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Multiple pathways in the synthesis of new annelated analogues of 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (emivirine)

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Condensation of 3-(3,5-dimethylphenyl)-2-oxocyclopentanecarboxamide (**11**) with oxalyl chloride and condensation of ethyl 2-benzylamino-5-methyl-3-phenylcyclopent-1-enecarboxylate (**17a**) with trimethylsilyl isothiocyanate gave 7-(3,5-dimethylphenyl)-6,7-dihydro-5*H*-cyclopenta[*e*][1,3]oxazine-2,4-dione (**12**) and 1-benzyl-5-methyl-7-phenyl-2-thioxo-1,2,3,5,6,7-hexahydrocyclopentapyrimidin-4-one (**18a**), respectively. Acid catalyzed ring-closure of 6-(4-methyl-1-phenylpent-3-enyl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (**26**) and radical mediated ring-closure of 1,3-bis(benzyloxymethyl)-5-bromo-6-(1-phenylbut-3-enyl)-1*H*-pyrimidine-2,4-dione (**32a**) gave 5,5-dimethyl-8-phenyl-5,6,7,8-tetrahydro-1*H*-quinazoline-2,4-dione (**28**) and 1,3-bis(benzyloxymethyl)-5-methyl-7-phenyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (**33**), respectively. Annelated emivirine analogues 7-(3,5-dimethylphenyl)-1-ethoxymethyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (**4**), 1-ethoxymethyl-5,5-dimethyl-8-phenyl-5,6,7,8-tetrahydro-1*H*-quinazoline-2,4-dione (**5**) and 1-ethoxymethyl-5-methyl-7-phenyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (**6**) were obtained in few steps from **12**, **28** and **18a/33**, respectively. These new analogues can be considered as conformationally locked analogues of emivirine. However, the compounds **4**–**6** showed lower activities against HIV-1 than emivirine and it is concluded that the locked conformation disfavours activity against HIV-1.

Introduction

6-Benzyl-1-(ethoxymethyl)-5-isopropyluracil[1] (emivirine, formerly MKC 442, **1**, Fig. 1) belongs to the non nucleoside[2] class (NNRTIs) of inhibitors that targets the retrovirus HIV-1 by binding allosterically to a hydrophobic pocket in the enzyme reverse transcriptase (RT).[3] The discovery of the binding site was reported in 1989 where the emivirine analogue 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymidine,[4] HEPT was found to have a different inhibition mechanism than the known nucleoside reverse transcriptase inhibitors (NRTIs).[5] Triangle Pharmaceuticals halted development of emivirine in January 2002 when a comparative study showed emivirine to be less potent than other antiretrovirals.[6] The importance of finding new analogues with higher binding affinity is obvious, because HIV-1 strains with RT mutations are shown to emerge rapidly upon treatment with existing drugs.[7] The mutated strains generally show good resistance to emivirine and other NNRTIs, but small changes in these 'first generation' NNRTIs have reduced the resistance.

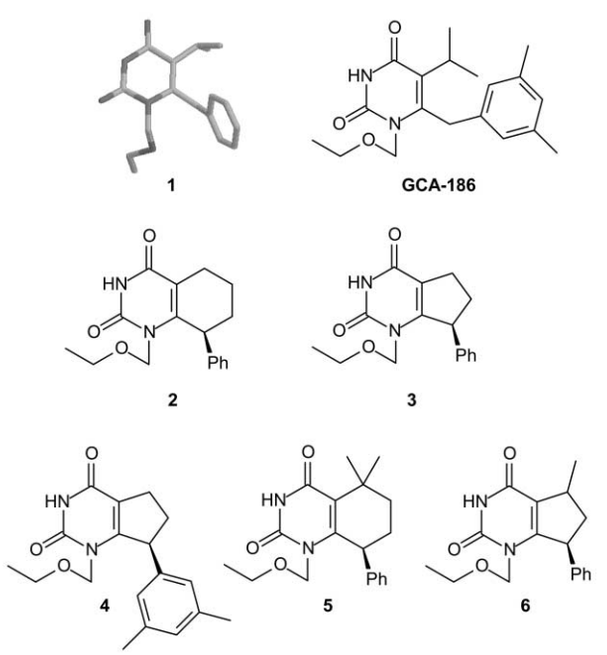

Fig. 1 Compound **1**: crystal structure of emivirine when bound to RT.[3] GCA-186. Compounds **2** and **3**: structures of previously synthesized, conformationally restricted emivirine analogues.[9] Compounds **4**,**5** and **6**: structures of target molecules.

In this paper, we investigate the effect of making conformationally restricted analogues of emivirine by locking the benzylic group in the C6 position. The energy gain from diminished flexibility (increase in ΔS) can lead to more active inhibitors, as observed in the inhibitor/enzyme system of imidazo[1,2-*a*]-pyridines and the gastric H^+/K^+-ATPase.[8]

Previously we described the syntheses of **2** and **3** (Fig. 1).[9] Compounds **2** and **3** showed *ca.* 10^3-fold (Table 1) lower activity than emivirine. It was believed that the low activity reflected the missing steric bulkyness around C5 of the uracil.[4] To investigate this hypothesis, we have now synthesized compounds **5** and **6** with extra methyl groups next to the C5 position of the uracil (Fig. 1).

Furthermore we have synthesized compound **4** which has 3,5-dimethyl substituents on its phenyl ring. This substitution pattern is also found in GCA-186 (Fig. 1) and for the latter it is the only difference from emivirine. This change of molecular structure tolerates the presence of Y181C or K103N RT mutations better than emivirine itself.[10]

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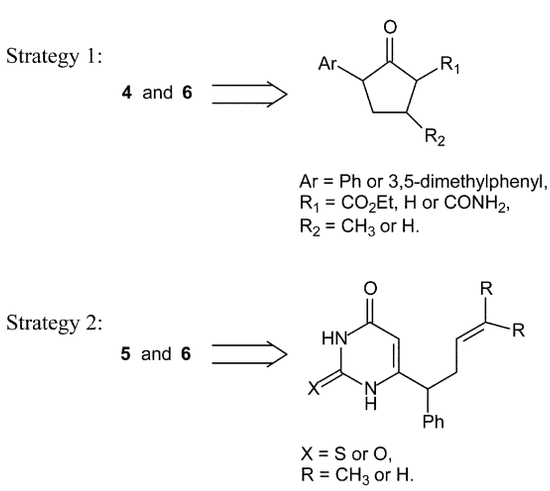
Table 1 Anti-HIV-1 activity of emivirine analogues

Compound	EC_{50}[d]/μM (HIV-III_B)	EC_{50}[d]/μM (HIV-$III_{B\text{-}Y181C}$)	EC_{50}[e]/μM
2[a]	29	NT[f]	>100
3[a]	36	NT[f]	>100
4[a]	0.35	7	>100
5[a]	9	NT[f]	>100
6[b]	4	NT[f]	>100
6[c]	24	NT[f]	>100
Emivirine	0.02	44	>100

[a] Racemic mixture. [b] *Cis*/*trans* ratio of 1 : 1. [c] *Cis*/*trans* ratio of 4 : 1. [d] 50% effective concentration. [e] 50% cytotoxic concentration. [f] Not tested.

Results and discussion

In order to synthesize target molecules (TM) **4**–**6** several synthetic strategies were considered. The bicyclic uracil derivatives **2** and **3** were synthesized by firstly building up the aliphatic ring followed by a ring-closing reaction to give the final bicyclic uracil derivatives.[9] In spite of an often low yielding ring-closing step this strategy was used for TM **4** and **6** (Scheme 1, strategy 1). Another strategy considered was to synthesize the uracil ring and then ring-close to the C5 position of the uracil to form the bicyclic system. The second strategy was used for TM **5** and **6** (Scheme 1, strategy 2).

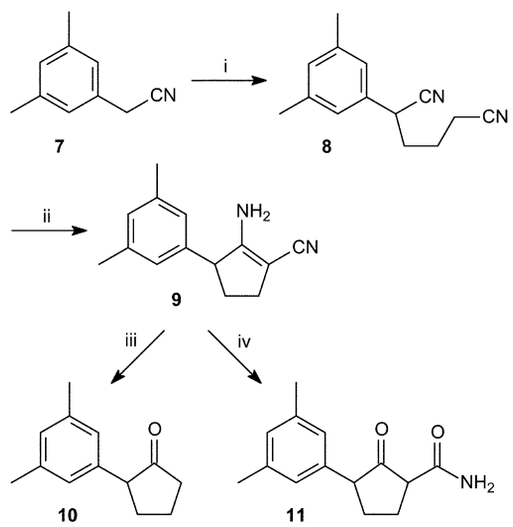


Scheme 1

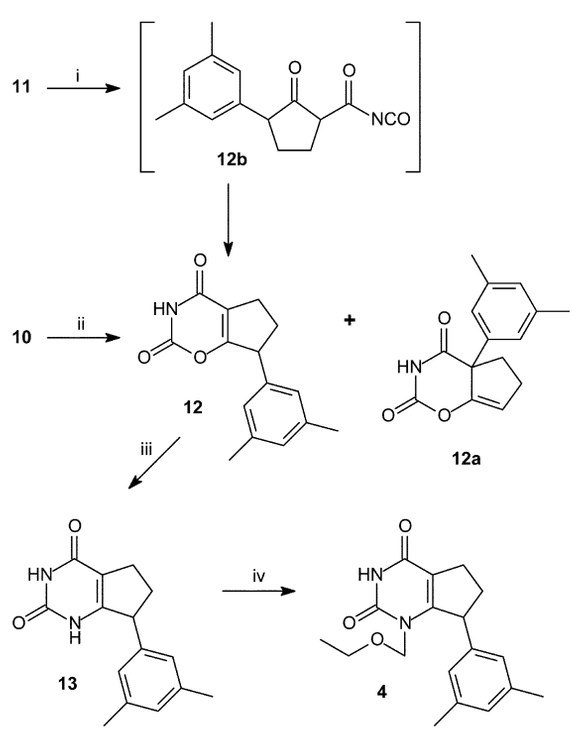
For the synthesis of TM **4**, the key intermediate 2-amino-1-cyano-3-(3,5-dimethylphenyl)cyclopent-1-ene (**9**) was synthesized in two steps from (3,5-dimethylphenyl)acetonitrile (**7**) (Scheme 2). First **7** was α-alkylated using a modified procedure of Wallingford *et al.*[11] to give 2-(3,5-dimethylphenyl)hexanedinitrile (**8**) in 61% yield. A subsequent ring-closure reaction with sodium hydride in a Thorpe–Ziegler reaction using the method of Kulp *et al.*[12] afforded **9** in 93% yield.

Compound **9** was then hydrolyzed in two different ways yielding two useful intermediates (Scheme 2) which could both be used for the synthesis of the key intermediate **12** of TM **4**. Treatment of **9** with conc. HCl in acetic acid under reflux[13] produced 2-(3,5-dimethylphenyl)cyclopentanone (**10**) in 55% yield, whereas conc. sulfuric acid at rt[14] gave 3-(3,5-dimethylphenyl)-2-oxocyclopentanecarboxamide (**11**) in 57% yield.

7-(3,5-Dimethylphenyl)-6,7-dihydro-5*H*-cyclopenta[*e*][1,3]-oxazine-2,4-dione (**12**) was synthesized from **10** by treatment with *N*-(chlorocarbonyl)isocyanate[15] in 35% yield (Scheme 3). The isomeric oxazine **12a** was isolated in 11% yield as a by-product because the aromatic conjugated enol tautomer is most likely the preferred enol tautomer of **10**, which undergoes a reaction with *N*-(chlorocarbonyl)isocyanate. The isomeric oxazine **12a** being the minor product is probably due to steric reasons. Compound **11** was reacted with oxalyl chloride to form **12** in 40% yield. A possible intermediate in the latter reaction is



Scheme 2 i, 1. NaOEt, $EtOCO_2Et$, $Cl(CH_2)_3CN$; 2. KOH–EtOH, 61%; ii, NaH, dioxane, 93%; iii, conc. HCl, AcOH, reflux, 55%; iv, conc. H_2SO_4, rt, 57%.

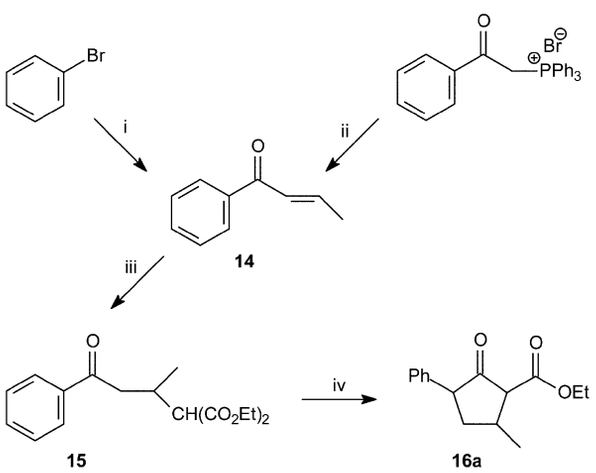


Scheme 3 i, $(CO)_2Cl_2$, DCE, 40%; ii, ClCONCO, 35% of **12** and 11% of **12a**; iii, conc. NH_3, 90%; iv, BSA, $CHCl_3$, $ClCH_2OEt$, 80%.

the 2-oxo-3-phenyl-cyclopentanecarbonyl isocyanate (**12b**), which is the typical product of the reaction of an amide with oxalyl chloride.[16] The conversion from a β-ketoamide to an oxazine is, to our knowledge, not reported elsewhere in the literature.

