Trisubstituted Olefins via Ester-Derived (Silyloxy)acetylenes: A Highly Stereoselective Alternative to the Horner–Wadsworth–Emmons Reaction

Conrad J. Kowalski* and Santi Sakdarat[1]

Synthetic Chemistry Department, SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, King of Prussia, Pennsylvania 19406

Received January 30, 1990

Summary: Crude ((triisopropylsilyl)oxy)acetylenes **2**, prepared in one step from common esters **1**, react with aldehydes in 60–65% overall yield after methanol quench to afford α,β-unsaturated esters **3** with very high E/Z stereoselectivity.

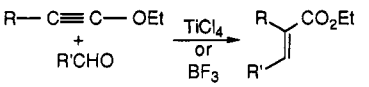
Both Arens[2] and Miginiac[3] have previously reported that ethoxyacetylenes will react with certain aldehydes under Lewis acid conditions to afford α,β-unsaturated esters possessing E-olefin geometry (Scheme I). Only examples in which R = CH_3 or CH_2SiMe_3 were presented, however, and subsequent utilization of this chemistry in a broader sense has not occurred. Very likely this is due to the fact that no really general, direct syntheses of alkoxyacetylenes exist.[4] Herein we report that a wide variety of crude (silyloxy)acetylenes **2**, prepared in a single step from esters **1**, also react with aldehydes and afford unsaturated esters **3** with extremely high E/Z selectivity. The directness of this new process, coupled with its remarkable stereoselectivity, renders it an attractive alternative to the classical Horner–Wadsworth–Emmons reaction.

Ester **1a** (R = *n*-pentyl) was converted using our standard one-pot procedure[5] into the ((triisopropylsilyl)oxy)acetylene **2a**, which was isolated but not purified. Reaction of **2a** with 1.2 equiv of 3-phenylpropanal in methylene chloride was effected at −78 °C for 10 min in the presence of 1.0 equiv of $TiCl_4$. In an attempt to isolate the likely intermediate **4** (R = C_5H_{11}, R′ = CH_2CH_2Ph), an extremely mild workup was employed (dilution at −78 °C with triethylamine/ether followed by sodium bicarbonate and brine washes). What was obtained, however, exclusively as the E isomer, was the unsaturated triisopropylsilyl ester **5a** (R = C_5H_{11}, R′ = CH_2CH_2Ph) in 45% yield. This failure to isolate any intermediate products having an intact 4-membered ring, as well as the observed E stereochemistry, both parallel earlier observations in the alkoxyacetylene series.[2,3]

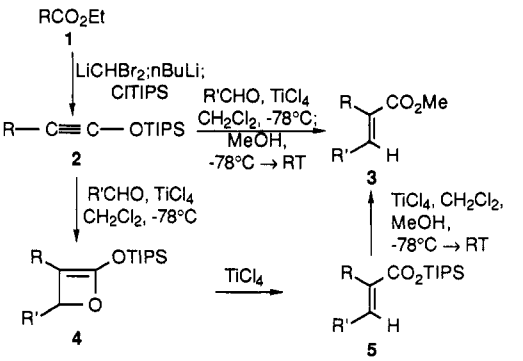
When the silyl ester **5a** was treated at room temperature with methanol in the presence of $TiCl_4$, clean transesterification to the methyl ester **3** occurred in 91% yield (rather than cleavage to the carboxylic acid). This suggested it might be possible to effect an overall transformation of **2** to **3** in a single pot. When crude (silyloxy)acetylene **2a** (R = C_5H_{11}) was treated with 3-phenylpropanal and $TiCl_4$ at −78 °C, followed by addition of methanol and warming to room temperature, ester **3a** was indeed obtained. The yield was 65%, based on starting ethyl hexanoate, and only the E isomer was observed (even prior to purification).

As evidenced by the examples in Table I, this two-pot preparation[6] of α,β-unsaturated esters **3** appears to be quite general for a variety of starting esters (**1**) and starting aldehydes. The carbethoxy group of **1** may be attached to primary, secondary, or aromatic R groups, with similar variations allowed in the aldehyde R′ group. For the two-step procedure, utilizing crude (silyloxy)acetylene intermediate, overall yields are generally in the range of 60–65% from the starting ester.

