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An Alternative Procedure for the Stereoselective Formation of Tetrahydropyran Derivatives *via* 6-Endo Ring Closure

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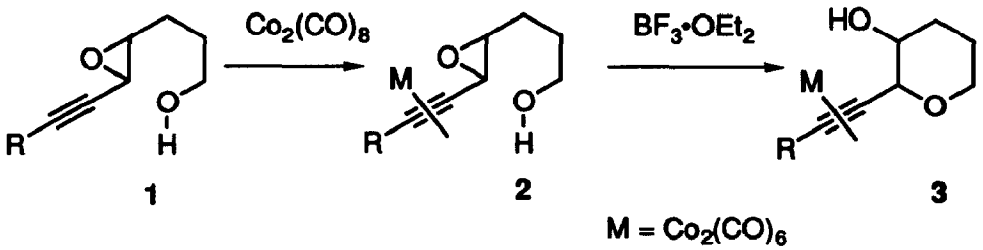
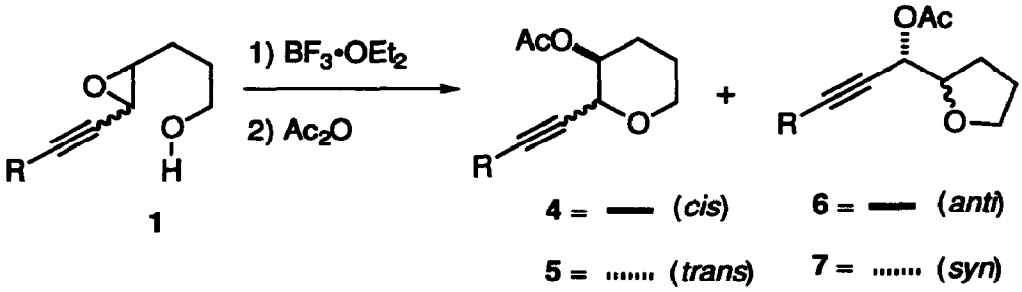
Abstract: Treatment of the acetylenic epoxides **1** having electron-donating groups at the acetylenic terminus with a catalytic amount of BF_3•OEt_2 afforded 6-endo products with inversion of stereochemistry at the propynyl position in a highly stereoselective manner, whereas the acetylenic epoxides **1** possessing electron-withdrawing substitutents at the acetylenic terminus provided under similar acidic condition the corresponding tetrahydrofuran derivatives in a highly selective way.

In the preceding paper,[1] we described an entirely novel method for the regio- and stereoselective formation of 3-hydroxy-2-ethynyltetrahydropyrans **3** through the 6-endo mode ring closure of the cobalt complexes **2**, derived from 4,5-epoxy-6-heptyn-1-ols **1**. The ring closure occurred exclusively at the propynyl position regardless of the properties of terminal substituents to give 6-endo products with retention of configuration at the propynyl stereogenic center. In order to explore further utility of the acetylenic epoxides **1**, we investigated direct ring closure of acetylenic epoxides **1** under acidic condition. This communication deals with (i) highly regio- and stereoselective 5-exo mode ring closure of acetylenic epoxides **1** having electron-deficient groups at the acetylenic terminus: (ii) highly regio- and stereoselective construction of tetrahydropyran ring from the acetylenic epoxides **1** possessing terminal electron-donating groups. In both cases *inversion of stereochemistry at the newly formed propynyl position was observed.*



To a solution of *trans*-**1a**[2] (1.0 mmol) in dry CH_2Cl_2 (30 mL) was added a solution of BF_3•OEt_2 in dry CH_2Cl_2 (0.1 M solution; 0.1 mmol) at -78°C. After being stirred at -78°C for 10 min, the cooling bath was removed and the reaction mixture was allowed to stand at room temperature with stirring (30 min). The reaction mixture was quenched by addition of H_2O and work-up gave an inseparable mixture of the 6-endo and 5-exo products. These compounds were subsequently acetylated with acetic anhydride and *N,N*-dimethylaminopyridine to furnish, after chromatographic separation, **5a** and **6a** in a ratio of 10 to 90 in 92% yield (Entry 1). Similar treatment of *cis*-**1a**[3] afforded **7a** exclusively in 89% yield (Entry 7). Treatment of other epoxides **1** with a catalytic amount of BF_3•OEt_2 in CH_2Cl_2 at -78°C to room temperature brought about an intriguing observation.



