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Asymmetric Synthesis of Highly Functionalized Tetrahydropyran DPP-4 Inhibitor

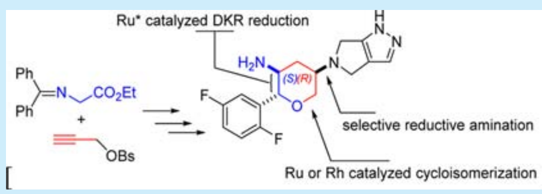
Feng Xu,*[†] Michael J. Zacuto,*[†] Yoshinori Kohmura,[†] Jon Rosen,[†] Andrew Gibb,[‡] Mahbub Alam,[‡] Jeremy Scott,[‡] and David Tschaen[†]

[†]Process Chemistry, Merck Research Laboratories, Rahway, New Jersey 07065, United States

[‡]Process Research Preparative Laboratory, Merck Sharp & Dohme Research Laboratories, Hoddesdon, Hertfordshire, EN11 9BU, U.K.

S *Supporting Information*

ABSTRACT: A practical synthesis of a highly functionalized tetrahydropyran DPP-4 inhibitor is described. The asymmetric synthesis relies on three back-to-back Ru-catalyzed reactions. A Ru-catalyzed dynamic kinetic resolution (DKR) reduction establishes two contiguous stereogenic centers in one operation. A unique dihydropyran ring is efficiently constructed through a preferred Ru-catalyzed cycloisomerization. Hydroboration followed by a Ru-catalyzed oxidation affords the desired functionalized pyranone core scaffold. Finally, stereoselective reductive amination and subsequent acidic deprotection afford the desired, potent DPP-4 inhibitor in 25% overall yield.

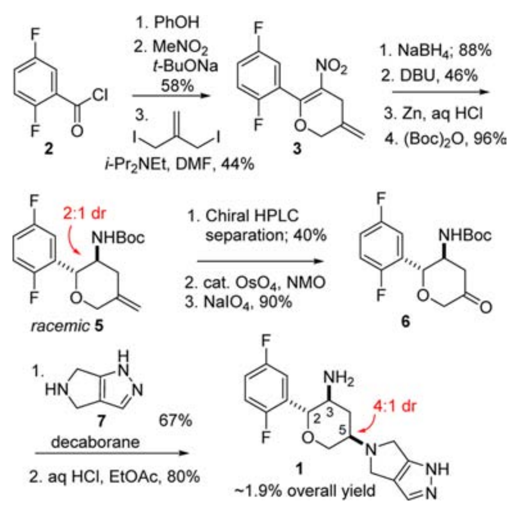


Type 2 diabetes mellitus is a growing worldwide epidemic affecting more than 347 million people.[1] The clinical application of dipeptidyl peptidase-4 (DPP-4) inhibitors has recently proved to be an effective new therapy for the treatment of type 2 diabetes.[2] Due to the clinical success of DPP-4 inhibitors, interest in this area has grown. As a result of the efforts to discover structurally diversified potent drug candidates with additional benefits over current DPP-4 inhibitors, Merck laboratories recently discovered highly functionalized tetrahydropyran **1**, which represents a new class of structurally differentiated DPP-4 inhibitors.[3] Tetrahydropyran **1** possesses a unique core scaffold required for achieving the desired selectivity and efficacy in the tested diabetes model, but it raises the chemical complexity of accessing the evolved new generation of DPP-4 inhibitor drug candidates.

To support the drug development program, an efficient synthesis of **1** suitable for large scale preparation was required. The main synthetic challenge in preparing **1** was the effective and practical construction of three stereogenic centers. In particular, the unique structure of **1** possesses a contiguous *R*,*S* (C2, C3) stereochemical array with an *R* (C5) functionalized amino group in the tetrahydropyran ring. In fact, the central problem of the initial racemic synthesis[3] of **1** essentially was the arduous nature of establishing the desired relative C2,C3 stereochemistry (Scheme 1). Also, reductive amination between **6** and **7** suffered from low diastereoselectivity in establishing the C-5 stereogenic center. The overall yield of the synthesis was only ~1.9%.

