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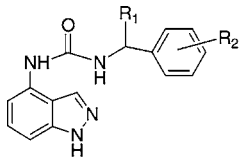
Development of a Large Scale Asymmetric Synthesis of Vanilloid Receptor (TRPV1) Antagonist ABT-102

Kirill Lukin,* Margaret C. Hsu, Gilles Chambournier,† Brian Kotecki, C. J. Venkatramani, and M. Robert Leanna
GPRD Process Chemistry, Abbott Laboratories, R-13, North Chicago, Illinois 60064-6291, U.S.A.

Abstract:
A highly efficient asymmetric synthesis of TRPV1 antagonist ABT-102 was developed and successfully demonstrated on a multi-kilogram scale. This process incorporates a new asymmetric synthesis of (*R*)-*tert*-butylaminoindan, which is based on a chiral auxiliary induced diastereoselective reduction of its iminoindan precursor.

Introduction

Vanilloid receptor TRPV1 has been identified as a promising target for the development of innovative medicines designed for treatment of chronic pain.[1] The available experimental data suggest that compounds targeting the TRPV1 receptor could provide pain relief without causing such side effects as addiction.[1] Subsequent efforts identified the indazole based ureas **1** as a class of potent TRPV1 antagonists.[2]



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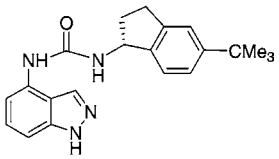


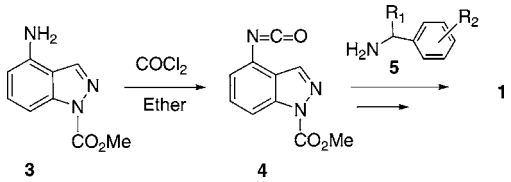
2

Further SAR optimization of these leads resulted in the discovery of ABT-102 (**2**) which possessed an excellent set of properties suitable for its further development as a clinical candidate.[3] In order to support this clinical program the process chemistry group was challenged to develop a robust and scalable synthesis of enantiopure compound **2**.

The original general approach for the preparation of indazyl ureas **1**, including ABT-102 (**2**), is outlined in Scheme 1.[2]

This synthesis is based on the preparation of an appropriately protected 4-amino substituted indazole derivative **3**, its conversion into isocyanate intermediate **4**, followed by coupling of the isocyanate with the desired benzylamine

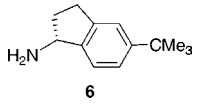
Scheme 1. **General synthesis of indazyl ureas 1**



3 **4** **5** **1**

5. In those cases, when the benzyl amine counterpart had a chiral center (e.g., **5**, $R_1 \neq H$) the separation of the resulting racemic ureas into the two pure enantiomers was achieved by a preparative chiral HPLC method.

In order to develop a reliable and robust large scale synthesis of enantiopure compound **2**, we decided to utilize the convenience of the convergent synthetic approach outlined in Scheme 1 while identifying and incorporating into the process an asymmetric synthesis of the R-enantiomer of 5-*tert*-butylaminoindan **6**.



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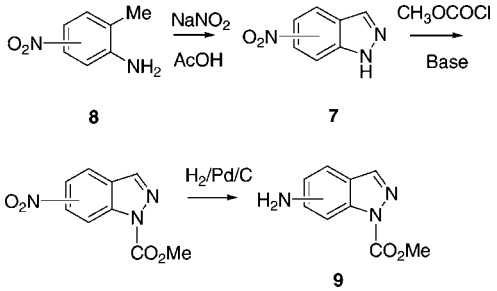
Further elaboration of the above approach resulted in an efficient asymmetric synthesis of ABT-102 suitable for multi-kilogram scale preparations. The details of this work are discussed in this manuscript.

Results and Discussion

1. Preparation of 1-*N*-Protected 4-Aminoindazole 3. Scheme 2 outlines a general synthetic approach to 1-*N*-protected aminoindazoles reported in the literature.[2,4] Following this approach, nitroindazole **7** was prepared via diazotation/cyclization of the corresponding nitrotoluidine **8**, protection of the indazole nitrogen using a suitable group, and reduction of the nitro group to amine **9**.

Scheme 2. **General synthesis of aminoindazoles 9**



8 **7** **9**

* To whom correspondence should be addressed. E-mail: kirill.lukin@abbott.com.

† Current address: Cayman Chemical Company, Ann Arbor, Michigan.

(1) For a review, see: Szallasi, A.; Appendino, G. *J. Med. Chem.* **2004**, *47*, 2717.

(2) Drizin, I.; Gomtsyan, A.; Bayburt, E. K.; Schmidt, R. G.; Zheng, G. Z.; Perner, R. J.; Didomenico, S.; Koenig, J. R.; Turner, S. C.; Jinkerson, T. K.; Brown, B. S.; Keddy, R. G.; McDonald, H.A.; Honore, P.; Wismer, C. T.; Marsh, K. C.; Wetter, J. M.; Polakowski, J. S.; Segreti, J. A.; Jarvis, M. F.; Faltynek, C. R.; Lee, C.-H. *Bioorg. Med. Chem.* **2006**, *14*, 4740.

