

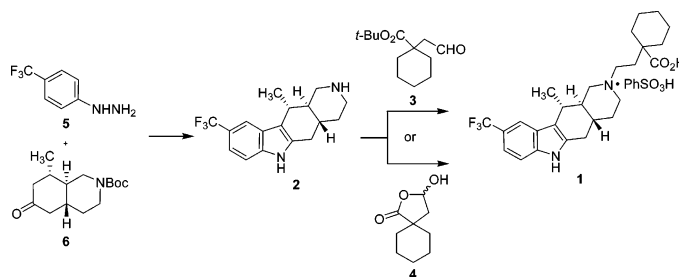
## Stereoselective Synthesis of a MCHr1 Antagonist

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Melanin-concentrating hormone (MCH) is implicated in the feeding behavior in mammals affording a potential target to control overeating in people. Compound **1** (AMG 076) has been identified as a potent MCHr1 antagonist for the treatment of obesity. A synthesis suitable for the large-scale preparation of this lead candidate was developed to support preclinical studies. A Robinson annulation of benzylpiperidone and resolution of the desired enone from a mixture of the diastereomers afforded key intermediate **6** after a stereoselective hydrogenation. Subsequent Fischer indole synthesis with hydrazine **5** then provided the advanced intermediate, indole **2**. Two complementary reductive amination strategies employing either aldehyde **3** or lactol **4** led to the synthesis of title compound **1**.

## Introduction

Melanin-concentrating hormone (MCH), a cyclic nonadecapeptide, plays a key role in eating behavior and energy homeostasis.<sup>1</sup> In rodents, intracerebraventricular administration of MCH leads to increased food intake<sup>2</sup> while MCH-deficient or MCH-knockout mice are lean, hypophagic, and hypermetabolic.<sup>3</sup> The action of MCH is believed to be the result of binding to MCH receptor 1 (MCHr1), which is a member of the G-protein-coupled receptors and is highly expressed in the lateral hypothalamus and zona incerta of the CNS.<sup>1</sup> Antagonism of MCHr1 has the potential to lead to weight loss through the

combined effects of reduced food intake and increased metabolism. As a result, a large scientific effort has been placed on the development of MCHr1 antagonists.<sup>4</sup> Discovery efforts

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(3) (a) Shimada, M.; Tritos, D.; Aitken, A.; Donella-Deana, A.; Hemmings, B. A.; Parker, P. J. *Nature* **1998**, *396*, 670. (b) Shimada, M.; Tritos, D.; Aitken, A.; Donella-Deana, A.; Hemmings, B. A.; Parker, P. J. *Eur. J. Biochem.* **1982**, *124*, 21. (c) Chen, Y.; Hu, C.; Hsu, C. K.; Zhang, Q.; Bi, C.; Asnicar, M.; Hsiung, H. M.; Fox, N.; Sliker, L. J.; Yang, D. D.; Heiman, M. L.; Shi, Y. *Endocrinology* **2002**, *143*, 2469. (d) Marsh, D. J.; Weingarth, D. T.; Novi, D. E.; Chen, H. Y.; Trumbauer, M. E.; Chen, A. S.; Guan, X. M.; Jiang, M. M.; Feng, Y.; Camacho, R. E.; Shen, Z.; Frazier, E. G.; Yu, H.; Metzger, J. M.; Kuca, S. J.; Shearman, L. P.; Gopal-Truter, S.; Macneil, D. J.; Strack, A. M.; MacIntyre, D. E.; Van der Ploeg, L. H.; Qian, S. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 3240.

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<sup>§</sup> Pharmaceutical Products PPG-Sipsy.

<sup>||</sup> Current address: Wyeth Research, Chemical Development, 401 N. Middletown Road, Pearl River, NY 10965.

(1) (a) Cambers, J.; Ames, R. S.; Bergsma, D.; Muir, A.; Fitzgerald, L. R.; Hervieu, G.; Dytko, G. M.; Foley, J. J.; Martin, J.; Liu, W.-S.; Park, J.; Ellis, C.; Ganguly, S.; Konchar, S.; Cluderays, J.; Leslie, R.; Wilson, S.; Sarau, H. M. *Nature* **1999**, *400*, 261. (b) Saito, Y.; Nothacker, H.-P.; Wang, Z.; Lin, S.; Leslie, F.; Civelli, O. *Nature* **1999**, *400*, 265.

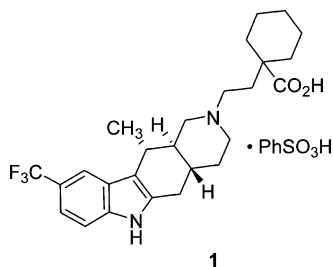
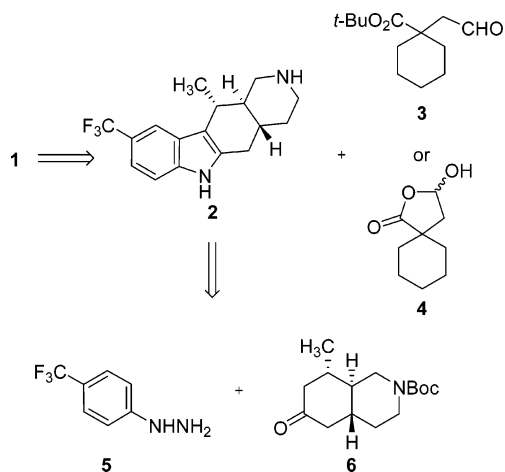


FIGURE 1. MCHr1 antagonist AMG 076.

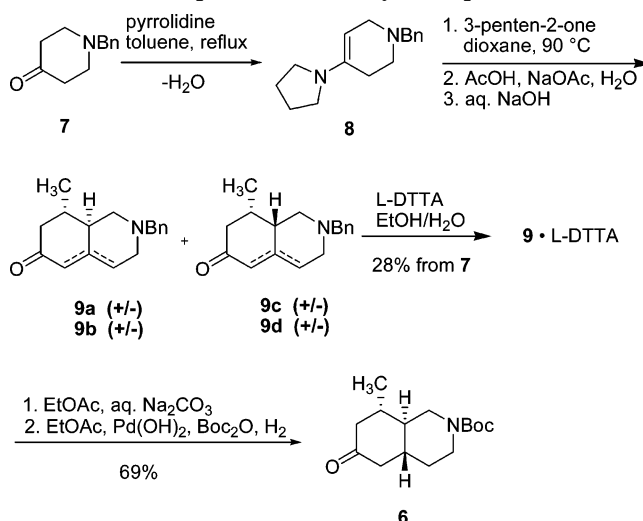
## SCHEME 1. Retrosynthetic Analysis of AMG 076



resulted in the identification of compound **1** (AMG 076) as a potent, bioavailable MCHr1 antagonist (Figure 1).<sup>5</sup>

The synthetic route to compound **1** has proceeded through three key building blocks (Scheme 1). A Fischer-indolization between hydrazine **5** and octahydroisoquinolinone **6**<sup>6</sup> provided the indole ring of penultimate intermediate **2**. Reductive

## SCHEME 2. Preparation of Octahydroisoquinolinone 6



amination with cyclohexylacetaldehyde derivative **3** or **4** completed the synthesis of AMG 076. This sequence of steps was sufficient for preparing initial quantities of material for testing but the process was not capable of supporting further preclinical and clinical development. Specifically, the indolization and the means for converting **2** to **1** were major bottlenecks. Furthermore, preparation the octahydroisoquinolinone presented a unique challenge in establishing the relative and absolute stereocenters for the drug candidate. Herein, we describe the development of an effective and productive synthesis of the MCHr1 antagonist AMG 076 (**1**).

