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Microwave-assisted solution phase synthesis of dihydropyrimidine C5 amides and esters

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Abstract—Multifunctionalized dihydropyrimidine-5-carboxylic amides and esters are generated in a multistep sequence integrating a variety of enabling and high throughput technologies such as automated or parallel microwave synthesis, the use of polymer-supported reagents, fluorous synthesis and purification strategies, and a continuous flow hydrogenation system. The key dihydropyrimidine-5-carboxylic acid intermediates are obtained in two steps by Biginelli multicomponent condensation of benzyl or allyl β-ketoesters with aldehydes and urea/thioureas, followed by suitable benzyl or allyl deprotection strategies. Further functionalization of the acid cores with amines using polymer-supported coupling reagents or with alcohols utilizing Mitsunobu chemistry provides the desired amides or esters, respectively.

1. Introduction

Modern drug discovery steadily relies on high speed organic synthesis and combinatorial chemistry techniques for the rapid generation of compound libraries. Microwave-assisted organic synthesis[1,2] and combinatorial chemistry together with high throughput screening (HTS) methods are being instrumental for the rapid synthesis, screening, and identification of compounds with new and improved biological activities.[3]

Over the years, research interest in multifunctionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs), viz. the Biginelli scaffold, has surged rapidly, owing to the pharmacological properties associated with many derivatives of this privileged heterocyclic core.[4–7] Reports describe several DHPMs that have been identified, for example, calcium channel modulators,[5] or small molecules targeting the mitotic machinery.[6] Notably, 4-aryldihydropyrimidinone heterocycles attached to an aminopropyl-4-piperidine moiety via a C5 amide linkage (see Chart 1) have proven to be excellent templates for selective α_{1a} receptor subtype antagonists to warrant further consideration for the treatment of Benign Prostatic Hyperplasia (BPH).[7] In the synthesis of these DHPM-5-carboxamides, amide bond formation between the requisite amines and the corresponding DHPM acids was performed using standard solution phase amide coupling chemistry involving carbodiimide coupling reagents.[7,8]

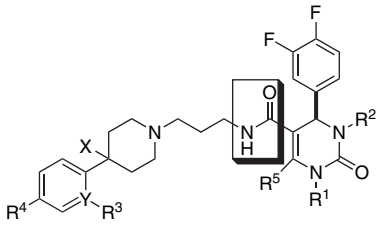

Chart 1.

This approach of introducing structural diversity appealed to our ongoing interest in the microwave-induced high speed synthesis[9] and decoration[10] of the Biginelli scaffold. In the present work we describe a rapid microwave-induced polymer-assisted solution phase synthesis (PASP) and high throughput purification of diverse DHPM C5 amides starting from a corresponding set of structurally diverse DHPM C5 acid cores and selected amines (see Scheme 1). With a high diversity of commercially available amines but limited availability of β-ketoamides, the synthesis of amides via the acid precursors has been chosen. In addition, the acid cores generated would also serve as excellent precursors for other interesting chemistries.

To introduce more diversity at the C5 position, we also synthesized a set of DHPM C5 esters **7** starting from the acids using Mitsunobu chemistry (Scheme 1). Via this protocol more diverse and novel ester-functionalities could be established by using the corresponding alcohols. Besides the standard Mitsunobu conditions, a fluorous Mitsunobu protocol was employed to facilitate the product isolation and purification.

Keywords: Microwave synthesis; Continuous flow techniques; Pyrimidines; Amide couplings; Fluorous synthesis; Mitsunobu reaction.
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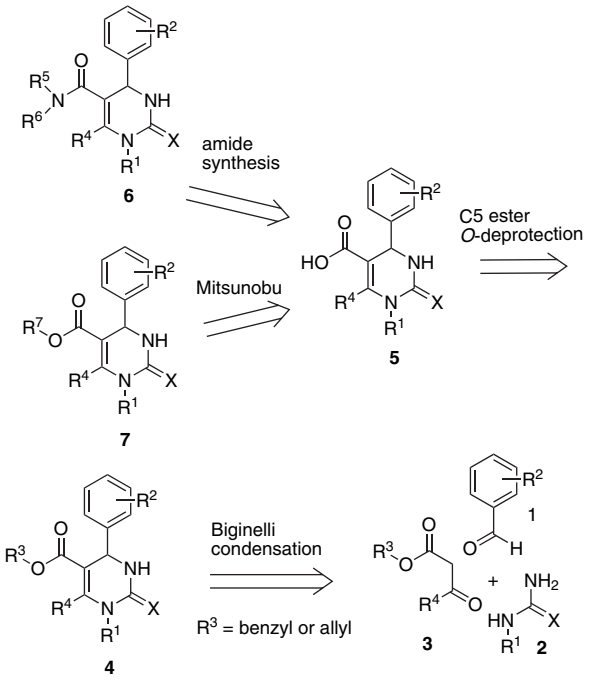


Scheme 1. Retrosynthetic strategy toward DHPM amide and ester libraries.

A microwave-induced combinatorial set and a parallel scale-up synthesis of structurally diverse DHPM C5 benzyl and allyl ester form the starting point in the synthesis of the DHPM C5 acid cores (Scheme 1).

2. Results and discussion

2.1. Microwave-assisted synthesis of DHPM esters 4

The Lewis acid-catalyzed multicomponent cyclocondensation of an aldehyde **1**, urea **2**, and a β-ketoester **3** (Biginelli condensation) constitutes the most elegant synthesis of multifunctionalized 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) of type **4** and has been extensively reported in the literature.[11,12] By far, library generation through automated sequential microwave-assisted Biginelli multicomponent condensation is most attractive in combining speed, diversity, and efficiency.[9] Improvements in the classical Biginelli multicomponent protocol have favored the more tolerant Lewis acids over a mineral acid viz. conc. HCl as the catalyst for yield improvements.[13] The use of solvents such as ethanol, acetic acid, THF, dioxane, acetonitrile, environmentally benign ionic liquids or solvent-free protocols has also been reported.[12]

As a starting point in our study, we have generated a small set (11 examples) of 4-aryl-DHPM C5 benzyl (Bn) and allyl (All) esters **4** using six different aldehydes **1A–F**, three urea/thiourea **2a–c**, and three CH-acidic carbonyl **3α–γ** building blocks (Figs. 1 and 2). This set of esters were synthesized in order to conveniently prepare DHPM acids **5**. In the synthesis of DHPM benzyl/allyl esters **4**, $Yb(OTf)_3$ as the Lewis acid catalyst and acetonitrile as the reaction solvent were chosen based on previous optimization studies on a larger and more diverse set of microwave-induced Biginelli multicomponent cyclocondensations.[9,10] Synthesis of both the DHPM C5 benzyl and allyl esters was performed to allow for a subsequent C5 O-deprotection using classical debenzylation and deallylation strategies (see below). The microwave-assisted sequential synthesis of DHPM esters **4** (4 mmol scale) utilized an excess (6 mmol) of the CH-acidic carbonyl building blocks **3**, which has led to improved yields in other Biginelli condensations.[12] In our case, the cyclocondensation has also been translated to 40 mmol scale using microwave-assisted parallel synthesis under nearly identical reaction conditions. For this scale-up synthesis (40 mmol) in a multimode cavity, the reaction mixtures were irradiated in parallel at preset conditions to afford the structurally diverse set of DHPM benzyl/allyl esters **4**.[14] The small scale (4 mmol) synthesis of the 4-aryl-DHPM C5 benzyl/allyl esters **4** involved sequential heating (120 °C for 20 min) of the corresponding reaction mixtures in a single-mode microwave reactor. The isolated yields obtained from each of the microwave (MW) heating runs are described in Table 1.

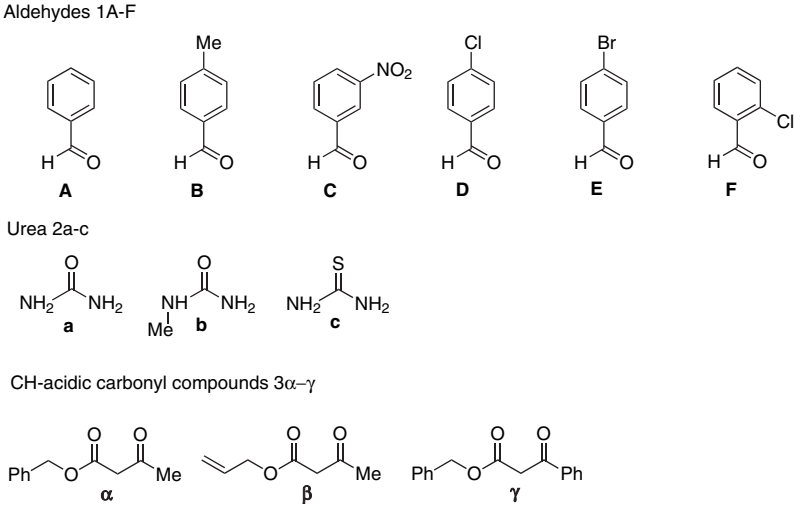


Figure 1. Aldehyde, urea, and β-ketoester building blocks.

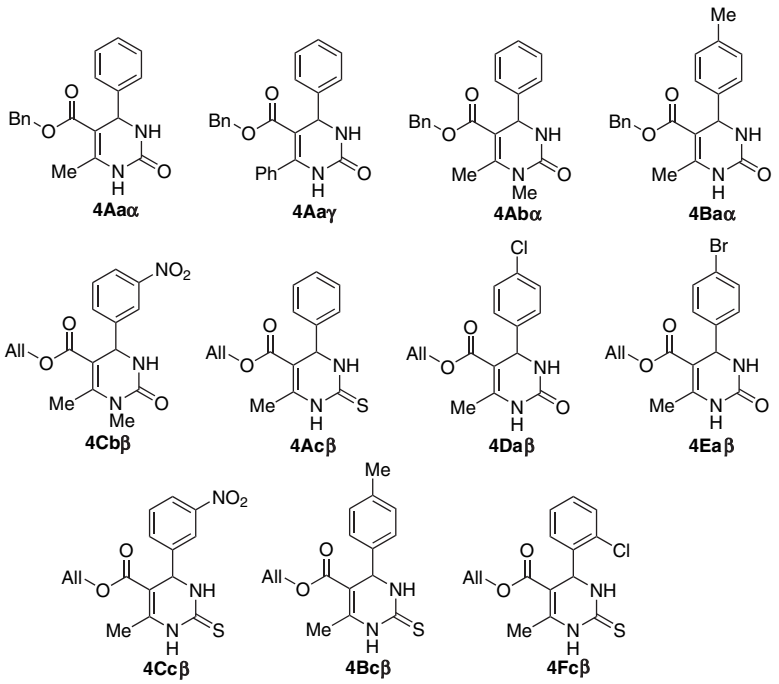
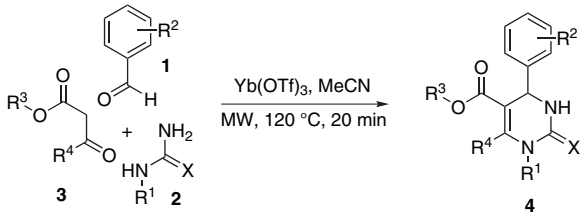


Figure 2. Dihydropyrimidine esters generated by Biginelli multicomponent condensations.