The oxazine **12** was reacted with 25% aqueous ammonia[17] to give 7-(3,5-dimethylphenyl)-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (**13**) in 90% yield (Scheme 3). Compound **13** was silylated with *N,O*-bis(trimethylsilyl)acetamide (BSA) and alkylated with chloromethyl ethylether[18] to give TM 7-(3,5-dimethylphenyl)-1-ethoxymethyl-1,5,6,7-tetrahydro-cyclopentapyrimidine-2,4-dione (**4**) in 80% yield.

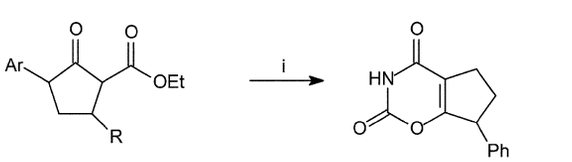
With the 5-methyl group in TM **6** compared to TM **4**, it was not straightforward to synthesize the dinitrile corresponding to compound **8**. Therefore we used another strategy where the key intermediate ethyl 5-methyl-2-oxo-3-phenylcyclopentanecarboxylate (**16a**) was synthesized in 2 steps from *trans*-1-phenylbut-2-en-1-one (**14**). Compound **14** was obtained from either phenacyl triphenylphosphonium bromide or bromobenzene (Scheme 4). Using a modified procedure of Bansal *et al.*[19] phenacyl triphenylphosphonium bromide was reacted with aqueous sodium hydroxide and acetaldehyde in a Wittig reaction to give *trans*-1-phenylbut-2-en-1-one (**14**) in 87% yield. Alternatively compound **14** was also synthesized in a Grignard reaction between bromobenzene and *trans*-crotonaldehyde[20] followed by a manganese dioxide oxidation to **14** in 69% overall yield. Compound **14** underwent a Michael addition with the sodium salt of diethyl malonate to give diethyl 2-(1-methyl-3-oxo-3-phenylpropyl)malonate (**15**) in 51% yield. Compound **15** was reacted in a McMurry coupling with activated Zn and $TiCl_4$ to give **16a** in 72% yield after hydrolysis using the method of Shi *et al.*[21]



Scheme 4 i, 1. Mg, I_2, THF, 2. *trans*-$CH_3CHCHCHO$, 3. MnO_2, 69%; ii, 1. 2 M NaOH, CH_2Cl_2, 2. CH_3CHO, 87%; iii, $CH_2(CO_2Et)_2$, NaOEt, EtOH, Et_2O, 51%; iv, 1. Zn, $TiCl_4$, THF, 2. 1 M HCl, 72%.

Ring-closure of compound **16a** was attempted without success with both thiourea and 2-(*S*-methylthio)isourea (Scheme 5). Although a ring-closure has been observed in a reaction of 2-(*S*-methylthio)isourea with ethyl 2-oxo-3-phenylcyclopentanecarboxylate (**16b**) to give an oxazine[9] neither **16a** nor ethyl 3-(3,5-dimethylphenyl)-2-oxocyclopentanecarboxylate[22] (**16c**) displayed any reactivity towards 2-(*S*-methylthio)isourea.

To investigate a possible ring-closure of **16a**, ethyl 2-oxocyclopentanecarboxylate (**16d**) was chosen as a model compound.

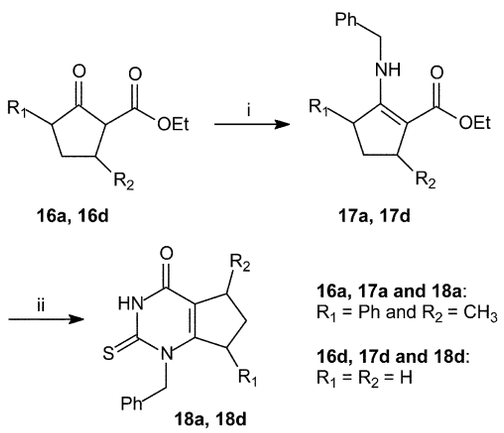


16a, Ar = Ph and R = CH_3,
16b, Ar = Ph and R = H
16c, Ar = 3,5-dimethylphenyl and R = H

No reaction for **16a** and **16c**.

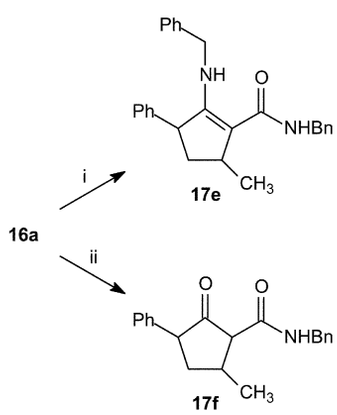
Scheme 5 i, $CH_3SC(NH)NH_2$, KOH, H_2O, 51% for **16b**.

It was found that **16d** in neat benzylamine was easily converted to the corresponding benzylenamine **17d** in 96% yield (Scheme 6). Compound **17d** was easily ring-closed with trimethylsilyl isothiocyanate to produce 1-benzyl-2-thioxo-1,2,3,5,6,7-hexahydro-cyclopentapyrimidin-4-one (**18d**) in 83% yield. It was not possible to obtain a complete conversion in the reaction of **16a** in neat benzylamine, but it gave the best result, which was a 27% yield of ethyl 2-benzylamino-5-methyl-3-phenylcyclopent-1-enecarboxylate (**17a**). No improvements were seen when the synthesis of **17a** was performed under other reaction conditions. Reacting **16a** in neat benzylamine using either excess benzylamine, addition of *p*-toluenesulfonic acid (PTSA)[23] or Al_2O_3[24] were tried.



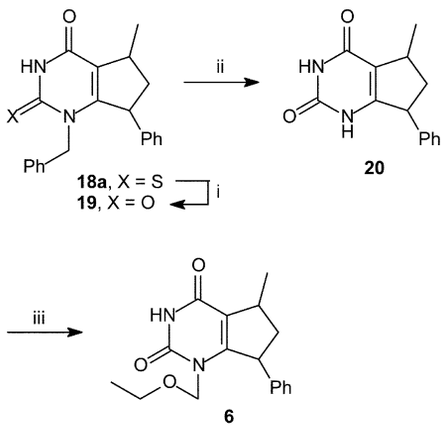
Scheme 6 i, 1.05 eq. $BnNH_2$, 27% for **17a** and 96% for **17d**; ii, 1. $(CH_3)_3SiNCS$, 2. $NaHCO_3$, 92% for **18a** and 83% for **18d**.

An attempt was also made to react **16a** and benzylamine in benzene/molecular sieves[25] and in toluene/PTSA.[26] In the case of toluene/PTSA and 1.5 equivalents of benzylamine, a conversion to **17e** was observed where both the ketone and the ester were converted to the enamine and amide, respectively (Scheme 7). Compound **17e** was isolated in 50% yield. Using 0.8 equivalents of benzylamine the β-keto amide **17f** was isolated as the sole product in 53% yield. Compound **17a** was ring-closed, in the same way as **17d**, to 1-benzyl-5-methyl-7-phenyl-2-thioxo-1,2,3,5,6,7-hexahydro-cyclopentapyrimidin-4-one (**18a**) in 92% yield (Scheme 6).

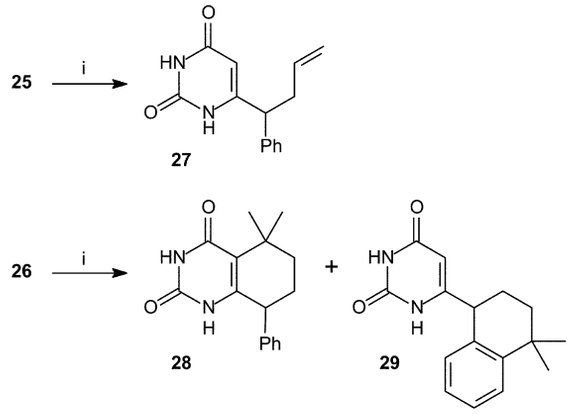


Scheme 7 i, 1.5 eq. $BnNH_2$, PTSA, toluene, 50%; ii, 0.8 eqv $BnNH_2$, PTSA, toluene, 53%.

Compound **18** was desulfurized with chloroacetic acid[18] to 1-benzyl-5-methyl-7-phenyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (**19**) in 32% yield (Scheme 8). The debenzylation of **19** was carried out with polyphosphoric acid (PPA) to give 5-methyl-7-phenyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (**20**) in 39% yield. Compound **20** was alkylated[18] to give TM 1-ethoxymethyl-5-methyl-7-phenyl-



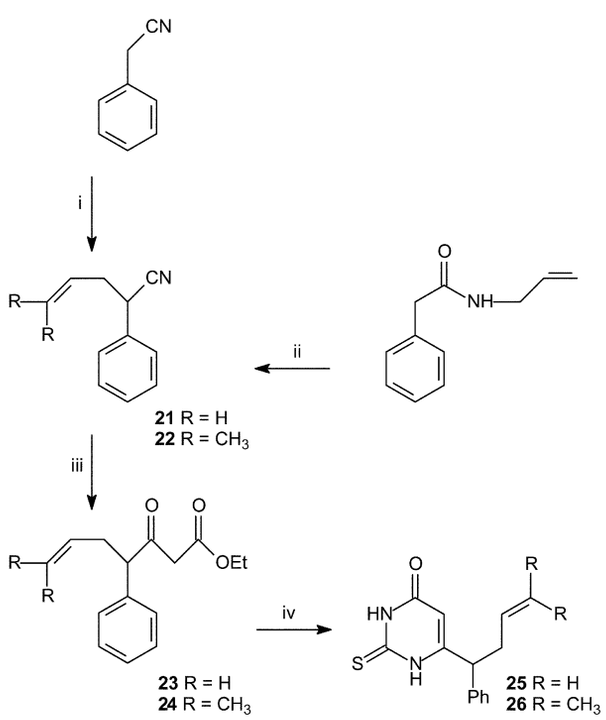
Scheme 8 i, $ClCH_2CO_2H$, 32%; ii, PPA, 39%; iii, 1. BSA, MeCN, 2. TMS triflate, $CH_2(OEt)_2$, 86%.



Scheme 10 i, $ClCH_2CO_2H$, 50% overall of **27** from **21**; 94% crude yield of a 1 : 1 mixture of **28** and **29**.

1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (**6**) in 86% yield.

To synthesize TM **5** and **6** using strategy 2, the key intermediates 6-(1-phenylbut-3-enyl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (**25**) and 6-(4-methyl-1-phenylpent-3-enyl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (**26**) were synthesized (Scheme 9). 2-Phenylpent-4-enenitrile (**21**) was synthesized from *N*-allyl-1-phenylacetamide by a 3-aza-Cope reaction in 81% yield.[27] 5-Methyl-2-phenylhex-4-enenitrile (**22**) was obtained in 74% yield from phenylacetonitrile using the modified procedure of Wallingford *et al.*[11] for obtaining **8**. The corresponding β-keto esters **23** and **24** were obtained in a Blaise reaction in quantitative yields.[18] Ring-closures of **23** and **24** with thiourea under basic conditions gave **25** and **26** in 54% and 48% yields from **21** and **22**, respectively.[18]

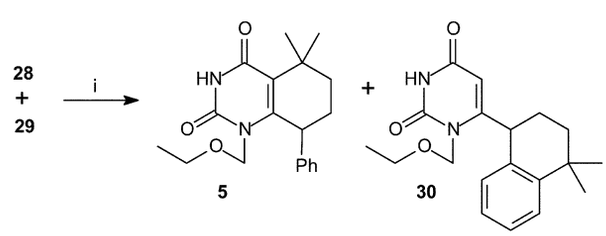


Scheme 9 i, 1. NaOEt, $EtOCO_2Et$, $BrCH_2CHC(CH_3)_2$, 2.30% KOH–EtOH, 74% of **22**; ii, PPh_3, CCl_4, Et_3N, CH_2Cl_2, 81% of **21**; iii, 1. $BrCH_2CO_2Et$, Zn, THF, 2. HCl (aq); iv, $SC(NH_2)_2$, NaOEt, EtOH, 54% and 48% overall from **21** and **22**, respectively.

