into the branch leading to 3. Whether the remaining steps required to produce 3, C-6/C-15 bond formation, enolization, and pyrone ring closure, occur spontaneously or require additional enzyme(s) is not yet clear. The fact that neither the granaticin producer, *S. violaceoruber* Tü 22,[12] nor a transformant of the daunomycin producer, *S. galilaeus* ATCC 31133 bearing plasmid pANT 12 carrying the *act I, III, IV,* and *VII* genes,[13] synthesized 3 favors the secondary possibility.

Experimental Section

General Procedures and Materials. NMR spectra were acquired at 303 K on acetate-d_6 solutions of mutactin with an IBM AF-300 FT-NMR spectrometer operating at a field strength of 7.1 T. FT mass spectra were obtained on a Nicolet FT-MS-1000 spectrometer operating at a field strength of 3.0 T using laser desorption. UV spectra were recorded on a Varian DMS-90 double-beam UV-vis spectrophotometer, and CD spectra on a JASCO J-500A spectropolarimeter, using methanol as solvent. HPLC separations and quantitations were carried out on an Alltech C-18 reverse-phase column connected to a Waters 590 solvent delivery system and a Waters R401 refractive index detector, using methanol–water–acetic acid (50:50:0.01) as solvent. Peak areas were integrated on a Hitachi D-2000 integrator. Elemental analyses were obtained from Midwest Microlab, Indianapolis, IN, and antimicrobial testing was carried out at Huashang Hospital, Shanghai, China.

Cultures of *S. coelicolor* B_{1190} (wild type), B_{40} (*act VII* mutant), B_{17} (*act I* mutant, lacking PKS), and B_{41} (*act III* mutant, lacking PKR) were obtained from Prof. D. A. Hopwood, Norwich, and were maintained on slants of CM medium[5] containing 1.5% Bacto-agar (Difco). *S. violaceoruber* Tü 22 was obtained from Prof. H. Zähner, Tübingen, and maintained as previously described,[12,14] and *S. galilaeus* ATCC 31133 {pANT 12}[13] was provided by Prof. W. R. Strohl, The Ohio State University. Sodium [1,2-$^{13}C_2$]acetate (99% ^{13}C) was obtained from Cambridge Isotopes, Inc.

Fermentation. Seed cultures were grown in 500-mL Erlenmeyer flasks containing 150 mL of CM medium inoculated with 2–5 mL of spore suspension from a well-sporulated slant of *S. coelicolor* B_{40}. The flasks were incubated for 36 h at 30 °C on a New Brunswick Controlled Environment gyratory shaker (300 rpm), and 25 mL of seed culture were then used to inoculate each production culture containing 150 mL of CM medium in a 500-mL Erlenmeyer flask. These were incubated with shaking as described above and harvested 5 days later. To produce larger quantities of 3, a 14-L New Brunswick Microferm fermentor containing 8 L of CM medium was inoculated with 4 seed cultures (600 mL). The fermentation was conducted for 5 days at 30 °C with agitation at 250 rpm and aeration at 1000 mL/min.

Fermentations of the other cultures were conducted in shake flasks using the same protocol. For the biosynthetic feeding experiment, 1 g of sodium [1,2-$^{13}C_2$]acetate was dissolved in 20 mL of water and added in equal portions to 12 36 h old production flasks. The cultures were harvested 84 h later; workup gave 80 mg of ^{13}C-labeled 3 with an average enrichment of about 1.2–1.5% per carbon.

Isolation of 3. The 5 day old cultures of *S. coelicolor* B_{40} were filtered first through Whatman 3MM filter paper and then through Celite, and the pH of the clear filtrate was adjusted to 3.0 with 1 N HCl. This solution was then extracted three times with equal volumes of ethyl acetate; the combined extracts were dried and evaporated to a syrup on a rotary evaporator at a bath temperature up to 50 °C. The residue was loaded onto a column of Sephadex LH-20, which was developed with methanol. Fractions containing 3 were located by analytical TLC (silica gel, $CHCl_3/CH_3OH$, 4:1, R_f 0.35), and the material was further purified by preparative layer chromatography in the same system.

