Stereocontrolled Syntheses of Substituted Tetrahydrofurans via S_N' O-Cyclization

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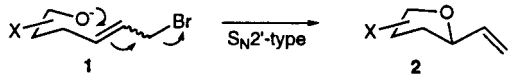
Tetrahydrofuran rings are a common structural motif present in a variety of natural products, pharmaceuticals, and diverse synthetic intermediates.[1−3] An effective approach to the synthesis of these heterocyclic compounds involves the formation of carbon−oxygen or carbon−carbon bonds via intramolecular S_N1, S_N2, or S_N' reactions.[4−6] The intramolecular S_N' reaction of alkoxide **1**, which is a nucleophilic displacement with a simultaneous allylic rearrangement (Scheme 1), offers a potential route to the stereoselective construction of vinyl tetrahydrofurans. The ring cyclization of **1** might proceed selectively from one face of the double bond because the transition state requires appropriate alignment of several atoms to liberate a single isomer of **2**. The rigid cyclic transition state of the S_N' processes can impose necessary geometric restraints for the stereoselective construction of a variety of bicyclic systems.[6,7] Herein we report an efficient method for the preparation of mono-heterocyclic compounds such as substituted tetrahydrofurans with high stereoselectivity via intramolecular S_N' O-cyclization of alkoxides.

Scheme 1



Our general strategy involves tandem reactions: addition of metallic or hydride reagents to carbonyl groups followed by an intramolecular S_N' O-cyclization to form tetrahydrofuran rings (Table 1). Reduction of **3a** or **4a**−**b** by DIBAL formed a primary alcohol which subsequently cyclized to give *2,4-disubstituted* THF **5a** or **5b** (entries 1−3). It was anticipated that the desired steric interactions in the transition state could be tuned by the use of trans or cis olefinic geometry. *E*-Allyl bromide **3a** was converted to **5a** with a slightly *cis*-favored diastereoselectivity (entry 1).[8,9] The selectivity was increased for *Z*-derivative **4a** (entry 2) and was magnified by selecting a large alkyl group such as the cyclohexyl group (entry 3).

For *2,5-disubstituted* THFs (entries 4−6), reaction of lithium reagents with 6-bromo-4-hexenal **3b** or **4c** gave alkoxide intermediates which cyclized in situ to produce a pair of isomers **5c**−**e**. Similarly, the olefin geometry of the starting materials appears to have an influence on the resulting stereochemistry of THFs. For example, the *E*-olefin **3b** reacts with 4-chlorophenyllithium to generate a 1:1 ratio of products (entry 4), whereas the *Z*-olefin **4c** produces 2,5-disubstituted THFs in favor of the trans products (entries 5−6).[8,9] The ratios of the trans/cis products increase dramatically by using bulky organometallic reagents (entry 6). A feature worth mentioning is that the dithiolanyl product **5e** can serve as an advantageous substrate for diastereoselective synthesis of other 2,5-disubstituted THFs.

On the basis of the encouraging results obtained above, we speculated that the stereochemical preferences observed in 2,4- and 2,5-disubstituted THF systems could be efficaciously exploited to provide superior stereocontrol in the formation of *2,3,5-trisubstituted* THFs. Indeed, treatment of 6-bromo-2-phenyl-4-hexenal **3a** or **4a** with metallic reagents such as allylmagnesium bromide and methyllithium gave trisubstituted tetrahydrofurans **5f**−**g** (entries 7−9) with complete control of stereochemistry.

This strategy was successfully applied to construct *tetrasubstituted* THFs (entries 10−16). The results parallel those observed for trisubstituted THFs and the addition of methyl organometallic agents to ketones **3c** or **4d** gave a dimethyl alkoxide intermediate which cyclized with the formation of the 2,4-cis isomers as the major products (entries 10−11). The reaction of **3d** or **4d**−**g** with other metallic agents rather than methyl derivatives generated two new stereocenters, but one isomer was predominantly produced (entries 12−16). Preferable formation of the 2,4-cis products **5a,b** can be tentatively explained by considering possible chairlike intermediates **A** and **B** (R′ = H) for the *Z* starting olefin (Scheme 2).[4l,5c] Only intermediates **A** and **B** were considered so that the bulky R groups occupy equatorial positions. The 1,3-diaxial interaction of hydrogen and vinyl in **B** is larger than that of two hydrogens in **A**, thus engendering cis diastereoselectivity for the 2,4-disubstituted THFs. The impressive stereocontrol, observed for the formation of the trisubstituted THFs, is attributed to the rigid chairlike transition states of the alkoxyl anion **A** (R,

