Synthesis and reactions of Biginelli-compounds. Part 14.[1] A rhodium-induced cyclization–cycloaddition sequence for the construction of conformationally rigid calcium channel modulators of the dihydropyrimidine type

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Conformationally rigid polyheterocycles **14a**,**b** which mimic the putative receptor-bound conformation of dihydropyridine type calcium channel modulators are prepared in a six-step reaction sequence starting from urea, ethyl acetoacetate and 2-alkenylbenzaldehydes. The key step in the synthesis involves the regio- and diastereoselective intramolecular 1,3-dipolar cycloaddition reaction of a dihydropyrimidine-fused isomünchnone dipole. Deprotection of the CBZ-protected intermediates **13a**,**b** leads to the desired target molecules **14a**,**b**. Prolonged exposure of these cyclic enamines in solution to the atmosphere results in oxidation to the corresponding α-hydroxy imines **16a**,**b**. Catalytic hydrogenation of the related *N*-benzyl-protected polycycle **19** furnishes the fully saturated hexahydropyrimidine derivative **20**. The relative stereochemistry in **20** was established by an X-ray crystallographic analysis.

Introduction

Calcium channel antagonists of the 1,4-dihydropyridine type (DHPs) are among the most extensively used therapeutics worldwide and today are almost indispensable for the clinical treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias, or angina pectoris. These substances exert their therapeutic effect by reversibly blocking L-type calcium channels in the cardiovascular system. Although much information about the molecular architecture of the calcium ion channel and the specific amino acids involved in drug binding has been obtained in recent years, a definitive model of the 3D-structure of the biological receptor remains a significant challenge.[2]

DHP calcium channel antagonists (*e.g.* **1**, nifedipine) are flexible molecules, in which the C4-aryl moiety and the C3/C5 ester substituents can rotate, and the conformation of the 1,4-dihydropyridine ring can change.[3] Despite many studies on the structure–activity relationships for DHPs with respect to calcium channel antagonist–agonist modulation, there still remains debate on the exact stereochemical/conformational requirements for activity.[3–5] It was recently proposed that calcium channel modulation (antagonist *vs.* agonist activity) is dependent on the absolute configuration at C4, whereby the orientation of the 4-aryl group (*R*- *versus* *S*-enantiomer) acts as a "molecular switch" between antagonist and agonist activity.[4] In the receptor-bound conformation the substituted aryl ring should be positioned axially, perpendicular to, and bisecting the boat-like dihydropyridine ring, with the 4-aryl substituent (X) prefering the synperiplanar (sp) orientation relative to C4-H (Fig. 1).[4] A *cis*-carbonyl ester orientation (with respect to the C5=C6 bond) was also found mandatory for calcium channel modulatory activity.[4] Although it was proposed that the "right-hand-side" of DHPs is non-essential for activity, further studies are required to confirm this hypothesis.[5]

1 nifedipine

2 SQ 32,926

3

Apart from nifedipine (**1**) and other second-generation DHP analogs,[6] interest has also focused on structurally closely related 3,4-dihydro-2(1*H*)-pyrimidone analogs (DHPMs), *e.g.* **2** (SQ 32,926),[7] which show a very similar pharmacological profile to classical DHP calcium channel modulators.[8] Due to the inherent asymmetry of DHPMs the investigation of structural/conformational requirements and the effect of absolute stereochemistry on the biological activity is facilitated.[7,8] Furthermore, from the synthetic point of view, the selective structural functionalization of the "right-hand" side of this heterocyclic system is much easier than with the corresponding DHP analogs.[9]

In the present article we detail the synthesis of novel conformationally rigid, polycyclic dihydropyrimidine calcium channel modulators of type **3** (R = H), mimicking the proposed bioactive DHP conformation (Fig. 1), where two of the three flexible bonds in DHPs/DHPMs are constrained simultaneously.

Results and discussion

Our synthetic strategy towards DHPM derivatives of type **3** is based on an intramolecular 1,3-dipolar cycloaddition reaction of an *o*-alkenylaryl-tethered dihydropyrimidine-fused isomünchnone dipole (see below). In a recent publication[10] we

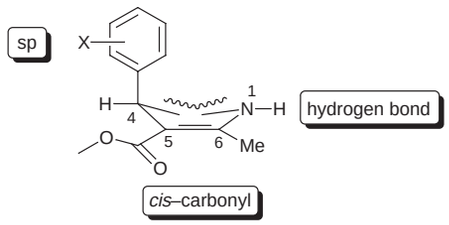
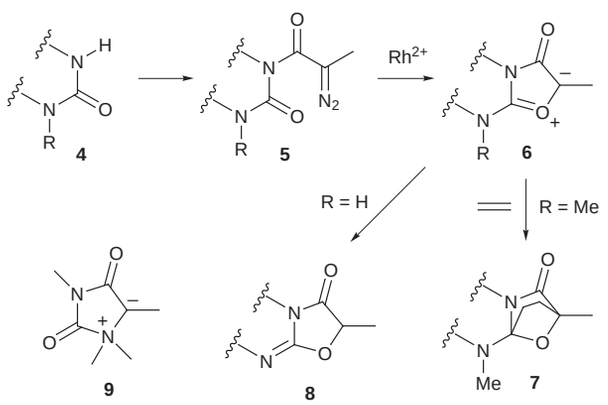


Fig. 1 Proposed receptor-bound conformation of DHP calcium channel modulators (antagonist form shown).[4]

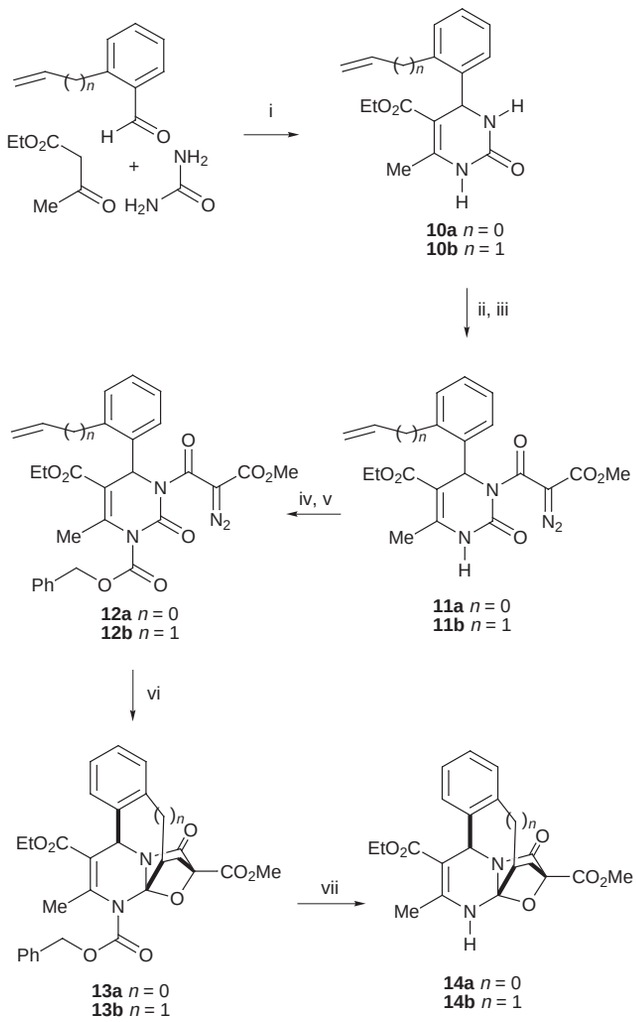
have described model studies dealing with bimolecular and intramolecular dipolar cycloaddition reactions of a variety of dihydropyrimidine-fused mesomeric betaines, including 1,3-thiazolium-4-olates (isothiomünchnones), 1,3-oxazolium-4-olates (isomünchnones), and cross-conjugated heteroaromatic 1,3-thiazinium betaines. These studies have led to the synthesis of biologically inactive polyheterocycles of type **3** where the crucial *N*1 position of the pyrimidine nucleus (*cf.* Fig. 1) is blocked by a methyl group (**3**; R = Me).[10] The overall reaction sequence used for this annulation–cycloaddition protocol is summarized in Scheme 1: diazo imide precursors **5**—which are