(3) Gomtsyan, A.; Bayburt, E. K.; Koenig, J. R.; Lee, C.-H. U.S. Pat. Appl. 2004254188, Dec 16, 2004.

(4) (a) Porter, H. D.; Peterson, W. D. *Org. Synth.* **1940**, *20*, 73. (b) Benchidmi, M.; Bouchet, P.; Lazaro, R. *J. Heterocycl. Chem.* **1979**, *16*, 1599.

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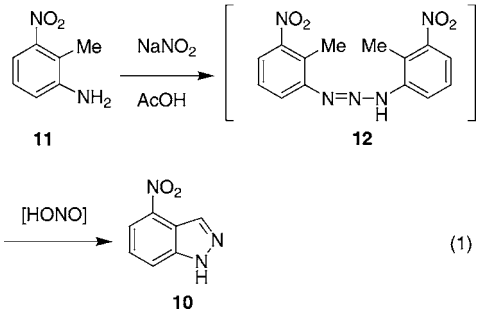
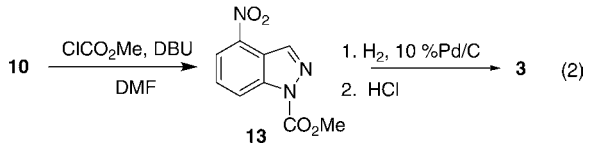
Although this synthetic sequence could be easily reproduced on a gram scale, several issues have been uncovered during the development of a kilogram scale process. Specifically, step 1 nitroindazole **10**[4] formation was particularly challenging.



(1)

Thus, according to the literature procedure,[4] a fast, one portion addition of the sodium nitrite solution to the mixture of nitrotoluidine **11** and acetic acid was required in order to obtain acceptable yields of **10** (eq 1). A slower addition of the sodium nitrite solution resulted in a massive precipitation of an unknown compound and incomplete reaction. However, the desired fast addition of the nitrite reagent produced a large exotherm (58 °C adiabatic temperature increase), which was very difficult to control on a scale. As a first step to resolve this issue, we isolated the intermediate precipitate and identified its structure as triazene **12**.[5] Then it was found that the triazene formation was reversible and that it could be converted into nitroindazole **10** by the addition of excess sodium nitrite (eq 1). Based on these observations we were able to develop a new protocol for the preparation of **10** which included a slow addition (over 1 h period) of the sodium nitrite solution to the preheated reaction mixture at 50 °C. This process provides good control of the exotherm and prevents the intermediate triazene precipitation. The optimized synthesis was reproducibly conducted on a kilogram scale and gave nitroindazole **10** in 95% isolated yield upon its precipitation from the reaction mixture with water.

For the second step of the synthesis, nitroindazole protection, we selected the methoxycarbonyl group because it could be selectively installed on the 1-*N* position, provided sufficient stability of intermediates throughout the process, and was easy to remove. The installation of the protection group was consequently achieved by the addition of methyl chloroformate to a solution of nitroindazole **10** in DMF in the presence of DBU as a base (eq 2). Resulting compound **13** was then precipitated from the reaction mixture by water addition. On a kilogram scale intermediate **13** was reproducibly isolated in 88% yield.

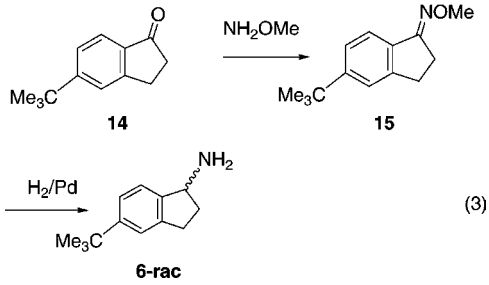


(2)

The next synthetic step, nitro group reduction, was initially conducted under standard hydrogenation conditions utilizing palladium on carbon as a catalyst and methanol as a solvent (eq 2). However, during the subsequent process optimization, it was found that up to 30% of aminoindazole **3** could be deprotected under the reaction conditions in alcoholic solvents. The problem was resolved by changing the reaction solvent to THF or ethyl acetate. Upon catalyst filtration, aminoindazole **3**[2] was isolated from the reaction mixture in the form of a stable hydrochloride salt via HCl addition.

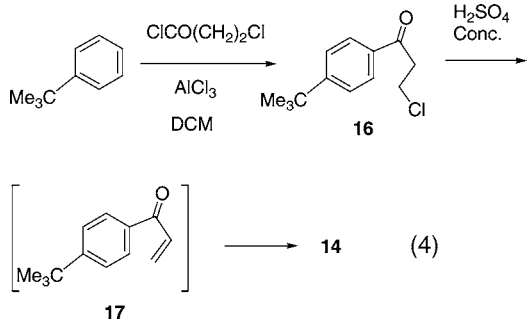
Overall, the three-step synthesis gave the indazole **3** building block in 77% yield on a kilogram scale.

2. Asymmetric Synthesis of *R*-(*tert*-Butylindanyl)amine 6. Preparation of the chiral aminoindan **6** was investigated next. Our synthetic approach to **6** was based on the utilization of 5-*tert*-butylindanone **14**[6] as a starting material. We thought that this ketone could be converted into chiral amine **6** either through the preparation of the corresponding racemic amine **6-rac** (eq 3), followed by its resolution, or, hopefully more efficiently, via a direct asymmetric synthesis.



