Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 1953–1958

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

# SYNTHESIS AND STRUCTURE–ACTIVITY RELATIONSHIPS OF 2-PYRIDONES: II. 8-(FLUORO-SUBSTITUTED PYRROLIDINYL)-2-PYRIDONES AS ANTIBACTERIAL AGENTS[1]

Qun Li,* Weibo Wang, Kristine B. Berst, Akiyo Claiborne, Lisa Hasvold, Kathleen Raye, Michael Tufano, Angela Nilius, Linus L. Shen, Robert Flamm, Jeff Alder, Kennan Marsh, DeAnne Crowell, Daniel T. W. Chu and Jacob J. Plattner

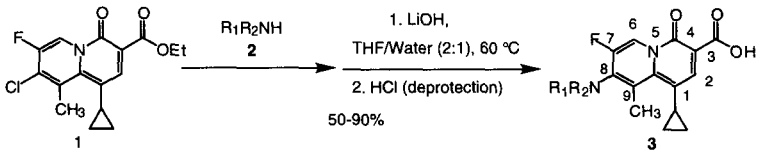
*Infectious Diseases Research, Pharmaceutical Products Division*
*Abbott Laboratories, 100 Abbott Park Road, Abbott Park, Illinois 60064-3500, U.S.A.*

Received 13 February 1998; accepted 3 June 1998

**Abstract**: The 8-position side chain of 2-pyridones is believed to be involved in the binding with bacterial DNA gyrase to form the ternary complex, making them very important for the activity of 2-pyridones. A series of 2-pyridones having fluoro-substituted amines at the 8-position has been synthesized and their antibacterial activities and parmacokinetic properties are reported. 

**Introduction**. 2-Pyridones (**1**) are a class of newly discovered potent antibacterial agents that are of particular interest due to their effectiveness against resistant bacteria.[2,3] The 8-position side chain of these compounds is thought to be involved in binding with bacterial DNA gyrase in the ternary complex,[4] making the substituent at the 8-position a key factor in the activity of the 2-pyridones.[2] The 7-position fluorine atom, which is highly electronegative, yet similar in size to hydrogen, has also proven to be very important to the activity of 2-pyridones,[2] as well as their quinolone[5] predecessors. Our continued efforts in the area of 2-pyridones led us to combine these two important findings such that we have synthesized a series of compounds possessing fluoropyrrolidines at the 8-position. Syntheses of these compounds as well as their antibacterial activity and pharmacokinetic properties are reported.[6]

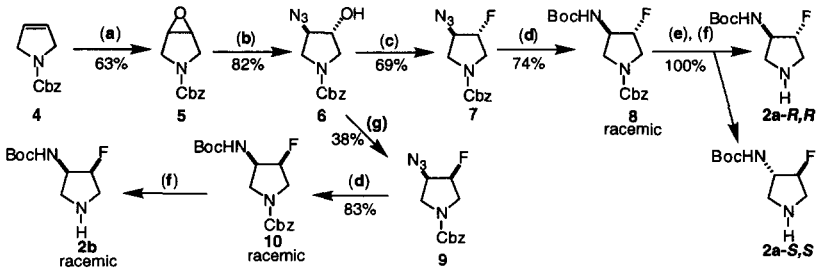
**Chemistry**. The synthesis of 2-pyridones **3** with fluoro-substituted pyrrolidines at the 8-position was achieved through the same route reported in our previous paper.[2] The synthesis required nucleophilic displacement of 8-chloropyridone **1** with fluoroamine **2** in acetonitrile or DMF. Lithium hydroxide mediated hydrolysis of the ester, followed by acid mediated removal of the amine-protecting Boc group afforded desired compound **3** in good yield (Scheme 1).




