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A concise synthesis of HIV integrase inhibitors bearing the dipyridone acid motif

Michelle Y. Platts *, Christopher G. Barber, Jean-Yves Chiva, Rachel L. Eastwood, David R. Fenwick, Kerry A. Paradowski, David C. Blakemore

Pfizer Global Research and Development, Sandwich Laboratories, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK

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ABSTRACT

An efficient route to dipyridone acid HIV integrase inhibitors is developed. The key steps include a one-pot three-step formation of the core template (containing one point of structural diversity) followed by a regioselective benzylation and in situ deprotection to afford the title compounds.

In connection with a programme to discover novel HIV integrase inhibitors,[1] we report our successful exploits in the preparation of 6-benzyl-1-alkyl-4,7-dioxo-1,4,6,7-tetrahydro-1,6-naphthyridine-3-carboxylic acids (dipyridone acids) **1**, Figure 1. From the outset, we desired a facile and reliable method for the preparation of dipyridone acids **1**, which would allow rapid access to a range of analogues in order to study the structure–activity relationships (SARs) in this series.

Our retrosynthetic analysis (Scheme 1) reveals that **1** may be derived from the hydrolysis and alkylation of pyridine ester **2**. The bromo analogue of **2** (X = Br, R = CH_2CH_3) has been previously reported by Strehlke and was synthesised in nine steps from 2-amino-5-methylpyridine.[2] We required a more concise route to **2**, which we believed could be formed from the addition of a suitable amine to ethyl (2*E*/*Z*)-2-[(4,6-dichloropyridin-3-yl)carbonyl]-3-(dimethylamino)prop-2-enoate (**3**), followed by ring-closure onto the chloropyridine moiety. Compound **3** should be accessible from 4,6-dichloronicotinic-3-carboxylic acid (**4**), which can be prepared from diethyl 1,3-acetonedicarboxylate (**5**).

As outlined in Scheme 2, acid **4** was synthesised in three-steps from commercially available 1,3-acetonedicarboxylate **5**. Reaction of **5** with triethyl orthoformate in acetic anhydride, followed by cyclisation with aqueous ammonia, gave **6**.[3] Treatment of **6** with phosphorus oxychloride under reflux conditions followed by ester hydrolysis under basic conditions gave the desired acid **4**.[4] Compound **4** was readily converted into the acid chloride **7**[5] and was subsequently treated with ethyl 3-dimethylaminoacrylate, using the conditions developed by Shinkai and co-workers,[6] to provide enaminoate **3**. Enaminoate **3** reacted readily with a series of amines. In this example it reacts with L-(+)-valinol to provide **8**, and after cyclisation under basic conditions, afforded ketoester **9** in moderate yield. This step was unoptimised, but allowed access to sufficient material to provide key analogues for our SAR analysis.

We then attempted chloropyridine–ketoester hydrolysis to the corresponding pyridone acids directly. We anticipated that hydrolysis of intermediate **10**, for example (prepared from 2,4-dimethoxybenzylamine using the route outlined in Scheme 2), using sodium hydroxide would be straightforward. However, initial work suggested that this reaction was far from trivial and a range of both acidic and basic hydrolysis conditions met with little success; our most successful attempt to form a pyridone acid utilised potassium *tert*-butoxide in *t*-butanol, which converted ketoester **10** into the desired compound **11**, albeit in poor isolated yield (Scheme 3).

As expected, in the presence of sodium hydroxide it appeared that the initial ester hydrolysis was facile (by LCMS) while displacement of the chloro substituent was hampered due to the poor solubility of the intermediate chlorocarboxylates in the reaction solvents used (water, DMSO and DMF). This led us to investigate

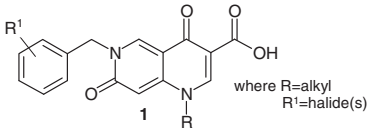

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Figure 1.

* Corresponding author. Tel.: +44 130 464 9141; fax: +44 130 465 1821.
E-mail address: michelle.platts@pfizer.com (M.Y. Platts).

