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Scalable Non-Aqueous Process to Prepare Water Soluble 3-Amino-pentan-1,5-diol

Thimma Rawalpally,* Yaohui Ji, Thomas Cleary, and Billy Edwards

Pharmaceutical Technical Development Actives (PTDA-FL), Roche Carolina Inc., 6173 East Old Marion Highway, Florence, South Carolina 29506-9330, U.S.A.

Abstract:

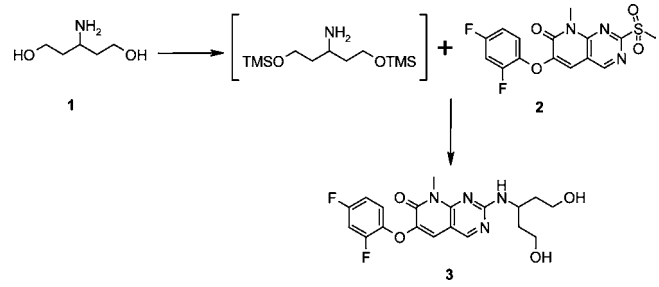
The development of a nonaqueous process for the synthesis of 3-amino-pentan-1,5-diol is described. Beginning with dimethyl acetone-1,3-dicarboxylate, a telescoped sequence of reductive amination, Boc protection, sodium borohydride reduction, and acidic resin-mediated deprotection generates the title compound. The key to this efficient process is the telescoped deprotection, purification and nonaqueous isolation of the 3-amino-pentan-1,5-diol. The process involves four optimized chemical reactions using two solvents in 89% overall yield and 97−98 area % purity.

Introduction

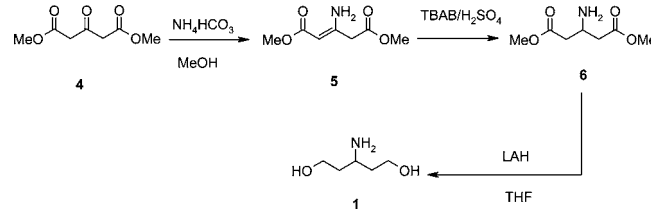
Biological agents that selectively neutralize pro-inflammatory cytokines (tumor necrosis factors such as TNFα and interleukin [IL]-1β) have been shown to reduce the number of swollen and tender joints and to retard the destruction of joint tissue in patients with rheumatoid arthritis.[1] p38 inhibitors of the pyridinylimadazole class block the destruction of joint tissue and the production of the TNFα and IL-1β in monocytes and in animal models of arthritis. Currently, there are no marketed, orally active, safe and effective agents that act primarily to inhibit TNFα or IL-1β. The active pharmaceutical ingredient (API) **3** can be prepared by coupling 3-amino-pentan-1,5-diol (**1**) (referred to as "aminodiol") and the sulfone intermediate **2** as shown in Scheme 1.

The original investigational new drug application (IND) synthesis of **1** is shown in Scheme 2. Dimethyl 3-aminoglutaconate (**5**) was prepared starting from dimethyl acetone-1,3-dicarboxylate (**4**) via amination. The enamine reduction of **5** under acidic conditions using borane-*tert*-butylamine complex (TBAB) provided the amino-diester **6**. Dimethyl 3-aminoglutarate (**6**) was reduced using lithium aluminum hydride (LAH) based on a literature[2] method; however, its isolation from the aluminum salts was operationally demanding, and the high water solubility of the aminodiol led to poor recovery. The aluminum salts were saturated with diethyl amine and propyl amine to improve the isolation of **1**. The IND synthesis was developed by our colleagues at Roche Bioscience, and this process enabled us to make API for initial clinical supplies. The purity of **1** was poor, and further purification by thin film evaporation was necessary prior to coupling with sulfone **2**. This synthetic route suffers from high manufacturing costs, low overall yield (57%), adverse environmental impact, poor

Scheme 1



Scheme 2. **Original IND synthesis of aminodiol 1**



recovery of the aminodiol from the aqueous workup, and challenging handling of LAH on a commercial scale.

