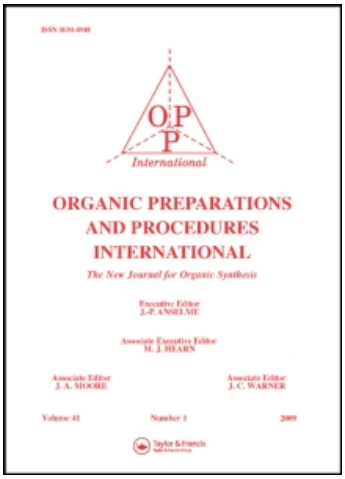


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

Chemistry of 3-Alkynals. A Review

Ronald Blankespoor[a]
[a] Department of Chemistry and Biochemistry, Calvin College, Grand Rapids, Michigan, U.S.A.

Online publication date: 01 October 2010

To cite this Article Blankespoor, Ronald(2010) 'Chemistry of 3-Alkynals. A Review', Organic Preparations and Procedures International, 42: 5, 467 — 477
To link to this Article: DOI: 10.1080/00304948.2010.513929
URL: http://dx.doi.org/10.1080/00304948.2010.513929

Organic Preparations and Procedures International, 42:467–477, 2010

ISSN: 0030-4948 print
DOI: 10.1080/00304948.2010.513929

Chemistry of 3-Alkynals. A Review

Ronald Blankespoor

Department of Chemistry and Biochemistry, Calvin College, Grand Rapids, Michigan, U.S.A.

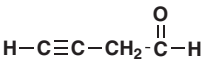
Chemistry of 3-Alkynals. A Review

Ronald Blankespoor

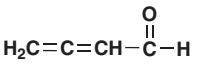
Department of Chemistry and Biochemistry, Calvin College, Grand Rapids, Michigan, U.S.A.

Introduction

Underlying the chemistry of *unsubstituted 3-alkynals* (*i. e.*, 3-alkynals unsubstituted at the 2-position) is their tendency to rearrange to 2,3-dienals in which one of the carbon-carbon π bonds is conjugated to the carbonyl. The relative energies of 3-butynal (**1**) and 2,3-butadienal (**2**), determined using density functional theory (DFT) and Hartree-Fock theory, show that conjugation of the aldehyde to the allene in **2** makes it 5–10 kcal/mol more stable than **1** where the π systems are not conjugated.[1] It is not surprising, therefore, that 3-alkynals are much less prominent in the literature than conjugated 2-alkynals, and some higher alkynals (*i. e.*, 4-alkynals, 5-alkynals, etc.), which have two or more sp^3 carbons separating their triple bond and carbonyl.



1



2

With methods now available to make 3-alkynals in gram quantities, contaminated by only small percentages of their 2,3-alkadienals, these compounds will undoubtedly play a more important role in synthesis having a triple bond that can undergo, for example, cyclization reactions,[2–6] and a carbonyl that can react with nucleophiles such as Wittig reagents[7] and enolates.[8,9] This review describes the chemistry of 3-alkynals reported in the literature through 2009. Unsubstituted 3-alkynals, which are prone to isomerization and consequently more difficult to synthesize, are treated separately from 3-alkynals that have substituents at the 2-position thereby "blocking" their rearrangement to 2,3-alkadienals.

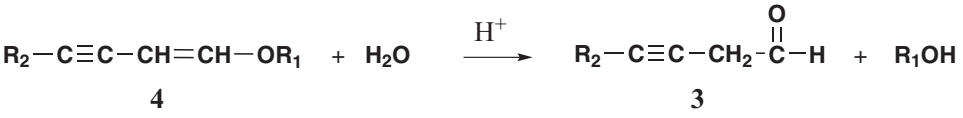
Received January 29, 2010; in final form June 4, 2010.

