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STEREOSELECTIVE APPROACH TO TRISUBSTITUTED TETRAHYDROPYRANS

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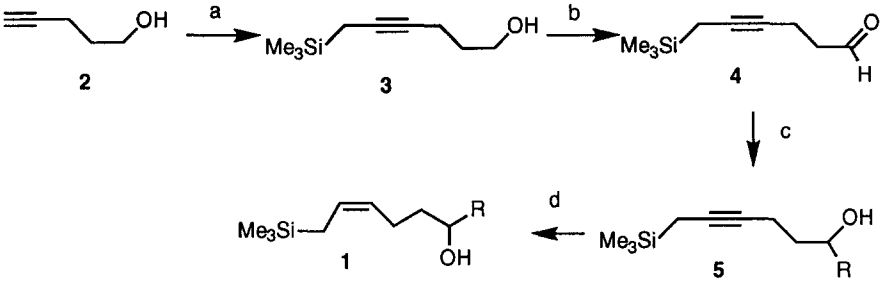
Summary: Functionalized allylsilanes of general structure 1 undergo with acetals 6 under mild Broensted acid catalysis a transacetalization-ring closure reaction to afford in moderate to good yield and high diastereoselectivity tetrahydropyrans 8 having all three substituents in an equatorial position.

Recently we reported the H^+-catalyzed intramolecular addition of an allylsilane to an oxocarbenium ion generated in situ by a transacetalization/ionization process leading in good yield and high selectivity to all-cis-tetrahydrofurans.[1] In an extension of this study we briefly examined the behaviour of the homologous substrates **1**. Our preliminary results are described in this Letter.

The precursors **1** were readily prepared from commercially available 4-pentyn-1-ol **2** according to Scheme 1.

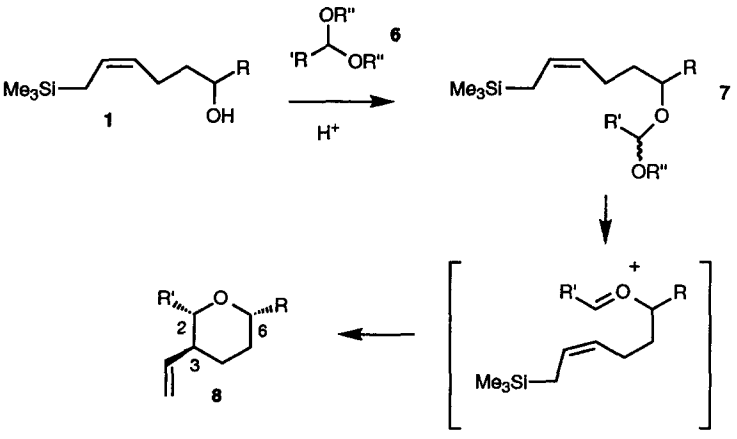


a) 2.1 eq. nBuLi, THF, DMPU; Me_3SiCH_2I; b) 1.25 eq. Oxalyl-Cl, 2.5 eq. DMSO, CH_2Cl_2; 5 eq. NEt_3; c) RMgX (**5a**, **5b**, **5c**, **5f**) or AcOEt/LDA (**5d**) or AcOMe/LDA (**5e**), THF; d) H_2, Lindlar catalyst, EtOH, chinoline.

Scheme 1

Double deprotonation of **2** followed by selective C-alkylation with trimethylsilyl-methyl iodide[2] yielded the desired propargylsilane **3**. *Swern* oxidation led to the aldehyde **4** which was reacted with either a *Grignard* reagent or the Li-enolate of methyl or ethyl acetate. *Lindlar* hydrogenation completed the synthesis of the substrates **1**.[3]

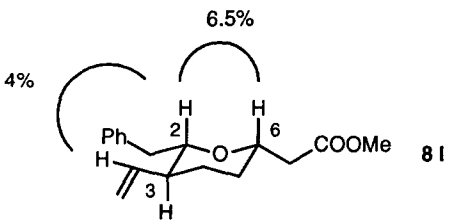
Treatment of **1** with 4 - 5 eq. of an acetal **6** in the presence of 0.33 eq. of pTsOH·H_2O triggered at ambient temperature, as summarized in Scheme 2, the expected transacetalization - intramolecular addition process to afford in moderate to good yield the tetrahydropyrans **8**.



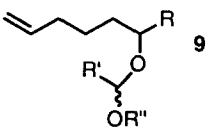
Scheme 2

The results are compiled in the Table. The two new asymmetric centres are formed with high stereochemical control. The relative stereochemistry was easily deduced from the ^1H NMR spectra which indicated an axial position for the hydrogens at C(2), C(3), and C(6), respectively, and was further corroborated by NOE experiments with **8 l**.[4]

The following features are noteworthy: the asymmetric induction is satisfactory irrespective of the size of R and R'[5] and comparable to the tetrahydrofuran analogues.[1] The ring closure rate, however, is roughly ten times slower[6] leading to somewhat diminished yields, especially if electronically destabilized oxocarbenium ions are involved (e.g. entry 2). Main competing side reaction is protodesilylation of the intermediate **7** leading to the terminal olefins **9** which are sometimes difficult to remove from the desired product.

