Tetrahedron Letters,Vol.23,No.27,pp 2719-2722,1982 0040-4039/82/272719-04$03.00/0
Printed in Great Britain

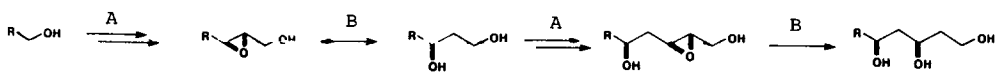
REDUCTIVE RING OPENINGS OF ALLYL-ALCOHOL EPOXIDES

James M. Finan and Yoshito Kishi*
Department of Chemistry, Harvard University, Cambridge, Mass. 02138, U.S.A

Abstract Red-Al reduction of allyl-alcohol epoxides was shown to yield 1,3-diols in high regioselectivity, while DIBAL reduction was shown to yield 1,2-diols.

A 1,3-polyhydroxylated chain is often found on the backbone of important natural products including polyene macrolide antibiotics.[1] However, to the best of our knowledge, there has been no general method for synthesizing such a system in a regio- and stereocontrolled fashion.[2] In this communication, we would like to report a simple solution for this problem.

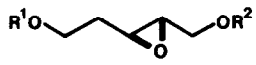
Encouraged by successful application of the chain extension approach for the synthesis of polyether antibiotics[3], ansamycin antibiotics[4], and carbohydrates[5], it was decided to examine the feasibility of the synthetic approach shown below, consisting of a repetition of two major steps, i.e., A and B. With respect to step A, Sharpless asymmetric epoxidation of allylic alcohols[6] seemed to provide a practical and reliable method of synthesizing either R- or S-epoxides Thus, we began to study a selective method to achieve step B. The regioselectivity



of the ring opening of epoxide 1[7] (racemic) by various hydride reagents was examined. From the results summarized in the table, it is clear that the Red-Al [$NaAlH_2(OCH_2CH_2OCH_3)_2$] conditions satisfy the present purposes. The primary factor controlling this remarkable regioselectivity seems to be the hydroxy group in 1, because the epoxide 4 was recovered unchanged under the same conditions and also because the epoxide 5 yielded exclusively[8] the alcohol 6. The scope of this reaction seemed to be very good, the Red-Al ring opening (Red-Al/THF/0°C) of three additional substrates 7 through 9 yielded exclusively[8] the expected 1,3-diols in excellent yield.[9]

In contrast to the Red-Al case, DIBAL reduction of the epoxide 1 yielded the 1,2-diol 3 as the major product (see table). Although the degree of regioselectivity varies by substrate, this seems to be a general trend, the results of DIBAL ring opening (DIBAL/C_6H_6/RT) on the three additional substrates 7 through 9 are indicated in the structures.[9]

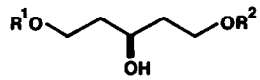
Coupled with Sharpless asymmetric epoxidation, the Red-Al reduction provides a stereo- and regiocontrolled route to 1,3-polyhydroxylated systems, as demonstrated in the synthesis of the alcohols 17 and 19 (see scheme) The stereoselectivity of the Horner-Emmons modification of Wittig reaction using $(i\text{-PrO})_2P(O)CH_2CO_2Et$[10] was 98:2 or better. The Red-Al reduction of the epoxides 12, 16 and 18 yielded the expected 1,3-dihydroxy products exclusively [8] The optical purity of the epoxide 12 and the alcohol 13 was very high [11] However, asymmetric induction in the epoxidation of the allylic alcohol 15 by using either natural (+)- or unnatural (-)-diethyl



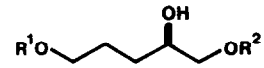
1: $R^1=CH_2C_6H_5$, $R^2=H$

4. $R^1=CH_2C_6H_5$, $R^2=Me$

5. $R^1=H$, $R^2=CH_2C_6H_5$

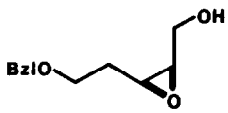


2 $R^1=CH_2C_6H_5$, $R^2=H$



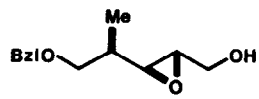
3 [12] $R^1=CH_2C_6H_5$, $R^2=H$

6: [12] $R^1=H$, $R^2=CH_2C_6H_5$



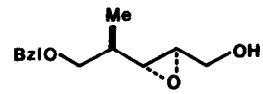
7 Red-Al = >20:1[8,14]

