Asymmetric hetero-Diels–Alder reactions of alkenyldihydro-oxazoles. Synthesis of oxazolo[3,2-*c*]pyrimidines and related compounds

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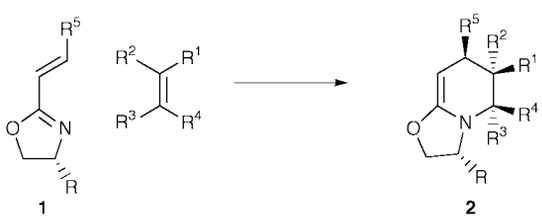
Alkenyldihydrooxazoles undergo a highly diastereoselective formal aza-Diels–Alder reaction with aryl and arenesulfonyl isocyanates to give oxazolo[3,2-*c*]pyrimidines. Depending on the substitution pattern of the alkenyldihydrooxazole, these compounds may then undergo addition of a second equivalent of the isocyanate to give either tetrahydrooxazolo[3,2-*c*]pyrimidine-8-carboxamides or octahydroazeto[2,3-*d*]oxazolo[3,2-*c*]pyrimidines. The second addition is sensitive to steric and electronic factors, and can be prevented in some cases.

Introduction

The Diels–Alder reaction has proven its synthetic utility numerous times since its discovery over 70 years ago.[1] Much recent work has focussed on asymmetric variations of this reaction, whether diastereoselective as a result of chiral starting materials[2] or enantioselective through catalysis.[3] In contrast to this, aza-Diels–Alder reactions, and particularly asymmetric aza-Diels–Alder reactions,[4] have received much less attention. In fact, prior to our own work in this area,[5] the only example of a chiral 1-azadiene in a Diels–Alder reaction was the use of unsaturated SAMP-hydrazones reported by Ghosez and co-workers,[6] while Waldner has reported an asymmetric aza-Diels–Alder reaction of a 1-azadiene with a homochiral thiazolinone dienophile.[7]

We felt that alkenyldihydrooxazoles **1** had much to offer as azadienes, given their ready preparation from amino acid derivatives, and that these reactions would allow the generation of up to three stereogenic centres in a single step (Scheme 1),

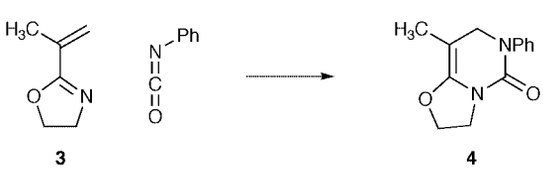


1 **2**

Scheme 1

with the opportunity to introduce further functionality by modification of potentially versatile products **2**.

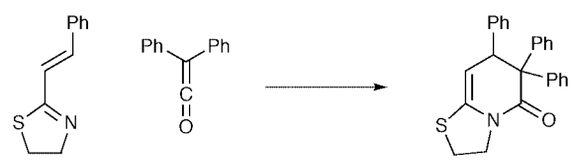
We were somewhat surprised to find only a single example of the use of alkenyldihydrooxazoles as azadienes in the literature, this being the work of Hellmann and co-workers (Scheme 2),[8]



3 **4**

Scheme 2

while Sakamoto had reported the use of alkenylthiazolines as azadienes in reactions with diphenylketene (Scheme 3).[9] In



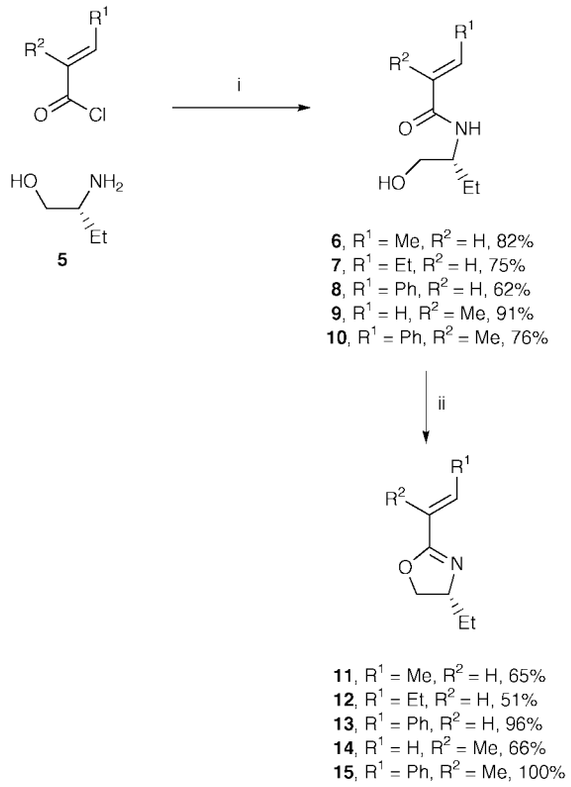
Scheme 3

related work, Richter and Ulrich reported reactions of *N*,*N*-dimethyl-*N*′-(Δ^2-thiazolin-2-yl)formamidine with phenyl isocyanate.[10] Cross-conjugated azatrienes were used by Saito *et al.*[11] with isocyanates in a tandem process.

All these reactions share the common factor of a heterocumulene reacting as the dienophilic component, and since isocyanates are more readily accessible than ketenes, we decided to use the study of Hellmann as a basis for our own work. We were initially hindered by the lack of experimental detail in the report of Hellmann, and unable to reconcile the single piece of spectroscopic data reported, an infrared stretching frequency of 1760 cm^{-1}, with the proposed structure **4**.

Results and discussion

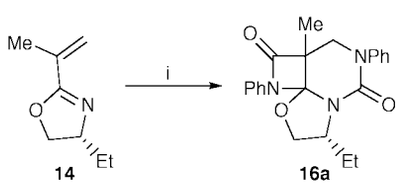
The many methods for the preparation of dihydrooxazoles have been reviewed by Meyers and Gant.[12] We were mindful of the potential problem of conjugate addition of excess amino alcohol to the desired alkenyldihydrooxazoles, and so chose to pursue a two step route involving formation and cyclisation of the corresponding amides (Scheme 4). Starting with the readily available (2*R*)-2-aminobutan-1-ol **5** of 64.4% ee the amides **6**–**10** were obtained in 62–91% yield from the appropriate acid chloride under Schotten–Baumann conditions according to the procedure of Langlois *et al.*[13] These were used without further purification with the exception of **10** which was recrystallised from diethyl ether. A number of methods can be used for the cyclisation to the dihydrooxazole,[14] but we have found the use of methanesulfonyl chloride and triethylamine in dichloromethane to be most convenient. Dihydrooxazole **13** surprisingly decomposed on attempted distillation or prolonged contact with silica gel. Rapid chromatography gave only a minor



Scheme 4 *Reagents and conditions*: i, Na_2CO_3, CH_2Cl_2, H_2O; ii, $MeSO_2Cl$, Et_3N, CH_2Cl_2.

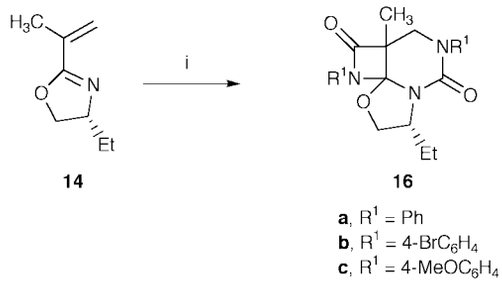
improvement, but fortunately the crude product was pure enough to use directly.[15] Dihydrooxazoles **11**, **12** and **14** were purified by short path distillation. Compound **15** was formed essentially quantitatively, and no purification was required.

Dihydrooxazole **3**, used earlier by Hellmann and prepared in a similar manner to that shown in Scheme 4, was used initially. Reaction with phenyl isocyanate under a wide range of conditions gave either recovered dihydrooxazole or complex mixtures from which we were unable to isolate products. In no instance did we observe the 1760 cm^{-1} band in the infrared spectrum even of the crude reaction mixture. Since this dihydrooxazole is quite volatile, we moved next to **14**, although due to the substitution pattern this was not expected to lead to the generation of a new stereogenic centre. In the event, this proved to be a fortuitous choice, since the products obtained when **14** was heated to 150 °C with phenyl isocyanate appeared to be a mixture of diastereoisomers in which two equivalents of the isocyanate had been incorporated. The NMR data for these compounds was not particularly conclusive, and we were unable to separate the diastereoisomers. However, based on the tentative assumption that the initial reaction would be a formal hetero-Diels–Alder, we reasoned that the second equivalent of the isocyanate might add to the electron-rich double bond in the initial adduct to give compounds **16** containing the previously unknown azeto[2,3-*d*][1,3]oxazolo[3,2-*c*]pyrimidine ring system (Scheme 5). These structures appear to fit the available data, and have been supported by later results (*vide infra*), although



Scheme 5 *Reagents and conditions*: i, 2 equivalents PhNCO, 150 °C, 65 h.