**Scheme 1.**

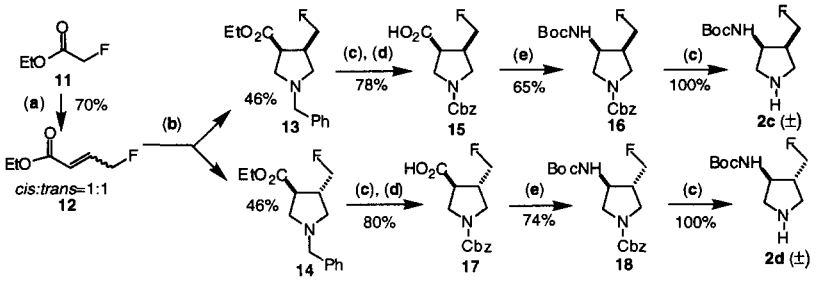
The syntheses of the fluoropyrrolidines **2** are illustrated in Schemes 2–8. The *cis*- and *trans*-fluoroaminopyrrolidines (**2a** and **2b**) were prepared by modified procedures of Bouzard[7] (Scheme 2). Epoxide **5**, which was prepared from Cbz-pyrroline **4** in 63% yield, was treated with sodium azide to give *trans*-azidohydroxypyrrolidine **6** in 82% yield. When alcohol **6** was reacted with DAST in methylene chloride at –78 °C, the reaction unexpectedly proceeded with retention of configuration to give *trans*-azidofluoropyrrolidine **7**. The *cis*-azidofluorpyrrolidine **9** was obtained by an alternate two step procedure via $S_N2$ substitution of the corresponding mesylate with sodium azide in 38% yield. Reduction of the azido groups of **7** and **9** and subsequent protection with $Boc_2O$ provided racemic **8** (74%) and **10** (83%), respectively. The isomers of compound **8** were separated by chiral preparative HPLC.[8] Hydrogenation gave the final products **2a** and **2b**.

0960-894X/98/$ - see front matter 
*PII:* S0960-894X(98)00355-2



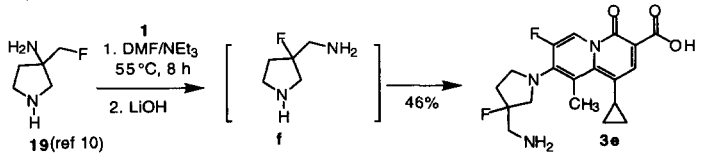
**Scheme 2.** (a) MCPBA, $CH_2Cl_2$, reflux; (b) $NaN_3$, acetone/water, reflux; (c) DAST, $CH_2Cl_2$, –78 °C to rt; (d) 1. $H_2$ (4 atm), Ra Ni, MeOH, rt; 2. $(Boc)_2O$, MeOH/water, rt; (e) chiral HPLC separation;[8] (f) $HCO_2NH_4$, 10% Pd-C, MeOH, reflux; (g) 1. MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C to rt; 2. 1.0 N $Bu_4NF$ in THF, 65 °C.

Synthesis of **2c** and **2d** (Scheme 3) began with ethyl fluoroacetate that was reduced with DIBAL. The resulting aldehyde was reacted with a Wittig reagent to give a mixture (70%, 1:1) of *cis*- and *trans*-fluorocrotonate **12**. The 1,3-dipolar addition reaction of **12** with the azomethine ylide[9] produced, after chromatographic separation, pyrrolidines **13** (46%) and **14** (46%). Conversion of the benzyl group of **13** to the Cbz group (for ease of operation) and subsequent hydrolysis of the ester gave **15** in 78% yield. **15** then underwent a Curtius rearrangement and subsequent hydrogenation to afford 4-fluoromethyl-3-aminopyrrolidine **2c** in 65% yield. The same reaction sequence was repeated starting with **14** to afford the *trans*-isomer **2d**.

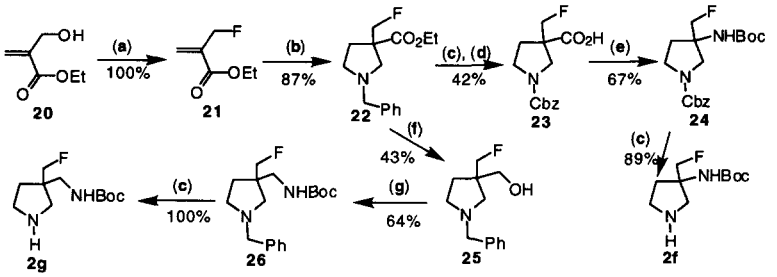


**Scheme 3.** (a) 1. DIBAL, $CH_2Cl_2$, –78 °C; 2. $Ph_3PCH_2CO_2Et$, NaH, THF; (b) $(MeOCH_2)(TMSCH_2)NCH_2Ph$, TFA, $CH_2Cl_2$, –78 °C to rt, column chromatographic separation; (c) $HCO_2NH_4$, 10% Pd-C, MeOH, reflux; (d) 1. Cbz-Cl, $Na_2CO_3$, dioxane-$H_2O$, 0 °C; 2. LiOH, THF-$H_2O$, 0 °C to rt; (e) DPPA, $Et_3N$, *t*-BuOH, reflux.

