Graphical Abstract

To create your abstract, type over the instructions in the template box below.

A useful methoxyvinyl cation equivalent: α -*t*-butyldimethylsilyl- α -methoxyacetaldehyde

Leave this area blank for abstract info.

Christopher D. McCune, Matthew L. Beio, Jacob A. Friest, Sandeep Ginotra and David B. Berkowitz*

A useful methoxyvinyl cation equivalent: α -t-butyltrimethylsilyl- α -methoxyacetaldehyde

Christopher D. McCune,^{a,§} Matthew L. Beio,^{a,§} Jacob A. Friest,^a Sandeep Ginotra and David B. Berkowitz^{a,*}

^aDepartment of Chemistry, University of Nebraska, Lincoln, NE 68588-0304, USA

[§]Note: These authors contributed equally to these studies.

ARTICLE INFO

Article history:

Received
Received in revised form
Accepted
Available online

Keywords:

methoxyvinylation
chelation control
Peterson elimination
 α -silyl- α -methoxyacetaldehyde
steric Felkin-Anh model

ABSTRACT

Described are the synthesis and application of α -t-butyltrimethylsilyl- α -methoxyacetaldehyde as a formal methoxyvinyl cation equivalent. Addition of Grignard reagents to the title aldehyde, followed by treatment of the intermediate β -hydroxysilanes with KH, gives good yields of large Z-methoxyvinylated products. Assuming a Peterson-like elimination mechanism, one can infer that the Grignard addition proceeds with high *syn* selectivity. These results are consistent with a chelation control model involving coordination to the α -methoxy group in the title aldehyde rather than an alternative stereoelectronic Felkin-Anh-type model. It must be noted that a steric Felkin-Anh model also accounts for the observed stereochemistry. All told, the title reagent can be employed to efficiently append a Z-configured methoxyvinyl group to an appropriate R-M species, in two steps.

2009 Elsevier Ltd. All rights reserved.

* Corresponding author. Tel.: +1-402-472-2738; fax: +1-402-472-9402; e-mail: dberkowitz1@unl.edu

The methoxyvinyl group is a functionality of importance both as a component of bioactive natural products and as an essential element of a number of synthetic reagents. Figure 1 illustrates several examples this functional group in both such contexts. Specifically, in

Figure 1. Naturally occurring and synthetically useful compounds bearing terminal methoxyvinyl groups. **a** - *E*-methoxyvinylglycine (natural; PLP enzyme inhibitor); **b** *Z*-methoxyvinylglycine (synthetic; SAM synthetase inhibitor); **c** isoquinoline anti-tumor agent; **d** fungal antibiotic eupenicinical B; **e** megistoquinone II antibiotic (natural); **f** asymmetric methoxyallylating agent (synthetic); **g** inverse electron demand dienophile (synthetic)

benzoazepinoisoquinolones, itself displays significant antitumor activity. On the other hand, compounds **f** and **g** bear methoxyvinyl groups as useful components of synthons being exploited for asymmetric methoxyallylation⁵ and inverse-electron demand Diels-Alder chemistry,⁶ respectively.

Interest in the *Z*-methoxyvinyl group, in particular, in our own research program is also stimulated by the finding that the *Z*-fluorovinyl group, among a range of vinylic functionalities,⁷ serves as a useful trigger for the mechanism-based inactivation of PLP-dependent enzymes.⁸ In synthesizing such vinylic PLP enzyme inhibitors initially, we had developed an approach whereby ethylene oxide, when combined with phenylselenolate anion, serves as a formal vinyl cation equivalent.⁹ It was therefore of interest for us

1 illustrates several examples this functional group in both such contexts. Specifically, in an amino acid context, *E*-methoxyvinylglycine (also known as 2-amino-4-methoxy-3-butenic acid = AMB; Figure 1, **a**) is biosynthesized by the opportunistic pathogen, *Pseudomonas aeruginosa*. Recently, it has been demonstrated that *E*-AMB strongly inhibits the growth of *Erwinia amylovora*, the causal agent of the devastating orchard crop disease known as fire blight.¹ On the other hand, synthetic *Z*-methoxyvinylglycine (**b**) is known to serve as an inhibitor of methionine adenosyltransferase,² the enzyme catalyzing the biosynthesis of S-adenosylmethionine as the first step in the important transulfuration pathway. Antibiotic scaffolds bearing terminal methoxyvinyl groups include the terpenoid natural product **d** from the plant source, *S. megistophylla*³ and the quinolone **e**, isolated from a *Eupenicillium* fungus.⁴ Significantly, the latter shows good activity against *S. aureus*. Finally, compound **c**, though a synthetic intermediate toward