Scheme 1

readily available by functionalization of the cyclic urea moiety in **4**—undergo Rh^{2+}-catalyzed decomposition to yield "amino-isomünchnone" dipoles of type **6**. In the presence of a suitable dipolarophile (*i.e.* an internal π-bond) for R = Me spontaneous 1,3-dipolar cycloaddition takes place to furnish cycloadducts **7**. In sharp contrast, for R = H a rapid, thermally allowed 1,5-sigmatropic hydrogen shift in the isomünchnone occurs (**6**→**8**) before cycloaddition can take place.[10] Therefore, the modified strategy reported in the present article has been developed in order to access the desired cycloadducts **3** (R = H). It should be pointed out that this *cyclization–cycloaddition* cascade sequence[11] (**5**→**6**→**7**) can only be applied to cyclic ureas. In the case of a conformationally flexible urea (*e.g. N*,*N*,*N*′-trimethylurea) the initially formed rhodium carbenoid intermediate (not shown) cyclizes preferentially to the corresponding isomeric ammonium ylide **9**.[12]

For the preparation of the desired conformationally restricted calcium channel modulators of type **3** several different protection group strategies were initially considered. Originally, we anticipated that the use of *N*-benzylurea in the sequence outlined in Scheme 2 would allow the preparation of the corresponding *N*-benzyl protected cycloadducts **3** (R = benzyl) which subsequently could be debenzylated by a variety of well-known methods. Since this protocol ultimately failed (*cf.* Scheme 4) we developed the CBZ-based (benzyloxycarbonyl) protection method shown in Scheme 2 to obtain the desired polycyclic DHPMs **14a**,**b**. The required starting dihydropyrimidones **10a**,**b** were synthesized by standard Biginelli condensation[9] of ethyl acetoacetate, with urea, and 2-vinylbenzaldehyde (or 2-allylbenzaldehyde, respectively).[10] The reaction could either by carried out using ethanol–HCl[9] or polyphosphate ester–THF[13] as a reaction medium, producing nearly identical yields. Diazo imides **11a**,**b** were readily prepared in high overall yield by *N*-malonyl acylation of pyrimidones **10a**,**b** with methyl malonyl chloride in refluxing benzene,[14] followed by a standard diazo-transfer reaction with mesyl azide.[15] Even when a large excess of acylating reagent was used, the *N*3-acylated product was obtained in a regiospecific manner, without any *N*1- or bis-acylation products being formed. However, subsequent *N*1-protection could easily be performed by careful deprotonation of the enamidic NH in **11a**,**b** with sodium hydride in THF at 0 °C, followed by addition of benzyloxycarbonyl chloride (CBZ-Cl) as acylating reagent.[16] Decomposition of the protected diazo imides **12a**,**b** with a catalytic amount of rhodium acetate in benzene (reflux, 30 min) furnished directly the CBZ-protected pentacyclic dihydropyrimidine analogs **13a**,**b**, without isolation of the initially generated transient isomünchnone dipoles (*cf.* Scheme 1). The reaction temperature in this *cyclization–cycloaddition* cascade could be significantly reduced by switching to more reactive catalysts such as rhodium trifluoroacetate or rhodium perfluorobutyrate[17] (CH_2Cl_2, reflux, 90 min). The nature of the ligand on the transition metal had no influence on the regio- and diastereoselectivity of the cycloaddition process.[17] Regardless of the catalyst, both analogs **13a**,**b** were obtained as single diastereoisomers which is the result of an extremely favourable transition state alignment



Scheme 2 *Reagents and conditions*: i, MeOH, HCl, reflux; ii, $ClCOCH_2CO_2Me$, benzene, reflux; iii, MsN_3, Et_3N, CH_2Cl_2, rt; iv, NaH, THF, 0 °C; v, CBZ-Cl, THF, rt; vi, $Rh_2(OAc)_4$, benzene, reflux; vii, H_2, 10% Pd–C, rt, 1 atm.

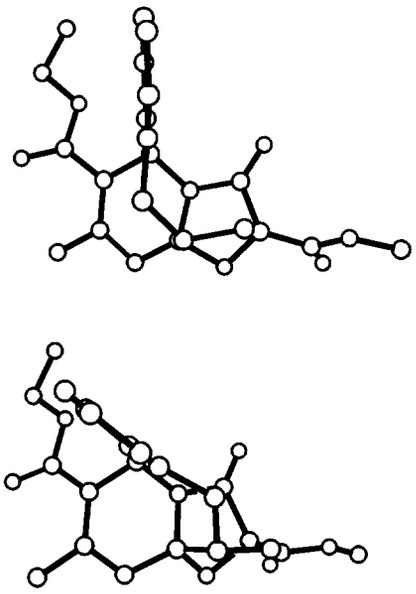
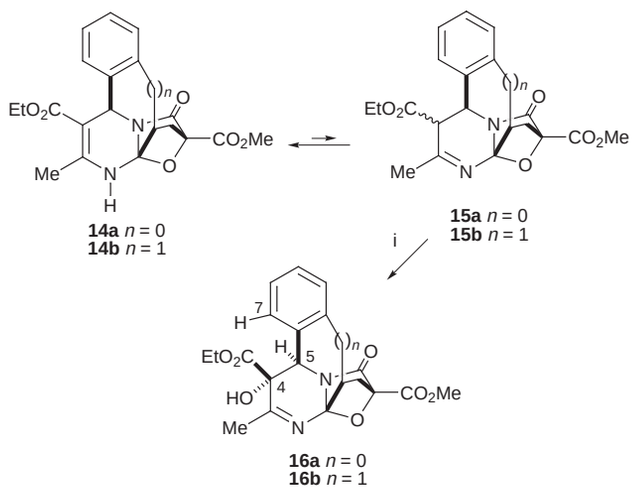


Fig. 2 AM1 optimized geometries for the two possible conformers of **14b**, *i.e.* **14b-A** (top, $\Delta H_f = -140.26$ kcal mol^{-1}) and **14b-B** (bottom, $\Delta H_f = -135.16$ kcal mol^{-1}). Hydrogen atoms omitted for clarity.

of the olefinic tether ($n = 0$, 1) relative to the carbonyl ylide dipole embedded into the isomünchnone system.[10] Finally, removal of the CBZ group by catalytic hydrogenation over Pd–C provided the desired conformationally rigid dihydropyrimidine derivatives **14a**,**b** in high yield.[16] The structures of these polycycles were confirmed by comparison of their ^{1}H and ^{13}C NMR spectra with spectroscopic data obtained for the corresponding *N*-methyl analogs for which X-ray structure determinations had been carried out.[10]

Molecular models of **14a**,**b** based on the solid-state structures obtained for the *N*-methyl analogs demonstrate that the geometries of these conformationally restricted DHPM derivatives are in good agreement with the proposed bioactive conformation for dihydropyridine-type calcium channel modulators (Fig. 1). Whereas non-rigid DHPMs are rather flexible molecules,[18] in the rigid analogs **14a,b** the aryl group is "tied" into the axial position, and is perpendicular to and (nearly) bisecting the dihydropyrimidine ring. At the same time the amide functionality on the "right-hand" side of these molecules is fixed into the "*trans*" position. Whereas the polycyclic framework of **14a** (n = 0) is completely rigid, disallowing any movement of the aryl ring, for homolog **14b** ($n = 1$) with an additional methylene group two conformational minima can be located by semi-empirical AM1 molecular orbital calculations (Fig. 2). The lower energy conformer **14b-A** where the aryl ring is bisecting the pyrimidine ring in half corresponds to the geometrical arrangement found in the solid-state structure of the *N*-methyl analog.[10] In contrast, in the higher energy conformer **14b-B** ($\Delta E = 5.10$ kcal mol^{-1}) the aryl ring is twisted away from the proposed ideal bioactive geometry[4] found in **14b-A** (*ca.* 70° deviation). Due to the relatively large calculated energy difference between the two conformers it can be assumed that in solution or under physiological conditions the putative bioactive conformer **14b-A** is the predominating one.

