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[a019]

Stereocontrolled preparation of substituted oxazolidin-2-one scaffold as the chiral building block for the synthesis of FTY720 analogues.

Kvetoslava Pomikalová, Miroslava Martinková and Jozef Gonda

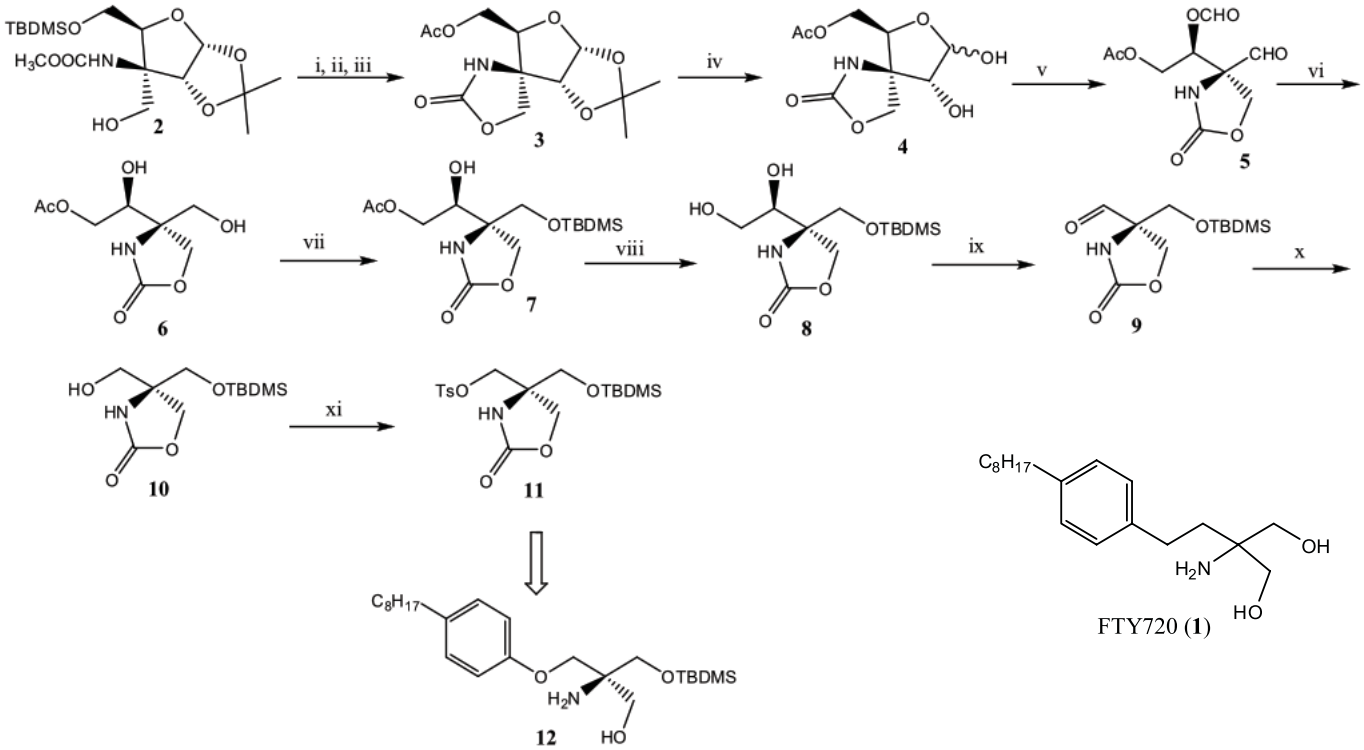
Institute of Chemical Sciences, Department of Organic Chemistry, P. J. Šafárik University, Moyzesova 11, Košice, Slovak Republic

Abstract:
*An efficient strereocontrolled synthesis of substituted oxazolidin-2-one synthon **11** as the key intermediate in the synthesis of FTY720 analogues starting from the highly functionalized furanose scaffold **2**[1] is reported.*

Introduction:

In recent years, many immunosuppressants have been developed, some of which have been introduced in clinical organ transplantation. FTY720 **1**[2] is an immunosuppressive compound, which is efficacious in various models of autoimmune diseases and also transplantation.[3] The development of FTY720 analogues (chiral and achiral) is desired in the investigation for the new immunomodulators.

Synthesis:



Reagents and conditions: (i) NaH, THF, 0 °C→RT, 30 min, 93%; (ii) TBAF, THF, 4Å molecular sieves, 0 °C→RT, 45 min, 85%; (iii) Ac_2O, pyridine, DMAP, RT, 40 min, 93%; (iv) TFA/H_2O (4:1), RT, 2 h, 79%; (v) $NaIO_4$, MeOH/H_2O (1:1), RT, 30 min, 96%; (vi) $NaBH_4$, MeOH, 0 °C, 2 h, 35%; (vii) TBDMSCl, DMAP, Et_3N, DMF, RT, 6 h, 62%; (viii) K_2CO_3, MeOH, 0 °C, 20 min, 48%; (ix) $NaIO_4$, MeOH/H_2O (1:1), RT, 3 h, 94%; (x) $NaBH_4$, MeOH, 0 °C, 45 min, 30%; (xi) TsCl, CH_2Cl_2, DMAP, Et_3N, RT, 6 h, 63%

Conclusion:

We have found an efficient route to interesting chiral building block **11**. We have also shown that this synthon **11** has suitable structure for further synthetic manipulations toward the FTY720 analogue **13**.

General experimental:

All commercially available reagents were used without purification, and solvents were dried by distillation from standard drying agents (under N_2). Thin layer chromatography (TLC) was used to monitor the progress and purity of compounds and performed on Merck Silica Gel 60 F_{254} analytical plates. The compounds were visualized with a solution of *p*-anisaldehyde (**2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**) or with a solution of phosphomolybdic acid (**10**, **11**), with subsequent heating. Column chromatography was done by using the flash chromatography technique, and was performed on silica gel 60 (0.040-0.063 mm, 230-400 mesh, Merck). Solvents for flash chromatography (hexane, dichloromethane, methanol and ethyl acetate) were distilled before using.
^1H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400 FT NMR spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) using CD_3OD or $CDCl_3$ as the solvents and TMS as the internal standard. For ^1H chemical shifts are reported in parts per million relative to TMS (0 ppm) or CD_3OD (δ=4.84) and for ^{13}C, they are reported relative to $CDCl_3$ (δ=77.0) or CD_3OD (δ=49.05). The melting points were determined on the Kofler block and are uncorrected. Optical rotations were measured with a P3002 Krüss polarimeter and reported as follows: $[\alpha]_D^{25}$ (*c* in grams per 100 mL, solvent).

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