A novel [3 + 2] annulation: synthesis and X-ray crystallographic structure of a novel tetrahydropyrazolo[1,5-*a*]quinoline, an intermediate towards new tricyclic quinolone antibacterials

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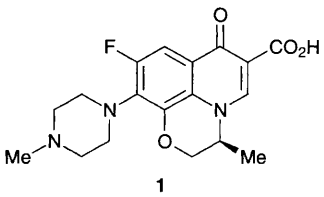
The synthesis and X-ray crystallographic structure of tetrahydropyrazolo[1,5-*a*]quinoline 10, an intermediate for novel DNA gyrase inhibitors, *via* a tandem 1,4-conjugate addition-Michael ring closure protocol are described.

Selective inhibitors of bacterial DNA gyrase are prominently featured in the available repertoire of anti-infective agents.[1] Whilst excellent broad spectrum activity is displayed by the fluoroquinolone members of this class, as exemplified by Levofloxacin **1**, resistance problems and relatively weak efficacy against significant Gram-positive pathogens indicates a continuing need to design and prepare new structural types.[2] As part of our program we sought to prepare the new tetrahydropyrazolo[1,5-*a*]quinolines **2**; however, whilst intermediates for some related dihydro compounds have been reported,[3] no obvious method exists for their conversion to our targets. Here we describe a new approach for construction of the pyrazolo[1,5-*a*]quinoline skeleton and the synthesis and X-ray crystallographic structure of **10**, a key intermediate for compounds **2** *via* a novel tandem 1,4-conjugate addition-Michael [3 + 2] annulation protocol.

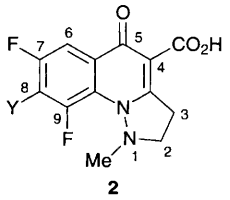
We recently reported a concise route to some novel 1,8-bridged tricyclic quinolones.[4] Malonate **4**, obtained by a Lewis-acid mediated conjugate addition reaction, underwent exclusive cyclisation to C(8) to give tricycle **5**. Hydrolysis and decarboxylation completed the synthesis of the key pyrido[3,2,1-*i,j*]cinnoline intermediate. Seeking to extend the scope of suitable electrophilic partners in the conjugate addition reaction, we have discovered that in sharp contrast to **4**, the ester **6**, obtained by reaction of amine **3** with *tert*-butyl acrylate, is not isolable and undergoes spontaneous cyclisation under the conditions used for the coupling, to the C(2)-position of the quinolone moiety. This observation was unexpected and presented us with a novel approach to construction of the pyrazolo[1,5-*a*]quinoline skeleton.

Amine **3** did not react with *tert*-butyl acrylate under Lewis acid-mediated conditions, such as those used for preparation of **4**, however reaction under basic conditions gave tricyclic β-keto ester **7** in 97% yield (NaH, DMF, 0 °C). Conjugate addition to give **6** being followed by spontaneous intramolecular cyclisation to C(2) to give the sodium salt of **7**, cyclisation occurring presumably due to the greater thermodynamic stability of the β-keto ester anion compared to the simple ester enolate. Hitherto in the quinolone area, the only report of an N(1) tethered carbanion undergoing cyclisation to C(2) involved an *in situ* generated Grignard reagent, leading to a 6-membered ring.[5] Compound **7** existed as a complex mixture of keto–enol and stereoisomeric forms; however, DDQ oxidation (1 equiv.) gave **8** smoothly (80%). ^{1}H NMR indicated a 2:1 mixture of diastereoisomers presumably due to slow nitrogen inversion.† TFA hydrolysis at room temperature followed by heating at 50 °C to complete decarboxylation of the intermediate acid **9** gave **10** in quantitative yield.‡

A single crystal X-ray analysis unequivocally established the N(1)–C(2) bridged tricyclic nature of **10** (Fig. 1).§ Of particular interest, the *N*-methyl group was essentially perpendicular to the plane of the quinolone ring. It has previously been shown for some 1,8-bridged tricyclic quinolones that a perpendicularly oriented methyl group is critical for good affinity to DNA gyrase.[6] A potent series of 1,2-bridged thiazeto[3,2-*a*]quinolines have also been shown to have a similarly oriented methyl group.[7] Accordingly, compounds of the type **2** may well be attractive targets as structurally novel potential antibacterial agents.