(3)

A large scale, robust preparation of indanone **14** was subsequently developed to support the synthetic efforts toward chiral amine **6**. The synthesis of 5-*tert*-butylindanone **14** was previously reported in the literature,[6] as part of a general methodology for the preparation of indanones, as shown in eq 4.[7]



(4)

This synthesis includes Fridel−Crafts acylation of *tert*-butylbenzene, followed by a Nazarov type cyclization of the intermediate β-chloroketone **16** in concd sulfuric acid.[7] While the first step of this synthesis was easily scalable and produced intermediate **16** in >90% yield, the following cyclization step required substantial optimization prior to scaleup. Thus, small-scale cyclization reactions had to be conducted at a fairly high dilution (0.2 M) using concd

(5) Benes, J.; Beranek, V.; Zimprich, J.; Vetesnik, P. *Coll. Czech. Chem. Commun.* **1977**, *42*, 702.

(6) Hannig, E. *Pharmazie* **1965**, *20*, 762.

(7) For example, see: Bartmann, W.; Konz, E.; Rueger, W. *J. Heterocycl. Chem.* **1987**, 677.

sulfuric acid as a solvent to prevent polymerization of the intermediate enone **17**. The subsequent workup of these reactions with water created a very large exotherm and required unacceptably high process volumes. With optimization, this reaction was conducted at higher concentrations (0.7 M), and the polymerization of **17** was minimized by adding chloroketone **16** to preheated sulfuric acid at 90 °C at a rate comparable to the rate of enone **17** cyclization (see Experimental Section for details). This method of the reagent addition maintained a low concentration of the enone intermediate in the mixture throughout the synthesis and, thus, prevented its polymerization.

Under the optimized conditions the synthesis of *tert*-butylindanone was successfully conducted on a kilogram scale and gave an 83% assayed yield of indanone **14** for the two-step sequence.

Resolution of Racemic Amine 6-rac. The possibility of resolving racemic amine **6-rac** was examined initially as a most straightforward approach to chiral amine **6**. Racemic **6-rac** was prepared from indanone **14** via the formation of oxime **15**, followed by hydrogenation in the presence of Raney nickel and ammonia, as shown in eq 3.

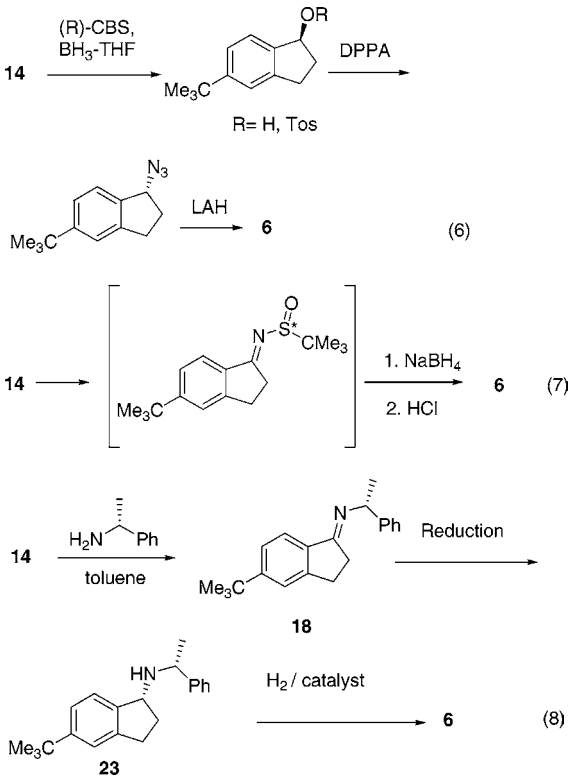
To resolve the racemate we utilized a method previously reported in the literature for the resolution of the unsubstituted analogue of **6**, i.e., 1-aminoindan.[8] Following this procedure, a methanolic solution of 5-*tert*-butyl-aminoindan (**6-rac**, 1 equiv) and *N*-acetyl-L-leucine (0.5 equiv) were combined to give the (*S*)-enantiomer as a crystalline salt. This first crop of this salt was isolated in 30% yield and ~80% ee chiral purity.

$$\textbf{6-rac} \xrightarrow[0.5\ \text{equiv}]{N\text{-Ac-D-leucine}} \textbf{6} \times N\text{-Ac-D-leucine} \qquad (5)$$

The preparation of the desired (*R*)-enantiomer **6** was then accomplished in a similar manner using *N*-acetyl-D-leucine (eq 5). The latter resolving agent was not commercially available but could be easily prepared by *N*-acetylation of D-leucine with acetic anhydride.[9] Upon further optimization of the resolution parameters, we were able to isolate the corresponding salt of **6** with >97% ee chiral purity in 18% yield. This resolution approach was used in the preparation of the first gram size batches of **6**. However, the method was unsuitable for a kilogram scale process due to the high cost of unnatural D-leucine and less than desired resolution efficiency.

