Alkylation of 1-[*N*-(Hydroxymethyl)-*N*-methylamino]-4-quinolones. An Improved Preparation of Intermediates for Novel Potent Tricyclic Quinolone Antibacterial Agents

David Barrett,* Hiroshi Sasaki, Takayoshi Kinoshita,† Hideo Tsutsumi,† and Kazuo Sakane

New Drug Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532

†Basic Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532

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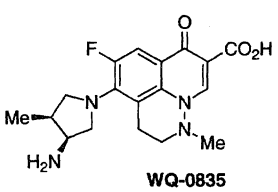
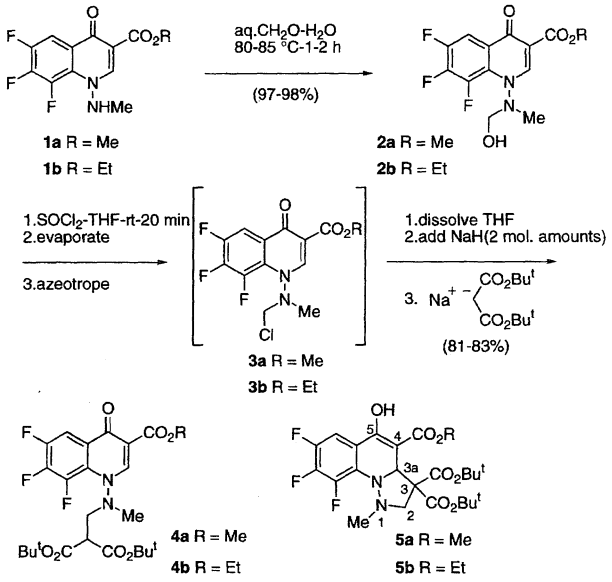
A new and improved method for the preparation of the key cyclization precursors for novel pyrido[3,2,1-*ij*]cinnoline antibacterial agents that avoids the use of di-*t*-butyl methylenemalonate is described. The key process is the alkylation of 1-[*N*-(hydroxymethyl)-*N*-methylamino]-4-quinolones with di-*t*-butyl malonate via the intermediate chloromethyl derivatives. Unexpectedly, this process produced labile pyrazolo[1,5-*a*]quinoline derivatives that were subsequently shown to undergo ring opening and cyclization to C8 to produce the pyrido[3,2,1-*ij*]cinnoline key intermediates.

We recently reported concise methodology for the preparation of key intermediates for the newly discovered pyrido-[3,2,1-*ij*]cinnoline class of DNA gyrase inhibitors.[1,2] This series (Chart 1), exemplified by WQ-0835[3,4] displays excellent broad spectrum antibacterial activity and high oral absorption and thus has good potential for clinical development. Our synthesis involved as a key step, the one-step preparation of malonate **4b** from amine **1b** and di-*t*-butyl methylenemalonate by a novel propylene oxide-mediated $TiCl_4$ reaction.[1] Whilst this is a reliable procedure, we encountered difficulties related to stability when preparing the methylenemalonate on large scale; this was attributed to a variable tendency to undergo spontaneous polymerization depending on batch and batch size, presumably due to the presence of trace amounts of impurities. We therefore required a new synthesis of malonate **4b** as well as the corresponding methyl ester **4a**; herein, we disclose a new approach that led to an improved process suitable for large scale preparations.



WQ-0835

Chart 1.



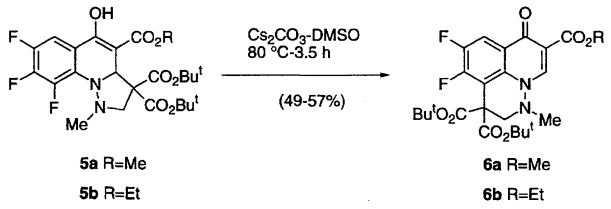
Scheme 1.

Results and Discussion

To circumvent the problems associated with large scale preparation of **4b** by our reported route, we were driven by the recognition that it can be considered as a Mannich base. As such, we can envisage it to be derivable from the reaction of di-*t*-butyl malonate with an iminium species or its equivalent.[5] Our new synthesis, summarized in Scheme 1, thus required an efficient method for the alkylation of a 1-[*N*-(hydroxymethyl)-*N*-methylamino]-4-quinolone such as **2a** or **2b**. Despite the fact that in general *N*-hydroxymethylamines are not stable entities, compound **2b** has been reported previously[6] to be a stable, isolable material, a feature attributed in part to a similarity with *N*-hydroxymethylated amides, which are well known, useful, stable synthetic intermediates.[7] The only previously reported chemistry of **2b** is a novel intramolecular cyclization to C-8 of the quinolone moiety to yield a novel series of benzoxadiazines;[6] no other chemistry of this potentially useful intermediate has yet appeared.