Both polycycles **14a**,**b** are stable compounds in the solid state and were fully characterized by spectroscopic and analytical data. Surprisingly however, we discovered that in *e.g.* chloroform solution on exposure to atmospheric oxygen enamine **14a** was slowly (1–2 weeks) oxidized to the corresponding α-hydroxy imine **16a** in a diastereoselective fashion. Since all *N*-substituted analogs in this series (**13a**,**b**, **19**, and the corresponding *N*-methyl derivatives[10]) are resistant to oxidation it is reasonable to assume that the imine tautomer **15a** is involved in this oxidative process. In fact, the autoxidation of cyclic imines by molecular oxygen has been observed previously in several instances, and is believed to follow an uncatalyzed radical chain reaction pathway.[19] The proposed stereochemistry on the new stereocenter in **16a** was confirmed by NOE measurements (360 MHz, $CDCl_3$): irradiation of the aromatic C7-H signal at δ 6.95 led to a small but significant NOE enhancement of the multiplet at δ 4.09 for the ester OCH_2 group at C4. At the same time an expected strong enhancement for the C5-H singlet at δ 5.12 was observed (Scheme 3). Note that for a related example in the



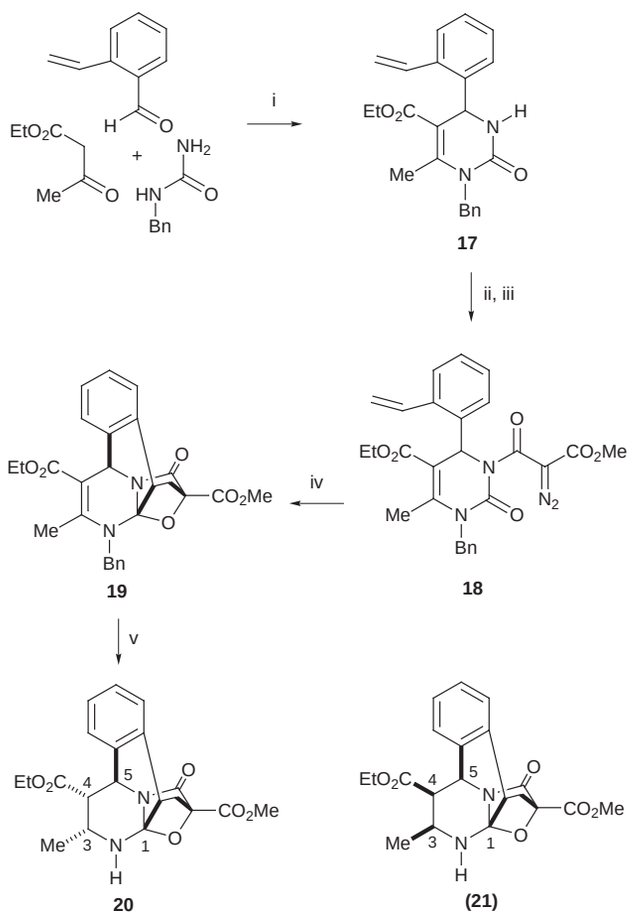
Scheme 3 *Reagents and conditions*: i, atmospheric O_2, $CHCl_3$, rt.

dihydropyridine series an analogous stereochemical arrangement has been confirmed by an X-ray structure determination.[20] Interestingly, under identical reaction conditions enamine **14b** proved to be considerably more stable and remained virtually unchanged for several days (^{1}H-NMR) in chloroform solution. Complete conversion under these conditions to **16b** took 5 weeks.

Since individual enantiomers of DHPMs (*i.e.* **14a**,**b**) may have opposing biological effects[4,5] (see above) access to enantiomerically pure derivatives is an important requirement for developing suitable model compounds for pharmacological tests. In recent work we have reported the successful chromatographic enantioseparation of a variety of racemic DHPMs using direct enantioselective analytical HPLC.[21] In this context resolution of the above conformationally rigid analogs was attempted. For reasons of stability we chose to employ the CBZ-protected analogs **13a** and **13b**, rather than the oxidation-sensitive target compounds **14a**,**b**. Testing a variety of commercially available chiral stationary phases (CSPs) in analytical HPLC experiments we found that both **13a** and **13b** were nicely separated using the carbohydrate-based Chiralcel OD-H column in normal-phase HPLC mode. For both homologs baseline separation could be achieved using mixtures of propan-2-ol and heptane (40 : 60) as mobile phase (for **13a**: $\alpha = 1.51$, Rs = 2.47; for **13b**: $\alpha = 1.31$; Rs = 2.07). Although the present experiments were performed on analytical HPLC columns (separations were not optimized), the reasonably high separation coefficients (α) and resolution values (Rs) suggest that DHPMs of this structural type could also be separated in a preparative HPLC experiment if required.

Finally, we wish here to report the generation of a fully saturated conformationally rigid pyrimidine derivative (*i.e.* **20**) with an axially oriented ester substituent at the C4 position. In general, for both dihydropyridines and dihydropyrimidines the sp^2-carbon atom of the vinylogous carbamate moiety enforces a coplanar "equatorial"-type arrangement of the ester functionality (Fig. 1), which has been found to be essential for biological activity.[3] During our exploratory work in this area

we have prepared the *N*-benzyl substituted polycycle **19**. The synthesis of this derivative is outlined in Scheme 4 and is essentially analogous to the preparation of **13a**,**b** presented in Scheme 2, with the exception that here the protection group can be introduced in the first step, *via* Biginelli condensation employing *N*-benzylurea instead of urea (→**17**). *N*-Malonyl acylation, followed by diazo transfer and $Rh_2(OAc)_4$-catalyzed decomposition provided *N*-benzyl dihydropyrimidine analog **19** in good overall yield. Surprisingly, catalytic hydrogenation of this *N*-benzyl derivative over 10% Pd–C (3 atm H_2, 35 °C, 4 days) did not lead to the expected unprotected analog **14a**, but furnished the fully saturated "hexahydropyrimidine" derivative **20** in 65% yield as the only isolable diastereoisomer. Several modifications of the hydrogenation conditions were investigated in order to access structure **14a**, but ultimately proved unsuccessful. ^{1}H NMR monitoring of the reaction mixture after specific time intervals indicated that enamine **14a** was indeed formed as an intermediate in this process, but at the same time was being further reduced to amine **20**. It should be noted that all other attempts to selectively debenzylate **19** (*e.g.* with Na/liq. NH_3) [16] also failed.



Scheme 4 *Reagents and conditions*: i, polyphosphate ester, THF, reflux; ii, $ClCOCH_2CO_2Me$, benzene, reflux; iii, MsN_3, Et_3N, CH_2Cl_2, rt; iv, $Rh_2(OAc)_4$, benzene, reflux; v, H_2, 10% Pd–C, 35 °C, 3 atm, 4 d.

