Synthesis of trovafloxacin using various (1α,5α,6α)-3-azabicyclo[3.1.0]hexane derivatives

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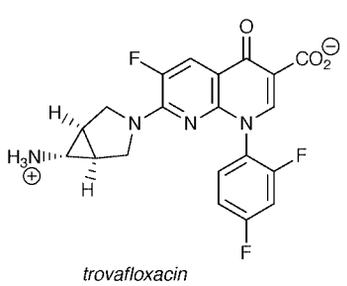
Trovafloxacin, a novel broad spectrum antibacterial, contains the unusual (1α,5α,6α)-3-azabicyclo[3.1.0]hexane ring system. The prototype of the industrial synthesis of this ring system and possible mechanistic pathways to exclusive formation of the *exo* or 6α-nitro derivative **4** are described, which leads to the key 6α-nitro-3-azabicyclo[3.1.0]hexane intermediate **10**. The synthesis of 6α-amino-3-azabicyclo[3.1.0]hexane **16** and useful protected *exo* 6-amino derivatives **15** and **17** follows from **10**. These can be coupled with the 7-chloronaphthyridone **18** to yield protected trovafloxacin compounds **20**–**22** in good yield. The ethyl ester of trovafloxacin **21** can also be accessed from the product of coupling **19**, derived from **18** and the *exo* 6-nitro-3-azabicyclo[3.1.0]hexane compound **12**. Removal of protecting groups from **20**–**22** with methanesulfonic acid yields trovafloxacin mesylate from which trovafloxacin zwitterion **1** can be liberated with base treatment. Zwitterion **1** can also be prepared directly from **16** tosylate salt and naphthyridone-2-carboxylic acid **26**.

Trovafloxacin **1** is a new and powerful antibiotic that is active



trovafloxacin

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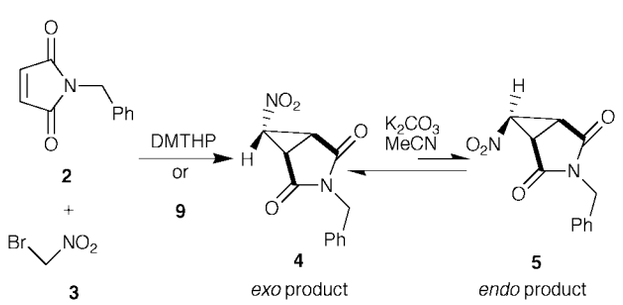
against a wide variety of microorganisms.[1] It contains the interesting 3-azabicyclo[3.1.0]hexane ring system.[2] This paper describes the synthesis and chemistry of a number of new (1α,5α,6α)-3-azabicyclo[3.1.0]hexanes and new naphthyridone coupled intermediates that can be used to make trovafloxacin. Possible mechanisms to interesting intermediates and the formation of some side products are also discussed.

The reaction of *N*-benzylmaleimide **2** and bromonitromethane **3** in the presence of base[3] is used to assemble the bicyclic ring system of **4**. Many bases can be used, but yields are often below 15%. Amidine bases are useful, particularly 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine[4] (DMTHP). This base improves the yield to the 30–35% range when the reaction is carried out at about −10 °C. The reaction can be carried out in many solvents but toluene is preferred because removal of the many tar like side products formed during the reaction is somewhat easier. It appears that the reaction produces almost exclusively the *exo* or 6α-nitro product **4**. The *endo* or 6β-nitro product **5** is detected at very low level, in the range 0.5–1.5% relative to *exo* **4**, in the presence of a base. The *endo* compound **5** can be formed by epimerization of **4** in the presence of potassium carbonate in acetonitrile. The equilibrium favours the *exo* form to a very significant extent and the *endo*–*exo* equilibrium is approximately 2:98 when measured by HPLC. The *endo* compound **5** has been isolated from the mother liquors of an equilibrium mixture by fractional crystallization and fully characterized by X-ray crystallography (see Fig. 1b).

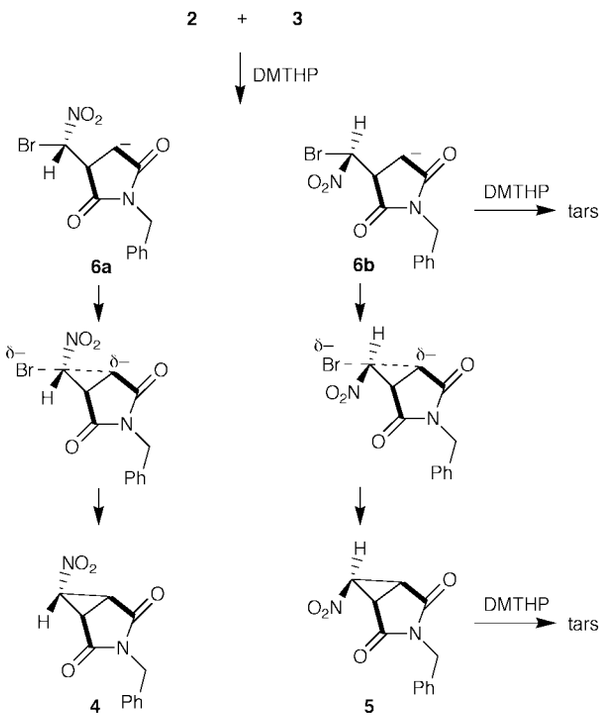


Steric hindrance is not a complete barrier to the synthesis of 6-substituted *endo* 3-azabicyclo[3.1.0]hexane products. For example, ethyl diazoacetate reacts with 1-benzyloxycarbonyl-2,5-dihydropyrrole in the presence of rhodium acetate to form both the 6α-ethoxycarbonyl and 6β-ethoxycarbonyl substituted 3-azabicyclo[3.1.0]hexane derivatives.[5] In this case the 6β- or *endo* isomer is a significant minor product, and the observed *endo*:*exo* ratio is 1:2. Recently, other workers have described a synthesis of 6β-isomers of the 3-azabicyclo[3.1.0]hexanes starting from amino-chloroenamines, such as 1-benzyl-3-chloro-4-(dibenzylamino)-1,2,3,6-tetrahydropyridine.[6]

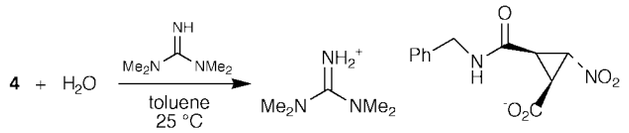
We cannot definitively account for the selectivity of the reaction between **2** and **3** in the presence of DMTHP to form **4** in terms of a mechanistic pathway, but some pertinent comments may be noted. The stereoselectivity in favour of the *exo* isomer **4** exceeds the thermodynamic ratio of 98:2 observed when equilibrating **4** with potassium carbonate in acetonitrile. It is possible that the cyclopropane ring forming reaction proceeds mainly by an insertion process in which both bonds of the cyclopropane ring are formed concomitantly. In this case, it might be anticipated that at least some *endo* product **5** should be formed as a measurable minor isomer in excess of 2% relative to *exo* product **4**, since there is no great steric inhibition to its formation. Similarly, if the cyclopropane bond forming processes occurs consecutively, a diastereomeric pair of carbanions **6a** and **6b**, would be expected to form, which will give rise to *exo*

and *endo* products **4** and **5**, respectively (see Scheme 1). For similar steric reasons that would also be true of the concomitant bond forming process, it seems improbable that kinetic stereoselectivity could arise from face selectivity in the initial Michael additon. In order to account for the observed selectivity† it may be that a more favoured reaction fate for carbanion **6b** or its resultant *endo* product **5** (formed by either concomitant or consecutive bond forming pathway) is the formation of polymeric reaction tars. Certainly, in examples where reactions are stressed, especially using reduced amounts of **3** and by leaving the reaction mixture to stir for >12 hours at room temperature prior to work up, even the *exo* product **4** decomposes. The major monomeric product observed from this decomposition process is the unexpected pyrrolo[3,4-*e*]isoindole-1,3,6,8-(2*H*,7*H*)-tetrone derivative **7**, isolated in 12% yield. Scheme 2 shows a possible pathway for its formation. In contrast, a more expected hydrolysis of the imide group resulting from the strained bicyclic ring system of **4** is not observed in the presence of DMTHP under the reaction conditions described. This reaction can be observed with excess bases and water, for example **4** gives rise to the cyclopropane hydrolysis product **8** in the presence of 1,1,3,3-tetramethylguanidine (Scheme 3). The structures of **7** and **8** have been confirmed by X-ray crystallography.

