Organic Process Research & Development **2002**, *6,* 42–48

Practical Large-Scale Synthesis of 3,4-Isopropylidenedioxypyrrolidine Hydrotosylate: Atom Economical Self-Hydrogenolysis of a Crystalline Borane−Benzylamine Adduct

Michel Couturier,* Brian M. Andresen, Jeffrey B. Jorgensen, John L. Tucker, Frank R. Busch, Steven J. Brenek, Pascal Dubé, David J. am Ende, and Joanna T. Negri

Chemical Research and Development, Pfizer Inc., Eastern Point Road, Groton, Connecticut 06340, U.S.A.

Abstract:

An efficient four-step sequence has been developed for the synthesis of 3,4-isopropylidenedioxypyrrolidine hydrotosylate starting from inexpensive *N*-benzylmaleimide. This approach features a novel *N*-debenzylation procedure that utilizes the corresponding borane−benzylamine complex as an internal hydrogen-transfer source. This palladium-catalyzed tandem protonolysis/hydrogenolysis allows cleavage of the borane−amine adduct and debenzylation in a single operation.

Introduction

In a recent development program of a drug candidate, we required large quantities of 3,4-isopropylidenedioxypyrrolidine, **1**, as the tosylate salt. Although the corresponding free-base has been reported in the literature,[1] close inspection of the lengthy six-step sequence from L-arabinose (**2**) revealed potential scale-up issues. In fact, the described procedures are not applicable to manufacturing since tedious work-ups are involved and the intermediates do not lend themselves to easy isolations, thereby requiring chromatographic purifications. Also, the critical information on the purity of the material is not addressed in these reports. This prompted us to investigate alternative routes. Several commodity chemicals were considered as starting materials, including: 3-pyrrolidene (**3**), 1,4-dibromobutane-2,3-dione (**4**), butan-1,2,3,4-tetraol (**5**), *cis*- and *trans*-1,4-dichloro-2-butene (**6**, **7** respectively), *meso*-tartaric acid (**8**), and D-ribose (**9**) (Figure 1). Although initial bulk lots were manufactured using the two former raw materials, they did not meet our long-term goal to develop a manufacturing process that would meet our cost objectives. We then set our attention on *N*-benzylmaleimide (**10**), a relatively inexpensive commodity chemical used in the trovafloxacin synthesis.[2] Transformation of this material to the title compound would require four steps: dihydroxylation, imide reduction, ketalization, and debenzylation, the sequence of which needed to be established. As such, this raw material met our criteria of an inexpensive compound that could be transformed to pyrrolidine **1** in relatively few operations.

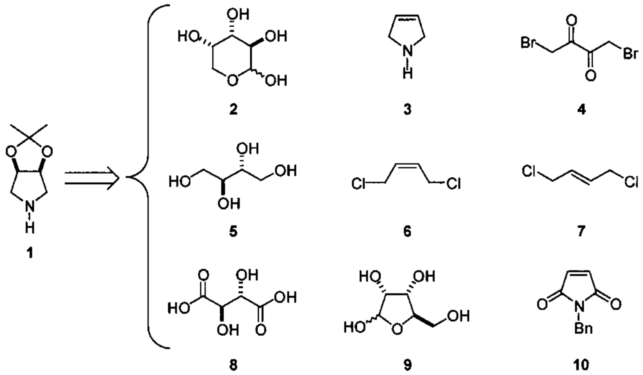
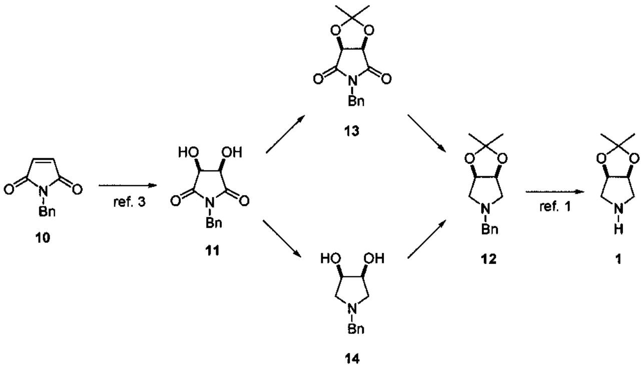


Figure 1. **Starting materials considered for the preparation of pyrrolidine 1.**

Results and Discussion

Route Selection. Sequencing the steps to convert *N*-benzylmaleimide (**10**) to the desired pyrrolidine **1** would prove straightforward. The *syn*-dihydroxylation of the former to diol **11** has already been described in the literature,[3] as has the *N*-benzyl hydrogenolysis of the penultimate intermediate **12**.[1] The key strategy was to determine whether to protect the diol **11** prior to the reduction, or install the acetonide on diol **14** following the imide reduction. Since the former approach avoids unnecessary consumption of hydride source by diol **11**, it would be advantageous to perform the imide reduction after ketalization of the diol, provided that the acetonide **13** would survive the reduction conditions. Initial experimentation on this route demonstrated the concept and exhibited potential for scale-up (Scheme 1).

Scheme 1



---

(1) (a) McCraig, A. E.; Meldrum, K. P.; Wightman, R. H. *Tetrahedron* **1998**, *54*, 9429. (b) McCraig, A. E.; Wightman, R. H. *Tetrahedron Lett.* **1993**, *34*, 3939. (c) Thompson, D. K.; Hubert, C. N.; Wightman, R. H. *Tetrahedron* **1993**, *49*, 3840.

