STEREO- AND REGIOSELECTIVE SYNTHESIS OF DIFLUORINATED CYCLIC β-AMINO ACID DERIVATIVES

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Amino acid 2 derived from lactam 1 by stereo- and regioselective iodolactonization, followed by HI elimination resulted in lactone 4. Lactone opening with NaOEt at 0 °C afforded all cis hydroxylated amino ester 5, while at 20 °C amino ester 6, stereoisomer of 5 was formeda,b (Scheme 1).

In order to prepare other difluorinated β-aminoacyclohexane carboxylate isomers cis-amino acid 14 with a cyclohexane skeleton, derived from bicyclic lactam 13 was first subjected to iodolactonization, HI elimination and lactone ring-opening producing 3-difluorinated 2-aminoacyclohexane carboxylates 17 (Scheme 4). By using similar protocol trans amino acid 18 afforded 5-hydroxylated amino ester 19 which on treatment with Deoxofluor afforded difluorinated 2-aminocyclohexane carboxylate stereoisomers 20 (Scheme 5).

In the stereoselective synthesis of difluorinated β-aminoacyclohexane carboxylate isomers 17 stereoisomers 20 were next transformed by C-C ring double bond saturation under transfer hydrogenation conditions and oxidation of the hydroxyl function with pyridinium-sulfur trioxide complex to the corresponding oxo amino esters 21 and 22 furnished the corresponding geminal 5,5-difluorinated 2-aminocyclohexane carboxylate stereoisomers 23 and 24 (Schemes 6 and 7).

Summary: Starting from bicyclic lactams 1 and 13 difluorinated cyclohexane β-amino ester regio- and stereoisomers have been prepared in six or seven steps. The method was based on stereo- and regioselective hydroxylation, hydroxyl group oxidation and oxo-fluorine interconversion.


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Bicyclic ester 8, which on treatment with Deoxofluor provided difluorinated 2-aminocyclohexene-carboxylate 9, was subjected to iodolactonization, HI elimination and lactone opening with NaOEt at 0 °C to afford cis-hydroxylated amino ester 10 (Scheme 2). Following a similar pathway from 3-hydroxylated amino ester 5, trans-hydroxylated amino ester 11 was generated (Scheme 3).