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Complementary Asymmetric Routes to (*R*)-2-(7-Hydroxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate

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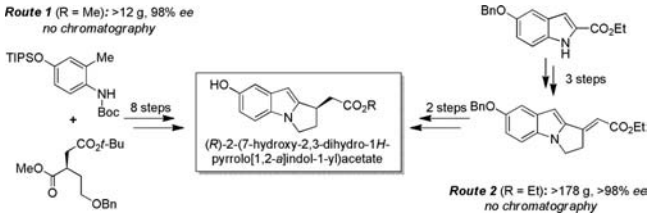
ABSTRACT



Two distinct and scalable enantioselective approaches to the tricyclic indole (*R*)-2-(7-hydroxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate, an important synthon for a preclinical $S1P_1$ receptor agonist, are reported. Route 1 employs a modified version of Smith's modular 2-substituted indole synthesis as the key transformation. Route 2 involves a highly enantioselective CuH-catalyzed 1,4-hydrosilylation as the stereodefining step. Both routes can be performed without chromatography to provide multigram quantities of the tricycle in ≥98% *ee*.

Members of the S1P receptor subfamily of G-protein coupled receptors represent highly attractive targets for drug discovery due to the numerous biological functions they elicit.[1] In particular, the $S1P_1$ receptor agonist FTY720 (**1**, Gilenya, Scheme 1) is currently used to treat relapsing forms of multiple sclerosis (MS).[2] Site-selective phosphorylation of FTY720 (**1**) to its active metabolite FTY720-P (**2**) results in $S1P_1$ dependent sequestration of lymphocytes into the lymphoid tissues, thereby limiting the concentration of immune cells in circulation.[3] This general mechanism of immunomodulation may be useful for the treatment of other autoimmune and neurodegenerative disorders.[4]

The therapeutic potential for $S1P_1$ agonists has prompted the development of a number of second generation $S1P_1$ agonists with improved selectivity and safety profiles.[5] An internal discovery program has identified a number of novel tricyclic indoles (**3**) as potent and selective agonists of the $S1P_1$ receptor.[6] Originally prepared as racemates, separation of the individual enantiomers of **3** by chiral

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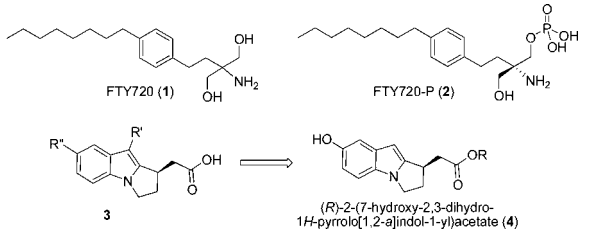
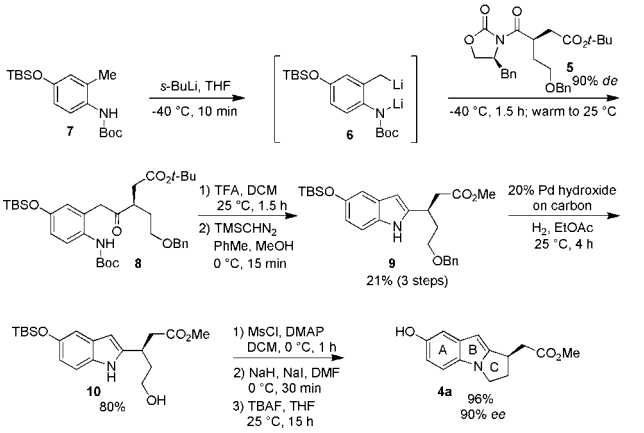
chromatography revealed that one enantiomer possessed superior activity. To further investigate this chemical series in preclinical studies, a scalable asymmetric synthesis of chiral tricyclic indole precursor (*R*)-2-(7-hydroxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (**4**), or its enantiomer, was required. Because the absolute configurations of the active enantiomers were unknown, a route incorporating the stereogenic carbon in a precursor of known configuration would serve as a stereochemical structure proof. Two separate and complementary routes to tricycle **4** are described herein.