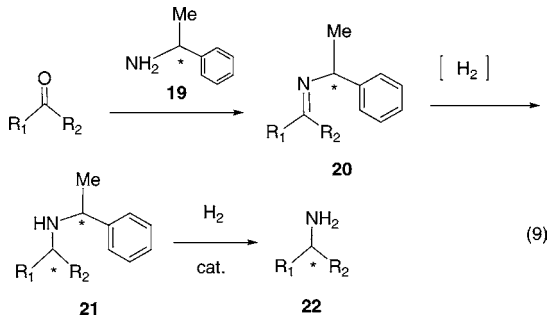
Our research efforts were consequently shifted to a chiral synthesis of **6**. The two primary approaches were (1) asymmetric reduction of indanone **14** followed by stereoselective amination (eq 6) and (2) auxiliary induced diastereoselective reduction of iminoindans, as shown in eqs 7 and 8.

Although all three explored approaches ultimately gave desired chiral amine **6**,[10−13] only the latter one, based on



diastereoselective reduction of chiral iminoindan **18**, was selected for a kilogram scale process development as the most practical and efficient.

Diastereoselective Reduction of Chiral Iminoindan 18. The use of enantiopure α-methylbenzylamines **19** as chiral auxiliaries in stereoselective reductive amination reactions (eq 9) has been well documented.[14]



According to this approach, chiral imine intermediate **20**, prepared from corresponding ketone and amine auxiliary, is

(8) Smith, H. E.; Willis, T. C. *Tetrahedron* **1970**, *26*, 107.
(9) DeWitt, H. D.; Ingersoll, A. W. *J. Am. Chem. Soc.* **1951**, *73*, 3359.
(10) A three-step sequence including asymmetric reduction of **14** with (*R*)-CBS-BH_3[11] and azidation of the resulting alcohol with DPPA, followed by the azide reduction with LAH, gave **6** in a 66% overall yield and 79% ee chiral purity.
(11) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. *J. Org. Chem.* **1993**, *58*, 2880.
(12) Utilizing Ellman's methodology[13] amine **6** (92 % ee) was prepared in 21% yield for a three-step sequence including conversion of **14** into an (*R*)-(+)-*tert*-butylsulfinimide derivative, followed by diastereoselective reduction with $NaBH_4$ and the auxiliary cleavage with concd HCl .
(13) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.
(14) (a) Bringmann, G.; Geisler J.-P. *Tetrahedron Lett.* **1989**, *30*, 317. (b) Bringmann, G. B.; Kunkel, G; Geuder, T. *Synlett* **1990**, 253. (c) Bringmann, G.; Geisler, J.-P. *J. Fluorine Chem.* **1990**, *49*, 67. (d) Bringmann, G.; Geisler, J.-P.; Geuder, T.; Küenkel, G.; Kinzinger, L. *Liebigs Ann. Chem.* **1990**, 795. (e) Kanai, M.; Yasumoto, M.; Kuriyama, Y.; Inomiya, K.; Katsuhara, Y.; Higashiyama, K.; Ishii, A. *Org. Lett.* **2003**, *5*, 1007. (f) Gutman, A. L.; Etinger, M.; Nisnevich, G.; Polyak, F. *Tetrahedron: Asymmetry* **1998**, *9*, 4369. (g) Storace, L.; Anzalone, L.; Confalone, P. N.; Davis, W. P.; Fortunak, J. M.; Giangiordano, M.; Haley, J. J.; Kamholz, K.; Li, H.-Y.; Ma, P.; Nugent, W. A.; Parsons, R. L.; Sheeran, P. J.; Silverman, C. E.; Waltermire, R. E.; Wood, C. C. *Org. Process Res. Dev.* **2002**, *6*, 54.

Table 1. **Diastereoselectivity of imine 18 reduction**

entry	reaction conditions	% de **23**
A	$NaBH_4$, EtOH, 0 °C, 2 h	94
B	$NaBH_4$, MeOH, 0 °C, 2 h	93
C	$Na(OAc)_3BH$, MeOH, 0 °C, 93 h	97
D	$Na(OPiv)_3BH^i$, MeOH, 0 °C, 93 h	97
E	Dibal-H, THF, 0 °C, 22 h	80
F	5% Pd/C (10 wt %), MeOH/toluene, 40 psi H_2, ambient	93
G	5% Pt/C (10 wt %), MeOH/toluene, 40 psi H_2, ambient	95
H	5% $Pd(OH)_2$/C (20 wt %), MeOH/toluene, 40 psi H_2, ambient	91
I	10% Pt/C (5 wt %), MeOH/toluene, 40 psi H_2, 0−12 °C	96
J	PtO_2 (10 mol %)/HOAc, MeOH/toluene, 40 psi H_2, 0 °C	96
K	5% Pd/C (5 wt %), MeOH/toluene, 40 psi H_2, 0−12 °C	96
L	5% $Pd(OH)_2$/C (10 wt %), MeOH/toluene, 40 psi H_2, 0−12 °C	95

subjected to a diastereoselective reduction with the formation of a secondary amine intermediate **21**, possessing a new stereogenic center. The auxiliary is then debenzylated affording chiral amine **22**.[14]

However, in those cases where R_1 or R_2 of amine **21** is an aryl substituent, the debenzylation reaction could proceed in a nonselective fashion with the formation of a mixture of desired amine and the deaminated side product.[15]

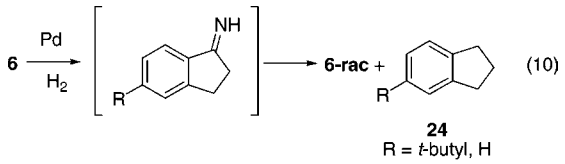
Although, the possibility of a nonselective debenzylation also exists in the case of secondary amine intermediate **23** (our precursor to **6**, eq 8), we were pleased to observe only minor undesired cleavage of the C1−N bond under the reaction conditions. The success of the debenzylation reaction ultimately allowed us to apply the above methodology to the large-scale synthesis of chiral amine **6** (eq 8).

