Pergamon

Tetrahedron Letters, Vol. 35, No. 14, pp. 2179-2182, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0267-2

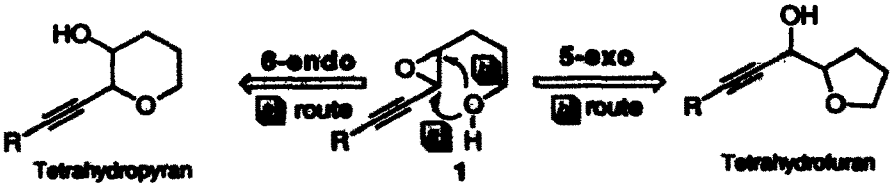
Regioselective and Stereospecific Formation of 2-Ethynyl-3-hydroxytetrahydropyran Derivatives *via* 6-Endo Ring Closure

Chisato Mukai, Yoshitaka Ikeda, Yu-ichi Sugimoto, and Miyoji Hanaoka*

Faculty of Pharmaceutical Sciences, Kanazawa University
Takara-machi, Kanazawa 920 Japan

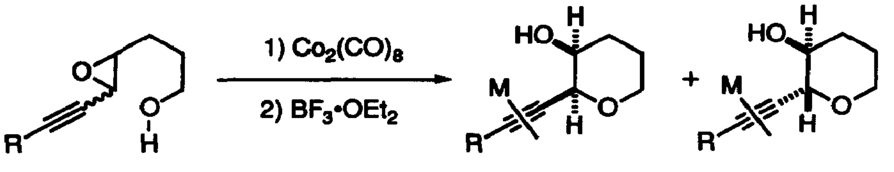
Abstract: Efficient access to tetrahydropyran derivatives *via* highly regio- and stereoselective 6-endo tet mode ring opening of an epoxide by an internal hydroxy group has been developed. Cobalt complexes, derived from *trans*-4,5-epoxy-6-heptyn-1-ols and dicobalt octacarbonyl were treated with a catalytic amount of $BF_3 \cdot OEt_2$ in CH_2Cl_2 at -78°C to afford *cis*-2-ethynyl-3-hydroxytetrahydropyran derivatives in a highly regio- and stereoselective manner. Similar treatment of *cis*-4,5-epoxides provided the corresponding *trans*-tetrahydropyrans selectively.

Tetrahydropyran systems[1] are frequently significant targets for synthesis[2,3,4] because they are components of many biologically important natural products.[5] Highly regio- and stereoselective 6-endo mode of ring opening of an epoxide by an internal hydroxy group would be the most attractive and straightforward access to 3-hydroxy-2-substituted-tetrahydropyran systems. Successful contributions in line with this strategy are Nicolaou's elegant protocol[3a] taking advantage of the activation of *trans* epoxides[6] by an adjacent vinyl moiety leading to *trans*-3-hydroxy-2-vinyltetrahydropyran derivatives and Hirama's palladium-catalyzed procedure[4,7] both of which display preference for the 6-endo mode of ring closure over usually favored 5-exo mode.[8] In addition to these two procedures, an antibody catalyst[9] has very recently attracted us because of its extreme effectiveness for 6-endo process over 5-exo one.



1

Described herein are the results of our initial investigation that disclose highly regio- and stereoselective formation of 2-ethynyl-3-hydroxytetrahydropyran derivatives through the 6-endo mode of ring closure of hydroxy epoxides possessing an acetylenic moiety adjacent to the epoxide ring. We found that the cobalt-complexed epoxides, prepared from the reaction of acetylenic epoxides **1** with dicobalt octacarbonyl, provided upon treatment with a catalytic amount of Lewis acid *6-endo products exclusively with retention*[10] *of configuration at the propynyl position.*



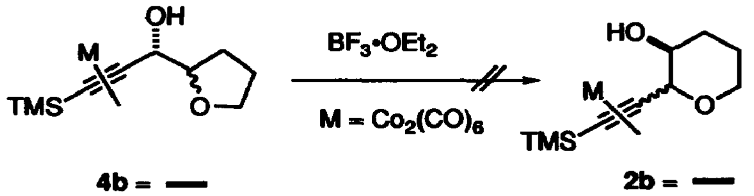
1 M = $Co_2(CO)_6$ **2** (*cis*) **3** (*trans*)

