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Asymmetric hetero-Diels–Alder reactions. Reactions of oxazolo[3,2-*c*]pyrimidines

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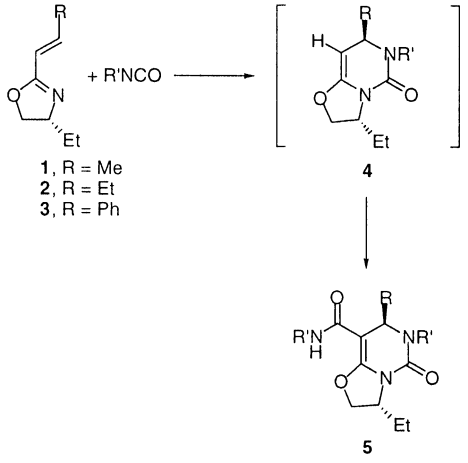
Abstract—Diastereomerically pure oxazolo[3,2-*c*]pyrimidines can be readily prepared by the reaction of alkenyloxazolines with isocyanates. The mechanism of this transformation has been investigated computationally. These compounds undergo epimerisation upon prolonged heating, a reaction which is consistent with the proposed stepwise mechanism. Hydrolysis reactions of these compounds have been investigated.

1. Introduction

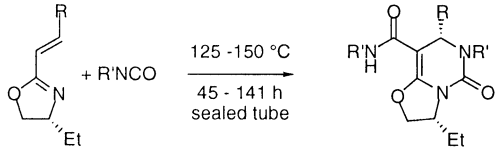
The oxazoline ring system is important in heterocyclic chemistry, and more recently in asymmetric synthesis.[1] In particular there are a wide range of reactions in which azolines and heterocumulenes combine in various proportions.[2] We recently reported the reaction of alkenyloxazolines **1**–**3** with aryl and arylsulfonyl isocyanates as a stereocontrolled entry into the oxazolo[3,2-*c*]pyrimidine ring system present in compounds **5** (Scheme 1).[3] This presumably occurs by addition of a second equivalent of isocyanate to compounds **4**. Although the formation of **4** can be written as a concerted hetero-Diels–Alder reaction,[4] we felt a stepwise mechanism was more consistent with this type of reaction,[5] and now present in full our experimental and computational results which support this assumption.[6] During the course of this work we undertook a preliminary study into the chemistry this little-studied ring system.[7] These results are also described herein.



Scheme 1.

During the early part of our investigations into the reactions of alkenyloxazolines with isocyanates, we noticed discrepancies between products obtained under differing reaction conditions. We had initially studied the reactions at elevated temperature, and quickly realised that better results were obtained if the reactions were carried out at room temperature. However, it became apparent that the products obtained under these differing conditions were actually diastereoisomers, so that the reactions were clearly operating under kinetic and thermodynamic control. While the (3*R*,7*R*) products (hereafter referred to as *trans*) were obtained at low temperature or short reaction times as previously reported, the (3*R*,7*S*) isomers (*cis*) were produced upon extended heating (Scheme 2). Furthermore, it is possible to convert the pure isolated *trans* isomer into the *cis* isomer upon heating.

Under these conditions, a 4:1 mixture of diastereoisomers was obtained in all cases, the ratio being determined by ^{1}H



a R = Me, R' = Ph, 32%
b R = Me, R' = 4-BrC_6H_4, 22%
c R = Me, R' = MeOC_6H_4, 20%
d R = Et, R' = 4-BrC_6H_4, 25%

Scheme 2.

Keywords: asymmetric reactions; Biginelli reactions; pyrimidones; oxazolines.

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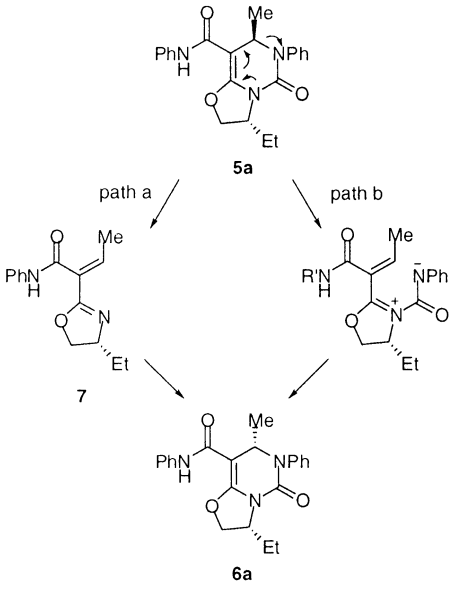
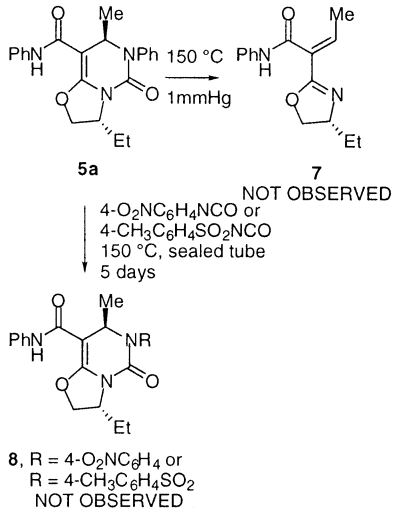


Scheme 3.

NMR analysis of the crude reaction mixtures. For convenience only the *cis* isomer was isolated by column chromatography from these mixtures. It is not entirely surprising, given the harsh conditions, that this isomerisation is accompanied by some decomposition, although NMR data are fully consistent with the proposed structures, and show the change of stereochemistry quite clearly. The major changes are in the oxazolo ring, suggesting that the conformation of the pyrimidine ring is similar between the two isomers. There is a balance between isomerisation and decomposition. The isomerisations must be carried out above the melting point of the pure (3*R*,7*R*) (*trans*) isomer (**5a**, 150°C; **5b**, 220°C; **5c**, 140°C; **5d**, 68°C), although if this is above 150°C decomposition predominates and only a trace of the (3*R*,7*S*) (*cis*) isomer can be detected (with the exception of **6b** which can be prepared directly from the alkenyloxazoline at 170°C despite **5b** having a melting point of 220°C).

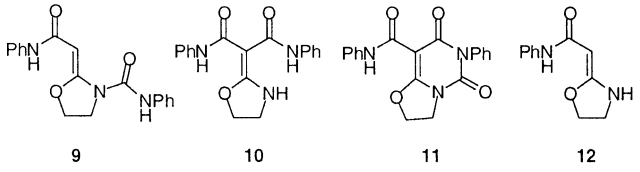


Scheme 4.

