Tetrahedron Letters, Vol.31, No.26, pp 3687-3690, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

ALKALINE HYDROLYSIS OF SOME ERYTHRONOLIDE A DERIVATIVES

Kunio Sakan[1a,b], Stefan A. Babirad[* 1b,c], Douglas A. Smith[1b,d], and K.N. Houk[* 1e]
Department of Chemistry, Carnegie-Mellon University, Pittsburgh, PA 15213
and
Department of Chemistry and Biochemistry, University of California, Los Angeles
Los Angeles, CA 90024-1569

Abstract: The saponification of certain protected benzylidene C.3-C.5, C.9-C.11 erythronolide-A derivatives is described. A remarkable solvent effect was noted which eliminates the formation of side-products during the alkaline hydrolysis.

The synthesis of complex natural products requires the initial investigation of degradation fragments of the parent substance to confirm the structure and stereochemistry of the corresponding synthesized fragments. This technique was most recently reported from the Kishi laboratories in the total synthesis of palytoxin.[2]

In performing fragmentation and/or degradation reactions, conditions should be chosen such that a high yield of material is obtained, since the abundance of the natural product is usually limited. Therefore, mild synthetic routes should be employed to ensure that the stereochemistry is maintained and possible side reactions are minimized.

In our investigation of macrolactonization efficacy of certain protected erythronolide A seco-acids, we observed a surprising outcome in the alkaline hydrolysis of the macrolide.[3] Reported herein are our findings in this area of research.

The saponification of erythronolide derivatives has been well documented in structure elucidation and confirmation of synthetic fragments from various laboratories. Corey has reported the use of mild alkaline hydrolysis conditions employing a system of tetrahydrofuran, 30% hydrogen peroxide, and 1N aqueous lithium hydroxide to provide a clean saponification product as a key synthetic intermediate in the total synthesis of erythronolide B.[4] The use of peroxide accelerates the hydrolysis of the lactone functionality. However, more stringent conditions were needed to open the fourteen-membered ring natural product (erythronolide B). Conditions for saponification required the use of 2.3N sodium hydroxide in dimethyl sulfoxide-water (4:3) at 115°C for seven hours to afford the seco-acid as a reference sample in their synthesis.[4] Masamune has also reported that efficient alkaline hydrolysis of 6-deoxyerythronolide B can be achieved utilizing the Corey conditions.[5]

In the total synthesis of erythromycin A, two independent saponification methodologies have been reported. The Woodward group utilized mild hydrolysis conditions of sodium hydroxide in a solvent mixture of tert-butanol/ethanol (4:1) at room temperature

to minimize epimerization of the C.2 stereocenter as well as to inhibit the formation of the C.12-C.13 epoxy seco-acid.[6] Deslongchamps employed the conditions of sodium methylate in methanol at room temperature for five hours to yield cleanly the methyl ester of erythronolide A.[7]

Employing the saponification conditions reported by the Woodward group on the protected C.3-C.5, C.9-C.11 erythronolide substrates **1-3**, the desired hydroxy seco-acids **4-6** and the C.12-C.13 epoxy seco-acids **7-9** were obtained. Table 1 lists ratios of the desired product seco-acid to epoxy seco-acids.[8] For the bis-mesitylidene acetal **1**, temperature had litttle effect on the product distribution of **4** and **7**. Changing the protecting group to either the phenyl or p-methoxyphenyl shows a decrease in the ratio of desired hydroxy seco-acid to C.12-C.13 epoxide formation. Thus, an approximately 1:1 mixture of **5** and **8** was observed in the alkaline hydrolysis of bis-benzylidene acetal **2**, and a 1: 5 ratio of **6** to **9** was observed for the p-methoxybenzylidene acetal **3**.[9]

Table 1: Product Distribution from Saponification employing NaOH in t-BuOH/EtOH (4:1)

Substrate	Reaction Temperature	Ratio (hydroxy seco-acid: epoxy seco-acid)	
1	25°C	87 : 13	**(4 : 7)**
	32°C	89 : 19	
	80°C	78 : 22	
2	25°C	51 : 49	**(5 : 8)**
3	65°C	16 : 84	**(6 : 9)**

The alkaline hydrolysis of "simple" lactones (ie. 4-7 membered rings) has been investigated for at least thirty years.[10] The classical report by Huisgen and Ott provides the broadest survey of the alkaline hydrolysis of five- to sixteen-membered ring lactones.[11] Most of these reports use saponification conditions in protic solvents such as water, methanol, ethanol, or a combination thereof to study kinectic effects or strain effects in the hydrolysis reactions.

