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DEGRADATION OF AMPHOTERICIN B: CLEAVAGE OF THE GLYCOSIDIC LINKAGE WITH ALUMINUM AMALGAM [Al(Hg)] OR DICHLORODICYANOQUINONE (DDQ)

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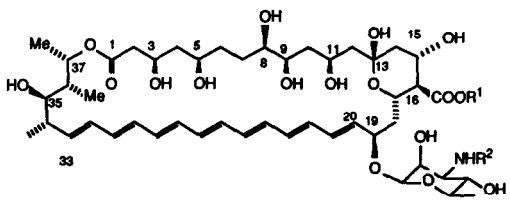
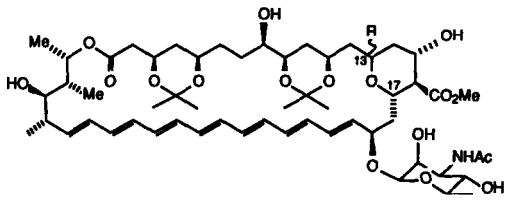
Summary: After appropriate protection of the hydroxyl and other functional groups present in amphotericin B, reductive and oxidative cleavages of the glycosidic linkage are effected with Al(Hg) and DDQ to obtain the C(1)-C(19) fragment and the C(19)-ketone corresponding to the aglycone, respectively.

More than 100 polyenemacrolide antibiotics have been isolated and characterized.[1] Of this large family of antibiotics amphotericin B(1)[2] is the only member whose stereostructure is clearly defined.[2b] Perhaps for this reason it has been the object of synthetic[3] and degradative[4] studies in this and other laboratories. This Note describes below two methods that effect smooth (reductive or oxidative) cleavage of the glycosidic linkage of 1 to obtain (i) the C(1)-C(19) fragment which comprises the majority of the stereogenic centers of 1 and (ii) the ketone corresponding to the aglycone. These methods will be, in all likelihood, applicable to degradation of other polyenemacrolides.





AMPHOTERICIN B

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

1a : $R^1 = Me$, $R^2 = Ac$

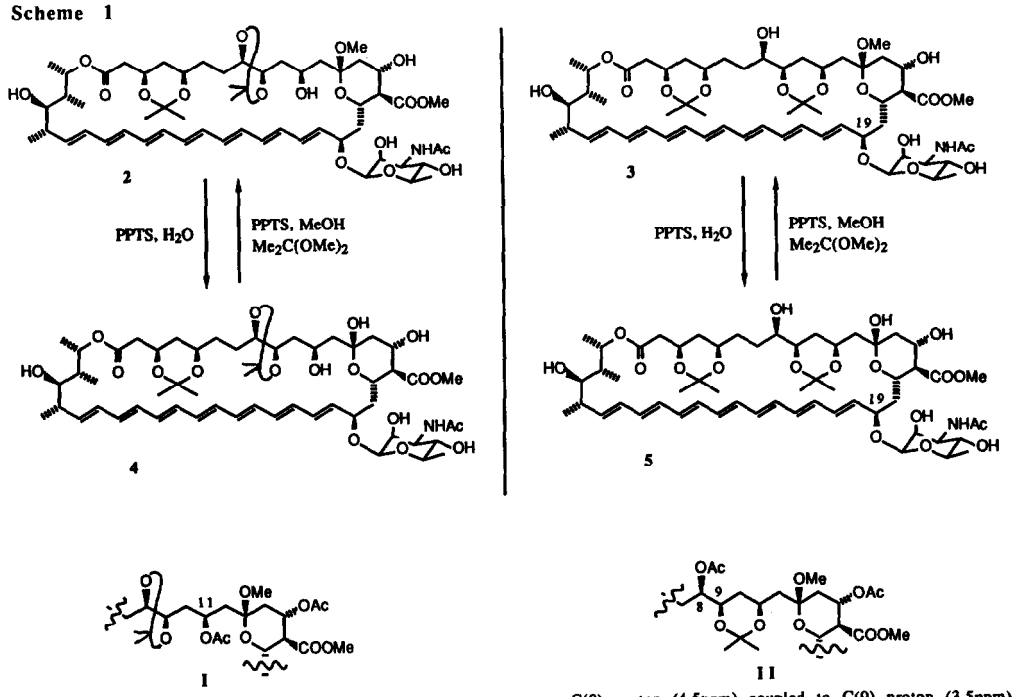
1b : R = β - OMe

1c : R = α - OMe

Ketalization of the Methyl Ester, N-Acetamide (1a) of Amphotericin B[5]