Compounds **25** and **26** were desulfurized with chloroacetic acid (Scheme 10). In this way 6-(1-phenylbut-3-enyl)-1*H*-pyrimidine-2,4-dione (**27**) was obtained in 50% overall yield from **21**. During the desulfurization under acidic conditions, the double bond of **26** was concomitantly protonated leading to an intramolecular attack on either C5 of the uracil or on the *ortho* position of the phenyl ring. 5,5-Dimethyl-8-phenyl-5,6,7,8-tetrahydro-1*H*-quinazoline-2,4-dione (**28**) and 6-(4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-1*H*-pyrimidine-2,4-dione (**29**) were obtained as a 1 : 1 product mixture in 94% crude yield.

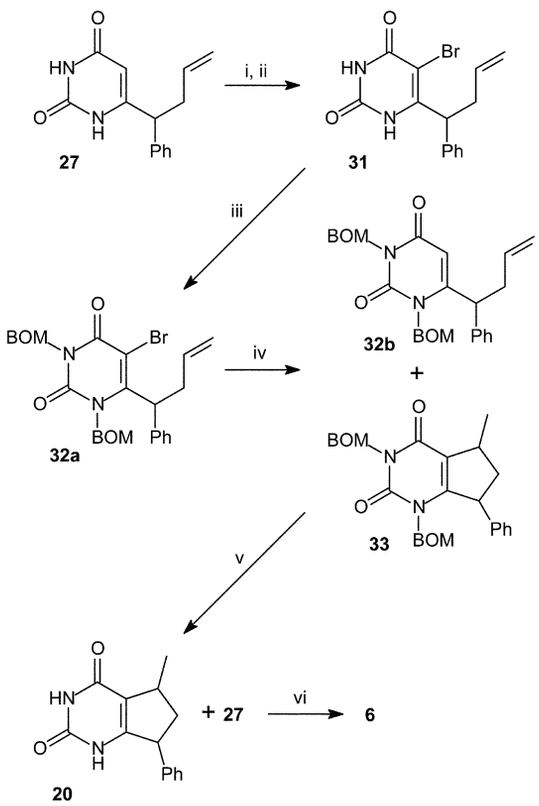
The product mixture was more easily separated after N1 alkylation to give TM **5** in 24% yield from **26** whereas **30** was only isolated as a product contaminated with **5** (Scheme 11).

The strategy to obtain TM **6** from **27** was to introduce a bromine at the C5 position of the uracil followed by a radical mediated ring-closure to the double bond. Compound **27** was triple brominated followed by a regeneration of the double bond by the action of NaI using the method of Marvel *et al.*[28] giving **31** in 78% yield (Scheme 12). Attempts to ring-close **31** by treatment with Bu_3SnH in the presence of AIBN[29] were unsuccessful. Therefore, the two free nitrogens of **31** were protected with benzyloxymethyl groups[30] to give **32a** in 61% yield. Treatment of **32a** with Bu_3SnH in the presence of AIBN[29] produced the ring-closed product 1,3-bis(benzyloxymethyl)-5-methyl-7-phenyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (**33**). Unfortunately, during the reaction conditions of ring-closure, reduction with replacement of bromine with hydrogen also took place and the debrominated product **32b** was formed in the same amount as **33**. The product mixture isolated in 71% yield could not be separated. The two BOM groups were removed in refluxing CF_3CO_2H[31] giving a 1 : 1 mixture of **20** and **27** in 42% yield. The mixture was N1 alkylated using the method of Cleary *et al.*[32] and TM **6** was isolated in 29% yield.



Scheme 11 i, 1. BSA, MeCN, 2. TMS triflate, $CH_2(OEt)_2$, 24% overall of **5** from **26**.

For TM **4**, **5** and **6** to correspond closely to the structure of emivirine in RT, the stereochemistry of C7 (C8 for TM **5**) must be the *S*-form. Furthermore, the phenyl group must adopt a pseudo-axial conformation. Because of the possible steric strain with the methyl group (in TM **6**) this is expected to be most favourable for the *trans*-5*R*,7*S* stereoisomer of TM **6**. The ring-closing reactions in the two strategies resulting in **18a** and **33** produced two different ratios of the two possible diastereomeric pairs. The radical ring-closure using Bu_3SnH



Scheme 12 i, 2 eq. Br_2, LiBr, AcOH; ii, excess NaI, acetone, 78%; iii, BOM-Cl, DBU, DMF, 61%; iv, Bu_3SnH, AIBN, toluene, 71% (1 : 1 mixture of **33** (~80% *cis*) and **32b**); v, CF_3CO_2H, 42% (1 : 1 mixture of **20** and **27**); vi, 1. HMDS, $(NH_4)_2SO_4$, 2. $CH_2(OEt)_2$, H_2SO_4, MeCN, 29%.

giving **33** produced a *cis*/*trans* ratio of 4 : 1 while the ionic ring-closure using the trimethylsilyl isothiocyanate giving **18a** produced a *cis*/*trans* ratio of 2 : 3. The excess of *trans* isomers in **18a** isomerized later on under the treatment with PPA to give a 1 : 1 ratio.

Biological activity

The compounds **4**–**6** were tested for their activity against HIV-1 in MT-4 cells infected with wild type HIV-1 strain IIIB and **4** was also tested in NNRTI resistant strain N119 with the Y181C RT mutation.[33]

TM **6** was obtained in a *cis*/*trans* ratio of 4 : 1 and 1 : 1. The biological activities (Table 1) obtained from these mixtures were 24 μM and 4 μM respectively, which correlate with the expectation of the *trans* 5*R*,7*S* stereoisomer to be the active molecule.

The activities of TM **5** and **6** show that, at most, a 10-fold increase in activity is gained by introducing extra methyl groups next to the C5 position of the uracil compared to **2** and **3**.

Interestingly, an increase of the steric bulkyness in the phenyl ring by 3,5-dimethyl substitution shows a 10^2-fold higher activity for **4** when compared to **3**. This should be compared with GCA-186 which differentiates from emivirine by 3,5-dimethyl substitution in the phenyl ring of emivirine. In this case the activity is only 3-fold higher compared to emivirine.[10]

Furthermore the cytotoxicity and the relative loss of activity towards the mutant virus with the Y181C RT mutation is lower for TM **4** compared to both emivirine and GCA-186.[10,33]

Conclusion

In the work of synthesizing TM **4**–**6** we have developed several new synthetic approaches in reaching C5 and C6 annelated structures of uracil with aliphatic 5 and 6 membered rings. These include: a. Formation of an oxazine from a cyclic β-keto amide and oxalyl chloride; b. A ring-closure of a β-enamine ester with trimethylsilyl isothiocyanate; c. A radical mediated ring-closure from C5 of a protected uracil to an allylic double bond; d. An acid catalysed ring-closure from C5 of a uracil to a substituted double bond.

The increase in steric bulkyness next to the C5 of the uracil seems not to be particularly favourable, as the biological activities obtained for TM **5** and **6** are only slightly better than those for **2** and **3**. The extra methyl groups are probably shifting the equilibrium between the different conformers to a lower amount of the phenyl group in the pseudo-axial position, which is needed to obtain optimal binding interaction with RT.

TM **4** showed a surprisingly high activity compared to the acitivies of **2**, **3**, **5** and **6**. Furthermore the activity towards the Y181C RT mutation only dropped 20-fold which is less than what is observed for emivirine.

Experimental

NMR spectra were recorded on a Bruker AC-300 FT NMR spectrometer at 300 MHz for ^{1}H-NMR and at 75 MHz for ^{13}C-NMR. The internal standards used in ^{1}H-NMR were TMS (δ 0.000) for $CDCl_3$ and DMSO-d_6. The internal standards used in ^{13}C-NMR were $CDCl_3$ (δ 77.0) and DMSO-d_6 (δ 39.4). Mass spectra were recorded on a Finnigan Mat SSQ 710 (EI), Kratos MS50RF instrument (FAB) or on an Ionspec 4.7 Tesla Ultima Fourier Transform Mass Spectrometer (MALDI). Elemental analyses were performed at Atlantic Microlab, Inc., Atlanta, Georgia or at Mikroanalytisk Afdeling, University of Copenhagen, Copenhagen. Merck silica gel (0.040–0.064 mm) was used for column chromatography. Solvents for chromatography were bought as HPLC grade or distilled prior to use. Chloroform, dichloromethane, carbon tetrachloride and 1,2-dichloroethane were dried over 4 Å sieves. Acetonitrile was dried over 3 Å sieves. DMF was dried by reflux over P_2O_5 (5 g L^{-1}) and distilled on 4 Å sieves. Toluene and diethyl ether were dried by sodium wire. THF was distilled from Na–benzophenone. Dioxane was predried with KOH pellets, decanted to and distilled from sodium and stored over 4 Å sieves. Triethylamine was dried over KOH pellets. Petroleum ether: bp 60–80 °C. Zn was activated by washing Zn dust, < 10 microns, sequentially with 3 × 50 ml of 4 M HCl, H_2O, EtOH and dry diethyl ether.

2-(3,5-Dimethylphenyl)hexanedinitrile (8)

Sodium (2.62 g, 114 mmol) was dissolved in 50 ml of absolute EtOH, and the excess EtOH was removed *in vacuo*. Diethyl carbonate (55 ml, 480 mmol) and (3,5-dimethylphenyl)acetonitrile **7** (13.84 g, 95.3 mmol) were added. The flask was equipped for distillation and heated to 120 °C. The solution was cooled to rt after the formed EtOH had evaporated from the reaction mixture. 4-Chlorobutyronitrile (9.5 ml, 106 mmol) was added and the solution was refluxed overnight. Dilute HCl was added until pH = 1–2. The mixture was extracted with diethyl ether (3 × 50 ml). The combined extracts were washed with brine (25 ml), dried and evaporated under reduced pressure which gave an orange oil. The oil was suspended in EtOH (10 ml), 8 M KOH (15 ml) and refluxed for 0.5 h. The solution was evaporated under reduced pressure and extracted with diethyl ether (3 × 50 ml). The combined extracts were dried and evaporated under reduced pressure to give the dinitrile **8** (12.4 g, 61%) as a yellow oil; (Found: C, 78.8; H, 7.6; N, 12.9. $C_{14}H_{16}N_2$ requires C, 79.2; H, 7.6; N, 13.2%); R_f 0.60 (CH_2Cl_2); δ_H($CDCl_3$) 1.82 (2 H, quintet, *J* 6.9, $CHCH_2CH_2$), 2.05 (2 H, quintet, *J* 6.9, $CHCH_2$), 2.33 (6 H, s, 2 × CH_3), 2.40 (2 H, t, *J* 6.9, CH_2CN), 3.78 (1 H, t, *J* 6.9, CH), 6.94 (2 H, s, Ar), 6.98 (1 H, s, Ar); δ_C(75 MHz) 16.6 ($CHCH_2CH_2$), 21.1 (2 × CH_3), 22.6 ($CHCH_2$), 34.3 (CH_2CN), 36.4 (CH), 118.6, 120.14 (2 × CN),

124.9, 129.9, 134.4, 138.9 (Ar); *m*/*z* (EI) 212 (M^+, 100%), 144 (89).

2-Amino-1-cyano-3-(3,5-dimethylphenyl)cyclopent-1-ene (9)

Sodium hydride (0.48 g, 18.8 mmol) washed with diethyl ether was heated to reflux in dry dioxane (20 ml). 2-(3,5-Dimethylphenyl)hexanedinitrile **8** (2.66 g, 12.5 mmol) in dry dioxane (20 ml) was added dropwise over 1 h and the resulting solution was refluxed for another 2.5 h. Water (25 ml) was added cautiously to the cooled reaction mixture, which was then neutralised with acetic acid. Brown solid precipitated, which was further purified by recrystallisation from EtOH to give **9** (2.47 g, 93%) as a brown solid; Mp 140–142 °C (EtOH); R_f 0.70 (10% MeOH–CH_2Cl_2); δ_H($CDCl_3$) 1.83–1.98, 2.30–2.42 (2 H, 2 × m, CHCH_2), 2.32 (6 H, s, 2 × CH_3), 2.55–2.70 (2 H, m, =CHCH_2), 3.75 (1 H, t, *J* 8.6, CH), 4.32 (2 H, br s, NH_2), 6.81 (2 H, s, Ar), 6.96 (1 H, s, Ar); δ_C($CDCl_3$) 21.2 (2 × CH_3), 29.7 (CHCH$_2$), 32.8 (=CHCH$_2$), 52.4 (CH), 75.3 (*C*CN), 118.9 (CN), 125.7, 129.1, 138.6, 140.6 (Ar), 163.6 (*C*NH_2); *m*/*z* (EI) 212 (M^+, 100%), 211 (59).