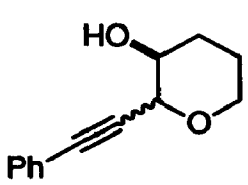
1

Table Ring Closure of Acetylenic Epoxides

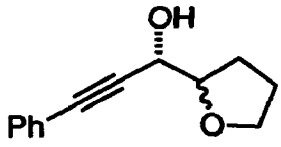
Entry	Substrate	R	6-endo/5-exo[a]	4 : 5[b]	6 : 7[b]	Yield (%)[c]
1	*trans*-**1a**	H	10 / 90	0 : 100	100 : 0	92
2	*trans*-**1b**[d]	TMS	62 / 38	2 : 98	90 : 10	91
3	*trans*-**1c**	Bu^n	95 / 5	0 : 100	100 : 0	96
4	*trans*-**1d**	C_6H_5	100 / 0	4 : 96	----	94
5	*trans*-**1e**	*p*-CH_3-C_6H_4	100 / 0	17 : 83	----	96
6	*trans*-**1f**	C_6H_5CO	1 / 99	0 : 100	100 : 0	96
7	*cis*-**1a**	H	0 / 100	----	0 : 100	89
8	*cis*-**1b**	TMS	20 / 80	96 : 4	0 : 100	90
9	*cis*-**1c**	Bu^n	72 / 28	100 : 0	0 : 100	96
10	*cis*-**1d**	C_6H_5	100 / 0	100 : 0	----	95
11	*cis*-**1e**	*p*-CH_3-C_6H_4	100 / 0	86 : 14	----	91
12	*cis*-**1f**	C_6H_5CO	0 / 100	----	0 : 100	89

[a] Ratio of total amount of **4** and **5** to that of **6** and **7**. [b] Ratio was determined by ^1H NMR.
[c] The specific yields are total yields of **4**, **5**, **6** and **7**. [d] A mixture of *trans*-**1b** and *cis*-**1b** in a ratio of 96 to 4 was employed.

Results summarized in Table allow us to make the following comments. 6-Endo ring closure occurred *with inversion of stereochemistry at the propynyl position.* The ratio of 6-endo product to 5-exo product[4,5] strongly depends on the electronic properties of the terminal substituents. Electron-donating substituents such as phenyl and *p*-tolyl groups extremely favored the 6-endo mode over the 5-exo mode (Entries 4, 5, 10, 11), while electron-deficient substituent like benzoyl group[6,7] dramatically changed the sense of ring closure to produce the tetrahydrofuran derivatives in a highly selective way (Entries 6, 12). Alkyl groups (weak electron-donating functionality) favor the 6-endo mode over the 5-exo mode (Entries 3, 9). In the cases of trimethylsilyl and unsubstituted derivatives, both of which are not regarded as either an obvious electron-donating or electron-deficient functionality, reactions proceeded in the 5-exo mode preferentially (Entries 1, 7, 8) except for the case of *trans*-**1b** (Entry 2). It is noteworthy that this behavior is not affected by the geometry of the starting epoxide.[8] Complete regiocontrol (6-endo mode) in the cases of phenyl and *p*-tolyl groups was realized regardless of the geometry of the starting acetylenic epoxides **1**. This result is contrast to the ring closure of vinyl epoxides; namely *trans* vinyl epoxides exclusively formed the corresponding tetrahydropyrans (6-endo mode closure), while *cis* vinyl epoxides provided both the 5-exo mode product and the 6-endo mode product nonselectively.[6]



8d = ——
9d = ·····



10d = ——
11d = ·····

Tetrahydropyrans **8d** and **9d** (prepared from **4d** and **5d**, respectively) were independently exposed to the standard ring closure condition and found to be recovered intact. Similar treatment of tetrahydrofurans **10d** and **11d** (derived from compounds obtained in Table, Entries 1,7) disclosed that both **10d** and **11d** were stable under the epoxide ring opening condition employed. On the basis of these results, possibility of interconversion of these four regio- and stereoisomers could be excluded.

