JOC Article

A Scalable Synthesis of an Azabicyclooctanyl Derivative, a Novel DPP-4 Inhibitor

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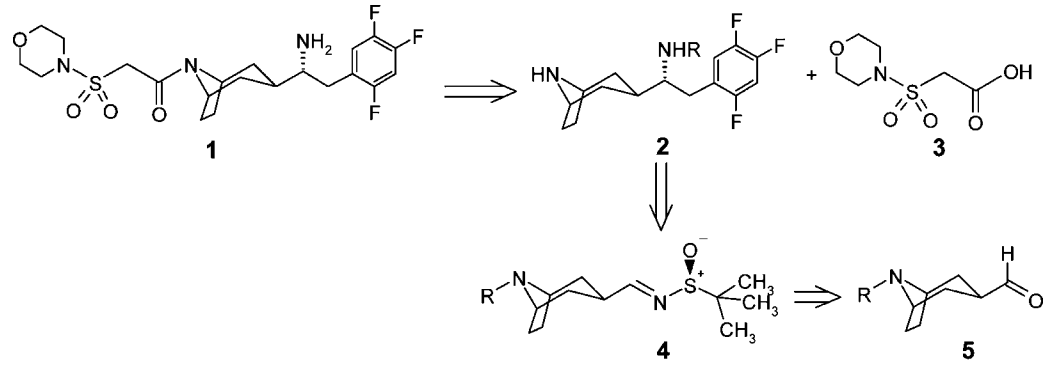

A practical synthetic strategy to a chiral azabicycclooctanyl derivative (**1**), a potent DPP-4 inhibitor, starting from a commercially available nortropine is described. The stereogenic center of **1** was established employing a modified protocol of Ellman's diastereoselective addition of a benzylic nucleophile to *tert*-butanesulfinimine. Other key steps include Corey−Chaykovsky reaction, Meinwald rearrangement, and CDMT-promoted amide bond formation involving a sterically hindered amine **2**.

Introduction

Dipeptidyl peptidase 4 (DPP-4) is a clinically validated target for regulating glycemia. Inhibiting DPP-4 will lead to a reduction in elevated blood glucose levels (hyperglycemia) that is a characteristic feature of type 2 diabetes.[1] Galvus (Novartis) and Januvia (Merck), both functioning as DPP-4 inhibitors, have been approved in several countries for the treatment of type 2 diabetic patients. Compound **1** was identified as another novel and potent DPP-4 inhibitor at Novartis.[2] To assess its efficacy and safety in man, we needed to develop a commercially viable route for the production of the active pharmaceutical ingredient for diabetic clinical trials.

Our strategy for the synthesis of **1** is outlined in Scheme 1, involving an attempt to assemble the target molecule by the condensation of bicyclic amine **2** with acid **3**. To establish the stereogenic center of **2**, we considered the asymmetric addition of a benzylic nucleophile to *tert*-butanesulfinimine **4**, a methodology developed by Ellman.[3] Azabicyclooctanyl aldehyde **5**, the precursor to aldimine **4**, could be synthesized from a commercially available starting material bearing the required azabicyclic skeleton.

Results and Discussion

Synthesis of Azabicyclooctane Aldehyde. The first route we considered for the synthesis of aldehyde **9** is shown in Scheme 2. Tropinone **6** was concomitantly protected and demethylated to afford **7** in 51% yield. Wittig olefination of **7** furnished enol

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(1) Drucker, D. J. *Diabetes Care* **2007**, *30* (6), 1335–1343.
(2) Baeschlin, D. K.; Fenton, G.; Namoto, K.; Ostermann, N.; Sedrani, R.; Sirockin, F. *Chem. Abstr.* **2007**, *147*, 448757; *WIPO*, WO 2007/115821.
(3) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.

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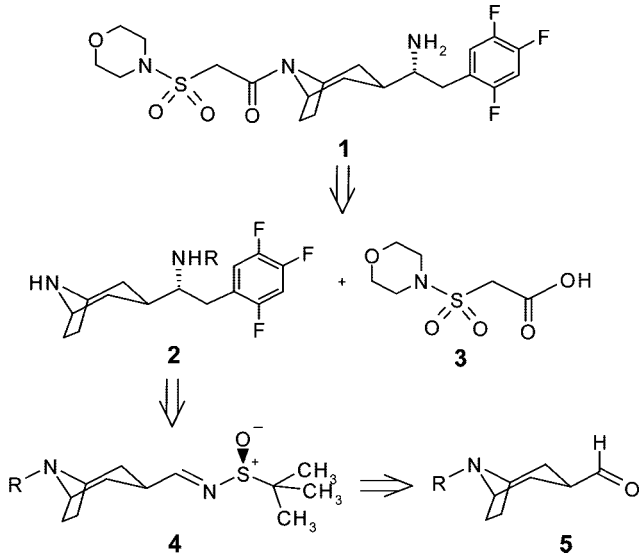
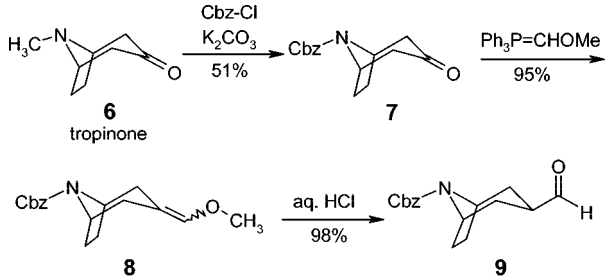
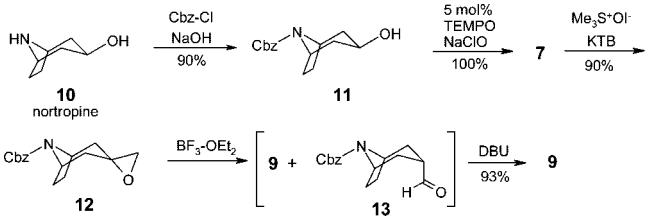
SCHEME 1. Retrosynthetic Analysis of 1



