ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Full Paper

First Kilogram-Scale Application of the Lanthanum Catalyzed Asymmetric Amination to Synthesis of the Chiral Succinimide Derivative, A Key Intermediate for the Preparation of AS-3201

Minoru Toshima, Shoji Watanabe, Katsuya Uchiyama, Tsuyoshi Takasaki, Nandkumar N Bhogle, Hang Zhao, Mike Filios, Kazuhiko Takahashi, John R Snoonian, and Kostas Saranteas

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.6b00053 • Publication Date (Web): 17 May 2016

ACS Publications

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

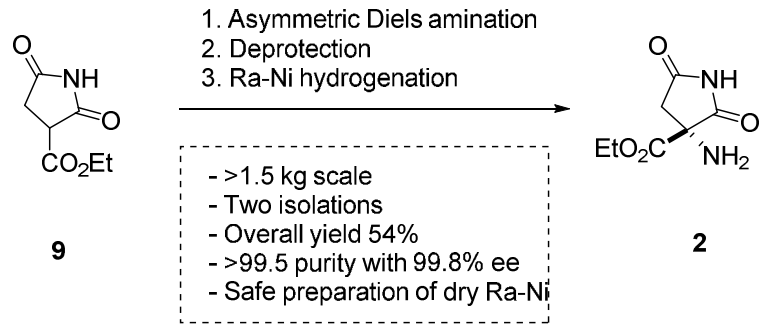
First Kilogram-Scale Application of the Lanthanum Catalyzed Asymmetric Amination to Synthesis of the Chiral Succinimide Derivative, A Key Intermediate for the Preparation of AS-3201

Minoru Toshima[†], *Shoji Watanabe*[†], *Katsuya Uchiyama*[†], *Tsuyoshi Takasaki*[†], *Nandkumar N. Bhogle*[*#], *Hang Zhao*[#], *Mike Filios*[#], *Kazuhiko Takahashi*[†], *John R. Snoonian*[#], *and Kostas Saranteas*[#]

[†]Process Chemistry Research and Development Laboratories, Sumitomo Dainippon Pharma Co., Ltd., 3-1-98 Kasugade-naka, Konohana-ku, Osaka 554-0022, Japan.

[#]Chemical and Pharmaceutical Sciences, Sunovion Pharmaceuticals, Marlborough, Massachusetts 01752, United States

Table of Contents Graphic

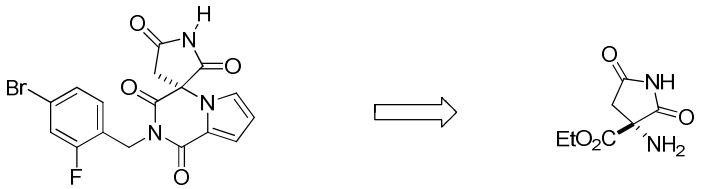


ABSTRACT. The process development of ethyl-(*R*)-3-amino-2,5-dioxopyrrolidine-3-carboxylate (2), the chiral intermediate for the manufacture of AS-3201 (1), is described. A practical and scalable Shibasaki asymmetric amination that generates the chiral quaternary center was developed and demonstrated on kilogram scale. A safe, convenient and large scale hydrogenation of the hydrazine intermediate was also developed.

INTRODUCTION

AS-3201 (1) is an aldose reductase inhibitor (ARI) that acts by reducing sorbitol accumulation in the cells.[1] AS-3201 exhibits better efficacy and low toxicity compared to most other ARIs and is currently in the Phase III clinical trials in Japan. AS-3201 is a highly functionalized heterocycle with a spirocyclic tetrasubstituted stereocenter and two imide moieties. The main synthetic challenge is the construction of the chiral intermediate 2 (Figure 1).

Figure 1. Structures of AS-3201 and Chiral Intermediate 2

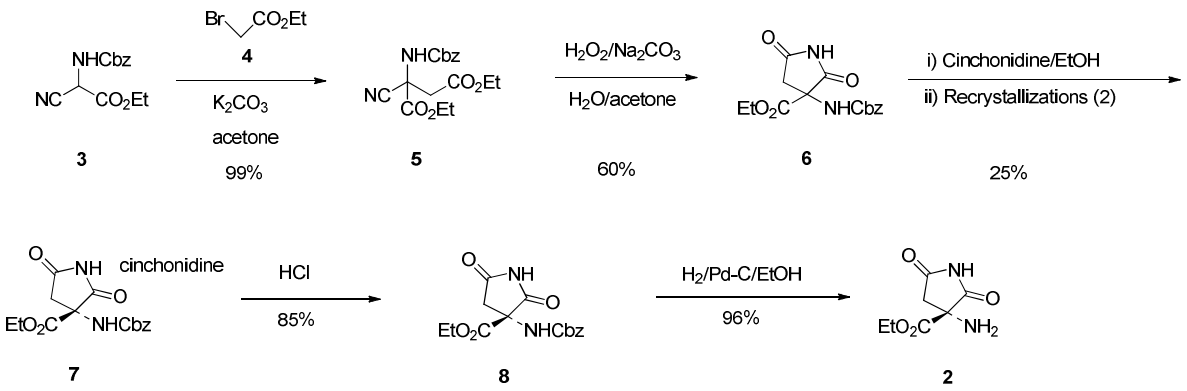


1
AS-3201

2

Currently, **2** is produced by the route shown in the Scheme 1.[1a] Alkylation of ethyl [(benzyloxycarbonyl)amino]cyanoacetate **3** with ethyl bromoacetate **4** furnished **5**. Hydrolysis of **5** using hydrogen peroxide and sodium carbonate followed by cyclization produced succinimide **6**. Resolution of **6** was carried out by forming cinchonidium salt **7**. Crude salt **7** was crystallized twice from ethanol to afford the diastereomerically enriched cinchonidium salt. This salt after treatment with aqueous hydrochloric acid yielded **8** with >99.5% ee. Carbobezyloxy group of the compound **8** was removed by hydrogenolysis with palladium on carbon to give **2**. The overall isolated yield of **2** is <12% due to the low yielding hydrolysis step, resolution step and two recrystallizations of the diastereomeric salt. Additionally, difficulty in recycling the used cinchonidine and limited world supply of cinchonidine make this route undesirable for the commercial production of 2.