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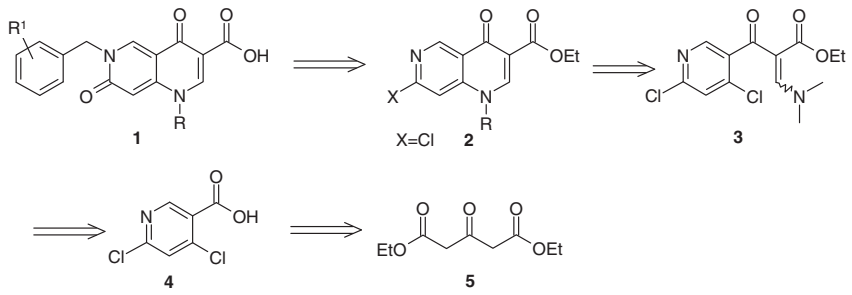
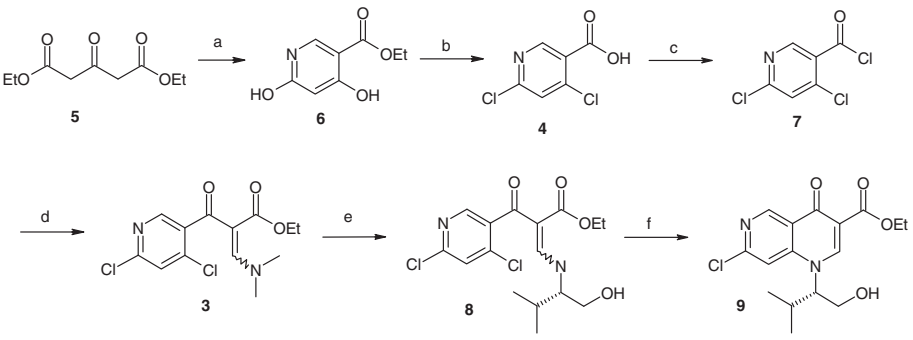
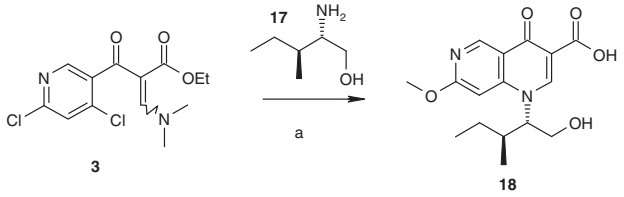


Scheme 1. Retrosynthesis of compounds of type **1**.

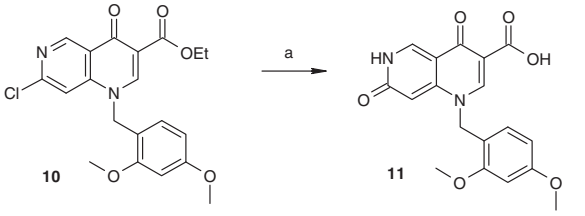


Scheme 2. Reagents and conditions: (a) $CH(OEt)_3$, Ac_2O, 145 °C then aq NH_3 61%; (b) (i) $POCl_3$, reflux 73%; (ii) LiOH, H_2O, THF, rt 96%; (c) $SOCl_2$, DMF, toluene, reflux, quantitative; (d) ethyl 3-dimethylaminoacrylate, Et_3N, THF, 65 °C, 79%; (e) L-(+)-valinol, THF, rt 78%; (f) K_2CO_3, DMF, 100 °C, 35%.

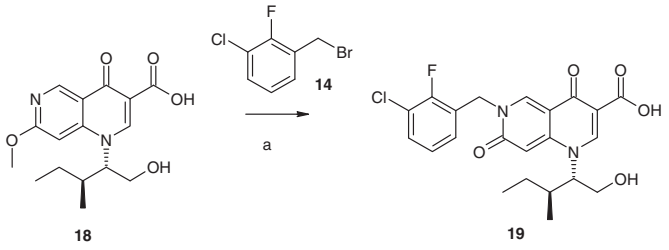
alcohol solvent systems for the hydrolysis. The use of hydroxide in methanol showed evidence for the formation of the corresponding methoxypyridine, and it was found that the formation of methoxypyridine **12** from the reaction of **9** with sodium methoxide in methanol occurred readily and in high yield (Scheme 4). With **12** in hand, the desired product **16** was now accessible. Demethylation with TMSI in CH_2Cl_2 gave pyridone **13**, and when treated with **14** under basic conditions, led to a mixture of *N*- and *O*-benzylated pyridone products (~1:1), as well as benzylation of the carboxylic acid. Separation of the desired *N*-benzyl isomer **15** followed by es-