Thus, refluxing a solution of **14** and (*R*)-(+)-α-methylbenzylamine in toluene resulted in the formation of imine **18**. The equivalent of water produced in this reaction had to be removed via a slow azeotropic distillation at ambient pressure to achieve the desired (better than 90%) conversion of the starting material. The whole process typically required 15 to 24 h and was accompanied by some imine degradation as judged by HPLC analysis. Our attempts to further improve the imine formation rate under acid catalysis conditions demonstrated that trace amounts of acid (e.g., TFA) accelerated the reaction; however, they also catalyzed the degradation of **18**. On the other hand, the presence of excess (*R*)-(+)-α-methylbenzylamine resulted in improved stability of this imine. Under the optimized conditions the process was carried in the presence of 2 equiv of the amine reagent, and the resulting imine solution was then subjected to the diastereoselective reduction without further purification.

Select results for the optimization of the diastereoselective reduction of imine **18** are presented in Table 1. The desired level of diastereoselectivity (>90% de) was achieved using either borohydride reagents (entries A−D) or catalytic hydrogenation conditions (entries F−L). In particular, we have found that the $NaBH_4$/EtOH system (entry A) was especially convenient for the lab scale preparations of amine **6**. Upon the reaction quench, secondary amine **23** was isolated from the mixture as a tosylate salt in 77% yield. During this isolation the chiral purity of **23** was further enhanced to >97% de as a result of the diastereomeric salt rejection.

At the same time, heterogeneous hydrogenation conditions using Pd/C, $Pd(OH)_2$/C, Pt/C, and PtO_2 (entries F−L) were most suitable for a pilot plant scale process. Although the platinum catalyst gave slightly better reduction selectivity, utilization of a palladium based catalyst in the process was more desirable due to its lower cost and the possibility of combining the reduction step and the debenzylation step into a one-pot process (both steps could be conducted in the presence of the same catalyst). Upon further optimization we have found that the diastereoselectivity of the imine reduction in the presence of a palladium catalyst could be improved when the reaction was conducted at lower temperatures (compare entries H and L, Table 1). The latter conditions were selected for a kilogram scale process.

Chemoselective debenzylation of amine **23** was examined next. We were pleased to find that both Pd/C and $Pd(OH)_2$/C catalysts gave highly selective auxiliary cleavage under hydrogenation conditions yielding the desired amine **6**. Surprisingly though, we observed a substantial erosion of the chiral purity of **6** upon reaction completion. Thus, debenzylations of amine **23** with 97% de purity typically gave amine **6** with only ~80% ee purity. We suspected that the deterioration of the amine chiral purity could occur via its partial racemization through the imine intermediate,[16] as shown in eq 10.



To support this hypothesis a high purity sample of **6** was subjected to the debenzylation conditions in the presence of $Pd(OH)_2$/C catalyst (eq 10). Indeed, after 24 h the recovered **6** showed significant loss of its enantiomeric purity, along with formation of *tert*-butylindan (**24**, R = *tert*-butyl) as a side product (entry A in Table 2). Interestingly, when the unsubstituted analogue of aminoindan **6** (R = H) was subjected to the same reaction conditions (entry B in Table 2), very little enantiomeric deterioration and deamination were observed, indicating that these side reactions were primarily induced by a *tert*-butyl substituent of **6**. An optimal control over the debenzylation of amine **23** was achieved upon extensive optimization of the reaction parameters. It was found that utilization of a less active catalyst (Pd/C vs $Pd(OH)_2$/C) and the interruption of the reaction at ~96% conversion of the starting material helped to maintain the chiral purity of **6** at the better than 90% ee level (entry C, Table 2).

(15) For example, see ref 14a, c, e, f.

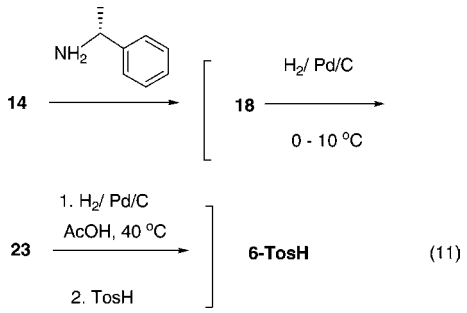
(16) Murahashi, S.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002.

Table 2. **1-Aminoindans racemization in the presence of palladium catalysts**

entry	substrate	initial % ee	conditions	final % ee	deamination (%)
A	**6**, R = *tert*-butyl	99	5% $Pd(OH)_2$, MeOH, HOAc, H_2O, 40 psi H_2, ambient, 24 h	66	36
B	R = H	99	5% $Pd(OH)_2$, MeOH, HOAc, H_2O, 40 psi H_2, ambient, 24 h	96	<10
C	**6**, R = *tert*-butyl	>99	5% Pd/C, MeOH, HOAc, 40 psi H_2, 40 °C, 20 h	90	12

These debenzylation conditions were successfully demonstrated in the kilogram scale process. The desired purity of isolated **6** could be achieved upon its crystallization in the form of a tosylate salt (**6-TosH**). Such isolation also resulted in the enhancement of the enantiomeric purity of **6** to better than 95% ee (see Experimental Section for details).