Alternatively, the residue from the ethyl acetate extract was dissolved in CH_3OH, an equal volume of water was added, and the pH was adjusted to 7–8. This solution was extracted successively with $CHCl_3$ and with EtOAc, and the extracts were discarded. The aqueous methanol solution was then adjusted to pH 2–3 and extracted twice with ethyl acetate. The extract was treated with activated charcoal (0.5–1.0%), filtered, and taken to dryness on a rotary evaporator. The residue was dissolved in a small volume of acetone and kept in the refrigerator until crystals deposited. Yield: about 40–50 mg/L. Mp: 192–193 °C. Molecular formula $C_{16}H_{14}O_6$ (MS: MH^+ calc 303.08687, obsd 303.08270). Anal. Obsd: C, 63.57; H, 4.72. Calc for $C_{16}H_{14}O_6 \cdot H_2O$: C, 63.58; H, 4.64. UV (λ, ϵ: 222 nm, 24300 mM^{-1} cm^{-1}; 265, 16900; 290, 9600 (sh). CD: no signal at 6.4 mg/mL in methanol over range of 250–600 nm. NMR: see Table I. Antimicrobial activity: at 100 μg/mL no inhibitory activity against *S. aureus* (3 strains), *E. coli* (3 strains), *P. aeruginosa* (2 strains), *K. pneumoniae* (2 strains), *Citrobacter* (2 strains), *Saccharomyces sake* (2 strains), *Candida albicans*, *Rhizopus nigricans*, *Aspergillus niger*, *A. oryzae*, *Penicillium citrinum*.

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(12) Barcza, S.; Brufani, M.; Keller-Schierlein, W.; Zähner, H. *Helv. Chim. Acta* **1966**, *49*, 1736.
(13) Bartel, P. L.; Zhu, C.-b.; Lampel, J. S.; Dosch, D. C.; Strohl, W. R.; Beale, J. M.; Floss, H. G., submitted.
(14) Snipes, C. E.; Chang, C.-j.; Floss, H. G. *J. Am. Chem. Soc.* **1979**, *101*, 107.

Synthesis of (*S*,*S*)- and (*R*,*R*)-2-Alkyl-2,5-diazabicyclo[2.2.1]heptanes

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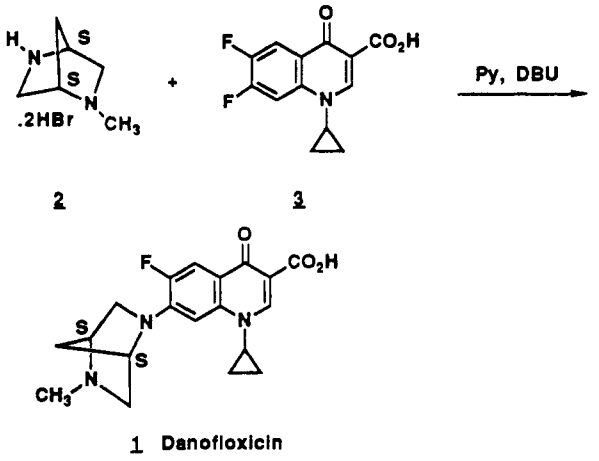
Danofloxacin (1)[1] is a member of a growing family of the totally synthetic antibacterials known as the quinolones,[2] the synthesis of which is accomplished by the nucleophilic introduction of (*S*,*S*)-2-methyl-2,5-diazabicyclo[2.2.1]heptane (2) to the nucleus moiety 3.[3] This paper describes a new efficient synthesis of 2 and its enantiomer (see Scheme I).

The synthesis of 2 has been reported previously,[4] from *trans*-4-hydroxy-L-proline (see Scheme II). In this synthesis, the tritosyl intermediate 4 was prepared from 4-hydroxy-L-proline by N-tosylation, esterification, and reduction with $LiBH_4$ followed by ditosylation of the resulting diol. Intermediate 4 was then cyclized with benzylamine, and the sulfonamide was cleaved with HI.[5] The

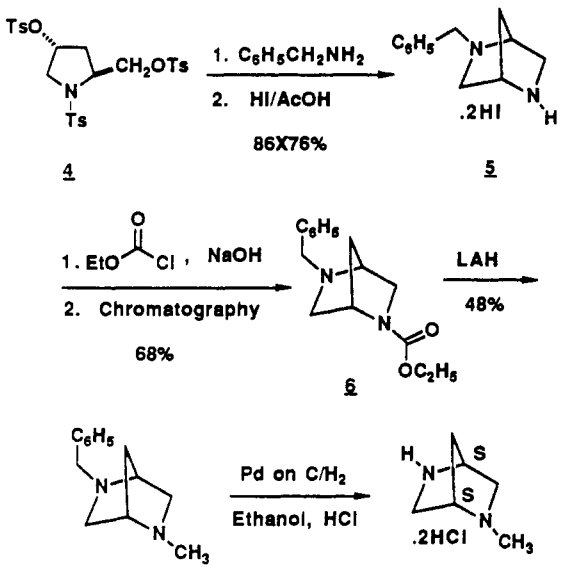
(1) Eur. Pat. Appl. EP215650 (Pfizer).
(2) *The Quinolones*; Andriole, V. T., Ed.; Academic Press: London, 1988.
(3) For other quinolones that are synthesized from the nucleus 3 and 2-alkyl(or hydrogen)-2,5-diazabicyclo[2.2.1]heptanes, see: Eur. Pat. Appls. EP251308 (Chemie Linz) and EP159,174 (Warner Lambert) and Int. Publication Number WO 88/02627 (Bristol-Myers).
(4) Strum, P. A.; Henry, D. W.; Thompson, P. E.; Ziegler, J. B.; McCall, J. W. *J. Med. Chem.* **1974**, *17*, 481.
(5) The chemistry up to this step was followed closely to that reported by Portoghese, P. S.; Mikhail, A. A. *J. Org. Chem.* **1966**, *31*, 1059.