Our first task was the efficient preparation of quinolones **2a** and **2b**. The method of Dax and Wei[6] involves treatment of **1b** with paraformaldehyde in water at reflux for 36 h, followed by extraction. We have discovered a superior method for this hydroxymethylation reaction. Simply heating a suspension of **1a** or **1b** in water with a large excess of 35% aqueous formaldehyde for 1—2 h, followed by cooling, filtration, washing, and drying, gave **2a** and **2b** in 97—98% yield as analytically pure stable solids. We have stored these compounds for more than 4 years at room temperature without any sign of decomposition. Use of 1.5 molar amounts of formaldehyde in water at 85 °C for 7 h led to only ca. 25% of **2b** indicating a need for a large excess.

For coupling with malonates, all attempts to employ acidic conditions (TFA, r.t. to reflux) to convert **2b** to an iminium ion, followed by trapping by the malonate were unsuccessful. Conversion of **2b** to the corresponding *O*-acetate to facilitate activation under Lewis acid catalysis ($TiCl_4$, −78 °C to r.t.), likewise failed to afford any **4b**. However, we were pleased to discover that **2b** could be smoothly converted to the corresponding chloro derivative **3b** by treatment with trichloromethylsilane in dichloromethane (97%).[8] The optimum conditions, however, involved simple treatment with thionyl chloride in THF at room temperature for 20 min. Whilst **3a** and **3b** could be isolated under these conditions, for practical purposes, it was unnecessary, since the crude evaporated residue was used directly in the next step. Optimum conditions for the coupling with di-*t*-butyl malonate involved adding the pre-formed malonate sodium salt (equimolar amount of NaH per malonate) in THF to a solution of the chloride in THF at 0 °C that had been pre-



5a R=Me
5b R=Et

6a R=Me
6b R=Et

Chart 2.

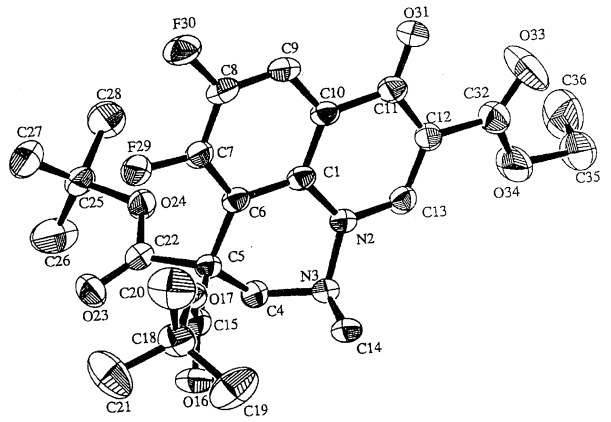


Fig. 1. ORTEP drawing of **6b** with crystallographic numbering scheme. Thermal ellipsoids are drawn at the 40% probability level. Hydrogen atoms are omitted for clarity.

treated with two molar amounts of sodium hydride. In this way smooth coupling occurred to give **4a** and **4b**. Without an excess of base, the reaction could not reach completion due to proton transfer from the product to the remaining malonate. An attempt to use potassium carbonate was not effective for this coupling (K_2CO_3–DMF −60 °C).

An interesting feature of this new method was the observation that since an excess of base is present, variable amounts of the labile C2-cyclized pyrazolo[1,5-*a*]quinoline derivatives **5a** and **5b** were also obtained in addition to **4a** and **4b**. These coupling reactions were quenched with water before adjusting to pH 7 with dilute hydrochloric acid. In our earlier, $TiCl_4$-mediated approach to **4b**, after quenching the pH was acidic; basic conditions are necessary to produce a C2-cyclized species.[9] In the case of methyl ester **2a**, 58% of **5a**, and 25% of **4a** were obtained by trituration of the crude product, for a total yield of 83%. For ethyl ester **2b**, the crude

Table 1. Fractional Coordinates and Equivalent Isotropic Thermal Parameters (B_{eq}/Å^2)[a] for Non-Hydrogen Atoms (esd's in parentheses)