Venkatasubramanian showed that the rate of alkaline hydrolysis of certain lactones is increased in aprotic solvents such as dimethylsulfoxide (DMSO). They attribute this enhancement to the poorly solvated hydroxide ion in DMSO, and to the ability of DMSO to solvate effectively the transition states of the saponification intermediates.[12]

In view of these experimental results, we felt that the Woodward alkaline hydrolysis conditions under protic conditions (t-BuOH/EtOH) would favor a solvated hydroxide ion that could either open the fourteen membered lactone ring or, conversely, abstract a hydrogen from the C.12 hydroxyl moiety yielding the C.12-C.13 epoxy seco-acid. However, under aprotic solvent conditions, the undesired epoxide formation should be less favored over the desired ring opening. We felt that the poorly solvated hydroxide ion would preferentially act as a nucleophile to the C.1 carbonyl center rather than abstract a hydrogen from the C.12 hydroxyl moiety.

A variety of aprotic solvents such as 1,2-dimethoxyethane, 1,4-dioxane, dimethylsulfoxide, and tetrahydrofuran were examined in the saponification of the protected macrolide. In this investigation, tetrahydrofuran gave the best results. A dramatic effect was observed regarding the amount of base solution with relation to the amount of tetrahydrofuran used. Volume ratios of base solution to THF ranging from 20-65% were investigated. Table 2 reveals that as the amount of base increased, the amount of epoxide formation also increased. Thus, at low volume percents of base, ie. 20% of 1N NaOH/EtOH in THF, virtually 100% of the desired hydroxy seco-acid was obtained without any epoxy formation.[13]

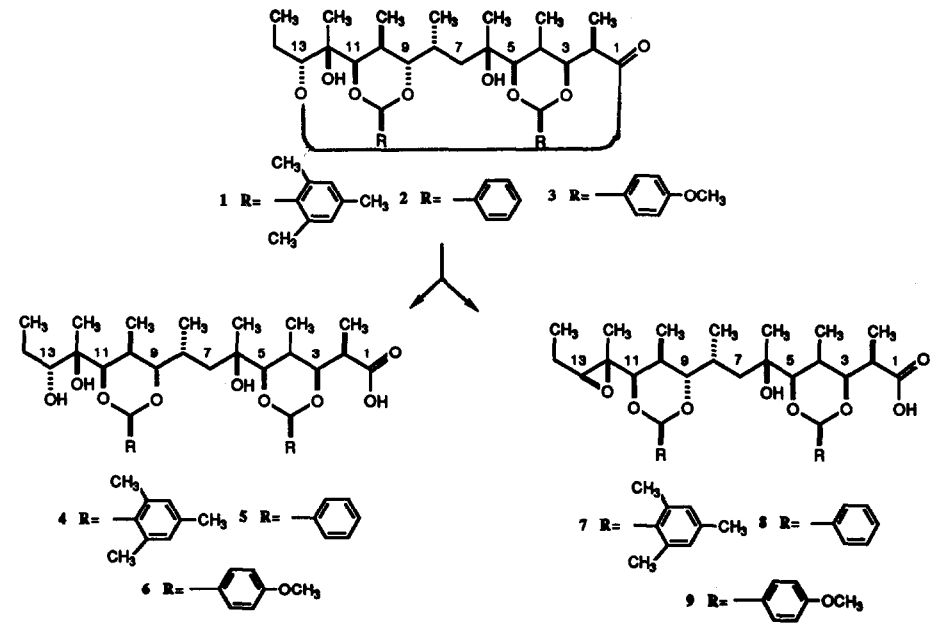

Table 2: Saponification of Erythronolide-A 3 in THF at Various Volume Percentages of 1N NaOH/EtOH

% NaOH	Ratio (hydroxy seco-acid : epoxy seco-acid)
20	100 : 0 (6 : 9)
35	83 : 17
50	72 : 28
65	63 : 37

A typical experimental procedure for the saponification of C.3-C.5, C.9-C.11 protected benzylidene erythronolide-A derivate is as follows: The C.3-C.5, C.9-C.11 benzylidene erythronolide-A derivative 2 (72.3 mg, 0.13 mmoL) in THF (27.5 ml) was treated with a 1 N ethanolic sodium hydroxide solution (6.9 ml, 6.9 mmoL). The reaction was allowed to stir at room temperature for 72 hours at which time TLC (5% MeOH/$CHCl_3$) indicated consumption of starting material. The reaction mixture was treated with saturated potassium dihydrogen phosphate solution (15 mL). The resulting mixture was concentrated under reduced pressure to half the original volume and the crude product was extracted into dichloromethane (100 mL). The layers were separated and the organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (5% MeOH/CH_2Cl_2) gave 66.6 mg (89%) of the C.3-C.5, C.9-C.11 benzylidene erythronolide-A seco acid 4 as an oil.

In conclusion, we feel that employing the above conditions to the saponification of complex macrolides, such as erythromycin, will generate excellent yields and high purity of the desired hydroxy seco-acids without the formation of side products. Our efforts on the conformational preference of the hydroxy seco-acids to adopt conformations similar to the fourteen-membered ring lactone will be reported in due course.

ACKNOWLEDGEMENT: The 600 MHz ^{1}H-NMR spectra were obtained at CMU using the facilities by the National Institutes of Health (GM 27390, RR00272). We are indebted to Dr. A.A. Bothner-By for his help in obtaining these spectra.

