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Stereoselection in Radical Cyclization of β-Alkoxyvinyl Sulfoxides: Synthesis of Tetrahydrofuranyl Allyl Carbinols

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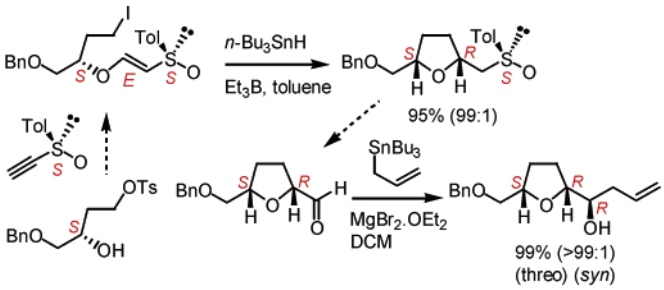
ABSTRACT



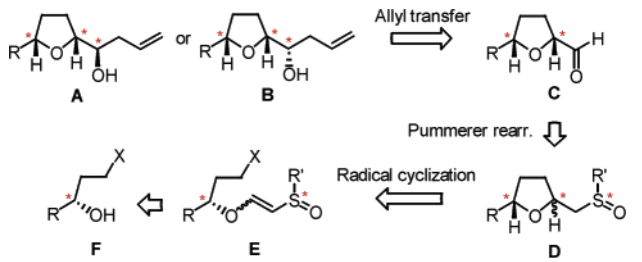
Tetrahydrofuranyl allyl carbinols may be prepared stereoselectively via radical cyclization of β-alkoxyvinyl sulfoxides, Pummerer rearrangement, and reaction with allylstannane.

Tetrahydrofuranyl carbinols are familiar motifs in numerous natural product structures with high biological activities.[1] We were interested in developing general methods for generation of the tetrahydrofuranyl carbinol derivatives **A** and **B**. One possibility would be allylation of the tetrahydrofuranyl aldehydes **C**, which may be obtained from Pummerer rearrangement of the corresponding sulfoxides **D**. Radical cyclization of β-alkoxyvinyl sulfoxides **E** prepared from secondary alcohols **F** would then be the first reaction of the sequence (Scheme 1).

Stereochemical aspects of radical cyclization of β-alkoxyvinyl sulfoxides have already been discussed. Malacria and co-workers reported that radical cyclization reactions of optically pure β-alkoxyvinyl sulfoxides led to significant diastereoselection.[2] In their work, radical cyclization of the substrate **1a** resulted in the formation of the products **3a** and **4a** in 70:30 ratio. The (*Z*)-derivative **2a** was converted into a 12:88 mixture of **3a** and **4a** (Scheme 2). The stereoselectivity was explained invoking *s-trans* vinyl sulfoxide transition-state conformations for radical cyclization. Better stereoselectivities were obtained for dimethyl derivatives **1b** and **2b**.

In the 5-exo radical cyclization reactions of β-alkoxyvinyl sulfoxides prepared from secondary alcohols, the intrinsic preference for the formation of *cis*-2,5-disubstituted tetrahy-

Scheme 1. Tetrahydrofuranyl Allyl Carbinols



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(1) Annonaceous acetogenins are representative examples. See, for example: Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, 275−306.

(2) Zahouily, M.; Journet, M.; Malacria, M. *Synlett* **1994**, 366−368.

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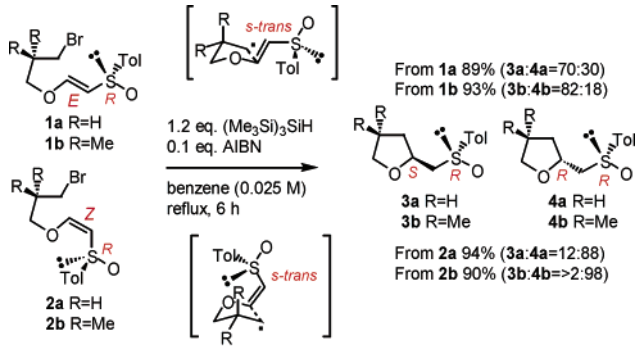
Scheme 2. Radical Cyclization of β-Alkoxyvinyl Sulfoxides



