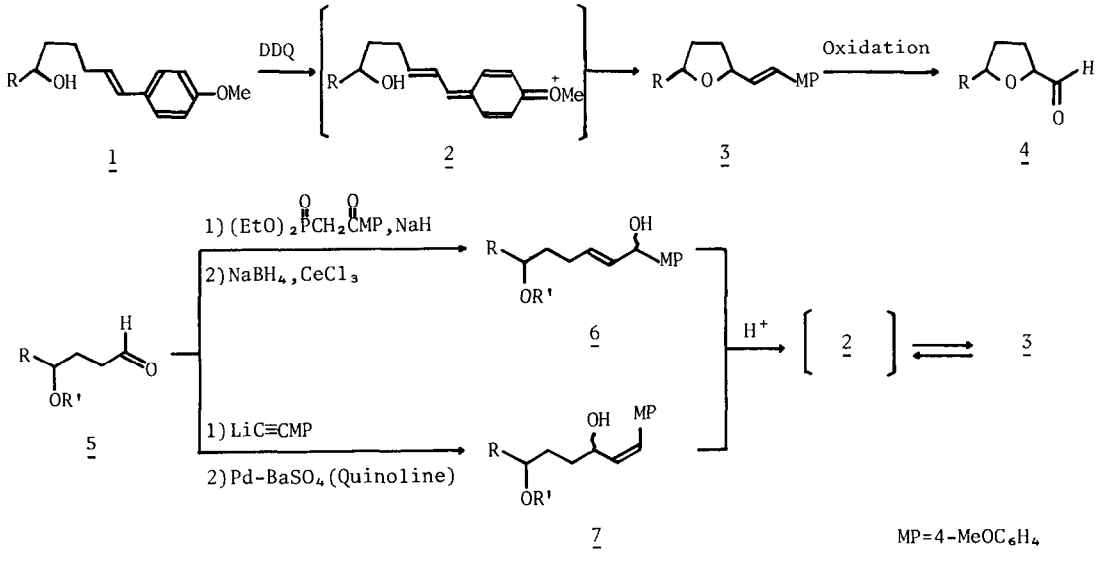
Tetrahedron Letters,Vol.27,No.17,pp 1917-1920,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF SUBSTITUTED TETRAHYDROFURANS AND TETRAHYDROPYRANS. 2. STEREOCONTROLLED ACID-CATALYZED CYCLIZATIONS