REFERENCES AND NOTES

1. (a) Deceased 12 January, 1984. (b) Carnegie-Mellon University. (c) Current address: 3M Company, 3M Center Bldg. 201-2N-20, St. Paul, MN 55144-1000. (d) Current address: Department of Chemistry; University of Toledo, Toledo, OH 43606. (e) University of California at Los Angeles.

2. (a) For the stereochemistry assignment of palytoxin primarily based on organic synthesis, see: Cha, J.K., Christ, W.J., Finan, J.M., Fujioka, H., Kishi, Y., Klein, L.L., Ko, S.S., Leder, J., McWhoter, W.W., Jr., Pfaff, K.-P., Yonaga, M., Uemura, D., and Hirata, Y., *J. Am. Chem. Soc.*, **1982**, *104*, 7369; and preceding papers. (b) For synthetic studies on palytoxin, see: Jin, H., Uenishi, J.-I., Christ, W.J., and Kishi, Y., *J. Am. Chem. Soc.*, **1986**, *108*, 5644; and references cited therein. (c) For the total synthesis of palytoxin, see: Armstrong, R.W., Beau, J.M., Cheon, S.H., Christ, W.J., Fujioka, H., Ham, W-H., Hawkins, L.D., Jin, H., Kang, S.H., Kishi, Y., Martinelli, M.J., McWhorter, W.W., Jr., Mizuno, M., Nakata, M., Stutz, A.E., Talamas, F.X., Taniguchi, M., Tino, J.A., Ueda, K., Uenishi, J.-I., White, J.B., and Yonaga, M., *J. Am. Chem. Soc.*, **1989**, *111*, 7530; and preceding paper.

3. Taken in part from: Babirad, S.A., Ph.D. Dissertation, Carnegie-Mellon University, 1987.

4. Corey, E.J., Kim, S., Yoo, S.-E., Nicolaou, K.C., Melvin, L.S., Jr., Brunelle, D.J., Falck, J.R., Trybulski, E.J., Lett, R., and Sheldrake, P.W., *J. Am. Chem. Soc.*, **1978**, *100*, 4620.

5. Masamune, S., Hirama, M., Mori, S., Ali, S.A.A., and Garvey, D.S., *J. Am. Chem. Soc.*, **1981**, *103*, 1568.

6. Woodward, R.B., Logusch, E., Nambiar, K.P., Sakan, S., Ward, D.E., Au-Yeung, B.-W., Balaram, P., Browne, L.J., Card, P.J., Chen, C.H., Chenevert, R.B., Fliri, A., Frobel, K., Gais, H.-J., Garratt, D.G., Hayakawa, K., Heggie, W., Hesson, D.P., Hoppe, D., Hoppe, I., Hyatt, J.A., Ikeda, D., Jacobi, P.A., Kim, K.S., Kobuke, Y., Kojima, K., Krowicki, K., Lee, V.J., Leutert, T., Malchenko, S., Martens, J., Matthews, R.S., Ong, B.S., Press, J.B., Rajan Babu, T.V., Rousseau, G., Sauter, H.M., Suzuki, M., Tatsuta, K., Tolbert, L.M., Truesdale, E.A., Uchida, I., Ueda, Y., Uyehara, T., Vasella, A.T., Vladuchick, W.C., Wade, P.A., Williams, R.M., and Wong, H.N.-C., *J. Am. Chem. Soc.*, **1981**, *103*, 3213.

7. Bernet, B., Bishop, P.M., Caron, M., Kawamata, T., Roy, B.L., Ruest, L., Sauve', G., Soucy, P., and Delongchamps, P., *Can. J. Chem.*, **1985**, *63*, 2814.

8. Satisfactory spectroscopic data were obtained for all new compounds reported in this paper.

9. The product distribution ratios were determined by high field ^{1}H NMR (600 MHz) analysis.

10. (a) Blackburn, G.M. and Dodds, L.H., *J.C.S. Perkin Trans. II*, **1974**, 377. (b) Storm, D.R. and Koshland, D.E., Jr., *J. Am. Chem. Soc.*, **1972**, *94*, 5815. (c) Brown, J.M., Conn, A.D., Pilcher, G., Leitao, M.L.P., and Meng-Yan, Y., *J.C.S. Chem. Commun.*, **1989**, 1817.

11. Huisgen, R. and Ott, H., *Tetrahedron*, **1959**, *6*, 253.

12. Balakrishnan, M., Rao, G.V., and Venkatasubramanian, N., *J.C.S. Perkin Trans. II*, **1974**, 1093.

13. An authentic sample of the C.12-C.13 epoxy seco-acid 9 was prepared by treating macrolide 3 with potassium hydride in THF. The epoxy seco-acid 9 was identical by TLC and NMR analysis to the epoxide generated from the reaction conditions described herein.

(Received in USA 18 April 1990)