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A Scalable Synthesis of a 1,7-Naphthyridine Derivative, a PDE-4 Inhibitor

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Abstract:

A six-step synthesis of a 4-[8-(3-fluorophenyl)[1,7]naphthyridin-6-yl]-*trans*-cyclohexanecarboxylic acid with an overall yield of 27% starting from 2-cyano-3-methylpyridine, cyclohexane-1,4-dicarboxylic acid dimethyl ester, and 3-fluorophenylboronic acid is described. The trans stereochemistry in the cyclohexane moiety was achieved through a series of equilibration steps at different stages of the synthesis.

Introduction

Phosphodiesterase-4 (PDE-4) inhibitors are potential candidates for treatment of respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma.[1] Two compounds in this class, *i.e.*, roflumilast[2] and silomilast[3] have been investigated in clinical trials. Unfavorable side effects such as nausea, diarrhea and headache have limited their use for the treatment of COPD and asthma. COPD is a major cause of chronic morbidity and mortality throughout the world, being currently the fourth leading cause of death[4] and projected to be the third most important cause of death by 2020.[5] Although effective therapies for the management of asthma, such as inhaled glucocorticosteroids[6] and β_2-agonists, are available, their use is limited because of side effects. A new class of PDE-4 inhibitors matching the effectiveness of existing treatments with a more favorable safety profile is still needed. After a detailed study, compound **1** was selected as a potential drug candidate in this area for further development.[7]

Results and Discussion

Research Synthesis. The synthesis used by medicinal chemists for preparing small quantities of **1** is shown in Scheme 1. The overall yield[7] from 3-pyridylacetonitrile (**2**) was 2.7%. The zinc/palladium-mediated alkyl iodide coupling step was not reproducible, and byproducts resulting from homocoupling, detriflation, and hydrolysis were a major concern. In addition, the reagents TMS-CN and Me_2NCOCl that were used for introducing the cyano group in **3** were toxic. A fundamental drawback of this synthesis was the isolation of *trans*-**13** using tedious chromatography as the crude was a mixture of *cis*- and *trans*-isomers in the ratio of 1:4. The *trans*-enriched iodide **12** was in turn obtained from **11** in a tiresome manner using iodine/triphenylphosphine/CCl_4/imidazole. Attempts to use pure *trans*-**12** in coupling with **9** invariably resulted in a *trans*/*cis* mixture. In addition, **2** was not readily available in multikilo quantities that were needed. In view of this, we looked for an alternative synthesis, and the results are summarized in this publication.

Retrosynthesis. On the basis of retrosynthetic analysis, a new route (Scheme 2) was developed.[8] An important feature of the proposed route is to use **14** and the readily available **16** with a 1:4 *trans/cis* ratio with the hope of achieving the desired *trans* configuration of the 1,4-cyclohexane system during the preparation of intermediate **18** by isomerization of the product as the condensation of **15** with **17** is run under strongly basic conditions. As a result, the proposed new synthesis was expected to be simple and economical, a significant improvement over the existing process. Compound **15** in its dianion form has earlier been used in the synthesis of loratidine.[9] Cyclohexane derivative **17** was selected as it offered the best differentiation in the reactivities of two carboxyl functions after screening several related compounds and is readily obtainable[10] from the commercially available **16**.

Synthesis of Intermediate 15. Compound **15** was prepared from **14** under Ritter reaction conditions[11] using *tert*-butyl alcohol and sulfuric acid following a literature procedure.[9] As it was difficult to control the isobutylene emission rate under these conditions and the isolation of **15** required multiple extractions, we replaced *tert*-butanol with *tert*-butyl acetate as the source of *tert*-butyl cation, on the basis of a recent report.[12] This change facilitated the isolation of **15** by direct precipitation from the reaction mixture. Under optimized reaction conditions, **14** was dissolved into acetic acid/H_2SO_4 followed by a controlled addition of *tert*-BuOAc. Use of glacial AcOH as a solvent helped in making the reaction mixture homogeneous before the addition of *tert*-butyl acetate. Product **15** was isolated in 90% yield (>99% HPLC purity) by direct precipitation using aqueous NaOH solution. It is worth noting that a mechanistic study (Scheme 3) using $Na^{18}OH$ as the quenching reagent showed no incorporation of ^{18}O in the product **15**, suggesting

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(1) (a) Hersperger, R.; Bray-French, K.; Mazzoni, L.; Muller, T. *J. Med. Chem.* **2000**, *43*, 675–682. (b) Brown, W. M. *Int. J. Chronic Obstruct. Pulm. Dis.* **2007**, *2* (4), 517.
(2) (a) Huang, Z.; Ducharme, Y.; Macdonald, D.; Robichaud, A. *Curr. Opin. Chem. Biol.* **2001**, 5 (4), 432. (b) Mclvor, R. A. *Expert Rev. Respir. Med.* **2008**, *2* (5), 539.
(3) Kroegel, C.; Foerster, M. *Expert Opin. Invest. Drugs* **2007**, *16* (1), 109.
(4) *World Health Report*, World Health Organization: Geneva, Switzerland, 2000.
(5) Murray, C. J.; Lopez, A. D. *Lancet* **1997**, *349* (9604), 1498.
(6) Barnes, P. J. *N. Engl. J. Med.* **1995**, *332*, 868.
(7) Denholm, A.; Keller, T. H.; McCarthy, C.; Press, N. J.; Taylor, R. J. WO/2003/039544, 2003; *CAN* **2003**, *138*, 368878.
(8) Jiang, X.; Kapa, P.; Lee, G.; Villhauer, E. *CAN* **2006**, *144*, 331421.
(9) Schumacher, D. P.; Murphy, B. L.; Clark, J. E.; Tahbaz, P.; Mann, T. A. *J. Org. Chem.* **1989**, *54*, 2242.
(10) Blum, C. A.; Zheng, X. E.; De Lombaert, S. *J. Med. Chem.* **2004**, *47*, 2318.
(11) Ritter, J. J.; Kalish, J. *Org. Synth.* **1973**, *5*, 471.
(12) Reddy, K. L. *Tetrahedron Lett.* **2003**, *44*, 1453–1455.

