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A Flexible Radical-Based Approach to TMS-Substituted Propargyl Alcohols and to 2,3-Allenols

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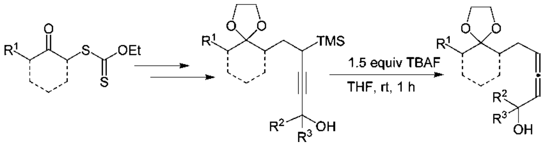
ABSTRACT

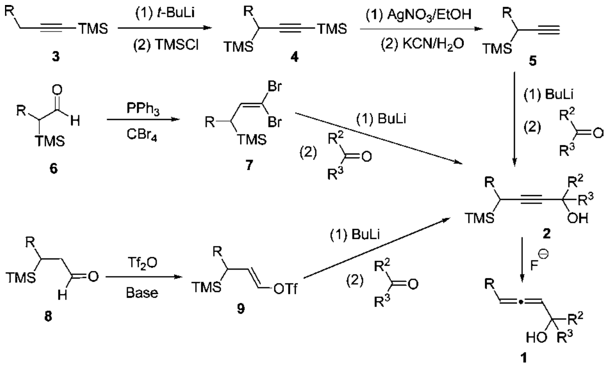


The radical reaction of TMS-substituted xanthates with 2,2-dichlorovinyl ethyl sulfone afforded TMS-substituted homodichlorovinyl compounds that can be transformed into TMS-substituted propargyl alcohols. Various 2,3-allenols were efficiently prepared from the reaction of these TMS-substituted propargyl alcohols with TBAF.

2,3-Allenols[1] are versatile building blocks for the synthesis of 2,5-dihydrofurans,[2] vinylic epoxides,[3] α,*β*-unsaturated ketones,[4] and numerous other valuable compounds. They represent important intermediates in the total synthesis of natural products such as the (+)-furanomycin[5] and peridinin.[6] Furthermore, 2,3-allenols are substructures in a number of natural products or pharmaceutical substances,[7a] such as mimulaxanthin,[7b] "Grasshopper Ketone",[7c] (*R*)-cytallene,[7d] and (*R*)-adenallene.[7e]

One efficient method for accessing 2,3-allenols **1** is the reaction of TMS-substituted propargyl alcohols **2** with TBAF (tetra-*n*-butylammonium fluoride).[8] However, except for the simplest derivatives, these precursors are not readily available, as indicated in Scheme 1, which summarizes previously described synthetic routes.

Scheme 1. Approaches to TMS-Substituted Propargyl Alcohols



The most frequently explored approach relies on the generation of the propargylic anion from alkyne **3** followed by its capture with TMSCl to give key intermediate **4**.[9] Selective removal of the terminal TMS group requires treatment with silver nitrate followed by destruction of the

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(1) For general reviews, see: (a) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (b) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (c) Deng, Y. Q.; Gu, Z. H.; Ma, S. *Chin. J. Org. Chem.* **2006**, *26*, 1468.

(2) (a) Gelin, R.; Gelin, S.; Albrand, M. *Bul1. Soc. Chim. Fr.* **1972**, 1946. (b) Olsson, L. I.; Claesson, A. *Synthesis* **1979**, 743.

(3) (a) Kang, S.-K.; Yamaguchi, T.; Pyun, S.-J.; Lee, Y.-T.; Bail, T.-G. *Tetrahedron Lett.* **1998**, *39*, 2127. (b) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943.

(4) Shimizu, I.; Sugiura, T.; Tsuji, J. *J. Org. Chem.* **1985**, *50*, 537.

(5) Vanbrunt, M. P.; Standaert, R. F. *Org. Lett.* **2000**, *2*, 705.

(6) (a) Furuichi, N.; Hara, H.; Osaki, T.; Mori, H.; Katsumura, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1023. (b) Furuichi, N.; Hara, H.; Osaki, T.; Nakano, M.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2004**, *69*, 7949.