2-(3,5-Dimethylphenyl)cyclopentanone (10)

2-Amino-1-cyano-3-(3,5-dimethylphenyl)cyclopent-1-ene **9** (2.14 g, 10.1 mmol) was dissolved in a mixture of glacial acetic acid (16 ml) and conc HCl (16 ml). The reaction mixture was refluxed for 6 h and subsequently extracted with diethyl ether (3 × 20 ml). The combined extracts were washed with water (2 × 15 ml), saturated aqueous $NaHCO_3$ (2 × 15 ml) and water (2 × 15 ml). Drying and evaporation under reduced pressure gave the ketone **10** (1.04 g, 55%) as a yellow oil; R_f 0.65 (CH_2Cl_2); δ_H($CDCl_3$) 1.83–1.99, 2.03–2.19, 2.21–2.37, 2.42–2.53 (6 H, 4 × m, 3 × CH_2), 2.31 (6 H, s, 2 × CH_3), 3.24 (1 H, t, *J* 8.9, CH), 6.80 (2 H, s, Ar), 6.90 (1 H, s, Ar); δ_C($CDCl_3$) 20.7 (CH_2*C*H_2CH_2), 21.1 (2 × CH_3), 31.84 (CH*C*H_2), 38.3 (*C*H_2CO), 55.2 (CH), 126.0, 128.6, 138.0, 138.5 (Ar), 218.6 (CO); *m*/*z* (EI) 188 (M^+, 67%), 133 (100).

3-(3,5-Dimethylphenyl)-2-oxocyclopentanecarboxamide (11)

2-Amino-1-cyano-3-(3,5-dimethylphenyl)cyclopent-1-ene **9** (0.50 g, 2.4 mmol) was stirred in conc. sulfuric acid (10 ml) for 2 days at rt. The reaction mixture was poured into icewater (40 ml) and neutralised with 25% aqueous ammonia. The formed precipitate was collected and dried which gave the amide **11** (0.31 g, 57%) as a brown solid; mp 127–133 °C; R_f 0.45 (10% MeOH–CH_2Cl_2); δ_H($CDCl_3$) 2.00–2.52 (4 H, m, CH_2CH_2), 2.31 (6 H, s, 2 × CH_3), 3.15–3.43, 3.67–3.75 (2 H, 2 × m, 2 × CH), 5.85 (2 H, br s, NH_2), 6.75–6.95 (3 H, m, Ar); δ_C($CDCl_3$) 21.2 (2 × CH_3), 23.2, 23.4 (CH_2CHCONH_2), 28.6, 30.1 (ArCHCH_2), 53.9, 54.6, 55.7, 56.0 (2 × CH), 125.9, 129.0, 137.2, 137.5, 138.2 (Ar), 168.2, 169.2 ($CONH_2$), 214.1, 215.4 (CO).

7-(3,5-Dimethylphenyl)-6,7-dihydro-5*H*-cyclopenta[*e*][1,3]-oxazine-2,4-dione (12) and 4a-(3,5-dimethylphenyl)-5,6-dihydro-4a*H*-cyclopenta[*e*][1,3]oxazine-2,4-dione (12a) from 10

2-(3,5-Dimethylphenyl)cyclopentanone (**10**) (0.76 g, 4.0 mmol) and *N*-(chlorocarbonyl)isocyanate (0.43 g, 4.1 mmol) were heated to 55 °C in an atmosphere of nitrogen for 1.5 h. The mixture was heated for another 1.5 h at 130 °C after which it was cooled and quenched by addition of diethyl ether (25 ml) and by careful addition of water (5 ml). The diethyl ether phase was washed with water (2 × 10 ml), saturated aqueous $NaHCO_3$ (2 × 10 ml) and water (2 × 10 ml). After drying and evaporation under reduced pressure, the product mixture was purified by column chromatography on silica using dichloromethane and methanol (0–10%) as eluent which gave the oxazine **12** (0.37 g, 35%) as white crystals and the isomeric oxazine **12a** (0.12 g, 11%) as light brown crystals; **12**: mp 196–198 °C; (Found: C, 69.6; H, 5.9; N, 5.4. $C_{15}H_{15}NO_3$ requires C, 70.0; H, 5.9; N, 5.4%); R_f 0.65 (10% MeOH–CH_2Cl_2); δ_H($CDCl_3$) 2.09–2.18 (1 H, m, CHCH_aH), 2.31 (6 H, s, 2 × CH_3), 2.56–2.95 (3 H, m, =CCH_2 and CHCHH_b), 4.11 (1 H, t, *J* 8.9, CH), 6.81, 6.95 (3 H, 2 × s, Ar), 9.04 (1 H, s, NH); δ_C($CDCl_3$) 21.3 (2 × CH_3), 24.1 (=C*C*H_2), 30.4 (CH*C*H_2), 49.3 (CH), 112.6 (C4a), 125.2, 129.4, 138.6, 139.3 (Ar), 148.8, 160.7, 170.0 (C2, C4 and C7a); *m*/*z* (EI) 257 (M^+, 100%) 214 (76); **12a**: mp 148–150 °C; (Found: C, 69.8; H, 5.9; N, 5.3. $C_{15}H_{15}NO_3$ requires C, 70.0; H, 5.9; N, 5.4%); R_f 0.75 (10% MeOH–CH_2Cl_2); δ_H($CDCl_3$) 2.10–2.19 (1 H, m, =CHCH_2CH_aH), 2.31 (6 H, s, 2 × CH_3), 2.57–2.92 (3 H, m, =CHCH_2CHH_b), 4.11 (1 H, t, *J* 8.7, =CH), 6.80, 6.93 (3 H, 2 × s, Ar); δ_C($CDCl_3$) 21.2 (2 × CH_3), 25.2, 35.1 (2 × CH_2), 56.2 (C), 113.2 (=CH), 123.5 130.0, 137.0, 138.8 (Ar), 146.9, 147.7, 171.6 (C2, C4 and O*C*=C); *m*/*z* (EI) 257 (M^+).

7-(3,5-Dimethylphenyl)-6,7-dihydro-5*H*-cyclopenta[*e*][1,3]-oxazine-2,4-dione (12) from 11

3-(3,5-Dimethylphenyl)-2-oxocyclopentanecarboxamide (**11**) (0.35 g, 1.7 mmol) was dissolved in 1,2-dichloroethane (10 ml) and cooled to 0 °C in an atmosphere of nitrogen. Oxalyl chloride (0.30 ml, 3.4 mmol) was added dropwise over 0.5 h. The reaction mixture was refluxed for 12 h, cooled and evaporated under reduced pressure which gave a brown residue. Purification by column chromatography on silica using dichloromethane and methanol (0–10%) as eluent gave **12** (0.18 g, 40%) as white crystals.

7-(3,5-Dimethylphenyl)-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (13)

7-(3,5-Dimethylphenyl)-6,7-dihydro-5*H*-cyclopenta[*e*][1,3]-oxazine-2,4-dione (**12**) (0.40 g, 1.6 mmol) was refluxed with aqueous ammonia (11 ml, 25%) for 24 h. Cooling to rt gave a light brown precipitate which was filtered off and purified by recrystallisation in EtOH which gave **13** (0.37 g, 90%) as light brown crystals; mp 299–300 °C (EtOH); (Found: C, 69.8; H, 6.3; N, 10.8. $C_{15}H_{16}N_2O_2$, 0.1 H_2O requires C, 69.8; H, 6.3; N, 10.9%); R_f 0.25 (10% MeOH–CH_2Cl_2); δ_H(DMSO-d_6) 1.77–1.85 (1 H, m, CHCH_aH), 2.24 (6 H, s, 2 × CH_3), 2.45–2.72 (3 H, m, =CCH_2 and CHCHH_b), 4.01–4.08 (1 H, m, CH), 6.76, 6.87 (3 H, 2 × s, Ar), 10.84 (1 H, s, NH), 10.87 (1 H, s, NH); δ_C(DMSO-d_6) 20.9 (2 × CH_3), 25.5 (=C*C*H_2), 32.1 (CH*C*H_2), 49.1 (CH), 110.7 (C4a), 125.1, 128.3, 137.6, 141.8 (Ar), 152.5, 156.7, 162.2 (C2, C4 and C7a); *m*/*z* (EI) 256 (M^+, 100%), 241 (40).

7-(3,5-Dimethylphenyl)-1-ethoxymethyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (4)

7-(3,5-Dimethylphenyl)-1,5,6,7-tetrahydrocyclopenta-pyrimidine-2,4-dione (**13**) (105 mg, 0.41 mmol) and BSA (0.30 ml; 1.23 mmol) were stirred in dry chloroform (10 ml) in an atmosphere of nitrogen at rt. As the reaction mixture became homogeneous (~5 min) chloromethyl ethyl ether (0.06 ml, 0.62 mmol) was added. The reaction was followed by TLC and quenched after 5 h with cold saturated aqueous $NaHCO_3$ (5 ml). The mixture was evaporated under reduced pressure to near dryness and the residue was stirred with diethyl ether (10 ml) for 1 h. The suspension was filtered and the filtrate was evaporated under reduced pressure. Purification by column chromatography on silica using dichloromethane and methanol (0–5%) as eluent gave **4** (100 mg, 80%) as white crystals; mp 170–175 °C; (Found: C, 68.7; H, 7.2; N, 8.7. $C_{18}H_{22}N_2O_3$ requires C, 68.8; H, 7.0; N, 9.0%); R_f 0.35 (10% MeOH–CH_2Cl_2); δ_H($CDCl_3$) 1.18 (3 H, t, *J* 7.0, CH_2CH_3), 1.96–2.05 (1 H, m, CHCH_aH), 2.30 (6 H, s, 2 × CH_3), 2.53–2.92 (3 H, m, =CCH_2 and CHCHH_b), 3.47–3.61 (2 H, m, CH_2CH$_3$), 4.39 (1 H, d, *J* 9.4, CH), 4.45 (1 H, d, *J* 10.7, NCH_aH), 5.33 (1 H, d, *J* 10.7, NCHH_b), 6.70, 6.90 (3 H, 2 × s, Ar), 9.19 (1 H, s, NH); δ_C($CDCl_3$) 15.0 (CH_2*C*H_3), 21.3 (2 × CH_3), 25.6 (=C*C*H_2), 33.0 (CH*C*H_2), 49.6 (CH), 64.8 (*C*H_2CH_3), 72.6 (NCH_2), 115.1 (C4a), 124.4, 129.3, 139.0, 140.8 (Ar), 152.9, 157.6, 161.5 (C2, C4 and C7a); *m*/*z* (EI) 314 (M^+, 47%), 268 (100).

Trans 1-phenylbut-2-en-1-one (14)

Method A. Phenacyl triphenylphosphonium bromide (6.12 g, 13.3 mmol) was stirred overnight in dichloromethane (30 ml) and 2 M NaOH (15 ml). The phases were separated and the water phase was extracted with dichloromethane (10 ml). To the combined extracts was added acetaldehyde (3 × 1.5 ml, 80 mmol, in intervals of 0.5 h). The reaction mixture was stirred for 1 h and then evaporated under reduced pressure. Purification by column chromatography on silica using dichloromethane as eluent gave the ketone **14** (1.69 g, 87%) as a clear colourless oil; R_f 0.35 (CH_2Cl_2); ^{1}H and ^{13}C-NMR spectra are as previously reported.[34] *Method B*. To phenylmagnesium bromide prepared from Mg (9.2 g, 0.38 mol) and bromobenzene (49.3 g, 0.31 mol) in dry THF (230 ml) was added *trans* crotonaldehyde (21.1 g, 0.30 mol) in dry THF (60 ml) at 0 °C over 15 min. The cooling bath was removed and the solution was stirred for one additional hour. Saturated aqueous NH_4Cl (60 ml) was added and after stirring for 0.5 h the THF was decanted. The residue was washed/decanted with THF (3 × 100 ml). The combined THF phases were concentrated under reduced pressure and the residue dissolved in dichloromethane (300 ml). The dichloromethane phase was washed with saturated aqueous $NaHCO_3$ (3 × 50 ml), brine (100 ml), dried and evaporated under reduced pressure. The resulting orange oil was purified by vacuum distillation (bp 76–78 °C/0.01 mbar; lit.,[35] 85–87 °C/1.2 Torr), which gave *trans* 1-phenylbut-2-en-1-ol (36.3 g, 78%) as a clear oil. *Trans* 1-phenylbut-2-en-1-ol (12.0 g, 81 mmol) and MnO_2 (64 g, 0.74 mmol) were stirred for 2 h at rt in dry diethyl ether (250 ml). The black slurry was filtered through Celite. The filtercake was washed with diethyl ether (4 × 150 ml) and the combined phases of diethyl ether were dried and evaporated under reduced pressure, which gave the ketone **14** (10.4 g, 88%) as an orange oil.