SCHEME 2. Initial Route for Aldehyde 9



SCHEME 3. Preferred Route to Aldehyde 9



ether **8** in 95% yield. Hydrolysis of **8** with aqueous HCl solution furnished **9** in 98% yield. Although yields of the last two steps were excellent, a tedious procedure that was needed to remove triphenylphosphine oxide byproduct discouraged us from using this method on a large scale. As a result, an alternative route according to Scheme 3 was developed.

Treating commercially available nortropine **10** with Cbz-Cl in the presence of sodium hydroxide afforded alcohol **11** as a white crystalline solid in 90% yield. Oxidation of **11** with a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) in the presence of aqueous sodium hypochlorite solution cleanly generated ketone **7** in quantitative yield. Epoxidation of **7** employing Corey−Chaykovsky reaction[4] provided epoxide **12** as an oil in 90% yield. Meinwald rearrangement[5] of **12** with BF_3−OEt furnished a mixture of isomers **9** and **13** (8:1). This mixture was treated with DBU at rt for 1 h and the thermodynamically more stable **9** was obtained in 93% isolated yield.

SCHEME 4. Addition of Grignard Reagent to Imine 15

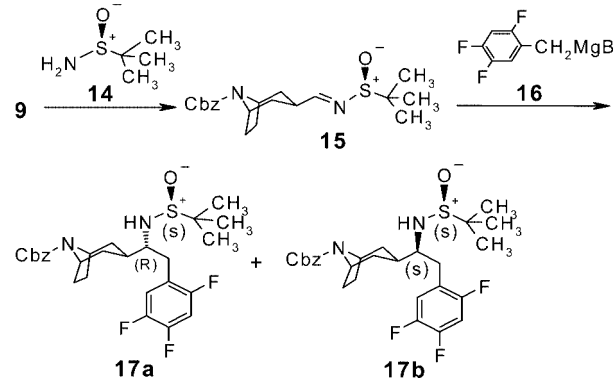
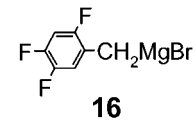


TABLE 1. Influence of Solvent and Temperature on Diastereoselectivity



entry	solvent	temp (°C)	**17a**:**17b**
1	Et_2O	25	40:60
2	$MeOCH_2CH_2OMe$	25	45:55
3	toluene	25	48:52
4	THF	25	42:58
5	CH_2Cl_2	25	55:45
6	CH_2Cl_2	10	62:38
7	CH_2Cl_2	−78	70:30

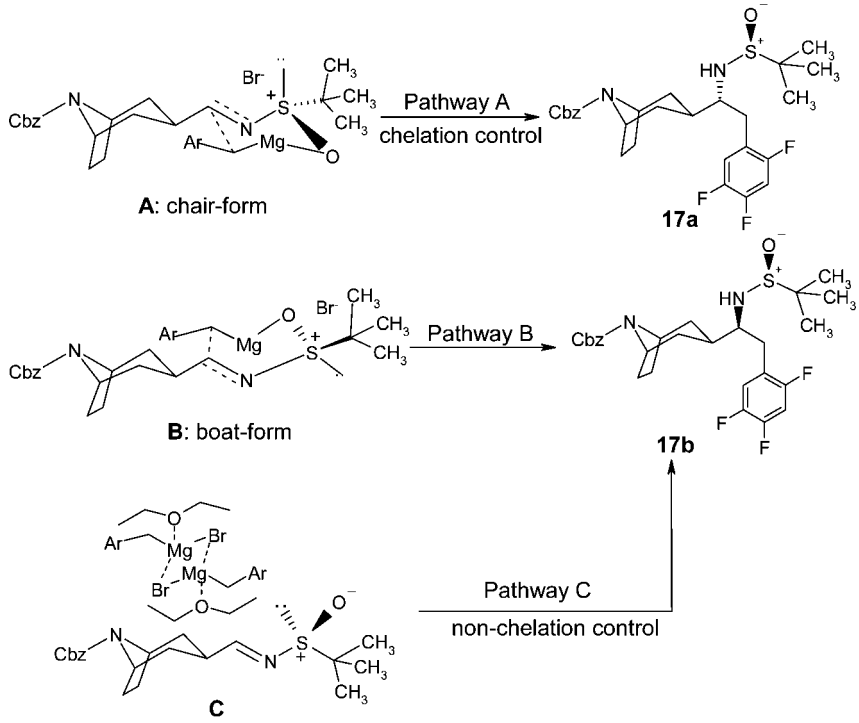
This route with an overall yield of 75% was employed for our large scale production of **9**.

