Stereocomplementary Construction of 2-Ethynyl-3-hydroxytetrahydrofuran Derivatives *via endo*-mode Ring Closure of 3,4-Epoxy-6-substitutedhex-5-yn-1-ols

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

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

Treatment of 3,4-epoxy-6-substitutedhex-5-yn-1-ols with $BF_3{\cdot}OEt_2$ gave the *endo*-mode cyclization products with inversion of stereochemistry, whereas conversion of the epoxides to the corresponding hexacarbonyldicobalt complexes, followed by Lewis-acid treatment provided the *endo*-mode products with retention of configuration at the newly formed stereogenic centre.

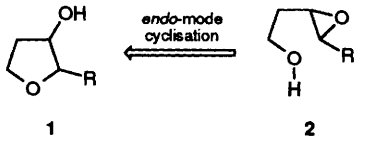
Tetrahydrofurans have been well known to be components of many biologically significant natural products[1] such as polyether antibiotics and acetogenins. One of the most straightforward processes to build up the substituted tetrahydrofuran skeletons **1**[2] would be ring opening of an epoxide by a terminal hydroxy group of **2** *via endo*-mode ring closure[3] which is generally regarded as an unfavourable pathway.[4] In order to override this disadvantageous process, we noticed the inherent properties of a triple bond to favour the *endo*-mode pathway over the 4-*exo*-mode in the cyclization reaction of **2**. Namely (*i*) a triple bond is susceptible to reaction with dicobalt octacarbonyl to form the corresponding alkyne-hexacarbonyldicobalt species[5] which can stabilise the propynyl cation and (*ii*) the π orbital of a triple bond should stabilise the adjacent propynyl cation by delocalization, although the stabilising ability of a triple bond due to delocalization might be less effective than that of a double bond.[6]

Described herein is a highly stereoselective and stereocomplementary method for the preparation of 2-ethynyl-3-hydroxytetrahydrofuran derivatives from 3,4-epoxy-6-substitutedhex-5-yn-1-ols through *endo*-mode type ring closure.

Exposure of *trans*-3,4-epoxy-6-trimethylsilhex-5-yn-1-ol (*trans*-**3a**, *trans*:*cis* = 92:8) to dicobalt octacarbonyl in CH_2Cl_2 at room temperature gave the labile cobalt-complexed product **4a**,[4] which was subsequently cooled to −78 °C and treated with a catalytic amount of $BF_3{\cdot}OEt_2$ (0.1 equiv.) to produce the cobalt complexed cyclized products. The resulting cobalt-complexed tetrahydrofurans were demetalated by exposure to cerium(IV) ammonium nitrate (CAN) at −78 °C to afford the *cis*-2-ethynyl-3-hydroxytetrahydrofuran derivative, *cis*-**5a**† (*cis*:*trans* = 92:8) in 84% yield. No 4-*exo*-mode cyclization products were detected in the reaction mixture. Complete regio- as well as stereo-control could be realised. Similar treatment of the *n*-butyl and phenyl analogues, *trans*-**3b** and **c** provided the corresponding *cis*-tetrahydrofuran derivatives in a highly stereocontrolled manner. The results from *cis*-epoxides are summarised along with those from *trans*-epoxides in Table 1.

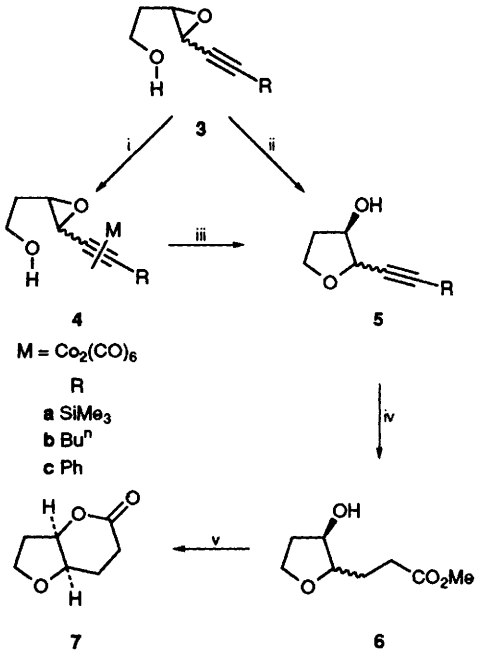
It should be noted here that (*i*) this cyclization *via* the cobalt-complexed intermediate is completely regioselective and yields the *endo*-mode products exclusively, (*ii*) cyclization proceeds with retention of the stereochemistry at the C-2 position of tetrahydrofuran skeleton, (*iii*) high stereoselectivity is observed irrespective of the geometry of either the starting epoxide or substituent at the alkynyl terminus. The stereochemical result may be tentatively interpreted as a double-inversion process[7] which involves epoxy-ring opening by neighbouring group participation arising from cobalt complexation, followed by capture of the resulting propynyl cation species by the terminal hydroxy group.‡

