Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 2107

www.rsc.org/obc

PAPER

A new diversity oriented and metal-free approach to highly functionalized 3*H*-pyrimidin-4-ones

Renata Riva,* Luca Banfi, Andrea Basso and Paola Zito

Received 3rd November 2010, Accepted 13th December 2010
DOI: 10.1039/c0ob00978d

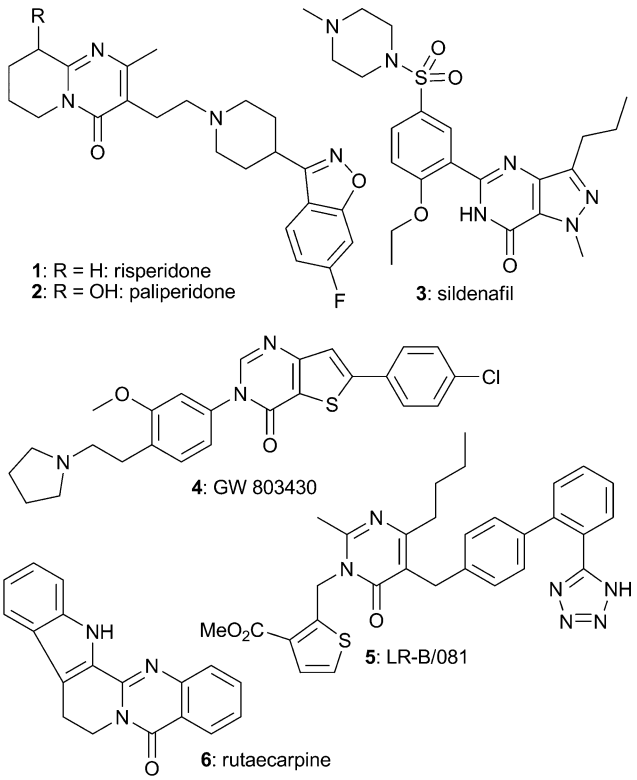
A new synthesis of 3*H*-pyrimidin-4-ones, characterized by four different sets of decorations, is presented. The strategy is based on the synthetic elaboration of readily available α-substituted β-ketoesters that, upon transformation into the corresponding acyl enamines, have been cyclized to give 6*H*-1,3-oxazin-6-ones. These reactive intermediates have been in turn cleanly converted into highly functionalized pyirimidinones, by treatment with an appropriate primary amine. The whole sequence does not need the use of any metal mediator or catalyst.

Introduction

The pyrimidin-4-one moiety is the *core* structure of many biologically active compounds. Some examples of compounds in clinical use are reported in Scheme 1: they include atypical antipsychotics risperidone **1** and its follow-up paliperidone **2**,[1,2] the phosphodiesterase type 5 inhibitor sildenafil **3** (best known as Viagra™),[3] the anxiolytic and antidepressant (also endowed with antiobesity activity) GW-803430 **4**,[4] the angiotensin II receptor antagonist LR-B/081 **5**,[5] and the indolequinazoline alkaloid rutaecarpine **6**, characterized by several interesting properties, including antiinflammatory activity.[6] Moreover, 3*H*-pyrimidin-4-ones, are also used as agrochemicals, owing to their activity as herbicides.[7,8] Finally, 3*H*-pyrimidin-4-ones are synthetic intermediates for the preparation of 4-aminopyrimidines, an essential fragment in very important molecules such as the antitumor antibiotics bleomycins.[9] Thus the pyrimidin-4-one ring is definitely a *privileged structure*, and the availability of efficient routes that allow a combinatorial entry to this scaffold, varying the substituents at all free positions (2, 3, 5, and 6), will be particularly useful.

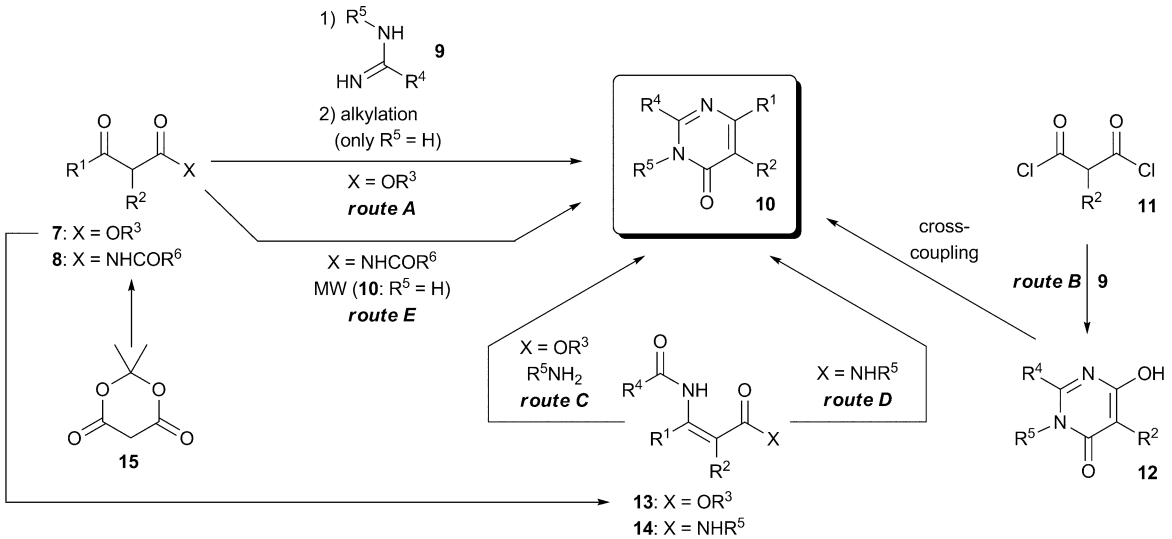
Several methods have been reported for preparing both pyrimidinones and quinazolinones. In this paper however we will focus our attention only on the synthesis of 2,3,5,6-tetrasubstituted 3*H*-pyrimidin-4-ones.

In the literature, a series of different approaches can be found. They mostly differ for the nature of the acyclic reagents that provide the necessary nitrogen atoms, whereas in most cases the three carbon atom fragment (C_4-C_5-C_6 in the pyrimidinone) is introduced employing an appropriate β-dicarbonyl derivative. Scheme 2 summarizes some of these strategies: β-ketoester **7** can be condensed with amidine **9** (R^5 = H) to give 3-unsubstituted 3*H*-pyrimidinones **10** (*route A*). However, this reaction was reported only with commercially available amidines (R^4 = H, Me). The fourth diversity point (R^5) is then introduced by N-alkylation.[5] This latter reaction is however critical because of the competitive O-alkylation, a typical behaviour of heterocyclic ambident anions.[10] To avoid the alkylation of the pyrimidinone, a N-substituted amidine ($R^5 \neq$ H) can be employed as well. The reaction was initially limited to α-unsubstitued **7**,[11] but recently, working under pressure, the protocol showed a more general scope.[7]



Scheme 1 Examples of biological relevant 3*H*-pyrimidin-4-ones.

Department of Chemistry and Industrial Chemistry, University of Genova, via Dodecaneso 31, 16146 Genova, Italy. E-mail: riva@chimica.unige.it; Fax: +39 010 3536118; Tel: +39 010 3536106



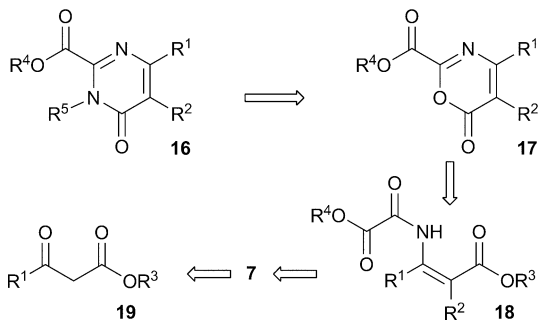
Scheme 2 Literature survey on the synthesis of 2,3,5,6-tetrasubstituted 3*H*-pyrimidin-4-ones.

Compounds **9** ($R^5 \neq H$) react smoothly also with malonyl dichlorides **11** to give **12** (*route B*), which can be converted into **10**, after cross-coupling of the corresponding triflate with a higher order cuprate.[12] This strategy is however hampered by the high reactivity and scarce availability of compounds **11**.

The two nitrogen atoms can also derive from two different acyclic substrates: β-ketoesters **7** are converted into the acylenamino esters **13**, which can be easily cyclized in the presence of trimethylaluminium and of the hydrochloride of a primary amine (*route C*).[13]

On the other hand, in *route D* the intramolecular dehydration is performed directly on the acylenamino amide **14**.[14] Protocols *C* and *D* are efficient, but both have some drawbacks: the first one represents a fast entry to pyrimidinones (only three steps), but the entire process is poorly sustainable. Because of the mechanism proposed by the authors, at least 3 equivalents of Me_3Al (a well known pyrophoric organometallic derivative) and of the primary amine are required, thus producing a lot of waste, a condition in contrast with atom economy. Moreover, in the final pyrimidinone (*route C*) only simple alkyl or aryl groups can be introduced on carbon 2. In the latter strategy (*route D*) eight steps from the β-ketoester are necessary and substituent R^5 is introduced early in the synthesis (fourth step). This means that, for each R^5 group, five synthetic steps have to be performed independently. Recently, a method for preparing isomers of **12** (with the OH group in position 5 instead of 6), through the thermal rearrangement of O-substituted amidoximes under microwave heating, was reported.[15] Finally, a very recent microwave assisted methodology allowed the transformation of Meldrum's acid **15** into **10** going through *N*-acyl-β-ketoamides **8** (*route E*). This strategy has however been reported only to prepare compounds with $R^5 = H$.[16]

In this paper we propose a third possibility in which a stepwise introduction of the two N atoms is performed, with the last one entering after the cyclization. This approach is illustrated in the retrosynthetic Scheme 3. A great advantage of our synthetic plan is that the various diversity inputs are introduced sequentially (one for each synthetic step). This means the possibility to use common intermediates for preparing several products with a

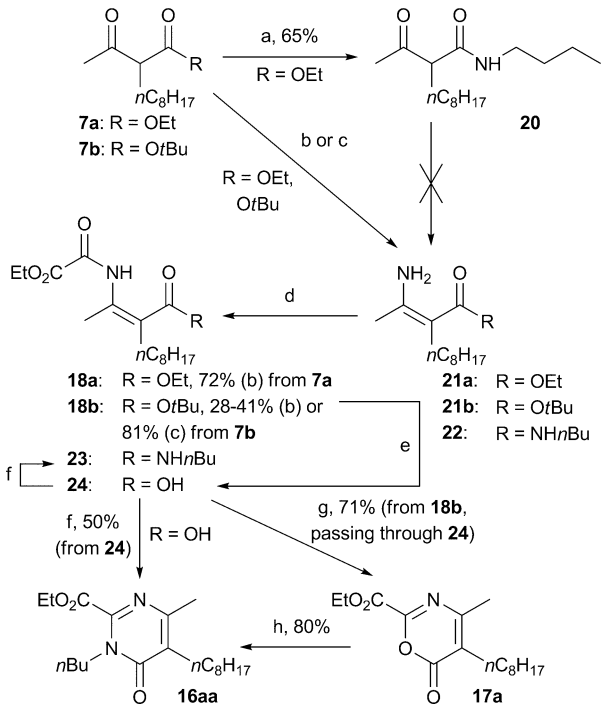


Scheme 3 Retrosynthetic plan.

gradual increase of the diversity of the system. This is clearly more advantageous, in combinatorial chemistry, than performing several synthetic steps after the introduction of all diversity inputs, as it happens for *route C* and, especially, for *route D*. Moreover, it is also possible to add further diversity, by modifying the final compounds **16**, through reactions involving the CO_2R^4 group. Finally, we wanted to develop a method that could be easily scaled up for the kilogram synthesis of these compounds, thus avoiding dangerous or expensive reagents, very low temperatures or metals that could contaminate the final products.

Results and Discussion

When this project started, we were interested in particular in synthesizing 2-carbalkoxy pyrimidinones like **16**. We initially followed more closely the previously reported *routes C* and *D*, studying an alternative synthesis of *N*-acylenaminoamides such as **23** that avoids the use of Me_3Al (Scheme 4). Our preliminary efforts started therefore from β-ketoester **7a**, prepared in 82% yield by alkylation of ethyl acetoacetate.[17] The transformation into amide **20** was accomplished by ester hydrolysis followed by coupling with nBuNH$_2$ to give the desired product in acceptable yield, notwithstanding the propensity of the intermediate β-ketoacid to undergo decarboxylation if inappropriate reaction and work-up conditions are employed. Nevertheless every effort to convert **20**



Scheme 4 *Reagents and conditions*: a) i. KOH, EtOH; ii. CDI, nBuNH$_2$, THF, r.t.; b) NH_4OAc, toluene, reflux; c) NH_3 (2.8 M in EtOH), NH_4OAc, 60 °C, sealed tube; d) $ClCOCO_2Et$, Py, CH_2Cl_2/Et_2O 2 : 1, r.t.; e) CF_3CO_2H, CH_2Cl_2, r.t.; f) i. CDI, THF, 20 min, r.t.; ii. nBuNH$_2$, r.t.; g) CDI, THF, r.t.; h) nBuNH$_2$, THF, r.t.

into **22** (and then into **23**) failed, either using NH_4OAc[13,18] or ammonia in the presence of a Lewis acid, such as, for example, $AlCl_3$.[14]

So we chose to work on the corresponding ester **18a**, planning to transform the ester into an amide later. The method proposed by Jeong *et al.* (ammonium acetate in refluxing toluene)[13] worked this time well, affording the enamine **18a** in a good 72% yield from **21a** after acylation with ethyl 2-chloro-2-oxoacetate,[19] although we were never able to drive the reaction to completion (conversion was always ≤90%). The formation of the enamine was highly stereoselective, giving almost exclusively the more hindered *Z* stereoisomer (>97%), whose formation is most likely favoured by the stabilization through an intramolecular H bond. The presence, in **18a**, of two ethyl ester groups could make selective hydrolysis troublesome, although the oxalic ester was expected to be more reactive according to literature data.[20] Thus we repeated the sequence starting from *tert*-butyl β-ketoester **7b**, prepared in 72% yield by alkylation of *t*-butyl acetoacetate.[21] To our surprise the formation of enamine **21a** under Jeong conditions[13] was this time rather sluggish. Conversions never went over 70–80% and long reaction times were detrimental because of decomposition of starting material. As a result, the yield was always ≤ 41%.

We therefore tried to optimize this reaction, inspired by the methods that employ gaseous ammonia and an appropriate acid.[14,20] For practical reasons we decided to avoid bubbling a stream of ammonia into the reaction, preferring instead a freshly prepared 2.8 M solution of ammonia in ethanol, that was added to a solution of the substrate in an appropriate solvent (diethyl ether, dioxane, hexane). Working in the presence of $AlCl_3$ we did not, however, obtain the expected results. We explored other acids, obtaining acceptable results with camphorsulfonic acid working at 60 °C in diethyl ether under MW heating in a closed vessel. Although a very clean reaction occurred, the conversion was always around 50% and addition of more catalyst was not beneficial, also because of poor solubility of ammonium camphorsulfonate. After a careful optimization we found ammonium acetate to be the ideal catalyst. In this case no need of an additional solvent was necessary and the conversion into **21b** resulted almost complete after heating a solution of **7b** in the presence of 9 equivalents of ethanolic ammonia and 4 equivalents of NH_4OAc in a sealed tube at 60 °C. With this procedure **18b** was isolated with a high purity and an overall 81% yield after acylation.

The following step was the hydrolysis of the *t*-butyl ester **18b** with CF_3CO_2H and the transformation of the resulting acid **24** into amide **23**, by treatment with *N*,*N*′-carbonyl diimidazole (CDI) and nBuNH$_2$. We were surprised to obtain a complex mixture containing pyrimidinone **16aa** (48%), oxazinone **17a** (11%), acid **24** (21%), 2-undecanone (from decarboxylation of **24**, 2%) and a small amount (about 10%) of a mixture of products (among them only traces of the expected amide **23** were identified). Moreover, it is fundamental to stir the solution of the acid in the presence of CDI for at least 20 min before adding the amine; otherwise no reaction takes place.

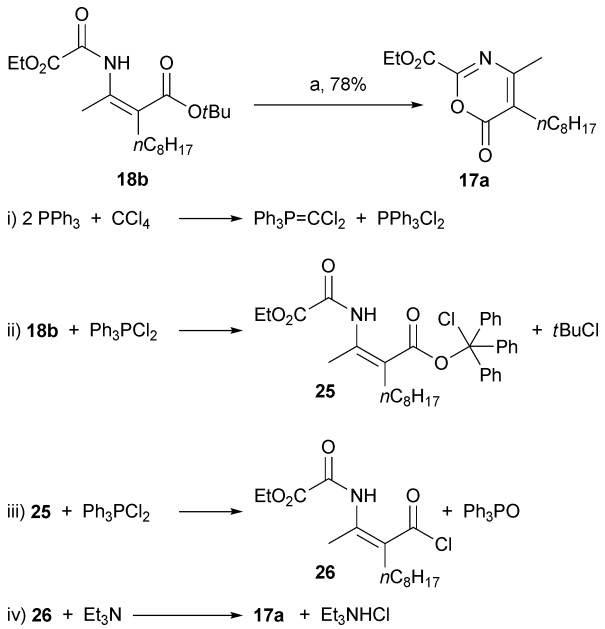
Interestingly, treatment of **24** with CDI without adding the amine, promoted a smooth transformation into **17a** (71% from **18b**). This allowed us to establish that oxazinone **17a**, rather than the amide **23**, is the intermediate of this cyclization reaction. This result was not completely unexpected since these heterocycles have been demonstrated to be intermediates in the Me_3Al mediated synthesis of **10**.[13] The isolated oxazinone **17a** is however quite reactive, being smoothly converted into **16aa** upon treatment with nBuNH$_2$ at room temperature without the need of any catalyst. This behaviour supports the scarce available literature data on these heterocyclic systems: actually, in only two other cases, oxazinones have been used as intermediates for the synthesis of very specific pyrimidinones,[22,23] thanks to their propensity to react with N-nucleophiles.

The synthesis of **17a** by treatment of **24** with CDI has however some drawbacks: even in the presence of an excess of condensing agent the reaction never reached completion and variable amounts of decarboxylation product were always identified. In order to overcome this undesired outcome, we examined the possibility to transform directly **18b** or **18a** into **17a**, avoiding the involvement of **24** as intermediate. Treatment of **18b** with a base such as EtONa, however, did not promote the O-cyclization, probably due to the weak nucleophilic power of the reacting species. Only cleavage of the amide bond to give a mixture of **21b** and **7b** occurred.

