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Facile Entry to an Efficient and Practical Enantioselective Synthesis of a Polycyclic Cholesteryl Ester Transfer Protein Inhibitor

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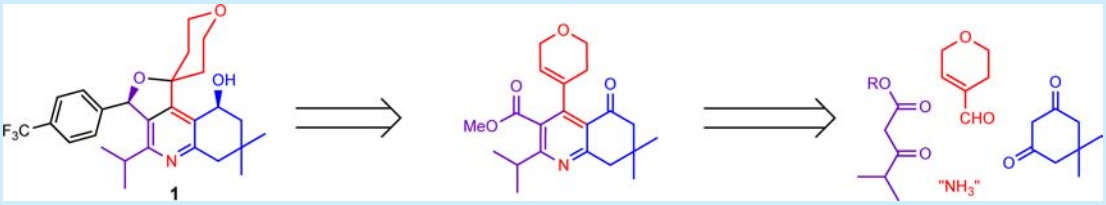
Supporting Information



ABSTRACT: An efficient enantioselective synthesis of the chiral polycyclic cholesteryl ester transfer protein (CETP) inhibitor **1** has been developed. The synthesis was rendered practical for large scale via the development of a modified Hantzsch-type reaction to prepare the sterically hindered pyridine ring, enantioselective hydrogenation of hindered ketone **6** utilizing novel BIBOP-amino-pyridine derived Ru complex, efficient ICl promoted lactone formation, and a BF_3 mediated hydrogenation process for diastereoselective lactol reduction. This efficient route was successfully scaled to produce multikilogram quantities of challenging CETP drug candidate **1**.

Compound **1** is a clinical candidate used as an inhibitor of cholesteryl ester transfer protein (CETP) for the treatment of cardiovascular disorders.[1,2] It is intended to reduce the risk of atherosclerosis by improving the HDL/LDL ratio.[2] In order to support early clinical development, a scalable process to produce **1** was required.

The target compound **1** possesses a crowded tricyclic pyridine core with an embedded chiral dihydrofuran moiety. The discovery route for its synthesis suffers from not only low yields and low stereoselectivity but also tedious steps for the construction of the pyridine core.[1c] While the Hantzsch reaction has been used extensively for the synthesis of pyridines and a number of improved protocols that were reported recently,[3] its application to the synthesis of highly substituted pyridine derivatives remains a challenge. To develop a cost competitive process, rapid construction of the tricyclic pyridine core was required. Herein, we describe an efficient enantioselective synthesis of **1** by building the fully substituted pyridine in one step followed by a catalytic asymmetric ketone reduction, lactonization, and diastereoselective spirocycle formation.

Our retrosynthetic strategy (Scheme 1) focused on the synthesis of the advanced chiral intermediate **3**. The construction of the challenging chiral spirocycle could be accomplished by a diastereoselective reduction of lactol **2** directed by the chiral alcohol, and **3** could be prepared either by asymmetric reduction of **4** or from chiral intermediate **5**. The lactone in **3** or **4** could be accessible by an acid promoted lactonization with the adjacent ester and olefin. Both **4** and **5** could be derived from the pyridine intermediate **6** which in turn could be prepared by a four-component coupling reaction (Hantzsch) of aldehyde **7**, ketoester **8**, dimedone **9**, and an appropriate ammonium salt.

The initial focus was to develop an efficient route to install the required carbon framework in a single step for the fully