Scheme I



Scheme II



The trisubstituted olefin products in Table I are the same type obtained from the classical Horner–Wadsworth–Emmons reaction.[11] To make these same products via the latter reaction, however, would require ester

(1) SK&F Postdoctoral Scientist.

(2) Vieregge, H.; Schmidt, H. M.; Renema, J.; Bos, H. J. T.; Arens, J. F. *Recueil* **1966**, *85*, 929–951.

(3) Pornet, J.; Khouz, B.; Miginiac, L. *Tetrahedron Lett.* **1985**, *26*, 1861–1862. For related work, see also: Pornet, J.; Rayadh, A.; Miginiac, L. *Ibid.* **1986**, *27*, 5479–5482.

(4) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693–3695, ref 3.

(5) Kowalski, C. J.; Lal, G. S.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127–7128.

(6) In a typical procedure, performed under N_2, 8.8 mmol of 2.5 M *n*-butyllithium solution in hexane was added dropwise to a stirred solution of 9.6 mmol of 2,2,6,6-tetramethylpiperidine in 8 mL of dry THF with ice-bath cooling. This mixture was then added dropwise via cannula over about a 5-min period to a stirred solution of 8.8 mmol of dibromomethane in 8 mL of dry THF, cooled with a −78 °C (dry ice/acetone) bath. After 5 min, a solution of 4.0 mmol of ethyl hexanoate (**1a**) in 1 mL of THF was added dropwise, and 30 min later a solution of 20 mmol of 2.5 M *n*-butyllithium in hexane was added dropwise. The −78 °C bath was replaced with a warm (30 °C) water bath for 45 min and then returned, after which 20.0 mmol of chlorotriisopropylsilane was added. The mixture was then stirred at about 0 °C (ice bath) for 2 h, diluted with 300 mL of petroleum ether, and washed with three 80-mL portions of aqueous sodium bicarbonate solution and one 100-mL portion of brine. After drying over anhydrous sodium sulfate, removal of the solvent in vacuo, and removal of remaining chlorosilane under high vacuum overnight, the crude (silyloxy)acetylene **2a** was used in the next step. Titanium tetrachloride (1.0 mmol) was added dropwise over 2–3 min to a stirred, −78 °C solution containing exactly one-fourth (nominally 1.0 mmol) of the crude (silyloxy)acetylene **2a** from above and 1.2 mmol of 3-phenylpropanal in 8 mL of dichloromethane. After 10 min, 5 mL of absolute methanol was added and the dry ice/acetone bath was removed. After 2 h, the mixture was diluted with 80 mL of ether, washed with water and brine, and dried over anhydrous sodium sulfate. Removal of the solvent and purification via prepative TLC on silica gel afforded 170 mg of ester **3a** (65% from **1a**).

(7) All new compounds afforded satisfactory IR and NMR spectroscopic data, as well as proper exact mass determination. In most cases, stereochemistry was assigned via NOE experiments on the major isomer, and sometimes on the minor isomer as well when both were available (e.g. **13** and **14**).

(8) Vaidyanathaswamy, R.; Parmer, B. S.; Attri, B. S.; Singh, R. P.; Mukerjee, S. K. *J. Agric. Food. Chem.* **1977**, *25*, 1401–1404.

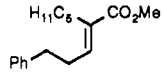
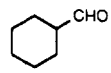
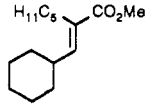
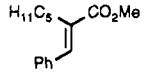
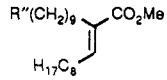
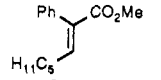
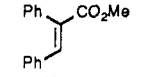
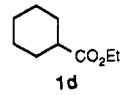
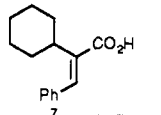
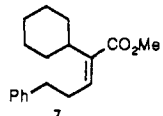
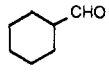
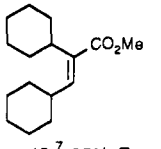
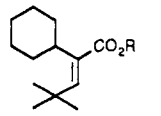
(9) Rousseau, G.; Slougui, N. *Tetrahedron* **1985**, *41*, 2653–2664.

