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# A Novel Synthesis of the Pyrazolo[1,5-*a*]quinoline Ring System. New N1-C2 Bridged DNA Gyrase Inhibitors via a Novel Tandem 1,4-Conjugate Addition-Michael [3+2] Annulation Process

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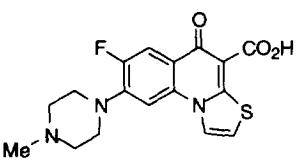
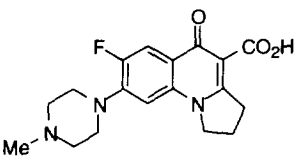
***Abstract***: A novel tandem 1,4-conjugate addition-intramolecular Michael addition [3+2] annulation process for synthesis of the pyrazolo[1,5-*a*]quinoline ring system is described. Reaction of N-methylaminoquinolones with various acrylate derivatives in the presence of NaH leads to pyrazolo[1,5-*a*]quinolines in excellent yield. Transformation of the adducts into novel N1-C2 bridged tricyclic DNA gyrase inhibitors is also described. Copyright © 1996 Elsevier Science Ltd

## INTRODUCTION

Fluoroquinolones are particularly effective antibacterial agents against a large number of common pathogens.[1] However, despite possessing excellent, broad spectrum activity against both Gram positive and Gram negative bacteria, poor activity against clinically significant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) dictates a need to find new structural types.[2] In the N1-C2 bridged tricyclic series, variable biological results due to apparently rigid steric and electronic limitations in the linking moiety have left this particular subset only partially explored.[3] As part of our program, we sought to prepare the novel N1-C2 linked tricyclic pyrazolo[1,5-*a*]quinoline[4,5] series **3** and **4**, modelled upon the well known thiazolo[3,2-*a*]quinoline **1**[3a] and pyrrolo[1,2-*a*]quinoline **2**.[3b]



**1**



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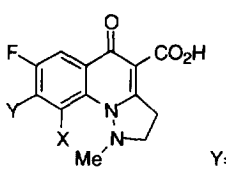
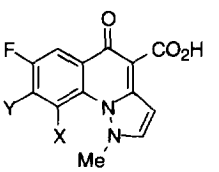


**3**

Y= secondary amine
X= H,F

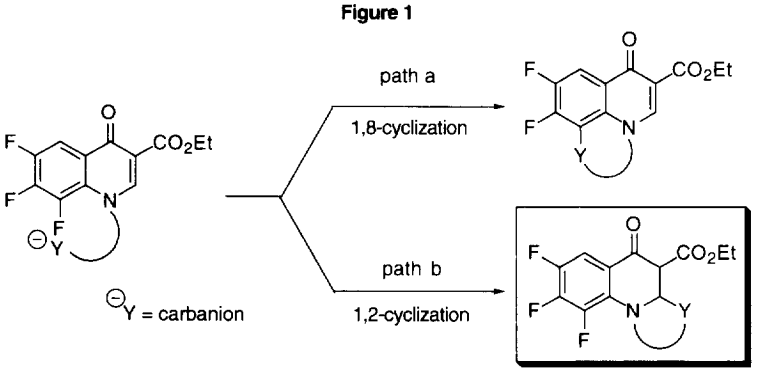


**4**

The most common approach to N1-C2 bridged quinolones involves intramolecular nucleophilic substitution of a suitably functionalized vinylogous amide, obtained by reaction of a benzoyl acetate with an imino ether. Alkylation is usually followed, without isolation of intermediates, by cyclization to obtain the tricyclic system.[3,6] A second major method involves intramolecular Friedel-Crafts cyclization via the Gould-Jacobs reaction.[3a,3d] Attempts to apply such methodology to the synthesis of **3** and **4** were however, unsuccessful and necessitated the design of a new synthesis that would hopefully allow preparation of both series from a common intermediate.

In recent studies[7] on the synthesis of novel 1,8-bridged tricyclic quinolones, we reported the first examples of intramolecular arylation reactions of N1-tethered carbon centered nucleophiles to C8 (path a, Figure 1). In one case,[7a] the cyclization precursor was obtained by a Lewis acid-mediated Michael reaction involving a N-methylamino quinolone and di-*tert*-butylmethylenemalonate. As a potential approach to **3** and **4**, we became intrigued by the possibility of a competing intramolecular Michael ring closure to C2 (path b, Figure 1) since such a mode of ring closure, which is poorly represented in the field of quinolones,[4b,7c,8] may lead, by combining inter- and intramolecular Michael reactions, to a very rapid assembly of the requisite skeletal framework.

**Figure 1**

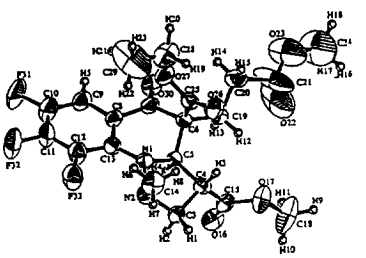


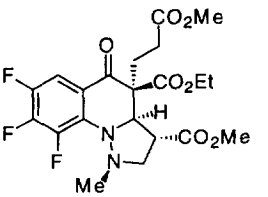

In this paper we wish to disclose full details of the realization of this concept and thereby the development of novel methodology for preparation of the pyrazolo[1,5-*a*]quinoline ring system.[9] Utilization of this methodology led efficiently to intermediates suitable for preparing **3** and **4**. A novel tandem 1,4-conjugate addition-Michael [3+2] annulation process[10,11] involving reaction of N-methylaminoquinolones with simple acrylate derivatives, followed by an oxidation-decarboxylative hydrolysis sequence leads smoothly to the required intermediates for **3**. Dehydrogenation then affords intermediates for **4**. Application of this process to the synthesis of some new tricyclic quinolones as potential antibacterial agents is also described.

## RESULTS AND DISCUSSION

We initially envisaged sequential 1,4-conjugate addition-Michael addition reactions between readily available N-methylaminoquinolones **5** and **6**[12] and simple acrylates such as methyl acrylate. However, attempts to prepare the 1,4-addition products under Lewis acid mediated conditions were unsuccessful, in contrast to our earlier work with di-*tert*-butyl methylenemalonate. Turning to basic conditions, similarly, no reaction occurred in the presence of triethylamine at reflux in 1,2-dichloroethane. However, in the presence of

DBU, amine **5** reacted slowly with methyl acrylate at room temperature to afford low yields (12-26%) of a 1:1 adduct, assigned structure **8a**, as a mixture of isomers **8a'**(trace) and **8a"**(major), and not the expected simple addition product. The major product in all cases was a single diastereoisomer of a 1:2 adduct, that was assigned the structure **7** on the basis of spectroscopic and crystallographic analysis. Using 3 equivalents of the acrylate gave **7** as the only product in 70% yield. The formation of **7** as the sole product can be rationalized on the basis that the initial 1,4-conjugate addition is followed by facile intramolecular Michael reaction to afford **8a** and is then followed by a further Michael reaction from the least hindered face to give the 1:2 adduct.

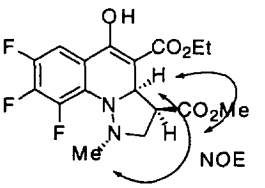




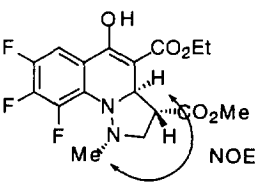

7

**Figure 2:** ORTEP drawing (40%-ellipsoids) of **7** with crystallographic numbering scheme. Selected bond lengths (Å), bond angles (deg), and torsion angles (deg): N(1)-N(2)=1.463(7), N(2)-C(14)=1.48(1), N(2)-C(3)=1.482(9), C(3)-C(4)=1.526(9), C(4)-C(5)=1.524(9); N(1)-N(2)-C(3)=102.2(5), N(1)-N(2)-C)14)=107.4(6), N(2)-N(1)-C(5)=112.6(6), N(1)-C(5)-C(4)=103.0(6), C(3)-C)4)-C(5)=100.3(6); C(13)-N(1)-N(2)-C(14)=-101.7(8), C(5)-N(1)-N(2)-C(14)=113.7(7), N(1)-C(5)-C(4)-C(3)=34.1(7), C(3)-C(4)-C(5)-C(6)=154.9(7), N(2)-N(1)-C(13)-C(12)=16(1).

NaH proved to be a more suitable choice of base. The 1:1 adduct could be obtained exclusively by simply treating a mixture of the amine and acrylate in DMF at 0°C with NaH in a single portion. Work-up gave the tricyclic adduct **8a** in 92% yield. $^1$H NMR analysis of the adduct revealed an 8:1 mixture of diastereoisomers. Using the same conditions, adducts **8b** and **8c** were obtained in 97 and 88% yields respectively from the appropriate amine and *tert*-butyl acrylate. Assignment of the relative stereochemistry of the major and minor isomers of **8a** could be achieved by $^1$H-$^1$H NOESY at 500 MHz, as shown below. The major isomer had the structure **8a'**, whist the minor isomer is represented by **8a"**. The observed relative stereochemistry of the major isomer in this tandem 1,4-conjugate addition-Michael annulation reaction indicates that after the initial intermolecular addition, the resulting nucleophile attacks the β-position of the enone moiety so that steric interaction between the β-hydrogen and methoxycarbonyl group is minimized leading to the endo-orientation for the ester group. In the DBU experiments that led only to **7**, equilibration of the major (kinetic adduct) **8a'** to the thermodynamic product **8a"**, presumably accounts for the observed stereochemistry, however, at this stage we cannot rule out an equilibration after the second alkylation.[13,14]