When *trans*-**3a** was directly treated with $BF_3{\cdot}OEt_2$ in



1 **2**

Scheme 1



Scheme 2 *Reagents*: i, $Co_2(CO)_8$; ii, $BF_3{\cdot}OEt_2$; iii, $BF_3{\cdot}OEt_2$ then CAN; iv, Bu^tMe_2SiCl–imidazole then K_2CO_3–MeOH then $LiBu^n$–$ClCO_2Me$ then H_2/Pd-C then $(Bu^n)_4NF$; vi, HCl–THF

Table 1 Preparation of 2-ethynyl-3-hydroxytetrahydrofuran derivatives **5**

Epoxide	R	Ratio of **3**[a] *trans*:*cis*	Method[b]	Product[c] (%)	Ratio of **5**[a] *trans*:*cis*
trans-**3a**	$SiMe_3$	92:8	a	**5a** (84)	8:92
trans-**3b**	Bu^n	99:1	a	**5b** (90)	3:97
trans-**3c**	Ph	98:2	a	**5c** (90)	8:92
cis-**3a**	$SiMe_3$	5:95	a	**5a** (62)	96:4
cis-**3b**	Bu^n	6:94	a	**5b** (78)	88:12
cis-**3c**	Ph	4:96	a	**5c** (77)	93:7
trans-**3a**	$SiMe_3$	92:8	b	**5a** (90)	98:2
trans-**3b**	Bu^n	99:1	b	**5b** (98)	99:1
trans-**3c**	Ph	98:2	b	**5c** (98)	93:7
cis-**3a**	$SiMe_3$	5:95	b	**5a** (44)	27:73
cis-**3b**	Bu^n	6:94	b	**5b** (73)	21:79
cis-**3c**	Ph	4:96	b	**5c** (73)	39:61

[a] Ratios were determined by ^1H NMR spectroscopy. [b] Method a, epoxide **3** was treated with $Co_2(CO)_8$ in CH_2Cl_2 at room temperature to give the corresponding cobalt-complexed alkyne which was exposed to $BF_3{\cdot}OEt_2$ (0.1 equiv.) at −78 °C. The reaction was quenched by addition of a solution of CAN in MeOH to the reaction mixture at −78 °C; method b, $BF_3{\cdot}OEt_2$ (0.1 equiv.) was added to a solution of epoxide **3** in CH_2Cl_2 at −78 °C and the reaction mixture was gradually warmed to room temperature. [c] *trans*- and *cis*-**5** could be separated by silica-gel column chromatography and characterised.

CH_2Cl_2, the *trans*-tetrahydrofuran, *trans*-**5a** was obtained in a highly selective way. In this case the configuration of the newly formed stereogenic centre of **5a** was inverted in sharp contrast to the result obtained from the cyclization reaction *via* cobalt complexation. Other *trans*-epoxides, *trans*-**3b,c**, on exposure to Lewis acids, furnished diastereoselectively *trans*-**5b,c**, in high yields, respectively (Table 1). For a series of *cis*-epoxides, cyclization occurred through the *endo* mode to yield tetrahydrofurans **5**, but the degree of stereoselectivity§ was somewhat lower compared with the case of *trans*-epoxides.