Diethyl 2-(1-methyl-3-oxo-3-phenylpropyl)malonate (15)

Sodium (0.40 g, 17 mmol) was dissolved in absolute EtOH (10 ml), and dry diethyl ether (10 ml) and diethyl malonate (16 ml, 95 mmol) were added. The reaction mixture was stirred 1 h at rt under nitrogen. *Trans* 1-phenylbut-2-en-1-one (**14**) (10.2 g, 70 mmol) in dry diethyl ether (10 ml) was added. After 1 h the reaction was quenched with glacial acetic acid (2 ml). Diethyl ether (100 ml) was added and the resulting solution was washed with water (2 × 25 ml), dried and evaporated under reduced pressure. The resulting orange oil was purified by a fast vacuum distillation, which gave **15** (10.9 g, 51%) as a slightly green-coloured oil; bp 148 °C (0.02 mbar); (Found: C, 66.7; H, 7.3. $C_{17}H_{22}O_5$ requires C, 66.6; H, 7.2%); R_f 0.75 (CH_2Cl_2); δ_H($CHCl_3$), 1.10 (3 H, d, *J* 6.6, CHCH_3), 1.26, 1.27 (6 H, 2 × t, *J* 7.0, CH_2CH_3), 2.88–3.00 (2 H, m, CH_aHCH), 3.29 (1 H, dd, *J* 3.2 and 15.5, CHH_bCH), 3.48 (1 H, d, *J* 6.6, $CHCO_2$), 4.16–4.25 (4 H, m, 2 × CH_2CH_3), 7.46 (2 H, t, *J* 7.3, Ar), 7.56 (1 H, t, *J* 7.3, Ar), 7.99 (2 H, d, *J* 7.3, Ar); δ_C($CDCl_3$) 14.1 (2 × CH_2CH_3), 17.7 (CHCH_3), 29.5 (CH_2CH), 42.7 (CH_2CH), 56.5 ($CHCO_2$), 61.3 (2 × CH_2CH_3), 128.1, 128.6, 133.1, 136.9 (Ar), 168.6, 168.7 (2 × CO_2), 198.8 (PhCO); *m*/*z* (EI) 306 (M^+, 8%), 105 (100).

Ethyl 5-methyl-2-oxo-3-phenylcyclopentanecarboxylate (16a)

To activated Zn (17.5 g, 0.268 mol) in dry THF (200 ml) was added $TiCl_4$ (14.7 ml, 0.134 mol) dropwise and the solution became dark and solidified. The mixture was heated to reflux to give an almost homogeneous purple solution. Reflux was continued for 2 h and after cooling the mixture solidified. A minor portion (~2–3 ml) of diethyl 2-(1-methyl-3-oxo-3-phenylpropyl)malonate (**15**) (20.5 g, 67 mmol) in dry THF (40 ml) was added. The mixture was heated to 50 °C, where the exothermic reaction was observed as effervescence from the surface of the purple solid. The rest of **15** in THF was added during 5 min. After 0.5 h the effervescence ceased and the mixture was heated under reflux for a further 1.5 h. After cooling the solution was stirred with 1 M HCl (100 ml) for 0.5 h. The mixture was extracted with diethyl ether (3 × 200 ml) and the combined organic phases were washed with brine (50 ml). Drying and evaporation under reduced pressure gave an orange oil. Purification by column chromatography on silica using dichloromethane as eluent gave the cyclopentanone ester **16a** (11.9 g, 72%) as a clear colourless oil; (Found: C, 69.8; H, 7.1, $C_{15}H_{18}O_3$·0.65 H_2O requires C, 69.8; H, 7.0%); R_f 0.35 (CH_2Cl_2); δ_H($CDCl_3$) 1.11–1.32 (6 H, m, 2 × CH_3), 1.57–1.73 (1 H, m, CH_aHCH), 2.35–2.64 (2 H, m, CHH_bCH, CHCH$_3$), 2.83 (1 H, d, *J* 11.6, $CHCO_2$), 3.48 (1 H, dd, *J* 7.4 and 12.9, PhCH), 4.09–4.24 (2 H, m, CH_2CH$_3$), 7.09–7.28 (5 H, m, Ar); δ_C($CDCl_3$) 14.1, 14.2 (CH_2CH_3), 19.0, 19.8 (CHCH_3), 33.8, 33.9 (CH_2-CH), 37.8, 37.9 (CH_3CH), 53.3, 56.2 (PhCH), 61.3 ($CHCO_2$), 62.8, 63.3 (CH_2CH_3), 126.9, 127.1, 127.9, 128.0, 128.5, 128.6, 137.3 (Ar), 169.0 (CO_2), 209.6 (PhCO); *m*/*z* (EI) 246 (M^+, 88%), 104 (100).

Ethyl 2-benzylamino-5-methyl-3-phenylcyclopent-1-enecarboxylate (17a)

Ethyl 5-methyl-2-oxo-3-phenylcyclopentanecarboxylate (**16a**) (509 mg, 2.07 mmol) was added to benzylamine (244 mg, 2.27 mmol). The mixture was rotated on a rotary evaporater (65 °C, 30 mbar) for 1.5 h. The cooled mixture was purified by column chromatography on silica using dichloromethane and petroleum ether (1 : 1) as eluent, which gave the enamine **17a** (184 mg, 27%, *cis*/*trans* ratio 4 : 3) as a clear slightly green-coloured oil, which is stable in the freezer for a few weeks; R_f 0.50 (CH_2Cl_2); δ_H($CDCl_3$) 1.10 (3 H, d, *J* 6.7, CHCH_3(*cis*)), 1.14 (3 H, d, *J* 6.7, CHCH_3(*trans*)), 1.30 (3 H, t, *J* 7.2, CH_2CH_3(*cis*)), 1.31 (3 H, t, *J* 7.2, CH_2CH_3(*trans*)), 1.39 (1 H, td, *J* 3.5 and 13.3, CHCH_aH-(*cis*)), 1.82–1.95 (2 H, m, CHCH_2(*trans*)), 2.55–2.67 (1 H, m, CHCHH_b(*cis*)), 2.96–3.12 (1 H, m, CHCH$_3$), 3.91–4.05 (1 H, m, PhCH), 4.00 (2 H, d, *J* 6.4, CH_2N), 4.09–4.29 (2 H, m, CH_2CH$_3$), 7.03–7.35 (10 H, m, Ar), 7.89–7.91 (1 H, m, NH); δ_C($CDCl_3$) 14.5, 14.6 (CH_2CH_3), 21.7, 22.9 (CHCH_3), 35.2, 36.2 (CHCH_2), 40.7, 42.3 ($CHCH_3$), 47.7 (CH_2N), 49.2, 49.5 (PhCH), 58.6 (CH_2CH_3), 100.7, 101.4 (=CCO), 126.5, 126.7, 126.9, 127.1, 127.2, 127.5, 128.5, 128.8, 128.9, 139.0, 139.1, 143.1, 144.2 (Ar), 163.7, 164.8 (NC=), 168.8, 168.9 (CO); *m*/*z* (EI) 335 (M^+, 35%), 320 (100).

Ethyl 2-benzylaminocyclopent-1-enecarboxylate (17d)

Ethyl 2-oxocyclopentancarboxylate (**16d**) (4.7 ml, 32 mmol) was added to benzylamine (3.6 ml, 33 mmol). A white precipitate formed immediately. The mixture was rotated on a rotary evaporater (55 °C, 30 mbar) for 2 h. The cooled mixture was purified by column chromatography on silica using dichloromethane as eluent, which gave the enamine **17d** (7.5 g, 96%) as a clear oil, which is stable in the freezer for a few weeks; (Found: C, 73.5; H, 7.9; N, 5.7. $C_{15}H_{19}NO_2$, requires C, 73.4; H, 7.8; N, 5.7%); R_f 0.50 (CH_2Cl_2); δ_H($CDCl_3$), 1.26 (3 H, t, *J* 7.2, CH_3), 1.80 (2 H, quintet, *J* 7.5, $CH_2CH_2CH_2$), 2.54 (4 H, t, *J* 7.5, $CH_2CH_2CH_2CH_2$), 4.15 (2 H, q, *J* 7.2, CH_2CH_3), 4.38 (2 H, d, *J* 6.4, CH_2N), 7.24–7.36 (5 H, m, Ar), 7.76 (1 H, br s, NH); δ_C($CDCl_3$) 14.7 (CH_3), 20.8 ($CH_2CH_2CH_2$), 29.1, 32.0 ($CH_2CH_2CH_2CH_2$), 48.4 (CH_2N), 58.5 (CH_2CH_3), 93.5 (=CCO), 126.7, 127.2, 128.6, 139.2 (Ar), 164.5 (NC=), 168.5 (CO); *m*/*z* (EI) 245 (M^+, 71%), 91 (100).

N-Benzyl-2-benzylamino-5-methyl-3-phenylcyclopent-1-enecarboxamide (17e)

Ethyl 5-methyl-2-oxo-3-phenylcyclopentanecarboxylate (**16a**) (1.08 g, 4.40 mmol), benzylamine (0.72 ml, 6.60 mmol) and PTSA (55 mg, 0.43 mmol) were refluxed 5 h in dry toluene (40 ml) in a Dean–Stark setup under an atmosphere of nitrogen. Evaporation under reduced pressure yielded a yellow

oil. Purification by column chromatography on silica using dichloromethane as eluent gave the enamine amide **17d** (1.02 g, 50%, *cis*/*trans* ratio 1 : 1) as a clear oil; R_f 0.15 (CH_2Cl_2); δ_H($CDCl_3$) 1.06, 1.15 (3 H, 2 × d, *J* 6.7, CH_3), 1.44 (1 H, td, *J* 2.2 and 13.1, CHCH_aH(*cis*)), 1.89–2.01 (2 H, m, CHCH_2-(*trans*)), 2.59–2.69 (1 H, m, CHCHH_b(*cis*)), 2.82–2.99 (1 H, m, C*H*CH_3), 3.93–4.03 (3 H, m, PhC*H*, CH_2NHCC), 4.44–4.66 (2 H, m, CH_2NHCO), 5.33–5.36 (1 H, m, CONH), 7.04–7.37 (15 H, m, Ar), 8.52–8.60 (1 H, m, NH); δ_C($CDCl_3$) 22.0, 23.0 (CH_3), 34.8, 36.0 (*C*HCH_3), 40.5, 42.8, 42.9, 43.0, 47.7, 47.6, 49.0 (CH*C*H_2, 2 × NCH_2, PhCH), 102.2, 102.3 (=*C*CO), 126.5, 126.6, 126.9, 127.2, 127.3, 127.5, 127.6, 128.4, 128.5, 128.6, 128.7, 128.8, 139.3, 139.4, 139.5, 139.6, 143.6, 144.1 (Ar), 161.0, 161.9 (NC=), 168.6, 168.7 (CON); *m*/*z* (MALDI-peak matching) 419.20840 (MNa^+). $C_{27}H_{28}N_2ONa$ requires 419.20938.

N-Benzyl-5-methyl-2-oxo-3-phenylcyclopentanecarboxamide (17f)

Ethyl 5-methyl-2-oxo-3-phenylcyclopentanecarboxylate (**16a**) (2.13 g, 8.65 mmol), benzylamine (0.75 ml, 6.90 mmol) and PTSA (82 mg, 0.43 mmol) were refluxed for 1.5 h in dry toluene (55 ml) in a Dean–Stark setup under an atmosphere of nitrogen. Evaporation under reduced pressure yielded a pink solid. Purification by recrystallisation in toluene and petroleum ether (1 : 1) gave **17e** (1.13 g, 53% according to **16a**) as white crystals; mp 128.5–132.5 °C (toluene–petroleum ether); (Found: C, 78.1; H, 6.9; N, 4.6. $C_{20}H_{21}NO_2$, requires C, 78.2; H, 6.9; N, 4.6%); R_f 0.10 (CH_2Cl_2); δ_H($CDCl_3$) 1.33 (3 H, d, *J* 6.2, CH_3), 1.69 (1 H, dd, *J* 12.8 and 14.2, CHCH_aH), 2.51–2.60 (1 H, m, CHH_b), 2.66 (1 H, d, *J* 11.0, $CHCO_2$), 2.71–2.80 (1 H, m, C*H*CH_3) 3.50 (1 H, dd, *J* 8.2 and 12.8, PhCH), 4.45 (2 H, d, *J* 5.9, CH_2N), 6.95 (1 H, br s, NH), 7.13–7.35 (10 H, m, Ar); δ_C($CDCl_3$) 20.2 (CH_3), 32.1 (*C*HCH_3), 37.2 (*C*H_2CH), 43.6 (CH_2N), 56.5 (PhCH), 61.9 (*C*HCO_2), 127.2, 127.3, 127.5, 128.1, 128.5, 128.6, 137.1, 137.9 (Ar), 166.5 (CO_2), 213.5 (CO); *m*/*z* (EI) 307 (M^+, 63%), 91 (100).