Although initial results showed that the dr of the reductive amination was low, the convergent endgame strategy was logically sound. Based on the stereofacial bias of the reduction of the corresponding iminium species derived from **6**, in principle, an improvement in C5 (*R*) selectivity could be achieved by optimizing proper reduction conditions, including

Scheme 1. Racemic Synthesis of 1



modification of reduction reagents. Therefore, a straightforward approach to prepare ketone **8** became the main focus of our efforts (Scheme 2).

We envisioned **8** to arise from dihydropyran **9** through a hydroboration[4] followed by oxidation, as **9** could be prepared via a cycloisomerization of **10**. In particular, several metal catalyzed cycloisomerization protocols[5] recently developed for the preparation of 2,3-disubstituted dihydropyrans were promising, although the competitive cyclization between *N* vs *O* selectivity had not been well studied at the time of our initial research.[6]

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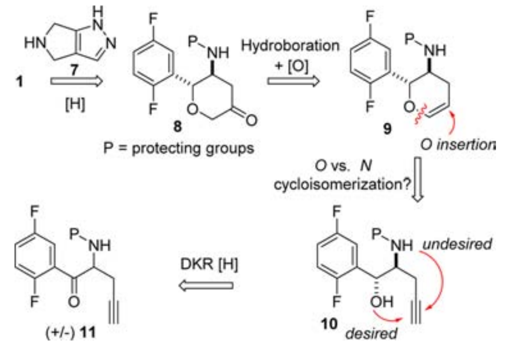
Scheme 2. Retrosynthetic Analysis of Tetrahydropyran 1

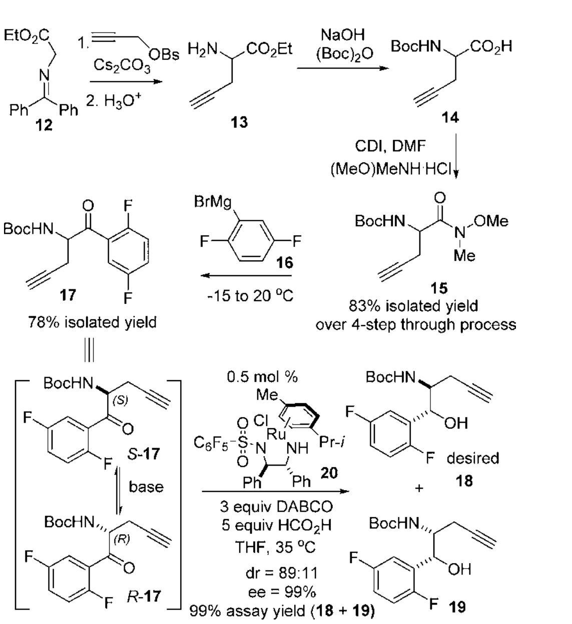


Furthermore, with the recent progress in dynamic kinetic resolution (DKR) reduction,[7] we envisioned that the two *O* and *N* bearing contiguous stereogenic centers in **10** could be established in one operation by applying an asymmetric DKR reduction. Thus, the challenge to achieve an asymmetric synthesis of **1** was retrosynthetically bridged to a racemic preparation of amino ketone **11**.

A key intermediate of our synthetic approach to amino ketone **11** was Boc propargylglycine **14**, which is commercially available, but expensive. After evaluating the reported preparations,[8−10] we quickly settled on a strategy for the preparation of **14** through alkylation of glycine benzophenone imine with propargyl besylate.[11] The use of phase transfer catalyst Bu_4NBr in the presence of Cs_2CO_3 in MTBE was crucial to achieve a reproducible conversion and reaction rate for this heterogeneous alkylation. Interestingly, the addition order of the reagents had a significant impact on yield, as we noticed that the formation of byproducts could be effectively suppressed when Cs_2CO_3 was charged to the reaction mixture last.[12] Thus, under this optimal addition order >99% conversion and >95% yield were obtained.