Atom	*x*	*y*	*z*	B_{eq} [a]
F(29)	0.7358(2)	0.8196(1)	0.2670(2)	4.57(6)
F(30)	0.9174(2)	0.7708(2)	0.0921(3)	5.44(6)
O(16)	0.5849(3)	0.8106(2)	0.7251(3)	4.72(7)
O(17)	0.7523(2)	0.8602(2)	0.6097(3)	3.77(6)
O(23)	0.4640(3)	0.8007(2)	0.3924(3)	5.56(8)
O(24)	0.4932(2)	0.6664(2)	0.2140(3)	3.84(6)
O(31)	1.0104(3)	0.4660(2)	0.1950(3)	5.05(8)
O(33)	0.9709(3)	0.2979(2)	0.3022(5)	8.6(1)
O(34)	0.8133(3)	0.2890(2)	0.4436(4)	7.2(1)
N(2)	0.7429(3)	0.5493(2)	0.4786(3)	3.05(7)
N(3)	0.6623(3)	0.5809(2)	0.5977(3)	3.18(7)
C(1)	0.7865(3)	0.6067(2)	0.3816(4)	2.97(8)
C(4)	0.5670(3)	0.6248(3)	0.5245(5)	3.28(9)
C(5)	0.6225(3)	0.7127(2)	0.4692(4)	3.04(8)
C(6)	0.7340(3)	0.6892(2)	0.3798(4)	3.00(8)
C(7)	0.7827(3)	0.7411(3)	0.2804(4)	3.59(9)
C(8)	0.8766(4)	0.7143(3)	0.1863(4)	3.91(9)
C(9)	0.9222(4)	0.6330(3)	0.1839(4)	3.77(9)
C(10)	0.8779(3)	0.5776(2)	0.2836(4)	3.21(8)
C(11)	0.9262(3)	0.4874(3)	0.2779(4)	3.70(9)
C(12)	0.8651(3)	0.4304(3)	0.3735(4)	3.47(8)
C(13)	0.7794(3)	0.4652(3)	0.4709(4)	3.35(8)
C(14)	0.7408(4)	0.6417(3)	0.7493(5)	4.0(1)
C(15)	0.6505(4)	0.8007(3)	0.6196(4)	3.56(9)
C(18)	0.7931(4)	0.9526(3)	0.7369(5)	4.9(1)
C(19)	0.8292(8)	0.9324(5)	0.8997(7)	7.7(2)
C(20)	0.9059(7)	0.9947(4)	0.6721(9)	7.2(2)
C(21)	0.6901(8)	1.0113(5)	0.737(1)	8.5(2)
C(22)	0.5160(4)	0.7336(3)	0.3548(4)	3.67(9)
C(25)	0.3980(4)	0.6708(3)	0.0783(4)	4.3(1)
C(26)	0.2677(5)	0.6644(7)	0.1288(8)	7.5(2)
C(27)	0.4383(7)	0.7603(4)	0.0275(7)	6.5(2)
C(28)	0.4103(6)	0.5840(4)	−0.0568(6)	6.0(1)
C(32)	0.8917(4)	0.3332(3)	0.3663(5)	4.4(1)
C(35)	0.8279(8)	0.1911(4)	0.4441(8)	7.7(2)
C(36)	0.7488(9)	0.1242(5)	0.303(1)	9.0(3)

a) $B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$.

Table 2. Selected Bond Lengths and Angles for **6b** (esd's in parentheses)

Bond length/Å			Bond angle/°				Bond angle/°			
F(29)	C(7)	1.348(4)	C(15)	O(17)	C(18)	120.4(3)	C(22)	O(24)	C(25)	121.1(3)
O(16)	C(15)	1.190(4)	C(32)	O(34)	C(35)	117.0(4)	N(3)	N(2)	C(1)	120.8(3)
O(17)	C(18)	1.489(4)	N(3)	N(2)	C(13)	117.2(3)	C(1)	N(2)	C(13)	121.9(3)
O(24)	C(22)	1.325(4)	N(2)	N(3)	C(4)	108.4(3)	N(2)	N(3)	C(14)	109.0(3)
O(31)	C(11)	1.230(4)	C(4)	N(3)	C(14)	115.8(3)	N(2)	C(1)	C(6)	119.7(3)
O(34)	C(32)	1.321(5)	N(2)	C(1)	C(10)	117.9(3)	C(6)	C(1)	C(10)	122.4(3)
N(2)	N(3)	1.430(3)	N(3)	C(4)	C(5)	113.9(3)	C(4)	C(5)	C(6)	108.6(3)
N(2)	C(13)	1.339(4)	C(4)	C(5)	C(15)	108.6(3)	C(4)	C(5)	C(22)	107.2(3)
N(3)	C(14)	1.478(5)	C(6)	C(5)	C(15)	115.9(3)	C(6)	C(5)	C(22)	111.1(3)
C(1)	C(10)	1.396(4)	C(15)	C(5)	C(22)	105.0(3)	C(1)	C(6)	C(5)	121.7(3)
C(5)	C(6)	1.519(4)	C(1)	C(6)	C(7)	115.5(3)	C(5)	C(6)	C(7)	122.5(3)
C(5)	C(22)	1.550(5)	F(29)	C(7)	C(6)	119.8(3)	F(29)	C(7)	C(8)	117.7(3)
C(7)	C(8)	1.391(5)	C(6)	C(7)	C(8)	122.5(3)	F(30)	C(8)	C(7)	117.5(3)
C(9)	C(10)	1.392(5)	F(30)	C(8)	C(9)	121.2(3)	C(7)	C(8)	C(9)	121.3(4)
C(11)	C(12)	1.449(5)	C(8)	C(9)	C(10)	119.0(4)	C(1)	C(10)	C(9)	119.2(3)
C(12)	C(32)	1.486(5)	C(1)	C(10)	C(11)	122.0(3)	C(9)	C(10)	C(11)	118.8(3)
C(18)	C(20)	1.505(7)	O(31)	C(11)	C(10)	120.0(4)	O(31)	C(11)	C(12)	125.5(4)
C(25)	C(26)	1.506(6)	C(10)	C(11)	C(12)	114.4(3)	C(11)	C(12)	C(13)	120.1(3)
C(25)	C(28)	1.520(6)	C(11)	C(12)	C(32)	121.3(3)	C(13)	C(12)	C(32)	118.5(4)
F(30)	C(8)	1.355(4)	N(2)	C(13)	C(12)	123.3(4)	O(16)	C(15)	O(17)	127.3(3)
O(17)	C(15)	1.330(4)	O(16)	C(15)	C(5)	121.7(3)	O(17)	C(15)	C(5)	111.0(3)
O(23)	C(22)	1.192(4)	O(17)	C(18)	C(19)	108.7(4)	O(17)	C(18)	C(20)	101.1(4)
O(24)	C(25)	1.493(4)	O(17)	C(18)	C(21)	108.9(4)	C(19)	C(18)	C(20)	112.1(5)
O(33)	C(32)	1.169(4)	C(19)	C(18)	C(21)	114.2(6)	C(20)	C(18)	C(21)	111.0(5)
O(34)	C(35)	1.473(5)	O(23)	C(22)	O(24)	126.8(4)	O(23)	C(22)	C(5)	123.4(3)
N(2)	C(1)	1.393(4)	O(24)	C(22)	C(5)	109.8(3)	O(24)	C(25)	C(26)	110.6(4)
N(3)	C(4)	1.459(4)	O(24)	C(25)	C(27)	108.7(4)	O(24)	C(25)	C(28)	102.2(3)
C(1)	C(6)	1.411(4)	C(26)	C(25)	C(27)	113.1(5)	C(26)	C(25)	C(28)	112.0(5)
C(4)	C(5)	1.551(4)	C(27)	C(25)	C(28)	109.8(4)	O(33)	C(32)	O(34)	122.6(4)
C(5)	C(15)	1.546(4)	O(33)	C(32)	C(12)	126.2(4)	O(34)	C(32)	C(12)	111.2(4)
C(6)	C(7)	1.372(4)	O(34)	C(35)	C(36)	109.5(6)				
C(8)	C(9)	1.352(5)								
C(10)	C(11)	1.483(5)								
C(12)	C(13)	1.367(4)								
C(18)	C(19)	1.518(7)								
C(18)	C(21)	1.499(7)								
C(25)	C(27)	1.510(6)								
C(35)	C(36)	1.453(9)								

