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Synthesis of 2-Methyl-2,5-diazabicyclo[2.2.1]heptane, Side Chain to Danofloxacin[1]

Tamim F. Braish*

Chemical Research and Development, Pfizer Global Research and Development, Groton, Connecticut 06340, U.S.A.

Abstract:

Various syntheses of the side chain of the quinolone antibiotic danofloxacin are described. The realization that the *N*-methyl substitution on the side chain 2-methyl-2,5-diazabicyclo[2.2.1]heptane can reside on either nitrogen, due to the symmetry of the molecule, played a major role in the design of the commercial synthetic route.

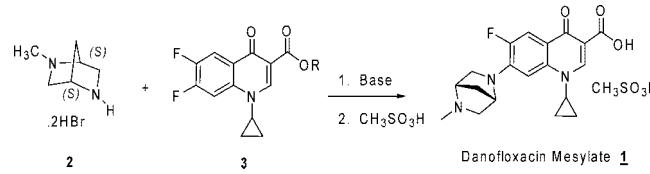
Danofloxacin mesylate, **1**, is a fluoroquinoline antibiotic that is sold under the trade name Advocin and is used in the area of veterinary medicine.[2] It is administered intravenously or as an intramuscular injection and is particularly effective in cattle and pigs against respiratory and enteric diseases. Danofloxacin activity, like that of other fluoroquinolones,[3] is due to the inhibition of microbial DNA gyrase, thus inhibiting replication and transcription of bacterial cells.[4]

Danofloxacin, **1**, is synthesized via the reaction of the side chain **2** and the fluoroquinolone nucleus **3** which is followed by the formation of the methanesulfonic acid salt[5] (Scheme 1). The nucleus is readily available from several vendors, and its synthesis will not be discussed in this manuscript.[6]

The side chain **2** is unique due to the presence of bridgehead carbon and the (*S*,*S*) configuration.[7] When the project was nominated into development, the medicinal chemistry synthesis started with the protection of 4-hydroxy(L)-proline with carbobenzyloxy chloride, reduction of the acid with borane·dimethylsulfide, followed by ditosylation and cyclization with benzylamine.[8] Installation of the methyl group was achieved by the reduction of the benzoyl group with Red-Al and was followed by chromatography to enable the isolation of **9**. Hydrogenation of **9** in the presence of Perlman's catalyst removed the benzyl group and provided the desired side chain as a free base which was converted to the hydrochloride salt in an overall yield of 20% (Scheme 2). The process was reasonably efficient and allowed us to make more than 10 kg of the side chain for the toxicology studies and early clinical trials.

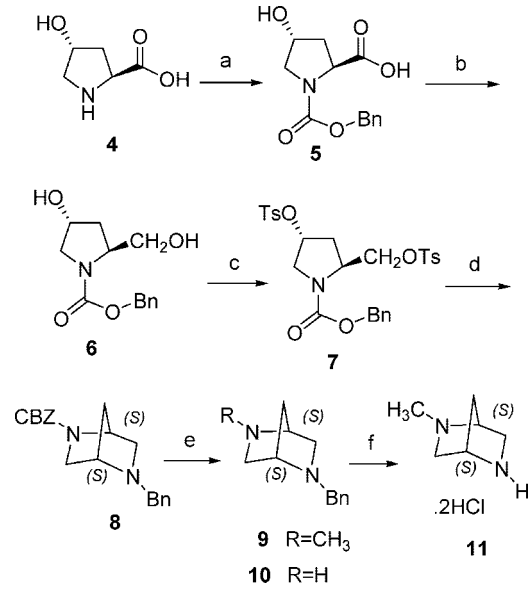
The requirements to make more danofloxacin for additional testing quickly escalated to hundreds of kilos. While the synthesis in Scheme 2 was efficient, it suffered from several drawbacks. First, the use of borane·dimethylsulfide was very undesirable due to the odor and cost of this reagent. Addition-

Scheme 1. **Synthesis of danofloxacin**



2 3

Scheme 2. **Medicinal chemistry route to 11**[a]