## Results and Discussion

**Octahydroisoquinolinone Preparation.** The traditional methodology for the synthesis of such a bicyclic enone would be the Robinson annulation.<sup>7</sup> However, the relative stereochemistry to be expected with pentenone was uncertain.<sup>8</sup> The protocol was applied to the starting material, *N*-benzyl-4-piperidone (**7**), which was converted to enamine **8** before alkylation by using pyrrolidine in refluxing toluene over a Dean–Stark trap to remove water (Scheme 2).<sup>9</sup> Rapid heating of the toluene was not an option since pyrrolidine could be lost in the distillate. However, by gradually increasing the temperature of the reaction mixture to 84 °C and holding the temperature for 1 h, the pyrrolidine was contained in the mixture. The resultant adduct was formed completely with only 1.5 equiv of the reagent. The heating was

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(5) (a) Leping, L.; Fan, P.; Chen, X.; Mihalic, J.; Fu, Y.; Dai, K.; Liang, L.; Reed, M.; Wright, M.; Timmermans, P.; Chen, J.-L.; Laen, J. *Abstracts of Papers*, 231st National Meeting of the American Chemical Society, March 26–30, 2006; American Chemical Society: Washington, DC, 2006. (b) Chen, X.; Chen, X.; Fan, P.; Jaen, J.; Li, L.; Mihalic, J. T. Patent WO 04/043958 A1, 2004.

(6) For an alternative strategy for the formation of a similar, tetracyclic isoquinolinone system, see: Le Goffic, F.; Gouyetts, A.; Ahoud, A. *Tetrahedron* **1973**, *29*, 3357.

(7) Gawley, R. E. *Synthesis* **1976**, 777.

(8) Annulation of *N*-methyl-4-piperidone with pentenone was reported to give the *N*-Me analogue of **9**. However, the stereochemistry was not defined, see: (a) Bergman, J.; Goonewardena, H. *Acta. Chem. Scand. Ser. B* **1980**, *34*, 763. For the reaction of 2-methylcyclohexanones with pentenone, see: (b) Kikughi, M.; Yoshikoshi, A. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3420. (c) Coates, R. M.; Shaw, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 5657. Robinson annulation of cyclohexanone with  $\beta$ -aryl methyl vinyl ketones has been reported but the stereochemistry was not defined, see: (d) Eiden, F.; Gmeiner, P. *Arch. Pharm.* **1988**, *321*, 397. (e) Eiden, F.; Gmeiner, P. *Liebigs Ann. Chem.* **1988**, 125.

(9) (a) Djerassi, C.; Pettit, G. R. *J. Org. Chem.* **1957**, *22*, 393. (b) Danishefsky, S.; Cavanaugh, R. *J. Org. Chem.* **1968**, *33*, 2959. (c) The reaction was monitored by gas chromatography for the consumption of *N*-benzyl-4-piperidone. It was critical to the success of this process to leave <2.5% of the starting material at this stage.

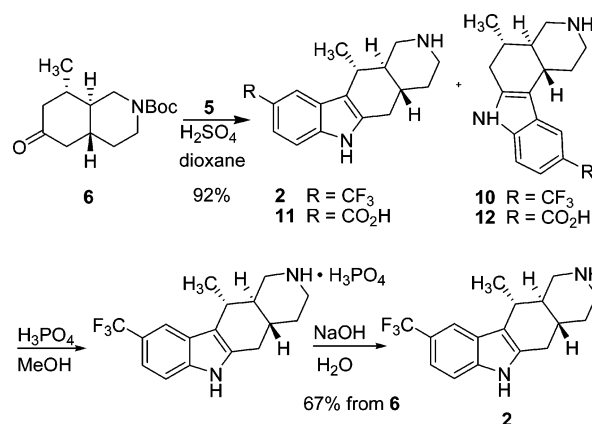
then increased to reflux to complete the dehydration. The Michael addition and cyclization were accomplished by heating the crude enamine with 3-penten-2-one<sup>10</sup> in dioxane at 90 °C. The reaction mixture contained alkylated piperidone intermediates and pyrrolidine adducts of the cyclized product.<sup>11</sup> Addition of aqueous acetic acid/sodium acetate converted these intermediates to the enone **9**, which was a racemic mixture of the *syn*- and *anti*-isomers of the methyl and bridgehead positions. The enone was also a mixture of the  $\alpha,\beta$ - and  $\beta,\gamma$ -isomers. Analysis of the crude product showed a 17:76:6:1 mixture by gas chromatography of the four possible isomers (compounds **9a–d**). The relative stereochemistry for the enone isomers was not determined, rather, the mixture was used directly in the subsequent chemical resolution step.

Treatment of the mixture of **9a–d** with di-*p*-toluoyl-L-tartaric acid (L-DTTA) in 80% ethanol/water resulted in the crystallization of the desired diastereomeric salt as an off-white solid.<sup>12</sup> Analysis of the optical purity revealed that the desired (8*S*,8*aR*)-enantiomer of **9** was obtained with 96.7% ee in 25–28% overall yield from *N*-benzyl-4-piperidone, which was sufficient for further processing.<sup>13</sup> Fortuitously the Robinson annulation procedure was suitable for establishing the relative stereochemistry of the two key chiral centers and we could easily access the pure enantiomer through resolution.

After salt-break of the enone **9** with aqueous sodium carbonate, hydrogenation of the enone over 10% Pd(OH)<sub>2</sub> on carbon in the presence of Boc<sub>2</sub>O effected not only reduction of the enone to set the final chiral center but in situ debenzylation followed by *N*-acylation to afford the desired product **6**. After removal of the catalyst, crystallization of the product by addition of heptane provided the octahydroisoquinolinone **6** in 69% yield and >99% ee.<sup>14</sup>

**Indole Synthesis.** The Fischer-indole reaction<sup>15</sup> between octahydroisoquinolinone **6** and 4-trifluoromethylphenylhydra-

SCHEME 3. Fischer-Indolization to **2**

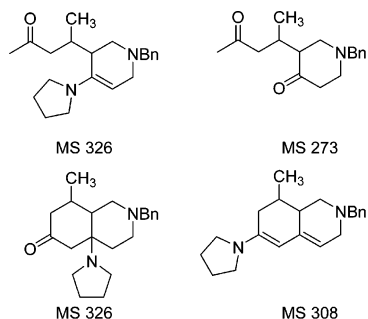


zine **5** was performed in dioxane at 70 °C with sulfuric acid,<sup>16</sup> which gratifyingly provided an ~8:1 mixture of desired linear indole **2** and undesired angular indole **10** in 92% yield (Scheme 3).<sup>17</sup> An extensive screen of a variety of acids and solvents did not improve the ratio. Depending on the reaction temperature variable amounts of the hydrolyzed byproducts **11** and **12**, along with HF, were generated.<sup>18</sup> Control of the reaction temperature between 67 and 72 °C resulted in full conversion while minimizing the hydrolysis of the CF<sub>3</sub> group to <5%. To avoid the hydrolysis side reaction, and perhaps improve the isomer ratio, an alternative to acid-catalyzed indolization of a ketone with a hydrazine would be the palladium-catalyzed indolization of 2-haloanilines, which is run under basic conditions.<sup>19</sup> Unfortunately, coupling of isoquinolinone **6** and 2-iodo-4-trifluoromethylphenylhydrazine only gave a 1:1 ratio of the indole products.

The indole isomers cocrystallized from the product mixture after pH adjustment (>12) with no appreciable enrichment of **2**. Crystallization of **2** as either the (*R*)-2-chloromandelic acid or phosphoric acid salt effectively rejected the indole byproduct **10**. Ultimately, the latter salt was selected as optimal. Thus, formation of the phosphate in methanol followed by salt-break

(10) The geometric purity of the pentenone is >95% by <sup>1</sup>H NMR. It was essential to check the quality of the 3-penten-2-one used carefully. A thorough analytical analysis revealed that it can contain variable amounts of acetic acid and water. These impurities caused hydrolysis of enamine **8**, regenerating *N*-benzyl-4-piperidone, which lowered the yield of the tartrate salt dramatically. Experimentation revealed that <0.10 wt % of acetic acid and <1.0 wt % of water were tolerated.

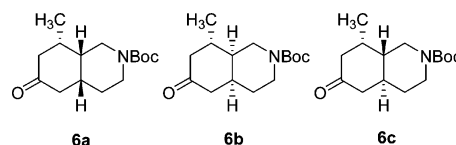
(11) The structures were surmised by the GC/MS and literature precedent, see: Stork, G.; Brizzolara, A.; Landesman, H.; Szmuskovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *55*, 207. All the intermediates were converted to the enone after addition of acetic acid.



(12) The amount of piperidone was detrimental to the isolated yield of the tartrate salt of **9**. With >10% of *N*-benzyl-4-piperidone, the resolution yield of **9** dropped from 28% overall yield to <12%, and in some cases, the tartrate salt failed to crystallize. In the event that the *N*-benzyl-4-piperidone was outside the set specification, unreacted material could be removed by washing the crude enone mixture with 1 M aqueous citric acid at pH 5.4.