Table. Ring Closure[a] of Cobalt Complexed Acetylenic Epoxides

Entry	Substrate	R	Products	(Ratio)[b]	Yield (%)[c]
1	*trans*-**1a**	H	**2a** : **3a**	(96 : 4)	65
2	*trans*-**1b**[d]	TMS	**2b** : **3b**	(91 : 9)	86
3	*trans*-**1c**	Bu^n	**2c** : **3c**	(97 : 3)	97
4	*trans*-**1d**	C_6H_5	**2d** : **3d**	(99 : 1)	96
5	*trans*-**1e**	*p*-CH_3-C_6H_4	**2e** : **3e**	(98 : 2)	98
6	*trans*-**1f**	C_6H_5CO	**2f** : **3f**	(98 : 2)	90
7	*cis*-**1a**	H	**2a** : **3a**	(1 : 99)	92
8	*cis*-**1b**	TMS	**2b** : **3b**	(0 : 100)	88
9	*cis*-**1c**	Bu^n	**2c** : **3c**	(1 : 99)	92
10	*cis*-**1d**	C_6H_5	**2d** : **3d**	(1 : 99)	93
11	*cis*-**1e**	*p*-CH_3-C_6H_4	**2e** : **3e**	(3 : 97)	95
12	*cis*-**1f**	C_6H_5CO	**2f** : **3f**	(3 : 97)	89

[a] To a solution of **1** (1.0 mmol) in dry CH_2Cl_2 (30 mL) was added $Co_2(CO)_8$ (1.1 mmol) at rt after being stirred (for 30~60 min; consumption of **1** was monitored by TLC), the reaction mixture was cooled down to -78°C and held at the same temperature for 30 min. A solution of $BF_3 \cdot OEt_2$ in dry CH_2Cl_2 (0.1M solution; 0.1 mmol) was then added to the reaction mixture, which was further stirred at -78°C for 10 min. The reaction was quenched at -78°C by addition of H_2O. Work-up and chromatography afforded cyclized products. [b] Compounds **2** and **3** could be separated by silica gel column chromatography as pure form. Ratio was determined on the basis of isolated amount of each compound **2** and **3**. [c] The specific yields are isolated yields of **2** and **3**. [d] A mixture of *trans*-**1b** and *cis*-**1b** in a ratio of 96 to 4 was employed.

trans Epoxide (*trans*-**1a**) was treated with dicobalt octacarbonyl to give the labile cobalt-complexed derivative which was subsequently exposed to a catalytic amount of BF$_3$•OEt$_2$[11] in CH$_2$Cl$_2$ at -78°C producing the 6-endo products[12] in 65% yield.[13] The ratio of **2a** to **3a** (*cis* : *trans*) was found to be 96 : 4 (Entry 1). No 5-exo cyclization products could be detected. The corresponding *cis* epoxide (*cis*-**1a**) gave 6-endo products exclusively in 92% yield in a highly *trans* selective manner (*cis* : *trans* = 1 : 99)(Entry 7). Further examples of 6-endo cyclization of epoxides **1** *via* the corresponding hexacarbonyldicobalt complexes under standard conditions are presented in Table. The following features deserve comment. (i) Exclusive formation of 6-endo products was observed regardless of geometry of the starting acetylenic epoxide **1**. (ii) Ring formation took place with retention of configuration at the propynyl position resulting in a highly stereoselective formation of *trans*-2-ethynyl-3-hydroxytetrahydropyran systems from *cis* epoxides, whereas *cis* congeners form *trans* epoxides. (iii) Irrespective of the electronic properties of the terminal substituent on the triple bond, ring closure proceeded in the 6-endo mode exclusively and 5-exo products were never found in more than trace quantities. It should be mentioned here that two possible isomerization processes during cyclization, *i.e.* epimerization of **2** to **3** and *vice versa*, and ring transformation of cobalt-complexed five membered products (tetrahydrofuran derivatives) to **2** and/or **3** (tetrahydropyran derivatives), were completely ruled out by the following experiments. (i) Pure **2b** and **3b** were independently exposed to BF$_3$•OEt$_2$ (0.1 equiv.) in CH$_2$Cl$_2$ at -78°C. Reactions quenched at the same temperature[14] revealed that no reaction took place and cobalt-complexed **2b** and **3b** were respectively recovered intact. (ii) Independent treatment of tetrahydrofurans **4b** and **5b**[15] with BF$_3$•OEt$_2$ at -78°C provided only **4b** and **5b** respectively intact again. These isomerization experiments strongly indicate that 6-endo cyclization products **2** and **3** are kinetically controlled in these cyclization reactions.



4b = ——
5b = ...

2b = ——
3b = ...

Preferential formation of tetrahydropyran ring systems over tetrahydrofuran derivatives could be explained by the intermediacy of a propynyl cation stabilized by the cobalt-complexed acetylenic moiety (Nicholas reaction).[16] Retention of configuration at the propynyl position implies that the intermediate carbenium ion does not undergo isomerization prior to nucleophilic attack. This is contrary to the findings of Schreiber[17] in his studies of the mechanism of intermolecular additions to cobalt stabilized carbenium ions.

Thus, we developed a new procedure for the preparation of *trans*- and *cis*-2-ethynyl-3-hydroxytetrahydropyran derivatives from acetylenic *cis* and *trans* epoxides, respectively, *via* the corresponding cobalt-complexed species.

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

References and Notes

1 For recent reviews, see (a) Rao, A.S.; Paknikar, S.K.; Kirtane, J.G. *Tetrahedron* **1983**, *39*, 2323. (b) Boivin, T.L.B. *Tetrahedron* **1987**, *43*, 3309.