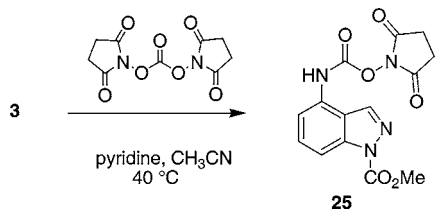
For pilot plant scale preparations the synthesis of chiral amine **6** from indanone **14** was further streamlined into a one-pot process (eq 11).



(11)

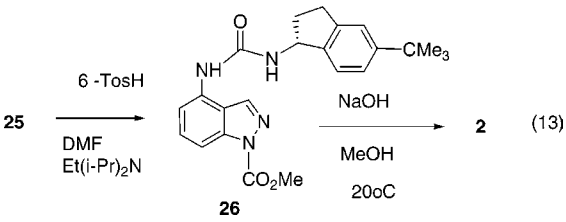
Thus, following imine **18** formation, the product solution was concentrated under a vacuum, diluted with methanol, and hydrogenated at 0−8 °C in the presence of a palladium catalyst. Upon completion of the reduction, acetic acid was added to the mixture and the hydrogenation was continued over the same catalyst at 40 °C achieving the chemoselective auxiliary cleavage. Using this highly practical method for a kilogram scale preparation of chiral amine **6**, the tosylate salt **6-TosH** was isolated in a 70% overall yield (for four chemical steps starting from **14**) with 100% chemical purity and >97% ee chiral purity.

3. Final Coupling Strategy. Preparation of ABT-102. With both building blocks (**3** and **6**) needed for ABT-102 preparation in hand, the final urea coupling process was investigated. In small-scale experiments, the original discovery method utilized phosgene for isocyanate **4** formation from aminoindazole **3**, followed by coupling with chiral aminoindan **6** (Scheme 1) to give the desired product in high yield. However, due to the low stability of the isocyanate intermediate this process could only be efficiently conducted in ether under high dilution conditions. For a kilogram scale process the unstable isocyanate was replaced with shelf stable succinimidyl carbamate derivative **25**.[17] Carbamate **25** was conveniently prepared by reacting aminoindazole hydrochloride **3** with disuccinimidylcarbonate in the presence of pyridine as a base (eq 12). Using acetonitrile as the solvent, the product directly precipitated from the reaction mixture upon cooling and was typically isolated in 80% yield on a kilogram scale.



(12)

The coupling of **25** with chiral aminoindan was achieved in DMF at rt using diisopropylethylamine as a base (eq 13).[17] The final deprotection step was accomplished by the reaction of the penultimate intermediate **26** with methanolic sodium hydroxide.



(13)

It was later found that both coupling and deprotection steps could be conveniently incorporated into a one-pot process. The product was precipitated from the reaction mixture with addition of a methanol/water mixture. The crude isolated **2** was then recrystallized from methanol or aqueous ethanol in 90% yield to afford the API with desirable physical properties. Chiral HPLC analysis of **2** showed the enantiomeric purity of **2** to be >99% ee.

Conclusions

A highly efficient asymmetric synthesis of ABT-102 was developed and successfully demonstrated on a multi-kilogram scale. This process features a very practical asymmetric synthesis of (*R*)-*tert*-butylaminoindan **6** as a key intermediate. A high level of asymmetric induction was achieved through the auxiliary induced stereoselective reduction of the corresponding iminoindan. Amine **6** was efficiently elaborated into ABT-102 via coupling with a succinimidylcarbamate derivative of the corresponding aminoindazole.

Experimental Section

Reaction mixtures and purities of the isolated products were monitored by GC or HPLC method (Zorbax Rx C8 colum, detection at 205 nm).

(17) Takeda, K.; Akagi, Y.; Saiki, A.; Tsukahara, T.; Ogura, H. *Tetrahedron Lett.* **1983**, *24*, 4569.

4-Nitro-1*H*-indazole (10).[4] A sodium nitrite (2.37 kg, 34.3 mol) solution in water (6.0 kg) is slowly added to a preheated to 50 °C solution of 2-methyl-3-nitroaniline (2.5 kg, 16.4 mol) in acetic acid (53 kg) while maintaining the internal temperature between 45 and 55 °C. The mixture is stirred for an additional 1 h at 50 °C and then concentrated under reduced pressure to an approximate volume of 10 L. Water (30 kg) is charged to the reactor. The contents of the reactor are distilled again to an approximate volume of 10 L. Water (30 kg) is charged to the reactor, and the resulting orange slurry is cooled to 20 °C. The product was filtered, washed with water (30 kg), and dried to 2.6 kg (95% yield).

If the above reaction was conducted at ambient temperature, precipitation of triazene intermediate **12** was observed: ^{1}H NMR (DMSO-d_6, δ, ppm): 2.45 (s, 6H), 7.40 (t, 2H), 7.61 (d, 2H), 7.81 (d, 2H).