Grignard Addition to *tert*-Butanesulfinimine. Two methodologies were investigated for the condensation of aldehyde **9** with (*S*)-*tert*-butanesulfinamide **14** (Scheme 4). Under homogeneous conditions, $Ti(OEt)_4$ was employed as both Lewis acid and water scavenger[6] affording **15** as a solid in 92% yield (HPLC purity 97%). Under heterogeneous conditions where pyridinium-*p*-toluenesulfonate and magnesium sulfate were utilized as a catalyst and as a water scavenger, respectively, **15** was obtained in 80% yield. Although the yield of the latter approach is slightly lower, it is the one adopted for scale-up.

To explore the diastereoselectivity of 1,2-addition of Grignard reagent **16** to *tert*-butanesulfinimine **15**, we decided to prepare **16** from *tri*-fluorobenzyl bromide and magnesium turnings in diethyl ether (Ellman utilized a 3.0 M solution of Grignard reagent in Et_2O in his protocol[7]). Grignard reagent **16** was then added to a solution of aldimine **15** in methylene chloride at 25 °C and resulted in the formation of a diastereomeric mixture of **17a** and **17b** (55:45). The desired **17a** was separated from **17b** in 30% yield by chromatography, which was a difficult operation due to the closeness of their R_f values. To improve the diastereoselectivity, solvent and temperature effects were probed and results were outlined in Table 1. The Grignard reagent was generated in ethyl ether and then added to the solution of **15** in a variety of solvents at 25 °C. The selectivity was better in a relative sense when methylene chloride was used (Table 1, entry 5). By lowering the addition temperature from 25 to −78 °C, an improved selectivity of **17a** over **17b** was observed (entries

(4) Corey, E. J.; Chaykovsky, M. J. *J. Am. Chem. Soc.* **1962**, *84*, 867–868.
(5) Meinwald, J.; Labana, S. S.; Chadha, M. S. *J. Am. Chem. Soc.* **1963**, *85*, 582–585.
(6) Ellman, J.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995.
(7) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883–8904.

SCHEME 5. Postulated Transition States of Grignard Addition

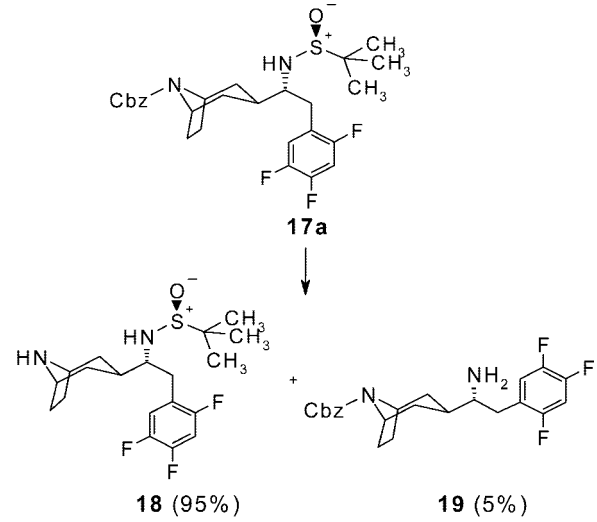


5 and 7). The effect of solvent and temperature on diastereoselectivity presumably could be explained by transition states theory postulated in Scheme 5. In a coordinating solvent, such as diethyl ether, the solvent−Grignard reagent cluster is strongly stabilized and uncoordinated to the sulfoxide group (pathway C). As a result, more **16** presumably adds to aldimine **15** from the sterically less-hindered side leading to **17b** as the major product. At a lower temperature in a noncoordinating solvent, such as methylene chloride, the chair-form transition state is postulated to be the favorable one contributing to the formation of more **17a** via pathway A.

Diethyl ether (boiling point 33 °C, flash point −40 °C) is an unsafe solvent for a manufacturing plant. To replace it with a safer solvent that could stabilize a Grignard reagent, we prepared **16** in toluene employing 1 equiv of cyclopentyl methyl ether (CPME) as a stabilizer. CPME is a safer replacement due to its higher boiling point (101 °C) and flash point (−1 °C). The resulting Grignard reagent was diluted with methylene chloride and cooled to −70 °C. A solution of imine **15** in methylene chloride was added. By employing these conditions (1 equiv CPME/toluene/CH_2Cl_2/−70 °C), the selectivity of **17a** over **17b** was increased to 85:15, which is superior to that of 70:30 with Et_2O/CH_2Cl_2/−78 °C conditions (Table 1, entry 7). The improvement in diastereoselectivity was so significant that we were able to isolate **17a** with high diastereomeric purity (99.8:0.2 dr) by crystallization of the crude mixture from methanol, which eliminated expensive and time-consuming chromatographic operations. This process was successfully employed on plant scales. It is noteworthy that attempts to improve the stereoselectivity by employing a Lewis acid[7] were not fruitful. The Lewis acids $TiCl_4$, BF_3−Et_2O, Me_3Al, $Zn(OTf)_2$, $Mg(OTf)_2$ were probed, and no significant advantages were found.