Particular attention should be paid to the stereochemical arrangement of the four stereocenters on the hexahydropyrimidine ring in **20**. The relative stereochemistry was established unequivocally by an X-ray crystallographic analysis (Fig. 3). As one would expect the ester and methyl groups at C4 and C3, respectively, have a *syn*-relationship consistent with a *cis*-hydrogen addition to the olefinic double bond in **19**. Catalytic hydrogenations of cyclic vinylogous carbamates are known in the literature and in most cases show *cis* selectivity when standard Pd–C conditions are employed.[22] The observed facial selectivity in **20** (with respect to the existing stereogenic centers at C5 and C1) is more difficult to rationalize. Solid-state geometries obtained for conformationally rigid DHPMs of type **3** clearly demonstrate that due to the steric effect of the axial aryl moiety the "top-face" of the molecule is sterically severely hindered and that therefore any attack to this face of the molecule should be disfavoured. According to the currently accepted mechanism [23,24] of the heterogenous catalytic hydrogenation the olefin is in the first step adsorbed onto the surface of the metal. Due to steric reasons this adsorption takes place with its less-hindered side attached to the catalyst surface.[23] In most cases subsequent addition of hydrogen follows also from this less-hindered side of the molecule, although some exceptions to this general rule are known.[24] Note that the catalytic reduction **19**→**20** apparently is such an exception where hydrogen (and therefore also Pd) have added from the more-hindered face of the molecule. Semi-empirical molecular orbital calculations (AM1) demonstrate that the diastereoisomer resulting from the alternative H_2-addition mode (*i.e.* **21**) is 5.53 kcal mol^{-1} less stable than **20**.

In conclusion, a protection group strategy has been devised in order to synthesize conformationally rigid dihydropyrimidine calcium channel modulators *via* a rhodium-induced cyclization–cycloaddition cascade protocol. Preliminary electrophysiological measurements have confirmed that *rac*-**14a** has calcium channel antagonistic activity in the micromolar range. Further structural modifications on these dihydropyrimidine analogs are currently being considered in our laboratory in order to increase their activity.

Experimental

General procedures and materials

Mps were determined on a Gallenkamp melting point apparatus, Mod. MFB-595 and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer as KBr pellets. ^{1}H and ^{13}C NMR spectra were obtained on a Varian XL-200 Gemini instrument at 200 and 50 MHz, respectively

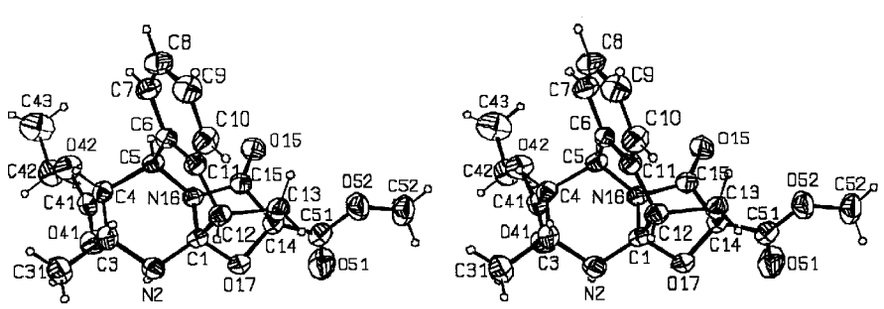


Fig. 3 Stereoscopic ORTEP plot showing the atomic numbering scheme and conformation of **20**. The probability ellipsoids are drawn at the 50% probability level, the hydrogen atoms are drawn with arbitrary radii.

(*J* values are given in Hz). NOE experiments were performed on a Bruker AMX 360 instrument at 360 MHz. Mass spectra were recorded on a VG ZAB-2SEQ instrument. Microanalyses were obtained on a Fisons Mod. EA 1108 elemental analyzer. HPLC measurements employed a Hewlett Packard HP 1050 compact system with variable wavelength detector (VWL) and a HP 2D-HPLC Chemstation version A.02.05. The Chiralcel OD-H column (250 × 4.6 mm i.d.) was supplied by J. T. Baker. *n*-Heptane and propan-2-ol for preparation of the moble phases were HPLC grade and purchased from Aldrich Chemical Co. Reactions were monitored by thin layer chromatography (TLC) on 0.2 mm silica gel F-252 (Merck) plates. Flash chromatography was performed with silica gel 60 (40–63 μm, Aldrich) using mixtures of light petroleum and ethyl acetate as eluent. Methylene chloride, benzene and THF were distilled and dried over 4 Å molecular sieves. Triethylamine was distilled from KOH before use. All moisture-sensitive reactions were carried out under a dry argon atmosphere employing flame-dried glassware. 2-Vinylbenzaldehyde,[25] 2-allylbenzaldehyde[26] and mesyl azide[27] were prepared according to literature procedures. Methyl malonyl chloride, benzyloxycarbonyl chloride (CBZ-Cl), rhodium acetate and rhodium trifluoroacetate were purchased from Aldrich Chemical Co. Pyrimidine derivatives **10a** and **11a** were prepared as previously described.[10]

Computational methods

Semi-empirical AM1[28] calculations were carried out using the PC Spartan Plus package (Version 1.0)[29] on a Pentium PC. Starting geometries were obtained using Spartans interactive building mode, and preoptimized using the SYBYL force field. For pentacycle **14b-A** and **20** the starting geometries were obtained from X-ray structure coordinates.[10] Geometries were completely optimized without molecular mechanics corrections for amide bonds. Convergence was achieved in all optimizations.

Ethyl 4-(2-allylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 10b

A mixture of ethyl acetoacetate (6.89 g, 53 mmol), freshly distilled 2-allylbenzaldehyde (5.11 g, 53 mmol) urea (3.18 g, 53 mmol) and methanol (40 cm^3) containing two drops of conc. HCl was heated under reflux for 15 h. After the mixture was allowed to stand at rt overnight, the precipitate was filtered and recrystallized from ethanol to give the pyrimidine **10b** (4.14 g, 39%) as a colorless solid, mp 160 °C (Found: C, 67.78; H, 6.89; N, 9.35; $C_{17}H_{20}N_2O_3$ requires: C, 67.98; H, 6.71; N, 9.33%); ν_{max}/cm^{-1} 3250, 3100, 1680, 1640; δ_H (200 MHz; $CDCl_3$) 1.08 (3 H, t, *J* 7.5, CH_3-CH_2), 2.40 (3 H, s, CH_3), 3.30–3.48 and 3.70–3.88 (2 H, 2 m, CH_2-CH=CH_2), 4.01 (2 H, q, *J* 7.5, CH_2-CH_3), 4.98–5.20 (2 H, m, CH_2-CH=CH_2), 5.38 (1 H, br s, NH), 5.67 (1 H, s, C4-H), 6.00–6.20 (1 H, m, CH_2-C*H*=CH_2), 7.10–7.28 (4 H, m, ArH), 8.58 (1 H, s, NH).

Ethyl 4-(2-allylphenyl)-3-[2-diazo-2-(methoxycarbonyl)acetyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 11b

A mixture of pyrimidine **10b** (3.20 g, 10.7 mmol), distilled methyl malonyl chloride (3.44 g, 25.3 mmol) and benzene (120 cm^3) was heated at reflux for 30–60 min. After all starting material had been consumed (TLC), the solution was cooled to ambient temperature. The solvent was evaporated under reduced pressure and the crude product triturated with ether to give, after recrystallization from ethanol, ethyl 4-(2-allylphenyl)-6-methyl-3-[2-(methyloxycarbonyl)acetyl]-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3.86 g, 91%) as colorless needles, mp 171 °C (Found: C, 62.94; H, 6.24; N, 6.99; $C_{21}H_{24}N_2O_6$ requires: C, 62.99; H, 6.04; N, 6.99%); ν_{max}/cm^{-1} 3250, 3140, 1750, 1710, 1640; δ_H (200 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.5, CH_3-CH_2), 2.41 (3 H, s, CH_3), 3.66 (3 H, s, OCH_3), 3.70–3.98 (2 H, m, CH_2-CH=CH_2), 3.80 and 4.05 (2 H, 2 d, *J* 16.0, $COCH_2CO$), 4.05–4.28 (2 H, m, CH_2-CH_3), 5.13–5.25 (2 H, m, CH_2-CH=CH_2), 5.90–6.10 (1 H, m, CH_2-C*H*=CH_2), 6.80 (1 H, s, C4-H), 7.10–7.40 (4 H, m, ArH), 8.03 (1 H, br s, NH).