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(9) The relative relationship of substituents for compounds **5** was studied by using NOESY techniques on several samples such as **5a**, **5k**, and **5l** . Both 2,4- and 2,5-disubstituted tetrahydrofurans exhibited regular patterns of chemical shifts of ^{1}H NMR spectra data. For example, the allylic protons of 2,4- and/or 2,5-disubstituted tetrahydrofuran are generally more upfield for the cis isomer than for the trans one.[5c,8a]

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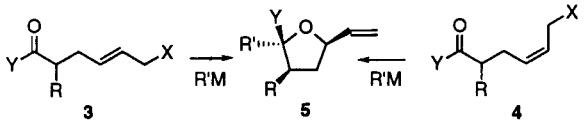
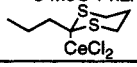
Table 1. Diastereoselective Synthesis of Substituted Tetrahydrofurans

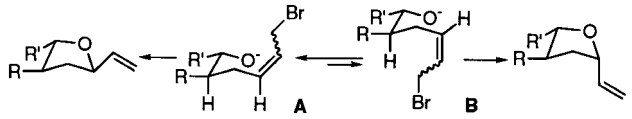


3 5 4

entry	olefin	X	Y	R	R'M	product	yield[a] (ratio)[b]
1	**3a**	Br	H	Ph	$HAl(i\text{-}Bu)_2$	**5a**	75% (3:2)
2	**4a**	Br	H	Ph	$HAl(i\text{-}Bu)_2$	**5a**	52% (4:1)
3	**4b**	Br	H	Cyh	$HAl(i\text{-}Bu)_2$	**5b**	74% (9:1)
4	**3b**	Br	H	H	*p*-Cl-PhLi	**5c**	72% (1:1)
5	**4c**	Br	H	H	*o*-MeO-PhLi	**5d**	92% (9:1)
6	**4c**	Br	H	H		**5e**	60% (20:1)
7	**3a**	Br	H	Ph	AllylMgBr	**5f**	71% (>20:1)
8	**4a**	Br	H	Ph	MeLi	**5g**	54% (>20:1)
9	**4a**	Br	H	Ph	AllylMgBr	**5f**	60% (>20:1)
10	**3c**	Br	Me	Cyh	MeLi	**5h**	80% (12:1)
11	**4d**	Br	Me	Ph	$MeCeCl_2$	**5l**	73% (10:1)
12	**3d**	Br	Me	Ph	AllylMgBr	**5j**	66% (>20:1)
13	**4d**	Br	Me	Ph	$n\text{-}BuCeCl_2$	**5k**	57% (>20:1)
14	**4e**	Br	*n*-Bu	Ph	$MeCeCl_2$	**5l**	66% (>20:1)
15	**4f**	Cl	Me	Ph	$n\text{-}BuCeCl_2$	**5k**	85% (12:1)
16	**4g**	Cl	Me	*p*-MeO-Ph	$n\text{-}BuCeCl_2$	**5m**	83% (15:1)

[a] Isolated yield. [b] Determined by ^1H NMR on the crude reaction mixture.

Scheme 2

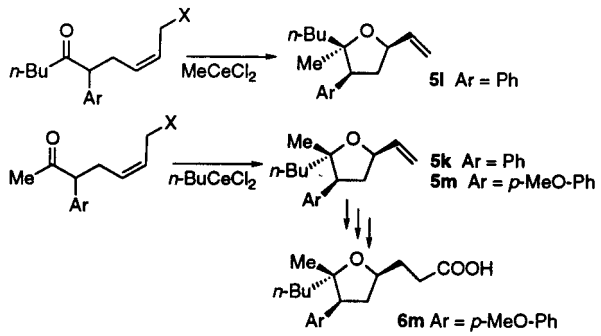


R′ = alkyl groups), in which a maximum number of the substituents are equatorially situated, thereby locking the conformation to give a single isomer.