**8a'** Major Isomer



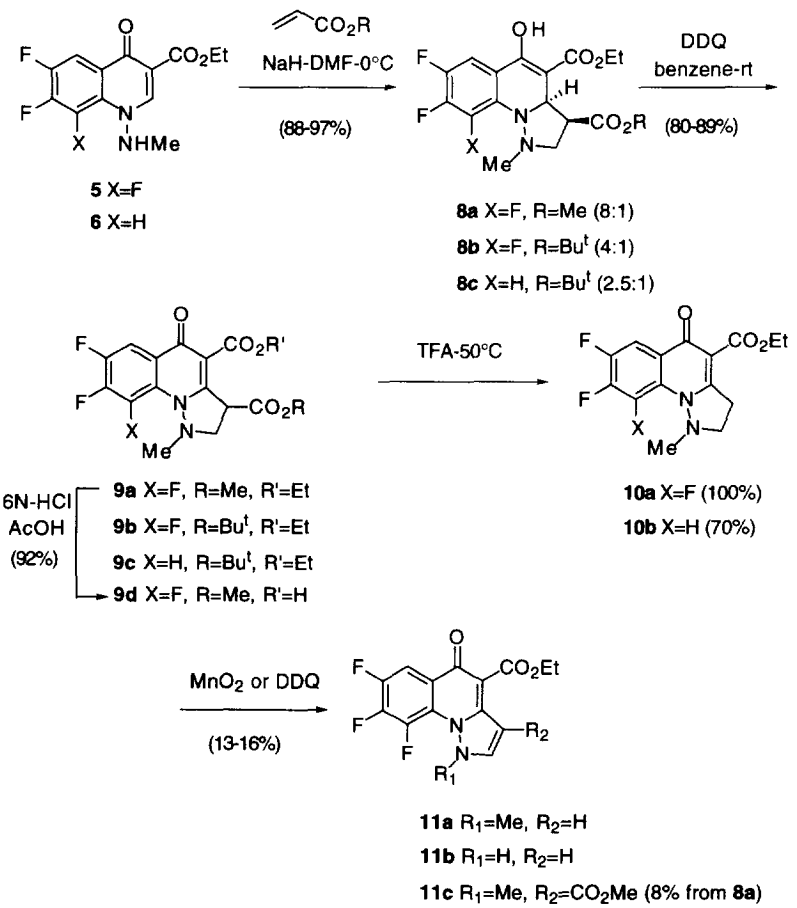

**8a"** Minor Isomer

Elaboration of [3+2] adducts **8a-c** to intermediates suitable for preparation of novel gyrase inhibitors required (a) regeneration of the oxoquinoline moiety and (b) decarboxylative hydrolysis of the 3-ester groups. Initial attempts to effect oxidation of **8a** to regenerate the oxoquinoline moiety[15] employed activated $MnO_2$ in

acetone at room temperature and produced desired **9a** in 38% isolated yield, along with 8% of an over-oxidized material identified as pyrazolo[1,5-*a*]quinoline **11c**, obtained from **9a** by dehydrogenation of the 2,3-bond. Performing the reaction at reflux led only to 14% of the by-product and none of desired **9a**. Controlled oxidation with a single equivalent of the more powerful reagent DDQ led to better results; **9a** was obtained in 82% yield after only 30 minutes at room temperature. DDQ oxidation was similarly effective in the case of **8b** and **8c**, producing **9b** and **9c** in 80 and 89% yields respectively. Compounds **9a-c** existed as 2:1 mixtures of stereoisomers in chloroform solution as shown by NMR (see Experimental Section).

Turning attention to producing intermediates suitable for preparation of **3** and **4**, we envisaged a chemoselective hydrolysis of the 3-ester moiety followed by decarboxylation of the thus produced vinylogous malonate derivative. In the event, treatment of **9a** with 6N-HCl in acetic acid at 110°C gave an unexpected result. The only product (92%) was ester **9d** in which only the ethyl ester had been hydrolyzed. Hydrolysis of *tert*-butyl esters **9b** and **9c** was however successful using trifluoroacetic acid. Hydrolysis occurred smoothly at room temperature however, decarboxylation was relatively slow at ambient temperature thus short heating at 50°C served to complete this hydrolysis-decarboxylation sequence. Key tricycles **10a** and **10b** were thus obtained in 100% and 70% yields respectively.

**Scheme 1**

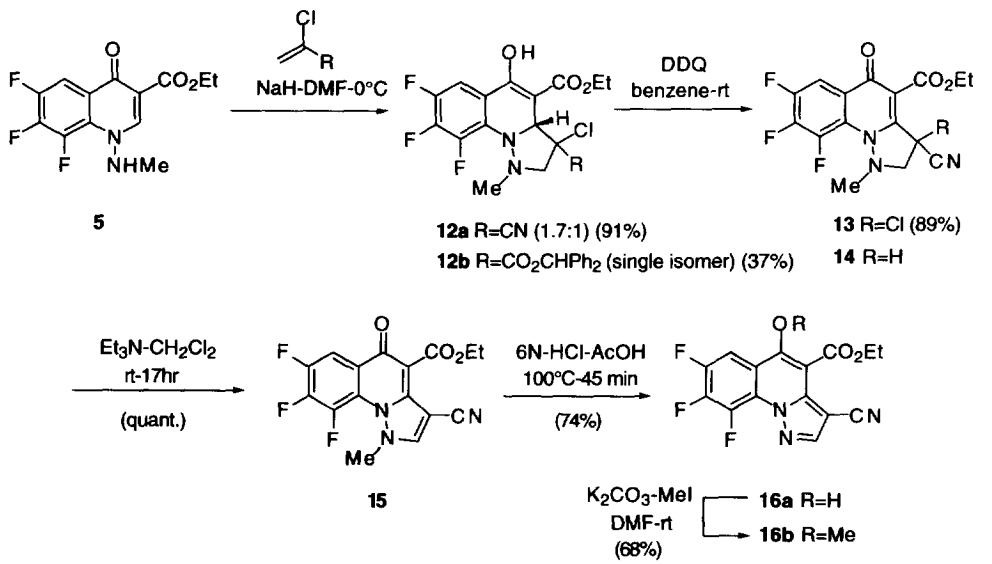


Oxidation of **10a** was effective for producing **11a**, an intermediate suitable for dihydro derivatives **4**. Using DDQ in acetone at reflux produced **11a** (13%) and a small amount of N-demethylated derivative **11b** (2%),[16] along with recovered **10a** (27%). The best conditions involved reaction with $MnO_2$ in toluene at reflux for 25 hours. **11a** was obtained in 28% yield (based on recovered **10a**, 16% isolated). Spectral analysis of **11a** showed two 1-proton doublets at δ 7.62 and 7.43 ($J$ = 3.7 Hz) for the olefin hydrogens. The N-methyl group appeared as a 3-proton doublet at δ 3.57 ($J$ = 2.8 Hz) due to long-range $^{19}$F-coupling. This contrasts with δ 2.83 (s) for **10a**. Additionally, the $^{13}$C NMR signal for the N-methyl carbon appeared at 43.0 ppm as a doublet ($J$ = 22 Hz).

An alternative method for introduction of a double bond into these tricycles was also examined. Selection of a 2-chloro acrylate derivative such as 2-chloroacrylonitrile led, after tandem 1,4-conjugate addition-Michael reaction and DDQ oxidation to **13** in high yield. Exposure of **13** to base (DBU) in $CH_2Cl_2$ at room temperature gave dihydro compound **15** in 40% yield along with 26% of the reduced derivative **14**.[17] In contrast, use of triethylamine led to a quantitative yield of **15**, although reaction was somewhat slow (17 h compared to 10 min for DBU). Like **10a**, compound **15** also displayed a 3-proton doublet at δ 3.90 ($J$ = 5.9 Hz) for the N-methyl group due to long range coupling with the C9-F atom. Employing diphenylmethyl-2-chloroacrylate (prepared from 2-chloroacrylic acid and diphenyldiazomethane, see Experimental Section) in the [3+2] annulation led to 37% of a single diastereoisomer of **12b**. The conventional 1,4-conjugate addition product was the major product (42%) in this case, indicating steric limitations to this process.[18]

Attempts to convert **15** to novel DNA gyrase inhibitors by reaction with secondary amines gave intractable mixtures that contained N-demethylated derivative **16a**. Interestingly, **16a** was the only product obtained when acidic conditions were employed in an attempted hydrolysis of the 4-ester group (45 min, reflux, 74%). Extended reaction times (16 h, reflux), intended to convert **16a** to a mono or diacid led only to unchanged **16a** (80%). An alkylation of **16a** intended to regenerate **15**, returned only the *O*-methyl derivative **16b**(68%).

**Scheme 2**




**5**

**12a** R=CN (1.7:1) (91%)
**12b** R=$CO_2CHPh_2$ (single isomer) (37%)

**13** R=Cl (89%)
**14** R=H

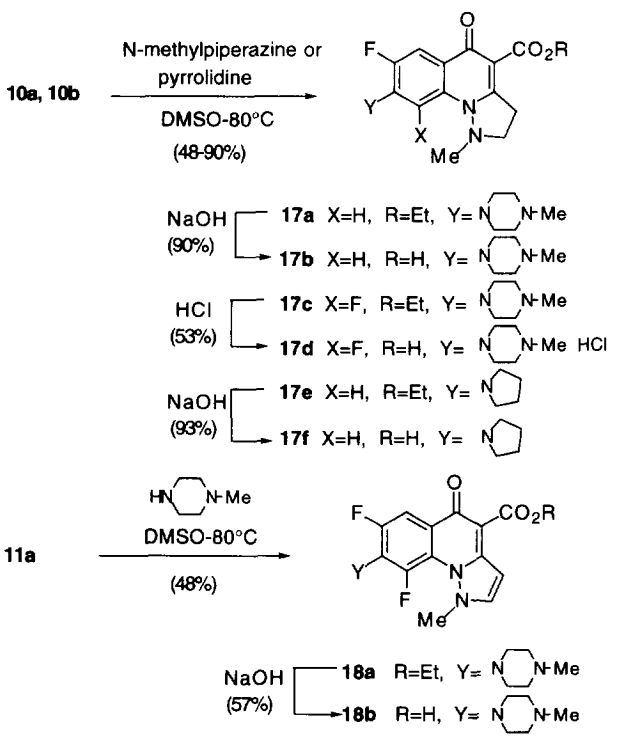
**15**

**16a** R=H
**16b** R=Me

**Synthesis of Novel DNA Gyrase Inhibitors.**

Illustration of the utility of these novel tricyclic quinolones for the preparation of the potential DNA gyrase inhibitors **3** and **4** was readily demonstrated. Compounds **10a**, **10b**, and **11a** reacted smoothly with typical secondary amines such as N-methylpiperazine or pyrrolidine in DMSO at 110°C to give exclusive displacement of the 8-fluorine to yield the derivatives **17a**, **17c**, **17e**, and **18a** in 48-90% yields (Scheme 3). Confirmation of the position of substitution was evident from inspection of $^1H$-$^{19}F$ coupling constants. 7,9-Difluoro compounds **17c** and **18a** showed signals for the C6-H at δ 7.64-7.74 as dd ($J_{ortho}$ = 12.3 Hz, $J_{para}$ = 1.7-1.8 Hz). The 7-fluoro compounds **17a** and **17e** showed d at δ 7.61-7.70 ($J_{ortho}$ = 13.5-14.7 Hz) for the C6-H, and at δ 6.58-7.02 ($J_{meta}$ = 7.5-7.8 Hz) for the C9-H. Ester hydrolysis proceeded uneventfully using either acidic or basic conditions. Novel DNA gyrase inhibitors **17b**, **17d**, **17f**, and **18b** were thus obtained in 53-93% yields. Spectroscopic and analytical properties were in accord with the assigned structures, however, pyrrolidine derivative **17f** showed an interesting feature in the $^1H$ NMR spectrum in $CF_3CO_2D$. Only the C6-H (δ 8.08, d, $J$ = 13.4 Hz) was observed; the C9-H was not observed, presumably due to deuterium exchange. The corresponding spectrum in DMSO containing a trace of NaOD showed both protons clearly (C6-H: δ 7.66, d, $J$ = 15 Hz; C9-H: δ 6.56, d, $J$ = 7.9 Hz). *In vitro* antibacterial activity of these new quinolone derivatives[19] indicates that these new derivatives are weak compared to the benchmark quinolone, levofloxacin.[1,2]