So we turned our attention on a completely different approach. Wamhoff *et al.* reported the serendipitous synthesis of hetero-condensed 6*H*-1,3-oxazin-6-ones arising from treatment of a very peculiar family of *N*-acylenamine esters, quite different from ours, with PPh_3 in hexachloroethane in the presence of Et_3N.[24,25] The authors, relying on the previous reports by Appel,[26] envisaged dichlorotriphenylphosphorane, generated by the combination of PPh_3 with C_2Cl_6, as the promoter of the whole sequence. We reasoned that a similar protocol could have been applied to our compounds, simply using carbon tetrachloride instead of hexachloroethane and working initially in 1,2-dichloroethane as

solvent. The choice of the solvent was made on the basis of two considerations: a) the possibility to explore a wider range of temperatures, compared to dichloromethane; b) a higher dielectric constant and dipole moment, which was expected to favour the formation of dichlorotriphenylphosphorane.[26]

We performed therefore two experiments under the same conditions on **18a** and **18b** respectively. Both were converted into the same oxazinone **17a** working at reflux, but with quite different rate: after 30 min the reaction resulted complete only for **18b**, while no complete conversion of **18a** was reached even after heating for several hours. The isolated yields were different too: 60% from **18a** and 78% from **18b**. Since the transformation from **18b** appeared to be more promising, the optimization was performed only on this compound. At the end of the tuning process we found that 1,2-dichloroethane can be conveniently substituted by the less toxic dichloromethane, since the temperature can be lowered to about 40 °C, with only an acceptable increase in the reaction time (2.5 h) and a comparable yield (78%) (Scheme 5).



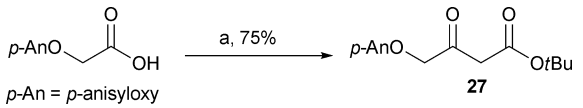
Scheme 5 *Reagents and conditions*: a) PPh_3/CCl_4, Et_3N, CH_2Cl_2, reflux.

A possible condensed mechanism, which ensues from previous findings and from our results,[24] is depicted in Scheme 5. It's important to notice that at least 2 equivalents of phosphine are required, because only 0.5 mole of dichlorodiphenylphosporane is produced from 1 mole of PPh_3. The reactive precursor of **17a** is most likely acyl chloride **26**. The faster reaction of the *t*-butyl ester **18b** is probably due to a faster conversion into **25**, facilitated by the exit of a *t*-butyl cation, which is then trapped by a chloride ion.

An important feature of oxazinone **17a** is its limited stability: this means that it can be isolated and purified by chromatography, but it is not stable enough to be stored for a long time, even at −25 °C. We therefore preferred to submit it immediately to the following reaction, just after a very rapid purification by chromatography, which is necessary to remove Ph_3PO. On the other side, this chromatography can not be avoided, because direct treatment of crude oxazinone with the amine gave an overall lower yield.

Having previously demonstrated that oxazinones **17** can be easily transformed into pyrimidinones **16**, the following step was to expand the scope of this method, introducing different decorations on the final 3*H*-pyrimidin-4-ones.

The starting materials were commercially available β-ketoesters, with the exception of **27**, which was synthesized in good overall yield (75% isolated, 94% considering recovered unreacted starting material) by treatment of (*p*-methoxyphenoxy)acetic acid, previously activated as the imidazolide, with Meldrum acid **15**,[27] followed by monodecarboxylation and esterification (Scheme 6).

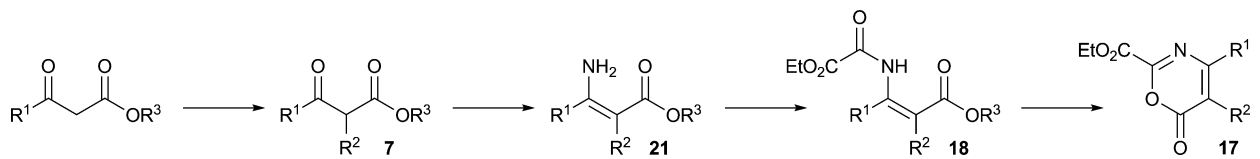


Scheme 6 *Reagents and conditions*: a) i. CDI, CH_2Cl_2, r.t.; ii. **15**, DMAP, CH_2Cl_2/Py, r.t.; iii. 2 M HCl, r.t.; iv. *t*BuOH, toluene, 85 °C.

Alkylation of the β-ketoesters was performed following different procedures, in order to achieve the highest yields (Table 1). A careful monitoring of the experimental conditions was necessary in order to suppress as much as possible the double alkylation.

The most critical example is represented by **7d** (entry 4). Bases that are usually employed for this kind of reaction gave only

Table 1 Synthesis of a small library of oxazinones **17**



Entry	R^1	R^2	R^3	Conditions of alkylation of β-ketoester	Yield % (**7**)	Yield % (**18**)[a]	Yield % (**17**)[b]
1	Me	nC_8H_{17}	Et	EtONa, $nC_8H_{17}Br$, KI, EtOH, reflux	82 (**7a**)	72 (**18a**)	60 (**17a**)
2	Me	nC_8H_{17}	*t*Bu	NaH, $nC_8H_{17}Br$, toluene-DMF, 100 °C	72 (**7b**)	81 (**18b**)	78 (**17a**)
3	Me	*i*Bu	*t*Bu	NaH, *i*BuBr, toluene-DMF, 100 °C	69 (**7c**)	82 (**18c**)	74 (**17c**)
4	Me	CH_2CH_2OBn	*t*Bu	Cs_2CO_3, $BnOCH_2CH_2Br$, *t*BuOH, reflux	70 (**7d**)	60 (**18d**)	57 (**17d**)
5	*p*-AnO[c]	Et	*t*Bu	NaH, EtBr, toluene-DMF, 100 °C	70 (**7e**)	43 (**18e**)[c]	55 (**17e**)

[a] i. NH_4OAc, toluene, reflux (**21a**), NH_3 (2.8 M in EtOH), NH_4OAc, 60 °C, sealed tube (**21b–d**); ii. $ClCOCO_2Et$, Py, CH_2Cl_2/Et_2O 2 : 1, r.t. (**18**); [b] PPh_3/CCl_4, Et_3N, CH_2Cl_2, reflux; [c] *p*-AnO = *p*-anisyloxy; [d] the isolated yield refers only to the *Z* isomer (see also text).

Table 2 Transformation of oxazinones **17** into pyrimidinones **16**

Entry	R^1	R^2	R^3	Yield % (**16**)[a]
1	Me	nC_8H_{17}	*n*Bu	80 (**16aa**)
2	Me	nC_8H_{17}	$(CH_2)_3CO_2tBu$	89 (**16ab**)
3	Me	nC_8H_{17}	$(CH_2)_3CO_2Et$	81 (**16ac**)
4	Me	nC_8H_{17}	*i*Bu	66 (**16ad**)
5	Me	*i*Bu	*i*Bu	68 (**16ca**)
6	Me	*i*Bu	(2-furyl)methyl	62 (**16cb**)
7	Me	*i*Bu	(2-thienyl)methyl	72 (**16cc**)
8	Me	*i*Bu	(4-methoxy)benzyl	75 (**16cd**)
9	Me	CH_2CH_2OBn	$(CH_2)_3CO_2tBu$	75 (**16d**)
10	*p*-$AnOCH_2$	Et	*n*Bu	77 (**16ea**)
11	*p*-$AnOCH_2$	Et	Bn	77 (**16eb**)

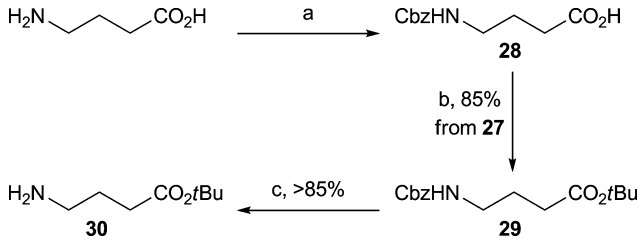
[a] amine, THF, r.t.

moderate yields (for example 51% under conditions employed for preparing **7b**, **7c** or **7e**). So we turned our attention on alkaline carbonates and we noticed a strict dependence upon the nature of the counterion: while with Na_2CO_3 the reaction did not start, with K_2CO_3 the yield was again around 50%. The best results (70%) were however obtained with Cs_2CO_3 under conventional reflux in *t*BuOH, while the same reaction, performed under microwave heating in DMF, gave only 52% yield. The formation of *N*-acyl enamines **18** gave good results in most cases, the only exception being represented by **18e**. The poorer yield is most likely to ascribe to a less stereoselective enamine formation. The higher steric hindrance of the *p*-anisyloxy group compared with the methyl can explain this different behaviour. It is worth noting that *Z*-**18e** is the only stereoisomer able to be transformed into **17e**, and therefore the isomeric *E*-**18e**, chromatographically separated from *Z*-**18e**, had to be discared.

The following cyclization mediated by the PPh_3/CCl_4 system, allowed to prepare a series of representative oxazinones **17**. As experienced before for the parent compound **17a**, all these heterocycles are quite unstable and must be isolated and purified as soon as possible and immediately submitted to the following reaction for avoiding an extended decomposition, which heavily affects the overall yield.

For the synthesis of **16** we chose a series of amines having different structures (Table 2). We employed either simple, commercially available, linear (entries 1, 10) or branched (entries 4, 5) primary amines, but we used also amines with aromatic (entries 8, 11) or heteroaromatic (entries 6, 7) groups. Moreover bi-functional amines have been tested too (entries 2, 3, 9). Ethyl 4-aminobutyrate is commercially available as the hydrochloride and, for this reason, the addition of one equivalent of triethylamine was necessary. On the contrary, the corresponding *t*Bu ester **30** had to be synthesized from γ-aminobutyric acid as depicted in Scheme 7. After protecting the amino group as Cbz (**28**),[28] the ester function was introduced.[29] Amine **30** could not be stored because it is not very stable. For this reason the protecting group was removed by hydrogenolysis just before the reaction with oxazinone **17a** or **17b**.

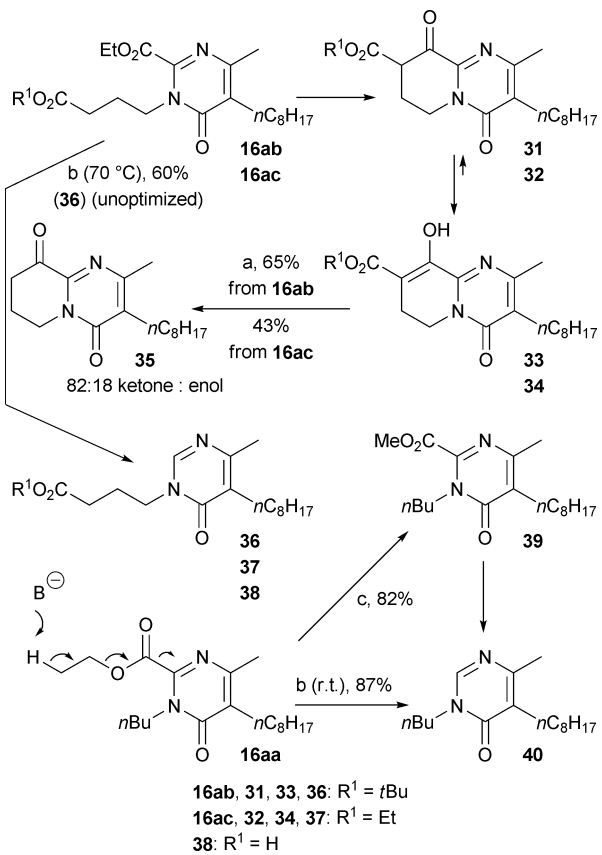
The protocol leading to pyrimidinones **16**, showed to be very efficient in most cases, as summarized in Table 2.



Scheme 7 *Reagents and conditions*: a) BnOCOCl, $NaOH/H_2O$, r.t.; b) *t*BuOH, DCC, DMAP, CH_2Cl_2, r.t.; c) H_2, Pd/C, MeOH, r.t.

Moreover, the possibility to tune the nature of the R groups, together with the presence of an ester function on C_2 disclosed also the opportunity to submit **16** to following transformations in order to increase the accessible diversity around the pyrimidinone scaffold.

In particular bi-functionalized amines gave very good yields (entries 2, 3, 9) and this prompted us to investigate the Dieckmann reaction involving the two ester functionalities on **16ab** and **16ac**, as depicted in Scheme 8. To the best of our knowledge this approach was used on similar compounds only in a recently reported total synthesis of rutaecarpine **6**.[6] It is however important to notice that the reported precursor is characterized by a benzene ring condensed with the pyrimidinone instead of having two R^1 and R^2 groups.



Scheme 8 *Reagents and conditions*: a) from **16ab**: i. *t*BuOK, THF, r.t.; ii. 0.5 M HCl, dioxane, reflux; from **16ac**: i. *t*BuONa, THF, r.t.; ii. 6 M HCl, reflux; b) NaH, DMF; c) MeONa, MeOH, r.t.

When we submitted **16ab** to the same conditions (NaH, 1.2 equivalents, DMF with heating overnight at 70 °C) we obtained

a complex reaction mixture of at least four compounds in the following ratio (GC-MS): 14% of unreacted starting material, 79% of decarboxylated **36** (60% isolated yield), about 3% of desired **31** and about 4% of **37** in which, in addition to the decarboxylation, a transesterification occurred too. We were quite surprised by these results and, in particular by the formation of **36** and **37**, and therefore we decided to further investigate the reaction. Changing the conditions and working in the presence of EtONa (1.5 equivalents) in toluene at 70 °C only a mixture of **31** and **37** was obtained. Switching to lithium bis(trimethylsilyl)amide (1.1 equivalents) in THF at room temp. the reaction was slow, affording again **36** as major product, **31**, and traces of **37**. By warming at reflux, the starting material and **36** disappeared and the major product was again **37**.

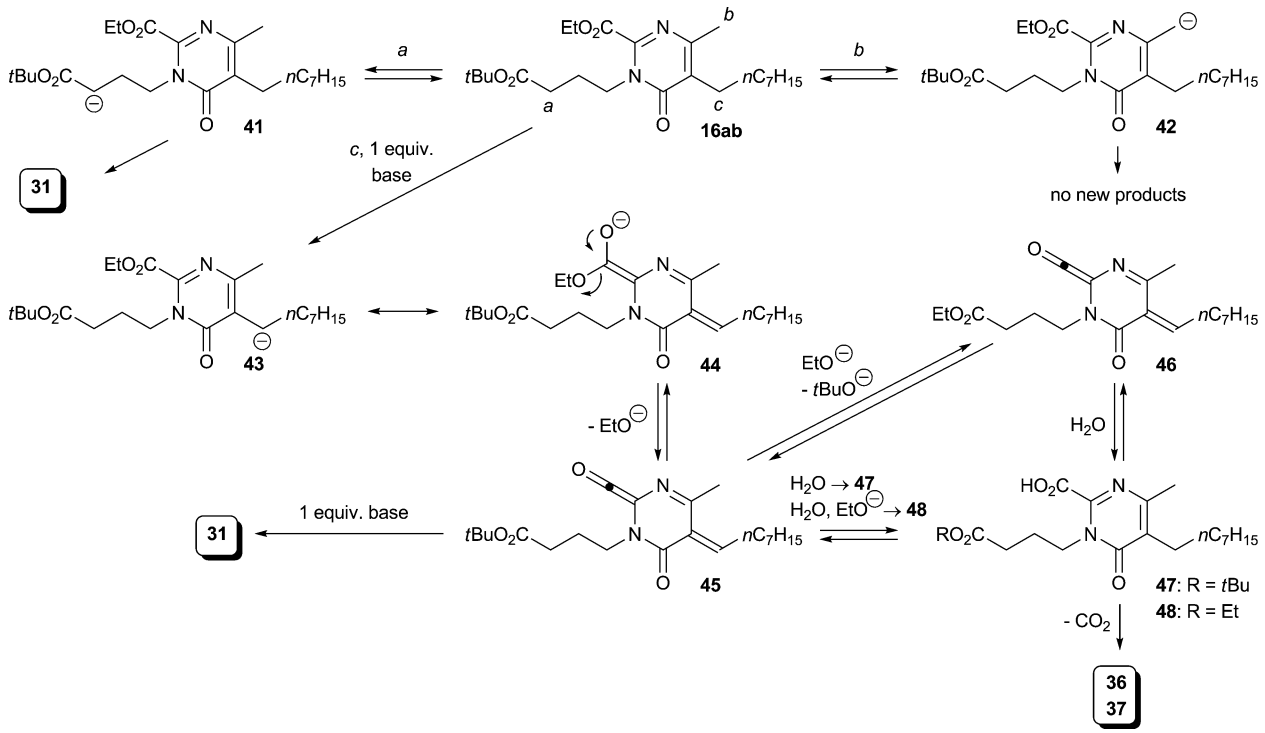
We demonstrated also that this decarboxylation is not peculiar of **16ab** only: actually, **16aa**, which is not a substrate for the Dieckmann reaction, underwent exactly the same fast decarboxylation to give exclusively **40** in excellent yield.

While decarboxylation of pyrimidinones bearing a COOH group on C_2 is known to be a spontaneous transformation,[9] the same reaction under basic conditions is however unlikely and is hard to justify.

Initially, we hypothesized the formation of a carbanion on C_2 through an E_2 process promoted by the attack of the base at the terminal carbon of the ethyl group as depicted in Scheme 8 on compound **16aa**. Such a reactive intermediate should however react easily with an electrophile, an example being an alkyl halide or an aldehyde, but all attempts to trap it failed. Moreover, we were able to exclude a mechanism proceeding through E_2 elimination, because methyl ester **39** (prepared through an unusually fast transesterification under very mild basic conditions) was converted into **40** too, even faster than **16aa**. The involvement of a radical mechanism during the decarboxylation was excluded too, because basic treatment in the presence of a radical inhibitor, such as 2-*tert*-butyl-4-((3-(2-hydroxypropan-2-yl)-4,5-dimethylphenyl)sulfanyl)-6-methylphenol, led again to **40**.