The importance of protecting the aminopyrrolidines was discovered when unprotected fluoromethylpyrrolidine **19**, which was prepared by patent procedure,[10] rearranged under the coupling conditions[6] to give the unexpected fluoropyrrolidinyl 2-pyridone **3e** (Scheme 4). Scheme 5 depicts an alternate route that was developed for the preparation of the Boc-protected 3-fluoromethylpyrrolidines, **2f** and **2g**. Hydroxymethacrylate **20** was treated with DAST to yield fluoromethacrylate **21** quantitatively. Cycloaddition of **21** with the azomethine ylide[9] produced pyrrolidine **22** in 87% yield. **2f**, the Boc-protected version of **19**, was prepared from **22** by the same reaction sequence described in Scheme 3. Alternately, ester **22** was reduced to alcohol **25** with LAH in 43% yield. Conversion of **25** to **26** was achieved by Mitsunobu reaction with phthalimide followed by hydrazinolysis and subsequent protection with $(Boc)_2O$ (64%). Hydrogenation of **26** produced **2g** (Scheme 5).[11]

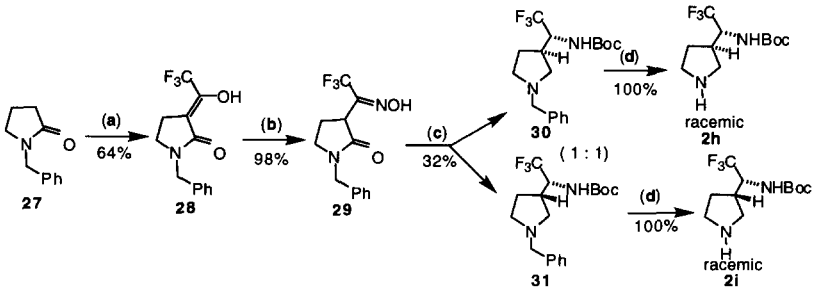


**Scheme 4.**



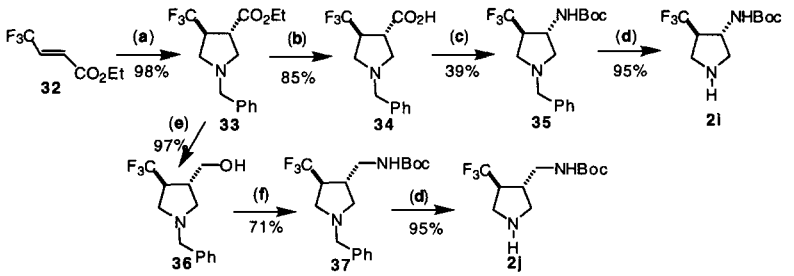
**Scheme 5.** (a) DAST, $CH_2Cl_2$, –78 °C to rt; (b) $(MeOCH_2)(TMSCH_2)NCH_2Ph$, TFA, $CH_2Cl_2$, 0 °C; (c) $HCO_2NH_4$, 10% Pd-C, MeOH, reflux; (d) 1. Cbz-Cl, $Na_2CO_3$, dioxane/$H_2O$, 0 °C; 2. LiOH, THF/$H_2O$, 0 °C to rt; (e) DPPA, $Et_3N$, *t*-BuOH/dioxane, reflux; (f) $LiBH_4$, MeOH/$Et_2O$, reflux (g) 1. DEAD, phthalimide, THF, rt; 2. $NH_2NH_2$, EtOH, reflux; 3. $(Boc)_2O$, MeOH/$H_2O$, rt.

Synthesis of trifluoroethyl pyrrolidines **2h** and **2i** is shown in Scheme 6. Trifluoroacetylation of *N*-benzylpyrrolidinone **27** produced **28** in 64% yield. Conversion of **28** to oxime **29**, followed by reduction with LAH and subsequent Boc-protection gave a mixture of **30** and **31** in 32% yield. Separation of the two diastereoisomers[12] by column chromatography, followed by removal of the benzyl groups from **30** and **31** afforded **2h** and **2i**, respectively. This convenient method for the preparation of racemic pyrrolidines should be applicable to other substituted aminomethylpyrrolidines.



