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Routes to HIV-integrase inhibitors: efficient synthesis of bicyclic pyrimidones by ring expansion or amination at a benzylic position

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ABSTRACT

Ring expansion of [6,6] bicyclic pyrimidones led, through an aziridinium intermediate, to potent HIV-integrase inhibitors with a [7,6] core. A more flexible and diversity-oriented synthesis of functionalized pyrimidohexahydrodiazepines was then developed; the key benzylic substituent was introduced in *one pot* by using sequentially DDQ and BnMeNH. Both synthetic routes are described.

In our drug discovery project on HIV-integrase, bicyclic pyrimidones (**1A** in Fig. 1) were identified as potent inhibitors,[1] and we reasoned that an additional heteroatom in the tetrahydropyridine ring would give us another handle to modulate the physico-chemical properties of this class of compounds. With this idea in mind we started the synthesis of tetrahydropirazopyrimidones **1B**.

The fused bicyclic core was obtained in five steps as depicted in Schemes 1 and 4 could be isolated in 44% yield from intermediate **2**[2] without the need to purify at intermediate stages using the following sequence: reaction with 2 equiv of *p*-fluorobenzylamine both formed the carboxamide and cleaved the benzoate-protecting group. TFA promoted removal of the Boc group then afforded the free amine. Imine formation by reaction with 1 equiv of chloroacetaldehyde and removal of volatiles, followed by reduction in MeOH then gave crude **3**. Base-mediated cyclization, followed by chromatographic purification, afforded **4**. After protection of the secondary amine as a carbamate and deprotection of the benzyl group by hydrogenation, the primary alcohol **5** was activated as

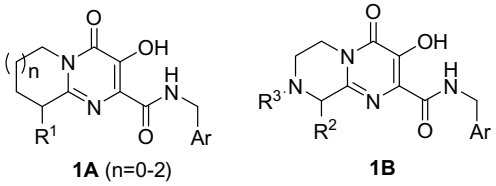
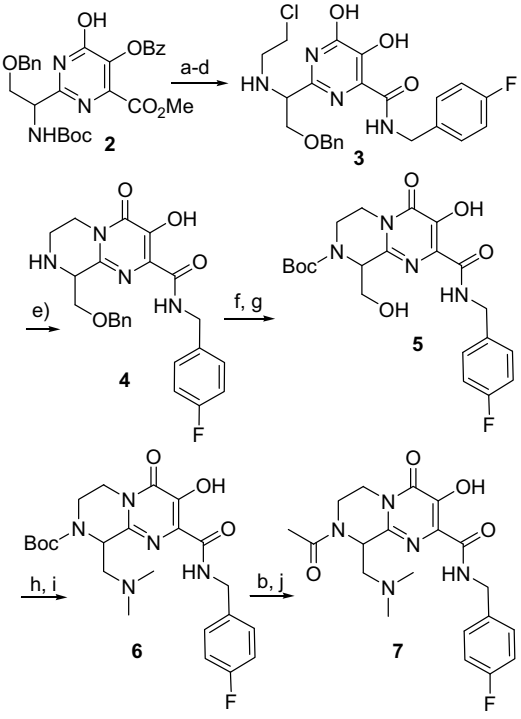


Figure 1.



Scheme 1. Reagents and conditions: Tetrahydropirazopyrimidones: synthetic scheme and conditions. (a) 4-Fluorobenzylamine, MeOH, rt; (b) TFA, DCM; (c) aq $ClCH_2CHO$, $CH(OMe)_3$; (d) $NaCNBH_3$, AcOH, MeOH; (e) *t*-BuOK, dioxane, reflux; (f) Boc_2O, MeOH; (g) 10% Pd/C, H_2, MeOH; (h) MsCl, TEA, $CHCl_3$; (i) 2 M Me_2NH, THF, rt; (j) Ac_2O, TEA, DCM.