Address correspondence to Ronald Blankespoor, Department of Chemistry and Biochemistry, Calvin College, Grand Rapids, MI 49546-4403. E-mail: blan@calvin.edu

I. Synthesis of Unsubstituted 3-Alkynals

1. Hydrolysis of Enol Ethers

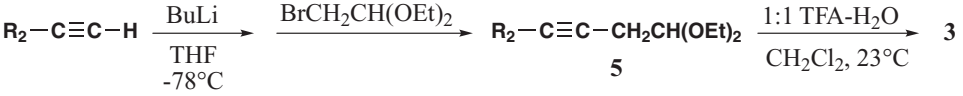
Some of the first attempts to prepare 3-alkynals (**3**) in the literature utilized the acid-catalyzed hydrolysis of enol ethers **4** *(Scheme 1)*. Heating **4** (R_1 = Me; R_2 = H, Et) in the presence of 4–10% H_2SO_4 for short times led to 3-butynal and 3-hexynal in low yields.[10,11] Durand and Piaux obtained 3-hexynal and 3-hepytnal in yields of ca. 25% when they hydrolyzed **4** (R_1 = Et; R_2 = Pr) using oxalic acid and hydroquinone.[13] None of these early workers commented on the purity of the 3-alkynals made by this method or their possible rearrangement to 2,3-alkadienals. In light of more recent work on 3-alkynals, though, it is likely that this method also results in rearrangement to their isomers in yields that depend upon the acid catalyst and conditions used in the hydrolysis.



Scheme 1

2. Hydrolysis of Acetals

Accessing 3-alkynals *via* the acid-catalyzed hydrolysis of their acetals has been more successful, not only in terms of yields and purity from the hydrolysis, but also because the acetals can be prepared in good yields from 1-alkynes (*Scheme 2)*. Roush and Park were able to prepare acetal **5** (R_2 = *n*-hexyl) in 75% yield,[14] and its hydrolysis led to a 95% yield of 3-decynal with less than 5% of 2,3-decadienal.[14,15]

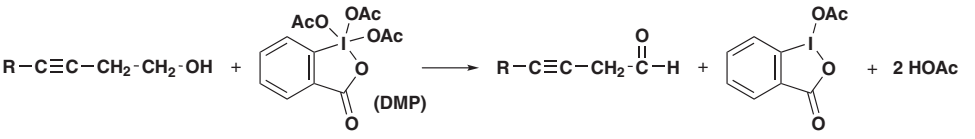


Scheme 2

Hydrolysis of **5** (R_2 = *n*-butyl, *n*-pentyl) in pentane/HCO_2H for 1 h at 20°C gave 3-octynal and 3-nonynal in yields of 50% and 57%, respectively, with less than 10% of their corresponding 2,3-dienals.[16] Interestingly, Sayre *et al*. report that their attempts to hydrolyze 4,4-diethoxy-1-butyne to 3-butynal with different acids either failed due to insufficient acid strength or generated 3-butynal with significant amounts of 2,3-butadienal.[17]

3. Dess-Martin Periodinane Oxidation

Two laboratories have used Dess-Martin periodinane (DMP), a hypervalent iodine (V) compound, to oxidize readily available 3-alkyn-1-ols to 3-alkynals (*Scheme 3*). Wavrin and Viala prepared 3-hexynal and 3-nonynal in yields of 95% and 96%, respectively, with this oxidizing agent in CH_2Cl_2 at 0°C.[18] These workers noted that the NMR spectra of these alkynals showed "no trace of allenic aldehydes or starting alcohols" when reaction mixtures

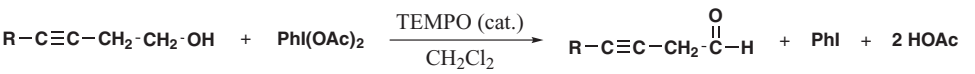


Scheme 3

were rapidly filtered through silica gel at low temperatures (−40 to −50°C) followed by drying *via* azeotropic vacuum distillation. More recently, Orru *et al.* were able to make 3-decynal quantitatively from 3-decyn-1-ol using DMP.[15] Although the filtration/evaporation procedures using DMP are somewhat cumbersome, the high yields of 3-alkynals from readily available alcohols without significant rearrangement to their 2,3-alkadienals certainly make this mild oxidation method an important one for synthesizing 3-alkynals.

4. TEMPO/PhI(OAc)$_2$ Oxidation

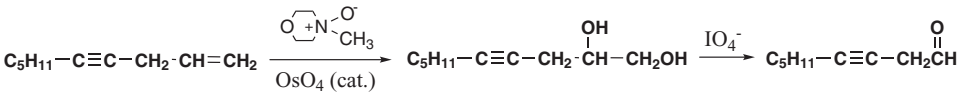
Orru *et al.* have used another mild oxidizing agent, 2,2,6,6-tetramethyl-1-piperidinyloxyl radical (TEMPO), to convert 3-alkyn-1-ols to 3-alkynals (*Scheme 4*), albeit in much lower yields.[19] Thus, catalytic amounts of TEMPO were used in combination with PhI(OAc)$_2$ to convert 3-pentyn-1-ol to 3-pentynal in 41% yield. Interestingly, only a trace of 3-butynal was obtained from the oxidation of 3-butyn-1-ol using this method due to its low reactivity.