**Scheme 6.** (a) $CF_3CO_2Et$, NaH, THF; (b) $NH_2OH$; (c) 1. LAH, THF; 2. $(Boc)_2O$, MeOH/$H_2O$, column separation; (d) $H_2$, 10% Pd-C, MeOH.

Synthesis of trifluoromethyl pyrrolidines **2j** and **2k** is illustrated in Scheme 7, in which *trans*-trifluorocrotonate underwent reactions analogous to these described in Scheme 3 and Scheme 5.

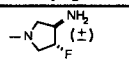
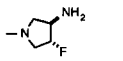
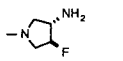
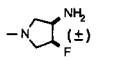
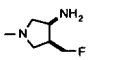
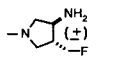
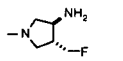
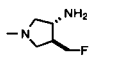
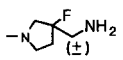
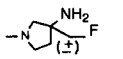
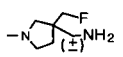
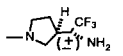
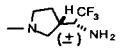
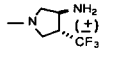
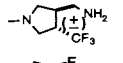
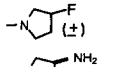
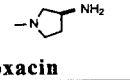


**Scheme 7.** (a) $(MeOCH_2)(TMSCH_2)NCH_2Ph$, TFA, $CH_2Cl_2$, 0 °C to rt; (b) LiOH, THF/$H_2O$, 60 °C; (c) DPPA, $Et_3N$, *t*-BuOH/dioxane, reflux; (d) $H_2$, 10% Pd-C, MeOH, rt; (e) LAH, THF, 0 °C to rt; (f) 1. DEAD, phthalimide, THF, 0 °C; 2. $NH_2NH_2$, EtOH, reflux; 3. $(Boc)_2O$, MeOH/$H_2O$, rt.

**Results and discussion**. The minimum inhibitory concentrations (MIC)[13] of fluoro-substituted pyrrolidinyl-pyridones **3a–l** against several representative Gram-positive and Gram-negative bacteria are

summarized in Table 1, along with data for ABT-719 and ciprofloxacin. In general, incorporation of fluorine atoms into pyrrolidines resulted in a decrease in the in vitro and in vivo activity, especially against Gram-negative organisms. However, the activity against staphylococci including methicillin-resistant *Staphylococcus aureus* (MRSA) remained almost unchanged. In general, activity against Gram-negative organisms, such as *Pseudomonas* species, is sensitive to the size of the substituents on the pyrrolidine rings. Our results confer this, since the trifluoro-substituted analogs were less active than the monofluoro-substituted compounds against Gram-negative bacteria. We found the aminomethylpyrrolidine series (**3e**, **3g**, and **3k**) to be more active than the