It is worthwhile to note that diastereoisomers **5l** and **5k** have the reversed orientations of methyl and *n*-butyl groups, and are also prepared from sequential reactions of organometallic coupling and intramolecular S_N' cyclization (Scheme 3). The tandem reaction is triggered by the metallic reagent (R′M) attacking the carbonyl from the less-hindered side according to Cram's or Felkin-Anh's model.[10] The resulting alkoxyl anion attacks the distant allyl bromide via S_N' pathway to produce the corresponding compounds with three chiral centers in the ring. The relative stereochemistry of compound **5m** was investigated by X-ray analysis of its *p*-methoxyphenyl derivative **6m**,[11] a single isomer

(10) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

Scheme 3



of which was obtained from **5m** by successive ozonolysis, Wittig reaction, hydrogenation, and hydrolysis.

The method reported here is useful for the preparation of a variety of multi-substituted tetrahydrofurans in terms of its simplicity and its attainment of uniformly high yield. The resulting terminal vinyl group provides functionality for further elaboration to complex substrates. The insight gained from these studies will allow for an extension of this methodology to the stereospecific construction of more elaborate tetrahydropyran and pyrrolidine systems, thus paving the way to the synthesis of naturally occurring products. We have applied this method to the synthesis of the bistetrahydrofuran core of acetogenins, and these results will be reported shortly.

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Supporting Information Available: Synthetic procedures and characterization data for all new products, NOESY spectra for compounds **5a**, **5k**, and **5l**, and tables listing crystallographic data for **6m** (45 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(11) Crystal data for compound **6m** ($C_{19}H_{28}O_4$): orthorhombic space group $Pca2_1$ (No. 29), $a = 9.109(3)$ Å, $b = 17.163(3)$ Å, $c = 22.733(5)$ Å, $V = 3554.0(15)$ Å^3, $Z = 8$, $D_{calcd} = 1.198$ g/cm^3, μ (Mo Kα) = 0.82 cm^{-1}. The 2821 data were collected at −120 °C on an Enraf-Nonius CAD4 diffractometer equipped with graphite-monochromatized M*o* Kα ($\lambda = 0.710\ 73$ Å) radiation and using the ω:θ scan mode to the limit of $2\theta = 46°$. The structure was solved by direct methods (SHELXS-97, G. M. Sheldrick, University of Göttingen, 1997) and refined using a full-matrix least-squares procedure that minimized the function $\sum[w(F_o^2 - F_c^2)^2]$, where $w = 1/[\sigma^2(F_o^2) + 0.035P^2]$, and $P = [0.33333\mathrm{MAX}(0,F_o^2) + 0.66667F_c^2]$ and used all 2529 nonzero F^2 values and 422 parameters (SHELXL-97, G. M. Sheldrick, University of Göttingen, 1997). The final cycle of refinement converged with $R(F) = \sum||F_o| - |F_c||/\sum|F_o| = 0.061$, $wR(F^2) = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{0.5} = 0.094$, GOF $= \{\sum[w(F_o^2 - F_c^2)^2]/(N_{obs} - N_{par})\}^{0.5} = 1.006$ for the 1377 data with $I > 2\sigma(I)$. An extinction correction was made, such that F_c was multiplied by the overall scale factor and $[1 + 0.001xF_c^2\lambda^3/\sin(2\theta)]^{-0.25}$, where x is the refined extinction coefficient. The large, indeterminate value for the absolute structure (Flack) parameter, −1(4), agrees with the presence of a racemate in the crystal structure. All non-H atoms were refined with anisotropic displacement parameters; all H atoms bonded to C atoms were fixed at their calculated positions; the carboxylic H atoms were restrained to positions one-half the distance to either carboxylic group involved in the "head-to-head" hydrogen bonding.