December 1994 Notes Chem. Pharm. Bull. 42(12) 2629—2632 (1994)

Practical Synthesis of T-3761, (*S*)-10-(1-Aminocyclopropyl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic Acid

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Received June 24, 1994; accepted August 1, 1994

An economical 11-step synthesis of T-3761 (1), a new quinolone antibacterial agent discovered by us, has been developed. Commercially available 2,3,4,5-tetrafluorobenzoic acid (2) has been transformed to 4-(1-acetamino-cyclopropyl)-2,3,5-trifluorobenzoic acid (10) in 6 steps (68% yield), including cyclopropane-ring formation of the 4-cyanomethylbenzoate intermediate (6) at its side chain. Conversion of 10 to the β-keto ester 11 and a subsequent 2-step pyridoxazine annulation procedure afforded 13 (80% yield), which, on *N*,*O*-deprotection, provided 1 (48% overall yield from 2). The overall reaction sequence can be carried out without chromatographic purification of intermediates.

Keywords fluoroquinolone; synthesis; aminocyclopropyl substituent; pyridobenzoxazine; antibacterial agent

Recently we have developed a structurally unique new fluoroquinolone antibacterial agent (**1** or T-3761)[1a] which not only displays potent broad-spectrum activity *in vitro* and *in vivo*, but also has excellent overall pharmacological and pharmacokinetic profiles, superior to those of currently marketed quinolones such as ofloxacin[2] and tosufloxacin.[3] Another notable property of **1** is that its methanesulfonate (T-3762),[1a] presently under Phase II clinical trials, possesses a high degree of water solubility that allows the agent to be employed intravenously for treatment of serious infections.

We wished to establish a practical synthetic method for **1** amenable to large-scale production. Our previous synthesis of **1**[1] utilized, as a key intermediate, the *N*-benzyloxycarbonyl (*Z*) derivative **4** of 4-(1-aminocyclopropyl)-2,3,5-trifluorobenzoic acid (Chart 1). This compound was prepared from commercially available tetrafluorobenzoic acid (**2**) in 11 steps (28% overall yield), involving cyclopropanation of the acrylate intermediate (**3**) with dimethylsulfoxonium methylide. It was our first goal to improve the multi-step transformation of **2** to **4** by utilizing an alternative cyclopropanation technique. We also planned to improve the subsequent steps for the construction of the pyridobenzoxazine framework in terms of both overall yield and operational feasibility. A revised synthetic route to fulfill these criteria has been established, leading to 48% overall yield of **1** from **2** in 11 steps without chromatographic purification of intermediates.

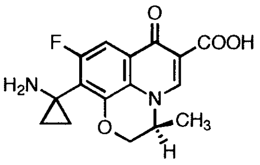
Treatment of the starting material (**2**) with ethyl bromide and then with *tert*-butyl cyanoacetate in the presence of K_2CO_3 in dimethyl sulfoxide (DMSO) in one flask afforded the arylated cyanoacetate **5**,[4] which, without purification, was heated in toluene in the presence of *p*-toluenesulfonic acid to give the 4-cyanomethylbenzoate **6** in 90% yield. Cyclopropane ring-formation at the benzylic position of **6** was performed by α,α-dialkylation with 2 eq of 1,2-dibromoethane under phase-transfer conditions[5] to afford 4-(1-cyanocyclopropyl)benzoic acid **7**. For conversion of **7** to the aminocyclopropyl compound **9**, the nitrile **7** was first subjected to hydration with alkaline H_2O_2 to afford the carboxamide **8** (81% overall yield from **6**), which, upon Hofmann rearrangement by treatment with NaOCl, gave **9** in 96% yield. The primary amino group of **9** was protected for the next reaction as its *N*-acetyl derivative **10** (97% yield), instead of using *Z*-protection as in **4**. Thus, the key intermediate **10** was obtained in 6 steps from **2**, in 68% overall yield.