Finally, we treated compound **16ab** with *t*BuOK (2 equivalents) in THF at room temp.: after addition of the base we noticed a sudden colour change from pale yellow to brick red and, after 10 min, the initial colour was established again. The reaction resulted complete after half an our and the only product we found was **31**. The same result was obtained working at 0 °C, even if the reaction mixture resulted less clean. On the contrary, working at 0 °C, but in the presence of only 1.2 equivalents of base, the crude resulted a 62 : 38 mixture of **31** and **36** respectively. Similar results were obtained substituting *t*BuOK with NaH (always 2 equivalents), including colour changes, which occurred this time only after refluxing the mixture. Comparing the precursor of rutaecarpine **6** with **16ab** the most significant difference is the presence, in our compound, of a CH_2 group bonded to C_5. At this point we were able to hypothesize a mechanism which agrees with all the experimental data reported above (Scheme 9).

Compound **16ab** has 3 acidic sites. Deprotonation on carbon *a* leads to the Dieckmann product (**31**), through enolate **41**. Deprotonation on carbon *b* gives carbanion **42**, which is stabilized by resonance but which is not able to give any new product. On the contrary, deprotonation on carbon *c* gives a highly delocalized carbanion (**43** ↔ **44**, the most likely candidate responsible for the brick red colour we observed), which, upon loss of ethylate through a E_{1cb} mechanism, is transformed into ketene **45**. During work-up, if no Dieckmann reaction occurred, a molecule of water adds to **45**, giving acid **47**, which soon decarboxylate to give **36**, whereas ethylate, produced during the formation of **45**, is responsible for the observed transesterification, following one of the paths displayed



Scheme 9 A possible mechanism for explaining the behaviour in bases of compound **16ab**.

in the Scheme 9. The exclusive formation of **31**, when 2 equivalents of base are employed, can be explained by the irreversible attack of the enolate of **45** to the highly electrophilic ketene moiety. Of course, when less than 2 equivalents of base are used, the conversion into **31** cannot be complete.

Compound **31** was shown to exist almost exclusively in the enolic form **33**, as proved at ^{1}H NMR by the chemical shift of the enol proton resonating at 12.06 ppm,[6,30] and at ^{13}C NMR by the absence of the ketone and of *C*HCO$_2$*t*Bu and by the presence of a quaternary carbon at 104.8 ppm for = *C*CO$_2$*t*Bu. This result is perfectly in accord with literature data on similar compounds. β-Ketoester **31**, moreover, is not very stable and decomposed quite rapidly even during chromatography. For this reason its structure was demonstrated on the crude and then it was directly submitted to a hydrolysis-decarboxylation protocol, leading to **35** in 65% overall yields. It is worth noting that **35** possesses the same bicyclic skeleton present in important drugs such as risperidone **1** and paliperidone **2**.

Encouraged by our findings we tried to extend the same protocol on **16ac**. Under exactly the same conditions used for **16ab**, we obtained a 6 : 4 mixture of **32** and **38** (in which, in addition to the decarboxylation, the hydrolysis of the ethyl ester occurred too). Harsher conditions for the hydrolysis of the ethyl ester were required and finally **35** was isolated in only 22% overall yield. The yield was however improved up to 43% switching to *t*BuONa.

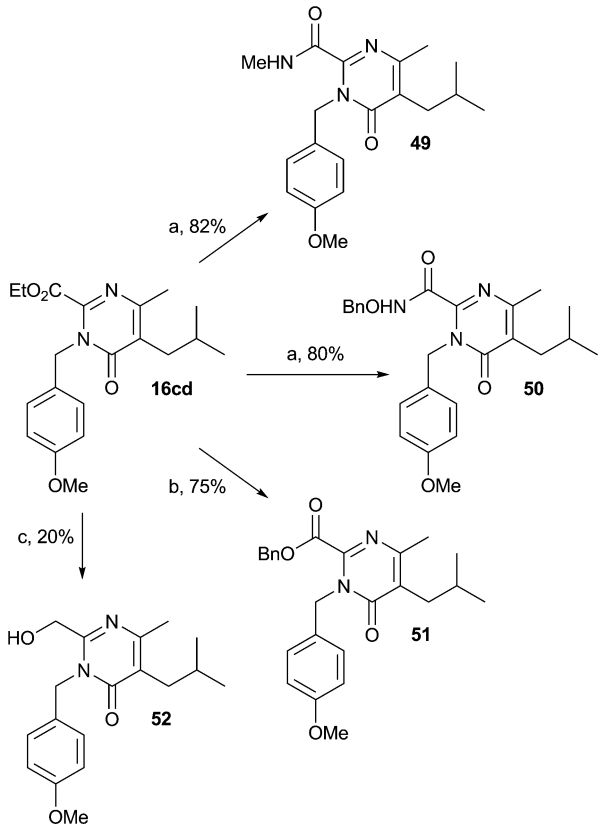
The clean decarboxylation reaction, achieved on compounds **16** by treatment with 1 equivalent of base, allows the access to 2-unsubstituted pyrimidinones, as exemplified by the synthesis of **40** from **16aa** in 86% yield. These unsubstituted compounds are not easily prepared using the strategies depicted in Scheme 2. Apart from this useful reaction, the high reactivity of the ester function bonded to C$_2$ prompted us to study other types of transformations, that are summarized in Scheme 10 starting from compound **16cd**.

For example, exploiting trimethylaluminium mediated reactions, the ester group was directly converted into an amide (**49**) or into an O-protected hydroxamate (**50**), in the presence of the hydrochlorides of a primary amine or of an *O*-alkyl hydroxylamine respectively. These functional groups are not directly accessible from the beginning, since only few mono-oxalyl chlorides are available. Nevertheless, every transformation of the ester function, passing through the carboxylic group has to be avoided, to prevent the very fast decarboxylation. Also the transesterification reaction was shown to be possible on **16cd** to give **51** under basic conditions. Generally speaking this procedure allows a fast entry to different carboxylates attached to C$_2$.

Treatment of these pyrimidin-3*H*-ones with mild reducing agents, such as NaBH$_4$, showed, on the contrary, not be consistent with the heterocyclic system. For example the ester function of **16cd** was rapidly reduced to give alcohol **52** even with a mild reagent as NaBH$_4$, but in very modest yield. This is most likely due to not complete stability of the heterocyclic moiety under reducing conditions.

Conclusions

In this paper we described a new, convergent and combinatorial four step synthesis of a family of differently substituted 3*H*-pyrimidin-4-ones from readily available β-ketoesters. Starting from few common intermediates a sequential increase of chemical diversity can be realized step by step under an efficient procedure carried out under mild conditions, tolerated by most functional groups. Moreover, with some limitations, these compounds showed to be *pluripotent substrates*[31] as demonstrated by the possibility to elaborate them after the formation of the heterocyclic scaffold. Apparently, our method seems to be suited only for the preparation of 3*H*-pyrimidin-4-one-2-carboxylic esters. We demonstrated however that the carbalkoxy group can be efficiently removed, leading to 2-unsubstituted compounds, or transformed into different carboxylic derivatives. Moreover, if a potential C-nucleophile is placed in the substituent at position 3, a cyclization onto the electrophilic 2-CO$_2$R group is possible, allowing the preparation of bicyclic systems. For the simplicity and the mildness of our conditions we think therefore that our methodology should find possible applications as a fast entry in the development of possible drug-like structures.



Scheme 10 *Reagents and conditions*: a) Me$_3$Al, CH$_2$Cl$_2$, MeNH$_2$·HCl (for **49**) or BnONH$_2$·HCl (for **50**), r.t.; b) BnOH, NaH, benzene, reflux; a) NaBH$_4$, MeOH, r.t.

Experimental Section

NMR spectra were measured at room temp. in CDCl$_3$ at 300 MHz (^{1}H), and 75 MHz (^{13}C), with TMS as internal standard for ^{1}H NMR and the central peak of CDCl$_3$ (at 77.02 ppm) for ^{13}C NMR spectroscopy. Chemical shifts are reported in ppm (δ scale); coupling constants are reported in hertz. Peak assignments were made with the aid of DEPT and gHSQC experiments. Peak assignment in ^{1}H NMR spectra was also made with the aid of gCOSY experiments. In AB systems the proton A is considered upfield and B downfield. GC-MS were carried out using an

HP-1 column (11.85 m long, 0.2 mm wide), electron impact at 70 eV, and a mass temperature of about 170 °C. Only $m/z >$ 33 were detected. All analyses were performed (unless otherwise stated) with a constant He flow of 0.9 mL min^{-1} with initial temp. 100 °C, init. time 2 min, rate 20 °C min^{-1}, final temp. 290 °C, inj. temp. 250 °C, det. temp. 280 °C. HR-MS were recorded employing ESI ionization method. IR spectra were recorded as $CHCl_3$ solutions and absorptions are reported in cm^{-1}. Melting points are uncorrected. TLC analyses were carried out on silica gel plates and viewed under **a**) UV (254 nm) or developed by dipping into a solution of **b**) $(NH_4)_4MoO_4{\cdot}4\ H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4\ H_2O$ (1 g) in H_2SO_4 (31 mL) and H_2O (469 mL) or into a solution of **c**) ninhydrin (900 mg dissolved in 300 mL of *n*BuOH and 9 mL of acetic acid) and warming. R_f were measured after an elution of 7–9 cm. Column chromatographies were done with the "flash" methodology using 220–400 mesh silica. Petroleum ether (40–60 °C) is abbreviated as PE. In extractive work-up, aqueous solutions were always reextracted three times with the appropriate organic solvent. Organic extracts were always dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen atmosphere.

Ethyl 2-octyl-3-oxobutanoate 7a

Sodium ethoxide (5.64 g, 82.9 mmol) was suspended in absolute ethanol (65 mL). After cooling to 0 °C ethyl acetoacetate (10 mL, 79.1 mmol) was dropped through an addition funnel over a period of 10 min using 5 mL of EtOH for a complete addition of the reagent. After 5 min the reaction was allowed to stir at room temp. for 15 min. Then solid KI (1.25 g, 7.53 mmol) was rapidly added followed by dropping, over a period of 5 min, of 1-bromooctane (15.6 mL, 90.3 mmol). The reaction was refluxed for 24 h. The reaction mixture was partitioned between water and Et_2O and extracted three times. After solvent removal the crude was purified by distillation under reduced pressure to give **7a** (15.76 g, 82%) as a pale yellow oil. This compound, such as other esters **7**, is sometimes contaminated by small amounts of dialkylated product, which can however be separated by chromatography. B.p. 60 °C, 0.35 mbar. R_f 0.36 (PE/Et_2O 9 : 1, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 3675, 3612, 3017, 2973, 2924, 1706, 1509, 1469, 1418, 1212, 1042, 925. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.87 (3 H, t, *J* 6.6, $CH_3(CH_2)_7$), 1.25–1.32 (12 H, m, $CH_3(CH_2)_6$), 1.27 (3 H, t, *J* 7.1, CH_3CH_2O), 1.79–1.90 (2 H, m, $CHCH_2$), 2.22 (3 H, s, CH_3CO), 3.40 (1 H, t, *J* 7.5, $CHCH_2$), 4.20 (2 H, q, *J* 7.1, CH_3CH_2O). δ_C(75 MHz; $CDCl_3$) 14.1 (2 C, CH_3CH_2), 22.6 ($CH_3CH_2CH_2$), 27.4 ($CHCH_2CH_2$), 28.2 ($CHCH_2CH_2$), 28.7 (CH_3CO), 29.1, 29.2 and 29.3 (3 C, $CH_3CH_2CH_2(CH_2)_3$), 31.8 ($CH_3CH_2CH_2$), 59.9 ($CHCH_2$), 61.2 (OCH_2), 169.9 (CO_2Et), 203.4 ($COCH_3$). GC-MS: R_t 5.75 min; m/z (EI) 242 (M^+, 0.61%), 200 (18), 157 (23), 143 (19), 131 (12), 130 (78), 115 (13), 102 (18), 101 (60), 98 (6.8), 97 (9.0), 88 (11), 85 (7.2), 84 (9.6), 83 (5.4), 73 (39), 71 (6.5), 69 (9.8), 55 (25), 43 (100), 42 (5.5), 41 (23), 39 (6.3). m/z (ESI^-) 241.1803 ($M - H^+$. $C_{14}H_{25}O_3$ requires 241.1804).

tert-Butyl 2-octyl-3-oxobutanoate 7b

In a two necked flask NaH (60% in mineral oil, 1.74 g, 43.5 mmol) was suspended in a mixture of dry toluene (25 mL) and DMF (20 mL). Then *t*-butyl acetoacetate (6.49 mL, 39.1 mmol) was dropped over a period of 30 min (so that the reaction mixture resulted just lukewarm), while the reaction was vigorously stirred. After 15 min 1-bromooctane (6.76 mL, 39.1 mmol) was added and the resulting yellow solution was heated at 100 °C for 3 h. The orange suspension was partitioned between saturated aq NH_4Cl and PE/Et_2O 1 : 1 and the pH of the aqueous layer was adjusted to 7–8 by addition of a small amount of concentrated HCl. After complete extraction the organic layers were washed with water and brine. After solvent evaporation, the crude was purified by chromatography with PE/Et_2O 9 : 1 to give pure **7b** (7.60 g, 72%) as a colourless oil. R_f 0.40 (PE/Et_2O 85 : 15, **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 3675, 3610, 3015, 2974, 2931, 1700, 1506, 1474, 1418, 1368, 1230, 1042, 924. δ_H(300 MHz; $CDCl_3$) 0.88 (3 H, t, *J* 6.9, $CH_3(CH_2)_7$), 1.22–1.32 (12 H, m, $CH_3(CH_2)_6$), 1.46 (9 H, s, $(CH_3)_3C$), 1.74–1.84 (2 H, m, $CHCH_2$), 2.21 (3 H, s, CH_3CO), 3.29 (1 H, t, *J* 7.4, $CHCH_2$). δ_C(75 MHz; $CDCl_3$; Me_4Si) 14.0 ($CH_3(CH_2)_7$), 22.6 ($CH_3CH_2CH_2$), 27.2 ($CHCH_2CH_2$), 27.8 (3 C, $(CH_3)_3C$), 28.0 ($CHCH_2CH_2$), 28.5 (CH_3CO), 29.1, 29.2 and 29.3 (3 C, $CH_3CH_2CH_2(CH_2)_3$), 31.8 ($CH_3CH_2CH_2$), 60.9 ($CHCH_2$), 81.6 ($OC(CH_3)_3$), 169.1 (CO_2tBu), 203.6 ($COCH_3$). GC-MS: R_t 6.13 min; m/z (EI) 214 ($M^+ - 56$, 1.3%), 197 (7.7), 158 (7.6), 115 (6.8), 112 (11), 103 (43), 102 (42), 98 (48), 97 (5.6), 84 (8.2), 73 (6.9), 71 (14), 58 (8.8), 57 (100), 56 (8.0), 55 (15), 43 (69), 41 (27). m/z (ESI^-) 269.2124 ($M - H^+$. $C_{16}H_{29}O_3$ requires 269.2117).

tert-Butyl 2-isobutyl-3-oxobutanoate 7c

It was prepared by the same methodology employed for **7b**, using this time isobutyl bromide, to give **7c** as a colourless oil in 69% yield after distillation. B.p. 96–97 °C, 7 mbar. R_f 0.48 (PE/Et_2O 8 : 2, **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 3545, 2926, 1727, 1631, 1267, 1116. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.90 and 0.92 (6 H, 2 d, *J* 1.8 and 1.5, $(CH_3)_2CH$), 1.46 (9 H, s, $(CH_3)_3C$), 1.51–1.80 (3 H, m, $(CH_3)_2CHCH_2$), 2.21 (3 H, s, CH_3CO), 3.39 (1 H, dd, *J* 8.4, 6.6, $CHCH_2CH(CH_3)_2$). δ_C(75 MHz; $CDCl_3$) 22.1 and 22.5 (2 C, $(CH_3)_2CH$), 26.1 ($(CH_3)_2CH$), 27.8 (3 C, $(CH_3)_3C$), 28.4 (CH_3CO), 36.8 ($CH_2CH(CH_3)_2$), 59.2 ($CHCH_2CH(CH_3)_2$), 81.6 ($OC(CH_3)_3$), 169.2 (CO_2tBu), 203.6 ($COCH_3$). GC-MS: R_t 2.95 min; m/z (EI) 214 (M^+, 0.023%), 158 (11), 141 (19), 116 (5.6), 115 (6.3), 103 (29), 102 (20), 99 (9.3), 98 (26), 73 (16), 71 (14), 70 (8.0), 69 (17), 58 (5.7), 57 (100), 56 (9.5), 55 (25), 43 (76), 41 (31), 39 (8.2). m/z (ESI^-) 213.1486 ($M - H^+$. $C_{12}H_{21}O_3$ requires 213.1491).

tert-Butyl 2-(2-benzyloxyethyl)-3-oxobutanoate 7d

A solution of *t*-butyl acetoacetate (2.34 g, 14.8 mmol) in dry *t*BuOH (30 mL) was treated with benzyl 2-bromoethyl ether (2.58 mL, 16.3 mmol). Then solid Cs_2CO_3 (7.25 g, 22.2 mmol) was added and the mixture was refluxed for 18 h. Cs_2CO_3 was filtered over a celite pad and washed with Et_2O. The resulting yellow solution was poured into a separatory funnel together with a 1 : 1 mixture of H_2O:sat. aq NH_4Cl. After extraction, washing of the organic layers with brine and solvent removal, the crude was chromatographed with PE/Me_2CO 98 : 2 → 9 : 1 to give **7d** (3.06 g, 70%) as a colourless oil. R_f 0.37 (PE/Me_2CO 9 : 1, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 3008, 2868, 1709, 1218, 1140, 920. δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.44 (9 H, s, $(CH_3)_3C$), 2.12 (2 H, quintet, *J* 6.5,$CHCH_2$), 2.22 (3 H, s, CH_3CO), 3.48 (2 H, t, *J* 5.9, CH_2OBn) 3.61 (1 H, t, *J* 7.2, $CHCH_2$), 4.46 (2 H, s, CH_2Ph), 7.25–7.38 (5 H, m, Ph). δ_C(75 MHz; $CDCl_3$) 27.8 (3 C, $(CH_3)_3C$), 28.0 ($CHCH_2$),

29.2 (CH_3CO), 57.5 ($CHCH_2$), 67.5 (CH_2OBn), 72.9 (CH_2Ph), 81.8 ($OC(CH_3)_3$), 127.57 (*CH para* of Ph), 127.64 (2 C, *CH ortho* of Ph), 128.3 (2 C, *CH meta* of Ph), 138.1 (*C ipso* of Ph), 168.7 (CO_2tBu), 203.4 ($COCH_3$). GC-MS: R_t 7.32 min; *m/z* (EI) 236 (M^+ – 56, 0.26%), 129 (46), 107 (8.7), 102 (8.2), 92 (10), 91 (100), 87 (5.9), 69 (11), 65 (7.0), 57 (28), 43 (19), 41 (9.5). *m/z* (ESI^-) 291.1605 (M – H^+. $C_{17}H_{23}O_4$ requires 291.1596).

tert-Butyl 2-ethyl-4-(4-methoxyphenoxy)-3-oxobutanoate 7e

It was prepared by the same methodology employed for **7b**, using this time ethyl iodide, to give **7e** as a colourless oil in 70% yield after chromatography (PE/Et_2O 9 : 1). R_f 0.42 (PE/Et_2O 7 : 3, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 2969, 2930, 2877, 1721, 1499, 1455, 1239, 1153, 1064, 1034. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.96 (3 H, t, *J* 7.5, CH_3CH_2), 1.43 (9 H, s, $(CH_3)_3C$), 1.90 (2 H, centre of m, CH_3CH_2), 3.55 (1 H, t, *J* 7.1, $CHCH_2$), 3.77 (3 H, s, OCH_3), 4.59 and 4.61 (2 H, AB system, *J* 16.6, OCH_2CO), 6.83 (4 H, s, aromatics). δ_C(75 MHz; $CDCl_3$) 11.8 (CH_3CH_2), 20.9 (CH_3CH_2), 27.9 (3 C, $(CH_3)_3C$), 55.7 (OCH_3), 57.6 ($CHCH_2$), 73.0 ($ArOCH_2$), 82.0 ($OC(CH_3)_3$), 114.7 and 115.5 (2 × 2C, aromatic *CH*), 151.7 and 154.5 (2 C, aromatic *C*), 168.5 (CO_2tBu), 203.0 ($COCH_2O$). GC-MS (based on the usual method but with final temp. 280 °C): R_t 7.88 min; *m/z* (EI) 308 (M^+, 18%), 308 (18), 235 (18), 137 (21), 129 (7.2), 125 (8.5), 124 (100), 109 (11), 107 (8.7), 92 (7.7), 77 (12), 57 (41), 55 (5.2), 41 (15). *m/z* (ESI^-) 307.1543 (M – H^+. $C_{17}H_{23}O_5$ requires 307.1545).