**Table 1**. In vitro antibacterial[13] and gyrase[14] activity of pyridones.

| | | MIC, μg/mL* | | | | | | | | | | Gyrase |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Gram-Positive organisms | | | | | Gram-negative organisms | | | | | $CC_{50}$[13] |
| Compd | $R_1R_2N$ | *S.a* | *S.a(R)* | *E.f.* | *S.b.* | *S.p* | *E.c* | *E.a* | *K.p.* | *P.s.* | *P.a* | μg/mL |
| **3a** |  | 0.02 | 0.78 | 0.1 | 0.2 | 0.2 | 0.02 | 0.05 | 0.02 | 1.56 | 0.78 | 0.7 |
| **3a-*R,R*[7]** |  | 0.05 | 1.56 | 0.2 | 0.39 | 0.2 | -- | 0.2 | 0.02 | 1.56 | 1.56 | - |
| **3a-*S,S*[7]** |  | 0.05 | 1.56 | 0.39 | 0.39 | 0.39 | -- | 0.2 | 0.02 | 0.78 | 0.78 | - |
| **3b** |  | 0.02 | 1.56 | 0.1 | 0.2 | 0.1 | 0.02 | 0.05 | 0.05 | 0.78 | 0.39 | - |
| **3c** |  | 0.01 | 1.56 | 0.1 | -- | 0.02 | 0.005 | 0.02 | 0.005 | 0.39 | 0.2 | - |
| **3d** |  | 0.02 | 3.1 | 0.1 | -- | 0.1 | 0.01 | 0.05 | 0.005 | 0.78 | 0.39 | - |
| **3d-*R,S*[7]** |  | 0.02 | 1.56 | 0.1 | 0.1 | 0.1 | 0.02 | 0.05 | 0.01 | 0.78 | 0.39 | - |
| **3d-*S,R*[7]** |  | 0.01 | 3.1 | 0.2 | 0.39 | 0.2 | 0.1 | 0.02 | 0.002 | 0.78 | 0.39 | - |
| **3e** |  | 0.01 | 0.39 | 0.02 | 0.02 | 0.02 | 0.02 | 0.05 | 0.005 | 0.78 | 0.39 | - |
| **3f** |  | 0.02 | 0.78 | 0.1 | 0.2 | 0.1 | 0.02 | 0.1 | 0.01 | 0.39 | 0.39 | - |
| **3g** |  | 0.02 | 1.56 | 0.1 | 0.1 | 0.05 | 0.05 | -- | 0.1 | 0.78 | 0.78 | - |
| **3h** |  | 0.02 | 0.78 | 0.39 | 0.39 | 0.2 | 0.78 | 1.56 | 0.39 | 6.2 | 6.2 | - |
| **3i** |  | 0.005 | 0.39 | 0.1 | 0.2 | 0.2 | 0.2 | 0.78 | 0.2 | 3.1 | 6.2 | - |
| **3j** |  | 0.02 | 1.56 | 0.2 | 0.39 | 0.2 | 0.05 | 0.2 | 0.05 | 3.1 | 0.78 | 3.8 |
| **3k** |  | 0.01 | 0.78 | 0.02 | 0.02 | 0.02 | 0.02 | 0.05 | 0.01 | 1.56 | 0.39 | 6.5 |
| **3l** |  | 0.02 | 1.56 | 0.05 | 0.1 | 0.1 | 0.1 | 0.39 | 0.1 | 0.78 | 1.56 | 0.6 |
| **ABT-719** |  | 0.01 | 0.78 | 0.02 | 0.02 | 0.02 | 0.002 | 0.005 | 0.005 | 0.2 | 0.05 | 0.03 |
| **ciprofloxacin** | | 0.39 | >100 | 0.78 | 0.78 | 0.78 | 0.02 | 0.02 | 0.02 | 1.56 | 0.2 | 0.24 |

**S.a: Staph. aureus* NCTC10649M; *S.a(R)*: *Staph. aureus* A1775; *E.f: Ent. faecium* ATCC8043; *S.b: Strep. bovis* A5169; *S.p: Strep. pyogenes* EES61; *E.c: E. coli* JUHL; *E.a: Enterobacter aerogenes* ATCC13048; *K.p: Klebsiella pneumoniae* ATCC8045; *P.s: Providentia Stuartii* CMX640; *P.a: Pseudomonas aeruginosa* A-5007.

compound **3l**, which had surprisingly good and balanced activity. Because of their good overall profiles, the racemic *trans*-fluoro- and *trans*-fluoromethylpyrrolidine analogs (**3a** and **3d**) were resolved.[8] However, no significant differences were found between the enantiomers (**3a-*S,S*** vs. **3a-*R,R*** and **3d-*S,S*** vs. **3d-*R,R***). The *E. coli* gyrase activity[14] decreased at least 20-fold for all the fluoropyrrolidinyl compounds tested.

The in vivo efficacy against *Staph. aureus* and *E-coli* of several of the compounds was determined in the acute murine lethal infections model.[2,15] The results along with pharmacokinetic properties are shown in Table 2. Most of our compounds were quite efficacious in vivo against *Staph.* In accordance with the in vitro results, the efficacy against *E. coli* was significantly lower. Compound **3l**, which lacks an amino group, was totally devoid of in vivo efficacy, despite its good in vitro potency. We observed that the regiochemistry of fluoro group affected the efficacy, since the *cis* analog **3b** was more efficacious than the *trans*-isomer **3a**. The fluoro-substituted analogs seemed to have improved pharmacokinetics in rat, as evidenced by the fact that they have longer half lives and better bioavailability than that of ABT-719.