† It is possible that if the kinetics of equilibrium between the *exo* and *endo* products, **4** and **5**, are extremely rapid, under the conditions of experimentation described, any *endo* **5** initially formed will be transformed predominantly to *exo* **4**.

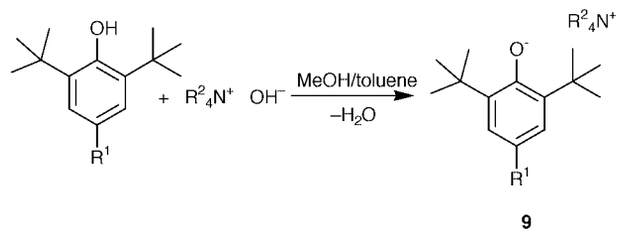


Scheme 1



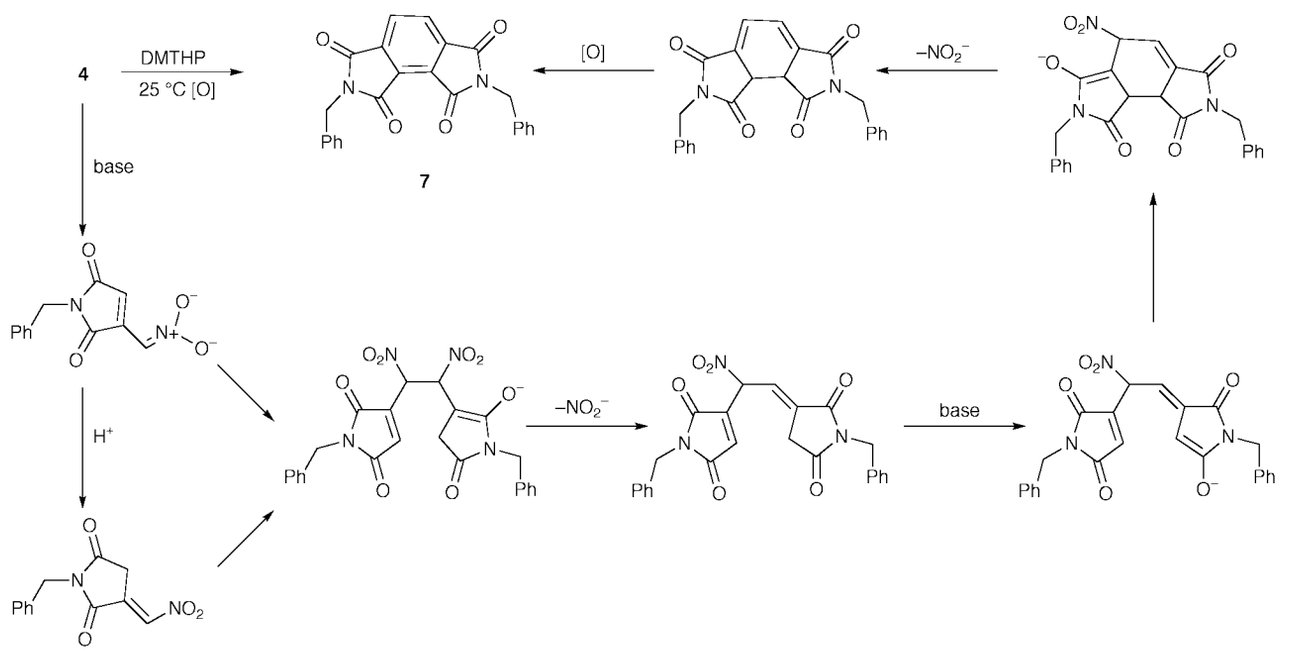
Scheme 3

Among anionic bases for the reaction of **2** with **3**, alkali metal phenoxides, alkoxides, and bis(trimethylsilyl)amides give lower yields of **4** than DMTHP. Considering that a non-associating cation might be beneficial, novel tetraalkylammonium 2,6-di-*tert*-butylphenoxide bases **9** were tested. These were prepared by combining the corresponding phenol and tetraalkylammonium hydroxide in methanol–toluene with azeotropic removal of water (Scheme 4). Tetrabutylammonium



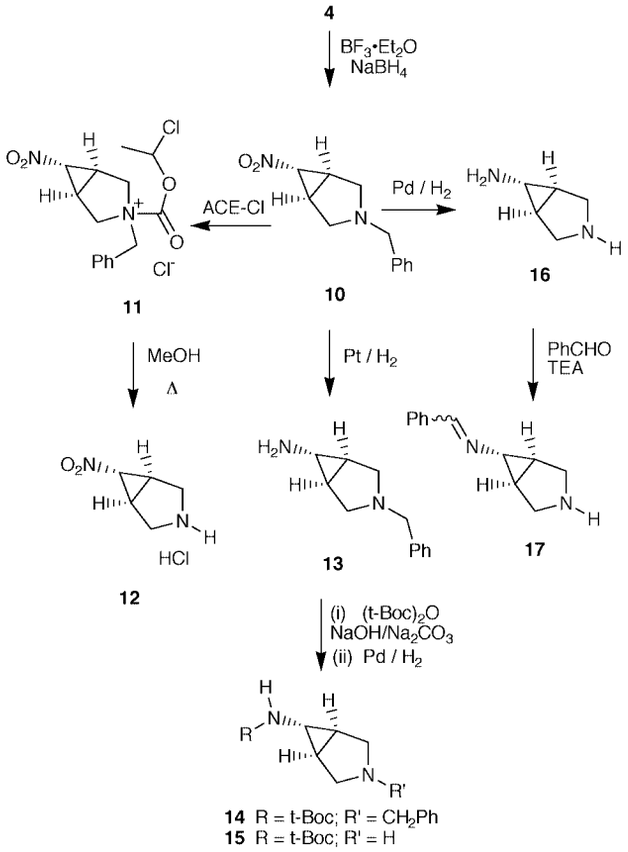
Scheme 4

2,6-di-*tert*-butylphenoxide **9** (R^1 = Bu, R^2 = H) gave 42–49% yields of **4** when used as base. Similar results have been obtained using quaternary ammonium fluoride salts.[7]



Scheme 2

Reduction of **4** with diborane[8] generated from sodium borohydride and boron trifluoride–diethyl ether in THF yields **10**, the key intermediate[9] in nearly quantitative yield (Scheme 5).



Scheme 5

This intermediate can be used to synthesize a number of derivatives (**12**, **15**, **16** and **17**) by four synthetic pathways that can be used to access trovafloxacin. The nitro compound **10** can be selectively reduced to the amine **13** using hydrogen at about 3–4 atm pressure, 50 °C in the presence of platinum on carbon catalyst. The reduction can also be carried out with zinc–hydrochloric acid or Raney nickel–hydrazine,[3] but the catalytic platinum reduction is most convenient. Products of cyclopropane ring opening are found in the reaction mixture using these reagents. When **13** is produced by the Pt catalyst method it can be used in synthesis without purification. Pure **13** can be induced to crystallize, but not readily and often remains as an oil. It is most readily purified and isolated in a crystalline form as the mono-mesylate salt from propan-2-ol, by treatment with an equivalent of methanesulfonic acid. Primary amine **13** is protected with a *tert*-butyloxycarbonyl (t-Boc) group introduced using di-*tert*-butyl dicarbonate (t-Boc anhydride) under Schotten–Baumann conditions to yield **14**. Compound **14** is readily converted to the corresponding secondary amine **15** by reductive removal of the *N*-benzyl function with hydrogen in the presence of palladium on carbon catalyst.

Reduction of **10** with hydrogen in the presence of palladium on carbon catalyst leads to the formation of the diamine **16**, which can be selectively protected on the primary amine by forming the imine **17** as a *syn* and *anti* mixture. The benzylidene functionality is introduced by refluxing **16** with benzaldehyde and triethylamine (TEA) in propan-2-ol. Both **16** and **17** are useful in further synthesis.

