Tetrahedron Letters, Vol. 34, No. 39, pp. 6251-6254, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

STEREOSELECTIVE APPROACH TO TRISUBSTITUTED TETRAHYDROFURANS

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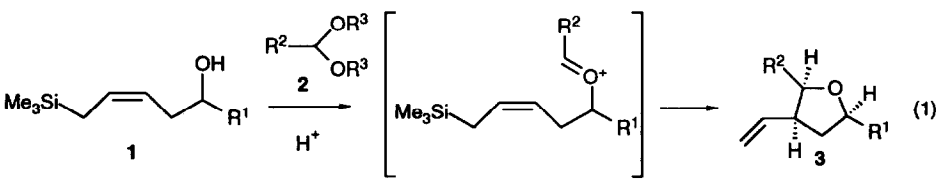
Summary: Functionalized allylsilanes 1 undergo with acetals 2 under mild Broensted acid catalysis a transacetalization-ring closure reaction to afford in fair to good yield and high diastereoselectivity all-cis-tetrahydrofurans 3. The stereochemical outcome is independent of the double bond geometry.

Key-Words: Allylsilane, Tetrahydrofuran, 1,3-Induction, Ring Closure

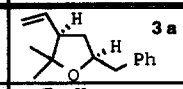
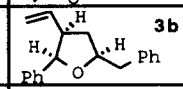
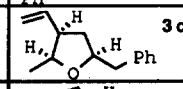
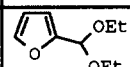
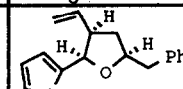
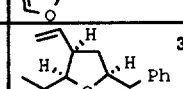
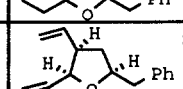
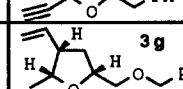
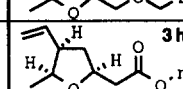
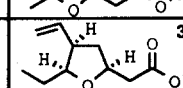
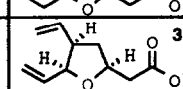
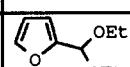
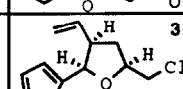
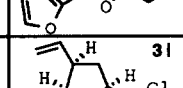
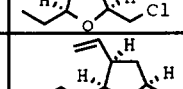
Since its discovery 20 years ago[1] the nucleophilic addition of allylsilanes to carbonyl groups or their synthetic equivalents has become an important carbon carbon bond forming reaction in the repertoire of synthetic organic chemistry[2]. In general, the transformation is performed in the presence of a strong Lewis acid, typically $TiCl_4$. Protic acids are less suited since they favour protodesilylation of the nucleophile as an undesired side-reaction[3]. In connection with our interest in polyfunctional allylsilanes[4] of type **1** we studied an intramolecular variant, namely the addition to an oxocarbenium ion formed *in situ* by transacetalization followed by acid-catalyzed ionization (eq. 1). We anticipated that the entropic gain would override the intrinsic tendency towards unproductive desilylation and could allow the stereoselective building of 5-membered rings under mild Broensted acid catalysis. In this Letter we disclose our preliminary results.



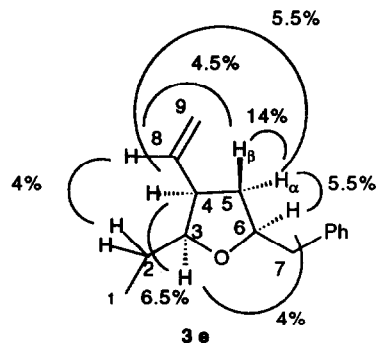
(1)

Substrates **1** were prepared as previously described[4]. They were treated at ambient temperature in the presence of 0.3 eq. of p-toluenesulfonic acid either neat with the corresponding acetal **2** (method A) or with 5 eq. of **2** in CH_2Cl_2 (method B) or , alternatively, with 0.3 eq. of camphorsulfonic acid and 5 eq. of **2** in CH_2Cl_2 (method C). As can be seen from the table, clean tandem transacetalization-intramolecular addition ensued and afforded in fair to good yield the all-cis-2,3,5-trisubstituted tetrahydrofurans **3** with high stereochemical purity[5]. The sum of the three other possible isomers amounted in all cases to five percent or less. The relative stereochemistry was deduced from the strong anisochronous behaviour of the methylene protons $H_2C(5)$[6] and finally proven by extensive NOE experiments with **3e** and **3l**.