Reaction mixtures with **3α** and **3γ** as the CH-acidic carbonyl component (R^3=benzyl) provided easy access to the desired DHPMs **4Aaα**, **4Aaγ**, **4Abα**, and **4Baα** in 24–62% isolated yields. In each of these cases, the reaction mixture becomes completely homogeneous over 20 min of microwave heating at the optimized temperature of 120 °C. A low solubility of the resulting cyclocondensed DHPMs upon overnight standing under refrigeration (4 °C) afforded complete precipitation of the desired corresponding DHPM benzyl esters in >95% HPLC purity. We also undertook a scale-up synthesis (4 mmol–40 mmol) of DHPM benzyl esters **4Aaα**, **4Aaγ**, **4Abα**, and **4Bbα**, switching from a single-mode microwave to a multimode microwave reactor capable of parallel synthesis.[14] Maintaining identical reaction conditions (catalyst, solvent and ratio of building blocks) in each of the cases provided the target compounds in multigram quantities and in similar yields (see Section 4 for details).

Table 1. Microwave-assisted synthesis of dihydropyrimidine benzyl/allyl esters **4**[a]



Entry	DHPM	R^1	R^2	R^3	R^4	X	Yield (%)[b]
1	**4Aaα**	H	H	Bn	Me	O	62
2	**4Aaγ**	H	H	Bn	Ph	O	17
3	**4Abα**	Me	H	Bn	Me	O	28
4	**4Baα**	H	4-Me	Bn	Me	O	43
5	**4Cbβ**	Me	3-NO_2	Allyl	Me	O	35
6	**4Acβ**	H	H	Allyl	Me	S	46
7	**4Daβ**	H	4-Cl	Allyl	Me	O	74
8	**4Eaβ**	H	4-Br	Allyl	Me	O	48
9	**4Ccβ**	H	3-NO_2	Allyl	Me	S	61
10	**4Bcβ**	H	4-Me	Allyl	Me	S	67
11	**4Fcβ**	H	2-Cl	Allyl	Me	S	37

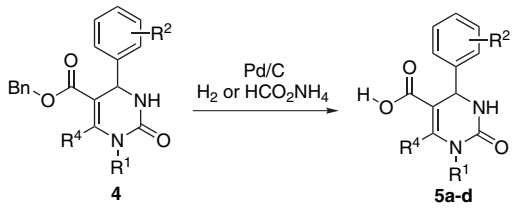
[a] Single-mode microwave on a 4 mmol scale.
[b] Isolated yield of pure compounds (>95% purity by HPLC at 215 nm).

The above generated DHPM benzyl esters exemplify a relative simplicity in terms of overall core diversity. The C6 phenyl substituent in **4Aaγ** and *N*1-methyl substituent in **4Abα** posed as robust diversity factors on the heterocyclic core. The synthesis of other DHPM C5 benzyl esters is similarly feasible by introducing diversity also in C2 (X=O or S) and the phenyl ring on C4 positions of the DHPM core. However, under identical deprotecting conditions this does not ensure to selectively carry out O-debenzylations without inadvertently affecting some of the other diversity points (the functional group substituents like NO_2, Cl, Br on the phenyl ring C4 position). The synthesis of DHPM allyl esters **4Cbβ**, **4Acβ**, **4Daβ**, **4Eaβ**, **4Ccβ**, **4Bcβ**, and **4Fcβ** became imperative for some of the structurally diverse building blocks, in particular with the aldehydes **1C–F** and/or thiourea **2c**, to retain the diversity in the resulting DHPM cores whilst selectively affording O-deprotections (deallylation) on the DHPM esters **4** under non-reducing conditions. The microwave-assisted synthesis (4 mmol and 40 mmol scale) was afforded under identical conditions as in the case of the 4-aryl-DHPM C5 benzyl esters, described in Table 1. In some cases, the relatively low yields of the DHPM allyl esters (e.g., for **4Fcβ**) may be attributed to the higher solubility of the DHPMs rendered by the allyl functionality.

2.2. Synthesis of DHPM acids 5a–d by catalytic transfer hydrogenation of DHPM benzyl esters 4

The next stage in our study was to gain access to compounds **5a–d** by devising a facile catalytic transfer hydrogenation of DHPM benzyl esters **4Aaα**, **4Aaγ**, **4Abα** and **4Baα**,

Table 2. Deprotection of DHPM benzyl esters **4**[a]



4 **5a-d**

DHPM	R^1	R^2	R^4	Conditions[a]	Yield (%)[b]	Product
4Aaα	H	H	Me	rt	66	**5a**
				MW	62	
				CF	95	
4Aaγ	H	H	Ph	rt	65	**5b**
				MW	60	
				CF	80	
4Abα	Me	H	Me	rt	57	**5c**
				MW	55	
				CF	85	
4Baα	H	4-Me	Me	rt	56	**5d**
				MW	53	
				CF	85	

[a] Conditions: rt: room temperature catalytic transfer hydrogenation ($HCOONH_4$, 25 °C, 8–10 h; 5 mmol); MW: microwave-assisted catalytic transfer hydrogenation ($HCOONH_4$, 120 °C, 20 min; 0.5 mmol); CF: continuous flow hydrogenation. For details see text.
[b] Yields are isolated yields of pure product.

respectively, in the presence of a suitable catalyst. So far, the synthesis of DHPM C5 carboxylic acids has been reported both in solution[15] and on solid phase.[16] The solution phase studies have involved Pd-catalyzed hydrogenation of benzyl esters using hydrogen or allyl deprotection. In our approach the DHPM benzyl esters were easily transfer hydrogenated in the presence of catalytic 5% Pd/C using ammonium formate as the in situ hydrogen source and methanol as the solvent. Within 20 min of microwave heating at 120 °C, the catalytic transfer hydrogenations afforded quantitative conversions and good to moderate isolated yields of the corresponding DHPM acids (Table 2). Similar results were obtained by carrying out the same reaction at room temperature in a sealed vessel for 8–10 h.

2.3. Hydrogenation of DHPM benzyl esters 4 in a flow manner

The hydrogenation for *O*-benzyl deprotection on DHPM benzyl esters **4Aaα**, **4Aaγ**, **4Abα**, and **4Baα** has additionally been carried out in a continuous flow manner using a continuous flow hydrogenation apparatus.[17]

This hydrogenation technology consists of a compact device capable to generate hydrogen gas in situ (up to 100 bars of H_2 pressure and 100 °C system temperature) and enabling catalytic hydrogenations in a flow mode. The electrolytic decomposition of water within the flow reactor (H-Cube™) generates hydrogen in the required quantity. The hydrogenation takes places within a heterogeneous catalyst (CatCart™) column. The exchangeable heterogeneous catalyst cartridges are advantageous for the final purification and isolation of the desired product over the conventional batch catalytic heterogeneous hydrogenations. Only homogeneous reaction mixtures are entered into the H-Cube via an HPLC injector (with up to 10 mL/min flow rate), allowing a continuous monitoring of reaction progress by sampling and also large scale hydrogenations in flow under optimized conditions.[18]

The *O*-benzyl deprotection of DHPM benzyl esters **4Aaα**, **4Aaγ**, **4Abα**, and **4Baα** was afforded in a flow manner in the H-Cube™ using a 5% Pd/C catalyst (CatCart™) column by preparing 0.025 M stock solutions using 30% AcOH in EtOH as solvent (25 mL). A continuous flow (1 mL/min flow rate) of 30% AcOH in EtOH is set through the H-Cube™ while maintaining a low (atmospheric) hydrogen pressure at 40–45 °C system temperature. After equilibrating the H-Cube™ with the above conditions of H_2 pressure and system temperature, the stock solution of substrate **4Aaα** was injected at 1 mL/min flow rate. A continuous sampling (reaction monitoring) enabled to identify quantitative conversion (by HPLC) to the desired corresponding DHPM acid **5a**. An entire cycle of 25 mL reaction mixture (**4Aaα**) extended for 25–30 min to provide a complete and clean conversion with 95% isolated yield of the desired product **5a** (Table 2). Similar conditions were applied to carry out transfer hydrogenations on DHPM benzyl esters **4Aaγ**, **4Abα**, and **4Baα** to afford quantitative conversions (by HPLC) to the corresponding DHPM C5 acids **5b**, **5c**, and **5d** (80%, 85%, and 85% isolated yields, respectively). The activity of 5% Pd/C catalyst column was retained for several cycles of similar and/or different chemistries (for a new example/substrate, the catalyst bed is rinsed with the reaction solvent prior to initiating a hydrogenation).

It was evident that transfer hydrogenation of DHPM benzyl esters **4Aaγ**, **4Abα**, and **4Baα** in the H-Cube™ flow system has a clear advantage to afford excellent yields of the desired acids **5a–d** by simple evaporation of the collected mixture after exposure of the reaction mixture to hydrogenation conditions. This makes the flow reactor an ideal candidate for automated generation of compound libraries from a library of its corresponding precursors.[18]

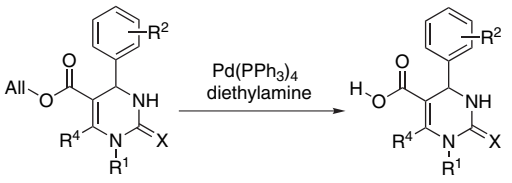
2.4. Microwave-assisted synthesis of DHPM acids 5e–k by Pd(0) catalyzed O-deallylation

The mild and selective method of Pd(0) catalyzed removal of allyl protecting groups[19] using 5 mol % of $Pd(PPh_3)_4$ as a catalyst and diethyl amine as a base formed the basis of transforming DHPM allyl esters **4Cbβ**, **4Acβ**, **4Daβ**, **4Eaβ**, **4Ccβ**, **4Bcβ**, and **4Fcβ** (ca. 0.5 mmol scale) to the corresponding DHPM acids **5e–k** under non-reducing conditions (Table 3).