A through process was then developed to carry the crude alkylation stream to Weinreb amide **15** (Scheme 3). Upon the completion of the alkylation, the reaction was quenched with water directly.[13] The crude stream was washed with 1 N HCl to afford hydrolyzed amine HCl salt **13** in aqueous phase, which, in one-pot, was treated with excess NaOH (2.5 equiv) followed by $(Boc)_2O$ in biphasic aqueous MTBE at ambient temperature to give the desired Boc protected acid **14**. The crude **14** was treated with CDI followed by Weinreb's amine in DMF to yield the desired amide **15**, which was directly crystallized upon addition of water to the reaction mixture. This practical through process afforded **15** in 83% yield over four steps. Grignard reagent **16** was then prepared through a halogen−metal exchange upon treatment of 1,4-difluoro-2-bromobenzene with *i*-PrMgCl or turbo Grignard (*i*-PrMgCl/LiCl) in THF or toluene.[14] Treatment of amide **15** with **16** gave the desired ketone **17**, which was isolated from heptane in 78% yield.

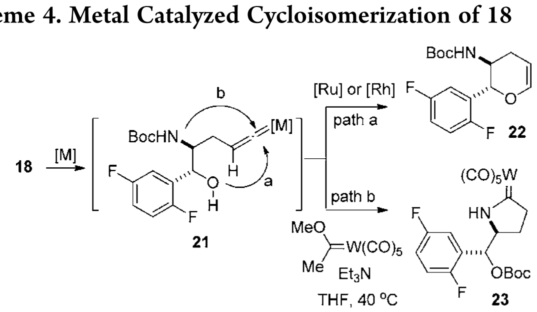
Scheme 3. Preparation of Ketone 17 and DKR Reduction



With **17** in hand, we explored opportunities to prepare the desired *anti* 1,2-amino alcohol **10** through a DKR reduction. The facial selectivity of ketone reduction is controlled by a chiral catalyst while the diastereoselectivity of the process is controlled by the relative ratio of the epimerization rate vs reduction rate of the desired enantiomer *S*-**17**. Attempts to apply DAIPEN type ligands and Ru-catalyzed DKR hydrogenation were unsuccessful.[9] Noyori's Ru-transfer hydrogenation system[15] gave low diastereoselectivity initially. However, the major diastereomer was desired compound **18**, and no over-reduction of the alkyne group was observed. After ligands available at the time were screened, pentafluorophenyl-DPEN was identified as a promising lead. Screening of bases showed that carbonates gave poor selectivity due to a slow epimerization, whereas amine bases such as DBU, DABCO, and morpholine gave improved results. Of these bases, DABCO was the best with no inhibition of the Ru catalyst. In the cases that either the reduction rate was accelerated faster than the epimerization rate or the epimerization rate was not competitive with the reduction rate, a higher catalyst loading or higher reaction temperature led to lower diastereoselectivity. Slow addition of formic acid did not improve the diastereomeric ratio. Solvent choice had a profound effect with THF and CH_2Cl_2 giving higher yields and diastereomeric ratios. In the presence of 0.5 mol % of **20** and 3 equiv of DABCO in THF at 35 °C, 9:1 dr and 95% ee were realized with near-quantitative assay yield. Attempts to upgrade stereochemical purity through direct crystallization of **18** were unsuccessful. Therefore, the crude DKR stream was directly used for subsequent cycloisomerization.

The investigation of the desired cycloisomerization began with studies on competitive cyclization of a vinylidene species **21** between *N* vs *O* selectivity (Scheme 4). To this end, purified

Scheme 4. Metal Catalyzed Cycloisomerization of 18



alcohol **18** was used for initial studies to evaluate several catalyst systems.[5,6,16] It was found that the use of $(CO)_4W{=}C(OMe)$-Me/Et_3N in THF at 40 °C under McDonald's conditions[5f,g] led to exclusive *N*-cyclization. Surprisingly, a 2-pyrroline carbene **23** with Boc group migration was obtained.[9]

