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A convergent synthesis of the immunosuppressant FTY720 employing aqueous Wittig chemistry

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ABSTRACT

A short, convergent synthesis of the immunosuppressant FTY720 is described involving the use of 4-hydroxymethylbenzaldehyde as a pivotal intermediate. A double Wittig strategy was developed to connect this dual-functional aldehyde with an alkyl-tether and to a readily available TRIS-derivative leading to an efficient synthesis of the target molecule.

Introduction

FTY720 **1** (Fig. 1 and **1**, R = H), also known as Fingolimod, has shown impressive activity, initially as an immunosuppressant in the survival of transplanted tissues (e.g., kidney, liver, heart).[1–3] FTY720 was first prepared as a synthetic analogue of myriocin **2**, a naturally occurring (fungal) palmitoyl transferase inhibitor that inhibits the *de novo* synthesis of ceramide.[4] FTY720 is also structurally related to the natural mediator lipid sphingosine **3**. The biological activity of FTY720 is essentially connected to modulation of those functions normally mediated through the analogous sphingosine adducts. Phosphorylation of sphingosine **3** (R = H) via sphingosine kinases (SphK1 or SphK2) yields sphingosine-1-phosphate (S1P) (Fig. 1 and compound **3**, $R = PO_3^{-2}$),[5–7] a lipid that has emerged as a central regulator in mammalian biology.[8] In a similar fashion, FTY720 is phosphorylated (SphK2) in vivo to give the active *S* enantiomer FTY720-P (Fig. 1 and **1**, $R = PO_3^{-2}$). Biological activity is associated with binding of the phosphorylated adducts to an expanding array of S1P receptors eliciting varied responses. Related to the immunosuppressant activity, FTY720 has also recently been investigated for the treatment of multiple sclerosis (MS) due to its ability to inhibit the autoimmune disintegration of the myelin sheath.[1,6,9] These findings have culminated in the approval of FTY720 (trade name Gilenya) as an orally administered agent that has shown impressive clinical efficacy in treating relapsing–remitting MS.[9] This activity is now linked to a complex interplay of agonism and antagonism of S1P receptors by FTY720-P,[9d] one of which ($S1P_1$ receptor subtype) inhibits antigen-activated lymphocyte egression. FTY720 has also been implicated in sensitizing prostate cancer cells to radiotherapy through the inhibition of SphK1,[10] as well as in promoting proteosomal degradation of prostate, breast and other cancer cell lines.[11] FTY720 and structural analogues have been shown to be pan-antagonists of S1P GPCR signalling.[12] Downstream events mediated through the binding of S1P to GPCRs are recognized as highly significant in the signalling network that regulates the survival and proliferation of cancer cells.[8] SphK1 has been labelled an 'oncogene' and is known to be upregulated in several solid tumors.[13]

While several syntheses of FTY720 have been reported,[7,14–16] new biologically active analogues continue to be discovered[12] and, in conjunction with this impressive array of selective biological activity, the development of a short efficient route became of interest. Of the reported syntheses of FTY720,[7,15,16] two make use of the inexpensive, readily available amine trishydroxymethylamino methane (Scheme 1, TRIS).[14] Both of these prior syntheses differentiate the hydroxyl groups of TRIS through the intermediacy of the *N*-Boc protected acetonide and convert the remaining primary alcohol to the aryl/alkyl side chain using Pd-mediated cross-coupling and Julia-olefination strategies. We have recently been investigating various aspects of aqueous Wittig olefination reactions with trialkylphosphine derived semi-stabilized ylides.[17] It occurred to us that the dual functional benzylic alcohol/aldehyde **6**[18] could potentially serve as a pivotal building block for the synthesis of FTY720 and analogues in conjunction with a suitable intermediate derived from TRIS. We have recently shown that olefination on the aldehyde of **6** can be carried out without protection of the 4-hydroxymethyl substituent under classic Wittig condi-

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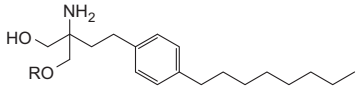
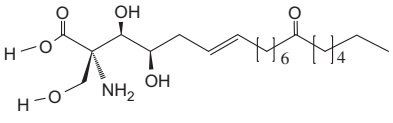
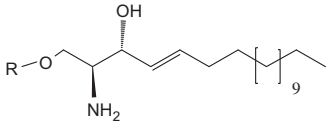


FTY720 (Fingolimod^{TM}) **1** (R=H)