Scheme 1. FTY720 (**1**), FTY720-P (**2**), $S1P_1$ Agonist Series **3**, and Chiral Precursor **4**



The methodology developed in the laboratories of Amos Smith in the mid-1980s for the construction of 2-substituted indoles served as the general approach to the target molecule (**4**).[7] Relevant to our work, in a later adaptation of A. Smith's work, Clark et al. performed an elegant synthesis of the achiral parent tricyclic indole 7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole.[8] The key two-step transformation in Clark's synthesis involved trapping the dianion generated from *N*-(*tert*-butoxycarbonyl)-4-methoxy-*o*-toluidine with the Weinreb amide of 4-chlorobutanoic acid, followed by TFA mediated cyclization to give 2-(3-chloropropyl)-5-methoxy-1*H*-indole. The full tricycle was then formed by intramolecular nucleophilic displacement of the tethered chloro substituent by the indole nitrogen. Our first generation asymmetric synthesis of **4**, shown in Scheme 2, is an extension of these methods where the electrophile employed in the key dilithiation reaction is the readily available chiral *N*-acyl oxazolidinone **5**.[9] Treatment of A ring precursor **7** (1.2 equiv) with *s*-BuLi (2.8 equiv) in THF at −40 °C followed by quench of the dianion (**6**) with *N*-acyl oxazolidinone **5**[10] gave the desired *N*-Boc ketoaniline **8**. TFA-mediated cyclization followed by re-esterification of the deprotected *tert*-butyl carboxylate with TMS-diazomethane gave indole **9** in an overall 21% yield (3 steps). The sequence was performed with little optimization and, to our knowledge, represents the first example of adding a dilithiated *o*-toluidine to an *N*-acyl oxazolidinone. Further experimentation to improve yields may significantly expand the scope of electrophiles employed in the modular indole synthesis protocol.

Scheme 2. Asymmetric Synthesis of Tricycle **4a**



The remaining steps involved closure of the C ring. Removal of the benzyl ether of **9** by hydrogenolysis with palladium hydroxide on carbon gave the free alcohol **10**. After mesylation of **10**, deprotonation of the indole N−H with sodium hydride in DMF effected ring closure. Finally, deprotection of the phenolic silyl ether with TBAF gave ester **4a** in excellent yield (96%, 3 steps). The high enantiomeric purity of **4a** (90% *ee*) revealed that no epimerization of the stereocenter had occurred.[11] The robust nature of this protocol highlights its relevance in the synthesis of 2-substituted indoles with a tertiary stereogenic center adjacent to the indole 2-position.[12] Further elaboration of tricycle **4a** to $S1P_1$ agonists (**3**) allowed for assignment of the absolute stereochemistry of these agonists (**3**).

(7) In Smith's modular indole synthesis protocol a dianion generated from an *N*-trimethylsilyl-*o*-toluidine is trapped with an ester or lactone and the resulting *N*-lithio ketoaniline undergoes intramolecular heteroatom Peterson olefination to give a 2-substituted indole. See: (a) Smith, A. B., III; Visnick, M. *Tetrahedron Lett.* **1985**, *26*, 3757–3760. (b) Smith, A. B., III; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957–2969. In some cases the heteroatom Peterson olefination does not proceed and the indole is produced by acid-promoted dehydration of the protonated ketoaniline intermediate. For an example, see: (c) Smith, A. B., III; Davulcu, A. H.; Cho, Y. S.; Ohmoto, K.; Kürti, L.; Ishiyama, H. *J. Org. Chem.* **2007**, *72*, 4596–4610.

(8) (a) Clark, R. D.; Muchowski, J. M.; Fisher, L. E.; Flippin, L. A.; Repke, D. B.; Souchet, M. *Synthesis* **1991**, *10*, 871–878. For a similar example, see also: (b) Peters, R.; Waldmeier, P.; Joncour, A. *Org. Process Res. Dev.* **2005**, *9*, 508–512.

(9) It was reasoned that selective nucleophilic addition of a carbanion to the exocyclic carbonyl adjacent to the oxazolidinone in **5** would be favored both sterically and stereoelectronically over addition to the *tert*-butyl ester.

(10) *N*-Acyl oxazolidinone **5** was prepared in 90% diastereomeric excess by stereoselective alkylation of (*S*)-4-benzyl-3-(4-(benzyloxy)-butanoyl)oxazolidin-2-one. See: (a) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem.* **1999**, *64*, 6411–6417. The synthesis of compound **5** was reported previously, but no analytical data were given. See: (b) Hepperle, M. E.; Campbell, D. A.; Winn, D. T.; Betancort, J. M. WO 2009102876, 2009.