(13) A second slurry in 80% ethanol/water could upgrade the material to 98.5% ee, if required. However, material of >96% ee will produce isoquinolinone **6** with >99% ee in the subsequent transformations.

(14) Minor amounts of the other diastereomers **6a** and **6b** were rejected in the filtrate. Compounds **6a** and **6b** were each isolated in ~0.25% yield by chromatography and identified by <sup>1</sup>H NMR. The remaining isomer **6c** was not isolated. The structure of **6c** was assumed based on the mass obtained from mass spectrometry and retention time comparison to the three characterized isomers **6**, **6a**, and **6b**. The stereochemistry of the methyl group was key to the selectivity in the hydrogenation to produce the *anti*-relationship between the two bridgehead positions. For comparison, the *des*-methyl-*N*-benzoyl analogue of **9** was converted to a mixture of the *syn,anti*-isomers: Rastogi, S. N.; Bindra, J. S.; Rai, S. N. *Indian J. Chem.* **1972**, *10*, 673.



(15) Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 667.

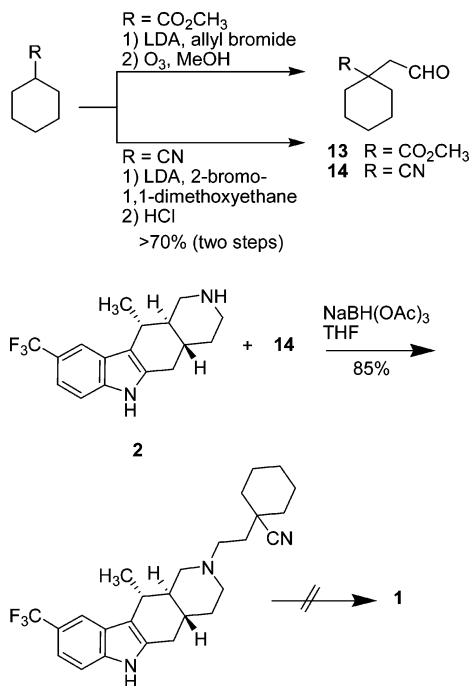
(16) Liazarzabura, M. E.; Shuttleworth, S. J. *Tetrahedron Lett.* **2004**, *45*, 4781.

(17) The Fischer-indolization of analogous decalinone systems has been reported to be selective for the formation of the linear isomer over the angular isomer: (a) Miller, F. M.; Lohr, R. A., Jr. *J. Am. Chem. Soc.* **1978**, *43*, 3388. (b) Rastogi, S. N.; Bindra, J. S.; Rai, S. N.; Anand, N. *Indian J. Chem.* **1972**, *10*, 673. (c) Christoffers, J. *Synthesis* **2006**, 318.

(18) At temperature of >72 °C there was significant glass erosion from HF evolution (>1.5 mg/m<sup>3</sup>).

(19) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2576.

## SCHEME 4. Coupling of Side Chain

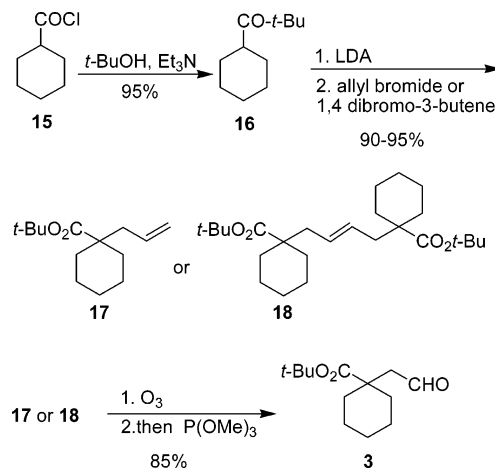
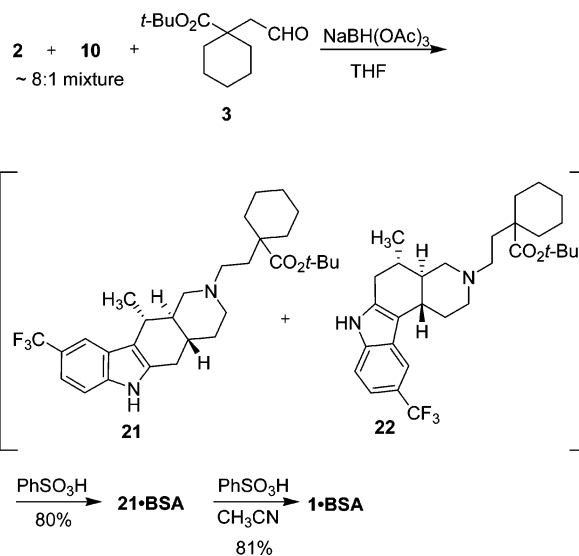


yielded 72% of pure indole **2** (Scheme 3). A crystal structure of the (*R*)-2-chloromandelate salt established the absolute stereochemistry of the molecule as 4*aR*,11*R*,11*aS*.

**Reductive Amination of Indole 2 with *tert*-Butyl Ester Aldehyde 3.** The final coupling of the indoloisquinoline **2** to the cyclohexyl-(1-carboxylic acid)-ethyl moiety relied on a reductive amination strategy. In preliminary studies the ester aldehyde **13** was prepared by allylation of the methyl ester of cyclohexylcarboxylic acid followed by ozonolysis (Scheme 4). However, the product suffered from poor stability and could not be isolated in pure form. Simply standing at room temperature resulted in the formation of degradants including the lactol **4**. Alternatively, the nitrile analogue 1-(2-oxoethyl)cyclohexanecarbonitrile **14**, which was easily prepared by alkylation of cyclohexylcarbonitrile followed by hydrolysis, was stable. Coupling proceeded quite well with NaBH(OAc)<sub>3</sub>. However, the nitrile group proved to be too hindered for hydrolysis to the desired carboxylic acid moiety under either acidic or basic conditions.

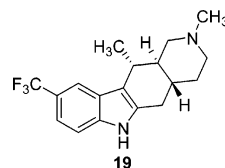
On the other hand, the *tert*-butyl ester group proved to be more stable to degradation and was easily removed after coupling. Deprotonation of **16**<sup>20</sup> with LDA and alkylation with allyl bromide provided the allyl derivative **17** as an oil (Scheme 5). Alternatively, alkylation of **16** with 1,4 dibromo-3-butene provided bis-adduct **18** as a crystalline solid in >90% yield.<sup>21</sup> Ozonolysis of either compound **17** or **18** in isopropanol provided *tert*-butyl 1-(2-oxoethyl)cyclohexane-carboxylate **3** as a light-yellow oil. A number of reducing agents, including Me<sub>2</sub>S, Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>, NH<sub>2</sub>CSNH<sub>2</sub>, and P(OMe)<sub>3</sub>, were tested for quenching the intermediate ozonide. The cleanest product was obtained with P(OMe)<sub>3</sub>.<sup>22</sup>

In the subsequent reductive amination step (Scheme 6), the crude 8:1 mixture of indole **2** and **10** was used directly as the undesired isomer **22** was easily rejected in the crystallization of **21**. The indoles and purified aldehyde **3** in THF were treated

SCHEME 5. *tert*-Butyl Ester Aldehyde SynthesisSCHEME 6. Coupling of Indole 2 with *tert*-Butylester Aldehyde 3

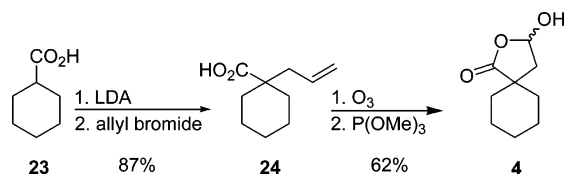
with NaBH(OAc)<sub>3</sub> at room temperature to afford the desired product **21** and corresponding regioisomer **22**. The pure product

(21) The formaldehyde from the ozonolysis of compound **17** was not easily separated. Despite wiped-film distillation of aldehyde **3** [see: (a) Cvengroš, J.; Valko, M.; Pollák, Š.; Lutišan, J. *Chem. Papers* **1999**, 53, 417] small amounts of formaldehyde always contaminated the product, which over time produced other byproducts. Aldehyde **3** was also prone to air oxidation. To improve stability, 1000 ppm of triethanolamine [see: (b) Ishihara, T.; Yamamoto, A.; Ohshima, M.; Aiba, N. Patent EP 0148648. (c) Weber, J.; Falk, V.; Kniep, C. Patent DE 2917789] was added to the distilled product, which was isolated in 78% yield and >95% purity as a light yellow oil. In contrast, no formaldehyde was generated in the ozonolysis of intermediate **18** to aldehyde **3**. Material prepared from this route was free of side products and was isolated in >95% yield and >99% GC purity without the need for wiped-film distillation. As mentioned, one problem with using the aldehyde **3** derived from **17** was the presence of small amounts of formaldehyde. This led to the formation of the *N*-Me derivative **19**. This impurity could be avoided by using **3** prepared from **18**.