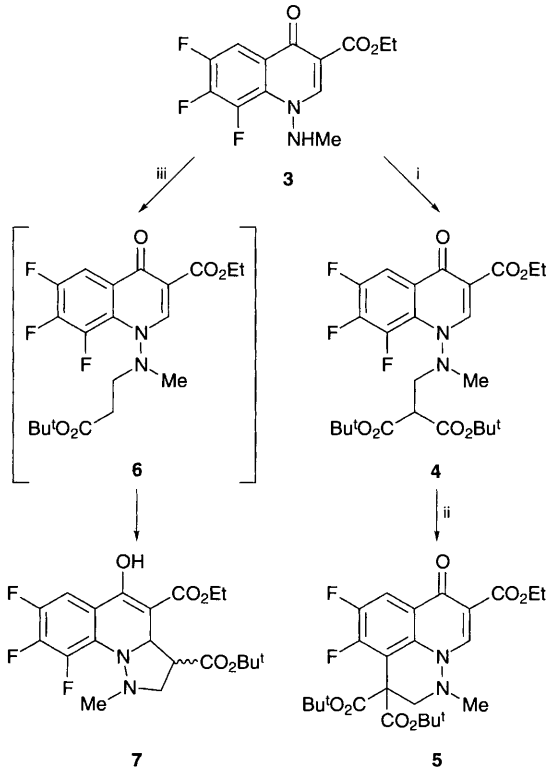


1



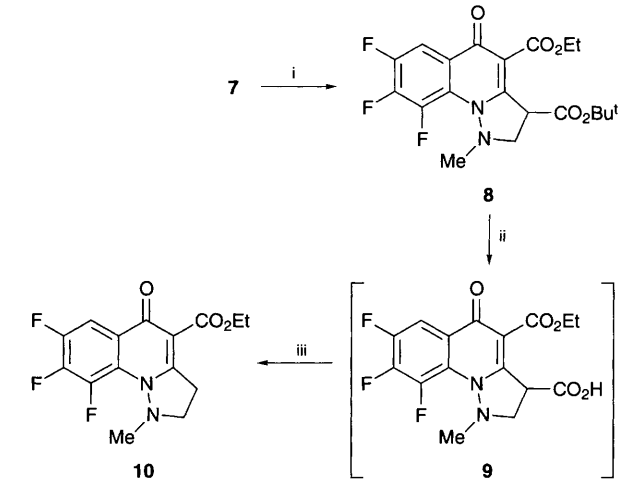
2

Y = secondary amine



Scheme 1 *Reagents and conditions*: i, $(Bu^tO_2C)_2C{=}CH_2$, $TiCl_4$, propylene oxide, CH_2Cl_2, 0 °C–room temp., 18 h, 89%; ii, Cs_2CO_3, Me_2SO, 80 °C, 4 h, 50%; iii, $Bu^tO_2CCH{=}CH_2$, NaH, DMF, 0 °C, 1 h, 97%

In summary, we have described a new strategy for the synthesis of pyrazolo[1,5-*a*]quinolines by exploiting the differential reactivity of an *N*-methylaminoquinolone with simple acrylates and methylidenemalonates.¶ Further conversion of **10** and related tricycles to novel DNA gyrase inhibitors by displacement of the C(8)-fluorine with amines, followed by ester hydrolysis occurs smoothly. For example **2** (Y = 4-methylpiperazin-1-yl, HCl) is readily obtained by reaction with *N*-methyl piperazine followed by acidic hydrolysis (6 mol dm^{-3} HCl–AcOH, reflux).‖



Scheme 2 *Reagents and conditions*: i, DDQ, C_6H_6, room temp., 15 min, 80%; ii, TFA, room temp., 1 h; iii, 50 °C, 2 h, 100%

