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An Efficient Enantiopure Synthesis of a Pivotal Precursor to Substance P Antagonists[1]

Thomas C. Nugent*,† and Robert Seemayer‡

Department of Chemistry, School of Engineering & Science, International University Bremen, Campus Ring 1, 28759 Bremen, Germany, and CV Therapeutics, Inc., Pharmaceutical Development and Manufacturing, 3172 Porter Drive, Palo Alto, California 94304, U.S.A.

Abstract:

Many substance P antagonists have a core structure based on the quinuclidine skeleton. Manufacture of these drug antagonists proceeds through the advanced intermediate (2*S*,3*S*)-*cis*-2-benzhydryl-3-aminoquinuclidine 1, and all previous syntheses of 2*S*,3*S*-1 proceed through quinuclidinone 2. The synthesis described herein provides a 40% improved synthetic yield of (2*S*,3*S*)-1 from quinuclidinone 2, when compared to all previously reported syntheses. The key process improvements originate from: (1) dynamic kinetic resolution of ketone *rac*-4, producing ketone (2*S*)-4 and (2) the subsequent reductive amination of ketone (2*S*)-4 without epimerization. The former dynamic kinetic resolution, the first demonstrated for this ketone (quinuclidinone) architecture, uses inexpensive (natural) L-tartaric acid to provide ketone (2*S*)-4 in high yield (90%) and enantiopurity (95% ee). The latter demonstrates the first use of $Ti(O^iPr)_4$/Pt-C/H_2 for reductive amination and is especially noteworthy for its ability to preserve the α-labile C2 stereocenter of ketone (2*S*)-4. The new reductive amination method is general in nature and should find broad applicability.

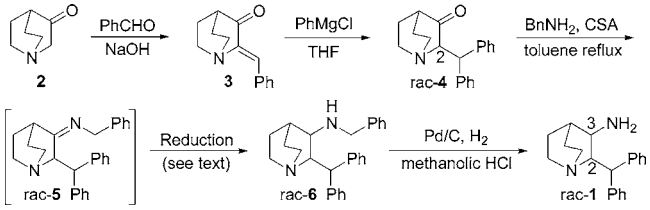
Introduction

Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides.[2] Quinuclidine derivatives are prepared for use as substance P receptor antagonists and treat many ailments ranging from gastrointestinal and central nervous system (psychotic) disorders to inflammatory diseases, pain, and migraine.[3] Their curative effects are perhaps unsurprising, since quinuclidine derivatives, both naturally occurring and synthetic, have long been associated with physiological properties.[4e] A brief review of the medical literature confirms the intense research effort invested in the use of these compounds and further reveals that many of these drugs contain the 3-amino-2-benzhydryl quinuclidine scaffold **1**.[4] A vast amount of literature regarding their synthesis is contained within pharmaceutical patents.[5,7]

Discussion and Results

Assessment of Prior Syntheses and Resolutions. To advance the clinical development programs of several lead drug candidates, larger quantities of (2*S*,3*S*)-**1** were required (Schemes 1 and 2). A review of the literature showed the most efficient route originating from the hydrochloride salt of quinuclidinone **2**.[2−4] To appreciate the chemistry involved we repeated the racemic synthesis of primary amine **1** following a literature preparation, which began with an aldol condensation of benzaldehyde and quinuclidinone **2** (Scheme 1).[4e,c] The resulting enone **3** was readily isolated from the aqueous reaction medium by simple Büchner funnel filtration. Reaction of this geometrically pure enone with phenylmagnesium chloride yielded the Michael addition product, benzhydryl ketone *rac*-**4**, as a well-behaved solid. Further treatment with benzylamine and camphorsulfonic acid (cat.) over 24 h enabled imine formation under the azeotropic conditions of refluxing toluene (Dean−Stark apparatus). The reaction is high yielding, but the resultant imine **5** is sensitive

Scheme 1. **Previous racemic synthesis of primary amine 1**



* To whom correspondence should be addressed. E-mail: t.nugent@iu-bremen.de.

† International University Bremen.

‡ CV Therapeutics, Inc., Pharmaceutical Development and Manufacturing.

(1) This research was performed at Catalytica Pharmaceuticals, 430 Ferguson Drive, Mountain View, CA 94043, U.S.A.

(2) Quinuclidine derivatives. Ito, F.; Kondo, H.; Nakane, M.; Shimada, K.; Lowe, J. A.; Rosen, T. J. (Pfizer Inc.). U.S. Patent 5,807,867, 1998.

(3) A process for preparing a quinuclidine derivative. Lowe, J. A. (Pfizer Inc., India). Patent number: IN173570, 1994.

(4) (a) Swain, C. J.; Seward, E. M.; Cascieri, M. A.; Fong, T. M.; Herbert, R.; MacIntyre, D. E.; Merchant, K. J.; Owen, S. N.; Owens, A. P.; Sabin, V.; Teall, M.; VanNiel, M. B.; Williams, B. J.; Sadowski, S.; Strader, C.; Ball, R. G.; Baker, R. *J. Med. Chem.* **1995**, *38*, 4793. (b) Lowe, J. A., III; Drozda, S. E.; Snider, R. M.; Longo, K. P.; Zorn, S. H.; Morrone, J.; Jackson, E. R.; McLean, S.; Bryce, D. K.; Bordner, J.; Nagahisa, A.; Kanai, Y.; Suga, O.; Tsuchiya, M. *J. Med. Chem.* **1992**, *35*, 2591. (c) Warawa, E. J.; Mueller, N. J.; Fleming, J. S. *J. Med. Chem.* **1975**, *18*, 587. (d) Warawa, E. J.; Mueller, N. J.; Gylys, J. A. *J. Med. Chem.* **1975**, *18*, 71. (e) Warawa, E. J.; Mueller, N. J.; Jules, R. *J. Med. Chem.* **1974**, *17*, 497.

