

## Tylosin Derivatives

### V. Electrochemical Opening of Oxirane Ring

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In the preceding paper<sup>1)</sup> we described the chemical deepoxidation of **1** with dissolving metal (Zn). Reductive oxirane cleavage was accompanied by simultaneous allylic rearrangement giving 10,13-dihydro-13-hydroxy desmycosin (**5**). It is noteworthy that preparation of **1** consists of two steps<sup>2)</sup>: oxidation of the 12,13-double bond with *m*-chloroperbenzoic acid with simultaneous formation of *N*-oxide, and reduction of the *N*-oxide with Ph<sub>3</sub>P.

Until now, electrochemical reduction of conjugated epoxy ketones has been described only in the case of steroid compounds<sup>3)</sup>. In this paper we report electro-

chemical reduction of **1** at mercury electrode. The mechanism of reduction has been investigated by cyclic voltammetry and preparative scale electrolysis has been carried out for the isolation and identification of products.

### Materials and Methods

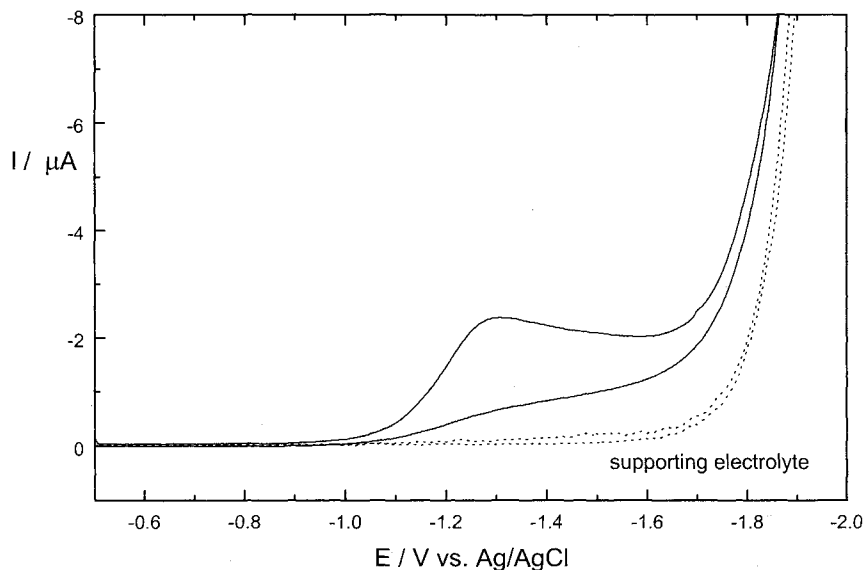
#### Cyclic Voltammetry

Cyclic voltammetry has been carried out at a hanging mercury drop electrode connected to the EG&G PAR potentiostat, Model 283. The reference electrode was an Ag/AgCl electrode and Pt wire served as a counter electrode. Phosphate and citrate buffers (0.1 mol/dm<sup>3</sup>) have been employed as supporting electrolytes. The concentration of **1** varied between 10<sup>-4</sup>~10<sup>-3</sup> mol/dm<sup>3</sup>.