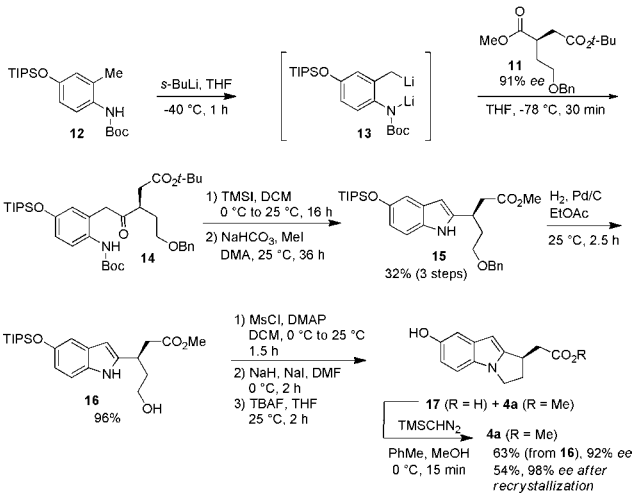
(11) Another significant feature of *N*-acyl oxazolidinone **5** is that epimerization at the α-stereogenic carbon in these systems is strongly discouraged, suggesting that the *R*-stereochemistry at the asymmetric carbon atom would remain unaffected by the strongly basic conditions encountered during the dilithiation reaction. See: Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23–32.

(12) The Smith indole synthesis protocol has been successfully applied to formal total syntheses of (+)-cinchonamine and (+)-*epi*-cinchonamine in which tertiary asymmetric carbon atoms adjacent to the indole 2-position are also located at the C2 position of bridged bicyclic quinuclidine rings. In both cases the indole formation proceeded by intramolecular heteroatom Peterson olefination. No epimerization was observed. For details, see ref 7b.

After some preliminary attempts to scale up the route, a number of modifications became necessary. It was found that TFA-mediated cyclization of *N*-Boc ketoaniline **8** to the indole was less successful on multigram scale.[13] Treatment with TMSI proved to be an acceptable means of cyclization to the indole. However, the highly acidic nature of this reagent caused deprotection of the TBS-protected phenol. Exchange for the more stable TIPS-protected phenol was warranted. Additionally, in order to avoid tedious purifications to remove the chiral auxiliary, methyl ester **11**[14] was examined as the electrophile in the dilithiation reaction (Scheme 3). In initial experiments on small scale (< 1 g), nucleophiles generated by dilithiation of either **7** or the TIPS protected variant **12** were quenched with the chiral acyclic ester **11** (91% *ee*) at −78 °C to give the desired *N*-Boc ketoaniline **8** or **14** respectively.[15] Analysis of the reaction mixtures of **8** and **14** by ^{1}H NMR spectroscopy and LC/MS after aqueous workup indicated selective addition of the benzyllithium anions (**6** or **13**) to the desired methyl ester carbonyl of bis(ester) **11**. When performed on 99 g scale, *N*-Boc-*o*-toluidine **12** (1.6 equiv) was treated with *s*-BuLi (3.7 equiv) at −40 °C and the resulting dianion (**13**) was quenched with bis(ester) **11** at −78 °C to deliver ketone **14**. TMSI-promoted cyclization and re-esterification of the hydrolyzed *tert*-butyl carboxylate under mild conditions gave methyl ester **15** in 32% overall yield from bis(ester) **11**.[16]

The final steps to form the C ring were performed on scale as described previously. The benzyl ether was removed using 10% palladium on carbon under 55 psi H_2 to give the free alcohol **16** in near-quantitative yield. Activation of **16** as its mesylate, C ring closure by deprotonation of the indole with sodium hydride, and deprotection of the phenolic TIPS-ether with TBAF gave a mixture of the final tricycle (**4a**) and the free acid (**17**).[17] Treatment of the mixture of acid (**17**) and methyl ester (**4a**) with TMS-diazomethane converted any free acid (**17**) to the ester (**4a**). Compound **4a** was obtained in 63% yield (4 steps from **16**) and 92% *ee*. Recrystallization of the product (**4a**) further improved the enantiopurity (54% yield, 98% *ee*). In total, over 12 g of **4a** were prepared from bis(ester) **11** in a single batch without the use of chromatography. This sequence demonstrated the successful application of an acyclic ester containing a tertiary asymmetric carbon atom at the α-position as the electrophilic component in the modular indole synthesis protocol. This highly useful intermediate

Scheme 3. Scale-up Synthesis of Tricycle **4a**



(**4a**) was used to prepare a number of important $S1P_1$ agonists (**3**) for examination in preclinical studies.