Transformation of the carboxylic acid **10** to the pyridoxazine **13** was carried out starting with conversion to the β-keto ester **11** (Chart 2). Reaction of **10** with imidazole in the presence of thionyl chloride and triethylamine (TEA) generated an imidazolide, which was allowed to react *in situ* with potassium ethyl malonate in the presence of $MgCl_2$, TEA, and *N*,*N*-dimethylformamide (DMF) to produce **11**.[6] This material was then converted to the enamine **12** by successive treatment with *N*,*N*-dimethylformamide dimethylacetal and (*S*)-(+)-2-aminopropanol. Cyclization of crude **12** to **13** was effected by heating in DMSO in the presence of K_2CO_3 as previously reported.[1] Lastly, the ethyl ester and acetamide groups in **13** were hydrolyzed under basic and acidic conditions, respectively, to afford **1** (T-3761) (71% overall yield from **10**, 5 steps). The methanesulfonate of **1** (T-3762) was obtained in 94% yield by treatment of **1** with CH_3SO_3H in ethanol.[1a]

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a JEOL FX-60 spectrometer. Chemical shifts are expressed in δ_{ppm} downfield from the internal tetramethylsilane. Resonance patterns are described as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. The optical rotations were recorded with a JASCO DIP-370 digital polarimeter. Column chromatography was carried out with Merck silica gel 60 (70—230 mesh). All organic solvent extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure with a rotary evaporator.

Ethyl 4-Cyanomethyl-2,3,5-trifluorobenzoate (6) A solution of **2** (200 g, 1.03 mol) in DMSO (1.0 l) was stirred at 65—70 °C for 2 h after addition of K_2CO_3 (164 g, 1.19 mol) and EtBr (135 g, 1.24 mol). *tert*-Butyl



1 (T-3761)
$MeSO_3H$ salt (T-3762)