Myriocin **2**

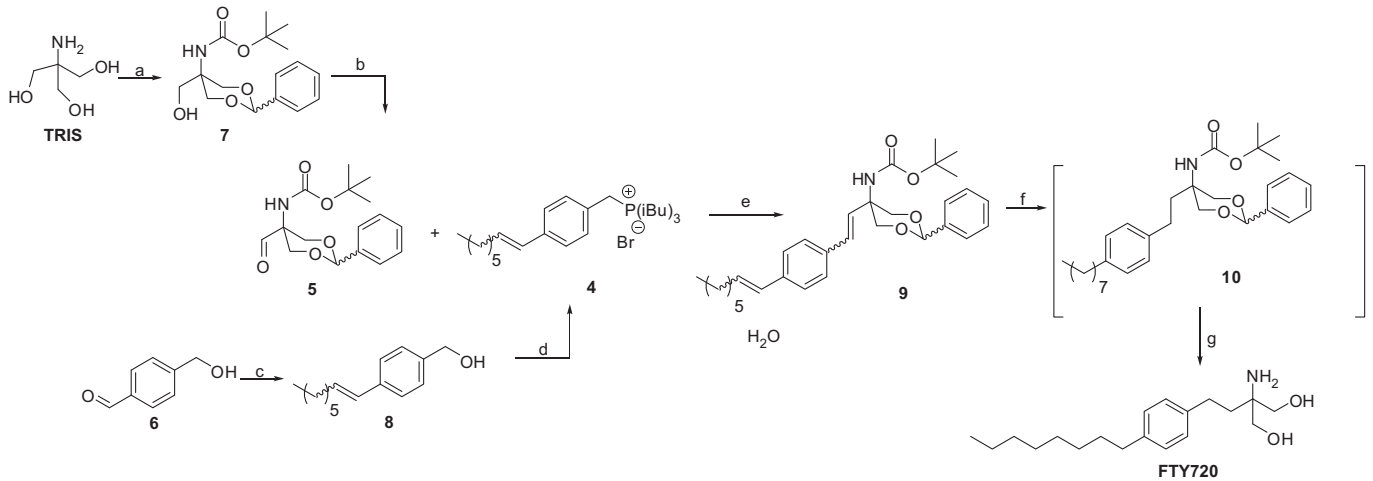


Sphingosine **3** (R=H)

Figure 1. FTY720 and related molecules.

tions,[18c] which in this case should lead to the alkene **8**. The second advantage that could be gained using **6** is the direct conversion of the benzylic alcohol in **8** to the benzylic phosphonium salt **4** using our recently reported trialkylphosphine hydrobromide protocol.[17c] We thus envisioned a convergent route to FTY720 involving an aqueous Wittig reaction between the ylide derived of **4** (Fig. 2) and aldehyde **5** that would proceed via **9**. Hydrogenation and global Boc/benzylidene deprotection would lead to FTY720 as the sole product. In this Letter, we report the successful, rapid, convergent synthesis of FTY720 from the bifunctional aldehyde **6** involving an aqueous Wittig olefination reaction with TRIS-derived aldehyde **5** as the critical point of assembly.

The overall convergent synthesis of FTY720 from aldehyde **6** and TRIS is shown in Scheme 1. The benzylidene acetal derivative of TRIS **7** has been previously prepared in a three step sequence from *tris*-(hydroxymethyl)-nitromethane through benzylidene formation,[19b] nitro-reduction and *N*-protection.[19a] In our hands, this derivative was readily accessed in two steps from TRIS via *N*-protection with Boc_2O and benzylidene formation using benzaldehyde dimethylacetal. The mono-alcohol **7** was isolated by crystallization as a mixture of *cis*- and *trans*-isomers in 81% yield (50:50 to 60:40 ratio). The two isomers were readily separable on chromatography and structures independently assigned.[16a] Swern oxidation was normally conducted on the mixture giving the *cis*- and *trans*-isomers of the fully protected aldehyde **5**. The three steps required to prepare **5** from TRIS can be conducted on a gram scale, requiring only one silica-gel chromatographic purification to obtain **5** in 59% overall yield as a colourless, amorphous solid. Aldehyde **5** proved to be very stable and could be stored for weeks without noticeable deterioration. The tail section of FTY720 was synthesized from the key building block 4-(hydroxymethyl)benzaldehyde **6** employing the double Wittig strategy. A standard (*Z*)-selective Wittig reaction using the non-stabilized ylide derived from triphenyl(heptyl)phosphonium bromide was employed for addition of the alkenyl sidechain. Protection of the hydroxyl group on **6** was not necessary; the olefinic benzyl alcohol **8** was isolated in 87–88% yield as a 10:1 mixture of (*Z*):(*E*)-olefins. The benzylic alcohol **8** was now subjected to our recently described one-step protocol[17c] yielding the triisobutylphosphonium salt **4** in quantitative yield. In this process, the use of a tertiary phosphine hydrobromide salt allows direct conversion of a benzylic alcohol to the Wittig salt without the requirement of formation of the intermediate benzylic bromide (or other activating group). The salt **4** was obtained in quantitative yield and was now subjected to an aqueous Wittig reaction with aldehyde **5** under our recently reported microwave conditions[17e] (30 min at 70 °C) using aqueous lithium hydroxide. The mixture of stereoisomers of **9** was obtained in high yield and was flushed through a short plug of silica to remove polar impurities giving **9** in 76% yield from the reaction of **4** and **5**. The aqueous Wittig reaction can also be conducted with standard thermal heating but is slower (64% isolated yield over 18 h at 70 °C). While the aqueous Wittig olefination protocol is (*E*)-selective, compound **9** was observed to be composed of four stereoisomers, *cis*/*trans* plus (*E*):(*Z*), observable by 600 MHz NMR spectroscopy. The mixture