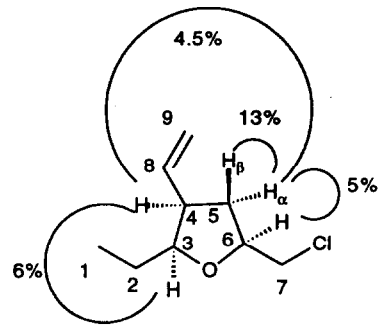
TABLE Acid Catalyzed Ring Closure to all-cis-Tetrahydrofurans 3

Entry	Allylsilane 1[a]	Acetal 2	Method[b]	Product 3[a]	Yield[c] (%)
1	**1a** R^1=CH_2Ph	$(CH_3)_2C(OMe)_2$	A	 **3a**	71
2	**1a** R^1=CH_2Ph	**2a** R^2=Ph R^3=Me	B	 **3b**	95
3	**1a** R^1=CH_2Ph	**2b** R^2=Me R^3=Me	B	 **3c**	81
4	**1a** R^1=CH_2Ph		B	 **3d**[d]	59
5	**1a** R^1=CH_2Ph	**2c** R^2=Et R^3=Et	B	 **3e**	83
6	**1a** R^1=CH_2Ph	**2d** R^2=HCC R^3=Et	B	 **3f**[d]	59
7	**1b** R^1=CH_2OCH_2Ph	**2b** R^2=Me R^3=Me	B	 **3g**	93
8	**1c** R^1=$CH_2COOnPr$	**2b** R^2=Me R^3=Me	C	 **3h**	62
9	**1c** R^1=$CH_2COOnPr$	**2c** R^2=Et R^3=Et	C	 **3i**	80
10	**1c** R^1=$CH_2COOnPr$	**2e** R^2=H_2CCH R^3=Me	B	 **3j**	85
11	**1d** R^1=CH_2Cl		B	 **3k**[d]	50
12	**1d** R^1=CH_2Cl	**2c** R^2=Et R^3=Et	B	 **3l**	66
13	**1d** R^1=CH_2Cl	**2f** R^2=$NCCH_2CH_2$ R^3=Et	B	 **3m**	41

[a]All compounds are racemates except those in entry 7 and eq. 3, where the absolute configuration is as indicated; [b]see text; [c]yields are not optimized and refer to chromatographically purified products which are contaminated in all cases with 5% or less of the other three possible isomers; [d]the furyl- and ethinyl-compounds are quite unstable which might explain the lower yield.

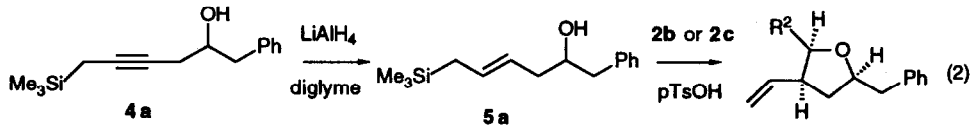


3e



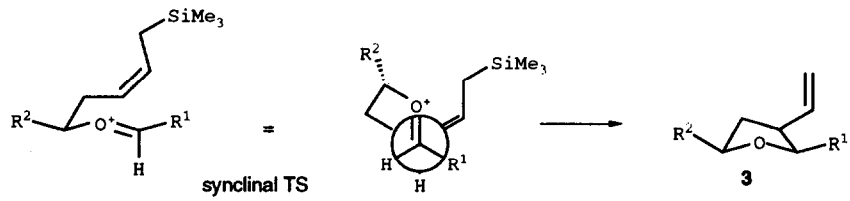
3l

We also briefly examined the behaviour of the E-allylsilane **5a**, whose synthesis was cumbersome. We were finally able to prepare it, albeit in low yield (ca. 30%), from propargylsilane **4a** according to the Rossi procedure[7] ($LiAlH_4$/diglyme, eq. 2). Even under these conditions substantial desilylation occurred. Exposure of **5a** to our standard conditions (acetal **2b** or **2c**, method B) provided the same all-cis-tetrahydrofuran **3c** and **3e**, respectively, albeit in somewhat lower yield and slightly worse stereoselectivity (eq. 2, cf. entry 3 and 5)[8].



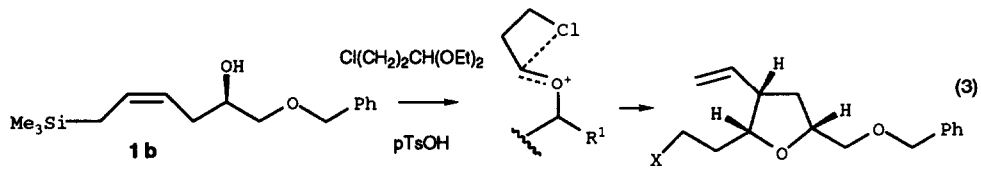
3c: R^2=Me, 52% yield
3e: R^2=Et, 63% yield

The following features are noteworthy: the stereoselectivity is good to excellent in all cases studied so far irrespective of the size of R^1 and R^2. The reaction requires only catalytic amounts of acid and is not sensitive towards traces of oxygen or moisture[9]. In cases where the oxocarbenium ion is destabilized (e.g. entry 13), the intermediate mixed acetal accumulates and its formation and disappearance can be followed by GLC and TLC. Crucial to success is the fact that transacetalization as well as ring closure is fast compared to intermolecular addition or protodesilylation of the starting allylsilane[10].