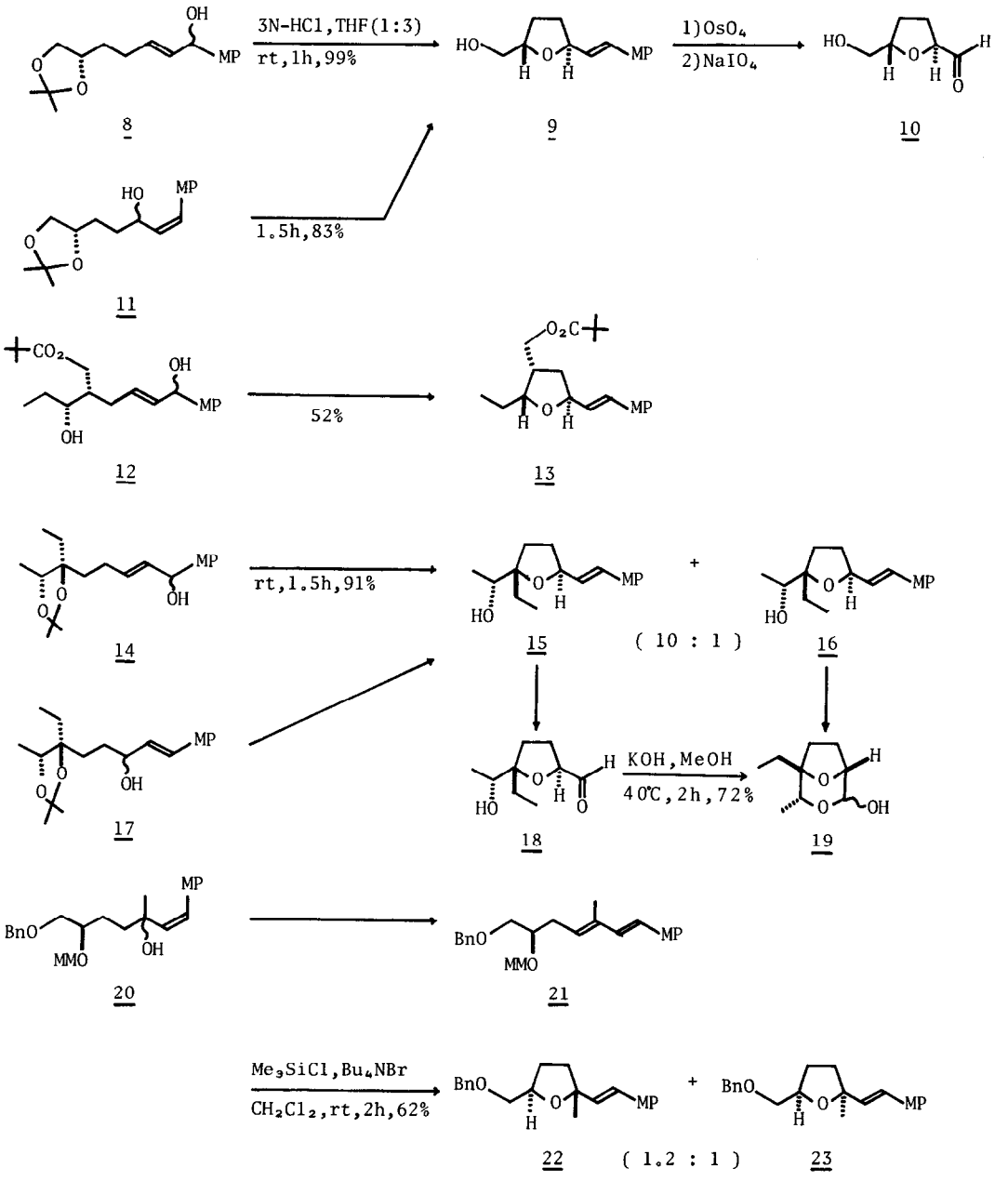
Ichio Noda, Kiyoshi Horita, Yuji Oikawa, and Osamu Yonemitsu*
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Summary A new acid-catalyzed synthesis of thermodynamically stable 2,5-substituted tetrahydrofurans and 2,6-substituted tetrahydropyrans was developed in order to apply to the synthesis of complex polyether antibiotics.

Because of the essential building blocks of complex polyether ionophore antibiotics, the stereocontrolled construction of substituted tetrahydrofurans and tetrahydropyrans has recently received much attention and many new methodologies have been published.[1] In connection with synthetic studies of polyether antibiotics such as isolasalocid A,[2] salinomycin,[3] etc. and macrolide antibiotics[4] from D-glucose by a common methodology, we recently reported a new synthesis of substituted tetrahydrofurans and tetrahydropyrans via an oxidative cyclization of p-methoxystyrene derivatives (1) with DDQ,[5] but both the yield and the stereoselectivity were unsatisfactory. One of the major problems was the inefficient formation of the intermediate 2, whose improvement was expected to provide a more promising method. We report here a stereocontrolled synthesis of tetrahydrofurans and tetrahydropyrans as exemplified by the acid-catalyzed formation of 3 via the same intermediate 2 from 6 or 7, which is readily derived from 5. Since the process from 2 to 3 must be reversible, the resulting products are presumably thermodynamically stable compounds, 2,5-trans-tetrahydrofurans and 2,6-cis-tetrahydropyrans.



When a solution of 8 in 3N-HCl and THF (1:3) was allowed to stand at room temperature for 1 h, the acid-catalyzed cyclization occurred quite smoothly to give only the 2,5-trans-tetrahydrofuran (9) in almost quantitative yield. The structure of 9 was confirmed by the conversion to the hydroxyaldehyde (10) [δ 9.64 (1H, d, J = 1.7 Hz)], not to a hemiacetal (see below). Under the same conditions 11 also gave 9 in high yield, but a little longer time was required to complete the reaction probably because of the configurational barrier from the Z-form 11 to the E-type intermediate 2. Similarly, 12 gave again the 2,5-trans compound 13, regardless of the C-4 substituent, though the yield was unsatisfactory.