(20) Chandrasekaran, S.; Tuner, J. V. *Synth. Commun.* **1982**, 12, 727.

## SCHEME 7. Lactol Synthesis

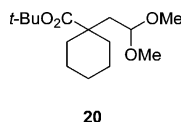


**21** was isolated by crystallization from ethyl acetate as the benzenesulfonic acid salt in 80% yield. Deprotection of the *tert*-butyl ester group was carried out by the addition of 0.25 equiv of benzenesulfonic acid to the salt **21** in acetonitrile and heating the mixture at 70 °C. AMG 076 was isolated as the benzenesulfonate salt in 81% yield. An excess of benzenesulfonic acid was required to improve the rate of the deprotection, as well as to prevent partial disproportionation of the desired salt to the free base.

**Reductive Amination of Indole 2 with Lactol 4.** Although lactol **4** was a degradant of methyl ester **13**, the compound had benefits over **3**. The intermediate would avoid the stability issues with the ester aldehydes, as well as a deprotection step (Scheme 7). Under forcing conditions with a strong acid, the methyl ester was not converted cleanly to **4**. Rather, the desired lactol was synthesized directly from cyclohexanecarboxylic acid (**23**).<sup>23</sup> To avoid the exothermic deprotonation, a THF solution of **23** was slowly added to LDA at −10 °C. To ensure complete dianion formation, it was crucial to stir the reaction mixture at 30–40 °C for several hours. The subsequent exothermic alkylation of the dianion with allyl bromide was performed at −10 to +10 °C. A catalytic amount of sodium iodide was needed for full consumption of the anion, otherwise, the reaction stalled at 80–90% conversion. The crude acid<sup>24</sup> was obtained as a clear yellow-orange oil in 87% yield. Allyl ester formation or *C,O*-dialkylation was not observed. Ozonolysis of the allyl group was carried out in MeOH at −45 °C. Trimethylphosphite was used to reduce the ozonide at −30 to −40 °C to afford lactol **4**, which was isolated as a white solid in 62% yield.

Five-membered-ring lactols such as **4** have been reported to be readily reduced to the corresponding lactone with a variety of reducing agents.<sup>24</sup> We were gratified that analogous to the coupling of indole **2** with aldehyde **3** (Scheme 6), reductive amination with lactol **4** by using NaBH(OAc)<sub>3</sub> in THF effectively produced compound **1**. Little over-reduction to the butyrolactone was observed. Product isolation, however, was very difficult. Compound **1** is a zwitterion, which formed a cloudy mixture of ultrafine particles upon aqueous quench. The solid could not be effectively isolated by filtration, leading to

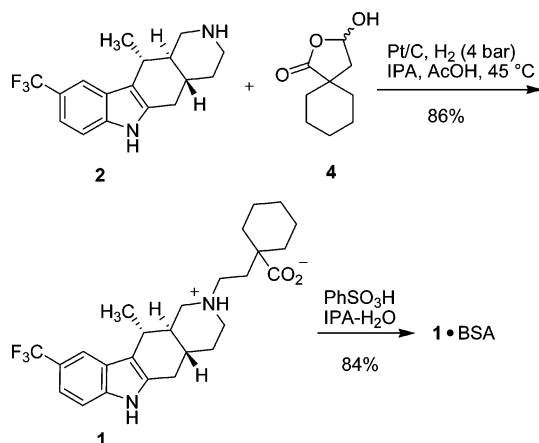
(22) Performing the ozonolysis step in methanol led to dimethyl acetal **20** byproduct formation since the pH of the product mixture became acidic due to the decomposition of P(OMe)<sub>3</sub>. By running the reaction in isopropanol and adding a mild base such as Na<sub>2</sub>CO<sub>3</sub> prior to the reducing agent, acetal formation was prevented.



(23) Direct alkylation of carboxylic acids has been reported previously: (a) Creger, P. L. *J. Org. Chem.* **1972**, 37, 1907. (b) Miller, R. D.; Goelitz, P. *J. Org. Chem.* **1981**, 46, 1616.

(24) For instance, see: (a) Sinhababu, A. K.; Borchardt, R. T. *J. Org. Chem.* **1983**, 48, 2356. (b) El-Shishtawy, R. M.; Fukunishi, K. *Synthesis* **1994**, 1411. (c) Tanino, H.; Fukuiishi, K.; Ushiyama, M.; Okada, K. *Tetrahedron* **2004**, 60, 3273.

## SCHEME 8. Coupling of Indole 2 with Lactol 4



very poor recoveries. Extraction of the product also was not practical as the product is highly insoluble in the typical solvents.

Catalytic hydrogenation was evaluated as this could offer improved separation of the product from the spent reagent (Scheme 8). From a screen of a number of homogeneous and heterogeneous catalysts, hydrogenation over Pt/C in isopropanol gave the most effective conversion.<sup>25</sup> The crystallization of the zwitterion **1** as it formed in the coupling was overcome by the addition of acetic acid. Thus, in a 70:30 mixture of IPA–AcOH, the zwitterion remained in solution throughout the hydrogenation. The spent catalyst was easily separated by filtration from the reaction mixture. The product was crystallized by a solvent switch to 1:15 AcOH/water. This produced a milky solution of the zwitterion as observed previously. However, with this system the fine particles could be reproducibly agglomerated into easily filterable particles by the slow addition of 3–7% of toluene with vigorous stirring to afford **1** in 86% yield. Salt formation with BSA in 75% aqueous isopropanol gave the desired final product **1** in 84% yield.

## Conclusions

Key to developing a productive synthesis of AMG 076 (**1**) were the preparation of chiral isoquinolinone **6**, the regioselectivity in the Fischer-indolization, the preparation of a suitable cyclohexylacetaldehyde equivalent, and a final reductive amination that allowed effective isolation of the drug substance. Two alternative building blocks **3** and **4** were employed for coupling the cyclohexylethyl side chain with the core heterocycle **2**. Although either endgame was suitable, the route through the lactol was optimal based on stability, robustness, and throughput. Kilogram quantities of **1** were prepared utilizing this chemistry.

## Experimental Section

**(8*S*,8*aR*)-2-Benzyl-8-methyl-1,3,4,7,8,8*a*-hexahydroisoquinolin-6(2*H*)-one di-*p*-toluoyl-L-tartaric Acid Salt (**9**).** A mixture of *N*-benzyl-4-piperidone (41.95 kg, 221 mol), toluene (145 kg, 126 L), and pyrrolidine (23.75 kg, 334 mol) was slowly heated to 84 °C over 2 h and held for 1 h, then the mixture was heated to reflux. Water was continuously removed by azeotropic distillation over a

(25) Only alcohol solvents performed well in this reaction. The *N*-ethyl byproduct of **2** was observed in ethanol due to the generation of acetaldehyde from oxidation of the solvent. Fortunately, isopropanol resulted in <1% of the corresponding *N*-alkylated byproduct. In *t*-BuOH and *sec*-BuOH the reactions were prohibitively sluggish.