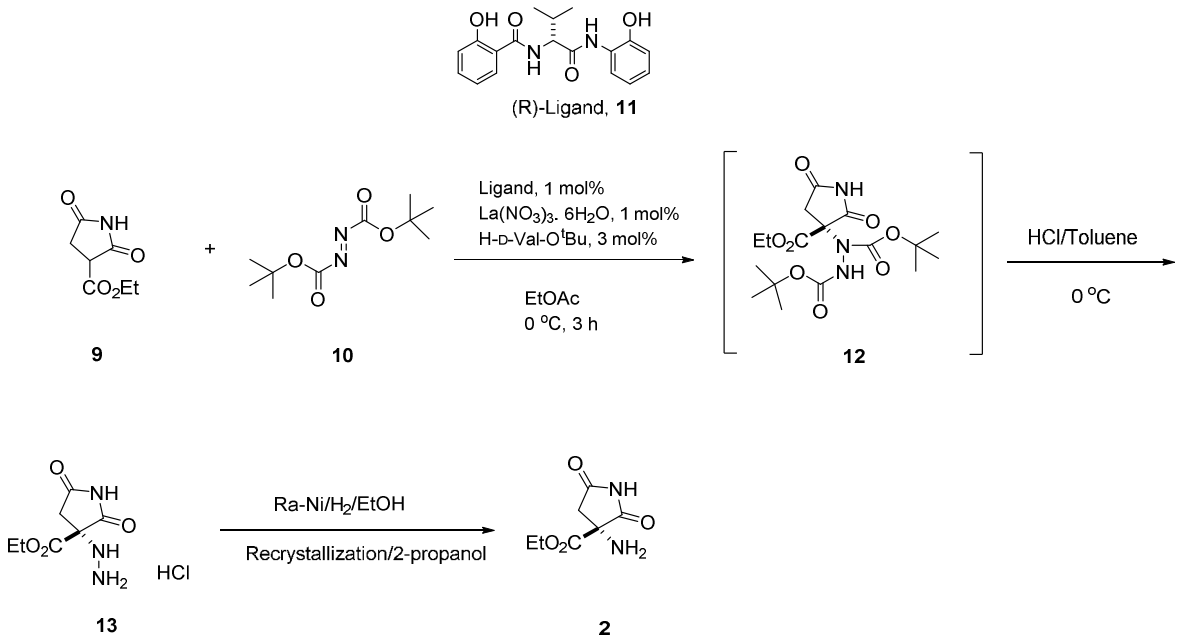
Scheme 1. Current Supply Route for 2



RESULTS AND DISCUSSION

Due to the limitations associated with the current route, we were interested in alternative routes to key intermediate **2** that would provide **2** in higher efficiency and security of supply for larger scale manufacture. The Shibasaki group has devised an elegant three-step sequence for the asymmetric synthesis of **2** and further demonstrated it on multigram scale (Scheme 2)[2]. Imide **9** was subjected to the asymmetric Diels amination to produce **12** in high conversion and chiral purity. Deprotection of **12** furnished **13** in 96% isolated yield and 91% ee (two steps). Hydrogenation of **13** to cleave the nitrogen-nitrogen bond with Raney Ni (Ra-Ni) furnished crude **2** that was further crystallized from 2-propanol to afford **2** in 63% overall yield with the desired chemical and enantiomericpurities.

Scheme 2. Shibasaki Asymmetric Synthesis of 2

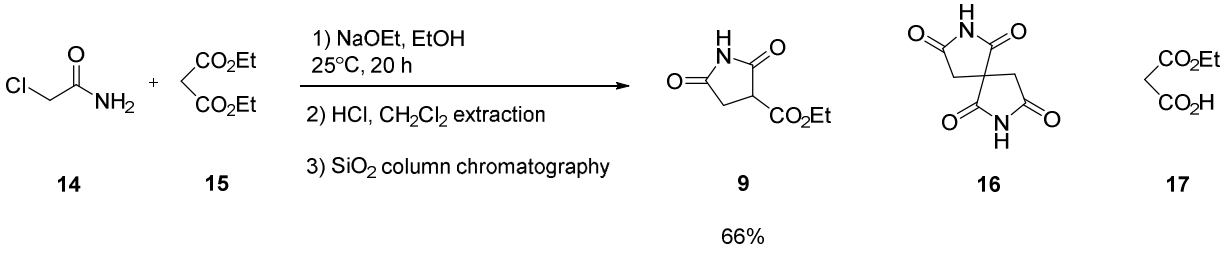


We were encouraged by the results for the Shibasaki synthesis of **2**. However, the conditions described in the papers were found to present challenges for large scale manufacture. First, the

deprotection reaction with HCl gas bubbling into a toluene solution of **12** followed by two isolations of hydrazine **13** after toluene evaporation and trichuration with three different solvents of makes this step somewhat lengthy and impractical. Second, Ra-Ni hydrogenation of the nitrogen-nitrogen bond for the conversion of **13** to **2** was carried with large quantities of pyrophoric Ra-Ni (substrate/Ra-Ni [dry] 2:1). All steps were further optimized to be able to produce multi-kilogram quantities of **2**. The details are described below.