product was almost exclusively the labile **5b** (^{1}H NMR), but after column chromatography **4b** was the only product (81% yield). We have previously shown[10] that reaction of **1b** with *t*-butyl acrylate affords irreversibly a similar tricycle by a novel tandem 1,4-conjugate addition-Michael reaction. In contrast, **5a** and **5b** were readily converted to the open-chain derivatives **4a** and **4b** simply by dissolution in DMSO. For example, ^{1}H NMR of **5a** in $CDCl_3$ revealed 1-proton singlets at $\delta = 12.62$ and 5.76 for the enol- and C3a-protons respectively, whilst the same material dissolved in DMSO-d_6 revealed only signals due to **4a**.

Illustration of this facile equilibration process was best achieved by base-mediated cyclization of **5a** at 80 °C to give pyrido[3,2,1-*ij*]cinnoline **6a** in 57% yield (Chart 2). In a similar manner, **5b** afforded tricycle **6b**[1] in 49% yield. Clearly **5a** and **5b** are functional equivalents of **4a** and **4b** respectively due to the rapid equilibration that takes place in polar aprotic solvents. We believe that this process is greatly facilitated by the steric congestion inherent in **5a** and **5b**. We have previously shown that **6b** is readily converted via hydrolysis and double-decarboxylation to the key intermediate for **1**.[1] Methyl ester **6a** undergoes similar transformation readily.[11]

Crystal Structure of 6b. In light of the novelty of the transformations **5a** to **6a** and of **5b** to **6b**, we undertook an X-ray crystallographic analysis of tricycle **6b** in order to unequivocally establish the structure of this novel heterocyclic system. Figure 1 shows the overall molecular structure of **6b**. Tables 1, 2, 3, and 4 summarize the atomic coordinates, bond lengths, bond angles, torsion angles, and crystal data obtained in this determination.[12] Of particular note, the *N*-methyl group is essentially perpendicular to the plane of the 4-quinolone moiety, as indicated by the C(13)–N(2)–N(3)–C(14) torsion angle of 93.1° (Table 3). This contracts sharply with our reported structure[2] for a pyrido[3,2,1-*ij*]cinnoline

Table 3. Selected Torsion Angles for **6b** (esd's in parentheses)