Scheme 4

5. Periodate Cleavage of Glycols

Although this method of preparing 3-alkynals first appeared in the literature in 1963, 3-hexynal was formed in only 30% yield, and no mention was made of the presence or absence of its dienal isomer.[12] More recently, Corey and Wright were able to prepare 3-nonynal, an intermediate needed for the synthesis of colneleic acid, in high yield using the sequence of reactions in *Scheme 5* starting with 1-decen-4-yne, which was made from 1-heptene



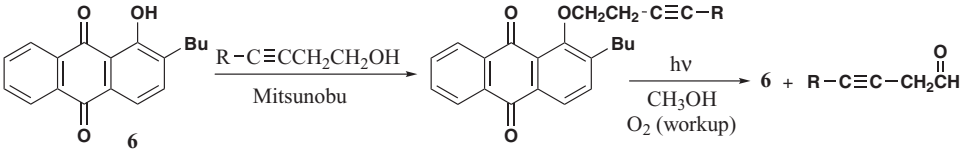
Scheme 5

using a literature method.[20] The oxidative cleavage in the last step (99% yield) was carried out in a two-phase reaction mixture composed of CH_2Cl_2 and aqueous sodium periodate in the presence of a catalytic amount of tetrabutylammonium periodate. The high yield of 3-nonynal, in gram quantities starting with a terminal alkyne, makes this method an excellent one for making 3-alkynals. Although NMR data was reported for 3-nonynal, these workers

did not comment on the presence or absence of 2,3-nonadienal in their final product, which was azeotropically dried with toluene before use in the next step of the synthesis.

6. Photochemically from 1-Alkynoxy-9,10-anthraquinones

3-Alkynals can also be prepared under very mild conditions using a photochemical process developed in our laboratory (*Scheme 6*).[21] Readily available 3-alkyn-1-ols are attached to the 1-position of 1-hydroxy-2-butyl-9,10-anthraquinone (**6**) using the Mitsunobu reaction. Irradiation of the resulting 1-alkynoxy-2-butyl-9,10-anthraquiones in methanol using 300–370 nm light followed by exposure to oxygen leads to the formation of 3-alkynals in isolated yields of 35–45% with only trace amounts of their 2,3-alkadienals. This method of making 3-alkynals could be useful in syntheses involving several hundred milligram quantities of substrates that have functional groups that are sensitive to acids, bases, or heating.



Scheme 6

II. Stability of Unsubstituted 3-Alkynals

Although it is clear from the literature that 3-alkynals should not be heated to high temperatures or stored for long periods at room temperature, they can be distilled under vacuum[16,18] and heated to 60°C in $CDCl_3$ solution for hours without significant rearrangement.[22] Heating a solution of **1** in $CDCl_3$, though, in a sealed NMR tube at 100°C for 4 hours resulted in almost complete rearrangement to **2**.[22] One laboratory reported that 3-octynal and 3-nonynal polymerized after one week at room temperature.[16] In our hands solutions of 3-alkynals in $CDCl_3$ were stable for weeks in a freezer.[22]

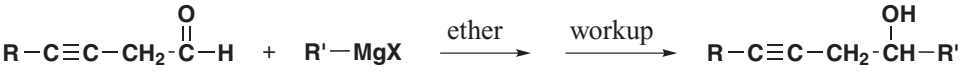
One reported attempt to purify 3-decynal using chromatography let to extensive decomposition.[14] Stirring chloroform solutions of this compound in silica gel for only 10 min at room temperature resulted in its partial rearrangement to 2,3-decadienal as evidenced by the NMR spectra of the aldehydic hydrogens.[21] As noted above, rapid filtration of 3-hexynal and 3-nonynal through a short pad of silica gel at low temperature (−40 to −50°C) did not result in significant rearrangement.[18]

There is considerable evidence in the literature that 3-alkynals rearrange to 2,3-alkadienals in the presence of acid. This was undoubtedly the reason early attempts to prepare these compounds by hydrolysis of enol ethers and acetals using dilute solutions of strong acids resulted in considerable rearrangement. Biphasic acidic mixtures (*e. g.*, formic acid/pentane[16] and aqueous TFA-$CHCl_3$[14]) do hydrolyze acetals to 3-alkynals at room temperature, but 5–10% of their 2,3-alkadienals are also obtained. Care should be taken to neutralize reaction mixtures before workup to prevent rearrangement (see, for example, Reference 19).