Optimization of imide 9 synthesis. Earlier batches of imide **9** were prepared by the following route depicted in the Scheme 3.[3] Low yield, use of dichloromethane for extraction and silica gel chromatography for purification of the crude product **9** were the issues associated with this route.

Scheme 3. Original Route for Imide 9



Closer examination of this synthetic route revealed formation of two byproducts **16** (21%) and **17** (6%) due to over alkylation and partial hydrolysis of diethylmalonate respectively. Further optimization with varying amounts of diethylmalonate and sodium ethoxide was conducted (Table 1). Use of >2.0 equivalents of sodium ethoxide resulted in formation of byproducts **16** and **17** in higher content (entries 2 and 3). A screen of diethylmalonate equivalents with 2.0

equivalents of sodium ethoxide revealed that the reaction proceeds with improved conversion and selectivity with higher equivalents of diethylmalonate (entry 7). Using <2.0 equivalents of sodium ethoxide with 5.0 equivalents of diethylmalonate resulted in lower conversion (entry 8). The optimal results were obtained when 2.0 equivalent of sodium ethoxide and 5.0 equivalents of diethylmalonate were used (entry 7). Higher conversion (>95%) and good selectivity were observed (>85%)

Table 1. Optimization of Imide 9 Synthesis

Entry	NaOEt (eq.)	Diethylmalonate (eq.)	14(%)[a]	9(%)[a]	16(%)[a]	17(%)[a]
1	2.0	2.0	6.6	63.8	21.3	6.3
2	3.0	2.0	2.4	29.4	55.4	9.8
3	4.0	2.0	1.7	14.4	63.8	15.6
4	2.0	1.1	20.3	63.4	5.8	4.3
5	2.0	1.5	11.9	71.3	10.0	5.0
6	2.0	3.0	6.3	79.8	9.8	2.6
7	2.0	5.0	4.9	86.4	4.9	2.9
8	1.1	5.0	19.0	73.9	3.0	2.4

a. HPLC A%

The sodium salt of **9** was isolated via filtration and further treated with 1M phosphate buffer. Crude **9** was extracted with ethyl acetate, and the resulting extract was concentrated and then crystallized from 2-propanol/-*n*-heptane mixture to furnish imide **9** with good purity. This procedure was scaled up to produce several 40 g batches of **9** with good yield (74%) and high purity (98.9%).

The optimized procedure was further employed for the kilo laboratory scale-up. The yield and quality data are depicted in the Table 2. The result of kilogram scale almost reproduced a result of laboratory scale. The reaction filtration and wet cake washing of sodium salt of **9** was slow enough that further attention is prudent to ensure success at larger scale.

Table 2. Data for kilolab run

Input of chloroacetamide (kg)	8.0
Output of **9** (kg)	10.7
Isolated Yield (%)	73.0
Purity by HPLC (A%)	97.88

Optimization of Asymmetric Diels Amination. Effect of additives. Effect of additives on the rate and selectivity of the reaction was explored. Water was proved to be detrimental. Addition of 10 mol% of water to the reaction indicated erosion in the stereochemical purity of the product and 30 mol% water in the reaction diminished the rate and selectivity significantly (Table 3,

entry 2). While ethanol and triethylorthoformate did not improve the ee there was also no loss of ee either (entries 3 and 4).

Table 3. Asymmetric Diels amination- Effect of additives

Entry	Additive	Quantity, mol%	Conversion, %[a]	12, er[a]
1	H_2O	10	>99.5	95.2:4.8
2	H_2O	30	62.0	61:39
3	EtOH	6	>99.5	96:4
4	Triethylorthoformate	10	>99.5	96.2:3.8

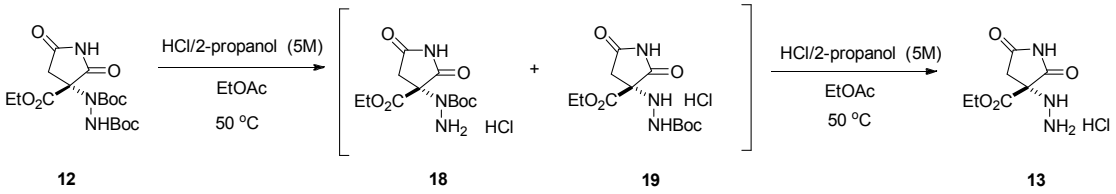
a. HPLC A%

Catalyst preparation, di-t-butylazodicarboxylate addition and work-up of the reaction. The catalyst preparation involves addition of ligand **11** and H-D-valine-O^{t}Bu successively to a solution of $(LaNO_3)_3.6H_2O$ in ethyl acetate at 20-25 ^oC. The imide **9** is then added at 20-25 ^oC and the resultant solution is then cooled to 0 ^oC and aged for 1h. Di-*t*-butylazodicarboxylate is then added in portions at 0 ^oC for the formation of the product **12**. After completion the reaction was quenched at 0 ^oC with the addition of 0.6M aqueous HCl and worked-up. Erosion of the selectivity of the Diels amination was observed when reaction was carried out at 20-25 ^oC (er 93.4:6.6 vs 96:4)). Catalyst preparation, addition of di-*t*-butylazodicarboxylate and aqueous HCl work-up exhibited very mild exotherms (rise of 5-7 ^oC).

Optimization of deprotection step. Evaporation of the amination reaction stream to dryness, HCl gas bubbling for deprotection, two purification steps, low volumetric productivity and use of four solvents were the major issues with this procedure. Thus, it was necessary to streamline and telescope the deprotection step into the prior amination reaction for the development of a practical process.