Within 20 min of microwave heating at 100 °C in THF, a smooth and selective *O*-allyl deprotection was possible in the presence of the Pd(0) catalyst and the nucleophilic amine. Under these conditions, the nucleophile selectively scavenges the allyl group to afford the desired DHPM acids **5e–k**. The *O*-allyl deprotections have also been performed at room temperature under otherwise similar conditions (Table 3), and on a ca. 5 mmol scale in parallel (rt) providing similar yields.

In summary, a set of 11 DHPM C5 carboxylic acids has been prepared on a multigram scale by either a Pd-catalyzed

Table 3. Microwave-assisted O-deallylation of DHPM allyl esters **4**



4 **5e-k**

DHPM	R^1	R^2	R^4	X	Conditions[a]	Yield (%)[b]	Product
4Cbβ	Me	3-NO_2	Me	O	rt	82	**5e**
					MW	49	
4Acβ	H	H	Me	S	rt	64	**5f**
					MW	59	
4Daβ	H	4-Cl	Me	O	rt	73	**5g**
					MW	60	
4Eaβ	H	4-Br	Me	O	rt	73	**5h**
					MW	58	
4Ccβ	H	3-NO_2	Me	S	rt	57	**5i**
					MW	56	
4Bcβ	H	4-Me	Me	S	rt	56	**5j**
					MW	61	
4Fcβ	H	2-Cl	Me	S	rt	63	**5k**
					MW	59	

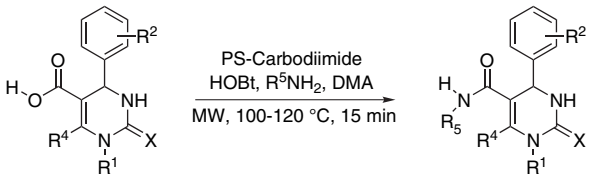
[a] Conditions: rt: room temperature deallylation with 5 mol % $Pd(PPh_3)_4$ in THF (ca. 5 mmol, 25 °C, 4–5 h); MW: microwave-assisted deallylation with 5 mol % $Pd(PPh_3)_4$ in THF (0.6–0.7 mmol, 100 °C, 20 min). See Section 4 for details.
[b] Yields are isolated yields of pure product.

debenzylation or a deallylation strategy. The acid cores **5a–k** were used as starting materials in a subsequent microwave-assisted decoration procedure to synthesize libraries of DHPM C5 amides.

2.5. Microwave-induced polymer-assisted solution phase synthesis of DHPM C5 amides from diverse DHPM acids 5 and selected amines

The multifunctionalized DHPM C5 carboxylic acids **5a–j** prepared by conventional and microwave-induced debenzylation and deallylation strategies were subsequently utilized as platforms to introduce structural diversity on the C5 position of the DHPM heterocycle. We subjected the DHPM acids **5a–j** to an existing rapid analoging amidation protocol[20] involving a polymer-assisted solution phase microwave-assisted synthesis and purification by solid-phase extraction (SPE). A simple representative set of amides was prepared in moderate to high yields, using benzylamine and propylamine as the starting amines. The polymer-assisted solution phase (PASP) microwave synthesis of the corresponding DHPM C5 amides was best afforded using DMA (*N*,*N*-dimethylacetamide) as the solvent. The highly polar DMA as the solvent ensured complete homogeneity of the reaction mixture (excluding the polymer-supported carbodiimide resin) and effective microwave heating of the reaction mixture. On the other hand, the use of solvents such as acetonitrile gave compromising yields, and at instances showed uncharacterizable by-products and/or incomplete conversions (by HPLC). In case of DMA as the solvent, 15 min of microwave heating was found sufficient to completely consume the starting DHPM acids (**5a–j**) and

Table 4. Microwave-assisted DHPM C5 amide synthesis[a]



5e-k **6a-j**

DHPM amides	R^1	R^2	R^4	R^5	X	Yields (%)[b]
6a	H	H	Me	Bn	O	84
6b	H	H	Ph	Bn	O	88
6c	Me	H	Me	Pr	O	89
6d	H	Me	Me	Bn	O	87
6e	H	2-Cl	Me	Bn	S	60
6f	H	4-Me	Me	Bn	S	51
6g	H	4-Br	Me	Pr	O	37
6h	H	3-NO_2	Me	Pr	S	57
6i	H	H	Me	Pr	S	52
6j	Me	3-NO_2	Me	Bn	O	54

[a] For conditions, see Section 4.
[b] Yields are isolated yields of pure product.

the amine component from the reaction mixture, affording a clean conversion to the corresponding DHPM amides (**6a–j**) (by HPLC monitoring). It was also evident that short term microwave heating (5 min) of the reaction mixture resulted mostly in the formation of the corresponding DHPM hydroxybenzotriazole active ester, retaining the unreacted starting amine (monitored by HPLC). The integration of a polymer-supported carbodiimide as an acid activating reagent (readily removed by simple post-reaction filtration) and a subsequent purification of the filtrate by filtering through a pre-packed Si-carbonate SPE cartridge,[20] aided a high throughput delivery of the corresponding DHPM amides **6a–j** (see Table 4) in high purity after solvent evaporation.[21]

2.6. Microwave-assisted Mitsunobu esterifications of DHPM C5 acids using fluorous synthesis and purification strategies

For the synthesis of DHPMs with more diverse and novel C5 ester moieties we wanted to perform esterification reactions employing a Mitsunobu protocol. The Mitsunobu reaction is a versatile method for the condensation of alcohols with various acidic nucleophiles promoted by triphenylphosphine (TPP) and diethyl- or diisopropyl azodicarboxylate (DEAD or DIAD) as the classical set of Mitsunobu reagents.[22] Since there are considerably more alcohols commercially available compared to β-ketoesters, diversity can potentially very rapidly be introduced at this position starting from DHPM C5 acids **5**. Nevertheless, the drawback of Mitsunobu protocol is the purification step, which usually requires a careful chromatography to separate the product from many by-products of this transformation (triphenylphosphine oxide, hydrazide, and excess alcohol) and therefore limits this reaction in the context of combinatorial/high throughput synthesis. Therefore, several strategies have been investigated to facilitate the purification step, employing, for example, polymer-bound or fluorous Mitsunobu reagents.[23–26]

For the esterification of DHPM C5 acids **5** we decided initially upon a protocol using a combination of the fluorous

Mitsunobu (F-Mitsunobu) reagents diphenyl-[4-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)phenyl]phosphine **8** (F-TPP) and bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorononyl) azodicarboxylate **9** (F-DIAD, Chart 2). Compared to polymer-bound reagents, which cannot be employed concurrently in this process and create heterogeneous reaction mixtures (therefore leading to slower reactions), fluorous reagents enable classical solution phase reaction conditions. They are soluble in most organic solvents like THF, DCM or MeOH, creating homogeneous reaction conditions, and due to the fluorous tag, product isolation can be easily performed by a fluorous solid-phase extraction (F-SPE) through fluorous silica gel.[27]

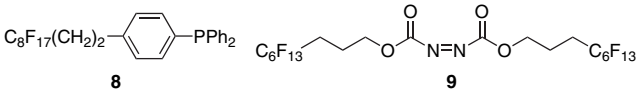
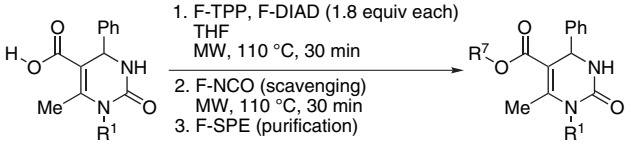


Chart 2.

For our initial optimization experiments we utilized the DHPM acid **5a** (R^1=H) and *n*-butanol as primary alcohol and made investigations on appropriate solvents, temperature, time, and molar ratios of the reaction partners. The best conditions turned out to be THF as solvent, 1.8 equiv each of the alcohol, F-TPP, and F-DIAD, and microwave irradiation at 110 °C for 10 min. With this set of conditions a conversion of 80% (HPLC) could be achieved. Reducing or increasing the temperature did not improve the conversion. By adding more equivalents of the reagents a slight increase in product concentration could be established by HPLC analysis, but due to the rather high cost of the fluorous reagents we decided to limit the amount of reagents to 1.8 equiv. Although it is known for Mitsunobu chemistry that the sequence of adding individual reagents can be crucial for the success of the reaction,[22,25] in our case a different order of reagent addition did not improve the conversion (for more details on the reaction conditions, see Section 4). After the completion of the reaction the F-reagents and F-by-products were removed by F-SPE. By eluting the reaction mixture with 80% MeOH in H_2O the F-reagents are retained on the F-silica and the 'organic' compounds can be easily separated. Since in our case only an 80% conversion was reached, some unreacted acid **5a** remained in the reaction mixture. For the removal of unreacted acid the mixture was subsequently passed through a cartridge filled with basic ion exchange Amberlite IRA-900 resin in carbonate form.[28] After evaporation of the solvent, the DHPM C5 ester **7a** was obtained in 95% purity. Unfortunately isolated product yields remained in the 30% region and could not be improved (Table 5). For secondary or other primary alcohols (like 3-fluorobenzyl alcohol), unsatisfactory conversion and very low isolated product yields were obtained. We assumed that perhaps the free *N*1–H moiety could somehow interfere with the reactivity of the acid, although no N1-alkylation was observed. In a previous publication we have shown that for the N1-alkylation of the DHPMs the more reactive Mitsunobu reagents tributylphosphine (TBP) in combination with *N*,*N*,*N*′,*N*′-tetramethyl azodicarboxamide (TMAD) have to be used since the pK_a of the nucleophilic NH was too high.[29]

Since the results for the esterification of the *N*1–H DHPM C5 acid **5a** have been rather disappointing, we turned our attention to the *N*1-substituted DHPM C5 acid **5c** (R^1=Me). The same reaction conditions have been employed for the reaction with 3-fluorobenzyl alcohol (Table 5). The only issue that had to be considered for this non-volatile alcohol was the removal of excess alcohol after the reaction, since 1.8 equiv of the alcohol were used. Therefore, we wanted to introduce a scavenging step by again using a fluorous reagent. We selected fluorous isocyanate **10** (F-NCO, 2-(perfluorooctyl)ethyl isocyanate, Chart 3) as electrophilic scavenger, which has been previously employed as scavenger for amines.[30] After some scavenging optimizations, we found that 3.2 equiv of the F-NCO reagent and 4 equiv of Et_3N (in relation to the DHPM C5 acid) were necessary to remove all the remaining acid. The scavenging step was best performed under microwave irradiation at 110 °C for 30 min. Note that the scavenging step for this particular reaction with 3-fluorobenzyl alcohol could be performed within 15 min, furnishing full conversion. In other cases (entry 5, Table 5) the time for scavenging of excess alcohol was prolonged to 30 min. Subsequent F-SPE and acid removal by filtration through a cartridge filled with Amberlite IRA-900 resin provided product **7b** in 69% isolated yield and 96% purity.