2 For some recent examples, see (a) Fukuyama, T.; Wang, C.-L.J.; Kishi, Y. *J. Am. Chem. Soc.* **1979,** *101*, 260. (b) Fukuyama, T.; Akasaka, K.; Karanewsky, D.S.; Wang, C.-L.J.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979,** *101*, 262. (c) Schultz, W.J.; Etter, M.C.; Purius, A.V.; Smith, S. *J. Am. Chem. Soc.* **1980,** *102*, 7981. (d) Dolle, R.E.; Nicolaou, K.C. *J. Am. Chem. Soc.* **1985,** *107*, 1691. (e) Bartlett, P.A.; Ting, P.C. *J. Org. Chem.* **1986,** *51*, 2230. (f) Trost, B.M.; Tenaglia, A. *Tetrahedron Lett.* **1988,** *29*, 2927. (g) Martín, V.S.; Nuñez, M.T.; Ramirez, M.A.; Soler, M. A. *Tetrahedron Lett.* **1990,** *31*, 763. (h) Kozikowski, A.P.; Lee, J. *J. Org. Chem.* **1990,** *55*, 863.

3 (a) Nicolaou, K.C.; Prasad, C.V.C.; Somers, P.K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989,** *111*, 5330. (b) Nicolaou, K.C.; Prasad, C.V.C.; Somers, P.K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989,** *111*, 5335.

4 Suzuki, T.; Sato, O.; Hirama, M. *Tetrahedron Lett.* **1990,** *31*, 4747.

5 For some recent reviews, see (a) Moore, R.E. *Marine Natural Products: Chemical and Biological Perspectives*; Scheuer, P.J., Ed.; Academic Press: New York, 1978, vol 2. (b) *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Westley, J.W., Ed.; Marcel Dekker: New York, 1982. (c) Faulkner, D.J. *Nat. Prod. Rep.* **1986,** *3*, 1.

6 The corresponding *cis* epoxides have been shown to disfavor 6-endo mode of ring closure.[3a,b]

7 Trost[2f] also reported palladium-catalyzed 6-endo cyclization of the hydroxy vinyl epoxide through π-allyl palladium complexes without definite statement of stereochemical outcome.

8 Baldwin, J.E. *J. Chem. Soc., Chem. Commun.* **1976,** 734.

9 Janda, K.D.; Shevlin, C.G.; Lerner, R.A. *Science*, **1993,** *259*, 490.

10 During preparation of this manuscript, Nicholas reported examples of carbon-carbon bond formation with retention of stereochemistry at the propynyl position of cobalt-complexed propargyl alcohols possessing tris(1,1,1,3,3,3-hexafluoroisopropyl)phosphite as a ligand. Caffyn, A.J.M.; Nicholas, K.M. *J. Am. Chem. Soc.* **1993,** *115*, 6438

11 The reaction with trifluoroacetic acid and methanesulfonic acid revealed the smilar chemical yield and stereoselectivity to those with BF_3•OEt_2. However, other Lewis acids ($SnCl_4$, $TiCl_4$, $EtAlCl_2$, Et_2AlCl) were found to be inferior to BF_3•OEt_2.

12 3-Hydroxytetrahydropyrans **2** and **3** were fully characterized by their conversion into corresponding *O*-acetyl compounds without cobalt complexation through successive CAN treatment and acetylation.

13 Ring opening of $Co_2(CO)_6$-complexed 1,2-epoxy-1-ethynylcyclohexane with excess of H_2O, MeOH, or Cl_3CCO_2H under acidic condition (HBF_4•Me_2O or H_2SO_4) had been investigated in Saha, M.; Nicholas, K.M. *J. Org. Chem.* **1984,** *49*, 417.

14 Even when *cis*-**1b** was exposed to 1.0 equiv. of BF_3•OEt_2 at -78°C, no conversion of *cis*-**1b** to *trans*-**1b** could be observed. However, isomerization of *cis*-**1b** to *trans* -**1b** (*cis* : *trans* = 26 : 74; 96% yield) occurred upon treatment of the former with 1.0 equiv. of BF_3•OEt_2 at rt for 30 min, whereas *trans*-**1b** was stable enough not to isomerize to *cis*-**1b** under these conditions examined.

15 Cobalt-complexed tetrahydrofurans **4b** and **5b** were derived from the corresponding tetrahydrofurans by treatment with $Co_2(CO)_8$: see the following manuscript.

16 For a review, see Nicholas, K.M. *Acc. Chem. Res.* **1987,** *20*, 207.

17 (a) Schreiber, S.L.; Sammakia, T.; Crowe, W.E. *J. Am. Chem. Soc.* **1986,** *108*, 3128. (b) Schreiber, S.L.; Klimas, M.T.; Sammakia, T. *J. Am. Chem. Soc.* **1987,** *109*, 5749.

(*Received in Japan* 23 *October* 1993; *accepted* 18 *January* 1994)