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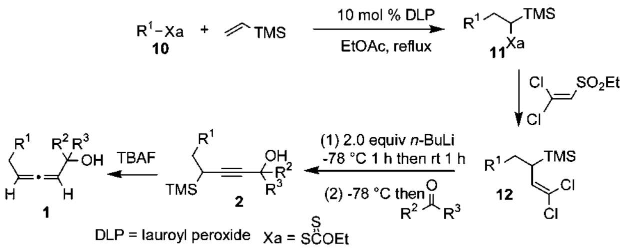
corresponding silver acetylide with cyanide. Finally, the resulting alkyne **5** is transformed into the desired allenyl alcohol **2** in the usual manner.

The two alternative approaches start with the rather inaccessible α- and *β*-TMS-substituted aldehydes **6** and **8**. The former is transformed into dibromide **7**, which is then converted into propargylic alcohol **2** through the Corey−Fuchs reaction.[10,11] The formation of the desired alkyne **2** from aldehyde **8** proceeds via enol triflate **9**.[12]

As part of our work on the degenerative xanthate transfer reaction,[13] we examined a potentially more flexible and more general route to allenyl alcohols **1**. Our synthetic approach, outlined in Scheme 2, hinges on the possibility of performing a radical addition of a xanthate **10** onto trimethyl vinyl silane to give the corresponding adduct **11** and then exchanging the xanthate group with a dichloro vinyl motif through reaction with dichlorovinyl ethyl sulfone.[14] The resulting product **12** could subsequently be processed into the desired allenyl alcohol **1** through the powerful Corey−Fuchs reaction.

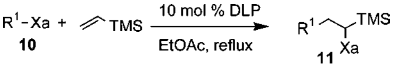
Scheme 2. Strategy to Synthesis of 2,3-Allenols from Xanthates

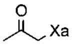
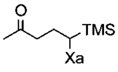
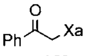
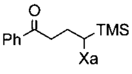
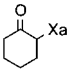
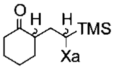


While we had previously performed additions of various xanthates to trimethyl vinyl silane,[15] the creation of a new C−C bond next to the bulky TMS group by radical addition to the somewhat sterically hindered dichloro-vinyl ethyl sulfone was far from obvious. It was therefore necessary to ascertain the viability of this key step in our proposed strategy.

The radical addition of xanthate **10a−c** to trimethyl vinyl silane proceeded smoothly as shown by the results in Table 1. In the case of xanthate **10c**, a 1:1 separable mixture of diastereoisomers **11c**/**11c′** was obtained. The lack of diastereoselectivity is not surprising, being typical of most intermoleculer radical additions.

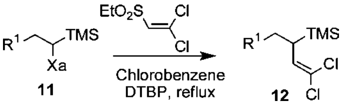
Table 1. Synthesis of TMS-Substituted Xanthates **11**

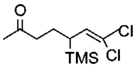
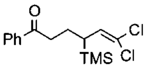
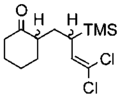


entry	xanthates **10**	xanthates **11**	yield[a] [%]
1	 **10a**	 **11a**	**86**
2	 **10b**	 **11b**	**87**
3	 **10c**	 **11c/11c’**	**60**[b]

[a] Isolated yield. [b] Total yield of **11c** and **11c′**, **11c**/**11c′** = 1/1. **11c**, R_f = 0.6, petroleum ether/EtOAc = 20:1. **11c′**, R_f = 0.5, petroleum ether/EtOAc = 20:1. This reaction was conducted in a mixture of EtOAc and DME (1:1 v/v).