The first-generation aminodiol synthesis, shown in Scheme 3, was developed by our colleagues at Roche Boulder. The IND synthesis was modified to include a benzyl protecting group on the amine, thereby decreasing its water solublity.[3,4]

Dimethyl 3-*N*-benzylamino-glutaconate (**7**) intermediate was purchased from Chemie Uetikon. The literature preparation of **7** started with dimethyl acetone-1,3-dicarboxylate (**4**).[3] The reduction of **7** was easily accomplished in good yields using TBAB in THF.[4] The crucial reduction of dimethyl 3-*N*-benzylamino-glutarate (**8**) to 3-*N*-benzylamino-pentan-1,5-diol (**9**) was achieved using sodium bis-(2-methoxyethoxy)aluminum hydride (Vitride). On a large scale, handling Vitride was easier than handling the LAH used in the IND synthesis.

Compound **9** was purified via its crystalline tosylate salt. This purification involved salt formation, isolation, and drying of the salt prior to regenerating the free base. In addition, achieving good recovery of compound **9** required six dichloromethane extractions (187 kg of dichloromethane/kg of product). Overall this process required a total of five different solvents, and the use of the Vitride reagent produced an aluminum salt-laden aqueous waste, which gelled if allowed to stagnate (40 kg of gel/kg of product). The reduction of compound **8** with inexpensive sodium borohydride required a long reaction time (72 h) and resulted in an impurity that was

* Author for correspondence. E-mail: Thimma_r.rawalpally@roche.com.

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(4) Cain, R. O.; Moorlag, H.; Tucker, C. E.; Wong, J.-W. U.S. Patent 20080154063; CAN 149:104406, 2008.

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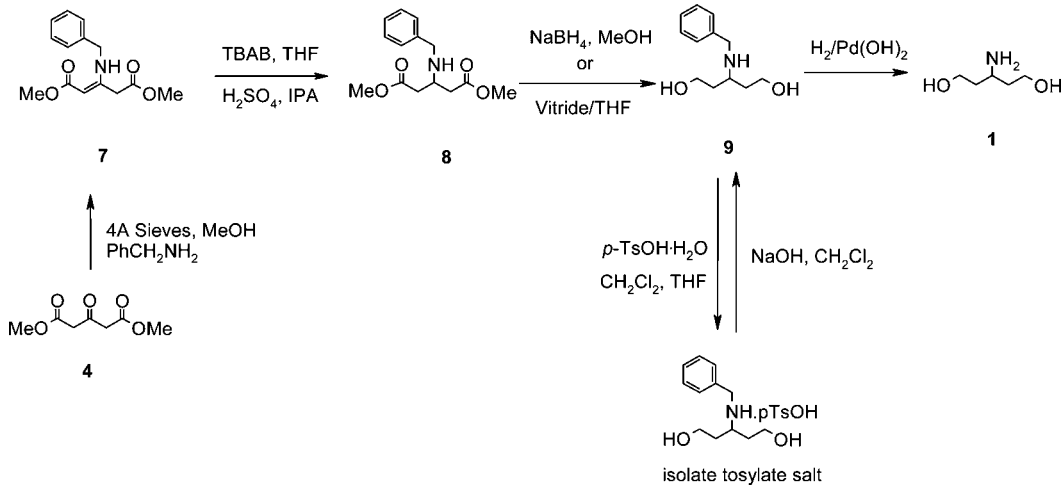
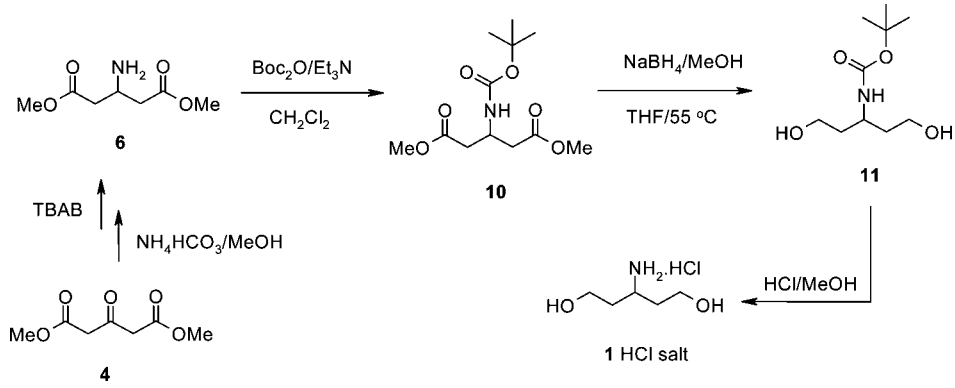
Scheme 3. **First-generation synthesis of aminodiol 1 (benzyl protected)**