The *N*-benzyl group attached to **10** can be removed using α-chloroethyl chloroformate[10] (ACE-Cl) to form the intermediate **11**; refluxing in methanol yields the hydrochloride salt **12**. Single crystal X-ray data have been obtained on the hydrochloride salt of **12**, Fig. 1a, illustrating the stereochemistry of

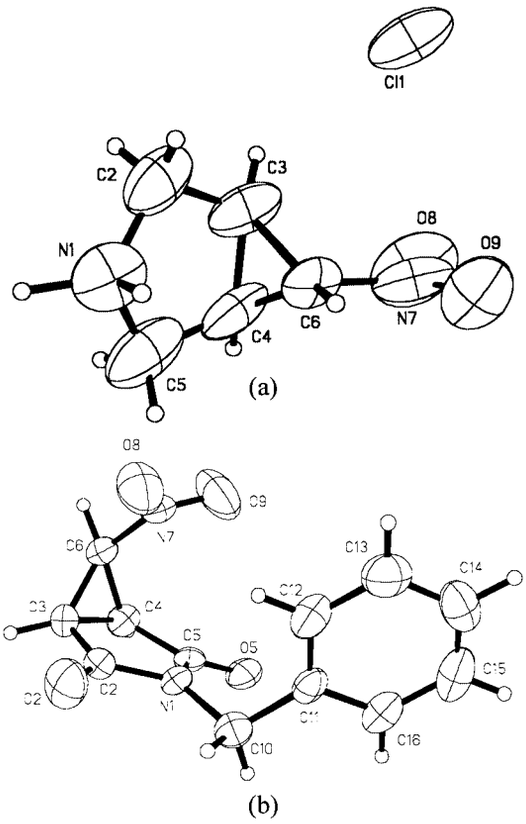


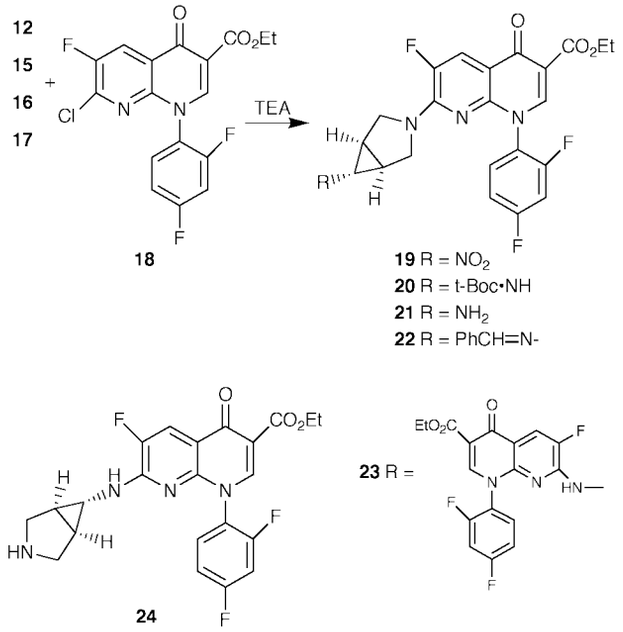
Fig. 1 (a) X-Ray derived molecular structure of **12** showing orientation of *exo* nitro group (atoms N7,O8,O9) and conformation of 3-azabicyclo[3.1.0]hexane ring system in its crystalline lattice. (b) X-Ray derived molecular structure of **5** showing orientation of *endo* nitro group in 2,4-dioxo-3-azabicyclo[3.1.0]hexane ring system in its crystalline lattice.

the compound. Interestingly, the plane of the nitro group atoms is nearly orthogonal to the plane of the cyclopropane ring. This is in contrast to **5** in which the *endo* nitro group is rotated 90° relative to the *exo* nitro group in **12** and is periplanar to the pyrrolidine ring.

Naphthyridone[11] **18** contains a reactive chlorine substituent at the C-7 position which is easily displaced by nucleophiles such as secondary amines. The 3-azabicyclo[3.1.0]hexane intermediates **12**, **15**, **16** and **17** can be coupled with **18** in the presence of TEA to yield a series of intermediates **19**–**22** (Scheme 6) in high yield which can be readily converted into trovafloxacin also in high yield.

The nitro compound **19** is reduced to amine **21** using Raney nickel–hydrazine, in 87% yield.[12] Raney nickel–hydrogen or zinc–methanesulfonic acid can be used also, but the yields are lower. The Boc and ethyl ester protecting groups from **20** are removed with methanesulfonic acid to yield trovafloxacin as its mesylate salt, directly. Interestingly, the conditions of the reaction can reverse the rate at which the two protecting groups are removed. Typically if methanesulfonic acid is in a modest excess with respect to **20** (mole ratio 3 : 1) and the reaction is carried out at reflux in THF–water 1 : 1 reaction monitoring by HPLC shows that the Boc group is lost first forming ethyl ester **21** as an intermediate. In contrast when the reaction is carried out under similar conditions, except that the THF : water ratio is adjusted to 9 : 1, then the rate of loss of the ethyl ester protecting group is significantly accelerated and the Boc-acid **25** is the predominant intermediate observed during reaction monitoring by HPLC.‡

‡ Compound **25** was independently synthesized by treating trovafloxacin mesylate salt with di-*tert*-butyl dicarbonate in the presence of triethylamine, for the HPLC study.



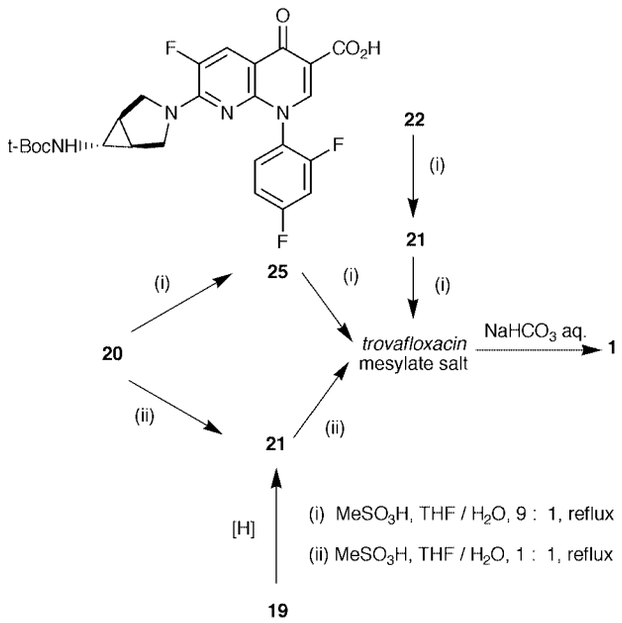
Scheme 6

Imines derived from (1α,5α,6α)-6-amino-3-azabicyclo[3.1.0]-hexane such as **17**, mentioned earlier, can be coupled with the 7-chloronaphthyridone **18** to yield the imine **22** which is very labile and and when treated with THF–water 1:1 at reflux produces trovafloxacin mesylate directly in 70% yield (Scheme 6). Trovafloxacin ethyl ester, **21**, is observed as an intermediate by HPLC, and forms readily during the initial stages of reaction.

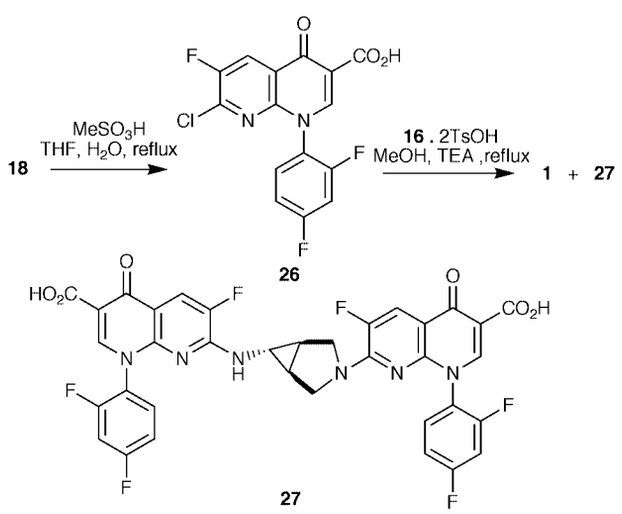
Perhaps most surprising is the coupling reaction of the potentially bidentate intermediate **16** with **18**, to yield mainly trovafloxacin ethyl ester **21**. Intermediate **16** contains a secondary and primary amine, both of which could potentially undergo nucleophilic substitution reactions with the active chlorine atom on the naphthyridone **18**. It is believed that the primary amine functionality is significantly less nucleophilic than would be the case normally, due to the presence of the adjacent banana bonds of the cyclopropyl moiety. A side product, **23**, derived from the coupling of **21** with another molecule of naphthyridone **18**, is formed in the reaction mixture to the extent of 5–10%, but no significant quantities of **24** derived from coupling through the primary amine have been measured.