Table 2. Synthesis of Dichlorovinyl Compounds **12**



entry	substrates **11**	products **12**	yield[a] [%]
1	**11a**	 **12a**	**55**
2	**11b**	 **12b**	**60**
3	**11c/11c’**	 **12c/12c’**	**54**[b]

[a] Isolated yield. [b] Total yield of **12c** and **12c′**, **12c**/**12c′** = 1/1. **12c**, R_f = 0.6, petroleum ether/EtOAc = 30:1. **12c′**, R_f = 0.5, petroleum ether/EtOAc = 30:1. The ratio of **12c** and **12c′** was determined from the ^{1}H NMR of the crude product. For reaction details, see Supporting Information.

With the TMS-substituted xanthates **11** in hand, we set out to assemble the α-TMS-substituted dichlorovinyl compounds **12** via the radical reaction of **11** with 2,2-dichlo-

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(7) (a) Krause, N.; Hoffmann-Röder, A. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, p 997. (b) Nitsche, H. *Phytochemistry* **1972**, *11*, 401. (c) Isoe, S.; Katsmura, S.; Hyeon, S. B. *Tetrahedron Lett.* **1971**, *16*, 1089. (d) Jones, B. C. N. M.; Silverton, J. V.; Simons, C. *J. Med. Chem.* **1995**, *38*, 1397. (e) Megati, S.; Goren, Z.; Silverton, J. V.; et al. *J. Med. Chem.* **1992**, *35*, 4098.

(8) (a) Pornet, J.; Randrianoelina, B.; Miginiac, L. *Tetrahedron Lett.* **1984**, *25*, 651. (b) Pornet, J.; Damour, D.; Randrianoelina, B.; Miginiac, L. *Tetrahedron* **1986**, *42*, 2501. (c) Chow, H.-F.; Cao, X.-P.; Leung, M.-K. *J. Chem. Soc., Chem. Commun.* **1994**, 2121. (d) Chow, H.-F.; Cao, X.-P.; Leung, M.-K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 193. (e) Wang, K. K.; Liu, B.; Lu, Y.-D. *J. Org. Chem.* **1995**, *60*, 1885. (f) Wang, K. K.; Liu, B.; Lu, Y.-D. *Tetrahedron. Lett.* **1995**, *36*, 3785. (g) Taing, M.; Moore, W. H. *J. Org. Chem.* **1996**, *61*, 329.

(9) (a) Rajagopalan, S.; Zweifel., G. *Synthesis* **1984**, 111. (b) Fleming, I.; Morgan, I. T.; Sarkar, A. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2749.

(10) (a) Tietze, L. F.; Neumann, T.; Kajino, M.; Pretor, M. *Synthesis* **1995**, 1003. (b) Haley, M. M.; Biggs, B.; Looney, W. A.; Gilbertson, R. D. *Tetrahedron Lett.* **1995**, *36*, 3457.

(11) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769.

(12) Fleming, I.; Mwaniki, J. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1237.

(13) For general reviews, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *153*, 137. (c) Zard, S. Z. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p 90. (d) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (e) Quiclet-Sire, B.; Zard, S. Z. *Chem. Eur. J.* **2006**, *12*, 6002. (f) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205.

(14) Bertrand, F.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1999**, *38*, 1943.

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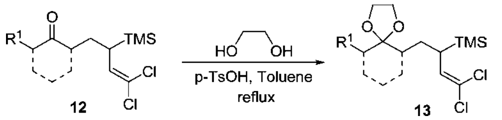
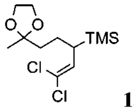
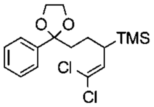
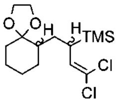
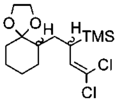
rovinyl ethyl sulfone.[16] After some extensive experimentation, we were pleased to find that it was possible to accomplish the desired transformation leading to α-TMS-substituted dichlorovinyl compounds **12**, albeit in moderate yield (Table 2). No diastereoselectivity was observed in the formation of **12c**/**12c′**, but it was possible to separate the two diastereoisomers by chromatography. It is worth noting that only a few instances of synthesis of α-TMS-substituted dichlorovinyl compounds[17a] or related derivatives[10a,17b−d] have been reported to date.