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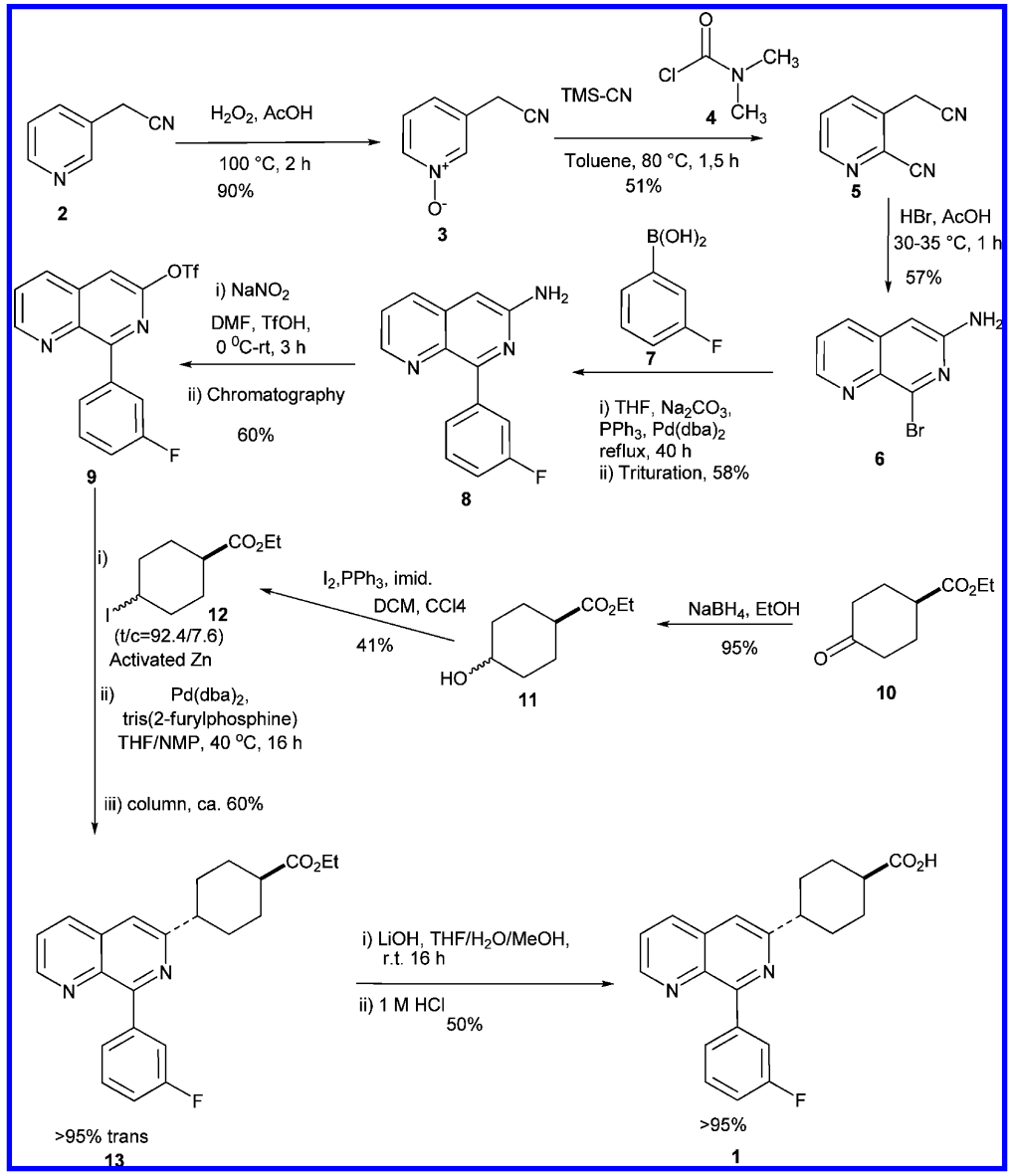
Scheme 1. **Research synthesis**