**Table 2**. In vivo efficacy and pharmacokinetics of selected pyridones.[2,15]

| | $ED_{50}$ in mice , (mg/kg/day)[a] | | | | PK after a 5 mg/kg single oral dose in rat | |
|---|---|---|---|---|---|---|
| | *S.aureus* NCTC10649M | | *E. coli* JUHL | | *Cmax*[e] | *F*[f] |
| Compd | SC[b] | PO[c] | SC | PO | (μg/mL) | (%) |
| **3a-*R,R***[8] | 4.8 | 7.3 | >5.0 | >10.0 | - | - |
| **3a-*S,S***[8] | 4.8 | 25.0 | >5.0 | >10.0 | - | - |
| **3b** | 1.5[b] | 7.7[d] | 1.8 | 7.4 | 0.9 | 34. |
| **3d-*R,S***[8] | 1.2 | -- | 0.8 | -- | - | - |
| **3d-*S,R***[8] | 1.2 | 11.5 | 0.4 | 3.0 | - | - |
| **3f** | 2.7 | 10.3 | 4.3 | 15.1 | 0.6 | 63 |
| **3g** | 1.50 | 3.8 | 1.5 | >10.0 | - | - |
| **3i** | 11.9 | 25.0 | >4.0 | >10.0 | 0.8 | 57 |
| **3j** | 4.8 | 25.4 | -- | -- | - | - |
| **3k** | 0.7 | 2.6 | -- | -- | - | - |
| **3l** | >12.0 | >50.0 | -- | -- | 0.35 | 13 |
| **ABT-719** | 0.6 | 3.4 | 0.1 | 0.6 | 0.27 | 32 |
| **Cipro** | 4.1 | 28.2 | 0.1 | 1.0 | 0.15 | 16 |

[a]Effective dosage that protect 50% of mice from lethal infection. Unless otherwise indicated, mice were infected at 100 × $LD_{50}$. [b]SC: subcutaneously administered. [c]PO: orally administered. [d]Mice were infected with 1000 × $LD_{50}$. [e]Maximal plasma concentration. [f]Bioavailability.

In summary, the synthesis and antibacterial activity of a series of 2-pyridones possessing fluoro-substituted pyrrolidine side chains has been described. It was found that the antibacterial activity of the fluoro-substituted compounds was excellent overall, especially against Gram-positive organisms, including MRSA. In particular, compounds **3b** and **3d** displayed the best overall and most balanced activity. However, the activity was decreased in comparison with the non-fluoro-substituted analogs. Therefore, it seems that the importance of fluoro-substitution to the 2-pyridone ring system is not conveyed to the 8-position side chain.

**Acknowledgment**: The authors wish to thank Ms. Beth Steiner and Dr. Curt Cooper for helpful discussions. We also wish to thank Mrs. Charlene Vojtko and Ms. Pauline Johnson for MIC testing and Mr. Michael Fitzgerald for HPLC separations. We acknowledge the support from the Structural Chemistry Department for analysis of the compounds.

## References and Notes

1. *This paper is dedicated to Professor Pang Zhang at Peking University on the occasion of his 80th birthday.*