Table 5. Synthesis of C5-esters using a fluorous Mitsunobu protocol



Entry	DHPM esters	R^1	R^7	Yield (%)[a]
1	**7a**	H	*n*-Bu	30[b,c]
2	**7b**	Me	3-F-PhCH$_2$	69[b]
3	**7c**	Me	*n*-Pr	44[c]
4	**7d**	Me	*i*-Pr	46[c]
5	**7e**	Me	Cyclohexyl	43

[a] Yields are isolated yields.
[b] Mitsunobu reaction at 110 °C for 10 min.
[c] No scavenging step.

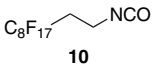


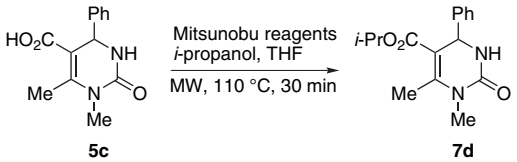
Chart 3.

For DHPM acid precursor **5c**, reasonable yields and purities≥94% could also be achieved for secondary alcohols such as *i*-propanol (46%) and cyclohexanol (43%) (Table 5), requiring an increased reaction time of 30 min at 110 °C as compared to 10 min for primary alcohols. However, the above mentioned fluorous protocol failed for more complex alcohols such as 1-butynol or longer chained alcohols like hexanol.

2.7. Reactivity studies of the fluorous Mitsunobu reagents F-TPP and F-DIAD

In summary, rather unsatisfactory results were obtained by applying the F-Mitsunobu protocol. Since full conversion could only be reached in a single case (entry 2, Table 5) and the subsequent purification steps turned out to be more

Table 6. Reactivities of F-TPP and F-DIAD



5c **7d**

Entry	Mitsunobu reagents	Yield (%)[a]
1	TPP/DIAD	75
2	F-TPP/DIAD	71
3	TPP/F-DIAD	49
4	TPP/F-DIAD	36[b]

[a] Yields are isolated yields.
[b] rt, overnight.

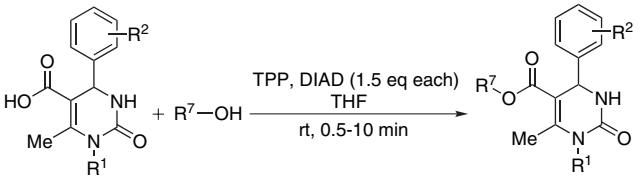
troublesome than expected, we performed reactivity studies on the F-Mitsunobu reagents. For these investigations, we examined Mitsunobu esterification of the *N*1-methyl-DHPM acid **5c** with *i*-propanol under several different conditions (Table 6). Initial experiments were performed with the classical Mitsunobu tandem TPP/DIAD using the optimized conditions of the F-Mitsunobu protocol for secondary alcohols (MW, 110 °C, 30 min). After column chromatography, product **7d** could be isolated in 75% yield with 99% purity, which was an improvement of 30% in yield compared to the F-Mitsunobu procedure. In a direct comparison experiment the combinations F-TPP/DIAD and TPP/F-DIAD were subsequently compared. By using the F-TPP/DIAD tandem nearly the same isolated yield (71%) was obtained after column chromatography compared to the 'all non-fluorous' TPP/DIAD combination (75% yield). Applying the TPP/F-DIAD combination, an isolated yield of only 49% after column chromatography could be achieved. We therefore conclude that F-DIAD has considerably lower reactivity in these esterifications as compared to standard DIAD. Longer reaction times did not lead to higher conversions. Similarly, performing the reaction at room temperature over night also did not increase the yield (entry 4, Table 6). As these studies indicate, it is the lower reactivity of the F-DIAD reagent, which limits the reaction progress.

2.8. Mitsunobu esterifications of DHPM C5 acids using classical reaction conditions

Since we could not achieve satisfactory results for the esterification of the DHPM acids **5** via the F-Mitsunobu reaction, we therefore decided to use the classical Mitsunobu conditions (TPP/DIAD), which have shown to be superior in yield (see Table 6).

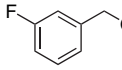
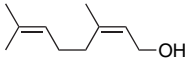
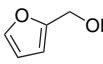
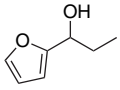
Further optimizations with respect to temperature, time, and molar equivalents of reagents with both *N*1–H (**5a**) and *N*1-methyl (**5c**) DHPM acids were performed with *n*-propanol and *i*-propanol using the TPP/DIAD reagent couple. Ultimately, we discovered that only 1.5 equiv each of propanol, TPP, and DIAD were sufficient at room temperature to obtain full conversion according to HPLC analysis. The reaction times for both **5a** and **5c** were surprisingly very short: 5 min for the *N*1–H analog **5a** and only 30 s for the *N*1-methyl DHPM acid **5c**. For the reaction with *i*-propanol 1.8 equiv each of alcohol, TPP, and DIAD were necessary for 10 min at room temperature for achieving 78% conversion in the case of *N*1-methyl (**5c**) and 50% for the *N*1-unsubstituted acid (**5a**). Longer reaction times or more equivalents of reagents did not improve the conversion.

Table 7. Synthesis of C5-esters via a classical Mitsunobu protocol



5a,c,e **7b-r**

17 examples

Entry	DHPM acid	Alcohol	*t* (min)	Yield (%)[a]	Product
1	**5a**		5	80	**7f**
2	**5c**		0.5	96	**7c**
3	**5a**		10	26[b]	**7g**
4	**5c**		10	75[b]	**7d**
5	**5a**		5	82	**7h**
6	**5c**		0.5	86	**7i**
7	**5a**		5	92	**7j**
8	**5c**		0.5	98	**7b**
9	**5a**		5	79	**7k**
10	**5c**		0.5	89	**7l**
11	**5a**		5	70	**7m**
12	**5c**		0.5	99	**7n**
13	**5a**		5	63	**7o**
14	**5c**		0.5	83	**7p**
15	**5c**		10	43[b]	**7e**
16	**5c**		10	56[b]	**7q**
17	**5e**		10	86	**7r**

[a] Yields are isolated yields.
[b] Alcohol, TPP, and DIAD, each of 1.8 equiv.

With these optimized protocols for primary and secondary alcohols we now prepared a set of 17 examples of DHPM C5 esters (Table 7). After purification by standard column chromatography, the products **7b–7r** could be obtained in moderate to excellent yields (26–99%) and in purities≥97%. The yields for the *N*1–H DHPM esters are in general somewhat lower than those for the *N*1-methyl products, especially if a secondary alcohol such as *i*-propanol is used (26% yield compared to 75%, see Table 7). If more hindered secondary alcohols, like cyclohexanol (entry 15) or the racemic 1-2(furyl)-1-propanol (entry 16) are employed in the reaction with *N*1-methyl DHPM acid, yields are moderate and in the case of cyclohexanol identical to that of the F-Mitsunobu protocol (43%, see also Table 5).

3. Conclusion

In conclusion, the efficiency of high speed sequential batch and parallel microwave synthesis has been applied to

generate a set of multifunctionalized dihydropyrimidinone esters. An easy access to the valuable carboxylic acid platform on the multifunctionalized DHPM heterocycle was found by microwave-assisted ester deprotections. The scope of flow methodology for high purity and throughput delivery of DHPM acid precursors have also been demonstrated. A rapid microwave-induced polymer-assisted solution phase (PASP) analoging protocol has been instrumental to introduce structural diversity, in the form of DHPM C5 amides. By applying a standard Mitsunobu protocol we were able to synthesize DHPM C5 esters with novel functionalities at the C5 position in excellent yields and in very short reaction times.

4. Experimental

4.1. General

Fluorous reagents were obtained from Fluorous Technologies Inc. (F-TPP: F017039, F-DIAD: F026100, F-NCO: F017032, F-Silica: 801-0100B). Amberlite IRA-900 Cl ion exchange resin was obtained from Acros (202315000). THF used for Mitsunobu reaction was obtained from Aldrich (puriss; over molecular sieve, 87371). Solvents for column chromatography have been distilled prior to use. TLC analysis was performed on Merck precoated 60 F_{254} plates. Melting points were obtained on a Gallenkamp melting point apparatus, Model MFB-595 in open capillary tubes. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX360 and 500 instruments in $CDCl_3$ or DMSO-d_6. IR spectra were taken on a Perkin–Elmer 298 spectrophotometer in KBr pellets. Mass spectra were taken on a Hewlett-Packard LC/MSD 1100 series instrument in the atmospheric pressure chemical ionization (negative or positive APCI) mode. HPLC analysis was carried out on two different Shimadzu systems. The Shimadzu LC-10 includes LC10-AT (VP) pumps, an autosampler (S-10AXL), and a dual wavelength UV detector. The separations were carried out using a C18 reversed phase analytical column, LiChrospher 100 (E. Merck, 100×3 mm, particle size 5 μm) at 25 °C and a mobile phase from (A) 0.1% TFA in 90:10 water/MeCN and (B) 0.1% TFA acid in MeCN (all solvents were HPLC grade, Acros; TFA was analytical reagent grade, Aldrich). The following gradient was applied: linear increase from solution 30% B to 100% B in 7 min, hold at 100% solution B for 2 min. The Shimadzu LC-20 system includes an LC-20AD pump, an SIL-20A autosampler, a diode array detector (SPD-M20A), a column oven (CTO-20A), and a degasser (DGU-20A5). The separations were carried out using a Pathfinder®AS100 reversed phase analytical column (150× 4.6 mm, particle size 5 μm) at 25 °C and a mobile phase from (A) 0.1% TFA in 90:10 water/MeCN and (B) 0.1% TFA acid in MeCN (all solvents were HPLC grade, Acros; TFA was analytical reagent grade, Aldrich). The following gradient was applied: linear increase from solution 20% B to 100% B in 7 min, hold at 100% solution B for 1 min.

4.2. Microwave irradiation experiments

Small scale microwave-assisted synthesis was carried out in an Emrys™ Synthesizer or Initiator 8 single-mode microwave instrument producing controlled irradiation at 2.450 GHz (Biotage AB, Uppsala).[9] Reaction times refer to hold times at the temperatures indicated, not to total irradiation times. The temperature was measured with an IR sensor on the outside of the reaction vessel.