**Scheme 3**



**Single Crystal X-Ray Structural Analysis of 11a.**

We reported earlier the single crystal X-ray structure of tetrahydropyrazolo[1,5-*a*]quinoline **10a**.[9] Of particular interest, the N-methyl group was oriented at 90° to the quinoline plane. Since the product of oxidation of **10a**, the dihydro derivative **11a** showed some unexpected long range coupling in the $^{1}H$ and $^{13}C$ NMR spectra for the N-methyl signal, we performed a single crystal X-ray structure determination. Figure 3 shows the ORTEP plot of the obtained structure. Overall, the tricyclic system is essentially planar, with the nitrogen atom of the pyrazole ring (N(2), Fig. 3) distorted slightly from planarity. Of particular note, the N-methyl group is oriented about 45° above the planar tricyclic system. This deviation from planarity is probably the result of steric interaction with the C9-fluorine atom since they have only a 2.71Å separation, compared to 3.01Å for **10a**. This close contact also probably accounts for the difficulty in forcing the oxidation reaction of **10a** to completion and the facile demethylation of **15** and of **11a**.

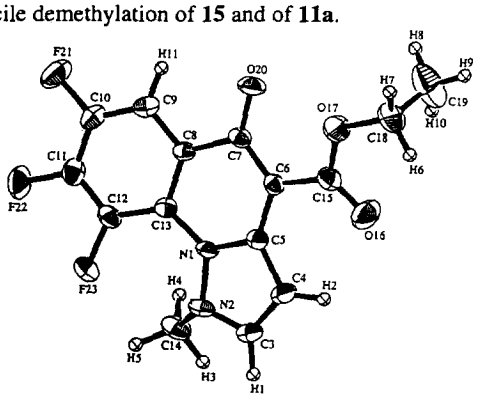



**Figure 3.** ORTEP drawing (41%-ellipsoids) of **11a** with crystallographic numbering scheme. Selected bond lengths (Å), bond angles (deg), and torsion angles (deg): N(1)-N(2)=1.395(3), N(2)-C(14)=1.489(5), N(2)-C(3)=1.352(5), C(3)-C(4)=1.354(5), C(4)-C(5)=1.412(5); N(1)-N(2)-C(3)=105.7(3), N(1)-N(2)-C(14)=120.4(3), N(2)-N(1)-C(5)=109.7(3), N(1)-C(5)-C(4)=105.9(3), C(3)-C(4)-C(5)=107.1(4); C(13)-N(1)-N(2)-C(14)=46.8(5), C(5)-N(1)-N(2)-C(14)=-142.4(3), N(1)-C(5)-C(4)-C(3)=1.0(4), C(3)-C(4)-C(5)-C(6)=-177.4(4), N(2)-N(1)-C(13)-C(12)=7.2(5).

## CONCLUSIONS

In this paper we have described a novel synthetic approach to the preparation of some pyrazolo[1,5-*a*]quinolines. A tandem 1,4-conjugate addition-Michael reaction of N-methylamino quinolones with simple acrylate derivatives leads to a single step [3+2] annulation of the pyrazole ring. Adjustment of oxidation level of the 5-membered ring may be acheived by simple dehydrogenation or by judicious choice of the coupling partner in the first step. Conversion of several of these novel pyrazolo[1,5-*a*]quinolines into new DNA gyrase inhibitors illustrated the usefulness of this methodology. We believe that further applications will lead to a variety of novel heterocycles of potential pharmaceutical interest.

## EXPERIMENTAL SECTION

**General Procedures.**

Melting points were measured on a Thomas-Hoover apparatus in open capilaries and are uncorrected. IR spectra were recorded on a Horiba Spectradesk FT-210 or a Hitachi IR-408 spectrometer as Nujol mulls or KBr disks as indicated. NMR spectra were measured on a Bruker AC200P ($^{1}H$, 200 MHz, $^{13}C$, 50.3 MHz).

$^1$H-$^1$H NOESY spectra were obtained at 500 MHz on a Bruker AMX500. The $^{13}$C NMR spectrum of **7** was recorded at 125.8 MHz on a Bruker AMX500. Chemical shifts are given in parts per million, and tetramethylsilane was used as the internal standard for spectra obtained in DMSO-$d_6$, $CDCl_3$, and $CF_3CO_2D$. DSS was used for spectra run in $D_2O$. All *J* values are given in Hz. Mass spectra were measured on a Hitachi Model M-80 mass spectrometer using EI or CI for ionization. Elemental analyses were carried out on a Perkin Elmer 2400 CHN Elemental Analyzer. Reagents and solvents were used as obtained from commercial suppliers without further purification. Column chromatography was performed using silica-gel, and the progress of reactions was determined by tlc analysis on silica-gel coated glass plates. Visualisation was with UV light (254 nm) or iodine.

**(3RS, 3aRS, 4SR) Ethyl 7,8,9-Trifluoro-3-methoxycarbonyl-4-(2-methoxycarbonyl)ethyl-1-methyl-5-oxo-1,2,3,3a,4,5-hexahydropyrazolo[1,5-*a*]quinoline-4-carboxylate (7).**

A solution of amine **5** (4.00 g, 13.33 mmol) and methyl acrylate (3.44 g, 40.0 mmol) in dichloromethane (40 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.44 g, 16.0 mmol) and the solution allowed to stand 72 h at room temperature then concentrated under vacuum and purified by silica gel chromatography (20% EtOAc-hexane elution) to give a single diasteroisomer of compound **7** (4.40 g, 70%) as a yellow oil that slowly crystallized on standing to give a yellow crystalline solid, mp 88-90°C; $^1$H NMR ($CDCl_3$) δ 7.55-7.47 (m, 1H), 4.43 (br s, 1H), 4.18-4.07 (m, 2H), 3.90-3.70 (m, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 3.58-3.40 (m, 1H), 3.20-3.00 (m, 1H), 2.65 (s, 3H), 2.60-2.15 (m, 4H), 1.18 (t, 3H, *J* = 7.1); $^1$H NMR (DMSO-$d_6$) δ 7.62-7.53 (m, 1H), 4.45 (br s, 1H), 4.09-4.02 (m, 2H), 3.80-3.60 (m, 1H), 3.70 (s, 3H), 3.58 (s, 3H), 3.42 (dd, 1H, *J* = 9.4, 11.8), 3.16 (dd, 1H, *J* = 5.3, 11.8), 2.54 (s, 3H), 2.60-2.00 (m, 4H), 1.08 (t, 3H, *J* = 7.1); $^{13}$C NMR ($CDCl_3$) 193.4 (s), 178.5 (s), 177.4 (s), 173.2 (s), 149.4 (ddd, *J* = 265, 16, 16, C7+C8), 144.8 (br d, *J* ~ 264), 139.8 (s), 118.8 (s), 112.7 (s), 66.3 (s), 63.8 (s), 60.6 (s), 60.0 (s), 54.1 (s), 53.15 (s), 47.0 (s), 44.1 (s), 30.25 (s), 28.8 (s), 14.25 (s); IR(KBr) *inter alia* 1730, 1687, 1637 cm$^{-1}$; MS *m/z* 473 ($MH^+$). Anal. Calcd for $C_{21}H_{23}F_3N_2O_7$: C, 53.39; H, 4.91; N, 5.93. Found: C, 53.36; H, 4.77; N, 5.85.

**Ethyl 7,8,9-Trifluoro-3-methoxycarbonyl-1-methyl-5-oxo-1,2,3,3a,4,5-hexahydropyrazolo[1,5-*a*]quinoline-4-carboxylate (8a).**

A solution of amine **5** (10.0 g, 33.3 mmol) in *N,N*-dimethylformamide (100 mL) at 0°C was treated with methyl acrylate (3.30 mL, 36.7 mmol) followed by sodium hydride (62% dispersion in oil) (1.42 g, 36.7 mmol). After 1 h, further methyl acrylate (0.33 mL) and 62% sodium hydride (0.14 g) were added. After an additional 30 minutes, the reaction was quenched with 1N-hydrochloric acid and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried ($MgSO_4$), evaporated and the residue triturated with isopropyl ether (iPE)-hexane to give the title compound **8a** (11.87 g, 92%) as a yellow powder that was pure enough to be used directly in the next reaction. An analytical sample was obtained by recrystallization from iPE-hexane. Yellow solid. mp 91.5-94°C; $^1$H NMR ($CDCl_3$)(8:1 mixture of stereoisomers) δ (major isomer) 12.50 (s, 1H), 7.24 (ddd, 1H, *J* = 2.2, 8.1, 10.3), 5.02 (d, 1H, *J* = 8), 4.46-4.24 (m, 2H), 3.63 (ddd, 1H, *J* = 6, 8, 8), 3.48 (s, 3H), 3.40 (ddd, 1H, *J* = 11.6, 6, 1.4), 2.97 (dd, 1H, *J* = 8, 11.6), 2.69 (s, 3H), 1.46 (t, 3H, *J* = 7.1); δ (minor isomer, partial) 4.98 (d, 1H, *J* ~ 8), 3.74 (s, 3H), 2.80 (s, 3H), 1.39 (t, 3H, *J* = 7.1). Other signals were obscured by the major isomer; $^1$H NMR (DMSO-$d_6$)(8:1

