A SYNTHETIC METHOD FOR PYRROLO[1,4]-BENZODIAZEPINE ANTITUMOR ANTIBIOTICS

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Pyrrolo[1,4] benzodiazepine antibiotics include anthramycin, sibiromycin, tomaymycin, and neothramycin, all of which contain either a carbinolamine or an imine structure at N10-C11. Our synthetic approach to this class of compounds focused on a selective reduction of the corresponding amides which are relatively easy to prepare. Based on a well-known conversion of thiazolines to thiazolidines, we developed a new and mild reduction method of amides using aluminum amalgam.

Thus, our model compound **1** was first converted to imino thioether **2** by thiation and alkylation. Treatment of **2** with aluminum amalgam gave thiocarbinolamine **3** which was converted to imine **4** upon silica gel chromatography. This method was applied in the conversion of oxotomaymycin (**5**), a biologically inactive fermentation byproduct, to tomaymycin (**6**). It was also applied in the total synthesis of a new pyrrolo[1,4] benzodiazepine antitumor agent, BBM-2040 (**7**). The nine-step synthesis was achieved in 10% overall yield starting with trans-4-hydroxy-L-proline.