(5) (a) Norris, T.; Santafianos, D.; Bordner, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3679 and patent citations therein. (b) Quinuclidine compound and medicinal use thereof. Shu, M.; Hiroshi, K.; Masahiko, K.; Hiroshi, Y. (Yoshitomi Pharmaceutical). Patent number: WO9309116, 1993.

(6) In our hands the stereoselectivity (*cis*/*trans* ratios) ranged from 20:1 to 1:1, depending on the reductant employed: $NaB(OAc)_3H$ > BH_3 ≅ Pt/C > $NaBH_4$. The use of 9-BBN has been reported to provide excellent *cis* product ratios, see ref 4b.

(7) For a classical resolution of *rac*-**1** see: (a) Production of optically active 3-amino-2-benzhydrylquinuclidine compound. Osamu, M.; Hiroshi, K. (Yoshitomi Pharmaceutical). Patent number: JP7025874, 1995. For a classical resolution of the *o*-methoxybenzyl derivatives of rac-**6**, see: (b) Process and intermediates for preparing azabicyclo[2.2.2]octane-3-imines. Godek, D. M.; Murtiashaw, C. W. (Pfizer. Inc.). U.S. Patent 5,138,060, 1992. (c) Resolution of 1-azabicyclo[2.2.2]octane-3-amine,2-(diphenylmethyl)-*N*-[[2-methoxy-5-(1-methylethyl)phenyl]methyl]. Tickner, D. L.; Meltz, M. (Pfizer, Inc.). Patent number: WO9703984, 1997.

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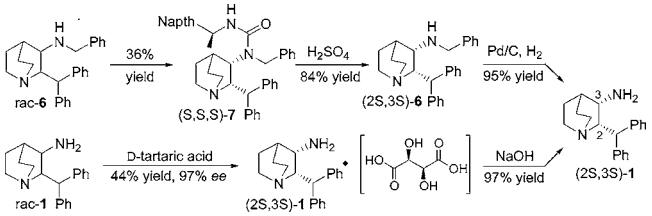
10.1021/op050213e CCC: $33.50

to moisture, thus we found it beneficial to reduce it without further purification.[5] A mixture of *cis* and *trans rac*-**6** resulted, and depending on the reductant employed, high diastereoselectivity (>20:1, *cis*/*trans*) could be achieved for racemic *cis*-**6**.[6] This level of diastereoselectivity was encouraging, but our experimental results and knowledge of the reported literature made it evident that no one reductant was ideal when considering the combined outcome of diastereoselectivity, yield, and rate of reaction. Finally, the title compound, primary amine *rac*-**1**, was cleanly produced upon hydrogenolysis of *rac*-**6** with Pd/C in methanolic hydrogen chloride (Scheme 1).[4a]

Two literature methods in particular are representative and descriptive for detailing the removal of the minor *trans* enantiomers (2*R*,3*S* and 2*S*,3*R* of **6** or **1**) and simultaneously resolving the *cis* enantiomers (2*S*,3*S* and 2*R*,3*R*) (Scheme 2). The first is a two-step process, requiring derivatization

Scheme 2. **Literature methods for the isolation of primary amine (2*S*,3*S*)-1**



of secondary amine *rac*-**6** with (*S*)-(+)-1-(1-naphthyl)ethyl isocyanate.[4b] The desired diastereomer is insoluble in the reaction solvent toluene and filtration allows unfettered isolation. The resulting urea derivative (*S*,*S*,*S*)-**7** is then hydrolyzed with concentrated H_2SO_4, yielding amine (2*S*,3*S*)-**6**. This product is assumed to be of high enantiopurity because further recrystallization did not improve the measured optical rotation of the material ($[\alpha]_D$ +67.4 (c = 1.0, DMSO)).[4b]

The second method is of greater utility, requiring only a static (classical) resolution of racemic amine **1** with unnatural D-(−)-tartaric acid (1.0 equiv) in hot methanol as described in a Japanese patent.[7] Filtration at room temperature provided a 44% yield of the desired diastereomeric salt (98.5% pure, 97% de), further treatment with aqueous alkali and extraction with methylene chloride provide the free amine(2*S*,3*S*)-**1** (97% ee). We did not examine either of these methods of resolution.

Despite the good resolution properties of rac-**1**, the most efficient synthesis remained too costly to be economically viable for large-scale production. From a process perspective the synthesis of (2*S*,3*S*)-**1** had several shortcomings, namely: (1) resolution of an advanced intermediate; (2) use of expensive resolving agents; (3) stepwise imine formation, isolation, and reduction thereof; and (4) mediocre, when considered in total, *cis/trans* diastereoselectivity, yield, and reaction time for the imine reduction step. Additionally, any potential solution would have to be amenable to scale-up and avoid expensive reagents and chemistries requiring low temperatures, and preferably have solid intermediates for ease of purification. This manuscript describes our approach to the aforementioned challenges, which were in large part met.

Identification of Weak Synthetic Points. Our improved route for the production of primary amine (2*S*,3*S*)-**1** would ultimately come from identifying the strengths and weaknesses of the known syntheses. These points can be summarized as follow. Alternatives exist for the incorporation of a benzhydryl moiety, but we found the demonstrated two-step process satisfactory both in ease of preparation and purification (Scheme 1). Next we questioned the need for stepwise imine formation, isolation, and then reduction. A significant decrease in processing time and a possible increase in yield might be realized if ketone **4** could be reductively aminated.

Although the last points concerned us, we identified the choice of resolving an advanced intermediate, e.g. *rac*-**6** or -**1**, as the most critical factor contributing to the low overall yield of all previous syntheses. Resolutions of these late-stage intermediates, while respectable in yield, were performed when a large amount of labor and expense had already been invested. As a consequence the overall yield of all previous syntheses were significantly compromised, since the undesired enantiomer could not be recycled and thus became part of the waste stream.