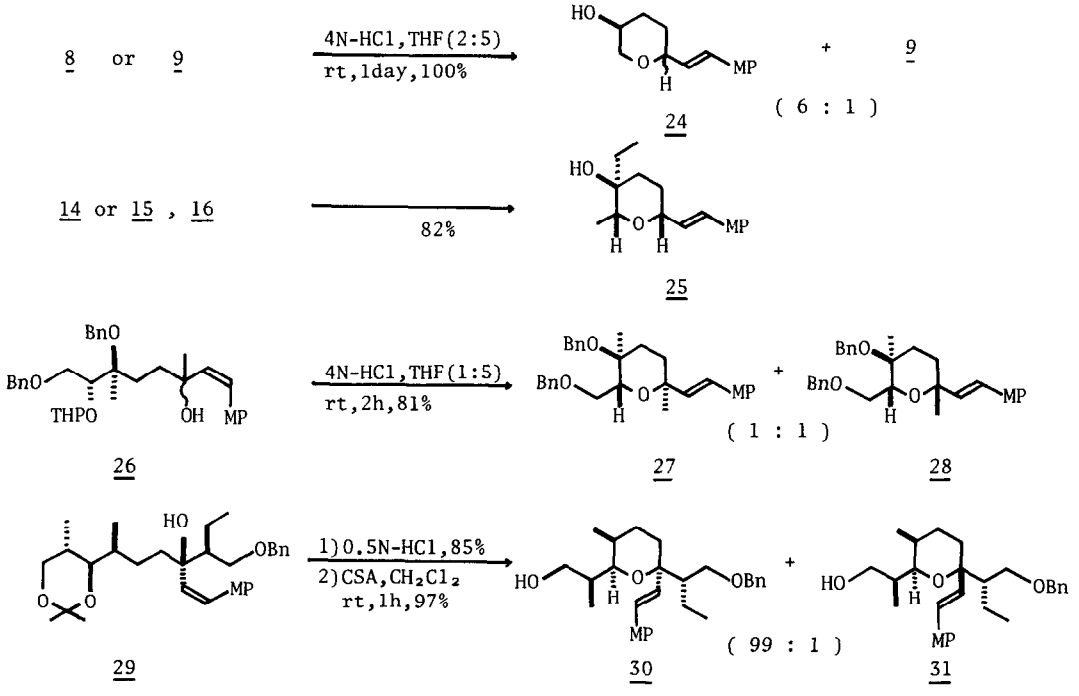


The acid-treatment of 14 gave a mixture of 2,5,5-trisubstituted tetrahydrofurans, 15 and 16, in high yield, and 17[6] gave the same result. The ratio of 15 and 16 (10:1) clearly reflects that the α-hydroxyethyl group is sterically larger than the ethyl group. The configurations of 15 and 16 were confirmed by the conversion to the hydroxyaldehyde (18) [δ 9.67 (1H, d, J = 2 Hz)] and the hemiacetal (19), respectively.[7]

In order to obtain 2,2,5-trisubstituted tetrahydrofurans, 20 was treated under similar conditions, but the diene (21) was only isolated. Under the conditions to cleave the MM (methoxymethyl) protection with Me_3SiBr,[8] a mixture (1.2:1) of 22 and 23 was obtained, indicating that methyl and p-methoxystyryl groups have comparable steric requirements.[9]

When 8 was treated with a higher concentration of the acid for a long time, interestingly the initially formed tetrahydrofuran (9) recyclized gradually to the thermodynamically more stable tetrahydropyrans (24; 1:1 mixture with respect to C-2), and after 24 h a 6:1 mixture of 24 and 9 was obtained in quantitative yield. Under the same conditions, the isolated 9 gave the same result. Compound 14 gave a practically useful result and the expected 2,6-cis-tetrahydropyran (25) with more than 92% stereoselectivity was obtained.[10]

The following two compounds gave only tetrahydropyrans, and not tetrahydrofurans. When 26 was treated with the acid under similar conditions, a 1:1 mixture of 27 and 28 was obtained in high yield. The steric requirement of methyl and p-methoxystyryl groups was again substantially equal. Compound 29 bearing a large branched substituent (1-ethyl-2-benzyloxy-



ethyl) gave only 30 with an axial 4-methoxystyryl group under similar conditions [4N-HCl, THF (1:2), rt, 4 h], but the cyclization proceeded much more smoothly and efficiently to give 30 with 99% stereoselectivity when the acetonide of 29 was first hydrolyzed with 0.5N-HCl and the resultant triol was treated with CSA (10-camphorsulfonic acid) in anhydrous CH_2Cl_2 at room temperature. Under rather kinetical conditions (CSA in toluene, -20°C), the product was a 1.3:1 mixture of 30 and 31, but when this mixture was treated again with CSA in CH_2Cl_2, the thermodynamic mixture (30 : 31 = 99 : 1) was also obtained.[11]