General procedure for the preparation of acylenamines 18

a) Formation of enamine **21a**: a solution of **7a** (2.50 mmol) in dry toluene (15 mL) was treated with NH_4OAc (14.5 mmol) and AcOH (9.68 mmol) and stirred with a Dean Stark apparatus. The solid slowly dissolved. After 2.3 h an additional amount of both NH_4OAc (10.48 mmol) and AcOH (6.99 mmol) was added and the reaction was refluxed for 0.7 h. The solution was diluted with CH_2Cl_2 and washed with 5% $NaHCO_3$. After solvent removal the crude was directly used in the next reaction.

b) Formation of enamines **21b–d**: for this reaction a saturated solution of NH_3, prepared by bubbling ammonia into absolute ethanol, was employed. The concentration of ammonia was established to be 2.8 M after titration. A solution of **7b–d** (3.14 mmol) in 2.8 M ammonia (10.1 mL, 28.3 mmol) was prepared in a pressure tube. After addition of NH_4OAc (968 mg, 12.6 mmol) the tube was sealed and stirred at 60 °C overnight. Disappearance of starting material and formation of **21b–d** was demonstrated by GC-MS. The crude was poured into brine (100 mL) and 1 M NaOH (10 mL) and an extraction with Et_2O was performed. After solvent evaporation the oily residue was dried at 0.2 mbar for 1.5 h and then directly submitted to the following reaction.

c) Formation of acylenamine **18**: crude **21** was dissolved in dry CH_2Cl_2 (10 mL) and treated with dry pyridine (762 µl, 9.42 mmol). After cooling to 0 °C ethyl 2-chloro-2-oxoacetate (4.56 µl, 4.08 mmol) was added. After 5 min the solution was allowed to stir at room temp. for 4 h. The crude was poured into a mixture of 5% aq $(NH_4)H_2PO_4$, brine (50 mL) and 1 M HCl (10 mL). After extraction with Et_2O the product was purified by chromatography.

(*Z*)-Ethyl 3-(2-ethoxy-2-oxoacetamido)-2-octylbut-2-enoate 18a

a) GC-MS (**21a**): R_t 6.63 min; *m/z* (EI) 241 (M^+, 6.7%), 196 (5.3), 143 (8.7), 142 (100), 129 (5.7), 96 (33), 70 (5.7), 55 (9.9), 42 (8.4). b) Chromatography of crude **18a** with PE/Et_2O 9 : 1 → 7 : 3 gave a pale yellow oil (72% from **7a**). R_f 0.28 (PE/AcOEt/CH_2Cl_2 90 : 5 : 5, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 2920, 2852, 1709, 1662, 1612, 1247, 1122. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.88 (3 H, t, *J* 6.7, $CH_3(CH_2)_7$), 1.24–1.36 (12 H, m, $CH_3(CH_2)_6$), 1.32 (3 H, t, *J* 7.1, CH_3CH_2OCO), 1.40 (3 H, t, *J* 7.1, CH_3CH_2OCOCO), 2.31 (2 H, br t, *J* 7.5, $CH_2(CH_2)_7CH_3$), 2.46 (3 H, s, CH_3CNH), 4.26 (2 H, q, *J* 7.2, CH_3CH_2OCO), 4.39 (2 H, q, *J* 7.2, CH_3CH_2OCOCO). δ_C(75 MHz; $CDCl_3$) 13.8 and 14.0 (2 C, $CH_3(CH_2)_7$ and CH_3CH_2OCOCO), 14.1 (CH_3CH_2OCO), 16.5 (CH_3CNH), 22.6 ($CH_3CH_2CH_2$), 26.9 ($CH_2(CH_2)_6CH_3$), 29.1, 29.2 and 29.3 (x 2) (4 C, $CH_2(CH_2)_4(CH_2)_2CH_3$), 31.7 ($CH_3CH_2CH_2$), 60.6 (CH_3CH_2OCO), 63.3 (CH_3CH_2OCOCO), 112.5 (CC_8H_{17}), 147.2 (*C*NHCO), 154.6 ($COCO_2Et$), 160.6 ($COCO_2Et$), 169.4 (CO_2Et). GC-MS: R_t 9.34 min; *m/z* (EI) 341 (M^+, 5.7%), 296 (8.3), 242 (28), 269 (18), 268 (100), 240 (23), 225 (8.4), 224 (13), 223 (5.5), 222 (31), 197 (10), 196 (79), 194 (16), 182 (5.7), 178 (6.8), 169 (12), 168 (14), 156 (14), 152 (5.1), 151 (22), 150 (16), 142 (9.8), 140 (6.2), 124 (12), 123 (6.5), 122 (21), 110 (8.2), 109 (9.1), 108 (5.3), 98 (6.9), 97 (14), 96 (49), 95 (12), 94 (9.2), 83 (6.9), 82 (6.6), 81 (17), 80 (5.4), 79 (6.2), 70 (19), 69 (16), 68 (10), 67 (12), 57 (10), 56 (5.0), 55 (39), 54 (7.2), 53 (10), 44 (7.3), 43 (35), 42 (44), 41 (40), 39 (8.0). *m/z* (ESI^-) 340.2133 (M – H^+. $C_{18}H_{30}NO_5$ requires 340.2124).

(*Z*)-*tert*-Butyl 3-(2-ethoxy-2-oxoacetamido)-2-octylbut-2-enoate 18b

a) GC-MS (**21b**): R_t 6.84 min; *m/z* (EI) 269 (M^+, 1.4%), 115 (7.0), 114 (100), 101 (10), 96 (14), 70 (5.8), 57 (8.5), 55 (7.2), 42 (7.6), 41 (8.3). b) Chromatography of crude **18b** with PE/Et_2O 8 : 2 → 75 : 25 gave a pale yellow oil (81% from **7b**). R_f 0.64 (PE/Et_2O 7 : 3, **a**). b) Chromatography of crude **18b** with PE/Et_2O 9 : 1 → 7 : 3 gave a pale yellow oil (72% from **7b**). R_f 0.28 (PE/AcOEt/CH_2Cl_2 90 : 5 : 5, a or b). $\nu_{max}(CHCl_3)/cm^{-1}$ 2917, 2852, 1704, 1609, 1451, 1367, 1194, 1010. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.88 (3 H, t, *J* 6.8, $CH_3(CH_2)_7$), 1.24–1.42 (12 H, m, $CH_3(CH_2)_6$), 1.40 (3 H, t, *J* 7.1, CH_3CH_2O), 1.52 (9 H, s, $(CH_3)_3C$), 2.26 (2 H, br t, *J* 7.5, $CH_2(CH_2)_7CH_3$), 2.42 (3 H, s, CH_3CNH), 4.38 (2 H, q, *J* 7.2, CH_3CH_2O). δ_C(75 MHz; $CDCl_3$) 13.8 and 14.0 (2 C, $CH_3(CH_2)_7$ and CH_3CH_2), 16.5 (CH_3CNH), 22.6 ($CH_3CH_2CH_2$), 27.4 ($CH_2(CH_2)_6CH_3$), 28.0 (3 C, $(CH_3)_3C$), 29.2, 29.3, 29.4 and 29.5 (4 C, $CH_2(CH_2)_4(CH_2)_2CH_3$), 31.7 ($CH_3CH_2CH_2$), 63.2 (CH_3CH_2O), 81.2 ($OC(CH_3)_3$), 114.1 (CC_8H_{17}), 146.0 (*C*NHCO), 154.5 ($COCO_2Et$), 160.6 ($COCO_2Et$), 168.8 (CO_2tBu). GC-MS: R_t 9.44 min; *m/z* (EI) 313 (M^+ –56, 0.81%), 214 (19), 212 (8.8), 197 (11), 196 (30), 151 (12), 140 (8.1), 128 (10), 124 (6.6), 122 (15), 118 (30), 114 (15), 110 (7.2), 109 (6.2), 97 (8.9), 96 (40), 95 (10), 94 (7.2), 83 (6.0), 81 (12), 70 (18), 69 (14), 68 (8.0), 67 (9.0), 58 (5.5), 57 (100), 56 (7.5), 55 (36), 53 (7.4), 44 (7.2), 43 (28), 42 (33), 41 (60). *m/z* (ESI^-) 368.2439 (M – H^+. $C_{20}H_{34}NO_5$ requires 368.2437).

(*Z*)-*tert*-Butyl 3-(2-ethoxy-2-oxoacetamido)-2-isobutylbut-2-enoate 18c

a) GC-MS (based on the usual method but with final temp. 280 °C) (**21c**): R_t 4.19 min; *m/z* (EI) 213 (M^+, 3.5%), 140 (6.6), 115

(6.7), 114 (100), 96 (22), 57 (7.0), 55 (8.5), 42 (16), 41 (9.0). b) Chromatography of crude **18c** with PE/Et_2O 95 : 5 → 8 : 2 gave a pale yellow oil (82% from **7c**). R_f 0.35 (PE/Et_2O 85 : 15, **a**). $\nu_{max}(CHCl_3)/cm^{-1}$ 3012, 2953, 2865, 1706, 1607, 1463, 1251, 1151, 1125. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.90 (6 H, d, *J* 6.6, $(CH_3)_2CH$), 1.41 (3 H, t, *J* 7.2, CH_3CH_2O), 1.52 (9 H, s, $(CH_3)_3C$), 1.71 (1 H, centre of m, $(CH_3)_2CH$), 2.20 (2 H, d, *J* 7.2, CH_2CH), 2.43 (3 H, s, CH_3CNH), 4.39 (2 H, q, *J* 7.1, CH_3CH_2O). δ_C(75 MHz; $CDCl_3$) 13.8 (CH_3CH_2O), 17.0 (CH_3CNH), 22.3 (2 C, $(CH_3)_2CH$), 27.8 (3 C, $(CH_3)_3C$), 29.2 ($(CH_3)_2CH$), 35.9 (CH_2CH), 63.2 (CH_3CH_2O), 81.2 ($OC(CH_3)_3$), 113.2 (CC_8H_{17}), 146.6 (*C*NHCO), 154.5 ($COCO_2Et$), 160.6 ($COCO_2Et$), 168.9 (CO_2tBu). GC-MS: R_t 7.54 min; *m*/*z* (EI) 313 (M^+, 2.0%), 257 (9.0), 240 (7.9), 215 (11), 214 (100), 212 (14), 197 (6.3), 196 (16), 184 (19), 166 (10), 156 (5.7), 140 (8.8), 122 (9.9), 114 (6.1), 97 (7.5), 96 (33), 95 (7.7), 70 (8.9), 57 (48), 55 (17), 53 (5.3), 43 (13), 42 (20), 41 (34), 39 (7.0). *m*/*z* (ESI^-) 312.1809 ($M - H^+$. $C_{16}H_{26}NO_5$ requires 312.1811).

(*Z*)-*tert*-Butyl 2-(2-benzyloxyethyl)-3-(2-ethoxy-2-oxoacetamido)-2-butenoate 18d

a) GC-MS (**21d**): R_t 8.04 min; *m*/*z* (EI) 291 (M^+, 6.9%), 170 (6.8), 157 (15), 115 (7.6), 114 (100), 101 (41), 96 (23), 91 (16), 65 (5.7), 57 (7.6), 55 (7.9), 42 (9.5), 41 (8.5). b) Chromatography of crude **18d** with PE/Et_2O 6 : 4 → 1 : 1 gave a pale yellow oil (60% from **7d**). R_f 0.49 (PE/Et_2O 1 : 1, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 3002, 1711, 1614, 1229, 1154, 1135, 1100. δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.40 (3 H, t, *J* 7.1, CH_3CH_2O), 1.47 (9 H, s, $(CH_3)_3C$), 2.47 (3 H, s, CH_3CNH), 2.63 (2 H, t, *J* 7.2, CH_2CH_2O), 3.48 (2 H, t, *J* 7.2, CH_2CH_2O), 4.38 (2 H, q, *J* 7.1, CH_3CH_2O), 4.51 (2 H, s, CH_2Ph), 7.25–7.37 (5 H, m, Ph). δ_C(75 MHz; $CDCl_3$) 13.9 (CH_3CH_2O), 16.8 (CH_3CNH), 28.0 (3 C, $(CH_3)_3C$), 28.1 (CH_2CH_2O), 63.3 (CH_3CH_2O), 69.0 (CH_2CH_2O), 72.8 (CH_2Ph), 81.6 ($OC(CH_3)_3$), 109.8 ($C(CH_2)_2$), 127.4 (2 C, *C*H *ortho* of Ph), 127.5 (*C*H *para* of Ph), 128.3 (2 C, *C*H *meta* of Ph), 138.3 (*C ipso* of Ph), 148.2 (*C*NHCO), 154.6 ($COCO_2Et$), 160.5 ($COCO_2Et$), 168.5 (CO_2tBu). GC-MS: R_t 7.54 min (not completely stable under the analysis conditions); *m*/*z* (EI) 318 ($M^+ - 73$, 0.070%), 274 (112), 229 (7.9), 218 (5.6), 214 (20), 196 (21), 173 (9.2), 156 (16), 128 (19), 122 (5.2), 96 (15), 92 (8.9), 91 (100), 70 (5.2), 65 (7.2), 57 (23), 55 (6.9), 42 (7.2), 41 (12). *m*/*z* (ESI^-) 390.1906 ($M - H^+$. $C_{21}H_{28}NO_6$ requires 390.1917).

(*Z*)-*tert*-Butyl 3-(2-ethoxy-2-oxoacetamido)-2-ethyl-4-(4-methoxyphenoxy)but-2-enoate 18e

a) GC-MS (based on the usual method but with final temp. 280 °C) (**21e**): R_t 8.67 min; *m*/*z* (EI) 303 (M^+, 3.3%), 234 (5.7), 137 (9.6), 128 (69), 125 (8.6), 124 (100), 123 (16), 109 (16), 57 (15), 42 (6.4), 41 (13). b) Chromatography of crude **18e** with PE/Et_2O 8 : 2 → 75 : 25 gave a white solid (43% of *Z* isomer from **7e**; *Z*+*E* overall yield 65%). Mp 65.8-67.8 °C (PE/Et_2O). R_f 0.27 (PE/Et_2O 7 : 3, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 3001, 1708, 1618, 1259, 1191, 1152, 1127. δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.07 (3 H, t, *J* 7.5, CH_3CH_2), 1.38 (3 H, t, *J* 7.2, CH_3CH_2O), 1.54 (9 H, s, $(CH_3)_3C$), 2.40 (2 H, q, *J* 7.4, CH_3CH_2), 3.77 (3 H, s, OCH_3), 4.37 (2 H, q, *J* 7.2, CH_3CH_2O), 5.16 (2 H, s, OCH_2CO), 6.87 (4 H, centre of m, aromatics), 12.44 (1 H, br s, N*H*). δ_C(75 MHz; $CDCl_3$) 14.0 (CH_3CH_2O), 14.8 (CH_3CH_2), 21.3 (CH_3CH_2), 28.1 (3 C, $(CH_3)_3C$), 55.7 (OCH_3), 63.3 and 63.4 (2 C, CH_2OAr, CH_3CH_2O), 82.3 ($OC(CH_3)_3$), 114.6 and 116.5 (2 × 2 C, aromatic *C*H), 121.2 (CCH_2CH_3), 141.7 (*C*NHCO), 152.5, 154.2 and 154.4 (3 C, 2 *C ipso* of Ar and $COCO_2Et$), 160.4 ($COCO_2Et$), 168.1 (CO_2tBu). GC-MS (based on the usual method but with final temp. 280 °C): R_t 10.39 min (not completely stable under the analysis conditions); *m*/*z* (EI) 334 ($M^+ - 73$, 1.2%), 229 (5.5), 228 (48), 189 (7.6), 184 (8.9), 182 (26), 125 (9.0), 124 (100), 123 (38), 110 (5.7), 109 (9.5), 57 (27), 56 (5.1), 41 (16), 39 (5.6). *m*/*z* (ESI^-) 406.1869 ($M - H^+$. $C_{21}H_{28}NO_7$ requires 406.1866).