Deprotection of Cbz-Protecting Group. Palladium-catalyzed hydrogenolysis was employed at the outset for the deprotection of the Cbz group from **17a** (Scheme 6) leading to the desired intermediate **18**. Owing to the presence of sulfoxide functionality

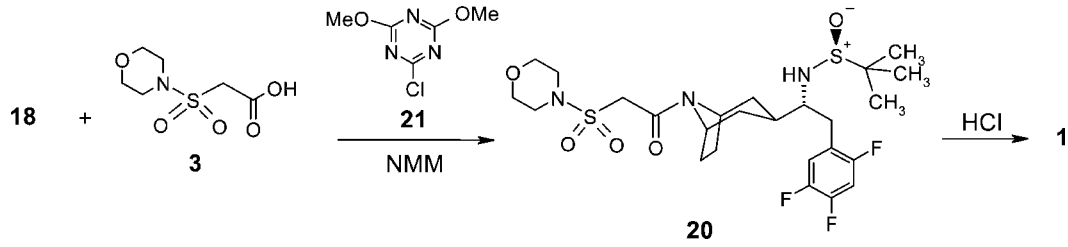
SCHEME 6. Deprotection of the Cbz-Protecting Group



in **17a**, the reaction needed a large amount of catalyst (two times the weight of the substrate). Even then, deprotection was still sluggish. Methansulfonic acid (MSA) was reported as an efficient reagent for the removal of the Cbz group when it is used neat.[8] It was also documented that other acid-labile protecting groups, such as Boc or benzyl, could potentially be cleaved by MSA. We discovered that neat MSA removed the Cbz group from **17a** cleanly without significant impact on the acid-labile *tert*-butanesulfinamide group. Under these conditions, we observed only a small amount (5%) of **19** in crude **18**. It is presumably formed during the quenching process when the reaction mixture (containing a large excess of MSA) was added to an aqueous $KHCO_3$ solution. This is supported by the fact that more **19** was observed if aqueous $KHCO_3$ solution was

(8) Yajima, H.; Kiso, Y.; Ogawa, H.; Fyjii, N.; Irie, H. *Chem. Pharm. Bull.* **1975**, *23*, 1164–1166.

SCHEME 7. Final Steps



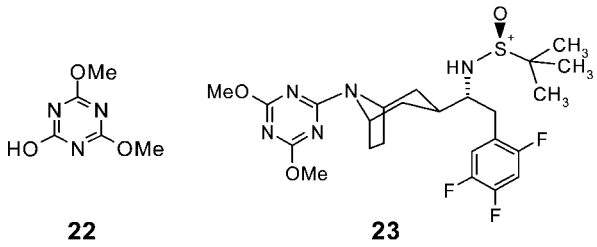


FIGURE 1. Byproducts of the synthesis of **20**.

added to the reaction mixture, where more *aqueous* acid could be present at the beginning of the quenching. In the optimized process, pure **18** was precipitated out from the reaction mixture after a subsequent treatment of the mixture with aqueous NaOH solution and was isolated as a crystalline solid in 90% yield (HPLC 99.8:0.2 dr).

Final Steps. 2-Chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) (**21**, Scheme 7) was found to be an excellent choice for the coupling of sterically hindered, bicyclic amine **18** and acid **3** in the presence of *N*-methylmorpholine (NMM), affording **20** (HPLC >98%) as a foamy solid in quantitative yield without any chromatography purifications. The major byproduct, 2-hydroxy-4,6-dimethoxy-1,3,5-triazine (**22**, Figure 1), was easily removed by aqueous $NaHCO_3$ wash. It is noteworthy that the order of reagent additions could have significant impact on the amount of byproduct **23** (Figure 1), which was generated from the arylation of **18** with CDMT. For instance, when **18**, acid **3**, NMM, and CDMT were charged in the order specified, a small amount (1.5%) of **23** was observed. When the order was changed to **18**, acid **3**, CDMT, and NMM, the undesired **23** was increased to 10%.

The last step involves the cleavage of the *tert*-butanesulfinyl group from **20**. We first followed Ellman's conditions by treating **20** with HCl in methanol.[3] The reaction was clean and fast. However, we had difficulties in separating byproduct methyl *tert*-butanesulfinate from **1** by aqueous workup, due to its poor hydrophilicity. This problem was easily overcome by cleaving the *tert*-butanesulfinyl group with aqueous HCl solution. Under these conditions, byproduct *tert*-butanesulfinic acid was completely removed by aqueous NaOH solution wash. Finally, crystallization of **1** from isopropyl acetate furnished crystalline **1** (HPLC >99%) as a solid in an overall yield of 80% from **18** over two steps.

Conclusion

We disclosed herein a practical synthetic strategy for the synthesis of an azabicyccloctanyl derivative **1**, an active pharmaceutical ingredient intended to be used in clinical trials in type 2 diabetes. Some notable features of our synthesis are as follows: (1) Ellman's protocol of 1,2-addition of a Grignard reagent to *tert*-butanesulfinimine was improved to satisfy our large scale operation, in terms of safety and diastereoselectivity, employing modified conditions (1 equiv CPME/toluene/CH_2Cl_2/−70 °C); (2) the azabicyccloctanyl aldehyde fragment was established from commercially available nortropine via Corey−Chaykovsky reaction and Meinwald rearrangement; and (3) CDMT was demonstrated to be an efficient coupling reagent for the condensation of sterically hindered, bicyclic amine **18** with acid **3** affording the desired amide in excellent yield and purity. The optimized synthetic route is economical, efficient, and incorporated green chemistry principles such as direct precipitation of the product by the addition of water where appropriate.