There are two main mechanistic possibilities for the formation of compounds **6**, either extrusion of the isocyanate to give **7** in the reverse of a hetero-Diels–Alder reaction followed by recombination (Scheme 3, path a), or scission of the C–N bond followed by ring closure to give the diastereoisomer (Scheme 3, path b).

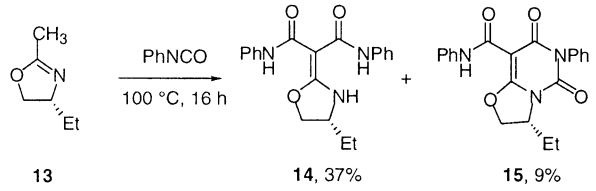
Reaction of **5a** with 4-nitrophenyl isocyanate or 4-toluenesulfonylisocyanate under isomerisation conditions did not lead to formation of mixed products **8**. Similarly heating of **5a** under vacuum showed no evidence for the formation of the alkenyloxazoline **7** (Scheme 4). While the lack of such compounds does not rigorously exclude path a, we take this as strong corroboration, and see no reason why the initial formation of **4** should not proceed by a similar pathway.

If compound **7** was involved in this reaction, it is possible that **6a** is actually the kinetic product formed by reaction of this compound with phenyl isocyanate. In order to investigate this possibility, we sought to prepare **7**. While a number of routes were considered, all of which were ultimately unsuccessful, one result is noteworthy. The reaction of 2-methyl-4,5-dihydrooxazole with phenyl isocyanate has been investigated by Nehring and Seeliger,[8] and subsequently by Richter and Ulrich.[9] Compounds **9**, **10** and **11** were claimed in the latter report, while **9** (later re-assigned as **10**) and **12** were claimed in the former. Clearly compounds similar to **9** and **12** could be useful in the preparation of **7**, so we reinvestigated this chemistry using (4*R*)-4-ethyl-2-methyl-4,5-dihydro-1,3-oxazole **13**.[10]



Reaction of **13** with phenyl isocyanate in chloroform at room temperature or at 50°C gave little or no reaction. However, upon heating these compounds for 16 h at 100°C in the absence of solvent, compounds **14** and **15** were formed as shown in Scheme 5. The structure of **14** was established unambiguously by single-crystal X-ray diffraction (Fig. 1).

While comparison of the data of **10** and **14** is difficult, the chemical shifts observed for **14** are certainly much closer to those reported for **10** than to **9**. Therefore we are confident of the structural assignments made by Richter and Ulrich, which were originally erroneously assigned by Nehring and Seeliger.



Scheme 5.

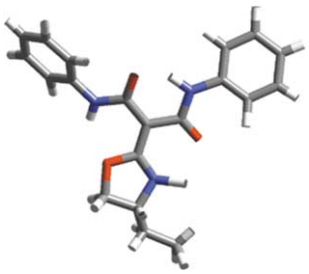
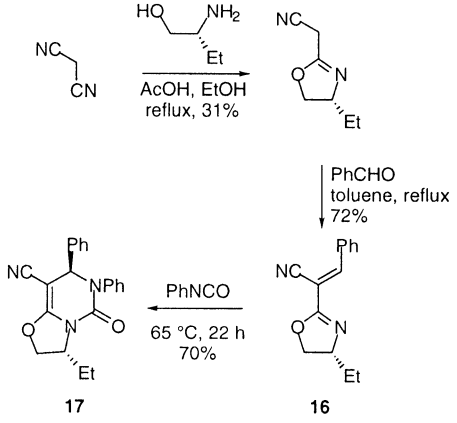


Figure 1. 3D representation of compound **14** from crystallographic data.

In a further attempt to investigate the effect of an electron-withdrawing group on the stereochemistry of the aza-Diels–Alder reaction, compound **16** was prepared as shown in Scheme 6. While this compound could not be obtained analytically pure, it underwent reaction with phenyl isocyanate under relatively mild conditions to give **17**. Again, while this is not conclusive, it does establish that an electron-withdrawing group on the double bond adjacent to the oxazoline is not responsible for the formation of the stereoisomeric products.

Hydrolysis reactions of oxazolo[3,2-*c*]pyrimidines have been previously reported.[7] Since this approach could provide a method for removing the chiral auxiliary, we undertook a brief investigation of these reactions. Hydrolysis of **5a** with concentrated hydrochloric acid or hydrobromic acid led to cleavage of the oxazolo ring in essentially quantitative yield giving only a single stereoisomer of **18** and **19** respectively (stereochemical assignment supported by nOe data, Fig. 2. While this data is not absolutely conclusive, the lack of observed coupling between H^1 and H^2 suggests a dihedral angle consistent with this conclusion). Treatment of **18** with 20% aqueous sodium hydroxide solution gave back **5a** (Scheme 7).



Scheme 6.

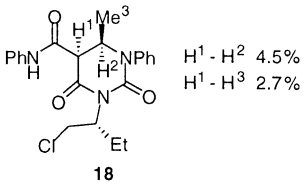
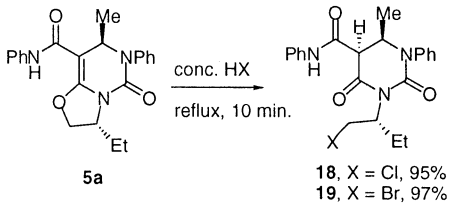


Figure 2. nOe enhancements for compound **18**.

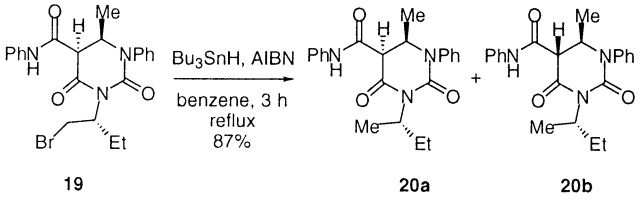


Scheme 7.