mixture of stereoisomers) δ (major isomer) 12.41 (s, 1H), 7.28 (ddd, 1H, *J* = 2.2, 8.3, 10.6), 5.01 (d, 1H, *J* = 8), 4.44-4.17 (m, 2H), 3.70 (dt, 1H, *J* = 8, 8), 3.40 (s, 3H), 3.09 (d, 2H, *J* = 8), 2.59 (s, 3H), 1.32 (t, 3H, *J* = 7.1); δ (minor isomer, partial) 4.90 (d, 1H, *J* = 7), 3.67 (s, 3H), 2.67 (s, 3H), 1.22 (t, 3H, *J* = 7.1). Other signals were obscured by the major isomer; IR(KBr) *inter alia* 1732, 1662 $cm^{-1}$; MS *m/z* 386 ($M^+$). Anal. Calcd for $C_{17}H_{17}F_3N_2O_5$: C, 52.85; H, 4.43; N, 7.25. Found: C, 52.96; H, 4.37; N, 7.22. A small sample of the pure major and minor isomers for NOESY experiments were obtained by silica gel chromatography (iPE-hexane, 1:1 elution). $^1H$ NMR signals for the minor isomer were as follows: $^1H$ NMR ($CDCl_3$) δ 12.52 (s, 1H). 7.29 (ddd, 1H, *J* = 2.2, 8, 10.3), 4.98 (d, 1H, *J* = 7.8), 4.48-4.14 (m, 2H), 3.73 (s, 3H), 3.32 (dd, 1H, *J* = 9.5, 10.8), 3.18-3.14 (m, 1H), 2.96 (dd, 1H, *J* = 4.8, 10.8), 2.80 (s, 3H), 1.32 (t, 3H, *J* = 7.1). NOESY experiments were used to assign the stereostructures of the isomers of **8a**. The major isomer displayed cross-peaks between the C3a-H at δ 5.02 and the N-methyl signal at δ 2.69 and the C3-H at δ 3.63. The minor isomer displayed a cross-peak between the N-methyl signal at δ 2.80 and the C3a-H signal at δ 4.98; no cross-peak between the C3a and C3 protons was observed.

The following pyrazolo[1,5-*a*]quinolines were obtained using a similar procedure from the appropriate amine, using the indicated acrylate derivative.

**Ethyl 7,8,9-Trifluoro-3-*tert*-butoxycarbonyl-1-methyl-5-oxo-1,2,3,3a,4,5-hexahydropyrazolo[1,5-*a*]quinoline-4-carboxylate (8b).**

From amine **5** (5.00 g) and *tert*-butylacrylate (2.68 mL). Yield: 6.95 g (97%). Yellow solid. mp 104-105°C(from hexane); $^1H$ NMR ($CDCl_3$)(4:1 mixture of stereoisomers) δ (major isomer) 12.52 (br s, 1H), 7.22 (ddd, 1H, *J* = 2.2, 8.1, 10.3), 4.96 (d, 1H, *J* = 7.7), 4.45-4.30 (m, 2H), 3.51-3.38 (m, 2H), 2.98-2.84 (m, 1H), 2.68 (s, 3H), 1.40 (t, 3H, *J* = 7.1), 1.24 (s, 9H); δ (minor isomer, partial) 12.59 (br s, 1H), 5.07 (d, 1H, *J* = 7), 2.77 (s, 3H), 1.49 (s, 9H), 1.33 (t, 3H, *J* = 7.1). Other signals were obscured by the major isomer; IR(KBr) *inter alia* 1724, 1662, 1595 $cm^{-1}$; MS *m/z* 428 ($M^+$). Anal. Calcd for $C_{20}H_{23}F_3N_2O_5$: C, 56.07; H, 5.41; N, 6.54. Found: C, 55.79; H, 5.34; N, 6.54.

**Ethyl 7,8-Difluoro-3-*tert*-butoxycarbonyl-1-methyl-5-oxo-1,2,3,3a,4,5-hexahydropyrazolo-[1,5-*a*]quinoline-4-carboxylate (8c).**

From amine **6** (5.00 g) and *tert*-butylacrylate (2.72 mL). Yield: 6.43 g (88%). Yellow solid. mp 81-88°C(from iPE-hexane); $^1H$ NMR ($CDCl_3$)(2.5:1 mixture of stereoisomers) δ (major isomer) 12.51 (br s, 1H), 7.33 (dd, 1H, *J* = 8.5, 10.6), 7.13 (dd, 1H, *J* = 7.1, 12.7), 4.92 (d, 1H, *J* = 7.3), 4.40-4.28 (m, 2H), 3.47-3.35 (m, 2H), 2.86-2.74 (m, 1H), 2.61 (s, 3H), 1.39 (t, 3H, *J* = 7.1), 1.20 (s, 9H); δ (minor isomer, partial) 12.59 (br s, 1H), 7.41 (dd, 1H, *J* = 8.5, 10.6), 7.20 (dd, 1H, *J* = 7.2, 12.8), 4.88 (d, 1H, *J* = 7.2), 3.22 (dd, 1H, *J* = 9.6, 11), 2.73 (s, 3H), 1.50 (s, 9H), 1.33 (t, 3H, *J* = 7.1). Other signals were obscured by the major isomer; IR(KBr) *inter alia* 1718, 1662, 1637, 1591 $cm^{-1}$; MS *m/z* 410 ($M^+$). Anal. Calcd for $C_{20}H_{24}F_2N_2O_5$: C, 58.53; H, 5.89; N, 6.82. Found: C, 58.46; H, 5.99; N, 6.68.

**Ethyl 3-Chloro-3-cyano-7,8,9-trifluoro-1-methyl-5-oxo-1,2,3,3a,4,5-hexahydropyrazolo-[1,5-*a*]quinoline-4-carboxylate (12a).**

From amine **5** (1.24 g) and 2-chloroacrylonitrile (438 mg). Yield: 1.46 g (91%). Light yellow solid. mp 104-104.5°C(from hexane); $^1H$ NMR (DMSO-$d_6$)(1.7:1 mixture of stereoisomers) δ 12.70 (br s, 1H), 7.54-7.41

(m, 1H), 5.57 (s, 0.63H), 5.53 (s, 0.37H), 4.46-4.26 (m, 2H), 4.26 and 3.38 (each d, total 1.26H, AB system, $J$ = 13.5), 3.89 and 3.61 (each d, total 0.74H, AB system, $J$ = 14.4), 2.88 and 2.77 (each s, 3H total), 1.35 (t, 3H, $J$ = 7.1); IR(KBr) *inter alia* 1668, 1651, 1597 $cm^{-1}$; MS *m/z* 387, 389 ($M^+$). Anal. Calcd for $C_{16}H_{13}ClF_3N_3O_3$: C, 49.56; H, 3.38; N, 10.84. Found: C, 49.72; H, 3.24; N, 10.65.

**Ethyl 3-Chloro-3-diphenylmethoxycarbonyl-7,8,9-trifluoro-1-methyl-5-oxo-1,2,3,3a,4,5-hexahydropyrazolo[1,5-*a*]quinoline-4-carboxylate (12b).**

From amine **5** (5.00 g) and diphenylmethyl 2-chloroacrylate (5.45 g). The crude product was a ca. 1:1 mixture of two products and was purified by silica gel chromatography (500g, 10:1 hexane-EtOAc elution). The first-eluted material, yield: 3.50 g (37%), light yellow solid, was the title compound as a single isomer. mp 170-172°C(from hexane); $^1H$ ($CDCl_3$)(single diastereoisomer) δ 12.77 (br s, 1H), 7.43-7.29 (m, 11H), 7.00 (s, 1H), 5.48 (s, 1H), 3.91 (dq, 1H, $J$ = 10.8, 7.1), 3.59 (dq, 1H, $J$ = 10.8, 7.1), 3.54 (d, 1H, $J$ = 13), 3.46 (dd, 1H, $J$ = 13, 1.3), 2.77 (s, 3H), 0.96 (t, 3H, $J$ = 7.1); IR(KBr) *inter alia* 1747, 1660 $cm^{-1}$; MS *m/z* 573, 575 ($MH^+$). Anal. Calcd for $C_{29}H_{24}ClF_3N_2O_5$: C, 60.79; H, 4.22; N, 4.89. Found: C, 60.88; H, 4.34; N, 4.66. After elution of **12b**, the column was eluted with EtOAc to give a second product, isolated as a white solid (4.0 g, 42%), identified as the conventional 1,4-conjugate addition product.[18] $^1H$ NMR ($CDCl_3$) (1:1 mixture of rotational isomers) δ 8.61 and 8.56 (each s, 1H total), 8.11-7.95 (m, 1H), 7.28-7.19 (m, 10H), 6.90 and 6.80 (each s, 1H total), 4.40 (q, 2H, $J$ = 7.1), 4.43-4.15 (m, 1H), 3.84-3.49 (m, 2H), 2.98 and 2.96 (each s, 3H total), 1.42 (t, 3H, $J$ = 7.1); MS *m/z* 573, 575 ($MH^+$).

**Diphenylmethyl 2-chloroacrylate.**

A solution of 2-chloroacrylic acid (9.87 g, 92.7 mmol) in ethyl acetate (100 mL) was treated with diphenyldiazomethane (18.9 g, 97.3 mmol) with ice-cooling over 15 minutes. After a further 2 h at the same temperature, the solution was evaporated and the residue triturated with hexane to give the title compound (25.3 g, 100%) as a light yellow solid that was pure enough for the subsequent transformation. An analytical sample was obtained by crystallization from hexane as a white solid. mp 74.5-75.5°C; $^1H$ NMR ($CDCl_3$) δ 7.40-7.29 (m, 10H), 6.95 (s, 1H), 6.63 (d, 1H, $J$ = 1.5), 6.05 (d, 1H, $J$ = 1.5); IR(KBr) *inter alia* 1726, 1653, 1608 $cm^{-1}$. Anal. Calcd for $C_{16}H_{13}ClO_2$: C, 70.46; H, 4.80. Found: C, 70.81; H, 4.62.