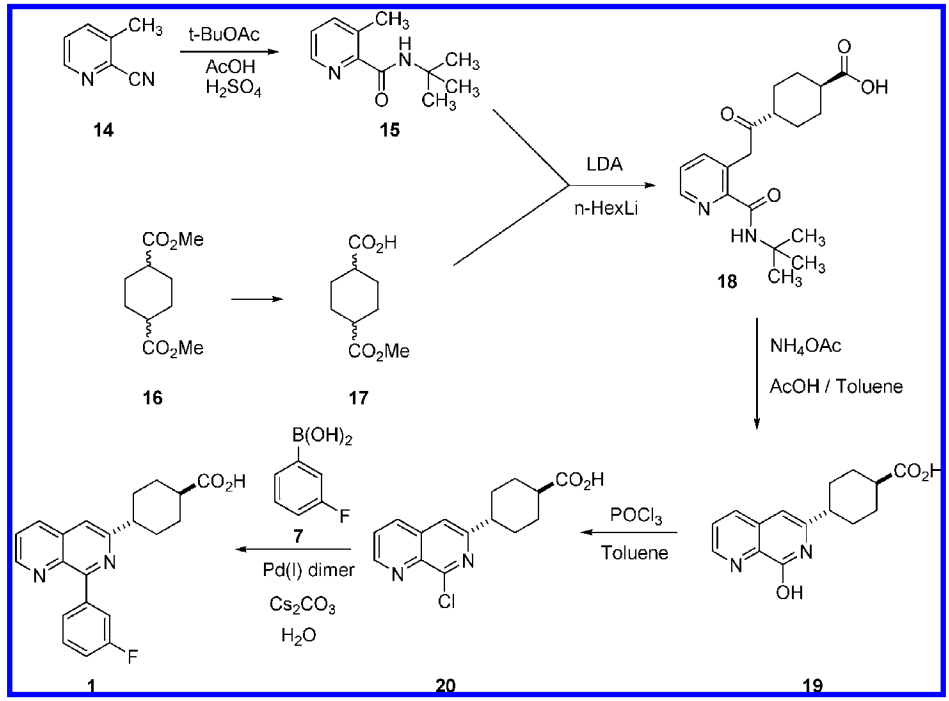


that the amide oxygen in **15** is from acetic acid. The water content in sulfuric acid that was used accounted for only 0.27 equiv with respect to **14**.

Synthesis of Intermediate 17. Compound **16** (a 20/80 mixture of *trans/cis*) was treated with 0.5 equiv of 10.5% solution of potassium hydroxide in methanol while maintaining the temperature below 20 °C.[10] After maintaining the mixture at 65 °C for 2 h followed by concentration to remove methanol, the crude was partitioned between water and heptane. The unreacted dimethyl ester (~25%) from the heptane layer was recycled for the next run. The aqueous solution containing the potassium salt of **17** after acidification with HCl and saturation with sodium chloride followed by extraction with *tert*-butyl-methyl ether gave **17** (*trans*/*cis* 36/64) in 67% yield. Obviously, the hydrolysis rates of the *trans*- and the *cis*-isomers were different, resulting in different isomer ratios in the product and in the unhydrolyzed **16**. This isomer change has no consequence as the *cis/trans* ratio was in flux in subsequent steps. A minor byproduct, *i.e.*, the corresponding cyclohexane dicarboxylic acid, was left in the aqueous layer if the pH was controlled at 5.5.

Main Sequence. For the number of equivalents of base required in the formation of **18**, one must consider the easily exchangeable protons in **15**, the readily enolizable carbonyl group of the expected product **18**, and the COOH group of **17**. In view of this, a mixture of LDA (2.5 eqiv.) and *n*-hexyllithium (2.54 equiv.) in THF at −40 °C was used for generating the dianion of **15**. A solution of compound **17** in THF was added to the above dianion mixture over 7−10 min, allowing the temperature to rise. This was found critical as the lower temperature resulted in the precipitation of the salt of **17** leading to an incomplete reaction. The color change from pink to yellow was used for monitoring the progress of the reaction. Product **18** was isolated by neutralizing the reaction mixture with 6 N HCl followed by extraction with ethyl acetate. The ratio of *trans*- to *cis*-isomer (35/64) remained essentially unchanged compared to **17**, not an encouraging result for our expectation of isomerization to the desired *trans*-isomer. However, serendipitously, the water-quenched reaction mixture on aging showed better *trans* selectivity, and this triggered a detailed study of this *trans*-enrichment (Table 1). The best *trans*

Scheme 2. **Proposed synthesis**



Scheme 3. **Mechanism of 15 formation through a Ritter reaction**

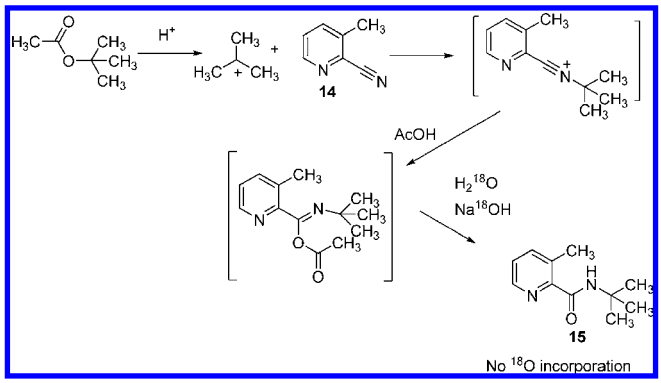


Table 1. ***trans/cis*** **Ratios of 18 after quenching with water**

time, min	temp., °C	conditions	*trans*, %	*cis*, %
10	25	add **8** and hold	34.5	65.5
30	−58	quench with water and hold	35.5	64.5
30	3	quench with water and hold	65	35
480	20	quench with water and hold	95	5

selectivity occurred after leaving the water-quenched reaction mixture at room temperature over 8 h.

