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Unprecedented single-pot protocol for the synthesis of N1, C6-linked bicyclic 3,4-dihydropyrimidinones via lithiation of Biginelli compounds

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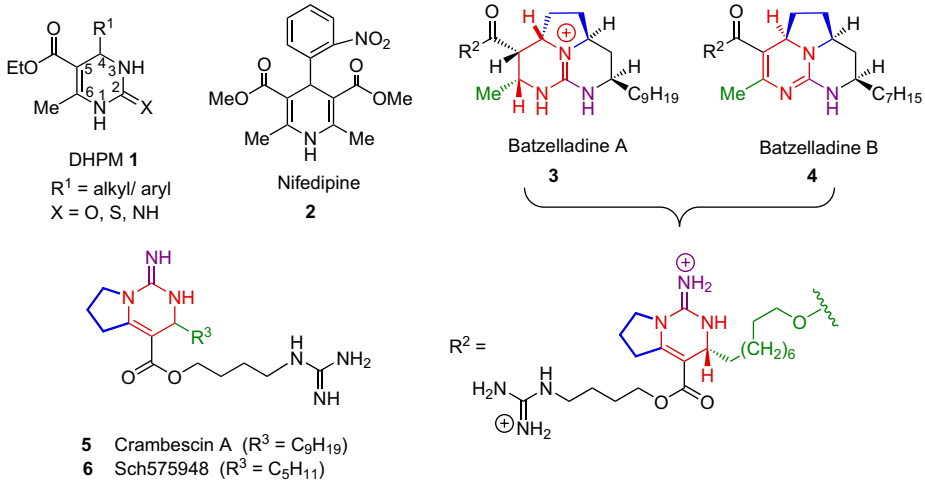
ABSTRACT

4-Aryl/alkyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one ester derivatives readily undergo metalation at the C6 methyl (vinylogous ester) position along with two acidic NHs upon treatment with *n*-butyllithium at −10 °C. The trianion of DHPMs thus obtained react smoothly with various terminal dibromoalkanes to afford N1, C6-linked bicyclic DHPM derivatives, which represent key structural features of the medicinally potent marine alkaloids such as batzelladine A and crambescin A.

1. Introduction

Functionalized 3,4-dihydropyrimidin-2(1*H*)ones (DHPMs, Biginelli compounds **1**) represent a class of heterocyclic system that has attracted a considerable interest of organic and medicinal chemists because of interesting pharmacological[1] and structural[2] profiles. Apart from their structural similarity with the calcium channel blockers of the 1,4-dihydropyridine category such as nifedipine **2**, this scaffold constitute an important structural component of medicinally potent marine alkaloids such as batzelladine alkaloids,



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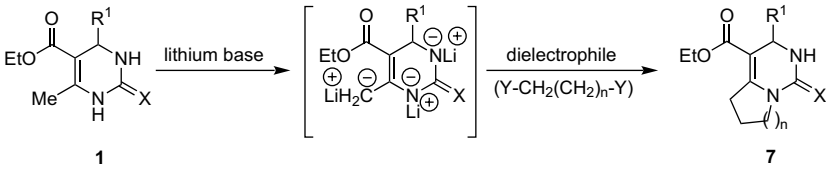


Scheme 1. Proposed hypothesis for synthesis of bicyclic DHPM **7**.

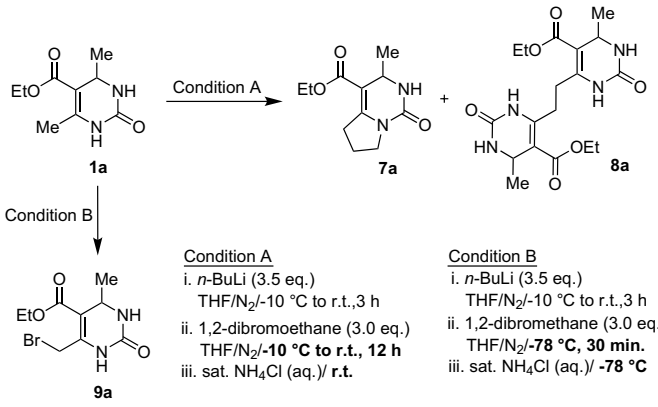
which are obtained from bright red Caribbean sponge Batzella species.[3] Among the various fragments obtained from methanolic extracts of this sponge, batzelladine A **3** and B **4** inhibit the binding of HIV surface glycoprotein gp120 to the CD4 receptor of human T-cells and therefore are of therapeutic interest for the treatment of HIV-AIDS.[3] The tricyclic framework of **3**/**4**, their side chains R^2 as well as other biologically important natural products such as crambescin A[4] (crambine A **5**) and Sch575948 **6**[5] contain a bicyclic unit reminiscent of an iminopyrimidine having N1, C6-link through a three-carbon bridge.

Synthesis of this important bicyclic system has gained considerable attention in the recent past in order to develop a total synthesis of **3** and its analogues. Although a general approach to link N1 and C6 positions of Biginelli DHPMs is still elusive, stepwise building[6] of a pyrrolo-pyrimidine structure, which serves as a template for further modification to produce bicyclic guanidine fragment of batzelladine A has been adopted. We recently reported on highly regioselective functional elaboration of DHPM core at key C6, C4, N3, N1 positions. Herein we report that N1, C6-positions of **1** could be linked in a single step to obtain bicyclic analogues **3**–**6** and offer a practical and synthetically useful route.