Trovafloxacin ethyl ester, **21** produced from the coupling of **16** and **18** is converted to trovafloxacin mesylate salt by treatment with aqueous methanesulfonic acid. Various ratios of THF–water at reflux can also be used as the reaction solvent system. This mesylate salt readily yields trovafloxacin zwitterion **1** on treatment with sodium bicarbonate and water of hydration can be removed as an azeotrope with a suitable water imiscible solvent, such as hexane or ethyl acetate. The conversion of coupled intermediates **19**–**22** into **1** is noted in Scheme 7. The use of protecting groups on the side chain and the naphthyridone is not absolutely essential. Zwitterion **1** can also be prepared directly in 75% yield by refluxing the di-tosylate salt of diamine **16** with carboxylic acid **26** in methanol in the presence of TEA. Compound **27**, the carboxylic acid analogue of **23**, is similarly formed as a side product, but most of it remains in the mother liquor and trovafloxacin zwitterion **1** containing only traces of **27** is precipitated from the reaction liquor as it is formed. Carboxylic acid **26** was easily prepared from the ester **18** by refluxing it in THF–water 9:1 in the presence of excess methanesulfonic acid (Scheme 8).

These studies are illustrative of the many approaches that can be used to synthesize this broad spectrum antibacterial agent trovafloxacin, and collectively, help to establish its chemistry and process impurity profile for routine manufacturing.



Scheme 7



Scheme 8

Experimental

Melting points were determined with an Electrothermal 9100 capillary melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) were obtained with a Bruker 360 instrument. Diffuse Reflectance Infrared Fourier Transform spectra (DRIFTS) were recorded on a Nicolet Magna IR Spectrometer 550. GC/MS were completed on a Hewlett Packard 5890 Series II Gas Chromatograph with a Hewlett Packard 5971 Series Mass Selective Detector. Column chromatography was performed on Scientific Adsorbents Inc. silica gel (63–200 mesh). Thin-layer chromatography (TLC) was run on E. Merck glass plates silica gel 60 F_{254}, 250 μm layer thickness with detection by 254 nm UV light. Microanalysis was performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY. Solvents were used as supplied without further purification or drying, except where noted. Hydrogenations were carried out in a standard Parr shaker apparatus. Platinum and nickel catalysts were purchased from Precious Metal Corp., Serverville, TN, USA and palladium catalysts from Engelhard, Senaca, SC, USA.

Bromonitromethane was purchased from Great Lakes Chemical Co., West Lafayette, IN, USA. *N*-Benzylmaleimide was made using the method of Arnold *et al.*[13] Ethyl 7-chloro-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyr-

idine-3-carboxylate, **18**, was purchased from Abbot Laboratories, Chicago, IL. 1,2-Dimethyl-1,4,5,6-tetrahydropyrimidine was obtained from Pfizer Ltd., Sandwich, England. Trovafloxacin is the WHO approved name for (1α,5α,6α)-7-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid zwitterion.

(1α,5α,6α)-3-Benzyl-6-nitro-2,4-dioxo-3-azabicyclo[3.1.0]-hexane, 4

(a) Using DMTHP. *N*-Benzylmaleimide (500 g, 2.67 mol), 90% bromonitromethane (831 g, 5.34 mol), powdered molecular sieves, 200 mesh (2020 g) and toluene (12 dm^3) were stirred under nitrogen at −10 °C. 1,2-Dimethyl-1,4,5,6-tetrahydropyrimidine (616 g, 5.49 mol) was added slowly over about 3 hours maintaining the reaction temperature at <−8 °C throughout the addition. After completion of the addition the reaction mixture was stirred for 1.5 h at 25 °C, filtered under a nitrogen atmosphere in a sealed pressure filter to remove sieves and tar, and the sieves washed with toluene (2 dm^3). The combined filtrates were washed with 2 M dilute hydrochloric acid (3 × 750 cm^3), carbon treated (50 g) at 70 °C, 1 h, filtered, concentrated, and triturated with propan-2-ol (~4 dm^3) to obtain crystals of **4** (223 g, 34%), mp 116–118 °C (Found: C, 58.2; H, 4.1; N, 11.3. $C_{12}H_{10}N_2O_4$ requires C, 58.5; H, 4.1; N, 11.4%); *m*/*z* 246 (M^+), 200 ($M^+ - NO_2$, 100%); δ_H(300 MHz; $CDCl_3$) 7.3 (m, 5H, Ph), 4.54 (s, 2H, benzylic), 4.45 (s, 1H, 6β), 3.35 (s, 2H, 3-ring). This process has been carried out at industrial scale.

(b) Using 9 (where R^1 = H, R^2 = Bu). A slurry of tetrabutylammonium 2,6-di-*tert*-butylphenoxide, **9** (33.58 g, 75 mmol) in dry toluene (450 cm^3) was added to a stirred mixture of *N*-benzylmaleimide (8.77 g, 47 mmol), bromonitromethane (4.25 cm^3, 61 mmol) and powdered 4 Å molecular sieves (30 g) in dry toluene (30 cm^3) under nitrogen at −19 °C over 1.5 h. After stirring for 1 h at −19 °C, the reaction mixture was warmed to 0 °C, filtered using filter aid, stirred with cold 2 M dilute hydrochloric acid (250 cm^3), and filtered again using filter aid. The organic layer was washed with water and brine, treated with activated charcoal, and concentrated to a semisolid (~23 g) which was recrystallized from toluene–propan-2-ol yielding **4** (4.93 g, 43%), mp 116.5–117 °C. Analytical data as noted above.

Tetra-*n*-butylammonium 2,6-di-*tert*-butylphenoxide, 9 (where R^1 = H, R^2 = Bu)

A solution of 2,6-di-*tert*-butylphenol (22.69 g, 110 mmol) in toluene (10 cm^3) was treated with a 1 M solution of tetrabutylammonium hydroxide in methanol (100 cm^3, 100 mmol) under nitrogen at ambient temperature. The resultant dark green solution was stirred for 1 h, concentrated under vacuum to a thick residue, treated with toluene (2 × 100 cm^3) and each aliquot concentrated under vacuum to yield a green solid **9** (52.08 g, 116% weight recovery) which was used in the next step without further purification. δ_H (300 MHz; $CDCl_3$) 7.13 (d, *J* 9 Hz, 2H), 6.77 (t, *J* 9 Hz, 1H), 3.30 (m, 8H), 1.61 (m, 8H), 1.41 (s, 18H), 1.40 (m, 8H), 0.96 (t, *J* 7 Hz, 12H).

(1α,5α,6β)-3-Benzyl-6-nitro-2,4-dioxo-3-azabicyclo[3.1.0]-hexane, 5

Isolation from equilibrium mixture. Compound **4**, (60 g), acetonitrile (400 cm^3) and potassium carbonate were stirred at room temperature for 1 h, the mixture was filtered and glacial acetic acid (1 cm^3) and water (1.6 dm^3) were added to the filtrate to crystallize out **4** which was removed by filtration. The filtrate was extracted with toluene (1.2 dm^3). The organic layer was concentrated to yield a white solid (2.66 g) shown to contain approximately 1 : 1 ratio of **4** and **5**. Fractional crystallization from ethyl acetate–hexane gave crystals of *endo* isomer **5** (288 mg), mp 111–112 °C (Found: C, 58.5; H, 4.1; N, 11.4. $C_{12}H_{10}N_2O_4$ requires C, 58.5; H, 4.1; N, 11.4%); *m*/*z* 246 (M^+), 200 ($M^+ - NO_2$, 100%); δ_H(300 MHz; $CDCl_3$) 7.3 (m, 5H, Ph), 4.82 (t, 1H, 6α), 4.54 (s, 2H, benzylic), 3.08 (d, 2H, 3-ring). The *endo* structure was confirmed by single crystal X-ray analysis.

2,7-Dibenzylpyrrolo[3,4-*e*]isoindole-1,3,6,8(2*H*,7*H*)-tetrone, 7

DMTHP (2.28 cm^3, 20.0 mmol) and toluene (10 cm^3) were added to a stirred mixture of *N*-benzylmaleimide (1.87 g, 10.0 mmol), bromonitromethane (0.56 cm^3, 8.0 mmol), powdered 4 Å molecular sieves (6.74 g) and toluene (50 cm^3) on an ice bath over 7 minutes. The reaction mixture was allowed to slowly warm to room temperature with stirring overnight, filtered through filter aid, washed with 2 M dilute hydrochloric acid, water, and brine, and concentrated to a foam. Flash chromatography on silica (25–40% ethyl acetate–hexane) yielded a yellow solid **7** (0.19 g, 12%), mp 204–206 °C. Recrystallization from dichloromethane–ether yielded yellow needles for X-ray crystallography. δ_H(300 MHz; d_6-DMSO) 8.25 (s, 2H), 7.3 (m, 10H), 4.8 (s, 4H).