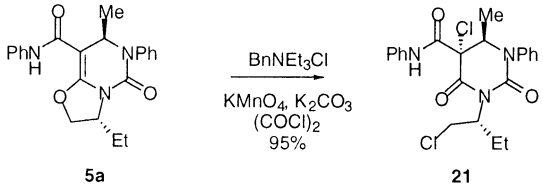
Compound **18** underwent slow epimerisation when left in solution ($CDCl_3$ with a drop of D_2O) to give, after 2 weeks, a 1:1 mixture of diastereoisomers, naturally with deuterium exchange at H^1 (numbering as shown in Fig. 2). Surprisingly, drying this solution over sodium sulfate, and removing the solvent in vacuo followed by immediate addition of fresh $CDCl_3$ gave only the isomer shown in the ^1H NMR spectrum. Presumably this effect is due to crystallization, since drying the solution alone did not change the isomer ratio. Addition of DCl did not accelerate the epimerisation.

Treatment of **19** with tributyltin hydride/AIBN gave a 2:1 mixture of **20a** and **20b**, both of which were obtained pure by careful fractional crystallization (Scheme 8).

Similarly to the formation of **18**, chlorination of **5a** under conditions reported by Markô[11] gave compound **21**. The stereochemistry is assumed to be the same as **18** due to the close similarity of their ^1H NMR spectra. Treatment of **21** with base again led to regeneration of **5a** (Scheme 9).



Scheme 8.

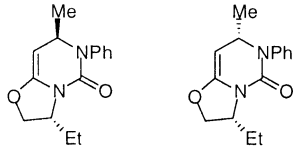


Scheme 9.

2. Computational data

The lack of rigorous experimental support for the stepwise mechanism for this new aza-Diels–Alder reaction prompted us to undertake a computational study. Semi-empirical calculations at the PM3 level[12] estimate the heat of formation of **5a** to be -51.3 kcal mol^{-1} while that of its diastereoisomer **6a** is -52.4 kcal mol^{-1}. From this we can see that the expected ratio of stereoisomers in a thermodynamic mixture is 4:1, as is observed. Further calculations showed a similar energy difference for the diastereoisomers

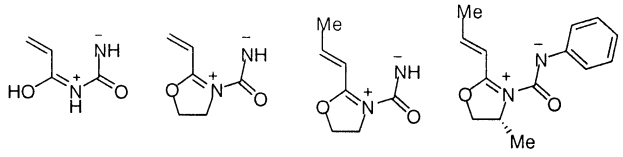
22 and **23**, so that if the first addition of the isocyanate were under thermodynamic control a similar diastereoselectivity would be obtained. The stereoselectivity in the first step must, then, be under kinetic control and so we calculated the transition states leading to each of the diastereoisomers.



22 **23**

Transition state searches were again undertaken using the semi-empirical[13] approach with the program MOPAC (PM3 parameterisation). The Cerius[2] graphical interface was employed for the preparation of the structures in both cartesian and z-matrix form. A frequency analysis at the same level of theory was used to check the nature of structures identified, minima being recognised by a complete set of positive normal modes and transition states by a single negative (imaginary force constant) mode.

Initial attempts to locate the transition state directly proved less than satisfactory, so the structure was simplified to **24** in which only the heavy atoms involved in the final 6-membered ring, the carbonyl and oxazolo oxygen atoms were included, all unsatisfied bonds being taken up by hydrogen atoms. The starting point based on the structure as drawn and the product structure with the 6-membered ring fully formed were optimised and a standard procedure used to step through intermediate structures to give a rough transition state structure (MOPAC SADDLE option). From this point the eigenvector follower method was used to refine the transition state which was then confirmed using a frequency calculation. Animation of the single negative vibrational mode confirmed that this corresponded to a transition state for ring closure.



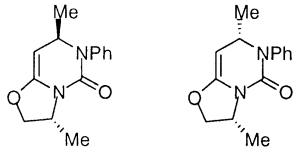
24 **25** **26** **27**

The molecule was then built up from this point in a series of steps: completing the five membered ring (without functionalisation at the 4-position) to give **25**. Then adding the methyl at the double-bond terminus (**26**), giving a chiral transition state for ring closure, and finally introducing the *N* phenyl group and the stereogenic methyl group at the 4-position of the oxazoline (**27**, giving the two required diastereomeric transition states). Methyl was used in place of ethyl to study the ring closure leading to the two diastereoisomers without the added complication of the conformations of the ethyl group which may affect the relative energies of the alternative transition states. At each stage the preceding transition state structure was used as the basis for modification and the transition state re-optimised. In this way it was possible to arrive at a transition for ring-closure for the proposed stepwise pathway. In addition the starting point for each molecule and the product structure were geometry optimised to allow the change in energy (ΔE) for the reaction to be calculated and to give the energy of the transition state relative to the starting point ($\Delta E^{\dagger}$). This data is shown for each structure in Table 1.

Table 1. The calculated energetics of ring closure

Structure	ΔE (kcal mol^{-1})	$\Delta E^{\dagger}$ (kcal mol^{-1})
24	−53.2	9.9
25	−50.0	9.4
26	−45.5	9.6
27 (3*R*,7*S*)	−35.0	14.0
27 (3*R*,7*R*)	−35.7	11.2

The barriers to reaction for structures **24**–**26** are in the range 9.4–9.9 kcal mol^{-1}, some 1 kcal mol^{-1} below the lowest barrier calculated for **27**. This probably arises from the steric interaction between the *N*-phenyl and the methyl at the double bond terminus. In addition there is a 2.8 kcal mol^{-1} difference in the calculated barrier for the transition states leading to **28** (3*R*,7*R*) and **29** (3*R*,7*S*). The optimised transition state geometries for these two cases are shown in Figs. 3 and 4.



28 **29**

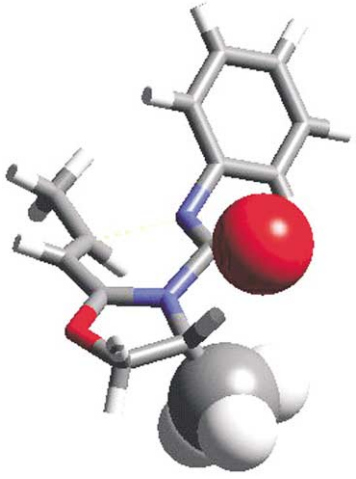


Figure 3. Transition state leading to (3*R*,7*R*) product **28**.