All microwave scale-up synthesis has been performed in a Synthos 3000 multimode batch reactor (Anton Paar GmbH).[14] The instrument is equipped with two magnetrons, operating at a frequency of 2.45 GHz with continuous microwave output power from 0 to 1400 W. The reactor cavity encompasses a 16-vessel rotor and its protection lid. The rotor carries 16 reaction vessels, which are 100 mL PTFE–TFM (maximum filling volume 60 mL) made, equipped with a pressure release valve on its seal and individually resting inside ceramic jackets, to enable reactions under high pressure (maximum pressure 40 bars). The temperature is monitored using an internal gas balloon thermometer placed in one reference vessel and additionally by exterior IR thermography.

4.3. Continuous flow hydrogenations

All hydrogenations (*O*-benzyl deprotections) were conducted in a flow manner using the H-Cube™ (Thales Nanotechnology Inc.)[18] operating at 0–100 bars of in situ H_2 pressure and up to 100 °C of maximum temperature with an HPLC-like platform and a maximum flow rate of 9 mL/min. The benzyl deprotections were catalyzed by 10% Pd/C (average particle size: 32–40 microns) catalyst beds (CatCart™), used as available from Thales and were deactivated after usage by introduction into sodium bisulfite solution.

4.4. General procedure for microwave-assisted synthesis of DHPM benzyl/allyl esters 4 (4 mmol)

A microwave process vial (2–5 mL) equipped with a magnetic stirrer bead was charged with the aldehyde **1A–F** (4 mmol), β-ketoester **3α–γ** (6 mmol), urea/thiourea **2a–c** (4 mmol), and $Yb(OTf)_3$ (248 mg, 10 mol %) as the catalyst in acetonitrile (3 mL). The process vial was sealed using an aluminum crimp equipped with a Teflon septum. The sealed vial was introduced in the microwave cavity using a robotic gripper and microwave irradiated at a set temperature of 120 °C for 20 min. After completion of irradiation time, the reaction mixture was cooled to room temperature through rapid gas-jet cooling and the desired DHPM was isolated (Fig. 2). In most instances the DHPM products precipitated from the reaction mixture upon cooling to room temperature. In the synthesis of compounds **4Abα**, **4Cbβ**, **4Acβ**, **4Daβ**, **4Eaβ**, **4Ccβ**, and **4Fcβ** the reaction mixture was poured over crushed ice after the irradiation to induce complete precipitation of product. The precipitates were filtered and washed with crushed ice–ethanol mixture to yield HPLC pure products. For isolated yields see Table 1.

4.5. General procedure for microwave-assisted synthesis of DHPM benzyl/allyl esters 4 (40 mmol)

Scale-up synthesis has been performed in a Synthos 3000 multimode batch reactor. The PTFE–TFM reaction vessels are charged with Teflon coated stirrer bars. Reaction mixtures were prepared in individual vessels with a set of corresponding aldehydes **1A–F** (40 mmol), urea/thiourea **2a–c** (40 mmol), and β-diketoester **3α–γ** (60 mmol) components

in 20 mL of acetonitrile (see Fig. 1 for building blocks). The PTFE vessels were introduced in ceramic jackets, appropriately sealed, and fitted into the rotor positions. The rotor fitted with the sealed reaction vessels is equipped with its protection lid and introduced in the reactor cavity. The reaction mixtures are then irradiated at a preset temperature of 120 °C for 20 min (with 3 min programmed ramp). After completion of the reaction, the mixture is allowed to cool to 40 °C by a built-in fan-assisted cooling. The reaction mixtures are worked up individually and the product yields evaluated upon isolation.

Isolated yields: **4Aaα** (48%), **4Aaγ** (25%), **4Abα** (36%), **4Baα** (39%), **4Cbβ** (59%), **4Acβ** (60%), **4Daβ** (59%), **4Eaβ** (66%), **4Ccβ** (47%), **4Bcβ** (76%), and **4Fcβ** (17%).

4.5.1. Benzyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Aaα). Mp 166 °C (lit.[15d] 168 °C). ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3H), 5.01–5.03 (m, 2H), 5.15 (d, J=2.8 Hz, 1H), 7.13–7.29 (m, 10H), 7.75 (br s, 1H), 9.26 (br s, 1H). MS (ES$^+$) m/z 323.1 (M+1).

4.5.2. Benzyl 4,6-diphenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Aaγ). Mp 210 °C (lit.[15d] 209 °C). ^{1}H NMR (DMSO-d_6) δ 4.79 (m, 2H), 5.26 (d, J=3.6 Hz), 6.79–7.38 (m, 15H), 7.88 (br s, 1H), 9.33 (s, 1H). MS (ES$^+$) m/z 385.2 (M+1).

4.5.3. Benzyl 1,6-dimethyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Abα). Mp 119–120 °C (lit.[15d] 118 °C). ^{1}H NMR (DMSO-d_6) δ 2.51 (s, 3H), 3.10 (s, 3H), 5.03–5.11 (m, 2H), 5.17 (d, J=3.6 Hz, 1H), 7.16–7.29 (m, 10H), 7.96 (d, J=3.8 Hz, 1H). MS (ES$^+$) m/z 337.2 (M+1).

4.5.4. Benzyl 6-methyl-4-tolyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Baα). Mp 170–171 °C. ^{1}H NMR (DMSO-d_6) δ 2.25 (s, 3H), 2.26 (s, 3H), 3.32 (s, 3H), 4.97–5.06 (m, 2H), 5.12 (d, J=3.2 Hz, 1H), 7.06–7.28 (m, 9H), 7.69 (br s, 1H), 9.22 (br s, 1H). MS (ES$^+$) m/z 337.2 (M+1).

4.5.5. Allyl 1,6-dimethyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Cbβ). Mp 125–126 °C (lit.[9a] 122–123). ^{1}H NMR (DMSO-d_6) δ 2.49 (s, 3H), 3.11 (s, 3H), 4.53 (m, 2H), 5.08–5.13 (m, 2H), 5.31 (d, J=3.9 Hz, 1H), 5.81–5.88 (m, 1H), 7.64–7.67 (m, 2H), 8.06 (br s, 1H), 8.12–8.18 (m, 2H). MS (ES$^+$) m/z 332.1 (M+1).

4.5.6. Allyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Acβ). Mp 154–155 °C. ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H), 4.50 (br, 2H), 5.05–5.10 (m, 2H), 5.19 (br, 1H), 5.78–5.86 (m, 1H), 7.20–7.34 (m, 5H), 9.67 (s, 1H), 10.37 (s, 1H). MS (ES$^+$) m/z 288.9 (M+).

4.5.7. Allyl 6-methyl-4-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Daβ). Mp 174–176 °C. ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3H), 4.48 (m, 2H), 5.06–5.11 (m, 2H), 5.15–5.16 (d, J=3.2 Hz, 1H), 5.77–5.88 (m, 1H), 7.23–7.40 (m, 4H), 7.79 (br s, 1H), 9.30 (br s, 1H). MS (ES$^+$) m/z 306.9 (M+1).

4.5.8. Allyl 6-methyl-4-(4-bromophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Eaβ). Mp 195–196 °C. ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3H), 4.48 (m, 2H), 5.07–5.12 (m, 2H), 5.13–5.14 (d, J=3 Hz, 1H), 5.77–5.88 (m, 1H), 7.17–7.53 (m, 4H), 7.79 (br s, 1H), 9.30 (br s, 1H). MS (ES$^+$) m/z 351 (M+1).

4.5.9. Allyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Ccβ). Mp 182–183 °C. ^{1}H NMR (DMSO-d_6) δ 2.33 (s, 3H), 4.51 (m, 2H), 5.07–5.12 (m, 2H), 5.34 (d, J=3.6 Hz, 1H), 5.77–5.88 (m, 1H), 7.67–8.18 (m, 4H), 9.97 (br s, 1H), 10.55 (br s, 1H). MS (ES$^+$) m/z 333.9 (M+1).

4.5.10. Allyl 6-methyl-4-tolyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Bcβ). Mp 161–162 °C. ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3H), 2.29 (s, 3H), 2.49 (s, 3H), 4.49 (m, 2H), 5.08–5.13 (m, 2H), 5.14–5.15 (d, J=3.9 Hz, 1H), 5.78–5.88 (m, 1H), 7.08–7.15 (m, 4H), 9.64 (br s, 1H), 10.34 (br s, 1H). MS (ES$^+$) m/z 303 (M+1).

4.5.11. Allyl 6-methyl-4-(2-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4Fcβ). Mp 107–108 °C. ^{1}H NMR (DMSO-d_6) δ 2.340 (s, 3H), 4.43 (m, 2H), 4.93–5.05 (m, 2H), 5.65 (d, J=3.2 Hz, 1H), 5.68–5.79 (m, 1H), 7.27–7.42 (m, 4H), 9.61 (br s, 1H), 10.41 (br s, 1H). MS (ES$^+$) m/z 323.1 (M+1).

4.6. General procedure for the microwave-assisted synthesis of DHPM acids 5a–d by catalytic transfer hydrogenation

A microwave process vial (2–5 mL) equipped with a magnetic stirrer bead was charged with 0.60 mmol of the appropriate DHPM C5 benzyl ester **4Aaα**, **4Aaγ**, **4Abα** or **4Baα**, 5% Pd/C (10% w/w), and ammonium formate (0.37 mg, 10 equiv) in methanol (3 mL). The process vial was sealed with an aluminum crimp equipped with a Teflon septum. The sealed vial was introduced in the microwave cavity using a robotic gripper and microwave irradiated at a set temperature of 120 °C for 20 min. After completion of the irradiation, the reaction mixture was cooled to room temperature, the contents transferred to a round bottom flask, and evaporated to dryness. The residue was treated with 0.5 M KOH solution (5–8 mL), stirred vigorously, and filtered under gravity. The filtrate was acidified with 2 M HCl to pH 4–5 and the resulting precipitates of the corresponding 4-aryl-DHPM C5 acids **5a–d** were collected by suction filtration and recrystallized from ethanol. For yields refer to Table 2.