Scheme 4. **Second-generation synthesis of aminodiol 1 (Boc protected)**



difficult to remove from the downstream process. This five-step process, starting from **7**, resulted in an overall yield of 69% of aminodiol **1** (purity >99 area % by GC). The API for midstage clinical supplies was produced using this modified process. This first-generation aminodiol process was not suitable for large-scale production due to its poor throughput and inherent environmental impact.

Results and Discussion

Upon reviewing the literature,[5] it appeared that the reduction of *N*-Boc-aminodiester **10** with sodium borohydride should proceed smoothly, thus suggesting a second-generation aminodiol synthesis (Scheme 4). The *tert*-butyloxycarbonyl (Boc) protection of **6** was easily achieved with Boc_2O and triethylamine in methylene chloride following literature procedures.[5] In turn, the required **6** was prepared by following the IND synthesis (Scheme 1) as described earlier.

The sodium borohydride reduction of **10** in THF solvent afforded **11** in 83% isolated yield with 96% purity (NMR/GC). In a typical procedure, methanol was added slowly to a slurry of **10** and sodium borohydride at 55 °C in THF. After reaction completion (<0.5% **10**), the excess reducing agent was quenched with water. The methanol and THF were distilled, and the aqueous layer was extracted with 1-butanol. After a solvent exchange, Boc-aminodiol **11** was obtained as a solution in MeOH. Maintaining the reaction temperature between 55 and 65 °C afforded good conversion (>99%), while lower temperatures led to incomplete reactions. In spite of high reaction conversion, low yields of **11** were observed because it was difficult to extract the product from the aqueous layer.

Deprotection of Boc-protected amines is usually achieved by using an acid such as HCl or TFA. In this case, the Boc group was easily removed under acidic conditions (HCl/MeOH or PTSA), but the isolation of free base **1** was difficult. Aminodiol **1** was highly water soluble which resulted in a poor recovery from the aqueous workup. Aminodiol **1** partitions preferably to the aqueous phase; hence, extraction of **1** as a free base in organic solvent is not practical. Deprotecting the Boc group and isolating **1** under nonaqueous conditions were required for a successful process.

Strongly acidic ion-exchange resins could deprotect the Boc group,[6] suggesting that isolation of water-soluble **1** from nonaqueous systems is possible. Treatment of **11** with strongly acidic Amberlyst-15 ion-exchange resin at 40 °C in MeOH afforded 36% deprotection in 24 h (Scheme 5). In the second step, the resin-bound aminodiol was released by exchange with ammonia. The process was further optimized with respect to the type of resins, resin loading, reaction temperature, 7 N methanolic ammonia extraction volume, and reaction time. The optimized conditions led to Boc deprotection in 18 h and utilized 150% resin loading in methanol at 60 °C. Comparable results

(5) Tomori, H.; Hibutani, K.; Ogura, K. *Heterocycles* **1997**, *44*, 213.