Commercially available 5 M HCl in 2-propanol was employed in the deprotection step (Scheme 4). Process stream generated from 1g scale Diels amination reaction was subjected to deprotection with 5M HCl (8 eq.) at 50 ^{o}C. The reaction proceeds through formation of two mono Boc intermediates **18** and **19** and was found to be complete in about 10 h. The reaction slurry was filtered to afford the hydrazine HCl salt **13** as white solid in 86% yield (2 steps) and >98% purity.

Scheme 4. Deprotection of 12



Prior to deprotection, the organic phase derived from Diels amination is washed with water and 5 wt% sodium chloride solution successively, and is then dried via azeotropic distillation under reduced pressure to achieve well below the target maximum of 0.50% water. HCl equivalence and reaction completion data from significant scale laboratory experimentation are summarized here in Table 3. With 4.5 eq. of HCl the reaction is essentially complete in about 13 h at 50^{o}C.

Fortunately, most of the impurities are soluble in the reaction solvents. The high isolated yields and purities of hydrazine **13** were observed (Table 4).

Table 4. Deprotection of 12 at 50°C[a]

Entry	Imide 9	Eq. of HCl	Reaction Time (h)	Isolated yield of 13 (%)	Purity of isolated 13 (%)[b,c]
1	30 g	8.8	9	94	99.0
2	180 g	4.3	10	95	99.1
3	200 g	4.5	13	94	99.0

a. After completion of Diels amination reaction work-up the process stream was subjected to azeotropic distillation and then exposed to HCl/IPA. b. HPLC A%. c. remainder is only one impurity-mono BOC intermediate.

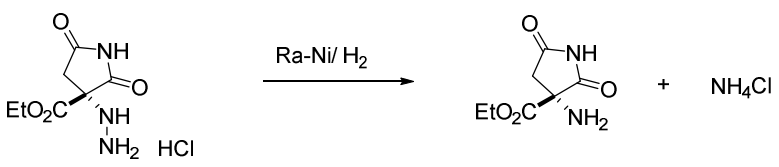
Both the asymmetric Diels amination and deprotection reactions worked very well at kilogram scale. Robustness of the process was evident by good performance and reproducibility. Significant loss of volatile hydrogen chloride which drives deprotection was observed and is attributed to evolution of 2 equivalents each of non-condensable reaction byproducts carbon dioxide and isobutene. The impact of hydrogen chloride loss on the reaction profile was mitigated by a modified addition of HCl/2-propanol solution such that some acid is added only after partial conversion (and non-condensable gas evolution) is achieved. As indicated in the Table 5 both the kilolab runs produced **13** consistently in high yield and good quality with complete removal of Lanthanum.

Table 5. Data for kilolab runs

Item	Run 1	Run 2
Input of imide **9** (kg)	2.0	2.0
Output of **13** (kg)	2.66	2.67
Isolated yield (%)	95.8	96.2
Purity by HPLC (A%)	99.13	98.95
Chiral purity (er, HPLC A%)	96.2:3.8	96:4
Lanthanum, ppm	<0.1	<0.1

Hydrogenation of hydrazine-Conversion of 13 to 2. The Shibasaki group utilized Ra-Ni catalyst for the hydrogenation step (Scheme 5).[2a] This procedure was carried out at 12 g scale of **13** with 6 g of Ra-Ni(dry basis) and at a hydrogen pressure of 50 psi. The crude product isolated after work-up was subjected to recrystallization with 2-propanol to afford **2** in 66% yield with the desired purity. Two areas of focus for optimization for this step were to first, lower catalyst loading for the hydrogenation and second, integrate the work-up and isolation to simplify the isolation procedure.

Scheme 5. Hydrogenation of hydrazine 13



13 **2**

Optimization of Ra-Ni catalyzed hydrogenation. The effect of variations in Ra-Ni quantity, reaction temperature and water content were explored for the rate and conversion of the reaction. Higher catalyst loading resulted in better reaction profile and higher conversions (Table 6, entries 1, 2 and 3). Higher temperature was better for reaction conversions (entries 4 and 6). Concentration of the reaction did not have much impact on the conversion (entries 4 and 5; 6 and 7; 8 and 9). Larger catalyst loadings at moderate temperature, the conditions reported by the Shibasaki group, were found to perform better than other conditions (entry 1).

Table 6. Hydrogenation at different catalyst loadings, temperature and concentration[a]

Entry	13	T ^{o}C	Ratio of 13/Raney Ni (dry basis)[b]	2 (%)[c]	13 (%)[c]
1	0.290 g	50	2/1	97.2	0

2	0.120 g	50	4/1	84.7	6.3
3	0.400 g	50	6/1	73.3	20.6
4	0.154 g	70	4/1	91.2	0.3
5	0.466 g	70	4/1	90.2	0.1
6	0.195 g	70	6/1	87.8	0.3
7	0.546 g	70	6/1	88.5	0.3
8	0.256 g	70	8/1	79.5	0.5
9	0.556 g	70	8/1	82.6	0.3
10	0.280 g	70	10/1	77.0	1.1

a. The substrate was dissolved in 5 mL of EtOH and hydrogenated at 115 psi for 5h. b. EtOH wash performed to remove water from the catalyst. c. HPLC A%

Effect of water. Presence of water in the reaction was found to be detrimental. Higher content of water produced more impurities, thus, affecting the conversion to **2** (Figure 2). Since Ra-Ni is a

50% water wet slurry a good wash procedure is required to remove most of the water from the catalyst.