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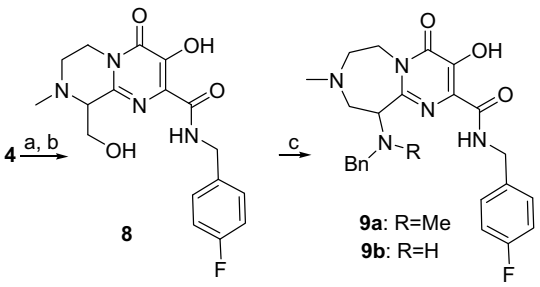
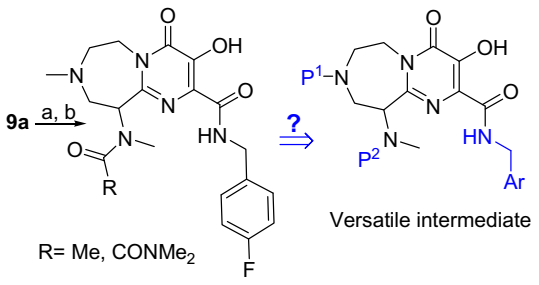


Scheme 2. Pyrimidohexahydrodiazepines by ring expansion of the [6,6] system. Reagents and conditions: (a) aq HCHO, AcOH, $NaCNBH_3$, MeOH; (b) 10% Pd/C, H_2, MeOH; (c) MsCl, TEA, CH_3CN, 0 °C to rt; then MeBnNH (or $BnNH_2$ for **9b**), 60 °C.



Scheme 4. Reagents and conditions: Final steps and an alternative intermediate to this class of compounds. Reagents and conditions: (a) 10% Pd/C, H_2, MeOH, aq HCl; (b) ClCOR, TEA, DCM.

the corresponding mesylate. Displacement with dimethylamine went cleanly to give **6**; Boc cleavage and final acetylation then led to isolation of **7**.[3]

The scaffold **1B** is versatile, opening up the possibility for diverse functionalization of the endo- and exo-cyclic amines. We decided to evaluate analogs complementary to **7**, bearing the basic amine on the core and an acyl substituent at the outside of the ring. To this end, amine **4** was methylated by reductive amination, followed by hydrogenation of the benzyl ether, mesylation and reaction with MeBnNH; but to our initial surprise instead of the anticipated [6,6] system, a hexahydrodiazepine was obtained in this case (Scheme 2).

Under optimized reaction conditions, bis-amine **9a** was isolated in ca. 25% yield from primary alcohol **8**.[4] Furthermore, use of different amines was disappointing: benzylamine afforded only 15% of **9b**, and similar or lower yield resulted when aliphatic primary amines (e.g., cyclohexyl and benzyl) were used.

A potential rationale for this (not entirely unexpected[5]) finding, can be found by invoking the participation of the ring nitrogen to form an aziridinium ion (*path a*, Scheme 3) from mesylate **10a**. The corresponding quinoid-like species depicted in Scheme 3 could also be involved in this reaction.