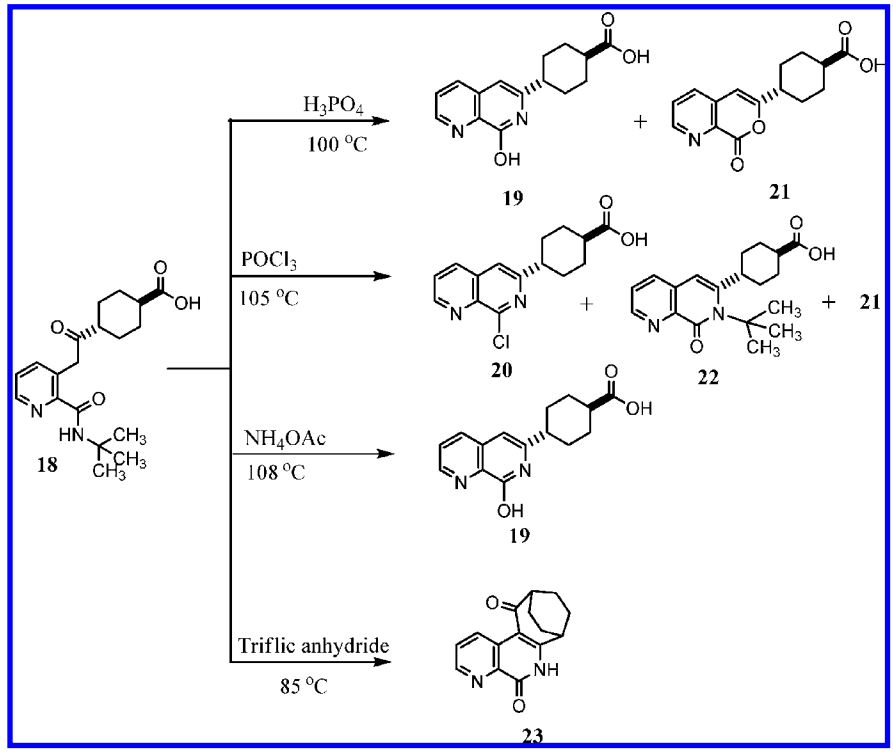
On the basis of the relative reactivity of the two methine protons in cyclohexane that are adjacent to carboxy and carbonyl groups, we believe the proton next to the ketone is participating in these isomerzations. This equilibration process essentially drives the isomeric ratio to the preferred *trans* isomer. Compound **18** was isolated by bringing the pH to 5−6, at which stage the product precipitated out in 80% yield with a HPLC purity of 98% (*trans* + *cis*).

The cyclization of **18** to **19** was extensively investigated as the product formed depended on the conditions used. Preliminary results on converting different analogues of **18** to their corresponding 8-hydroxy-6-substituted-1,7-naphthyridines using ammonium acetate and conversion of compound **18** to fused bicyclo[3.2.2]nonenones by treatment with triflic anhydride were reported earlier by us.[13] A summary of our investigations in converting **18** to **19** leading to the final optimized conditions, *i.e.*, ammonium acetate in acetic acid are shown in Scheme 4. Treatment of compound **18** with phosphoric acid at 100 °C afforded the desired compound **19**, along with byproduct **21**. With phosphorus oxychloride, it was possible to obtain **20** in one step but the formation of byproduct **21** and **22** made this condition impractical. With triflic anhydride a tricyclic compound was formed. Finally using ammonium acetate as an amine source we accomplished the desired cyclization in 81% yield.

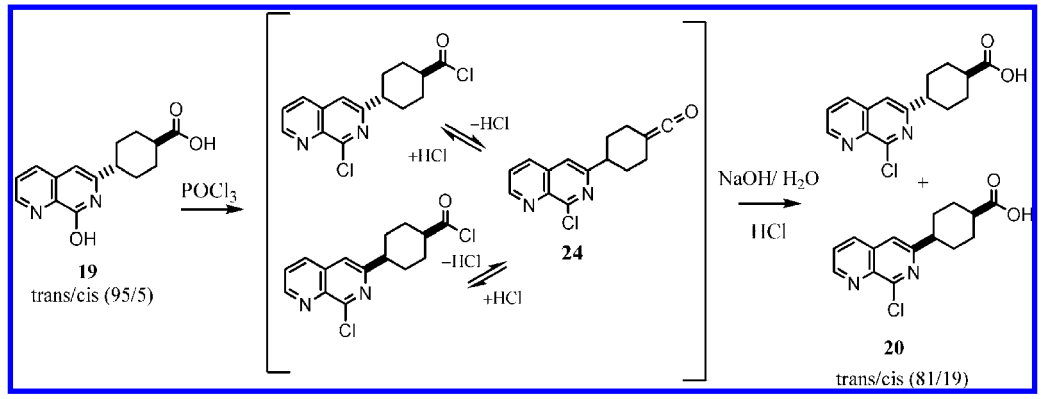
Attempts to convert compound **19** to compound **20** with oxalyl chloride or thionyl chloride were not successful. However, compound **19** on treatment with phosphorus oxychloride alone or in a combination with phosphorus pentachloride gave the desired compound **20** in good yield and in high purity. In the final process, compound **19** and 10 equiv of phosphorus oxychloride were dissolved in toluene and heated at 108 °C for 6.5 h. Chloride **20** was isolated, in 93% yield as a 81:19 *trans/cis* mixture, by a slow addition of the reaction mixture to water at 5 ± 3 °C followed by neutralization with 50% sodium hydroxide to pH 3.1 and filtration. It is important to note that the temperature of the addition of the reaction mixture to water was critical since the hydrolysis of compound **20** back to compound **19** was observed at >5 °C. Unexpectedly, product **20** that was isolated was found to be a 81:19 *trans*/*cis* mixture as the acid chloride intermediate **24** was re-equilibrated through a ketene intermediate[14] (Scheme 5) under these conditions.

(13) Jiang, X. L.; Chen, G. P.; Prasad, K.; Repič, O.; Blacklock, T. *J. Heterocycl. Chem.* **2006**, *43* (6), 1725.
(14) Fujii, T.; Hoshino, S.; Kotou, K. JP56120636; *CAN*, 1981, *96*, 51873.