An early stage resolution could impart a significant economic benefit, but no literature precedent could be established. Thus we were intrigued by the possibility of performing a static or better yet a dynamic kinetic resolution (DKR) of racemic benzhydryl ketone **4**. An immediate beneficial consequence of a dynamic kinetic resolution would be a theoretical doubling of the yield, a benefit that could not be ignored. In the event such a resolution could be realized, we faced one more significant hurdle, preservation of the α-keto stereocenter upon introduction of nitrogen, i.e. could enantiopure benzhydryl quinuclidinone (2*S*)-**4** [ketone (2*S*)-**4**] be further elaborated to (2*S*,3*S*)-**6** without epimerization. In our final analysis we deemed the benefits of such an approach outweighed the downside of lost research time in the event of failure.

Finally, the source of nitrogen, benzylamine, was questioned. Reductive amination with ammonia would provide the product directly from ketone (2*S*)-**4**, obviating the need for a debenzylation step. While it was an interesting idea, we were uncertain of the diastereoselectivity (*cis/trans*) associated with the reduction of a non-N-alkylated imine intermediate and our ability to mitigate further alkylation of the desired reaction product primary amine-**1**.[8] In the end, benzylamine would prove to be a convenient source of nitrogen.

Dynamic Kinetic Resolution of Benzhydryl Ketone 4. Overcoming the need for a late-stage static resolution for the production of (2*S*,3*S*)-**1** was the key and tactical point we focused on. A literature search revealed that no attempts at early-stage resolutions or early- or late-stage dynamic kinetic resolutions had been reported for the synthesis of quinuclidine derivatives. Benzhydryl quinuclidinone *rac*-**4** met our requirements for an early-stage dynamic kinetic resolution study, and to investigate this possibility we

(8) Over alkylation is probably not a concern, see: (a) Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463. (b) Hirayama, Y.; Ikunaka, M.; Matsumoto, J. *Org. Process Res. Dev.* **2005**, *9*, 30.

prepared kilogram quantities of *rac*-**4** without event.[4c] By doing so, we were able to liberally examine the dynamic kinetic resolution properties of *rac*-**4** with a variety of enantiopure, inexpensive, and commercially available carboxylic acids on a tens of gram scale. An initial screen of economically viable chiral carboxylic acids soon led to the observation that natural L-tartaric acid allowed (2*S*)-**4** to precipitate as its tartrate acid salt in 80−85% yield (92−94% ee) from hot 2-propanol. A static (classical) resolution provides a maximum 50% yield of one enantiomer; thus, our yield and ee clearly demonstrated that a dynamic kinetic resolution had been achieved. The dynamic kinetic nature of this resolution was further supported by analysis of the mother liquor of the resolution reaction after isolation of the tartrate salt. It showed that the remaining ketone-**4**, in the solvent, is indeed a racemate. Analysis of the precipitated tartrate salt showed the molar ratio between ketone-**4** and L-tartaric acid to be 1:1.

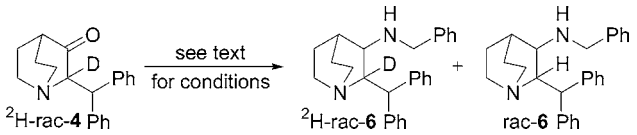
As initially observed, L-tartaric acid is efficient at selectively precipitating only the (2*S*)-**4** L-tartrate salt, but it is rather slow at converting the undesired (2*R*)-**4** enantiomer into the (2*S*)-**4** enantiomer even in refluxing 2-propanol (>24 h). Adding more equivalents of an appropriate acid, to accelerate the rate of racemization, could mitigate this problem. Keeping the cost of the process in mind, we then studied the effect of adding a commodity carboxylic acid, e.g., acetic acid.[9] This and other 1-alkanoic acids served the stated purpose and additionally had the desired property of not precipitating salts of ketone-**4**.

After further experimentation and optimization we found that L-tartaric acid (1.0 equiv) with acetic acid (1.0 equiv) in refluxing ethanol efficiently converted ketone rac-**4** to the (2*S*)-**4**-L-tartrate salt in 85−90% yield (94−96% ee) within 12 h. These reaction conditions allowed timely removal of the desired enantiomer, i.e. precipitation of the (2*S*)-**4** L-tartrate salt, from the solution-phase racemization equilibrium.

The enantioenriched ketone (2*S*)-**4** was obtained from its salt form by suspending it in an organic solvent (e.g. toluene, ethyl acetate, or methyl *tert*-butyl ether) and then dropwise adding an alkaline aqueous base ($NaHCO_3$, Na_2CO_3 or NaOH—potassium salts are also acceptable) until the pH of the aqueous layer was approximately 9 (±0.5). Generally, the temperature was maintained below 25 °C during the neutralization. This is particularly important if a hydroxide base is used because elevated temperatures lead to deterioration of the optical purity of ketone (2*S*)-**4**. The free base of (2*S*)-**4** is recovered as a solid after concentration of the organic extract. Using this procedure and utilizing sodium hydroxide as the base we produced several 0.5 kg batches of benzhydryl ketone (2*S*)-**4** in near quantitative yield and with uncompromised enantiopurity (free ketone ee = 95%) without event.