III. Reactions of Unsubstituted 3-Alkynals

1. Grignard Addition

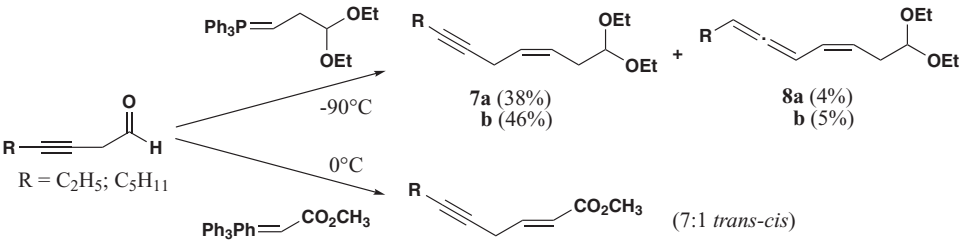
3-Alkynals react with Grignard reagents to form alkynols without significant prior rearrangement to their 2,3-alkadienals (*Scheme 7*). Reaction of 3-octynal and 3-nonynal with allylmagnesium bromide led to 4-hydroxy-1-undecen-6-yne and 4-hydroxy-1-dodecen-6-yne in yields of 50 and 57%, respectively.[16] 4-Octyn-2-ol and 4-undecyn-2-ol were obtained in overall yields of 35–40% starting with their anthraquinones (*Scheme 6*, R = C_3H_7 and C_6H_{13}).[21] Given that the photochemical step occurs in yields of 35–45%, the addition of methylmagnesium bromide to 3-heptynal and 3-decynal occurs in yields of at least 70%.



Scheme 7

2. Wittig Addition

Wittig reagents react with 3-alkynals to form 1-en-4-ynes in moderate yields (*Scheme 8*). Wavrin and Viala reacted 3-hexynal (R = C_2H_5) and 3-nonynal (R = C_5H_{11}) with (3,3-

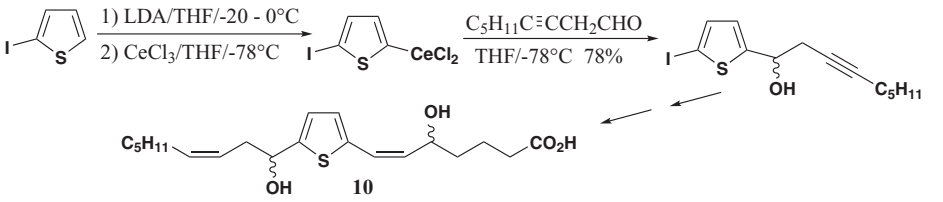


Scheme 8

diethoxypropylidene)triphenylphosphorane at −90°C to give *(Z)*-enynes **7** along with small amounts of their rearranged isomers, the (*Z*)-trienes **8**.[18] Interestingly, reaction of 3-heptynal and 3-decynal with the methyl ester of (triphenylphosphoranylidene)acetate gave mostly the (*E*)-enynes (**9**) without significant amounts of the corresponding trienes.[21] These results nicely affirm the observation that unstabilized ylides give predominately (*Z*)-alkenes, whereas stabilized ylides give mainly (*E*)-alkenes.[23]

