A New Efficient Synthesis of the Immunosuppressive Agent FTY−720

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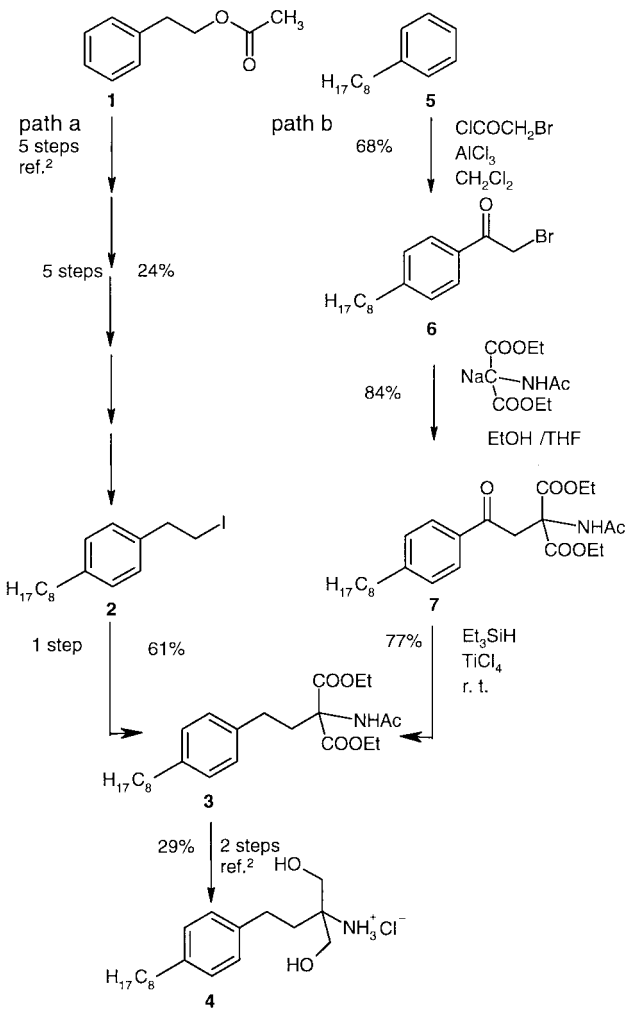
Abstract: A new efficient five-step synthesis of the immunosuppressive agent FTY−720 is described.

Key words: FTY−720, immunosuppressive agent, acylations, reductions

We are interested in studying the pharmacological profile of FTY−720 **4**, a new immunosuppressive agent endowed with an original mechanism of action.[1] For this purpose a multigram quantity of FTY−720 was required. We first used the only synthetic scheme described in the patent literature,[2] an eight step, 4% overall yield synthesis (Scheme, path a).



Scheme

Using this synthetic pathway, we faced a major difficulty during the condensation step of 2-iodophenylethyl derivative **2** with the sodium salt of diethyl acetamidomalonate. In some experiments, elimination leading to a styrene derivative was the major reaction observed. To alleviate this side reaction, we decided to use an α-haloacetophenone such as **6** instead of the 2-halophenylethyl derivative **2**.

In this article, we describe a shorter and more efficient synthesis of FTY−720 (Scheme, path b). Friedel−Crafts acylation of 1-phenyloctane with bromoacetyl chloride in dichloromethane using $AlCl_3$ afforded the α-bromoacetophenone derivative **6** in 68% yield. An alternative but more expensive route to this α-bromoketone consists of the bromination of 1-(4-octylphenyl)ethanone.[3] Condensation of **6** with the sodium salt of diethyl acetamidomalonate afforded the new ketone derivative **7** in 84% yield. For its full characterisation, this compound was purified by flash chromatography. However, for large-scale preparations it could be used after removal of the slight excess of diethyl acetamidomalonate by precipitation in petroleum ether. The conversion of the ketone into methylene moiety using Et_3SiH and CF_3CO_2H[4] failed under different reaction temperatures and even in the presence of a large excess of the silane reagent. Such a lack of reactivity of a ketone carrying an aminoester function has already been described by Yato et al.[5] They solved the problem using the more oxophilic Lewis acid $TiCl_4$ instead of trifluoroacetic acid. Using the same conditions, we obtained the desired intermediate **3** as a crystalline compound in 77% yield. Completion of the synthesis of FTY−720 was performed as described by Fujita et al.[2]

In conclusion, we have developed a new efficient multigram synthesis of FTY−720 in five steps and in a 13% overall yield, starting from commercially available 1-phenyloctane.

All chemicals were purchased from commercial sources and were used without further treatment except when specified. Mps were uncorrected. ^{1}H NMR spectra were determined 300 MHz with TMS as internal standard. ^{13}C NMR spectra were recorded at 75 MHz. The chemical shifts are expressed in δ values relative to TMS. Elemental analyses were performed with an elemental analyser Perkin−Elmer 2400 CHN.

2-Bromo-1-(4-octylphenyl)-1-ethanone (6)

Bromoacetyl chloride (28.2 g, 180 mmol) in CH_2Cl_2 (60 mL) was added dropwise to a cooled solution (−10 °C) of 1-phenyloctane **5** (34.2 g, 180 mmol) and $AlCl_3$ (24.0 g, 180 mmol) in CH_2Cl_2 (50 mL). The solution was then allowed to return to r.t. and stirred for a further 3 h. The mixture was poured slowly onto ice (100 g), the

aqueous phase was extracted with CH_2Cl_2 (60 mL) and the organic phases were collected, dried ($MgSO_4$) and concentrated. The product was crystallised twice (CH_3OH:H_2O) to give **6** (38.3 g, 68%) as white crystals; mp 45−50 °C (Lit.[3] mp 39−40 °C).