Scheme 4. **Cyclization of 18**



Scheme 5. **Isomerization of 24**



Although this was a set-back from the point of view of losing some *trans* selectivity from what was achieved during the dianion chemistry, it provided a way for recycling the undesired *cis*-isomer in the final step.

For the Suzuki coupling of **20** with **7**, palladium catalysts[15] such as $Pd(OAc)_2$, POPd, POPd1, POPd2, PS-Pd, FiberCat-1001, and FiberCat-1000-D7 were screened, but none of them gave the desired **1** in good yield. As shown in Table 2, FiberCat 1000-D7 and FiberCat 1001 gave no desired product even with 10% catalyst loading.

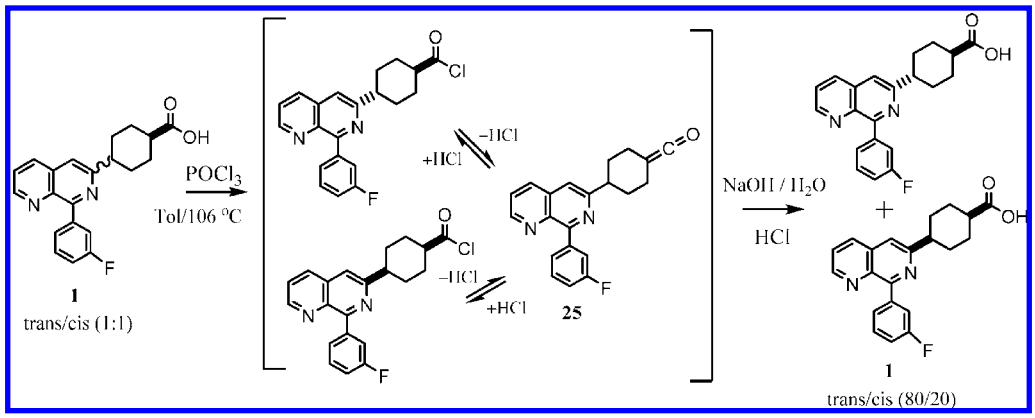
Table 2. **Screening Pd catalysts for Suzuki coupling reaction**

entry	Pd cat. molar ratio to **2**	ligand	temp., °C	time, h	% conversion to **1**
1	$Pd(OAc)_2$, 10%	P(*o*-tolyl)$_3$	80	1.5	40
2	$Pd(OAc)_2$, 1%	P(*o*-tolyl)$_3$	80	1.5	14
3	FiberCat-1000-D7, 10%	no	80	6	No
4	FiberCat-1001, 10%	no	80	6	No
5	POPd, 10%	no	80	18	30
6	POPd1, 6%	no	80	21	5.3
7	POPd2, 6%	no	80	18	75
8	PS-Pd, 10%	no	80	20	94
8	PS-Pd, 0.4%	no	80	22	68
9	**Pd-Dimer, 0.4%**	**no**	**80**	**1.7**	**~100**

A very low yield was obtained with $Pd(OAc)_2$, POPd1 and POPd. The catalyst PS-Pd worked well, but it is not readily available in the quantity we needed. Finally we settled on using Pd(I) tri*tert*-butyl phosphine bromide (Pd(I) dimer) as the catalyst, as the coupling was completed within 2 h in water at 80 °C in the presence of

(15) Details on these catalysts are as follows: POPd = dihydrogen dichlorobis(di-*tert*-butylphosphinito-*k*P)palladate (2-), CAS # 391683-95-7 (supplier: Combiphos Catalysts Inc.); POPd1 = dihydrogen di-μ-chlorotetrakis(di-*tert*-butylphosphinito-*k*P)palladate (2-), CAS # 386706-31-6 (supplier: Combiphos Catalysts Inc.); POPd2 = dihydrogen di-μ-dichlorodichlorobis(di-*tert*-butylphosphinito-*k*P)palladate (2-), CAS # 386706-32-7 (supplier: Combiphos Catalysts Inc.); PS-Pd = Allyl-palladium dimer supported on poly(ethyleneglycol)polystyrene graft copolymer beads (supplier: Strem Chemicals, Inc.); FiberCat-1001 and Fibercat-1000-D7 are palladium catalysts anchored onto the polyethylene-based supported ligands (supplier: Johnson Matthey).

Scheme 6. **Isomerization of mother liquors of 1**



potassium carbonate. The Pd(I) dimer, when added last, was found to be quite stable to aqueous reaction conditions.

The isolation of compound **1** from the reaction mixture proved to be quite challenging as the crude potassium salt of **1** had low solubility in water and started precipitating during further handling of the reaction mixture. In an optimized process, the reaction mixture was first extracted with *tert*-butyl methyl ether (TBME), followed by 6 N HCl solution. Treatment with Smopex 110 at 60 °C for removing residual palladium, filtration of this hot solution through a pad containing activated carbon and Celite, followed by neutralization with NaOH to pH 10 with stirring for 4 h and readjusting the reaction mixture pH back to 2−3, afforded **1** as a 82:18 *trans/cis* mixture in 88% yield. For removing palladium, we found Smopex 110 to be superior to Smopex 112 under aqueous acidic conditions, and with one treatment, the Pd level was reduced from 1300 ppm to ≤1 ppm. Since the crude **1** obtained from the Suzuki reaction contained 19% of the undesired *cis*-isomer, a series of crystallization conditions were screened, and the best conditions were found to be the use of 10% water in acetonitrile where the product was isolated in 51% yield (over two steps) in a reproducible manner with the *cis*-isomer being <1%.