Trost's Rh based catalytic system[5c] led to the desired *O*-cycloisomerization exclusively. The use of a preprepared fluorinated analog of Wilkinson's catalyst $[(3\text{-F-Ph})_3P]_3RhCl$ showed a remarkable improvement of the reaction rate and yield over the catalyst prepared *in situ* from $[Rh(COD)Cl]_2/P(3\text{-F-Ph})_3$. Following optimization, a 93% assay yield was obtained by heating **18** to 80 °C in DMF in the presence of 1.5 mol % of $[(3\text{-F-Ph})_3P]_3RhCl$. Attempts to further reduce the catalyst loading resulted in incomplete conversion. When these optimized conditions were applied to the crude mixture of diastereomers (**18**:**19** = 9:1) produced through the DKR reduction, diminished performance of the catalyst was observed, characterized by incomplete conversion of **18** and **19**. A successful solution to overcome this issue was to preserve the effective catalyst concentration through slow addition of the substrates. As such, the intermolecular side reactions were suppressed. Under optimized conditions a solution of a 9:1 mixture (**18**:**19**) in DMF was added over 2−3 h to a solution of 2 mol % Rh catalyst at 80 °C to achieve >98% conversion.

We further extended our cycloisomeration studies to inexpensive, commercially available Ru catalysts. We were also interested in expanding upon the identification of *O*-selectivity observed with Rh vinylidenes.[5c] Our preliminary results showed that carbamate *N*H capture of Ru vinylidene was disfavored and therefore inefficient compared to the desired *O*-cyclization to form dihydropyran under Trost's conditions.[6] After examining several conditions, promising results were obtained with $RuClCp(PPh_3)_2$ (Table 1, entry 6). However, the reaction was

Table 1. Selected Results of Ru-Catalyzed Cycloisomerization of 18[a]

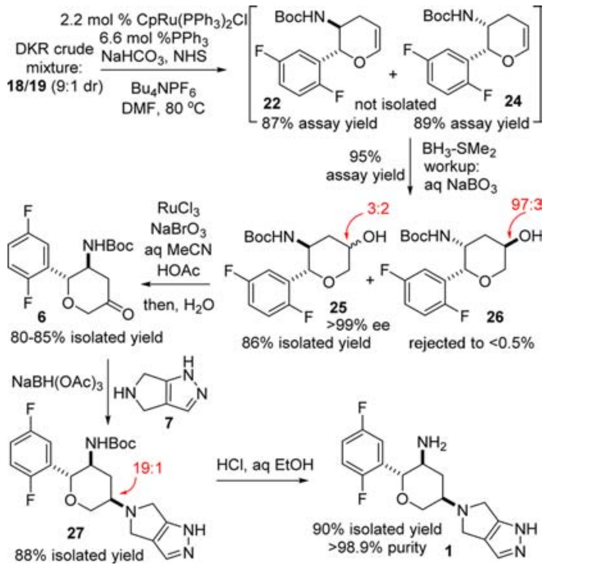
entry	Ru complex	R_3P	time (h)	conv (%)[b]	yield (%)[b]
1	$[RuCl_2(C_{10}H_{14})]_2$	BINAP	30	62	–
2	$[RuCl_2(C_{10}H_{14})]_2$	$(3\text{-FPh})_3P$	30	73	–
3	$[RuCl_2(CO)_3]_2$	$(3\text{-FPh})_3P$	40	97	38
4	$RuCl_3$	$(3\text{-FPh})_3P$	40	98	41
5	$RuCl_3$	PPh_3	16	99	20
6	$RuClCp(PPh_3)_2$	None	24	98	89

[a]Unless otherwise mentioned, all reactions were carried out at 85 °C in DMF (0.4 M) in the presence of a Ru complex (5 mol %), Bu_4NPF_6 (50 mol %), $NaHCO_3$ (50 mol %), and R_3P (20 mol %). [b]Determined by HPLC analysis.[9]

very sensitive with poor reproducibility. After various studies, we finally found that the attainment of a high catalytic Ru cycle for the desired cycloisomerization could be achieved by simply introducing 6.6 mol % PPh_3 into the reaction system (Scheme 5); presumably, the active Ru species was further stabilized with more phosphine ligand available in the reaction mixture.