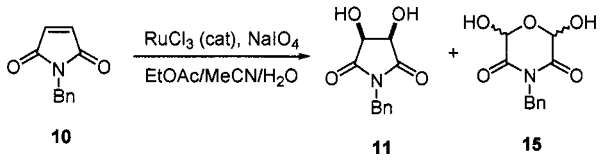
(2) (a) Norris, T.; Braish, T. F.; Butters, M.; DeVries, K. M.; Hawkins, J. M.; Massett, S.; Rose, P. R.; Santafianos, D.; Sklavounos, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, *10*, 1615. (b) Braish, T. F.; Castaldi, M.; Chan, S.; Fox, D. E.; Keltonic, T.; McGarry, J.; Hawkins, J. M.; Norris, T. *Synlett* **1996**, 1100. (c) Brighty, K. E.; Castaldi, M. J. *Synlett* **1996**, 1097.

(3) Miller, S. A.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 8100.

10.1021/op0102161 CCC: $22.00

Step 1: Dihydroxylation. The precedented *syn*-dihydroxylation of *N*-benzylmaleimide (**10**) has been reported using OsO_4.[3] In addition to a modest yield of 51%, this procedure has major drawbacks, including the use of osmium, a product isolation which requires a Florisil filtration followed by a silica gel chromatographic purification, and lack of information on the purity.[4] Recently, Shing et al. reported a ruthenium-catalyzed flash-dihydroxylation procedure using sodium periodate as the co-oxidant.[5] Small-scale application of this methodology on *N*-benzylmaleimide (**10**) quickly revealed that this procedure would be more practical and higher-yielding than the published osmium method (Scheme 2).

Scheme 2



Not unexpectedly, several process-related issues needed to be addressed prior to implementation of this reaction on pilot-plant scale. For instance, the original dihydroxylation procedure utilized an aqueous solution of sodium periodate. Since it is only sparingly soluble in water, 1 equiv of oxidant would require over 11 vol of water at saturation point. This would translate into low reactor throughput and excessive aqueous waste. In fact, the original literature procedure entails a 75 vol reaction with 125 vol at quench. Another issue arose when a 50 °C temperature increase was measured when the reaction was performed under adiabatic conditions. Both of these issues were resolved by adding the periodate portionwise as a solid to the reaction mixture containing 5 vol of water and an equal amount of organics. Under these favorable conditions, the oxidation performs equally well as in the original procedure, and the reaction exotherm can be safely controlled. For example, 12 successive charges of periodate led to a series of easily controlled 3−5 °C exotherms. From an engineering standpoint, vigorous agitation with a low minimum stir volume is necessary to avoid caking of dense sodium periodate at the bottom of the vessel.

The effect of reducing the catalyst loading on the reaction outcome was also investigated. Although the literature procedure suggested using 7 mol % of ruthenium chloride, decreasing the loading to 0.5 mol % on a 100 g scale had no significant impact on the yield. However, further reduction of the catalyst loading led to increased amounts of the hydrated dialdehyde **15** that arose from oxidative cleavage of the diol. Considering that excess periodate has a deleterious effect on the diol product, we further needed to determine the amount of co-oxidant needed to give the optimal yield. For this purpose, the reaction profile was established by HPLC, where the reaction mixture was analyzed after successive 0.1 equiv additions of periodate. The data showed that the maximal yield could be achieved using 1.3 equiv of the periodate co-oxidant (Figure 2).

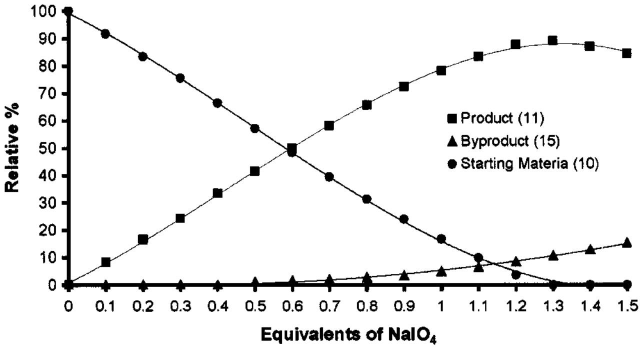


Figure 2. **Relative percentages of 10, 11, and 15 as a function of equivalents of periodate added.**

Safety analysis of the ruthenium-catalyzed dihydroxylation led to a concern about ruthenium exposure. Although ruthenium is routinely utilized in industrial chemical processes[6] and the reactors can be efficiently decontaminated with citrates,[7] the active species, ruthenium tetraoxide, is highly reactive, toxic, and volatile and therefore requires rigorous exposure control. However, it has been postulated by Sharpless that acetonitrile binds to lower-valent ruthenium.[8] In this case, the oxidant is kept in solution and should not be present in the headspace of the reactor. To substantiate this hypothesis and to address operator safety, a nitrogen bleed over the headspace at a rate of 20 mL min^{-1} was scrubbed through an aqueous sodium thiosulfate solution. Analysis of this solution by atomic absorption did not show detectable amounts of ruthenium (LOQ 0.1 ppm). From this perspective, this process is safe to run with appropriate safety protocols.