4.7. General procedure for the continuous flow hydrogenation of DHPM C5 benzyl esters 4

A hydrogenation flow apparatus (H-Cube™) capable of generating hydrogen gas in situ (100 bars and 100 °C system temperature) has been utilized for the synthesis of the DHPM C5 carboxylic acids **5a–d** by a continuous flow *O*-benzyl deprotection of DHPM C5 benzyl esters **4** (Table 2). Stock solutions (0.60 mmol, 0.025 M) of the DHPM benzyl esters (**4Aaα**, **4Aaγ**, **4Abα**, **4Baα**, Fig. 2) were prepared in 30% AcOH in EtOH (25 mL). The H-Cube™ was equipped with a fresh 5% Pd/C catalyst (CatCart™) column and then purged with the solvent mixture (30% AcOH in

EtOH). Initially, the solvent flow is regulated to 1 mL/min while maintaining a low hydrogen pressure (ca. atmospheric pressure) and the system temperature set to 40–45 °C. The solvent flow is allowed to equilibrate with the set conditions. Thereafter, the reaction mixture stock solution is injected at 1 mL/min flow rate and exposed to the preset hydrogenation conditions. The injected mixture is analyzed by continuous sampling and the progress of the reaction is monitored by HPLC. The entire cycle of 25 mL stock solution is completed in 25–30 min. The corresponding DHPM carboxylic acids **5a–d** were isolated in ca.100 mg quantities and yields determined after evaporating the solvent from the collected mixture after exposure to the hydrogenation conditions in the H-Cube™ (Table 2).

4.8. General procedure for the room temperature synthesis of DHPM acids 5a–d by catalytic transfer hydrogenation

In 50 mL single neck round bottom flasks equipped with magnetic stirrer beads, individual reaction mixtures of 6.0 mmol of the corresponding DHPM benzyl esters **4Aaα**, **4Aaγ**, **4Abα**, and **4Baα**, 5% Pd/C (10% w/w) and ammonium formate (3.78 g, 10 equiv) are suspended in 15 mL of methanol. The reaction flask is sealed with a rubber septum and a balloon maintained on it. After allowing the reaction mixture to stir at room temperature for 8–10 h to enable complete reaction, the solvent is completely evaporated under reduced pressure. The solid residue is treated with 0.5 M KOH solution (10–15 mL), vigorously stirred, and filtered under gravity. The filtrate is acidified by 2 M HCl till pH 4–5 and the resulting precipitates of the corresponding DHPM carboxylic acids **5a–d** are collected by suction filtration and recrystallized from ethanol. For yields, see Table 2.

4.9. General procedure for the microwave-assisted synthesis of DHPM acids 5e–k by palladium-catalyzed O-deallylation

A microwave process vial (2–5 mL) equipped with a magnetic stirrer bead was charged with 0.60 mmol of the corresponding DHPM allyl esters **4Cbβ**, **4Acβ**, **4Daβ**, **4Eaβ**, **4Ccβ**, **4Bcβ**, and **4Fcβ**, 5 mol % of $Pd(PPh_3)_4$ (0.034 g), and diethyl amine (0.438 mg, 10 equiv) in THF (3 mL) as the solvent. The process vial was sealed using an aluminum crimp equipped with a Teflon septum. The sealed vial was introduced in the microwave cavity using a robotic gripper and microwave irradiated at a set temperature of 100 °C for 20 min. After completion of irradiation time, the reaction mixture is cooled to room temperature through rapid gas-jet cooling and the reaction mixture is transferred into a round bottom flask and evaporated to dryness. To this residue 0.5 M KOH (5–8 mL) is added, vigorously stirred, and filtered under gravity. The filtrate is acidified with 2 M HCl to pH 4–5 and the resulting DHPM C5 carboxylic acid precipitates are filtered under suction and recrystallized from ethanol. For yields, see Table 3.

4.10. General procedure for the room temperature synthesis of DHPM acids 5e–k by palladium-catalyzed O-deallylation

In 50 mL single neck round bottom flasks equipped with a magnetic stirrer bead, individual reaction mixtures containing 6.0 mmol of the corresponding DHPM allyl esters **4Cbβ**, **4Acβ**, **4Daβ**, **4Eaβ**, **4Ccβ**, **4Bcβ**, and **4Fcβ**, 5 mol % of $Pd(PPh_3)_4$ (0.346 mg), and diethyl amine (4.38 g, 10 equiv) are prepared in 15 mL THF. The reaction mixture is stoppered and allowed to stir at room temperature for 4–5 h to enable complete conversion. Thereafter, the reaction mixture is evaporated to dryness under reduced pressure and the solid residue is treated with 0.5 M KOH solution (10–15 mL), vigorously stirred, and filtered under gravity. The filtrate is acidified by 2 M HCl till pH 4–5 and the resulting precipitates of the corresponding 4-aryl-DHPM C5 carboxylic acids **5e–k** are collected by suction filtration and recrystallized from ethanol. For yields, see Table 3.

4.10.1. 1,2,3,4-Tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylic acid (5a). Mp 210 °C (lit.[15d] 210–213 °C). ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 3H), 5.09 (br s, 1H), 7.22–7.66 (m, 5H), 7.66 (br s, 1H), 9.07 (br s, 1H), 11.88 (br s, 1H). MS (ES$^+$) *m*/*z* 233.2 (M+1).

4.10.2. 1,2,3,4-Tetrahydro-2-oxo-4,6-diphenylpyrimidine-5-carboxylic acid (5b). Mp 160 °C (lit.[15d] 163 °C). ^{1}H NMR (DMSO-d_6) δ 5.22 (d, J=3.6 Hz, 1H), 7.30–7.39 (m, 10H), 7.89 (br s, 1H), 9.13 (s, 1H). MS (ES$^+$) *m*/*z* 295 (M+1).

4.10.3. 1,2,3,4-Tetrahydro-1,6-dimethyl-2-oxo-4-phenylpyrimidine-5-carboxylic acid (5c). Mp 235 °C (lit.[15d] 237 °C). ^{1}H NMR (DMSO-d_6) δ 2.48 (s, 3H), 3.07 (s, 3H), 5.12 (d, J=3.9 Hz, 1H), 7.20–7.30 (m, 5H), 7.89 (d, J=3.2 Hz, 1H). MS (ES$^+$) *m*/*z* 247 (M+1).

4.10.4. 1,2,3,4-Tetrahydro-6-methyl-2-oxo-4-*p*-tolylpyrimidine-5-carboxylic acid (5d). Mp 220–223 °C. ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 3H), 2.25 (s, 3H), 5.14 (d, J=3.6 Hz, 1H), 7.11–7.12 (m, 4H), 7.62 (br s, 1H), 9.04 (br s, 1H), 11.84 (s, 1H). MS (ES$^+$) *m*/*z* 247 (M+1).

4.10.5. 1,2,3,4-Tetrahydro-1,6-dimethyl-4-(3-nitrophenyl)-2-oxopyrimidine-5-carboxylic acid (5e). Mp 200–201 °C. ^{1}H NMR (DMSO-d_6) δ 2.49 (s, 3H), 3.08 (s, 3H), 5.26 (d, J=3.9 Hz, 1H), 7.62–8.10 (m, 4H), 8.13 (br s, 1H), 12.34 (br s, 1H). MS (ES$^+$) *m*/*z* 292.2 (M+1).

4.10.6. 1,2,3,4-Tetrahydro-6-methyl-4-phenyl-2-thioxopyrimidine-5-carboxylic acid (5f). Mp 209–210 °C. ^{1}H NMR (DMSO-d_6) δ 2.27 (s, 3H), 5.14 (d, J=3.6 Hz, 1H), 7.20–7.34 (m, 5H), 9.72 (br s, 1H), 10.24 (br s, 1H). MS (ES$^+$) *m*/*z* 249.1 (M+1).

4.10.7. 4-(4-Chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylic acid (5g). Mp 199–200 °C. ^{1}H NMR (DMSO-d_6) δ 2.23 (s, 3H), 5.13 (d, J=3.4 Hz, 1H), 7.23–7.39 (m, 4H), 7.71 (br s, 1H), 9.16 (br s, 1H), 11.92 (br s, 1H). MS (ES$^+$) *m*/*z* 267 (M+1).

4.10.8. 4-(4-Bromophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylic acid (5h). Mp 174–175 °C. ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 3H), 5.08 (d, J=3.2 Hz, 1H), 7.17–7.53 (m, 4H), 7.70 (br s, 1H), 9.13 (br s, 1H), 11.92 (br s, 1H). MS (ES$^+$) *m*/*z* 311.1 (M+1).

4.10.9. 1,2,3,4-Tetrahydro-6-methyl-4-(3-nitrophenyl)-2-thioxopyrimidine-5-carboxylic acid (5i). Mp 204–205 °C. ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H), 5.30 (d, J=3.6 Hz, 1H), 7.16–8.16 (m, 4H), 9.72 (br s, 1H), 10.42 (br s, 1H), 12.39 (br s, 1H). MS (ES$^+$) m/z 294.1 (M+1).

4.10.10. 1,2,3,4-Tetrahydro-6-methyl-2-thioxo-4-*p*-tolyl-pyrimidine-5-carboxylic acid (5j). Mp 208–209 °C. ^{1}H NMR (DMSO-d_6) δ 2.25 (s, 3H), 2.26 (s, 3H), 2.49 (s, 3H), 5.09 (d, J=3.6 Hz, 1H), 7.08–7.15 (m, 4H), 9.54 (br s, 1H), 10.20 (br s, 1H), 12.14 (br s, 1H). MS (ES$^+$) m/z 262.9 (M+1).

4.10.11. 4-(2-Chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidine-5-carboxylic acid (5k). Mp 206–208 °C. ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H), 5.58 (d, J=3.4 Hz, 1H), 7.25–7.43 (m, 5H), 9.49 (br s, 1H), 10.29 (br s, 1H), 12.12 (br s, 1H). MS (ES$^+$) m/z 283 (M+1).

4.11. General procedure for the amidation of acids to DHPM amides

In a small microwave process vial (0.5–2.5 mL), a mixture of the corresponding DHPM acids **2a**–**d** (0.050 mmol), polymer-supported carbodiimide (PS-carbodiimide, 1.29 mequiv/g loading, Argonaut part no. 800370) (150 mg, 0.1 mmol, 2.0 equiv), 1-hydroxybenzotriazole (7 mg, 0.051 mmol), and benzylamine or *n*-propylamine (0.050 mmol) was suspended in *N*,*N*-dimethylacetamide (DMA) (2 mL). The process vial was sealed appropriately, introduced into the single-mode microwave cavity, and microwave irradiated at 100 °C for 15 min. After completion of the irradiation time, the reaction vial was rapidly cooled to room temperature by compressed air (gas-jet cooling) and the mixture was diluted with MeOH (2 mL). The reaction mixture was filtered through a pre-packed column of Si-carbonate (1 g, 0.8 mmol/g loading, Silicycle Inc.) and washed with several aliquots of MeOH (3×3 mL) under gravity. The filtrate collected was evaporated under reduced pressure to yield the corresponding DHPM amides as colorless solids in 37–89% yield. The purity of those compounds was >95% by HPLC (215 nm) and ^{1}H NMR analysis.