1-Methoxycarbonyl-4-nitro-1*H*-indazole (13).[2] A solution of nitroindazole **10** (2.4 kg, 14.7 mol) in DMF (17 kg) is cooled to 5 °C. DBU (2.45 kg, 16.1 mol) is then charged to the reactor while maintaining the internal temperature below 15 °C. Methyl chloroformate (1.65 kg, 17.4 mol) is then charged to the reactor over ~1.5 h while maintaining the internal temperature below 25 °C. The reaction mixture is stirred for 30 min at 20 °C and quenched by the addition of aqueous KH_2PO_4 (1 kg in 11 kg of water) while maintaining the internal temperature below 25 °C. The brown precipitate is filtered and washed with water (30 kg). The wet cake is then charged back into the reactor and slurried in isopropyl acetate (14 kg), and the mixture is then concentrated in vacuo to an approximate volume of 10 L. The mixture is diluted with isopropyl acetate (20 kg). The product is filtered, washed with isopropyl acetate, and dried to 2.8 kg of **13** (88% yield).

1-Methoxycarbonyl-4-amino-1*H*-indazole Hydrochloride (3).[2] A slurry of nitroindazole **13** (2.8 kg, 11.0 mol) in ethyl acetate (50 kg) is transferred into a hydrogenator containing 5% Pd/C (0.24 kg) while maintaining a nitrogen atmosphere. The reactor is then gassed with hydrogen, and the mixture is stirred under 40 psi of hydrogen while maintaining the internal temperature 40−45 °C. Upon the reaction completion the catalyst is filtered off. The filtrate is then treated with gaseous HCl (0.58 kg, 15.9 mol). The precipitated salt is filtered, washed with ethyl acetate, and dried under a vacuum to afford **3** (2.36 kg, 92% yield).

5-*tert*-Butylindan-1-one (14).[6] 3-Chloropropionyl chloride (3.2 kg, 25.2 mol) is added over 15−30 min to a slurry of aluminum chloride (3.3 kg, 24.8 mol) in methylene chloride (40 kg) at 0−5 °C under a nitrogen atmosphere. Then *tert*-butylbenzene (32 kg, 23.9 mol) is charged to the above mixture over ~1 h maintaining the internal temperature below 5 °C. The mixture is stirred at 0−5 °C for an additional 0.5 h. The reaction mixture is quenched by transferring into a reactor containing 10% aqueous hydrochloric acid (52 kg) while maintaining the internal temperature below 10 °C. After the phase separation the organic layer is diluted with heptanes. The resulting solution is then concentrated via vacuum distillation to an ~10 L volume, and the residue is diluted with heptanes. The heptanes solution is concentrated in vacuo. The residue is then diluted with methylene chloride (0.5 kg) for direct use in the cyclization step, as follows.

Chloroketone **16** solution is slowly added over a 1 h period to concd sulfuric acid (59 kg) preheated to 90 °C. After an additional 1 h at 90 °C the reaction mixture is checked by an HPLC method for the reaction completion and cooled to 15−20 °C. The reaction mixture is then quenched by slow transfer into a mixture of water−MTBE−heptanes (30:5.5:5.0 kg) while maintaining the internal temperature below 10 °C. The organic layer is then separated and washed with 5% aqueous potassium carbonate. The organic layer is concentrated in vacuo, and the resulting oil is assayed for ketone **14** (3.7 kg, 83% yield from *tert*-butylbenzene) and is used directly in the imine formation step.

Synthesis of (*R*)-(5-*tert*-Butylindan-1-yl)amine 6. (A) Imine 18 Formation. To a solution of **14** (3.66 kg by assay, 19.5 mol) in toluene (26 kg) is added (*R*)-(+)-α-methylbenzylamine (**19**, 4.8 kg, 40 mol). The solution is then heated to reflux and slowly distilled under atmospheric pressure to an approximately 12 L volume. If the conversion of **14** has not reached 90%, more toluene is added, and the atmospheric pressure distillation is continued until the conversion target is achieved. The resulting solution of **18** is then cooled to rt and used directly in the reduction step.

(B) Preparation of Chiral Aminoindan 6. The solution of imine **18**, prepared as described above in part A, is diluted with methanol (30 kg) and transferred under a nitrogen atmosphere into a hydrogenator charged with 5% Pd/C catalyst (1.15 kg).

The mixture is cooled to 0 °C and hydrogenated at ~40 psi pressure while maintaining the reaction temperature below 10 °C. Upon the reaction completion the internal temperature was adjusted to 20 ± 5 °C and acetic acid (2.92 kg) is added to the reaction mixture. The reaction mixture is then further hydrogenated at 40 °C until ~96% conversion of amine **23** was achieved, as judged by an HPLC method.