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, 3H, *J* = 6.5 Hz, CH_3), 1.20−1.40 (m, 10H, CH_2), 1.56−1.66 (m, 2H, C*H*$_2$CH$_2$Ar), 2.67 (t, 2H, *J* = 7.5 Hz, CH_2C*H*$_2$Ar), 4.43 (s, 2H, C*H*$_2$Br), 7.29 (d, 2H, *J* = 8.3 Hz, H_{arom}), 7.90 (d, 2H, *J* = 8.3 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 14.0, 22.6, 29.1, 29.2, 29.3, 30.9, 31.8, 36.0, 128.8, 129.0, 131.6, 149.9, 190.8.

Anal: $C_{16}H_{23}BrO$ (311.27): Calc C, 61.74; H, 7.45. Found C, 62.07; H, 7.46.

2-(Acetylamino)-2-[2-(4-octylphenyl)-2-oxo-ethyl]propanedioic Acid Diethyl Ester (7)

To a solution of NaOEt (0.68 g, 10 mmol) in EtOH (10 mL) diethyl acetamidomalonate (3.50 g, 16 mmol) was added in portions at 60 °C. The mixture was stirred for a further 40 min and a solution of the bromo derivative **6** (1.00 g, 3.2 mmol) in EtOH (5 mL) was added. The mixture was stirred further for 45 min at 60 °C, cooled to r.t. and poured onto ice (60.0 g). The aqueous phase was extracted with EtOAc (3 × 50 mL), the organic phases were collected, washed with brine, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography on silica gel (EtOAc/cyclohexane, 8:2) gave **7** as a colourless oil (1.20 g, 84%).

^{1}H NMR ($CDCl_3$): δ = 0.87 (t, 3H, *J* = 6.5 Hz, CH_3), 1.20−1.40 (m, 16H, (C*H*$_2$)$_5$, 2 C*H*$_3$CH$_2$O), 1.61 (m, 2H, C*H*$_2$CH$_2$Ar), 1.96 (s, 3H, C*H*$_3$CO), 2.65 (t, 2H, *J* = 7.5 Hz, CH_2C*H*$_2$Ar), 4.24 (s, 2H, C*H*$_2$CO), 4.26 (q, 4H, *J* = 6.5 Hz, 2 CH_3C*H*$_2$O), 7.10 (s, 1H, NH), 7.26 (d, 2H, *J* = 8 Hz, CH_{arom}), 7.87 (d, 2H, *J* = 8 Hz, CH_{arom}).

^{13}C NMR ($CDCl_3$): δ = 13.9, 14.1, 22.6, 22.9, 29.2, 29.4, 31.1, 31.8, 36.0, 42.2, 62.8, 64.0, 128.4, 128.7, 133.9, 149.6, 167.4, 169.4, 196.5.

Anal: $C_{25}H_{37}NO_6$ (447.58): Calc C, 67.09; H, 8.33; N, 3.13. Found C, 66.96; H, 8.35; N, 3.23.

2-(Acetylamino)-2-[2-(4-octylphenyl)ethyl]propanedioic Acid Diethyl Ester (3)

A solution of the ketone **7** (20.0 g, 45 mmol) in CH_2Cl_2 (70 mL) was added dropwise to a solution of Et_3SiH (19.8 g, 170 mmol) in CH_2Cl_2 (200 mL) at r.t. under N_2 atm. $TiCl_4$ (32.4 g, 170 mmol) was added with a syringe and the reaction mixture was stirred for 12 h at r.t. The solution was poured slowly onto ice (100g) and the aqueous phase was extracted with CH_2Cl_2 (60 mL). The organic phases were collected and dried ($MgSO_4$). The solvent was removed under vacuum and the product was then crystallised twice from petroleum ether to yield **3** as a colourless solid (15.1 g, 77%); mp 53 °C (Lit.[2] mp 49−50 °C).

^{1}H NMR ($CDCl_3$): δ = 0.87 (t, 3H, *J* = 6.5 Hz, CH_3), 1.20−1.40 (m, 16H, (C*H*$_2$)$_5$ and 2 CH_3), 1.56 (m, 2H, C*H*$_2$CH$_2$Ar), 1.97 (s, 3H, CH_3CO), 2.45 (m, 2H, C*H*$_2$C(COOEt)$_2$NHAc), 2.55 (t, 2H, *J* = 7.5 Hz, C*H*$_2$Ar), 2.68 (m, 2H, C*H*$_2$CH$_2$C(CO$_2$Et)$_2$NHAc), 4.14−4.25 (m, 4H, OC*H*$_2$CH$_3$), 6.75 (s, 1H, NH), 7.02−7.09 (m, 4H, CH_{arom}).

^{13}C NMR ($CDCl_3$): δ = 13.8, 14.0, 22.5, 22.8, 29.1, 29.2, 29.3, 29.6, 31.3, 31.5, 31.7, 33.2, 35.4, 62.4, 66.3, 128.2, 128.3, 137.5, 141.1, 167.9, 168.9.

Anal: $C_{25}H_{39}NO_5$ (433.59): Calc C, 69.25; H, 9.07; N, 3.23. Found C, 68.65; H, 9.03; N, 3.30.

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