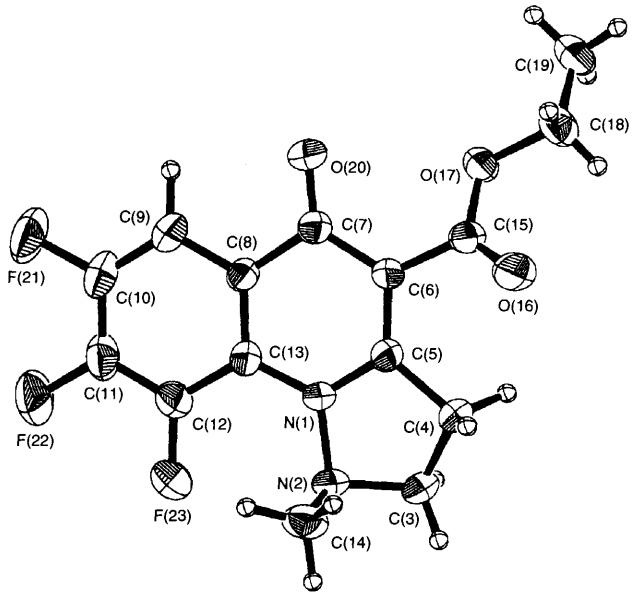


Fig. 1 ORTEP drawing (40%-ellipsoids) of **10** with crystallographic numbering scheme. Selected bond lengths (Å), bond angles (°), and torsion angles (°): N(1)–N(2) 1.453(4), C(4)–C(5) 1.510(5), C(3)–C(4) 1.545(6), N(2)–C(3) 1.487(5), N(2)–C(14) 1.482(6); N(1)–N(2)–C(14) 107.6(3), N(1)–N(2)–C(3) 101.2(3), N(2)–C(3)–C(4) 105.0(3); C(13)–N(1)–N(2)–C(14)–85.7(4), C(5)–N(1)–N(2)–C(14) 95.8(4), F(23)–C(12)–C(13)–C(8) 179.5(4).

Footnotes

† *Selected data* for **8**: δ_H (200 MHz, [$^2H_6$]Me_2SO) (2:1 mixture of diastereoisomers) 8.03–7.93 (1H, m), 5.23 (0.33 H, dd, *J* 11.7, 8 Hz), 4.81 (0.67 H, d, *J* 8.7 Hz), 4.28–4.14 (2 H, m), 4.08–3.84 (1 H, m), 3.73 (0.67 H, d, *J* 13 Hz), 3.48 (0.33 H, dd, *J* 11.7, 11.7 Hz), 2.81 and 2.78 (3 H total, each s), 1.43 and 1.40 (9 H total, each s), 1.27 (3 H, t, *J* 7.1 Hz).

‡ *Selected data* for **10**: δ_H (200 MHz, [$^2H_6$]Me_2SO) 8.09 (1 H, ddd, *J* 10.2, 8.0, 2.3 Hz), 4.40 (2 H, q, *J* 7.1 Hz), 3.97–3.39 (4 H, m), 2.83 (3 H, s), 1.42 (3 H, t, *J* 7.1 Hz).

§ *Crystal data* for **10**: Crystal dimensions 0.20 × 0.05 × 0.05 mm, $C_{15}H_{13}F_3N_2O_3$, *M* = 326.27, monoclinic, *a* = 18.568(2), *b* = 12.522(2), *c* = 16.630(1) Å, β = 132.665(3)°, *V* = 2843.4(5) $Å^3$, space group *C*2/*c*(#15), *Z* = 8, D_c = 1.524 g cm^{-3}, μ(Cu-Kα) = 11.58 cm^{-1}, *F*(000) = 1344. Data were obtained at 25 ± 1 °C on a Rigaku AFC5R diffractometer using graphite monochromatized Cu-Kα radiation. A total of 2647 reflections (2559 unique) were collected using the ω-2θ scan technique within a 2θ range of 130.2°. The structure was solved by direct methods and refined by a full-matrix least-squares method using 1607 reflections [$I_o > 3.0\,\sigma(I)$]. The final refinement converged to R = 0.047 and R_w = 0.038. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

¶ The sodium salt of **7** was stable in DMF up to 80 °C. Even upon heating to 120 °C no cyclisation to C(8) occurred, however slow decomposition was observed. Reaction of **7** with Cs_2CO_3 under the conditions used for cyclisation of **4** returned only unchanged starting material.

‖ This compound showed moderate antibacterial activity, for example, minimum inhibitory concentration (MIC) against *P. vulgaris* IAM 1025, 0.78 μg cm^{-3}, compared to < 0.025 μg cm^{-3} for Levofloxacin **1**. *Selected data* for **2** (Y = 4-methylpiperazin-1-yl, HCl): δ_H (200 MHz, [$^2H_6$]Me_2SO) 15.59 (1 H, s), 11.03 (1 H, br s), 7.89 (1 H, dd, *J* 11.9, 1.8 Hz), 3.99–3.89 (2 H, m), 3.65–3.05 (10 H, m), 2.83 (3 H, s), 2.81 (3 H, s).

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