Thus, either *trans*- or *cis*-2-ethynyl-3-hydroxytetrahydropyran species are now easily available from acetylenic epoxides **1** by judicious choice of the starting epoxide and/or reaction condition (with or without cobalt complexation[1]). The stereocomplementarity between cobalt-complexed[1] and cobalt free procedures in the cases of acetylenic epoxides **1** having electron-donating groups enhances the value of the procedure developed here. Therefore, both reactions (cobalt-complexed and cobalt free methods) should be considered attractive not only from regio- and stereochemical points of view but also from the synthetic perspective, and may be added as new useful additions to the list of stereoselective tetrahydropyran syntheses. Further mechanistic details and the synthetic utility of these reactions will be reported in due course.

Acknowledgment: We thank Takeda Science Foundation for generous financial support.

References and Note

1 Mukai, C.; Ikeda, Y.; Sugimoto, Y.; Hanaoka, M. *Tetrahedron Lett.* in this issue.

2 *trans* Epoxides **1** were prepared from 4-(*tert*-butyldimethyl-silyloxy)-1-butanal (Nicolaou, K.C.; Prasad, C.V.C.; Hwang, C.-K.; Duggan, M.E.; Veale, C.A. *J. Am. Chem. Soc.* **1989**, *111*, 5321) as follows: (i) olefination with $CHI_3/CrCl_2$; (ii) palladium coupling with acetylene derivatives; (iii) epoxidation with *m*-CPBA; (iv) desilylation.

3 *cis* Epoxides **1** were prepared from (*Z*)-2-bromo-1-iodopropene (Ziegler, F.E.; Jeroncic, L.O. *J. Org. Chem.* **1991**, *56*, 3479) as follows: (i) reaction with lithium enolate of *tert*-butyl acetate; (ii) reduction with $LiAlH_4$; (iii) silylation with *tert*-$BuMe_2SiCl$; (iv) palladium coupling with acetylene derivatives; (v) epoxidation with *m*-CPBA; (vi) desilylation.

4 *Anti* and *syn* stereochemistry refers to that depicted in structures **6** and **7**, respectively. Stereochemistry of **6** and **7** was determined by anaology to literature precedents.[5,6]

5 For examples, see (a) Karakhanov, R.A.; Vartanyan, M.M.; Soloveva, T.Yu.; Lapuka, L.F. *Khim. Geterotsiki. Soedin.* **1983**, 1602 [*CA.* **1984**, *100*, 174555h]. (b) Wright, A.E.; Schäfer, M.; Midland, S.; Munnecke, D.E.; Sims, J.J. *Tetrahedron Lett.* **1989**, *30*, 5699. (c) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K.B.; Sinha, S.C.; Sinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407. (d) Borhan, B.; Nourooz-Zadeh, J.; Uematsu, T.; Hammock, B.D.; Kurth, M.J. *Tetrahedron* **1993**, *49*, 2601. (e) Grese, T.A.; Hutchinson, K.D.; Overman, L.E. *J. Org. Chem.* **1993**, *58*, 2468.

6 (a) Nicolaou, K.C.; Duggan, M.E.; Hwang, C.-K.; Somers, P.K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359. (b) Nicolaou, K.C.; Prasad, C.V.C.; Somers, P.K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (c) Nicolaou, K.C.; Prasad, C.V.C.; Somers, P.K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335.

7 Nicolaou[6] reported exclusive 5-exo ring closure of **1** having bromo functionality at acetylenic terminus under similar condition.

8 In cases of **1b** and **1c**, *trans* compounds yielded 6-endo products more selectively compared with *cis* analogues (Entries 2,3,8,9). This observation may be due in part to steric congestion and worse overlapping effect between triple bond and C-O bond of epoxide in *cis* epoxide structure.

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