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Efficient chromatography-free synthesis of the oxy-analogue of fingolimod

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Dedicated to Professor Dr. Dr. Dr. W. Schunack on the occasion of his 75th birthday

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ABSTRACT

Fingolimod (FTY720) and its analogue derivatives are not only promising therapeutics in sphingolipid signaling but also valuable tools for understanding the roles of sphingolipids in (patho)physiological conditions. A practical method for the synthesis of the ether analogue of FTY720 is described. Our final synthetic approach allows high yield and efficient synthesis of O-FTY in only four steps without chromatographic purifications.

The role of sphingolipids in chemical biology as important modulators of diverse body functions has raised increased therapeutic interest. Within the sphingolipid pathways different important potential targets such as S1P receptors, sphingosine kinases, and ceramide synthases are actually widely explored.[1] Fingolimod (FTY720, Gilenia®) as parent prodrug compound for S1P receptor agonist is the most advanced drug in this group.

Numerous comparable synthetic approaches for FTY720 have been described[2–11] but in our hands none of those offered chemical approaches was fast enough for derivatization of FTY720. Therefore, for the development of FTY720 derivatives as a pharmacological tool its oxy-analogue (*R*)-AAL can be taken as comparable lead structure (Fig. 1).[12] The goal of our approach was to provide easy access to the ether analogues to FTY720 (O-FTY, Fig. 1).

Route A in Figure 2 shows the original synthesis of the O-FTY[3] and route B the first synthesis that we developed because of the poor overall yield obtained with route A of about 25%. In our attempts to develop a more practicable and more cost effective synthesis of targeted compounds we combined different method variations adopted to the literature in the synthesis of comparable structural elements (Fig. 2).[2–11] Synthesis started from *p*-hydroxyacetophenone (**9**) which was first alkylated (**10**) and then brominated (**11**). Compound **11** upon substitution of bromine with diethyl acetamidomalonate, subsequent reduction, and following deprotection gave O-FTY (**3**). Route B significantly reduced costs of O-FTY (**3**) synthesis but failed to improve overall yield (maintained approximately 25%) and reduced a number of chromatographic purifications that were necessary for almost each reaction step for route A.

To overcome these difficulties we started the synthesis in routes C and D from the 4-(2-bromoethyl)phenol (**13**) (Fig. 3). The reaction to both Boc-protected aminomalonate (**14**, route C) and acetamidomalonate compound (**15**, route D) was accomplished with NaH in DMF using corresponding N-protected aminomalonate compound. After varying reaction time and temperature we were able to synthesize both compounds after 48 h at 45 °C with a yield of about 75%. Compound **17** (route D) was isolated pure after

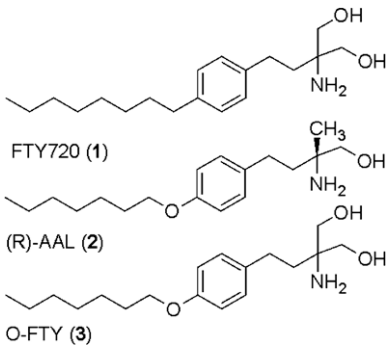

Figure 1. Fingolimode (FTY720) and its analogues.

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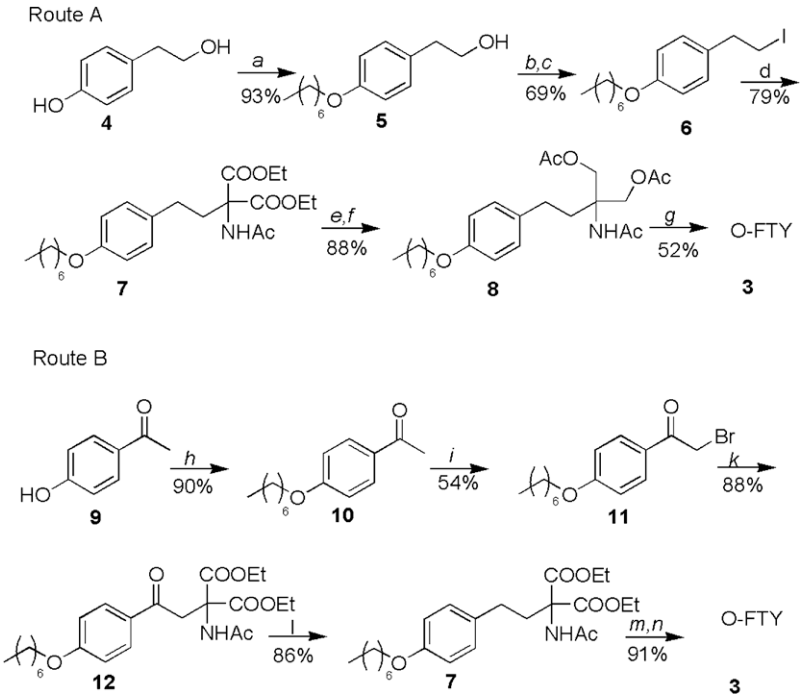