Introduction of Nitrogen to Benzhydryl Quinuclidinone (2*S*)-4. Intent on reductively aminating ketone (2*S*)-**4**, we were baffled to find a total lack of precedent for reductive amination in the quinuclidine literature. Due to the time restraints imposed, we needed to examine the dynamic kinetic resolution of ketone rac-**4** and its reductive amination chemistries in parallel. To do so, we found it useful to use the readily prepared α-deuterated ketone **4**, as a surrogate for (2*S*)-**4**, at the beginning of our reductive amination research effort (Scheme 3). All previous researchers chose

Scheme 3. **Use of ^{2}H-*rac*-4 as a probe for assessing the propensity of (2*S*)-4 to epimerize during reductive amination**



to incorporate the exoskeletal nitrogen in a stepwise fashion (i.e., imine formation, isolation, then reduction), thus we initiated a one-pot reductive amination feasibility study using α-deuterated benzhydryl ketone **4** (^{2}H-*rac*-**4**). Using standard ^{1}H NMR experiments we were able to measure the level of deuterium remaining in the subsequent product (secondary amine ^{2}H-**6**) and thus drew immediate conclusions concerning the propensity of (2*S*)-**4** to epimerize during reductive amination.

A variety of reductive amination protocols exist in the literature and are procedurally similar in that a Brønsted acid is used to facilitate "imine" formation, while a coexisting reductant reduces the imine. Using the standard literature conditions, we examined the reductive amination of ^{2}H-*rac*-**4** in THF with benzylamine (1.1 equiv), $NaB(OAc)_3H$ (1.4 equiv), and AcOH (1.0 equiv).[10] After 11 h the desired product was obtained in 40% yield after purification by column chromatography (Scheme 3). Extending the reaction time (6 d) and/or adding additional AcOH and/or $NaB(OAc)_3H$ provided only marginal improvements in yield. That said, a significant improvement in yield occurred when the initial conditions were as follows: $BnNH_2$ (1.5 equiv), $NaB(OAc)_3H$ (2.5 equiv), and AcOH (1.7 equiv) in THF (0.4 M), with heating at 35 °C for 25 h (Table 1, entry 1). Unfortunately, these Brønsted acid conditions allowed gross exchange of the deuterium label that we were trying to preserve.

Next we investigated the ability of a Lewis acid, $Ti(O^iPr)_4$, in combination with a borohydride-based reducing agent, to reductively aminate ^{2}H-*rac*-ketone **4**. This method of reductive amination was first demonstrated by Mattson et al. and calls for the neat reaction of a ketone, an amine and $Ti(O^iPr)_4$ in approximately equal molar quantities.[11,12] After 1 h of stirring, EtOH and $NaBH_3CN$ are added, allowing amine product formation. The method has since been championed by Bhattacharyya, using the reductant $NaBH_4$,[13,14] and is noted for its ketone/amine substrate breadth and tolerance of several spectator functional groups.[15]

(9) We have recently become aware that this general strategy has been employed before: see specifically p 803 of Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788.

(10) 1,2-Dichloroethane was the solvent of choice for most of their reactions, although they mention that THF, CH_2Cl_2, or CH_3CN may be also be used, see: Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

(11) Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552.

Table 1. **Ti(O^{i}Pr)$_4$ vs AcOH-catalyzed reductive amination with NaB(OAc)$_3$H**

catalyst	temp (°C)	time (h)	product **6** (%)[a]	% ^{2}H in **6**[b]	*cis/trans* of **6**[c]
AcOH	35	25	70	28	16:1
Ti(O^{i}Pr)$_4$	25	11	85	51	17:1

[a] Isolated yields after chromatography. [b] Starting ketone 94% ^{2}H. [c] ^{1}H NMR data.

Aware of the aforementioned reductants, in combination with Ti(O^{i}Pr)$_4$, we first decided to investigate the use of NaB(OAc)$_3$H as a reductant.[16] Our initial experiments employed Ti(O^{i}Pr)$_4$ (1.2 equiv), BnNH$_2$ (1.1 equiv), and NaB(OAc)$_3$H (2.3 equiv), producing the secondary amine **6** in <11 h at room temperature. Again the reductive amination product showed gross loss of deuterium at C2 (Table 1). It is valuable to note that both methods provided very respectable and very similar *cis/trans* diastereoselectivity. While we found the procedure using Ti(O^{i}Pr)$_4$ more reliable and convenient, the goal of enantiopreservation (or retention of deuterium in this case) was clearly not feasible using this combination of reagents.

Next we examined the use of NaBH$_4$ and NaBH$_3$CN as reductants for the titanium (IV)-mediated method. Thus reaction of ^{2}H-*rac*-**4** with Ti(O^{i}Pr)$_4$ (1.2 equiv) and BnNH$_2$ (1.1 equiv) in THF (1.0 M) for 2.5 h, followed by removal of THF (rotary evaporator), addition of EtOH (0.25 M) and NaBH$_4$ or NaBH$_3$CN (2.0 equiv) allowed the smooth formation of amine **6** (Table 2). No byproducts were formed (^{1}H NMR of crude product), and significantly the deuterium label was fully preserved when using either of these reductants. Unfortunately, the *cis/trans* diastereoselectivity was poor at best, and in the case of NaBH$_4$ decreased on cooling (Table 2, entry 3). These results were edifying and clearly established that Ti(O^{i}Pr)$_4$ was not responsible for the earlier observed deuterium/hydrogen exchange (epimerization) at C2 of ketone ^{2}H-*rac*-**4**.