0022-3263/90/1955-1684$02.50/0

Scheme I



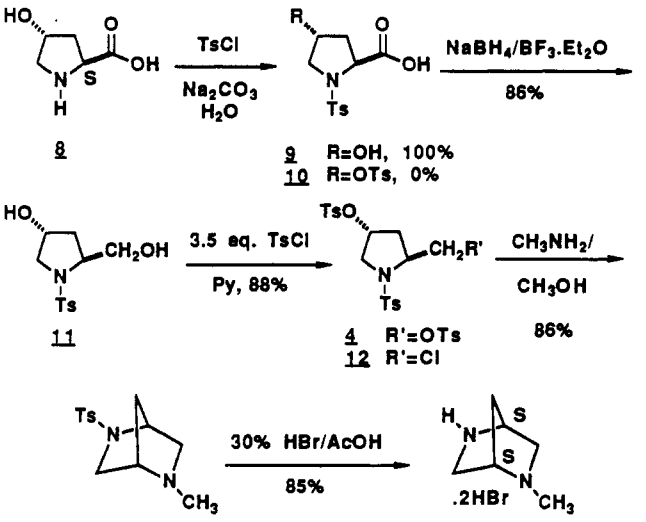
Scheme II



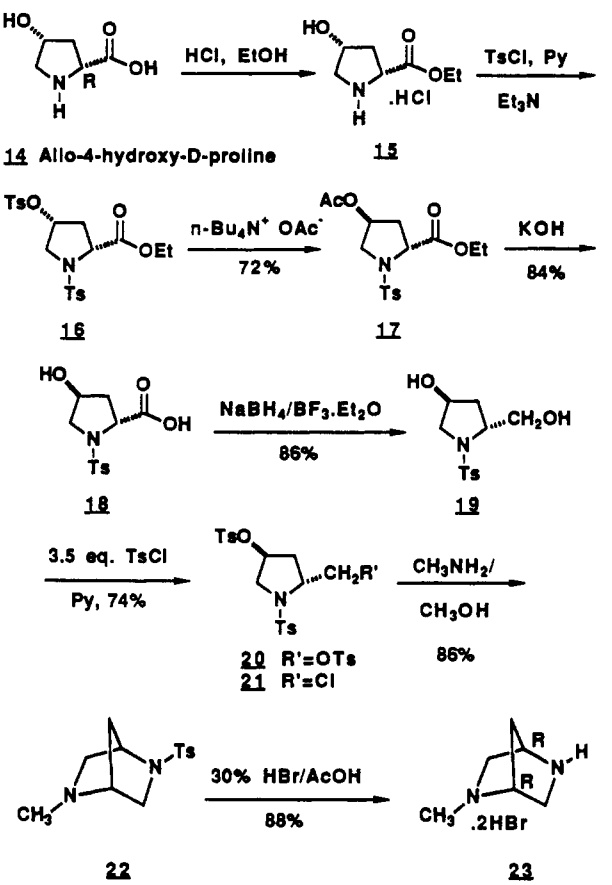
resulting salt **5** was then treated with ethylchloroformate and reduced with lithium aluminum hydride, and the benzyl group was hydrogenated to give **2** as the HCl salt.

Since this synthesis was long and required several purifications, a more efficient synthesis was of interest. Other reported syntheses of the same ring system[6] suffered due to the use of azide intermediates. Our synthesis also started with the N-tosylation of *trans*-4-hydroxy-L-proline. This was achieved quantitatively and without the formation of the N,O-ditosylated product **10** by stirring an aqueous solution of the amino acid in the presence of *p*-toluenesulfonyl chloride and sodium carbonate as a base.[7] Acidification of the reaction mixture allowed for the direct isolation of the product via filtration. Reduction of the N-tosylated hydroxyproline **9** with diborane generated in situ (sodium borohydride and borontrifluoride etherate)[8] provided the diol **11** in 86% yield (see Scheme III). Bis tosylation of **11** in pyridine at 0 °C provided the crystalline tritosyl intermediate **4** in 85% yield. When this reaction was run at room temperature appreciable amounts

Scheme III



Scheme IV



of the chloro intermediate **12** could be isolated. The presence of the monochloro **12**, however, did not impact the next reaction since both the tritosyl **4** and the monochloro **12** could be cyclized with methylamine in a sealed container[9] to afford the bicyclic intermediate **13** in 86% yield. This intermediate was then deprotected with 30% anhydrous hydrogen bromide in acetic acid to provide the (*S,S*)-2-methyl-2,5-diazabicyclo[2.2.1]heptane (**2**) as the dihydrobromide salt in 85% yield.