Table 1 Reactions of **14** with selected isocyanates



Reagents and conditions: i, 2 equivalents R^1NCO, see below.

Entry	R	R^1	*t*/h	*T*/°C	Compound (yield %)
1	Et	Ph	65	150	**16a** (81)
2	Et	4-BrC_6H_4	18	150	**16b** (42)
3	Et	4-$MeOC_6H_4$	25	150	**16c** (see text)
4	Et	4-$NO_2C_6H_4$	—	—	(0)

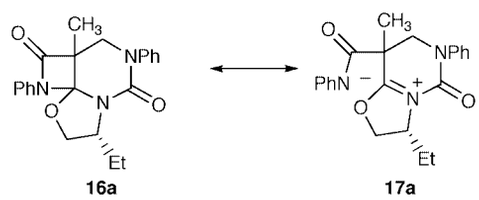


Fig. 1

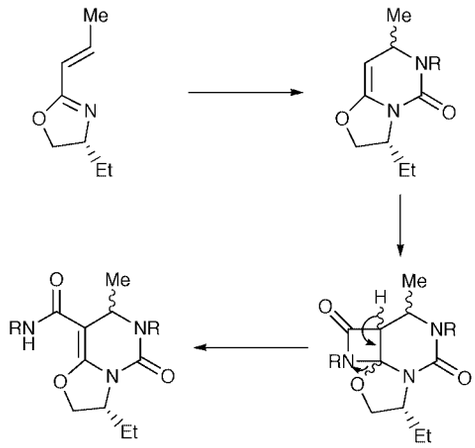
we do feel that the data we have is not conclusive and have been unable to assign the stereochemistry of the major isomer.

Compounds **16a–c** were formed from **14** (Table 1, entries 1–3), in each case as an approximately 1.7 : 1 mixture of diastereoisomers. Reaction of **14** with 4-nitrophenyl isocyanate led to no isolable products, presumably due to the ease of hydrolysis of the β-lactam (entry 4).

In each case we were unable to separate the diastereoisomers by either crystallisation or chromatography. Not surprisingly these compounds decomposed extensively upon chromatography over silica gel. Chromatography over neutral alumina gave essentially pure compounds, although traces of the *N*,*N*′-diarylurea, a hydrolysis product of the isocyanate, could not completely be removed. In the case of **16a**, the compound was obtained essentially pure simply by extracting the reaction mixture with chloroform and filtering and evaporating. Very little improvement was observed upon chromatography. In the case of **16c**, the reaction was extremely capricious. On one occasion we were able to obtain a 70% yield of reasonably pure material by dissolving the crude reaction mixture in chloroform. On a number of other occasions only a small amount of product was observed, along with extensive decomposition.

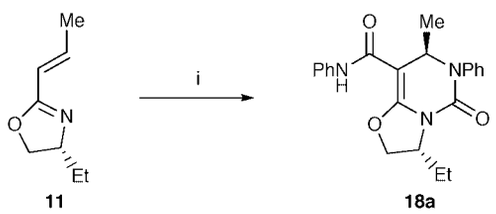
These compounds exhibit some unusual spectroscopic features. For example, the infrared stretch of the β-lactam carbonyl is lower than might be expected (typically 1730 cm^{-1}). Also, the quaternary carbon bearing the three heteroatoms is significantly deshielded in the ^{13}C NMR spectrum (around 150 ppm). Both these features can be rationalised by the contribution of a zwitterionic resonance form **17** (Fig. 1). The existence of compounds **16** as full zwitterionic species seems unlikely on the grounds of polarity.

Due to our difficulty in satisfactorily characterising compounds **16**, we reasoned that moving the methyl group in **14** to the terminus of the double bond would lead to the formation of a new stereogenic centre in the addition of the first equivalent of the isocyanate, and if a β-lactam were formed during the second addition, it would be expected to fragment as shown in Scheme 6.



Scheme 6

Gratifyingly this proved to be the case, so that when **11** was heated with two equivalents of phenyl isocyanate at 150 °C (sealed tube) for 1 hour, the 2:1 adduct **18a** formed as only a single diastereoisomer within the detection limits of 400 MHz ^{1}H NMR spectroscopy (Scheme 7). Subsequent experiment-



Scheme 7 *Reagents and conditions*: i, 2 equivalents PhNCO, 150 °C, 1 h.

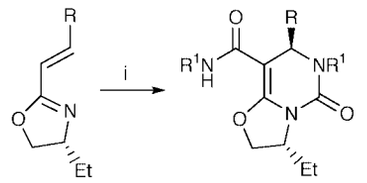
ation showed that the reaction also proceeds, albeit slowly, at room temperature. At either temperature, only the same single diastereoisomer was observed. Results from a range of isocyanates are summarised in Table 2. The stereochemistry of **18c**, **18e** and **20e** were confirmed by single crystal X-ray analysis.[16] The other compounds are assumed, on the basis of similar spectroscopic data, to have the same stereochemistry. Based on these results, we feel that the β-lactam structures **16** are correct.

Reactions with toluene-4-sulfonyl isocyanate were particularly rapid, while those with 4-methoxyphenyl isocyanate were much slower (with compound **19d** only a trace of the desired product was visible in the ^{1}H NMR spectrum of the crude reaction mixture). Reactions with *tert*-butyl isocyanate and benzyl isocyanate were unsuccessful, reflecting the lower reactivity of these compounds.

We were intrigued by the possibility of preparing mixed adducts using two isocyanates in appropriate proportions. Unfortunately reaction of **11** with 5 equivalents of either phenyl isocyanate or 4-methoxyphenyl isocyanate and 1 equivalent of toluene-4-sulfonyl isocyanate gave only the adduct derived from double addition of toluene-4-sulfonyl isocyanate. Clearly while the second addition is faster than the first, it is still slow enough to permit selective reaction of a more reactive isocyanate.

With these results in hand, we felt that if we were to use a substrate such as **15** it should give complete stereocontrol in the first step. As a result of this, the β-lactam formation in the second step would be directed by an adjacent stereocentre rather than a remote one, and so we might expect better stereocontrol. Although this did prove to be the case, the reactions were not as simple as expected. Reaction of this dihydrooxazole with 2 equivalents of phenyl isocyanate at 65 °C resulted in the formation of a single adduct **21** in 62% yield. Conducting the

Table 2 Reactions of 2-alkenyldihydrooxazoles **11**–**13** with selected isocyanates



a, R^1 = Ph
b, R^1 = 4-BrC_6H_4
c, R^1 = 4-$O_2NC_6H_4$
d, R^1 = 4-$MeOC_6H_4$
e, R^1 = 4-$CH_3C_6H_4SO_2$

11, R = Me
12, R = Et
13, R = Ph

18, R = Me
19, R = Et
20, R = Ph

Reagents and conditions: i, 2 equivalents R^1NCO, see below.

R	R^1	*t*/h	*T*/°C	Compound (yield %)
Me	Ph	48	25	**18a** (58)
Me	4-BrC_6H_4	24	25	**18b** (61)
Me	4-$O_2NC_6H_4$	21	25	**18c** (82)
Me	4-$MeOC_6H_4$	120	25	**18d** (65)
Me	4-$MeC_6H_4SO_2$	0.5	25	**18e** (66)[a]
Et	Ph	46	25	**19a** (53)
Et	4-BrC_6H_4	1.25	150	**19b** (69)
Et	4-$O_2NC_6H_4$	1	150	**19c** (71)
Et	4-$MeOC_6H_4$	—	—	(0)
Et	4-$MeC_6H_4SO_2$	0.5	25	**19e** (90)
Ph	Ph	1	150	**20a** (76)
Ph	4-BrC_6H_4	1	150	**20b** (59)
Ph	4-$O_2NC_6H_4$	1	150	**20c** (74)
Ph	4-$MeOC_6H_4$	1	150	**20d** (10)[b]
Ph	4-$MeC_6H_4SO_2$	0.5	25	**20e** (94)

[a] Reaction carried out in toluene solution. [b] Not fully purified.

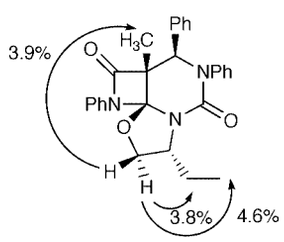
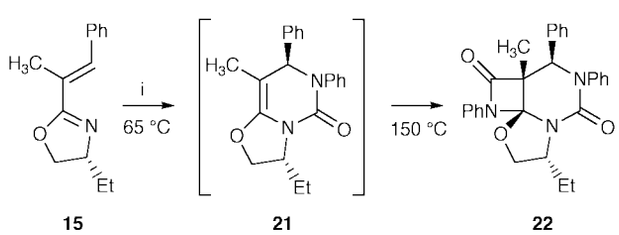


Fig. 2

reaction at 150 °C, or addition of another equivalent of phenyl isocyanate to the single adduct resulted in the formation of the double adduct **22** as a single diastereoisomer (Scheme 8), the



Scheme 8 *Reagents and conditions*: i, PhNCO, see Discussion.