4 5 6 7 8 9 R=CH3 10 R=H 11

[a] **Reagents and conditions for the Medicinal route:** (a) CBZ-Cl, Py, RT. (b) BH_3·DMS, chromatography. (c) Ts-Cl, Py, 0 °C then RT, 24 h. (d) 3 equiv of benzylamine, toluene, reflux. (e) 3 equiv of Red-Al, toluene, 0 °C, chromatography. (f) $Pd(OH)_2$, H_2, 2 equiv of HCl, toluene; 20% overall yield from hydroxyproline. **Reagents and conditions for the modified Medicinal route:** (a) CBZ-Cl, Et_3N, RT. (b) $NaBH_4$, BF_3·etherate, THF, 0 °C then RT, methanol quench, then heat to reflux; 78% yield from hydroxyproline. (c) 2.1 equiv of Ts-Cl, Et_3N, 0 °C then RT, 24 h, 81% yield. (d) 3 equiv of benzylamine, toluene, reflux, 70% yield. (e) 3 equiv of Red-Al, toluene, −10 °C, 2 h; then, 0 °C 6 h, chromatography, 68% yield. (f) 10% Pd/C, H_2, 2 equiv of HCl, toluene, 90% yield.

* E-mail: tamim.f.braish@pfizer.com.

(1) In Memory of Chris Schmid, a colleague and a friend.
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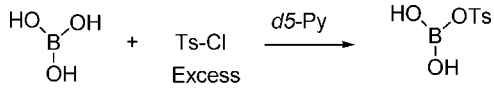
Scheme 3. **Reaction of TsCl with boric acid**



12

ally, the ditosylation step never went to completion even with 3 equiv of *p*-toluenesulfonyl chloride, and chromatography was therefore necessary after this step. Also the Red-Al step was exothermic and required very careful control and monitoring in order to obtain the *N*-methyl derivative **9** exclusively without contaminations with the hydrogen analogue **10**. Debenzylated **10** can react with the fluoroquinolone fragment **3** on both nitrogens to form a dimer which is impossible to remove from danofloxacin. Finally, all the intermediates in the synthesis were oils, and several purifications via chromatography to isolate intermediates **7** and **9** were absolutely necessary to obtain the side chain **11** in good quality.

It was first decided to fine-tune the current route to overcome the deficiencies. The reduction of intermediate **5** with a reagent other than borane·dimethylsulfide became our first priority. This was achieved through the addition of sodium borohydride to **5** followed by the careful addition of BF_3·etherate at 0 °C.[9] This reagent generates borane in situ and is an excellent alternative to buying and storing diborane. The reaction mixture was carefully quenched with water and extracted in toluene to provide **6** in 80% yield.

The focus was then shifted to understanding the tosylation reaction which we felt should go to completion with only 2 equiv of *p*-toluenesulfonyl chloride instead of the 3 equiv required. Interestingly, there was never any excess *p*-toluenesulfonyl chloride left at the end of the reaction which implied that this material was being consumed mysteriously in the reaction mixture. It was postulated that the TsCl was perhaps reacting with residual boric acid from the previous step. To test this theory, boric acid and *p*-toluenesulfonyl chloride were mixed in various solvents and in different ratios, and we found that the reaction between these two reagents is instantaneous and **12** was the only species observed by NMR in d_5-pyridine even when excess TsCl was used[10] (Scheme 3).

We quickly changed the workup conditions to isolate intermediate **6** by quenching the reaction with methanol and heating the mixture for several hours to remove residual borate esters as the trimethylborate. This modified workup allowed for the isolation of **6** in 78% yield, and when this material was reacted with only 2.1 equiv of *p*-toluenesulfonyl chloride in toluene in the presence of NaOH, intermediate **7** could be isolated in 81% yield from **6**.

The cyclization of **7** with benzylamine to make intermediate **8** proceeded uneventfully with 3 equiv of benzylamine (1 equiv is involved with the cyclization, and 2 equiv acts as a base). Attempts to modify the conditions with benzylamine and 2 equiv of another base (such as triethylamine or di-isopropylethyl amine) failed to drive the reaction to completion, and the conditions were left unchanged.

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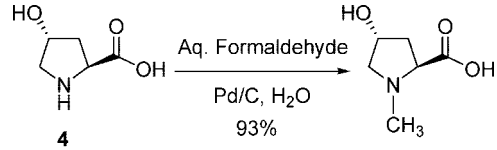
Scheme 4. **Introduction of the methyl group**



4 **13**

We then turned our attention to the problematic Red-Al reduction to make intermediate **9**. The reaction proceeded smoothly, but the product was always contaminated with the carbamate hydrolysis material **10**, requiring a chromatography step to remove this impurity. Adding the Red-Al at cooler temperatures reduced the impurity but did not eliminate it. To make the side chain **11**, the chromatography step was found to be absolutely necessary before proceeding further to the palladium-catalyzed benzyl group removal step.