(6) Rosen, T.; Lico, I. M.; Chu, D. T. *J. Org. Chem.* **1988**, *53*, 1580–82. Sepulchre, A. M.; Cleophax, J.; Hildesheim, J.; Gero, S. D. *C. R. Acad. Sci. Paris, Ser. C* **1969**, 849–51.

(7) When NaOH was used as the base (see ref 3) appreciable amounts of *N,O*-ditosylhydroxylproline **10** were formed.

(8) Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1969**, *82*, 681–86.

(9) A sealed tube was used on a small scale and a parr bottle was used on larger scales. A pressure as high as 30 psi may be generated during this reaction.

The enantiomer of **2** was also synthesized from the *allo*-4-hydroxy-D-proline by inversion of the 4-hydroxy moiety of intermediate **16** with tetrabutylammonium acetate as reported.[10] Saponification of **17** with KOH at 0 °C provided the *N*-tosyl-*trans*-4-hydroxy-D-proline (**18**), which is the enantiomer of compound **9**. By carrying intermediate **18** through the same reaction sequence as that described for **9**, the (*R*,*R*)-2-methyl-2,5-diazabicyclo-[2.2.1]heptane (**23**) was obtained (Scheme IV).

The above described synthesis is a very efficient method for the synthesis of the title compounds, and it has been demonstrated on a multigram scale successfully. The synthesis may be extended to the synthesis of any *N*-H or *N*-alkyl derivative of 2,5-diazabicyclo[2.2.1]heptanes depending on the alkylamine (or ammonia) used in the cyclization of the tritosyl intermediate **4**. Several other alternative syntheses of the 2,5-diazabicyclo[2.2.1]heptane ring system are currently under investigation, and this chemistry will be reported in due course.

Experimental Section

Melting points were determined with Thomas-Hoover capillary melting point apparatus and were uncorrected. NMR spectra were recorded on a Brucker 300-MHz spectrometer in $CDCl_3$ unless noted otherwise. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer in $CHCl_3$. Microanalyses were performed by the Pfizer Analytical Department. All reagents were used as they were received without any purification. *allo*-4-Hydroxy-D-proline was purchased from Sigma.

1-(4-Tolylsulfonyl)-4-hydroxy-L-proline (9). To a solution of 4-hydroxy-L-proline (100 g, 763 mmol) in 750 mL of water were added Na_2CO_3 (169.9 g, 1602 mmol) at 0 °C and 4-toluenesulfonyl chloride (174.5 g, 916 mmol; added in three portions over a period of 1 h). The slurry was then warmed to room temperature and allowed to stir for 48 h. The reaction was acidified with concentrated HCl solution to pH 2, and the product was isolated via filtration. The filter cake was washed with pH 2 buffer and dried in a vacuum oven at 60 °C for 16 h to obtain 215.3 g of the product as a white crystalline solid in 99% yield. Mp: 149–151 °C. NMR (CD_3OD): δ 7.75 (d, 2 H), 7.40 (d, 2 H), 4.32 (m, 1 H), 4.21 (t, 1 H), 3.57 (dd, 1 H), 3.3 (m, 2 H), 2.45 (s, 3 H), 2.1 (m, 2 H). $[\alpha]_D$: −116.2° (*c* = 1.85, C_2H_5OH) [lit. $[\alpha]_D$ −116.5° (*c* = 1.86, C_2H_5OH)].

(2*S*,4*R*)-2-(Hydroxymethyl)-4-hydroxy-1-(4-tolylsulfonyl)pyrrolidine (11). Sodium borohydride (57.6 g, 1523 mmol) was added to 2 L of THF, and the mixture was cooled to 10 °C before borontrifluoride etherate (250 mL, 1980 mmol) was added dropwise over a period of 1 h. Then *N*-(4-tolylsulfonyl)-4-hydroxy-L-proline (215.3 g, 755.4 mmol) was added carefully in 100 mL of THF, and the mixture was allowed to stir for 16 h. The reaction was quenched with methanol, a 10% aqueous HCl solution was added, and the mixture was gently heated to 60 °C for 1 h. The pH of the reaction was adjusted to neutral with 50% aqueous sodium hydroxide solution, and the volatiles were evaporated under reduced pressure. The product was then isolated via filtration, and the filter cake was washed with water. Drying under vacuum at 60 °C for 12 h yielded 164 g of the product as a white solid in 85% yield. Mp: 132–133 °C. NMR ($CDCl_3$): δ 7.75 (d, 2 H), 7.30 (d, 2 H), 4.3 (m, 1 H), 3.75–3.65 (m, 2 H), 3.6 (m, 2 H), 3.35 (m, 1 H), 3.1 (m, 1 H), 2.42 (s, 3 H), 1.9 (m, 2 H). Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.14; H, 6.27; N, 5.17; S, 11.81. Found: C, 52.98; H, 6.36; N, 5.16; S, 11.80. $[\alpha]_D$: −43.3° (*c* = 1.85, C_2H_5OH) [lit. $[\alpha]_D$ −43.4° (*c* = 1.86, C_2H_5OH)].