Concurrent with the development of the dilithiation route, a second generation asymmetric route to compound **4** was being investigated. While the dilithiation route was able to serve as a stereochemical structure proof and provide material for preclinical testing of a number of advanced $S1P_1$ agonists (**3**), an inexpensive and more efficient route to our most advanced drug candidate was desired.

The second approach to tricycle **4** was based on the original medicinal chemistry route.[6] An optimized route to a key intermediate, the β,β-disubstituted enoate **18**, as a pure *E*-isomer is shown in Scheme 4.[18] Starting from readily available hydrazine **19**, ethyl 5-(benzyloxy)-1*H*-indole-2-carboxylate (**20**) was prepared via the classic Fischer-indole approach.[19] 1,4-Addition/Dieckmann condensation of **20** with ethyl acrylate and KO*t*-Bu in THF at reflux followed by decarboxylation in acetic acid/water gave pure ketone **21** in 60% yield after precipitation from the cooled reaction mixture. Olefination of the ketone (**21**) with triethylphosphonoacetate (**22**) and KO*t*-Bu proceeded with excellent *E*/*Z* selectivity (*E*/*Z* > 35:1) to give the α,β-unsaturated ester **18** exclusively as the *E*-isomer. Each reaction in this optimized linear sequence was performed on > 0.30 mol scale without the use of chromatography.

With a convenient route to pure olefin isomer **18** established, efforts were focused on identifying an asymmetric reduction of **18**. Because of the highly unique nature of the substrate (**18**), there was little precedent to achieve this transformation.[20] Asymmetric hydrogenations of β,β-disubstituted enoates lacking an adequate coordinating group involve high catalyst loadings and hydrogen pressures in excess of 500 psig and often proceed with low

(13) Similar results were observed by the F. Hoffman-La Roche group during scale up of their 5-HT_{2c} agonist precursor. See ref 8b.

(14) Bis(ester) **11** was prepared in two steps from *N*-acyl oxazolidinone **5** by peroxolysis followed by methylation. For removal of the chiral auxiliary by lithium hydroxide/hydrogen peroxide, see: Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144. Also see Supporting Information.

(15) It is noteworthy Clark et al. reported in ref that attempts to effect the reactions of dilithiated *N*-Boc-*o*-toluidines with esters were unsuccessful. For an example of addition of a poly-lithiated *N*-(*tert*-butoxycarbonyl)-*o*-toluidine to a lactone with a quaternary α-stereogenic center, see ref 7c.

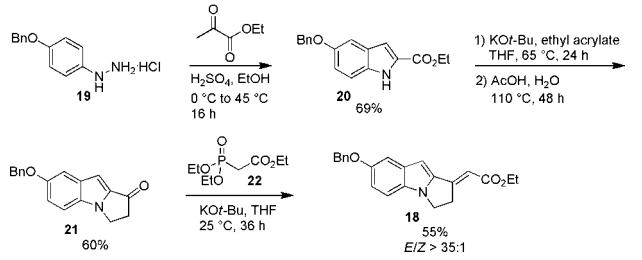
(16) In some cases, on 1−2 g scale, the TMSI conditions caused deprotection of the TIPS ether.

(17) Some ester hydrolysis occurred during workup of the C ring cyclization.

(18) The medicinal chemistry route had produced *tert*-butyl 2-(7-hydroxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ylidene)acetate as an inseparable mixture of olefin isomers. See ref 6b.

(19) Ethyl 5-(benzyloxy)-1*H*-indole-2-carboxylate (**20**) could be purchased from Amfinecom, Inc. for $6,800/kg. The hydrazine precursor (**19**) was purchased from Astatech, Inc. for only $700/kg.