The exact mechanistic picture of allylsilane additions remains controversial and obscure[11]. Our stereochemical results can best be rationalized based on the synclinal transition state model proposed by Seebach and Golinski[12,13]. If one further assumes an E-configurated oxocarbenium ion and a pseudoequatorial position of the group R^1 within the developing 5-ring one predicts the all-cis product **3** starting from either the E- or Z- allylsilane, as is experimentally observed.

Finally, we note that functional groups which are capable of anchimeric stabilization of the oxocarbenium ion may thwart the success of the reaction. Allylsilane **1b**, for example, afforded with 3-chloro-1,1-diethoxypropane a 2:3 mixture of the expected **3n** and the corresponding ethoxy-derivative **3o** besides some minor unidentified side-products (eq. 3).



3n : X=Cl
3o : X=EtO

I am grateful to Prof. A. Vasella for stimulating and helpful discussions and to Dr. W. Arnold for the NMR experiments.

REFERENCES AND NOTES

1. A. Z. Shikhmamedbekova and R. A. Sultanov, *J. Gen. Chem. USSR* (Engl. Transl.) **1970**, *40*, 72.
2. For recent reviews see: a) I. Fleming, J. Dunogues, and R. Smithers, *Organic Reactions* **1989**, *37*, 57; b) G. L. Larson in *"The Chemistry of Organic Silicon Compounds"*; S. Patai and Z. Rappoport, Eds.; Wiley & Sons: New York, **1989**; Chapter 11; c) A. Hosomi, *Acc. Chem. Res.* **1988**, *21*, 200.
3. There are only scarce literature precedents for protic acid catalysis, see e. g. a) V. Gevorgyan, I. Kadota, and Y. Yamamoto, *Tetrahedron. Lett.* **1993**, *34*, 1313; b) D. Schinzer and M. Ruppelt, *Chem. Ber.* **1991**, *124*, 247; c) A. Itoh, K. Oshima, and H. Nozaki, *Tetrahedron Lett.* **1979**, *20*, 1783.
4. P. Mohr, *Tetrahedron Lett.* **1992**, *33*, 2455.
5. The products were analyzed by capillary GC on a 25m *HP Ultra1* column.
6. Arbitrary numbering; ^{1}H-NMR (400 MHz, $CDCl_3$): **3e**: δ 0.90 (t, J=7.5, H_3(C1)) , 1.38 (quin, J=7.5, H_2(C2)), 1.46 (m, HβC(5)), 2.03 (m, HαC(5)), 2.70 (dxd, J=7.0, J=13.5, H(C7)), 2.78 (quin, J=8.0, HC(4)), 2.99 (dxd, J=6.0, J=13.5, H(C7)), 3.71 (q, J=7.0, H(C3)), 4.02(m, H(C6)), 4.93(s, HC9)), 4.96 (m, HC(9)), 5.63-5.72(m, HC(8)), 7.14-7.26 (m, arom. H); **3m**: δ 0.93 (t, J=7.5, H_3C(1)), 1.45 (m, H_2(C2)), 1.66 (m, Hβ(C5)), 2.26 (m, Hα(C5)), 2.90 (quin, J=8.0, H(C4)), 3.54 (dxd, J=6.0, J=11, H(C7)), 3.62 (dxd, J=5.5, J=11, H(C7)), 3.82 (q, J=6.5, H(C3)), 4.13 (quin, J=7.0, H(C6)), 5.03 (s, H(C9)), 5.06 (m, H(C9)), 5.72-5.81 (m, H(C8)).
7. R. Rossi and A. Capita, *Synthesis* **1977**, 561.
8. **3c** and **3e** contained 3.4% and 3.5%, respectively, of a minor isomer (unknown stereochemistry).
9. pTsOH was used as monohydrate.
10. In the case of formaldehyde dimethylacetal (primary oxocarbeniumion as intermediate) protodesilylation and intermolecular addition can compete effectively with ring closure (unpublished observation).
11. See ref. 2 and e. g. a) J. S. Panek and N. F. Jain, *J. Org. Chem.* **1993**, *58*, 2345; b) J. S. Panek and P. F. Cirillo, *J. Org. Chem.* **1993**, *58*, 999; c) S. Aoki, K. Mikami, M. Terada, and T. Nakai, *Tetrahedron* **1993**, *49*, 1783; d) R. L. Danheiser, B. R. Dixon, and R. W. Gleason, *J. Org. Chem.* **1992**, *57*, 6094.
12. D. Seebach and J. Golinski, *Helv. Chim. Acta* **1981**, *64*, 1413.
13. S. E. Denmark and E. J. Weber, *Helv. Chim. Acta* **1983**, *66*, 1655.

(Received in Germany 24 June 1993; accepted 28 July 1993)