(2*S*,4*R*)-1-(4-Tolylsulfonyl)-2-(((4-tolylsulfonyl)oxy)-methyl)-4-((4-tolylsulfonyl)oxy)pyrrolidine (4). To an ice-cold solution of (2*R*,4*S*)-2-(hydroxymethyl)-4-hydroxy-*N*-(*p*-tolylsulfonyl)pyrrolidine (170 g, 626.5 mmol) in 0.5 L of pyridine was added 4-toluenesulfonyl chloride (250 g, 1.32 mol) in three portions in order to keep the temperature of the reaction below 15 °C for 1 h, and the reaction was kept at 0 °C for 12 h. An additional 125 g (656 mmol) of *p*-toluenesulfonyl chloride was then added, and the mixture was allowed to stir at 0 °C for 16 additional hours. The mixture was then cooled with an ice bath, and 3 L of 10% aqueous HCl solution was carefully added. A white precipitate formed which was isolated via filtration and then taken in 1 L of ethanol and heated to reflux for 30 min. The mixture was then cooled, and the solids were filtered and dried under reduced pressure to give 213 g of product in 80% yield. Mp: 134–135 °C. NMR ($CDCl_3$): δ 7.8–7.3 (m, 12 H), 4.78 (m, 1 H), 4.32 (m, 1 H), 4.1 (m, 1 H), 3.8 (m, 2 H), 2.45 (s, 6 H), 2.41 (s, 3 H), 2.04 (m, 2 H). $[\alpha]_D$: −56.0° (*c* = 1.168, acetone) [lit. $[\alpha]_D$ −52.5° (*c* = 1.92, acetone)].

(2*S*,4*R*)-1-(4-Tolylsulfonyl)-2-(chloromethyl)-4-((4-tolylsulfonyl)oxy)pyrrolidine (12). To an ice-cold solution of (2*R*,4*S*)-2-(hydroxymethyl)-4-hydroxy-1-(4-tolylsulfonyl)-pyrrolidine (**4**) (170 g, 626.5 mmol) in 0.5 L of pyridine was added *p*-toluenesulfonyl chloride (250 g, 1.32 mol) in one portion, and the reaction was warmed to 50 °C. After 6 h the mixture was cooled with an ice bath, and 3 L of 10% aqueous HCl solution was carefully added. A white precipitate formed which was isolated via filtration and then taken in 1 L of ethanol and heated to reflux for 30 min. The mixture was then cooled, and the solids were filtered and dried under reduced pressure to give 195 g of product in 70% yield. Mp: 145–146 °C. NMR ($CDCl_3$): δ 7.70 (d, 2 H), 7.56 (d, 2 H), 7.30 (m, 4 H), 4.82 (m, 1 H), 3.75–4.0 (m, 2 H), 3.75 (m, 1 H), 3.60 (m, 2 H), 2.45 (s, 3 H), 2.42 (s, 3 H), 2.10 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 145.3, 144.3, 129.98, 129.86, 127.71, 127.67, 78.2, 58.8, 55.12, 47.67, 36.9, 21.68, 21.62. Anal. Calcd for $C_{19}H_{22}NClO_5S_2$: C, 51.4; H, 4.99; N, 3.15; S, 14.68. Found: C, 51.32; H, 5.01; N, 3.07; S, 14.83. $[\alpha]_D$: −34.1° (*c* = 1.0, acetone).

(1*S*,4*S*)-2-(4-Tolylsulfonyl)-5-methyl-2,5-diazabicyclo-[2.2.1]heptane (13). A Parr bottle was charged with the (2*S*,4*R*)-1-(4-tolylsulfonyl)-2-(((*p*-tolylsulfonyl)oxy)methyl)-4-((4-tolylsulfonyl)oxy)pyrrolidine (**4**) (250 g, 1.32 mol) and 690 mL of methanol, and the bottle was then tared. Methylamine gas was then bubbled through the methanol solution until 62 g (2 mol) of the gas had dissolved. The bottle was then sealed and heated to 80 °C. After heating for 16 h the reaction was cooled, and the solvent was evaporated at reduced pressure. The residual solids were then partitioned between 500 mL of methylene chloride and 400 mL of 10% aqueous NaOH solution. The layers were separated, and the organic layer was washed with an additional 400 mL of 10% aqueous NaOH solution and then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure provided 47.5 g of the desired product, which represents a 90% yield. Mp: 87–88 °C. NMR ($CDCl_3$): δ 7.70 (d, 2 H), 7.30 (d, 2 H), 4.23 (m, 1 H), 3.55 (dd, 1 H), 3.30 (m, 1 H), 3.0 (dd, 1 H), 2.85 (dd, 1 H), 2.63 (m, 1 H), 2.40 (s, 3 H), 2.33 (s, 3 H), 1.65 (d, 1 H), 1.06 (d, 1 H); ^{13}C NMR ($CDCl_3$): δ 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, 58.73; H, 6.90; N, 10.51; S, 12.26. $[\alpha]_D$: +18.69° (*c* = 1.18, CH_3OH).