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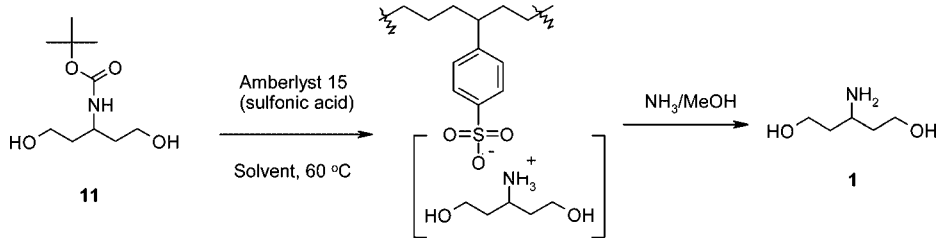
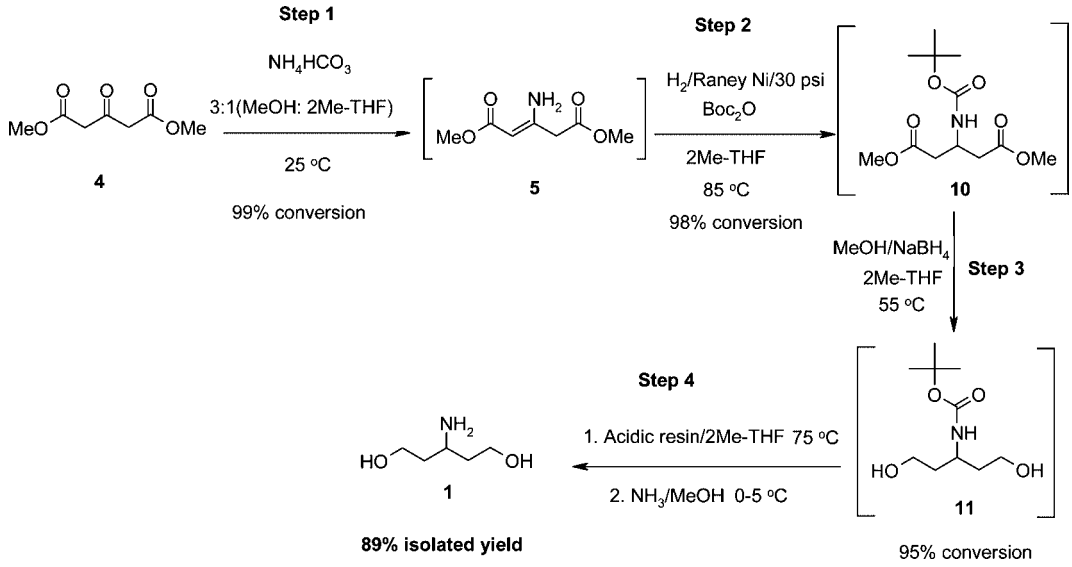
Scheme 5. **Deprotection of Boc group using acidic resin/liberation of free amine 1**



Scheme 6. **Telescoped second-generation aminodiol process**



were obtained using either FPC22H or FPC23H; both are Amberlite resins with sulfonic acid functional groups on a styrene−divinylbenzene copolymer. The desired aminodiol was then released by treating the resin with 7 N methanolic ammonia solution for 4 h.

In this second-generation process, we demonstrated a facile sodium borohydride reduction of **10** and Boc deprotection, purification, and nonaqueous isolation of the aminodiol **1** using a strongly acidic ion-exchange resin. An 83% overall yield was obtained from compound **4** (Schemes 4 and 5).

Development of a Telescoped Second-Generation Synthesis of Aminodiol 1. The process depicted in Schemes 4 and 5 requires several solvents, multiple solvent exchanges, and the use of expensive TBAB reagent[7] for the reduction of **5**. Further development work was undertaken to telescope these steps to improve cycle time and capacity and to reduce waste as shown in Scheme 6.

Dimethyl 3-aminoglutaconate (**5**) was prepared following the IND synthesis. The reaction was optimized with ammonium hydrogen carbonate serving as an ammonia source in methanol. During the course of development work, it was observed that protic solvents, such as residual methanol and ammonia from Step 1, would react with di-*tert*-butyl dicarbonate (Boc_2O) in the subsequent hydrogenation/Boc protection step to form impurities. For the Step 1 process, 2-methyltetrahydrofuran (2Me-THF) became the solvent of choice because it does not react with Boc_2O in Step 2. Unfortunately, liberated ammonia from ammonium hydrogen carbonate had poor solubility in 2Me-THF. To achieve complete conversion, a 3:1 mixture of methanol/2Me-THF was required. At the end of the reaction, a constant volume distillation was performed to exchange the methanol for 2MeTHF and to remove the ammonia gas. The resulting 2Me-THF solution of **5** was carried directly into the Step 2 process.