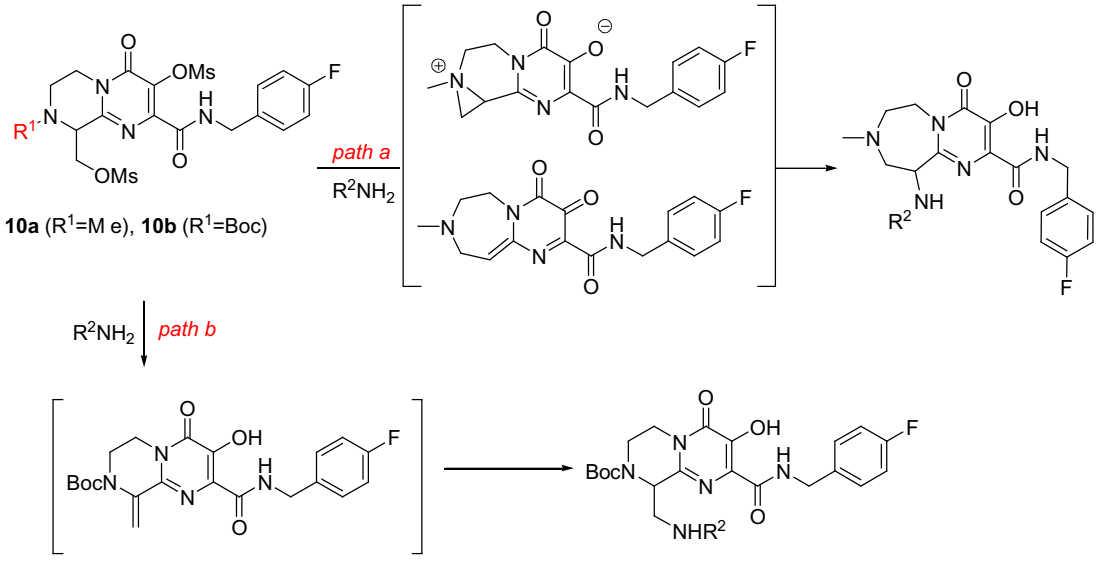
For carbamate **10b** this mechanism is unlikely, due to the electron-withdrawing nature of the carbamate; elimination seems to take place (*path b*, Scheme 3), and addition of the amine to the double bond (intermediate compatible with mass spectrum) would lead to the expected [6,6] bicyclic system.

To finish the synthesis, the benzyl group of **9a** was removed by hydrogenation, and the exocyclic amine was acylated as shown in Scheme 4 to provide the first analogs in the series. Preliminary SAR proved sufficiently encouraging to warrant a more extensive exploration of this novel structural class.

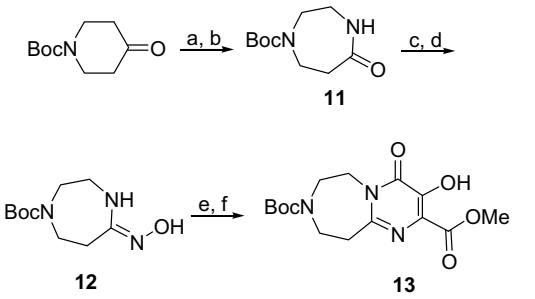
To facilitate a more complete SAR, a better synthesis of a more versatile intermediate (Scheme 4) with the [7,6] core was needed, ideally fulfilling the following requirements:

(1) Flexibility: potential for the introduction of diversity (orthogonal P_1, P_2, and formation of the carboxamide as late as possible).
(2) Acceptable overall yield.
(3) Trouble-free purification of intermediates (suitable for multi-gram scale).

Based on our previous experience,[6] we decided to use *N*-Boc-4-piperidone as the starting material. Lactam **11** was prepared by Beckmann rearrangement according to a published procedure,[7] and then converted to amidoxime **12** and reacted with DMDA under conditions previously optimized[6,8] to afford **13** in 19% overall yield on a 25 g scale (Scheme 5). Conveniently, for large-scale purposes, no chromatography was needed to obtain pure **13**.



Scheme 3. The two different reaction pathways leading to either [7,6] or [6,6] system depending on the nature of R^1.



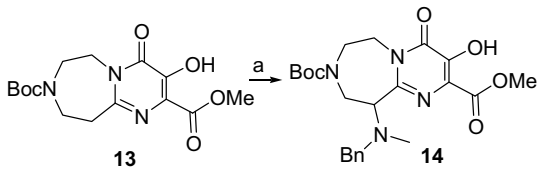
Scheme 5. Pyrimidohexahydrodiazepine core from commercially available, *N*-Boc-4-piperidone. Reagents and conditions: (a) NH_2OH (1.2 equiv), MeOH, 55 °C, 2 h; (b) TsCl, (1.5 equiv), K_2CO_3 (2.5 equiv), DME/water 1.5:1, 82 °C, 3 h; (c) P_4S_{10} (0.2 equiv), hexamethyldisiloxane (2 equiv), DCM, 1 h; (d) NH_2OH (1.2 equiv), MeOH, 55 °C, 2 h; (e) Dimethyl acetylenedicarboxylate, CH_3CN; (f) Xylenes, 145 °C.