1-Benzyl-5-methyl-7-phenyl-2-thioxo-1,2,3,5,6,7-hexahydrocyclopentapyrimidin-4-one (18a)

Ethyl 2-benzylamino-5-methyl-3-phenylcyclopent-1-enecarboxylate (**17a**) (680 mg, 2.03 mmol) and trimethylsilyl isothiocyanate (4.3 ml, 30 mmol) were refluxed for 3.5 h in an atmosphere of nitrogen. The cooled reaction mixture was quenched with dropwise addition of saturated aqueous $NaHCO_3$ (15 ml) and water (10 ml). The mixture was extracted with dichloromethane (3 × 25 ml). The combined organic phases were dried and evaporated under reduced pressure. Purification by column chromatography on silica using dichloromethane and methanol (2.5%) as eluent gave the thiouracil **18a** (648 mg, 92%) as a light brown solid. On recrystallisation from EtOH the *cis*/*trans* ratio of **18a** changed from ~2 : 3 to ~1 : 4 and the mixture was isolated as a slightly yellow solid; mp 212–213 °C (EtOH); (Found: C, 72.2; H, 5.8; N, 8.1. $C_{21}H_{20}N_2OS$, requires C, 72.4; H, 5.8; N, 8.0%); R_f 0.50 (5% EtOH–CH_2Cl_2); δ_H($CDCl_3$), 1.29 (3 H, d, *J* 7.1, CHCH_3(*cis*)), 1.34 (3 H, d, *J* 7.1, CHCH_3(*trans*)), 1.56 (1 H, td, *J* 3.3 and 13.7, CHCH_aH(*cis*)), 1.92–2.03, 2.09–2.17 (2 H, 2 × m, CHCH_2(*trans*)), 2.76 (1 H, td, *J* 9.9 and 13.7, CHCHH_b(*cis*)), 3.20–3.25 (1 H, m, C*H*CH_3(*cis*)), 3.36 (1 H, sextet, *J* 7.1, C*H*CH_3(*trans*)), 3.96–4.02 (1 H, m, PhCH), 4.30, 6.22 (2 H, 2 × d, *J* 16.2, CH_2N(*cis*)), 4.38, 6.19 (2 H, 2 × d, *J* 16.2, CH_2N-(*trans*)), 7.03–7.15, 7.26–7.42 (10 H, m, Ar), 10.05 (1 H, br s, NH); δ_C($CDCl_3$) 19.3, 20.6 (CH_3), 35.0, 35.2 (*C*HCH_3), 41.0 42.5 (CH*C*H_2), 49.8, 50.2 (PhCH), 52.4, 52.6 (CH_2N), 124.0, 125.1 (C4a), 125.8, 125.9, 126.6, 126.8, 127.7, 127.8, 127.9, 128.9, 129.0, 129.6, 129.7, 134.9, 134.9, 140.1, 141.8 (Ar), 158.0, 158.2 (C4 and C7a), 178.2 (C2); *m*/*z* (EI) 348 (M^+, 100%), 91 (20).

1-Benzyl-2-thioxo-1,2,3,5,6,7-hexahydrocyclopentapyrimidin-4-one (18d)

Ethyl 2-benzylaminocyclopent-1-enecarboxylate (**17d**) (1.0 g, 4.1 mmol) and trimethylsilyl isothiocyanate (3.0 ml, 21 mmol) were refluxed for 3 h in an atmosphere of nitrogen. The cooled reaction mixture was quenched with dropwise addition of saturated aqueous $NaHCO_3$ (10 ml) and water (10 ml). The mixture was extracted with dichloromethane (3 × 50 ml). The combined organic phases were dried and evaporated under reduced pressure. Purification by column chromatography on silica using dichloromethane and methanol (5%) as eluent gave the thiouracil **18d** (878 mg, 83%) as a light brown solid; mp 222–228 °C; (Found: C, 65.3; H, 5.6; N, 10.6. $C_{14}H_{14}N_2OS$, requires C, 65.1; H, 5.5; N, 10.8%); R_f 0.45 (5% EtOH–CH_2Cl_2); δ_H($CDCl_3$) 1.92 (2 H, quintet, *J* 7.5, $CH_2CH_2CH_2$), 2.57, 2.78 (4 H, 2 × t, *J* 7.5, CH_2CH_2CH_2), 5.58 (2 H, s, PhCH_2), 7.21–7.39 (5 H, m, Ar), 12.59 (1 H, br s, NH); δ_C($CDCl_3$) 20.5 (CH_2-*C*H_2CH_2), 27.2, 32.6 (*C*H_2CH_2*C*H_2), 52.8 (CH_2N), 117.9 (C4a), 126.0, 127.2, 128.6, 135.6 (Ar), 157.6, 158.3 (C4 and C7a), 177.2 (C2); *m*/*z* (EI) 258 (M^+, 100%), 91 (82).

1-Benzyl-5-methyl-7-phenyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (19)

1-Benzyl-5-methyl-7-phenyl-2-thioxo-1,2,3,5,6,7-hexahydrocyclopentapyrimidin-4-one (**18a**) (648 mg, 1.86 mmol, with a *cis*/*trans* ratio of 2 : 3) was refluxed for 36 h in 25% aqueous chloroacetic acid. A precipitate was formed on cooling the reaction mixture. Purification by column chromatography on silica using dichloromethane and methanol (3%) as eluent gave the uracil **19** (195 mg, 32%, with a *cis*/*trans* ratio of 2 : 3) as a white solid; mp 146–148 °C; (Found: C, 75.6; H, 6.2; N, 8.3. $C_{21}H_{20}N_2O_2$, requires C, 75.9; H, 6.1; N, 8.4%); R_f 0.40 (5% EtOH–CH_2Cl_2); δ_H($CDCl_3$) 1.28 (3 H, d, *J* 6.9, CHCH_3(*cis*)), 1.32 (3 H, d, *J* 6.9, CHCH_3(*trans*)), 1.54 (1 H, td, *J* 3.6 and 13.7, CHCH_aH(*cis*)), 1.94–2.05, 2.10–2.18 (2 H, 2 × m, CHCH_2-(*trans*)), 2.78 (1 H, td, *J* 9.9 and 13.7, CHCHH_b(*cis*)), 3.15–3.22 (1 H, m, C*H*CH_3(*cis*)), 3.32 (1 H, sextet, *J* 6.9, C*H*CH_3(*trans*)), 3.96–4.01 (1 H, m, PhCH), 4.07, 5.26 (2 H, 2 × d, *J* 16.1, CH_2N), 7.02–7.12, 7.23–7.40 (10 H, m, Ar), 8.51 (1 H, br s, NH); δ_C($CDCl_3$) 19.7, 21.0 (CH_3), 34.7, 34.9 (*C*HCH_3), 41.4, 42.8 (CH*C*H_2), 46.8, 47.0 (PhCH), 49.2, 49.6 (CH_2N), 118.3 (C4a), 126.3, 126.4, 126.7, 127.0, 127.6, 127.7, 127.8, 127.8, 128.9, 128.9, 129.5, 129.5, 136.1, 140.6, 142.1 (Ar), 152.6, 157.5, 160.8 (C2, C4 and C7a); *m*/*z* (EI) 332 (M^+, 9%), 91 (100).

5-Methyl-7-phenyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (20)

1-Benzyl-5-methyl-7-phenyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (**19**) (127 mg, 0.38 mmol, with a *cis*/*trans* ratio of 2 : 3) was heated at 165 °C for 30 min in PPA. The dark green solution was cooled and water added. As the PPA dissolved in the water, a brown solid crystallised. The solid was filtered off and washed with water. Purification by column chromatography on silica using dichloromethane and ethanol (2.5%) as eluent gave the uracil **20** (36 mg, 39%, with a *cis*/*trans* ratio of 1 : 1) as a slightly brown-coloured solid; (Found: C, 68.8; H, 5.7; N, 11.4. $C_{14}H_{14}N_2O_2$, 0.1 H_2O requires C, 68.9; H, 5.8; N, 11.5%); mp 233–236 °C; R_f 0.20 (5% EtOH–CH_2Cl_2); δ_H(DMSO-d_6) 1.18, 1.20 (3 H, 2 × d, *J* 6.4, CHCH_3), 1.36 (1 H, td, *J* 5.3 and 13.3, CH_aH(*cis*)), 2.01–2.08 (2 H, m, CH_2(*trans*)), 2.80 (1 H, td, *J* 9.2 and 13.3, CHH_b(*cis*)), 2.98, 3.12 (1 H, 2 × sextet, *J* 6.4, C*H*CH_3), 4.11–4.19 (1 H, m, PhCH), 7.08–7.37 (5 H, m, Ar), 10.82, 10.90 (2 H, 2 × br s, NH); δ_C(DMSO-d_6) 19.7, 20.6 (CH_3), 34.0, 34.2 (*C*HCH_3), 41.8 (CH*C*H_2), 47.8, 48.3 (PhCH), 114.4, 115.0 (C4a), 126.6, 126.8, 127.3, 127.6, 128.5, 128.6, 141.8, 142.4 (Ar), 152.4, 152.5, 155.4, 156.2, 162.0, 162.1 (C2, C4 and C7a); *m*/*z* (MALDI-peak matching) 265.0948 (MNa^+). $C_{14}H_{14}N_2O_2Na$ requires 265.0948.

1-Ethoxymethyl-5-methyl-7-phenyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (6)

5-Methyl-7-phenyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (**20**) (30 mg, 0.124 mmol) was suspended in dry acetonitrile (3 ml) under nitrogen and BSA (0.11 ml, 0.43 mmol) was added. The reaction mixture was stirred for 10 min at rt and then cooled to −45 °C. Diethoxymethane (18 mg, 0.25 mmol) in dry acetonitrile (0.1 ml) and TMS-triflate (29 mg, 0.13 mmol) in dry acetonitrile (0.1 ml) were added to the reaction mixture, which was slowly warmed to rt for 2.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (1 ml) followed by evaporation under reduced pressure. Water (5 ml) was added followed by extraction with diethyl ether (3 × 15 ml). The combined diethyl ether phases were dried and evaporated under reduced pressure. Purification by column chromatography on silica using dichloromethane and ethanol (2%) as eluent gave **6** (32 mg, 86%, with a *cis*/*trans* ratio of 1 : 1) as a white solid; R_f 0.30 (5% EtOH–CH_2Cl_2); δ_H($CDCl_3$) 1.14 (3 H, t, *J* 7.0, CH_2CH_3(*cis*)), 1.17 (3 H, t, *J* 7.0, CH_2CH_3(*trans*)), 1.30 (3 H, d, *J* 6.8, $CHCH_3$(*cis*)), 1.35 (3 H, d, *J* 6.6, $CHCH_3$(*trans*)), 1.61 (1 H, td, *J* 4.0 and 13.6, $CHCH_aH$(*cis*)), 2.14–2.22 (2 H, m, $CHCH_2$(*trans*)), 2.93 (1 H, td, *J* 9.7 and 13.6, $CHCH_bH$(*cis*)), 3.16–3.26 (1 H, m, $CHCH_3$(*cis*)), 3.29–3.36 (1 H, m, $CHCH_3$(*trans*)), 3.38–3.59 (2 H, m, CH_2CH_3), 4.29, (1 H, d, *J* 10.5, NCH_aH(*cis*)), 4.39–4.47 (1 H, m, PhCH), 4.41 (1 H, d, *J* 10.6, NCH_aH(*trans*)) 5.28 (1 H, d, *J* 10.5, NCH_bH(*cis*), 5.30 (1 H, d, *J* 10.6, NCH_bH(*trans*)), 7.10–7.38 (5 H, m, Ar), 9.19 (1 H, br s, NH); δ_C($CDCl_3$) 15.0 (CH_2CH_3), 19.7, 20.9 ($CHCH_3$), 34.6, 34.9 ($CHCH_3$), 41.6, 42.8 ($CHCH_2$), 48.7, 49.2 (PhCH), 64.8, 64.9 (CH_2CH_3), 72.3, 72.5 (NCH_2), 118.7, 119.6 (C4a), 126.8, 127.1, 127.4, 127.6, 129.3, 129.4, 141.0, 142.4 (Ar), 152.8, 153.0, 155.8, 157.0, 160.9, 161.3 (C2, C4 and C7a); *m*/*z* (MALDI-peak matching) 323.1370 (MNa^+). $C_{17}H_{20}N_2O_3Na$ requires 323.1366.

2-Phenylpent-4-enenitrile (21)

N-Allyl-1-phenylacetamide (41.1 g, 0.235 mol), triphenylphosphine (123 g, 0.469 mol), dry carbon tetrachloride (67 ml, 0.69 mol), dry triethylamine (96 ml, 0.69 mol) and dry dichloromethane (400 ml) were stirred for 19 h using a $CaCl_2$ drying tube. The organic phase was washed with water (4 × 100 ml), dried and evaporated under reduced pressure, which gave 118 g of a dark brown solid. Purification by vacuum distillation gave the nitrile **21** (30.2 g, 81%) as a clear colourless oil; bp 78–87 °C/0.2 mbar (lit.,[36] 80 °C/0.5 mbar).