To improve the cost efficiency and scalability of the process, we turned our attention toward catalytic reduction of the enamine.[8] It was difficult to achieve complete conversion with Pd/C despite high H_2 pressure (350 psi) and high catalyst loading (10% to 20%). Based on earlier work,[9] Raney-nickel-catalyzed hydrogenation of **5** was achieved with 10% loading at 200 psi hydrogen pressure under slightly acidic conditions to afford **10** after 18 h (<0.5 area % of **5**). Acetic acid was required as a cocatalyst to drive the Raney-Ni hydrogenation reaction to completion. In the next step, the free amine was protected with a Boc protecting group. We thought to use the Boc protecting reaction to drive the equilibrium towards completion. On the basis of this concept, we attempted to telescope these steps into a one-pot process.[10]

The hydrogenation/Boc protection telescoped sequence was optimized in 2Me-THF by varying equivalents of Boc_2O, catalyst loading, pressure, and temperature (Table 1 and Scheme 6). The Step 2 reaction was optimized with 1.1 equiv of Boc_2O

(7) The bulk commercial cost of TBAB is $220/kg ($20/mol).

(8) Augustine, R. L.; Bellina, R. L. *J. Org. Chem.* **1968**, *33*, 1287.
(9) Saliou, C.; Fleurant, A.; Celerier, J. P.; Lhommet, G. *Tetrahedron Lett.* **1991**, *32*, 3365.
(10) For a similar approach to this problem, see: Zhu, W.; Ma, D. *Org. Lett.* **2003**, *26*, 5063.

Table 1. **Optimization of reductive amination/Boc protection**

entry	equiv Boc_2O	H_2 pressure (Raney-Ni % loading)	temp (0 °C)	rxn time (h)	IPC(GC A% of **5**)
1	1.0	200 psi (10 wt %)	65−85	7	3
2	1.1	200 psi (10 wt %)	85	3.5	0.5
3	1.1	30 psi (10 wt %)	85	21	3
4	1.3	30 psi (15 wt %)	85	11	0.3
5	1.3	30 psi (15 wt %)	85	3.5	9
6[a]	1.3	30 psi (15 wt %)	85	4	0.3

[a] System was purged with hydrogen after 2 h.

at 85 °C with 10% Raney-Ni catalyst loading and 200 psi hydrogen pressure to afford complete conversion in 3.5 h.

To allow the Step 2 hydrogenation reaction to be performed in standard glass-lined vessels, reduced pressures were evaluated. Accordingly, at 30 psi with 1.3 equiv of Boc_2O, a slightly higher catalyst loading (15 wt %) was required for complete conversion after 11 h (Table 1, entry 4). An attempt to improve the reaction rate by increasing the reaction temperature to 95 °C appeared to cause decomposition of the Boc_2O reagent. Purging the reaction vessel with hydrogen after 2 h improved the reaction rate (entry 6). In order to avoid handling dry, pyrophoric catalyst on large scale, the effect of water on the Step 2 process was evaluated, and wetting the Raney-Ni catalyst with up to 50% water was well tolerated. After filtering to remove the catalyst, the 2Me-THF solution of Step 2 intermediate **10** was carried forward into the Step 3 process.

After the pilot-plant scaleup of the Step 3 sodium borohydride reduction, several opportunities for improvement were identified. The methanol addition to $NaBH_4$ generated hydrogen gas, and the reaction became viscous as the solvent was evaporated by the hydrogen purge. The viscosity of the reaction mixture also led to agitation, sampling, and foaming problems. In addition, the reaction quench was also slow, and hydrogen evolution persisted for more than two days. Removal of the THF solvent via distillation to facilitate good layer separation and product recovery was difficult due to the continuing hydrogen effervescence. Additionally, due to the high boiling point and viscous nature of 1-butanol, its solvent exchange with lower-boiling methanol on large scale was problematic.