Dean–Stark trap. The consumption of starting material was monitored by GC. When the amount of *N*-benzyl-4-piperidone was <2.5%, the toluene was distilled to <25% from the reaction mixture at 30 Torr and 50–60 °C. 1,4-Dioxane (174 kg, 174 L) and 3-penten-2-one (29.30 kg, 267 mol) were then charged to the thick, dark oil and the solution was stirred at 90 °C for 14 h. Approximately 50% of the dioxane was then removed by vacuum distillation and a mixture of sodium acetate (17.35 kg, 211 mol), acetic acid (33.80 kg, 563 mol), and water (35.05 kg, 1945 mol) was added slowly, while maintaining the temperature at <50 °C. The temperature of the reaction mixture was then adjusted to 90 °C and the solution was stirred for 2 h. The remaining dioxane was removed by vacuum filtration and the pH was adjusted to pH 8 with sodium hydroxide (50.25 kg, 353 mol) in water (45.25 kg, 2511 mol). Isopropyl acetate (110 kg, 126 L) was charged into the mixture, the phases were separated, and the aqueous phase was extracted once more with isopropyl acetate (110 kg, 126 L). The pooled organic phases were concentrated by vacuum distillation and the crude product mixture was analyzed by GC. The crude enone mixture contained 2.4% of *N*-benzyl-4-piperidone. This material was left in the reactor and was used as is in the resolution. The crude enone was charged with ethanol (70 kg, 100 L) and water (23 kg, 23 L).

A mixture of di-*p*-toluoyl-*L*-tartaric acid (73.0 kg, 188.9 mol), water (30 kg, 30 L), and ethanol (95 kg, 120 L) was heated to 40 °C to ensure complete dissolution. The prepared solution was added to the enone solution at 70 °C. During the addition a precipitate formed. The suspension was cooled to 20 °C over 4 h and aged for 8 h. The product was isolated by filtration and washed with 80:20 ethanol–water (2 × 71 kg). The wet filter cake was sampled and analyzed by chiral HPLC (96.7% ee). The salt was added to 80:20 ethanol–water (203 kg) and the mixture was heated at reflux for 1 h, cooled to 20 °C over 4 h, and aged for 8 h. The product was isolated by filtration, washed with 80:20 ethanol–water (70 kg), and vacuum-dried to give 79 kg of technical grade salt (28% overall yield from **7**), which contained ~5% water: 98.5% ee; chemical purity 99.5%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.09 (br s, 1H), 7.29 (d, *J* = 7.6 Hz, 4H), 6.79–6.70 (m, 9H), 5.18 (m, 3H), 3.21 (d, *J* = 13.1 Hz, 1H), 3.07 (d, *J* = 13.1 Hz, 1H), 2.76 (dd, *J* = 11.3, 5.5 Hz, 1H), 2.41 (m, 1H), 1.80 (s, 6H) superimposed on 1.91–1.72 (m, 3H), 1.62–1.46 (m, 3H), 1.34 (t, *J* = 11.3 Hz, 1H), 1.19–1.10 (m, 1H), 0.34 (d, *J* = 6.6 Hz, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 198.0, 167.6, 164.7, 161.7, 144.3, 135.9, 129.5, 129.4, 128.2, 127.3, 127.6, 126.1, 124.2, 71.6, 60.6, 56.5, 51.5, 44.5, 42.2, 32.6, 32.1, 21.2, 18.8; IR (neat) 1719, 1670, 1611 cm<sup>−1</sup>. Anal. Calcd for C<sub>37</sub>H<sub>39</sub>NO<sub>9</sub>: C, 69.25; H, 6.13; N, 2.18. Found: C, 68.97; H, 6.13; N, 2.16.

**(8S,8aR)-2-Benzyl-8-methyl-1,3,4,7,8,8a-hexahydroisouquinolin-6(2H)-one (9)**. An aliquot of the isolated di-*p*-toluoyl-*L*-tartaric acid salt **9** was treated with 10% aqueous sodium carbonate in water to provide a salt-free, analytical standard of compound **9** as a light yellow oil: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.39–7.32 (m, 5H), 7.30 (m, 1H), 5.84 (br s, 1H), 3.65 (d, *J* = 13.3 Hz, 1H), 3.52 (d, *J* = 13.3 Hz, 1H), 3.30 (ddd, *J* = 11.1, 5.6, 1.9 Hz, 1H), 2.99 (dddd, *J* = 11.0, 5.6, 2.1, 2.1 Hz, 1H), 2.65–2.50 (m, 1H), 2.40–2.35 (m, 2H), 2.32–2.27 (m, 1H), 2.14 (dd, *J* = 15.9, 13.5 Hz, 1H), 2.04 (ddd, *J* = 11.0, 9.5, 2.9 Hz, 1H), 1.90–1.80 (m, 1H), 1.76 (t, *J* = 11.0 Hz, 1H), 1.04 (d, *J* = 6.5 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 199.4, 163.2, 138.0, 128.9, 128.3, 127.2, 124.6, 62.6, 58.3, 52.8, 45.2, 44.0, 34.6, 32.8, 19.3; IR (neat) 1715, 1677 cm<sup>−1</sup>. HRMS calcd for C<sub>17</sub>H<sub>22</sub>NO 256.1701 [M + H]<sup>+</sup>, found 256.1686 [M + H]<sup>+</sup>.

**(4aR,8S,8aR)-8-methyl-6-oxo-octahydroisouquinoline-2-carboxylic Acid *tert*-Butyl Ester (6)**. A reactor was charged sequentially with a 4.7 wt/wt solution of sodium carbonate in water (210 kg, 141.5 mol), resolved di-*p*-toluoyl-*L*-tartaric acid salt **9** (78.2 kg, 66.3 wt %, 84.2 mol), and EtOAc (156 kg, 169 L). The biphasic mixture was stirred at 25 °C for 1 h, the layers were separated, and the aqueous layer was extracted with a second portion of EtOAc

(182 kg, 197 L). The organic layers were combined, washed with a 4.7 wt/wt solution of sodium carbonate in water (2 × 51 kg, 22.6 mol), and concentrated to 300 L by distillation. This sequence was repeated for an additional 89.4 mol of di-*p*-toluoyl-*L*-tartaric acid salt **9** and the free base solutions were combined and used directly in the next step.

Di-*tert*-butyl carbonate (41.6 kg, 190.3 mol) and 10% Pd(OH)<sub>2</sub> (3.4 kg, 2.4 mol) were charged into the crude reaction mixture. The reaction vessel was pressurized with hydrogen (3 bar) and the mixture was stirred at 40 °C. Conversion to product was monitored by HPLC (12–17 h). The Pd catalyst was removed by adding Celite (1.5 kg) to the reaction mixture and filtering through a bed of Celite (0.7 kg). The excess Boc anhydride was destroyed by refluxing the filtrate with water (38.9 kg, 2159 mol) for 8 h and discarding the aqueous phase. The organic layer was concentrated to 130 L and heptane was added (184 L). The reaction mixture was concentrated (25–35 °C, 30 Torr) to a final volume of 85 L and seeded to induce crystallization. The slurry was cooled to 0 °C, aged for 30 min, filtered, and washed with cold heptane (16 kg). The wet cake was dried to give 31.8 kg (69% yield) of ketone **6** as a white solid: mp (DSC) 86.7 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.44 (br s, 1H), 4.16 (br s, 1H), 2.69 (br t, *J* = 11.5 Hz, 1H), 2.38 (dddd, *J* = 14.2, 14.2, 4.6, 2.0 Hz, 2H), 2.33–2.23 (m, 1H), 2.11 (ddd, *J* = 13.0, 13.0, 2.5 Hz, 2H), 1.65–1.50 (m, 2H), 1.47 (s, 9H), 1.32 (ddd, *J* = 13.0, 13.0, 4.6 Hz, 1H), 1.27–1.21 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 209.2, 154.6, 79.5, 49.6, 47.7, 47.1, 46.0, 43.9, 41.2, 35.9, 32.9, 28.3, 19.0; IR (neat) 1664, 1124 cm<sup>−1</sup>. HRMS calcd for C<sub>11</sub>H<sub>18</sub>NO<sub>3</sub> 212.1287 [M – *tert*-butyl + H]<sup>+</sup>, found 212.1272 [M – *tert*-butyl + H]<sup>+</sup>. Anal. Calcd for C<sub>11</sub>H<sub>18</sub>NO<sub>3</sub>: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.43; H, 9.52; N, 5.18.