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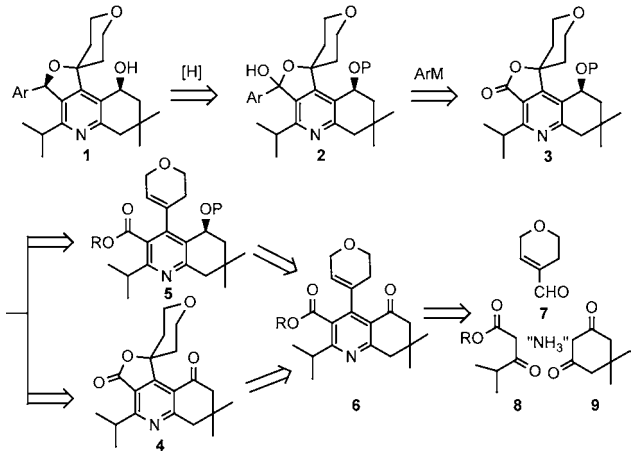
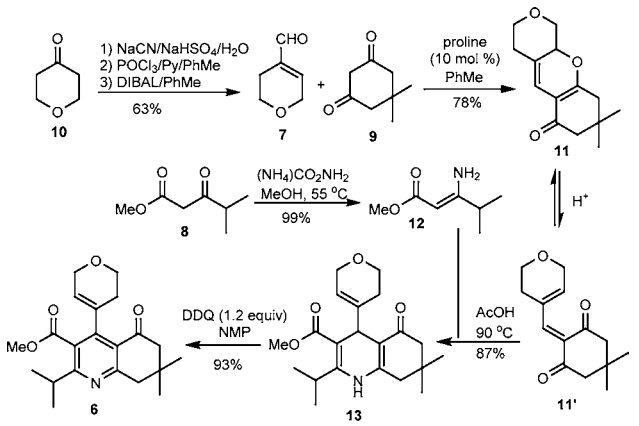
Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of 6 *via* Hantzsch-Type Reaction

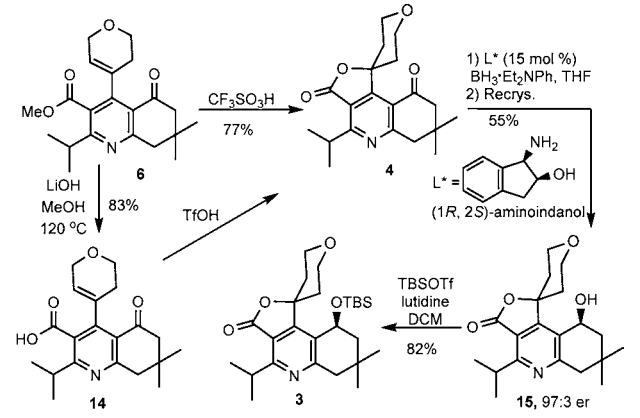


substituted pyridine core **6** by a Hantzsch reaction (Scheme 2). The required aldehyde **7** was prepared from the readily available pyranone **10** in three steps and a 63% overall yield.[4] Preliminary studies for the four-component coupling reactions were unsuccessful for the parent example. When a mixture of **7**, **8**, **9**, and NH_4OAc was subjected to various reported protocols,[3] no desired product **13** was formed, but instead **11** was isolated as the major product. Consequently, the pyridine synthesis via two-component coupling of **11** and **12** was investigated.

Condensation of α,β-unsaturated aldehyde **7** with dimedone **9** was catalyzed by either 10 mol % of 2,6-lutidine or L-proline to provide cyclic product **11** in 78% yield.[4,5] Concurrently, enamine **12** was prepared in 99% yield by reacting ketoester **8** with ammonium carbamate in MeOH.[4] Unexpectedly, no reaction was observed when **11** and **12** were subjected to the reported reaction conditions in which EtOH, acetonitrile, or 1,2-dichloroethane were used as solvents in the presence or absence of a Lewis acid additive at different temperatures.[3a,b,4] Interestingly, moderate conversion was observed when a mixture of tricycle **11** and enamine **12** in methyldiglyme was heated to a higher reaction temperature of 140 °C. A higher conversion (95%) to **13** was later identified once the reaction was carried out in refluxing AcOH (100−110 °C). We believed that the use of AcOH would drive the equilibrium toward the active coupling intermediate **11′**. Furthermore, it was found that the yield was affected by the amount of enamine **12** and 4 equiv of **12** were required in order to consume **11**. The large amount of enamine **12** required was due to the competitive decomposition of **12** at high reaction temperatures. It was determined that the optimal conditions included performing the reaction at 90 °C with 2 equiv of enamine **12** in which complete conversion was obtained in 4 h to furnish dihydropyridine **13** in 87% isolated yield. Subsequent aromatization of **13** with DDQ in NMP afforded the fully substituted pyridine **6** in 93% isolated yield.

With the fully substituted pyridine core **6** in hand, the synthesis of chiral intermediate **3** was investigated (Scheme 3).