DIBAL = 1 1 2[13,14]



8: Red-Al = >20.1[8,14]

DIBAL = 1.6[13,14]



9: Red-Al = >20 1[8,14]

DIBAL = 1.8[13,14]

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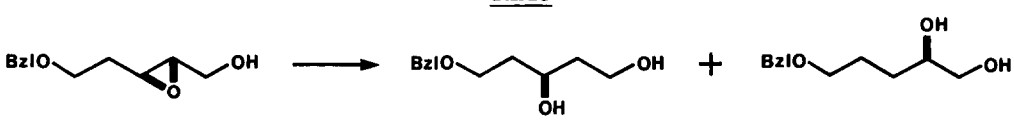
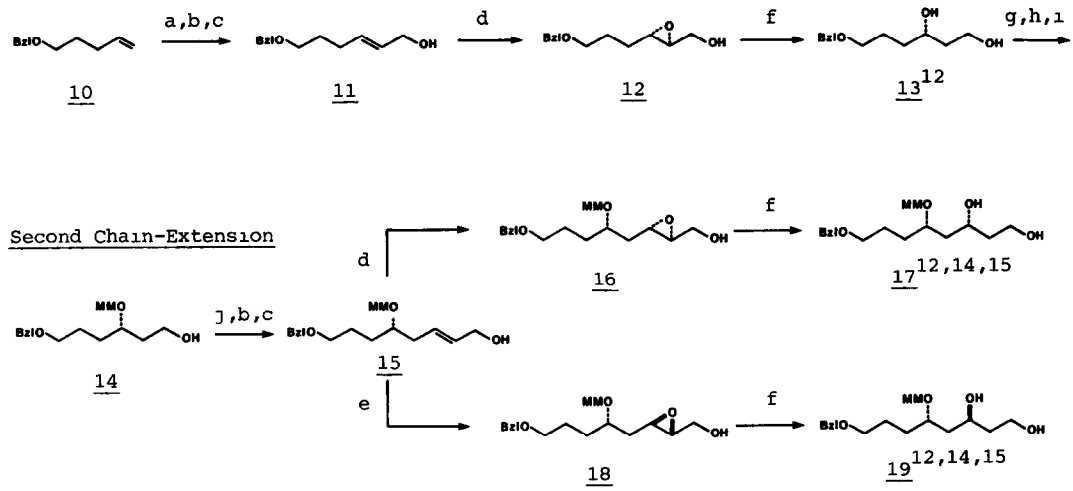
Table



1 2[12] 3[12]

Reagent and Reaction Conditions	Product Ratio[13] 2 : 3
Red-Al/benzene/RT	19 · 1
Red-Al/ether/RT	12 : 1
Red-Al/THF/RT	22 . 1
Red-Al/THF/0°C	40 · 1
Red-Al/THF/-20°C	150 : 1
DIBAL/hexane/RT	1 : 7
DIBAL/benzene/RT	1 13
DIBAL/ether/RT	1 . 7
DIBAL/ether/0°C	1 5
DIBAL/ether/-20°C	1 3
LAH/ether/RT	1 : 1
LAH/THF/RT	1 . 1