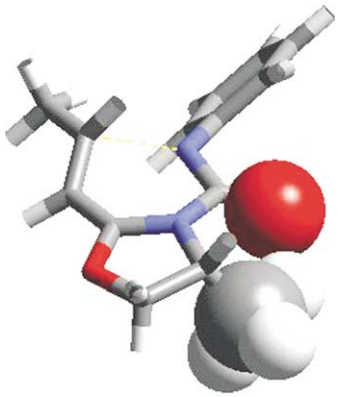
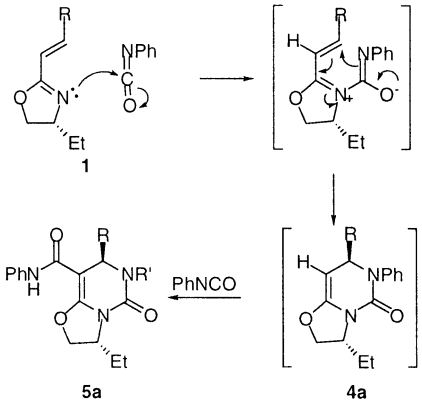


Figure 4. Transition state leading to (3*R*,7*S*) product **29**.

In both cases the propenyl group and the isocyanate are twisted out of the plane of the oxazoline ring to allow a close approach of the carbon and nitrogen atoms forming the new bond. The space filling representation is used to emphasize the isocyanate oxygen and the methyl group at the 4-position of the oxazoline in each structure. The transition state leading to the (3*R*,7*S*) product **29** shows that the twist of the isocyanate leads to steric interactions between the oxygen of the isocyanate and the substituent at the 4-position of the oxazoline which are not present for the transition state leading to the (3*R*,7*R*) product **28**. This interaction appears to lead to the difference in the calculated transition state energies suggesting kinetic selectivity for the (3*R*,7*R*) isomer. This is the form observed experimentally at lower temperatures and with shorter reaction times. From the calculated transition state energy difference we would expect the selectivity to be about 98:2 in favour of the (3*R*,7*R*) isomer. Furthermore, since substituents on the methyl group can orient themselves away from the oxygen of the isocyanate, we would not expect a large difference in selectivity in the series methyl, ethyl, 2-propyl. Clearly, since ethyl gives essentially complete selectivity, this will be difficult to probe experimentally, although 2-propyl does give a similar result. Interestingly, the oxazoline with a gem-dimethyl group at the 4-position is unreactive towards isocyanates, even at elevated temperatures.

We also investigated the possibility of this reaction being a concerted Diels–Alder reaction, but were unable to locate a transition state.

Clearly the calculations are in good agreement with experimental data, both for the kinetically and thermodynamically controlled reactions. We therefore feel that the reaction proceeds in a stepwise manner as originally proposed (Scheme 10).



Scheme 10.

3. Conclusions

The oxazolo[3,2-*c*]pyrimidine ring system has been shown to undergo a number of interesting reactions. Study of these reactions points to a stepwise mechanism for the formation of these compounds in a formal hetero-Diels–Alder reaction of alkenyloxazolines with isocyanates. This mechanism is supported by computational data.

4. Experimental

4.1. General

All melting points were determined on a Gallenkamp melting point apparatus, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a Fisons VG Platform II spectrometer. High-resolution mass spectra were recorded at the EPSRC National Mass Spectrometry Service Centre in Swansea. Elemental analyses were recorded using a Perkin Elmer 240 C elemental analyser. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C at 25°C. All chemical shifts are reported in ppm downfield from TMS. Flash chromatography was performed on Matrex silica 60 35–70 μm.

4.1.1. (3*R*,7*S*)-*N*,6-Diphenyl-3-ethyl-7-methyl-5-oxo-2,3,6,7-tetrahydrooxazolo[3,2-*c*]pyrimidine-8-carboxamide (6a). A mixture of phenyl isocyanate (346 mg, 2.90 mmol) and (4*R*)-ethyl-2-(1-propenyl)-4,5-dihydrooxazole **1** (202 mg, 1.45 mmol) were heated in a sealed tube at 150°C for 65 h. The residue was purified by column chromatography (eluent 3:1 diethyl ether/hexane) to afford the *title compound* (175 mg, 32%) as a light yellow solid, mp 59–61°C (Found: C, 69.73; H, 5.84; N, 10.33. $C_{22}H_{23}N_3O_3$ requires C, 70.01; H, 6.14; N, 11.13%); $\nu_{max.}$ ($CHCl_3$) (cm^{-1}) 3413, 1682, 1652, 1595, 1534 and 694; δ_H (400 MHz; $CDCl_3$) 8.21 (1H, s, N–H), 7.46 (2H, d, *J*=8.2 Hz, aromatic CH), 7.29 (7H, m, aromatic CH), 6.96 (1H, t, *J*=7.2 Hz, aromatic CH), 4.88 (1H, q, *J*=6.3 Hz, MeC*H*), 4.57 (1H, apparent t, *J*=8.1 Hz, one of OCH_2), 4.46 (1H, m, *H*CEt), 4.35 (1H, dd, *J*=8.2, 4.5 Hz, one of OCH_2), 1.87–1.81 (1H, M, one of CH_2CH$_3$), 1.78–1.73 (1H, m, CH_2CH$_3$), 1.24 (3H, d, *J*=6.3 Hz, CH$_3$) and 0.90 (3H, t, *J*=7.4 Hz, CH$_3$); δ_C (100 MHz; $CDCl_3$) 160.9 (C=O), 151.6 (C=O), 149.6 (C), 139.4 (C), 137.6 (C), 128.1 (CH), 127.9 (CH), 126.2 (CH), 126.0 (CH), 122.4 (CH), 119.7 (CH), 83.3 (C), 73.2 (OCH$_2$), 54.3 (CH), 54.0 (CH), 25.4 (CH$_2$), 18.1 (CH$_3$) and 7.8 (CH$_3$); *m*/*z* (EI) 377 (M^+, 21%), 362 (100), 285 (34) and 166 (73).