Experimental Section

Benzyl 8*H*-Spiro[8-azabicyclo[3.2.1]octane-3,2′-oxirane]-8-carboxylate (12). To a 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a thermometer, and a condenser was charged THF (anhydrous, 163 mL), potassium *tert*-butoxide (6.6 g, 95% pure, 55.9 mmol,) and trimethylsulfoxonium iodide ($Me_3S^+OI^-$) (13.0 g, 57.9 mmol) under nitrogen atmosphere. The mixture was heated to reflux and stirred for an additional 3 h. A solution of **7** (10.0 g, 38.6 mmol) in THF (37 mL) was added in one portion. The reaction was refluxed for another 2 h. The mixture was cooled to rt and diluted with toluene (100 mL) and water. The water layer was separated and extracted with toluene (2 × 50 mL). The combined organic layers were washed with water (3 × 40 mL) and evaporated under vacuum to dryness to give **12** (10.6 g, 90%) as an oil: HPLC assay 95%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 5.16 (s, 2H), 4.42 (d, J = 10.4 Hz, 2H), 2.43 (s, 3H), 2.31 (m, 1H), 1.91−2.04 (m, 4H), 1.23 (d, J = 14.0 Hz, 2H); HRMS calcd for $C_{16}H_{20}NO_3$ $[M + H]^+$ 274.1443, found 274.1433. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.21; H, 6.90; N, 5.11. HPLC for **7** (t_R = 9.1 min), **12** (t_R = 9.9 min): Agilent Zorbax Eclipse XDB-C18 5 μm 150 mm × 4.6 mm, flow rate = 1.0 mL/min, 40 °C, gradient elution from 10:90 A:B to 80:20 A:B over 9 min then held for an additional 3 min (A = acetonitrile; B = 0.1% H_3PO_4).

Benzyl 3-Formyl-8-azabicyclo[3.2.1]octane-8-carboxylate (9). To a cold (−3 °C) solution of epoxide **12** (0.5 g, 1.8 mmol) in THF (anhydrous, 5 mL) was added BF_3−OEt_2 (120 mL, 0.9 mmol) under nitrogen atmosphere, maintaining the batch temperature at <2 °C. The mixture was stirred at 3−5 °C for 3 h. A 5% aqueous solution of $NaHCO_3$ (5 mL) was added, followed by ethyl acetate (15 mL). The organic layer was separated, washed with water (2 × 5 mL), and evaporated to dryness. Toluene (5 mL) was added and evaporated to dryness. The crude product was dissolved in a solution of THF−MeOH (2.6 mL, 1:1 v/v) and treated with DBU (14 mg, 0.09 mmol) at rt for 1 h. To the mixture were added 2% HCl (5 mL) and ethyl acetate (15 mL). The organic layer was separated, washed with water (5 mL), 2% $NaHCO_3$ (5 mL), and water (5 mL), and evaporated to dryness. Toluene (5 mL) was added and evaporated under vacuum to obtain **9** (0.22 g, 80%) as an oil: IR ν_{max} (KBr) 3033, 2968, 2886, 2814, 2710, 1698, 1416, 1326, 1211, 1101, 1081, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55

(d, J = 1.3 Hz, 1H), 7.25−7.40 (m, 5H), 5.16 (s, 2H), 4.45 (br s, 2H), 2.76 (m, 1H), 2.06 (m, 2H), 1.65−1.95 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 153.2, 136.6, 128.3, 127.8, 127.7, 66.6, 52.6, 41.7, 30.6, 29.9, 28.3, 27.4. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.19; H, 7.34; N, 5.07. HPLC for **9** (t_R = 3.1 min): Phenomenex Prodigy ODS-2 5 μm C-18 150 mm × 4.6 mm, flow rate = 1.0 mL/min, 40 °C, isocratic, 65:35 A:B (A = acetonitrile; B = 0.05 M NaH_2PO_4 (pH 2.5)).

Azabicyclooctanyl Imine (15). A 50-mL, three-necked, round-bottomed flask was charged with aldehyde **9** (1.6 g, 3.6 mmol), toluene (8 mL), (*s*)-*tert*-butanesulfinamide **14** (0.5 g, 3.9 mmol), pyridine toluenesulfonate (46 mg, 0.18 mmol), and $MgSO_4$ (860 mg, 7.2 mmol) under nitrogen atm. The suspension was stirred at rt for 16 h. the solids were removed by filtration. The filtrate was washed with water (2 × 8 mL) and evaporated under vacuum to dryness. To the suspension were added isopropyl acetate (0.5 mL) and *n*-heptane (2 mL). The suspension was filtered to obtain **15** (1.1 g, 80%) as a white solid: mp 77−79 °C; HPLC assay >99%; IR ν_{max} (KBr) 2974, 2947, 2880, 1697, 1623, 1451, 1405, 1326, 1212, 1100, 1078, 1020 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 4.4 Hz, 1H), 7.29−7.38 (m, 5H), 5.15 (s, 2H), 4.43 (br s, 2H), 2.95−3.05 (m, 1H), 2.01−2.09 (m, 2H), 1.70−1.80 (m, 6H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 153.3, 136.7, 128.4, 127.9, 127.8, 66.6, 56.5, 53.0, 35.6, 33.9, 33.2, 28.3, 27.6, 22.2, 22.0. Anal. Calcd for $C_{20}H_{28}N_2O_3S$: C, 63.80; H, 7.50; N, 7.44; S, 8.52. Found: C, 63.52; H, 7.81; N, 7.41; S, 8.53. HPLC for **9** (t_R = 3.1 min); **15** (t_R = 4.8 min): Phenomenex Prodigy ODS-2 5 μm C-18 150 mm × 4.6 mm, flow rate = 1.0 mL/min, 40 °C, isocratic, 65:35 A:B (A = acetonitrile; B = 0.05 M NaH_2PO_4 (pH 2.5)).