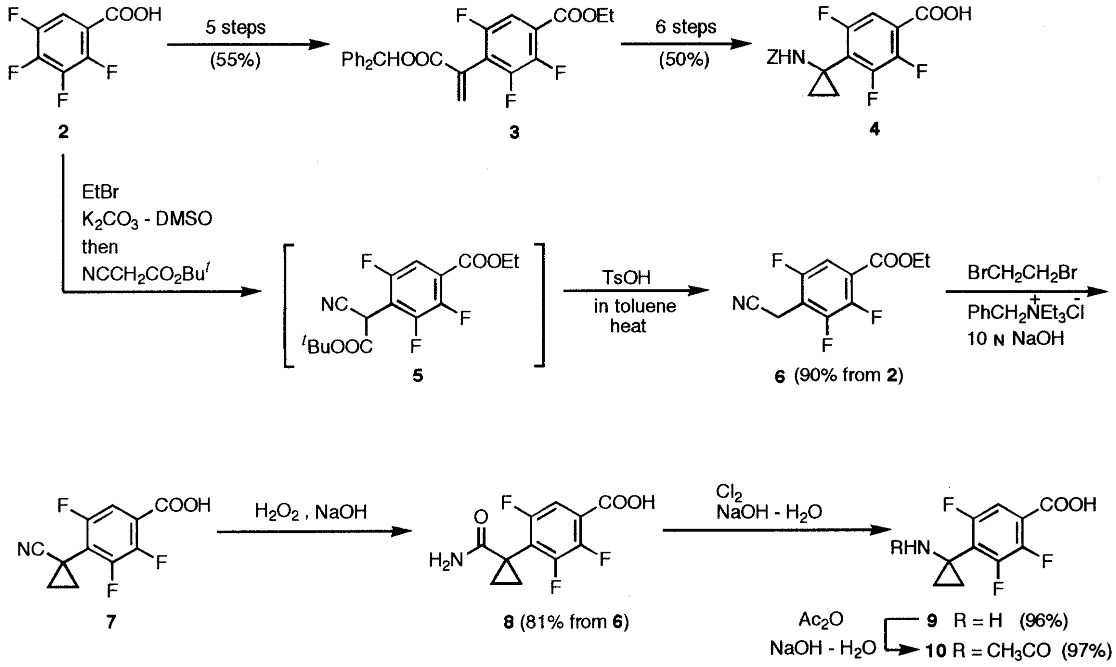


Chart 1

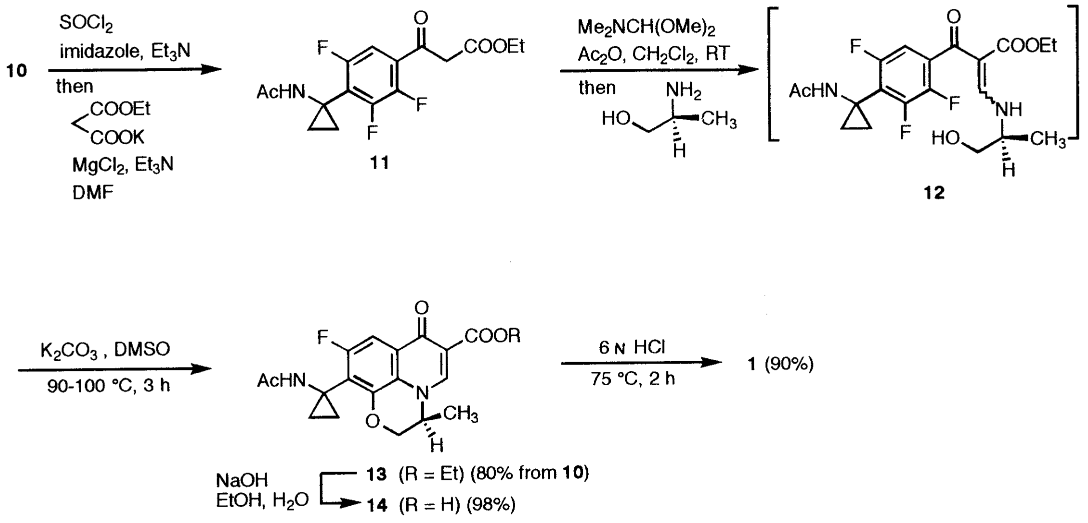


Chart 2

cyanoacetate (175 g, 1.24 mol) and K_2CO_3 (342 g, 2.47 mol) were then added, and stirring of the mixture at the same temperature was continued for 2 h. The mixture was poured into a stirred mixture of ice-water (4.0 l) and toluene (2.0 l), and the whole was acidified to pH 3 by addition of 6 N HCl. The aqueous layer was separated, and the organic layer was washed successively with water and saturated brine, dried, and filtered. The filtrate containing **5** was heated under reflux for 6 h after addition of *p*-toluenesulfonic acid monohydrate (1.0 g, 5.3 mmol). The mixture was poured into ice-water (400 ml) and the organic layer was separated, washed successively with water and saturated brine, dried, and concentrated. The oily residue was purified by distillation to give **6** (226 g, 90%) as a colorless oil, bp 130—131 °C (1.1 mmHg). IR (neat): 2262, 1732 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.86 (2H, s, CH_2CN), 4.43 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.49 (1H, ddd, J=9.5, 5.5, 2.5 Hz, Ar-H). *Anal.* Calcd for $C_{11}H_8F_3NO_2$: C, 54.33; H, 3.32; N, 5.76. Found: C, 54.28; H, 3.22; N, 5.78.