Without isolation of dihydropyran **22**, the crude stream after aqueous workup was directly subjected to hydroboration. In order to achieve full conversion, 2.5 equiv of $BH_3{\cdot}SMe_2$ were used (Scheme 5).[17] Presumably, the NHBoc functionality consumed/deactivated 1 equiv of borane. The hydroboration proceeded efficiently between −10 and 0 °C. Following an oxidative workup ($NaBO_3$),[18] the assay yield of **25** was >95%. At this point, development of an effective crystallization process was desired to isolate the desired **25** from the crude mixture of diastereomers. After several experiments the desired crystalline **25** with >98% purity was successfully isolated as a 3:2 mixture of diastereomers from toluene/heptane, along with nearly complete

Scheme 5. Through-Process to Pyranone 27 and Endgame



rejection of the undesired product **26** (<0.5%). In addition, the introduction of Bu_3P (20 mol %) during the crystallization allowed for an effective rejection of residual Rh and Ru to lower the burden of controlling the level of heavy metals in final product **1**, as residual heavy metals are strictly regulated for active pharmaceutical ingredients. Thus, starting from ketone **17**, pyranol **25** was isolated in 64% yield and >99% ee over three steps without isolating any intermediates.

With a practical route to pyranol **25** in place, we turned our attention to an oxidation to afford pyranone **6**. Attempts to oxidize **25** with catalytic TEMPO under various conditions were plagued by incomplete conversion; only one of the diastereomers was oxidized.[9] Fortunately, we discovered that Ru-catalyzed oxidations converted both diastereomers of **25** with equal efficiency. In the presence of 0.2 mol % $RuCl_3$[19] and 0.55 equiv of $NaBrO_3$, the oxidation proceeded smoothly in aqueous HOAc−MeCN at 0 °C.[20] Upon completion of the oxidation, *i*-PrOH was added to quench the excess oxidants, because other reducing reagents such as Na_2SO_3 and NaS_2O_3 could cause the reaction mixture to turn to a gel during the aqueous workup. With the appropriate ratio of MeCN−water determined, the desired ketone **6** was crystallized in >98% purity by adding water to the reaction mixture directly.

To complete the construction of the skeleton of **1**, a highly diastereoselective reductive amination of **6** with **7** was desired, since the dr with decaborane was low in the initial synthesis.[3] Surprisingly, a breakthrough in improving diastereoselectivity came from an unexpected, significant salt/acid buffer effect (Table 2). Among the various catalysts/conditions examined, the reductive amination with $NaBH(OAc)_3$ was best carried out in the presence of a weak acid such as HOAc.[21] In particular, when MsOH or pTSA salt **7** was neutralized with a tertiary amine base followed by pH buffering with HOAc, the dr selectivity was dramatically improved in amide solvents (Table 2, entries 5−8). With a combination of Et_3N and HOAc in DMA, reductive amination of bis pTSA salt **7** afforded **27** in 19:1 selectivity (Table 2, entry 7). The desired crystalline product **27** was directly isolated in 88% yield simply by adding aqueous ammonia to the crude reaction mixture. It is important to note that the filtration rate was significantly improved when the reaction slurry

Table 2. Selected Results of Reductive Amination of 6[a]

entry	7	additives	solvents	dr[b]
1	free base	5 equiv HOAc	DMA	6.4:1
2		5 equiv HOAc	NMP	9.5:1
3		2.5 equiv HOAc	*i*-PrOH	3.6:1
4	HCl salt	5 equiv HOAc	10% H_2O/DMF	8:1
5	MsOH salt[c]	3 equiv Et_3N, 5 equiv HOAc	DMF	16:1
6		3 equiv Et_3N, 5 equiv HOAc	DMF	14:1
7	pTSA salt	3 equiv Et_3N, 5 equiv HOAc	DMA	19:1
8		3 equiv Et_3N, 5 equiv HOAc	NMP	12:1

[a]Unless otherwise noted, all reactions were carried out at 20 °C with $NaBH(OAc)_3$. [b]Determined by HPLC analysis.[9] [c]Hygroscopic.

was heated to 70 °C to dissolve/digest fine particle solids before the batch was cooled to ambient temperature for filtration.