A New Method for Reductive Amination: Synthesis of Primary Amine (2*S*,3*S*)-1. Our earlier research results revealed that reductive amination catalyzed by Ti(O^{i}Pr)$_4$ is strongly dependent upon the nature of the reductant. Yet,

Table 2. **Ti(O^{i}Pr)$_4$-mediated reductive aminations with various borohydrides**

borohydride	temp (°C)	% loss of ^{2}H in **6**	*cis/trans*	yield (%)
NaB(OAc)$_3$H	22	41	17:1	85
NaBH$_4$	22	0	6:4	a
NaBH$_4$	0	0	1:1	a
NaBH$_3$CN	22	1	6:5	a

[a] The chromatographic yield was not determined for this reaction, but the mass recovery was good and the ^{1}H NMR of the crude product showed only product.

none of the borohydrides we examined were able to simultaneously provide nonepimerizing conditions, adequate *cis/trans* diastereoselectivity, and sufficient rate of reaction. We then turned our attention to the use of hydrogen as a reductant. Our first experiment was as follows: ketone (2*S*)-**4** (1.0 mmol, 94% ee), THF, BnNH$_2$, and Ti(O^{i}Pr)$_4$ were stirred for 2.5 h and subsequently hydrogenated at 50 psi with Pt/C (25 wt %). The reaction yielded the product in 75% yield, 91% ee, and with a respectable *cis/trans* ratio of 7:1.[17,18]

Further refinements (see Experimental Section) increased the diastereomeric yield (85%), improved the diastereoselectivity (9:1, *cis/trans*), and maintained a high ee (≥92%) for the desired *cis* enantiomer.[19,20] This was possible while also reducing the amount of heterogeneous hydrogenation catalyst required. A large number of experiments were performed and can be summarized by stating that: (1) Pt/C (10 wt %, 60% water content) is a superior hydrogenation catalyst[21] for this ketone substrate regarding the yield and enantiomeric excess of (2*S*,3*S*)-**6**; (2) Pd/C provides excellent diastereoselectivity (*cis/trans* ratios as high as 40:1), but the reactions failed to go to completion,[22] and lower optical purities (50−75% ee) were observed with increasing reaction

(12) Similar Ti(IV) methods using TiCl$_4$ have been described; in our hands these methods proved unhelpful, see: (a) Barney, C. L.; Huber, E. W.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 5547. (b) Johansson, A.; Lindstedt, E.-L.; Olsson, T. *Acta Chem. Scand.* **1997**, *51*, 351.

(13) For examples of reductive amination using Ti(O^{i}Pr)$_4$ and NaBH$_4$ see: ref 8a and (a) Neidigh, K. A.; Avery, M. A.; Williamson, J. S.; Bhattacharyya, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2527. (b) Bhattacharyya, S. *J. Org. Chem.* **1995**, *60*, 4928. (c) Bhattacharyya, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1845. (d) Bhattacharyya, S. *Synth. Commun.* **1995**, *25* (1), 9. (e) Bhattacharyya, S. *Tetrahedron Lett.* **1994**, *35*, 2401. (f) Bhattacharyya, S.; Chatterjee, A.; Williamson, J. S. *Synlett* **1995**, 1079.

(14) For an example of reductive amination using Ti(O^{i}Pr)$_4$ and polymethylhydrosiloxane (PMHS), see: Chandrasekhar, S.; Reddy, R. C.; Ahmed, M. *Synlett* **2000**, 1655.

(15) For substrate breadth and compatible functional groups, e.g. carbamates, urethanes, tertiary amides, acetonides, silyl ethers, esters, etc., see: refs 8a, 13a,f, and Seebach, D.; Hungerbuehler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zueger, M. *Synthesis* **1982**, 138.

(16) At the time of the following research, 1998, the use of NaB(OAc)$_3$H in combination with Ti(O^{i}Pr)$_4$ was unreported. It has since been reported, but the researchers additionally added AcOH, see: Breitenbucher, J. G.; Hui, H. C. *Tetrahedron Lett.* **1998**, *39*, 8207.

(17) We simultaneously found that a stepwise imine formation/isolation/reduction pathway was possible. Thus, the ^{2}H-*rac*-**4** was condensed with benzylamine under the conditions of (1) catalytic CSA acid with azeotropic water removal, (2) neat at 145 °C under N$_2$, (3) alumina (basic) or anhydrous MgSO$_4$ in a dry THF. The first two conditions provided the imine, albeit with gross loss of deuterium, and the last two reactions failed to provide imine, even under forcing conditions, i.e., higher temperature. Despite these setbacks we did find that imine formation was possible without loss of deuterium using Ti(O^{i}Pr)$_4$ at room temperature (2.5 h), followed by workup with sat. NaHCO$_3$ or H$_2$O. Yields varied from 60 to 95%; this likely reflects the short workup times required to avoid imine hydrolysis but which are suspected of being insufficient to free all of the product from the titanium salts. Workup using NaOH (1.0 M) led to a 29% decrease in the percent of deuterium.

(18) All crucial previous experiments with ^{2}H-*rac*-**4** were reexamined using (2*S*)-**4**; no inconsistencies were observed.

(19) The new reductive amination protocol described herein, Ti(O^{i}Pr)$_4$/H$_2$/Pt−C, has been used internally at Catalytica Pharmaceuticals (and later at DSM and Pfizer) since 1998 as a trade secret. The patent application process took its own course as mergers and acquisitions occurred. Process for the preparation of (*S*,*S*)-*cis*-2-benzhydryl-3-benzylaminoquinuclidine: Nugent, T. C.; Seemayer, R. (Pfizer Products, Inc. and DSM Pharmaceuticals, Inc.). Patent number: WO2004035575, 2004.

(20) Related research has since been published, see: (a) Nugent, T. C.; Wakchaure, V. N.; Ghosh, A. K.; Mohanty, R. R. *Org. Lett.* **2005**, *7*, 4967. (b) Alexakis, A.; Gille, S.; Prian, F., Rosset, S.; Ditrick, K. *Tetrahedron Lett.* **2004**, *45*, 1449.

(21) Further attempts to improve the *cis/trans* selectivity proved to be futile, e.g. (1) hydrogenation at 0 °C, (2) use of Pt on alternative supports, e.g. alumina powder or sulfide carbon, and (3) prereduction of the Pt/C catalyst.

(22) Even with high Pd catalyst loadings and higher pressure (e.g., 125 psi) and/or heating, yields in the range of 10−35% were observed. Nevertheless, since the reason for incomplete reaction using Pd/C is not understood, further catalyst screening should be considered.