(1*S*,4*S*)-2-(4-Tolylsulfonyl)-5-methyl-2,5-diazabicyclo-[2.2.1]heptane (13). A Parr bottle was charged with (2*S*,4*R*)-*N*-(4-tolylsulfonyl)-2-(chloromethyl)-4-((4-tolylsulfonyl)oxy)-pyrrolidine (**12**) (3.8 g, 8.56 mmol) and 25 mL of methanol, and the bottle was then tared. Methylamine gas was then bubbled through the methanol solution until 2.65 g (85.6 mmol) of the gas has dissolved. The bottle was then sealed and heated to 90 °C. After heating for 16 h the reaction was cooled and the solvent was evaporated at reduced pressure. The residual solids were then partitioned between 50 mL of methylene chloride and 40 mL of 10% aqueous NaOH solution. The layers were separated, and the organic layer was washed with an additional 30 mL of 10% aqueous NaOH solution and then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure provided 1.73 g of the desired product, which represents a 76% yield. Mp: 87–88 °C. NMR ($CDCl_3$): δ 7.70 (d, 2 H), 7.30 (d, 2 H), 4.23 (m, 1 H), 3.55 (dd, 1 H), 3.30 (m, 1 H), 3.0 (dd, 1 H), 2.85 (dd, 1 H), 2.63 (m, 1 H), 2.40 (s, 3 H), 2.33 (s, 3 H), 1.65 (d, 1 H), 1.06 (d, 1 H); ^{13}C NMR ($CDCl_3$): δ 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, 58.73; H, 6.90; N, 10.51; S, 12.26. $[\alpha]_D$: +18.69° (*c* = 1.18, CH_3OH).

(1*S*,4*S*)-2-Methyl-2,5-diazabicyclo[2.2.1]heptane Dihydrobromide (2). (1*S*,4*S*)-2-(4-Tolylsulfonyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane (**13**) (60 g, 225 mmol) was suspended

(10) Baker, G. L.; Fritschel, S. J.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954.

in 900 mL of 30% hydrogen bromide in acetic acid, and the mixture was allowed to stir at room temperature. After 6 h the acetic acid was removed under aspirator pressure to $^1/_4$ of the original volume, and 1800 mL of ethylacetate was then added. A solid precipitated and was then filtered under an inert atmosphere. The product was recrystallized by dissolving it in a minimum amount of methanol at reflux. Cooling followed by the addition of 400 mL of isopropyl alcohol provided a white solid, which was filtered and dried under reduced pressure. The product weighed 48 g, which represents an 81% yield. Mp: 258–259 °C (coloration occurs at 234 °C). NMR (D_2O): δ 4.73 (m, 1 H), 4.62 (m, 1 H), 3.8–3.6 (m, 4 H), 3.08 (s, 3 H), 2.65 (m, 1 H), 2.35 (m, 1 H). Anal. Calcd for $C_6H_{12}N_2$·2HBr: C, 26.30; H, 5.15; N, 10.22; Br, 58.33. Found: C, 26.26; H, 5.15; N, 10.08; Br, 58.58. $[\alpha]_D$: +13.21° (c = 0.946, CH_3OH).

***allo*-4-*cis*-Hydroxy-D-proline Ethyl Ester Hydrochloride (15)** (Baker, D. L.; Fritschel, S. J.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954–2960). 4-*cis*-Hydroxy-D-proline (80 g, 0.61 mol) was suspended in 500 mL of anhydrous ethanol, and anhydrous HCl gas was allowed to bubble through the mixture until the reaction mixture became homogeneous. The reaction was then heated to reflux for 5 h, and the volume of the solvent was reduced by half; 100 mL of diethyl ether was then added, and the mixture was kept in a freezer overnight. The resulting precipitate was filtered and washed with diethyl ether and dried under reduced pressure to yield 111 g of product (93% yield). Mp: 152–153 °C (lit. mp 157–158.4 °C).