2. Results and discussion

Lithiation of a number of dihydropyrimidinones derivatives **1** with selected lithium bases and quenching with a variety of hard[7]/soft[8] electrophiles led to the regioselective elaboration of key diversity oriented (C6 and N3) positions of the DHPM core. While nucleophiles regioselectively add at the C4 position to offer C4 elaborated **1** in a synthetically useful manner.[9] It was expected that under appropriate lithiation conditions if more than 3 equiv of a base are employed to deprotonate **1**, in situ generation of tri-lithiated (N1, N3, and C6) species could be envisaged, which upon treatment with a dihaloalkane might lead to the formation of N1, C6-linked bicyclic DHPM **7** (Scheme 1). It would also offer an opportunity to probe the effect of hydrocarbon chain length intercepting the two electrophilic centers of the dielectrophile on the reaction pathway.

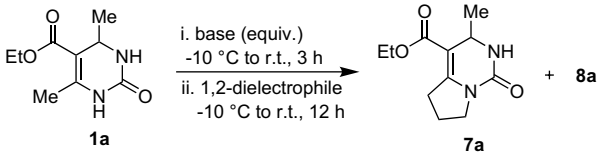
DHPM **1a** (Scheme 2) was treated with 3.5 equiv of freshly prepared *n*-BuLi (2.1 N in hexane) in anhydrous THF at −10 °C, under a blanket of dry nitrogen gas followed by stirring at room temperature for 3 h. The resultant colored anionic suspension was subsequently quenched with 3.0 equiv of 1,2-dibromoethane at −10 °C, which upon stirring for 12 h at room temperature furnished **7a** in 35% yield (Table 1). However, the formation of **7a** was accompanied by formation of a dimeric DHPM **8a** in 55% yield. Evidently, intramolecular cyclization (through N1 anion) of the initially formed C6-elaborated 3-bromopropyl derivative, due to excess equivalent of base may result in the formation of DHPM **7a**. The dimeric species **8a** could arise through the in situ formation of 6-bromomethyl DHPM **9a** (Scheme 2) through bromination of C6 methyl of **1a** by 1,2-dibromoethane.[10] In turn, **9a** could serve as an electrophile to quench a part of metalated **1a** to furnish the dimer **8a**. To provide an unequivocal support to the proposed mechanism, and in order to isolate **9a**, the above reaction was quenched at −78 °C followed by subsequent stirring for 30 min at the same temperature, whereby instead of **7a** or **8a**, **9a** was isolated in 35% yield, along with unreacted **1a**. Compound **9a** could be readily transformed to 4-methyl-4,7-dihydro-1*H*,3*H*-furo[3,4-*d*]pyrimidin-2,5-dione[11] and when independently reacted with the metalated **1a**, led to the exclusive formation of dimeric DHPM **8a**.



Scheme 2. Reaction of **1a** with 1,2-dibromoethane under different conditions.

In order to circumvent the formation of dimeric DHPM **8a** and improve the yield of **7a**, various other bases such as LDA or combination of *n*-BuLi with TMEDA, K-OBu^t, NaH, HMPA were used (Table 1), but the formation of **8a** could not be avoided and using 3.5 equiv of *n*-BuLi **7a** was obtained in maximum of 35% yield. Even changing 1,2-dibromoethane with 1,2-dichloroethane, 1-bromo-2-chloroethane,[12] and 2-chloroethanol toluene-4-sulfonate failed to

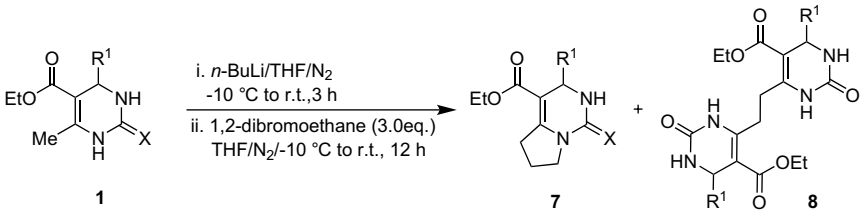
Table 1
Condition optimization for the synthesis of bicyclic DHPM **7a**



Entry	Base (equiv)	Electrophile	Product	Isolated yield (%)[a]
1	*n*-BuLi (1.1)	1,2-Dibromoethane	—	—
2	*n*-BuLi (2.1)	1,2-Dibromoethane	—	—
3	*n*-BuLi (3.5)	1,2-Dibromoethane	**7a**	35[b]
4	*n*-BuLi (4.0)	1,2-Dibromoethane	**7a**	28[b]
5	*n*-BuLi (3.5)	1,2-Dichloroethane	**7a**	Trace
6	*n*-BuLi (3.5)	1-Bromo-2-chloroethane	**7a**	10
7	*n*-BuLi (3.5)	2-Chloroethanol toluene-4-sulfonate	—	—
8	LDA (3.5)	1,2-Dibromoethane	**7a**	23[b]
9	LDA (4.0)	1,2-Dibromoethane	**7a**	15[b]
10	*n*-BuLi/TMEDA (3.5)	1,2-Dibromoethane	—	—
11	*n*-BuLi/K(OBu)^t (3.5)	1,2-Dibromoethane	—	—
12	*n*-BuLi/NaH (3.5)	1,2-Dibromoethane	**7a**	20[b]
13	*n*-BuLi/HMPA (3.5)	1,2-Dibromoethane	**7a**	26[b]

[a] After chromatographic purification.
[b] More than 50% of starting DHPM gets converted into dimer **8a**.