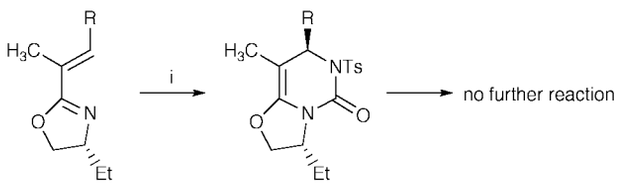
relative stereochemistry of which was supported by NOE experiments (Fig. 2), although these can hardly be considered conclusive. The ^{13}C NMR spectrum of **22** shows 11 distinct resonances corresponding to aromatic methines; presumably these arise due to hindered rotation of one of the phenyl groups.

The α-hydrogen on the dihydrooxazole CH_2 group is significantly shielded (δ_H 3.2), presumably by the phenyl group attached to the β-lactam nitrogen, although this was not observed in compounds **16a**–**16c**.

On the basis of the available data, we assume that the stereo-

chemistry of **22** is as shown, although this assignment owes more to predictions based upon the known stereochemistry of compounds **18**–**20** and to our difficulty in rationalising any other stereochemical outcome than to unambiguous evidence.

Reaction between either **14** or **15** with toluene-4-sulfonyl isocyanate gave adducts in which only a single equivalent of the isocyanate added (Scheme 9). We have considered the possibility that the second addition may be reversible, although the lack of reactivity of **24** with phenyl isocyanate does cast doubt on this. It is possible that the reactivity of the double bond is attenuated by the electron-withdrawing effect of the toluene-4-sulfonyl group, and this, in conjunction with steric hindrance due to the methyl group, prevents the second addition. Compound **23** was produced essentially pure, and decomposed upon attempted purification; in particular on removal of the last traces of toluene, the compound rapidly decomposed. Nevertheless, acceptable spectroscopic data have been obtained. Compound **24** undergoes a retro-Diels–Alder reaction to produce **15** when kept in solution ($CDCl_3$ or benzene-d_6) for 10–14 days.[17] Presumably this reaction is driven by the hydrolysis of toluene-4-sulfonyl isocyanate by traces of water in the solvent.



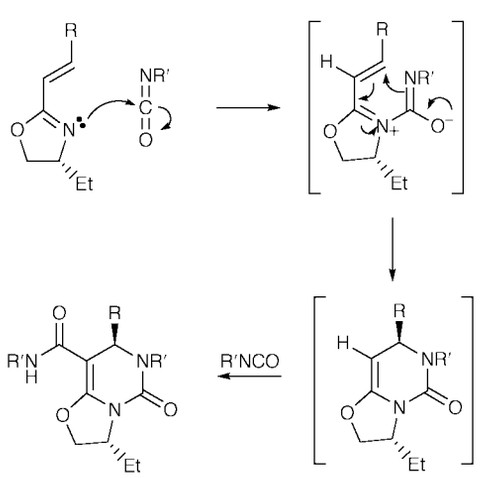
14, R = H
15, R = Ph

23, R = H
24, R = Ph

Scheme 9 *Reagents and conditions*: i, TsNCO, toluene, 25 °C.

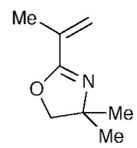
In the IR spectra of compounds **21**, **23** and **24**, a signal was observed at approximately 1760 cm^{-1} which could not be readily explained. It seems likely that this is due to an impurity, possibly the azetidinedione formed by dimerisation of the isocyanate.[18] This may also explain the observations of Hellmann.[8]

The Diels–Alder reaction has been the subject of numerous computational studies, with concerted and stepwise (biradical and ionic) pathways being considered.[19] Tietze *et al.*[20] have studied the Diels–Alder reaction of 1-azabuta-1,3-dienes at both semiempirical and *ab initio* levels, their results suggesting a two-step cycloaddition mechanism. Our own recent computational study on the reactions of alkenyldihydrooxazoles with isocyanates[21] is in agreement with a similar study by Fabian and Kollenz[22] on the reaction of 1-azadienes with ketene in that a stepwise reaction as shown in Scheme 10 is supported. The origin of the asymmetric induction appears to be reduction of steric interactions between the isocyanate oxygen and the substituent at the 4-position of the dihydrooxazole.



Scheme 10

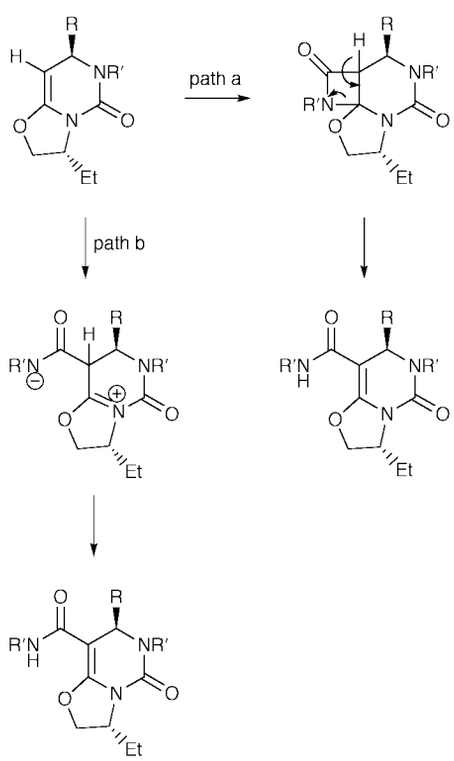
In order to test the sensitivity of the reaction to steric effects, dihydrooxazole **25** was prepared *via* the corresponding amide.



25

This compound did not react with aryl and arenesulfonyl isocyanates, even under forcing conditions. This observation is consistent with our transition state model (*vide infra*), where for ring closure to occur, the isocyanate oxygen would be particularly close to the *gem*-dimethyl group.

The second addition may proceed either by a direct $[2\pi_s + 2\pi_a]$ thermally allowed cycloaddition followed by the cleavage of the β-lactam (Scheme 11, path a) or by a stepwise enamine acylation[23] (Scheme 11, path b). We have no evidence to allow us to distinguish between these mechanisms at the present time, although computational studies are underway.



Scheme 11

In conclusion, alkenyldihydrooxazoles undergo a novel stereoselective formal hetero-Diels–Alder reaction with isocyanates. These reactions have been used to prepare a number of novel heterocyclic systems, and we have outlined the scope and limitations of the reaction.

Experimental

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; *J* values are given in Hz. Flash chromatography was performed unless otherwise stated on Matrex silica 60 35–70 micron.

2-(Propen-2-yl)-4,5-dihydro-1,3-oxazole (3)

Triethylamine (9.16 g, 88 mmol) and methacryloyl chloride (8.86 g, 88 mmol) were added to 2-aminoethanol (5.35 g, 88 mmol) in dichloromethane (50 ml) and the solution stirred for 15 h. After cooling to 5 °C, triethylamine (9.16 g, 88 mmol) and methanesulfonyl chloride (10.03 g, 88 mmol) were added and the resulting suspension was stirred for 24 h. The organic layer was washed twice with saturated $NaHCO_3$ (25 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by short path distillation to afford the *title compound* (1.64 g, 17%) as a colourless oil, bp 110 °C/1 mmHg; ν_{max} (neat)/cm^{-1} 2989, 1655, 1609 and 1141; δ_H (400 MHz; $CDCl_3$) 5.85 (1 H, s, alkene C*H*), 5.47 (1 H, s, alkene C*H*), 4.29 (2 H, t, *J* 9.5, OCH_2), 3.81 (2 H, t, *J* 9.5, NCH_2) and 2.01 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 165.9 (C), 133.0 (alkene C), 122.0 (alkene CH_2), 67.7 (OCH_2), 55.4 (CH_2) and 19.7 (CH_3).

(*E*)-*N*-[(2*R*)-1-Hydroxybutan-2-yl]but-2-enamide (6)

(*E*)-Crotonyl chloride (17.26 g, 0.17 mol) was added to a mixture of (2*R*)-2-aminobutan-1-ol (13.38 g, 0.15 mol) in dichloromethane (200 ml) and saturated aqueous sodium carbonate solution (120 ml). The mixture was stirred overnight after which the aqueous layer was saturated with sodium chloride and extracted three times with dichloromethane (75 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the *title compound* (19.34 g, 82%) as a yellow solid, mp 73–75 °C, which was used without further purification (Found: MH$^+$, 158.1181. $C_8H_{16}NO_2$ requires M$^+$, 158.1181); ν_{max} ($CHCl_3$)/cm^{-1} 3392, 1674, 1631, 1545; δ_H (400 MHz; $CDCl_3$) 6.78 (1 H, dq, *J* 15.2 and 6.8, alkene C*H*), 5.75 (1 H, apparent dd, *J* 15.2 and 1.6, alkene C*H*), 5.61 (1 H, s, N*H*), 3.93–3.88 (1 H, m, C*H*), 3.68 (1 H, dd, *J* 11.0 and 3.1, one of OCH_2), 3.55 (1 H, dd, *J* 11.0 and 5.5, one of OCH_2), 2.93 (1 H, broad s, O*H*), 1.78 (3 H, dd, *J* 6.8 and 1.6, CH_3), 1.62–1.50 (2 H, m, CH_2) and 0.89 (3 H, t, *J* 7.5, CH_3); δ_C (100 MHz; $CDCl_3$) 167.3 (C=O), 140.9 (alkene CH), 125.3 (alkene CH), 65.8 (OCH_2), 53.8 (CH), 24.6 (CH_2), 18.1 (CH_3) and 11.0 (CH_3); *m*/*z* (EI) 158 (MH$^+$, 89%), 86 (17) and 58 (100).