Product isolation from the reaction mixture is relatively straightforward. Upon completion, the reaction is conveniently quenched with the sodium thiosulfate solution previously utilized as the scrubber system. Following removal of sodium iodate by filtration,[9] the product is extracted in ethyl acetate. The combined organics are atmospherically distilled using ethyl acetate to ensure complete azeotropic removal of the acetonitrile[10] and water.[11] The product is then crystallized by the addition of hexane as an anti-solvent, and any remaining ash will be removed by a spec-free filtration in the last step (vide infra).

Armed with these facts, this chemistry was demonstrated by processing 50 kg lots in the pilot plant. Although the first run, using 0.5 mol % catalyst loading, did not give rise to

---

(4) Residual levels of osmium were not addressed and measured in the report.

(5) (a) Shing, T. K. M.; Tam, E. K. W.; Tai, V. W.-F.; Chung, I. H. F.; Jiang, Q. *Angew. Chem. Eur. J.* **1996**, *2*, 50. (b) Shing, T. K. M.; Tai, V. W.-F.; Tam, E. K. W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2312.

(6) Harre, M.; Haufe, R.; Nickisch, K.; Weinig, P.; Weinmann, H. *Org. Process Res. Dev.* **1998**, *2*, 100.

(7) Row, T. H. *Nucl. Sci. Abstr.* **1967**, *21*, 27690.

(8) Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(9) In an effort to eliminate the filtration process to remove the sodium iodate, a screen was conducted to test oxidants other than sodium periodate. In agreement with Shing's previous observation (ref 5), however, co-oxidants such as 30% hydrogen peroxide, *tert*-butylhydroperoxide, or bleach solutions were not efficient co-oxidants for this methodology.

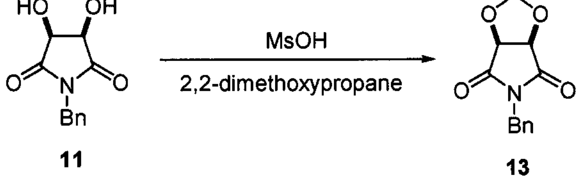
(10) (76.1 °C, 33% MeCN) Mato, F.; Sanchez, M. *An. R. Soc. Esp. Fis. Quim.* **1967**, *63B*, 971.

(11) (70.4 °C, 30% water) Ellis, S. R. M.; Garbett, R. D. *Ind. Eng. Chem.* **1960**, *52*, 385.

technical difficulties, the yield was a modest 50%, lower than the 75% obtained in laboratory pilots. It became apparent that insufficient amounts of catalyst led to considerable oxidative cleavage to **15**. In the next run, the loading of catalyst was increased to 1 mol %, which gratifyingly led to a 65% yield for the first crop. As laboratory experiments continued to work well with 0.5 mol % catalyst, this lead to a development dilemma. Our goal was to use the smallest possible $RuCl_3$ charge, while maintaining a robust process and good yield. Since the laboratory-scale experiments were not predictive of the outcome in the pilot plant, an attempt to fine-tune the procedure by varying the catalyst charge was conducted on-scale to determine the optimal catalyst charge for this process. Through a succession of minor modifications, the optimum catalyst charge was determined to be 0.9 mol %. The yield was further improved by decreasing the polarity of the isolation liquor by using less ethyl acetate, leading to a 74% one-crop isolation process.

Step 2: Ketalization. The second step involves the protection of the diol as an acetonide. Initial experiments using the standard procedure with acetone and *p*-toluenesulfonic acid quickly revealed a reaction halted by an unfavorable thermodynamic acetonide/diol ratio of 7:3, respectively. We reasoned, however, that the use of 2,2-dimethoxypropane would entropically favor the product by releasing 2 equiv of methanol.[12] Indeed, lab experiments using *p*-toluenesulfonic acid in neat 2,2-dimethoxypropane showed 98% conversion to the desired acetonide. Isolation of the product proved straightforward. Since both the diol **11** and the acetonide **13** are sparingly soluble in 2,2-dimethoxypropane, the reaction is run as a slurry-to-slurry. We therefore expected that an aqueous neutralization work-up procedure could be avoided by the addition of an anti-solvent, which would fully crystallize the product. For this purpose, isopropyl ether was found to be the cosolvent of choice to achieve a high yield of 90%. Furthermore, to avoid contaminating the product with *p*-toluenesulfonic acid, a catalyst that would be soluble in this solvent system was sought and methanesulfonic acid successfully met this criterion. Hence, the diol is slurried in two volumes of inexpensive 2,2-dimethoxypropane in the presence of 10 mol % of methanesulfonic acid. When the reaction is deemed complete, 8 volumes of isopropyl ether are added and the stable, crystalline intermediate **13** is isolated by filtration (Scheme 3).

Scheme 3



11

13

With this procedure in hand, diol **11** was processed in the pilot plant to give acetonide **13**, but this initial lot was contaminated with 2.5% of starting material. At that time, purge of the latter in the subsequent steps was unknown, and purification by recrystallization was of no avail. Since the actual reaction process is not more complicated than a recrystallization, the material was resubmitted to similar reaction conditions in order to consume any remaining diol **11** and to drive the reaction to completion. Unfortunately, initial laboratory pilots quickly revealed a rapidly decomposing reaction mixture. In an effort to understand why resubjecting the product to the exact same reaction conditions led to decomposition, a similar reaction was performed in the absence of acetonide **13**. It was determined that dimethoxypropane is unstable to methansulfonic acid and this was the source of our problem. We therefore reasoned that the methanol liberated from the initial ketalization reaction must have a beneficial effect in stabilizing the dimethoxypropane. This could be attributed to the additional methanol providing the right equilibrium between the ketal and the corresponding oxonium, thereby minimizing aldol type self-condensations (Figure 3).