Scheme 1. Synthesis of the title aldehyde **5**

to develop a complementary “methoxyvinyl cation equivalent” strategy here. Inspired by the pioneering work of Hudrlik¹⁰ that leverages Peterson olefination-type reactivity, we set out to construct an α -silyl- α -methoxy acetaldehyde suitable for condensation with appropriate nucleophiles. As is illustrated in Scheme 1, the desired methoxyvinyl cation equivalent could be assembled in a half dozen straightforward steps from propargyl alcohol. The key operation involves introduction of

Table 1

Representative additions to methoxyvinyl cation equivalent **5**

Entry	R	Metal/Solvent	dr	Yield 6 (%)
a		Li/THF	20:1	90 ^a
b		Mg/THF	6:1	80 ^a
c		Mg/THF	20:1	75
d		Mg/THF	10:1	96 ^a
e		Mg ⁺ /THF	6:1	69 ^b
f		Mg ⁺ /THF	8:1	76 ^b
g		Mg ⁺ /THF	6:1	81 ^b
h		Mg/THF	5:1	91
i		Mg/THF	12:1	72
j		Mg ⁺ /THF	20:1	63 ^b

Diastereoselectivity determined by ¹H-NMR. ^aYield estimated by NMR vs. CH₃CN as internal standard; ^bNote: Rieke magnesium (Mg⁺) was used to make the Grignard reagents in these cases.

Lewis acid-catalyzed opening of epoxide **3** α -to silicon, regiochemistry that is well preceded.¹¹ Compound **4** proved a convenient stage at which store the reagent. The title aldehyde **5** could then be unmasked oxidatively with Pb(OAc)₄ very cleanly, consistent with the observations of Chauret *et al.* in related systems.¹²

Table 2

Representative examples of the two step addition/elimination protocol

Entry	R	Metal/Solvent	Z:E	Yield 7 (%)
a		Li/THF	20:1	83
b		Mg/THF	6:1	72
c		Mg/THF	20:1	55
d		Mg/THF	10:1	86 ^a
e		Mg ⁺ /THF	6:1	65 ^b
f		Mg ⁺ /THF	8:1	68 ^b
g		Mg ⁺ /THF	6:1	70 ^b
h		Mg/THF	5:1	86
i		Mg/THF	12:1	65
j		Mg ⁺ /THF	20:1	53 ^b

E:*Z*-ratio determined by ¹H-NMR. ^aYield estimated by NMR vs. CH₃CN as internal standard; ^bNote: Rieke magnesium (Mg⁺) was used in these examples.

As can be seen from Table 1, upon condensing **5** with aryl Grignard reagents or lithium phenylacetylide, smooth aldehyde addition occurs and that addition is quite diastereoselective (from 5:1 to 20:1) as judged by crude NMR (see Figure 2 for a view of a representative NMR, for **6d**, in this case). Note that it was found particularly convenient to utilize Rieke magnesium (Mg^*)¹³ to generate the Grignard reagents at low T, e.g. leading to **6e-g** and **6j**. In some cases, the intermediate β -silyl alcohols **6** were isolated and purified chromatographically. However, yields were generally better if the crude β -silyl alcohol **6**, after workup, was treated with KH in THF to generate the methoxyvinyl compound directly. This efficiency of this two step addition/elimination protocol for the rapid methoxyvinylation of a metalated carbon nucleophile is documented in Table 2. Note that the diastereomeric ratio seen in the aldehyde addition adducts is reflected in the *Z:E* ratio seen in the elimination products, providing strong evidence in support of a stereospecific mechanism for the elimination, as expected for Peterson-type chemistry.

Figure 2. ¹H NMR (700 MHz, CDCl₃) spectra for the formation of both addition compounds **6d** and elimination products **7d**. The diastereomeric ratio remains constant (@ 10:1) suggestive of a stereospecific *syn* Peterson-type elimination wherein the predominant *syn*-addition product gives the *Z*-alkene and the minor *anti*-addition product gives the minor *E*-alkene.