In conjunction with synthetic studies, Nicolaou and coworkers recently reported the ketalization of 1a with $Me_2C(OMe)_2$, MeOH, and camphorsulfonic acid.[4b] Two major compounds obtained from this reaction were thought to be epimeric at the C(13) center as shown in 1b and 1c. This assignment was in apparent conflict with our observation that a synthetic pyran intermediate[6] having a substitution pattern similar to the C(13)-C(17) unit of 1 showed, upon ketalization [PPTS, CH_2Cl_2, $MeC(OMe)_3$], a strong preference for the axial methoxy configuration. The following two lines of evidence have, in fact, led us to conclude that the two products obtained upon ketalization of 1a are five and six-membered acetonides (2 and 3 in Scheme 1). (i) Both 2 and 3 were separately hydrolyzed (PPTS, THF, H_2O) to provide hemiketals 4 and 5, which were, again, separately ketalized [PPTS, MeOH, $Me_2C(OMe)_2$] back to 2 and 3, respectively.[7] (ii) ^1H COSY spectra for the pentaacetates I and II derived from 2 and 3, respectively, revealed an additional 3.5-4.5 ppm cross peak for II, resulting from coupling between the protons on C(8) and C(9).

Scheme 1



I

^{1}H NMR: C(11) proton not coupled to ~3.5ppm proton

II

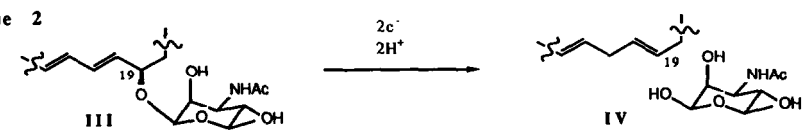
C(8) proton (4.5ppm) coupled to C(9) proton (3.5ppm)

Reductive Cleavage of 2 and 3

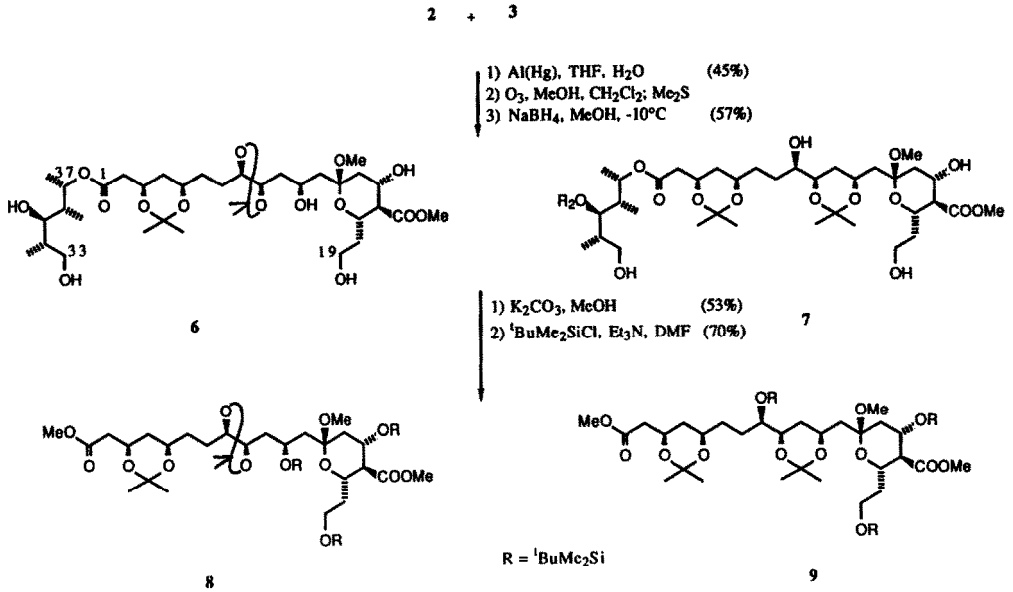
Cleavage of the glycosidic bond is the single most problematic step in degradation of polyenemacrolides because the allylic ether is more susceptable to acid hydrolysis than the glycosidic bond. Although Nicolaou had reported an ingenious, multi-step sequence for cleavage of the glycosidic linkage,[4b] it was anticipated that donation of electrons to the allylic ether moiety would be a more direct solution to this problem (conversion of III to IV in Scheme 2). The mycosamine would then be ejected as an alkoxide with concommitant migration of the olefin(s). Indeed, reduction of a mixture of 2 and 3 [Al(Hg), 2% H_2O, 4h, 25°C, 45%][8] afforded a mixture of olefinic isomers which were subjected to ozonolysis. The resultant C(19,33)-bis-aldehydes were then reduced with $NaBH_4$ to provide a mixture of 6 and 7 (Scheme 3).