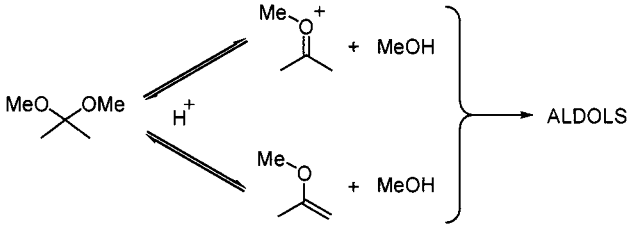


Figure 3. **Potential decomposition pathway of 2,2-dimethoxypropane with MsOH.**

To substantiate this hypothesis, one equivalent of methanol was added prior to the methanesulfonic acid charge, and the reaction proceeded without the deleterious side reactions. With these highly favorable conditions, the rework could then be accomplished in 94% yield providing over 104 kg of pure acetonide **13**, free from diol **11**.[13]

Step 3: Imide Reduction. The third step involves a borane-mediated reduction of imide **13** to the corresponding amine **12**.[14] Using commercial borane−tetrahydrofuran,[15] followed by a methanol quench,[16] this transformation can be achieved very efficiently, and provides the desired product in almost quantitative yield. However, the desired amine is generally contaminated with 3−5% of isopropyl ether, resulting from reduction of the ketal. Fortunately, this impurity can be purged in the final crystallization (vide infra). In this salt-free process, all traces of boron are conveniently removed from the reaction mixture as trimethylborate by full displacement in methanol. The trimethylborate forms an azeotrope with methanol (70% $B(OMe)_3$ at 59 °C), and under these conditions, even boric acid can be removed from the

---

(12) (a) Lorette, N. B.; Howard, W. L. *J. Org. Chem.* **1960**, *25*, 521. (b) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252.

(13) It was later demonstrated by purging experiments that marginal quantities of diol had no impact on the quality of the last-step product; thus, material with low levels of starting material may be used directly in the next steps.

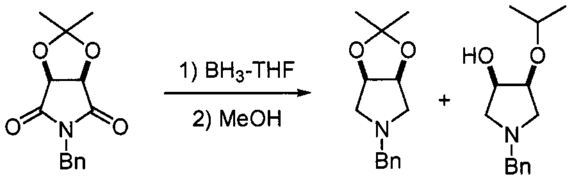
(14) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912.

(15) Commercial bulk of borane−tetrahydrofuran adduct can be supplied by Callery Chemical Company as a 2 M solution in THF.

(16) The methanolysis of residual hydrides occurs in a stepwise process. First, the excess reagent is consumed, followed by the borane−amine complex at higher temperature, from which 3 equiv of hydrogen gas is evolved.

reaction mixture.[17] This provided the advantage of avoiding another aqueous work-up (Scheme 4).

Scheme 4



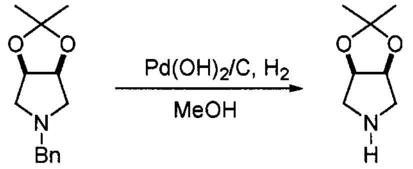
13 **12** **16**

In an effort to develop a more economically efficient process, we investigated the in-situ preparation of borane−THF with sodium borohydride and boron trifluoride. Using stoichiometic quantities,[18] a considerably higher proportion of isopropyl ether was observed, ca. 15%. We further investigated this deleterious side reaction by examinating the effect of excess sodium borohydride versus excess boron trifluoride on the reaction profile. Using 1 mol excess of sodium borohydride, a far greater amount of reduced ketal was formed, ca. 80%. Alternatively, 1 mol excess of boron trifluoride led to only 19% of the isopropyl ether. These experiments suggest that the catalytic effect of boron trifluoride is much less deleterious than stoichiometric reduction with sodium borohydride. As such, we have not succeeded in mimicking commercial quality borane−THF using the in-situ method outlined above.[19] It is noteworthy that the industrial preparation of borane−THF uses diborane gas, and therefore neither borohydride nor boron trifluoride is present in the solution (aside from 0.002 M quantity of the former as a stabilizer, preventing THF ring-opening).[20]

Exemplification of this chemistry on 47.5 kg scale was performed using 300 L of a 2 M BH_3−THF solution in tetrahydrofuran, which translates to 3.3 equiv. The exothermic reaction was controlled by a slow, portion-wise addition of the borane solution, and these favorable conditions led to a 5 °C exotherm. The reaction mixture was carefully quenched with methanol, and after complete removal of trimethylborate by azeotrope, the crude solution of pyrrolidine **12** in methanol was used as such for the next transformation. In a representative experiment, the HPLC purity of pyrrolidine **12** was 93.6% with only 5.5% of the side product **16**.