Phenylmethyl (3-*exo*)-3-[(1*R*)-1-[[(*S*)-(1,1-Dimethylethyl)-sulfinyl]amino]-2-(2,4,5- trifluorophenyl)ethyl]-8-azabicyclo-[3.2.1]octane-8-carboxylate (17a). Magnesium (42 g, 1.8 mol), iodine (420 mg, 1.6 mmol), and cyclopentyl methyl ether (154 g, 1.54 mol) were charged to a 2-L, four-necked, round-bottomed flask equipped with a mechanical stirrer, a thermocouple, and an addition funnel under nitrogen atmosphere. The mixture was stirred at 20−23 °C for 5 min. 2,4,5-Trifluorobenzyl bromide (4.7 g, 20 mmol) was added over 15 min to initiate the formation of the corresponding Grignard reagent. After the addition, the mixture was stirred for an additional 5 min at rt until the iodine color dissipated [Note: the batch temperature slowly increased and was maintained at 20−28 °C with an ice bath]. Toluene (560 mL) was added to the mixture. Additional 2,4,5-trifluorobenzyl bromide (310.3 g, 1.4 mol) was added, maintaining the temperature between 20 and 28 °C with an ice bath. The mixture was stirred for an additional 30 min at rt to obtain a gray suspension. [Note: The Grignard reagent formation was monitored by quenching a sample with water and checked with HPLC: Phenomenex Ultracarb ODS-30 5 μm C-18 250 mm × 4.6 mm, flow rate = 1.0 mL/min, 20 °C, isocratic, 65:35 A:B, A = acetonitrile, B = water, until the disappearance of 2,4,5-trifluorobenzyl bromide, t_R = 10.9 min.] A 12-L, four-necked, round-bottomed flask equipped with a mechanical stirrer, a thermocouple, and an addition funnel was charged with anhydrous CH_2Cl_2 (3.8 L). The solvent was cooled to −78 °C. The freshly prepared solution of 2,4,5-trifluorobenzylmagnesium bromide in toluene was added to methylene chloride, while keeping the batch temperature below −55 °C. The mixture was cooled to −70 °C. A solution of aldimine **15** (210 g, 0.56 mol) in CH_2Cl_2 (350 mL) was added to the reaction mixture, while keeping the temperature below −55 °C. The mixture was allowed to warm to rt over 1.5 h and stirred for an additional 16 h. The reaction was monitored by HPLC until the ratio of **15** to (**17a** + **17b**) was determined to be <1%. The mixture was cooled to 10 °C. Saturated NH_4Cl solution (1.5 L) was slowly added to the mixture, while keeping the batch temperature below 18 °C. The resulting gray emulsion was broken by adjusting the pH to 4.6−5.0 with 20% aqueous citric acid (350 mL). The organic layer containing product was separated and saved. The aqueous layer was extracted one more time with CH_2Cl_2 (375 mL). The organic layers were combined and solid citric acid was added. (Note: Approximately 8 g of solid citric acid was used for 1 L of CH_2Cl_2 solution in order to break the emulsion.) To the mixture was added water (375 mL) and the resulting mixture was stirred at rt for 10 min. The organic layer was separated and washed with saturated $NaHCO_3$ (1 × 750 mL) and NaCl (1 × 750 mL). The organic layer was concentrated to a final volume of 1.5 L and filtered. The filtrate was evaporated to give a thick orange oil (362 g). To the orange oil was added warm methanol (40 °C, 1.2 L). The mixture was stirred at 40−45 °C for an additional 10 min. The solution was cooled to rt over 30 min. The resulting suspension was cooled to −15 °C and stirred for an additional 40 min. The solids were collected by filtration and rinsed with methanol−water (300 mL, 3:2 v/v). The solids were dried under vacuum at 35 °C for 16 h to give **17a** (189 g, 65%) as a white solid: mp 89−92 °C; HPLC assay >99.5%; IR ν_{max} (KBr) 3472, 3169, 2956, 1701, 1520, 1472, 1447, 1330, 1211, 1152, 1094, 1077, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.40 (m, 5H), 7.15 (m, 1H), 6.95 (m, 1H), 5.05−5.20 (m, 2H), 4.35 (br s, 2H), 3.45 (s, 1H), 3.10−3.30 (m, 2H), 2.81−2.98 (m, 2H), 1.80−2.00 (m, 4H), 1.50−1.70 (m, 4H), 1.17 (s, 9H); MS (ESI) m/z 523.225 (M + H$^+$). Anal. Calcd for $C_{27}H_{33}F_3N_2O_3S$: C, 62.05; H, 6.36; N, 5.36; F, 10.91; S, 6.14. Found: C, 61.96; H, 6.49; N, 5.26; F, 10.88; S, 5.98. HPLC for **15** (t_R = 14.6 min); **17a** (t_R = 19.4 min); **17b** (t_R = 19.8 min): Alltech Inertsil ODS-2 5 μm C-18 150 mm × 4.6 mm, flow rate = 1.0 mL/min, 40 °C, 35:65 A:B 5 min then gradient elution from 35:65 A:B to 65:35 A:B over 10 min (A = acetonitrile; B = 0.05 M NaH_2PO_4 (pH 2.5)). Chiral HPLC assay 99.8:0.2 er, sample **17a** was treated with aqueous HCl solution to remove the *tert*-butanesulfinamide group and the resulting enantiomer was analyzed: Chiral Technologies Chiralpak AD, 5 μm 250 mm × 4.6 mm, flow rate = 0.6 mL/min, 20 °C, isocratic, 2-propanol−hexane−diethylamine = 20:80:0.1: (*S*)-enantiomer, t_R = 15.5 min; (*R*)-enantiomer, t_R = 16.4 min. Analytical sample of **17b**: mp 137−140 °C; IR ν_{max} (KBr) 3258, 3060, 2956, 1678, 1519, 1462, 1426, 1330, 1207, 1152, 1113, 1060 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.45 (m, 5H), 7.07 (m, 1H), 6.93 (m, 1H), 5.18 (s, 2H), 4.41 (br s, 2H), 3.20 (m, 2H), 2.75 (d, J = 14.2 Hz, 1 H), 2.54 (dd, J = 13.8, 10.1 Hz, 1H), 2.38 (m, 1H), 2.00 (m, 2H), 1.50−1.80 (m, 6H), 1.07 (s, 9H). Anal. Calcd for $C_{27}H_{33}F_3N_2O_3S$: C, 62.05; H, 6.36; N, 5.36; F, 10.91; S, 6.14. Found: C, 62.19; H, 6.37; N, 5.30; F, 10.60; S, 5.93.