***trans*-Enrichment of Mother Liquors of 1.** Upon treating the *cis*-enriched mother liquor residue with 3.0 equiv of phosphorus oxychloride at 110−125 °C for 2 h followed by quenching with NaOH crude, **1** with a *trans*/*cis* ratio of 85/15 (91% yield) was obtained (Scheme 6). This recycling through the intermediacy of **25** made the overall process highly practical and economical.

Conclusions

An efficient new synthesis of **1** with an overall yield of 27% was described. The key intermediate **18** was prepared in 80% isolated yield with a 95/5 *trans/cis* ratio by adding compound **17** to the dianion of compound **15** prepared by treatment with LDA and *n*-hexyllithium in THF at −40 °C, followed by holding the water-quenched reaction mixture for at least 8 h at 23 °C. Drug substance **1** was obtained by treatment of compound **20** with **7** in the presence of palladium(I) dimer, and potassium carbonate in water at 85 °C. The desired **1** was obtained in 58% yield containing less than 1% of the *cis*-isomer using 10% water in acetonitile as a recrystallization medium; the undesired *cis*-isomer was largely isomerized to the *trans*-isomer using phosphorus oxychloride at 110 °C.

Experimental Section

General. HPLC methods: compound **16**: Agilent 1100 system using YMC ODS-AQ columns (150 mm ×3 mm, 3 μm, 45 °C) and a mixture of acetonitrile with trifluoroacetic acid as mobile phase (gradient at a flow rate of 0.8 mL/min and UV detector at 215 nm); retention times **16**: *trans*-isomer 2.38 min and *cis*-isomer 2.678 min. Compounds **1**, **15**, **18**, **19**, and **20**: Dynamax model SD-200, column: Symmetry, C18/5 μm, 4.6 mm ×250 mm; flow rate: 1.0 mL/min; eluents: A:B = 90:10, isocratic, A is water with 0.05% TFA (v/v), B is acetonitrile with 0.05% TFA (v/v). Retention times for compounds are as follows: Compound **1**: *trans*-isomer 12.37 min, *cis*-isomer 12.85 min; compound **15** 10.1 min; compound **18** 11.28 min; compound **19** 7.68 min; compound **20**: *trans*-isomer 10.72 min and *cis*-isomer 11.05 min.

3-Methylpyridine-2-carboxylic Acid *tert*-Butylamide (15). 2-Cyano-3-methylpyridine (**14**, 94.4 g, 0.8 mol) and acetic acid (2.62 mol, 150.0 mL) were stirred at RT at a rate of 250 rpm while concentrated sulfuric acid (1.8 mol, 96.0 mL) was added over 0.5 h at ≤30 °C. During the addition, the solution was first an opaque, white solution and then became clear and colorless by the end of the addition. *tert*-Butyl acetate (1.6 mol, 215.6 mL) was added over 45 min, while the reaction was kept under a constant and gentle N_2 stream and the temperature at 25 ± 4 °C. After addition, the resulting clear, colorless solution was stirred at RT for 4 h. The reaction mixture was held at RT for another 8 h to guarantee complete reaction. The reaction was quenched by addition into 9.0% aqueous NaOH solution (360 g of NaOH in 3.64 kg of water) over 40 min at 8 ± 4 °C. The mixture was stirred at RT for another1.5 h, and the solid was collected by filtration. The collected solids were suspended in water (600 g) and stirred for 0.5 h, collected by filtration, and dried under vacuum (44 ± 5 °C, 25 mbar) for 14 h to afford 138.44 g of **15** in 90% yield as a white crystalline solid; mp: 58−60 °C; *m*/*z* (M + 1) 193; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 2.72 (s, 3 H), 7.21−7.28 (m, 1 H), 7.52−7.60 m, 1 H), 8.05 (br s, 1 H), 8.30−8.32 (m, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.72, 28.79, 50.17, 125.62, 135.0, 140.89, 145.13, 148.38, 165.38.

Cyclohexane-1,4-dicarboxylic Acid Monomethyl Ester (17). This compound was prepared on the basis of the literature procedure[12] with few modifications. To a solution of 1,4-cyclohexanecarboxylic acid dimethylester (**16**, 1.01 kg, 4.79 mol, *trans/cis* 20/80) and methanol (79 g) was added a warm

solution (47 °C) of potassium hydroxide (158.2 g, 2.39 mol) in methanol (1.343 kg) at 16−19 °C. The resulting pale-yellow solution was warmed slowly to 65 °C over 1.5 h and maintained at this temperature for 2 h. The mixture was cooled to 35 ± 3 °C and concentrated at this temperature to a hazy, viscous oil. Heptane (926 g) and water (2.5 kg) were added and stirred for 15 min (pH ≈ 8.5). The pH of the mixture was adjusted to pH 10.5 by adding potassium carbonate (20 g) and water (100 g), the aqueous layer was separated, and the organic layer containing the starting material **16** was washed with water (100 g) and saved for recycling. The combined aqueous layers were extracted with heptane (686 g), and the aqueous layer was saturated with sodium chloride (250 g), followed by the addition 2.34 kg of *tert*-butyl methyl ether. The pH of the mixture was adjusted to 5.5 by adding conc. hydrochloric acid (209 g) in water (174 g), and the aqueous layer was separated. The organic layer was washed with water (100 g) and concentrated at 50−71 °C under atmospheric pressure to give a viscous oil. Addition of heptane (997 g) to the oil at 60 °C, and holding at 54 °C or 1 h, then cooling to 9 ± 3 °C over 1.5 h, followed by filtration and drying at 60 °C (15 mbar) gave 299 g of **17** as a white solid (a *trans*/*cis* 36/64 mixture) in 67% yield with 98.4% purity by HPLC; mp: 85−87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43−1.51 (m, 4 H), 2.08−2.10 (m, 4 H), 2.2−2.37 (m, 2 H), 3.67−3.68 (s, 3 H), 4.60−5.20 (br, 1 H).