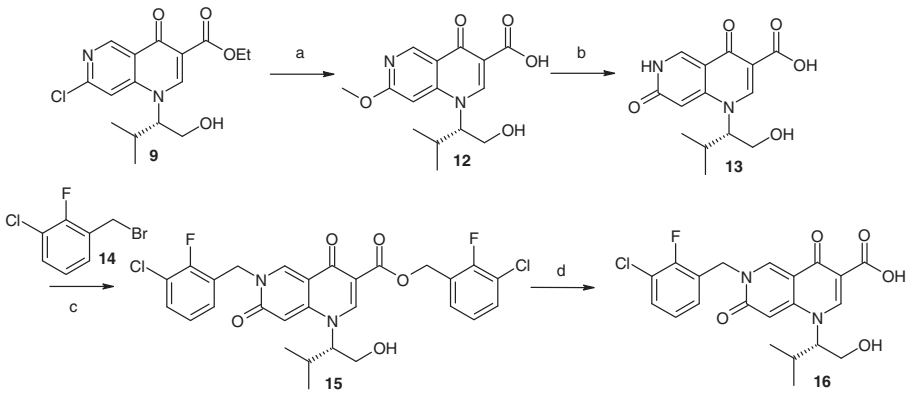
Scheme 5. Reagents and conditions: (a) **17**, NaOMe, MeOH, reflux then aqueous work-up, 70%.



Scheme 3. Reagents and conditions: (a) KO^{t}Bu, *t*-BuOH, 90 °C, 10–15%.



Scheme 6. Reagents and conditions: **14**, NaI, MeCN, MW, 170 °C, 1 h, 57%.



Scheme 4. Reagents and conditions: (a) NaOMe, MeOH, reflux, then aqueous work-up, 85%; (b)TMSI, CH_2Cl_2, rt, 65%; (c) **14**, K_2CO_3, DMF, 60 °C, 28%; (d) 1 N $NaOH_{(aq)}$, THF, rt, 60%.

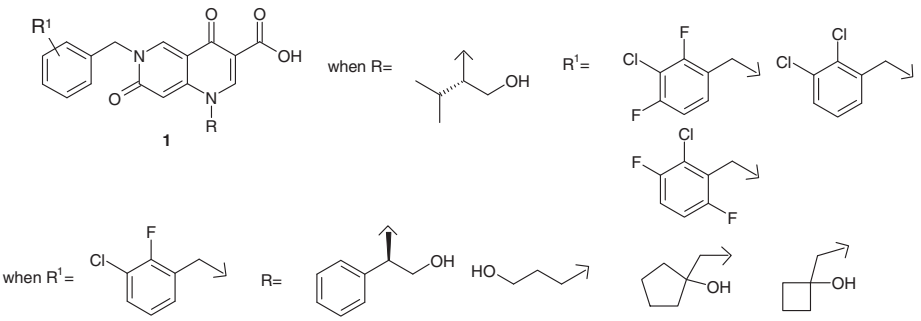


Figure 2.

ter hydrolysis afforded dipyridone acid **16** in reasonable yield. Given the difficult isolation of intermediate **13** and the subsequent low yielding unselective alkylation we decided to investigate a more direct and selective route to compounds of type **1**, since the synthetic complexity of the existing route precluded an efficient elaboration of the SAR.

