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Crystallization Based Resolution of Enantiomeric and Diastereomeric Derivatives of myo-Inositol

Authors : Nivedita T. Patil, M. T. Patil, M. S. Shashidhar, R. G. Gonnade

Abstract : Cyclitols are cycloalkane polyols which have raise attention since they have numerous biological and pharmaceutical properties. Among these, inositols are important cyclitols, which constitute a group of naturally occurring polyhydric alcohols. Myo, scyllo, allo, neo, D-chiro- are naturally occurring structural isomer of inositol while other four isomers (L-chiro, allo, epi-, and cis-inositol) are derived from myo-inositol by chemical synthesis. Myo-inositol, most abundant isomer, plays an important role in signal transduction process and for the treatment of type 2 diabetes, bacterial infections, stimulation of menstruation, ovulation in polycystic ovary syndrome, improvement of osteogenesis, and in treatment of neurological disorders. Considering the vast application of the derivatives, it becomes important to supply these compounds for further studies in quantitative amounts, but the synthesis of suitably protected chiral inositol derivatives is the key intermediates in most of the synthesis which is difficult. Chiral inositol derivatives could also be of interest to synthetic organic chemists as they could serve as potential starting materials for the synthesis of several natural products and their analogs. Thus, obtaining chiral myo-inositol derivatives in a more eco-friendly way is need for current inositol chemistry. Thus, the resolution of nonracemates by preferential crystallization of enantiomers has not been reported as a method for inositol derivatives. We are optimistic that this work might lead to the development of the two tosylate enantiomers as synthetic chiral pool molecules for organic synthesis. Resolution of racemic 4-O-benzyl 6-O-tosyl myo-inositol 1, 3, 5 orthoformate was successfully achieved on multigram scale by preferential crystallization, which is more scalable, eco-friendly method of separation than other reported methods. The separation of the conglomeric mixture of tosylate was achieved by suspending the mixture in ethyl acetate till the level of saturation is obtained. To this saturated clear solution was added seed crystal of the desired enantiomers. The filtration of the precipitated seed was carried out at its filtration window to get enantiomerically enriched tosylate, and the process was repeated alternatively. These enantiomerically enriched samples were recrystallized to get tosylate as pure enantiomers. The configuration of the resolved enantiomers was determined by converting it to previously reported dibenzyl ether myo-inositol, which is an important precursor for mono- and tetraphosphates. We have also developed a convenient and practical method for the preparation of enantiomeric 4-O and 6-O-allyl myo-inositol orthoesters by resolution of diastereomeric allyl dicamphante orthoesters on multigram scale. These allyl ethers can be converted to other chiral protected myo-inositol derivatives using routine synthetic transformations. The chiral allyl ethers can be obtained in gram quantities, and the methods are amenable to further scale-up due to the simple procedures involved. We believe that the work described enhances the pace of research to understand the intricacies of the myo-inositol cycle as the methods described provide efficient access to enantiomeric phosphoinositols, cyclitols, and their derivatives from the abundantly available myo-inositol as a starting material.

Keywords : cyclitols, diastereomers, enantiomers, myo-inositol, preferential crystallization, signal transduction
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