[*S*(*S*)]-*N*-[(1*R*)-1-(3-*exo*)-8-Azabicyclo[3.2.1]oct-3-yl-2-(2,4,5-trifluorophenyl)ethyl]-2-methyl-2-propanesulfinamide (18). To a 5-L, round-bottomed flask was charged methanesulfonic acid (1.4 kg, 14.6 mol). While the acid was stirred moderately, **17a** (350 g, 0.67 mol) was added in portions (~6 g each portion) at 19−27 °C over 60 min [Note: exotherm and evolution of CO_2 were observed]. After the addition, the mixture was stirred at 24−27 °C for an additional 2 h [Note: a mild evolution of CO_2 continued during this period]. The reaction was monitored by HPLC until the ratio of **17a** to (**18** + **19**) was determined to be <0.5%. The mixture was quenched in two equal parts. Each part was added to a solution of $KHCO_3$ (875 g) in H_2O (5.25 L) in a 22-L, round-bottomed flask over a period of 30 min, maintaining both temperature below 25 °C and foaming under control [Note: a 22-L flask was used to provide large headspace for the vigorous gas evolution that occurred]. The aqueous layers from the two quenches were combined and washed with *tert*-butyl methyl ether (TBME) (2 × 2.5 L). The aqueous layer was separated and treated with 50% (w/w) NaOH (445 g) until pH 14 was reached. The mixture was stirred at rt for 1 h. The solids were collected by filtration, rinsed with water (3 L), and dried under vacuum at 45 °C for 16 h to afford amine **18** (234.2 g, 90% yield) as a pinky white solid: mp 114−117 °C; HPLC assay 99%; $[\alpha]^{25}_D$ +39.7 (*c* 1.0, CH_3OH); IR ν_{max} (KBr) 3421, 3156, 3057, 2936, 2918, 2304, 1676, 1634, 1521, 1474, 1423, 1323, 1204, 1153, 1056 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (m, 1H), 6.83 (m, 1H), 3.47 (m, 2H), 3.16 (m, 1H), 3.10 (d, J = 8.1 Hz, 1H), 2.75−2.90 (m, 2H), 1.20−1.90 (m, 10H), 1.10 (s, 9H); MS (ESI) m/z 389.188 (M + H$^+$). Anal. Calcd for

$C_{19}H_{27}F_3N_2OS$: C, 58.74; H, 7.01; N, 7.21; S, 8.25. Found, C, 58.48; H, 7.12; N, 7.14; S, 8.44. HPLC for **17a** (t_R = 6.9 min); **18** (t_R = 1.7 min); **19** (t_R = 2.0 min): Alltech Inertsil ODS-2 5 μm C-18 150 mm × 4.6 mm, flow rate = 1.0 mL/min, 40 °C, isocratic, 65:35 A:B (A = acetonitrile; B = 0.05 M NaH_2PO_4 (pH 2.5)). HPLC assay for diastereomeric ratio = 99.8:0.2: Gemini C18, 3 μm 150 mm × 3.0 mm, flow rate = 1.0 mL/min, 40 °C, UV 210 nm, gradient elution from 10:90 A:B to 90:10 A:B over 16 min, held for an additional 4 min, then to 10:90 A:B over 5 min (A= acetonitrile; B = 20 mM $NaClO_4$ in 0.1% (v/v) $HClO_4$). (*R*,*S*)-Diastereomer, t_R = 7.15 min; (*S*,*S*)-diastereomer, t_R = 8.05 min.