4-(1-Cyanocyclopropyl)-2,3,5-trifluorobenzoic Acid (7) Benzyltriethylammonium chloride (187 g, 0.821 mol) and 10 N NaOH (1.6 l) were added to a stirred mixture of **6** (200 g, 0.822 mol) and 1,2-dibromoethane (324 g, 1.74 mol) at 10 °C. The mixture was then stirred at room temperature for 2 h before acidification to pH 1 with 6 N HCl and extraction with a mixture of toluene (2.6 l) and AcOEt (1.0 l). The organic extract was washed with aqueous $NaHCO_3$ (2.6 l, pH 8), and the aqueous layer was acidified to pH 1 with 6 N HCl. The resulting crystalline precipitate was collected by filtration to give crude **7** (178 g) as a pale yellow solid of mp 154—156 °C. This crude product was used for the next step without further purification. An analytical sample was obtained by recrystallization from benzene, mp 159—160 °C, colorless prisms. IR (KBr): 2237, 1699 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.1—2.2 (4H, m, cyclopropane), 7.50 (1H, ddd, J=10, 5.5, 2.5 Hz, Ar-H), 10.08 (1H, br s, COOH). *Anal.* Calcd for $C_{11}H_6F_3NO_2$: C, 54.78; H, 2.51; N, 5.81. Found: C, 54.84; H, 2.40; N, 5.88.

4-(1-Carbamoylcyclopropyl)-2,3,5-trifluorobenzoic Acid (8) A solution of crude **7** (170 g, 0.705 mol) in 1 N NaOH (1.4 l) was stirred at room temperature, and 35% H_2O_2 (137 g, 1.41 mol) was added over 1 h. Thirty minutes after the addition was completed, the mixture was acidified to pH 2 with 6 N HCl. The crystalline precipitate was collected by filtration and dried to give **8** (164 g, 81% from **6**) as a white solid of mp 264—265 °C. An analytical sample was obtained by recrystallization from MeOH, mp 265—266 °C, colorless prisms. IR (KBr): 1706, 1683 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.7—1.8 (4H, m, cyclopropane), 6.92 (3H, br s, NH_2, COOH), 7.42 (1H, ddd, J=10, 5.5, 2 Hz, Ar-H). *Anal.* Calcd for $C_{11}H_8F_3NO_3$: C, 50.98; H, 3.11; N, 5.40. Found: C, 50.96; H, 3.05; N, 5.41.

4-(1-Aminocyclopropyl)-2,3,5-trifluorobenzoic Acid (9) Compound **8** (150 g, 0.579 mol) was added to a stirred mixture of 13% aqueous NaOCl (332 g, 0.580 mol) and 2.5 N NaOH (1.16 l) at room temperature. After 1 h the reaction mixture was heated at 50 °C for 2.5 h, then cooled to 20 °C and brought to pH 5 with 6 N HCl. The resulting precipitate was collected by filtration and dried to give **9** (128 g, 96%) as a white powder of mp 256—257 °C. IR (KBr): 1626 cm^{-1}. ^{1}H-NMR (CF_3COOD) δ: 1.3—2.2 (4H, m, cyclopropane), 7.4—8.0 (1H, m, Ar-H). *Anal.* Calcd for $C_{10}H_8F_3NO_2$: C, 51.96; H, 3.49; N, 6.06. Found: C, 51.85; H, 3.41; N, 6.01.

4-(1-Acetylaminocyclopropyl)-2,3,5-trifluorobenzoic Acid (10) Acetic anhydride (57.0 g, 0.558 mol) and 2 N NaOH (250 ml) were added simultaneously in a dropwise manner (over 30 min) to a stirred solution of **9** (100 g, 0.433 mol) in 2 N NaOH (320 ml) at room temperature at a controlled pH of 11.5—12.0. Thirty minutes after the addition was completed, the mixture was acidified to pH 1 with 6 N HCl, and the resulting precipitate was collected by filtration and dried to give **10** (115 g, 97%) as a white solid of mp 239—241 °C. An analytical sample was obtained by recrystallization from aqueous EtOH, mp 240—242 °C, colorless prisms. IR (KBr): 1711, 1697 cm^{-1}. ^{1}H-NMR (CF_3COOD) δ: 1.2—1.9 (4H, m, cyclopropane), 2.38, 2.55 (3H, each s, $NHCOC\underline{H}_3$), 7.3—7.8 (1H, m, Ar-H). *Anal.* Calcd for $C_{12}H_{10}F_3NO_3$: C, 52.76; H, 3.69; N, 5.13. Found: C, 52.68; H, 3.67; N, 5.15.