Methanolysis with K_2CO_3 removed the polypropionate [C(33)-C(37)] fragment from 6 and 7 to provide the corresponding methyl esters. Silylation in DMF with t-$BuMe_2SiCl$ resulted in the isomers 8 and 9 which were now readily separated on a multigram scale.

Scheme 2



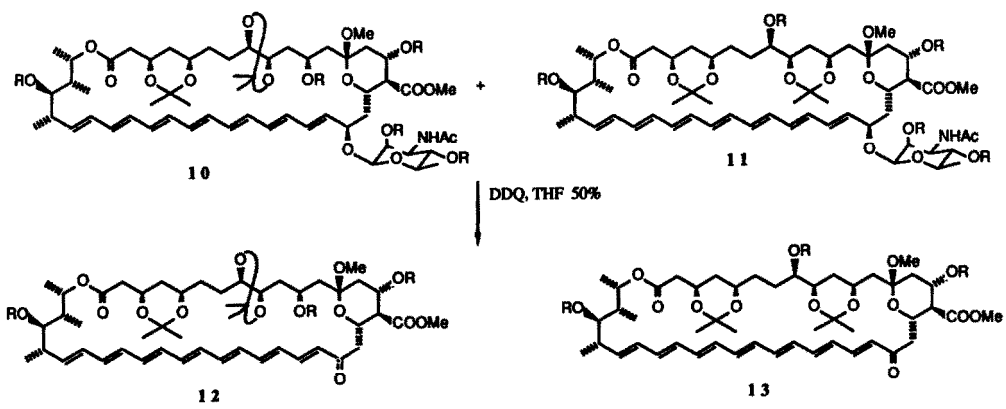
Scheme 3



Oxidative Cleavage of 2 and 3

The aglycone with the polyene moiety intact can also be obtained from degradation of amphotericin B. Thus, silylation of acetonides 2 and 3 affords a mixture of compounds 10 and 11 which was treated with DDQ[9] in dry THF at 25°C to provide 12 and 13 in 50% combined yield (Scheme 4). At this stage the acetonides 12 and 13 were most conveniently separated by flash chromatography. It was noted that upon addition of DDQ, the color of the reaction mixture became intensely red and then partially faded. This observation suggests the formation of a charge-transfer complex and is taken as possible evidence for electron transfer as opposed to hydride transfer. The liberated mycosamyl moiety, probably covalently bound to the reduced DDQ, was not recovered.

Scheme 4



The above two reaction sequences leading to a mixture of 8 and 9 and a mixture of 12 and 13 take advantage of the unique reactivity of the allyl ether in 1, and the products 9 and 13 have served to establish the stereochemistry of synthetic intermediates described in the following Note.

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References and Footnotes

§ The work of A.A. was carried out at the Chemistry Department, Hokkaido University, Sapporo, Japan.

