



A stereoselective and scalable synthesis of a conformationally constrained S1P₁ agonist

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ABSTRACT

A scalable and enantioselective synthesis of a potent S1P₁ agonist containing two stereogenic centers on a cyclopentane ring is described. Control of the absolute chirality of an amino alcohol precursor, generated via a robust phase-transfer catalyzed alkylation protocol, allows for substrate directed hydrogenation to install the second stereogenic center providing access to gram-quantities of compound **2**.

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Agonism of sphingosine-1-phosphate (S1P) receptors, specifically the S1P₁ receptor, has been linked to many diverse cellular functions including sequestration of lymphocytes into secondary lymph organs thereby preventing them from causing an autoimmune response.¹ FTY720 represents a new class of immunomodulating agents that act via agonism of the S1P₁ receptor and has been shown to be active in Phase II clinical trials for multiple scler-

osis.² Compound **1** (see Fig. 1) is a conformationally constrained analog of FTY720 that has been shown to induce sequestration of lymphocytes in mice.³ Two diastereomers, (1*R*,3*S*) (**2**) and (1*R*,3*R*) (**3**, Fig. 1), have been prepared in milligram-quantities and confirmed to be the stereoisomers that are active in vivo. Herein, we disclose a gram-scale, enantioselective route to one of the active stereoisomers which provides intermediates suitable for analog synthesis to establish structure–activity relationships.

A synthetic route was chosen that would set the conserved (1*R*) stereogenic center of the two diastereomers that induce lymphopenia while allowing for late-stage induction of the benzylic stereocenter through either chirality transfer or reagent control (see Scheme 1). In addition, an alkene such as compound **4**, which could be prepared via ring-closing metathesis (RCM), would likely be amenable to stereoselective hydrogenation allowing access to either the (3*R*) or (3*S*) stereoisomers.

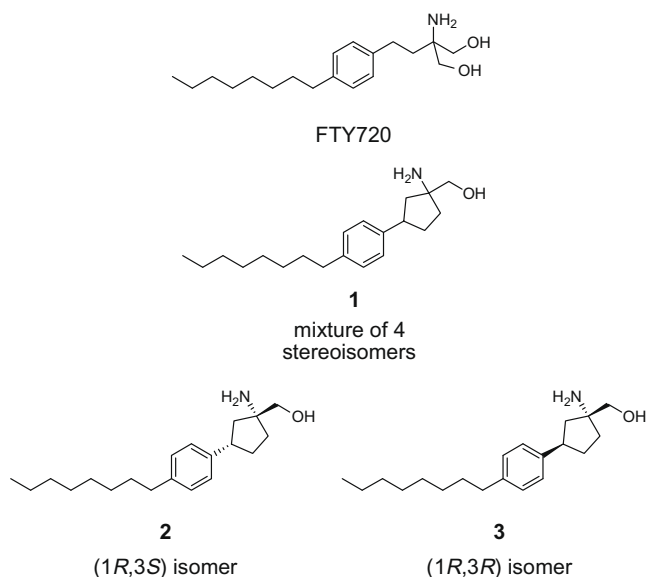
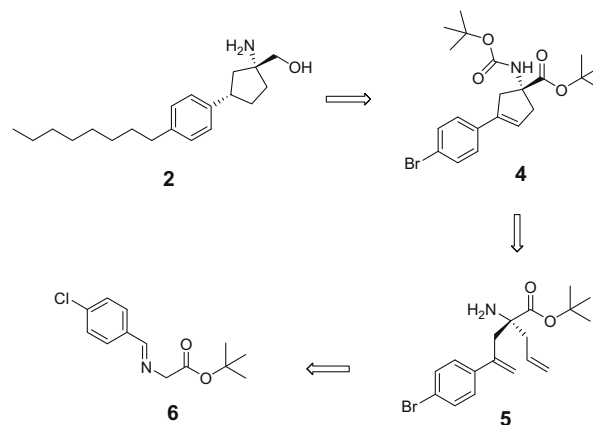


Figure 1. FTY720 and conformationally constrained analogs.