The reaction mixture is cooled to rt, and the catalyst is filtered off. Chiral analysis determined ~82% ee purity of **6** at this point. The methanolic solution of **6** is then added to a solution of tosic acid (3.4 kg, 17.8 mol) in methanol (5.1 kg). The resultant solution is distilled under reduced pressure to an approximately 20 L volume. The internal temperature is adjusted to ~65 °C, and water (32 L) is added while maintaining the internal temperature above 60 °C. The product crystallizes out during the addition. The mixture is held at ~65 °C for 1 h and then slowly cooled to ~20 °C. After mixing at ~20 °C the crude salt **6-TosH** is collected by filtration. The wetcake is washed with water (5 kg) and purged with nitrogen. The crude salt **6-TosH** is then charged back to the reactor and diluted with toluene (21 kg) and methanol (2.3 kg), and the mixture is heated to ~65 °C and then gradually cooled to ~20 °C. The product is filtered, washed with toluene, and dried under a vacuum to give **6-TosH** (4.9 kg, 70% yield for three steps starting with **14**, 97% ee chiral purity). ^{1}H NMR (CD_3OD, δ, ppm): 1.31 (s, 9H), 1.98−2.13 (m, 1 H), 2.36 (s, 3H), 2.48−2.63 (m, 1H),

2.88−3.01 (m, 1H), 3.06−3.19 (m, 1H), 4.67−4.76 (m, 1H), 7.21 (d, 2H), 7.28−7.35 (m, 1H), 7.36−7.43 (m, 2H), 7.68 (d, 2H).

Sodium Borohydride Reduction of Imine 18. Preparation of (*R*)-5-*tert*-Butyl-*N*-((*R*)-1-phenylethyl)-1-indanyl-1-amine Tosylate (23-TosH). The solution of imine **18** (0.46 kg by assay, 1.58 mol), prepared as described above, is slowly added to a slurry of sodium borohydride (0.137 kg, 3.16 mol) in ethanol (2.0 kg) while maintaining the reaction temperature below 10 °C. The mixing is continued at 10 °C until the reaction is complete (HPLC method). The reaction mixture is then quenched by careful addition of 10% aqueous KH_2PO_4 (4.1 kg) while maintaining the reaction temperature below 10 °C.

The organic layer is separated and washed with 10% aqueous KH_2PO_4 (2.0 kg). The organic layer is concentrated in vacuo and diluted with ethyl acetate (0.7 kg). The resulting amine solution is then added to a solution of tosic acid (0.35 kg, 1.83 mol) in ethyl acetate (2.6 kg.). The internal temperature is adjusted to ∼65 °C and then slowly cooled to ∼20 °C. After the solution mixed at 20 °C, the crude salt **23-TosH** is collected by filtration. The wetcake is washed with ethyl acetate (2 × 0.7 kg) and dried under a vacuum to give **23-TosH** (0.6 kg, 71% yield). ^{1}H NMR (CD_3OD, δ, ppm): 1.31 (s, 9H), 1.69 (d, 3H), 2.10−2.26 (m, 1H), 2.36 (s, 3H), 2.37−2.51 (m, 1H), 2.83−2.97 (m, 1H), 3.06−3.24 (m, 1H), 4.50−4.62 (m, 1H), 4.62−4.69 (m, 1H), 7.21 (d, 2H), 7.30−7.37 (m, 1H), 7.37−7.52 (m, 5H), 7.52−7.61 (m, 2H), 7.69 (d, 2H).

Preparation of Methyl 4-[(2,5-Dioxopyrrolidine-1-yloxy)carbonylamino]-1*H*-indazole-1-carboxylate (25). A slurry of aminoindazole hydrochloride **3** (1.95 kg, 8.6 mol) and *N*,*N*′-dissuccinimidylcarbonate (2.4, kg, 9.4 mol) in acetonitrile (25 kg) is cooled to 10 °C. Pyridine (0.74 kg, 9.4 mol) is charged to the reactor while maintaining the internal temperature below 25 °C. The reaction mixture is then heated to 40 °C for not less than 5 h. Upon the reaction completion, the mixture is cooled back to room temperature. The precipitate is filtered, washed with acetonitrile, and dried under a vacuum to give intermediate **25** (2.6 kg, 86% yield).

Synthesis of (*R*)-1-(5-*tert*-butylindan-1-yl)-3-(1*H*-indazol-4-yl)urea (ABT-102, 2).[3] Diisopropylethylamine (1.4 kg, 2.1 equiv) is added over 0.5 h to a slurry of active carbamate **25** (1.54 kg, 4.6 mol) and chiral aminoindan salt **6-TosH** (1.72 kg, 4.76 mol) in DMF (7.2 kg) while maintaining the internal temperature below 20 °C. After an additional 30 min a sodium hydroxide (0.45 kg, 11.2 mol) solution in methanol (7.5 kg) is added to the mixture over 10−20 min while maintaining the internal temperature below 20 °C. After an additional 30 min at rt the mixture is diluted with methanol (5.4 kg) and the product is precipitated via slow addition of water (16.5 kg). The product is then filtered off and washed with methanol−water (1:1). The crude **2** is dried under a vacuum and redissolved in ethanol (3A, 200 proof, 20 kg) at reflux. The solution is then distilled under an ∼200 mmHg vacuum to an ∼16 L volume. The reaction mixture temperature is adjusted to 40 ± 5 °C, and water (6.3 kg) is added over 1 h to the resulting slurry. The mixture is cooled to rt, and the product is filtered off, washed with ethanol−water (70:30), and dried under a vacuum to give ABT-102 (**2**, 1.38 kg, 86% yield, >99% ee chiral purity).

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