3. Organocerium Addition

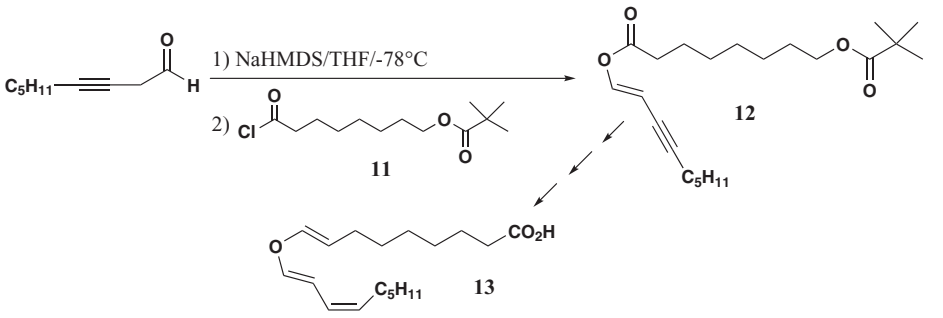
An important step in the synthesis of 8,11-thioleukotriene B_4 (**10**) is the reaction of an organocerium reagent with 3-nonynal (*Scheme 9*),[24] which was prepared by hydrolysis of its diethyl acetal.[16] The addition of the organocerium reagent to the carbonyl goes in high yield (78%) without prior rearrangement of 3-nonynal to 2,3-nonadienal.



Scheme 9

4. Enolate Formation

Not surprisingly, 3-alkynals can be converted to enolates by treatment with strong, non-nucleophilic bases (*Scheme 10*). In the synthesis of colneleic acid (**13**) Corey and Wright[20] prepared the enolate of 3-alkynal and reacted it with acid chloride **11** to form ester **12** in a 22% yield (not optimized). Several more steps were needed to achieve their goal of colneleic acid.



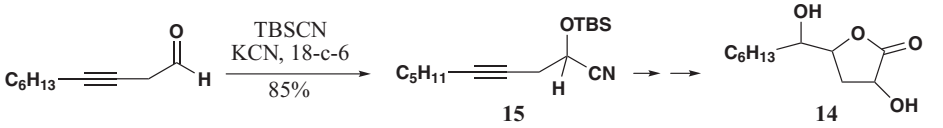
Scheme 10

5. Acetal Formation

Wavrin and Viala have shown that the method of forming 3-alkynals from acetals (*Scheme 2*) can be reversed.[18] Reaction of 3-hexynal with triethyl orthoformate in the presence of catalytic amounts of camphorsulfonic acid generated 1,1-diethoxyhex-3-yne in 65% yield. According to these workers, this is an efficient way to make homopropargylic acetals with different alkyl groups.

6. Cyanide Addition

Vugts *et al.* recently reported the synthesis of 3'-deoxyribolactone **14** in a 44% overall yield from commercially available 3-decyn-1-ol, which was oxidized to 3-decynal using DMP (*Scheme 11*).[15] A key step in this sequence of reactions is the addition of cyanide to the carbonyl of 3-decynal using *t*-butyldimethylsilyl cyanide (TBSCN) to form protected alcohol **15**.



Scheme 11

IV. Reactions and Synthesis of 2,2-Disubstituted 3-Alkynals

When both hydrogens at the 2-position (*i. e.*, α-hydrogens) in 3-alkynals are substituted, rearrangement to 2,3-alkadienals is no longer an obstacle to using these compounds as synthetic tools. As shown in *Table 1*, some of these alkynals undergo cyclization reactions to form 6-, 9-, and 10-membered rings in moderately good yields.[25–29] Others have been