4.11.1. *N*-Benzyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenyl-pyrimidine-5-carboxamide (6a). Mp 210–212 °C (MeCN). ^{1}H NMR (DMSO-d_6) δ 2.02 (s, 3H), 4.22 (br, 2H), 5.30 (br, 1H), 6.96–7.31 (m, 10H), 7.49 (s, 1H), 8.10 (br, 1H), 8.56 (s, 1H); ^{13}C NMR δ 17.4, 42.5, 55.5, 105.2, 126.9, 127.0, 127.4, 127.7, 128.5, 128.8, 138.0, 140.2, 144.7, 153.0, 166.8. MS (pos. APCI) m/z 322.3 (M+1). Anal. Calcd ($C_{19}H_{19}N_3O_2$): C, 71.01; H, 5.96; N, 13.08. Found: C, 70.83; H, 5.96; N, 12.97.

4.11.2. *N*-Benzyl-1,2,3,4-tetrahydro-2-oxo-4,6-diphenyl-pyrimidine-5-carboxamide (6b). Mp 175–177 °C (MeCN). ^{1}H NMR (DMSO-d_6) 3.83–3.89 (dd, J=5.07, 5.42 Hz, 1H), 3.98–4.04 (dd, J=6.21, 6.00 Hz, 1H), 5.26 (br, 1H), 6.67 (br, 2H), 7.10 (br, 3H), 7.34–7.36 (m, 10H), 7.49 (br, 1H), 7.55 (s, 1H), 8.68 (s, 1H); ^{13}C NMR δ 42.6, 56.5, 107.4, 126.8, 127.3, 127.3, 127.9, 128.4, 128.5, 128.8, 128.9, 129.4, 134.5, 144.1, 153.2, 166.9. MS (pos. APCI) m/z 384.6 (M+1).

4.11.3. *N*-Propyl-1,2,3,4-tetrahydro-1,6-dimethyl-2-oxo-4-phenyl-pyrimidine-5-carboxamide (6c). Mp 239–241 °C (MeCN). Anal. Calcd ($C_{16}H_{21}N_3O_2$) C, 66.88; H, 7.37; N, 14.62. Found: C, 66.85; H, 7.44; N, 14.62. ^{1}H NMR (DMSO-d_6) δ 0.74 (br, 3H), 1.33 (m, 2H), 2.09 (s, 3H), 3.02 (br, 5H), 5.15 (s, 1H), 7.18–7.30 (m, 5H), 7.60 (s, 1H), 7.81 (br, 1H); ^{13}C NMR δ 11.8, 16.8, 22.7, 29.7, 41.0, 54.3, 110.0, 126.5, 127.7, 128.8, 138.0, 144.2, 154.6, 167.3. MS (pos. APCI) m/z 288.2 (M+1).

4.11.4. *N*-Benzyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-*p*-tolylpyrimidine-5-carboxamide (6d). Mp 223–226 °C (MeCN). Anal. Calcd ($C_{20}H_{21}N_3O_2$): C, 71.62; H, 6.31; N, 12.53. Found: C, 71.04; H, 6.22; N, 12.22. ^{1}H NMR (DMSO-d_6) δ 2.00 (s, 3H), 2.28 (s, 3H), 4.21 (br, 2H), 5.25 (br, 1H), 6.97–7.17 (m, 9H), 7.43 (s, 1H), 8.06 (br, 1H), 8.53 (s, 1H); ^{13}C NMR δ 17.4, 21.1, 42.2, 55.2, 105.4, 126.9, 127.4, 128.4, 129.3, 136.8, 137.8, 140.2, 141.8, 153.0, 166.8. MS (pos. APCI) m/z 336.4 (M+1).

4.11.5. *N*-Benzyl-1,2,3,4-tetrahydro-6-methyl-2-thioxo-4-(2-chlorophenyl)-pyrimidine-5-carboxamide (6e). Mp 235–237 °C. ^{1}H NMR (DMSO-d_6) δ 1.98 (s, 3H), 4.13 (br, 1H), 4.26 (br, 1H), 5.68 (1H), 6.92–7.40 (m, 9H), 8.29 (s, 1H), 9.17(br, 1H), 9.86 (br, 1H); ^{13}C NMR δ 16.6, 42.5, 53.6, 106.6, 126.9, 127.2, 128.0, 128.5, 130.0, 132.2, 134.2, 139.7, 140.2, 166.2, 174.3. MS (pos. APCI) m/z 372.6 (M+1).

4.11.6. *N*-Benzyl-1,2,3,4-tetrahydro-6-methyl-2-thioxo-4-*p*-tolyl-pyrimidine-5-carboxamide (6f). Mp 216–217 °C. ^{1}H NMR (DMSO-d_6) δ 2.03 (s, 3H), 2.28 (s, 3H), 4.17–4.28 (m, 2H), 5.27 (s, 1H), 6.98–7.19 (m, 9H), 8.26 (m, 1H), 9.30 (br, 1H), 9.81 (s, 1H); ^{13}C NMR δ 16.8, 21.1, 42.5, 55.2, 107.2, 126.9, 127.0, 127.4, 128.4, 129.4, 135.0, 137.3, 139.9, 140.5, 166.4, 174.2. MS (pos. APCI) m/z 352.5 (M+1).

4.11.7. *N*-Propyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-(4-bromophenyl)-pyrimidine-5-carboxamide (6g). Mp 234–236 °C. Anal. Calcd ($C_{15}H_{18}BrN_3O_2$): C, 51.15; H, 5.15; N, 11.93. Found: C, 50.67; H, 4.95; N, 11.45. ^{1}H NMR (DMSO-d_6) δ 0.70 (t, J=7.2 Hz, 3H), 1.32 (m, 2H), 1.97 (s, 3H), 2.90 (m, 2H), 5.21 (s, H), 7.15–7.18 (d, 2H), 7.49–7.52 (br, 2H), 7.55 (br, 1H), 7.57 (t, J=5 Hz, 1H), 8.55 (s, 1H); ^{13}C NMR δ 11.7, 17.2, 22.7, 54.9, 105.3, 120.7, 129.0, 131.6, 134.4, 144.1, 153.0, 166.5. MS (pos. APCI) m/z 352.5 (M+1).

4.11.8. *N*-Propyl-1,2,3,4-tetrahydro-6-methyl-2-thioxo-4-(3-nitrophenyl)-pyrimidine-5-carboxamide (6h). Mp 240–241 °C. ^{1}H NMR (DMSO-d_6) δ 0.68 (t, J=7.5 Hz, 3H), 1.30 (m, 2H), 2.03 (s, 3H), 2.96 (m, 2H), 5.40 (s, 1H), 7.65–7.70 (m, 2H), 7.81 (t, J=5.2 Hz, 1H), 8.07 (s, 1H), 8.14 (d, J=7.2 Hz, 1H), 9.45 (br, 1H), 10.0 (s, 1H); ^{13}C NMR δ 11.7, 16.8, 22.6, 54.7, 106.6, 121.6, 123.0, 130.7, 133.5, 135.6, 145.5, 148.2, 165.9, 174.7. MS (pos. APCI) m/z 335.4 (M+1).

4.11.9. *N*-Propyl-1,2,3,4-tetrahydro-6-methyl-2-thioxo-4-phenyl-pyrimidine-5-carboxamide (6i). Mp 174–176 °C. ^{1}H NMR (DMSO-d_6) δ 0.71 (t, J=7.2 Hz, 3H), 1.31 (m, 2H), 1.99 (s, 3H), 2.49–2.99 (m, 2H), 5.25 (s, 1H),

7.18–7.35 (m, 5H), 7.75 (t, J=5.2 Hz, 1H), 9.30 (br, 1H), 9.81 (s, 1H); ^{13}C NMR δ 11.7, 16.7, 22.6, 55.9, 107.6, 108.4, 126.8, 128.0, 128.9, 139.4, 166.3. MS (pos. APCI) m/z 290.4 (M+1).

4.11.10. *N*-Benzyl-1,2,3,4-tetrahydro-1,6-dimethyl-2-oxo-4-(3-nitrophenyl)-pyrimidine-5-carboxamide (6j). Mp 241–242 °C. ^{1}H NMR (DMSO-d_6) δ 2.16 (s, 3H), 3.05 (s, 3H), 4.17–4.23 (dd, J=5.7, 5.7 Hz, 1H), 4.25–4.31 (dd, J=6.12, 6.12 Hz, 1H), 5.35 (s, 1H), 6.99–7.01 (m, 1H), 7.16–7.18 (m, 3H), 7.59–7.67 (m, 2H), 7.82 (d, J=2.5 Hz, 1H), 8.06 (br, 1H), 8.13–8.15 (m, 1H), 8.38–8.42 (m, 1H); ^{13}C NMR δ 17.0, 29.8, 53.9, 108.0, 121.5, 122.8, 127.0, 127.4, 128.5, 130.5, 133.6, 139.8, 140.0, 146.2, 148.2, 153.5, 167.0. MS (pos. APCI) m/z 381.6 (M+1).

4.12. General procedure for the synthesis of DHPM C5 esters using a fluorous Mitsunobu protocol

A small microwave vial (0.5–2 mL) was charged with 0.07 mmol of the corresponding DHPM acid **5a** or **c**, F-TPP (89 mg, 1.8 equiv), and anhydrous THF (0.5 mL). After stirring for a few seconds, the corresponding alcohol (1.8 equiv) and F-DIAD (106 mg, 1.8 equiv) were added, the vial was capped, flushed with argon, and heated at 110 °C for the times given in Table 5. After cooling to 50 °C, F-NCO reagent (110 mg, 3.2 equiv, 0.22 mmol) and Et_3N (39 μL, 4 equiv, 0.28 mmol) were added and the vial was again heated in the microwave reactor at 110 °C for 30 min (entries 2 and 5, Table 5). Subsequently, the solvent was evaporated, the mixture dissolved in ca. 300–400 μL MeOH, and passed through a cartridge filled with 2.5 g of F-silica, which was pre-conditioned with 5 mL THF and 15 mL H_2O, with 8 mL of 80% MeOH in H_2O. The solvent was evaporated then the residue was dissolved in 0.5 mL of THF and passed through a cartridge filled with 700 mg Amberlite IRA-900 resin in carbonate form (1.5 g for entries 3–5), which was pre-conditioned with 8 mL MeOH and 10–20 mL THF, with 10 mL THF. The solvent was evaporated and the residue was washed two times with toluene, which was also removed by evaporation. For yields and purities see text and Table 5.