**Ethyl 7,8,9-Trifluoro-3-methoxycarbonyl-1-methyl-5-oxo-1,2,3,5-tetrahydropyrazolo[1,5-*a*]quinoline-4-carboxylate (9a).**

A solution of **8a** (5.00 g, 12.95 mmol) in benzene (100 mL) at room temperature was treated with 2,3-dichloro-5.6-dicyano-1,4-benzoquinone (DDQ) (2.94 g, 12.95 mmol) and the mixture stirred 30 minutes, filtered, and the precipitated material washed thoroughly with benzene. The evaporated filtrate was then purified by silica gel chromatography ($CH_2Cl_2$-EtOAc, 9:1-5:1) and the product triturated with hexane to give the title compound **9a** (4.09 g, 82%) as a white powder. mp 155-157°C; $^1H$ NMR ($CDCl_3$)(2:1 mixture of stereoisomers) δ 8.17-8.07 (m, 1H), 5.10 (t, 0.33H, $J$ = 10.1), 4.88 (d, 0.67H, $J$ = 9), 4.38 (q, 2H, $J$ = 7.1), 4.08-3.93 (m, 1H), 3.82 and 3.76 (each s, 3H total), 3.76-3.67 (m, 1H), 2.88 and 2.82 (each s, 3H total), 1.39 (t, 3H, $J$ = 7.1); IR(KBr) *inter alia* 1751, 1685, 1649, 1620, 1545 $cm^{-1}$; MS *m/z* 384 ($M^+$). Anal. Calcd for $C_{17}H_{15}F_3N_2O_5$: C, 53.13; H, 3.93; N, 7.29. Found: C, 53.28; H, 3.86; N, 7.25.

Using the same procedure, the following compounds were also obtained from the indicated tricycle.

**Ethyl 7,8,9-Trifluoro-3-*tert*-butoxycarbonyl-1-methyl-5-oxo-1,2,3,5-tetrahydropyrazolo-[1,5-*a*]quinoline-4-carboxylate (9b).**

From **8b** (29.0 g). Yield: 21.7 g (80%). White powder. mp 176.5-177°C; $^1$H NMR (DMSO-$d_6$)(2:1 mixture of stereoisomers) δ 8.03-7.93 (m, 1H), 5.23 (dd, 0.33H, *J* = 11.7, 8), 4.81 (d, 0.67H, *J* = 8.7), 4.28-4.14 (m, 2H), 4.08-3.84 (m, 1H), 3.73 (d, 0.67H, *J* = 13), 3.48 (dd, 0.33H, *J* = 11.7, 11.7), 2.81 and 2.78 (each s, 3H total), 1.43 and 1.40 (each s, 9H total), 1.27 (t, 3H, *J* = 7.1); IR(KBr) *inter alia* 1736, 1685, 1649, 1622, 1560, 1487 cm$^{-1}$; MS *m/z* 426 ($M^+$). Anal. Calcd for $C_{20}H_{21}F_3N_2O_5$: C, 56.34; H, 4.96; N, 6.57. Found: C, 56.21; H, 4.96; N, 6.44.

**Ethyl 7,8-Difluoro-3-*tert*-butoxycarbonyl-1-methyl-5-oxo-1,2,3,5-tetrahydropyrazolo[1,5-*a*]quinoline-4-carboxylate (9c).**

From **8c** (6.30 g). Yield: 5.57 g (89%). White powder. mp 169-171°C; $^1$H NMR (DMSO-$d_6$)(2:1 mixture of stereoisomers) δ 8.06 (dd, 1H, *J* = 10.6, 8.7), 7.79 (dd, 1H, *J* = 11, 6.6), 5.30-5.10 (m, 0.33H), 4.85-4.75 (m, 0.67H), 4.30-3.60 (m, 4H), 2.81 (s, 3H), 1.42 (s, 9H), 1.27 (t, 3H, *J* = 7.1); IR(KBr) *inter alia* 1739, 1684, 1647, 1618, 1560, 1491 cm$^{-1}$; MS *m/z* 408 ($M^+$). Anal. Calcd for $C_{20}H_{22}F_2N_2O_5$: C, 58.82; H, 5.43; N, 6.86. Found: C, 59.10; H, 5.45; N, 6.70.

**Ethyl 3-Chloro-3-cyano-7,8,9-trifluoro-1-methyl-5-oxo-1,2,3,5-tetrahydropyrazolo[1,5-*a*]-quinoline-4-carboxylate (13).**

From **12a** (1.10 g). Yield: 971 mg (89%). Light yellow powder. mp 156.5-158°C(from $Me_2CO$-hexane); $^1$H NMR ($CDCl_3$)(2:1 mixture of stereoisomers) δ 8.08 (ddd, 1H, *J* = 9.9, 7.9, 2.2), 4.53 (q, 2H, *J* = 7.1), 4.47 (d, 1H, *J* = 13.8), 4.18 (d, 1H, *J* = 13.8), 3.28 and 3.17 (each s, total 3H), 1.45 (t, 3H, *J* = 7.1); IR(KBr) *inter alia* 1711, 1645, 1620, 1574 cm$^{-1}$; MS *m/z* 386 ($MH^+$). Anal. Calcd for $C_{16}H_{11}ClF_3N_3O_3$: C, 49.82; H, 2.87; N, 10.89. Found: C, 50.02; H, 2.63; N, 10.84.

**Ethyl 7,8,9-Trifluoro-3-methoxycarbonyl-1-methyl-5-oxo-1,5-dihydropyrazolo[1,5-*a*]quinoline-4-carboxylate (11c).**

A solution of **8a** (5.0 g, 13 mmol) in acetone (100 mL) was treated with $MnO_2$ (11.3 g, 130 mmol) and the heterogeneous mixture stirred 64 h at room temperature. The insoluble residue was removed by filtration and the evaporated filtrate triturated with diethyl ether (100 mL). The collected solid was washed with hexane, dried, and purified by silica gel chromatography ($CH_2Cl_2$-EtOAc, gradient elution) to give **9a** (1.89 g, 38%), identical with the material prepared by DDQ oxidation, and 386 mg (8%) of a white solid identified as the title compound **11c**. mp 247°C; $^1$H NMR ($CDCl_3$) δ 8.12 (ddd, 1H, *J* = 10.1, 8, 2.2 Hz), 8.08 (s, 1H), 4.29 (q, 2H, *J* = 7.2 Hz), 3.82 (d, 3H, *J* = 4 Hz), 3.81 (s, 3H), 1.30 (t, 3H, *J* = 7.2 Hz); IR(KBr) *inter alia* 1734 br cm$^{-1}$; MS *m/z* 382 ($M^+$). Anal. Calcd for $C_{17}H_{13}F_3N_2O_5 \cdot 0.2H_2O$: C, 52.91; H, 3.50; N, 7.26. Found: C, 52.92; H, 3.25; N, 7.21.

**Ethyl 7,8,9-Trifluoro-1-methyl-5-oxo-1,2,3,5-tetrahydropyrazolo[1,5-*a*]quinoline-4-carboxylate (10a).**

A solution of ester **9b** (20.0 g, 46.9 mmol) in trifluoroacetic acid (100 mL) was stirred 1 h at room temperature then 2 h at 50°C. After evaporation, iPE (200 mL) was added and, after 30 minutes stirring at ambient temperature, the resulting precipitate collected by filtration, washed thoroughly with iPE and hexane and dried to give the title compound **10a** (15.3 g, 100%) as a white powder. mp 186-188°C; $^1$H NMR ($CDCl_3$) δ 8.09 (ddd, 1H, *J* = 10.2, 8.0, 2.3), 4.40 (q, 2H, *J* = 7.1), 3.97-3.39 (m, 4H), 2.83 (s, 3H), 1.42 (t, 3H, *J* = 7.1); IR(KBr) *inter alia* 1695, 1655, 1620, 1556, 1487 cm$^{-1}$; MS *m/z* 326 ($M^+$). Anal. Calcd for $C_{15}H_{13}F_3N_2O_3$: C, 55.22; H, 4.02; N, 8.58. Found: C, 55.19; H, 3.92; N, 8.43.

Using the same procedure, the following compound was also obtained

**Ethyl 7,8-Difluoro-1-methyl-5-oxo-1,2,3,5-tetrahydropyrazolo[1,5-*a*]quinoline-4-carboxylate (10b).**

From **9c** (5.50 g). Yield: 2.92 g (70%). White powder. mp 168-169°C; $^1$H NMR (DMSO-$d_6$) δ 8.01 (dd, 1H, *J* = 10.8, 8.6), 7.73 (dd, 1H, *J* = 11.2, 6.8), 4.24 (q, 2H, *J* = 7), 4.05-3.80 (m, 1H), 3.70-3.40 (m, 3H), 2.75 (s, 3H), 1.29 (t, 3H, *J* = 7); $^{13}$C NMR ($CDCl_3$) 173.0, 165.8, 155.4, 153.8 (dd, *J* = 256, 15.3), 148.5 (dd, *J* = 250, 13.8), 132.5 (dd, *J* = 10, 1.4), 124.2 (dd, *J* = 5.2, 2.4), 115.5 (dd, *J* = 19, 2.3), 108.1, 104.5 (d, *J* = 22.9), 60.9, 53.5, 43.5, 32.5, 14.4; IR(KBr) *inter alia* 1724, 1687, 1637, 1612 cm$^{-1}$; MS *m/z* 309 ($MH^+$). Anal. Calcd for $C_{15}H_{14}F_2N_2O_3$: C, 58.44; H, 4.58; N, 9.09. Found: C, 58.70; H, 4.47; N, 9.04.

**Ethyl 7,8,9-Trifluoro-1-methyl-5-oxo-1,5-dihydropyrazolo[1,5-*a*]quinoline-4-carboxylate (11a).**

A mixture of ester **10a** (14.5 g, 44.5 mmol) and activated $MnO_2$ (58 g) in toluene (360 mL) was heated at reflux for 25 h. After evaporation, the residue was treated with dichloromethane (300 mL), stirred 5 minutes then filtered. The filter cake was washed with dichloromethane (200 mL) and the evaporated filtrate purified by silica gel chromatography (350 g, $CH_2Cl_2$-MeOH, 50:1-25:1 elution) to give recovered **10a** (6.10 g) and the title compound **11a** (2.30 g, 16%, 28% based on recovered **10a**) as an off-white powder. mp 248-250°C(dec.); $^1$H NMR ($CDCl_3$) δ 8.23 (ddd, 1H, *J* = 10.2, 8, 2.3), 7.62 (d, 1H, *J* = 3.7), 7.43 (d, 1H, *J* = 3.7), 4.40 (q, 2H, *J* = 7.1), 3.57 (d, 3H, *J* = 2.8), 1.42 (t, 3H, *J* = 7.1); $^{13}$C NMR ($CDCl_3$+TFA) 167.9, 164.7, 150.3 (ddd, *J* = 258, 11, 2.6), 146.9, 145.5, 144.1 (ddd, *J* = 265, 17, 17), 140.7 (ddd, *J* = 257.9, 16.6, 3.2), 120.3 (dd, *J* = 8.4, 3), 117.6 (dd, *J* = 8, 2.8), 110.0 (dd, *J* = 20.4, 3.4), 105.0, 97.6, 64.0, 43.0 (d, *J* = 22), 13.9; IR(KBr) *inter alia* 1699, 1585, 1541, 1479 cm$^{-1}$; MS *m/z* 325 ($MH^+$). Anal. Calcd for $C_{15}H_{11}F_3N_2O_3$: C, 55.56; H, 3.42; N, 8.64. Found: C, 55.70; H, 3.42; N, 8.53.

