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A stereoselective and scalable synthesis of a conformationally constrained $S1P_1$ agonist

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ABSTRACT

A scalable and enantioselective synthesis of a potent $S1P_1$ 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**.

Agonism of sphingosine-1-phosphate (S1P) receptors, specifically the $S1P_1$ 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 $S1P_1$ receptor and has been shown to be active in Phase II clinical trials for multiple sclerosis.[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.

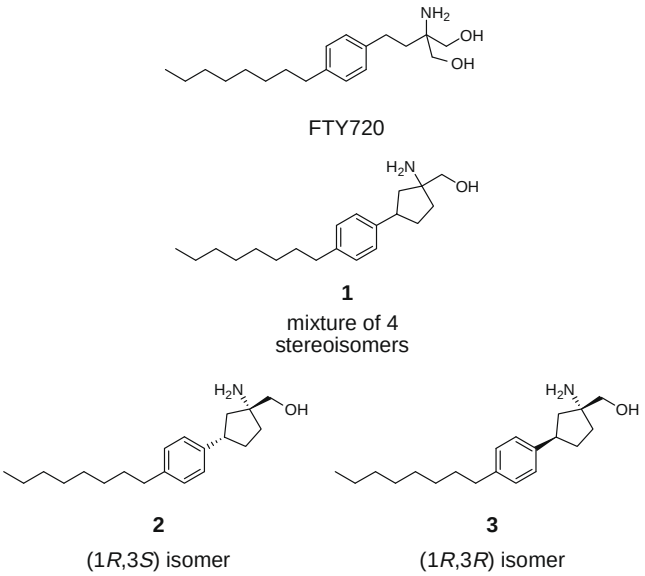
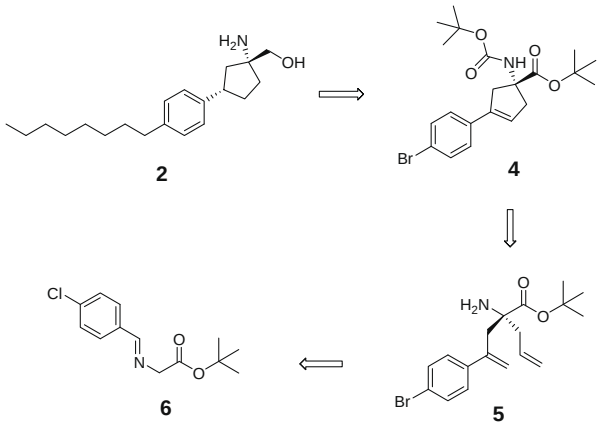


Figure 1. FTY720 and conformationally constrained analogs.

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.



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

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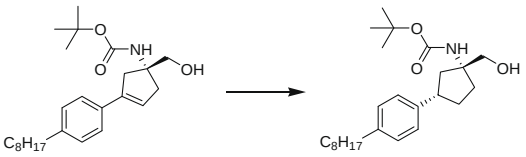
Table 1
Evaluation of hydrogenation catalysts



7 **8**

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)[c]
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 CH_2Cl_2.
[d] >95% ee was observed for the reduction of 1-methylstilbene.
[e] Reaction run in MeOH.

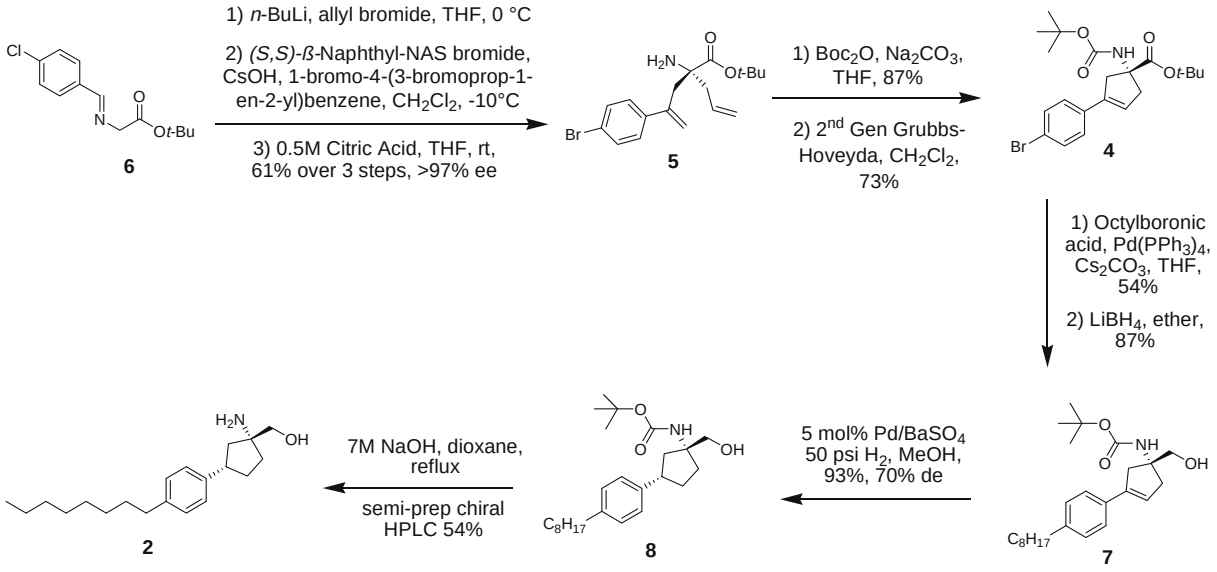
Synthesis of an amino alcohol precursor with control of absolute stereochemistry could be achieved through a variety of methods including selective-Strecker reactions,[4] the use of chiral auxiliaries such as the Williams diphenyloxazinone,[5] or through recently developed techniques such as the DuBois 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 protocol[8] led to incomplete alkylation. However, employing the standard two-step protocol using *n*-BuLi to install the allyl group followed by $CsOH{\cdot}H_2O$ and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide[9] to enable the second alkylation with 1-bromo-4-(3-bromoprop-1-en-2-yl)benzene[10] 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 $LiBH_4$ 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 catalyst[14] 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 it's *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 $Pd/BaSO_4$ as a promising reagent (Table 1, entry 6). The $Pd/BaSO_4$ 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 recrystalization 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 $S1P_1$ 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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