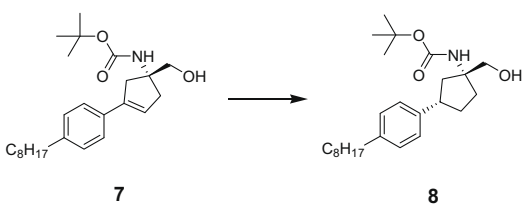


Scheme 1. Retrosynthesis of the (1*R*,3*S*) isomer.

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Table 1
Evaluation of hydrogenation catalysts



Entry	Compound	H ₂ (psi)	Catalyst ^a	% conv ^b (% de)
1	7	50	Ir(COD)ThrePHOX	0 ^c
2	7	970	Ir(COD)ThrePHOX	0 ^c
3	1-Methylstilbene	50	Ir(COD)ThrePHOX	100 ^{c,d}
4	7 , 1-Methylstilbene	50	Ir(COD)ThrePHOX	0, 100 ^{c,d}
5	7	15	Ir(COD)Py(PCy ₃)	100 (33) ^e
6	7	15	Pd/BaSO ₄	100 (70) ^e
7	7	15	1% Pt/C	100 (20) ^e
8	7	15	5% Pd/CaCO ₃	100 (50) ^e
9	7	15	PtO ₂	100 (33) ^e
10	7	15	2% Pd/SrCO ₃	100 (60) ^e

^a All reactions were conducted at rt using 5 mol % of catalyst.

^b Diastereomeric excess as measured by chiral HPLC.

^c Reaction run in CH₂Cl₂.

^d >95% ee was observed for the reduction of 1-methylstilbene.

^e Reaction run in MeOH.

Synthesis of an amino alcohol precursor with control of absolute stereochemistry could be achieved through a variety of methods including selective-Strecker reactions,⁴ the use of chiral auxiliaries such as the Williams diphenyloxazinone,⁵ or through recently developed techniques such as the DuBois nitrene insertion protocol.⁶ In addition, phase-transfer catalysts, such as those developed by Maruoka and co-workers, have been shown to be effective in preparing quaternary amino acid precursors with high enantioselectivity and chemical yield.⁷ Initial attempts at bis-alkylation of the known glycine imine **6** using a chiral phase-transfer catalyst via the reported one-pot protocol⁸ led to incomplete alkylation. However, employing the standard two-step protocol using *n*-BuLi to install the allyl group followed by CsOH·H₂O and (*S,S*)-3,4,5-trifluorophenyl-NAS bromide⁹ to enable the second alkylation with 1-bromo-4-(3-bromoprop-1-en-2-yl)benzene¹⁰ led to greater conversion and higher isolated yields.¹¹ The chiral

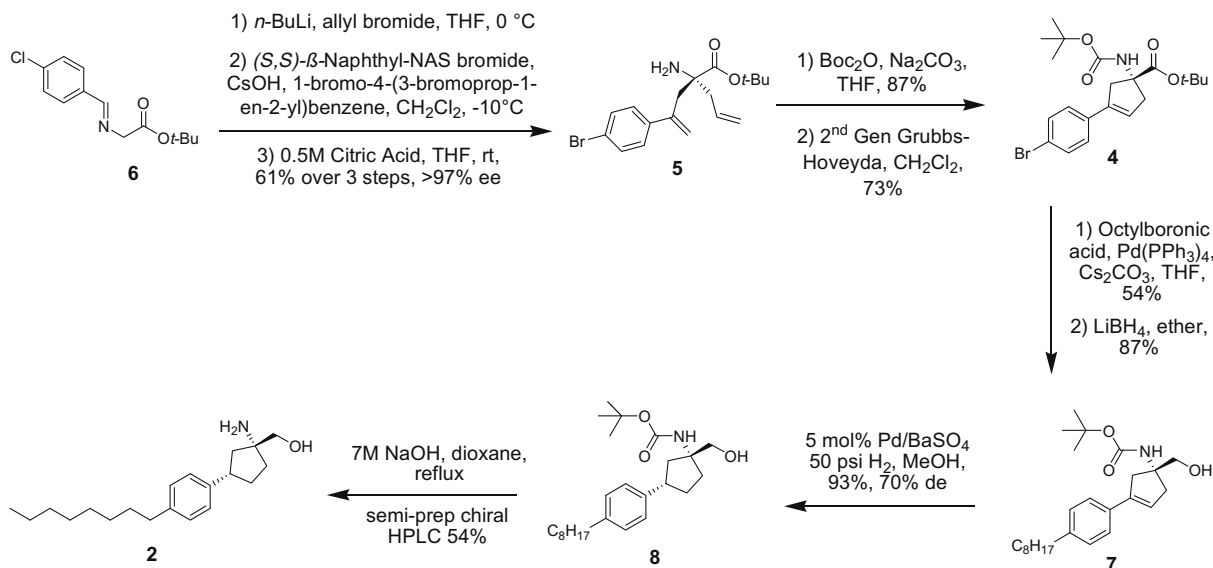
imine intermediate was hydrolyzed with citric acid to provide the quaternary amino ester **5** in 97% ee on a multi-gram scale. Protection of the amine as the Boc carbamate facilitated a Ru-catalyzed ring-closing metathesis using the Grubbs–Hoveyda second generation catalyst.¹²