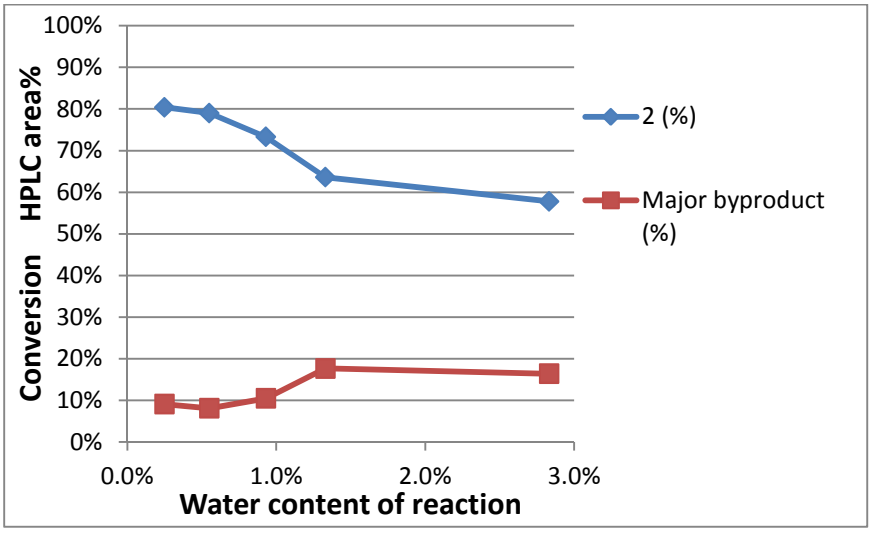


Figure 2: Effect of water on hydrogenation of **13** to **2**

Scale up of hydrogenation. Larger catalyst loadings [(2:1, substrate:Ra-Ni (dry basis)] and moderate temperature of 50 ^{o}C were used for further scale up of hydrogenation at 90 psi. For practical purposes water content of the hydrogenation mixture was set at not more than 1.0% at the ethanol wash step. Further dilution of the reaction mixture with absolute ethanol was expected to bring the water content of the reaction well below 1%. After maximum amount of liquid was removed from the settled Ra-Nivia a dip tube under positive nitrogen pressure absolute ethanol was added to the Ra-Ni and the slurry was stirred for 10-15 minutes and allowed to settle. The supernatant ethanol was removed repeating the above procedure. After performing the ethanol wash procedure three more times the water content of the Ra-Ni slurry in ethanol was consistently found well below 1%.

Hydrogenation scale-up experiments were conducted on 25 g scale of **13**. The reactions were stirred under hydrogen at about 25°C for 30 minutes and then warmed to 50°C and continued for about 4.5 h. Good conversion with very little side reactions were observed (Table 7). After completion the reaction was passed through Celite and mass balance of **2** in the reaction solution was determined by wt/wt% HPLC assay.

Table 7. Scale up of Hydrogenation[a]

Entry	Raney Ni (dry basis)	H_2O wt%[b]	T°C	Time	2 (%)[c]	13 (%)[c]	Mass balance of 2 (Wt %)[c]
1	12.5 g	0.94	25	0.5 h			
			50	4.5 h	96.8	0	90
2	12.5 g	0.57	25	0.5 h			
			50	4.5 h	96.7	0.5	91

a. 25 g of **13** was added to the catalyst slurry in 300 mL of EtOH and hydrogenated at 90 psi. b. Water Wt% determined after catalyst wash with EtOH. c. HPLC A%

Isolation of 2. Major impurities present in the hydrogenation process stream are the undesired enantiomer of **2** (~4%) and NH_4Cl (1 equivalent). The undesired enantiomer is formed in the asymmetric Diels amination reaction in about 4% and then it is carried through deprotection and hydrogenation steps finally converting to the undesired enantiomer of **2**. Recrystallization of

crude **2** from 2-propanol removes the undesired enantiomer efficiently but it does not remove residual NH_4Cl completely. Usually about 1% NH_4Cl is detected in the final isolated sample of **2**.