Table 3. **Effect of water on the product yield profile (HPLC[a] data)[b]**

entry	H_2O (equiv)	(2*S*,3*S*)-**6** (%)	(2*S*,3*R*)-**6** (%)	(2*R*,3*R*)-**6** (%)	ee
1	none	75.7	14.3	1.58	96
2	0.4	77.7	9.0	3.37	92
3	0.6	80.6	8.8	3.20	92
4	1.2	80.2	8.4	4.57	89
5	1.8	79.7	8.2	4.49	89
6	3.0	77.7	8.0	4.87	88

[a] Ultron ES OVM HPLC column (chiral) and Waters Symmetry C_8 HPLC column (nonchiral) data. [a] 1.0 mmol scale, 5% Pt/C (10 wt %, 1−4% water content)

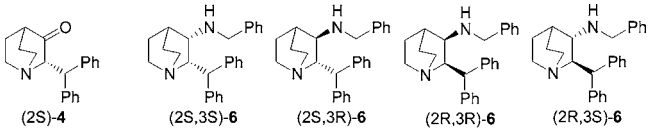


Figure 1. **Possible diastereomeric amine products from reductive amination of ketone (2*S*)-4 with benzylamine.**

Table 4. **Reaction yield and optical purity versus $Ti(O^iPr)_4$ stoichiometry[a]**

entry	$Ti(O^iPr)_4$ (equiv)	yield (%)	ee
1	1.05	78	91
2	1.1	80	90
3	1.2	79	89
4	1.3	83	93
5	0.34	36	79

[a] Ultron ES OVM HPLC column (chiral) and Waters Symmetry C_8 HPLC column (nonchiral) data; 60 psi, all reactions stopped at 10 h.

time; (3) control of the water content allows the overall yield of (2*S*,3*S*)-**6** to be maximized (Table 3, Figure 1). Finally, (4) lower grade $Ti(O^iPr)_4$ (Aldrich, TYZOR 97%, 2.0 L = $109.00, neat) works equally well as highly purified $Ti(O^iPr)_4$ (99.999%). Stoichiometric quantities are required for complete reaction (Table 4).

Another avenue to change the diastereoselectivity of the reduction could potentially arise from the use of alternative solvents and/or cosolvents. A very brief study of these factors follows. Addition of 25 equiv (based on the limiting reagent: ketone (2*S*)-**4**) of anhydrous CH_3OH, a protic solvent, essentially left the product profile unchanged, compare entry 1 (Table 5) with entry 1 (Table 3), the same result as if no water had been added. Replacing THF with toluene slowed the reaction down, and the addition of further cosolvents did not improve the reaction profile (Table 5).

The crude product **6** could be recrystallized from a toluene/*n*-hexane mixture once and consistently provided the product (2*S*,3*S*)-**6** in 61% yield with >99.5% chemical purity (HPLC) and ≥99% de and ≥99% ee (chiral HPLC, see Experimental Section). Interestingly, the use of hexanes or heptanes, in place of *n*-hexane, proved deleterious, resulting in a slightly poorer impurity profile that did not meet our target specifications for (2*S*,3*S*)-**6**.

Secure in our ability to produce reliable batches of enantiopure (2*S*,3*S*)-**6**, we next examined its debenzylation (Table 6). Reaction of amine (2*S*,3*S*)-**6**, at room temperature,

Table 5. **Effects of solvent and cosolvent on reaction profile[a]**

entry	solvent	additive[b]	(2*S*,3*S*)-**6** (%)	(2*S*,3*R*)-**6** (%)	(2*R*,3*R*)-**6** (%)	ee
1	THF	MeOH (25 equiv)	77.9	12.1	1.68	96
2	toluene	none	67.2	8.6	1.69	95
3	toluene	H_2O (3 equiv)	72.2	6.3	3.00	92
4	toluene	HOiPr (6 equiv)	68.9	8.6	1.68	95

[a] Ultron ES OVM HPLC column (chiral) and Waters Symmetry C_8 HPLC column (nonchiral) data. [b] Additives added at start of hydrogenation.

Table 6. **Debenzylation of (2*S*,3*S*)-6[a]**

entry	solvent	acid/equivalents	time (h)	conversion[b]
1	CH_3OH	*p*-TsOH/1.05	9.0	99
2	CH_3OH	CH_3SO_3H/1.05	12	100
3	CH_3OH	HCl/1.05	12	100
4	H_2O	HCl/1.05	14	52
5	H_2O	HCl/2.4	6.5	100

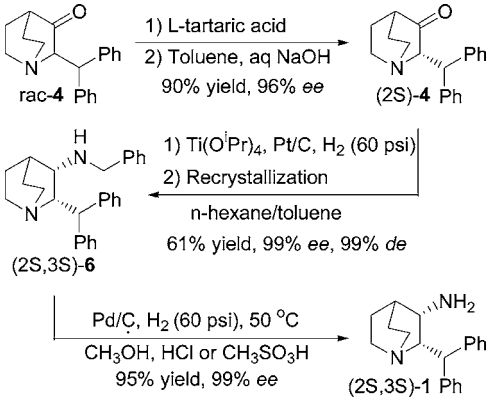
[a] All reactions 1 mmol scale, 1/10 wt % of 5% Pd/C (50% wet), 50 ± 5 °C, 50 ± 5 Psi H_2, 0.25 M. [b] First aliquot showing 100% conversion or last aliquot examined.

with $Pd(OH)_2$ or Pd/C in the presence of an acid resulted in incomplete reaction. Next we examined the hydrogenolysis at elevated temperature. Regardless of the acid employed the debenzylations were quantitative.[23] From a manufacturing point of view, methanesulfonic acid was more attractive than HCl because it allows more flexibility in the potential equipment trains to be used.

