Acid catalyzed hydrolysis of glycosides is amply documented. Application of this method to erythromycin A oxime and erythromycin B so as to remove the glycoside cladinose is well known. However, during our examination of the erythromycin A methoxime base-decomposition studies, we found an unusual and unexpected cladinose-displaced product 2 in >50% yield (Scheme 1).

Thus, 2.1 g (1.88 mmol) of 2',4'' bis TMS erythromycin A methoxime (1) was dissolved in THF/DMSO, followed by addition of powdered KOH (0.24 g, 3.6 mmol) at room temperature. The solution slowly turned dark on stirring overnight and was quenched by pouring into a chilled (10-15°C) mixture of heptane and 2N sodium hydroxide. The layers were separated and the heptane portion, after being washed with water, was dried with anhydrous magnesium sulfate. Removal of the solvent by vacuum distillation gave 0.84 g of 2 (68% pure, 52% yield). The structure of 2 was determined by the shifts of the ^1H and ^13C NMR spectra. The ^1H NMR spectrum clearly showed the N(CH_3)_2 group of the desosamine present at 2.30 ppm, but the usually salient resonances of the 3''-OCH_3 and the 1'' proton of cladinose were absent. The ^1H and ^13C spectra were assigned (Table 1) using two-dimensional double quantum-filtered COSY, ROESY, HMQ C, and HMBC spectra. The ^13C shifts of C3 and C6 are both indicative of an ether linkage being present at C3 and C6. The ^13C shift of C5 shows that C5 is part of the five-membered ring formed by the 3~6 ether linkage. Further evidence for the 3~6 ether linkage comes from an NOE observed between C3H and C6-Me, which is normally not seen for erythromycin A, indicating that these two groups are in proximity to each other due to being in the axial positions across from each other in the five-membered ring. Further confirmation of the structure of 2 was obtained from the IR spectrum which indicated strong C-O-C stretching vibrations, characteristic of the ether linkage, and from the HR-MS (M+H)^+ 587.3912 (calc. M+H, C_{30}H_{55}N_{2}O_{9}: 587.3908).

Only one literature reference relevant to the formation of the 3~6 epoxy product 2 was found. In 1975, LeMahieu and colleagues reported a multi-step preparation of Compound 3. First, cladinose was cleaved from erythromycin A oxime by means of dilute acid. Acetylation provided the 2'-acetyl-5-(9-desosaminylerythronolid A acetoxime. This compound was then converted to its 3-mesylate. A final reaction (LiCl/DMF) produced the 3,6 ether, 3. In contrast, this note shows a novel one step displacement of the entire cladinose moiety from erythromycin A methoxime.

There are two possible mechanisms that we can perceive for the formation of 2. One entails the elimination of cladinose with the formation of a C2-C3 double bond and subsequent C6 alkoxy reaction with the double bond. The alternative mechanism is a direct displacement of the cladinose by the C6 alkoxy moiety providing 2. Evidence for the direct displacement was obtained by decomposition of a derivative of 1: 2',4'' bis TMS 6-O-methyl erythromycin A methoxime (4). When 4 was subjected to the same basic conditions as 1, only desilylation occurred; the subsequent 6-O-methyl erythromycin A methoxime remained stable for days. This
The phenomenon demonstrated that when C6 alkoxy is blocked with a methyl group no displacement takes place. The stability of the compound demonstrates that no other chemical transformation, i.e. enone formation, is taking place on the aglycone ring. Similarly, erythromycin A methoxime also provided 2, indicating that the silyl moiety is not crucial in this displacement reaction.

Another piece of evidence that supports this proposed direct displacement reaction was obtained by the X-ray analysis of the methiodide of 3, prepared by starting with the base decomposition of a 2',4'-O-bis(trimethylsilyl)-erythromycin A 9-[O-ketal oxime], showing that the configuration of the C2 position remained unchanged.

Preliminary data from the experiments employing different protecting groups on the oxime functionality show that this base degradation pathway is common to \( \text{NO}-R \) (R-alkyl, ketal, ortho ester, etc.), and the yield data indicate this displacement is an important reaction pathway. The extension of this base degradation method to erythromycin B, C, and D is expected to promote understanding of this fourteen membered ring macrolide system.

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References