Table 2
Reaction of metalated DHPMs **1b–d** with 1,2-dibromoethane



1 **7** **8**

Entry	DHPM	R/X	Equiv of *n*-BuLi	Product (isolated yield %)[a]	
				7	**8**
1	**1b**	Ph/O	3.5	**7b** (30)	**8b** (50)
2	**1c**	H/O	4.5	**7c** (15)	**8c** (48)
3	**1d**	Ph/S	3.5	**7d** (15)	—

[a] After chromatographic purification.

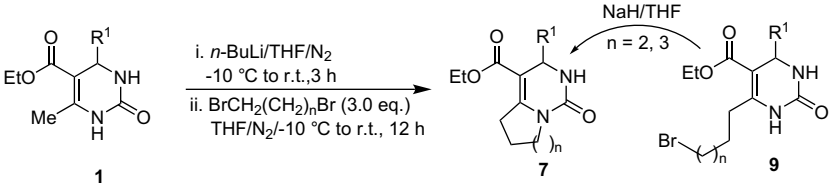
further improve the yield of **7a** (Table 1). Several other experiments using prolonged lithiation time, inverse addition of reactants, high dilution, and change in solvent did not show any appreciable improvement in the yield of **7a**. Inverse addition was also plagued by the formation of precipitates of anionic species, which even upon dilution did not run very smoothly through cannula making the procedure impracticable.

To determine the scope and limitations of this reaction, we subsequently studied the reaction of **1b** (R^1=Ph, X=O, Table 2) with 1,2-dibromoethane under the same set of conditions. Both bicyclic **7b** and dimeric **8b** DHPM derivatives were obtained in 30% and 50% yield, respectively[13] (Table 2). However, DHPM **1c** (R^1=H, X=O, Table 2) furnished **7c** (15%) and **8c** (48%), respectively, even upon increasing the equivalent of the base from 3.5 to 4.5 equivalent.[13] Use of rather reactive pyrimidine-2-thione derivative **1d** (R=Ph, X=S, Table 2) furnished a complex mixture of products, out of which the N1, C6-linked bicyclic DHPM **7d** was obtained in only 15% yield.

Further, in order to monitor the effect of hydrocarbon chain length of the dielectrophile on the reaction profile, the metalated DHPM **1a** was treated with 1,3-dibromopropane under optimized conditions. However, only one product i.e., N1, C6-linked bicyclic DHPM analogue **7e** was obtained in 71% yield (Table 3). In the event of dibromoalkanes other than 1,2-dibromoethane the formation of **8**-type dimer is not probable. Apart from a reactive alkyl halide, 1,2-dibromoethane is a potent source of electrophilic bromine for bromination of carbanions,[10,14] a feature not feasible when the two bromines are intercepted by methylenes in excess of two. A similar reaction of metalated **1b** with 1,3-dibromopropane also furnished the corresponding N1, C6-linked DHPM derivative **7f** in 74% yield. However, when the reaction was stirred at −10 °C only for 30 min, instead of 12 h at rt (Table 3), the C6-bromobutyl derivative of DHPM **9b** was obtained in 75% yield. By increasing the chain length further, e.g., using 1,4-dibromobutane as dielectrophile for quenching metalated **1b**, in addition to the N1, C6-linked product **7g** (28%), C6-bromopentyl DHPM derivative **9c** was obtained in 58% yield. However, the reaction of metalated DHPM **1b** with higher homologues of the dielectrophile, such as 1,5-dibromopentane and 1,6-dibromohexane, only led to C6-elaborated products **9d** and **9e** in 68% and 72% yields, respectively. The formation of N3 alkylated product was not detected in any case, which is well in agreement with our previous findings wherein N3 lithiated DHPM derivatives were found to reactive exclusively with hard electrophiles,[7] only whereas least acidic C6 methyl anion preferentially reacted with soft electrophiles.[8]

Thus whereas, all attempts to isolate C6-elaborated 3-bromopropyl DHPM in the reaction of **1a** with 1,2-dibromoethane failed owing to the favorable proximity of the nucleophilic N1 anion and electrophilic bromopropyl center leading to instant cyclization to the five membered ring of the thermodynamically more stable **7a**, the derivative **9c** could be isolated and cyclized to the corresponding **7g**. However, the greater flexibility of the long alkyl

Table 3
Effect of dielectrophile chain length on formation of bicyclic DHPM **7**



1 **7** **9**

Entry	DHPM	R^1	Electrophile $BrCH_2(CH_2)_nBr$	Product (isolated yield %)[a]	
				7	**9**
1	**1a**	Me	*n*=2	**7e** (71)	—
2	**1b**	Ph	*n*=2	**7f** (74)	**9b** (0)[b]
3	**1b**	Ph	*n*=3	**7g** (28)	**9c** (58)[b]
4	**1b**	Ph	*n*=4	—	**9d** (68)
5	**1b**	Ph	*n*=5	—	**9e** (72)

[a] After chromatographic purification.
[b] Electrophile addition at −10 °C followed by stirring for 30 min and quenching at rt furnish **9b** in 75% and **9c** 73% yields, exclusively.

chains in **9d** and **9e** did not affect cyclization to the corresponding bicyclic DHPM derivatives.