Tetramethylguanidinium (1α,2α,3β)-2-(*N*-benzylcarbamoyl)-3-nitrocyclopropanecarboxylate, 8

Tetramethylguanidine (2.6 cm^3, 21 mmol) was added to a slurry of **4** (0.5 g, 2.1 mmol) in toluene (5 cm^3). After stirring for 2 days at room temperature a solid was isolated by filtration to yield **8** (0.665 g, 83%). A portion was recrystallized from ethanol–ethyl acetate yielding fine white needles for X-ray crystallography. δ_H(300 MHz; d_6-DMSO) 9.95 (t, 1H), 8.05 (s, 2H), 7.28 (m, 5H), 4.90 (t, 1H), 4.25 (d, 2H), 2.90 (s, 12H), 2.75 (dd, 1H), 2.60 (dd, 1H).

(1α,5α,6α)-3-Benzyl-6-nitro-3-azabicyclo[3.1.0]hexane, 10

Tetrahydrofuran (350 cm^3), sodium borohydride (14.1 g, mmol) and **4** (35.0 g, mmol) were stirred under nitrogen for 0.25 h and then treated dropwise with boron trifluoride–THF complex containing 21.5% BF_3 (44.9 cm^3) so that the exotherm was controlled to <40 °C. After addition was completed the reaction mixture was stirred for 3 h at 40 °C, quenched slowly with water–THF 1 : 1 (70 cm^3) to avoid excessive foaming and stirred for 0.5 h at 50 °C to ensure the quench of unreacted diborane generated *in situ* was completed. The quench formed a salt slurry which was filtered and washed with THF (140 cm^3), the combined filtrate was partially concentrated, diluted with water (350 cm^3) and further concentrated to remove most of the THF and extracted with ethyl acetate (140 cm^3). The ethyl acetate was concentrated to a clear product oil **10** (30.6 g, 97%). Elemental analysis obtained from mesylate salt (Found: C, 49.8; H, 6.0; N, 9.1; S, 10.2. $C_{12}H_{14}N_2O_2 \cdot CH_4O_3S$ requires C, 49.7; H, 5.8; N, 8.9; S, 10.2%); *m*/*z* 218 (M^+); δ_H(300 MHz; $CDCl_3$) 7.3 (m, 5H, Ph), 4.63 (s, 1H, 6β), 3.6 (s, 2H, benzylic), 3.14 (d, 2H, 5-ring), 2.51 (m, 2H, 3-ring).

3-Azabicyclo[3.1.0]hexane derivatives derived from 10

(1α,5α,6α)-6-Nitro-3-azabicyclo[3.1.0]hexane hydrochloride, 12. Compound **10** (25.1 g, 115 mmol) and 1,2-dichloroethane (115 cm^3) were cooled to 0–5 °C and treated dropwise with 1-chloroethyl chloroformate (25.3 g, 177 mmol) over 20 minutes. The reaction mixture was warmed to 50–55 °C for 2–3 h, and concentrated under vacuum to give a black residue. The residue was dissolved in methanol (100 cm^3) and heated to 55–60 °C for 3 h to yield a slurry, which was cooled to room temperature, stirred for 18 h, treated with concentrated hydrochloric acid (10 cm^3, 115 mmol) and stirred for 1.5 h. The product was isolated by filtration, washed with chloroform (25 cm^3) and dried under vacuum to yield **12** (9.99 g, 53%). White crystals from water, mp 215–216 °C (decomp.) (Found: C, 36.4; H, 5.35; Cl, 21.9; N,

16.8. $C_5H_8N_2O_2$·HCl requires C, 36.5; H, 5.5; Cl, 21.5; N, 17.0%); *m/z* 128 ($M^+ + 1$); δ_H(300 MHz; $CDCl_3$) 9.78 (br s, 2H), 4.95 (t, *J* 2.0 Hz, 1H), 3.51 (d, *J* 12.1 Hz, 2H), 3.41 (dt, *J* 1.8 and 12.8 Hz, 2H), 2.87 (s, 2H). Structure confirmed by single crystal X-ray analysis.

(1α,5α,6α)-3-Benzyl-6-amino-3-azabicyclo[3.1.0]hexane, 13. (1α,5α,6α)-3-Benzyl-6-nitro-3-azabicyclo[3.1.0]hexane, **10** (25.05 g, 114.8 mmol), 5% platinum on carbon catalyst, water content 66% (10.02 g), and methanol (250 cm^3) were hydrogenated in a Parr apparatus at 50 °C, 3.5 atm, 24 h. The catalyst was filtered off and the filtrate concentrated under vacuum to obtain a product oil, **13** (20.24 g, 93.6%), purity GC 81.5%. White crystals can be obtained from hexane, mp 99–102 °C (hexanes). δ_H(300 MHz; $CDCl_3$) 7.31–7.18 (m, 5H), 3.53 (s, 2H), 2.94 (d, *J* 8.8 Hz, 2H), 2.64 (s, 1H), 2.36 (dm, *J* 8.6 Hz, 2H), 1.53 (s, 2H), 1.32 (dd, *J* 1.9 and 3.3 Hz); δ_C (75.5 MHz; $CDCl_3$) 139.5, 128.5, 128.1, 126.7, 59.2, 54.5, 32.5, 25.8; *m/z* 189 $(M + H)^+$. Elemental analysis obtained on mesylate salt (Found: C, 54.7; H, 7.1; N, 9.75; S, 11.5. $C_{12}H_{16}N_2$·CH_4O_3S requires C, 54.9; H, 7.1; N, 9.85; S, 11.3%).

(1α,5α,6α)-3-Benzyl-6-*tert*-butyloxycarbonylamino-3-azabicyclo[3.1.0]hexane, 14. Ethyl acetate (225 cm^3), di-*tert*-butyl dicarbonate (30.8 g, 141 mmol) and **13** (21.6 g, 115 mmol) were stirred at room temperature and a solution of sodium carbonate (24.7 g, 233 mmol) and sodium hydroxide (9.35 g, 234 mmol) in water (200 cm^3) was added at <30 °C. The two phase reaction mixture was stirred for 3 h at 30 °C then separated and the organic phase concentrated to 25% of its original volume and treated with hexane (150 cm^3). The resultant crystals were isolated by filtration, washed with hexane (50 cm^3) to obtain **14** as white needles (18.4 g, 56%), mp 132–133 °C (EtOAc–hexane) (Found: C, 71.0; H, 8.45; N, 9.8. $C_{17}H_{24}N_2O_2$ requires C, 70.8; H, 8.4; N, 9.7%); *m/z* 289 ($M^+ + 1$); δ_H(300 MHz; $CDCl_3$) 7.29 (m, 5H, Ph), 4.62 (br s, NH), 3.61 (s, 2H benzylic) 3.1 (d, 2H, 5-ring), 2.92 (s, 1H, 6β), 2.50 (d, 2H, 5-ring), 1.56 (s, 2H, 3-ring), 1.4 (s, 9H); ν_{max}(DRIFTS)/cm^{-1} 3370 (NH), 1687 (urethane carbonyl).

(1α,5α,6α)-6-*tert*-Butyloxycarbonylamino-3-azabicyclo[3.1.0]-hexane, 15. Methanol (200 cm^3), catalyst 10% palladium on charcoal containing 55% water (10 g) and **14** (20 g, 101 mmol) were hydrogenated on a Parr apparatus at room temperature overnight, catalyst was filtered off, washed with methanol (20 cm^3) and the combined filtrate concentrated and displaced with cyclohexane (300 cm^3). The resultant crystal slurry was further concentrated to about 100 cm^3 and the product isolated as white crystals of **15** (12.2 g, 89%), mp 119–125 °C (cyclohexane) (Found: C, 60.35; H, 9.3; N, 14.1. $C_{10}H_{18}N_2O_2$ requires C, 60.6; H, 9.15; N, 14.1%); *m/z* 199 ($M^+ + 1$); δ_H(300 MHz; $CDCl_3$) 4.8 (br s, NH), 3.13 (d, 2H, 5-ring), 3.0 (s, NH), 2.9 (d, 2H, 5-ring), 2.29 (s, 1H, 6β), 1.57 (s, 2H, 3-ring), 1.39 (s, 9H); ν_{max}(DRIFTS) cm^{-1} 3321 (NH), 3174 (NH).