Despite being precedent with related pyrimidone substrates,[9] attempts to functionalize the benzylic position via bromination failed, resulting only in Boc deprotection under forcing conditions.

We turned our attention to DDQ (Scheme 6) because of its known ability to selectively oxidize activated benzylic positions. We optimized the reaction conditions using different stoichiometries of the reagent, and we found that upon treating **13** with 2.1 equiv of DDQ and 6 equiv of benzylmethylamine the desired amine **14** was obtained in greater than 50% yield.[10]

During these trials, we discovered two main side products that were characterized as **15a** and **15b**, excess of the nucleophile being essential to minimize their formation (Fig. 2).

It is generally accepted that quinones (Q) react with C–H bonds abstracting a hydrogen to give a radical, a second electron is transferred from the quinol radical (QH·) to form a carbocation or a donor–acceptor complex.[11a] However, also electrophilic intermediates such as **16**, in which there is a covalent bond between DDQH and the substrate, have been proposed.[11b]



Scheme 6. Reagents and conditions: (a) DDQ (2–2.5 equiv), dioxane, reflux; then MeBnNH (6 equiv), dioxane, 65 °C.

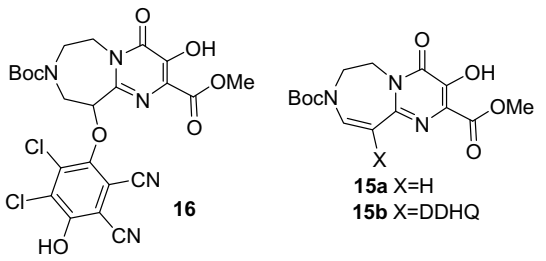


Figure 2. A possible intermediate in the formation of **14** is derivative **16**. **15a** and **15b** were identified as by-products of the reaction.

Even though the use of other nucleophiles was less successful,[12] **14** itself still represents a versatile intermediate since it bears three orthogonal-protecting groups (carbamate, benzyl amine and methyl ester). Thus, R^1, R^2, and Ar groups could be incorporated sequentially passing via through either **19** or **21** (Scheme 7) as appropriate, based on the SAR requirements. Details of these studies will be reported in due course.[13]

Acknowledgements

We thank Silvia Pesci and Edith Monteagudo for the assignment of several compounds with [7,6] cores. We also thank Ian Stansfield for revision of this manuscript.