Scheme 4. Large-Scale Preparation of α,β-Unsaturated Ester **18**



enantioselectivities.[21] After some preliminary screening of conditions to reduce **18**, we decided to further examine the CuH-catalyzed asymmetric 1,4-hydrosilylation (Scheme 5) as an alternative to hydrogenation.[22] In this procedure, a CuH complex ligated with a chiral phosphine is the active catalyst and a silane serves as the stoichiometric hydride donor. High substrate/ligand ratios and the use of environmentally benign and inexpensive hydride sources such as tetramethyldisiloxane (TMDS) and polymethylhydrosiloxane (PHMS) make this an attractive procedure for scale up. A screen of chiral phosphines, solvents, and reaction temperatures was performed on small scale (100 mg of **18**) using PHMS as the hydride source and *t*-BuOH as an additive.[23] The ferrocenyl based JOSIPHOS ligand (*R,S*)-PPF-P(*t*-Bu)$_2$ (**23**) and (*R*)-DTBM-SEGPHOS gave superior results (95−99% *ee*) to the BINAP based bis-phosphines (*R*)-BINAP and (*R*)-xylyl-BINAP (69−89% *ee*). The temperature and solvent seemed to have little effect, although

(20) Subsequent to this work, the iridium-Walphos-catalyzed enantioselective hydrogenation of a related tricyclic enoate was reported. See: Tudge, M.; Savarin, C. G.; DiFelice, K.; Maligres, P.; Humphrey, G.; Reamer, B.; Tellers, D. M.; Hughes, D. *Org. Process Res. Dev.* **2010**, *14*, 787–798.

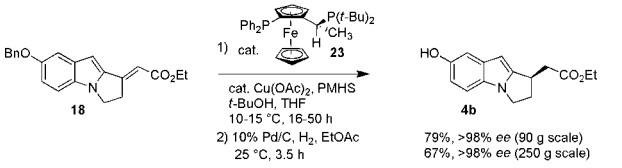
(21) (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069. Chiral iridium N,P complexes have performed well in the high pressure hydrogenations of unfunctionalized olefins. For reviews, see: (b) Woodmansee, D. H.; Pfaltz, A. *Chem. Commun.* **2011**, *47*, 7912–7916. (c) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267–1277.

(22) (a) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352–8353. (b) Deng, J.; Hu, X.-P.; Huang, J.-D.; Yu, S.-B.; Wang, D.-Y.; Duan, Z.-C.; Zheng, Z. *J. Am. Chem. Soc.* **2008**, *73*, 6022–6024. (c) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916–2927.

(23) See Supporting Information.

(24) The 250 g scale reduction proceeded more slowly and required the infusion of additional CuH (1.5 mol %) and ligand **23** (1.5 mol %) as well as a higher temperature (15 °C) in order for the reaction to go to completion.

Scheme 5. Large Scale Asymmetric 1,4-Hydrosilylation



THF was superior to PhMe in solubilizing the enoate (**18**). Ultimately, the CuH catalyzed reduction proved to be quite scalable. When performed on a 90 g scale with 0.5 mol % of (*R,S*)-PPF-P(*t*-Bu)$_2$ (**23**) and 0.5 mol % Cu(OAc)$_2$ with THF as solvent, the reaction gave **4b** in overall 79% yield after benzyl group removal. The sequence was also performed on a 250 g scale with a two-step yield of 67%.[24] Both batches produced the tricycle (**4b**) in >98% *ee* after recrystallization. The remarkable enantioselectivity, reaction efficiency, and scalability of the asymmetric 1,4-hydrosilylation of enoate **18** clearly demonstrates the utility of this technology in preclinical drug development.

In conclusion, two complementary and scalable routes to the S1P$_1$ tricyclic agonist precursor, (*R*)-2-(7-hydroxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate (**4**), have been developed. The first generation dilithiation route served as a stereochemical structure proof and provided material for characterizing a number of promising S1P$_1$ agonist drug candidates (**3**). The second route showcased a highly enantioselective CuH-catalyzed asymmetric 1,4-hydrosilylation to generate the stereogenic center. In total, the optimized route produced in excess of 178 g of tricycle **4b** in >98% *ee* without the use of chromatography. The material obtained enabled a number of preclinical studies for a highly advanced drug candidate.

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Supporting Information Available. Characterization data and full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.