Step 4: *N*-Benzyl Hydrogenolysis. Using the crude methanol solution of benzylamine **13** described above, hydrogenolysis of the benzyl protective group can be accomplished without incident using 10% weight loading of Pearlman's catalyst at room temperature. Alternatively, standard 10% palladium on carbon can be used, but at a higher temperature of 60 °C. The crude methanol solution obtained after removal of the catalyst is then taken directly into the salt formation/purification sequence. Interestingly, the initial dark-brown solution is found completely decolorized after the hydrogenolysis (Scheme 5).

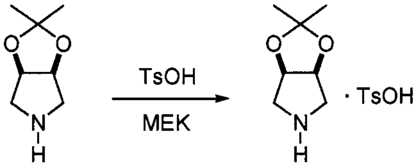
Scheme 5



12 **1**

Step 5: Salt Formation. At this stage, it is of importance to purge undesired isopropyl ether impurity and to remove ash from previous steps to obtain high-quality material that would meet specifications. We determined that acetone, methyl ethyl ketone (MEK), and methyl isobutyl ketone (MIBK) would be suitable solvents for the salt formation. They freely dissolve *p*-toluenesulfonic acid and, more importantly, the corresponding salt is only sparingly soluble in these solvents. Prior to the salt formation, however, the solvents from the previous reaction, ca. methanol and water from the wet catalyst, must be completely displaced to ensure an efficient, high-yielding crystallization of the product. Incidentally, MEK provides particularly efficient azeotropes for both methanol[21] and water.[22] Furthermore, the boiling point of the free amine **1** was observed at 180 °C, and no azeotrope was detected with MEK (Scheme 6).

Scheme 6



1 **17**

Accordingly, the crude methanol solution of pyrrolidine **1** was concentrated to a minimum volume, after which the remaining methanol and water were removed by azeotrope with MEK. At this stage, all remaining insoluble ash was removed by a speck-free filtration. Following addition of a freshly prepared *p*-toluenesulfonic acid solution in MEK, the resulting crystalline tosylate salt **17** was crystallized and isolated by filtration. The yield for the three-step sequence from imide **12** (reduction, debenzylation, and salt formation) was in the range 70−74% with a 99.5% purity well within specifications.[23] Atomic absorption analysis showed that ruthenium and palladium were undetected at ppm levels in the hydrotosylate salt **17** (LOQ 0.1 ppm).[24]

---

(17) Schlesinger, H. I.; Brown, H. C.; Mayfield, D. L.; Gilbreath, J. R. *J. Am. Chem. Soc.* **1953**, *75*, 213.

(18) The borane−THF was prepared at room-temperature according to the following equation: $3NaBH_4 + 4BF_3\text{-}OEt_2 + 4THF \rightarrow 4BH_3\text{-}THF + 3NaBF_4 + 4Et_2O$, and stirred for 1 h at the same temperature prior to the addition of imide **13**.

(19) Our research efforts continue to investigate alternate reducing reagents with the goal of minimizing the formation of this over-reduction by-product.

(20) Since the complex **18** has been observed from the reaction using generated borane, there may be a point of economic tradeoff in which the less expensive in situ borane reaction conditions compensate for the increased formation of ether **16**.

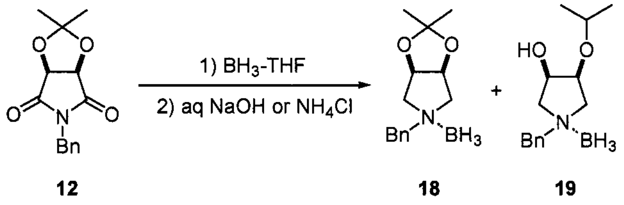
(21) (63.6 °C, 84% MeOH) Hill, D. W.; Van Winkle, M. *Ind. Chem. Eng. Chem.* **1952**, *9*, 319.

(22) (73.6 °C, 35% H_2O) Ellis, S. R. M.; Garbett, R. D. *Ind. Eng. Chem.* **1960**, *52*, 385.

(23) GC Purity: 99.5%; Counterion: 54.9% (54.5% theory); Boron: 0.9 ppm; Total solvent: 0.4%; Water: 0.03%; Total impurities 0.18%.

Tandem Methanolysis/Hydrogenolysis of the Crystalline *N*-Benzylamine−Borane Adduct. As mentioned above, the cost of commercial borane−THF significantly adds to the cost of the product. Efforts to utilize in situ borane preparation methods were undermined by the formation of by-product **16** in 15% yield. A solution became apparent when we discovered that the borane−amine complex **18** formed in the reaction is a stable, crystalline compound and purges this side product. This complex can be isolated following either an ammonium chloride quench (pH = 1) or 6 M potassium hydroxide quench (pH = 14) (Scheme 7).

Scheme 7



The complex **18** is surprisingly stable to prolonged stirring and can be easily crystallized from ethyl acetate. Its identity has been established by X-ray crystallography (Figure 4), and DSC analysis has determined that this compound is safe to be handled (55 J/g at an onset temperature of 125 °C). Interestingly, only one diastereomer is formed in this reduction.