It became a top priority to eliminate the Red-Al reduction of intermediate **8**, and we elected to do so by an early introduction of the required methyl group. Consequently, L-4-hydroxyproline was hydrogenated with aqueous formaldehyde in the presence of palladium on carbon to provide the *N*-methy-4-hydroxyproline, **13**, in 93% yield (Scheme 4). Attempts to reduce **13** proved very difficult due to the lack of solubility of **13** in organic solvents that were compatible with reducing agents.

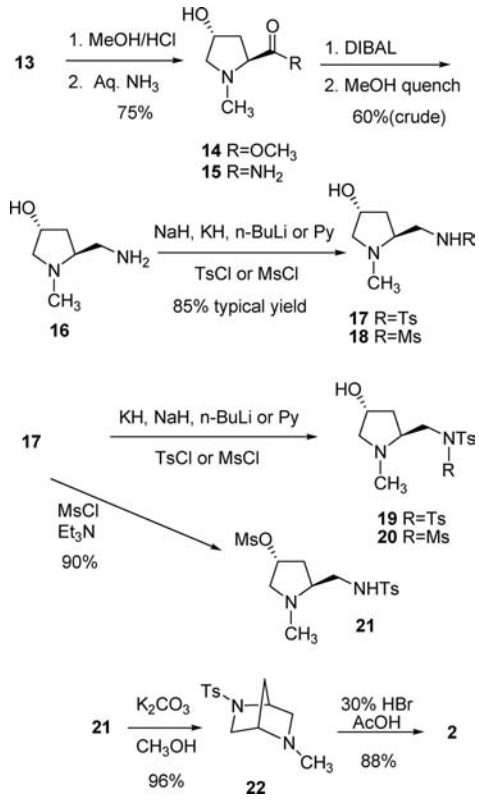
The carboxylic acid **13** was then converted to the amide **15** in 75% overall yield by first bubbling anhydrous HCl in the methanol solution of **4** to make the ester **14**, followed by adding 28% commercial aqueous ammonia solution to the ester and filtering the amide directly from the reaction mixture (Scheme 5). The amide reduction was achieved with DIBAL; however, the isolation of intermediate **16** proved challenging due to its extreme aqueous solubility. Repetitive extractions proved futile, and the isolation issue was resolved by carefully quenching the reaction with 2 equiv of methanol, allowing the aluminum salts to precipitate, and isolating the product as a solution in THF after filtration. Evaporation of the solvents allowed for the isolation of **16** in 60% crude yield.

We envisioned at this stage a scenario where intermediate **16** is tosylated on oxygen and the primary nitrogen would act as an intramolecular nucleophile to close the ring. All attempts to *O*-sulfonylate **16** resulted in *N*-sulfonylation to intermediates **17** and **18**. Bases other than the traditional amine bases were also attempted (KH, NaH, and *n*-BuLi), all resulting in *N*-sulfonylation as well.

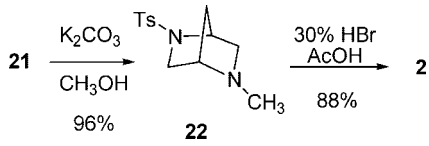
Attempts to tosylate the amide **15** directly resulted in complete decomposition. It was reasoned at this point that the *N*-monosulfonate intermediate **17** would *O*-sulfonylate with another equivalent of sulfonylating agent. However excess *p*-toluenesulfonyl chloride or methanesulfonyl chloride under the same reaction conditions where *N*-monosulfonylated product **17** was produced, only provided the *N*,*N*-disulfonylated products **19** and **20** under a variety of conditions. Only when **17** was treated with triethylamine and methanesulfonyl chloride were we able to isolate the desired intermediate **21** in 90% yield.

Intermediate **21** was cyclized with potassium carbonate in methanol to provide the bicyclic intermediate **22** in 90% isolated yield as a crystalline intermediate. Removal of the tosyl

Scheme 5. **Tosylation efforts**



Scheme 6. **Cyclization and Ts removal**



protecting group of **22** required some experimentation and was finally achieved with aqueous 30% HBr solution in acetic acid, and the desired side chain **2** was isolated in 88% yield as the dihydrobromide salt (Scheme 6).

The side chain **2** made by this route was coupled with the fluoroquinolone **3**, and the danofloxacin **1** that was isolated from the reaction mixture, met all the required analytical specification for that candidate.