(*E*)-*N*-[(2*R*)-1-Hydroxybutan-2-yl]pent-2-enamide (7)

A solution of (*E*)-pentenoic acid (1.97 g, 20 mmol) in thionyl chloride (25 ml) was heated under reflux overnight. The thionyl chloride was removed *in vacuo*, to afford the corresponding acid chloride, which was added to a solution of (2*R*)-2-aminobutan-1-ol (1.60 g, 18 mmol) in dichloromethane (50 ml). Saturated aqueous sodium carbonate solution (30 ml) was added and the resulting mixture stirred overnight. The aqueous layer was saturated with sodium chloride and extracted three times with dichloromethane (50 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the *title compound* (2.48 g, 75%) as a light brown solid, which was used without further purification; ν_{max} ($CHCl_3$)/cm^{-1} 3288, 1666, 1628, 1542; δ_H (400 MHz; $CDCl_3$) 6.82 (1 H, dt, *J* 15.2 and 6.4, alkene C*H*), 5.91 (1 H, broad d, *J* 7.7, N*H*), 5.74 (1 H, d, *J* 15.2, alkene C*H*), 3.84 (1 H, m, *H*CEt), 3.62 (1 H, dd, *J* 11.0 and 3.4, one of OCH_2), 3.52 (1 H, dd, *J* 11.0 and 5.6, one of OCH_2), 3.41 (1 H, broad s, O*H*), 2.16–2.12 (2 H, m, CH_2), 1.60–1.53 (1 H, m, one of CH_2), 1.48–1.41 (1 H, m, one of CH_2), 0.99 (3 H, t, *J* 7.4, CH_3) and 0.89 (3 H, t, *J* 7.4, CH_3); δ_C (100 MHz; $CDCl_3$) 167.5 (C=O), 147.1 (alkene CH), 122.8 (alkene CH), 65.6 (OCH_2), 53.8 (CH), 25.5 (CH_2), 24.6 (CH_2), 12.8 (CH_3) and 11.0 (CH_3).

(*E*)-*N*-[(2*R*)-1-Hydroxybutan-2-yl]-3-phenylprop-2-enamide (8)

(*E*)-Cinnamoyl chloride (9.66 g, 58 mmol) was added to a solution of (2*R*)-2-aminobutan-1-ol (4.70 g, 52 mmol) in dichloromethane (50 ml). Saturated aqueous sodium carbonate solution (30 ml) was added and the resulting mixture stirred overnight. The aqueous layer was then saturated with sodium chloride and extracted three times with dichloromethane (50 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the *title compound* (7.20 g, 62%) as a white solid, mp 93–96 °C, which was used without further purification (Found: M$^+$, 219.1259. $C_{13}H_{17}NO_2$ requires M, 219.1259); ν_{max}($CHCl_3$)/cm^{-1} 3020, 1662, 1622; δ_H (400 MHz; $CDCl_3$) 7.55 (1 H, d, *J* 15.6, alkene C*H*), 7.38 (2 H, m, aromatic C*H*), 7.31–7.29 (3 H, m, aromatic C*H*), 6.42 (1 H, d, *J* 15.6, alkene C*H*), 6.20 (1 H, broad d, *J* 7.9, N*H*), 3.96–3.91 (1 H, m, C*H*), 3.68 (1 H, dd, *J* 11.2 and 3.5, one of OCH_2), 3.57 (1 H, dd, *J* 11.2 and 5.6, one of OCH_2), 3.51 (1 H, broad s, O*H*), 1.63–1.53 (1 H, m, one of CH_2), 1.51–1.44 (1 H, m, one of CH_2) and 0.91 (3 H, t, *J* 7.4, CH_3); δ_C (100 MHz; $CDCl_3$) 167.3 (C=O), 141.8 (alkene CH), 135.1 (aromatic C), 130.1, 129.3, 128.2 (all aromatic CH), 121.0 (alkene CH), 65.5 (OCH_2), 54.0 (CH), 24.7 (CH_2) and 11.1 (CH_3); *m*/*z* (EI) 219 (M$^+$, 14%), 188 (100), 131 (100), 103 (100) and 77 (100).

***N*-[(2*R*)-1-Hydroxybutan-2-yl]-2-methylprop-2-enamide (9)**

Methacryloyl chloride (20.14 g, 0.19 mol) was added to a mixture of (2*R*)-2-aminobutan-1-ol (15.61 g, 0.18 mol) in dichloromethane (200 ml) and saturated aqueous sodium carbonate solution (120 ml). The mixture was stirred overnight, after which the aqueous layer was saturated with sodium chloride and extracted three times with dichloromethane (50 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the *title compound* (25.02 g, 91%) as a pale yellow oil, mp 7–9 °C, which was used without further purification; ν_{max} (neat)/cm^{-1} 3349, 1667, 1624, 1533; δ_H (400 MHz; $CDCl_3$) 6.23 (1 H, broad s, N*H*), 5.64 (1 H, s, alkene C*H*), 5.26 (1 H, s, alkene C*H*), 3.84 (1 H, m, C*H*), 3.63 (1 H, broad s, O*H*), 3.61 (2 H, m, OCH_2), 1.89 (3 H, s, CH_3), 1.63–1.41 (2 H, m, CH_2) and 0.88 (3 H, t, *J* 7.5, CH_3); δ_C (100 MHz; $CDCl_3$) 171.3 (C=O), 142.0 (alkene C), 121.9 (alkene CH_2), 67.0 (OCH_2), 55.3 (CH), 27.4 (CH_2), 20.3 (CH_3) and 12.7 (CH_3); *m*/*z* (EI) 158 (MH$^+$, 100%), 140 (100) and 69 (50).

(*E*)-*N*-[(2*R*)-1-Hydroxybutan-2-yl]-2-methyl-3-phenylprop-2-enamide (10)

A solution of (*E*)-2-methyl-3-phenylpropenoic acid (3.98 g, 24.5 mmol) in thionyl chloride (25 ml) was heated under reflux for 15 h. After cooling, the excess thionyl chloride was removed *in vacuo* to afford (*E*)-2-methyl-3-phenylpropenoyl chloride (4.38 g, >99%) as a brown liquid, which was used without further purification. Saturated sodium carbonate solution (30 ml) was added to a solution of (2*R*)-2-aminobutan-1-ol (2.31 g, 25.9 mmol) in dichloromethane (50 ml). The (*E*)-2-methyl-3-phenylpropenoyl chloride was added and the mixture stirred overnight. The aqueous layer was saturated with sodium chloride and extracted twice with dichloromethane (50 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to afford a yellow solid which was then washed with diethyl ether to give the *title compound* (4.57 g, 76%) as a white solid, mp 88–91 °C; ν_{max}(neat)/cm^{-1} 3344, 3054, 1713 (C=O) and 1652; δ_H (400 MHz; $CDCl_3$) (OH not observed) 7.38–7.29 (6 H, m, aromatic and alkene C*H*), 4.02–3.97 (1 H, m, *H*CEt), 3.79 (1 H, dd, *J* 11.0 and 3.4, one of OCH_2), 3.70–3.66 (1 H, dd, *J* 11.0 and 5.8, one of OCH_2), 2.12 (3 H, s, CH_3), 1.73–1.59 (2 H, m, CH_2) and 1.02 (3 H, t, *J* 7.4,

CH_3); δ_C (100 MHz; $CDCl_3$) 170.9 (C=O), 136.5 (aromatic C), 134.5 (alkene CH), 132.3 (alkene C), 129.7, 128.7, 128.4 (all aromatic CH), 65.2 (OCH_2), 53.9 (CH), 24.7 (CH_2), 14.7 (CH_3) and 11.1 (CH_3); *m/z* (EI) 234 (MH^+, 30%), 202 (41), 145 (86), 117 (90) and 115 (100).