(1α,5α,6α)-6-Amino-3-azabicyclo[3.1.0]hexane, 16. *From compound **15**.* (1α,5α,6α)-6-*tert*-Butyloxycarbonylamino-3-azabicyclo[3.1.0]hexane, **15** (15.0 g, 75.8 mmol), methanol (300 cm^3) and toluene-4-sulfonic acid (28.8 g, 151.6 mmol) were heated to reflux for 2 h. The reaction solution was concentrated to a crystal slurry, and the crystals isolated by filtration, washed with methanol and dried under vacuum to yield the di-tosylate salt of **16** (25.6 g, 76%), mp 247–248 °C (methanol) (Found: C, 51.5; H, 6.0; N, 6.3; S, 14.55. $C_5H_{10}N_2$·$C_{14}H_{16}O_6S_2$ requires C, 51.8; H, 5.9; N, 6.3; S, 14.5%); *m/z* 96 ($M^+ - 2$); δ_H(400 MHz; d_6-DMSO) 8.49 (br s, 5H, NH and SO_3H), 7.51 (d, 2H, ABq), 7.12 (d, 2H, ABq), 3.3 (m, 4H 5-ring), 2.6 (s, 1H, 6β), 2.27 (s, 6H, ArMe), 2.11 (s. 2H, 3-ring).

*From compound **10**.* (1α,5α,6α)-3-Benzyl-6-nitro-3-azabicyclo[3.1.0]hexane, **10** (25.2 g, 115.5 mmol), 10% palladium on carbon catalyst, water content 55% (10.0 g), water (125 cm^3) and propan-2-ol (250 cm^3) were hydrogenated in a Parr apparatus at 50 °C, 3.5 atm, 24 h. The catalyst was filtered off and the filtrate concentrated under vacuum to obtain a product oil, **16** (10.4 g, 91.7%), purity GC 83%. Material produced in this way is convenient and satisfactory for direct use in synthesis. Purification by column chromatography on silica gel using $CHCl_3$–CH_3OH–concentrated NH_4OH (55:35:10) yielded a clear oil; *m/z* 96 ($M^+ - 2$); δ_H(300 MHz; d_4-CH_3OH) 4.86 (s, NHs and MeOH), 2.97 (2H, d, *J* 11.4 Hz), 2.77 (2H, dt, *J* 1.4 and 11.4 Hz), 2.06 (1H, t, *J* 2.2 Hz), 1.42 (2H, td, *J* 1.4 and 2.2 Hz); δ_C(75.5 MHz; d_4-CH_3OH) 48.9, 32.5, 27.5.

(1α,5α,6α)-6-Benzylideneamino-3-azabicyclo[3.1.0]hexane, 17. Compound **17** is formed *in situ* as an oil that readily undergoes hydrolysis and is a mixture of *syn* and *anti* isomers. See preparation of **22**. It can be crystallized from propan-2-ol. Its ^1H and ^{13}C NMR were obtained. δ_H(300 MHz; $CDCl_3$) 8.42 (s, 0.8H), 8.33 (s, 0.2H), 7.68–7.64 (m, 1.8H), 7.53 (t, *J* 7.4 Hz, 0.2H), 7.38–7.30 (m, 3H), 3.90 (s, 0.4H), 3.32 (s, 0.8H), 3.20 (d, *J* 9.0 Hz, 0.8H), 3.15 (s, 0.2H), 3.07 (d, *J* 11.2 Hz, 0.2H), 2.94 (d, *J* 9.0 Hz, 0.8H), 2.86 (s, 0.2H), 2.58 (dd, *J* 9.0 and 3.0 Hz, 0.8H), 2.26 (dd, *J* 9.0 and 3.0 Hz, 0.8H), 2.02 (s, 0.4H), 1.90–1.86 (m, 1.8H); δ_C(75.5 MHz; $CDCl_3$) major isomer 157.6, 136.0, 130.0, 128.5, 127.6, 83.1, 51.8, 51.0, 26.6, 26.0.

Coupling reactions

Ethyl (1α,5α,6α)-7-(6-nitro-3-azabicyclo[3.1.0]hexan-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate, 19. Acetonitrile (190 cm^3), **18** (19.07 g, 50 mmol), **12** (9.88 g, 60 mmol), and triethylamine (15.3 g, 151 mmol) were heated to reflux (82 °C) for 6.5 h. The reaction slurry was cooled to room temperature and treated with water (115 cm^3). The resulting product slurry was granulated at 0–5 °C for 1 h. The product was collected by filtration as a white solid, washed with 1:1 MeCN–water (50 cm^3) and dried under vacuum at 40 °C, to yield **19** (21.17 g, 89%), mp 248–249 °C (Found: C, 55.5; H, 3.48; F, 12.0; N, 11.7. $C_{22}H_{17}F_3N_4O_5$ requires C, 55.7; H, 3.6; F, 12.0; N, 11.8%); *m/z* 475 ($M^+ + 1$); δ_H(300 MHz; $CDCl_3$) 8.4 (s, 1H), 8.1 (d, 1H), 7.4 (m, 1H), 7.05 (m, 1H), 4.35 (q, 2H), 4.1 (s, 1H), 3.95 (m, 2H), 3.65 (m, 2H), 2.75 (s, 3H), 1.35 (t, 3H).

Ethyl (1α,5α,6α)-7-(6-*tert*-butyloxycarbonylamino-3-azabicyclo[3.1.0]hexan-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate, 20. Methanol (75 cm^3), **15** (5.5 g, 27.7 mmol), **18** (10.0 g, 26.1 mmol) and triethylamine (4.7 cm^3, 33.7 mmol) were heated to reflux for 1 h. The reaction mixture was cooled to room temperature and white product crystals isolated by filtration, washed with methanol and dried under vacuum to yield **20** (14.2 g, 99%), mp 218–219.5 °C (Found: C, 58.65; H, 5.3; F, 9.6; N, 10.2. $C_{27}H_{27}F_3N_4O_5$·CH_4O requires C, 58.3; H, 5.4; F, 9.9; N, 9.7%); *m/z* 545 ($M^+ + 1$); δ_H(300 MHz; $CDCl_3$) 8.49 (s, 1H), 8.0 (d, 1H), 7.43 (m, 1H), 7.02 (m, 2H), 4.33 (q, 2H), 3.79 (br s, 2H), 3.51 (br s, 2H), 2.56 (br s, 1H), 2.22 (s, 1H, 6β-H), 1.78 (br s, 2H), 1.40 (s, 9H), 1.33 (t, 3H).

Ethyl (1α,5α,6α)-7-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate, Trovafloxacin ethyl ester, 21. *From **16** and **18**.* Methanol (75 cm^3), triethylamine (10 cm^3, 71.7 mmol) and **16** (5.0 g, 51 mmol) were stirred at 50 °C and treated with a slurry of **18** (15.0 g, 39.3 mmol) in methanol (150 cm^3) over 3 h. The reaction mixture was held at 50 °C for 3 h, concentrated, treated with water (150 cm^3), extracted with ethyl acetate (200 cm^3) and washed with 0.1 M dilute hydrochloric acid and water. The organic layer was concentrated to dryness to yield crude trovafloxacin ethyl ester **21** (16.35 g, 93.6%). Crude product

(HPLC 74%) was purified by chromatography using a silica gel column eluted with ethyl acetate and then methanol to yield pure trovafloxacin ethyl ester **21**, *m*/*z* 445 ($M^+ + 1$) (Found: C, 59.4; H, 4.3; N, 12.7; F, 12.5. $C_{22}H_{18}F_3N_4O_3$ requires C, 59.5; H, 4.3; F, 12.8; N, 12.6%); δ_H(300 MHz; $CDCl_3$) 8.35 (s, 1H), 7.8 (d, 1H), 7. 35 (m, 1H), 7.05 (m, 2H), 4.35 (q, 2H), 3.6 (br s, 2H), 3.5 (br s, 2H), 2.05 (s, 1H), 1.57 (m, 2H), 1.51 (s, 2H), 1.39 (t, 3H).

This reaction also forms **23**. This can be formed as a significant product by adjusting the mole ratio of **16**:**18** to 1:2 in the above procedure.

Ethyl (1α,5α,6α)-7-(6-{[6-ethoxycarbonyl-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-amino}-3-azabicyclo[3.1.0]hexan-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate, 23. (Found: C, 58.0; H, 3.6; F, 13.8; N, 10.7. $C_{39}H_{28}F_6N_6O_6{\cdot}H_2O$ requires C, 57.9; H, 3.7; F, 14.1; N, 10.4%); δ_H(300 MHz; d_6-DMSO) 8.53 (s, 1H), 8.47 (s, 1H), 8.16 (br s, 1H), 7.91 (d, *J* 9.0 Hz, 1H), 7.87 (d, *J* 6.9 Hz, 1H), 7.84–7.76 (m, 2H), 7.61 (td, *J* 9.7 and 2.7 Hz, 1H), 7.37–7.32 (m, 1H), 7.22 (br t, *J* 8.6 Hz, 1H), 4.16–4.25 (m, 4H), 3.45 (m, 4H), 2.07 (s, 1H), 1.79 (br s, 2H), 1.23–1.29 (m, 6H); *m*/*z* 791 $(M + H)^+$; ν_{max}(DRIFTS)/cm^{-1} 3325, 3116, 3075, 3060, 2983, 2936, 2919, 2871, 1723, 1694, 1633, 1571, 1550, 1511.