General procedure for the preparation of oxazinones 17

A solution of acylenamine **18** (2.80 mmol) in dry CH_2Cl_2 (15 mL) was treated sequentially with triphenyl phosphine (1.54 g, 5.87 mmol), tetrachloromethane (377 µl, 3.91 mmol) and triethylamine (817 µl, 5.86 mmol) and then refluxed until complete reaction was observed (typically 4–5 h). After dilution with CH_2Cl_2 the organic layer was washed with 5% aq $Na_2S_2O_5$. After solvent evaporation a very fast chromatography was performed and the corresponding oxazinone was immediately submitted to the following reaction, due to its limited stability. Only compound **17a** was characterized, while for all other derivatives only ^1H NMR and, when feasible, GC-MS have been recorded.

Ethyl 4-methyl-5-octyl-6-oxo-6*H*-1,3-oxazine-2-carboxylate 17a

The reaction on **18a** was performed in 1,2-dichloroethane at reflux (2.5 h). The isolated yield, after chromatography with PE/Et_2O 100 : 0 → 6 : 4, gave a pale yellow oil in 60% (67% on unrecovered starting material) yield. Starting from **18b** the reaction in 1,2-dichloroethane was complete after 30 min. The solvent was however successfully substituted by CH_2Cl_2, with no appreciably affecting the yield. Oxazinone **17a** was isolated in 78% yield. R_f 0.24 (PE/Et_2O 7 : 3, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 3002, 2868, 1744, 1630, 1390, 1300, 1185. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.88 (3 H, t, *J* 6.8, $CH_3(CH_2)_7$), 1.21–1.56 (12 H, m, $CH_3(CH_2)_6$), 1.42 (3 H, t, *J* 7.2, CH_3CH_2O), 2.35 (3 H, s, CH_3C-N), 2.51 (2 H, t, *J* 7.6, $CH_2(CH_2)_6CH_3$), 4.64 (2 H, q, *J* 7.1, CH_3CH_2O). δ_C(75 MHz; $CDCl_3$) 14.0 and 14.1 (2 C, $CH_3(CH_2)_7$ and CH_3CH_2O), 20.8 (CH_3C-N), 22.6 ($CH_3CH_2CH_2$), 26.6 ($CH_2(CH_2)_6CH_3$), 27.8 ($CH_2CH_2(CH_2)_5CH_3$), 29.2, 29.3 and 29.6 (3 C, $(CH_2)_2(CH_2)_3(CH_2)_2CH_3$), 31.8 ($CH_3CH_2CH_2$), 63.7 ($CH_3CH_2O$), 124.7 (*C*(C═O)N), 149.8 (*C*═N), 157.4, 158.4, 158.5 (3 C, 2 *C*O and CH_3C-N). GC-MS: R_t 8.51 min; *m*/*z* (EI) 295 (M^+, 0.11%), 223 (16), 222 (100), 197 (6.8), 196 (16), 169 (6.2), 151 (11), 126 (23), 125 (17), 124 (19), 97 (6.5), 96 (33), 95 (12), 94 (5.3), 93 (5.8), 82 (5.6), 81 (20), 79 (6.8), 70 (7.8), 69 (13), 68 (8.7), 67 (15), 57 (7.5), 56 (5.7), 55 (23), 54 (9.8), 53 (12), 43 (21), 42 (19), 41 (32), 39 (7.9).

Ethyl 5-isobutyl-4-methyl-6-oxo-6*H*-1,3-oxazine-2-carboxylate 17c

Chromatography with PE/Et_2O 8 : 2 gave a pale yellow oil (74%). R_f 0.23 (PE/Et_2O 7 : 3, **a** or **b**). δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.95 (6 H, d, *J* 6.6, $(CH_3)_2CH$), 1.42 (3 H, t, *J* 7.1, CH_3CH_2O), 1.99 (1 H, nonuplet, *J* 6.8, $(CH_3)_2CH$), 2.34 (3 H, s, CH_3C-N), 2.42 (2 H, d, *J* 7.5, CH_2CH), 4.47 (2 H, q, *J* 7.2, CH_3CH_2O). GC-MS: R_t 6.25 min; *m*/*z* (EI) 239 (M^+, 9.0%), 167 (11), 166 (100), 140 (5.7),

138 (5.1), 124 (7.6), 123 (12), 97 (6.1), 96 (9.6), 95 (16), 81 (8.1), 67 (10), 55 (9.5), 54 (9.8), 53 (7.3), 43 (18), 42 (19), 41 (18), 39 (8.5).

Ethyl 5-(2-(benzyloxy)ethyl)-4-methyl-6-oxo-6*H*-1,3-oxazine-2-carboxylate 17d

Chromatography with PE/Et_2O 6 : 4 → 1 : 1 gave a yellow–orange oil (57%). R_f 0.33 (PE/Et_2O 1 : 1, **a** or **b**). δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.42 (3 H, t, *J* 7.1, CH_3CH_2O), 2.39 (3 H, s, CH_3C-N), 2.84 (2 H, t, *J* 6.2, CH_2CH_2O), 3.69 (2 H, t, *J* 6.3, CH_2CH_2O), 4.70 (2 H, q, *J* 7.1, CH_3CH_2O), 4.74 (2 H, s, CH_2Ph), 7.24–7.35 (5 H, m, Ph). GC-MS: R_t 9.42 min; *m*/*z* (EI) 317 (M^+, 0.15%), 214 (5.1), 211 (20), 183 (9.1), 138 (10), 96 (4.4), 92 (10), 91 (100), 65 (11), 42 (6.2).

Ethyl 4-((4-methoxyphenoxy)methyl)-5-ethyl-6-oxo-6*H*-1,3-oxazine-2-carboxylate 17e

Chromatography with PE/AcOEt 7 : 3 gave a yellow oil (55%). R_f 0.35 (PE/AcOEt 7 : 3, **a** or **b**). δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.17 (3 H, t, *J* 7.5, CH_3CH_2), 1.43 (3 H, t, *J* 7.2, CH_3CH_2O), 2.67 (2 H, q, *J* 7.5, CH_3CH_2), 3.78 (3 H, s, OCH_3), 4.47 (2 H, q, *J* 7.1, CH_3CH_2O), 4.92 (2 H, s, OCH_2C-N), 6.87 (4 H, centre of m, aromatics). GC-MS: unsuitable for this analysis.

General procedure for the preparation of 3*H*-pyrimidin-4-ones 16

A solution of oxazinone **17** (2.00 mmol) in dry THF (5 mL) was treated at room temp. with 1.3 equivalents of the desired primary amine. The solution was allowed to stir until complete. Usually 4 h are enough but, since in most cases **16** and **17** are not well separated in tlc, the reaction was allowed to stir overnight. The resulting solution was partitioned between H_2O and Et_2O and extracted. The excess of amine can be removed by washing the organic layers with slightly acid (HCl) brine. Chromatography with the appropriate solvent (see below) furnished **16**.

Ethyl 3-butyl-6-methyl-5-octyl-3*H*-pyrimidin-4-one-2-carboxylate 16aa

Starting oxazinone: **17a**. Amine: *n*butylamine. Chromatography with PE/Et_2O 8 : 2 gave a pale yellow oil (80%). R_f 0.34 (PE/Et_2O 7 : 3, **a**). ν_{max}($CHCl_3$)/cm^{-1} 2957, 2923, 2852, 1736, 1655, 1598, 1442, 1381, 1210, 1108. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.88 (3 H, t, *J* 6.8, $CH_3(CH_2)_7$), 0.94 (3 H, t, *J* 7.2, $CH_3(CH_2)_3N$), 1.22–1.49 (14 H, m, $CH_3(CH_2)_6$ and $CH_3CH_2(CH_2)_2N$), 1.43 (3 H, t, *J* 7.2, CH_3CH_2O), 1.71 (2 H, centre of m, $CH_3CH_2CH_2CH_2N$), 2.31 (3 H, s, CH_3C-N), 2.52 (2 H, t, *J* 7.8, $CH_2(CH_2)_6CH_3$), 3.97 (2 H, centre of m, CH_2N), 4.46 (2 H, q, *J* 7.2, CH_3CH_2O). δ_C(75 MHz; $CDCl_3$) 13.6 (CH_3CH_2O), 14.0 ($CH_3(CH_2)_7$), 14.1 ($CH_3(CH_2)_3N$), 20.1 ($CH_3CH_2(CH_2)_2N$), 21.1 (CH_3C-N), 22.6 ($CH_3CH_2(CH_2)_6$), 26.6 ($CH_2(CH_2)_6CH_3$), 28.0 ($CH_2CH_2(CH_2)_5CH_3$), 29.3, 29.4 and 29.8 (3 C, $(CH_2)_2(CH_2)_3(CH_2)_2CH_3$), 30.9 ($CH_3CH_2CH_2CH_2N$), 31.8 ($CH_3CH_2CH_2(CH_2)_5$), 45.5 ($CH_2N$), 63.1 ($CH_3CH_2O$), 126.9 (C(=O)N), 147.7 (C=N), 157.2 (CH_3C-N), 161.1 (C(C=O)N), 161.3 (CO_2Et). GC-MS: R_t 9.48 min; *m*/*z* (EI) 350 (M^+, 8.4%), 335 (14), 321 (5.3), 295 (9.9), 279 (9.1), 278 (20), 277 (100), 265 (11), 253 (15), 252 (100), 251 (7.4), 223 (6.1), 221 (5.2), 209 (5.9), 207 (6.3), 197 (10), 196 (13), 195 (8.9), 193 (5.6), 180 (5.6), 179 (40), 177 (6.4), 163 (6.1), 151 (11), 150 (26), 149 (11), 138 (6.9), 137 (11), 135 (9.8), 124 (43), 123 (35), 122 (14), 121 (10), 96 (27), 95 (7.8), 94 (6.6), 93 (5.4), 81 (7.6), 80 (5.2), 79 (7.4), 69 (9.6), 67 (17), 57 (13), 56 (8.9), 55 (41), 53 (22), 43 (32), 42 (26), 41 (56), 39 (10). *m*/*z* (ESI^-) 349.2507 (M – H^+. $C_{20}H_{33}N_2O_3$ requires 349.2491).

Ethyl 3-(3-(*tert*-butoxycarbonyl)propyl)-6-methyl-5-octyl-3*H*-pyrimidin-4-one-2-carboxylate 16ab

Starting oxazinone: **17a**. Amine: freshly prepared **30**, obtained by deprotection of **29** (see below), was employed. Chromatography with PE/Et_2O 9 : 1 → 6 : 4 gave a yellow–brown oil (89%). R_f 0.45 (PE/Et_2O 6 : 4, **a** or **b**). ν_{max}($CHCl_3$)/cm^{-1} 3675, 3611, 3018, 2971, 2925, 2893, 1724, 1653, 1506, 1473, 1424, 1195, 1044, 924. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.88 (3 H, t, *J* 6.9, $CH_3(CH_2)_7$), 1.19–1.52 (12 H, m, $CH_3(CH_2)_6$), 1.44 (9 H, s, $(CH_3)_3C$), 1.44 (3 H, t, *J* 6.9, CH_3CH_2O), 2.00 (2 H, centre of m, $CH_2CH_2CH_2N$), 2.29 (2 H, t, *J* 7.2, $CH_2CH_2CH_2N$), 2.32 (3 H, s, CH_3C-N), 2.52 (2 H, t, *J* 7.5, $CH_2(CH_2)_6CH_3$), 4.03 (2 H, centre of m, CH_2N), 4.48 (2 H, q, *J* 7.1, CH_3CH_2O). δ_C(75 MHz; $CDCl_3$) 13.8 (CH_3CH_2O), 14.0 ($CH_3(CH_2)_7$), 21.0 (CH_3C-N), 22.5 ($CH_3CH_2(CH_2)_6$), 24.2 ($CH_2CH_2CH_2N$), 26.4 ($CH_2(CH_2)_6CH_3$), 27.8 ($CH_2CH_2(CH_2)_5CH_3$), 27.9 (3 C, $(CH_3)_3C$), 29.2, 29.3 and 29.7 (3 C, $(CH_2)_2(CH_2)_3(CH_2)_2CH_3$), 31.7 ($CH_3CH_2CH_2(CH_2)_5$), 32.4 ($CH_2CH_2CH_2N$), 44.8 ($CH_2N$), 63.2 ($CH_3CH_2O$), 80.4 ($(CH_3)_3C$), 126.8 (C(C=O)N), 147.5 (C=N), 157.2 (CH_3C-N), 160.9 (C(C=O)N), 161.1 (CO_2Et), 171.6 (CO_2tBu). GC-MS: R_t 11.25 min; *m*/*z* (EI) 436 (M^+, 2.3%), 380 (12), 365 (10), 363 (21), 338 (6.4), 295 (6.5), 293 (12), 283 (15), 282 (100), 196 (17), 191 (6.0), 163 (8.1), 123 (7.9), 96 (5.4), 69 (8.7), 57 (14), 43 (5.1), 41 (12). *m*/*z* (ESI^-) 435.2849 (M – H^+. $C_{24}H_{39}N_2O_5$ requires 435.2859).

Ethyl 3-(3-(ethoxycarbonyl)propyl)-6-methyl-5-octyl-3*H*-pyrimidin-4-one-2-carboxylate 16ac

Starting oxazinone: **17a**. Amine: commercially available ethyl 4-aminobutyrate hydrochloride was used. This time an addition of triethylamine (1.15 equiv. with respect to the hydrochloride) was necessary. Chromatography with PE/Et_2O 6 : 4 → 1 : 1 gave a yellow oil (81%). R_f 0.30 (PE/Et_2O 6 : 4, **a**). ν_{max}($CHCl_3$)/cm^{-1} 2919, 2851, 1730, 1649, 1597, 1445, 1370, 1205, 1084, 1016. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.88 (3 H, t, *J* 6.8, $CH_3(CH_2)_7$), 1.24–1.50 (12 H, m, $CH_3(CH_2)_6$), 1.26 (3 H, t, *J* 6.9, $CH_3CH_2OCOCH_2$), 1.44 (3 H, t, *J* 6.9, CH_3CH_2OCOC=N), 2.05 (2 H, centre of m, $CH_2CH_2CH_2N$), 2.32 (3 H, s, CH_3C-N), 2.38 (2 H, t, *J* 7.2, $CH_2CH_2CH_2N$), 2.52 (2 H, t, *J* 7.6, $CH_2(CH_2)_6CH_3$), 4.05 (2 H, centre of m, CH_2N), 4.13 (2 H, q, *J* 7.2, $CH_3CH_2OCOCH_2$), 4.48 (2 H, q, *J* 7.2, CH_3CH_2OCOC=N). δ_C(75 MHz; $CDCl_3$) 13.9 (CH_3CH_2OCOC=N), 14.1 ($CH_3(CH_2)_7$), 14.2 ($CH_3CH_2OCOCH_2$), 21.1 (CH_3C-N), 22.6 ($CH_3CH_2(CH_2)_6$), 24.1 ($CH_2CH_2CH_2N$), 26.6 ($CH_2(CH_2)_6CH_3$), 28.0 ($CH_2CH_2(CH_2)_5CH_3$), 29.3, 29.4 and 29.8 (3 C, $(CH_2)_2(CH_2)_3(CH_2)_2CH_3$), 31.3 ($CH_3CH_2CH_2(CH_2)_5$), 32.4 ($CH_2CH_2CH_2N$), 44.9 ($CH_2N$), 60.6 ($CH_3CH_2OCOCH_2$), 63.4 ($CH_3CH_2OCOC$=N), 127.0 (C(C=O)N), 147.6 (C=N), 157.3 (CH_3C-N), 161.1 (C(C=O)N), 161.2 (N=CCO_2Et), 172.5 (CH_2CO_2Et). GC-MS: R_t 10.88 min; *m*/*z* (EI) 408 (M^+, 2.3%), 408 (6.5), 363 (15), 335 (6.8), 311 (10), 310 (59), 293 (15), 264 (6.6), 207 (5.1), 196 (14), 191 (12), 165 (7.6), 164 (6.5), 163 (13), 150 (6.7), 124 (7.6), 123 (13), 122 (5.1), 116 (7.0), 115 (100), 96

(8.0), 87 (60), 69 (20), 55 (12), 53 (7.8), 45 (9.4), 43 (27), 42 (9.8), 41 (25). *m/z* (ESI$^+$) 409.2720 (M + H$^+$. $C_{22}H_{37}N_2O_5$ requires 409.2702).

Ethyl 3-isobutyl-6-methyl-5-octyl-3*H*-pyrimidin-4-one-2-carboxylate 16ad

Starting oxazinone: **17a**. Amine: isobutylamine. Chromatography with PE/Et_2O 9 : 1 → 6 : 4 gave a pale yellow oil (66%). R_f 0.28 (PE/Et_2O 7 : 3, **a**). ν_{max}($CHCl_3$)/cm^{-1} 2920, 2851, 1735, 1649, 1597, 1422, 1369, 1183, 1136, 1113, 1023. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.87 (3 H, t, *J* 6.9, CH_3(CH$_2$)$_7$), 0.89 (6 H, d, *J* 6.9, (CH_3)$_2$CH), 1.21–1.50 (12 H, m, CH$_3$(CH_2)$_6$), 1.42 (3 H, t, *J* 7.2, CH_3CH$_2$O), 2.05 (1 H, nonuplet, *J* 6.9, (CH$_3$)$_2$C*H*), 2.32 (3 H, s, CH_3C-N), 2.52 (2 H, t, *J* 7.6, CH_2(CH$_2$)$_6$CH$_3$), 3.96 (2 H, d, *J* 7.5, NCH_2CH), 4.45 (2 H, q, *J* 7.2, CH$_3$CH_2O). δ_C(75 MHz; $CDCl_3$) 14.0 (*C*H$_3$CH$_2$O), 14.1 (*C*H$_3$(CH$_2$)$_7$), 19.9 (2 C, (*C*H$_3$)$_2$CH), 21.1 (*C*H$_3$C-N), 22.7 (CH$_3$*C*H$_2$(CH$_2$)$_6$), 26.6 (*C*H$_2$(CH$_2$)$_6$CH$_3$), 28.0 (CH$_2$*C*H$_2$(CH$_2$)$_5$CH$_3$), 28.3 ((CH$_3$)$_2$*C*H), 29.3, 29.4 and 29.8 (3 C, (CH$_2$)$_2$(*C*H$_2$)$_3$(CH$_2$)$_2$CH$_3$), 31.8 (CH$_3$CH$_2$*C*H$_2$(CH$_2$)$_5$), 51.4 (*C*H$_2$N), 63.1 (CH$_3$*C*H$_2$O), 126.9 (*C*(C=O)N), 147.7 (*C*=N), 156.9 (CH$_3$*C*-N), 161.38 and 161.41 (2 C, C(*C*=O)N and *C*O$_2$Et). GC-MS: R$_t$ 9.25 min; *m/z* (EI) 350 (M$^+$, 6.2%), 335 (5.3), 296 (19), 295 (100), 277 (16), 253 (6.7), 252 (40), 223 (6.4), 221 (6.8), 209 (7.2), 197 (16), 196 (24), 195 (8.4), 151 (6.4), 150 (22), 149 (6.4), 137 (7.8), 135 (6.2), 124 (17), 123 (31), 122 (9.2), 121 (6.9), 96 (17), 95 (5.3), 67 (11), 57 (12), 56 (8.8), 55 (24), 53 (12), 43 (24), 42 (15), 41 (41), 39 (7.7). *m/z* (ESI$^+$) 351.2654 (M + H$^+$. $C_{20}H_{35}N_2O_3$ requires 351.2648).