(4*R*)-4-Ethyl-2-propenyl-4,5-dihydro-1,3-oxazole (11)

(*E*)-*N*-[(2*R*)-1-Hydroxybutan-2-yl]but-2-enamide (**6**) (4.21 g, 27 mmol) in dichloromethane (75 ml) was cooled to 5 °C. Triethylamine (5.42 g, 54 mmol) and methanesulfonyl chloride (3.07 g, 27 mmol) were added and the solution was stirred overnight. The solution was then washed twice with saturated $NaHCO_3$ (50 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by Kugelrohr distillation to afford the *title compound* (2.41 g, 65%) as a colourless oil, bp 120 °C/water pump; ν_{max} (neat)/cm^{-1} 1674 and 1616; δ_H (400 MHz; $CDCl_3$) 6.53 (1 H, dq, *J* 15.8 and 6.9, alkene C*H*), 5.95 (1 H, dq, *J* 15.8 and 1.7, alkene C*H*), 4.23 (1 H, dd, *J* 9.2 and 8.2, one of OCH_2), 4.02 (1 H, m, *H*CEt), 3.85 (1 H, apparent t, *J* 8.0, one of OCH_2), 1.78 (3 H, dd, *J* 6.9 and 1.6, CH_3), 1.62–1.41 (2 H, m, CH_2) and 0.90 (3 H, t, *J* 7.4, CH_3); δ_C (100 MHz; $CDCl_3$) 163.0 (C), 139.1 (alkene CH), 119.5 (alkene CH), 71.9 (OCH_2), 67.9 (CH), 28.9 (CH_2), 18.6 (CH_3) and 10.3 (CH_3); *m/z* (EI) 140 (MH^+, 39%), 126 (25) and 83 (100).

(4*R*,*E*)-4-Ethyl-2-but-1-enyl-4,5-dihydro-1,3-oxazole (12)

(*E*)-*N*-[(2*R*)-1-Hydroxybutan-2-yl]pent-2-enamide (**7**) (2.33 g, 20 mmol) was dissolved in dichloromethane (75 ml.). After cooling with an ice–water bath, triethylamine (3.99 g, 39 mmol) and methanesulfonyl chloride (2.26 g, 20 mmol) were added and the solution was stirred overnight. The organic layer was washed twice with saturated $NaHCO_3$ (25 ml) and quickly dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by Kugelrohr distillation to afford the *title compound* (1.68 g, 51%) as a colourless oil, bp 120 °C/1 mmHg (Found: M^+, 153.1154. $C_9H_{15}NO$ requires M, 153.1154); ν_{max} (neat)/cm^{-1} 2965, 2926, 1674 and 1612; δ_H (400 MHz; $CDCl_3$) 6.56 (1 H, m, alkene C*H*), 5.94–5.89 (1 H, d, *J* 12.6, alkene C*H*), 4.26 (1 H, apparent t, *J* 8.2, one of OCH_2), 4.00 (1 H, m, *H*CEt), 3.81 (1 H, apparent t, *J* 7.9, one of OCH_2), 2.14 (2 H, m, CH_2), 1.62–1.57 (1 H, m, one of CH_2), 1.47–1.44 (1 H, m, one of CH_2), 0.99 (3 H, t, *J* 8.0, CH_3) and 0.91 (3 H, t, *J* 7.4, CH_3); δ_C (100 MHz; $CDCl_3$) 163.1 (C), 145.7 (alkene CH), 117.2 (alkene CH), 72.1 (OCH_2), 68.0 (CH), 29.0 (CH_2), 26.0 (CH_2), 12.8 (CH_3) and 10.5 (CH_3); *m/z* (EI) 153 (M^+, 44%), 108 (73), 96 (100) and 82 (39).

(4*R*,*E*)-4-Ethyl-2-(2-phenylethenyl)-4,5-dihydro-1,3-oxazole (13)

(*E*)-*N*-[(2*R*)-1-Hydroxybutan-2-yl]-3-phenylprop-2-enamide (**8**) (6.35 g, 29 mmol) in dichloromethane (75 ml) was cooled to 5 °C. Triethylamine (5.88 g, 58 mmol) and methanesulfonyl chloride (3.33 g, 29 mmol) were added and the solution stirred overnight. The solution was then washed twice with saturated $NaHCO_3$ (35 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the *title compound* (5.63 g, 96%) as a brown oil which was used without further purification, mp 4–7 °C (Found: M^+, 201.1154. $C_{13}H_{15}NO$ requires M, 201.1153); ν_{max} (neat)/cm^{-1} 1654 and 1608; δ_H (400 MHz; $CDCl_3$) 7.42–7.39 (2 H, dd, aromatic C*H*), 7.31–7.24 (4 H, m, aromatic C*H* and alkene C*H*), 6.57 (1 H, d, *J* 16.3, alkene C*H*), 4.32 (1 H, apparent t, *J* 8.3, one of OCH_2), 4.08 (1 H, m, *H*CEt), 3.88 (1 H, apparent t, *J* 7.9, one of OCH_2), 1.68–1.59 (1 H, m, one of CH_2), 1.56–1.47 (1 H, m, one of CH_2) and 0.92 (3 H, t, *J* 7.4, CH_3); δ_C (100 MHz; $CDCl_3$) 163.6 (C=O), 140.2 (alkene CH), 135.6 (aromatic C), 130.1, 129.3, 127.8 (all aromatic CH), 115.7 (alkene CH), 72.3 (OCH_2), 68.3 (CH), 29.0 (CH_2) and 10.6 (CH_3); *m/z* (EI) 201 (M^+, 39%), 172 (100), 144 (26), 115 (39) and 77 (43).

(4*R*)-4-Ethyl-2-propen-2-yl-4,5-dihydro-1,3-oxazole (14)

N-[(2*R*)-1-Hydroxybutan-2-yl]-2-methylprop-2-enamide (**9**) (7.46 g, 47 mmol) in dichloromethane (75 ml) was cooled to 5 °C. Triethylamine (9.60 g, 95 mmol) and methanesulfonyl chloride (5.44 g, 47 mmol) were added and the solution stirred overnight. The solution was then washed twice with saturated $NaHCO_3$ (50 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by short path distillation to afford the *title compound* (4.33 g, 66%) as a colourless oil, bp 120 °C/water pump (Found M^+, 139.0997. $C_8H_{13}NO$ requires M, 139. 0997); ν_{max} (neat)/cm^{-1} 1652 and 1616; δ_H (400 MHz; $CDCl_3$) 5.72 (1 H, s, alkene C*H*), 5.34 (1 H, s, alkene C*H*), 4.22 (1 H, dd, *J* 9.4 and 8.2, one of OCH_2), 4.03 (1 H, m, *H*CEt), 3.85 (1 H, apparent t, *J* 7.8, one of OCH_2), 1.95 (3 H, s, CH_3), 1.66–1.60 (1 H, m, one of CH_2), 1.52–1.43 (1 H, m, one of CH_2) and 0.87 (3 H, t, *J* 7.5, CH_3); δ_C (100 MHz; $CDCl_3$) 164.7 (C), 133.1 (alkene C), 121.9 (alkene CH_2), 702.2 (OCH_2), 68.4 (CH), 28.8 (CH_2), 19.8 (CH_3) and 10.3 (CH_3); *m/z* (EI) 139 (M^+, 25%), 110 (74), 94 (24) and 55 (100).

(4*R*,*E*)-4-Ethyl-2-(1-phenylpropen-2-yl)-4,5-dihydro-1,3-oxazole (15)

(*E*)-*N*-[(2*R*)-1-Hydroxybutan-2-yl]-2-methyl-3-phenylprop-2-enamide (**10**) (4.90 g, 21.0 mmol) was dissolved in dichloromethane (50 ml). After cooling with an ice–water bath, triethylamine (4.25 g, 42.0 mmol) and methanesulfonyl chloride (2.41 g, 21.0 mmol) were added and the solution was stirred overnight. The organic layer was washed twice with saturated aqueous sodium hydrogen carbonate (50 ml) and quickly dried over Na_2SO_4, filtered and concentrated *in vacuo*, to afford the *title compound* (4.80 g, quant.) as a yellowish oil which was used without further purification (Found: M^+, 214.1238. $C_{14}H_{17}NO$ requires M, 214.1232); ν_{max} (neat)/cm^{-1} 3056, 1644 and 1614; δ_H (400 MHz; $CDCl_3$) 7.26 (1 H, s, alkene C*H*), 7.22–7.18 (5 H, m, aromatic C*H*), 4.21 (1 H, dd, *J* 9.4 and 8.1, one of OCH_2), 4.06–3.97 (1 H, m, *H*CEt), 3.81 (1 H, apparent t, *J* 7.9, one of OCH_2), 2.08 (3 H, s, CH_3), 1.65–1.55 (1 H, m, one of CH_2), 1.47–1.37 (1 H, m, one of CH_2) and 0.82 (3 H, t, *J* 7.4, CH_3); δ_C (100 MHz; $CDCl_3$) 166.0 (C), 136.7 (aromatic C), 135.5 (alkene CH), 129.7, 128.7, 128.1 (all aromatic CH), 125.8 (alkene C), 72.2 (CH_2), 68.2 (CH), 28.9 (CH_2), 15.5 (CH_3) and 10.3 (CH_3); *m/z* (EI) 216 (MH^+, 54%), 214 (100), 186 (53) and 115 (100).