(10) Picard, J. P.; Dunogues, J.; Calas, R. *J. Organomet. Chem.* **1974**, *77*, 167–176.

(11) Wadsworth, W. S. *Org. React.* **1977**, *25*, 73–253.

0022-3263/90/1955-1977$02.50/0

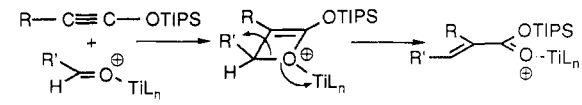
Table I

ester	aldehyde	product, % E_c[a] (yield; % E_p)
$H_{11}C_5CO_2Et$ **1a**	$Ph(CH_2)_2CHO$	 **3a**,[7] 100% E_c (65%; 100% E_p)
		 **6**,[7] 91% E_c (63%; 100% E_p)
	PhCHO	 **7**,[8] 84% E_c (64%; 93% E_p)
$C_{10}H_{21}CO_2Et$ **1b**	$H_{17}C_8CHO$	 **8**,[7] 100% E_c (66%; 100% E_p)
$PhCO_2Et$ **1c**	$H_{11}C_5CHO$	 **9**,[9] 100% E_c (65%; 100% E_p)
	PhCHO	 **10**,[10] 97% E_c (62%; 100% E_p)
 **1d**	PhCHO	 **11**,[7] 80% E_c (56%; 98% E_p)[b]
	$Ph(CH_2)_2CHO$	 **12**,[7] 100% E_c (63%; 100% E_p)
		 **13**,[7] 95% E_c (64%; 97% E_p)
		 **14**,[7] (61%; 39% E_p)[c]

[a] E_c and E_p indicate the percent of E isomer observed in the E/Z mixture of crude and purified product, respectively; these values were assigned by NMR and/or capillary GC and are only approximate for E_c. [b] This compound, for unexplained reasons, was obtained as the acid (not ester). NOE was performed on the corresponding methyl ester. [c] 85:15 mixture of acid and ester.

starting materials different from 1 to prepare the phosphonates (since our procedure involves a homologation step). This new chemistry, therefore, is complimentary

Scheme III



to the classical approach in terms of starting material. Perhaps more significant, however, is the extremely high ratio of E to Z products obtained. While the Horner–Wadsworth–Emmons reaction proceeds very well to afford the E product **3** when R = H (and in many cases CH_3), the stereochemistry often deteriorates for larger R and R′ groups.[12] For example, Marshall has published some model studies in which he tried numerous variants (classical and modern) of the Horner–Wadsworth–Emmons reaction to prepare the unsaturated ester **8** (R″ = vinyl) bearing two long hydrocarbon chains. The best E:Z ratio he was able to obtain via phosphonate reactions with nonanal was 85:15.[12] In order to compare our chemistry in a closely related case, the (silyloxy)acetylene **2b** (prepared from ester **1b**, R = $C_{10}H_{21}$) was also reacted with nonanal; in the resulting product **8** (R″ = CH_3), only the E isomer was obtained, with none of the Z compound observed even in the crude product.

Perhaps the most impressive stereochemical result obtained was in the formation of ester **13**, in which the isomer having *cis*-cyclohexyl groups was predominant in the crude product by almost 20:1. Semiempirical MO calculations indicated that this major E product was about 1.6 kcal less stable than the corresponding Z isomer. Indeed, treatment of a 4:1 mixture of E- and Z-**13** under isomerizing conditions ($LiSCHMe_2$, THF, Δ) afforded a 96% yield of recovered **13**, but with an E/Z ratio of 1:4. While this may not represent a final equilibrium mixture, it clearly demonstrates that the initially obtained E product is thermodynamically less stable.