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1. Muraglia, E.; Kinzel, O. D.; Gardelli, C.; Crescenzi, B.; Donghi, M.; Ferrara, M.; Nizi, E.; Orvieto, F.; Pescatore, G.; Laufer, R.; Gonzalez-Paz, O.; Di Marco, A.; Fiore, F.; Monteagudo, E.; Fonsi, M.; Felock, P. J.; Rowley, M.; Summa, V. *J. Med. Chem.* **2008**, *51*, 861–874.
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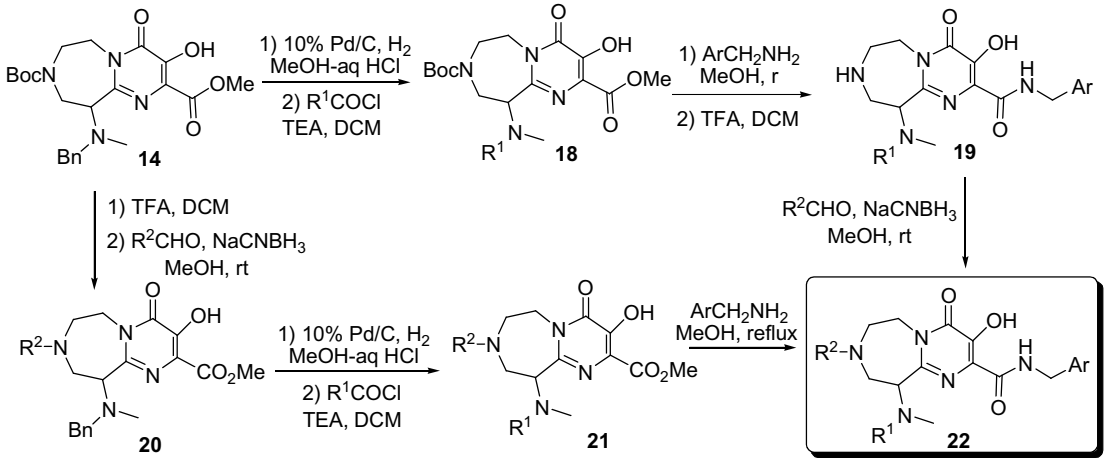
3. Data for **7**: ^{1}H NMR (300 MHz, CD_3CN) δ 8.59 (1H, br s), 7.44–7.41 (2H, m), 7.13 (2H, t, J = 8.8 Hz), 5.73–5.69 (1H, m) 4.60 (2H, br s), 4.13–4.09 (1H, m), 4.04–4.00 (1H, m), 3.97–3.90 (1H, m), 3.71–3.52 (3H, m), 2.99 (6H, br s), 2.17 (3H, s) ppm; MS m/z: 418 $(M+H)^+$.
4. *Experimental procedure*: To a solution of starting **8** (662 mg, 1.7 mmol) in chloroform (30 mL) and TEA (0.5 mL, 2.2 equiv), MsCl (0.15 mL, 1.2 equiv) was added, and the mixture was stirred for 1 h at rt. Solvent was removed at 25 °C; the residue (fully mesylated at primary alcohol and partly mesylated at phenolic OH) was taken up in dry acetonitrile (30 mL) and treated with methylbenzylamine (0.7 mL, 4 equiv) overnight at 70 °C. Volatiles were then



Scheme 7. Further transformations of key intermediate **14** leading to HIV-integrase inhibitors.

removed under vacuum, and the residue was purified by RP-HPLC to afford, after lyophilization, 190 mg (20%) of **9a**. Data for **9a**: ^{1}H NMR (300 MHz, CD_3CN) δ 8.21 (1H, br s), 7.54–7.34 (7H, m), 7.09 (2H, t, J = 8.8 Hz), 5.33 (1H, dd, J = 17.0, 4.6 Hz) 5.17 (1H, d, J = 9.9 Hz), 4.69–4.48 (4H, m), 4.09 (1H, d, J = 13.5 Hz), 3.93–3.82 (2H, m), 3.68–3.60 (1H, m), 3.34–3.26 (1H, m), 3.06 (3H,s), 3.04 (3H, s) ppm; MS m/z: 466 $(M+H)^+$.