To address the above scale-up issues and enable telescoping with Steps 1 and 2, we decided to explore the use of 2Me-THF as the solvent in Step 3. On a small scale, the Step 3 reaction in 2Me-THF was complete within 30 min after methanol addition. Good layer separation was achieved at room temperature after the aqueous quench, and the product was isolated in 93% yield. On scale-up, the Step 3 product recovery was poor (76%); however, the product recovery was improved to 91% by extracting the aqueous layer at 60 °C and reducing the amount of water used for the reaction quench.

The rate of hydrogen evolution was controlled by diluting the methanol with 2Me-THF to allow a more controllable addition. The reduction was optimized with 3 equiv of sodium borohydride. The excess reducing agent was treated with acetone prior to quenching with water; acetone reacts with borane instantaneously to form 2-propanol, and therefore generates less hydrogen than treatment with water. Adding the reaction mixture to an acidic aqueous solution (pH 4) at 60 °C provided rapid but controllable hydrogen evolution.

Table 2. **Comparison of environmental assessment for routes of aminodiol 1**

material consumption - ecology	IND synthesis	first generation	second generation (telescoped)
overall kg solvents/kg of **1**	48	252	52
dichloromethane kg/kg of **1**	10	192	0
overall kg input material (excl. solvents and water)/ kg of **1**	20	38	7
organic liquid waste (incineration) kg/kg of **1**	56	252	3
solid waste kg/kg of **1**	5	40	9
number of steps	3	6	4
number of isolations	3	6	1
number of solvents used	6	5	2
yield	57%	69%	89%

By incorporating these modifications, the Step 3 process was easily scalable without any major safety concerns. Hydrogen evolution was more controllable, both during methanol addition and upon quench. Heat and mass transfer were much more efficient, and the long-lasting effervescence after the water quench was effectively eliminated, giving a better layer separation and good product recovery.

To further streamline the process, we explored the use of 2Me-THF as the solvent in the Step 4 Boc deprotection reaction as well. In fact, complete Boc deprotection was achieved in 4 h at 75 °C (as compared to 18 h at 60 °C in MeOH) to provide aminodiol **1** in 89% overall yield (based on the charge of **4**) and 96−98 GC area % purity. The telescoped second-generation process (Scheme 6) was successfully demonstrated on pilot-plant scale.[11]

Handling the viscous and hygroscopic aminodiol **1** was difficult. A distilled aminodiol sample (>99 GC area % purity) solidified upon standing at room temperature. We focused our attention on developing a crystallization process to resolve the handling issue. After some experimentation, a preliminary crystallization process was developed using a methanol/THF mixture with 80% recovery. Alternative to crystallization as a means of purification, a short-path distillation process was developed on a small scale. Unfortunately, neither the crystallization nor the distillation process was scaled-up due to project termination.

Environmental Assessment of the Synthetic Routes. This synthesis of 3-amino-pentan-1,5-diol (**1**) involves a single isolation with four chemical reactions starting from the readily available and inexpensive dimethyl acetone-1,3-dicarboxylate (**4**). All four chemical steps were optimized using two solvents, 2Me-THF/MeOH, which could be easily recovered and recycled. The key operations involved were an easily scalable, inexpensive sodium borohydride reduction of Boc-aminodiester **10**, a telescoped deprotection, and the purification and isolation of **1** using an acidic ion-exchange resin under nonaqueous conditions. From the viewpoint of an environmental assessment, the preparation of **1** via the three different routes is compared in Table 2.

(11) Cleary, T.; Ji, Y.; Lee, L.; Rawalpally, T.; Sarma, K. PCT Int. Appl. WO/2008/0151992 A2 20081218, 2008.