(3*R*)-6,9-Diphenyl-3-ethyl-7a-methyl-2,3,5,6,7,7a,8,9-octahydroazeto[2,3-*d*][1,3]oxazolo[3,2-*c*]pyrimidine-5,8-dione (16a)

A mixture of phenyl isocyanate (504 mg, 2.24 mmol) and (4*R*)-4-ethyl-2-propen-2-yl-4,5-dihydro-1,3-oxazole **(14)** (295 mg, 2.12 mmol) was heated in a sealed tube at 150 °C for 65 hours. The reaction mixture was dissolved in chloroform, filtered, and the chloroform was removed *in vacuo* to afford the essentially pure *title compound* (649 mg, 81%) as a light yellow solid (1.7:1 mixture of diastereoisomers), mp 58–60 °C (Found: M^+, 377.1737. $C_{22}H_{23}N_5O_3$ requires M, 377.1739); ν_{max} ($CHCl_3$)/cm^{-1} 1729 and 1686; δ_H (400 MHz; $CDCl_3$) 7.70–6.90 (10 H, m, aromatic C*H*), 4.40–4.20 (1 H, m), 4.14–4.04 (2 H, m), 3.95–3.85 (2 H, m), 1.58–1.46 (5 H, m, CH_2 and CH_3), 0.90 (3 H of major isomer, t, *J* 7.4, CH_3) and 0.85 (3 H of minor isomer, t, *J* 7.5, CH_3); δ_C (100 MHz; DMSO-d_6) 170.1 (C=O), 165.2 (2 peaks, C=O), 152.6 (2 peaks, C-9a), 142.9, 142.7, 137.7, 137.6 (all aromatic C), 129.8, 129.7, 129.6, 129.5, 128.7, 127.3, 127.1, 126.3, 126.0 (all aromatic CH), 73.1, 72.9 (both CH_2), 67.7 (2 peaks, CH), 53.6, 53.1 (both CH_2), 45.1 (2 peaks, C-7a), 29.1, 28.6 (both CH_2), 18.4, 18.0, 10.6 and 10.2 (all CH_3); *m/z* (EI) 377 (M^+, 27%), 362 (27), 290 (90) and 124 (100).

(3*R*)-6,9-Bis(4-bromophenyl)-3-ethyl-7a-methyl-2,3,5,6,7,7a,8,9-octahydroazeto[2,3-*d*][1,3]oxazolo[3,2-*c*]pyrimidine-5,8-dione (16b)

A mixture of 4-bromophenyl isocyanate (489 mg, 2.47 mmol)

and (4*R*)-4-ethyl-2-propen-2-yl-4,5-dihydro-1,3-oxazole **(14)** (172 mg, 1.24 mmol) was heated in a sealed tube at 150 °C for 18 hours. After cooling, the resulting solid was purified by column chromatography (neutral alumina; eluent 3:1 diethyl ether–hexane) to afford the *title compound* (196 mg, 42%) as a colourless solid (1.7:1 mixture of diastereoisomers), mp 86–88 °C; ν_{max} ($CHCl_3$)/cm^{-1} 1733 and 1691; δ_H (400 MHz; $CDCl_3$) 7.66–7.53 (4 H, m, aromatic C*H*), 7.26–7.17 (4 H, m, aromatic C*H*), 4.42 (1 H of major diastereoisomer, dd, *J* 9.4 and 8.5, one of OCH_2), 4.36 (1 H of minor diastereoisomer, dd, *J* 9.4 and 8.2, one of OCH_2), 4.18–4.09 (2 H, m), 4.02–3.92 (2 H, m), 1.64–1.57 (5 H, m, CH_2 and CH_3), 1.00–0.88 (3 H of major diastereoisomer, t, *J* 7.4, CH_3) and 0.85 (3 H of minor diastereoisomer, t, *J* 7.4, CH_3); δ_C (100 MHz; $CDCl_3$) 169.9, 169.8, 164.8, 164.7 (all C=O), 152.2 (2 peaks, C-9a), 141.0, 140.9, 135.6, 135.5 (all aromatic C), 133.1, 132.8, 132.7, 132.6, 130.9, 130.5, 127.2, 126.9 (all aromatic CH), 122.8, 122.8, 120.6, 120.6 (all C-Br), 73.4, 73.3 (both CH_2O), 68.2, 68.1 (both CH), 53.8, 53.4 (both CH_2N), 45.2, 45.1 (both C-7a), 29.2, 28.8 (both CH_2), 18.5, 18.2, 10.4 and 10.2 (all CH_3); *m*/*z* (EI) 537 (M^+, 11%), 535 (M^+, 16), 533 (12), 521 (100), 518 (84), 450 (19), 448 (42), 446 (20), 352 (63), 350 (73), 199 (66) and 197 (65).

(3*R*)-6,9-Bis(4-methoxyphenyl)-3-ethyl-7a-methyl-2,3,5,6,7,7a,8,9-octahydroazeto[2,3-*d*][1,3]oxazolo[3,2-*c*]pyrimidine-5,8-dione (16c)

A mixture of 4-methoxyphenyl isocyanate (418 mg, 2.80 mmol) and (4*R*)-4-ethyl-2-propen-2-yl-4,5-dihydro-1,3-oxazole **(14)** (195 mg, 1.40 mmol) was heated in a sealed tube at 150 °C for 25 hours. After cooling, the reaction mixture was dissolved in chloroform (5 ml), filtered and concentrated *in vacuo* to afford the *title compound* (429 mg, 70%) as a colourless waxy solid (*ca*. 1.7:1 mixture of diastereoisomers); ν_{max} ($CHCl_3$)/cm^{-1} 1733 and 1691. NMR data were broadly in line with compounds **16a** and **16b**, although the presence of decomposition products arising from 4-methoxyphenyl isocyanate makes reporting this data meaningless.

(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 (18a)

A mixture of phenyl isocyanate (363 mg, 3.05 mmol) and (4*R*)-4-ethyl-2-propenyl-4,5-dihydro-1,3-oxazole (**11**) (212 mg, 1.52 mmol) was stirred in a sealed tube for 48 hours. The resulting solid was dissolved in dichloromethane and precipitated with diethyl ether. The precipitate was collected by filtration to afford the *title compound* (334 mg, 58%) as a colourless solid, mp 150–152 °C (Found: C, 70.16; H, 6.36; N, 11.44. $C_{22}H_{23}N_3O_3$ requires C, 70.01; H, 6.14; N, 11.13%); ν_{max} ($CHCl_3$)/cm^{-1} 3424, 1686, 1649, 1595 and 1535; δ_H (400 MHz; $CDCl_3$) 8.32 (1 H, s, N*H*), 7.47 (2 H, d, *J* 7.8, aromatic C*H*), 7.35 (2 H, d, *J* 8.0, aromatic C*H*), 7.28–7.22 (5 H, m, aromatic C*H*), 7.00 (1 H, apparent t, *J* 7.4, aromatic C*H*), 4.91 (1 H, q, *J* 6.1, MeC*H*), 4.60 (1 H, apparent t, *J* 7.6, one of OCH_2), 4.48 (1 H, dd, *J* 8.4 and 1.6, one of OCH_2), 4.32 (1 H, m, *H*CEt), 1.99–1.93 (1 H, m, one of CH_2), 1.88–1.81 (1 H, m, one of CH_2), 1.22 (3 H, d, *J* 6.2, CH_3) and 0.87 (3 H, t, *J* 7.5, CH_3); δ_C (100 MHz; $CDCl_3$) 162.6, 152.1 (both C=O), 150.4 (alkene C), 140.3, 139.0 (both aromatic C), 129.6, 129.3, 128.3, 127.0, 123.9, 120.2 (all aromatic CH), 83.8 (alkene C), 74.1 (OCH_2), 57.3, 56.2 (both CH), 23.7 (CH_2), 21.2 and 9.0 (both CH_3); *m*/*z* (EI) 377 (M^+, 14%), 362 (57), 285 (11), 166 (18), 119 (72) and 55 (100).