Ethyl 3,5-diisobutyl-6-methyl-3*H*-pyrimidin-4-one-2-carboxylate 16ca

Starting oxazinone: **17c**. Amine: isobutylamine. Chromatography with PE/Et_2O 9 : 1 → 85 : 15 gave a yellow oil (68%). R_f 0.56 (PE/Et_2O 8 : 2, **a or b**). ν_{max}($CHCl_3$)/cm^{-1} 3675, 3610, 3021, 2973, 1732, 1650, 1596, 1511, 1471, 1418, 1191, 1043. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.86 (6 H, d, *J* 6.9, (CH_3)$_2$CHCH$_2$N) 0.90 (6 H, d, *J* 6.6, (CH_3)$_2$CHCH$_2$C), 1.40 (3 H, t, *J* 7.2, CH_3CH$_2$O), 1.93 (1 H, nonuplet, *J* 6.8, (CH$_3$)$_2$C*H*CH$_2$C), 2.02 (1 H, nonuplet, *J* 7.0, (CH$_3$)$_2$C*H*CH$_2$N), 2.30 (3 H, s, CH_3C-N), 2.41 (2 H, d, *J* 7.2, CCH_2CH), 3.93 (2 H, d, *J* 7.5, NCH_2CH), 4.43 (2 H, q, *J* 7.1, CH$_3$CH_2O). δ_C(75 MHz; $CDCl_3$) 13.9 (*C*H$_3$CH$_2$O), 19.9 (2 C, (*C*H$_3$)$_2$CHCH$_2$N), 21.5 (*C*H$_3$C-N), 22.6 (2 C, (*C*H$_3$)$_2$CHCH$_2$C), 27.9 ((CH$_3$)$_2$*C*HCH$_2$C), 28.2 ((CH$_3$)$_2$*C*HCH$_2$N), 35.4 (C*C*H$_2$CH), 51.3 (N*C*H$_2$CH), 63.1 (CH$_3$*C*H$_2$O), 126.0 (*C*(C=O)N), 147.7 (*C*=N), 157.6 (CH$_3$*C*-N), 161.4 (C(*C*=O)N), 161.6 (*C*O$_2$Et). GC-MS: R_t 7.25 min; *m/z* (EI) 294 (M$^+$, 6.3%), 251 (7.7), 240 (15), 239 (100), 221 (16), 197 (5.2), 196 (12), 195 (31), 167 (7.1), 166 (18), 165 (21), 150 (15), 123 (15), 122 (9.4), 121 (8.4), 96 (24), 67 (11), 57 (6.5), 56 (7.1), 55 (25), 53 (20), 43 (19), 42 (18), 41 (34), 39 (11). *m/z* (ESI$^-$) 293.1864 (M – H$^+$. $C_{16}H_{25}N_2O_3$ requires 293.1865).

Ethyl 3-((furan-2-yl)methyl)-5-isobutyl-6-methyl-3*H*-pyrimidin-4-one-2-carboxylate 16cb

Starting oxazinone: **17c**. Amine: furfurylamine. Chromatography with PE/Et_2O 9 : 1 → 85 : 15 gave a yellow oil (62%). R_f 0.38 (PE/Et_2O 1 : 1, **a**). ν_{max}($CHCl_3$)/cm^{-1} 3010, 2956, 1731, 1658, 1595, 1415, 1292, 1174, 1037. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.93 (6 H, d, *J* 6.6, (CH_3)$_2$CH), 1.40 (3 H, t, *J* 7.0, CH_3CH$_2$O), 1.97 (1 H, nonuplet, *J* 6.8, (CH$_3$)$_2$C*H*), 2.32 (3 H, s, CH_3C-N), 2.45 (2 H, d, *J* 7.5, CH_2CH), 4.45 (2 H, q, *J* 7.2, CH$_3$CH_2O), 5.47 (2 H, s, CH_2(furan-2-yl)), 6.29 (1 H, dd, *J* 3.3, 1.8, C*H*(CH)$_2$-O), 6.32 (1 H, d, *J* 3.0, CHC*H*CH-O), 7.30 (1 H, dd, *J* 1.8, 0.6, (CH)$_2$C*H*-O). δ_C(75 MHz; $CDCl_3$) 13.9 (*C*H$_3$CH$_2$O), 21.6 (*C*H$_3$C-N), 22.6 (2 C, (*C*H$_3$)$_2$CH), 27.9 ((CH$_3$)$_2$*C*H), 35.5 (*C*H$_2$CH), 39.6 (*C*H$_2$(furan-2-yl)), 63.2 (CH$_3$*C*H$_2$O), 109.7 (*C*H(CH)$_2$-O), 110.5 (CH*C*HCH-O), 126.4 (*C*(C=O)N), 142.7 ((CH)$_2$*C*H-O), 146.8 (*C*=N), 148.9 (*C* of furyl), 157.7 (CH$_3$*C*-N), 161.0 (C(*C*=O)N), 161.3 (*C*O$_2$Et). GC-MS (based on the usual method but with final temp. 280 °C): R_t 8.33 min; *m/z* (EI) 319 (7.9), 318 (M$^+$, 38%), 245 (6.4), 237 (11), 195 (11), 165 (5.6), 163 (9.4), 82 (12), 81 (100), 53 (22), 43 (5.9), 41 (6.3). *m/z* (ESI + Na$^+$) 341.1465 (M + Na$^+$. $C_{17}H_{22}N_2NaO_4$ requires 341.1477).

Ethyl 5-isobutyl-6-methyl-3-((thien-2-yl)methyl)-3*H*-pyrimidin-4-one-2-carboxylate 16cc

Starting oxazinone: **17c**. Amine: 2-thiophenemethylamine. Chromatography with PE/Et_2O 6 : 4 gave a yellow oil (72%). R_f 0.29 (PE/Et_2O 6 : 4, **a**). ν_{max}($CHCl_3$)/cm^{-1} 3010, 2950, 2864, 1727, 1645, 1594, 1415, 1366, 1330, 1290, 1247, 1143. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.94 (6 H, d, *J* 6.6, (CH_3)$_2$CH), 1.36 (3 H, t, *J* 7.2, CH_3CH$_2$O), 1.97 (1 H, nonuplet, *J* 6.8, (CH$_3$)$_2$C*H*), 2.31 (3 H, s, CH_3C-N), 2.46 (2 H, d, *J* 7.2, CH_2CH), 4.43 (2 H, q, *J* 7.2, CH$_3$CH_2O), 5.56 (2 H, s, CH_2(thien-2-yl)), 6.91 (1 H, dd, *J* 5.1, 3.6, CHC*H*CH-S), 7.03 (1 H, dd, *J* 3.6, 1.2, C*H*(CH)$_2$-S), 7.22 (1 H, dd, *J* 5.1, 1.2, (CH)$_2$C*H*-S). δ_C(75 MHz; $CDCl_3$) 13.8 (*C*H$_3$CH$_2$O), 21.5 (*C*H$_3$C-N), 22.5 (2 C, (*C*H$_3$)$_2$CH), 27.9 ((CH$_3$)$_2$*C*H), 35.3 (*C*H$_2$CH), 42.0 (*C*H$_2$(thien-2-yl)), 63.2 (CH$_3$*C*H$_2$O), 126.37 and 126.40 (2 C, CH(*C*H)$_2$-S), 126.5 (*C*(C=O)N), 127.9 (*C*H(CH)$_2$-S), 137.6 (*C* of thienyl), 146.4 (*C*=N), 157.7 (CH$_3$*C*-N), 161.0 (C(*C*=O)N), 161.1 (*C*O$_2$Et), GC-MS: R_t 9.12 min; *m/z* (EI) 335 (5.9), 334 (M$^+$, 27%), 261 (6.0), 237 (13), 195 (9.6), 165 (5.6), 163 (7.7), 99 (5.2), 98 (12), 97 (100), 53 (9.5), 45 (7.5), 43 (5.0), 41 (5.1). *m/z* (ESI$^+$) 335.1426 (M + H$^+$. $C_{17}H_{23}N_2O_3S$ requires 335.1429).

Ethyl 5-isobutyl-3-(4-methoxybenzyl)-6-methyl-3*H*-pyrimidin-4-one-2-carboxylate 16cd

Starting oxazinone: **17c**. Amine: (4-methoxybenzyl)amine. Chromatography with PE/Et_2O 8 : 2 gave a yellow oil (75%). R_f 0.18 (PE/Et_2O 7 : 3, **a**). ν_{max}($CHCl_3$)/cm^{-1} 3005, 1732, 1655, 1498, 1415, 1192, 1029, 922. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.93 (6 H, d, *J* 6.6, (CH_3)$_2$CH), 1.22 (3 H, t, *J* 7.0, CH_3CH$_2$O), 1.97 (1 H, nonuplet, *J* 6.8, (CH$_3$)$_2$C*H*), 2.31 (3 H, s, CH_3C-N), 2.45 (2 H, d, *J* 7.2, CH_2CH), 3.75 (3 H, s, OCH_3), 4.28 (2 H, q, *J* 7.2, CH$_3$CH_2O), 5.30 (2 H, s, CH_2Ar), 6.80 (2 H, dt *J* 8.7, 2.1, *H ortho* to OCH$_3$), 7.13 (2 H, dt *J* 8.7, 2.4, *H meta* to OCH$_3$). δ_C(75 MHz; $CDCl_3$) 13.7 (*C*H$_3$CH$_2$O), 21.6 (*C*H$_3$C-N), 22.6 (2 C, (*C*H$_3$)$_2$CH), 27.9 ((CH$_3$)$_2$*C*H), 35.5 (*C*H$_2$CH), 46.6 (*C*H$_2$Ar), 55.2 (O*C*H$_3$), 63.1 (CH$_3$*C*H$_2$O), 114.0 (2 C, *C*H *ortho* to OCH$_3$), 126.3 (*C*(C=O)N), 128.0 (*C para* to OCH$_3$), 129.2 (2 C, *C*H *meta* to OCH$_3$), 147.5 (*C*=N), 157.8 (CH$_3$*C*-N), 159.2 (*C*-OCH$_3$), 161.4 (C(*C*=O)N), 161.5 (*C*O$_2$Et). GC-MS: R_t 10.02 min; *m/z* (EI) 358 (M$^+$, 6.9%), 122 (16), 121 (100), 77 (5.9). *m/z* (ESI$^-$) 357.1801 (M – H$^+$. $C_{20}H_{25}N_2O_4$ requires 357.1814).

Ethyl 5-(2-(benzyloxy)ethyl)-3-(3-(*tert*-butoxycarbonyl)propyl)-6-methyl-3*H*-pyrimidin-4-one-2-carboxylate 16d

Starting oxazinone: **17d**. Amine: freshly prepared **30** (see below). Chromatography with PE/Et_2O 6 : 4 → 4 : 6 gave an amber-coloured oil (75%). R_f 0.68 (PE/AcOEt 1 : 1, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 2969, 2863, 1721, 1657, 1599, 1443, 1367, 1190, 1077. δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.44 (3 H, t, *J* 7.1, CH_3CH$_2$O), 1.44 (9 H, s, (CH_3)$_3$C), 1.98 (2 H, centre of m, CH$_2$CH_2CH$_2$N), 2.28 (2 H, t, *J* 7.4, CH_2CH$_2$CH$_2$N), 2.36 (3 H, s, CH_3C-N), 2.88 (2 H, t, *J* 6.8, CH_2CH$_2$O), 3.65 (2 H, t, *J* 6.6, CH$_2$CH_2O), 4.01 (2 H, centre of m, CH_2N), 4.49 (2 H, q, *J* 7.2, CH$_3$CH_2O), 4.50 (2 H, s, CH_2Ph), 7.23–7.35 (5 H, m, Ph). δ_C(75 MHz; $CDCl_3$) 13.8 (*C*H$_3$CH$_2$O), 21.5 (*C*H$_3$C-N), 24.2 (CH$_2$*C*H$_2$CH$_2$N), 27.3 (*C*H$_2$CH$_2$O), 28.0 (3 C, (*C*H$_3$)$_3$C), 32.5 (*C*H$_2$CH$_2$CH$_2$N), 44.9 (*C*H$_2$N), 63.3 (CH$_3$*C*H$_2$O), 67.9 (CH$_2$*C*H$_2$O), 72.8 (*C*H$_2$Ph), 80.4 ((CH$_3$)$_3$*C*), 123.2 (*C*(C═O)N), 127.4 (3 C, *C*H *ortho* and *para* of Ph), 128.2 (2 C, *C*H *meta* of Ph), 138.3 (*C ipso* of Ph), 148.0 (*C*═N), 159.1 (CH$_3$*C*-N), 160.9 (C(*C*═O)N), 161.0 (*C*O$_2$Et), 171.6 (*C*O$_2$*t*Bu). GC-MS: R$_t$ 13.07 min; *m*/*z* (EI) 385 (M$^+$ – 73, 9.1%), 312 (5.5), 311 (34), 296 (16), 295 (7.6), 293 (7.5), 281 (9.1), 225 (24), 223 (9.4), 210 (13), 209 (14), 196 (5.7), 195 (17), 163 (9.0), 138 (6.9), 135 (6.0), 123 (6.9), 96 (14), 92 (9.1), 91 (100), 87 (5.8), 69 (12), 65 (8.7), 57 (28), 56 (7.4), 55 (9.7), 53 (7.1), 43 (6.3), 42 (7.1), 41 (27.6), 40 (5.5), 39 (7.4). *m*/*z* (ESI$^-$) 457.2339 (M – H$^+$. $C_{25}H_{33}N_2O_6$ requires 457.2339).

Ethyl 3-butyl-5-ethyl-6-((4-methoxyphenoxy)methyl)-3*H*-pyrimidin-4-one-2-carboxylate 16ea

Starting oxazinone: **17e**. Amine: *n*butylamine. Chromatography with PE/AcOEt 9 : 1 → 85 : 15 gave a yellow oil (77%). R_f 0.56 (PE/AcOEt 7 : 3, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 2962, 2867, 1734, 1658, 1462, 1245, 1195, 1016. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.95 (3 H, t, *J* 7.4, CH_3(CH$_2$)$_3$N), 1.16 (3 H, t, *J* 7.5, CH_3CH$_2$CC═O), 1.38 (2 H, centre of m, CH$_3$CH_2(CH$_2$)$_2$N), 1.43 (3 H, t, *J* 7.1, CH_3CH$_2$O), 1.66–1.78 (2 H, m, CH$_3$CH$_2$CH_2CH$_2$N), 2.65 (2 H, q, *J* 7.4, CH$_3$CH_2CC═O), 3.77 (3 H, s, OCH_3), 4.00 (2 H, centre of m, CH_2N), 4.47 (2 H, q, *J* 7.1, CH$_3$CH_2O) 4.89 (2 H, s, OCH_2C-N), 6.88 (4 H, centre of m, aromatics). δ_C(75 MHz; $CDCl_3$) 13.0 (*C*H$_3$CH$_2$CC═O), 13.6 (*C*H$_3$CH$_2$O), 14.0 (*C*H$_3$(CH$_2$)$_3$N), 19.8 (CH$_3$*C*H$_2$CC═O), 20.1 (CH$_3$*C*H$_2$(CH$_2$)$_2$N), 30.8 (CH$_3$CH$_2$*C*H$_2$CH$_2$N), 45.7 (*C*H$_2$N), 55.7 (O*C*H$_3$), 63.2 (CH$_3$*C*H$_2$O), 69.3 (*C*H$_2$OAr), 114.6 and 115.8 (2 × 2 C, aromatic *C*H), 131.4 (*C*(C═O)N), 148.4 (*C*═N), 152.5, 153.9 and 154.2 (3 C, 2 *C ipso* of Ar and OCH$_2$*C*-N), 161.0 (C(*C*═O)N), 161.3 (*C*O$_2$Et). GC-MS (based on the usual method but with init. temp. 70 °C and final temp. 260 °C): R$_t$ 12.55 min; *m*/*z* (EI) 388 (M$^+$, 2.2%), 135 (6.1), 124 (17), 123 (100), 121 (6.4), 109 (5.4), 95 (12), 67 (16), 65 (6.7), 57 (5.8), 55 (6.1), 41 (22). *m*/*z* (ESI$^-$) 387.1912 (M – H$^+$. $C_{21}H_{27}N_2O_5$ requires 387.1920).

Ethyl 3-benzyl-5-ethyl-6-((4-methoxyphenoxy)methyl)-3*H*-pyrimidin-4-one-2-carboxylate 16eb

Starting oxazinone: **17e**. Amine: benzylamine. Chromatography with PE/Et_2O 8 : 2 gave a pale yellow oil (77%). R_f 0.15 (PE/Et_2O 7 : 3, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 2976, 2934, 1735, 1657, 1499, 1439, 1420, 1286, 1221, 1176, 1033. δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.16 (3 H, t, *J* 6.9, CH_3CH$_2$O), 1.18 (3 H, t, *J* 7.2, CH_3CH$_2$CC═O), 2.69 (2 H, q, *J* 7.4, CH$_3$CH_2CC═O), 3.77 (3 H, s, OCH_3), 4.25 (2 H, q, *J* 7.2, CH$_3$CH_2O) 4.90 (2 H, s, OCH_2C-N), 5.43 (2 H, s, CH_2N), 6.88 (4 H, centre of m, aromatics (C$_6$H$_4$OMe)), 7.18–7.39 (5 H, m, aromatics (Ph)). δ_C(75 MHz; $CDCl_3$) 13.0 and 13.6 (2 C, *C*H$_3$CH$_2$CC═O and *C*H$_3$CH$_2$O), 20.0 (CH$_3$*C*H$_2$CC═O), 47.2 (*C*H$_2$N), 55.7 (O*C*H$_3$), 63.1 (CH$_3$*C*H$_2$O), 69.2 (*C*H$_2$OAr), 114.6 and 115.7 (2 × 2 C, aromatic *C*H (C$_6$H$_4$OMe)), 127.8 (2 C, *C*H *ortho* of Ph), 128.0 (*C*H *para* of Ph), 128.7 (2 C, *C*H *meta* of Ph), 131.7 (*C*(C═O)N), 135.5 (*C ipso* of Ph), 148.1 (*C*═N), 152.5, 153.9 and 154.2 (3 C, 2 *C ipso* of C$_6$H$_4$OMe and OCH$_2$*C*-N), 161.0 (C(*C*═O)N), 161.5 (*C*O$_2$Et). GC-MS (based on the usual method but with init. temp. 200 °C, rate 35 °C min^{-1}, final temp. 280 °C). R$_t$ 6.36 min; *m*/*z* (EI) 422 (M$^+$, 32%), 124 (18), 123 (100), 95 (12), 92 (8.9), 91 (97), 65 (12), 41 (7.8). *m*/*z* (ESI$^+$) 423.1902 (M + H$^+$. $C_{24}H_{27}N_2O_5$ requires 423.1920).