4.1.2. (3*R*,7*S*)-*N*,6-Bis(4-bromophenyl)-3-ethyl-7-methyl-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide (6b). A mixture of 4-bromophenyl isocyanate (508 mg, 2.93 mmol) and (4*R*)-4-ethyl-2-(1-propenyl)-4,5-dihydro-1,3-oxazole **1** (204 mg, 1.47 mmol) was heated in a sealed tube at 170°C for 114 h. The resulting solid was purified by column chromatography (eluent 2:1 diethyl ether/hexane) to afford the title compound (170 mg, 22%) as a light yellow impure solid, mp 89–93°C (Found: (FAB) MH^+, 536.0018. $C_{22}H_{21}{}^{79}Br^{81}BrN_3O_3$ requires MH^+, 536.0007); $\nu_{max.}$ ($CHCl_3$) (cm^{-1}) 3414, 1682, 1646, 1590 and 1529; δ_H (400 MHz; $CDCl_3$) 8.20 (1H, s, N*H*), 7.45 (2H, dd, *J*=6.8, 1.6 Hz, aromatic CH), 7.40–7.33 (4H, m, aromatic CH), 7.17–7.14 (2H, dd, *J*=6.9, 1.6 Hz, aromatic CH), 4.86 (1H, q, *J*=6.2 Hz, MeC*H*), 4.68 (1H, apparent t, *J*=8.2 Hz, one of OCH_2), 4.56–4.49 (1H, m, *H*CEt), 4.42 (1H, dd, *J*=8.4, 4.5 Hz, one of OCH_2), 1.88–1.76 (2H, m, CH_2), 1.24 (3H, d, *J*=6.4 Hz, CH_3) and 0.97 (3H, t, *J*=7.4 Hz, CH$_3$); δ_C (100 MHz; $CDCl_3$) 162.1 (C=O), 153.1 (C=O), 150.7 (C), 139.7 (C), 138.1 (C), 132.7

(CH), 132.2 (CH), 129.2 (CH), 121.6 (CH), 120.9 (C), 116.3 (C), 84.6 (C), 74.8 (CH_2), 55.7 (CH), 55.6 (CH), 26.8 (CH_2), 20.0 (CH_3) and 9.2 (CH_3); *m/z* (EI) 535 (M^+, 1%), 363 (2), 199 (24), 197 (28) and 55 (100).

4.1.3. (3*R*,7*S*)-*N*,6-Bis(4-methoxyphenyl)-3-ethyl-7-methyl-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide (6c). A mixture of 4-methoxyphenyl isocyanate (420 mg, 2.82 mmol) and (4*R*)-4-ethyl-2-(1-propenyl)-4,5-dihydro-1,3-oxazole **1** (196 mg, 1.41 mmol) were stirred in a sealed tube for 45 h at 150°C. The resulting solid was purified by column chromatography (eluent 3:1 diethyl ether/hexane) to afford the title compound (120 mg, 20%) as a colourless impure solid, mp 74–77°C (Found: (FAB) MH^+, 438.2042. $C_{24}H_{27}N_3O_5$ requires MH^+, 438.2029); $\nu_{max.}$ ($CHCl_3$) (cm^{-1}) 3416, 1684, 1645, 1599 and 1538; δ_H (400 MHz; $CDCl_3$) 8.20 (1H, s, N*H*), 7.37 (2H, d, *J*=6.9 Hz, aromatic CH), 7.16 (2H, d, *J*=6.7 Hz, aromatic CH), 6.84 (2H, d, *J*=6.7 Hz, aromatic CH), 6.78 (2H, d, *J*=6.9 Hz, aromatic CH), 4.79 (1H, q, *J*=6.1 Hz, MeC*H*), 4.64 (1H, apparent t, *J*=8.1 Hz, one of OCH_2), 4.52–4.47 (1H, m, *HC*Et), 4.38 (1H, dd, *J*=8.2, 4.6 Hz, one of OCH_2), 3.74 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 1.82–1.76 (2H, m, CH_2), 1.25 (3H, d, *J*=6.4 Hz, CH_3) and 0.96 (3H, t, *J*=7.4 Hz, CH_3); δ_C (100 MHz; $CDCl_3$) 162.3 (C=O), 158.8 (C=O), 156.2 (C), 152.8 (C), 151.3 (C), 133.5 (C), 132.1 (C), 129.1 (CH), 122.0 (CH), 114.8 (CH), 114.5 (CH), 84.5 (C), 74.6 (CH_2), 56.0 (CH), 55.9 (2×OCH_3), 55.5 (CH), 26.9 (CH_2), 20.0 (CH_3) and 9.2 (CH_3); *m/z* (EI) 437 (M^+, 87%), 422 (96), 315 (95), 166 (100) and 149 (92).

4.1.4. (3*R*,7*S*)-*N*,6-Bis(4-bromophenyl)-3,7-diethyl-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide (6d). A mixture of 4-bromophenyl isocyanate (503 mg, 2.54 mmol) and (4*R*,*E*)-4-ethyl-2-(buten-1-yl)-4,5-dihydro-1,3-oxazole **2** (142 mg, 1.27 mmol) were stirred in a sealed tube at 125°C for 141 h. The resulting solid was purified by column chromatography (eluent 2:1 diethyl ether/hexane) to afford the title compound (189 mg, 25%) as a yellow impure solid. (Found: MH^+, 548.0180. $C_{23}H_{23}{}^{79}Br_2N_3O_3$ requires MH^+, 548.0184); $\nu_{max.}$ ($CHCl_3$) (cm^{-1}) 3413, 1683, 1652, 1589 and 1527; δ_H (400 MHz; $CDCl_3$) 8.27 (1H, s, N*H*), 7.44–7.33 (6H, m, aromatic CH), 7.17 (2H, m, aromatic CH), 4.92 (1H, m, EtC*H*), 4.64 (1H, apparent t, *J*=8.0 Hz, one of OCH_2), 4.48 (1H, m, *HC*Et), 4.42 (1H, dd, *J*=8.2, 4.2 Hz, one of OCH_2), 1.89–1.57 (4H, m, 2×CH_2) and 0.84–0.78 (6H, m, 2×CH_3); δ_C (100 MHz; $CDCl_3$) 162.9 (C=O), 154.0 (C=O), 151.5 (C), 140.5 (C), 138.5 (C), 133.2 (CH), 132.7 (CH), 129.8 (CH), 122.1 (CH), 121.3 (C), 116.7 (C), 82.5 (C), 75.1 (CH_2), 60.7 (CH), 56.1 (CH), 27.5 (CH_2), 27.2 (CH_2), 9.9 (CH_3) and 9.4 (CH_3); *m/z* (EI) 547 (M^+, 1%), 522 (42), 520 (100), 518 (49), 180 (89) and 55 (100).