5-Methyl-2-phenylhex-4-enenitrile (22)

Sodium (1.5 g, 66 mmol), diethyl carbonate (40 ml), benzyl cyanide (7.0 g, 60 mmol) and 4-bromo-2-methylbut-2-ene (7.5 ml, 66 mmol) were used following the procedure described for synthesizing **8**. The addition of 2-methylbut-2-ene was followed by stirring overnight at rt. The orange oil obtained as the crude product was further purified by Kugelrohr vacuum distillation which afforded the nitrile **22** as a colourless clear oil; bp 94–104 °C/0.09 mbar (lit.,[37] 94–96 °C/0.2 Torr); R_f 0.65 (CH_2Cl_2); δ_H($CDCl_3$) 1.53, 1.70 (3 H, 2 × s, $=C(CH_3)_2$), 2.53–2.61 (2 H, m, $CHCH_2$), 3.75 (1 H, dd, *J* 6.9 and 8.0, PhCH), 5.14–5.18 (1H, m, =CH), 7.24–7.37 (5 H, m, Ar); δ_C($CDCl_3$) 17.8, 25.7 (2 × CH_3), 34.5 ($CHCH_2$), 37.8 (PhCH), 118.4 (CH=), 120.8 (CN), 127.3, 127.9, 128.9, 135.6, 136.6 (Ar and =C); *m*/*z* (EI) 185 (M^+, 22%), 69 (100).

Ethyl 3-oxo-4-phenylhept-6-enoate (23)

Activated Zn (41 g, 0.627 mol) in dry THF (500 ml) was heated to reflux using a $CaCl_2$ drying tube. 2-Phenylpent-4-enenitrile (**21**) (14.8 g, 0.094 mol) and ethyl 2-bromoacetate (~2 ml of 26.2 ml, 0.236 mol) were added to the reaction mixture. As a green colour and/or a strong effervescence were observed, the remaining ethyl 2-bromoacetate was added dropwise to the reaction mixture. Reflux was continued for 1.5 h before cooling and addition of saturated aqueous K_2CO_3 (200 ml). The solution was stirred vigorously overnight. The upper THF phase was decanted from the thick lower aqueous phase. The aqueous phase was washed and decanted with THF (4 × 100 ml). The combined THF phases were stirred for 1 h with 1 M HCl (200 ml). Evaporation of the THF under reduced pressure was followed by extraction with dichloromethane (2 × 250 ml). The combined dichloromethane phases were gently (emulsion forms easily) washed with saturated aqueous $NaHCO_3$ (100 ml). Drying and evaporation under reduced pressure afforded **23** (25.3 g, 100%) as a brown oil; R_f 0.50 (10% ethyl acetate–cyclohexane); δ_H($CDCl_3$) 1.21 (3 H, t, *J* 7.2, CH_3), 2.45 (1 H, td, *J* 7.2 and 14.4, $=CHCH_aH$), 2.83 (1 H, td, *J* 7.2 and 14.4, $=CHCH_bH$), 3.28 (1 H, d, *J* 15.5, $COCH_aHCO$), 3.41 (1 H, d, *J* 15.5, $COCH_bHCO$), 3.87 (1 H, t, *J* 7.2, PhCH), 4.07–4.15 (2 H, m, OCH_2), 4.94–5.06 (2 H, m, $=CH_2$), 5.59–5.70 (1 H, m, =CH), 7.19–7.37 (5 H, m, Ar); δ_C($CDCl_3$) 13.9 (CH_3), 36.1 (=CH–CH_2), 48.0 ($COCH_2$), 58.7 (PhCH), 61.2 (OCH_2), 116.8 ($=CH_2$), 127.6, 128.4, 129.0, 135.2, 137.2 (Ar and =CH), 166.9 (CO_2), 201.6 (CO); *m*/*z* (EI) 246 (M^+, 26%), 131 (100).

Ethyl 7-methyl-3-oxo-4-phenyloct-6-enoate (24)

5-Methyl-2-phenylhex-4-enenitrile (**22**) (8.0 g, 43.3 mmol) was used following the procedure described for synthesizing **23**. The β-keto-ester **24** (12.5 g, 100%, NMR shows minor impurities) was isolated as a brown oil; R_f 0.50 (CH_2Cl_2); δ_H($CDCl_3$) 1.21 (3 H, t, *J* 7.1, CH_2CH_3), 1.52, 1.61 (6 H, 2 × s, $=C(CH_3)_2$), 2.38 (1 H, td, *J* 7.4 and 14.6, $=CHCH_aH$) 2.75 (1 H, td, *J* 7.4 and 14.6, $=CHCH_bH$), 3.29, 3.40 (2 H, 2 × d, *J* 15.4, $COCH_2CO$), 3.78 (1 H, t, *J* 7.4, PhCH), 4.07–4.18 (2 H, m, CH_2CH_3), 4.96–5.01 (1 H, m, =CH), 7.19–7.36 (5 H, m, Ar); δ_C($CDCl_3$) 14.0 (CH_2CH_3), 17.7, 25.6 ($=C(CH_3)_2$), 30.8 (=CH–CH_2), 48.3 (PhCH), 59.1 ($COCH_2CO$), 61.2 (OCH_2), 120.8 (=C), 127.5, 128.5, 128.9, 133.7, 137.7 (=CH and Ar), 167.0 (CO_2), 202.2 (CO); *m*/*z* (MALDI-peak matching) 297.1463. $C_{17}H_{22}O_3Na$ requires 297.1461 (MNa^+).

6-(1-Phenylbut-3-enyl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (25)

Sodium (25 g, 1.09 mol) was dissolved in absolute EtOH (600 ml). Thiourea (80 g, 1.05 mol) and ethyl 3-oxo-4-phenylhept-6-enoate (**23**) (24.3 g, 0.099 mol) was added to the solution which was refluxed for 4.5 h. The EtOH was carefully evaporated under reduced pressure to give a yellow solid. The solid was dissolved in water (150 ml). To the solution was added 3 M HCl until pH = 9–10 and then acetic acid until pH = 7–8. The precipitate formed was filtered off and washed with water, which gave **25** (13.7 g, 54%) as a grey solid. A small portion was recrystallised from EtOH, which gave **25** as a white compound; mp 198.5–199.5 °C (EtOH); (Found: C, 65.0; H, 5.5; N, 10.9. $C_{14}H_{14}N_2OS$ requires C, 65.1; H, 5.5; N, 10.8%); R_f 0.40 (5% MeOH–CH_2Cl_2); δ_H(DMSO-d_6) 2.62 (1 H, td, *J* 7.3 and 14.3, $=CHCH_aH$), 2.80 (1 H, td, *J* 7.3 and 14.3, $=CHCH_bH$), 3.88 (1 H, t, *J* 7.3, PhCH), 5.00 (1 H, d, *J* 10.1, $=CH_{trans}H$), 5.07 (1 H, d, *J* 17.1, $=CH_{cis}H$), 5.60–5.71 (1H, m, $=CHCH_2$), 5.94 (1 H, s, 5-H), 7.25–7.41 (5 H, m, Ar), 12.30, 12.38 (2 H, 2 × br s, 2 × NH); δ_C(DMSO-d_6) 36.4 ($=CHCH_2$), 46.2 (PhCH), 102.4 (C5), 117.3 ($=CH_2$) 127.2, 127.9, 128.5, 135.31, 139.8 (Ar and =CH), 158.2, 161.0 (C4 and C6), 175.9 (C2); *m*/*z* (EI) 258 (M^+, 100%), 174 (23).

6-(4-Methyl-1-phenylpent-3-enyl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (26)

Ethyl 7-methyl-3-oxo-4-phenyloct-6-enoate (**24**) (11.7 g, 42.6 mmol) was used following the procedure described for the synthesis of **25**. Compound **26** (5.90 g, 48%) was isolated as a

slightly purple coloured solid. A sample was recrystallised in EtOH to give off-white crystals; mp 195–196 °C (EtOH); R_f 0.45 (5% MeOH–CH_2Cl_2); δ_H(DMSO-d_6) 1.55, 1.60 (6 H, 2 × s, =C(CH_3)$_2$), 2.51–2.75 (2 H, m, =CH–CH_2), 3.78 (1 H, t, *J* 8.0, PhCH), 4.96 (1 H, t, *J* 6.8, =CH), 5.94 (1 H, s, 5-H), 7.23–7.41 (5 H, m, Ar), 12.25, 12.36 (2 H, 2 × br s, 2 × NH); δ_C(DMSO-d_6) 17.7, 25.4 (=C(*C*H_3)$_2$), 31.2 (CH_2), 46.9 (PhCH), 102.3 (C5), 121.0 (=C), 127.1, 127.9, 128.4, 133.2, 140.1 (Ar and =CH), 158.6, 161.1 (C4 and C6), 175.9 (C2); *m*/*z* (MALDI-peak matching) 309.10400. $C_{16}H_{18}N_2OSNa$ requires 309.10320 (MNa^+).

6-(1-Phenylbut-3-enyl)-1*H*-pyrimidine-2,4-dione (27)

Crude 6-(1-phenylbut-3-enyl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (**25**) (obtained from 14.8 g of **21** in two steps) was refluxed for 20 h in 10% aqueous chloroacetic acid (400 ml). White precipitate was formed as the reaction mixture was cooled. Filtration and washing with water gave the uracil **27** (11.40 g, 50% from **21**) as a white solid. A sample was recrystallised in EtOH; mp 175.5–177 °C (EtOH); (Found: C, 69.3; H, 5.8; N, 11.5. $C_{14}H_{14}N_2O_2$ requires C, 69.4; H, 5.8; N, 11.6%); R_f 0.25 (5% MeOH–CH_2Cl_2); δ_H(DMSO-d_6) 2.64 (1 H, td, *J* 7.4 and 14.4, =CHCH_aH), 2.81 (1 H, td, *J* 7.4 and 14.4, =CHCHH_b), 3.74 (1 H, t, *J* 7.4, PhCH), 4.99 (1 H, d, *J* 10.2, =CH_{trans}H), 5.08 (1 H, d, *J* 17.1, =CHH_{cis}), 5.56 (1 H, s, 5-H), 5.60–5.73 (1 H, m, =CH), 7.24–7.41 (5 H, m, Ar), 10.87, 10.97 (2 H, 2 × br s, 2 × NH); δ_C(DMSO-d_6) 35.9 (=CH*C*H_2), 47.0 (PhCH), 97.7 (C5), 117.2 (=CH_2), 127.1, 127.8, 128.5, 135.4, 140.0 (=CH and Ar), 151.6, 157.9, 164.1 (C2, C4 and C6); *m*/*z* (EI) 242 (M^+, 100%), 201 (79).

5,5-Dimethyl-8-phenyl-5,6,7,8-tetrahydro-1*H*-quinazoline-2,4-dione (28) and 6-(4,4-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-1*H*-pyrimidine-2,4-dione (29)

6-(4-Methyl-1-phenylpent-3-enyl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (**26**) (0.90 g, 3.1 mmol) was refluxed for 4 days in 10% aqueous chloroacetic acid (75 ml). TLC showed three products after 1 day and only two products after 4 days, where 20 ml water was added. A precipitate was formed when the reaction mixture was cooled. Filtration at 0 °C and washing with water (3 × 10 ml) gave the crude uracils **28** and **29** (0.80 g, 94%, ~1 : 1 mixture, pure on NMR) as a light brown solid. Purification and separation by column chromatography on silica using dichloromethane and ethanol (2.5%) as eluent gave small amounts of pure **28** and **29**, which were recrystallised in EtOH to give white crystals; **28**: mp > 250 °C (EtOH); R_f 0.25 (5% EtOH–CH_2Cl_2); δ_H(DMSO-d_6) 1.19–1.33 (2 H, m, CH_2), 1.23, 1.33 (6 H, 2 × s, 2 × CH_3), 1.52–1.67, 1.97–2.08 (2 H, m, CH_2), 3.78–3.84 (1 H, m, CH), 7.08–7.37 (5 H, m, Ar); δ_C(DMSO-d_6) 26.3, 28.2 (2 × CH_3), 26.5 (CH*C*H_2), 31.7 (C*C*H_2), 34.3 (C), 41.9 (PhCH), 114.9 (C4a), 126.4, 128.1, 128.2, 141.8 (Ar), 148.9, 150.6, 163.6 (C2, C4 and C8a); *m*/*z* (MALDI-peak matching) 271.14380 (MH^+). $C_{27}H_{29}N_2O$ requires 271.14410; **29**: mp > 250 °C (EtOH); R_f 0.20 (5% EtOH–CH_2Cl_2); δ_H(DMSO-d_6) 1.23, 1.30 (6 H, 2 × s, 2 × CH_3), 1.51–1.64, 1.95–2.01 (4 H, m, 2 × CH_2), 3.81 (1 H, dd, *J* 5.5 and 11.4, PhCH), 4.70 (1 H, s, 5-H), 6.97 (1 H, d, *J* 7.6, Ar), 7.11 (1 H, t, *J* 7.6, Ar), 7.24 (1 H, t, *J* 7.6, Ar), 7.43 (1 H, d, *J* 7.6, Ar), 10.97, 11.00 (2 H, 2 × br s, 2 × NH); δ_C(DMSO-d_6) 24.0 (CH*C*H_2), 31.4, 31.6 (2 × CH_3), 33.5 (C*C*H_2), 35.0 (C), 42.5 (PhCH), 100.1 (C5), 125.5, 126.8, 127.3, 129.1, 133.0, 146.0 (Ar), 151.7, 159.9, 163.8 (C2, C4 and C6); *m*/*z* (MALDI-peak matching) 293.12580 (MNa^+). $C_{27}H_{28}N_2ONa$ requires 293.12605.