Bonds angle/°					Bonds angle/°				
F(29)	C(7)	C(6)	C(1)	178.0(3)	F(29)	C(7)	C(6)	C(5)	3.9(5)
F(29)	C(7)	C(8)	F(30)	2.2(5)	F(29)	C(7)	C(8)	C(9)	−175.3(3)
F(30)	C(8)	C(7)	C(6)	179.8(3)	F(30)	C(8)	C(9)	C(10)	179.6(3)
O(16)	C(15)	O(17)	C(18)	−2.2(6)	O(16)	C(15)	C(5)	C(4)	−35.1(5)
O(16)	C(15)	C(5)	C(6)	−157.7(3)	O(16)	C(15)	C(5)	C(22)	79.3(4)
O(17)	C(15)	C(5)	C(4)	146.0(3)	O(17)	C(15)	C(5)	C(6)	23.4(4)
O(17)	C(15)	C(5)	C(22)	−99.6(3)	O(23)	C(22)	O(24)	C(25)	2.7(6)
O(23)	C(22)	C(5)	C(4)	108.9(4)	O(23)	C(22)	C(5)	C(6)	−132.6(4)
O(23)	C(22)	C(5)	C(15)	−6.5(5)	O(24)	C(22)	C(5)	C(4)	−70.7(4)
O(24)	C(22)	C(5)	C(6)	47.8(4)	O(24)	C(22)	C(5)	C(15)	173.9(3)
O(31)	C(11)	C(10)	C(1)	−177.1(3)	O(31)	C(11)	C(10)	C(9)	5.0(5)
O(31)	C(11)	C(12)	C(13)	174.9(4)	O(31)	C(11)	C(12)	C(32)	−6.1(6)
O(33)	C(32)	O(34)	C(35)	−1.0(7)	O(33)	C(32)	C(12)	C(11)	9.2(7)
O(33)	C(32)	C(12)	C(13)	−171.8(5)	O(34)	C(32)	C(12)	C(11)	−170.9(3)
O(34)	C(32)	C(12)	C(13)	8.0(5)	N(2)	N(3)	C(4)	C(5)	−60.8(4)
N(2)	C(1)	C(6)	C(5)	−5.6(5)	N(2)	C(1)	C(6)	C(7)	−179.9(3)
N(2)	C(1)	C(10)	C(9)	179.3(3)	N(2)	C(1)	C(10)	C(11)	1.4(5)
N(2)	C(13)	C(12)	C(11)	3.2(6)	N(2)	C(13)	C(12)	C(32)	−175.7(3)
N(3)	N(2)	C(1)	C(6)	−11.1(6)	N(3)	N(2)	C(1)	C(10)	171.6(3)
N(3)	N(2)	C(13)	C(12)	−173.9(3)	N(3)	C(4)	C(5)	C(6)	44.9(4)
N(3)	C(4)	C(5)	C(15)	−82.0(4)	N(3)	C(4)	C(5)	C(22)	165.0(3)
C(1)	N(2)	N(3)	C(4)	43.5(4)	C(1)	N(2)	N(3)	C(14)	−83.4(4)
C(1)	N(2)	C(13)	C(12)	2.6(5)	C(1)	C(6)	C(5)	C(4)	−11.1(4)
C(1)	C(6)	C(5)	C(15)	111.5(4)	C(1)	C(6)	C(5)	C(22)	−128.8(3)
C(1)	C(6)	C(7)	C(8)	0.5(5)	C(1)	C(10)	C(9)	C(8)	0.8(5)
C(1)	C(10)	C(11)	C(12)	3.8(5)	C(4)	N(3)	N(2)	C(13)	−140.0(3)
C(4)	C(5)	C(6)	C(7)	162.7(3)	C(5)	C(4)	N(3)	C(14)	62.1(4)
C(5)	C(6)	C(1)	C(10)	171.6(3)	C(5)	C(6)	C(7)	C(8)	−173.6(3)
C(5)	C(15)	O(17)	C(18)	176.6(3)	C(5)	C(22)	O(24)	C(25)	−177.7(3)
C(6)	C(1)	N(2)	C(13)	172.5(3)	C(6)	C(1)	C(10)	C(9)	2.0(5)
C(6)	C(1)	C(10)	C(11)	−175.8(3)	C(6)	C(7)	C(8)	C(9)	2.2(6)
C(7)	C(6)	C(1)	C(10)	−2.7(5)	C(7)	C(6)	C(5)	C(15)	−74.7(4)
C(7)	C(6)	C(5)	C(22)	45.0(4)	C(7)	C(8)	C(9)	C(10)	−2.9(6)
C(8)	C(9)	C(10)	C(11)	178.7(3)	C(9)	C(10)	C(11)	C(12)	−174.1(3)
C(10)	C(1)	N(2)	C(13)	−4.8(5)	C(10)	C(11)	C(12)	C(13)	−6.0(5)
C(10)	C(11)	C(12)	C(32)	172.9(3)	C(12)	C(32)	O(34)	C(35)	179.2(4)
C(13)	N(2)	N(3)	C(14)	93.1(4)	C(15)	O(17)	C(18)	C(19)	63.6(6)
C(15)	O(17)	C(18)	C(20)	−178.3(4)	C(15)	O(17)	C(18)	C(21)	−61.4(6)
C(22)	O(24)	C(25)	C(26)	−63.7(6)	C(22)	O(24)	C(25)	C(27)	61.0(5)
C(22)	O(24)	C(25)	C(28)	177.0(4)	C(32)	O(34)	C(35)	C(36)	−90.4(7)

containing an oxo group adjacent to the *N*-methyl substituent in which a near planar arrangement is observed for the tricyclic array. Of further interest, the N(3)–C(14) bond length of 1.459 Å, characteristic of a pyramidal nitrogen, is longer than the 1.365 Å distance obtained for the oxo compound, which is indicative of a typical amide structure.