To supplement the yield of the desired N1, C6-linked DHPM derivatives **7f** and **7g**, each of the corresponding C6-bromoalkyl products **9b** and **9c** were cyclized. Thus, C6-bromobutyl DHPM **9b** upon treatment with 2.1 equiv of NaH in THF at 0 °C furnished **7f** (TLC monitoring) in 72% yield. Similarly, C6-bromopentyl DHPM **9c** was also transformed to the corresponding N1, C6-linked DHPM **7g** in 55% yield, using relatively harsh reaction conditions as this reaction was required to be refluxed for 2 h. However, reaction of C6-bromohexyl DHPM **9d** and C6-bromoheptyl DHPM **9e** derivatives remained unaffected even upon prolonged treatment with NaH.

3. Conclusions

Thus, we have found that using *n*-BuLi (3.5 equiv) at −10 °C DHPM derivatives upon metalation and subsequent reaction with dielectrophiles furnish N1, C6-linked bicyclic DHPM derivatives, which constitute an important structural feature of alkaloids. The hydrocarbon chain length flanked by two halides guides the cyclization to the N1, C6-linked bicyclic DHPMs. Thus using $BrCH_2(CH_2)_nBr$, for n=1 to n=3 cyclization proceeds in the reaction itself, however, if n exceeds 3 i.e., n=4, 5; N1, C6-linked DHPM derivatives are not formed even if treated with a base, separately. This single-pot approach furnish access to N1, C6-linked DHPM derivatives in moderate yields.

4. Experimental

4.1. General information

Melting points were determined in open capillaries and are uncorrected. $^1H/^{13}C$ NMR (300/75 MHz as well as 200/50 MHz; $CDCl_3$+DMSO-d_6/TFA) spectra were recorded using commercial deuterated solvents on multinuclear spectrometer Jeol FT-AL-300 instrument using tetramethylsilane as internal standard. Data are reported as follows: chemical shifts (δ, ppm), multiplicity [singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), AB quartet (ABq), broad (br), and multiplet (m)], coupling constant [Hz], integration. Mass spectra (MS) were recorded on Bruker Daltonics esquire 3000 spectrometer. IR spectra were recorded on Shimadzu FTIR 8400 S spectrophotometer. Elemental analyses were performed on FLASH EA 1112 (Thermo electron corporation) analyzer.

Thin layer chromatography (TLC) was performed on Merck ($60F_{254}$, 0.2 mm) using an appropriate solvent system. The chromatograms were visualized under UV light. Separation of various products was carried out by flash chromatography on silica gel (60–120 mesh). All solvents and electrophiles were dried with appropriate reagents before use. Reactions were run under a blanket of dry nitrogen gas in a sealed (rubber septum, Aldrich) round-bottomed flasks. Organometallic reagents were added using cannula. The low temperature (−10 °C and −78 °C) was attained in Dewar flasks using organic solvent–liquid N_2 slush.

4.2. General procedure

To a suspension of DHPM **1** (5 mmol) in dry THF (50 ml) under a blanket of dry N_2, 2.1 N *n*-BuLi (17.5 mmol, 8.33 ml) was added drop-wise at −10 °C. After the addition, reaction mixture was warmed to room temperature and stirred for additional 3 h until colored anionic species was generated. To this solution, appropriate dielectrophile (dibromoalkane) (15 mmol), dissolved in 10 ml dry THF was added drop-wise using cannula at 10 °C. Upon addition of the electrophile, the red color was quenched in most of the cases, indicating the consumption of the anions. Reaction was warmed to room temperature and stirring was continued for additional 12 h, to complete the reaction, after which a saturated aqueous solution of NH_4Cl was introduced to terminate the reaction. The reaction was extracted with ethyl acetate (3×25 ml) treated in sequence with brine and water. The extracts were dried over anhydrous Na_2SO_4 and the mixture concentrated under reduced pressure. The products were isolated by flash chromatography using silica gel-G (60–120 mesh) and mixtures of ethyl acetate and hexane as eluent. For preparing samples for micro-analytical analysis, crystallization was done using combinations of dry DCM and hexane or methanol and petroleum ether (40–60 °C).

The following compounds have been prepared.