The first improvement made to the route was to telescope the three-steps of amine addition, ring-closure and chloro to methoxy conversion into a single step. This was achieved by reacting enaminoate **3** with the desired amine, in this case **17**, in the presence of sodium methoxide in methanol at reflux, to afford the corresponding product **18** in an impressive overall yield, (Scheme 5). The ability to utilise the methoxide as base and nucleophile in such a sequence is, to our knowledge, unprecedented.

We then explored a further improvement to the route which involved direct benzylation of the methoxypyridine intermediate **18**.[7] It was anticipated that benzylation would occur selectively on the pyridine nitrogen and that the resulting quaternary ammonium salt would be readily demethylated using an appropriate nucleophile. Under the conditions reported by Bowman and Bridge, who had shown a similar reaction with 2-methoxypyridine to be successful,[8] we attempted the regioselective synthesis of *N*-benzyl pyridone **19**. Our initial results in refluxing MeCN showed no reaction, although pleasingly, at the higher temperature achieved under microwave conditions, the desired reaction did occur, indicating that the pyridine nitrogen in our system was less nucleophilic than that of methoxypyridine (Scheme 6).[9] Under these conditions *N*-benzylation and demethylation occurred exclusively to afford dipyridone acid **19**.[10]

Similar methodology was applied to prepare further analogues of compound **19** (Fig. 2). These derivatives possessed potent anti-HIV integrase activity and a further explanation of the SAR will be described elsewhere.

In summary, a novel and concise synthetic route to dipyridone acids of type **1** has been achieved. Significant improvements made to the initial route made for a highly efficient synthesis of cyclised methoxypyridine intermediates and regioselective *N*-benzyl dipyridone acid preparation. Late stage *N*-benzyl variation has allowed rapid access to a range of analogues. A key feature of this work has been the reduction of the route complexity as a means to explore rapidly the SAR.

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7. Preparation of **18**.
   To a stirred suspension of **3** (100 mg, 0.32 mmol) in MeOH (10 mL) was added **17** (41 mg, 0.35 mmol) and the mixture was stirred at rt for 1 h. NaOMe (170 mg, 3.15 mmol) was added portionwise and the mixture was stirred at reflux for 4 h. The resulting mixture was concentrated under reduced pressure and diluted and acidified to pH 1 with 2 N HCl (aq). The aqueous was extracted with 5% MeOH and CH_2Cl_2 (15 mL) and the organics dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by chromatography (silica gel, eluting with 100% heptane–100% EtOAc) to provide **18** as a white foam (71 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.34 (1H, s), 8.82 (1H, s), 6.79 (1H, s), 4.34 (1H, m), 4.17–4.05 (5H, m), 2.19 (1H, m), 1.24 (1H, m), 1.13 (3H, d, J = 6.6 Hz), 1.03 (1H, m), 0.82 (3H, t, J = 7.4 Hz). LRMS (Cl^-): 319 $[M-H]^-$.
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10. Preparation of **19**.
    To a stirred suspension of **18** (71 mg, 0.22 mmol) in MeCN (1 mL) was added **14** (109 mg, 0.49 mmol) and NaI (66 mg, 0.44 mmol) and the mixture was heated under microwave irradiation (Biotage, Initiator 8) at 170 °C for 1 h. The resulting mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2 (5 mL), washed with 10% aqueous $Na_2S_2O_3$ solution (5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by reverse phase HPLC (MeCN/H_2O/TFA 5%/95%/0.1%, flow rate 20 mL/min, column: Phenomenex C18 100A 150 × 15 mm, 10 micron) to provide **19** as a yellow solid (57 mg, 57% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.15 (1H, s), 8.67 (1H, s), 7.54 (1H, dt, J = 7.36, 2.32 Hz), 7.26–7.17 (2H, m), 6.78 (1H, s), 5.43 (2H, s), 5.15 (1H, t, J = 5.13 Hz), 4.45 (1H, m), 3.84 (1H, m), 3.65 (1H, m), 2.07 (1H, m), 1.24 (1H, m), 1.04 (3H, d, J = 6.50 Hz), 1.03 (1H, m), 0.77 (3H, t, J = 7.40 Hz). LRMS (Cl^+): 449/451 $[M+H]^+$.