**(4aR,11R,11aS)-11-Methyl-9-(trifluoromethyl)-2,3,4,4a,5,6,11,11a-octahydro-1H-pyrido[4,3-*b*]carbazole (2) and (4aR,5S,11cS)-5-Methyl-10-(trifluoromethyl)-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,4-*c*]carbazole (10)**. The ketone **6** (195.4 g, 0.731 mol) and 4-(trifluoromethyl)phenylhydrazine **5** (180.6 g, 0.738 mol) were mixed in dioxane (1.4 L). A solution of premixed concentrated sulfuric acid (125 mL, 2.34 mol) and water (6.5 mL, 0.36 mol) was added slowly to the yellow heterogeneous reaction mixture while keeping the temperature of the vessel at <45 °C. When the addition was complete, the reaction mixture was heated over 1 h to 70 °C. Off-gassing of carbon dioxide and isobutylene from the loss of the Boc group was observed at the beginning of the reaction. The consumption of the hydrazone from the initial condensation of ketone **6** and hydrazine **5** was monitored by HPLC and after ~19 h there was <1%. The reaction was cooled to rt over 3 h and NaOH (2.48 L of a 1.9 N solution in water, 4.75 mol) was added. A beige precipitate formed and the mixture was aged at rt for 2 h. The slurry was filtered, washed with water (3 × 0.5 L), and dried at 60 °C with a nitrogen bleed for 24 h to give 207.4 g (92% yield) of an 8.1:1 mixture of indoles **2** and **10**.

For the coupling of the indole with the *tert*-butyl ester **3** the crude indole mixture can be used as is. For coupling of **2** with the lactol **4** the indole isomer **10** must be removed.

The crude mixture of indoles **2** and **10** (207.8 g, 0.67 mol) was heated in methanol (2.0 L) at 60 °C to give a homogeneous solution. Concentrated phosphoric acid (75 mL, 1.1 mol) was added over 20 min to the solution while maintaining the temperature at <65 °C. The reaction mixture was cooled over 2 h to 25 °C. The phosphate salt of **2** was filtered, washed with methanol (2 × 0.4 L), and dried under vacuum with a nitrogen stream for 1 h. A mixture of the crude phosphoric acid salt of compound **2**, water (3.2 L), and THF (0.8 L) was warmed to 35 °C and NaOH (142 mL of a 10 N solution in water, 1.42 mol) was added. The beige slurry was stirred vigorously for 2 h then filtered and the filter cake was washed with water (3 × 0.2 L). The wet filter cake was dried to give 149 g (72% yield, 99.7 LCAP) of purified indole **2**: mp (DSC) 232.4 °C; <sup>1</sup>H NMR (300 MHz, MeOH-*d*<sub>4</sub>) δ 7.77 (s, 1H), 7.37 (d, 8.5 Hz, 1H), 7.26 (dd, *J* = 8.5, 1.3 Hz, 1H), 3.36

(dd,  $J = 12.4, 3.7$  Hz, 1H), 2.98 (br d,  $J = 12.3$  Hz, 1H), 2.63 (dd,  $J = 16.1, 4.3$  Hz, 1H), 2.56–2.47 (m, 2H), 2.34 (ddd,  $J = 16.1, 10.7, 2.1$  Hz, 1H), 2.23 (dd,  $J = 12.3, 11.1$  Hz, 1H), 1.75–1.70 (m, 1H), 1.50–1.40 (m, 1H), 1.37 (d,  $J = 6.5$  Hz, 3H), 1.29 (dd,  $J = 12.0, 4.1$  Hz, 1H), 1.24–1.11 (m, 1H);  $^{13}\text{C}$  NMR (75 MHz, MeOH- $d_4$ )  $\delta$  139.3, 136.9, 127.8, 127.3 (q,  $J_{\text{C-F}} = 270$  Hz), 121.4 (q,  $J_{\text{C-F}} = 31$  Hz), 117.7 (q,  $J_{\text{C-F}} = 4$  Hz), 117.2 (q,  $J_{\text{C-F}} = 5$  Hz), 114.6, 112.0, 51.5, 48.2, 47.0, 38.5, 34.5, 33.1, 31.3, 20.0; IR (neat) 3100, 1105  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{17}\text{H}_{20}\text{F}_3\text{N}_2$ : 309.1573 [ $\text{M} + \text{H}$ ] $^+$ , found 309.1567 [ $\text{M} + \text{H}$ ] $^+$ . Anal. Calcd for  $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_2$ : C, 66.22; H, 6.21; N, 9.06. Found: C, 66.19; H, 6.24; N, 9.06.

An analytical standard of the regioisomer **10** was prepared by concentrating the original mother liquor from the phosphoric acid salt formation and rinsing the precipitate well with methanol: mp (DSC) 249.3  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 (s, 1H), 7.33 (s, 2H), 3.36 (dd,  $J = 11.6, 3.0$  Hz, 1H), 3.25 (m, 1H), 2.89 (td,  $J = 12.0, 2.0$  Hz, 1H), 2.79 (dd,  $J = 16.3, 5.4$  Hz, 1H), 2.69 (m, 2H), 2.52 (m, 2H), 1.87–1.75 (m, 2H), 1.35 (qd,  $J = 10.7, 3.0$  Hz, 1H), 1.08 (d,  $J = 6.5$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  137.5, 135.7, 126.8, 125.7, 120.4 (q,  $J_{\text{C-F}} = 32$  Hz), 116.6, 116.2, 112.0, 110.5, 47.2, 42.8, 39.6, 32.2, 31.7, 31.6, 18.2, 3.70; IR (neat) 3150, 1105  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{17}\text{H}_{20}\text{F}_3\text{N}_2$ : 309.1573 [ $\text{M} + \text{H}$ ] $^+$ , found 309.1576 [ $\text{M} + \text{H}$ ] $^+$ .

**1-Allylcyclohexanecarboxylic Acid *tert*-Butyl Ester (17).** *n*-Butyllithium (195 mL of a 1.6 M solution in hexanes, 0.31 mol) was added to a solution of diisopropylamine (35.6 g, 0.35 mol) in THF (195 mL) at  $-20$  to  $0$   $^{\circ}\text{C}$  over 40 min and held at  $0$   $^{\circ}\text{C}$  for 30 min. The solution was cooled to  $-20$   $^{\circ}\text{C}$  and *tert*-butyl cyclohexanecarboxylate (**16**) (50.0 g, 0.27 mol) was added. The reaction mixture was stirred at  $0$   $^{\circ}\text{C}$  for 30 min and cooled to  $-20$   $^{\circ}\text{C}$ . Allyl bromide (26.0 g, 0.30 mol) was added and the reaction mixture was then warmed to rt over 90 min. The reaction was monitored by GC for the consumption of *tert*-butyl cyclohexanecarboxylate. When the level was  $<1\%$  the crude reaction mixture was cooled to  $0$   $^{\circ}\text{C}$  and the reaction was quenched by adding it to a solution of citric acid (67 g, 0.35 mol) in water (150 mL). The layers were separated and the organic phase was washed with 10% aqueous sodium carbonate solution, water (150 mL), and brine (150 mL) and concentrated to give 58 g (95% yield) of **17** as a yellowish oil: bp 47–49  $^{\circ}\text{C}$  (1 Torr);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.72 (m, 1H), 5.04 (m, 1H), 5.00 (m, 1H), 2.20 (d,  $J = 7.4$  Hz, 2H), 2.00 (br d, 13.4 Hz, 2H), 1.55 (m, 3H), 1.44 (s, 9H), 1.35 (m, 2H), 1.20 (m, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.4, 134.0, 117.3, 79.8, 47.1, 44.9, 34.0, 28.2, 26.0, 23.2; IR (neat) 1719, 1128  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{14}\text{H}_{24}\text{O}_2$ : C, 74.95; H, 10.78. Found: C, 74.83; H, 10.93.