Conclusions

In summary, we have developed a useful procedure for the alkylation of the potentially versatile 1-[*N*-(hydroxymethyl)-*N*-methylamino]-4-quinolones **2a** and **2b**, in order to obtain malonates **4a** and **4b**, key intermediates in the preparation of potent pyrido[3,2,1-*ij*]cinnoline DNA gyrase inhibitors. Apart from the simplicity and reliability of this new method for large scale preparations, an additional advantage is the ability to employ other malonates in the coupling step; an important consideration related to cost-efficacy. We have employed diethyl malonate in this sequence without trouble and believe that other nucleophiles should also undergo this coupling leading to novel series of quinolone antibacterial agents.

Experimental

General Procedures. Melting points were measured on a Thomas–Hoover apparatus and are uncorrected. IR spectra were recorded on a Horiba Spectradesk FT-210 or a Hitachi IR-408 spectrometer. ^{1}H NMR spectra were measured on a Bruker AC200P at 200 MHz. Chemical shifts are given in parts per million, and tetramethylsilane was used as the internal standard for spectra obtained in DMSO-d_6 and $CDCl_3$. Mass spectra were measured on a Hitachi

Table 4. Crystal Data and Data Collection Details for **6b**

Formula	$C_{25}H_{30}F_2N_2O_7$
Formula weight	508.52
Crystal system	Triclinic
Space group	$P\bar{1}$(♯2)
a/Å	10.788(1)
b/Å	14.720(1)
c/Å	8.5305(6)
α/°	104.669(6)
β/°	95.499(7)
γ/°	97.930(7)
V/Å^3	1285.7(2)
Z	2
D_{calcd}/g cm^{-3}	1.313
$F(000)$	536.00
μ(Cu $K\alpha$)/cm^{-1}	8.94
Crystal dimensions/mm^3	0.20 × 0.20 × 0.10
2θ range/°	130.1
Total no. of observed reflections	4633
No. of unique reflections with $I > 3\sigma(I)$	3505
Final no. of variables	445
Final residuals R	0.057
R_W	0.055

Model M-80 mass spectrometer using EI 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 purification. Column chromatography was performed using silica gel, and the progress of reactions was determined by TLC analysis on silica gel coated glass plates.

Methyl 6,7,8-Trifluoro-1-[*N*-(hydroxymethyl)-*N*-methylamino]-4-oxo-1,4-dihydroquinoline-3-carboxylate (2a). A suspension of amine **1a** (25.0 g, 87.4 mmol) in water (250 mL) was treated with 35% aqueous formaldehyde solution (250 mL), heated at 80—85 °C for 2 h, then cooled, filtered, and the collected solid washed thoroughly with water and then dried in a dessicator at 40—45 °C over diphosphorus pentaoxide to constant weight to give **2a** (26.7 g, 97%) as a white solid, mp 174—176.5 °C; ^{1}H NMR (DMSO-d_6) δ = 8.97 (s, 1H), 7.93 (ddd, 1H, J = 2.1, 8.4, 10.4 Hz), 6.30 (t, 1H, J = 6.5 Hz), 4.66—4.50 (m, 2H), 3.77 (s, 3H), 3.00 (s, 3H); IR(KBr) 3435, 1730, 1616 cm^{-1}; MS m/z 317 (MH$^+$). Found: C, 49.40; H, 3.34; N, 8.77%. Calcd for $C_{13}H_{11}F_3N_2O_4$: C, 49.37; H, 3.51; N, 8.86%. The following quinolone was obtained using the same procedure.

Ethyl 6,7,8-Trifluoro-1-[*N*-(hydroxymethyl)-*N*-methylamino]-4-oxo-1,4-dihydroquinoline-3-carboxylate (2b). From amine **1b** (50.0 g). Yield: 54.2 g (98%). Yellow solid, mp 140—142 °C (lit,[6] 138—139 °C); ^{1}H NMR (DMSO-d_6) δ = 8.95 (s, 1H), 7.92 (ddd, 1H, J = 2.2, 8.4, 10.5 Hz), 6.30 (t, 1H, J = 6.4 Hz), 4.66—4.50 (m, 2H), 4.25 (q, 2H, J = 7.1 Hz), 3.00 (s, 3H), 1.28 (t, 3H, J = 7.1 Hz); IR (Nujol) 3425, 1710, 1620 cm^{-1}; MS m/z 330 (M$^+$). Found: C, 50.70; H, 3.88; N, 8.42%. Calcd for $C_{14}H_{13}F_3N_2O_4$: C, 50.91; H, 3.97; N, 8.48%.