4-[2-(2-*tert*-Butylcarbamoylpyridin-3-yl)acetyl]cyclohexanecarboxylic Acid (18). To a solution of THF (1.9 L) and diisopropylamine (1.25 mol, 126.5 g) at −40 to −50 °C *n*-hexyllithium in hexane (4.54 equiv, 2.27 mol, 645 g) was added slowly over 30−40 min. 3-Methyl-pyridine-2-carboxylic acid *tert*-butylamide (**15**, 0.5 mol, 96 g) in THF (300 mL) was added while maintaining the temperature at −40 to −50 °C over 30 min. The mixture was stirred for another 30 min and warmed to 0−3 °C. A solution of cyclohexane-1,4-dicarboxylic acid monomethyl ester (**17**, 0.644 mol, 120 g) in THF (300 mL) was added over 7−10 min. During the addition, the internal temperature rose from about 3 °C to about 36 °C (vigorous stirring is necessary as solids tend to separate at this stage). Stirring was continued at this temperature for 1.5 h and then cooled to −5 to −20 °C. Water (1.25 L) was added slowly, and the mixture was warmed to 10−20 °C. The layers were separated, the aqueous layer was extracted with *tert*-butyl methyl ether (500 mL), and the aqueous solution was held at 20 °C for at 8 h. Aqueous hydrochloric acid (5 N HCl, 365 mL) was added at 10 ± 3 °C to adjust the pH to 5.8 ± 0.2. The mixture was stirred at this pH for 30 min or until solid formation was observed. Aqueous 6 N HCl was added slowly to reach a pH of 5.0. The suspension was stirred at 0−5 °C for 1 h, and the solids were collected by filtration. The solids were washed with water (300 mL) and dried at 50 °C (25 mbar) for 14 h to give **18** (139 g, 80% yield) as an off-white powder and about a 95:5 mixture of the *trans*- and *cis*-isomers by NMR (98% by HPLC, *trans* + *cis*); mp ≈ 160 °C; *m*/*z* (M + 1) 347; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12−1.47 (m, 4 H), 1.35 (s, 9 H), 2.03−2.08 (m, 4 H), 2.20−2.25 (m, 1 H), 2.51−2.58 (m, 1 H), 4.28 (s, 2 H), 7.24−7.26 (m, 1 H), 7.40 (d, J = 1.7 Hz, 1 H), 7.87 (b s, 1 H), 8.35 (d, J = 1.8 Hz, 1 H), 10.5 (br s, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 26.32, 26.98, 27.63, 41.40, 44.71, 48.51, 49.79, 124.31, 130.26, 140.42, 145.29, 147.75, 164.02, 180.42, 208.75.

4-(8-Oxo-7,8-dihydro[1,7]naphthyridin-6-yl)cyclohexanecarboxylic Acid (19). A mixture of **18** (0.136 kg, 0.393 mol), ammonium acetate (303 g, 3.93 mol), and acetic acid (275 g) was stirred until it became a thick homogeneous slurry. The mixture was heated to 108 ± 3 °C over 40 min and stirred at this temperature for another 12 h. The mixture was cooled to 50 °C, water (1.5 L) was added, and the mixture was cooled to 10 °C. After 1.5 h, the precipitated solids were collected by filtration, washed with a chilled (10 ± 5 °C) mixture of water (600 mL) and methanol (76 mL), and was dried under vacuum (60 ± 5 °C, 25 mbar) for 14 h to afford **19** 86.3 g (81% yield) as an off-white powder and about a 93:7 mixture of the *trans*- and *cis*-isomers (99% by HPLC); mp > 270 °C; *m*/*z* (M + 1) 273; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34−1.54 (m, 4 H), 1.91−1.99 (m, 4 H), 2.30−2.45 (m, 1 H), 2.50−2.52 (m, 2 H); 6.33 (s, 1 H), 7.60−7.64 (m, 1 H), 8.01−8.04 (m, 1 H), 8.68−8.69 (m, 1 H), 11.47 (br s, 1 H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 25.31, 28.88, 30.56, 42.24, 98.86, 127.09, 134.79, 134.83, 140.92, 148.18, 148.54, 161.63, 176.93.

4-(8-Chloro[1,7]naphthyridin-6-yl)cyclohexanecarboxylic Acid (20). A suspension of **19** (70.9 g, 0.257 mol), toluene (770 mL), and phosphorus oxychloride (247 mL, 2.671 mol) was heated to about 106 °C over 1 h, refluxed gently at 108 ± 3 °C for 6.5 h to give a dark homogeneous mixture. The reaction was cooled to 20 ± 3 °C over 30 min, and poured slowly into cold (about 2 °C) water (3.03 L). The temperature was maintained at 5 ± 3 °C for 1 h. The flask was rinsed once with toluene (350 mL), and the rinse solution was combined with the cooled reaction mixture. The combined mixture was stirred at 5 ± 3 °C for 1.5 h. A solution of sodium hydroxide (413 g) in water (413 mL) was added over 30−60 min while maintaining the temperature at 5 ± 3 °C to adjust the pH of the mixture to 3.1 ± 0.2 (end volume ∼4.7 L). The suspension was warmed to 7 ± 3 °C over 10 min, and the solids were collected by filtration, washed twice with water (2 × 250 mL). The solids were dried (50 °C, 15 mbar) for 18 h to give **20** (71.1 g, 93% yield) as a 81:19 mixture of the *trans*- and *cis*-isomers;: mp 213−214 °C (with decomposition); *m*/*z* (M + 1) 291; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59−1.78 (m, 4 H), 2.05−2.25 (m, 4 H), 2.30−2.40 (m, 1 H), 2.65−2.90 (m, 1 H), 7.35 (s, 1 H), 7.55−7.59 (m, 1 H), 8.07 (d, J = 1.5 Hz, 1 H), 9.02 (d, J = 1.68 Hz, 1 H), 11.02 (br s,1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 25.82, 27.96, 30.54, 41.39, 114.91, 124.78, 132.66, 134.18, 138.15, 150.74, 151.48, 158.24, 180.13.