**7,8,9-Trifluoro-3-methoxycarbonyl-1-methyl-5-oxo-1,2,3,5-tetrahydropyrazolo[1,5-*a*]quinoline-4-carboxylic Acid (9d).**

A solution of ester **9a** (2.00 g, 5.20 mmol) in acetic acid (30 mL) was treated with 6N-hydrochloric acid (30 mL) and heated at 110°C for 3 h then cooled to room temperature, treated with water (100 mL) and the precipitate collected by filtration, washed thoroughly with water and dried to constant weight to give **9d** (1.70 g, 92%) as a white powder. mp 250-255°C; $^1$H NMR (DMSO-$d_6$)(2.2:1 mixture of stereoisomers) δ 15.18 (s, 1H), 8.28-8.13 (m, 1H), 5.48 (dd, 0.31H, *J* = 11.7, 8), 5.06 (d, 0.69H, *J* = 8.7), 4.13-3.85 (m, 2H), 3.74

and 3.65 (each s, 3H total), 2.88 and 2.84 (each s, 3H total); IR(KBr) *inter alia* 1737, 1714, 1608 $cm^{-1}$; MS *m/z* 356 ($M^+$). Anal. Calcd for $C_{15}H_{11}F_3N_2O_5$: C, 50.57; H, 3.11; N, 7.86. Found: C, 50.96; H, 3.02; N, 7.98.

**Ethyl 3-Cyano-7,8,9-trifluoro-1-methyl-5-oxo-1,5-dihydropyrazolo[1,5-*a*]quinoline-4-carboxylate (15).**

A solution of chloride **13** (152 mg, 0.394 mmol) in dichloromethane (3 mL) was treated with triethylamine (80 mg, 0.788 mmol) and stirred at room temperature for 17 h. The mixture was diluted with ethyl acetate, washed with 1N-hydrochloric acid, water, brine, dried ($MgSO_4$), evaporated, to give the title compound **15** (137 mg, 100%) as a white powder. An analytical sample was obtained by crystallization from acetone-hexane. mp 230-233°C; $^1H$ NMR (DMSO-$d_6$) δ 9.20 (s, 1H), 8.02 (dd, *J* = 10.3, 8.1, 2.2), 4.24 (q, 2H, *J* = 7.1), 3.90 (d, 3H, *J* = 5.9), 1.28 (t, 3H, *J* = 7.1); IR(KBr) *inter alia* 2231, 1703, 1649, 1577 $cm^{-1}$; MS *m/z* 349 ($M^+$). Anal. Calcd for $C_{16}H_{10}F_3N_3O_3$: C, 55.02; H, 2.89; N, 12.03. Found: C, 55.06; H, 2.93; N, 11.56.

**Ethyl 3-Cyano-7,8,9-trifluoro-5-oxo-1,5-dihydropyrazolo[1,5-*a*]quinoline-4-carboxylate (16a).**

A solution of **15** (50 mg, 0.143 mmol) in acetic acid (1 mL) was treated with 6N-hydrochloric acid (1 mL) and the mixture heated at 100°C for 45 minutes, cooled, evaporated, and the residue treated with water. The resulting solid was collected by filtration, washed with water and dried to give the title compound **16a** (35.4 mg, 74%) as a white powder. mp 181-183 °C; $^1H$ NMR ($CDCl_3$) δ 13.67 (s, 1H), 8.34 (s, 1H), 8.05 (ddd, 1H, *J* = 9.8, 7.5, 2.4), 4.74 (q, 2H, *J* = 7.1), 1.55 (t, 3H, *J* = 7.1); IR(KBr) *inter alia* 2227, 1660, 1579 $cm^{-1}$; MS *m/z* 335 ($M^+$). Anal. Calcd for $C_{15}H_8F_3N_3O_3$: C, 53.74; H, 2.40; N, 12.53. Found: C, 54.09; H, 2.39; N, 12.08.

**Ethyl 3-Cyano-7,8,9-trifluoro-5-methoxypyrazolo[1,5-*a*]quinoline-4-carboxylate (16b).**

A solution of **16a** (58.5 mg, 0.174 mmol) in *N,N*-dimethylformamide (2.0 mL) was treated with potassium carbonate (24.1 mg, 0.174 mmol) and methyl iodide (50 mg, 0.35 mmol) and the mixture stirred at room temperature for 48 h. The reaction was then diluted with ethyl acetate and washed with water (5x), brine (1x), dried ($MgSO_4$), filtered, and the evaporated residue purified by silica gel chromatography ($CH_2Cl_2$-MeOH 20:1 elution) to give the title compound **16b** (41.5 mg, 68%) as a white solid. mp 163-165°C; $^1H$ NMR ($CDCl_3$) δ 8.34 (s, 1H), 7.86 (ddd, 1H, *J* = 10, 7.5, 2.4), 4.61 (q, 2H, *J* = 7.2), 4.20 (s, 3H), 1.48 (t, 3H, *J* = 7.2); IR(KBr) *inter alia* 2223, 1728, 1581 $cm^{-1}$; MS *m/z* 350 ($MH^+$). Anal. Calcd for $C_{16}H_{10}F_3N_3O_3$: C, 55.02; H, 2.88; N, 12.03. Found: C, 54.73; H, 2.86; N, 11.64.

**Ethyl 7,9-Difluoro-1-methyl-8-(1-methyl-4-piperazinyl)-5-oxo-1,2,3,5-tetrahydropyrazolo-[1,5-*a*]quinoline-4-carboxylate (17c).**

A solution of **10a** (200 mg, 0.613 mmol) in dimethylsulfoxide (3 mL) was treated with N-methylpiperazine (0.204 mL, 1.84 mmol) and heated at 110°C for 4 h then evaporated under high vacuum. The residue was triturated with iPE, collected, washed with water and dried to give the title compound **17c** (194 mg, 78%) as a white powder. mp 156-158°C; $^1H$ NMR (DMSO-$d_6$) δ 7.64 (dd, 1H, *J* = 12.3, 1.8), 4.23 (q, 2H, *J* = 7), 3.87-3.73 (m, 1H), 3.60-3.39 (m, 3H), 3.29 (br s, 4H), 2.72 (s, 3H), 2.44 (br s, 4H), 2.23 (s, 3H), 1.28 (t,

3H, $J$ = 7); IR(KBr) *inter alia* 1716, 1687, 1631, 1604, 1479, 1454 $cm^{-1}$; MS *m/z* 407 ($MH^+$). Anal. Calcd for $C_{20}H_{24}F_2N_4O_3$: C, 59.10; H, 5.95; N, 13.78. Found: C, 58.75; H, 5.97; N, 13.70.

Using a similar procedure, the following compounds were also prepared from the appropriate quinolone and the indicated amine.

**Ethyl 7-Fluoro-1-methyl-8-(1-methyl-4-piperazinyl)-5-oxo-1,2,3,5-tetrahydropyrazolo[1,5-*a*]quinoline-4-carboxylate (17a).**

From quinolone **10b** (1.50 g) and N-methylpiperazine (1.63 mL). Yield: 996 mg (53%). White powder. mp 204-205°C; $^1H$ NMR (DMSO-$d_6$) δ 7.70 (d, 1H, $J$ = 13.5), 7.02 (d, 1H, $J$ = 7.5), 4.22 (q, 2H, $J$ = 7), 4.00-3.70 (m, 1H), 3.60-3.36 (m, 3H), 3.28-3.15 (m, 4H), 2.75 (s, 3H), 2.24 (s, 3H), 1.28 (t, 3H, $J$ = 7); IR(KBr) *inter alia* 1685, 1631, 1610, 1577, 1491 $cm^{-1}$; MS *m/z* 388 ($M^+$). Anal. Calcd for $C_{20}H_{25}FN_4O_3$: C, 61.84; H, 6.49; N, 14.42. Found: C, 61.62; H, 6.47; N, 14.27.

**Ethyl 7,9-Difluoro-1-methyl-8-(1-methyl-4-piperazinyl)-5-oxo-1,5-dihydropyrazolo[1,5-*a*]-quinoline-4-carboxylate (18a).**

From quinolone **10a** (500 mg) and N-methylpiperazine (0.512 mL). Yield: 300 mg (48%). White powder. mp 168-171°C (from $Me_2CO$-hexane); $^1H$ NMR (DMSO-$d_6$) δ 8.24 (d, 1H, $J$ = 3.6), 7.74 (dd, 1H, $J$ = 12.3, 1.7), 7.12 (d, 1H, $J$ = 3.6), 4.20 (q, 2H, $J$ = 7), 3.56 (d, 3H, $J$ = 3.3), 3.33 (br s, 4H), 2.50 (br s, 4H), 2.24 (s, 3H), 1.27 (t, 3H, $J$ = 7); IR(KBr) *inter alia* 1693, 1668, 1628, 1595 $cm^{-1}$; MS *m/z* 404 ($M^+$). Anal. Calcd for $C_{20}H_{22}F_2N_4O_3 \cdot 1.2H_2O$: C, 56.38; H, 5.77; N, 13.15. Found: C, 56.13; H, 5.23; N, 13.14.

**Ethyl 7-Fluoro-1-methyl-5-oxo-8-(1-pyrrolidinyl)-1,2,3,5-tetrahydropyrazolo[1,5-*a*]quinoline-4-carboxylate (17e).**

From quinolone **10b** (500 mg) and pyrrolidine (0.407 mL). Yield: 527 mg (90%). White powder. mp 183-185°C; $^1H$ NMR (DMSO-$d_6$) δ 7.61 (d, 1H, $J$ = 14.7), 6.58 (d, 1H, $J$ = 7.8), 4.20 (q, 2H, $J$ = 7), 3.88-3.31 (m, 8H), 2.73 (s, 3H), 1.95 (br s, 4H), 1.27 (t, 3H, $J$ = 7); IR(KBr) *inter alia* 1718, 1680, 1630, 1601 $cm^{-1}$; MS *m/z* 359 ($M^+$). Anal. Calcd for $C_{19}H_{22}FN_3O_3$: C, 63.50; H, 6.17; N, 11.69. Found: C, 63.77; H, 6.26; N, 11.63.