4.2.1. 3-Methyl-1-oxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]-pyrimidine-4-carboxylic acid ethyl ester ***7a***

Yield: 35%; amorphous white solid; mp (CH_2Cl_2/hexane) 141 °C; [Found: C, 59.01; H, 7.32; N, 12.24. $C_{11}H_{16}N_2O_3$ requires: C, 58.92; H, 7.14; N, 12.51%.] R_f (40% ethyl acetate/hexane) 0.24; ν_{max} (KBr) 3275, 1685, 1665 cm^{-1}; ^1H (300 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.6 Hz, CH_3), 1.29 (3H, t, *J* 7.2 Hz, CH_3), 2.02–2.04 (2H, m, CH_2), 3.12–3.22 (2H, m, CH_2), 3.70–3.72 (2H, m, CH_2), 4.18–4.20 (2H, m, –OCH_2), 4.40–4.43 (1H, m, C4-H), 5.11 (1H, br, D_2O exchangeable, N3-H); ^{13}C (75 MHz, $CDCl_3$) 14.4, 21.3, 24.0, 31.9, 46.5, 47.9, 59.8, 153.1, 165.7; *m*/*z* 224 (M^+).

4.2.2. 1-Oxo-3-phenyl-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]-pyrimidine-4-carboxylic acid ethyl ester ***7b***

Yield: 30%; crystalline solid; mp (CH_2Cl_2/hexane) 185 °C; [Found: C, 67.23; H, 6.33; N, 10.04. $C_{16}H_{18}N_2O_3$ requires: C, 67.13; H, 6.29; N, 9.79%.] R_f (50% ethyl acetate/hexane) 0.3; ν_{max} (KBr) 3200, 1670, 1655 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 1.18 (3H, t, *J* 7.2 Hz, CH_3), 2.04–2.07 (2H, m, CH_2), 3.10–3.13 (1H, m, CH), 3.24–3.26 (1H, m, CH), 3.77–3.79 (2H, m, CH_2), 4.07–4.09 (2H, m, OCH_2), 5.32 (1H, br, D_2O exchangeable, N3-H), 5.40 (1H, d, *J* 3.0 Hz, C4-H), 7.26–7.29 (5H, m, ArH); ^{13}C (75 MHz, $CDCl_3$) δ 14.2, 21.3, 32.1, 46.7, 55.8, 59.9, 126.4, 127.8, 128.6, 129.5, 152.1; *m*/*z* 286 (M^+).

4.2.3. 1-Oxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]-pyrimidine-4-carboxylic acid ethyl ester ***7c***

Yield: 15%; white solid; mp (CH_2Cl_2/hexane) 132 °C; [Found: C, 56.98; H, 6.52; N, 13.24. $C_{10}H_{14}N_2O_3$ requires: C, 57.14; H, 6.66; N, 13.33%.] R_f (45% ethyl acetate/hexane) 0.5; ν_{max} (KBr) 3100, 1670, 1665 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 1.28 (3H, t, *J* 7.2 Hz, CH_3), 1.97–1.99 (2H, m, CH_2), 3.09–3.11 (2H, m, CH_2), 3.69 (2H, t, *J* 7.2 Hz, CH_2), 4.16 (2H, s, C4), 4.17 (2H, q, *J* 7.2 Hz, OCH_2), 4.88 (1H, br, D_2O exchangeable, N3-H); ^{13}C (75 MHz, $CDCl_3$) δ 14.4, 21.3, 31.8, 41.5, 46.4, 59.8, 102.1, 153.1, 165.7; *m*/*z* 210 (M^+).

4.2.4. 3-Phenyl-1-thioxo-1,2,3,5,6,7-hexahydropyrrolo[1,2-c]-pyrimidine-4-carboxylic acid ethyl ester ***7d***

Yield: 15%; yellow crystalline solid; mp (CH_2Cl_2/hexane) 178 °C; [Found: C, 63.29; H, 6.24; N, 9.05; S 10.60. $C_{16}H_{18}N_2O_2S$ requires: C, 63.57; H, 5.96; N, 9.27; S, 10.59%.] R_f (35% ethyl acetate/hexane) 0.5; ν_{max} (KBr) 3165, 1645, 1610 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 1.18 (3H, t, *J* 7.2 Hz, CH_3), 2.04–2.06 (2H, m, CH_2), 3.09–3.11 (1H, m, CH), 3.31–3.34 (1H, m, CH), 4.08–4.11 (4H, m, 2×CH_2), 5.37 (1H, d, *J* 3.0 Hz, C4-H), 6.95 (1H, br, D_2O exchangeable, N3-H), 7.26–7.30 (m, 5H, ArH); ^{13}C (75 MHz, $CDCl_3$) δ 14.1, 21.0, 32.1, 52.1, 55.7, 60.3, 100.7, 126.6, 128.2, 128.8, 142.9, 149.3, 165.3, 175.4; *m*/*z* 302 (M^+).