Prior to conducting the Corey−Fuchs reaction, it was necessary to protect the ketone group as the corresponding ketal. This was accomplished by treatment with ethylene glycol under standard acid catalysis. Unfortunately, under these conditions, the two separated diastereoisomers **12** and **12c′** gave the same mixture of **13c**/**13c′** (Table 3, entries 3 and 4) through epimerization of the center vicinal to the acetal group.

Table 3. Protection of Dichlorovinyl Compounds **12**



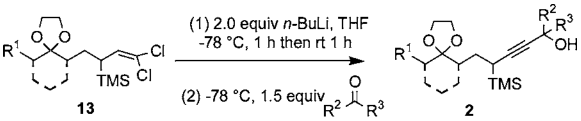
entry	substrates **12**	products **13**	yield^a [%]
1	**12a**	 **13a**	**84**
2	**12b**	 **13b**	**80**
3	**12c**	 **13c/13c'** = 3/5	**70**^{b}
4	**12c'**	 **13c/13c'** = 3/5	**60**^{b}

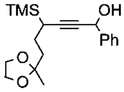
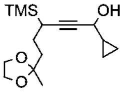
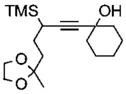
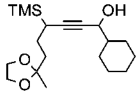
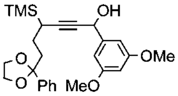
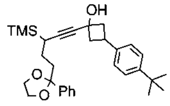
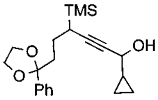
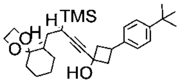
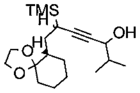
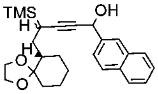
^{a} Isolated yield. ^{b} Total yield of **13c** and **13c′**. **13c**, R_f = 0.5, petroleum ether/EtOAc = 30:1. **13c′**, R_f = 0.4, petroleum ether/EtOAc = 30:1. The ratio of **13c** and **13c′** was determined from the ^{1}H NMR of the crude product. For reaction details, see Supporting Information.

Acetals **13** were subjected to the general procedure of the Corey−Fuchs reaction, and the acetylide was subsequently quenched with various aldehydes (Table 4, entries 1, 2, 4, 5, 7, 9, and 10) or ketones (entries 3, 6, and 8). Consequently, a broad assortment of TMS-substituted propargyl alcohols **2** were obtained in moderate to good yield (Table 4).

After reacting with 1.5 equiv of TBAF in THF at room temperature, the TMS-substituted propargyl alcohols **2** were transformed into the 2,3-allenols **1** in good to excellent yields (Table 5). The α position of the 2,3-allenols can bear aryl (Table 5, entries 1 and 5), naphth-2-yl (entry 10), aliphatic alkyl (entry 9), and cyclic alkyl (entries 2, 4, and 7). The alcohols can be secondary (entries 1, 2, 4, 5, 7, 9, and 10) or tertiary (entries 3, 6, and 8). The presence of the masked ketone allows the installation of a carbonyl group that might have further reaction potential in combination with the allene moiety.[18,19]

Table 4. Synthesis of TMS-Substituted Propargyl Alcohols **2**



entry	acetals **13**	products **2**	yield^a [%]
1	**13a**	 **2a**	**64**^{b}
2	**13a**	 **2b**	**55**^{b}
3	**13a**	 **2c**	**63**
4	**13a**	 **2d**	**55**^{b}
5	**13b**	 **2e**	**59**^{b}
6	**13b**	 **2f**	**54**
7	**13b**	 **2g**	**52**^{b}
8	**13c**	 **2h**	**71**
9	**13c'**	 **2i**	**50**^{b}
10	**13c'**	 **2j**	**71**^{b}

^{a} Isolated yield. ^{b} dr = 1:1.