Conclusion

The synthesis outlined in Scheme 4 has enabled us to increase the yield of primary amine (2*S*,3*S*)-**1** by 40% when compared to the previous best synthetic methods reported for its synthesis. Paramount to achieving this overall yield increase was the identification of racemic benzhydryl quinuclidinone **4** for dynamic kinetic resolution studies, that culminated in an efficient method for the conversion of ketone *rac*-**4** to (2*S*)-**4**. All previous resolution strategies used advanced intermediates that were not capable of dynamic kinetic resolution.

Scheme 4. **Synthesis of (2*S*,3*S*)-1 from racemic ketone 4**



Introduction of the exoskeletal nitrogen was not trival because it required preservation of the existing α-labile (2*S*) stereocenter of ketone (2*S*)-**4**, good cis diastereoselectivity, and good yield for the amine product (2*S*,3*S*)-**6**. To maximize these desired attributes, we developed a new method for diastereoselective reductive amination [$Ti(O^iPr)_4$/Pt−C/H_2].[19] This reagent combination is a powerful tool for reductively aminating α-chiral ketones with retention of stereochemical information. To our knowledge this is the first example of such a feat, albeit no negative examples were found in the literature. Finally, this new method is noteworthy because it demonstrates the first reported use of $Ti(O^iPr)_4$/Pt−C/H_2 for reductive amination. Previously, chemists had only examined the use of hydride reagents[11,13,14] in combination with $Ti(O^iPr)_4$ for reductive amination.[20]

The aforementioned combined advances, as outlined above, now allow the efficient large-scale synthesis of amine (2*S*,3*S*)-**1** for the synthesis of quinuclidine derivatives.

Experimental Section

General Remarks. The NMR spectra were recorded on a Brueker instrument at 300 MHz for ^1H and 75 MHz for ^{13}C, with tetramethylsilane as an internal standard. All melting points were measured on a capillary melting point apparatus and are uncorrected. All reactions were performed under a positive pressure of nitrogen. All chemicals and reagents were purchased and used without further purification unless otherwise mentioned. Dry solvents were used as purchased.

HPLC Methods. Reaction progress was monitored by HPLC with purities being determined by peak area percent. A Hewlett-Packard (Agilent) 1100 with variable UV/Vis detector was used for all analyses.

*HPLC analysis for compounds racemic-**4** and racemic cis- and trans-**6**:* Waters Symmetry C8 column; dimensions: 3.9 mm × 150 mm; mobile phase: pH 5.0 buffer/MeCN = 65:35 (v/v) [buffer prepared as follows: dissolve NH_4OAc (1.93 g) in H_2O (950 mL), add Et_3N (1.0 mL) and adjust pH to 5 with HOAc, dilute to 1000 mL with H_2O]; flow: 1.0 mL/min; detection wavelength: 220 nm (bandwidth 8 nm), ref 360 nm (bandwidth 100 nm); temperature: 23 °C; injection volume: 20 μL/mL; sample preparation: sonicate 20 mg of sample in MeCN (20 mL), dilute with mobile phase to 100 mL. Retention time (min). *rac*-**4**: 8.5 min; (2*S*,3*R*)- and (2*R*,3*S*)-**6** (enantiomeric *trans* products): 15.3; (2*S*,3*S*)- or (2*R*,3*R*)-**6** (enantiomeric cis products): 16.4.

*Chiral HPLC analysis for (2R)- or (2S)-ketone-**4**:* Chiral-Pak-AD column; dimensions: 4.6 mm × 250 mm (and guard column); mobile phase: 95 vol % hexane, 5 vol % 2-propanol, 0.1 vol % diethylamine; flow: 1.0 mL/min; detection wavelength: 220 nm; temperature: 20 °C; injection volume: 10 μL/mL; sample diluent: 20 vol % 2-propanol, 80% mobile phase. Sample preparation: sonicate 20 mg of sample in 2-propanol (20 mL), dilute with mobile phase to 100 mL. Retention time (min). (2*S*)-ketone-**4**: 7.45; (2*R*)-ketone-**4**: 8.02.

*Chiral HPLC analysis for racemic cis- and trans-**6**:* Ultron ES-OVM column; dimensions: 4.6 mm × 150 mm (add guard column); mobile phase: pH 6.2 buffer/MeCN, 82:18 (v/v) [buffer prepared as follows: dissolve KH_2PO_4 (1.36 g) in H_2O (950 mL), adjust pH to 6.2 with H_3PO_4, dilute to 1000 mL with H_2O]; flow rate: 1.0 mL/min; detection wavelength: 210 nm; temperature: 25 °C; injection volume: 20 μL; sample preparation: sonicate 20 mg of sample in MeCN (20 mL), then dilute to 100 mL with mobile phase. Retention time (min). (2*S*,3*S*)-**6** (*cis* desired): 16.61; (2*R*,3*R*)-**6** (*cis* undesired): 23.44.

(2*S*)-Benzhydryl-3-quinuclidinone 4 L-Tartaric Acid Salt. Racemic 2-benzhydryl-3-quinuclidinone **4** (52.45 g, 180 mmol) was dissolved in denatured ethanol (5% methanol, 5% 2-propanol) (525 mL, 0.35 M) with acetic acid (10.4 mL, 180 mmol), and L-tartaric acid (27 g, 180 mmol) was added. The mixture was heated to reflux for 12 h and then allowed to cool to room temperature and held for 1 h. The solids were filtered, collected, and dried under vacuum at 40 °C for 12 h. The desired 1:1 L-tartaric acid salt of (2*S*)-ketone **4** weighed 69.9 g (88% yield).