The two-step addition/elimination protocol lends itself well to examination by ¹H NMR as is illustrated in Figure 2. Thus, addition of *p*-fluorophenylmagnesium bromide to the title aldehyde results in a 10:1 ratio of aldehyde addition adducts. Subsequent treatment with KH in THF at 0 °C delivers a 10:1 product distribution of *Z*- to *E*-methoxyvinylated arenes, with *J* values of 7.0 Hz and 12.6 Hz, respectively. Notice that the chemical shift windows for addition adducts and elimination products are well resolved, allowing for convenient mapping of the transformation of individual β -silyl- β -methoxy-alcohol adducts onto their derivative methoxyvinyl elimination products by ¹H NMR. A particularly interesting example is represented by the formation of the dienyl methyl ether from α -bromostyrene, utilizing Mg^* to generate the corresponding vinyl Grignard reagent, and employing the two step procedure.

Given the definitive identification of the Z-methoxyvinyl product as the major elimination product in each case under classic Peterson elimination conditions (KH, THF), it is presumed that the elimination occurs in a stereospecific *syn*-fashion, via the intermediacy of an pentacoordinate ate-addition complex at silicon (Figure 3).¹⁴ Logically then, it follows that the initial additions of aryl Grignard or lithiated acetylide nucleophiles to the title α -methoxy- α -silyl aldehyde must proceed in a highly *syn*-selective manner. The prevailing models for diastereoselection in the nucleophilic additions to chiral α -substituted aldehydes are presented in Figure 3. When an α -substituent bearing an electron-withdrawing heteroatomic substituent X is present, a Felkin-Anh model¹⁵ in which stereoelectronic effects predominate is often posited. There are two views of the nature of that stereoelectronic interaction in the transition state. If the transition state is late, then it is argued, the develop C-Nu σ -bonding orbital overlaps with the C-X σ^* -anti-bonding orbital. On the other hand, for early transition state, the Cieplak picture holds that C-X σ -bonding orbital overlaps with the C-Nu σ^* -anti-bonding orbital associated with the newly forming bond.¹⁶ Both of these stereoelectronic models require that the incoming nucleophile approach the carbonyl from an angle opposite to the C-X bond, albeit at the Bürgi-Dunitz angle. In the case at hand, this would mean approach opposite to the C-OMe bond, at that face of the carbonyl presenting the H-substituent, rather than the large TBS-substituent, thereby giving the *anti*-diastereomeric addition product, as shown in Figure 3. In all cases, this is the minor product, indicating that the stereoelectronic Felkin-Anh model does not apply here.

Figure 3. Comparison of the predictions made by the stereoelectronic Felkin-Anh model, the Cornforth-Evans model and by the chelation control model for the addition of RMgBr to the title methoxyvinyl cation equivalent, to form adduct **6**. Experimental results indicate that there is generally high *syn* selectivity in these additions suggesting that chelation contributions by the α -methoxy group in the electrophile outweigh stereoelectronic effects here.

Evans¹⁷ has recently put forth a modification of the traditional Cornforth model that is in keeping with widely accepted view that nucleophilic attack must proceed at the Bürgi-Dunitz¹⁸ angle. The Cornforth model¹⁹ postulates that for such electronegative substituents X, dipole-dipole interactions predominate. That is to say, in this view, there is a strong predilection for the C-X dipole to oppose the C=O dipole in the lowest energy transition state. Attack would then occur from the least hindered trajectory, i.e. opposite the TBS substituent here, subject to the aforementioned dipolar constraints. Once again, this model predicts the *anti*-product here and therefore cannot describe the predominant transition state.

On the other hand, a chelation control model,²⁰ in which the α -methoxy substituent and the aldehyde carbonyl are bridged by a chelating MgX or Li metal ion, is consistent with the observed stereochemistry here, in that attack from the least hindered face in this model would give the *syn*-product. It is important to note, however, that these results are also consistent with a steric-Felkin-Anh model,²¹ in which the sterics of the TBS group are postulated to override favorable stereoelectronic interactions involving the C-OMe bond.

As it stands, the methodology reported herein serves as a nice complement to existing methods for the installation of an alkoxyvinyl group. These include Horner-Wittig olefinations with $\text{Ar}_2\text{P}(\text{O})\text{CRH}(\text{OMe})$ reagents,²² as well as Julia olefination approaches with $\text{ArSO}_2\text{CH}_2(\text{OMe})$ reagents.²³ Finally, as is shown in Figure 4, this methoxyvinyl cation approach, though employing a Peterson-type elimination step following the condensation reaction, represents a different bond disconnection from traditional Peterson olefination approaches,^{14, 24} some of which have been developed for enol ether synthesis.²⁵ What differentiates the methodology reported herein from all of these approaches is, indeed, the bond disconnection, whereby the title reagent serves as a true methoxyvinyl cation equivalent, supplying the methoxy group and both carbons of the π -bond for convergent condensation with a nucleophile of choice. As such, we believe that this reagent has the potential for broad application in synthesis.

