Synthesis of Optically Active Dimethylphosphinoyl Analogues of Fotemustine

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Organophosphorus compounds have been used as drugs for decades, many of them have achieved commercial success. Among them is an anticancer drug - fotemustine, a cytotoxic alkylating and carbamylating agent. The main problem in finding new drugs among organophosphorus compounds is the low water solubility of their esters. This applies to fotemustine, which is administered as a solution in dextrose, which limits its use in treatment of people with diabetes. In addition, fotemustine is a racemate, which can be attributed to the disadvantages of the drug, because it is well known that optical antipodes often have opposite biological effects. A unique synthetic approach to enantiomerically pure dimethylphosphinoyl analogues of fotemustine was developed. The results of spectroscopic and elemental analysis of the compounds were obtained at each stage. It was established that the key stage of synthesis of dimethylphosphinoylnitrosourea, asymmetric addition of dimethylphosphine oxide to the double C=N bond of N-(tert-butyl) sulfinilimines, is realized in the presence of titanium tetraisopropylate by stereoselective mechanism – Re-face attack. The absolute configuration of the aminophosphine oxides was determined by comparison with analogues, which were synthesized according to the same scheme and studied by X-ray structural analysis. The enantiomeric excess amounted to 98%. Enantiomerically pure forms of N-chloroethyl nitrosourea containing a dimethylphosphine oxide group were isolated individually with preparative yields and found to be readily soluble in water. Thus, the obtained compounds have the potential for use as drugs and will be transferred for research to the Institute of Biomolecules Max Mousseron (IBMM), France.

Awards Won:

Fourth Award of $500

American Chemical Society: Fourth Award of $1,000