Scheme 3. Synthesis of 3 *via* Lactone−Ketone Reduction



An initial attempt was to form the spirocyclic γ-lactone **4** via an intramolecular cyclization of either the ester **6** or acid **14** with the alkene of the pyran ring. Nonhindered γ-lactone synthesis from an olefin and acid has been reported although strong acids are normally required to achieve high conversion.[6] Acid **14** was first investigated for the synthesis of **4**, but as anticipated, its conversion to **4** was found to be difficult. Among the many acids surveyed,[4] only neat H_2SO_4 or trifluoromethanesulfonic acid (TfOH) could promote the cyclization. The reaction in H_2SO_4 was sluggish, and an 80% conversion was obtained after 4 days at ambient temperature. Attempts to accelerate the process with elevated temperatures generated many side products. A clean reaction was observed in neat TfOH, and the reaction was complete after 12 h at ambient temperature to afford the desired lactone **4**. However, presumably due to the steric hindrance of pyridine **6**, the synthesis of acid **14** by ester hydrolysis was not a viable process, as the reaction needed to be conducted in MeOH with LiOH at 120 °C in a pressure reactor. A more direct protocol was later developed by the cyclization of ester **6** with neat TfOH in 18 h at rt to afford **4** in 77% isolated yield.[4] This effective transformation may account for the TfOH promoted formation of the carbocationic species of the alkene, followed by addition of the methoxy or carbonyl oxygen atom, and the efficiently triflate induced demethylation of the resultant oxonium species.[6b]

Due to the hindered environment around the ketone no reduction was observed when **4** was subjected to asymmetric hydrogenation or transfer hydrogenation conditions. Thus, we explored borane reagents for the asymmetric reduction of **4**.[4,7] The optimal conditions were found using 2 equiv of a borane−diethylaniline complex (BH_3·Et_2NPh) with 10 mol % of either (*R*)-*tert*-leucinol or (1*R*,2*S*)-1-amino-2-indanol as a ligand in THF. The reaction completed in 24 h at rt to provide chiral alcohol **15** in an 80%−85% assay yield and 94:6 er. A higher selectivity of 97:3 er was obtained when 15 mol % of (1*R*, 2*S*)-

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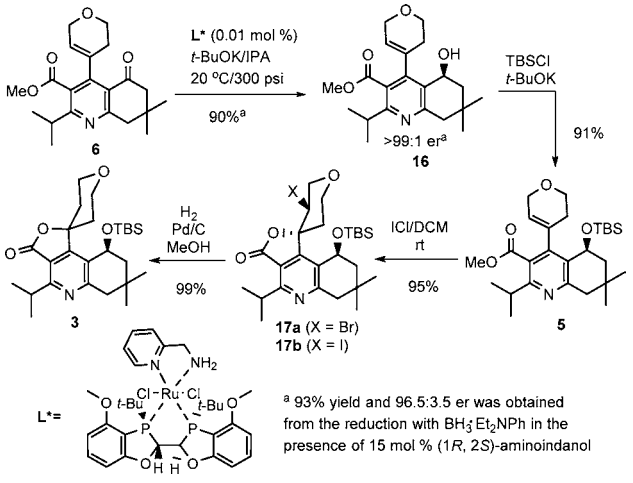
1-amino-2-indanol was used. This protocol, however, provided the product with 15%−20% of byproducts resulting from over-reduction of the lactone. To obtain pure **15**, two recrystallizations were needed to remove the byproducts, and the isolated yield of **15** was a modest 55%. Treatment of alcohol **15** with TBSOTf and 2,6-lutidine afforded the TBS ether **3** in 82% yield. Use of TBSCl failed to provide the desired product.