While this was not a viable process, the amount of knowledge that was aquired during a period of less than three months, allowed us to quickly refocus our efforts on the next phase of the redesign of the process, and intermediate **22** became the new target of our efforts. Also, upon further analysis of the structure **2**, we realized that, with the symmetry of this molecule, it did not matter which of the two nitrogens ended up with the methyl group. The structures in Figure 1 with the rotation and as mirror images are only to help visualize and illustrate this symmetry element.

Thus, an alternate strategy where the methyl group is introduced with the nitrogen nucleophile as methylamine became the new goal. This was reduced to practice by first protecting the L-4-hydroxyproline on nitrogen with *p*-toluenesulfonyl chloride in the presence of sodium carbonate in water to provide intermediate **23** in quantitative yield by the direct filtration of the product from the reaction mixture. Intermediate **23** was reduced via the reaction with sodium borohydride in

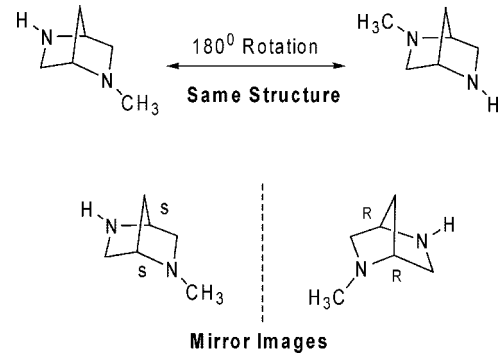


Figure 1. **Simple rotation vs mirror images.**

the presence of BF_3·etherate which was worked up with methanol at reflux to remove the residual boronic acid, generating the diol **24** in 85% yield. The subsequent ditosylation step proceeded with 2.2 equiv of *p*-toluenesulfonyl chloride in the presence of triethylamine. The tritosylate **25** was isolated as crystalline intermediate in 90% yield. Cyclization of **25** with methylamine[11] as a solution in methanol provided the intermediate **22** which was synthesized earlier in Scheme 6. Removal of the *N*-tosyl protecting group proceeded as expected with the 30% HBr solution in acetic acid (Scheme 7).

Summary

This new process was scaled up quickly to make several batches of the side chain **2** that were a 100 kg each. The only modification was to replace the BF_3·etherate with BF_3·THF complex which allowed manufacturing to recycle the THF for the reduction step without any contaminations with another solvent. Danofloxacin that was obtained from this route met all the analytical specification that were set for this product.

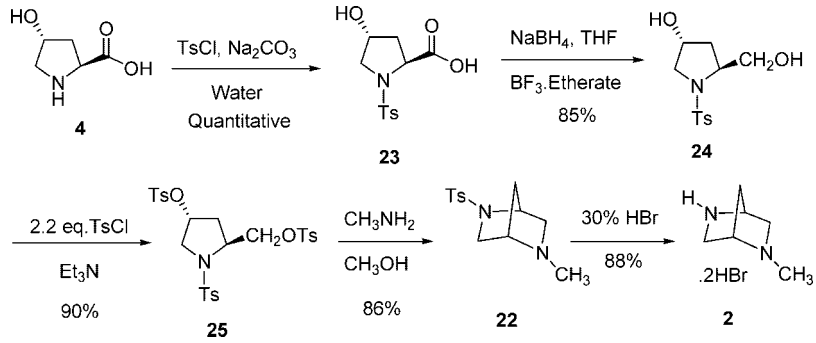
One obvious question remained, and that was whether the starting material L-4-hydroxyproline could be reduced to the hydroxyl prolinol which upon treatment with excess *p*-toluenesulfonyl chloride would provide the tritosylate intermediate **25** directly. However, all attempts to make the prolinol failed due to the lack of solubility of the hydroxyl proline in organic solvents that were compatible with any of the reducing agents needed to achieve this reduction; moreover, the price of the prolinol was at least 10 times the price of the L-4-hydroxyproline, and this approach was not pursued further.

The new commercial route had several advantages. First, all the intermediates in this route were crystalline, and if a mishap were to happen during a scale-up, purification could be achieved after any of the steps if necessary. Additionally, as we gained more knowledge with the new route, we quickly realized that isolation of any of the intermediates was not necessary, and the process became very streamlined. The overall yield of **2** from purchased *N*-tosyl-4-hydroxyproline is usually 60−65% without a single isolation.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and were uncorrected. NMR spectra were recorded on a Brucker 300 MHz spectrometer in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in ppm relative to residual protons in the deuterated solvent.