Methyl 1-{*N*-[2,2-Bis(*t*-butoxycarbonyl)ethyl]-*N*-methylamino}-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (4a). A solution of **2a** (14.0 g, 44.3 mmol) in tetrahydrofuran (140 mL) at room temperature was treated dropwise with thionyl chloride (4.2 mL, 57.6 mmol), stirred for 20 min at the same temperature, evaporated, azeotroped with toluene (60 mL), and then dried under high vacuum to give the crude chloride. This material was dissolved in tetrahydrofuran (140 mL), cooled to 0 °C, treated with sodium hydride (62% dispersion in mineral oil) (3.78 g, 94.5 mmol), stirred 30 min and then treated with a preformed solution of the sodium salt of di-*t*-butyl malonate (prepared by treating a solution of malonate (11.1 g, 51.4 mmol) in tetrahydrofuran (140 mL) at 0 °C with 62% sodium hydride (1.89 g, 48.7 mmol), followed by stirring for 30 min at the same temperature) in a single portion. After 1.5 h, the reaction was quenched with water (60 mL), the clear solution adjusted to pH 7 with 6 M-hydrochloric acid (1 M = 1 mol dm^{-3}), and then extracted with ethyl acetate (600 mL). The organic layer was washed with water, brine and the insoluble material was removed by filtration to give pure **5a** (2.96 g, 13%). Trituration of the evaporated filtrate with diisopropyl ether provided an additional 10.28 g (45%) of pure **5a** as a light yellow powder after drying. Further trituration of the evaporated mother liquors gave 5.71 g (25%) of ring-opened, pure, **4a** as a white crystalline solid. Since **5a** is the functional equivalent of **4a** in the next reaction, total yield of desired product is 83%. Mp 119.5—120.5 °C; ^{1}H NMR ($CDCl_3$) δ = 8.66 (s, 1H), 8.10 (ddd, 1H, J = 2.2, 7.9, 10.2 Hz), 3.94 (s, 3H), 3.64—3.57 (m, 2H), 3.26 (t, 1H, J = 7.1 Hz), 3.01 (s, 3H), 1.45 (s, 9H), 1.38 (s, 9H); IR (KBr) 1739, 1705, 1653, 1624 cm^{-1}; MS m/z 514 (M$^+$). Found: C, 56.18; H, 5.56; N, 5.42%. Calcd for $C_{24}H_{29}F_3N_2O_7$: C, 56.03; H, 5.68; N, 5.44%.

Methyl 3,3-Bis(*t*-butoxycarbonyl)-7,8,9-trifluoro-5-hydroxy-1,2,3,3a-tetrahydropyrazolo[1,5-*a*]quinoline-4-carboxylate (5a). Mp 145—147 °C; ^{1}H NMR ($CDCl_3$) δ = 12.62 (s, 1H), 7.21 (ddd, 1H, J = 2.2, 8, 10.2 Hz), 5.71 (s, 1H), 3.95 (d, 1H, J = 12.9 Hz), 3.82 (s, 3H), 3.05 (d, 1H, J = 12.9 Hz), 2.70 (s, 3H), 1.51 (s, 9H), 1.33 (s, 9H); IR (KBr) 1743, 1722, 1655 cm^{-1}; MS m/z 515 (MH$^+$). Found: C, 55.24; H, 5.69; N, 5.33%. Calcd for $C_{24}H_{29}F_3N_2O_7$: C, 56.03; H, 5.68; N, 5.44%. Calcd for $C_{24}H_{29}F_3N_2O_7 \cdot 0.4H_2O$: C, 55.25; H, 5.76; N, 5.37%. Prolonged drying over diphosphorus pentaoxide did not improve this analysis.

Ethyl 1-{*N*-[2,2-Bis(*t*-butoxycarbonyl)ethyl]-*N*-methylamino}-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (4b). By application of the same procedure as above, and purification of the crude product by silica-gel chromatography (50 : 1 CH_2Cl_2: MeOH elution) **4b** (4.30 g, 81%) was obtained from hydroxymethyl derivative **2b** (3.30 g) as a white solid, mp 113—115 °C (lit,[1] 112—115 °C). ^{1}H NMR, IR, and MS spectral data were identical with those of a sample prepared by our previously reported method.[1] The crude product showed ^{1}H NMR signals only for the pyrazolo[1,5-*a*]quinoline derivative **5b**. For obtaining analytical data, a small portion of the crude product was crystallized from hexane to give pure **5b** as a yellow powder.