Table 1
Reactions of 2,2-Disubstituted 3-Alkynals

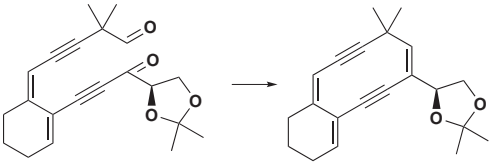
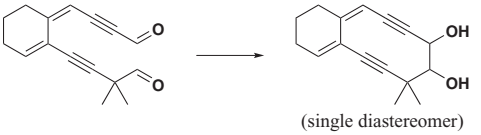
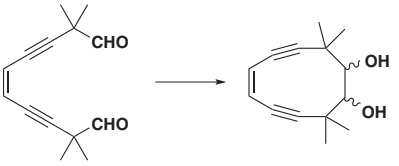
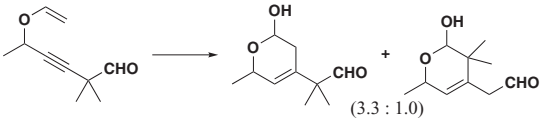
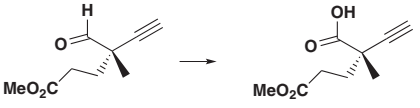
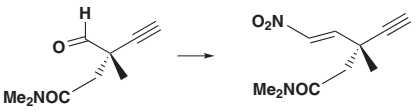
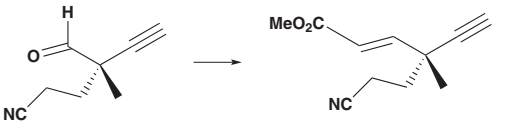
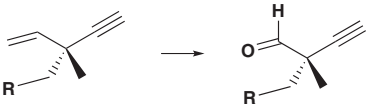
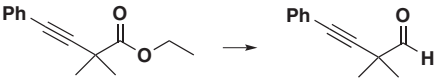
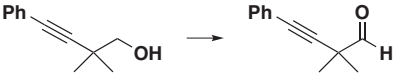
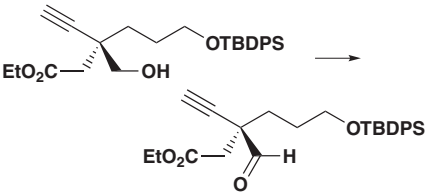
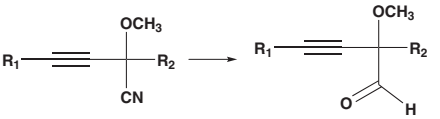
Reaction	Reagent/Catalyst	% Yield	Reference
	$Cl_3Ti(DME)_2$ Zn/Cu	42	25
	$CrCl_2/NiCl_2$	50	26
 (single diastereomer)	$Cl_3Ti(DME)_2$ Zn/Cu	56	27
	Ti/DME	45	28
 (3.3 : 1.0)	$[(Ph_3PAu)_3O]BF_4$	Not Reported	29
	CrO_3	61%	30
	1. CH_3NO_2, KF 2. MsCl, Et_3N	96%	30
	NaH $(MeO)_2\overset{O}{\overset{\|}{P}}CH_2CO_2Me$	64%	30

Table 2
Synthesis of 2,2-Disubstituted 3-Alkynals

Reaction	Reagent/Catalyst	% Yield	Reference
 R = CH_2CN, CO_2Me, $CONMe_2$	O_3 Me_2S or $(Me_3O)_3P$ −78°C	78–85%	30
	DIBAL-H −78°C	83%	31
	PCC	73%	32
	$(COCl)_2$ DMSO Et_3N −78°C	One of two steps with a total yield of 74%	33
 $R_1 = CH_3$ or $CH_3(CH_2)_5$; R_2 = H or CH_3	i-BuAlH H_3O^+	Not Reported	34

oxidized to 3-alkynoic acids with CrO_3 and condensed with nitromethane to form 1-nitro-1-alken-4-ynes.[30] *Table 2* shows that 2,2-disubstituted 3-alkynals can be prepared from 3-alkynoate esters by reduction using DIBAL-H,[30] from 3-alkynols by oxidation using PCC[31] or $(COCl_2)_2$/DMSO/Et_3N (Swern),[32] from 1-alken-4-ynes by ozonolysis/reduction,[33] and from 3-alkynenitriles by reduction with i-BuAlH followed by hydrolysis of the resulting imine.[34]

Conclusion

This review has shown that 3-alkynals are now accessible in gram quantities relatively free of their 2,3-alkadienal isomers. Although 3-alkynals are prone to rearrangement under acidic and basic conditions, and to decomposition with heating, they have been used successfully as intermediate compounds in a number of synthetic applications. It seems reasonable to expect 3-alkynals to play an increasingly important role as a synthetic tool in the future.

Acknowledgment

R.L.B. acknowledges support of the Brummel Chair at Calvin College.