Figure 4. Comparison of bond constructions and stereochemical consequences of the methoxyvinylation approach reported here vs. the traditional Peterson olefination approach.

Acknowledgments

This paper is dedicated to the memory of Professor Harry H. Wasserman, a true scholar, leader in the organic chemistry community and a real gentleman. HHW served as an inspiration to DBB during his postdoctoral time at Yale and beyond. We thank Reuben Rieke and Rieke Metals, Inc. for providing the Rieke magnesium (Mg^*) utilized herein and for helpful discussion. The authors thank the NSF (1214019) for support. This research was facilitated by the IR/D (Individual Research and Development) program associated with DBB's appointment at the NSF. The authors thank the NIH (SIG-1-510-RR-06307) and NSF (CHE-0091975, MRI-0079750) for NMR instrumentation support and the NIH (RR016544) for facilities renovation.

References and notes

1. Lee, X.; Reimann, C.; Greub, G.; Sufrin, J.; Croxatto, A., *Microbes Infect.* **2012**, *14*, 268-272.
2. (a) González, B.; Pajares, M. a. A.; Hermoso, J. A.; Guillerm, D.; Guillerm, G.; Sanz-Aparicio, J., *J. Mol. Biol.* **2003**, *331*, 407-416; (b) Berkowitz, D. B.; Charette, B. D.; Karukurichi, K. R.; McFadden, J. M., *Tetrahedron: Asymmetry* **2006**, *17*, 869-882; (c) Gonzalez, B.; Pajares, M. A.; Hermoso, J. A.; Alvarez, L.; Garrido, F.; Sufrin, J. R.; Sanz-Aparicio, J., *J. Mol. Biol.* **2000**, *300*, 363-75.
3. Fokialakis, N.; Magiatis, P.; Chinou, I.; Mitaku, S.; Tillequin, F., *Chem. Pharm. Bull.* **2002**, *50*, 413-414.
4. Li, G.; Kusari, S.; Lamshoft, M.; Schuffler, A.; Laatsch, H.; Spiteller, M., *J. Nat. Prod.* **2014**, *77*, 2335-41.
5. Munoz-Hernandez, L.; Soderquist, J. A., *Org. Lett.* **2009**, *11*, 2571-2574.
6. (a) Stehl, A.; Seitz, G.; Schulz, K., *Tetrahedron* **2002**, *58*, 1343-1354; (b) Che, D.; Wegge, T.; Stubbs, M. T.; Seitz, G.; Meier, H.; Methfessel, C., *J. Med. Chem.* **2001**, *44*, 47-57.
7. (a) Berkowitz, D. B.; Chisowa, E.; McFadden, J. M., *Tetrahedron* **2001**, *57*, 6329-6343; (b) Berkowitz, D. B.; McFadden, J. M.; Sloss, M. K., *J. Org. Chem.* **2000**, *65*, 2907-2918; (c) Berkowitz, D. B.; McFadden, J. M.; Chisowa, E.; Semerad, C. L., *J. Am. Chem. Soc.* **2000**, *122*, 11031-11032; (d) Berkowitz, D. B.; Smith, M. K., *Synthesis* **1996**, *1*, 39-41.
8. (a) Berkowitz, D. B.; Karukurichi, K. R.; de la Salud-Bea, R.; Maiti, G.; McFadden, J. M.; Morris, M. L., *ACS Symp. Ser.* **2009**, *1009*, 288-303; (b) Berkowitz, D. B.; Karukurichi, K. R.; de la Salud-Bea, R.; Nelson, D. L.; McCune, C. D., *J. Fluorine Chem.* **2008**, *129*, 731-742; (c) Karukurichi, K. R.; De la Salud-Bea, R.; Jahng, W. J.; Berkowitz, D. B., *J. Am. Chem. Soc.* **2007**, *129*, 258-259; (d) Berkowitz, D. B.; de la Salud-Bea, R.; Jahng, W.-J., *Org. Lett.* **2004**, *6*, 1821-1824; (e) Berkowitz, D. B.; Pedersen, M. L.; Jahng, W.-J., *Tet. Lett.* **1996**, *37*, 4309-4312; (f) Berkowitz, D. B.; Jahng, W.-J.; Pedersen, M. L., *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2151-2156.
9. Pedersen, M. L.; Berkowitz, D. B., *J. Org. Chem.* **1993**, *58*, 6966-75.
10. Hudrlik, P. F.; Kulkarni, A. K., *J. Am. Chem. Soc.* **1981**, *103*, 6251-6253.
11. (a) Yoshida, J.-i.; Maekawa, T.; Morita, Y.; Isoe, S., *J. Org. Chem.* **1992**, *57*, 1321-1322; (b) Croudace, M. C.; Schore, N. E., *J. Org. Chem.* **1981**, *46*, 5357-5363; (c) Hudrlik, P. F.; Hudrlik, A. M.; Rona, R. J.; Misra, R. N.; Withers, G. P., *J. Am. Chem. Soc.* **1977**, *99*, 1993-1996.
12. Chauret, D. C.; Chong, J. M.; Ye, Q., *Tetrahedron: Asymmetry* **1999**, *10*, 3601-3614.
13. (a) Rieke, R. D., *Aldrichimica Acta* **2000**, *33*, 52-60; (b) Lee, J.-s.; Velarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D., *J. Org. Chem.* **2000**, *65*, 5428-5430.
14. Peterson, D. J., *J. Org. Chem.* **1967**, *33*, 780-784.
15. (a) Yang, X.; Liu, P.; Houk, K. N.; Birman, V. B., *Angew. Chem. Int. Ed.* **2012**, *51*, 9638-42; (b) Frenking, G.; Koehler, K. F.; Reetz, M. T., *Tetrahedron* **1993**, *49*, 3983-94; (c) Cherest, M.; Felkin, H.; Prudent, N., *Tet. Lett.* **1968**, *18*, 2199-2204; (d) Anh, N. T., *Top. Curr. Chem.* **1980**, *88*, 145-162; (e) Anh, N. T. E., Odile, *Nouv. J. Chim.* **1977**, *1*, 61-70.