Ethyl 3,3-Bis(*t*-butoxycarbonyl)-7,8,9-trifluoro-5-hydroxy-1,2,3,3a-tetrahydroprazolo[1,5-*a*]quinoline-4-carboxylate (5b). Mp 114—116 °C; ^{1}H NMR ($CDCl_3$) δ = 12.80 (s, 1H), 7.22 (ddd, 1H, J = 2.2, 8.1, 10.3 Hz), 5.76 (s, 1H), 4.44—4.13 (m, 2H), 3.91 (d, 1H, J = 12.9 Hz), 3.07 (d, 1H, J = 12.9 Hz), 2.69 (s, 3H), 1.50 (s, 9H), 1.38 (t, 3H, J = 7.1 Hz), 1.33 (s, 9H); IR (KBr) 1743, 1722, 1662 cm^{-1}; MS m/z 529 (MH$^+$). Found: C, 56.19; H, 5.59; N, 5.33%. Calcd for $C_{25}H_{31}F_3N_2O_7$: C, 56.81; H, 5.91; N, 5.30%. Calcd for $C_{25}H_{31}F_3N_2O_7 \cdot 0.3H_2O$: C, 56.24; H, 5.96; N, 5.25%. As with the similarly labile **5a**, prolonged drying did not improve this analysis, however in both cases, homogeneity was indicated by NMR and the sharp melting points.

Methyl 3,3-Bis(*t*-butoxycarbonyl)-4,5-difluoro-1-methyl-7-oxo-2,3-dihydro-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-8-carboxylate (6a). A solution of **5a** (13.0 g, 25.3 mmol) in dimethyl sulfoxide (195 mL) was treated with cesium carbonate (4.12 g, 12.6 mmol) at 80 °C for 3.5 h then cooled and poured into ice-water (2 L). 1 M-

hydrochloric acid (26 mL) was added and the mixture was extracted with ethyl acetate (2 L). The separated organic layer was filtered to remove insoluble material then washed with water (3×2 L), brine, dried ($MgSO_4$) and concentrated under reduced pressure. Dichloromethane (200 mL) was added to the residue and the insoluble material discarded. The evaporated filtrate was triturated with diisopropyl ether (100 mL) and the solid collected and dried to give **6a** (7.14 g, 57%) as a white powder, mp 173—175 °C; ^{1}H NMR ($CDCl_3$) δ = 8.57 (s, 1H), 8.30 (dd, 1H, J = 8.4, 10.2 Hz), 4.07 (s, 2H), 3.93 (s, 3H), 2.78 (s, 3H), 1.48 (s, 18H); IR (KBr) 1736, 1637, 1612 cm^{-1}; MS *m/z* 495 (MH^+). Found: C, 57.81; H, 5.39; N, 5.81%. Calcd for $C_{24}H_{28}F_2N_2O_7$: C, 58.29; H, 5.71; N, 5.66%. The following tricycle was obtained using the same procedure.

Ethyl 3,3-Bis(*t*-butoxycarbonyl)-4,5-difluoro-1-methyl-7-oxo-2,3-dihydro-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-8-carboxylate (6b). From pyrazolo[1,5-*a*]quinoline **5b** (300 mg). Yield: 140 mg (49%), mp 177—178 °C (lit,[1] 175—177 °C). ^{1}H NMR, IR, and MS spectra were identical with an authentic sample.[1] Found: C, 58.80; H, 5.96; N, 5.44%. Calcd for $C_{25}H_{30}F_2N_2O_7$: 59.05; H, 5.95; N, 5.51%.

X-Ray Crystallographic Analysis of 6b. Colorless prismatic crystals of **6b** were grown by slow evaporation of an acetone solution. Diffraction measurements were performed on a Rigaku AFC-5R diffractometer using graphitemonochromatized Cu $K\alpha$ radiation (λ = 1.54178 Å). Data were collected at 25 °C using the ω–2θ scan technique within a 2θ range of 130.1°. Of the 4633 reflections collected, 4378 were unique; the structure was solved by direct methods[13] and refined by a full-matrix least squares method using 3505 reflections.

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8) For example, a solution of **2b** (3.0 g, 9.08 mmol) in dichloromethane (60 mL) at 0 °C was treated with trichloromethylsilane (1.18 ml, 9.99 mmol) for 1.5 h. After addition of diisopropyl ether (120 mL), the precipitate was collected and washed with diisopropyl ether and hexane to give chloride **3b** (3.07 g, 97%) as a moisture-sensitive yellow powder. ^{1}H NMR ($CDCl_3$) δ = 9.01 (s, 1H), 8.07 (ddd, 1H, J = 2.2, 8.1, 10.1 Hz), 5.47 and 5.43 (each d, 2H total, AB system, J = 11.1 Hz), 4.39 (q, 2H, J = 7.1 Hz), 3.20 (s, 3H), 1.41 (t, 3H, J = 7.1 Hz).

9) Treatment of **4b** with sodium hydride in tetrahydrofuran at 0 °C for 30 min, followed by water quench and adjustment to pH 7 gave after extraction a mixture of **4b** and **5b**. Trituration with hexane gave a pure sample of **5b**.

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11) Hydrolysis of **6a** with 6 M-hydrochloric acid-acetic acid at 100 °C gave the same diacid (94%) reported in our earlier paper.[1]

12) Complete details of the X-ray determination are deposited as Document No. 69027 at the Office of the Editor of Bull. Chem. Soc. Jpn.

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