2. Li, Q.; Chu, D. T.; Claiborne, A.; Cooper, C. S.; Lee, C. M.; Raye, K.; Berst, K. B.; Donner, P.; Wang, W., Hasvold, L.; Fung, A.; Ma, Z.; Tufano, M.; Flamm, R.; Shen, L. L.; Baranowski, J.; Nilius, A.; Alder, J.; Meulbroek, J.; Marsh, K.; Crowell, D.; Hui, Y.; Seif, L.; Melcher, L. M.; Henry, R.; Spanton, S.; Faghih, R.; Klein, L. L.; Tanaka, S. K.; Plattner, J. J. *J. Med. Chem.* **1996**, *39*, 3070.
3. For other 2-pyridone related papers, see: (a) Ma, Z.; Chu, D. T. W.; Li, Q.; Shen, L. L.; Fung, A.; Cooper, C. S.; Wang, W.; Wang, S.; Flamm, R. K.; Nilius, A.; Alder, J. D.; Tanaka, S. K.; Or, Y.; Plattner, J. J. *37th ICAAC*, 1997, Abstract F169. (b) Park, T-H.; Nam, K-S.; Ha, Y-H.; Choi, Y-K.; Choi, Y-J.; Kong, J-Y.; Kim, Y-H. 37th ICAAC, 1997, Abstract 173. (c) Klein, L. L.; DeGoey, D. A.; Thomas, S. A.; Yeung, C. M.; Leone, C. L.; Grampovnik, D. J.; Chu, D. T.; Lartey, P. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1167. (d) Flamm, R. K.; Vojtko, C.; Chu, D. T.; Li, Q.; Beyer, J.; Hensey, D.; Ramer, N.; Clement, J. J.; Tanaka, S. K. *Antimicrob. Agents Chemother.* **1995**, *39*, 964. (e) Eliopoulos, G. M.; Wennersten, C. B.; Cole, G.; Chu, D.; Pizzuti, D.; Moellering, R. C., Jr. *Antimicrob. Agents Chemother.* **1995**, *39*, 850. (f) Alder, J.; Clement, J; Meulbroek, J.; Shipkowitz, N.; Mitten, M.; Jarvis, K.; Oleksijew, A.; Hutch, T., Sr.; Paige, L.; Flamm, R.; Chu, D.; Tanaka, K. *Antimicrob. Agents Chemother.* **1995**, *39*, 971. (g) Fromtling, R. A. *Drugs Fut.* **1995**, *20*, 1103.
4. Shen, L. L. *Advances in Pharmacology* **1994**, *29a*, 285.
5. K. Hayashi and coworkers disclosed at 37th ICAAC that with certain combinations of substitutions at the 7- and 8-positions, the quinolones without the 6-fluorine were as active as the ones with the 6-fluorine, while having greatly reduced side effects. Hayashi, K.; Todo, Y.; Hamamoto, S.; Ojima, K.; Yamada, M.; Kito, T.; Takahata, M.; Watanabe, Y.; Narita, H. *37th ICAAC* **1997**, Abstract 158.
6 Li, Q.; Claiborne, A.; Chu, D. T. W.; Lee, C. M.; Raye, K. A.; Berst, K.; Ma, Z.; Wang, W.; Shen, L. L.; Flamm, R.; Nilius, A.; Alder, J.; Marsh, K.; Shortridge, V. D.; Tanaka, S. K.; Seif, L.; Cooper, C. S.; Fung, A.; Tufano, M.; Melcher, L. M.; Henry, R.; Klein, L.; Plattner, J. J. Presented in part at the *35th ICAAC* **1995**, Abstract F8.
7. Bouzard, D.; Cesare, P. Di; Essiz, M.; Jacquet, J. P.; Kiechel, J. R.; Remuzon, P.; Weber, A.; Oki, T.; Masuyoshi, M.; Kessler, R. E.; Fung-Tomc, J.; Desiderio, J. *J. Med. Chem.* **1990**, *33*, 1344.
8. Racemic **8** and **18** were separated by preparative HPLC using a Chiralpak column eluting with hexanes/ethanol (90/10). The compounds with lower retention time after cleavage of the benzyl group were assigned arbitrarily as 3*R*, 4*R* (**2a-*RR***) and 3*R*,4*S* (**2d-*RS***), respectively. The compounds with higher retention time after cleavage of the benzyl group were assigned arbitrarily as 3*S*,4*S* (**2a-*SS***) and 3*S*,4*R* (**2d-*SR***), respectively.
9. Laborde, E. *Tetrahedron Lett.* **1992**, *33*, 6607, and references therein.
10. Saito, A; Uesato, S; Iwata, H; Ao, H; Kuroda, T; Kawasaki, K; Morigushi, A; Ikeda, Y. WO 9514794-A1, **1994**.
11. Kitani, H.; Kuroda, T.; Moriguchi, A.; Ao, H.; Hirayama, F.; Ikeda, Y.; Kawakita, T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 515.
12. The configurations were assigned arbitrarily.
13. *National Committee for Clinical Laboratory Standards 1993. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A3*; National Committee for Clinical Laboratory Standards; Villanova, PA
14. (a) Shen, L. L.; Baranowski, J.; Fostel, J.; Montgomery, D. A.; Lartey, P. A. *Antimicrob. Agents Chemother.* **1992**, *36*, 2778. (b) Shen, L. L.; Kohlbrenner, W. E.; Weigl, D.; Baranowski, J. *J. Biol. Chem.* **1989a**, *264*, 2973.
15. Clement, J. C.; Tanaka, S. K.; Alder, J, D.; Vojtko, C.; Beyer, J.; Hensey, D.; Ramer, N.; McDaniel, D.; Chu, D. T. W. *Antimocrob. Agents Chemother.* **1994**, *38*, 1071.