A mixture of the above 1,3-dicarbonyl compound (3.86 g, 9.7 mmol), mesyl azide (1.40 g, 11.6 mmol) triethylamine (2.18 g, 21.6 mmol) and methylene chloride (40 cm^3) was stirred in the dark at rt for 24-48 h. After all starting material had been consumed (^{1}H NMR), the diazo-transfer reaction mixture was washed rapidly with ice-cold 5% aq. KOH (3 × 30 cm^3) and saturated aq. NaCl (3 × 50 cm^3). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (light petroleum–EtOAc, 2:1) to yield the diazo imide **11b** (3.38 g, 82%) as a yellow solid, mp 123 °C (Found: C, 59.25; H, 5.10; N, 13.33; $C_{21}H_{22}N_4O_6$ requires: C, 59.15; H, 5.20; N, 13.14%); ν_{max}/cm^{-1} 3240, 3140, 2140, 1750, 1710, 1650; δ_H (200 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7.5, CH_3-CH_2), 2.40 (3 H, s, CH_3), 3.75–3.85 and 3.90–3.98 (2 H, 2 m, CH_2-CH=CH_2), 3.79 (3 H, s, OCH_3), 4.00–4.25 (2 H, m, CH_2-CH_3), 5.13–5.28 (2 H, m, CH_2-CH=CH_2), 5.98–6.18 (1 H, m, CH_2-C*H*=CH_2), 6.33 (1 H, s, C4-H), 7.10–7.48 (4 H, m, ArH), 8.00 (1 H, br s, NH).

1-Benzyl 5-ethyl 6-methyl-3-[2-diazo-2-(methoxycarbonyl)-acetyl]-2-oxo-4-(2-vinylphenyl)-1,2,3,4-tetrahydropyrimidine-1,5-dicarboxylate 12a

To a stirred solution of diazo imide **11a** (300 mg, 0.7 mmol) in tetrahydrofuran (1.2 cm^3) was added sodium hydride (21 mg, 0.9 mmol) at 0 °C. After the suspension was stirred at 0°C for 20 min, a solution of distilled benzyloxycarbonyl chloride (150 mg, 0.9 mmol) in tetrahydrofuran (1 cm^3) was added. After additional stirring for 30 min at rt ethyl acetate (30 cm^3) was added to the reaction mixture which was subsequently extracted with saturated aq. NH_4Cl (2 × 50 cm^3). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to leave a crude product which was purified by flash chromatography (light petroleum–EtOAc, 2:1) to yield the protected diazo imide **12a** (300 mg, 86%) as a yellow solid, mp 103 °C (Found: C, 61.74; H, 4.90; N, 9.97; $C_{28}H_{26}N_4O_8$ requires: C, 61.53; H, 4.79; N, 10.25%); ν_{max}/cm^{-1} 2140, 1780,1720, 1710, 1660; δ_H (200 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.5, CH_3-CH_2), 2.40 (3 H, s, CH_3), 3.73 (3 H, s, OCH_3), 4.05–4.25 (2 H, m, CH_2-CH_3), 5.41 (2 H, s, OCH_2Ph), 5.38 (1 H, dd, *J* 1.5 and 11.0, CH=CH_2), 5.66 (1 H, dd, *J* 1.5 and 17.0, CH=CH_2), 6.36 (1 H, s, C4-H), 7.05–7.60 (10 H, m, ArH + C*H*=CH_2).

1-Benzyl 5-ethyl 4-(2-allylphenyl)-6-methyl-3-[2-diazo-2-(methoxycarbonyl)acetyl]-2-oxo-1,2,3,4-tetrahydropyrimidine-1,5-dicarboxylate 12b

This compound was prepared in a similar manner to analog **12a** described above, using diazo imide **11b** (2.31 g, 5.4 mmol) as a starting material. The CBZ-protected pyrimidine **12b** (2.10 g, 69%) was obtained as a yellow solid, mp 99 °C (Found: C, 62.35; H, 5.25; N, 9.84; $C_{29}H_{28}N_4O_8$ requires: C, 62.12; H, 5.03; N, 10.00%); ν_{max}/cm^{-1} 2140, 1770, 1720, 1710, 1650; δ_H (200 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7.5, CH_3-CH_2), 2.41 (3 H, s, CH_3), 3.63–3.98 (2 H, m, CH_2-CH=CH_2), 3.73 (3 H, s, OCH_3), 4.08–4.23 (2 H, m, CH_2-CH_3), 5.12–5.19 (2 H, m, CH_2-CH=CH_2), 5.41 (2 H, s, OCH_2Ph), 5.93–6.14 (1 H, m, CH_2-C*H*=CH_2), 6.34 (1 H, s, C4-H), 7.00–7.47 (9 H, m, ArH).

2-Benzyl 4-ethyl 14-methyl 3-methyl-15-oxo-17-oxa-2,16-diazapentacyclo[12.2.1.0^{1,12}.0^{5,16}.0^{6,11}]heptadeca-3,6,8,10-tetraene-2,4,14-tricarboxylate 13a

A solution of diazo compound **12a** (310 mg, 0.6 mmol) in benzene (15 cm^3) containing a catalytic amount of rhodium acetate

(<5 mg) was heated under reflux for 30–60 min. After all starting material was consumed (TLC), the solvent was evaporated under reduced pressure and the crude product purified by flash chromatography (light petroleum–EtOAc, 2:1) to give pentacycle **13a** (220 mg, 71%) as a colorless solid, mp 150 °C (Found: C, 64.66; H, 4.95; N, 5.29; $C_{28}H_{26}N_2O_8$ requires: C, 64.86; H, 5.05; N, 5.40%); ν_{max}/cm^{-1} 1770, 1740, 1700, 1610; δ_H (200 MHz; $CDCl_3$) 1.41 (3 H, t, *J* 7.5, C*H*$_3$-CH$_2$), 1.90 (1 H, dd, *J* 3.0 and 12.5, C13-H$_a$), 2.46 (3 H, s, CH$_3$), 2.71 (1 H, dd, *J* 11.0 and 12.5, C13-H$_b$), 3.80 (1 H, dd, *J* 3.0 and 11.0, C12-H), 3.92 (3 H, s, OCH$_3$), 4.20–4.40 (2 H, m, C*H*$_2$-CH$_3$), 5.13 and 5.48 (2 H, 2 d, *J* 12.0, OC*H*$_2$Ph), 6.02 (1 H, s, C5-H), 6.80–7.40 (9 H, m, ArH).

2-Benzyl 4-ethyl 15-methyl 3-methyl-16-oxo-18-oxa-2,17-diazapentacyclo[13.2.1.0^{1,13}.0^{5,17}.0^{6,11}]octadeca-3,6,8,10-tetraene-2,4,15-tricarboxylate 13b

This compound was prepared in a similar manner to analog **13a** described above, using diazo imide **12b** (1.10 g, 2.0 mmol) as a starting material. The CBZ-protected pentacycle **13b** (0.60 g, 56%) was obtained as a colorless solid, mp 138 °C (Found: C, 65.49; H, 5.54; N, 5.28; $C_{29}H_{28}N_2O_8$ requires: C, 65.41; H, 5.30; N, 5.26%); ν_{max}/cm^{-1} 1750, 1700, 1600; δ_H (200 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7.5, C*H*$_3$-CH$_2$), 1.43 (1 H, dd, *J* 5.5 and 13.0, C14-H$_a$), 2.38 (1 H, dd, *J* 10.0 and 13.0, C14-H$_b$), 2.56 (3 H, s, CH$_3$), 2.76 (1 H, dd, *J* 5.5 and 16.0, C12-H$_a$), 3.00–3.13 (1 H, m, C13-H), 3.25 (1 H, dd, *J* 2.0 and 16.0, C12-H$_b$), 3.85 (3 H, s, OCH$_3$), 4.00–4.19 (2 H, m, C*H*$_2$-CH$_3$), 5.27 and 5.35 (2 H, 2 d, *J* 12.0, OC*H*$_2$Ph), 5.72 (1 H, s, C5-H), 6.95–7.48 (9 H, m, ArH).