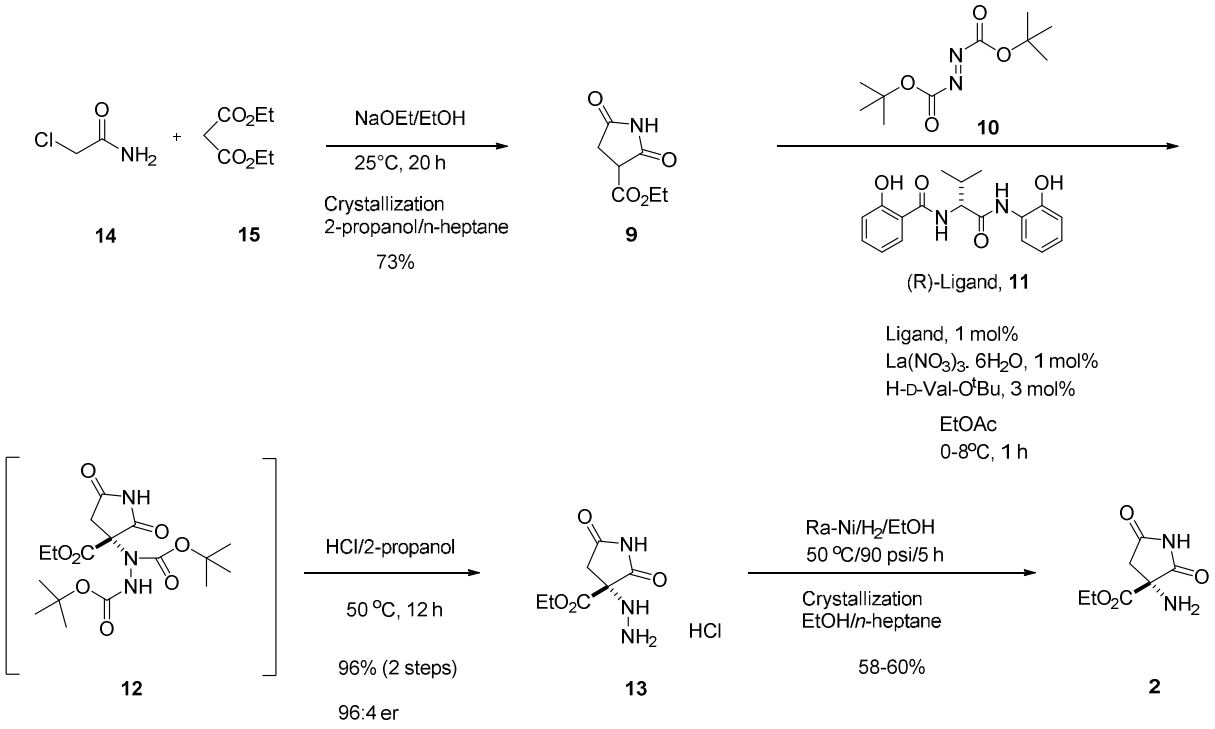
The process stream obtained after 25 g scale hydrogenation of **13** was worked-up, concentrated and subjected to a crystallization screen. The slurry of substrate in ethyl alcohol was heated up to 60 ^oC, then *n*-heptane was added and the mixture was heated up to 70 ^oC. After 30 minutes at 70 ^oC, the insoluble solid (NH_4Cl) was filtered off, washed with corresponding hot solvent mixture. The filtrate was cooled linearly to room temperature. The solid was filtered, washed, dried to give the final product. **2** was obtained in 56-59% yield with >99.5% purity. Further, hydrogenation was performed on 70 g scale and the crystallization was conducted with ethyl alcohol/ *n*-heptane (1:1). The product was isolated with good yield (65%) and high purity (chemical and chiral purities>99.5% with <0.1% NH_4Cl)

Three runs of hydrogenation of **13** were conducted in the kilo laboratory. Safe Ra-Ni handling and water removal procedures developed in the laboratory were demonstrated successfully in these runs. The integrated hydrogenation and crystallization steps worked smoothly in the kilolab. The undesired enantiomer of **2** was rejected with high efficiency during the crystallization. The yield and quality data for the kilolab runs are depicted in the Table 8.

Table 8. Data for kiloab runs

Item	**Run 1**	**Run 2**	**Run 3**
Input of **13** (kg)	1.86	1.55	1.64
Output of **2** (kg)	0.80	0.67	0.73
Isolated yield (%)	55.2	55.8	56.8
Purity by HPLC (A%)	99.94	100.00	99.84
Chiral purity (er, HPLC A%)	99.93:0.07	99.93:0.07	99.89:0.11
Ammonium chloride, wt%	<0.1	<0.1	<0.1

Scheme 6. Improved procedure for synthesis of 2



CONCLUSIONS

In summary, practical procedures for synthesis of imide **9**, Shibasaki asymmetric amination, N-Boc deprotection and hydrogenation of the hydrazine **13** were developed (Scheme 6). The amination step was successfully telescoped into the deprotection step thus obviating the need for isolation of the amination product **12**. Hydrazine **13** was isolated with high yield (96%) and high purity (chem. purity 99%, er 96:4). Safe procedures for handling large quantities of Ra-Ni were introduced. Hydrogenation followed by robust crystallization that rejects impurities with high efficiency was also developed. The target compound **2** was isolated with overall yield of 54% yield (3 steps) with high chemical (>99.5%) and chiral purities (>99.7%).

EXPERIMENTAL SECTION

All reactions were carried out under a nitrogen atmosphere. All solvents and reagents were purchased from commercial sources and were used without further purification. Chiral ligand **11** was prepared according to literature procedure.[2a] H-D-valine-O^{t}Bu .HCl was purchased from Watanabe Chemical Company, Hiroshima, Japan. It was neutralized with aqueous sodium bicarbonate and the free base was isolated after extraction with dichloromethane followed by evaporation of the solvent. ^{1}H and ^{13}C NMR chemical shifts were reported relative to residual proton solvent peaks. All yields are corrected for purity and determined by reverse-phase HPLC using purified standards. Chiral purities of **13** and **2** were determined by analysis of N-Boc derivative of **13** and N-Cbz derivative of **2** respectively.

HPLC method for **9** (reaction/purity): YMC ODS-A A-303, 5 μm (4.6 mmφ × 250 mm). Solvent A: phosphate buffer [(KH_2PO_4 (2.94 g) and K_2HPO_4 (2.94 g) were dissolved in H_2O (800 mL) and this solution was diluted fivefold]. Solvent B: acetonitrile. Gradient program; solvent A / solvent B hold 70:30 for 10 min, 70:30 to 10:90 over 5 min, 10:90 to 70:30 over 0 min hold 15 min, flow 0.5 mL/min, at 30 °C, detection at 210 nm, RT 8.3 min.

HPLC method for **12** (reaction/purity) and **13**. (reaction/purity): YMC ODS-A A-303, 5 μm (4.6 mmφ × 250 mm). Solvent A: phosphate buffer [(KH_2PO_4 (2.94 g) and K_2HPO_4 (2.94 g) were dissolved in H_2O (800 mL) and this solution was diluted fivefold]. Solvent B: acetonitrile. solvent A / solvent B 50:50, 30 min, flow 0.5 mL/min, at 30 °C, detection at 210 nm, RT 11.1 min (**12**), RT 5.1 min (**13**).