This provided rapid access to multi-gram quantities of **4** (Scheme 2), which could be used for analog synthesis via cross-coupling reactions of the aryl bromide moiety. To enable the synthesis of compound **2**, an *n*-octyl chain was installed using standard Suzuki coupling conditions followed by reduction of the ester to the corresponding alcohol with LiBH₄ resulting in cyclopentene intermediate **7**.

Compound **7** provided a reasonable scaffold with which to investigate methods for installing the second stereogenic center. A number of methods for asymmetric hydrogenation of olefins have been reported including the Iridium–threoninephosphinite-oxazoline (Ir(COD)ThrePHOX) catalysts developed by Pfaltz and co-workers that have been shown to provide excellent enantioselectivities for trisubstituted olefins without the need for substrate complexation.¹³ However, evaluation of the Pfaltz catalyst¹⁴ system on the functionalized cyclopentene **7** resulted, surprisingly, in no conversion of the starting material (Table 1, entries 1 and 2).¹⁵

Control experiments using 1-methylstilbene, both with and without the cyclopentene **7**, showed excellent conversion of the acyclic trisubstituted olefin, and no catalyst inhibition by the cyclopentene substrate **7** (Table 1, entries 3 and 4).

Crabtree's catalyst was also screened to evaluate a substrate directed approach utilizing either the primary alcohol or its *t*-butyl ester precursor moiety for catalyst complexation.¹⁶ However, only modest de's were observed, presumably due to the competing directing potential of the Boc carbamate group (Table 1, entry 5). A further screen of catalysts, which included heterogeneous hydrogenation catalysts, identified Pd/BaSO₄ as a promising reagent (Table 1, entry 6). The Pd/BaSO₄ hydrogenation system provided compound **8** as an 85:15 mixture of diastereomers, favoring the stereochemistry (1*R*,3*S*) found in compound **2**. This mixture could be further enriched to a 95:5 mixture by recrystallization from heptane.¹⁷ To complete the synthesis of compound **2**, the Boc group was removed via hydrolysis at elevated temperature. The remaining undesired stereoisomer was removed by semi-preparative chiral HPLC to furnish compound **2** in >98% de.



Scheme 2. Synthesis of the (1*R*,3*S*) isomer.

In conclusion, we have developed a stereoselective route that was used to successfully provide gram-quantities of the S1P₁ agonist **2**. This route demonstrates excellent enantioselectivity in setting the stereochemistry at the quaternary center which facilitates moderate stereo-induction at the benzylic site. This route also enabled the preparation of multi-gram quantities of **4**, an intermediate suitable for analog synthesis and SAR evaluation. Additional details of analog synthesis efforts will be published in due course.

Acknowledgments

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Supplementary data

Full experimental details for the preparation of compound **2**, ¹H NMR spectra, and chiral HPLC traces are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.099.

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