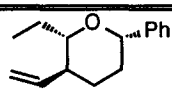
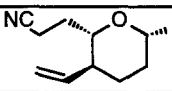
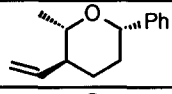
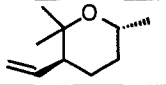
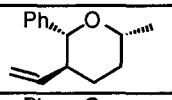
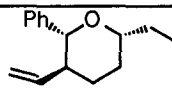
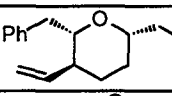
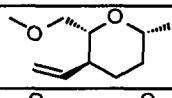
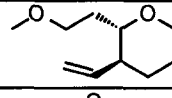
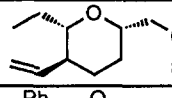
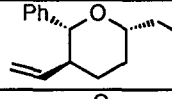
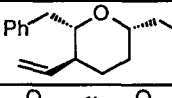
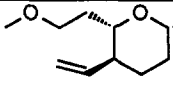


8 l



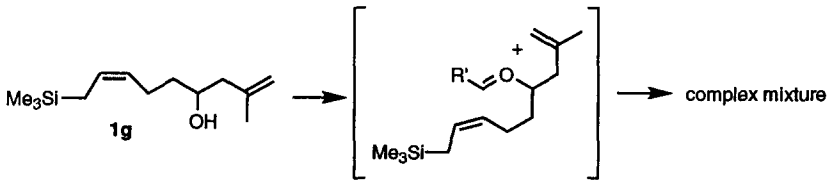
9

TABLE Acid Catalyzed Ring Closure to Tetrahydropyrans 8

Entry	Allylsilane 1[a]	Acetal 6	Product 8[a]	Yield[b] (%)
1	1a R=Ph	6a R'=CH_3CH_2 R"=Et	 8a	84
2	1a R=Ph	6b R'=$NCCH_2CH_2$ R"=Et	 8b	40
3	1a R=Ph	6c R'=CH_3 R"=Et	 8c	86
4	1b R=CH_3	$(CH_3)_2C(OMe)_2$	 8d	47[c]
5	1b R=CH_3	6d R'=Ph R"=Me	 8e	69
6	1c R=CH_3CH_2	6d R'=Ph R"=Me	 8f	64
7	1c R=CH_3CH_2	6e R'=$PhCH_2$ R"=Me	 8g	67
8	1c R=CH_3CH_2	6f R'=CH_3OCH_2 R"=Me	 8h	87
9	1c R=CH_3CH_2	6g R'=$CH_3OCH_2CH_2$ R"=Me	 8i	68
10	1d R=$EtOOCCH_2$	6a R'=CH_3CH_2 R"=Et	 8j	63
11	1e R=$MeOOCCH_2$	6d R'=Ph R"=Me	 8k	86
12	1e R=$MeOOCCH_2$	6e R'=$PhCH_2$ R"=Me	 8l	52
13	1f R=$(CH_3)_2CHCH_2$	6g R'=$CH_3OCH_2CH_2$ R"=Me	 8m	54

[a]All compounds are racemates; [b]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; [c]low yield due to the high volatility of the product.

Finally, we note that trisubstituted double bonds capable of intramolecular nucleophilic attack are not tolerated. Allylsilane **1g** led with acetal **6d** and **6f**, not unexpectedly[7], to untractable complex mixtures (cf. Scheme 3).



Scheme 3

The stereochemical outcome can easily be rationalized assuming an E-configurated oxocarbenium-ion and a chairlike transition state with a pseudoequatorial position of all three substituents R, R', and Me_3SiCH_2CH in the developing six-membered ring (cf. Scheme 4).

Scheme 4

Acknowledgment: I warmly thank Dr. W. Arnold for the NMR experiments.

REFERENCES AND NOTES

1. P. Mohr, *Tetrahedron Lett.* **1993**, *34*, 6251.
2. S. K. Chiu and P. E. Peterson, *Tetrahedron Lett.* **1980**, *21*, 4047.
3. Interestingly enough, primary alcohol **3** resisted in our hands attempted *Lindlar* hydrogenation. Therefore, the order of reaction steps could not be reversed.
4. Arbitrary numbering; ^1H NMR (400 MHz, $CDCl_3$): **8l**: δ 1.34, 1.47 (2xm, $H_{ax}C(4)$, $H_{ax}C(5)$), 1.68, 1.82 (2xm, $H_{eq}C(4)$, $H_{eq}C(5)$), 2.00 (m, *H*C(3)), 2.38 (dxd, J=5.0, J=14.6, H_2CCOOMe), 2.49 (dxd, J=8.4, J=14.6, H_2CCOOMe), 2.60 (dxd, J=9.2, J=14.6, H_2CPh), 2.94 (dxd, J=2.2, J=14.6, H_2CPh), 3.34 (dxt, J=2.2, J=9.5, *H*C(2)), 3.52 (s, H_3COOC), 3.65-3.72 (m, *H*C(6)), 5.07-5.14 (m, H_2CCHC(3)), 5.66 (dxdxd, J=8.8, J=9.4, J=18, H_2C*H*CC(3)), 7.14-7.26 (m, H_5C_6)).
5. The products were analyzed by capillary GC on a 25m *HP Ultra1* column.
6. Typical reaction time is 24h compared to 3h in the tetrahydrofuran series.
7. Allylsilanes of type **1** exhibit similar nucleophilicity as 1,1-disubstituted olefins; cf. H. Mayr and M. Patz, *Angew. Chem.* **1994**, *106*, 990.

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