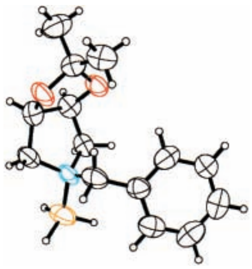
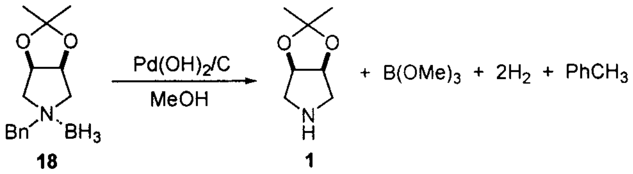


Figure 4. **ORTEP repesentation of amine−borane 18.**

An additional benefit of the borane−amine complex is that this crystalline compound can serve as an internal hydrogen source upon reaction with alcohols.[25−27] Indeed, in the presence of Pearlman's catalyst in methanol, the complex releases 3 equiv of hydrogen, which then conveniently hydrogenates the benzyl group (Scheme 8).

Scheme 8



This reaction was monitored by its pressure profile, and the plot clearly shows the initial evolution of hydrogen, which then partakes in the debenzylation. Over time, the stabilized pressure corresponds to the residual 2 equiv of hydrogen produced. The positive and negative slopes of pressure suggest that the rates of hydrogen evolution and debenzylation are relatively similar. In an effort to reduce the maximal pressure in the reactor, reaction conditions were sought where the rate of hydrogen evolution would be slower than debenzylation. We reasoned that a more sterrically hindered alcohol should decomplex the borane−amine adduct more slowly and perhaps not affect the debenzylation rate. The use of ethanol does decrease the alcoholysis of the borane amine **18**. Unfortunately, it also decreases the rate of hydrogenolysis to a similar extent and therefore does not relieve the pressure spike. Attempts at achieving this goal by lowering the reaction temperature also met with failure.

Another issue is the final pressure exerted by the residual 2 equiv of hydrogen. One option would be to physically vent the extra hydrogen from the reactor. A preferable approach would be to chemically scavenge some of the extra hydrogen with an additive. Indeed, by adding 1.5 equiv of allyl alcohol, the hydrogen is consumed practically as soon as it is formed, and this alleviated the maximal pressure to 125 psi, which is within limits of typical hydrogenation vessel. It is noteworthy that the experiment represents a 10 vol reaction with similar headspace, and therefore, throughput is not sacrificed (Figure 5).

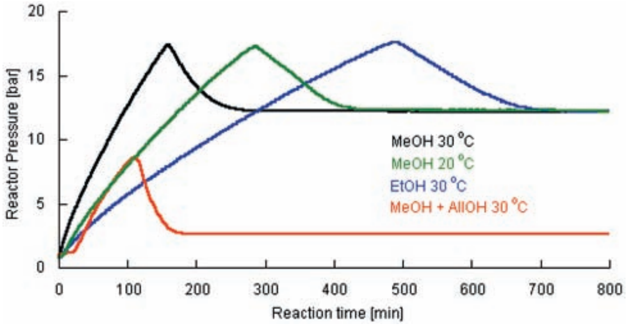


Figure 5. **Reactor pressure measured during the tandem alcoholysis/hydrogenolysis of borane−benzylamine 18 as a function of time.**

The use of this stable, crystalline adduct offers multiple benefits, including purge of a side product, lower cost, and ablility to serve as its own hydrogen source for the ensuing debenzylation. This atom economical approach is viable as a potential alternative method but has not yet been exemplified on pilot-plant scale. Work is currently in progress to understand the kinetics of the reaction to support potential implementation of this technology.

Conclusions

This work demonstrates an efficient and practical large-scale synthesis of pyrrolidine **1**. The synthesis described herein is shorter, higher-yielding, and less costly than the preparation of **1** from D-ribose. This route also avoids the use of stoichiometric osmium and successfully provided 194 kg of **17** for use in the preparation of a drug candidate in a

---

(24) Motojima, K.; Tatenuma, K.; Yoshida, Z.; Takeeishi, H.; Akatsu, E. *Anal. Chim. Acta* **1986**, *183*, 217.

(25) Couturier, M.; Tucker, J. L.; Andresen, B. M.; Dube, P.; Negri, J. T. *Org. Lett.* **2001**, *3*, 465.

(26) Couturier, M. Andresen, B. M.; Tucker, J. L.; Dubé, P.; Breneck, S. J.; Negri, J. T. *Tetrahedron Lett.* **2001**, *42*, 2763.

(27) Couturier, M.; Tucker, J. L.; Andresen, B. M.; Dubé, P.; Breneck, S. J.; Negri, J. T. *Tetrahedron Lett.* **2001**, *42*, 2285.

timely manner. Analytical testing of pyrrolidine **17** showed no Pd or Ru residue (LOQ < 1 ppm), with a GC purity of 99.5% well within specifications. As the manufacturing requirements increase, efforts are underway to further improve the process for future campaigns. Interestingly, the development of this process has set the stage for the discovery of a tandem methanolysis/hydrogenolysis of a borane−benzylamine adduct.

Experimental Section

General Procedures. Unless otherwise noted, all of the operations were performed in Clean-By-Test nitrogen-purged vessels. All charges and transfers are performed using isolated vacuum whenever possible. The hydrogenation equipment was prepared as directed by standard operating procedures.