Scheme 1. Convergent synthesis of FTY720 from TRIS. Reagents and conditions: (a) (1) Boc_2O, DMF, 24 h, (2) $PhCH(OMe)_2$, $PTSA_{(cat)}$, 24 h, 81% over both steps; (b) $(COCl)_2$, DMSO, −78 °C to rt, 4 h, 79%; (c) (1) $(Ph)_3P–C_7H_{15}$ + Br^-, LiHMDS, 0 °C, 1 h, (2) compound **6**, THF, −78 °C to rt, 18 h, 88%; (d) $(^tBu)_3PH+$ Br^-, 110 °C, 18 h. Quant; (e) LiOH, H_2O, MW, 70 °C, 30 min, 76%; (f) H_2, $Pd/C_{(cat)}$, THF, rt; (g) HCl, MeOH/DCM, rt, 92% over both steps.

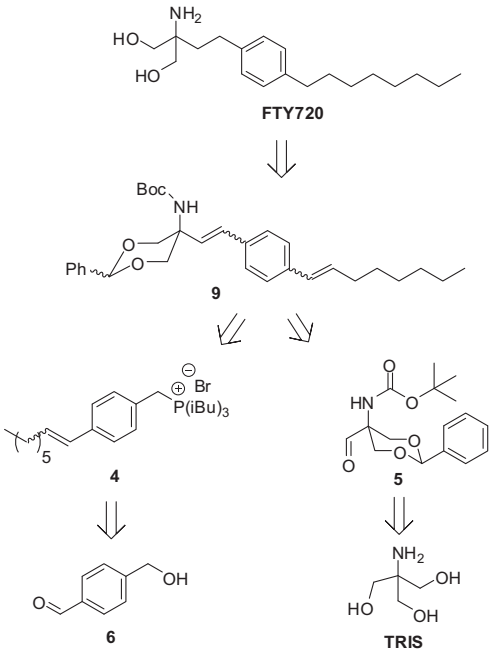


Figure 2. Retrosynthetic analysis of FTY720.

was hydrogenated over Pd/C to give the doubly reduced product **10** as the *cis*/*trans* isomers only. Hydrolysis of the benzylidene acetal and removal of the Boc-protecting group was now performed in a mixture of dichloromethane and hydrochloric acid in methanol, from which the HCl salt and subsequently free base of FTY720 could readily be isolated. The last two steps involve four separate transformations on the molecule, three of which eradicate all stereochemical complexities. Intermediate **10** was readily isolatable and fully characterized, however, these two steps were conducted sequentially and FTY720 isolated in 92% overall yield from **9**.

From an overall strategic synthesis viewpoint, the convergent fusion of benzylic alcohol **8** and TRIS-derived aldehyde **5** fuses the two essential 'halves' of the molecule in an efficient and straightforward process. The salt **4** is prepared in quantitative yield from **8** and is dissolved in water for the aqueous Wittig reaction with **5**, giving direct access to **9** as the mixture of stereoisomers. Hydrogenation and deprotection of **9** are carried out sequentially, involving four separate functional group interconversions that result in unravelling all stereoisomeric complications inherent in **9**. The process provides for the synthesis of FTY720 in 45% yield and only five steps from TRIS, or 62% yield and three steps from the aldehyde **6**. This compares favourably to the method of Kim et al.,[7,9f] that provides FTY720 in 64% yield but requires seven linear steps from TRIS. The readily available bifunctional aldehyde **6** proved to be an ideal building block for the rapid elaboration to FTY720 via the double Wittig strategy and this synthesis should be readily amenable to the preparation of truncated or functionalized analogues of FTY720 through their incorporation onto **6**.

In conclusion, a short efficient synthesis of FTY720 from the inexpensive readily available starting material TRIS and the bifunctional aldehyde **6** is reported. The synthesis employs an aqueous Wittig reaction at the point of convergence providing rapid entry to **9** as a mixture of stereoisomers. Hydrogenation and acidic hydrolysis of **9** yield FTY720 as the sole product in high yield. Aldehyde **6** proved to be a pivotal intermediate to access FTY720 employing the double Wittig strategy. Preparation and assessment of structural analogues of FTY720 employing this method are currently under investigation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.100.

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