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8. To a suspension of **12** (29.4 g, 0.12 mol) in 500 mL of acetonitrile, DMAD (15.6 mL, 1.05 equiv) was added in one portion, and the mixture was stirred for 1 h at rt. Solvent was evaporated, and the residue was dissolved in xylenes (1.2 L) and stirred overnight at 145 °C. Evaporation gave a residue that was taken up in EtOAc, a black solid was filtered off, and the filtrate was extracted with sat $NaHCO_3$. $CHCl_3$ was added to the aqueous phase, followed by 6 N HCl until acid pH; extraction with $CHCl_3$ afforded pure **13** (8 g, 19% from 4-piperidone). Data for **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.55 (1H, br s), 4.42–4.40 (2H, m), 4.03 (3H, s), 3.72–3.69 (4H, m), 3.12–3.09 (2H, m), 1.48 (9H, s) ppm; ^{13}C NMR (300 MHz, CD_3CN) δ 169.8, 158.8, 155.4, 153.1, 148.5, 125.2, 80.7, 53.5, 46.0 (br), 45.0, 43.3 (br), 38.8, 28.3 (3C) ppm; MS m/z: 340 $(M+H)^+$.
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10. DDQ (4.1 g, 2.1 equiv) was added to a solution of **13** (2.9 g, 8.5 mmol) in dry 1,4-dioxane (150 mL), and the mixture was stirred at 105 °C (oil bath temperature) overnight. After cooling to rt, benzylmethylamine (6.6 mL, 6 equiv) was added and stirring was continued at 65 °C for 6 h, before leaving to cool. Dihydro-DDQ was filtered off, dioxane and most of the excess amine were evaporated, and the residue was taken up in MeOH, acidified with AcOH and charged on a cationic exchange resin (Varian, Bond Elut SCX). Impurities were washed off with MeOH, and then elution with 2 M NH_3/MeOH gave, after removing volatiles, a residue that was taken up in EtOAc, washed with satd $NaHCO_3$, dried, and concentrated to afford 2.3 g (58%) of **14**. A sample of this compound was purified by RP-HPLC for characterization purposes: Data for **14**: ^{1}H NMR (300 MHz, CD_3CN) δ 7.69 (2H, br s), 7.48 (3H, br s), 5.04 (1H, bd, J = 14 Hz), 4.75–4.69 (2H, m), 4.37–4.20 (2H, m), 4.01 (3H,s), 3.96–3.84 (2H, m), 3.72 (1H, br s), 3.46 (1H, br s), 2.87 (3H, s), 1.43 (9H, s) ppm;.^{13}C NMR (300 MHz, CD_3CN) δ 168.0, 159.9 (br), 157.4, 154.2 (br), 148.4, 145.4, 130.6 (2C), 129.4, 128.7 (2C), 123.2, 81.0, 65.2, 57.2, 52.6, 44.4 (br), 42.6, 41.9 (br), 38.3, 27.1 (3C) ppm; MS m/z: 459 $(M+H)^+$.
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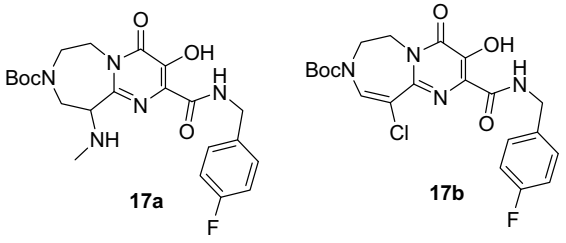
12. When methylamine was added to the activated intermediate, a 1:1 mixture of desired amine **17a** and chloride **17b** was obtained.



Reaction was done on the *p*-fluorobenzylamide to avoid reaction of methylamine with the methyl ester of **13**.

13. Data for **22** (R^1 = –COCONMe$_2$, R^2 = –SO$_2$Me): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (1H, br s, 9.58 (1H, br s), 7.37 (2H, dd, J = 8.6, 5.7 Hz), 7.14 (2H, t, J = 8.6 Hz), 5.30 (1H, br s), 5.12 (1H, dd, J = 15.7, 3.6 Hz), 4.54–4.44 (2H, m), 4.03 (1H, bd, J = 12.8 Hz), 3.91–3.76 (3H, m), 3.16–3.10 (1H, m), 2.99 (3H, s), 2.96 (3H, s), 2.95 (3H, s), 2.92 (3H, s) ppm; ^{13}C NMR (400 MHz, DMSO-d_6) δ 167.9, 166.5, 164.8, 161.3 (d, J = 965 Hz), 157.6, 146.8, 146.4, 134.6, 129.5, 129.4, 124.7, 115.2, 114.9, 59.4, 47.9, 46.5, 42.3, 41.5, 36.7, 36.3, 34.6 (br), 32.8 ppm; MS m/z: 539 $(M+H)^+$.