21 From nitro compound, 19. *(a) Zinc–methanesulfonic acid reduction.* Acetonitrile (50 cm^3), water (50 cm^3), **19** (10.0 g, 21.1 mmol) and zinc dust (6.9 g, 105.5 mmol) were treated with methanesulfonic acid (70%, 25.5 cm^3, 241 mmol) resulting in an exotherm to 40 °C. The orange-yellow reaction mixture was warmed to 50–55 °C for 3 h, cooled to room temperature, treated with water (100 cm^3) and filter aid (1 g), and stirred for 0.25 h. The resultant slurry was filtered to give a deep amber solution, basified to pH 10.1 using 50% NaOH, extracted with dichloromethane (250 cm^3) and filtered to remove insolubles. Dichloromethane was removed by evaporation to yield crude trovafloxacin ethyl ester **21** (2.57 g, 27.4%). Crude product was purified by chromatography and analytical data as reported above.

(b) Raney nickel–hydrazine reduction. Tetrahydrofuran (100 cm^3), Raney nickel A-5000 (0.87 g), **19** (2.0 g, 4.22 mmol) and water (100 cm^3) were stirred at 20 °C, a solution of 98% hydrazine (1 ml, ~31.2 mmol) in THF (5 cm^3) and water (5 cm^3) was added slowly at 20–30 °C. The reaction mixture was stirred at 25 °C for 1.5 h, catalyst was removed by filtration and the filtrate concentrated under vacuum to obtain a pale yellow solid, which was treated with ethyl acetate (100 cm^3) and further concentrated to give a slurry. Product was isolated by filtration, washed with water and dried under vacuum to yield **21** (1.64 g, 87%). Analytical data as reported above.

(c) Raney nickel–hydrogen reduction. Tetrahydrofuran (36 cm^3), Raney nickel A-5000 (0.86 g), **19** (2.0g) and water (8 cm^3) were hydrogenated in a Parr apparatus at 3.3 atm, 25 °C for 3 h, catalyst was removed by filtration and the filtrate concentrated under vacuum to dryness to obtain a pale yellow solid. This was treated with ethanol (30 cm^3) at reflux to give a clear solution, on cooling a slurry was obtained. White product was isolated by filtration, washed with water and dried under vacuum to yield **21** (863 mg, 46%). Analytical data as reported above.

Ethyl (1α,5α,6α)-7-(6-benzylideneamino-3-azabicyclo[3.1.0]-hexan-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate, 22. Nitro compound, **10** (30.9 g, 142 mmol), propan-2-ol (310 cm^3), water (30 cm^3), and 10% Pd on carbon, 50% water content (12.3 g) were hydrogenated at 50 psi and 50 °C for 18–24 h in a Parr shaker. The catalyst was filtered off and the pale yellow filtrate was azeotropically distilled at constant volume to remove water. The resulting solution was treated with triethylamine (46 g, 456 mmol) and heated to reflux. Benzaldehyde (15.0 g, 141 mmol) was added dropwise over 15 minutes. The reaction was held at reflux for 4 h to form imine **17** *in situ*. The orange solution was cooled to 40–50 °C, naphthyridine derivative **18** (42.45 g, 111 mmol) and triethylamine (13.1 g, 130 mmol) were added. The reaction slurry was held at reflux for 16–18 h, cooled to 20 °C and stirred for 5 h. The slurry was filtered and product isolated as a white solid to yield **22**, 57.12 g, 75.5% based on **5**, 96.6% based on **18**. White solid recrystallized from acetonitrile, mp 148–155 °C (decomp.) (Found: C, 63.5 ; H, 4.4; F, 10.35; N, 10.7. $C_{29}H_{23}F_3N_4O_3{\cdot}H_2O$ requires C, 63.3; H, 4.6; F, 10.35; N, 10.2%); *m*/*z* 533 $(M^+ + 1)$; δ_H(300 MHz; $CDCl_3$) 8.33 (s, 1H), 8.29 (s, 1H), 7.97 (d, *J* 7.1 Hz, 1H), 7.58–7.61 (m, 2H), 7.46 (td, *J* 5.7 and 8.6 Hz, 1H), 7.31–7.35 (m, 3H), 6.97–7.08 (m, 2H), 4.31 (q, *J* 7.1 Hz, 2H), 3.80 (br s, 2H), 3.64 (br s, 2H), 2.75 (t, *J* 1.8 Hz, 1H), 2.13 (s, 2H), 1.32 (t, *J* 7.1 Hz, 3H); ν_{max}(KBr)/cm^{-1} 1730, 1697, 1632.

Trovafloxacin mesylate salt

From 20. Tetrahydrofuran (125 cm^3), **20** (12.5 g, 23 mmol), and water (125 cm^3) were treated with 97% methanesulfonic acid (5.5 g, 55.5 mmol) and heated to reflux for 17–24 h. The reaction solution was cooled to 45 °C, treated with activated carbon (0.3 g) for 1 h and filtered. The filtrate was concentrated under vacuum to approximately 50% of its original volume to give a white crystal slurry, cooled to 5–10 °C, granulated for 4 h, washed with cold THF, filtered and dried to yield trovafloxacin mesylate (11.8 g, 90%), mp 253–256 °C (decomp.) (Found: C, 49.3; H, 3.75; F, 11.2; N, 11.0; S, 6.3. $C_{20}H_{15}F_3N_4O_3{\cdot}CH_4O_3S$ requires C, 49.2; H, 3.7; F, 11.1; N, 10.9; S, 6.3%); δ_H(300 MHz; d_6-DMSO) 8.85 (s, 1H), 8.17 (br m, 2H), 8.11 (d, 1H), 7.83 (m, 2H), 7.62 (m, 2H), 7.37 (m, 2H), 3.67 (br s, 3H), 2.45 (s, 1H), 2.37 (s, 3H), 2.08 (s, 2H). Trovafloxacin mesylate salt can also be isolated as a monohydrate.

From trovafloxacin ethyl ester, 21. Trovafloxacin ethyl ester **21** (1.54 g, 3.46 mmol) and water (25 cm^3) were treated with methanesulfonic acid (38.4 mmol) for 18 h at 45–50 °C. The reaction mixture was cooled to room temperature and the product was isolated by suction filtration and dried under vacuum to yield trovafloxacin mesylate salt (1.48 g, 83%). Analytical data as reported above.

From imine 22. Tetrahydrofuran (250 cm^3), **22** (25.05 g, 47 mmol), and water (250 cm^3) were treated with 97% methanesulfonic acid (13.3 g, 138 mmol) and heated to reflux for 24 h. The reaction solution was cooled to 45 °C, treated with activated carbon (2.5 g) for 1 h and filtered. The filtrate was concentrated under vacuum to approximately 25% of its original volume to give a white crystal slurry, cooled to 15–25 °C, granulated for 4 h and filtered to yield trovafloxacin mesylate (16.86 g, 70.0%). Analytical data as noted above.

Trovafloxacin zwitterion, 1

From mesylate salt of 1. Trovafloxacin mesylate salt (15.0 g, 29.3 mmol), and water (75 cm^3) were stirred at 50 °C and the pH adjusted to 8.5 by addition of saturated sodium hydrogen carbonate solution (~ 50 cm^3). The resultant slurry was cooled to 25 °C, filtered and the product residue, washed with water (120 cm^3), and the wet cake dried by refluxing in ethyl acetate to remove water azeotropically. It was then dried under vacuum to yield trovafloxacin zwitterion, **1** (11.5 g, 94%), mp 225–228 °C (decomp.) (Found: C, 57.4; H, 3.6; F, 13.9; N, 13.4. $C_{20}H_{15}F_3N_4O_3$ requires C, 57.7; H, 3.6; F, 13.7; N, 13.5%); δ_H(300 MHz; d_6-DMSO) 8.81 (s, 1H), 8.03 (d, *J* 12.7 Hz, 1H), 7.80 (td, *J* 6.0 and 8.7 Hz), 7.63 (m, 1H), 7.35 (tm, *J* 8.6 Hz, 1H), 3.2–3.8 (br m, 4H), 1.92 (s, 1H), 1.53 (s, 2H).