***(meso)-N*-Benzyl-3,4-dihydroxy-2,5-pyrrolidinedione (11).** To a stirred solution of ruthenium(III) chloride hydrate (499 g, 2.20 mol) in water (250 L) was added a solution of *N*-benzylmaleimide (**10**) (50.0 kg, 267 mol) in ethyl acetate (64 L) and acetonitrile (125 L). The vessel containing the latter solution was rinsed with ethyl acetate (61 L) and combined to the reaction mixture. The reaction vessel was configured to vent through a scrubber solution of sodium thiosulfate (45 kg, 285 mol) in water (38 L) and then cooled to 5 °C. Under vigorous agitation, 12 equal portions of sodium periodate (12 × 6.2 kg, 12 × 29 mol) were added, allowing the exothermic reaction to cool back to 5 °C between each charge. Upon completion, the reaction mixture was quenched with the aqueous sodium thiosulfate scrubber solution. The vessel containing the latter was rinsed with water (19 L) and combined with the reaction mixture. The slurry was then filtered to remove any solid material, transferring the filtrate to a nitrogen-purged isolation vessel. The reaction vessel was then rinsed with ethyl acetate (285 L) which was then transferred through the filter cake and combined with the filtrate. After the contents of the isolation vessel were allowed to separate (30 min), the aqueous layer was transferred to the reaction vessel, to which ethyl acetate (125 L) was added. The contents of the reaction vessel were stirred (15 min) and then allowed to settle and separate (15 min). The aqueous layer was removed and drummed for disposal, and the organic layers were combined in the isolation vessel. A solution of sodium chloride (8.0 kg) in water (72 L) was added to the isolation vessel, and the resulting biphasic mixture was stirred (15 min) and then allowed to settle (15 min). The aqueous layer was removed and drummed for disposal. The product rich organic layer was concentrated (final volume of 300 L) by atmospheric distillation and then cooled to 60 °C. Ethyl acetate (303 L) was then charged to the isolation vessel, and the solution was further concentrated (final volume of 250 L) by atmospheric distillation. The solution was then cooled to 15 °C, and the resulting slurry was stirred for 4 h. Upon addition of hexanes (360 L), the slurry was further cooled to 5 °C, and stirred for an additional hour. The crystalline product was isolated by filtration, and then the isolation vessel and the filter cake were successively rinsed with a cooled mixture of ethyl acetate (22 L) and hexanes (91 L) at 10 °C. The filter cake was unloaded and dried under vacuum (35 mmHg) at 40−45 °C for 12 h, providing the title compound **11** (59.1 kg, 73.3%) as an off-white crystalline solid, mp 129−131 °C; IR (neat, cm^{-1}) 3318, 3010, 1780, 1605, 1585, 1203, 1002, 795; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32−7.21 (m, 6H), 6.01 (br s, 2H), 4.52 (s, 2H), 4.39 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.0, 136.6, 129.1, 128.1, 68.7, 41.5.

Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.38; H, 4.85; N, 6.25.

***(meso)-N*-Benzyl-3,4-isopropylidenedioxy-2,5-pyrrolidinedione (13).** To a stirred suspension of *(meso)-N*-benzyl-3,4-dihydroxy-2,5-pyrrolidinedione (**11**) (79.9 kg, 361 mol) in 2,2-dimethoxypropane (160 L) was added methanesulfonic acid (2.35 L, 36.1 mol). The resulting slurry was stirred at 20 °C for 9 h, and upon reaction completion, diisopropyl ether (240 L) was added. The slurry was granulated for 2 h at 20 °C, cooled to −15 °C, and further stirred an addition 2 h. The product was isolated by filtering the mixture through a closed system. The reaction vessel and the filter cake were successively rinsed with diisopropyl ether (200 L). The filter cake was unloaded and dried under vacuum (35 mmHg) at 40−45 °C for 12 h, providing the title compound **13** (82.8 kg, 87.6%) as an off-white crystalline solid, mp 95−96 °C; IR (neat, cm^{-1}) 3112, 3090, 1722, 1586, 1001, 799; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.28 (m, 5H), 4.85 (s, 2H), 4.68 (m, 2H), 1.41 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 134.8, 129.2, 128.9, 128.5, 75.2, 42.7, 26.8, 25.8.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.29; H, 5.86; N, 5.30.

***(meso)-N*-Benzyl-3,4-isopropylidenedioxy-2,5-pyrrolidine (12).** A stirred solution of *(meso)-N*-benzyl-3,4-isopropylidenedioxy-2,5-pyrrolidinedione (**13**) (47.5 kg, 182 mol) in tetrahydrofuran (378 L) was concentrated to 75% of its original volume by atmospheric distillation. The solution was cooled to 10 °C, and a sample was removed for KF determination. A solution of borane−tetrahydrofuran complex (300 L, 2 M in THF, 600 mol) was slowly charged portion-wise, maintaining the temperature between 10 and 20 °C throughout the addition. The reaction mixture was then stirred an additional 4 h at 25 °C. Upon reaction completion determination, the reaction mixture was cooled to 10 °C and carefully quenched by slowly adding methanol (239 L) cooled to 10 °C. The reaction mixture was stirred at the same temperature for 1 h, warmed to 40 °C, and stirred an additional 2 h. At this stage, the reaction mixture was further warmed to reflux and stirred for an addition 2 h. The resulting solution was then concentrated by atmospheric distillation (final volume of 145 L). The solution was then cooled to 40 °C, diluted with methanol (473 L), and further concentrated atmospherically (final volume of 145 L). Upon cooling to room temperature, water (1.0 L) was added, and the resulting solution was stirred 2 h. The concentrated title compound **12** (HPLC assay: 93.6%) was drummed and used as such for the next transformation; IR (neat, cm^{-1}) 3085, 2743, 1603, 1347, 1071, 1028, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.23 (m, 5H), 4.64 (m, 2H), 3.61 (s, 3H), 3.03 (d, *J*

= 11.5 Hz, 2H), 2.14 (m, 2H), 1.57 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 128.7, 128.5, 127.1, 111.4, 79.8, 59.9, 59.5, 26.7, 25.3.