Although the above process provided the desired chiral product **3**, it was not preferable for large scale synthesis. The main drawbacks were the use of corrosive TfOH as solvent for the lactone formation and the low overall isolated yield. To overcome these issues, a more effective alternative was developed by using asymmetric reduction of ketone **6** to install the chiral alcohol first followed by lactone formation (Scheme 4). Similar to **4**, the reduction of **6** by $BH_3{\cdot}Et_2NPh$ (1.6 equiv)

Scheme 4. Synthesis of 3 *via* Ketone−Ester Reduction



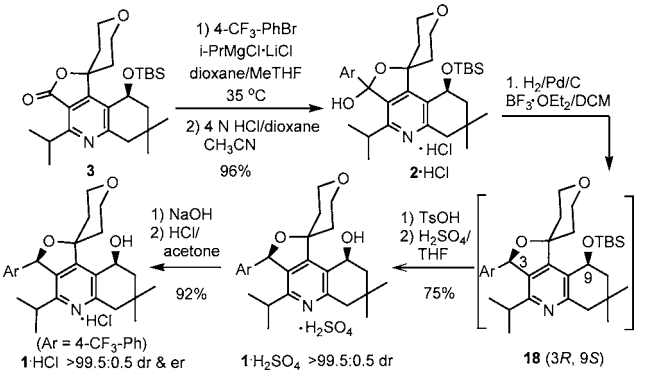
with (1*R*, 2*S*)-1-amino-2-indanol (15 mol %) as the ligand in THF afforded the desired product **16** in 96.5:3.5 er. Unlike **4**, reduction of **6** gave a clean reaction to afford **16** in 93% isolated yield and high purity.

To develop a greener and more efficient process, we investigated the catalytic asymmetric hydrogenation of ketone **6**. In contrast to lactone **4**, high conversions were obtained when **6** was subjected to different catalytic conditions with commercially available $RuCl_2$(diphosphine) (diamine) complexes.[8,9b] The best result was found using 0.5 mol % of a complex formed between $RuCl_2$(tol-BINAP) with 2-aminomethylpyridine (Ampy) in EtOH which afforded the chiral alcohol **16** in quantitative yield and 98:2 er. Attempts to decrease the catalyst loading resulted in low conversion. A more efficient catalytic system was later identified by using our in-house developed BIBOP ligand.[9a] Using the $RuCl_2$(MeO−BIBOP)−(Ampy) complex in isopropanol under 300 psi H_2 at 20 °C, the reaction was complete in 20 h to afford **16** in 90% isolated yield and >99:1 er. Furthermore, the yield and stereoselectivity were not affected even by lowering the catalyst loading to 0.01 mol %.

Treatment of **16** with TBSCl instead of TBSOTf in the presence of *t*-BuOK afforded **5** in 91% isolated yield. The lactone formation using the ester directly was studied. Since a strong acid was not compatible with the substrate, the use of a halogen-promoted lactonization was investigated. Using NIS or I_2 failed to deliver the desired product. Although NBS in dioxane/water afforded the lactone **17a** in 80% isolated yield, the subsequent debromination process generated about 28% side products. After a survey of other reagents and conditions, it was eventually found that treatment of **5** with ICl in DCM at rt afforded the desired product **17b** as a diastereomer in 95% isolated yield, from which the lactone **3** was obtained in quantitative yield by hydrogenative deiodination with the Pd/C catalyst in MeOH.

Having successfully prepared the key tetracycle **3** we next explored the construction of the chiral spirocycle **18** (Scheme 5). Addition of *p*-CF_3−PhLi (ArLi) to **3** was first investigated.

Scheme 5. Synthesis of 1 by Lactol Reduction



The reaction was performed by reverse addition of **3** in THF to an ArLi solution generated *in situ* by treatment of ArBr with *n*-BuLi at −70 °C. The reaction was completed in 30 min after warming to −35 °C to afford **2** in 95% yield. However, this protocol was not feasible for large scale production due to the limited thermal stability of the ArLi wherein up to 50% was decomposed after 2 h at −70 °C. In order to obtain complete conversion more than 3 equiv of the ArBr were required and the reaction needed to be completed in less than 2 h.

Due to the stability issues with the aryllithium substrate, the use of the corresponding Grignard reagent *p*-CF_3−PhMgX was investigated. The initial focus was to identify reaction conditions for the preparation of the stable Grignard reagent. Eventually, it was found that *p*-CF_3−PhMgCl can be prepared by treatment of ArBr with *i*-PrMgCl/LiCl and 2 equiv of dioxane in THF.[10] Although *p*-CF_3−PhMgCl has been previously reported as unstable,[11] the *in situ* prepared Grignard was found to decompose very slowly (<1%/h) at ambient temperature. Therefore, by using 2 equiv of *p*-CF_3−PhMgCl the addition reaction reached full conversion in 4 h at 40 °C. Attempts to isolate the addition product **2** directly were not successful because it was an oil. Gratifyingly, the desired lactol **2** was easily isolated as a crystalline HCl salt in 96% yield and high purity.