Chiral HPLC method for asymmetric Diels amination reaction. Daicel Chiralpak AD-H, methanol/hexane 5:95, flow 1.0 mL/min, at 40 °C, detection at 210 nm, RT 9.5 min (major) and

12.5 min (minor).

Chiral HPLC method for N-Boc derivative of **13**. Daicel Chiralcel OJ-H 2-propanol/hexane 1/9, flow 1.0 mL/min, at 40 °C, detection at 254 nm, RT 9.3 min (minor) and 12.1 min (major).

HPLC method for **2** (reaction): YMC ODS-A A-303, 5 μm (4.6 mmφ × 250 mm). Solvent A: phosphate buffer [(KH_2PO_4 (2.94 g) and K_2HPO_4 (2.94 g) were dissolved in H_2O (800 mL) and this solution was diluted fivefold]. Solvent B: acetonitrile. Gradient program; solvent A / solvent B 90 : 10 to 20 : 80 over 20 min, 20 : 80 to 90 : 10 over 0 min, hold 10 min, flow 0.5 mL/min, at 30 °C, detection at 210 nm, RT 9.8 min.

HPLC method for **2** (purity): SUMIPAX ODS D-210SLP, 3 μm (3.0 mmφ × 150 mm). Solvent A: phosphate buffer [KH_2PO_4 (0.74 g) and K_2HPO_4 (0.74 g) were dissolved in H_2O (1000 mL)]. Solvent B: acetonitrile. Gradient program; solvent A / solvent B 100 : 0 to 90 : 10 over 10 min, 90 : 10 to 40 : 60 over 20 min, 40 : 60 to 100 : 0 over 0 min, hold 15 min, flow 0.5 mL/min, at 25 °C, detection at 220 nm, RT 9.1 min.

Chiral HPLC method for N-Cbz derivative of **2**. Daicel Chiralpak AS-H, ethanol/hexane 1/9, flow 2.0 mL/min, at 40 °C, detection at 254 nm, RT 11.0 min (major) and 16.8 min (minor).

3-Ethoxycarbonylpyrrolidin-2,5-dione (9). Chloroacetamide (8.00 kg, 85.6 mol), diethyl malonate (68.5 kg, 428 mol, 5.00 eq.) and ethanol (100 kg) were charged at room temperature. 20% sodium ethoxide in EtOH (58.2 kg, 171 mol, 2.00 eq.) was added over 20 minutes and the mixture was stirred at 25°C for 23 h (HPLC condition A). The reaction slurry was filtered and the residue was washed with ethyl acetate (40.0 kg). The filtered residue was collected as sodium salt of **9** and ethyl acetate (80.0 kg) was added. The phosphate buffer (1 M, pH 6) was added and

adjusted pH to 8.2. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (80 kg) two times. The combined organic layer was concentrated under reduced pressure below 40°C to a weight of 22.2 kg 2-propanol (80.1 kg) was added to the concentrated residue and the mixture was concentrated under reduced pressure below 40°C to a weight of 22.2 kg. The concentrated residue was filtered and washed with 2-propanol to a weight of 29.3 kg *n*-heptane (7.32 kg) was added to the concentrated oil at room temperature and seed crystals of **9** (8.02 g) were added at 25°C. The mixture was stirred for 25°C and *n*-heptane (36.6 kg) was added over 1 h. The mixture was cooled to -10°C over 1 h and stirred for 1 h. The white slurry was filtered and the wet cake was washed with 2-propanol/*n*-heptane (1.78 kg/14.2 kg) at -10°C. The wet cake was dried under reduced pressure under 40°C for 21 h to give **9** as off-white solid in 73% yield (10.7 kg, 97.9% HPLC purity). ^{1}H NMR (400MHz, $CDCl_3$): 9.06 (brs, 1H), 4.28 (q, J = 7.2 Hz, 2H), 3.85 (dd, J = 4.8, 9.6 Hz, 1H), 3.15 (dd, J = 4.8, 18.4 Hz, 1H), 2.95 (dd, J = 9.6, 18.4 Hz, 1H), 1.32 (t, J = 7.2 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 172.8, 167.3, 62.8, 47.9, 33.4, 14.1. The NMR data are in agreement with the previously reported data.[3]

Preparation of ethyl-(*R*)-3-hydrazinyl-2,5-dioxopyrrolidine-3-carboxylate hydrochloride (13). To a stirred solution of $LaNO_3.6H_2O$ (51 g, 0.12 mol) in ethyl acetate (3.32 L) ligand **11** (40 g, 0.12 mol) and H-D-valine-O^{t}Bu (61.2 g, 0.36 mol were added successively. The solution was stirred for about 15 minutes until a thin white slurry was formed. Ethyl acetate (22.2 L) was added to get a clear solution. Imide **9** (2.0 kg, 11.8 mol) was added and the resulting solution was cooled to about 0 °C and aged for 1 h. Di-t-butylazodicarboxylate (3.24 kg, 14.1mol) was added maintaining the reaction temperature below 5 °C. The addition was complete in about 15 minutes. The reaction was stirred at 0-5 °C until <0.5% imide **9** remained in the reaction as judged by HPLC method (~ 1 h). It was then quenched with addition of 0.6M aqueous HCl (8.0