**7,9-Difluoro-1-methyl-8-(1-methyl-4-piperazinyl)-5-oxo-1,2,3,5-tetrahydropyrazolo[1,5-*a*]quinoline-4-carboxylic Acid Hydrochloride (17d).**

A solution of **17c** (150 mg, 0.37 mmol) in 1:1 acetic acid-6N-hydrochloric acid (3 mL) was heated at 110°C for 3 h then cooled and evaporated. Ethanol (10 mL) was added and the mixture heated at reflux for 10 minutes and the resulting white powder collected and dried to give the title compound **17d** (81.4 mg, 53%). mp 275-278°C(dec.); $^1H$ NMR (DMSO-$d_6$) δ 15.59 (s, 1H), 11.03 (br s, 1H), 7.89 (dd, 1H, $J$ = 11.9, 1.8), 3.99-3.89 (m, 2H), 3.65-3.05 (m, 10H), 2.83 (s, 3H), 2.81 (s, 3H); IR(nujol) *inter alia* 1690 br $cm^{-1}$; MS *m/z* 378 ($M^+$, free). Anal. Calcd for $C_{18}H_{20}F_2N_4O_3 \cdot HCl \cdot 0.35H_2O$: C, 51.34; H, 5.19; N, 13.30. Found: C, 51.35; H, 5.05; N, 13.22.

**7-Fluoro-1-methyl-8-(1-methyl-4-piperazinyl)-5-oxo-1,2,3,5-tetrahydropyrazolo[1,5-*a*]quinoline-4-carboxylic Acid (17b).**

A solution of **17a** (400 mg, 1.03 mmol) in 1,4-dioxane (2.2 mL) was treated with 1N-sodium hydroxide (2.2 mL) at 50-55°C for 1.5 h then cooled, treated with 1N-hydrochloric acid (2.2 mL) and water (10 mL) and the white powder collected, washed and dried to give **17b** (332 mg, 90%). mp 238-240°C; $^1$H NMR (DMSO-$d_6$) δ 16.00 (s, 1H), 7.90 (d, 1H, $J$ = 13.7), 7.16 (d, 1H, $J$ = 7.5), 4.00-3.80 (m, 2H), 3.75-3.50 (m, 2H), 3.34 (br s, 4H), 2.81 (s, 3H), 2.50 (br s, 4H), 2.30 (s, 3H); IR(KBr) *inter alia* 1701, 1628 cm$^{-1}$; MS *m/z* 360 ($M^+$). Anal. Calcd for $C_{18}H_{21}FN_4O_3$: C, 59.99; H, 5.87; N, 15.55. Found: C, 59.62; H, 6.06; N, 15.38.

Using a similar procedure, the following compounds were also obtained

**7,9-Difluoro-1-methyl-8-(1-methyl-4-piperazinyl)-5-oxo-1,5-dihydropyrazolo[1,5-*a*]quinoline-4-carboxylic Acid (18b).**

From **18a** (160 mg). Yield: 85 mg (57%). Off-white powder. mp 218-220°C(dec.); $^1$H NMR (DMSO-$d_6$) δ 15.07 (s, 1H), 8.50 (d, 1H, $J$ = 3.4), 7.89 (dd, 1H, $J$ = 11.9, 1), 7.43 (d, 1H, $J$ = 3.4), 3.81 (d, 3H, $J$ = 5), 3.39 (br s, 4H), 2.50 (br s, 4H), 2.26 (s, 3H); IR(KBr) *inter alia* 1693, 1622, 1585 cm$^{-1}$; MS *m/z* 376 ($M^+$). Anal. Calcd for $C_{18}H_{18}F_2N_4O_3$: C, 57.44; H, 4.82; N, 14.89. Found: C, 57.71; H, 4.86; N, 14.64.

**7-Fluoro-1-methyl-8-(1-pyrrolidinyl)-5-oxo-1,2,3,5-tetrahydropyrazolo[1,5-*a*]quinoline-4-carboxylic Acid (17f).**

From **17e** (500 mg). Yield: 427 mg (93%). White powder. mp 310°C(dec.); $^1$H NMR ($CF_3CO_2D$) δ 8.08 (d, 1H, $J$ = 13.4), 4.34-4.15 (m, 2H), 4.00-3.80 (m, 6H), 3.08 (s, 3H), 2.28-2.21 (m, 4H); $^1$H NMR (DMSO-$d_6$+NaOD) δ 7.66 (d, 1H, $J$ = 15), 6.56 (d, 1H, $J$ = 7.9), 3.58-3.38 (m, 8H), 2.69 (s, 3H), 1.96 (br s, 4H); IR(KBr) *inter alia* 1705, 1631, 1595, 1560 cm$^{-1}$; MS *m/z* 331 ($M^+$). Anal. Calcd for $C_{17}H_{18}FN_3O_3 \cdot H_2O$: C, 58.45; H, 5.77; N, 12.03. Found: C, 58.85; H, 5.28; N, 12.00.

**X-Ray Crystallographic Analysis.**

**General:** Diffraction measurements were performed on a Rigaku AFC-5R diffractometer using graphite-monochromatized CuK $\alpha$ radiation ($\lambda$ = 1.54178 Å). The structures were solved by direct methods and refined by a full-matrix least-squares method.

**Compound (7)**: Yellow crystals suitable for x-ray analysis were grown from hexane solution. Crystal data: $C_{21}H_{23}F_3N_2O_7$, $Mr$ = 472.42, triclinic, $P1$ (#2), $a$ = 12.122 (8) Å, $b$ = 13.099 (5) Å, $c$ = 8.171 (2) Å, $\alpha$ = 103.48 (3)°, $\beta$ = 107.51 (4)°, $\gamma$ = 107.17 (4)°, $V$ = 1105 (1) Å$^3$, $Z$ = 2, $D_{calc}$ = 1.419 gcm$^{-3}$, $\mu$ = 10.64 cm$^{-1}$, $F(000)$ = 492, $T$ = 297K. A total of 3981 reflections (3782 unique reflections) were collected using the ω-2θ scan technique within a 2θ range of 130.2°. The structure was solved using 2178 reflections (Io > 2.0 σ(I)). The final refinement converged to $R$ = 0.098 and $R_w$ = 0.093.

**Compound (11a)**: Colorless prismatic crystals were grown from acetone solution. Crystal data: $C_{15}H_{11}F_3N_2O_3$, $Mr$ = 324.26, monoclinic, $P2_1/n$ (#14), $a$ = 11.267 (1) Å, $b$ = 10.3327 (9) Å, $c$ = 11.6737 (8)

Å, $\beta = 93.566\ (7)°$, $V = 1356.4\ (2)$ Å$^3$, $Z = 4$, $D_{calc} = 1.588$ gcm$^{-3}$, $\mu = 12.13$ cm$^{-1}$, *F(000)* = 664, $T = 297$K. A total of 2587 reflections (2456 unique reflections) were collected using the ω-2θ scan technique within a 2θ range of 130.1°. The structure was solved using 2012 reflections (Io > 3.0 σ(I)). The final refinement converged to $R = 0.060$ and $R_w = 0.05$.

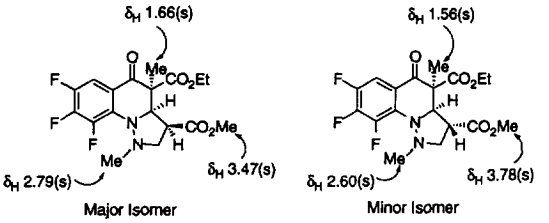
## REFERENCES AND NOTES


1. Wolfson, J.S.; Hooper, D.C. *Clin. Microbiol. Rev.* **1989**, *2*, 378.
2. For recent reviews on the structure-activity relationships of the quinolone antibacterials see (a) Chu, D.T.W.; Fernandes, P.B. "Recent Developments in the Field of Quinolone Antibacterial Agents" in *Advances in Drug Research*; Testa, B. Ed.; Academic Press: New York, Vol. 21, pp 39-144, 1991. (b) Asahina, Y.; Ishizaki, T.; Suzue, S. "Recent Advances in Structure Activity Relationships in New Quinolones" in *Progress in Drug Research*; Mitsuhashi, S. Ed.; Birkhäuser Verlag: Basel, Vol. 38, pp 57-106, 1992. For a recent review of the most frequently employed synthetic methods employed in quinolone chemistry, see: Radl, S.; Bouzard, D. *Heterocycles* **1992**, *34*, 2143.
3. For known N1-C2 bridged tricyclic quinolones see: (a) *thiazolo[3,2-a]quinolines*: Segawa, J.; Kitano, M.; Kazuno, K.; Tsuda, M.; Shirahase, I.; Ozaki, M.; Matsuda, M.; Kise, M. *J. Heterocyclic Chem.* **1992**, *29*, 1117 and references therein. (b) *pyrrolo[1,2-a]quinolines*: Chu, D.T.W.; Claiborne, A.K. *J. Heterocyclic Chem.* **1987**, *24*, 1537 and ref. 3c. (c) *pyrido[1,2-a]quinolines*: Newhouse, B.J.; Bordner, J.; Augeri, D.J.; Litts, C.S.; Kleinman, E.F. *J. Org. Chem.* **1992**, *57*, 6991, Zeigler, C.B.; Moran, D.B.; Fenton, T.J.; Lin, Y. *J. Heterocyclic Chem.* **1990**, *27*, 587 and refs 3b and 8 (d) *thiazeto[3,2-a]quinolines*: Segawa, J.; Kazuno, K.; Matsuoka, M.; Shirahase, I.; Ozaki, M.; Matsuda, M.; Tomii, Y.; Kitano, M.; Kise, M. *Chem. Pharm. Bull.* **1995**, *43*, 63 and references therein. (e) *thiazolo, oxazolo, and imidazolo[3,2-a][1,8]napthyridines*: Kondo, H.; Taguchi, M.; Inoue, Y.; Sakamoto, F.; Tsukamoto, G. *J. Med. Chem.* **1990**, *33*, 2012. For other N1-C2 bridged quinolones, that contain additional rings see: (f) *benzoxazolo[3,2-a]quinolines*: Chung, S.J.; Kim, D.H. *Tetrahedron* **1995**, *51*, 12549, and Kim, D.H.; Chung, S.J.; Yeon, S.W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1953. (g) *benzothiazolo[3,2-a]quinolines*: Chu, D.T.W.; Fernandes, P.B.; Pernet, A.G. *J. Med. Chem.* **1986**, *29*, 1531. (h) *C8-bridged thiazolo[3,2-a]quinolines*: Jinbo, Y.; Kondo, H.; Taguchi, M.; Sakamoto, F.; Tsukamoto, G. *J. Org. Chem.* **1994**, *59*, 6057 and references cited therein.
4. 3-Acylated compounds related to **4** (but lacking an N-alkyl group) have been obtained from the reaction of N-aminoquinolones with 1,3-diketones, but no report of their conversion to the final antibacterial agents has appeared. Additionally, adaptation of the route to our target compounds, notably **3**, is not obvious. See: (a) Azev, Y.A.; Shorshnev, S.V.; Alexeev, S.G.; Charushin, V.N.; Chupakhin, O.N. *Mendeleev Commun.* **1993**, 99. (b) Chupakhin, O.N.; Azev, Y.A.; Alexeev, S.G.; Shorshnev, S.V.; Tsoi, E.; Charushin, V.N. *Mendeleev Commun.* **1992**, 151.
5. Pyrazolo[1,5-*a*]quinolines are not a well characterized class of heterocycles. Syntheses of the skeletal framework, based predominantly on 1,3-dipolar cycloadditions of N-aminoquinolinium salts with olefins, are known, but are not readily adaptable to **3** or **4**. For some examples see: (a) Yamashita, Y.; Masumura, M. *Tetrahedron Lett.* **1979**, *20*, 1765. (b) Tominaga, Y.; Ichihara, Y.; Mori, T.; Kamio, C.; Hosomi, A. *J. Heterocyclic Chem.* **1990**, *27*, 263. (c) Tominaga, Y.; Ichihara, Y.; Hosomi, A. *Heterocycles* **1988**,