***allo*-1-(4-Tolylsulfonyl)-4-((4-tolylsulfonyl)oxy)-D-proline Ethyl Ester (16).** To 110 g (562 mmol) of the *allo*-4-hydroxy-D-proline ethyl ester hydrochloride were added 1 L of pyridine and 79 mL of triethylamine at 0 °C. After the mixture was stirred for 10 min, 242.1 g (1.24 mol) of *p*-toluenesulfonyl chloride was added in small portions as to control the temperature between 0–5 °C, and the reaction mixture was allowed to stir at 0 °C over night. The next day the reaction was added to 750 mL of ice-cold water, and the slurry was left to stir at room temperature for 1 h. The solids were filtered and dried in a vacuum oven at 30 °C for 48 h to provide 243.9 g of product (92% yield). NMR ($CDCl_3$): δ 7.73 (d, 2 H), 7.68 (d, 2 H), 7.27 (m, 4 H), 4.93 (m, 1 H), 4.49 (dd, 1 H), 4.10 (m, 2 H), 3.60 (dd, 1 H), 3.40 (dd, 1 H), 2.40 (s, 3 H), 2.37 (s, 3 H), 2.33 (m, 1 H), 2.20 (m, 1 H), 1.16 (t, 3 H). Mp: 122–123 °C.

4-(Acetyloxy)-1-(4-tolylsulfonyl)-D-proline Ethyl Ester (17). To 218 g (466 mmol) of *allo*-1-(4-tolylsulfonyl)-4-((4-tolylsulfonyl)oxy)-D-proline ethyl ester in 1500 mL of toluene was added 81 g (606 mmol) of tetramethylammonium acetate, and the mixture was heated to reflux for 2 h. The reaction was cooled, washed with 2 × 500 mL of water, and dried over Na_2SO_4. Evaporation of the solvent and drying the resulting solids in a vacuum oven over night at 30 °C provided 120.6 g of product (72% yield). NMR ($CDCl_3$): δ 7.75 (d, 2 H), 7.30 (d, 2 H), 5.10 (m, 1 H), 4.28 (dd, 1 H), 4.18 (dq, 2 H), 3.69 (dd, 1 H), 3.50 (m, 1 H), 2.40 (s, 3 H), 2.30 (m, 1 H), 2.17 (m, 1 H), 1.65 (s, 3 H), 1.27 (t, 3 H). ^{13}C NMR ($CDCl_3$): δ 171.46, 169.75, 143.77, 134.71, 129.61, 127.75, 72.62, 61.64, 59.80, 53.99, 36.62, 21.46, 20.47, 14.05. Anal. Calcd for $C_{16}H_{21}NO_6S$: C, 54.07; H, 5.96; N, 3.94; S, 9.02. Found: C, 54.20; H, 6.05; N, 4.0; S, 9.0. Mp: 82–83 °C.

1-(4-Tolylsulfonyl)-4-hydroxy-D-proline (18). To 4-(acetyloxy)-1-(4-tolylsulfonyl)-D-proline ethyl ester (17) (127.9 g, 359.9 mmol) in 640 mL of THF was added KOH (100 g, 1.8 mol) dissolved in 640 mL of water at 0 °C. The mixture was warmed to room temperature and allowed to stir for 2 h. The organic solvents were removed in vacuo, and the pH of the resulting mixture was adjusted to neutral with concentrated HCl. A precipitate formed which was filtered and dried over night in a vacuum oven at 25 °C to provide 86.2 g of product (84% yield). NMR (CD_3OD): 7.73 (d, 2 H), 7.38 (d, 2 H), 4.95 (broad m, OH), 4.33 (m, 1 H), 4.23 (dd, 1 H), 3.58 (dd, 1 H), 3.28 (m, 1 H), 2.40 (s, 3 H), 2.09 (m, 2 H). Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 50.52; H, 5.30; N, 4.91; S, 11.24. Found: C, 58.61; H, 5.30; N, 4.99; S, 11.35. Mp: 147–149 °C. $[\alpha]_D$: +100.07° (c = 1.1, CH_3OH).

(2*R*,4*S*)-2-(Hydroxymethyl)-4-hydroxy-1-(4-tolylsulfonyl)pyrrolidine (19). To 900 mL of THF was added sodium borohydride (21.75 g, 574.9 mmol), and the mixture was cooled to 10 °C before borontrifluoride etherate (97.92 mL, 776.2 mmol) was added dropwise over a period of 1 h. Then of *N*-(4-tolylsulfonyl)-4-hydroxy-D-proline (18) (82 g, 287.4 mmol) was added carefully in 330 mL of THF at 0 °C, and the mixture was warmed to room temperature and allowed to stir for 16 h. The reaction was then cooled 0 °C and quenched with methanol; 10% aqueous HCl solution was then added, and the mixture was gently heated to 60 °C for 1 h. The pH of the reaction was adjusted to neutral with 50% aqueous sodium hydroxide solution, and the volatiles were evaporated under reduced pressure. The product was then isolated via filtration, and the filter cake was washed with water. Drying under vacuum at 60 °C for 12 h yielded 78 g of the product as a white solid solid in 85% yield. Mp: 131–132 °C. NMR ($CDCl_3$): δ 7.75 (d, 2 H), 7.30 (d, 2 H), 4.3 (m, 1 H), 3.75–3.65 (m, 2 H), 3.6 (m, 2 H), 3.35 (m, 1 H), 3.1 (m, 1 H), 2.42 (s, 3 H), 1.9 (m, 2 H). Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.14; H, 6.27; N, 5.17; S, 11.81. Found: C, 52.81; H, 6.36; N, 5.16; S, 11.80.