References

1. Unpublished results obtained at Calvin College by Professor Roger DeKock and his student, Ben Brandsen, using DFT (B3LYP/cc-pVTZ and B3LYP/aug-cc- pVTZ) and Hartree Fock Theory (RHF/6–311G(d,p)).
2. K. K. Wang, *Chem. Rev.*, **96**, 207 (1996).
3. I. Ojima, M. Tzamarioudaki, Z. Li and R. Donovan, *Chem. Rev.*, **96**, 635 (1996).
4. K. Mikami and M. Shimizu, *Chem. Rev.*, **92**, 1021 (1992).
5. J. Marshall and M. Andersen, *J. Org. Chem.*, **57**, 2766 (1992).
6. J. Marshall and W. DuBay, *J. Org. Chem.*, **59**, 1703 (1994).
7. M. Journet and M. Malacria, *J. Org. Chem.*, **57**, 3085 (1992).
8. C. Mukai, O. Kataoka and M. Hanaoka, *Tetrahedron Lett.*, **32**, 7553 (1991).
9. Mukai, O. Kataoka and M. Hanaoka, *J. Chem. Soc., Perk. Trans. 1*, 563 (**1993**).
10. T. Herbertz, *Chem. Ber.*, **85**, 475 (1952).
11. T. Herbertz, *Chem. Ber.*, **92**, 541 (1959).
12. M. Winter, *Helv. Chim. Acta.*, **46**, 1754 (1963).
13. M. Durand and L. Piaux, *Comp. Ren.*, **246**, 1055 (1958).
14. W. R. Roush and J. C. Park, *Tetrahedron Lett*., **32**, 6285 (1991).
15. D. J. Vugts, H. Aktas, K. Al-Mafraji, F. J. J. de Kanter, E. Ruijter, M. B. Groen and R. V. A. Orru, *Eur. J. Org. Chem.*, 1336 (**2008**).
16. F. Barbot and P. Miginiac, *Synthesis*, 651 (**1983**).
17. C. Qiao, H.-B. Jeon and L. M. Sayre, *J. Am. Chem. Soc.*, **126**, 8038 (2004).
18. L. Wavrin and J. Viala, *Synthesis*, 326 (**2002**).
19. D. J. Vugts, L. Veum, K. Al-Mafraji, R. Lemmens, R. F. Schmitz, F. J. J. de Kanter, M. B. Groen, U. Hanfeld and R. V. A. Orru, *Eur. J. Org. Chem.*, 1672 (**2006**).
20. E. J. Corey and S. W. Wright, *J. Org. Chem.*, **55**, 1670 (1990).
21. R. L. Blankespoor, P. J. Boldenow, E. C. Hansen, J. M. Kallemeyn, A. G. Lohse, D. M. Rubush and D. Vrieze, *J. Org. Chem.*, **74**, 3933 (2009).
22. Unpublished results from the laboratory of R. Blankespoor, Calvin College, using 99.8 atom% D $CDCl_3$ from Aldrich (#225789) as solvent. Although calculations using the *ab initio* RHF level with the 6–311G(d,p) basis set gave a 38 kcal/mol (at the MP2 fixed level) transition state energy for a [1,5]-sigmatropic shift of the OH hydrogen in the enol of 3-butynal leading to 2,3-butadienal, acid-catalyzed rearrangement of 3-butynal to 2,3- butadienal due to trace amounts of DCl in $CDCl_3$ cannot be ruled out.
23. M. Schlosser and B. Schaub, *J. Am. Chem. Soc.*, **104**, 5821 (1982).
24. P. T. de Sousa, Jr. and R. J. K. Taylor, *J. Braz. Chem. Soc.*, **4**, 109 (1993); *Chem. Abstr.,* **122**, 9704 (1995).
25. F. Ferri and R. Brückner, *Liebigs Ann./Recueil*, 961 (**1997**).
26. K. R. Buszek and Y. Jeong, *Synth. Commun.*, **24**, 2461 (1994).

27. F. Ferri, R. Brückner and R. Herges, *New J. Chem.*, **22**, 531 (1998).

28. K. C. Nicolaou, E. J. Sorensen, R. Discordia, C.-K. Hwang, R. E. Minto, K. N. Bharucha and R. G. Bergman, *Angew. Chem. Int. Ed.*, **31**, 1044 (1992).

29. B. D. Sherry, L. Maus, B. N. Laforteza and F. D. Toste, *J. Am. Chem. Soc.*, **128**, 8132 (2006).

30. R. V. Stevens, N. Beaulieu, W. H. Chan, A. R. Daniewski, T. Takeda, A. Waldner, P. G. Williard and U. Zutter, *J. Am. Chem. Soc.*, **108**, 1039 (1986).

31. G.-Y. Lin, C.-Y. Yang and R.-S. Liu, *J. Org. Chem.*, **72**, 6753 (2007).

32. J.-M. Tang, T.-A. Liu and R.-S. Liu, *J. Org. Chem.*, **73**, 8479 (2008).

33. S. Sumi, K. Matsumoto, H. Tokuyama and T. Fukuyama, *Org. Lett.*, **5**, 1891 (2003).

34. K. Utimoto, *Pure & Appl. Chem.*, **55**, 1845 (1983).