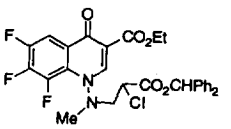
*27*, 2345. (d) Huisgen, R.; Grashey, R.; Krischke, R. *Liebigs Ann. Chem.* **1977**, 506. (e) Sundberg, R.J.; Ellis, J.E. *J. Heterocyclic Chem.* **1982**, *19*, 573. (f) Tsuchiya, T.; Sashida, H.; Konoshita, A. *Chem. Pharm. Bull.* **1983**, *31*, 4568. (f) Gelin, S.; Deshayes, C. *Synthesis* **1983**, 566.

6. (a) Coppola, G.M.; Damon, R.E. *J. Heterocyclic Chem.* **1980**, *17*, 1729. (b) Chu, D.T.W.; Fernandes, P.B.; Pernet, A.G. *J. Med. Chem.* **1986**, *29*, 1531.
7. (a) Barrett, D.; Sasaki, H.; Tsutsumi, H.; Murata, M.; Terasawa, T.; Sakane, K. *J. Org. Chem.* **1995**, *60*, 3928. (b) Barrett, D.; Tsutsumi, H.; Kinoshita, T.; Murata, M.; Sakane, K. *Tetrahedron* **1995**, *51*, 11125. (c) Barrett, D.; Sasaki, H.; Kinoshita, T.; Tsutsumi, H.; Sakane, K. *Bull. Chem. Soc. Jpn.* **1996**, in press.
8. For an intramolecular Michael reaction at C2 in the quinolone area see: Schroeder, M.C.; Kiely, J.S. *J. Heterocyclic Chem.* **1988**, *25*, 1769.
9. A portion of this work has been reported in preliminary form. Barrett, D.; Sasaki, H.; Kinoshita, T.; Sakane, K. *J. Chem. Soc., Chem. Commun.* **1996**, 61.
10. (a) For an excellent recent review of the intramolecular Michael reaction see: Little, R.D.; Masjedizadeh, M.R.; Wallquist, O.; McLoughlin, J.I. *Organic Reactions* Vol. 47, pp-315-552, 1995. (b) For a recent review of the utility of tandem reactions in organic synthesis see: Bunce, R.A. *Tetrahedron* **1995**, *51*, 13103.
11. For examples of tandem Michael-Michael reactions leading to cyclized products see: (a) Yoo, S-E.; Suh, J-H.; Yi, K.Y. *Bull. Korean Chem. Soc.* **1993**, *14*, 166. (b) Bunce, R.A.; Wamsley, E.J.; Pierce, J.D.; Shellhammer Jr, A.J.; Drumright, R.E. *J. Org. Chem.* **1987**, *52*, 464. (c) Barco, A.; Benetti, S.; Casolari, A.; Pollini, G.P.; Spalluto, G. *Tetrahedron Lett.* **1990**, *31*, 3039 and 4917. (d) Posner, G.H.; Mallamo, J.P.; Black, A.Y. *Tetrahedron* **1981**, *37*, 3921. (e) Spitzner, D.; Wagner, P.; Simon, A.; Peters, K. *Tetrahedron Lett.* **1989**, *30*, 547. (f) Posner, G.H.; Lu, S-B.; Asirvatham, E.; Silversmith, E.F.; Shulman, E.M. *J. Am. Chem. Soc.* **1986**, *108*, 511. (g) Danishefsky, S.; Harrison, P.; Silvestri, M.; Segmuller, B. *J. Org. Chem.* **1984**, *49*, 1319. (h) Richter, F.; Otto, H-H. *Tetrahedron Lett.* **1987**, *28*, 2945. (i) Barco, A.; Benetti, S.; Risi, C.D.; Pollini, G.P.; Romagnoli, R.; Spalluto, G.; Zanirato, V. *Tetrahedron* **1994**, *50*, 2583. (j) Barco, A.; Benetti, S.; Pollini, G.P.; Spalluto, G.; Zanirato, V. *Gazz. Chim. Ital.* **1993**, *123*, 185. (k) Ihara, M.; Ishida, Y.; Tokunaga, Y.; Kabuto, C.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2085. (l) Ihara, M.; Kirihara, T.; Kawaguchi, A.; Tsuruta, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc. Perkin Trans. 1*, **1987**, 1719.
12. Chu, D.T.W. *J. Heterocyclic Chem.* **1985**, *22*, 1033.
13. In a TLC control experiment (1:1 iPE-hexane elution), treatment of the 8:1 mixture of **8a'** and **8a''**, obtained from the NaH-reaction with a trace of DBU in $CH_2Cl_2$ at room temperature for 4 days led to a mixture rich in the minor isomer, indicating epimerisation at C3, along with a trace of **7**, indicating that the retro-reaction ie **8a** to **5** can occur to a certain degree.
14. Reaction of the 8:1 mixture of **8a** with methyl iodide-$Cs_2CO_3$ in acetone at room temperature afforded a separable mixture of two *C*-methylated products as shown below. $^1H$ NMR spectroscopy, in particular the *O*-methyl resonances, indicated simple alkylation of the respective isomers of **8a** without any C3 epimerization, further confirming the diastereisomeric nature of the components. Furthermore, exposure of the major isomer to DBU in dichloromethane at room temperature for 7 days resulted in smooth

isomerisation to a mixture rich in the minor isomer, confirming their isomeric nature.




15. (a) For a selenium-based re-oxidation method see: ref. 8. (b) For use of DDQ see: Domagala, J.M.; Hanna, L.D.; Heifetz, C.L.; Hutt, M.P.; Mich, T.F.; Sanchez, J.P.; Solomon, M. *J. Med. Chem.* **1986**, *29*, 394. (c) For use of chloranil-pyridine see: Miyamoto, T.; Egawa, H.; Matsumoto, J. *Chem. Pharm. Bull.* **1987**, *35*, 2280. (d) For use of bromine see: Miyamoto, T.; Egawa, H.; Shibamori, K.; Matsumoto, J. *J. Heterocyclic Chem.* **1987**, *24*, 1333.
16. Spectroscopic data for **11b**: $^1$H NMR ($CDCl_3$) δ 13.08 (s, 1H), 8.05 (d, 1H, $J$ = 2 Hz), 7.96 (ddd, 1H, $J$ = 2.4, 7.6, 10.1 Hz), 6.88 (d, 1H, $J$ = 2 Hz), 4.57 (q, 2H, $J$ = 7.1 Hz), 1.54 (t, 3H, $J$ = 7.1 Hz); MS *m/z* 310 ($M^+$).
17. Spectroscopic data for **14**: $^1$H NMR ($CDCl_3$)(3:1 mixture of diastereoisomers) δ 8.14-8.05 (m, 1H), 5.20-5.00 (m, 1H), 4.50-4.39 (m, 2H), 4.06-3.80 (m, 2H), 3.12 and 2.85 (each s, total 3H), 1.45 (t, 3H, $J$ = 7.1 Hz); IR(nujol) *inter alia* 1680 $cm^{-1}$; MS *m/z* 351 ($M^+$).
18. The lower yield of tricyclic product in this case is most likely attributable to the selective ring opening of one of the diasteroisomeric products, giving the 1,4-conjugate addition adduct below. The crude product contained two products of similar $R_f$, only one of which eluted from the column. The second-eluted material was much more polar than either of the two components in the crude product. We have previously shown that related bis-*tert*-butoxycarbonyl derivatives undergo ready ring opening in DMSO solution or upon silica gel chromatography.[7c] Compound **12b** did not ring open in DMSO solution.



19. *In vitro* antibacterial activity of the new N1-C2 bridged tricyclic quinolones prepared in this work is shown below. Whilst activity is reasonable against *P.vulgaris* IAM 1025, overall potency is moderate.

| | MIC (μg/ml) | | | | |
|---|---|---|---|---|---|
| Bacteria | **17b** | **17d** | **17f** | **18b** | **Levofloxacin** |
| *S.aureus* 209P JC-1 | 6.25 | 25 | 3.13 | 25 | 0.39 |
| *E.coli* NIHJ JC-2 | 0.78 | 6.25 | >100 | 6.25 | 0.05 |
| *P.vulgaris* IAM 1025 | 0.10 | 0.78 | 0.20 | 0.78 | <0.025 |
| *P.aeruginosa* IAM 1095 | 50 | >100 | >100 | >100 | 1.56 |

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