***tert*-Butyl 4-(4-methoxyphenoxy)-3-oxobutanoate 27**

A solution of Meldrum's acid **15** (2.07 g, 14.3 mmol) in dry CH_2Cl_2 was cooled to 0 °C; then dry pyridine (2.5 mL) was added. A suspension of (*p*-methoxyphenoxy)acetic acid (2.37 g, 13.0 mmol) in dry CH_2Cl_2 (5 mL) was treated portionwise with *N*,*N*′-carbonyldiimidazole (2.33 g, 14.3 mmol). After gas evolution stopped the colourless solution wad added to the solution of Meldrum's acid at 0 °C, with the help of additional 10 mL of CH_2Cl_2. Finally, 4-dimethylaminopyridine (80 mg, 652 µmol) was added and, after 1 h, the mixture was allowed to stir at room temp. overnight. The solution was poured into a separatory funnel containing 2 M HCl and extracted with CH_2Cl_2. After treatment with brine the organic layers were concentrated to give a pale yellow solid that was suspended in dry toluene (15 mL). Then *t*BuOH (1.87 mL, 19.6 mmol) was added and the suspension was refluxed for 1 h, becoming a pale yellow solution soon after heating started. After solvent evaporation the crude was purified by chromatography to give **27** (2.26 g, 75%) as a pale yellow oil and starting acid (474 mg, 20%), with a 94% overall yield based on unrecovered starting material. R_f 0.42 (PE/Et_2O 7 : 3, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 2971, 2891, 1717, 1496, 1368, 1322, 1205, 1148. δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.45 (9 H, s, (CH_3)$_3$C), 3.54 (2 H, s, COCH_2CO), 3.77 (3 H, s, OCH_3), 4.58 (2 H, s, ArOCH_2CO), 6.83 (4 H, s, aromatics). δ_C(75 MHz; $CDCl_3$; Me_4Si) 28.0 (3 C, (*C*H$_3$)$_3$C), 47.4 (CO*C*H$_2$CO), 55.7 (O*C*H$_3$), 73.2 (ArO*C*H$_2$), 82.3 (O*C*(CH$_3$)$_3$), 114.8 and 115.5 (2 × 2 C, aromatic *C*H), 151.7 and 154.6 (2 C, aromatic *C*), 165.9 (*C*O$_2$*t*Bu), 201.3 (*C*OCH$_2$O) ppm. GC-MS: unsuitable for this analysis. *m*/*z* (ESI$^-$): 279.1245 (M – H$^+$. $C_{15}H_{19}O_5$ requires 279.1232.

***tert*-Butyl 4-(benzyloxycarbonylamino)butanoate 29**

a) Formation of **28**: a solution of γ-aminobutyric acid (5.22 g, 50.6 mmol) in 2 M NaOH (25 mL) was cooled to 0 °C and treated with benzyl chloroformate (8.23 mL, 55.6 mmol), while pH is maintained around 10 by continuous addition of 3 M NaOH. After 15 min the reaction was allowed to stir at room temp for 4.5 h. After two extractions with Et_2O, the pH of the aqueous solution was adjusted to 1.5 by addition of 6 M HCl. After having saturated with solid NaCl compound **28** was extracted with AcOEt (**28** is not soluble enough in Et_2O). The combined organic layers were washed with brine, dried and concentrated.

The oily residue was taken up with Et_2O and the solvent removed again to give a white solid (10.01 g) which was directly submitted to the esterification. R_f 0.48 (PE/AcOEt 4 : 6 + 1% AcOH, **a** or **b**). b) Formation of **29**: compound **28** from the above reaction was dissolved in dry CH_2Cl_2 (100 mL). After addition of *t*BuOH (14.5 mL, 151.7 mmol) and 4-dimethylaminopyridine (618 mg, 5.06 mmol), the solution was cooled to 0 °C before adding dicyclohexylcarbodiimide (12.52 g, 60.7 mmol). A white solid suddenly precipitate. After 1 h the reaction was allowed to stir vigorously at room temp. for 8 h. Dicyclohexylurea was filtered and washed with AcOEt. The filtrate was washed with 1 M HCl, brine, 5% aqueous $NaHCO_3$ and again with brine. After solvent removal the crude was purified by chromatography (PE/AcOEt 85 : 15 → 75 : 25) to give a colourless oil that becomes a solid when stored at −25 °C (12.61 g, 85% from **27**). R_f 0.47 (PE/AcOEt 8 : 2, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 3668, 3446, 2968, 1709, 1499, 1366, 1248, 1148. δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.44 (9 H, s, $(CH_3)_3C$), 1.80 (2 H, quintet, *J* 7.1, $ZNHCH_2CH_2CH_2$), 2.27 (2 H, t, *J* 7.2, $ZNHCH_2CH_2CH_2$), 3.24 (2 H, q, *J* 6.5, $ZNHCH_2CH_2CH_2$), 4.89 (1 H, br s, N*H*), 5.09 (2 H, s, CH_2O), 7.31–7.37 (5 H, m, aromatics). δ_C(75 MHz; $CDCl_3$; Me_4Si) 25.1 ($ZNHCH_2CH_2CH_2$), 28.0 (3 C, $(CH_3)_3C$), 32.7 ($ZNHCH_2CH_2CH_2$), 40.4 ($ZNHCH_2CH_2CH_2$), 66.5 (CH_2O), 80.4 ($OC(CH_3)_3$), 127.9 (2 C, *C*H *ortho* of Ph), 128.4 (3 C, *C*H *meta* and *para* of Ph), 136.5 (*C ipso* of Ph), 156.4 (CO_2Bn), 172.5 (CO_2tBu) ppm. GC-MS: R_t 8.24 min; *m*/*z* (EI) 237 (M^+ - 56, 5.0%), 146 (5.1), 112 (6.1), 108 (42), 107 (30), 102 (9.7), 92 (8.7), 91 (100), 84 (12), 79 (7.1), 65 (9.1), 57 (30), 56 (6.1), 41 (13). *m*/*z* (ESI^-): 292.1556 ($M - H^+$. $C_{16}H_{22}NO_4$ requires 292.1549).

tert-Butyl 4-aminobutanoate 30

A solution of **30** (580 mg, 1.22 mmol) in methanol (5 mL) was treated with Pd/C (10%; 59 mg) and hydrogenated. After 1 h the catalyst was filtered over a celite pad and washed with CH_2Cl_2/MeOH 8 : 2. The solvent was carefully evaporated. Due to the volatility of the product, crude **30** was not dried under vacuum. It was actually transferred into a volumetric flask and diluted with THF to give a 0.33 M solution (concentration based on a supposed 100% yield in the hydrogenolysis), that was used as such for the formation of **16ab** and **16d**. R_f 0.04 (AcOEt/MeOH 8 : 2, **c**). GC-MS: R_t 1.57 min; *m*/*z* (EI) 159 (M^+, 0.065), 103 (46), 102 (36), 87 (5.9), 86 (100), 85 (7.6), 84 (60), 69 (43), 59 (6.4), 58 (6.8), 57 (95), 56 (26), 44 (17), 43 (39), 42 (11), 41 (69), 39 (16).

t-Butyl 6,7,8,9-tetrahydro-2-methyl-3-octyl-4,9-dioxo-4*H*-pyrido[1,2-*a*]pyrimidine-8-carboxylate 31

A solution of **16ab** (113 mg, 259 µmol) in dry THF (3 mL) was treated with *t*BuOK (58 mg, 518 µmol) at room temp. The initial pale yellow solution suddenly became brick red and went back to yellow after 10 min. After 0.5 h the reaction was complete. The solution was diluted with saturated aq NH_4Cl, extracted with Et_2O, washed with brine and concentrated to give a gold yellow oil. Due to the instability of **31** under chromatographic conditions, it was partially characterized only as crude derivative and then directly submitted to the decarboxylation procedure. R_f 0.44 (PE/Me_2CO 8 : 2, **a**, **b** or **c**). δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.88 (3 H, t, *J* 6.8, $CH_3(CH_2)_7$), 1.18–1.52 (12 H, m, $CH_3(CH_2)_6$), 1.56 (9 H, s, $(CH_3)_3C$), 2.40 (3 H, s, CH_3C-N), 2.55 (2 H, t, *J* 7.8, $CH_2(CH_2)_6CH_3$), 2.64 (2 H, t, *J* 7.0, CH_2CH_2N), 4.13 (2 H, t, *J* 7.0, CH_2CH_2N), 12.06 (1 H, s, O*H*). δ_C(75 MHz; $CDCl_3$) 14.1 ($CH_3(CH_2)_7$), 22.6 (2 C, CH_3C-N and $CH_3CH_2(CH_2)_6$), 26.8, 28.2, 28.3, 29.3, 29.5, 29.8 and 31.9 (7 C, 6 CH_2 of octyl and CH_2CH_2N), 28.1 (3 C, $(CH_3)_3C$), 38.5 (CH_2N), 83.6 ($(CH_3)_3C$), 104.8 (=CCO_2tBu) 126.5 (C(C=O)N), 145.7 (C=N), 155.9 (CH_3C-N), 157.8 (C(C=O)N), 161.0 (=COH), 170.3 (CO_2tBu). GC-MS: under the analysis conditions compound **31** underwent a clean decarboxylation. Retention time (9.75 min) and mass spectrum (290 (M^+)) resulted superimposable with the ones of ketone **35**.

Ethyl 2-methyl-3-octyl-4,9-dioxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-8-carboxylate 32

Exactly the same procedure described above for the preparation of **31** was followed, starting from **16ac** (102 mg, 250 µmol) and using *t*BuONa (60 mg, 624 mmol) instead of *t*BuOK. Due to the instability of **32** under chromatographic conditions, it was directly submitted to the decarboxylation procedure. R_f 0.11 (PE/Me_2CO 8 : 2, **a** or **c**). GC-MS: under the analysis conditions compound **32** underwent a clean decarboxylation. Retention time (9.75 min) and mass spectrum (290 (M^+, 17)) resulted superimposable with the ones of ketone **35** and compound **31**.

2-Methyl-3-octyl-7,8-dihydro-6*H*-pyrido[1,2-*a*]pyrimidine-4,9-dione 35

a) From **31**: a solution of crude **31** in a 0.5 M solution of HCl in dioxane was stirred 2.5 h at 60 °C and then refluxed for additional 2 h. The solution was poured into 5% aq $(NH_4)H_2PO_4$ and extracted with Et_2O. After washing with brine and solvent removal chromatography with PE/Et_2O 8 : 2 → 1 : 1 furnished **35** (49 mg) as a pale yellow oil in 65% overall yield from **16ab**. b) From **32**: crude **32** was treated with 6 M HCl and refluxed for 5 h. The pH was adjusted to 7 by addition of 3 M NaOH and K_2HPO_4. Extraction with AcOEt and chromatography as above furnished **35** (31 mg) as a pale yellow oil in 43% overall yield from **16ac**. R_f 0.24 (PE/Me_2CO 8 : 2, **c**). $\nu_{max}(CHCl_3)/cm^{-1}$ 2921, 2851, 1648, 1594, 1390, 1177. Note that NMR spectra show a 82 : 18 mixture of ketone (k) and enol (e). δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.86 (3 H (k + e), t, *J* 6.8, $CH_3(CH_2)_7$), 1.20–1.53 (12 H (k + e), m, $CH_3(CH_2)_6$), 2.27–2.35 (2 H (k), m, $CH_2CH_2CH_2N$), 2.28 (3 H (e), s, CH_3C-N), 2.40 (3 H (k), s, CH_3C-N), 2.47–2.58 (2 H (k + e) and 2 H (e), m, $CH_2(CH_2)_6CH_3$ and C(OH)=CH-CH_2), 2.84 (2 H (k), t, *J* 6.6, $CH_2CH_2CH_2N$), 4.10 (2 H (e), t, *J* 7.4, CH_2CH_2N), 4.18 (2 H (k), centre of m, $CH_2CH_2CH_2N$), 5.66 (1 H (e), t, *J* 4.6, CH=COH), 12.06 (1 H (e), s, O*H*). δ_C(75 MHz; $CDCl_3$) 14.1 (k + e) ($CH_3(CH_2)_7$), 20.2 (e) and 20.5 (k) (CH_2CH_2N), 21.0 (e) and 21.5 (k) (CH_3C-N), 22.6 (k + e) ($CH_3CH_2CH_2$), 26.6 (e) and 26.9 (k) ($CH_2(CH_2)_6CH_3$), 27.9 (k) and 28.2 (e) ($CH_2CH_2(CH_2)_5CH_3$), 29.2, 29.4, 29.5 and 29.8 (k + e) (3 C, $(CH_2)_2(CH_2)_3(CH_2)_2CH_3$), 31.83 (k) and 31.85 (e) ($CH_3CH_2CH_2$), 37.1 (k) and 39.0 (e) (CH_2N), 42.3 (k) (CH_2CO), 103.7 (e) (CH=CCO) 124.6 (e) and 129.0 (k) (C(C=O)N), 145.1 (k) and 146.8 (e) (C=N), 156.2 (e), 157.9 (k) and 161.1 (k + e) (CH_3C-N and C(C=O)N), 161.4 (e) (=COH), 189.6 (k) (CH_2CO). GC-MS: R_t 8.24 min; *m*/*z* (EI) 290 (M^+ - 56, 10), 219 (7.6), 205 (19), 193 (12), 192 (100), 191 (38), 164

(9.8), 163 (40), 135 (6.0), 96 (14), 69 (13), 68 (9.3), 67 (9.8), 55 (18), 53 (12), 43 (7.6), 42 (13), 41 (29), 39 (7.9). *m/z* (ESI⁻): 289.1921 (M – H⁺. $C_{17}H_{25}N_2O_2$ requires 289.1916.

3-(3-(*tert*-Butoxycarbonyl)propyl)-6-methyl-5-octyl-3*H*-pyrimidin-4-one 36

A solution of **16ab** (82 mg, 188 µmol) in dry DMF (1 ml) was treated with NaH (60% in mineral oil, 9.0 mg, 225 µmol) and heated at 70 °C overnight. The mixture was diluted with 5% aq $(NH_4)H_2PO_4$ and extracted with Et_2O, washed with brine and concentrated. Chromatography with PE/Et_2O 6 : 4 → Et_2O gave **36** (41 mg) as a pale yellow oil (60%). R_f 0.56 (Et_2O, **a**). $\nu_{max}(CHCl_3)/cm^{-1}$ 2922, 2850, 1720, 1649, 1602, 1415, 1367, 1145. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.86 (3 H, t, *J* 6.6, CH_3(CH$_2$)$_7$), 1.17–1.49 (12 H, m, CH$_3$(CH_2)$_6$), 1.42 (9 H, s, (CH_3)$_3$C), 2.00 (2 H, quintet, *J* 7.1, CH$_2$CH_2CH$_2$N), 2.26 (2 H, t, *J* 6.6, CH_2CH$_2$CH$_2$N), 2.28 (3 H, s, CH_3C-N), 2.48 (2 H, t, *J* 7.6, CH_2(CH$_2$)$_6$CH$_3$), 3.91 (2 H, centre of m, CH_2N), 7.89 (1 H, s, C*H*C=N). δ_C(75 MHz; $CDCl_3$) 14.1 (*C*H$_3$(CH$_2$)$_7$), 21.2 (*C*H$_3$C-N), 22.6 (CH$_3$*C*H$_2$(CH$_2$)$_6$), 24.3 (CH$_2$*C*H$_2$CH$_2$N), 26.2 (*C*H$_2$(CH$_2$)$_6$CH$_3$), 28.06 (3 C, (*C*H$_3$)$_3$C), 28.09 (CH$_2$*C*H$_2$(CH$_2$)$_5$CH$_3$), 29.3, 29.4 and 29.8 (3 C, (CH$_2$)$_2$(*C*H$_2$)$_3$(CH$_2$)$_2$CH$_3$), 31.8 and 32.0 (2 C, CH$_3$CH$_2$*C*H$_2$(CH$_2$)$_5$ and *C*H$_2$CH$_2$CH$_2$N), 46.3 (*C*H$_2$N), 80.8 ((CH$_3$)$_3$*C*), 125.6 (*C*(C=O)N), 146.9 (*C*H=N), 158.6 (CH$_3$*C*-N), 161.4 (C(*C*=O)N), 171.8 (*C*O$_2$*t*Bu). GC-MS: R$_t$ 10.12 min; *m/z* (EI) 364 (M⁺, 1.5%), 308 (11), 293 (15), 292 (5.5), 291 (28), 223 (7.8), 211 (12), 210 (100), 192 (34), 164 (8.4), 124 (7.6), 123 (11), 69 (6.2), 41 (9.0). *m/z* (ESI⁺): 365.2792 (M + H⁺. $C_{21}H_{37}N_2O_3$ requires 365.2804).