Experimental section

GC conditions. Instrument: Agilent 6890 equipped with FID. Column: Agilent HP-1MS, 30 mm × 2.5 mm × 0.25 μm. Inlet: 250 °C, split ratio 30:1. Detector: 300 °C, H_2 30 mL/min, helium 30 mL/min, air 300 mL/min. Oven temperature: 100 °C for 1 min, then 15 °C/min to 280 °C.

Synthesis of 5. 2Me-THF (51.6 g), ammonium hydrogen carbonate (72.6 g, 919 mmol), dimethyl acetone-1,3-dicarboxylate (**4**) (80.0 g, 460 mmol) were stirred in MeOH (144 g) at 20 °C for 18 h. The solids were removed by filtration, MeOH was distilled at atmospheric pressure, and the 2Me-THF solution of **5** was taken directly into the next step. ^{1}H NMR (DMSO-d_6) δ 3.18 (s, 2 H), 3.48 (s, 3 H), 3.60 (s, 3 H), 4.38 (s, 1 H), 7.04 (s, 1H), 7.68 (s, 1H).

Synthesis of 10. The 2Me-THF solution of **5** (79.5 g, 460 mmol, based on 99% recovery starting from **4**), di-*tert*-butyl dicarbonate (Boc_2O, 130 g, 597 mmol) dissolved in 2Me-THF (292 g), and sponge Raney-Ni (12.0 g plus 12.0 g of water) were charged to a 1 L autoclave. After several nitrogen purges and hydrogen purges, the reaction was heated to 85 °C at 30 psi H_2 for 6 h. After several nitrogen purges, the reaction was cooled to 20 °C and filtered through celite, and the organic filtrate containing **10** was carried forward directly into the next step. ^{1}H NMR (DMSO-d_6) δ 1.34 (s, 9 H), 2.46 (m, 4 H), 3.55 (s, 6 H), 4.09 (m, 1 H), 6.87 (d, 1H, J = 8.8).

Synthesis of 11. The 2Me-THF solution of **10** (~36.7 wt %) was combined with sodium borohydride (52.1 g, 1.38 mol) and heated to 55 °C. To this mixture was slowly added anhydrous methanol (66.1 g, 2.1 mol) diluted with Me-THF (86.0 g). The reaction temperature was maintained between 55 and 60 °C throughout the addition. After the MeOH addition, the batch was held at 55 °C for 3 h. The excess reducing agent was treated with 10 mL of acetone, and the reaction contents were quenched by slowly adding it to a preheated aqueous acidic solution (800 g of water and 130.0 g of 3 N HCl) in a separate vessel at 60 °C. The organic phase containing **11** was separated at 60 °C and taken directly into the next step. ^{1}H NMR (DMSO-d_6) δ 1.35 (s, 9 H), 1.47 (m, 4 H), 3.37 (q, 4 H, J = 5.6), 3.51 (m, 1H), 4.32 (t, 2 H, J = 5.2), 6.57 (d, 1 H, J = 8.8).

Synthesis of 1. The 2Me-THF solution of **11** and Amberlite FPC22H ion-exchange resin (302 g) was heated to 75 °C and held for 4 h. The batch was cooled to 20 °C, and the product-bound resin was collected by filtration. The resin was rinsed with an additional 400 g of fresh methanol. The resin was transferred to a separate reactor and charged with 4 °C 7 N ammonia in methanol solution (400 g); the reaction was exothermic. The reaction was warmed to room temperature and held for 1 h. The resin was removed by filtration, and the methanol solution containing the product was collected. To remove the light-yellow color, the methanolic solution was filtered through a bed of carbon/celite (Carbon black NORIT 211 from Acros). The methanol was removed by distillation at atmospheric pressure to obtain 49.7 g of **1** in 89% overall yield (GC purity = 98−99%); ^{1}H NMR (DMSO-d_6) δ 1.38 (m, 4 H), 2.81 (t, 1 H, J = 4.3, 8.6), 3.50 (m, 4 H), 6.87 (d, 1H, J = 8.8 Hz).

Acknowledgment

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