**1-(2-Oxo-ethyl)cyclohexanecarboxylic Acid *tert*-Butyl Ester (3).** Ozone gas was passed through a solution of allylcyclohexanecarboxylate **17** (100 g, 0.44 mol) in isopropanol (500 mL) at  $-25$   $^{\circ}\text{C}$  for 4 h. Nitrogen was then passed through the solution for 30 min at  $-25$   $^{\circ}\text{C}$  to remove any excess ozone. Solid sodium carbonate (47.3 g, 0.45 mol) was added first to the reaction mixture followed by trimethylphosphite (56.0 g, 0.45 mol) over 60 min at  $-15$   $^{\circ}\text{C}$ . The slurry was then filtered into a mixture of MTBE (1 L) and 5% aqueous sodium carbonate (1 L). The layers were separated and the organic phase was washed with water ( $2 \times 1$  L) and brine (100 mL). The crude solution of the product was concentrated and then purified by wiped-film distillation to afford 85 g (85% yield) of aldehyde **3** as a slightly yellow oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.75 (t,  $J = 2.4$  Hz, 1H), 2.54 (d,  $J = 2.5$  Hz, 2H), 2.00 (m, 2H), 1.52 (m, 6H), 1.45 (s, 9H), 1.38 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  201.1, 174.9, 80.9, 51.5, 45.1, 34.0, 28.0, 25.6, 22.4. The thermal instability of aldehyde **3** precluded further characterization.

**1-[2-((4aR,11R,11aS)-11-Methyl-9-trifluoromethyl-1,3,4,4a,5,6,11,11a-octahydropyrido[4,3-*b*]carbazol-2-yl)ethyl]cyclohexanecarboxylic Acid *tert*-Butyl Ester Benzenesulfonic Acid Salt (21).** The crude 8:1 mixture of indoles **2** and **10** (40.0 g, 130 mmol) and aldehyde **3** (38.2 g, 169 mmol) were mixed in THF (160 mL). The resultant mixture was stirred at rt for 1 h, then cooled to  $10$   $^{\circ}\text{C}$  and

sodium triacetoxyborohydride (55.0 g, 259 mol) was added. The mixture was stirred at rt for 4 h, diluted with EtOAc (200 mL), and washed with 10% aqueous sodium carbonate ( $2 \times 140$  mL), water ( $2 \times 150$  mL), and brine ( $2 \times 150$  mL). The product solution was treated directly with a solution of  $\text{PhSO}_3\text{H}$  (31 g, 146 mmol) in EtOAc (130 mL) at rt over 1 h at which time a white precipitate had formed. The product was isolated by filtration and dried to constant mass to give 70 g (80% yield) of compound **21** as a fluffy white solid: mp (DSC) 226.1  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  11.30 (s, 1H), 9.12 (br s, 1H), 7.81 (s, 1H), 7.61 (d,  $J = 2.0$  Hz, 2H), 7.46 (d,  $J = 8.5$  Hz, 1H), 7.31 (m, 4H), 3.83 (d,  $J = 11.0$  Hz, 1H), 3.57 (d,  $J = 11.5$  Hz, 1H), 3.13 (m, 2H), 3.05–2.77 (m, 5H), 2.70 (t,  $J = 7.5$  Hz, 1H), 2.45 (m, 1H), 2.08 (m, 1H), 1.98–1.84 (m, 6H), 1.45 (s, 9H), 1.42 (d,  $J = 6.5$  Hz, 3H), 1.36–1.19 (m, 7H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) 173.8, 148.1, 137.4, 135.4, 128.1, 127.4, 125.5 (q,  $J_{\text{C-F}} = 271.4$  Hz), 125.4, 125.2, 118.8 (q,  $J_{\text{C-F}} = 30.4$  Hz), 116.4, 115.5 ( $J_{\text{C-F}} = 3.5$  Hz), 111.8, 111.2, 80.0, 55.0, 52.2, 50.9, 45.0, 43.2, 33.9, 33.3, 32.7, 32.3, 30.8, 29.1, 28.3, 27.5, 25.0, 22.3, 22.2, 19.0; IR (neat) 3200, 1714, 1115  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{26}\text{H}_{34}\text{F}_3\text{N}_2\text{O}_2$  463.2572 [ $\text{M} - \text{tert-butyl} + \text{H}$ ] $^+$ , found 463.2588 [ $\text{M} - \text{tert-butyl} + \text{H}$ ] $^+$ .

**1-[2-((4aR,11R,11aS)-11-Methyl-9-trifluoromethyl-1,3,4,4a,5,6,11,11a-octahydropyrido[4,3-*b*]carbazol-2-yl)ethyl]cyclohexanecarboxylic Acid·Benzenesulfonic Acid (1).** Salt **21** (50 g, 74 mmol) and  $\text{PhSO}_3\text{H}$  (13 g, 81 mmol) were added to acetonitrile (500 mL). The vessel was made inert with three vacuum/nitrogen cycles and heated to  $70$   $^{\circ}\text{C}$ . After 5.5 h, toluene (500 mL) was added over 1 h and the reaction mixture was then cooled to ambient temperature over 1 h and  $0$   $^{\circ}\text{C}$  over 1 h. The slurry was stirred at  $0$   $^{\circ}\text{C}$  for a further 1 h and filtered. The filter cake was washed with a 1:1 mixture of acetonitrile and toluene ( $2 \times 100$  mL) and dried to give 37.4 g (81%) of the title compound **1** as a white solid: water (Karl Fischer) 1.4%, mp (DSC) 226.1  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  12.55 (br s, 1H), 11.32 (s, 1H), 9.15 (br s, 1H), 7.81 (s, 1H), 7.64–7.61 (m, 2H), 7.47 (d,  $J = 8.6$  Hz, 1H), 7.31 (m, 4H), 3.84 (d,  $J = 10.8$  Hz, 1H), 3.58 (d,  $J = 11.4$  Hz, 1H), 3.16 (m, 1H), 3.05–2.79 (m, 4H), 2.67 (t,  $J = 7.3$  Hz, 1H), 2.43 (m, 1H), 2.07 (d,  $J = 13.7$  Hz, 1H), 1.93 (m, 3H), 1.73 (m, 1H), 1.60–1.50 (m, 5H), 1.40 (d,  $J = 6.5$  Hz, 3H), 1.36–1.26 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ) 176.7, 148.1, 137.6, 135.6, 128.5, 127.6, 125.7 (q,  $J_{\text{C-F}} = 271.4$  Hz), 125.6, 125.5, 119.0 (q,  $J_{\text{C-F}} = 30.3$  Hz), 116.5, 115.7 (q,  $J_{\text{C-F}} = 3.5$  Hz), 112.0, 111.5, 55.3, 52.5, 51.1, 44.5, 43.4, 34.2, 33.2, 33.0, 32.1, 31.0, 29.3, 28.5, 25.2, 22.5, 19.2; IR (neat) 3463, 1735, 1694  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{32}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_5\text{S} + 0.5\text{H}_2\text{O}$ : C, 61.03; H, 6.40; N, 4.45. Found: C, 61.34; H, 6.47; N, 4.26.

**1-Allylcyclohexanecarboxylic Acid (23).** A reactor was charged with THF (3 L) and made inert with three vacuum/nitrogen cycles, then diisopropylamine (2.05 kg, 20.26 mol) was added. The reaction was cooled  $-30$  to  $-40$   $^{\circ}\text{C}$  and *n*-butyllithium (7.18 L of a 2.5 M solution in hexanes, 17.95 mol) was added at a rate to maintain a temperature of  $<0$   $^{\circ}\text{C}$ . The solution was then stirred at  $-10$   $^{\circ}\text{C}$  for 30 min and a solution of cyclohexanecarboxylic acid (1.0 kg, 7.8 mol) in THF (1.3 L) was added over 1 h. The reaction mixture was heated to reflux ( $\sim 42$   $^{\circ}\text{C}$ ) and held for 8 h. The reaction completion was determined by quenching an aliquot with allyl bromide and analysis for cyclohexylcarboxylic acid by GC. When the level was  $<5\%$  the slurry was cooled to  $-20$   $^{\circ}\text{C}$  and NaI (117.0 g, 0.78 mol) was added in one portion. Subsequently, allyl bromide (1.01 L, 11.7 mol) was added at a rate such that the temperature did not exceed  $10$   $^{\circ}\text{C}$ . When the addition was complete, the reaction mixture was warmed to rt and stirred until the conversion was  $>90\%$  by GC. The mixture was cooled to  $-10$   $^{\circ}\text{C}$  and water (3 L) and MTBE (5 L) were added. The layers were separated and the organic layer was extracted with 10% aqueous sodium carbonate (2.0 L). The aqueous layers were combined and cooled to  $10$   $^{\circ}\text{C}$  and the pH of the mixture was adjusted to 1–2 with 10% HCl ( $\sim 5.0$  L). The product separated out as an oil and was extracted with MTBE ( $2 \times 2.0$  L). The combined organic phases were washed

with 5 N NaCl solution ( $2 \times 2.0$  L) and evaporated to dryness to yield 1.28 kg of **24** (97% yield, 91.4% GC purity) as a clear, yellowish-orange oil:  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  11.80 (br s, 1H), 5.73 (m, 1H), 5.07 (m, 1H), 5.03 (m, 1H), 2.29 (m, 2H), 2.05 (m, 2H), 1.65–1.52 (m, 3H), 1.47–1.37 (m, 3H), 1.30–1.23 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  183.6, 133.4, 117.9, 47.2, 44.4, 33.5, 25.8, 23.1; IR (neat) 3078, 1697, 1641  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{10}\text{H}_{17}\text{O}_2$  169.1223  $[\text{M} + \text{H}]^+$ , found 169.1222  $[\text{M} + \text{H}]^+$ .