The stability of the allyl trimethylsilyl motif in **12a**−**c** toward acidic conditions, allowing ready formation of ketals **13a**−**c**, is remarkable. One of the initial aims of this project

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(15) For some recent examples, see: (a) Corbet, M.; Ferjancic, Z.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 3579. (b) Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 3279. (c) Corbet, M.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 2861. (d) Corbet, M.; de Greef, M.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 253.

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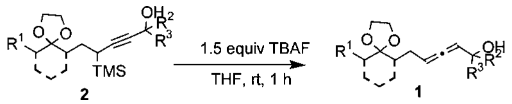
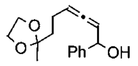
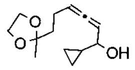
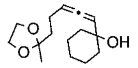
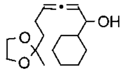
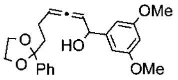
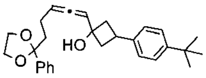
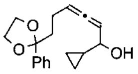
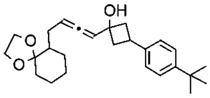
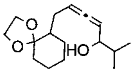
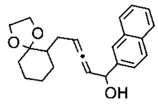
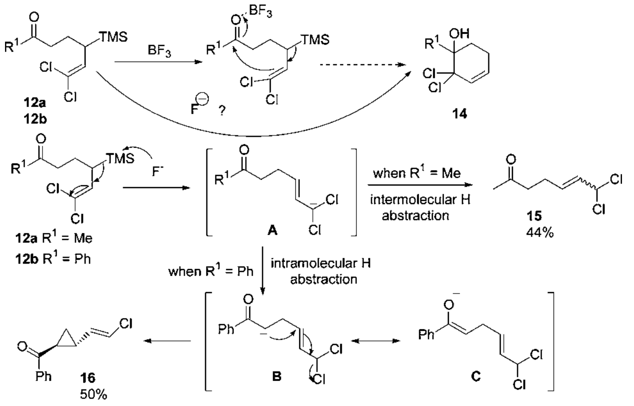
Table 5. Synthesis of 2,3-Allenols **1**



entry	substrate **2**	2,3-allenols **1**	yield[a] [%]
1	**2a**	 **1a**	85[b]
2	**2b**	 **1b**	85[b]
3	**2c**	 **1c**	88
4	**2d**	 **1d**	80[b]
5	**2e**	 **1e**	81[b]
6	**2f**	 **1f**	80
7	**2g**	 **1g**	93[b]
8	**2h**	 **1h**	95[b]
9	**2i**	 **1i**	78[c]
10	**2j**	 **1j**	83[c]

[a] Isolated yield. [b] dr = 1:1. [c] dr = 1:1:1:1.

Scheme 3. Reaction of **12a** and **12b** with TBAF



was to exploit the proximity of the ketone group to induce ring closure into dichlorocyclohexenol **14** by exposure to Lewis acid as indicated in Scheme 3. However, treatment of allylsilane **12a** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 did not result in any reaction. Indeed, compound **12a** was recovered essentially intact. When we attempted to promote the same ring formation with fluoride anion, we observed a different reaction. With **12a**, a simple desilylation took place to give unsaturated dichloro ketone **15** in 44% yield. In the case of **12b**, containing slightly more acidic hydrogen, the reaction proceeded further to furnish monochlorovinyl cyclopropane **16** in moderate yield via enolate **B**.

In summary, we have established an efficient route to polyfunctional 2,3-allenols by exploring the potential of the xanthate transfer process to bring together the various components, which then could be subjected to the Corey−Fuchs reaction. This flexibility opens access to a large variety of structures and complements existing strategies. Furthermore, it is interesting to note that converting the alcohol group in adduct **2** (Table 4) into a strong nucleofuge, such as a triflate, followed by treatment with fluoride, provides 1,2,3-trienes (see ref 8e). The present approach should allow a convenient entry to otherwise inaccessible [3]cumulenes.

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Supporting Information Available: Experimental procedures, full spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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