4-Ethyl 14-methyl 3-methyl-15-oxo-17-oxa-2,16-diazapentacyclo[12.2.1.0^{1,12}.0^{5,16}.0^{6,11}]heptadeca-3,6,8,10-tetraene-4,14-dicarboxylate 14a

A solution of the protected pentacycle **13a** (1.30 g, 2.5 mmol) in methanol (300 cm^3) containing a catalytic amount of 10% Pd–C was hydrogenated at rt under atmospheric pressure for 40 min. After the catalyst was removed by filtration the reaction mixture was evaporated under reduced pressure to leave pentacycle **14a** (920 mg, 96%) as a colorless solid, mp 141 °C (decomp.) (Found: C, 62.11, H, 5.10; N, 6.99; $C_{20}H_{20}N_2O_6$ requires: C, 62.49; H, 5.24; N, 7.29%); ν_{max}/cm^{-1} 3300, 1760, 1730, 1680, 1660, 1600, 1510; δ_H (200 MHz; $CDCl_3$) 1.39 (3 H, t, *J* 7.5, C*H*$_3$-CH$_2$), 1.92 (1 H, dd, *J* 3.0 and 12.5, C13-H$_a$), 2.26 (3 H, s, CH$_3$), 2.81 (1 H, dd, *J* 11.0 and 12.5, C13-H$_b$), 3.70 (1 H, dd, *J* 3.0 and 11.0, C12-H), 3.88 (3 H, s, OCH$_3$), 4.20–4.35 (2 H, m, C*H*$_2$-CH$_3$), 5.30 (1 H, br s, NH), 6.04 (1 H, s, C5-H), 7.05–7.50 (4 H, m, ArH); δ_C (50 MHz; $CDCl_3$) 14.6, 20.3, 39.7, 49.3, 50.6, 53.2, 60.0, 87.0, 95.3, 100.0, 126.8, 127.8, 127.9, 130.2, 132,5, 136.5, 149.9, 164.6, 165.8, 166.9.

4-Ethyl 15-methyl 3-methyl-16-oxo-18-oxa-2,17-diazapentacyclo[13.2.1.0^{1,13}.0^{5,17}.0^{6,11}]octadeca-3,6,8,10-tetraene-4,15-dicarboxylate 14b

A solution of the protected pentacycle **13b** (200 mg, 0.4 mmol) in methanol (70 cm^3) containing a catalytic amount of 10% Pd–C was hydrogenated at rt under atmospheric pressure for 40 min. After the catalyst was removed by filtration the reaction mixture was evaporated under reduced pressure to leave pentacycle **14b** (120 mg, 79%) as a colorless solid, mp 262 °C (decomp.) (Found: C, 63.49; H, 5.68; N, 6.85; $C_{21}H_{22}N_2O_6$ requires: C, 63.31; H, 5.63; N, 7.03%); ν_{max}/cm^{-1} 3280, 1740, 1680, 1660, 1600, 1510; δ_H (200 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7.5, C*H*$_3$-CH$_2$), 1.51 (1 H, dd, *J* 5.5 und 13.0, C14-H$_a$), 2.42 (3 H, s, CH$_3$), 2.39 (1 H, dd, *J* 10.0 and 13.0, C14-H$_b$), 2.55–2.68 (1 H, m, C13-H), 2.82 (1 H, dd, *J* 5.5 and 16.0, C12-H$_a$), 3.32 (1 H, dd, *J* 2.0 and 16.0, C12-H$_b$), 3.86 (3 H, s, OCH$_3$), 4.00–4.10 (2 H, m, C*H*$_2$-CH$_3$), 5.25 (1 H, br s, NH), 5.73 (1H, s, C5-H), 6.99–7.55 (4 H, m, ArH); δ_C (50 MHz; $CDCl_3$) 14.2, 20.7, 31.4, 32.3, 43.6, 53.0, 54.6, 59.8, 86.0, 95.5, 96.6, 126.5, 127.8, 132.1, 132.5, 133.4, 138.9, 150.1, 165.2, 166.0, 166.2.

4-Ethyl 14-methyl 4-hydroxy-3-methyl-15-oxo-17-oxa-2,16-diazapentacyclo[12.2.1.0^{1,12}.0^{5,16}.0^{6,11}]heptadeca-2,6,8,10-tetraene-4,14-dicarboxylate 16a

A solution of enamine **14a** (230 mg, 0.6 mmol) in chloroform (5 cm^3) was exposed to the atmosphere for 2 weeks. After evaporation under reduced pressure the solid residue was triturated with diethyl ether to leave hydroxy imine **16** (190 mg, 80%) as a colorless solid, mp 218 °C (Found: C, 59.70; H, 5.04; N, 6.84; $C_{20}H_{21}N_2O_7$ requires: C, 59.85; H, 5.27; N, 7.01%); ν_{max}/cm^{-1} 3240, 1780, 1745, 1670; δ_H (200 MHz; $CDCl_3$) 0.86 (3 H, t, *J* 7.5, C*H*$_3$-CH$_2$), 1.88 (1 H, dd, *J* 3.0 and 12.5, C13-H$_a$), 2.10 (3 H, s, CH$_3$), 2.90 (1 H, dd, *J* 11.0 and 12.5, C13-H$_b$), 3.48–3.66 and 4.00–4.18 (2 H, 2 m, C*H*$_2$-CH$_3$), 3.76 (1 H, dd, *J* 3.0 and 10.5, C12-H), 3.89 (1 H, s, OCH$_3$), 5.12 (1 H, s, C5-H), 6.90–7.00 (1 H, m, C7-H), 7.10–7.32 (3 H, m, ArH); δ_H (200 MHz; DMSO) 0.80 (3H, t, *J* 7.5, C*H*$_3$-CH$_2$), 1.51 (2 H, dd, *J* 3.0 and 12.5, C13-H$_a$), 2.00 (3H, s, CH$_3$), 2.97 (1 H, dd, *J* 11.0 and 12.5, C13-H$_b$), 3.48–3.70 and 3.80–4.03 (2 H, 2 m, C*H*$_2$-CH$_3$), 3.76 (1 H, dd, *J* 3.0 and 10.5, C12-H), 3.89 (1 H, s, OCH$_3$), 5.12 (1 H, s, C5-H), 6.90–7.00 (1 H, m, C7-H), 7.10–7.32 (3 H, m, ArH), 7.45 (1H, br s, OH, exchangeable with D_2O); δ_C (50 MHz; $CDCl_3$) 13.2, 22.6, 39.3, 45.2, 53.1, 61.3, 63.0, 76.6, 85.4, 99.2, 127.4 (2 carbons), 129.2, 129.5, 130.6, 134.8, 164.6, 169.3, 170.4, 170.7; *m*/*z* (EI) 400 (M$^+$, 75%), 313 (35), 299 (32), 271 (100), 256 (46), 230 (36), 197 (31), 128 (38), 115 (58), 29 (25).