4-[8-(3-Fluorophenyl)[1,7]naphthyridin-6-yl]cyclohexanecarboxylic Acid (Crude 1). A solution of water (400 mL), potassium carbonate (0.499 mol, 69 g), 4-(8-chloro[1,7]naphthyridin-6-yl)cyclohexanecarboxylic acid (**20**, 0.2 mol, 58.2 g), 3-fluorophenylbronic acid (**7**, 0.24 mol, 33.6 g), and palladium(I) tri-*tert*-butylphosphine bromide dimer (0.809 mmol, 629 mg) was heated to 83 ± 3 °C and maintained at this temperature for 2 h. The reaction was monitored by HPLC. After the completion of the reaction, water (400 mL) was added, and the mixture was extracted with *tert*-butylmethyl ether (3 × 240 mL). Hydrochloric acid (700 mL, 37%) was

added to the aqueous phase at 10−30 °C followed by addition of SMOPEX 110 (7.0 g), and the mixture was heated at 60 °C for 1 h. The hot solution was filtered through a column packed with Celite and activated carbon. The column was washed with a hot solution (40−50 °C) of aqueous HCl (6 N, 422.4 g), and the filtrate was neutralized with aqueous NaOH (727.2 g, 50%) to pH 9 at <20 °C. The mixture was stirred at this temperature for 3 h and then adjusted to a pH of 2 to 3 by adding aqueous HCl (6 N, 37.0 g), and stirring was continued for 3 h at 0−5 °C. The solids were collected by filtration, washed with water (200 mL), and dried at 60 °C for 14 h to give crude **1** (60 g, 88% yield) as a light-yellow solid and as a 82:18 mixture of the *trans*- and *cis*-isomers.

4-[8-(3-Fluorophenyl)[1,7]naphthyridin-6-yl]-*trans*-cyclohexanecarboxylic Acid (1). A mixture of crude **1** (76.0 g), acetonitrile (519 g), and water (53.0 g) was heated to 30−40 °C, and the pH of the mixture was adjusted to 2.0 ± 0.5 by adding sodium hydroxide (2 N, 18 mL) solution. If the volume of sodium hydroxide was less than 18 mL (2 N), more water was added to adjust the ratio of acetonitrile to water to about 7.86 to 1.0 g. Smopex 110 (7.6 g) was added, and the suspension was heated to 70 °C for 4 h. The hot solution was filtered and rinsed with hot acetonitrile (39.0 g). The seeds were added (0.076 g, 0.1% based on **1** by weight) at 35−40 °C (seeds must be added to an acetone/water solution that is above 30 °C), and the suspension was stirred at 18 ± 3 °C for 4 h. The solids were collected, washed with water (110 g), and dried at 50 °C for 14 h until LOD <1% to give 44.1 g (58% yield) of **1** (>99% *trans*-isomer) as a white solid;. mp 168−170 °C; *m*/*z* (M + 1) 351; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68−1.71 (m, 4 H), 2.13−2.24 (m, 4 H), 2.42−2.58 (m, 1 H), 2.85−3.12 (m, 1 H), 7.15−7.20 (m, 1 H), 7.40−7.62 (m, 3 H), 7.85−7.98 (m, 2H), 8.10−8.16 (m, 1 H), 8.99−9.01 (m, 1 H), 11.5 (br s, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.83, 31.82, 42.71, 44.85, 115.82, 118.17, 124.66, 126.95, 129.30, 132.80, 135.08, 140.60, 150.74, 157.78, 157.81, 159.02, 160.87, 164.11, 181.88.

Isomerization of Mother Liquor of 1. The mother liquor residue of **1** (134.1 g, 95.4% chemical purity, 0.363 mol, *trans*/*cis* = 1/1) was dissolved in 200 mL of toluene followed by the addition of phosphorus oxychloride (174 g, 1.12 mol). The suspension was heated to 122 °C over 1 h, and maintained at this temperature for 1.5 h. ^{1}H NMR was used to monitor the reaction. The reaction mixture was cooled to 45 °C, and toluene (350 mL) was added to obtain a homogeneous solution. Water (1000 mL) was slowly added over 30 min, and the mixture was stirred at this temperature for another 30 min. The pH of the mixture was adjusted to 5.5 by adding 50% sodium hydroxide solution (395 g) at 40 °C. The reaction mixture was cooled to 22 °C and stirred for 4 h. The solids were filtered, washed with toluene (50 mL) and water (300 mL), and dried in an oven at 70−75 °C under vacuum for 16 h to give 116 g of **1** in 91% yield with a *trans*/*cis* ratio 85 to 15. This *trans*-enriched mixture was used for isolating pure **1** as described in the earlier experiment.

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