One possible explanation for the high E/Z selectivity of this reaction, even to form less stable, kinetic products, would be a concerted, electrocyclic ring opening of the Lewis acid complexed oxetene (having a trans orientation of the titanium and R′ group). Allowed, conrotatory thermal opening might be expected to occur with outward rotation of the R′ group and the titanium/ligand complex, thus affording the observed E stereochemistry.[13] In the case of product **14**, in which such an opening would force a *tert*-butyl and cyclohexyl group to be cis on the olefin, the E/Z ratio drops to about 1:2. This may indicate the onset of a competitive ring-opening process, in which a discrete carbocation (with rotational freedom) is generated at the center bearing the R′ group. This would also be consistent with the lower E stereochemistry observed in products **7** and **11** in which a better carbocation stabilizing group (R′ = phenyl) was present. Despite the poor stereochemical results observed in formation of **14**, the fact that a 61% yield of this hindered product was obtained is in itself somewhat remarkable.

Additional work is needed to elucidate the exact mechanism of this trisubstituted olefin forming reaction. Regardless of the mechanism, however, it is clear from the results in Table I that this two step process (1 → 2 → 3) allows for efficient incorporation of the body (R) of an ester (RCO_2Et) at the α-position of an α,β-unsaturated ester. The directness of this procedure, coupled with the unusually high E/Z stereoselectivity, serves to make it a

(12) Marshall, J. A.; DeHoff, B. S.; Cleary, D. G. *J. Org. Chem.* **1986**, *51*, 1735–1741 and references therein.
(13) Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1985**, *107*, 2099–2111.

useful alternative to the classical Horner–Wadsworth–Emmons reaction.

Acknowledgment. We would like to thank Walter Johnson, Priscilla Offen, and Scott Dixon at SK&F for exact mass determination, NOE studies, and MO calculations, respectively, and both Paul Gassman and Larry Overman for stimulating discussions.

Supplementary Material Available: IR and NMR data given for *E*-**3a**, *E*-**5a**, *E*-**6**, *E*-**7**, *E*-**8** (R″ = Me), *E*-**9**, *E*-**10**, *Z*-**10**, *E*-**11**, *E*-**12**, *E*-**13**, *Z*-**13**, *Z*-**14** (R = H), *E*-**14** (R = H), *E*/*Z*-**14** (R = Me), with high-resolution mass spectral data for new compounds (2 pages). Ordering information is given on any current masthead page.

A Route to Glycals in the Allal and Gulal Series: Synthesis of the Thiosugar of Esperamicin A_1

Mark D. Wittman, Randall L. Halcomb, and Samuel J. Danishefsky*
Department of Chemistry, Yale University, New Haven, Connecticut 06511
Jerzy Golik and Dolatrai Vyas
Bristol-Myers Squibb Company, Wallingford, Connecticut 06492
Received December 7, 1989

Summary: Axial anomeric sulfoxides generated via thiophenol Ferrier rearrangement of glucal and galactal derivatives are used to synthesize glycals of the gulal and allal series. An application of the method led to the synthesis of the esperamicin thiosugar, thereby establishing its absolute configuration.

The advent of the potent DNA cutting antibiotics esperamicin (**1**)[1] and calicheamicin[2] raises numerous issues in biology and chemistry. Not the least of the challenges and opportunities for organic synthesis in this area is that of the carbohydrate sector (cf. esperamicin trisaccharide type, **2**). While the enediyne carbocyclic region presumably serves as the source of the chemically destructive properties,[3] the carbohydrate ensemble may well play an important role as a recognition marker for the oligonucleotide.[4] In this paper we describe a synthesis of the hexose containing the thiomethyl group.[5]

While the methyl glycoside **3** was the focus of the effort, a more general objective was that of providing access to glycals bearing 3-axial alcohol derivatives, with a range of substituents at C4 (see allal and gulal structures **4** and **5**, respectively).[6] Glycals of this type might be useful intermediates for reaching **3** and might serve as glycosyl donors pursuant to a projected synthesis of the larger goal, i.e. system **2** (see Scheme I).