4-Ethyl 15-methyl 4-hydroxy-3-methyl-16-oxo-18-oxa-2,17-diazapentacyclo[13.2.1.0^{1,13}.0^{5,17}.0^{6,11}]octadeca-2,6,8,10-tetraene-4,15-dicarboxylate 16b

A solution of enamine **14b** (50 mg) in chloroform (5 cm^3) was exposed to the atmosphere for 5 weeks. After evaporation under reduced pressure the solid residue was triturated with diethyl ether to leave hydroxy imine **16b** (40 mg, 80%) as a colorless solid, mp 149 °C (Found: C, 60.96; H, 5.32; N, 6.58; $C_{21}H_{22}N_2O_7$ requires C, 60.86; H, 5.35; N, 6.76%); ν_{max}/cm^{-1} 3250, 1770, 1750, 1730, 1660; δ_H (200 MHz; $CDCl_3$) 0.76 (3 H, t, *J* 7.5, C*H*$_3$-CH$_2$), 1.68 (1 H, dd, *J* 5.5 and 13.0, C14-H$_a$), 2.22 (3 H, s, CH$_3$), 2.60 (1 H, dd, *J* 10.0 and 13.0, C14-H$_b$), 2.84 (1 H, dd, *J* 5.5 and 16.0, C12-H$_a$), 2.82–3.03 (1 H, m, C13-H), 3.17 (1 H, dd, *J* 2.0 and 16,0, C12-H$_b$) 3.44–3.63 and 3.65–3.88 (2 H, 2 m, C*H*$_2$-CH$_3$), 3.87 (1H, s, OCH$_3$), 5.13 (1 H, d, C5-H), 7.09–7.22 (4 H, m, ArH).

Ethyl 1-benzyl-6-methyl-2-oxo-4-(2-vinylphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate 17

A mixture of ethyl acetoacetate (1.73 g, 13 mmol), freshly distilled 2-vinylbenzaldehyde (1.63 g, 19 mmol), *N*-benzylurea (2.82 g, 19 mmol), polyphosphate ester[13] (1.20 g) and tetrahydrofuran (25 cm^3) was heated under reflux for 15 h. After the mixture was extracted with saturated aq. $NaHCO_3$ (2 × 50 cm^3) the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (light petroleum–EtOAc, 1:1) to yield pyrimidone **17** (2.00 g, 47%) as a colorless solid, mp 114 °C (hexanes) (Found: C, 73.47; H, 6.48; N, 7.43; $C_{23}H_{24}N_2O_3$ requires: C, 73.38; H, 6.43; N, 7.44%); ν_{max}/cm^{-1} 3210, 3080, 1710, 1670, 1620; δ_H (200 MHz; $CDCl_3$) 0.98 (3 H, t, *J* 7.5 C*H*$_3$-CH$_2$), 2.46 (3 H, s, CH$_3$), 3.90 (2 H, q, *J* 7.5, C*H*$_2$-CH$_3$), 4.82 and 5.14 (2 H, 2 d, *J* 16.5, NCH$_2$), 5.36 (1 H, dd, *J* 1.5 and 11.0, C*H*$_2$=CH), 5.61 (1 H, dd, *J* 1.5 and 17.0, C*H*$_2$=CH), 5.70 (2 H, m, C4-H + NH), 7.70–7.40 (10 H, m, ArH + C*H*=CH$_2$); δ_C (50 MHz; $CDCl_3$) 13.9, 16.4, 45.9, 50.5, 60.1, 103.3, 118.3, 126.4, 126.6, 127.0, 127.2, 128.1, 128.3, 128.7, 133.8, 136.2, 138.0, 139.5, 149.7, 153.1, 165.8.

Ethyl 1-benzyl-3-[2-diazo-2-(methoxycarbonyl)]acetyl]-6-methyl-2-oxo-4-(2-vinylphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate 18

A mixture of pyrimidone **17** (1.67 g, 4.4 mmol) distilled methyl malonyl chloride (1.02 g, 7.5 mmol) and benzene (50 cm^3) was heated at reflux for 30–60 min. After all starting material had been consumed (TLC), the solution was cooled to ambient temperature, diluted with diethyl ether (50 cm^3), and washed in succession with saturated aq. $NaHCO_3$ (2 × 100 cm^3) and NaCl solution (2 × 100 cm^3). The solvent was removed under reduced pressure and the crude product purified by flash chromatography (light petroleum–EtOAc, 2:1) to give ethyl 1-benzyl-6-methyl-3-[2-(methoxycarbonyl)acetyl]-2-oxo-4-(2-vinylphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2.11 g, 98%) as colorless oil; ν_{max}/cm^{-1} 1740, 1690, 1640; δ_H (200 MHz; $CDCl_3$) 1.20 (3 H, t, *J* 7.5, CH_3-CH_2), 2.51 (3 H, s, CH_3), 3.65 (3 H, s, OCH_3), 3.75 and 4.12 (2 H, 2 d, *J* 16.5, N-CH_2), 4.05–4.20 (2 H, m, CH_2-CH_3), 5.05 (1 H, s, C4-H), 5.36 (1 H, dd, *J* 1.5 and 11.0, CH_2=CH), 5.62 (1 H, dd, *J* 1.5 and 17.0, CH_2=CH), 6.89 (1 H, s, ArH), 7.70–7.75 (9 H, m, ArH + CH_2=C*H*); δ_C (50 MHz; $CDCl_3$) 14.1, 16.4, 45.2, 47.5, 49.6, 52.2, 60.7, 110.6, 115.9, 126.7, 126.8, 127.0, 127.7, 128.1, 128.4, 128.8, 135.3, 136.3, 136.5, 136.9, 146.6, 152.4, 164.9, 166.9, 167.9.

A mixture of the above 1,3-dicarbonyl compound (2.11 g, 4.4 mmol), mesyl azide (640 mg, 5.3 mmol), triethylamine (1.10 g, 10.6 mmol), and methylene chloride (30 cm^3) was stirred in the dark at rt for 24–48 h. After all starting material had been consumed (^{1}H NMR), the diazo-transfer reaction mixture was washed rapidly with ice-cold 5% aq. KOH (3 × 30 cm^3) and saturated aq. NaCl (3 × 50 cm^3). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (light petroleum–EtOAc, 2:1) to yield the diazo imide **18** (1.89 g, 86%) as a yellow oil; ν_{max}/cm^{-1} 2120, 1730, 1690, 1650; δ_H (200 MHz; $CDCl_3$) 1.20 (3 H, t, *J* 7.5, CH_3-CH_2), 2.54 (3 H, s, CH_3), 3.78 (3 H, s, OCH_3), 4.05–4.25 (2 H, m, CH_2-CH_3), 5.00 and 5.11 (2 H, 2 d, *J* 16.5, NCH_2), 5.36 (1 H, dd, *J* 1.5 and 11.0, CH=CH_2), 5.64 (1 H, dd, *J* 1.5 and 17.0, CH_2=CH), 6.37 (1 H, s, C4-H), 6.90–7.60 (10 H, m, ArH + CH_2=C*H*); δ_C (50 MHz; $CDCl_3$) 14.2, 16.8, 47.6, 52.3, 52.4, 60.6, 77.2, 111.2, 115.8, 126.5, 126.6, 127.7, 127.8, 128.3, 128.7, 135.2, 136.4, 137.2, 146.8, 152.0, 161.5, 163.5, 165.0.

4-Ethyl 14-methyl 2-benzyl-3-methyl-15-oxo-17-oxa-2,16-diazapentacyclo[12.2.1.0^{1,12}.0^{5,16}.0^{6,11}]heptadeca-3,6,8,10-tetraene-4,14-dicarboxylate 19

A solution of diazo compound **18** (1.30 g, 2.6 mmol) in benzene (80 cm^3) containing a catalytic amount of rhodium acetate (<10 mg) was heated under reflux for 30–60 min. After all starting material was consumed (TLC), the solvent was evaporated under reduced pressure and the crude product purified by flash chromatography (light petroleum–EtOAc, 2:1) to give pentacycle **19** (720 mg, 58%) as a colorless solid, mp 163 °C (Found: C, 68.44; H, 5.48; N, 5.72; $C_{27}H_{26}N_2O_6$ requires: C, 68.34; H, 5.52; N, 5.90%); ν_{max}/cm^{-1} 1760, 1720, 1690, 1570; δ_H (200 MHz; $CDCl_3$) 1.43 (3 H, t, *J* 7.5, CH_3-CH_2), 1.93 (1 H, dd, *J* 3.0 and 12.5, C13-H_a), 2.32 (3 H, s, CH_3), 2.70 (1 H, dd, *J* 10.5 and 12.5, C13-H_a), 3.51 (1 H, dd, *J* 3.0 and 10.5, C12-H), 3.92 (3 H, s, OCH_3), 4.20–4.40 (2 H, m, CH_2-CH_3), 4.78 and 5.17 (2 H, 2 d, *J* 16.5, NCH_2), 6.13 (1 H, s, C5-H), 6.90–7.60 (9 H, m, ArH); δ_C (50 MHz; $CDCl_3$) 14.6, 15.6, 39.2, 46.2, 46.5, 50.1, 53.2, 60.0, 86.6, 98.2, 100.9, 125.2, 126.9, 127.3, 127.8, 128.1, 128.8, 130.0, 132.5, 136.2, 137.2, 153.2, 164.6, 166.0, 167.3.