Scheme 7. **Commercial route**



Microanalyses were performed by the Pfizer Analytical Department. All reagents obtained from commercial suppliers were used without further purification.

***trans*-*N*-Methyl-4-hydroxy-L-proline (13).** To *trans*-4-hydroxy-L-proline (40 g, 305 mmol) in water (80 mL) were added 80 mL of 30% aqueous formaldehyde solution and 7.0 g of 5% palladium on carbon catalyst (50% wet). The reaction was inerted with nitrogen twice and pressurized to 50 psi with hydrogen in a Parr shaker. The mixture was allowed to hydrogenate for 24 h after which the reaction was vented and inerted with nitrogen, and the catalyst was removed by filtration over diatomaceous earth. The filtrate was evaporated under reduced pressure to provide 43.5 g (93.3%) of title product; mp 140−142 °C dec. Anal. Calcd for $C_6H_{11}NO_3$: C, 49.66; H, 7.56; N, 9.66. Found: C, 49.82; H, 7.68; N, 9.72. ^{1}H NMR (D_2O): 4.65 (m, 1H), 4.20 (dd, 1H), 3.97 (dd, 1H), 3.2 (dm, 1H), 2.50 (m, 1H), 2.25 (m, 1H); $[\alpha]_D = -54.8°$ ($c = 1.18$, H_2O).

***trans*-*N*-Methyl-4-hydroxy-L-proline Methyl Ester (14).** The acid **13** (100 g, 690 mmol) was suspended in 600 mL of methano, and anhydrous HCI gas was bubbled through the reaction mixture until it became homogeneous (∼5 min). The reaction was then heated to reflux for 16 h, after which it was cooled and the solvent was evaporated and replaced with 150 mL of water. Potassium carbonate [200 g (1.44 mol)] was then added carefully at 0 °C, and the product was extracted with 4 × 200 mL portions of ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated to provide 87 g (75%) of product **14** as a white solid; mp 53−54 °C; ^{1}H NMR (D_2O) 4.85 (s, 38), 4.73 (m, 2H), 3.90 (s, 3H, *N*-methyl), 3.58 (m, 1H), 3.45 (m, 1H), 2.54 (m, 1H), 2.37 (m, 1H); $[\alpha]_D = -80.0°$ ($c = 1.038$, CH_3OH).

(2*S*,4*R*)-1-Methyl-2-carbamoyl-4-hydroxypyrrolodine (15). The methyl ester **14** (20 g, 126 mmol) was dissolved in 40 mL of ice-cold, saturated commercial NH_4OH solution, and the resulting solution was slowly warmed to room temperature over a period of 30 min. After stirring for 24 h the solvent was removed under high vacuum to produce a quantitive yield of present title product as a white, crystalline solid; mp 138−140 °C. Anal. Calcd for $C_6H_{12}N_2O_2$: C, 50.01; H, 8.33; N, 19.44. Found: C, 50.03; H, 8.28; N, 19.45. ^{1}H NMR (D_2O) 4.43 (m, 1H), 3.42 (dd, 1H), 3.25 (AB pattern, 1H), 2.36 (s, 3H), 2.33 (M, 1H), 2.1 (m, 2H); $[\alpha]_D = -105.48°$ ($c = 0.953$, CH_3OH).

(2*S*,4*R*)-1-Methyl-2-aminomethyl-4-hydroxypyrrolidine (16). The amide **15** (15 g, 104 mmol) was suspended in 75 mL of tetrahydrofuran, and 572.5 mL (572.5 mmol) of diisobutyl aluminum hydride (1 M solution in hexanes) was added over a period of 15 min. The mixture was then heated to reflux for two days and judged complete by monitoring with thin layer chromatography. Diatomaceous earth (30 g) was then added to the reaction, and while cooling with an ice bath, methanol (45 mL) was added dropwise. The slurry was then filtered, and the solvents were evaporated to provide 8.1 g of colorless, oily product (60%). This product could not be purified further and was used as is; ^{13}C NMR (D_2O) 69.5 (CH), 66.8 (CH), 64.9 (CH_2), 44.0 (CH_2), 41.0 (CH_3), 39.5 (CH_2); $[\alpha]_D = -61.94°$ ($c = 0.956$, CH_3OH).