The concept is well illustrated by the conversion of the commercially available triacetylglucal (**6**) to the allal derivative **11**. Treatment of **6** with benzenethiol (BF_3·OEt_2–methylene chloride −78 °C) afforded, by Ferrier type rearrangement,[7a,b] the α-(phenylthio)pseudoglycal[7c] in 72% yield. There was also produced ca. 8% of the corresponding β-phenylthio anomer. Compound **7** was oxidized with *m*-chloroperoxybenzoic acid (mCPBA) in methylene chloride at 0 °C.[8] Exposure of resultant sulfoxide **8** to piperidine at room temperature afforded a 70% yield of **11**.[9] In a similar way L-rhamnal derivative **12** was converted to α-sulfide **13**[9] (71% yield) and thence to **17**[9] in 30% overall yield.[10]

The most obvious formulation of these results involves [2,3] sigmatropic rearrangement of **8** and **14**,[11,12] leading to sulfenates **9** and **15**, respectively (Scheme II). These intermediates are interdicted with piperidine to give **10** and **16**, which undergo acyl transfer to provide the observed products **11** and **17**. An alternate formulation, which avoids the need to invoke an acyl transfer, contemplates neighboring group participation by the trans-dis-

(1) (a) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (b) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.

(2) (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466.

(3) For a review of the seminal experiments involving the generation of aromatic 1,4-diyls from cis-enediynes see: (a) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. For early applications of the generation of aromatic 1,4-diradicals to mimic the mode of action of the esperamicins and calicheamicins, see: (b) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921. (c) Magnus, P.; Carter, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 1626. (d) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866. For examples of the use of related 1,4-diyls, such as that derived from esperamicin, in DNA cleavage, see: (e) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Kataoka, H. *J. Am. Chem. Soc.* **1988**, *110*, 7247. (f) Mantlo, N. B.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 2781. (g) Zein, N.; McGahren, W. J.; Morton, G. O.; Ashcroft, J.; Ellestad, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 6888.

(4) (a) Hawley, R. C.; Kiessling, L. L.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 1105. (b) Zein, N.; Poncin, M.; Nilakantan, R.; Ellestad, G. A. *Science* **1989**, *244*, 697. (c) Long, B. H.; Golik, J.; Forenza, S.; Ward, B.; Rehfuss, R.; Dabrowiak, J. C.; Catino, J. J.; Musial, S. T.; Brookshire, K. W.; Doyle, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 2. (d) Sugiura, Y.; Uesawa, Y.; Takahashi, Y.; Kuwahara, J.; Golik, J.; Doyle, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 7672.

(5) A nonselective synthesis of the thiol analogue of the methylthio monosaccharide was recently reported: Scharf, H.-D.; Laak, K. V. *Tetrahedron* **1989**, *34*, 4505.

(6) All attempted reductions of the corresponding ketones lead to equatorial alcohols: (a) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. Attempts to directly invert the equatorial 3-OH using Mitsunobu conditions or by displacing equatorial leaving groups led only to S_n2' reactivity. For some previous preparations of allal and gulal derivatives, see: (b) Sharma, M.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 2825. (c) Lemieux, R. U.; Fraga, E.; Watanabe, K. A. *Can. J. Chem.* **1968**, *46*, 61.

(7) (a) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570. (b) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 199. (c) Valverde, S.; Garcia-Ochoa, S.; Martin-Lomas, M. *J. Chem. Soc., Chem. Commun.* **1987**, 383.

(8) The sulfoxides were isolated but were not characterized. They were immediately treated with piperidine without any attempt to isolate their corresponding sulfenates. For a striking demonstration of the lability of anomeric sulfoxides, see: Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

(9) All new compounds were characterized by IR and NMR spectroscopy, HRMS, and optical rotation.

(10) Complications arising from the votalility of glycal **17** rather than differences in chemistry are responsible for the decreased yields in this case.

(11) (a) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869. (b) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100.

(12) (a) Evans, D. A.; Andrews, G. C.; Sims, C. L. *J. Am. Chem. Soc.* **1971**, *93*, 4956. (b) Evans, D. A.; Bryan, C. A.; Sims, C. L. *J. Am. Chem. Soc.* **1972**, *94*, 2891. (c) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.

0022-3263/90/1955-1979$02.50/0