M. Malacria et al. *Synlett* **1994**, 366-368

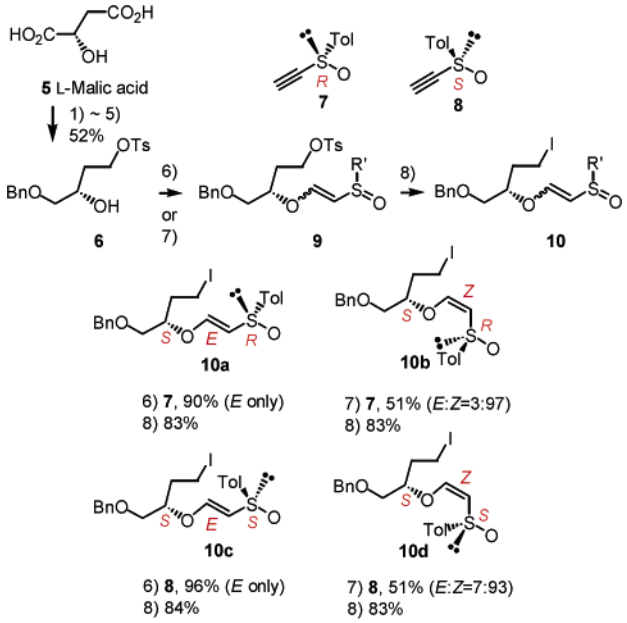
drofuran products in the vinyl ether radical cyclization reactions should also be considered,[3] and we intended to investigate the possibility of double stereoselection leading to higher stereoselectivity.

The tosylate **6** was obtained from L-malic acid (**5**) via a five-step sequence. Reaction of **6** with ethynyl *p*-tolyl (*R*)-sulfoxide (**7**)[4] in the presence of *N*-methylmorpholine and iodide substitution resulted in the formation of the (*E*)-vinyl sulfoxide **10a**. Reaction of the lithium alkoxide derived from **6** with **7** supplied mainly the (*Z*)-vinyl sulfoxide **10b** after iodide substitution. Employing the enantiomeric (*S*)-sulfoxide **8**, the alternative vinyl sulfoxides **10c** and **10d** were also obtained (Scheme 3).

When the substrate **10a** was treated with tributylstannane in the presence of triethylborane at −20 °C in toluene, a 94:6 mixture of the tetrahydrofuranyl products **11** and **12** was obtained. Under the same reaction conditions, the vinyl sulfoxide **10b** was converted almost exclusively into **11** (**11**:**12** = 99:1). The results show clearly that the intrinsic preference for formation of *cis*-2,5-disubstituted tetrahydrofurans predominated in both cases. The vinyl sulfoxide **10a** was a mismatched substrate, and the stereoselectivity suffered. On the contrary, the reaction of **10b** was a matched case and resulted in higher stereoselectivity. The situation reversed with the diastereomers **10c** and **10d** for synthesis of tetrahydrofurans **13** and **14**. The reaction of **10c** was more stereoselective (matched case) than the reaction of **10d** (mismatched case); in both cases, **13** was the predominant product (Scheme 4).

Preparatively, conversion of the vinyl sulfoxide **10c** to the tetrahydrofuran product **13** was the most efficient, from which the aldehyde **15** was prepared via Pummerer rearrangement reaction. Allylation reaction was investigated under a variety of conditions for chelation (leading to the *threo-syn*-tetrahydrofuranyl allyl carbinol **16**) or Felkin stereocontrol (leading to the *erythro-anti* product **17**). Reaction of **15** with allyl Grignard reagent in ether at −78 °C

Scheme 3. Preparation of β-Alkoxyvinyl Sulfoxides[a]

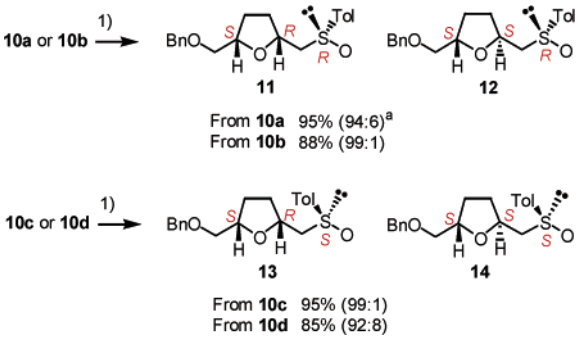


[a] Key: (1) $BH_3 \cdot SMe_2$, $(MeO)_3B$, THF; (2) $PhCH(OMe)_2$, CSA, DCM; (3) BnBr, NaH, THF; (4) $AcOH-H_2O$ (4:1); $NaIO_4$, $MeOH-H_2O$ (4:1); (5) TsCl, TEA, DCM, 0 °C; (6) 2.5 equiv of **7** or **8**, 1.0 equiv of NMM, DCM, rt, 18 h; (7) 3.0 equiv of **7** or **8**, 1.2 equiv of LHMDS, THF, −78 to −20 °C, 1 h; (8) 3.0 equiv of NaI, acetone, reflux, 3 h.