In conclusion, the acid-catalyzed synthesis of substituted tetrahydrofurans and tetrahydropyrans presented in this report may provide one of useful methods because of the following merits. 1) The starting compounds are readily prepared from aldehydes and ketones. 2) The configuration of the products can be predicted because thermodynamically stable products are mainly obtained. 3) The p-methoxystyryl group in the products is readily converted to the aldehyde group, which is favorable to further reactions.

Further applications in the synthesis of polyether antibiotics, isolasalocid A and salinomycin, will be reported soon.

REFERENCES AND NOTES

1) Semple, J. E.; Joullie, M. M. Heterocycles 1980, 14, 1825. Bartlett, P. A. "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York; 1984, Vol.3, pp 411-454. Stork, G.; Poivier, J. M. J. Am. Chem. Soc. 1983, 105, 1073. Batmangherlich, S.; Davidson, A. M.; Procter, G. Tetrahedron Lett. 1983, 24, 2889. Semmelhack, M. F.; Bodurow, C. J. Am. Chem. Soc. 1984, 106, 1496. Williams, D. R.; Harigaya, Y.; Moore, J. L.; D'sa, A. Ibid. 1984, 106, 2641. Ting, P. C.; Bartlett, P. A. Ibid. 1984, 106, 2668. Dolle, R. E.; Nicolaou, K. C. Ibid. 1985, 107, 1691. Nicolaou, K. C.; Duggan, M. E.; Hwang, C. -K.; Soners, P. K. J. Chem. Soc. Chem. Commun. 1985, 1359. Burke, S. D.; Armistead, D. M.; Fevig, J. M. Tetrahedron Lett. 1985, 26, 1163. Williams, D. R.; White, F. H. Ibid. 1985, 26, 2529. Tamaru, Y.; Kawamura, S.; Yoshida, Z. Ibid. 1985, 26, 2885.

2) Westley, J. W.; Beng, W.; Donahue, J.; Evans, R. H.; Scott, C. C.; Stempel, A.; Berger, J. J. Antibiot. 1974, 27, 744.

3) Kinashi, H.; Otake, N.; Yonehara, H. Tetrahedron Lett. 1973, 4955.

4) Omura, S. "Macrolide Antibiotics"; Academic Press; New York, 1984, pp 3-198.

5) Oikawa, Y.; Horita, K.; Yonemitsu, O. Heterocycles 1985, 23, 553.

6) In the early stage from 14 to 15 and 16, some 14 rearranged to 17, which was isolated by a column chromatography.

7) 19 [anomeric proton: δ 4.95 (3/7H, dd, J = 1.7, 6 Hz), 4.62 (4/7H, d, J = 10 Hz). m/e 172 (M^+, 14%) (HRMS, calcd for $C_9H_{16}O_3$: 172.1095. Found: 172.1100]. On treatment with KOH, 18 was readily isomerized to 19. Configurations of other tetrahydrofurans and tetrahydropyrans in this report were confirmed in the same way.

8) Woodward, R. B.; et.al. J. Am. Chem. Soc. 1981, 103, 3213. Hanessian, S.; Delorme, D.; Dufresne, Y. Tetrahedron Lett. 1984, 25, 2515.

9) The analogs of 20 having TMP (3,4,5-trimethoxyphenyl) and DMN (4,8-dimethoxynaphthyl) groups instead of the MP (4-methoxyphenyl) gave similar results.

10) Both the isolated 15 and 16 also gave the same results. 25 was converted to the corresponding aldehyde [δ 9.64 (1H, s)]. Under the same conditions, the minor trans-isomer gave a hemiacetal [δ 5.05 (5/6H, m), 5.47 (1/6H, m)].

11) 30 and 31 were confirmed by the conversion to a C-1∼C-9 segment of salinomycin.[12]

12) Horita, K.; Yonemitsu, O. to be published.

(Received in Japan 4 March 1986)