Scheme



Reagents

a. O_3/MeOH-CH_2Cl_2/-78°C, followed by $(Me)_2S$ work-up
b. $(i\text{-PrO})_2P(O)CH_2CO_2Et$/t-BuOK/THF/-78°C → 0°C[10]
c. DIBAL/THF/-78°C
d. t-BuOOH/(+)-diethyl tartrate/$(i\text{-PrO})_4Ti$/CH_2Cl_2/-23°C[6]
e. t-BuOOH/(-)-diethyl tartrate/$(i\text{-PrO})_4Ti$/CH_2Cl_2/-23°C[6]
f. Red-Al/THF/0°C
g $(t\text{-Bu})(C_6H_5)_2SiCl$/imidazole/DMF/RT
h. $MeOCH_2Br$/$(i\text{-Pr})_2(Et)N$/CH_2Cl_2/RT
i. $(n\text{-Bu})_4NF$/THF/RT
j. DMSO/$(COCl)_2$/CH_2Cl_2/-60°C, and then Et_3N[16]

tartrate yielded about a 3 1 mixture of the two diastereomers We are currently investigating improvement of this step by changing the protecting group of the secondary alcoholic group of 15.

Although further experiments will be necessary to provide a mechanistic explanation for the observed results, the Red-Al reduction seems to involve initial complexation of the reducing agent with the alcoholic group, followed by intramolecular hydride reduction. The DIBAL reduction also seems to involve initial formation of a complex with the alcoholic group, in which the aluminum serves as a Lewis acid to facilitate intermolecular hydride reduction. With respect to the practical application, it seems worth pointing out that 1,4- (or 1,2-) dihydroxylated systems (cf. 3 and 6) could also be obtained by either the Red-Al or DIBAL method.

Acknowledgment Financial assistance from the National Institutes of Health (NS 12108) and the National Science Foundation (CHE 78-06296) is gratefully acknowledged.

References and Footnotes

(1) For example, see W. Mechlinski, C. P Schaffner, P. Ganis and G. Avitabile, Tetrahedron Lett., 3873 (1970).

(2) For some works related to this problem, see P. A. Bartlett and K. K Jernstedt, J. Am. Chem. Soc., 99, 4829 (1977), P. A. Bartlett and K K. Jernstedt, Tetrahedron Lett., 1607 (1980), D. M. Floyd and C M. Cimarusti, Tetrahedron Lett , 4129 (1979), D. M. Floyd and A. W. Fritz, Tetrahedron Lett., 2847 (1981), K. Narasaka and H. C. Pai, Chem. Lett., 1415 (1980), G Cardillo, M. Orena, G. Porzi and S Sandri, J. C. S. Chem. Comm., 465 (1981).

(3) Y. Kishi, S Hatakeyama and M D. Lewis, Pure Appl. Chem , in press, T. Fukuyama, K. Akasaka, D. J. Karanewsky, C.-L J. Wang, G Schmid and Y. Kishi, J. Am. Chem. Soc., 101, 262 (1979).

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(6) T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 102, 5974 (1980). The most recent contribution to this method from the Sharpless laboratory is found in V. S. Martin, S S Woodard, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Sharpless, J. Am. Chem. Soc., 103, 6237 (1981), we thank Professor Sharpless for a preprint of this paper

(7) Satisfactory spectroscopic data were obtained for all new compounds described in this paper

(8) The ratio of the two possible regioisomers was greater than 20:1 (NMR).

(9) In connection with other research in our laboratories, we have found numerous examples which support this statement.

(10) See footnote 7 of the second paper quoted under reference 4.

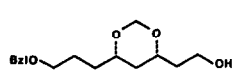
(11) Optical purity of 14 was examined by H-NMR and F-NMR analyses of its MTPA derivative, prepared according to the Mosher procedure [J. Org. Chem., 34, 2543 (1969)] No minor enantiomer was detected by these analyses.

(12) On sodium periodate treatment, the alcohol 3 smoothly yielded an aldehyde, but the alcohols 2, 6, 13, 17 and 19 were recovered unchanged.

(13) The ratio was determined by HPLC analysis

(14) This ratio represents the product ratio of 1,3-diol and 1,2-diol.

(15) On acid treatment (TFA/CH_2Cl_2/RT) the alcohols 17 and 19 yielded the acetals 1 and 11, respectively, which were easily separable by silica gel thin layer chromatography.



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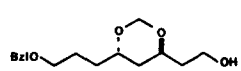

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(Received in USA 30 March 1982)