Figure 2. Alternative synthesis routes of O-FTY—comparison of route A[3] and novel route B. Reagents and conditions: (a) NaOEt, $C_7H_{15}Br$; (b) MsCl, TEA, DCM; (c) NaI, 2-butanone; (d) NaOEt/EtOH, diethyl acetamidomalonate; (e) $LiAlH_4$, THF; (f) Ac_2O, Py; (g) LiOH, MeOH, H_2O; (h) $C_7H_{15}Br$, K_2CO_3, CH_3CN; (i) Br_2, DCM; (k) NaH, diethyl acetamidomalonate, DMF; (l) $TiCl_4/Et_3SiH$, DCM; (m) $NaBH_4$, THF, MeOH; (n) LiOH/THF/MeOH.

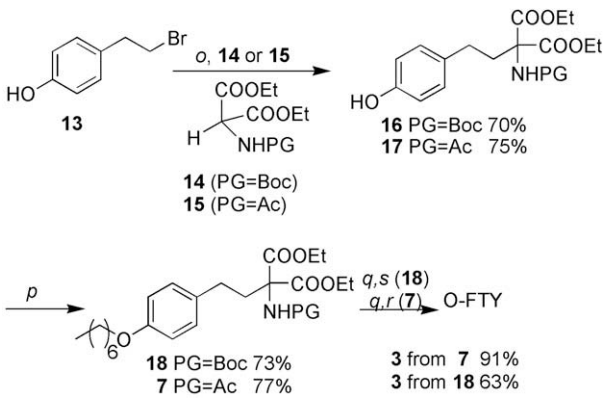

Figure 3. New synthesis of O-FTY (routes C and D). Reagents and conditions: (o) NaH, diethyl acetamidomalonate, DMF, **15** or **16** (rt, 1 h and then 48 h at 90 °C); (p) $C_7H_{15}Br$, K_2CO_3, CH_3CN, reflux, 12 h; (q) $NaBH_4$, $CaCl_2$, EtOH/H_2O; (r) LiOH/MeOH/H_2O; (s) TFA/THF, rt.

simple crystallization from EtOAc whereas the corresponding Boc-protected compound **16** (route C) had to be additionally purified by chromatographic separation. Under these conditions a small amount of the styrene derivative (⩽2%) could be isolated. No side reaction at the phenol moiety was observed. The further alkylation was done with K_2CO_3 and bromoheptan. Compound **7** (route D) was crystallized from petrol ether giving the pure product, where compound **18** (route C) had to be purified by column chromatography.

Compounds **18** and **7** were both reduced with $NaBH_4/CaCl_2$/EtOH and the crude product could be deprotected with LiOH for acetyl group (**7** to **3**, route D) or TFA for Boc-protecting group (**18** to **3**, route C). After both reactions, product **3** could be purified by re-crystallization from ethyl acetate.

The routes D and C can be accomplished with overall yield of 50%. In addition the route D, from **13** over intermediate compounds **17** and **7** is accomplished without a single purification step and easier to achieve than in any of previously described synthesis to best of our knowledge. Therefore, this synthetic approach is the most promising one for obtaining O-FTY and O-FTY derivatives as polyfunctionalized hydrophilic head groups (2-aminopropan-1,3-diol functionality) in our hands.

In conclusion, we have developed a new efficient multigram synthesis of the FTY720 analogue O-FTY in four steps and 50% overall yield without any chromatographic purification (route D).

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Supplementary data

Supplementary data (experimental details for the synthesis as well as analytical data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.051.

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