kg). After the separation of the lower aqueous phase the reaction stream was washed successively with water (1x8.0 kg) and 5% aqueous NaCl (2x8.0 kg) and subjected to azeotropic distillation under vacuum maintaining the batch temperature below 50 ^{o}C. The distillation was continued until the water content of the process stream was <0.5%. The process stream was then cooled to about 22 ^{o}C and polish filtered to a clean reactor. The batch was warmed to about 50 ^{o}C and 5M HCl in 2-propanol (8.0 kg, 60 mol) was added over a period of 1h. Caution! vigorous gas evolution occurs due to byproducts carbon dioxide and isobutene. Gas evolution can be controlled by reducing addition rate or pausing addition to allow vigorous evolution to subside. After the addition reaction was further stirred at 50±2 ^{o}C until <0.05% **13** and <0.75% of mono-Boc intermediate **19** remained in the reaction as judged by HPLC method (~ 12h). The reaction slurry was cooled linearly to 20±2 ^{o}C over a period of 1 h and filtered. The cake was washed with successively with ethyl acetate (6 L)/2-propanol (1.9 L) mixture, 2-propanol (7.9L) and ethyl acetate (8L) and dried in vacuo at 40±2 ^{o}C until constant weight to give 2.66 kg (95.8% yield) of **13** as white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 4.31-4.37 (m, 2H), 3.20 (d, J = 18.4 Hz, 1H), 2.87 (d, J = 18.4 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.1, 175.2, 170.0, 69.0, 65.3, 41.5, 14.8. The NMR data are in agreement with the previously reported data.[2a, b]

Preparation of (R)-ethyl 3-amino-2,5-dioxopyrrolidine-3-carboxylate (2). 50% wet Raney Ni (1.515 kg) was charged to a reactor and allowed to settle. Degassed ethanol (12 kg) in a charge pot was transferred to the reactor. The system was purged with nitrogen and the catalyst slurry was stirred for 10 minutes and allowed to settle. The supernatant ethanol was removed with the aid of a dip tube utilizing positive pressure of nitrogen. Another catalyst wash with degassed ethanol (8 kg) was performed. The analysis of water content of the ethanol washes indicated that

most of the water has been removed from the catalyst and ~1% water remains with the last ethanol wash. A slurry of **13** (1.55 kg, 6.52 mol) in ethanol (11.33 kg) was charged to the reactor and the reactor was purged with nitrogen. The reaction slurry was warmed to 25±5 ^{o}C with agitation and the reactor was pressurized with hydrogen to 90 psi. Hydrogenation was continued for about 0.5 h with monitoring of hydrogen gas uptake. Hydrogenation was further continued at 40±5 ^{o}C for about 1.5 h and at 50±5 ^{o}C for about 4h. The catalyst and residual ammonium chloride was filtered at 50±5 ^{o}C and the process stream was further concentrated to about 6.8L via vacuum distillation maintaining the batch temperature below 60 ^{o}C. *n*-heptane (4.2 kg) was charged to the reactor and the resulting slurry was heated to 70±2 ^{o}C. Reaction mixture was filtered at 70±2 ^{o}C to remove residual ammonium chloride and cooled to about 47 ^{o}C and aged for about 15 minutes. The resultant slurry was further cooled linearly to 20±2 ^{o}C over a period of 1h, aged for about 0.5 h and filtered. The cake was washed twice with ethanol (0.93 kg)/n-heptane (0.77 kg) mixture and dried in vacuo at 40±2 ^{o}C until constant weight to give 0.674 kg (55.6% yield) of **2** as a white to off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 4.22 (q, J = 7.0 Hz, 2H), 3.20 (d, J = 18.0 Hz, 1H), 2.67 (d, J = 18.0 Hz, 1H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 179.3, 177.8, 172.0, 65.9, 64.3, 43.9, 14.8. The NMR data are in agreement with the previously reported data.[2a]

AUTHOR INFORMATION

Corresponding Author

Telephone: +1-508-357-7581. Fax: +1-508-357-7808. E-mail: Nandkumar.bhogle@sunovion.com

Notes

The authors declare no competing interest.

ACKNOWLEDGMENT

We thank Mr. Takayuki Miyake for large scale manufacturing and Dr. Robert Bujalski for analytical support.

REFERENCES

(1) (a) Negoro, T.; Murata, M.; Ueda, S.; Fujitani, B.; Ono, Y.; Kuromiya, A.; Komiya, M.; Suzuki, K.; Matsumoto, J.-I. *J. Med. Chem.* **1998** *41*, 4118. (b) Kurono, M.; Fujiwara, I.; Yoshida, K. *Biochemistry* **2001**, *40*, 8216. (c) Bril, V.; Buchanan, R. A. *Diabetes Care* **2004**, *27*, 2369. (d) Kurono, M.; Fujii, A.; Murata, M.; Fujitani, B.; Negoro, T. *Biochem. Pharmacol.* **2006**, *71*, 338. (e) Giannoukakis, N. *Curr. Opin. Investig. Drugs* **2006**, *7*, 916. (f) Matsumoto, T.; Ono, Y.; Kurono, M.; Kuromiya, A.; Nakamura, K.; Bril, V. *J. Pharmacol. Sci.* **2008**, *107*, 231. (g) Bril, V.; Buchanan, R. A. *Diabetes Care* **2006**, *29*, 68–72. (h)Vera Bril, Toshiyuki Hirose, Sasagu Tomioka, Robert Buchanan, Diabetes Care. 2009 July; 32(7): 1256–1260

(2) (a) Mashiko, T.; Hara, K.; Tanaka, D.; Fujiwara, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 11342. (b) Mashiko, T.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2725. (c) Mashiko, T.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 14990.

(3) (a)Tanaka, D. PCT Int Appl. WO2008 / 004415 A1, 2008. (b) Tanaka, D. US Patent Appl. US20090253917A1