(3*R*,7*R*)-*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 (18b)

A mixture of 4-bromophenyl isocyanate (330 mg, 1.67 mmol) and (4*R*)-4-ethyl-2-propenyl-4,5-dihydro-1,3-oxazole (**11**) (116 mg, 0.83 mmol) was stirred in a sealed tube for 24 hours. The resulting solid was dissolved in dichloromethane, precipitated with diethyl ether and filtered to afford the *title compound* (270 mg, 61%) as a colourless solid, mp 219–221 °C (Found: C, 49.49; H, 3.70; N, 7.73. $C_{22}H_{21}Br_2N_3O_3$ requires C, 49.37; H, 3.95; N, 7.85%); ν_{max} ($CHCl_3$)/cm^{-1} 3413, 1685, 1650, 1588 and 1526; δ_H (400 MHz; $CDCl_3$) 8.28 (1 H, s, N*H*), 7.47 (2 H, d, *J* 8.6, aromatic C*H*), 7.38 (2 H, d, *J* 6.8, aromatic C*H*), 7.34 (2 H, d, *J* 6.8, aromatic C*H*), 7.16 (2 H, d, *J* 8.6, aromatic C*H*), 4.84 (1 H, q, *J* 6.2, MeC*H*), 4.59 (1 H, apparent t, *J* 8.1, one of OCH_2), 4.48 (1 H, dd, *J* 8.4 and 1.7, one of OCH_2), 4.31 (1 H, m, *H*CEt), 1.99–1.92 (1 H, m, one of CH_2), 1.87–1.78 (1 H, m, one of CH_2), 1.20 (3 H, d, *J* 6.2, CH_3) and 0.86 (3 H, t, *J* 7.4, CH_3); δ_C (100 MHz; $CDCl_3$) 162.4, 152.2 (both C=O), 150.1 (alkene C), 139.3, 138.1 (both aromatic C), 132.7, 132.2, 129.9, 121.7 (all aromatic CH), 121.2, 116.3 (both C-Br), 83.7 (alkene C), 74.2 (CH_2), 57.3, 56.1 (both CH), 23.7 (CH_2), 21.2 and 9.0 (both CH_3); *m*/*z* (EI) 537 ($M^+ - {}^{81}Br_2$, 8%), 535 (16), 533 (8), 522 (19), 520 (53), 518 (25), 365 (28), 363 (27), 199 (28), 197 (32), 171 (47) and 166 (100).

(3*R*,7*R*)-*N*,6-Bis(4-nitrophenyl)-3-ethyl-7-methyl-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide (18c)

A mixture of 4-nitrophenyl isocyanate (401 mg, 2.44 mmol) and (4*R*)-4-ethyl-2-propenyl-4,5-dihydro-1,3-oxazole (**11**) (174 mg, 1.22 mmol) was stirred in a sealed tube for 21 hours. The resulting solid was triturated with diethyl ether to afford the *title compound* (467 mg, 82%) as a yellow solid, mp 203–206 °C (Found: C, 56.57; H, 4.18; N, 14.66. $C_{22}H_{21}N_5O_7$ requires C, 56.53; H, 4.53; N, 14.98%); ν_{max} ($CHCl_3$)/cm^{-1} 3406, 1682, 1661, 1612, 1595, 1546, 1523, 1509, 1346, 1332 and 853; δ_H (400 MHz; $CDCl_3$) 8.67 (1 H, s, N*H*), 8.31 (2 H, d, *J* 9.0, aromatic C*H*), 8.23 (2 H, d, *J* 9.2, aromatic C*H*), 7.74 (2 H, d, *J* 9.2, aromatic C*H*), 7.60 (2 H, d, *J* 9.0, aromatic C*H*), 5.12 (1 H, q, *J* 6.2, MeC*H*), 4.78 (1 H, apparent t, *J* 8.1, one of OCH_2), 4.67 (1 H, dd, *J* 8.5 and 1.8, one of OCH_2), 4.49 (1 H, m, *H*CEt), 2.12–2.07 (1 H, m, one of CH_2), 2.00–1.89 (1 H, m, one of CH_2), 1.35 (3 H, d, *J* 6.3, CH_3) and 1.00 (3 H, t, *J* 7.4, CH_3); δ_C (100 MHz; DMSO-d_6) 162.2, 153.1 (both C=O), 149.0 (alkene C), 146.5, 145.5, 145.2, 142.1 (all aromatic C), 127.6, 124.9, 124.5, 119.0 (all aromatic CH), 82.5 (alkene C), 74.3 (OCH_2), 56.8, 55.0 (both CH), 23.0 (CH_2), 21.0 and 8.4 (both CH_3); *m*/*z* (EI) 303 (51%) and 166 (100).

(3*R*,7*R*)-*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 (18d)

A mixture of 4-methoxyphenyl isocyanate (782 mg, 5.24 mmol) and (4*R*)-4-ethyl-2-propenyl-4,5-dihydro-1,3-oxazole (**11**) (365 mg, 2.62 mmol) was stirred in a sealed tube for 120 hours. The resulting solid was triturated with diethyl ether to afford the *title compound* (752 mg, 65%) as a colourless solid, mp 140–142 °C (Found: C, 65.82; H, 6.41; N, 9.84. $C_{24}H_{27}N_3O_5$ requires C, 65.89; H, 6.22; N, 9.60%); ν_{max} ($CHCl_3$)/cm^{-1} 3415, 1686, 1644 and 1536; δ_H (400 MHz; $CDCl_3$) 8.20 (1 H, s, N*H*), 7.38 (2 H, d, *J* 8.9, aromatic C*H*), 7.17 (2 H, d, *J* 8.9, aromatic C*H*), 6.85 (2 H, d, *J* 8.9, aromatic C*H*), 6.78 (2 H, d, *J* 8.9, aromatic C*H*), 4.80 (1 H, q, *J* 6.2, MeC*H*), 4.58 (1 H, apparent t, *J* 8.2, one of OCH_2), 4.46 (1 H, dd, *J* 8.4 and 1.6, one of OCH_2), 4.29 (1 H, m, *H*CEt), 3.74 (3 H, s, OCH_3), 3.72 (3 H, s, OCH_3), 1.97–1.92 (1 H, m, one of CH_2), 1.87–1.81 (1 H, m, one of CH_2), 1.21 (3 H, d, *J* 6.2, CH_3) and 0.86 (3 H, t, *J* 7.5, CH_3); δ_C (100 MHz; $CDCl_3$) 164.7, 161.0 (both C=O), 158.4 (alkene C), 154.1, 152.9, 135.7, 134.2 (all aromatic C), 131.7, 124.6, 116.9, 116.6 (all aromatic CH), 85.7 (alkene C), 76.1 (OCH_2), 59.3, 58.5 (both CH), 58.0 (two coincident OCH_3), 25.9 (CH_2), 23.3 and 11.2 (both CH_3); *m*/*z* (EI) 437 (M^+, 14%), 422 (18), 272 (60), 149 (75), 134 (36) and 108 (100).

(3*R*,7*R*)-*N*,6-Bis((4-methylphenyl)sulfonyl)-3-ethyl-7-methyl-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide (18e)

A solution of toluene-4-sulfonyl isocyanate (510 mg, 2.59 mmol) and (4*R*)-4-ethyl-2-propenyl-4,5-dihydro-1,3-oxazole (**11**) (180 mg, 1.29 mmol) in dry toluene (20 ml) was stirred for 21 hours. After removing toluene *in vacuo*, the solid was recrystallised from ethanol to afford the *title compound* (453 mg; 66%) as a colourless solid, mp 172–175 °C (Found: C, 53.93; H, 5.07; N, 7.85. $C_{24}H_{27}N_3O_7S_2$ requires C, 54.02; H, 5.10; N, 7.87%); ν_{max} ($CHCl_3$)/cm^{-1} 3361, 1713, 1672, 1598 and 1042; δ_H (400 MHz; $CDCl_3$) 9.00 (1 H, s, N*H*), 7.91 (2 H, d, *J* 8.3, aromatic C*H*), 7.79 (2 H, d, *J* 8.3, aromatic C*H*), 7.26 (2 H, d, *J* 8.3, aromatic C*H*), 7.21 (2 H, d, *J* 8.3, aromatic C*H*), 5.41 (1 H, q, *J* 6.3, MeC*H*), 4.62 (1 H, apparent t, *J* 8.1, one of OCH_2), 4.42 (1 H, dd, *J* 8.7 and 2.0, one of OCH_2), 4.25 (1 H, m, *H*CEt), 2.35 (3 H, s, CH_3), 2.33 (3 H, s, CH_3), 1.69–1.66 (2 H, m, CH_2), 1.18 (3 H, d, *J* 6.3, CH_3) and 0.68 (3 H, t, *J* 7.3, CH_3); δ_C (100 MHz; $CDCl_3$) 162.1, 156.2 (both C=O), 149.4 (alkene C), 147.6, 147.3, 138.5, 138.4 (all aromatic C), 132.0, 131.8, 131.4, 131.0 (all aromatic CH), 86.1 (alkene C), 77.1 (OCH_2), 59.4, 53.4 (both CH), 25.4 (CH_2), 25.3, 24.2, 24.2 and 10.4 (all CH_3); *m*/*z* (EI) 377 (1%), 165 (49), 191 (99) and 84 (100).