4.2.5. 3-Methyl-1-oxo-2,3,5,6,7,8-hexahydro-1H-pyrido[1,2-c]-pyrimidine-4-carboxylic acid ethyl ester ***7e***

Yield: 71%; light brown solid; mp (CH_2Cl_2/hexane) 72 °C; [Found: C, 60.31; H, 7.32; N, 11.34. $C_{12}H_{18}N_2O_3$ requires: C, 60.50; H, 7.56; N, 11.76%.] R_f (45% ethyl acetate/hexane) 0.5; ν_{max} (KBr) 3260, 1695, 1645 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 1.23 (3H, d, *J* 6.3 Hz, CH_3),

1.27 (3H, t, *J* 7.2 Hz, CH_3), 1.74–1.77 (2H, m, CH_2), 3.00–3.03 (1H, m, CH), 3.12–3.14 (1H, m, CH), 3.55–2.57 (2H, m, CH_2), 3.79–3.81 (2H, m, CH_2), 4.14–4.16 (2H, m, OCH_2), 4.32–4.34 (1H, m, C4-H), 5.10 (1H, br, D_2O exchangeable, N3-H); ^{13}C (75 MHz, $CDCl_3$) δ 14.3, 18.7, 21.7, 23.4, 25.3, 40.5, 46.1, 59.8, 103.1, 132.4, 154.7, 165.9; *m*/*z* 238 (M^+).

4.2.6. 1-Oxo-3-phenyl-2,3,5,6,7,8-hexahydro-1H-pyrido[1,2-c]-pyrimidine-4-carboxylic acid ethyl ester ***7f***

Yield: 74%; amorphous white solid; mp (CH_2Cl_2/hexane) 132 °C; [Found: C, 67.89; H, 6.85; N, 9.63. $C_{17}H_{20}N_2O_3$ requires: C, 68.0; H, 6.66; N, 9.33%.] R_f (45% ethyl acetate/hexane) 0.7; ν_{max} (KBr) 3180, 1655, 1608 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 1.16 (3H, t, *J* 7.2 Hz, CH_3), 1.72–1.74 (3H, m, CH_2 and CH), 1.86–1.88 (1H, m, CH), 3.06–3.08 (1H, m, CH), 3.21–3.23 (1H, m, CH), 3.63–3.65 (1H, m, CH), 3.83–3.85 (1H, m, CH), 4.07 (2H, q, *J* 7.2 Hz, OCH_2), 5.36 (1H, s, C4-H), 5.36 (1H, br, D_2O exchangeable, N3-H), 7.26–7.28 (5H, m, ArH); ^{13}C (50 MHz, $CDCl_3$) δ 14.1, 18.7, 21.8, 25.4, 40.6, 54.2, 59.9, 101.7, 126.2, 127.8, 128.7, 143.7, 151.2, 153.1, 165.8; *m*/*z* 300 (M^+).

4.2.7. 1-Oxo-3-phenyl-1,2,3,5,6,7,8,9-octahydropyrimido[1,6-a]-azepine-4-carboxylic acid ethyl ester ***7g***

Yield: 28%; amorphous white solid; mp (CH_2Cl_2/hexane) 136 °C; [Found: C, 68.67; H, 7.27; N, 9.19. $C_{18}H_{22}N_2O_3$ requires: C, 68.78; H, 7.00; N, 8.91%.] R_f (35% ethyl acetate/hexane) 0.7; ν_{max} (KBr) 3100, 1685, 1660 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 1.18 (3H, t, *J* 7.2 Hz, CH_3), 1.72–1.74 (6H, m, 3×CH_2), 2.92–2.94 (1H, m, CH), 3.43–3.45 (1H, m, CH), 3.86–3.88 (2H, m, CH_2), 4.09 (2H, q, *J* 7.2 Hz, OCH_2), 5.36 (1H, d, *J* 3.3 Hz, C4-H), 5.45 (1H, br, D_2O exchangeable, N3-H), 7.24–7.26 (5H, m, ArH); ^{13}C (75 MHz, $CDCl_3$) δ 14.0, 26.7, 28.3, 28.7, 28.8, 43.2, 53.9, 60.1, 103.3, 126.2, 127.7, 128.6, 143.3, 153.6, 154.5, 166.1; *m*/*z* 314 (M^+).

4.2.8. 1,2-Bis-[(5-ethoxycarbonyl-4-methyl-3,4-dihydropyrimidin-2(1H)-one)-6-yl]ethane ***8a***

Yield: 55%; amorphous white solid, did not melt up to 300 °C; [Found: C, 55.03; H, 6.83; N, 13.97. $C_{18}H_{26}N_4O_6$ requires: C, 54.82; H, 6.59; N, 14.21%.] ν_{max} (KBr) 3260, 1680, 1625 cm^{-1}; ^1H (300 MHz, $CDCl_3$+TFA) δ 1.31 (6H, t, *J* 7.2 Hz, 2×CH_3), 1.33 (6H, d, *J* 6.3 Hz, 2×CH_3), 2.84–2.86 (2H, m, CH_2), 3.03–3.05 (2H, m, CH_2), 4.23–4.25 (4H, m, 2×OCH_2), 4.50–4.52 (2H, m, 2×C4-H), 7.13 (2H, br, D_2O exchangeable, N3-H), 8.43 (2H, br, D_2O exchangeable, N1-H); ^{13}C (75 MHz, $CDCl_3$+TFA) δ 14.0, 18.3, 23.3, 29.1, 47.5, 60.7, 104.4, 112.8, 116.6, 147.1, 156.4, 165.1; *m*/*z* 394 (M^+).