The initial rejection of the diastereomer of **27** from the reaction mixture was inefficient, as the isolated **27** contained about 4% of the diastereomer. However, the rejection of the corresponding diastereomer was excellent in the endgame. Thus, treatment of **27** with HCl in aqueous EtOH yielded **1** near-quantitatively. The bis HCl salt dihydrate **1** was directly isolated from the reaction stream in 90% yield and >98.9% purity. The corresponding minor diastereomer carried from the previous step was easily cleared to <0.5%.

In summary, an efficient asymmetric synthesis of tetrahydropyran DPP-4 inhibitor **1** has been developed. This practical synthesis features an application of Ru-catalyzed DKR reduction to establish two contiguous stereogenic centers of an *anti* aryl 1,2-amino alcohol in >99% ee in one step. A Ru-promoted *O*-selective cycloisomerization followed by hydroboration and a Ru-catalyzed oxidation prepares the desired functionalized pyranone **6**. Finally, stereoselective reductive amination and subsequent acidic deprotection complete the synthesis of **1**. Starting from inexpensive glycine ester **12**, the overall yield of this synthesis is 25%. This synthesis is also amenable to the preparation of various analogs of the title compound.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure/data and discussion. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: feng_xu@merck.com.
*E-mail: michael_zacuto@merck.com.

Notes

The authors declare no competing financial interest.

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(2) Since sitagliptin, the first DPP-4 inhibitor was approved by the FDA in 2006, several additional DPP-4 inhibitors, including valdagliptin, saxagliptin, linagliptin, and alogliptin are on the market.

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(4) For selectivity of hydroboration, see: Brown, H. C.; Prasad, J. V. N. V. *J. Am. Chem. Soc.* **1986**, *108*, 2049.

(5) For example, see: (a) Verela-Fernández, A.; González-Rodríguez, C.; Varela, J. A.; Sáa, C. *Org. Lett.* **2009**, *11*, 5350. (b) Koo, B.; McDonald, F. E. *Org. Lett.* **2007**, *9*, 1737. (c) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2003**, *125*, 7482. (d) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 2528. (e) McDonald, F. E.; Chatterjee, A. K. *Tetrahedron Lett.* **1997**, *38*, 7687. (f) McDonald, F. E.; Zhu, Y. H. *Tetrahedron* **1997**, *53*, 11061. (g) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648.

(6) For a preliminary communication of studies on selective cycloisomerization, see: Zacuto, M. J.; Tomita, D.; Pirzada, Z.; Xu, F. *Org. Lett.* **2010**, *12*, 684.

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(9) For a detailed discussion, see the Supporting Information.

(10) For example, the procedure reported in ref 8a was cumbersome to run and the yields obtained in our lab were not as high as quoted.

(11) It is not recommended to use propargyl bromide on large scale due to safety concerns.

(12) The addition mode has been studied in-depth, but its mechanism to suppress the formation of byproducts remains unclear.

(13) Alternatively, the inorganic salts could be removed by filtration.

(14) Scott, J. P.; Brewer, S. E.; Davies, A. J.; Brands, K. J. M. *Synlett* **2004**, *9*, 1646.

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(16) Preliminary results showed that Au-catalyzed cyclization led to an undesired 5-exo dig cyclization/isomerization.

(17) With <1 equiv $BH_3{\cdot}SMe_2$, no desired product was observed.

(18) The use of H_2O_2 was unsafe due to its exothermic and catalytic decomposition by residual Ru or Rh present in solution from the previous step. The use of $NaBO_3$, by contrast, was free of these concerns. For application of $NaBO_3$, see: Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.

(19) The two polymorph forms of $RuCl_3$ could dramatically affect the oxidation rate due to different dissolution rates.[9]

(20) Overoxidation of **6** was suppressed at 0 °C.

(21) The reductive amination could be carried out in the presence of a small amount of water in DMF. However, competitive reduction of **6** to the corresponding alcohol became significant if more water was introduced. Attempts to use strong acid salts of **7** directly for reductive amination were unsuccessful.