4.1.5. (4*R*)-2-[Bis(phenylcarbamoyl)methylene]-4-ethyloxazolidine (14) and (3*R*)-*N*,6-diphenyl-3-ethyl-5,7-dioxo-2,3,6,7-tetrahydrooxazolo-5*H*-[3.2-*c*]pyrimidine-8-carboxamide (15). A mixture of (4*R*)-4-ethyl-2-methyl-4,5-dihydro-1,3-oxazole **13**[10] (277 mg, 2.45 mmol) and phenyl isocyanate (584 mg, 4.90 mmol) were stirred in a sealed tube at 100°C for 20 h. The resulting solid was filtered through silica (eluent: 2:1 diethyl ether/hexane). The solvent was removed in vacuo and the residue recrystallised from hot methanol to afford **14** (315 mg, 37%) as a colourless solid, mp 139–142°C (Found: C, 68.16; H, 6.05; N, 12.41. $C_{20}H_{21}N_3O_3$ requires C, 68.36; H, 6.02; N, 11.96%); $\nu_{max.}$ ($CHCl_3$) (cm^{-1}) 3423, 1699 and 1641; δ_H (400 MHz; $CDCl_3$) 12.25 (1H, s, N*H*), 11.01 (1H, s, N*H*), 8.69 (1H, s, N*H*), 7.51 (2H, d, *J*=7.7 Hz, aromatic CH), 7.39 (2H, d, *J*=7.6 Hz, aromatic CH), 7.26–7.19 (4H, m, aromatic CH), 7.01 (1H, t, *J*=7.3 Hz, aromatic CH), 6.95 (1H, t, *J*=7.4 Hz, aromatic CH), 4.59 (1H, apparent t, *J*=8.5 Hz, one of OCH_2), 4.27 (1H, dd, *J*=8.3, 6.6 Hz, one of OCH_2), 3.93 (1H, m, *HC*Et), 1.62–1.51 (2H, m, CH_2) and 0.89 (3H, t, *J*=7.4 Hz, CH_3); δ_C (100 MHz; $CDCl_3$) 169.2 (C), 168.6 (C), 167.1 (C), 139.5 (C), 138.8 (C), 129.4 (CH), 129.1 (CH), 124.4 (CH), 123.5 (aromatic CH), 121.9 (CH), 121.2 (CH), 79.0 (C), 74.0 (CH_2), 56.6 (CH), 27.8 (CH_2) and 10.0 (CH_3); *m/z* (EI) 351 (M^+, 4%), 260 (13), 187 (22), 119 (49) and 93 (100).

The mother liquor was concentrated further and compound **15** was collected by filtration (88 mg, 9%); δ_H (400 MHz; $CDCl_3$) 10.78 (1H, s, N*H*), 7.56 (2H, d, *J*=7.9 Hz, aromatic CH), 7.52–7.42 (3H, m, aromatic CH), 7.27–7.21 (4H, m, aromatic CH), 7.00–6.97 (1H, t, *J*=7.3 Hz, aromatic CH), 4.95–4.88 (1H, apparent t, *J*=10.8 Hz, one of OCH_2), 4.69 (1H, dd, *J*=9.2, 4.1 Hz, one of OCH_2), 4.66–4.61 (1H, m, *HC*Et), 2.09–2.03 (1H, m, one of CH_2), 1.94–1.86 (1H, m, one of CH_2) and 0.95 (3H, t, *J*=7.5 Hz, CH_3); *m/z* (EI) 377 (M^+, 22%), 285 (22) and 55 (100).

4.2. Structure determination and refinement of (14)

A colourless crystal (0.21×0.11×0.07 mm^3) was glued on top of a capillary and transferred in the cold nitrogen stream of a fast area detector diffractometer with rotating anode. Final lattice parameters were determined by least-squares treatment, using the setting angles (SET) of well-centred reflections in the range $1.99<\theta<25.02°$. Selected crystallographic data are as follows: $C_{20}H_{21}N_3O_3$ (M_r 351.40), triclinic, $P\bar{1}$, a=8.192(2), b=10.525(6), c=10.919(10) Å. α=73.12(3), β=76.480(10), γ=80.17(3)°, Z=2, V=870.6(10) $Å^3$, D_c=1.341 g cm^{-3}, Mo Kα radiation, λ=0.71069 Å, $1.99<\Theta<25.02°$. 3103 reflections were collected of which 2195 were unique. 724 reflections having $I>2.0\sigma(I)$ were used for refinement (236 parameters), converging to R=0.0536 and R_W=0.1071. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 167845.

4.2.1. (4*R*,*E*)-4-Ethyl-2-(2-phenyl-1-cyanoethenyl)-4,5-dihydro-1,3-oxazole (16). Malononitrile (3.80 g, 57.5 mmol) was added to a solution of (2*R*)-2-aminobutan-1-ol (1.71 g, 19.2 mmol) in absolute ethanol (50 ml) and glacial acetic acid (2 ml). The mixture was heated under reflux overnight. The volatiles were removed in vacuo. The remaining solid was dissolved in chloroform and washed twice with saturated aqueous sodium hydrogencarbonate (25 ml) and quickly dried over Na_2SO_4, filtered and concentrated in vacuo to afford (4*R*)-4-ethyl-2-cyanomethyl-4,5-

dihydro-1,3-oxazole (815 mg, 31%) which was added to a solution of benzaldehyde (626 mg, 5.90 mmol) in toluene (50 ml). The mixture was heated under reflux under azeotropic removal of water overnight. The solid was removed in vacuo and purified by column chromatography (eluent: 2:1 diethyl ether/hexane) to afford the title compound (963 mg, 72%) as a yellowish slightly impure oil (Found: MH^+, 227.1185. $C_{14}H_{14}N_2O$ requires MH^+, 227.1184); $\nu_{max.}$ (neat) (cm^{-1}) 3061, 2212, 1640 and 1631; δ_H (400 MHz; $CDCl_3$); 7.85 (2H, m, aromatic CH), 7.82 (1H, s, alkene C*H*), 7.46–7.42 (3H, m, aromatic CH), 4.42 (1H, apparent t, J=8.4 Hz, one of OCH_2), 4.24–4.18 (1H, m, *HC*Et), 4.00 (1H, apparent t, J=8.0 Hz, one of OCH_2), 1.74–1.64 (1H, m, one of CH_2), 1.58–1.51 (1H, m, one of CH_2) and 0.91 (3H, t, J=7.4 Hz, CH_3); m/z (CI) 227 (MH^+, 100%).