From 16 di-tosylate salt and 26. Carboxylic acid **26** (500 mg, 1.41 mmol), di-tosylate salt of **16** (624 mg, 1.41 mmol), triethyl-

amine (0.6 cm³, 4.23 mmol) and methanol (5 cm³) were refluxed for 16 h. White solid was collected by filtration, refluxed in THF and re-isolated to give **1** (450 mg, 75%). Analytical data as reported above. Compound **27** was isolated from the mother liquor by chromatography. Analytical data for side product **27** reported below.

(1α,5α,6α)-7-(6-*tert*-Butyloxycarbonylamino-3-azabicyclo-[3.1.0]hexan-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 25

Trovafloxacin mesylate salt (15.6 g), triethylamine (5.6 g), tetrahydrofuran (135 cm³), and water (15 cm³) were treated with di-*tert*-butyl dicarbonate (7.6 cm³) over 0.5 h at 25 °C and held for 4 h at 25 °C to obtain a white slurry. The slurry was filtered, the white residue was stirred with water (100 cm³) for 16 h at 25 °C, re-isolated and re-treated. The white solid was dried under vacuum to remove water to yield **25**, mp 234–236 °C (Found: C, 58.0; H, 4.4; N, 10.9; F, 11.35. $C_{25}H_{23}F_3N_4O_5$ requires C, 58.1; H, 4.5; F, 11.0; N, 10.85%); *m*/*z* 517 ($M^+ + 1$); δ_H(300 MHz; $CDCl_3$) 8.55 (s, 1H), 7.92 (d, 2H), 7.35 (m, 1H), 7.04 (m, 2H), 4.1–3.1 (v br s, 2H exchange D_2O), 3.68 (t, 1H, 6β), 3.21 (br s, 2H, 5-ring), 2.13 (br s, 2H, 5-ring), 1.73 (m, 2H, 3-ring), 1.36 (s, 9H).

7-Chloro-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 26

Tetrahydrofuran (450 cm³), water (50 cm³), methanesulfonic acid (127 cm³) and **18** (50 g) were refluxed for 1 h, cooled to 25 °C, isolated product crystals, washed with tetrahydrofuran, and dried under vacuum at 100 °C to obtain **26** (41.3 g, 89%), mp 250 °C (Found: C, 50.4; H, 1.7; Cl, 9.9; F, 16.0; N, 8.0. $C_{15}H_6ClF_3N_2O_3$ requires C, 50.8; H, 1.7; Cl, 10.0; F, 16.1; N, 7.9%); δ_H(300 MHz; d_6-DMSO) 13.9 (s, 1H), 9.09 (s, 1H), 8.77 (d, *J* 7.5 Hz, 1H), 7.86 (td, *J* 5.9 and 8.8 Hz, 1H), 7.66 (ddd, *J* 2.7, 9.0 and 11.8 Hz, 1H), 7.39 (tm, *J* 8.6 Hz, 1H); ν_{max}-(DRIFTS)/cm^{-1} 3130, 3060, 2947, 2885, 2821, 2723, 2637, 2594, 1734, 1641, 1623, 1579, 1544, 1516.

(1α,5α,6α)-7-(6-{[6-Carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]amino}-3-azabicyclo-[3.1.0]hexan-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 27

Side product **27** was obtained from the mother liquor after chromatography as a sesquihydrate (Found: C, 55.2; H, 2.9; F, 15.3; N, 11.0. $C_{35}H_{20}F_6N_6O_6 \cdot 1\frac{1}{2}H_2O$ requires C, 55.2; H, 3.0; F, 15.0; N, 11.0%); δ_H(300 MHz; d_6-DMSO) 14.85 (br s, 2H) 2.85 (s, 1H), 8.80 (s, 1H), 8.56 (br s, 1H), 8.07 (d, *J* 5.7 Hz, 1H), 8.04 (d, *J* 3.6 Hz, 1H), 7.84–7.82 (m, 2H), 7.64 (td, *J* 9.7 and 2.5 Hz, 1H), 7.40–7.36 (m, 2H), 7.25 (br s, 1H), 3.50 (br s, 4H), 2.14 (s, 1H), 1.87 (br s, 2H); *m*/*z* 735 $(M + H)^+$; ν_{max}(DRIFTS)/cm^{-1} 3304, 3064, 2882, 1726, 1631, 1546, 1505.

Crystal data collected for compounds 5, 7, 8 and 12

$C_{12}H_{10}N_2O_4$, **5**, *M* = 246.2, monoclinic, *a* = 6.267(1) Å, *b* = 19.626(3) Å, *c* = 9.565(1) Å, *α* = 90.0°, *β* = 104.94(1)°, *γ* = 90.0°, *V* = 1142.1(3) Å³, space group $P2_1/n$, *Z* = 4, D_x = 1.432 g cm^{-3}, colorless needles, crystal dimensions 0.06 × 0.08 × 0.30 mm, *μ*(Cu-Kα) = 0.927 mm^{-1}.

$C_{24}H_{16}N_2O_4$, **7**, *M* = 396.4, monoclinic, *a* = 4.718(1) Å, *b* = 31.996(5) Å, *c* = 6.432(1) Å, *α* = 90.0°, *β* = 92.15(3)°, *γ* = 90.0°, *V* = 970.3(3) Å³, space group $P2_1$, *Z* = 2, D_x = 1.357 g cm^{-3}, yellow needles, crystal dimensions 0.04 × 0.11 × 0.28 mm, *μ*(Cu-Kα) = 0.769 mm^{-1}.

$C_5H_{14}N_3^+C_{12}H_{11}N_2O_5^-$, **8**, *M* = 380.4, orthorhombic, *a* = 20.135(1) Å, *b* = 9.706(1) Å, *c* = 20.318(4) Å, *α* = 90.0°, *β* = 90.0°, *γ* = 90.0°, *V* = 3970.8(9) Å³, space group *Pbca*, *Z* = 8, D_x = 1.273 g cm^{-3}, colorless prisms, crystal dimensions 0.10 × 0.11 × 0.22 mm, *μ*(Cu-Kα) = 0.792 mm^{-1}.

$C_5H_9N_2O_2^+Cl^-$, **12**, *M* = 164.6, monoclinic, *a* = 8.035(2) Å, *b* = 7.702(2) Å, *c* = 12.185(2) Å, *α* = 90.0°, *β* = 95.25 (3)°, *γ* = 90.0°, *V* = 750.9(3) Å³, space group $P2_1/c$, *Z* = 4, D_x = 1.456 g cm^{-3}, colorless needles, crystal dimensions 0.17 × 0.22 × 0.36 mm, *μ*(Cu-Kα) = 4.075 mm^{-1}.

Data collection and processing

Siemens R3m/v diffractometer, *ω*/2*θ* mode with *ω* scan width = 1.2° plus Kα-separation, *ω*-scan speed 4 deg min^{-1}, graphite monochromated Cu-Kα (*λ* = 1.54178 Å) radiation; for $C_{12}H_{10}N_2O_4$, (**5**), 1175 reflections measured with 892 ($I > 3.0\sigma$), for $C_{24}H_{16}N_2O_4$, (**7**), 1027 reflections measured with 808 ($I > 3.0\sigma$), $C_5H_{14}N_3^+C_{12}H_{11}N_2O_5^-$, (**8**), 2035 reflections measured with 1147 ($I > 3.0\sigma$), for $C_5H_9N_2O_2^+Cl^-$, (**12**), 764 reflections measured with 521 ($I > 3.0\sigma$).

Structure analysis and refinement

Trial structures were obtained using direct methods. These trial structures were refined in a full matrix least-squares fashion ultimately using anisotropic temperature factors for the non-hydrogen atoms. All crystallographic calculations were facilitated by the Siemens SHELXTL PLUS computer programs. The hydrogen positions were calculated wherever possible. Methyl hydrogens and hydrogen on nitrogen were located by difference Fourier techniques and then idealized by calculation. The hydrogen atoms were added to the structure factor calculations but were not refined. The final data fit criteria were as follows: for $C_{12}H_{10}N_2O_4$, (**5**), final difference map, +0.25 to −0.23 e Å^{-3}, *R* = 5.26%, GOF = 1.40; for $C_{31}H_{36}N_2O_3$, (**7**), final difference map, +0.27 to −0.25 e Å^{-3}, *R* = 7.29%, GOF = 1.03; for $C_5H_{14}N_3^+C_{12}H_{11}N_2O_5^-$, (**8**), final difference map, +0.31 to −0.29 e Å^{-3}, *R* = 7.86%, GOF = 1.06; for $C_5H_9N_2O_2^+Cl^-$, (**12**), final difference map, +0.49 to −0.36 e Å^{-3}, *R* = 9.57%, GOF = 1.92.

Full details of the crystallographic results have been deposited with the Cambridge Crystallographic Data Centre. CCDC reference number 207/416.

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