***(meso)*-3,4-Isopropylidenedioxy-2,5-pyrrolidine hydrotosylate (17).** To a water wet hydrogenation vessel containing Pearlman's catalyst (8.5 kg, 50% water wet) was added the crude foregoing solution of *(meso)*-*N*-benzyl-3,4-isopropylidenedioxy-2,5-pyrrolidine (**12**) in methanol (182 mol, based on *(meso)*-*N*-benzyl-3,4-isopropylidenedioxy-2,5-pyrrolidinedione). The drum containing the latter solution was rinsed with methanol (42 L) and added to the reaction mixture. The hydrogenation vessel was repeatedly purged with hydrogen, and the suspension was stirred at 20 °C under 50 psi for approximately 10 h. Upon completion, the reaction mixture was filtered through a pad of Celite, and the filtrate was transferred to a nitrogen-purged vessel. The reaction vessel was then rinsed with methanol (76 L), transferred through the filter cake, and combined to the filtrate. The resulting solution was concentrated by atmospheric distillation (final volume of 80 L). After cooling the solution to 40 °C, methyl ethyl ketone (288 L) was added, and the solution was atmospherically distilled to a final volume of 133 L. The resulting cloudy solution was cooled to 20 °C and then filtered through a Celite-coated filter, sending the filtrate to a nitrogen-purged vessel. The reaction vessel and the filter cake were successively rinsed with methyl ethyl ketone (27 L). In a separate vessel, a solution of *p*-toluenesulfonic acid monohydrate (34.6 kg, 182 mol) in methyl ethyl ketone (102 L) was freshly prepared and added to the stirred filtrate. The resulting slurry was cooled to 10 °C and stirred for 5 h. After further cooling to 0 °C, the mixture was stirred an additional 2 h and then filtered. The reaction vessel and the filter cake were successively rinsed with methyl ethyl ketone (117 L). The filter cake was unloaded and dried under vacuum (35 mmHg) at 40−45 °C for 12 h, providing the title compound **17** (44.8 kg, 78.1%) as a white crystalline solid, mp 186−187 °C; IR (neat, cm^{-1}) 3038 br, 1610, 1386, 1367, 1270, 1186, 896, 847, 573; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (br s, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 4.81 (br s, 2H), 3.59 (d, J = 12.5 Hz, 2H), 3.29 (br d, J = 12.5 Hz, 2H), 2.36 (s, 3H), 1.44 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.94, 138.62, 128.86, 126.19, 111.14, 78.33, 51.43, 26.04, 24.20, 21.50.

Anal. Calcd for $C_{14}H_{21}NO_5S$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.36; H, 6.73; N, 4.41.

***(meso)*-*N*-Benzyl-3,4-isopropylidenedioxy-2,5-pyrrolidine-borane (18).** To an ice-cold solution of *N*-benzyl-3,4-isopropylidenedioxy-2,5-pyrrolidinedione (**12**) (6.53 g, 25.0 mmol) in anhydrous THF (25.0 mL) was added a solution of 1 M borane−THF (87.5 mL, 87.5 mmol). The resulting mixture was allowed to warm to room temperature and further stirred for 2.5 h. The reaction was carefully quenched with methanol (25.0 mL) and concentrated to dryness. The residual crystalline material was then slurred in ethyl acetate/hexane (1:1, 20 mL), cooled to 0 °C, and filtered to give the borane−amine complex **18** (5.01 g, 83%) as a white crystalline solid, mp 125 °C (dec); IR (neat, cm^{-1}) 2985, 1440, 1297, 1085, 904; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.49 (m, 2H), 7.40−7.36 (m, 3H), 4.99 (m, 2H), 4.19 (s, 2H), 3.30 (dd, J = 5.5, 12.5 Hz, 2H), 3.25 (d, J = 12.5 Hz, 2H), 1.47 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.5, 131.8, 129.2, 128.3, 113.6, 79.8, 65.2, 63.5, 26.5, 24.2.

Anal. Calcd for $C_{14}H_{22}BNO_2$: C, 68.04; H, 8.97; N, 5.67. Found: C, 68.02; H, 8.96; N, 5.59.

Acknowledgment

We thank Mr. Paul Ahlijanian, Mr. Mark Barrila, and co-workers for their assistance in successfully transferring the process to the pilot plant, Ms. Christine Keating, Ms. Grace Vandel, Ms. Ioulia Loubkina, Mr. Richard Ferraina, and Dr. Michael Preigh for their analytical support, and Mr. John Bordner for X-ray crystallographic measurements. We also thank Drs. Stephane Caron, Timothy Norris, and Phillip Hammen for insightful comments and suggestions.

Received for review May 1, 2001.

OP0102161