(2*R*,4*S*)-1-(4-Tolylsulfonyl)-2-(((4-tolylsulfonyl)oxy)-methyl)-4-((4-tolylsulfonyl)oxy)pyrrolidine (20). This compound was prepared in a similar fashion as described for compound 4. Mp: 125–130 °C. NMR ($CDCl_3$): δ 7.8–7.3 (m, 12 H), 4.78 (m, 1 H), 4.32 (m, 1 H), 4.1 (m, 1 H), 3.8 (m, 2 H), 2.45 (s, 6 H), 2.41 (s, 3 H), 2.04 (m, 2 H). $[\alpha]_D$: +55.9° (c = 1.168, acetone).

(2*R*,4*S*)-1-(4-Tolylsulfonyl)-2-(chloromethyl)-4-((4-tolylsulfonyl)oxy)pyrrolidine (21). This compound was prepared in a similar fashion as described for compound 12. Mp: 141–143 °C. NMR ($CDCl_3$): δ 7.70 (d, 2 H), 7.56 (d, 2 H), 7.30 (m, 4 H), 4.82 (m, 1 H), 3.75–4.0 (m, 2 H), 3.75 (m, 1 H), 3.60 (m, 2 H), 2.45 (s, 3 H), 2.42 (s, 3 H), 2.10 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 145.3, 144.3, 129.98, 129.86, 127.71, 127.67, 78.2, 58.8, 55.12, 47.67, 36.9, 21.68, 21.62. Anal. Calcd for $C_{19}H_{22}NClO_5S_2$: C, 51.4; H, 4.99; N, 3.15; S, 14.68. Found: C, 51.34; H, 5.01; N, 3.10; S, 14.77. $[\alpha]_D$: +34.0° (c = 1.0, acetone).

(1*R*,4*R*)-2-(4-Tolylsulfonyl)-5-methyl-2,5-diazabicyclo-[2.2.1]heptane (22). This compound was prepared in a similar fashion as described for compound 13. Mp: 82–87 °C. NMR ($CDCl_3$): δ 7.70 (d, 2 H), 7.30 (d, 2 H), 4.23 (m, 1 H), 3.55 (dd, 1 H), 3.30 (m, 1 H), 3.0 (dd, 1 H), 2.85 (dd, 1 H), 2.63 (m, 1 H), 2.40 (s, 3 H), 2.33 (s, 3 H), 1.65 d, 1 H), 1.06 (d, 1 H); ^{13}C NMR ($CDCl_3$): δ 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).

(1*S*,4*S*)-2-Methyl-2,5-diazabicyclo[2.2.1]heptane Dihydrobromide (23). This compound was prepared in a similar fashion as described for preparation of compound 2. Mp: 260–262 °C (coloration occurs at 240 °C). NMR (D_2O): δ 4.73 (m, 1 H), 4.62 (m, 1 H), 3.8–3.6 (m, 4 H), 3.08 (s, 3 H), 2.65 (m, 1 H), 2.35 (m, 1 H). Anal. Calcd for $C_6H_{12}N_2$·2HBr: C, 26.30; H, 5.11; N, 10.23; Br, 58.33. Found: C, 26.40; H, 5.10; N, 10.19; Br, 58.42. $[\alpha]_D$: −13.0° (c = 0.972, CH_3OH).

Reactions of Azines. 14. Preparation of 5*H*,7*H*-Pyrazolo[1,5-*d*][2,4]benzoxazepin-7-ones

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The previous papers in this series have shown that unusual heterocyclic compounds containing a pyrazole ring with one of its nitrogen atoms in a bridgehead position may be readily prepared from azine ylides 1 (see Scheme I). It has been shown that pyrazolo[5,1-*c*]-1,4-oxazines 4,[1,2] 4,5-dihydropyrazolo[1,5-*b*]isoquinolines 5,[1-4] and 4,5- and 6,7-dihydropyrazolo[1,5-*a*]pyridines (6 and 7)[5] are produced from ketenes. Isocyanates have given 4,9-dihydropyrazolo[5,1-*b*]quinazolines 8,[6,7] 2,3-dihydro-1*H*-imidazo-[1,2-*b*]pyrazol-2-ones 9,[4,6] and 4*H*-pyrazolo[1,5-*c*][1,3,5]-

† For the X-ray data.

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