4.2.9. 1,2-Bis-[(5-ethoxycarbonyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one)-6-yl]ethane ***8b***

Yield: 50%; amorphous white solid, did not melt up to 300 °C; [Found: C, 64.60; H, 5.51; N, 10.53. $C_{28}H_{30}N_4O_6$ requires: C, 64.86; H, 5.79; N, 10.81%.] ν_{max} 3210, 1680, 1640 cm^{-1}; ^1H (300 MHz, $CDCl_3$+TFA) δ 1.14 (6H, t, *J* 7.2 Hz, 2×CH_3), 3.07–3.09 (2H, m, CH_2), 3.19–3.21 (2H, m, CH_2), 4.07 (4H, q, *J* 7.2 Hz, 2×–OCH_2), 5.51 (2H, d, *J* 3.0 Hz, 2×C4-H), 7.29 (10H, m, ArH+2H, D_2O exchangeable, N3-H), 8.58 (2H, br, D_2O exchangeable, N1-H); ^{13}C NMR (75 MHz, $CDCl_3$+TFA) δ 13.6, 29.2, 55.5, 61.6, 103.2, 108.8, 112.5, 116.3, 120.1, 126.5, 141.6, 147.4, 155.2, 165.7; *m*/*z* 518 (M^+).

4.2.10. 1,2-Bis-[(5-ethoxycarbonyl-3,4-dihydropyrimidin-2(1H)-one)-6-yl]ethane ***8c***

Yield: 48%; amorphous white solid, did not melt up to 300 °C; [Found: C, 52.18; H, 5.91; N, 15.39. $C_{16}H_{22}N_4O_6$ requires: C, 52.45; H, 6.01; N, 15.30%.] ν_{max} 3230, 1745, 1675 cm^{-1}; ^1H (300 MHz, $CDCl_3$+TFA) δ 1.30 (6H, t, *J* 7.2 Hz, 2×CH_3), 2.93–2.95 (4H, m, 2×CH_2), 4.22 (4H, q, *J* 7.2 Hz, 2×–OCH_2), 4.23 (4H, s, 2×C4-CH_2), 6.81 (2H, br, D_2O exchangeable, N3-H), 8.23 (2H, br, D_2O exchangeable, N1-H); ^{13}C (75 MHz, $CDCl_3$+TFA) δ 13.9, 29.3, 41.0, 61.4, 98.5, 112.6, 116.4, 148.4, 156.5, 159.9, 160.5, 165.5; *m*/*z* 366 (M^+).

4.3. Trapping of intermediates 9a and 9b

To a suspension of DHPM **1** (5 mmol) in 50 ml dry THF under a blanket of dry N_2, 2.1 N *n*-BuLi (8.33 ml, 17.5 mmol) was added drop-wise at −10 °C. After the addition, reaction mixture was warmed to room temperature and stirred for additional 3 h. For trapping **9a**, the reaction was shifted to −78 °C and 1,2-dibromoethane (1.3 ml, 15 mmol), dissolved in 10 ml dry THF was added drop-wise. Stirring was continued at the same temperature for additional 30 min, after which a saturated aqueous solution of NH_4Cl was introduced at −78 °C. However, for synthesis of **9b** the second step was executed at −10 °C, by using 1,3-dibromopropane (15 mmol) and stirring was continued for 30 min at rt. The reaction was treated with brine and extracted with ethyl acetate (3×25 ml). The extracts were dried over anhydrous Na_2SO_4 and the mixture concentrated under reduced pressure. The product was isolated by flash chromatography using silica gel-G (60–120 mesh) and mixtures of ethyl acetate/hexane as eluent.

4.3.1. 5-Ethoxycarbonyl-6-(bromomethyl)-4-methyl-3,4-dihydropyrimidin-2(1H)-one ***9a***

Yield: 35%; amorphous brown solid; mp (CH_2Cl_2) 137 °C; [Found: C, 39.18; H, 4.87; N, 9.91. $C_9H_{13}N_2O_3Br$ requires: C, 38.98; H, 4.69; N, 10.10%.] R_f (60% ethyl acetate/hexane) 0.4; ^1H (300 MHz, $CDCl_3$) δ 1.31 (3H, t, *J* 7.2 Hz, CH_3), 1.30 (3H, d, *J* 6.6 Hz, CH_3), 4.21–4.23 (2H, m, OCH_2), 4.41–4.43 (1H, m, C4-H), 4.57 (2H, ABq, *J* 10.5 Hz, CH_2Br), 5.71 (1H, br, D_2O exchangeable, N3-H), 8.05 (1H, br, D_2O exchangeable, N1-H); ^{13}C (75 MHz, $CDCl_3$) δ 14.3, 21.3, 31.8, 46.5, 47.9, 59.7, 104.7, 144.4, 153.0, 165.6; *m*/*z* 277 (M^+).