1. For an extensive review on the biochemistry and clinical application of 1, see Omura, S. "Macrolide Antibiotics, Chemistry, Biology and Practice", Academic Press, New York, 1984; Chapters 9-12, and references quoted therein.

2. (a) Isolation from Streptomycetes nodusus: Vandeputte, J.; Wachtel, J.L.; Stiller, E.T. Antibiot. Annu. 1956, 587. (b) X-ray analysis: Ganis, P.; Avitable, G.; Mechlinski, W.; Schaffner, C.P. J. Am. Chem. Soc. 1971, 93, 4560.

3. See references 1 and 2 in the following Note.

4. (a) Nicolaou, K.C.; Chakraborty, T.K.; Daines, R.A.; Simpkins, N.S.; Ogawa, Y.; J. Chem. Soc. Chem. Commun. 1987, 686. (b) Nicolaou, K.C.; Chakraborty, T.K.; Daines, R.A.; Simpkins, N.S.; J. Chem. Soc. Chem. Commun. 1986, 413. (This reference also describes assembly of the fragments obtained by degradation of 1. (c) Borowski, E.; Mechlinski, W.; Falkowski, L.; Ziminski, T.; Dutcher, J.D. Tetrahedron Lett. 1965, 473. (d) Cope, A.C.; Axen, U.; Burrows, E.P.; Weinlich, J. J. Am. Chem. Soc. 1966, 88, 4228. (e) Dutcher, J.D.; Walters, D.R.; Wintersteiner, O. J. Org. Chem. 1963, 28, 995. (f) Dutcher, J.D.; Young, M.B.; Sherman, J.H.; Hibbits, W.E.; Walters, D.R. Antibiot. Annu. 1957, 866. (g) von Satza, M.; Dutcher, J.D.; Reid, J.; Wintersteiner, O. J. Org. Chem. 1963, 28, 999. (h) Borowski, E.; Zielinsk, J.; Falkowski, L.; Ziminski, T.; Golik, J.; Kolodziejczk, P.; Jereczek, E.; Gdulewicz, M. Tetrahedron Lett. 1971, 685.

5. Amphotericin B (E.P. Squibb & Sons, Inc. SQ 9,468 Batch FGNM-029, 4/30/86) was generously supplied through the courtesy of Dr. C. Cimarusti to whom we are grateful.

6. See conversion of compound 7 to 8 in the following Note.

7. Hydrolysis and reketalization [PPTS, THF, H_2O; then PPTS, MeOH, $Me_2C(OMe)_2$] resulted in a 1:4.9 ratio of 2:3 from 3, while none of 3 was obtained from the same treatment of 2. Furthermore, extended treatment of 1a under the described ketalization conditions [CSA, MeOH, $Me_2C(OMe)_2$] resulted exclusively in 2, albeit in lower yield. These observations are consistent with the conclusion that the C(9,11) acetonide of 3 migrates to the thermodynamically more stable C(8,9) position to provide 2. This migration is likely to have occurred in the synthesis of amphotericin reported by Nicolaou, et al. See conversion of compound 10 to 12 in: Nicolaou, K.C.; Daines, R.A.; Chakraborty, T.K. J. Am. Chem. Soc. 1987, 109, 2208.

8. Aluminum foil (0.5 g, 20 strips, 5 x 1 cm) was dipped into 2% aqueous $HgCl_2$ for 30 sec and washed with H_2O, MeOH and ether successively. The amalgamated aluminum was cut in 1 cm squares into a solution of 1.2 g of a mixture of 2 and 3 in 100 mL of 2% aqueous THF. The mixture was stirred for 4 h, filtered through a pad of Celite and concentrated. The yellow oil was then filtered through SiO_2(CH_2Cl_2/MeOH, 10:1) to afford a pale yellow solution which was concentrated to yield 0.53 g of a yellow oil which was then directly treated with ozone and reduced with sodium borohydride (see Scheme 3) to afford a mixture of 6 and 7.

9. A similar oxidative cleavage has been affected through the employment of N-bromosuccinimide (NBS). See reference 4a.

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