Methyl 3-butyl-6-methyl-5-octyl-3*H*-pyrimidin-4-one-2-carboxylate 39

MeONa (25 mg, 463 µmol) was added to a solution of **16aa** (107 mg, 305 µmol) in dry methanol (4.5 mL) and the suspension was stirred for 1.25 h at room temp. The reaction was partitioned between 5% aq $(NH_4)H_2PO_4$ and Et_2O and extracted as usual. After washing with brine and solvent removal, chromatography with PE/Et_2O 6 : 4 gave **39** (84 mg, 82%) as a pale yellow oil. R_f 0.24 (PE/Et_2O 7 : 3, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 2960, 2920, 2855, 1737, 1650, 1600, 1440, 1381, 1105. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.88 (3 H, t, *J* 6.8, CH_3(CH$_2$)$_7$), 0.94 (3 H, t, *J* 7.4, CH_3(CH$_2$)$_3$N), 1.21–1.52 (14 H, m, CH$_3$(CH_2)$_6$ and CH$_3$CH_2(CH$_2$)$_2$N), 1.65–1.75 (2 H, m, CH$_3$CH$_2$CH_2CH$_2$N), 2.32 (3 H, s, CH_3C-N), 2.53 (2 H, t, *J* 7.5, CH_2(CH$_2$)$_6$CH$_3$), 4.00 (3 H, s, OCH_3), 4.00 (2 H, t, CH_2N). GC-MS: R$_t$ 9.24 min; *m/z* (EI) 336 (M⁺, 3.7%), 321 (7.5), 281 (8.5), 278 (13), 277 (64), 265 (5.1), 251 (9.9), 239 (15), 238 (100), 237 (7.1), 209 (5.5), 195 (12), 193 (5.1), 183 (16), 182 (23), 181 (18), 179 (36), 177 (7.2), 163 (8.4), 151 (9.0), 150 (35), 149 (14), 138 (6.7), 137 (8.9), 135 (14), 124 (41), 123 (25), 122 (18), 121 (16), 108 (5.3), 96 (41), 95 (7.2), 94 (7.1), 93 (6.8), 81 (8.2), 80 (5.8), 79 (8.9), 69 (11), 68 (5.7), 67 (21), 59 (6.9), 57 (15), 56 (9.9), 55 (48), 54 (8.1), 53 (25), 43 (27), 42 (34), 41 (57), 39 (3.4). *m/z* (ESI⁻) 335.2342 (M – H⁺. $C_{19}H_{31}N_2O_3$ requires 335.2335).

3-Butyl-6-methyl-5-octyl-3*H*-pyrimidin-4-one 40

A solution of **16aa** (81 mg, 231 µmol) in dry DMF (1 mL) was treated at 0 °C with NaH (60% in mineral oil, 19 mg, 475 µmol). After 5 min the resulting red solution was stirred at room temp. for 1 h. The reaction was partitioned between 5% aq $(NH_4)H_2PO_4$ and Et_2O and extracted as usual. The organic layers were washed with H_2O and then with brine. After solvent removal chromatography with Et_2O gave **40** (56 mg, 87%) as a pale yellow oil. R_f 0.41 (Et_2O, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 2920, 2851, 1647, 1603, 1438, 1234. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.88 (3 H, t, *J* 6.8, CH_3(CH$_2$)$_7$), 0.96 (3 H, t, *J* 7.2, CH_3(CH$_2$)$_3$N), 1.20–1.52 (14 H, m, CH$_3$(CH_2)$_6$ and CH$_3$CH_2(CH$_2$)$_2$N), 1.72 (2 H, centre of m, CH$_3$CH$_2$CH_2CH$_2$N), 2.30 (3 H, s, CH_3C-N), 2.51 (2 H, t, *J* 8.1, CH_2(CH$_2$)$_6$CH$_3$), 3.87 (2 H, t, *J* 7.5 CH_2N), 7.89 (1 H, s, C*H*=N). δ_C(75 MHz; $CDCl_3$) 13.6 (*C*H$_3$(CH$_2$)$_3$N), 14.1 (*C*H$_3$(CH$_2$)$_7$), 19.9 (CH$_3$*C*H$_2$(CH$_2$)$_2$N), 21.2 (*C*H$_3$C-N), 22.6 (CH$_3$*C*H$_2$(CH$_2$)$_6$), 26.2 (*C*H$_2$(CH$_2$)$_6$CH$_3$), 28.1 (CH$_2$*C*H$_2$(CH$_2$)$_5$CH$_3$), 29.3, 29.4 and 29.8 (3 C, (CH$_2$)$_2$(*C*H$_2$)$_3$(CH$_2$)$_2$CH$_3$), 31.2 (CH$_3$CH$_2$*C*H$_2$CH$_2$N), 31.8 (CH$_3$CH$_2$*C*H$_2$(CH$_2$)$_5$), 47.1 (*C*H$_2$N), 125.6 (*C*(C=O)N), 146.8 (*C*H=N), 158.4 (CH$_3$*C*-N), 161.4 (C(*C*=O)N). GC-MS: R$_t$ 8.37 min; *m/z* (EI) 278 (M⁺, 5.8%), 263 (6.7), 207 (9.2), 193 (17), 181 (12), 180 (100), 179 (32), 163 (6.5), 151 (9.7), 138 (40), 137 (15), 125 (15), 124 (41), 123 (51), 96 (11), 68 (5.5), 67 (7.6), 57 (12), 55 (23), 54 (5.2), 53 (13), 43 (13), 42 (22), 41 (40), 39 (8.3). *m/z* (ESI⁺) 279.2428 (M + H⁺. $C_{17}H_{31}N_2O$ requires 279.2436).

General procedure for the conversion of ethyl ester into amide or hydroxamate

The nitrogen reagent, as the corresponding hydrochloride (1.20 mmol), was put in a flask with 2 mL of dry CH_2Cl_2. After cooling to 0 °C a solution of Me_3Al (2 M in toluene, 600 µl) was added dropwise. At the end a colorless solution was obtained which was stirred ar room temp. for 15 min. Half of this solution was transferred into another flask and a solution of **16cd** (300 µmol) in CH_2Cl_2 (1 mL) was added dropwise. The mixture was stirred at room temp. for 4 h and then poured into a separatory funnel containing 1 M HCl and extracted with CH_2Cl_2. After washing with brine and solvent removal the crude was purified by chromatography.

5-Isobutyl-3-(4-methoxybenzyl)-*N*,6-dimethyl-3*H*-pyrimidin-4-one-2-carboxamide 49

Nitrogen nucleophile: methylamine hydrochloride. Chromatography: PE/AcOEt 8 : 2 → 75 : 25 gave **49** as a white solid (82%). Mp 91.8–93.9 °C (PE/AcOEt). R_f 0.15 (PE/AcOEt 7 : 3, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 3431, 2996, 2949, 1654, 1505, 1225, 1168, 1024. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.92 (6 H, d, *J* 6.9, (CH_3)$_2$CH), 1.97 (1 H, nonuplet, *J* 6.8, (CH$_3$)$_2$C*H*), 2.26 (3 H, s, CH_3C-N), 2.44 (2 H, d, *J* 7.2, CH_2CH), 2.91 (3 H, d, *J* 5.1, CH_3NH), 3.76 (3 H, s, OCH_3), 5.77 (2 H, s, CH_2Ar), 6.79 (2 H, dt, *J* 8.7, 2.5, *H ortho* to OCH$_3$), 7.27 (2 H, dt, *J* 8.7, 2.6, *H meta* to OCH$_3$), 7.39 (1 H, br d, *J* 3.9, N*H*). δ_C(75 MHz; $CDCl_3$) 21.4 (*C*H$_3$C-N), 22.6 (2 C, (*C*H$_3$)$_2$CH), 26.4 (*C*H$_3$NH), 27.9 ((CH$_3$)$_2$*C*H), 35.6 (*C*H$_2$CH), 45.7 (*C*H$_2$N), 55.2 (O*C*H$_3$), 113.7 (2 C, *C*H *ortho* to OCH$_3$), 126.3 (*C*(C=O)N), 129.5 (*C para* to OCH$_3$), 129.8 (2 C, *C*H *meta* to OCH$_3$), 147.3 (*C*=N), 156.4 (CH$_3$*C*-N), 158.9 (*C*-OCH$_3$), 161.7 (C(*C*=O)N), 162.4 (*C*ONHCH$_3$). GC-MS: R_t 10.78 min; *m/z* (EI) 343 (M⁺, 18%), 286 (14), 285 (12), 192 (5.5), 150 (10), 122 (12), 121 (100), 91 (5.2), 78 (5.5), 77 (8.0). *m/z* (ESI⁻) 342.1816 (M – H⁺. $C_{19}H_{24}N_3O_3$ requires 342.1818).

N-(Benzyloxy)-5-isobutyl-3-(4-methoxybenzyl)-6-methyl-3*H*-pyrimidin-4-one-2-carboxamide 50

Nitrogen nucleophile: *O*-benzylhydroxylamine hydrochloride. Chromatography: PE/AcOEt 8 : 2 → 75 : 25 gave **50** as a pale yellow oil (80%). R_f 0.30 (PE/AcOEt 7 : 3, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 3030, 2995, 2952, 1703, 1652, 1503, 1222. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.91 (6 H, d, *J* 6.6, $(CH_3)_2CH$), 1.95 (1 H, nonuplet, *J* 6.8, $(CH_3)_2CH$), 2.16 (3 H, s, CH_3C-N), 2.40 (2 H, d, *J* 7.8, CH_2CH), 3.77 (3 H, s, OCH_3), 4.88 (2 H, s, CH_2ONHCO), 5.71 (2 H, s, CH_2Ar), 6.81 (2 H, dt, *J* 8.7, 2.6, *H ortho* to OCH_3), 7.25 (2 H, dt, *J* 8.4, 2.6, *H meta* to OCH_3), 7.30–7.37 (5 H, m, Ph) 9.54 (1 H, br s, N*H*). δ_C(75 MHz; $CDCl_3$) 21.2 (CH_3C-N), 22.6 (2 C, $(CH_3)_2CH$), 27.9 ($(CH_3)_2CH$), 35.6 (CH_2CH), 45.3 (CH_2N), 55.2 (OCH_3), 78.4 (CH_2ONHCO), 113.8 (2 C, *C*H *ortho* to OCH_3), 127.1 (*C*(C═O)N), 128.6, 129.3, 129.9 (3 × 2 C, *C*H *ortho* to OMe and *C*H *ortho* and *meta* of Ph), 128.9 (*C*H *para* of Ph), 129.1 (*C para* to OCH_3), 134.8 (*C ipso* of Ph), 145.9 (*C*═N), 156.4 (CH_3C-N), 159.0 (*C*-OCH_3), 159.6 (C(*C*═O)N), 162.1 ($CONHCH_3$). GC-MS: unsuitable for this analysis. *m*/*z* (ESI^-) 434.2065 (M – H^+. $C_{25}H_{28}N_3O_4$ requires 434.2080).

3-Butyl-6-methyl-5-octyl-3*H*-pyrimidin-4-one 51

A solution of benzyl alcohol (116 µl, 1.12 mmol) in dry benzene (1 mL) was treated at 0 °C with NaH (60% in minera oil, 13.4 mg 335 µmol). A solution of **16cd** (100 mg, 279 µmol) in benzene (0.5 mL) was dropped into the benzylate solution, using 1 additional mL of benzene for complete transfer of the substrate. The resulting mixture was refluxed and a very slow azeotropic removal of ethanol was performed, adding additional benzene to avoid to concentrate too much the reaction. After 4 h the reaction was complete and the crude was partitioned between H_2O and Et_2O and extracted. Final washing with brine and solvent removal was followed by a double chromatography: PE/AcOEt 85 : 15 → 8 : 2 and CH_2Cl_2/Et_2O 97 : 3 to give **51** as a pale yellow oil (88 mg, 75%). R_f 0.58 (PE/Et_2O 7 : 3, **a** or **b**). $\nu_{max}(CHCl_3)/cm^{-1}$ 2957, 2866, 1735, 1650, 1597, 1510, 1274, 1248, 1172. δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.94 (6 H, d, *J* 6.6, $(CH_3)_2CH$), 1.97 (1 H, nonuplet, *J* 6.8, $(CH_3)_2CH$), 2.31 (3 H, s, CH_3C-N), 2.45 (2 H, d, *J* 7.2, CH_2CH), 3.74 (3 H, s, OCH_3), 5.26 (2 H, s, CH_2OCO), 5.27 (2 H, s, NCH_2Ph), 6.71 (2 H, dt, *J* 8.7, 3.0, *H ortho* to OCH_3), 7.29 (2 H, dt, *J* 9.0, 3.0, *H meta* to OCH_3), 7.23–7.37 (5 H, m, Ph). δ_C(75 MHz; $CDCl_3$) 21.6 (CH_3C-N), 22.6 (2 C, $(CH_3)_2CH$), 28.0 ($(CH_3)_2CH$), 35.5 (CH_2CH), 46.5 (CH_2N), 55.2 (OCH_3), 68.6 (CH_2OCO), 114.0 (2 C, *C*H *ortho* to OCH_3), 126.4 and 127.9 (2 C, *C*(C═O)N and *C para* to OCH_3), 128.6, 128.9, 129.3 (7 C, *C*H *ortho* to OMe and *C*H of Ph), 133.9 (*C ipso* of Ph), 147.2 (*C*═N), 157.9 (CH_3C-N), 159.2 (*C*-OCH_3), 161.2 (C(*C*═O)N), 161.5 ($CONHCH_3$). GC-MS (based on the usual method but with init. temp. 200 °C, rate 35 °C min^{-1}, final temp. 280 °C): R_t 6.25 min; *m*/*z* (EI) 420 (M^+, 1.2), 329 (16), 193 (13), 165 (14), 122 (14), 121 (100), 91 (17). *m*/*z* (ESI^-) 419.1978 (M – H^+. $C_{25}H_{27}N_2O_4$ requires 419.1971).

Acknowledgements

The authors thank Dr Francesca Musumeci and Ms Federica Gastaldo for their contribution to this work, Chemessentia Srl, Novara (Italy) for financial assistance and Fondazione S. Paolo for a contribution to the purchase of NMR instrument.

Notes and references

1 P. A. Janssen, C. J. Niemegeers, F. Awouters, K. H. Schellekens, A. A. Megens and T. F. Meert, *J. Pharmacol. Exp. Ther.*, 1988, **244**, 685–693.
2 F. H. L. Awouters and P. J. Lewi, *Arzneimittel-Forsch.*, 2007, **57**, 625–632.
3 N. K. Terrett, A. S. Bell, D. Brown and P. Ellis, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1819–1824.
4 D. R. Gehlert, K. Rasmussen, J. Shaw, X. Li, P. Ardayfio, L. Craft, T. Coskun, H. Y. Zhang, Y. Chen and J. M. Witkin, *J. Pharmacol. Exp. Ther.*, 2009, **329**, 429–438.
5 A. Salimbeni, R. Canevotti, F. Paleari, D. Poma, S. Caliari, F. Fici, R. Cirillo, A. R. Renzetti, A. Subissi, L. Belvisi, G. Bravi, C. Scolastico and A. Giachetti, *J. Med. Chem.*, 1995, **38**, 4806–4820.
6 S. P. Chavan and R. Sivappa, *Tetrahedron Lett.*, 2004, **45**, 997–999.
7 A. Jezewski, J. Jurczak, Z. Lidert and C. M. Tice, *J. Heterocycl. Chem.*, 2001, **38**, 645–648.
8 E. C. Taylor, P. Zhou, C. M. Tice, Z. Lidert and R. C. Roemmele, *Tetrahedron Lett.*, 1997, **38**, 4339–4342.
9 W. K. Hagmann, F. Z. Basha, M. Hashimoto, R. B. Frye, S. Kojo and S. M. Hecht, *J. Org. Chem.*, 1981, **46**, 1413–1423.
10 J. P. Jonak, G. C. Hopkins, H. J. Minnemeyer and H. Tickelmann, *J. Org. Chem.*, 1970, **35**, 2512–2516.
11 A. Sitte and H. Paul, *Chem. Ber.*, 1969, **102**, 615–622.
12 E. C. Taylor, H. Zhou and C. M. Tice, *Tetrahedron Lett.*, 1997, **38**, 4339–4342.
13 J. U. Jeong, X. Chen, A. Rahman, D. S. Yamashita and J. I. Luengo, *Org. Lett.*, 2004, **6**, 1013–1016.
14 I. Shcherbakova, G. Huang, O. J. Geoffroy, S. K. Nair, K. Swierczek, M. F. Balandrin, J. Fox, W. L. Heaton and R. L. Conklin, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2537–2540.
15 Y.-L. Zhong, H. Zhou, D. R. Gauthier and D. Askin, *Tetrahedron Lett.*, 2006, **47**, 1315–1317.
16 C. Guo, *Tetrahedron Lett.*, 2010, **51**, 548–549.
17 J. Gabard, M. Dvolaitzky and J. Jacques, *Bull. Chem. Soc. Fr.*, 1964, 27–30.
18 Y. Zhao, J. Zhao, Y. Zhou, Z. Lei, L. Li and H. Zhang, *New J. Chem.*, 2005, **29**, 769–762.
19 L. F. Tietze, A. Bergmann, G. Brill, K. Brüggemann, U. Hartfiel and E. Voss, *Chem. Ber.*, 1989, **122**, 83–94.
20 R. T. Buckler, H. E. Hartzler and B. M. Phillips, *J. Med. Chem.*, 1975, **18**, 509–513.
21 J. B. Bicking, C. M. Robb, E. J. Cragoe, E. H. Blaine, L. S. Watson and M. C. Dunlay, *J. Med. Chem.*, 1983, **26**, 335–341.
22 D. L. Temple, J. P. Yevich, R. R. Covington, C. A. Hanning, R. J. Seidehamel, H. K. Mackey and M. J. Bartek, *J. Med. Chem.*, 1979, **22**, 505–510.
23 Y. Yamamoto, Y. Morita and K. Minami, *Chem. Pharm. Bull.*, 1986, **34**, 1980–1986.
24 D. Achakzi, M. Ertas, R. Appel and H. Wamhoff, *Chem. Ber.*, 1981, **114**, 3188–3194.
25 H. Wamhoff, G. Hendrikx and M. Ertas, *Liebigs Ann. Chem.*, 1982, 489–498.
26 R. Appel, *Angew. Chem., Int. Ed. Engl.*, 1975, 801–811.
27 L. Banfi, G. Cascio, C. Ghiron, G. Guanti, E. Manghisi, E. Narisano and R. Riva, *Tetrahedron*, 1994, **50**, 11983–11994.
28 H. E. Carter, R. L. Frank and H. W. Johnston, *Org. Synth., Coll. Vol. 3*, 1955, **23**, 167–169.
29 M. Schmidt, E. Barbayianni, I. Fotakopoulou, M. Höhne, V. Constantinou-Kokotou, U. T. Bornscheuer and G. Kokotos, *J. Org. Chem.*, 2005, **70**, 3737–3740.
30 T. Breining, I. Hermecz, B. Podanyi and J. Sessi, *J. Heterocycl. Chem.*, 1985, **22**, 1253–1259.
31 M. D. Burke and S. L. Schreiber, *Angew. Chem., Int. Ed.*, 2004, **43**, 46–58.