Ethyl 4-(1-Acetylaminocyclopropyl)-2,3,5-trifluorobenzoylacetate (11) Thionyl chloride (47.9 g, 0.403 mol) was added to a stirred and cooled (ice-water) solution of **10** (100 g, 0.366 mol) in CH_2Cl_2 (1.0 l) containing imidazole (27.4 g, 0.402 mol) and TEA (122 g, 1.21 mol). The mixture was then stirred at room temperature for 1 h before addition of $MgCl_2$ (34.8 g, 0.366 mol), TEA (37.0 g, 0.366 mol), potassium ethyl malonate (125 g, 0.734 mol), and DMF (100 ml). After being heated under reflux for 2 h, the mixture was poured into a mixture of ice-water (2.0 l) and CH_2Cl_2 (1.0 l), and the whole was acidified to pH 1 by addition of 6 N HCl. The aqueous layer was separated, and the organic layer was washed successively with water, saturated $NaHCO_3$, 1 N HCl, and saturated brine, and dried. The solvent was evaporated under reduced pressure to give crude **11** (125 g) as a pale yellow solid of mp 118—120 °C. This crude product was used for the next step without further purification. An analytical sample was obtained by silica gel chromatography (toluene : AcOEt = 50 : 1). mp 120—121 °C (a white powder from toluene). IR (KBr): 1736, 1701, 1657 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.5 (7H, m, $CH_2C\underline{H}_3$, cyclopropane), 1.87, 2.15 (3H, each s, $NHCOC\underline{H}_3$), 3.8—4.0 (2H × 0.7, m, $COCH_2COO$), 4.21 (2H × 0.7, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.27 (2H × 0.3, q, J=7 Hz, $C\underline{H}_2CH_3$), 5.81 (1H × 0.3, s, $C(OH)=C\underline{H}COO$), 6.15 (1H, br s, NH), 7.1—7.6 (1H, m, Ar-H), 12.60 (1H × 0.3, br s, $C(O\underline{H})=CHCOO$). *Anal.* Calcd for $C_{16}H_{16}F_3NO_4$: C, 55.98; H, 4.70; N, 4.08. Found: C, 55.82; H, 4.67; N, 3.86.

Ethyl (*S*)-10-(1-Acetylaminocyclopropyl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (13) *N*,*N*-Dimethylformamide dimethylacetal (54.1 g, 0.454 mol) and acetic anhydride (46.3 g, 0.454 mol) were added to a stirred solution of crude **11** (120 g, 0.350 mol) in CH_2Cl_2 (1.2 l) at room temperature. After 2 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOH (600 ml), and the solution was stirred at room temperature after addition of (*S*)-2-amino-1-propanol (26.3 g, 0.350 mol). After 2 h, the reaction mixture was concentrated under reduced pressure to give crude **12** (150 g) (yellow oil), which was used for the next step. An analytical sample was obtained as an amorphous solid by silica gel chromatography (toluene : AcOEt = 50 : 1). IR (KBr): 1671 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.6—1.6 (10H, m, $CHC\underline{H}_3$, $CH_2C\underline{H}_3$, cyclopropane), 1.84, 2.15 (3H, each s, $NHCOC\underline{H}_3$), 3.2—4.3 (6H, m, $CH_3C\underline{H}C\underline{H}_2O\underline{H}$, $C\underline{H}_2CH_3$), 6.4—7.1 (2H, m, NHCO, Ar-H), 8.19 (1H, d, J=14.5 Hz, $=C\underline{H}NH$), 9.2—9.8 (1H × 0.3, m, $=CHN\underline{H}$), 10.5—11.2 (1H × 0.7, m, $=CHN\underline{H}$).