( $\pm$ ) **3-Hydroxy-2-oxa-spiro[4.5]decan-1-one (4)**. A 2 L, 3-necked Morton flask equipped with a thermocouple probe, a gas transfer tube, and a nitrogen inlet was charged sequentially with 1-allylcyclohexane carboxylic acid **24** (100 g, 0.594 mol) and methanol (750 mL) and cooled to  $-45^\circ\text{C}$ . Ozone was bubbled into the solution through the gas transfer tube until the blue color of ozone persisted ( $\sim 3$  h). The reaction progress can also be monitored by quenching an aliquot into an excess of  $\text{P}(\text{OMe})_3$  in methanol at  $-78^\circ\text{C}$  and monitoring the conversion by GC. Nitrogen was then bubbled into the solution until the reaction mixture was nearly colorless ( $\sim 45$  min) and then trimethylphosphite (84.1 mL, 0.713 mol) in methanol (84 mL) was added at  $-45$  to  $-20^\circ\text{C}$ . After the addition was complete, the solution was warmed to rt and stirred for 10 h. The solvent was switched to MTBE and the mixture was washed with water ( $3 \times 300$  mL). The solvent was switched again to cyclohexane and the volume was adjusted to 900 mL. The mixture was heated to reflux ( $\sim 80^\circ\text{C}$ ), cooled to  $35^\circ\text{C}$ , and seeded to induce crystallization. The resultant slurry was aged at  $0^\circ\text{C}$  for 2 h. The product was isolated by filtration, washed with cold cyclohexane (200 mL), and dried in a vacuum oven ( $30^\circ\text{C}$ , 30 Torr) for 16 h to give 63.1 g (62.3% yield) of lactol **4** as a white solid: mp (DSC)  $74.7^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{ACN}-d_3$ )  $\delta$  5.16 (br s, 1H), 5.76 (dd,  $J = 6.0, 3.6$  Hz, 1H), 2.33 (dd,  $J = 13.6, 6.0$  Hz, 1H), 1.95 (dd,  $J = 13.6, 3.6$  Hz, 1H), 1.68 (m, 3H), 1.64 (m, 1H), 1.62 (m, 1H), 1.58 (m, 1H), 1.50 (br d,  $J = 13.0$  Hz, 1H), 1.34 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{ACN}-d_3$ )  $\delta$  181.9, 97.5, 45.4, 41.2, 34.8, 34.6, 22.9, 22.8, 26.1; IR (KBr) 3465, 3314, 1763, 1731  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_9\text{H}_{15}\text{O}_3$  171.1022  $[\text{M} + \text{H}]^+$ , found 171.1026  $[\text{M} + \text{H}]^+$ .

**1-[2-((4aR,11R,11aS)-11-Methyl-9-trifluoromethyl-1,3,4,4a,5,6,11,11a-octahydropyrido[4,3-b]carbazol-2-yl)ethyl]cyclohexanecarboxylic Acid (1)**. A suspension of 5% Pt/C (2.5 g, 50% wet weight, 0.33 mmol) in acetic acid (22.5 mL) was purged sequentially with nitrogen and hydrogen. The mixture was stirred at  $40^\circ\text{C}$  and pressurized to 20 psi with hydrogen gas for 1 h to pre-hydrogenate the catalyst. A homogeneous mixture of indole **2** (10.00 g, 32.4 mmol) in IPA (105 mL), lactol **4** (6.07 g, 35.6 mmol) in

IPA (22.5 mL), and acetic acid was then added to the catalyst suspension. The mixture was vigorously stirred under 20 psi of hydrogen gas at  $40^\circ\text{C}$  for 24 h at which time the conversion of indole **2** to product was  $>99\%$ . The spent catalyst was removed by filtration and the filter cake was washed with AcOH ( $2 \times 10$  mL). The homogeneous reaction mixture was then concentrated to ca. half of the original volume and water (375 mL) was added. The resultant milky white suspension was vigorously stirred for 1 h at  $40^\circ\text{C}$  and cooled to rt. Toluene (15.7 mL) was slowly added to the rapidly stirred emulsion over 45 min. This resulted in the agglomeration of the fine suspension of particles and filtration furnished 12.8 g (86%) of zwitterion **1** as white granules: mp (DSC)  $276.3^\circ\text{C}$ ;  $^1\text{H}$  NMR (600 MHz, TFA- $d_1$  + DMSO- $d_6$ )  $\delta$  11.29 (s, 1H), 9.35 (br s, 1H), 7.79 (s, 1H), 7.44 (d,  $J = 8.5$  Hz, 1H), 7.29 (d,  $J = 8.5$  Hz, 1H), 3.85 (br d,  $J = 12.0$  Hz, 1H), 3.58 (br d,  $J = 11.4$  Hz, 1H), 3.17 (m, 1H), 3.04 (m, 1H), 2.95 (t,  $J = 11.4$  Hz, 1H), 2.87 (t,  $J = 12.0$  Hz, 1H), 2.82 (dd,  $J = 16.1, 4.4$  Hz, 1H), 2.67 (qui,  $J = 6.5$  Hz, 1H), 2.44 (dd,  $J = 16.1, 12.6$  Hz, 1H), 2.06 (d,  $J = 12.0$  Hz, 1H), 1.95 (m, 4H), 1.71 (m, 1H), 1.55 (m, 5H), 1.42 (d,  $J = 6.5$  Hz, 3H), 1.31 (m, 5H);  $^{13}\text{C}$  NMR (150 MHz, TFA- $d_1$  + DMSO- $d_6$ ) 176.8, 137.7, 135.6, 125.9 (q,  $J_{\text{C-F}} = 270.7$  Hz), 125.8, 119.4 (q,  $J_{\text{C-F}} = 30.8$  Hz), 116.8, 115.9, 112.2, 111.6, 55.4, 52.7, 51.2, 44.7, 43.7, 34.4, 33.4, 33.4, 33.3, 31.2, 29.5, 28.7, 25.4, 22.6, 22.6, 19.3; IR (KBr) 3253, 3059, 1668, 1626  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{26}\text{H}_{34}\text{F}_3\text{N}_2\text{O}_2$  463.2567  $[\text{M} + \text{H}]^+$ , found 463.2575  $[\text{M} + \text{H}]^+$ .

**1-[2-((4aR,11R,11aS)-11-Methyl-9-trifluoromethyl-1,3,4,4a,5,6,11,11a-octahydropyrido[4,3-b]carbazol-2-yl)ethyl]cyclohexanecarboxylic Acid·Benzenesulfonic Acid (1)**. Benzenesulfonic acid (4.9 g, 31.1 mmol) in water (15.6 mL) at  $70^\circ\text{C}$  was slowly added to a slurry of zwitterion **1** (12.0 g, 25.9 mmol) in IPA (65 mL). Additional water (49 mL) was added to the mixture and stirring was continued at  $70^\circ\text{C}$ . The homogeneous solution was cooled over 2 h to  $55^\circ\text{C}$  and seeded to induce crystallization. The solution was aged for 10 h at  $55^\circ\text{C}$  and then was cooled to  $5^\circ\text{C}$  and aged for a further 4 h. The product was isolated by filtration and washed with 50% IPA–water ( $2 \times 75$  mL) and dried to give 13.5 g (84%) of the salt **1**, which was identical with the sample synthesized from the *tert*-butyl ester aldehyde **3** (mp,  $^1\text{H}$  NMR).

**Supporting Information Available:** Experimental methods, X-ray crystallographic data, and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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