4.12.1. Butyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7a). ^{1}H NMR (DMSO-d_6) δ 0.78 (t, J=7.3 Hz, 3H), 1.09–1.19 (m, 2H), 1.39–1.47 (m, 2H), 2.25 (s, 3H), 3.86–3.99 (m, 2H), 5.13 (d, J=3.0 Hz, 1H), 7.21–7.35 (m, 5H), 7.73 (br s, 1H), 9.20 (br s, 1H). MS (ES$^+$) m/z 289.1 (M+1).

4.13. General procedure for the synthesis of DHPM C5 esters under classical Mitsunobu conditions

A small microwave vial (0.5–2 mL) was charged with 0.1 mmol of the corresponding DHPM acid **5a**, **5c** or **5e**, triphenylphosphine (TPP, 39 mg, 1.5 equiv), and anhydrous THF (0.7 mL). After stirring for a few seconds, the corresponding alcohol (1.5 equiv) and diisopropyl azodicarboxylate (DIAD, 29.5 μL, 1.5 equiv) were added and the mixture was stirred for the time given in Table 7. For secondary alcohols, 1.8 equiv each of alcohol, TPP, and DIAD was used. Subsequently, the solvent was evaporated and the reaction mixture was purified by column chromatography using DCM/EtOAc for *N*1-methyl substituted and $CHCl_3$/acetone for *N*1-unsubstituted products. For the products **7k** and **7l** a mixture of hexane/THF and for **7p** hexanes/EtOAc were used. For yields and purities see text and Table 7.

4.13.1. 3-Fluorobenzyl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7b). ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 3.26 (s, 3H), 5.01–5.05 and 5.09–5.13 (2m, 2H), 5.40 (d, J=2.9 Hz, 1H), 5.58 (br s, 1H), 6.79 (d, J=9.5 Hz, 1H), 6.91–7.01 (m, 2H), 7.19–7.31 (m, 6H). MS (ES$^+$) m/z 355.5 (M+1).

4.13.2. Propyl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7c). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J=7.4 Hz, 3H), 1.54–1.64 (m, 2H), 2.54 (s, 3H), 3.25 (s, 3H), 4.02 (t, J=6.6 Hz, 2H), 5.39 (d, J=2.9 Hz, 1H), 5.58 (br s, 1H), 7.25–7.33 (m, 5H). MS (ES$^+$) m/z 289.5 (M+1).

4.13.3. *i*-Propyl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7d). ^{1}H NMR ($CDCl_3$) δ 1.06 (d, J=6.2 Hz, 3H), 1.24 (d, J=6.2 Hz, 3H), 2.52 (s, 3H), 3.25 (s, 3H), 4.94–5.04 (m, 1H), 5.38 (d, J=2.7 Hz, 1H), 5.55 (br s, 1H), 7.25–7.33 (m, 5H). MS (ES$^+$) m/z 289.5 (M+1).

4.13.4. Cyclohexyl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7e). ^{1}H NMR ($CDCl_3$) δ 1.22–1.54 (m, 9H), 1.82–1.85 (m, 1H), 2.54 (s, 3H), 3.24 (s, 3H), 4.74–4.79 (m, 1H), 5.40 (d, J=2.8 Hz, 1H), 5.57 (br s, 1H), 7.25–7.33 (m, 5H). MS (ES$^+$) m/z 329.4 (M+1).

4.13.5. Propyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7f). ^{1}H NMR (DMSO-d_6) δ 0.74 (t, J=7.4 Hz, 3H), 1.47 (sex, J_1=6.9 Hz, J_2=7.1 Hz, 2H), 2.26 (s, 3H), 3.83–3.94 (m, 2H), 5.14 (d, J=3.0 Hz, 1H), 7.22–7.34 (m, 5H), 7.73 (br s, 1H), 9.19 (br s, 1H). MS (ES$^+$) m/z 275.7 (M+1).

4.13.6. *i*-Propyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7g). ^{1}H NMR (DMSO-d_6) δ 0.98 (d, J=6.2 Hz, 3H), 1.15 (d, J=6.2 Hz, 3H), 2.24 (s, 3H), 4.75–4.86 (m, 1H), 5.12 (d, J=2.8 Hz, 1H), 7.22–7.34 (m, 5H), 7.72 (br s, 1H), 9.16 (br s, 1H). MS (ES$^+$) m/z 275.3 (M+1).

4.13.7. 3-Butynyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7h). ^{1}H NMR (DMSO-d_6) δ 2.25 (s, 3H), 2.42–2.45 (m, 2H), 2.85 (br s, 1H), 3.95–4.07 (m, 2H), 5.14 (d, J=2.8 Hz, 1H), 7.21–7.33 (m, 5H), 7.77 (br s, 1H), 9.24 (br s, 1H). MS (ES$^+$) m/z 285.3 (M+1).

4.13.8. 3-Butynyl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7i). ^{1}H NMR ($CDCl_3$) δ 1.97 (t, J=2.5 Hz, 1H), 2.43–2.47 (m, 2H), 2.54 (s, 3H), 3.26 (s, 3H), 4.17 (t, J=6.6 Hz, 2H), 5.40 (d, J=3.0 Hz, 1H), 5.59 (br s, 1H), 7.26–7.33 (m, 5H). MS (ES$^+$) m/z 299.4 (M+1).

4.13.9. 3-Fluorobenzyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7j). ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H), 4.97–5.00 and 5.07–5.11 (2m,

2H), 5.19 (d, J=3.0 Hz, 1H), 6.88 (d, J=10.0 Hz, 1H), 6.96 (d, J=7.6 Hz, 1H), 7.06–7.11 (m, 1H), 7.20–7.34 (m, 6H), 7.77 (br s, 1H), 9.30 (br s, 1H). MS (ES^+) m/z 341.4 (M+1).

4.13.10. *cis*-3,7-Dimethyl-2,6-octadien-1-yl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7k). ^1H NMR (DMSO-d_6) δ 1.52 (s, 3H), 1.60 (s, 3H), 1.67 (s, 3H), 1.99 (br s, 4H), 2.23 (s, 3H), 4.44 (d, J=7.0 Hz, 2H), 5.03 (br s, 1H), 5.12 (d, J=2.6 Hz, 1H), 5.21 (t, J=7.0 Hz, 1H), 7.20–7.31 (m, 5H), 7.73 (br s, 1H), 9.19 (br s, 1H). MS (ES^+) m/z 369.3 (M+1).

4.13.11. *cis*-3,7-Dimethyl-2,6-octadien-1-yl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7l). ^1H NMR (DMSO-d_6) δ 1.52 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 2.00 (br s, 4H), 2.46 (s, 3H), 3.08 (s, 3H), 4.43–4.53 (m, 2H), 5.04–5.05 (m, 1H), 5.13 (d, J=3.5 Hz, 1H), 5.23 (t, J=6.8 Hz, 1H), 7.17–7.31 (m, 5H), 7.96 (br d, J=3.6 Hz, 1H). MS (ES^+) m/z 383.4 (M+1).

4.13.12. Furfuryl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7m). ^1H NMR (DMSO-d_6) δ 2.22 (s, 3H), 5.00 (s, 2H), 5.11 (d, J=3.1 Hz, 1H), 6.39–6.43 (m, 2H), 7.15–7.29 (m, 5H), 7.65 (d, J=0.8 Hz, 1H), 7.76 (br s, 1H), 9.28 (br s, 1H). MS (ES^+) m/z 313.5 (M+1).

4.13.13. Furfuryl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7n). ^1H NMR (DMSO-d_6) δ 2.47 (s, 3H), 3.09 (s, 3H), 5.06 (s, 2H), 5.12 (d, J=3.7 Hz, 1H), 6.43 (s, 2H), 7.12–7.29 (m, 5H), 7.67 (s, 1H), 7.98 (br d, J=3.8 Hz, 1H). MS (ES^+) m/z 327.2 (M+1).

4.13.14. (*R*)-(+)-Oxirane-2-methyl 6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7o). ^1H NMR (DMSO-d_6) δ 2.26 (s, 3H), 2.50 (br s, 1H), 2.70 (t, J=4.5 Hz, 1H), 3.07–3.15 (m, 1H), 3.76–3.83 (m, 1H), 4.28–4.32 (m, 1H), 5.16 (d, J=2.7 Hz, 1H), 7.24–7.35 (m, 5H), 7.79 (br s, 1H), 9.29 (br s, 1H). MS (ES^+) m/z 289.0 (M+1).

4.13.15. (*R*)-(+)-Oxirane-2-methyl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7p). ^1H NMR (DMSO-d_6) δ 2.50 (br s, 4H), 2.71–2.73 (m, 1H), 3.11–3.20 (m, 4H), 3.78–3.87 (m, 1H), 4.33–4.38 (m, 1H), 5.17 (d, J=2.6 Hz, 1H), 7.22–7.34 (m, 5H), 8.02 (br d, J=2.1 Hz, 1H). MS (ES^+) m/z 303.1 (M+1).

4.13.16. 1-(2-Furyl)-1-propyl 1-methyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7q). ^1H NMR ($CDCl_3$), mixture of diastereoisomers, δ 0.60 (t, J=7.3 Hz, 3H), 0.90 (t, J=7.3 Hz, 3H), 1.71–1.84 (m, 2H), 1.94–2.02 (m, 2H), 2.49 (s, 3H), 2.56 (s, 3H), 3.23+3.24 (2s, 6H), 4.94–5.01 (m, 2H), 5.36+5.41 (2s, 2H), 5.56+5.58 (2br s, 2H), 6.04 (d, J=2.4 Hz, 1H), 6.25+6.29+6.34 (3s, 3H), 7.13–7.30 (m, 11H), 7.39 (s, 1H). MS (ES^+) m/z 355.5 (M+1).

4.13.17. *i*-Propyl 1-methyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7r). ^1H NMR (DMSO-d_6) δ 1.01 (d, J=6.2 Hz, 3H), 1.19 (d, J=6.2 Hz, 3H), 2.50 (s, 3H), 3.11 (s, 3H), 4.82–4.93 (m, 1H), 5.28 (d, J=3.5 Hz, 1H), 7.63–7.69 (m, 2H), 8.06 (br s, 1H), 8.12–8.14 (m, 2H). MS (ES^+) m/z 334.5 (M+1).

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