4-Ethyl 14-methyl 3-methyl-15-oxo-17-oxa-2,16-diazapentacyclo[12.2.1.0^{1,12}.0^{5,16}.0^{6,11}]heptadeca-6,8,10-triene-4,14-dicarboxylate 20

A solution of the *N*-benzyl pentacycle **19** (200 mg, 0.4 mmol) in methanol (200 cm^3) containing 10% Pd–C (200 mg, containing 50% H_2O) was hydrogenated at 35 °C and 3 atm hydrogen pressure for 4 d. After all starting material was consumed (^{1}H NMR) the catalyst was removed by filtration and the reaction mixture evaporated under reduced pressure to leave hydrogenation product **20** (100 mg, 65%) as a colorless solid, mp 205 °C (from methanol) (Found: C, 62.33, H, 5.78; N, 7.16; $C_{20}H_{22}N_2O_6$ requires: C, 62.17; H, 5.74; N, 7.25%); ν_{max}/cm^{-1} 3300, 1760, 1740, 1720; δ_H (200 MHz; $CDCl_3$) 1.22 (3 H, d, *J* 6.5, C3-CH_3), 1.32 (3 H, t, *J* 7.5, CH_3-CH_2), 1.78 (1 H, dd, *J* 3.0 and 12.5, C13-H_a), 2.42 (1 H, dd, *J* 2.5 and 2.5, C4-H), 2.81 (1 H, dd, *J* 10.5 and 12.5, C13-H_a), 3.26 (1 H, br s, NH, exchangeable with D_2O), 3.10–3.20 (1 H, dq, *J* 2.5 and 6.5, C3-H), 3.56 (1 H, dd, *J* 3.0 and 10.5, C12-H), 3.87 (3 H, s, OCH_3), 4.25 (2 H, m, CH_3-CH_2), 5.44 (1 H, d, *J* 2.5, C5-H), 7.00–7.30 (4 H, m, ArH); δ_C (50 MHz; $CDCl_3$) 14.2, 18.6, 40.4, 45.5, 46.2, 48.0, 53.0, 56.3, 61.1, 85.0, 99.2, 126.6, 127.9, 128.7, 130.0, 132.4, 137.8, 165.0, 170.3, 170.3.

Table 1 Selected bond lengths (Å) and angles (°) for compound **20**

C(1)–N(2)	1.422(3)
N(2)–C(3)	1.485(3)
C(3)–C(4)	1.552(3)
C(4)–C(5)	1.565(3)
C(5)–C(6)	1.521(3)
C(6)–C(11)	1.400(3)
C(11)–C(12)	1.524(3)
C(12)–C(13)	1.567(3)
C(13)–C(14)	1.548(3)
C(14)–C(15)	1.551(3)
C(15)–N(16)	1.377(3)
N(16)–C(1)	1.492(3)
N(16)–C(5)	1.465(3)
C(1)–C(12)	1.556(3)
C(1)–O(17)	1.427(3)
O(17)–C(14)	1.445(3)
C(15)–O(15)	1.212(3)
O(17)–C(1)–N(2)	111.87(16)
N(16)–C(1)–C(12)	105.66(15)
O(17)–C(1)–C(12)	105.28(15)
N(16)–C(1)–O(17)	100.71(15)
C(1)–N(2)–C(3)	110.36(16)
C(1)–C(12)–C(13)	99.43(15)
C(12)–C(13)–C(14)	101.43(15)
O(17)–C(14)–C(13)	101.08(16)
O(17)–C(14)–C(15)	102.23(15)
O(15)–C(15)–N(16)	128.36(19)
N(16)–C(15)–C(14)	102.65(16)
C(15)–N(16)–C(1)	105.95(15)
C(1)–O(17)–C(14)	96.19(14)
O(17)–C(1)–N(16)–C(5)	−177.84(14)
N(2)–C(1)–O(17)–C(14)	175.21(16)
O(17)–C(1)–N(2)–C(3)	−169.50(15)
C(31)–C(3)–N(2)–C(1)	−179.37(17)
C(31)–C(3)–C(4)–C(5)	−177.45(18)
C(41)–C(4)–C(5)–C(6)	167.32(16)
C(4)–C(5)–N(16)–C(15)	173.15(16)
C(5)–C(6)–C(11)–C(12)	8.0(3)
C(6)–C(11)–C(12)–C(1)	−14.5(3)
C(1)–C(12)–C(13)–C(14)	7.27(18)
C(14)–C(15)–N(16)–C(1)	8.00(19)

X-Ray crystallographic structure determination of pentacycle 20

A colourless single crystal block of compound **20**, recrystallized from EtOH, was mounted on a glass fibre and transferred to the diffractometer.

Crystal data. $C_{20}H_{22}N_2O_6$, M_r = 386.40. Monoclinic, $P2_1/c$, a = 14.998(3), b = 9.397(2), c = 14.153(4) Å, β = 111.847(18)°, V = 1851.4(8) Å^3 (by least-squares refinement on diffractometer angles for 71 centered reflections with 12.57 ⩽ θ ⩽ 14.57°,

$\lambda = 0.71069$ Å, $T = 298$ K), $Z = 4$, $D_x = 1.386$ g cm^{-3}, colourless block (0.40 × 0.30 × 0.28 mm), μ (Mo-Kα) = 0.103 mm^{-1}.

Data collection and processing. Modified Stoe 4-circle diffractometer, graphite-monochromated Mo-Kα radiation, ω scans with scan width 1.0°, 5051 reflections measured ($2.6 \leqslant \theta \leqslant 27°$, $-19 \leqslant h \leqslant 18$, $-12 \leqslant k1$, $-1 \leqslant l \leqslant 18$), no crystal decay was detected, 4024 unique reflections ($R_{int} = 0.0227$), 2777 significant reflections with $I > 2\sigma(I)$, 4024 reflections were used in all calculations. No corrections for absorption were applied.

Structure solution and refinement. The structure was solved by direct methods.[30] Full-matrix least-squares refinement[31] on F^2 with anisotropic displacement parameters for all non-H atoms. The hydrogen atoms of the tertiary C–H groups were refined with all X–C–H angles equal, the H atoms of the CH_2 and CH_3 groups were refined with idealised geometry and common isotropic displacement parameters for the H atoms of the same group. The C atoms of the phenyl ring were refined without any constraints, the H atoms were constrained to parent sites and one common isotropic displacement parameter was refined for these H atoms. An extinction correction[31] refined to 0.0065(10). The final refinement cycles using a weighting scheme of $w^{-1} = [\sigma^2(F_o^2) + (0.0434P)^2 + 0.6168P]$, $P = [\max(F_o^2, 0) + 2F_c^2]/3$, showed no parameter shifts and resulted in R_1 [$F \geqslant 4\sigma$ (F)] = 0.0492, wR_2 [all data] = 0.1238, $S = 1.025$ for 268 refined parameters. The final ΔF synthesis showed no peaks outside the range −0.203 to +0.246 e Å^{-3}. Fig. 3 was produced using ORTEP.[32] See Table 1 for selected bond lengths and angles.†

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† Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/287. See http://www.rsc.org/suppdata/p1/1999/307/ for crystallographic files in .cif format.

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