4.3.2. 5-Ethoxycarbonyl-6-(4-bromobutyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one ***9b***

Yield: 75%; white solid; mp (CH_2Cl_2/hexane) 141 °C; [Found: C, 53.65; H, 5.71; N, 7.07. $C_{17}H_{21}N_2O_3Br$ requires: C, 53.54; H, 5.51; N, 7.34%.] R_f (45% ethyl acetate/hexane) 0.4; ν_{max} (KBr) 3100, 1690, 1630 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 1.15 (3H, t, *J* 7.2 Hz, CH_3), 1.77–1.79 (2H, m, CH_2), 1.93–1.95 (2H, m, CH_2), 2.75 (2H, t, *J* 7.5 Hz, CH_2), 3.41 (2H, t, *J* 6.Hz, CH_2), 4.06 (2H, q, *J* 7.2 Hz, OCH_2), 5.40 (1H, d, *J* 2.7 Hz, C4-H), 5.61 (1H, br, D_2O exchangeable, N3-H), 7.27–7.29 (5H, m, ArH), 8.04 (1H, br, D_2O exchangeable, N1-H); ^{13}C (75 MHz, $CDCl_3$) δ 14.0, 26.7, 30.7, 32.2, 33.1, 55.8, 60.0, 101.3, 126.5, 128.0, 128.7, 143.6, 149.7, 153.2, 165.2; *m*/*z* 381 (M^+).

4.3.3. 5-Ethoxycarbonyl-6-(5-bromopentyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one ***9c***

Yield: 58%; white solid; mp (CH_2Cl_2/hexane) 153 °C; [Found: C, 54.97; H, 6.09; N, 7.31. $C_{18}H_{23}N_2O_3Br$ requires: C, 54.68; H, 5.82; N, 7.08%.] R_f (35% ethyl acetate/hexane) 0.4; ν_{max} (KBr) 3185, 1665, 1615 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 1.15 (3H, t, *J* 7.2 Hz, CH_3), 1.55–1.57 (4H, m, 2×CH_2), 1.86–1.88 (2H, m, CH_2), 2.71–2.73 (2H, m, CH_2), 3.40 (2H, t, *J* 6.6 Hz, CH_2), 4.06 (2H, q, *J* 7.2 Hz, OCH_2), 5.39 (1H, d, *J* 2.7 Hz, C4-H), 5.70 (1H, br, D_2O exchangeable, N3-H), 7.27–7.29 (5H, m, ArH), 8.20 (1H, br, D_2O exchangeable, N1-H); ^{13}C (75 MHz, $CDCl_3$) δ 14.0, 27.1, 27.7, 31.4, 32.1, 33.6, 55.6, 60.0, 100.99, 126.5, 127.9, 128.7, 143.6, 150.1, 165.2; *m*/*z* 395 (M^+).

4.3.4. 5-Ethoxycarbonyl-6-(6-bromohexyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one ***9d***

Yield: 68%; white solid; mp (CH_2Cl_2/hexane) 121 °C; [Found: C, 55.93; H, 6.25; N, 6.90. $C_{19}H_{25}N_2O_3Br$ requires: C, 55.74; H, 6.11; N, 6.84%.] R_f (25% ethyl acetate/hexane) 0.5; ν_{max} (KBr) 3205, 1685, 1632 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 1.15 (3H, t, *J* 7.2 Hz, CH_3), 1.42–144 (4H, m, 2×CH_2), 1.62–1.64 (2H, m, CH_2), 1.83–1.85 (2H, m, CH_2), 2.71–2.73 (2H, m, CH_2), 3.39 (2H, t, *J* 6.6 Hz, CH_2), 4.07 (2H, q, *J* 7.2 Hz, OCH_2), 5.39 (1H, s, C4-H and 1H, D_2O exchangeable, N3-H), 7.13 (1H, br, D_2O exchangeable, N3-H), 7.30 (5H, m, ArH); ^{13}C

(75 MHz, $CDCl_3$) δ 14.0, 27.7, 27.9, 28.4, 31.5, 32.5, 33.9, 55.6, 59.9, 100.8, 126.5, 127.8, 128.6, 143.8, 150.6, 153.7, 165.3; *m*/*z* 410 (M^+).

4.3.5. 5-Ethoxycarbonyl-6-(7-bromoheptyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one **9e**

Yield: 72%; white solid; mp 111 °C (CH_2Cl_2/hexane); [Found: C, 56.83; H, 6.63; N, 6.71. $C_{20}H_{27}N_2O_3Br$ requires: C, 56.60; H, 6.36; N, 6.60%.] R_f (20% ethyl acetate/hexane) 0.4; ν_{max} (KBr) 3180, 1665, 1615 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 1.15 (3H, t, *J* 7.2 Hz, CH_3), 1.42–1.44 (6H, m, 3×CH_2), 1.60–1.62 (2H, m, CH_2), 1.82–1.84 (2H, m, CH_2), 2.70–2.72 (2H, m, CH_2), 3.38 (2H, t, *J* 6.6 Hz, CH_2), 4.07 (2H, q, *J* 7.2 Hz, OCH_2), 5.39 (1H, d, *J* 2.7 Hz, C4-H), 5.68 (1H, br, D_2O exchangeable, N3-H), 7.27–7.29 (5H, m, ArH), 7.85 (1H, br, D_2O exchangeable, N1-H); ^{13}C (75 MHz, $CDCl_3$) δ 14.0, 27.9, 28.0, 28.3, 29.1, 31.6, 32.6, 33.8, 55.6, 59.9, 100.9, 126.5, 127.9, 128.7, 143.7, 150.4, 165.3; *m*/*z* 424 (M^+).

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