4.2.2. (3*R*,7*R*)-8-Cyano-6,7-diphenyl-3-ethyl-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine (17). A mixture of phenyl isocyanate (257 mg, 2.16 mmol) and (4*R*,*E*)-4-ethyl-2-(2-phenyl-1-cyanoethenyl)-4,5-dihydro-1,3-oxazole **16** (244 mg, 1.08 mmol) was heated in a sealed tube at 65°C for 22 h. The resulting solid was purified by column chromatography (eluent 2:1 diethyl ether/hexane followed by dichloromethane) to afford the title compound (260 mg, 70%) as a white solid, mp 175–177°C (Found: M^+, 345.1474. $C_{21}H_{19}N_3O_2$ requires M, 345.1477); $\nu_{max.}$ ($CHCl_3$) (cm^{-1}) 2208 and 1694; δ_H (400 MHz; $CDCl_3$) 7.21 – 7.09 (8H, m, aromatic CH), 6.93 (2H, d, J=9.0 Hz, aromatic CH), 5.36 (1H, s, PhC*H*), 4.59 (1H, apparent t, J=7.4 Hz, one of OCH_2), 4.44–4.37 (2H, m, HCEt and one of OCH_2), 1.99–1.93 (1H, m, one of CH_2), 1.92–1.84 (1H, m, one of CH_2) and 0.90 (3H, t, J=7.5 Hz, CH_3); δ_C (100 MHz; $CDCl_3$) 158.5 (C═O), 149.4 (C), 140.0 (C), 139.7 (C), 129.6 (CH), 129.3 (CH), 129.3 (CH). 128.4 (CH), 128.1 (CH), 127.7 (CH), 116.2 (CN), 74.0 (CH_2), 64.0 (CH), 59.0 (C), 57.9 (CH), 24.7 (CH_2) and 8.9 (CH_3); m/z (APCI) 346 (MH^+, 100%).

4.2.3. (4*R*,5*R*)-1-((2*R*)-1-Chlorobutan-2-yl)-2,6-dioxo-4-methyl-3-phenyl-5-(*N*-phenylcarbamoyl)perhydropyrimidine (18). (3*R*,7*R*)-*N*,6-Diphenyl-3-ethyl-7-methyl-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide **5a** (25 mg, 0.007 mmol) was heated under reflux for 10 min in concentrated hydrochloric acid (10 ml). The resulting solution was extracted with chloroform (10 ml), and the chloroform dried over Na_2SO_4 before being removed in vacuo to afford the title compound (26 mg, 95%) as a colourless solid, mp 60–62°C (Found: C, 64.34; H, 6.07; N, 9.89. $C_{22}H_{24}ClN_3O_3$ requires C, 63.84; H, 5.84; N, 10.15%); $\nu_{max.}$ ($CHCl_3$) (cm^{-1}) 3383, 1706, 1668, 1599 and 1538; δ_H (400 MHz; $CDCl_3$) 8.06 (1H, s, N*H*), 7.44–7.25 (9H, m, aromatic CH), 7.09 (1H, t, J=7.4 Hz, aromatic CH), 4.99–4.91 (1H, m, *HC*Et), 4.57 (1H, q, J=7.0 Hz, MeC*H*), 4.25 (1H, apparent t, J=10.9 Hz, one of CH_2Cl), 3.70 (1H, dd, J=11.4, 3.6 Hz, one of CH_2Cl), 3.57 (1H, s, C*H*), 2.07–1.98 (1H, m, one of CH_2), 1.77–1.68 (1H, m, one of CH_2), 1.35 (3H, d, J=6.9 Hz, CH_3) and 0.88 (3H, t, J=7.4 Hz, CH_3); δ_C (100 MHz; $CDCl_3$) 169.7 (C═O), 162.2 (C═O), 149.1 (C═O), 140.9 (C), 137.2 (C), 129.7 (CH), 129.6 (CH), 128.8 (CH), 128.2 (CH), 125.6 (CH), 120.8 (CH), 57.7 (CH), 56.0 (CH), 52.6 (CH), 45.8 (CH_2), 23.5 (CH_2) and 18.3 (CH_3), 11.5 (CH_3); m/z (EI) 416 (M^+ (^{37}Cl), 6%), 414 (M^+, 21), 378 (85), 285 (48) and 119 (100).

4.2.4. (4*R*,5*R*)-1-((2*R*)-1-Bromobutan-2-yl)-2,6-dioxo-4-methyl-3-phenyl-5-(*N*-phenylcarbamoyl)perhydropyrimidine (19). (3*R*,7*R*)-*N*,6-Diphenyl-3-ethyl-7-methyl-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide **5a** (132 mg, 0.35 mmol) was heated under reflux for 10 min in concentrated hydrobromic acid (10 ml). The resulting solution was extracted with chloroform (10 ml), dried over Na_2SO_4. The solvent was removed in vacuo to afford the title compound (156 mg, 97%) as a colourless solid, mp 71–73°C; $\nu_{max.}$ ($CHCl_3$) (cm^{-1}) 3384, 1704, 1667, 1599 and 1538; δ_H (400 MHz; $CDCl_3$) 8.15 (1H, s, N*H*), 7.44–7.42 (4H, m, aromatic CH), 7.36–7.32 (2H, m, aromatic CH), 7.29–7.22 (3H, m, aromatic CH), 7.07 (1H, t, J=7.3 Hz, aromatic CH), 5.00–4.92 (1H, m, *HC*Et), 4.54 (1H, q, J=6.6 Hz, MeC*H*), 4.16 (1H, apparent t, J=10.6 Hz, one of CH_2Br), 3.59 (1H, s, C*H*), 3.52 (1H, dd, J=10.7, 5.8 Hz, one of CH_2Br), 2.06–2.00 (1H, m, one of CH_2), 1.79–1.72 (1H, m, one of CH_2), 1.35 (3H, d, J=7.0 Hz, CH_3) and 0.87 (3H, t, J=7.4 Hz, CH_3); δ_C (100 MHz; $CDCl_3$) 169.5 (C═O), 162.3 (C═O), 151.1 (C═O), 141.0 (C), 137.3 (C), 129.8 (CH), 129.6 (CH), 128.2 (CH), 125.5 (CH), 120.9 (CH), 120.8 (CH), 57.6 (CH), 55.9 (CH), 52.6 (CH), 34.3 (CH_2), 24.2 (CH_2), 18.5 (CH_3) and 11.7 (CH_3); m/z (EI) 459 (M^+, 4), 457 (8), 361 (100), 339 (34), 337 (34) and 203 (39).