(2*S*,4*R*)-1-Methyl-2-[(4-methylbenzenesulfonylamino)methyl]-4-hydroxypyrrolidine (17). To the amine **16** (7.3 g, 56.2 mmol) in 200 mL of tetrahydrofuran at −10 °C was added 22.46 mL of -butyllithium (56.2 mmol, 2.5 M in hexanes) over a period of 30 min. *p*-Toluenesulfonyl chloride (10.2 g, 53.3 mmol) in 10 mL of tetrahydrofuran was then added. After stirring the mixture for 2 h at −10 °C, water (20 mL) was added, and the reaction was extracted with 2 × 140 mL of methylene chloride. The combined organic layers were dried (Na_2SO_4) and evaporated at reduced pressure to provide 15 g (85%) of present title product as a light-yellow oil. A small sample was purified by silica gel chromatography for elemental analysis. Anal. Calcd for $C_{13}H_{20}N_2SO_3$: C, 54.93; H, 7.04; N, 9.86; S, 11.27. Found: C, 54.95; H, 7.01; N, 9.90; S, 11.31. ^{13}C NMR ($CDCl_3$) δ 7.80 (d, 2H), 7.34 (d, 2H), 3.30 (m, 1H, alpha to OH), 3.22 (m, 1H, alpha to N-Ts), 2.50 (m, 1H), 2.40 (m, 1H), 2.35 (s, 3H), 2.25 (s, 3H), 1.7 (m, 2H), 2.2 (m, 2H, OH and NH protons). ^{13}C NMR ($CDCl_3$) 143.4, 136.5, 129.7, 127.0, 69.1, 64.7, 62.4, 43.0, 40.0, 38.2, 21.5; $[\alpha]_D = -34.67°$ ($c = 0.90$, CH_3OH).

(2*S*,4*R*)-1-Methyl-2-[(4-methylbenzensulfonylamino)methyl]-4-(methane sulfonyloxy)pyrrolidine (21). To the *N*-tosyl compound **17** (1.0 g, 3.5 mmol) in 20 mL of tetrahydrofuran were added triethylamine (0.49 mL, 3.5 mmol) and methanesulfonyl chloride (0.27 mL, 3.5 mmol). After stirring at room temperature for 30 min, water (20 mL) was added, and the reaction was extracted with methylene chloride (2 × 40 mL). The combined organic layers were then dried (Na_2SO_4) and evaporated under reduced pressure to provide 1.2 g (95%) of product as an oil. A small sample was purified by silica gel

(11) Other amine nucleophiles were also used and have been reported recently. See: Melgar-Fernandez, R.; Gonzalez-Olvera, R.; Olivares-Romero, J. L.; Gonzalez-Lopez, V.; Romero-Ponce, L.; Ramirez-Zarate, M.; Demare, P.; Regla, I.; Juaristi, E. *Eur. J. Org. Chem.*, **2008**, *4*, 655.

chromatography for elemental analysis. Anal. Calcd for $C_{14}H_{22}N_2S_2O_5$: C, 46.41; H, 6.08; N, 7.77; S, 17.72. Found: C, 46.48; H, 6.01; N, 7.77; S, 17.72. ^{1}H NMR ($CDCl_3$) 7.73 (d, 2), 7.40 (d, 2H), 5.04 (m, 1H) 3.70 (m, 1H), 3.55 (dd, 1H), 3.05 (m, 1H), 3.0 (s, 3H), 2.83 (m, 1H), 2.62 (dd, 1H), 2.40 (s, 3H), 2.23 (s, 3H), 2.10 (m, 1H), 1.82 (m, 1H).

(1*S*,4*S*)-2-Methyl-5-(4methylbenzenesulfonyl)-2,5-diazabicyclo[2.2.1]heptane 22. Compound **21** (760 mg, 5.52 mmol) was dissolved in 30 mL of methanol, and K_2CO_3 (760 mg, 5.52 mmol) was added. After stirring the mixture for 24 h, the solvent was removed under reduced pressure, and 20 mL of water was added. The aqueous layer was then extracted with 2 × 40 mL of methylene chloride, and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to provide 470 mg (90%) of present title product as a solid. The reaction could be extracted with toluene as well; mp 87−88 °C; ^{13}C NMR ($CDCl_3$) 143.5, 135.4, 129.8, 127.4, 62.9, 61.1, 61.0, 49.9, 40.2, 34.9, 21.5. Anal. Calcd for $C_{13}H_{18}N_2O_2S$: C, 58.62; H, 6.81; N, 10.52; S, 12.04. Found: C, 58.75; H, 6.83; N, 10.55; S, 12.19. $[\alpha]_D = -16.8°$ ($c = 1.038$, CH_3OH).

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