(2*S*)-Benzhydryl-3-quinuclidinone 4. The L-tartaric acid salt from the previous example (69.9 g, 158 mmol) was suspended in toluene (700 mL) and cooled with an ice−water bath while a saturated solution of sodium bicarbonate (500 mL) was added dropwise. Note the use of NaOH avoids the often noted foaming associated with the use of bicarbonate. The temperature was maintained below a maximum of 25 °C. The clear, biphasic mixture was stirred for 20 min at 25 °C, and the layers were separated. The organic layer was washed with water (100 mL), the layers were separated, and the organics were dried over sodium sulfate. The organics were filtered and evaporated in vacuo to provide the desired, optically active ketone as a colorless solid (45.66 g; 99% yield). Mp = 145−146 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.86−2.00 (m, 4H), 2.41−2.43 (m, 1H), 2.54−2.59 (m, 2H), 3.08 (t, 2H), 3.98 (d, 1H), 4.55 (d, 1H), 7.17 (m, 8H), 7.38−7.41 (m, 2H).

(2*S*)Benzhydryl-(3*S*)-benzylamino-quinuclidine 6 [(2*S*,3*S*)-6]. *With Aluminum Tri-isoproxide*. Under nitrogen, (2*S*)-benzhydryl-3-quinuclidinone **4** (0.50 g, 1.0 equiv, 1.72 mmol) was dissolved in anhydrous THF (2.0 mL). Benzylamine (0.21 mL, 1.1 equiv, 1.89 mmol) was then added followed by a solution of aluminum isopropoxide (0.42 g, 1.2 equiv, 2.06 mmol) in anhydrous THF (2.0 mL). The solution was stirred for 3 h. To this colorless solution was then added a slurry of 5% Pt/C (0.063 g, Degussa F101RA/W, ∼60% wet) in anhydrous THF (1.0 mL). The reaction was placed in a Parr reactor, pressurized to 75 psi H_2, and allowed to react at room temperature for 15 h. The reaction mixture was poured into 15 mL of 2.0 M HCl, followed by filtration, basification with 1 M NaOH and extraction with 50 mL of methyl tertiary butyl ether (MTBE). The MTBE layer was dried with $MgSO_4$, followed by removal of solvent in vacuo, leaving a white crystalline solid. This was analyzed

(23) Transfer hydrogenation conditions were briefly examined for hydrogenolysis. The most useful reaction was one in which a methanolic solution (0.30 M) of (2*S*,3*S*)-**6** had ammonium formate (4.0 equiv) and 5% Pd/C (1/6 wt %, 50% wet) added to it. When this solution was heated at 50 °C for 2.5 h, a 70% conversion was noted. An additional 3 h at the increased temperature of reflux was required for full conversion.

as all *cis* isomer (<2% *trans* isomer), >99% ee (none of other enantiomer observed).

With Titanium Tetra-isoproxide. (2*S*)-Benzhydryl-3-quinuclidinone **4** (9.00 g, 30.9 mmol) was dissolved in anhydrous THF (75 mL, 0.40 M). The solution was transferred through a port to a 300-mL autoclave with the hydrogenation head secured while a positive flow of nitrogen was maintained. Through the same port on the hydrogenator head and under 300 rpm stirring was added benzylamine (3.7 mL, 33.9 mmol) followed by titanium (IV) isopropoxide (10.9 mL, 36.9 mmol). The port was closed, and the autoclave was pressure tested (90 psi nitrogen) while the reaction mixture was stirred at 300 rpm. After 3.0 h at 25 °C the N_2 pressure was released, and under a positive flow of nitrogen was added a slurry of 5% Pt/C (1.13 g; 59.4% wet) in THF (3.0 mL) via syringe (14-gauge needle) through the port. Additional THF (2 mL) was used to slurry the residual catalyst and was added to the reaction. The port was closed and the autoclave pressurized to 75 psi with hydrogen and then slowly vented. This was repeated three times. The final hydrogen pressure was adjusted to 75 psi and the reaction mixture hydrogenated overnight (12 h) with stirring maintained at 600 rpm. The vessel was then vented and subsequently pressurized with nitrogen (90 psi) and vented. The reactor was pressurized with nitrogen and vented three more times.

Under positive nitrogen flow 42 mL of ice-cold 12.4% hydrochloric acid (28 mL water + 14 mL 37% HCl) was added slowly and the reaction mixture stirred under nitrogen for 1 h at 25 °C and 900 rpm and subsequently pressure transferred into a 250-mL Erlenmeyer flask. The hydrogenator was charged with toluene (50 mL) and 30 mL of 10% hydrochloric acid. The mixture was agitated for 30 min at 900 rpm and again pressure transferred into an Erlenmeyer flask. The combined biphasic heterogeneous solution was filtered through a 1-cm Celite pad under vacuum to remove the Pt/C catalyst. The filter cake was further rinsed with aqueous 10% HCl (100 mL). The clear filtrate phase separated immediately, and the organic layer was removed and discarded. Under stirring and cooling, 50 mL of toluene was added and the pH adjusted to approximately 13 by slow addition of 50% NaOH (30 mL). The biphasic slurry was filtered through a 1-cm Celite pad to remove titanium salts. The filter cake was washed with toluene (2 × 50 mL), the layers were then separated, and the toluene layer was concentrated at 80 °C until the volume of toluene was reduced to 20 mL. Then, 40 mL of *n*-hexane was added, and the mixture was slowly cooled to 10 °C over 2−3 h (0.5 g of seeds (∼ 5%) was added at 55 °C). The precipitate was filtered, washed with 40 mL toluene/*n*-hexane 1/6 (v/v), and dried in a vacuum at 40 °C. The yield of colorless solid was 7.3 g, 61% of theory.[4a,c] This material matched the reported spectroscopic data (^{1}H and ^{13}C NMR) and was further analyzed by achiral HPLC (>99% de) and chiral HPLC (>99% ee).

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