4.2.5. (4*R*)-1-((2*R*)-Butan-2-yl)-2,6-dioxo-4-methyl-3-phenyl-5-(*N*-phenylcarbamoyl)perhydropyrimidine (20). To (4*R*)-1-((2*R*)-1-bromobutan-2-yl)-2,6-dioxo-4-methyl-3-phenyl-5-(*N*-phenylcarbamoyl)perhydropyrimidine **19** (94 mg, 0.21 mmol) in benzene (10 ml, degassed for 30 min with nitrogen) was added AIBN (1 mg) and tributyltin hydride (597 mg, 2.05 mmol). The mixture was heated under reflux for 3 h. The solvent was removed in vacuo and the remaining oil was dissolved in acetonitrile (10 ml) and washed with hexane (5×, 15 ml). The acetonitrile was removed in vacuo to afford the title compound (68 mg, 87%) as a colourless solid (2:1 mixture of diastereoisomers), mp 170°C (dec.) (Found: MH^+, 380.1978. $C_{22}H_{25}N_3O_3$ requires MH^+, 380.1974); $\nu_{max.}$ ($CHCl_3$) (cm^{-1}) 3379, 1704, 1659, 1598 and 1538; m/z (APCI) 380 (MH^+, 100%). Fractional crystallisation (2:1 diethyl ether/hexane) afforded both diastereoisomers pure.

20a: δ_H (400 MHz; $CDCl_3$) (NH not observed) 7.63 (2H, d, J=7.7 Hz, aromatic CH), 7.53 (2H, d, J=8.0 Hz, aromatic CH), 7.38–7.32 (5H, m, aromatic CH), 7.16 (1H, t, J=7.4 Hz, aromatic CH), 4.81–4.72 (1H, m, C*H*), 4.68–4.58 (1H, m, C*H*), 3.92 (1H, d, J=5.2 Hz, C*H*), 2.10 (1H, m, one of CH_2), 1.82 (1H, m, one of the CH_2), 1.48 (3H, d, J=6.9 Hz, CH_3), 1.33 (3H, d, J=6.5 Hz, CH_3) and 0.95 (3H, t, J=7.5 Hz, CH_3); δ_C (100 MHz; $CDCl_3$) 170.2 (C═O), 163.3 (C═O), 150.0 (C═O), 141.0 (C), 137.7 (C), 129.8 (CH), 129.5 (CH), 128.0 (CH), 127.2 (CH), 125.5 (CH), 120.8 (CH), 54.0 (CH), 53.3 (CH), 50.5 (CH), 26.5 (CH_2), 19.1 (CH_3), 15.2 (CH_3), 12.1 (CH_3).

20b: δ_H (400 MHz; $CDCl_3$) 8.28 (1H, s, N*H*), 7.54–7.52 (3H, m, aromatic CH), 7.46–7.42 (2H, apparent t,

J=8.1 Hz, aromatic CH), 7.38–7.32 (4H, m, aromatic CH), 7.18 (1H, t, J=7.5 Hz, aromatic CH), 4.78–4.70 (1H, m, C*H*), 4.66–4.60 (1H, m, C*H*), 3.60 (1H, s, C*H*), 2.12–2.07 (1H, m, one of CH_2), 1.81–1.77 (1H, m, one of the CH_2), 1.45 (3H, d, J=6.9 Hz, CH_3), 1.40 (3H, d, J=6.9 Hz, CH_3) and 0.91 (3H, t, J=7.4 Hz, CH_3); δ_C (100 MHz; $CDCl_3$) 169.3 (C=O), 162.2 (C=O), 150.9 (C=O), 141.1 (C), 137.3 (C), 129.7 (CH), 129.6 (CH), 129.1 (CH), 128.2 (CH), 120.6 CH), 120.4 (CH), 59.5 (CH), 53.0 (CH), 51.9 (CH), 26.5 (CH_2), 19.1 (CH_3), 18.3 (CH_3), 11.8 (CH_3).

4.2.6. (4*S*)-1-((2*R*)-1-Chlorobutan-2-yl)-2,6-dioxo-5-chloro-4-methyl-3-phenyl-5-(*N*-phenylcarbamoyl)perhydropyrimidine (21). Potassium permanganate (50 mg, 0.32 mmol) was added to a solution of benzyltriethylammonium chloride (73 mg, 0.32 mmol) in dry dichloromethane (15 ml). The purple mixture was stirred for 15 min and was then cooled to −45°C. Oxalyl chloride (80 mg, 0.64 mmol) was added. A vigorous gas evolution took place and the colour changed to dark brown. After 20 min (3*R*,7*R*)-*N*,6-Diphenyl-3-ethyl-7-methyl-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide **5a** (120 mg, 0.32 mmol) was added, after which the solution turned emerald green. After 30 min, the solution was quenched with a saturated aqueous solution of sodium thiosulphate (10 ml). The organic layer was separated, dried over magnesium sulfate, and the resulting solution filtered and concentrated in vacuo to give the title compound (136 mg, 95%) as a light brown solid, mp 68–70°C; (Found: M^+, 447.1116. $C_{22}H_{23}{}^{35}Cl^{37}ClN_3O_3$ requires M, 447.1116); $\nu_{max.}$ ($CHCl_3$) (cm^{-1}) 3493, 1726, 1695, 1659 and 1548; δ_H (400 MHz; $CDCl_3$) 10.78 (1H, s, N*H*), 7.57 (2H, d, J=7.7 Hz, aromatic CH), 7.37–7.31 (7H, m, aromatic CH), 7.14 (1H, t, J=7.4 Hz, aromatic CH), 4.97–4.90 (1H, m, *H*CEt), 4.52–4.47 (1H, q, J=6.7 Hz, MeC*H*), 4.28 (1H, apparent t, J=11.0 Hz, one of CH_2Cl), 3.66 (1H, dd, J=11.2, 4.9 Hz, one of CH_2Cl), 2.10–2.05 (1H, m, one of CH_2), 1.78–1.75 (1H, m, one of CH_2), 1.42 (3H, d, J=6.8 Hz, CH_3) and 0.95 (3H, t, J=7.5 Hz, CH_3); δ_C (100 MHz; $CDCl_3$) 168.3 (C=O), 161.9 (C=O), 150.8 (C=O), 140.6 (C), 137.2 (C), 130.0 (CH), 129.6 (CH), 128.6 (CH), 127.5 (CH), 125.9 (CH), 120.9 (CH), 61.1 (C-Cl), 60.4 (CH), 59.3 (CH), 45.1 (CH_2), 22.9 (CH_2), 15.9 (CH_3), 11.4 (CH_3); *m/z* (EI) 448 (MH^+, 1%), 413 (1), 363 (2), 119 (55), 77 (78) and 55 (100).

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