A mixture of crude **12** (140 g, 0.327 mol) and K_2CO_3 (135 g, 0.977 mol) in DMSO (700 ml) was stirred at 90—100 °C for 3 h. The mixture was poured into a mixture of ice-water (4.0 l) and $CHCl_3$ (5.0 l), and the whole was adjusted to pH 2 with 6 N HCl. The aqueous layer was separated, and the organic layer was washed successively with water and saturated brine, dried, and concentrated. The crystalline residue was washed with Et_2O to give **13** (102 g, 80% from **10**) as a pale yellow solid of mp 213—215 °C. An analytical sample was obtained by recrystallization from aqueous EtOH, mp 217—218 °C, a white powder. $[\alpha]_D^{20}$ −69.3° (c=1.0, $CHCl_3$). IR (KBr): 1713, 1668 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.7 (10H, m, CH_3-3, $CH_2C\underline{H}_3$, cyclopropane), 1.85, 2.16 (3H, each s, $NHCOC\underline{H}_3$), 4.0—4.6 (5H, m, $OC\underline{H}_2C\underline{H}$, $C\underline{H}_2CH_3$), 6.41 (1H, s, NH), 7.51 (1H, d, J=10.5 Hz, H-8), 8.28 (1H, s, H-5). *Anal.* Calcd for $C_{20}H_{21}FN_2O_5$: C, 61.85; H, 5.45; N, 7.21. Found: C, 61.79; H, 5.37; N, 7.24.

(*S*)-10-(1-Acetylaminocyclopropyl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic Acid (14) The ester **13** (100 g, 0.257 mol) was added to a mixture of EtOH (150 ml), H_2O (200 ml), and 1 N NaOH (330 ml), and the mixture was stirred at 45—50 °C for 2 h before acidification to pH 2 with 6 N HCl. The crystalline precipitate was collected by filtration and dried to give **14** (91.0 g, 98%) as a pale yellow solid of mp 271—273 °C. An analytical sample was obtained by recrystallization from aqueous EtOH, mp 274—275 °C, colorless needles. $[\alpha]_D^{20}$ −58.5° (c=1.0, 1.0 N NaOH). IR (KBr): 1734, 1648 cm^{-1}. ^{1}H-NMR (CF_3COOD) δ: 1.2—2.1 (7H, m, CH_3-3, cyclopropane), 2.34, 2.58 (3H, each s, $NHCOC\underline{H}_3$), 4.4—5.5 (3H, m, $OC\underline{H}_2C\underline{H}$), 8.01 (1H, d, J=9.5 Hz, H-8), 9.36 (1H, s, H-5). *Anal.* Calcd for $C_{18}H_{17}FN_2O_5$: C, 60.00; H, 4.76; N, 7.77. Found: C, 59.99; H, 4.73; N, 7.74.

(*S*)-10-(1-Aminocyclopropyl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic Acid (1) A suspension of **14** (50.0 g, 0.139 mol) in 6 N HCl (110 ml) was stirred at 70—75 °C for 20 h. The reaction mixture was concentrated under reduced pressure to give hydrochloride of **1**. This material was dissolved in a solution of KOH (18.0 g, 0.321 mol) in H_2O (600 ml) and EtOH (400 ml), and the solution was saturated with CO_2. The crystalline precipitate was collected by filtration to give **1** (39.7 g, 90%)[1a)] as colorless needles, mp 266—267 °C (dec.), $[\alpha]_D^{20}$ −81.0° (c=1.0, 1.0 N NaOH).

Acknowledgment The authors are grateful to Professor E. Yoshii, Toyama Medical and Pharmaceutical University, for his help and useful suggestions during the preparation of the manuscript.

References and Notes

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