16. Cieplak, A. S., *J. Am. Chem. Soc.* **1981**, *103*, 4540-4552.
17. Cee, V. J.; Cramer, C. J.; Evans, D. A., *J. Am. Chem. Soc.* **2006**, *128*, 2920-2930.
18. Buergi, H. B.; Dunitz, J. D., *Acc. Chem. Res.* **1983**, *16*, 153-61.
19. Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K., *J. Chem. Soc.* **1959**, 112-127.
20. (a) Raffier, L.; Stanton, G. R.; Walsh, P. J., *Org. Lett.* **2013**, *15*, 6174-6177; (b) Stanton, G. R.; Koz, G.; Walsh, P. J., *J. Am. Chem. Soc.* **2011**, *133*, 7969-7976; (c) Stanton, G. R.; Johnson, C. N.; Walsh, P. J., *J. Am. Chem. Soc.* **2010**, *132*, 4399-4408.
21. Lodge, E. P.; Heathcock, C. H., *J. Am. Chem. Soc.* **1987**, *109*, 3353-61.
22. (a) Mukai, K.; Urabe, D.; Kasuya, S.; Aoki, N.; Inoue, M., *Angew. Chem. Int. Ed.* **2013**, *52*, 5300-4; (b) Earnshaw, C.; Wallis, C. J.; Warren, S., *J. Chem. Soc.* **1979**, 3099-3106.
23. Surprenant, S.; Chan, W. Y.; Berthelette, C., *Org. Lett.* **2003**, *5*, 4851-4854.
24. (a) Hamlin, T. A.; Kelly, C. B.; Cywar, R. M.; Leadbeater, N. E., *J. Org. Chem.* **2014**, *79*, 1145-55; (b) Barbero, A. n.; Blanco, Y.; García, C.; Pulido, F. J., *Synthesis* **2000**, *9*, 1223-1228; (c) Welch, J. T.; Lin, J., *Tet. Lett.* **1998**, *39*, 9613-9616; (d) Welch, J. T.; Lin, J., *Tetrahedron* **1996**, *52*, 291-304.
25. (a) Seto, M.; Morihira, K.; Katagiri, S.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I., *Chem. Lett.* **1993**, *22*, 133-136; (b) Furukawa, T.; Seto, M.; Horiguchi, Y.; Kuwajima, I., *Chem. Lett.* **1993**, *22*, 1279-1282; (c) Magnus, P.; Roy, G., *J. C. S., Chem. Commun.* **1979**, 822-823.