was a stereorandom process. Use of (allyl)tri-*n*-butylstannane in the presence of boron trifluoride etherate proceeded to produce **17** stereoselectively in preference to **16**. When stannic chloride was used as the Lewis acid, **17** was still obtained in better than 10:1 ratio (Scheme 5).[5]

Use of zinc chloride and zinc iodide reversed the tendency, and a useful degree of stereoselection in favor of the *syn* product **16** was realized. Magnesium bromide etherate was the best additive in this case resulting in a complete

Scheme 4. Radical Cyclization of β-Alkoxyvinyl Sulfoxides[a]

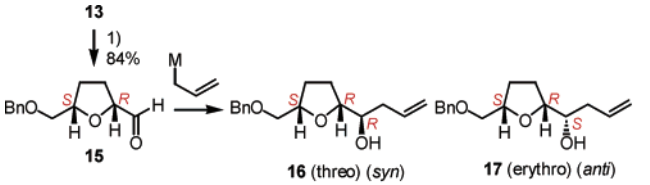


[a] Key: (1) 1.2 equiv of *n*-Bu_3SnH, 1.5 equiv of Et_3B, toluene, −20 °C, 30 min. (a) The product ratio was determined by HPLC analysis: Licrosorb, Hibar RT 250-4, Si 60, hexane/EtOAc = 50:50, flow rate = 2 mL/min, column temperature = 24.1 °C, detection at 254 nm.

(3) For references, see: Lee, E. In *Radicals in Organic Synthesis, Vol. 2: Applications*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; pp 303−333.

(4) Kosugi, H.; Kitaoka, M.; Tagami, K.; Takahashi, A.; Uda, H. *J. Org. Chem.* **1987**, *52*, 1078−1082.

Scheme 5. Pummerer Rearrangement and Allylation[a]



M	reaction conditions[a]	yield (%)	(**16**:**17**)
MgBr	ether, -78 °C, 2 h	69	42:58
$SnBu_3$	1.2 eq. $BF_3.OEt_2$, DCM, -78 °C, 2 h[b]	98	8:92
	1.2 eq. $BF_3.OEt_2$, DCM, -78 °C, 2 h	81	7:93
	3.0 eq. $BF_3.OEt_2$, DCM, -78 °C, 2 h	86	8:92
	3.0 eq. $SnCl_4$, DCM, -78 °C, 2 h	99	7:93
	1.0 eq. $SnCl_4$, DCM, -78 °C, 2 h	96	10:90
	3.0 eq. $ZnCl_2$ (1 M in ether), DCM, -78 °C,	98	84:16
	3.0 eq. ZnI_2, DCM, r.t. 2 h	98	67:33
	3.0 eq. $MgBr_2.OEt_2$, DCM, r.t. 3 h	99	>99:1
$SiMe_3$	3.0 eq. $BF_3.OEt_2$, DCM, -78 °C, 2 h	98	23:77
	3.0 eq. $MgBr_2.OEt_2$, DCM, r.t. 3 h	99	>99:1

[a] Key: (1) TFAA, pyridine, MeCN, 30 min; KOAc, H_2O, 2 h. (a) Addition of allylstannane or allylsilane into a solution containing **15** and Lewis acid. (b) Addition of Lewis acid into a solution containing **15** and allylstannane. (c) Diastereomeric ratio was determined by capillary GC analysis.

stereocontrol,[6] and **16** was obtained in high yield as the exclusive product. Reaction of (allyl)trimethylsilane in the presence of magnesium bromide etherate also proceeded stereoselectively producing **16** as the sole product in high yield.

In summary, double stereoselection in radical cyclization reaction of β-alkoxyvinyl sulfoxides presents a viable route for stereoselective synthesis of tetrahydrofuranyl allyl carbinols when coupled with subsequent Pummerer rearrangement and allylstannane reaction. Application of the strategy in the synthesis of oxacyclic natural products will be reported in due course.

Acknowledgment. We thank the Ministry of Science and Technology, Republic of Korea, and KISTEP for a National Research Laboratory grant (1999).

Supporting Information Available: Selected experimental procedures and ^1H and ^{13}C NMR spectra of **11**, **13**, and **15**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The results are contrary to expectation. There is an example of a related system in which $SnCl_4$ was used as a Lewis acid in chelation-controlled Sakurai reaction: Koert, U.; Stein, M.; Wagner, H. *Liebigs Ann.* **1995**, 1415−1426. In our case, it may be important to realize that there are three oxygen atoms per molecule for coordination.

(6) Use of magnesium bromide for chelation-controlled allyl transfer reaction for a α-benzyloxyaldehyde was reported: Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265−268.