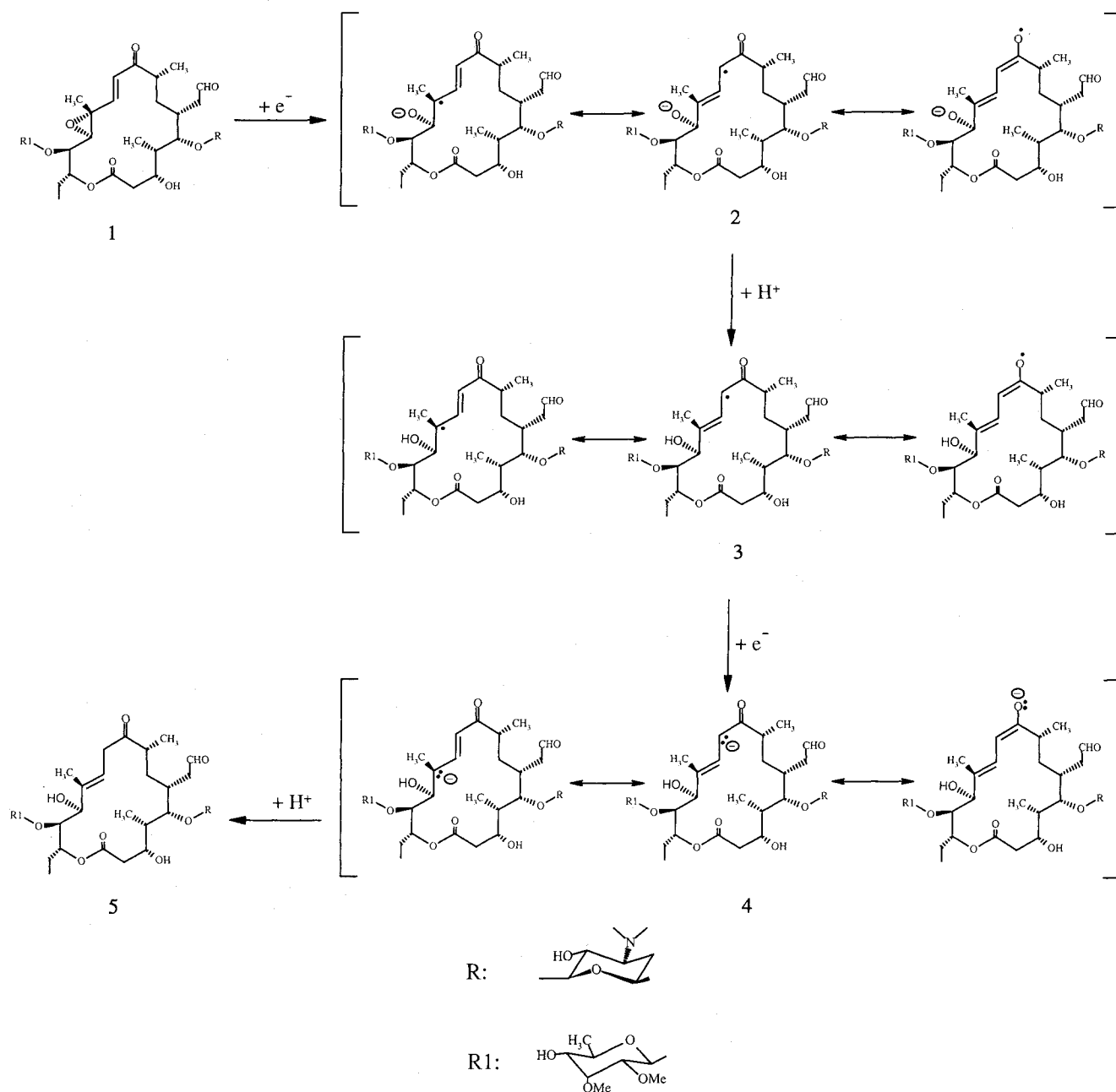
#### Preparative Scale Electrolysis

Preparative scale electrolysis has been carried out at constant potential with 100 mg of **1** in 30 ml 0.1 mol/dm<sup>3</sup> phosphate buffer, pH=5.5. Mercury pool and graphite rod have been employed as cathode and anode, respectively. A conventional H-type electrolysis cell was used with compartments separated by a glass frit. Reference Ag/AgCl electrode has been positioned in the catholyte as close as possible to the cathode. During the electrolysis, the solution was stirred with a magnetic stirrer. The potential of

Fig. 1. Cyclic voltammogram of 10<sup>-3</sup> M solution of **1** in phosphate buffer, pH=5.5 (—) in comparison to supporting electrolyte alone (-----);  $v=100$  mV/s.



Scheme 1. Electroreduction mechanism of 12,13-Epoxy-desmycosin.



electrolysis has been  $-1.4$  V vs. Ag/AgCl and has been kept constant during the electrolysis.

#### Isolation and Identification of Products

The product has been isolated from the reaction mixture at pH=8.5 (adjusted with NaOH) by extraction into  $\text{CHCl}_3$  followed by column chromatography. Identification of products has been carried out by MS and NMR and has been described in the previous paper<sup>1)</sup>.

#### Results and Discussion

Cyclic voltammograms obtained for a  $10^{-3}$  mol/dm<sup>3</sup> solution of **1** in phosphate buffer (pH=5.5) show a well defined, irreversible reduction wave at  $-1.3$  V (Fig. 1).

The irreversibility of the electrode process represented by the reduction wave in Fig.1 indicates that the electrode reaction is accompanied by a fast follow-up homogeneous

chemical reaction giving a product which is not electroactive under the experimental conditions studied. The homogeneous reaction is so fast that even at the highest scan rates employed ( $v=10$  V/s) there has been no sign of an oxidative wave in a reverse scan.

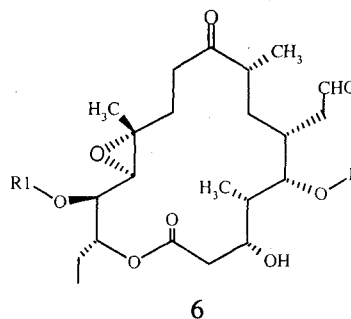
The reduction wave shifts toward more negative potentials with the increase of pH of the solution. The shift is linear with pH giving a slope of 60 mV/pH. This is consistent with the electrode mechanism in which the ratio of protons and electrons participating in the reaction is unity.

Preparative scale electrolysis consumes  $1.9 \pm 0.1$  electrons per molecule of **1** which together with the above mentioned pH dependence indicates a  $2e^-/2H^+$  reduction. From the reaction mixture **5** has been isolated in a high yield (85~90%).

Therefore the reduction follows an ECEC mechanism and can be presented as in Scheme 1.

After the uptake of the first electron, the C12-O bond is cleaved and the oxygen atom is protonated resulting in a resonantly stabilized radical **3**. The resonance stabilizes the intermediate in the reaction, making the cleavage of the C12-O bond energetically more favorable than cleavage of C13-O bond. The radical **3** is further reduced and the resulting anion **4** protonated yielding **5**. The absence of a second reduction wave at more negative potentials clearly shows that the standard potential of the second electron transfer is more positive than the first. This means that radical **3** is reduced as soon as it is formed, yielding **4**. The structure of product **5** confirmed the fact that the structure with a carbanion at C-12 is least significant in delocalised structure **4**.

It is worth noting that the resonantly stabilized intermediate is a prerequisite for the opening of the oxirane ring since 10,11-dihydro-12,13-epoxydesmycosin (**6**) is not reducible at the given experimental conditions.



#### References

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