1-Ethoxymethyl-5,5-dimethyl-8-phenyl-5,6,7,8-tetrahydro-1*H*-quinazoline-2,4-dione (5)

A ~1 : 1 mixture of compound **28** and **29** (400 mg, 1.48 mmol), acetonitrile (20 ml), diethoxymethane (0.26 ml, 2.96 mmol) and TMS-triflate (0.29 ml, 1.63 mmol) were used following the procedure described for synthesizing **6**. The solution was stirred overnight before work up. Purification by dry column vacuum chromatography on silica using petroleum ether and ethyl acetate (10–100%) gave **5** (123 mg, 51%) as a white solid; mp 165.5–167.5 °C; (Found: C, 68.7; H, 7.2; N, 8.2. $C_{19}H_{24}N_2O_3$, 0.25 H_2O requires C, 68.5; H, 7.3; N, 8.4%); R_f 0.30 (40% ethyl acetate–petroleum ether); δ_H($CDCl_3$) 1.17 (3 H, t, *J* 6.9, CH_2CH_3), 1.22–1.32, 1.46–1.54, 1.76–1.81, 2.11–2.22 (4 H, m, CH_2CH_2), 1.37, 1.47 (6 H, 2 × s, C(CH_3)$_2$), 3.51 (1 H, qd, *J* 6.9 and 9.6, CH_aHCH$_3$), 3.63 (1 H, qd, *J* 6.9 and 9.6, CHH_bCH$_3$) 4.36 (1 H, d, *J* 3.6, PhCH), 4.47, 5.47 (2 H, 2 × d, *J* 11.1, NCH_2O), 7.10–7.37 (5 H, m, Ar), 9.58 (1 H, br s, NH); δ_C($CDCl_3$) 15.1 (CH_2CH_3), 26.7 (C*C*H_3), 27.5 (CH_2CH_2), 28.7 (C*C*H_3), 33.3 (C), 34.0 (CH_2CH_2), 40.8 (PhCH), 65.0 (*C*H_2CH_3), 72.1 (NCH_2O), 119.6 (C4a), 127.1, 127.8, 129.0, 141.1 (Ar), 150.4, 152.0, 162.5 (C2, C4 and C8a); *m*/*z* (EI) 328 (M^+, 20%), 267 (100).

5-Bromo-6-(1-phenylbut-3-enyl)-1*H*-pyrimidine-2,4-dione (31)

To 6-(1-phenylbut-3-enyl)-1*H*-pyrimidine-2,4-dione (**27**) (1.89 g, 7.79 mmol), anhydrous LiBr (2.0 g, 23 mmol) and glacial acetic acid (100 ml), was added dropwise bromine (0.89 ml, 17.5 mmol) in glacial acetic acid (40 ml). The solution was stirred for 18 h and then evaporated under reduced pressure to a small volume (~10 ml). Water (100 ml) was added and white solid precipitated on stirring. Filtration and washing with water gave a white solid (3.77 g, 7.79 mmol, 100%) of the triple brominated derivative of **27**, which was stirred under reflux for 3.5 h with NaI (11.8 g, 78 mmol) in acetone (125 ml). The hot dark solution was filtered and the filtercake was washed with acetone (2 × 25 ml). The combined filtrates were evaporated under reduced pressure, which gave a dark coloured residue. Aqueous hot EtOH (125 ml, 80%) and aqueous saturated $Na_2S_2O_3$ (20 ml) were added, which gave a colourless two phase system. The alcohol layer was decanted and the aqueous layer was washed and decanted with EtOH (2 × 25 ml). The combined ethanol phases were evaporated under reduced pressure until precipitation started. The solution was cooled on ice and filtration gave **31** (1.96 g, 78%) as a white solid which pure according to NMR. A sample was recrystallised in EtOH; mp 206–208 °C (EtOH); (Found: C, 51.5; H, 4.1; N, 8.5. $C_{14}H_{13}N_2O_2Br$, 0.25 H_2O requires C, 51.6; H, 4.2; N, 8.6%); R_f 0.45 (75% ethyl acetate–petroleum ether); δ_H(DMSO-d_6) 2.80 (1 H, td, *J* 6.6 and 13.9, =CHCH_aH), 3.06 (1 H, td, *J* 9.1 and 13.9, =CHCHH_b), 4.59 (1 H, dd, *J* 6.6 and 9.1, PhCH), 5.05 (1 H, d, *J* 10.2, =CH_{trans}H), 5.13 (1 H, d, *J* 17.4, =CHH_{cis}), 5.71–5.80 (1 H, m, =CH), 7.27–7.54 (5 H, m, Ar), 11.04, 11.57 (2 H, 2 × br s, 2 × NH); δ_C(DMSO-d_6) 34.0 (=CH*C*H_2), 47.2 (PhCH), 96.8 (C5), 117.4 (=CH_2) 127.3, 127.5, 128.6, 135.0, 138.4 (Ar and =CH), 150.4, 154.05, 159.9 (C2, C4 and C6); *m*/*z* (EI) 320 (M^+, 100%), 322 (92), 241 (1050).

5-Bromo-1,3-bis(phenoxymethyl)-6-(1-phenylbut-3-enyl)-1*H*-pyrimidine-2,4-dione (32a)

5-Bromo-6-(1-phenylbut-3-enyl)-1*H*-pyrimidine-2,4-dione (**31**) (504 mg, 1.57 mmol) and DMF (8 ml) were stirred under an atmosphere of nitrogen. The reaction mixture became deep blue as DBU (0.83 ml, 5.6 mmol) was added. After 10 min of stirring, BOM-Cl (898 mg, 5.74 mmol) was added dropwise. The golden yellow solution was stirred for 23 h and then poured into water (200 ml). The water phase was extracted with diethyl ether (6 × 100 ml). The combined diethyl ether phases were washed with brine, dried and evaporated under reduced pressure, which gave a thick, light brown oil. Purification by column chromatography on silica using dichloromethane as eluent gave the bis protected compound **32a** (539 mg, 61%) as a clear colourless oil; (Found: C, 64.2; H, 5.3; N, 4.8. $C_{30}H_{29}N_2O_4Br$ requires C, 64.2; H, 5.2; N, 5.0%); R_f 0.15 (CH_2Cl_2); δ_H($CDCl_3$) 2.99–3.08 (2 H, m, =CHCH_2), 4.57–4.71 (3 H, m, PhC*H* and

NCH_2), 4.75 (2 H, s, $PhCH_2$), 4.90–5.49 (2 H, m, NCH_2), 5.08 (1 H, d, *J* 10.2, =CH_{trans}H), 5.19 (1 H, dd, *J* 1.2 and 17.4, =CHH_{cis}), 5.56 (2 H, s, $PhCH_2$), 5.76–5.90 (1 H, m, =CH), 7.16–7.43 (15 H, m, Ar); $\delta_C(CDCl_3)$ 33.9 (=CH*C*H_2), ~42 (broad, PhCH), 72.2 (broad, NCH_2), 72.5, 72.7 (2 × $PhCH_2$), 74.6 (NCH_2), 118.4 (=CH_2), 126.7, 127.3, 128.9, 134.2 (broad, Ar) 127.6, 127.7, 127.9, 128.0, 128.3, 128.4, 137.7, 137.8 (=CH and Ar), 151.9 (C2); *m*/*z* (FAB) 561 (M^+, 100%), 563 (85), 503 (645).

1,3-Bis(benzyloxymethyl)-5-methyl-7-phenyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (33) and 1,3-bis(benzyloxymethyl)-6-(1-phenylbut-3-enyl)-1*H*-pyrimidine-2,4-dione (32b)

5-Bromo-1,3-bis(phenoxymethyl)-6-(1-phenylbut-3-enyl)-1*H*-pyrimidine-2,4-dione (**32a**) (770 mg, 1.37 mmol) in dry toluene (40 ml) was degassed with nitrogen for 5 min. AIBN (45 mg, 0.27 mmol) and tributyltin hydride (0.44 ml, 1.3 mmol) were added and the solution was refluxed for 4 h under nitrogen. Evaporation under reduced pressure followed by column chromatography on silica using petroleum ether and dichloromethane (0–20%) as eluent gave a clear oil. To remove tin residues the oil was dissolved in ethyl acetate (10 ml) and triethylamine (1.5 ml) and stirred for 1.5 h until a fine white precipitate had formed, which was filtered off. The filtrate was evaporated under reduced pressure and further purified by preparative TLC on silica using dichloromethane and EtOH (2%) as eluent, which gave **33** and **32b** (470 mg, 71%, ~1 : 1 mixture, **33** with *cis*/*trans* ratio of ~4 : 1) as a clear colourless oil; R_f 0.20 (2% EtOH–CH_2Cl_2); **33**: characteristic NMR signals: $\delta_H(CDCl_3)$ 1.26 (3 H, d, *J* 7.0, CHCH_3(*cis*)), 1.27 (3 H, d, *J* 7.0, CHCH_3(*trans*)), 1.54 (1 H, td, *J* 3.9 and 13.5, CHCH_aH(*cis*)), 2.02–2.18 (2 H, m, CHCH_2(*trans*)), 2.84 (1 H, td, *J* 9.7 and 13.5, CHCHH_b(*cis*)), 3.10–3.17 (1 H, m, C*H*CH_3(*cis*)), 3.27–3.33 (1 H, m, C*H*CH_3-(*trans*)); **32b**: characteristic NMR signals: $\delta_H(CDCl_3)$ 2.48–2.64 (2 H, m, =CHCH_2), 5.86 (1 H, s, 5-H); **33** + **32b**: *m*/*z* (MALDI-peak matching) 505.2116. $C_{30}H_{30}N_2O_4Na$ requires 505.2098 (MNa^+).

5-Methyl-7-phenyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (20) and 6-(1-phenylbut-3-enyl)-1*H*-pyrimidine-2,4-dione (27)

A ~1 : 1 mixture of **33** (*cis*/*trans* ratio of ~4 : 1) and **32b** (406 mg, 0.72 mmol) was refluxed for 1.5 h in TFA (40 ml). Evaporation, followed by co-evaporation with toluene (40 ml), under reduced pressure gave a dark brown residue. Purification by column chromatography on silica using dichloromethane and EtOH (5%) as eluent gave a yellow oil. Recrystallisation in EtOH–water gave initially a small amount of brown solid (~5 mg) which was filtered off. The filtrate was evaporated under reduced pressure until precipitation of white solid was observed. The solution was cooled and after filtration and drying **20** and **27** (73 mg, 42%) were obtained as a ~1 : 1 mixture where **20** had a *cis*/*trans* ratio of ~4 : 1; NMR data are consistent with those of **20** obtained in the reaction from **19**.

1-Ethoxymethyl-5-methyl-7-phenyl-1,5,6,7-tetrahydrocyclopentapyrimidine-2,4-dione (6)

A ~1 : 1 mixture of compound **20** (*cis*/*trans* ratio of ~4 : 1) and **27** (62 mg, 0.26 mmol), HMDS (3 ml) and $(NH_4)_2SO_4$ (10 mg) were refluxed for 1 h to give a clear solution. The solution was evaporated under reduced pressure to a small volume (~1 ml), which was heated to 80 °C in dry acetonitrile (4 ml) where diethoxymethane (55 mg, 0.76 mmol) and conc H_2SO_4 (10 mg, 0.1 mmol) were added. After 16 h at 80 °C diethoxymethane (93 mg, 1.29 mmol) and conc H_2SO_4 (15 mg, 0.15 mmol) were also added. Although after stirring for another 24 h the reaction was not finished according to TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ (1 ml). The mixture was stirred vigorously and then extracted with ethyl acetate (2 × 15 ml). The combined ethyl acetate phases were washed with brine (10 ml), dried and evaporated under reduced pressure. Purification by preparative TLC on silica using dichloromethane and EtOH (2%) as eluent gave **6** (11 mg, 29%, *cis*/*trans* ratio of ~4 : 1) as a clear oil; NMR data are consistent with those of **6** obtained in two steps from **19**.

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