To complete the synthesis, a diastereoselective reduction of lactol **2** with various reducing reagents promoted by Lewis acids was first investigated. The main challenge was to identify conditions to achieve a significant level of desired diastereoselectivity, *presumably induced by the already existing chiral environment in* **2**. Initial results showed that the selectivity was very sensitive to the reaction conditions, specifically, the reagents, the Lewis acids, and the solvents used.[12] Using Et_3SiH, a reagent commonly used for lactol reduction,[13] with $TiCl_4$ in DCM an 83:17 dr of **18** was obtained favoring the undesired diastereomer ((3*S*, 9*S*)/(3*R*, 9*S*)). With $NaBH_3CN$ the selectivity was found to depend upon the solvent and Lewis

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acid employed.[12] The best selectivity of 80:20 dr favoring the desired diastereomer was obtained using $TiCl_4·(THF)_2$ in THF. However, the reaction required 4 equiv of $NaBH_3CN$ and a Lewis acid to achieve high conversion.

Gratifyingly, an improved selectivity of 85:15 dr was observed with the hydrogenation in the presence of either $BF_3·OEt_2$ or $BF_3·THF$ in DCM with 10 mol % wet Pd/C. The selectivity was further increased to 89:11 dr when 3 mol % of dry Pd/C was used, and the reaction was completed in 7.5 h at 40 °C to afford **18** in >99% conversion, which was used directly in the next step.

A one-pot protocol for the hydrogenation of **2** and deprotection of **18** was explored with the goal to avoid the use of TBAF.[14] Directly heating the reaction mixture after hydrogenation provided low conversion and numerous dehydration byproducts. A survey of other additives such as acids and bases showed that *p*-$TsOH·H_2O$ gave a complete reaction in 7.5 h at 35 °C to afford the crude desilylation product **1** in 89:11 dr.

Recrystallization of different salts of **1** was studied in order to upgrade its diastereomeric and enantiomeric purity. Recrystallizations of the HCl, H_3PO_4, and HBr salts of **1**, for example, failed to enrich the product. An efficient protocol was finally identified by the slow addition of H_2SO_4 to a solution of **1** in THF, from which **1**·H_2SO_4 was isolated in 75% overall yield in three steps with enrichment of the er from 96:4 (from borane reduction) to >99.5:0.5 and the dr from 89:11 to >99.5:0.5. The final drug substance **1**·HCl was prepared by treating the free base **1** in acetone with 4 N HCl in dioxane to provide **1**·HCl in 92% yield and 99% purity. The stereochemistry of **1** was unambiguously confirmed by a single crystal X-ray structure as shown in Figure 1. This process was utilized to prepare 4.2 kg of **1**·HCl.

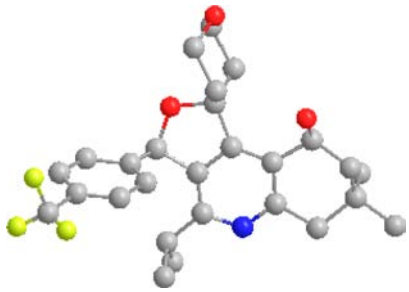

Figure 1. Single X-ray crystal structure of **1**.

In summary, an efficient enantioselective synthesis of the CETP inhibitor **1** was developed. Its main features include the development of an efficient Hantzsch-type reaction for the construction of the fully substituted pyridine tetracyclic core, a highly enantioselective ketone reduction via a newly developed BIBOP−amino−pyridine derived Ru complex, a novel ICl promoted lactonization, and BF_3 mediated diastereoselective lactol reduction. The asymmetric process was successfully scaled to produce multikilogram quantities of **1** to support preclinical drug development.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, detailed reaction condition survey results, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(4) See the SI for the synthesis of **7** and **11**, the results under different conditions for the Hantzsch reaction (Tables 1 and 2), lactone formation (Tables 3 and 4), and ketone reduction (Table 5).

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(12) See Table 6 in the SI for the results on lactol reduction under different conditions.

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(14) Details are provided in the SI.