Thus, we have developed two procedures for construction of 2-ethynyl-3-hydroxytetrahydrofuran derivatives *via endo*-mode type ring closure. The first procedure is direct cyclization of **3** to tetrahydrofurans **5** with stereoinversion at the C-2 position of **5** and the second is *via* cobalt-complexation which yields species **5** with retention of configuration at the C-2 position. This stereocomplementarity coupled with the fact that triple bonds can be easily transformed into various functionalities, strongly enhances our newly developed procedures for the preparation of substituted tetrahydrofuran derivatives. Further studies on applications of these reactions to biologically active compounds as well as details of the mechanism for retention of stereochemistry in the cobalt complexation procedure are now in progress.

Part of this work has been financially supported by the Takeda Science Foundation, to whom our thanks are due.

Received, 8th February 1994; Com. 4/00781F

Footnotes

† The structures of the cyclization products were determined on the basis of spectroscopy. Furthermore, *cis* and *trans*-**5a** were independently transformed into the corresponding hydroxy esters, *cis*- and *trans*-**6**, respectively as indicated in Scheme 2. Lactonisation of *cis*-**6** under mild acidic conditions gave the *cis*-lactone **7** with a smaller coupling constant (4.3 Hz) between the two protons at the ring juncture as expected. However, *trans*-**6** did not provide the corresponding loctone under either the above conditions for *cis*-**6** or by employing more drastic conditions.

‡ Retention of stereochemistry at the propynyl position implies that the plausible cobalt-complexed carbenium ion intermediate does not undergo isomerization prior to intramolecular attack of the terminal alcoholic moiety. This interpretation is contrary to that proposed in ref. 7 on the mechanism of intermolecular addition to cobalt-complexed propynyl ether species. Otherwise this result would be interpreted in terms of the diastereoselectivity of formation of the cobalt-stabilised propynyl cation intermediate.[7]

§ The reasons for low stereoselectivity observed in the cyclization of *cis*-**3** (method b) are as yet unclear. Non-bonding interactions between the alkyne moiety and the terminal hydroxy group would retard an approach of the latter to the propynyl position giving rise to partial isomerization of the cationic intermediate which leads to production of considerable amount of *trans*-**5**. Another possible factor for low stereoselectivity is the poorer delocalization of the triple bond of *cis*-**3** relative to *trans*-**3** owing to steric conjestion. By either method (a or b) the yields of the cyclization products **5** were higher for *trans*- over *cis*-**3**, perhaps reflecting these two factors.

References

1 J. W. Westle, in *Polyether Antiobiotics: Naturally Occurring Acid Ionophores*, Marcel Dekker, New York, 1982, vols. 1 and 2 M. H. D. Postema, *Tetrahedron*, 1992, **48**, 8545; A. Cavé, D. Cortes, B. Figadère, R. Hocquemiller, O. Laprévote, A. Laurens and M. Leboeuf, in *Phytochemical Potential of Tropical Plants; Recent Advances in Phytochemistry*, ed. K. R. Downum, J. Romeo and H. H. A. Stafford, Plenum, New York, 1993, vol. 27.

2 T. L. B. Boivin, *Tetrahedron*, 1987, **43**, 3309; J.-C. Harmange and B. Figadère, *Tetrahedron Asymmetry*, 1993, **4**, 1711.

3 For some examples, G. Stork, L. D. Cama and D. R. Coulson, *J. Am. Chem. Soc.*, 1974, **96**, 5258; G. Stork and J. F. Cohen, *J. Am. Chem. Soc.*, 1974, **96**, 5270; M. P. Cooke, Jr. and I. N. Houpis, *Tetrahedron Letters*, 1985, **26**, 3643; S. Hatakeyama, K. Sakurai, H. Numata, N. Ochi and S. Takano, *J. Am. Chem. Soc.*, 1988, **110**, 5201; V. Ratovelomanana, L. Vidal, J. Royer and H.-P. Husson, *Heterocycles*, 1991, **32**, 879; M. Yoshitake, M. Yamamoto, S. Kohmoto and K. Yamada, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2157.

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

5 K. M. Nicholas, *Acc. Chem. Res.*, 1987, **20**, 207.

6 K. C. Nicolaou, C. V. C. Prasad, P. K. Somers and C.-K. Hwang, *J. Am. Chem. Soc.*, 1989, **111**, 5330.

7 S. L. Schreiber, M. T. Klimas and T. Sammakia, *J. Am. Chem. Soc.*, 1987, **109**, 5749.