[*S*(*S*)]-*N*-[(1*R*)-1-(3-*exo*)-8-[2-(4-Morpholinylsulfonyl)acetyl]-8-azabicyclo[3.2.1]oct-3-yl-2-(2,4,5-rifluorophenyl)ethyl]-2-methyl-2-propanesulfinamide (20). To a 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and a thermocouple was charged **18** (30 g, 77.0 mmol), morpholinosulfonyl acetic acid **3** (17.1 g, 81.0 mmol), ethyl acetate (1.4 L), and *N*-methylmorpholine (15 g, 148 mmol) under nitrogen atmosphere. The mixture was stirred at rt for 15 min to obtain a hazy solution. To the mixture was added 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT, 20 g, 112 mmol) and the batch was stirred at rt for an additional 3 h. The mixture was washed with 10% aqueous citric acid (1 × 400 mL), 5% aqueous $NaHCO_3$ (1 × 400 mL), and saturated NaCl (1 × 400 mL). The organic phase was evaporated at 35 °C under vacuum (70−80 torr) to dryness to obtain **20** (44.2 g, 76.2 mmol, 99% yield) as a gummy oil: HPLC assay 96%; IR ν_{max} (KBr) 3269, 3047, 2977, 2862, 1641, 1519, 1455, 1424, 1348, 1211, 1162, 1114, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 1H), 6.93 (m, 1H), 4.72 (m, 1H), 4.37 (m, 1H), 3.85−4.05 (m, 2H), 3.74 (m, 4H), 3.20−3.45 (m, 6H), 2.83−3.00 (m, 2H), 1.42−2.20 (m, 9H), 1.20 (s, 9H); MS *m*/*z* 580.211 ($M + H^+$). Anal. Calcd for $C_{25}H_{36}F_3N_3O_5S_2$: C, 51.80; H, 6.26; N, 7.25; F, 9.83; S, 11.06. Found: C, 51.67; H, 6.49; N, 7.13; F, 9.54; S, 11.15. HPLC for **18** (t_R = 2.7 min); **20** (t_R = 5.5 min): Agilent Zorbax SB-C18 3.5 μm 150 mm × 3.0 mm, flow rate = 0.3 mL/min, 40 °C, isocratic, 50:50 A:B (A = acetonitrile; B = 0.1% TFA).

1-{3-[(*R*)-1-Amino-2-(2,4,5-trifluorophenyl)ethyl]-8-azabicyclo[3.2.1]oct-8-yl}-2-(morpholine-4-sulfonyl)ethanone (1). To a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and a thermocouple were charged **20** (44.2 g, 76.2 mmol), THF (50 mL), and 6 N aqueous HCl (39 mL) under nitrogen atm. The mixture was stirred at rt for an additional 30 min. A solution of 1 N NaOH (400 mL) was added. The product was extracted into isopropyl acetate (1 × 400 mL). The organic layer was separated and washed with 1 N NaOH (1 × 200 mL) and water (2 × 200 mL). The organic layer was evaporated at 50 °C under vacuum (110 Torr) until the final volume of 80 mL was obtained. To the concentrate were added seeds and the batch was stirred at rt for 1.5 h. The solids were collected by filtration, rinsed with isopropyl acetate (5 °C, 35 mL), and dried at 50 °C under vacuum for 16 h to obtain **1** (26.1 g, 72%) as a white solid: mp 117−119 °C; HPLC assay >99%; $[\alpha]^{20}_D$ −5.7 (*c* 1.0, CH_3OH); IR ν_{max} (KBr) 3385, 2974, 2959, 2927, 2857, 1643, 1518, 1453, 1422, 1341, 1328, 1301, 1235, 1210, 1161, 1124, 1112, 1074, 1044, 1013 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.05 (m, 1H), 6.90 (m, 1H), 4.75 (m, 1H), 4.41 (m, 1H), 4.05 (m, 2H), 4.00 (m, 2H), 3.75 (m, 4H), 3.45 (m, 4H), 2.70−2.85 (m, 2H), 2.40 (m, 1H), 2.15 (m, 1H), 1.95 (m, 2H), 1.20−1.85 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$, signals marked with an asterisk correspond to rotamers) δ 156.9, 156.1 (*J* = 243 Hz), 148.7 (*J* = 242 Hz), 146.6 (*J* = 243 Hz), 122.7, 118.7, 105.4, 66.6, 56.3, 55.6, 55.5*, 54.2, 52.0*, 51.9, 46.1, 35.9, 34.5*, 34.49, 34.43*, 34.40, 34.3*, 34.2, 32.8, 28.6*, 28.5, 27.2, 27.1*. Anal. Calcd for $C_{21}H_{28}F_3N_3O_4S$: C, 53.04; H, 5.94; N, 8.84; F, 11.99. Found: C, 52.98; H, 5.97; N, 8.81; F, 12.23. HPLC for **20** (t_R = 4.6 min); **1** (t_R = 1.8 min): Phenomenex Prodigy ODS-2 5 μm C-18 150 mm × 4.6 mm, flow rate = 1.0 mL/min, 40 °C, isocratic, 50:50 A:B (A = acetonitrile; B = 0.05 M NaH_2PO_4 (pH 2.5)).

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Supporting Information Available: Experimental details for the syntheses of compounds **7** and **11** and copies of ^1H and ^{13}C NMR spectra for compounds **1**, **7**, **9**, **11**, **12, 15**, **17a**, **17b**, **18**, and **20**, and HPLC spectra for compound **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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