(3*R*,7*R*)-*N*,6-Diphenyl-3,7-diethyl-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide (19a)

A mixture of phenyl isocyanate (100 mg, 0.84 mmol) and (4*R*,*E*)-4-ethyl-2-but-1-enyl-4,5-dihydro-1,3-oxazole (**12**) (70 mg, 0.42 mmol) was stirred in a sealed tube at 25 °C for 46 hours. After cooling, the resulting solid was purified by column chromatography (eluent 3 : 1 diethyl ether–hexane) to afford the *title compound* (90 mg, 53%) as a yellow solid, mp 64–66 °C (Found: C, 70.34; H, 6.30; N, 10.76. $C_{23}H_{25}N_3O_3$ requires C, 70.57; H, 6.44; N, 10.73%); ν_{max} ($CHCl_3$)/cm^{-1} 3418, 1685, 1649, 1596, 1535 and 693; δ_H (400 MHz; $CDCl_3$) 8.38 (1 H, s, N*H*), 7.48 (2 H, d, *J* 7.9, aromatic C*H*), 7.28 (7 H, m, aromatic C*H*), 6.99 (1 H, t, *J* 7.4, aromatic C*H*), 5.04 (1 H, m, EtC*H*), 4.56 (1 H, apparent t, *J* 8.2, one of OCH_2), 4.45 (1 H, dd, *J* 8.4 and 1.8, one of OCH_2), 4.31 (1 H, m, *H*CEt), 1.92–1.80 (2 H, m, CH_2), 1.62–1.59 (2 H, m, CH_2), 0.86 (3 H, t, *J* 7.5, CH_3) and 0.84 (3 H, t, *J* 7.5, CH_3); δ_C (100 MHz; $CDCl_3$) 162.7, 152.9 (both C=O), 151.0 (alkene C), 140.4, 139.0 (both aromatic C), 129.6, 129.3, 128.1, 127.6, 123.9, 120.1 (all aromatic CH), 80.5 (alkene C), 74.1 (OCH_2), 60.5, 57.2 (both CH), 26.4, 23.8 (both CH_2), 9.0 and 7.7 (both CH_3); *m*/*z* (EI) 391 (M$^+$, 2%), 362 (63), 272 (20), 244 (4), 180 (48) and 55 (100).

(3*R*,7*R*)-*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 (19b)

A mixture of 4-bromophenyl isocyanate (491 mg, 2.48 mmol) and (4*R*,*E*)-4-ethyl-2-but-1-enyl-4,5-dihydro-1,3-oxazole (**12**) (190 mg, 1.24 mmol) was stirred in a sealed tube at 150 °C for 75 minutes. The resulting solid was purified by flash column chromatography (eluent 1 : 1 dichloromethane–hexane) to give the *title compound* (472 mg, 69%) as a colourless solid, mp 68–70 °C (Found: C, 50.51; H, 4.01; N, 7.43. $C_{23}H_{23}Br_2N_3O_3$ requires C, 50.29; H, 4.22; N, 7.65%); ν_{max} ($CHCl_3$)/cm^{-1} 3412, 1681, 1653, 1589 and 1526; δ_H (400 MHz; $CDCl_3$) 8.35 (1 H, s, N*H*), 7.46 (2 H, d, *J* 6.7, aromatic C*H*), 7.39 (2 H, d, *J* 6.7, aromatic C*H*), 7.35 (2 H, d, *J* 6.7, aromatic C*H*), 7.20–7.18 (2 H, d, *J* 6.7, aromatic C*H*), 4.99 (1 H, m, EtC*H*), 4.59 (1 H, dd, *J* 8.4 and 7.0, one of OCH_2), 4.47 (1 H, dd, *J* 8.4 and 1.9, one of OCH_2), 4.30 (1 H, m, *H*CEt), 2.00–1.90 (1 H, m, one of CH_2), 1.85–1.75 (1 H, m, one of CH_2), 1.70–1.60 (1 H, m, one of CH_2), 1.54–1.48 (1 H, m, one of CH_2), 0.86 (3 H, t, *J* 7.4, CH_3) and 0.81 (3 H, t, *J* 7.4, CH_3); δ_C (100 MHz; $CDCl_3$) 161.1, 151.6 (both C=O), 149.2 (alkene C), 138.1, 136.7 (both aromatic C), 131.3, 130.7, 128.3, 120.3 (all aromatic CH), 119.6, 114.7 (both C-Br), 78.9 (alkene C), 72.8 (OCH_2), 58.9, 55.8 (both CH), 25.3, 22.3 (both CH_2), 7.6 and 6.3 (both CH_3); *m*/*z* (EI) 549 (M$^+$, 1%), 520 (23), 90 (52) and 55 (100).

(3*R*,7*R*)-*N*,6-Bis(4-nitrophenyl)-3,7-diethyl-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide (19c)

A mixture of 4-nitrophenyl isocyanate (316 mg, 1.93 mmol) and (4*R*,*E*)-4-ethyl-2-but-1-enyl-4,5-dihydro-1,3-oxazole (**12**) (161 mg, 0.96 mmol) was stirred in a sealed tube at 150 °C for 1 hour. On cooling, the resulting solid was recrystallised from hot ethanol to afford the *title compound* (330 mg, 71%) as a yellow solid, mp 203–206 °C (Found: M$^+$ − Et, 452.1198. $C_{21}H_{18}N_5O_7$ requires M, 452.1206); ν_{max} ($CHCl_3$)/cm^{-1} 3405, 1682, 1546 and 1508; δ_H (400 MHz; $CDCl_3$) 8.67 (1 H, s, N*H*), 8.20 (2 H, d, *J* 9.1, aromatic C*H*), 8.14 (2 H, d, *J* 9.1, aromatic C*H*), 7.63 (2 H, d, *J* 9.1, aromatic C*H*), 7.55 (2 H, d, *J* 9.1, aromatic C*H*), 5.16–5.14 (1 H, m, EtC*H*), 4.68 (1 H, dd, *J* 8.4 and 7.1, one of OCH_2), 4.58 (1 H, dd, *J* 8.4 and 1.9, one of OCH_2), 4.38 (1 H, m, *H*CEt), 2.00–1.90 (1 H, m, one of CH_2), 1.85–1.78 (1 H, m, one of CH_2), 1.70–1.62 (1 H, m, one of CH_2), 1.55–1.45 (1 H, m, one of CH_2), 0.88 (3 H, t, *J* 7.4, CH_3) and 0.82 (3 H, t, *J* 7.4, CH_3); δ_C (100 MHz; $CDCl_3$) 162.4, 153.5 (both C=O), 150.1 (alkene C), 146.5, 146.2, 144.9, 143.3 (all aromatic C), 128.0, 125.6, 125.0, 119.2 (all aromatic CH), 80.9 (alkene C), 74.7 (OCH_2), 60.1, 57.6 (both CH), 27.1, 23.7 (both CH_2), 9.0, 8.1 (both CH_3); *m*/*z* (EI) 134 (13%), 90 (37), 69 (52), 63 (57), 55 (93) and 46 (100).

(3*R*,7*R*)-*N*,6-Bis((4-methylphenyl)sulfonyl)-3,7-diethyl-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide (19e)

Toluene-4-sulfonyl isocyanate (312 mg, 1.58 mmol) was added to (4*R*,*E*)-4-ethyl-2-but-1-enyl-4,5-dihydro-1,3-oxazole (**12**) (132 mg, 0.79 mmol). The reaction was stirred for 30 min, during which time the exotherm subsided. The resulting solid was recrystallised from hot ethanol to afford the *title compound* (400 mg, 90%) as a colourless solid, mp 160–163 °C (Found: C, 54.63; H, 5.19; N, 7.84. $C_{25}H_{29}N_3O_7S_2$ requires C, 54.83; H, 5.34; N, 7.67%); ν_{max} ($CHCl_3$)/cm^{-1} 3361, 1713, 1668, 1598 and 1047; δ_H (400 MHz; $CDCl_3$) 8.89 (1 H, s, N*H*), 7.98 (2 H, d, *J* 8.2, aromatic C*H*), 7.89 (2 H, d, *J* 8.3, aromatic C*H*), 7.37 (2 H, d, *J* 8.2, aromatic C*H*), 7.26 (2 H, d, *J* 8.3, aromatic C*H*), 5.48 (1 H, t, *J* 5.0, EtC*H*), 4.63 (1 H, dd, *J* 8.7 and 7.6, one of OCH_2), 4.48 (1 H, dd, *J* 8.7 and 2.6, one of OCH_2), 4.28 (1 H, m, *H*CEt), 2.47 (3 H, s, CH_3), 2.43 (3 H, s, CH_3), 1.79–1.62 (4 H, m, 2 × CH_2), 0.74 (3 H, d, *J* 7.4, CH_3) and 0.66 (3 H, t, *J* 7.4, CH_3); δ_C (100 MHz; $CDCl_3$) 160.3, 154.8 (both C=O), 147.8 (alkene C), 145.5, 145.2, 136.4, 136.1 (all aromatic C), 129.8, 129.7, 129.2, 128.8 (all aromatic CH), 81.5 (alkene C), 75.1 (OCH_2), 57.2, 55.7 (both CH), 32.1, 29.6 (both CH_3), 23.2, 22.0 (both CH_2), 8.2 and 8.0 (both CH_3); *m*/*z* (EI) 106 (52%), 89 (80) and 63 (100).

(3*R*,7*R*)-3-Ethyl-5-oxo-*N*,6,7-triphenyl-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide (20a)

A mixture of phenyl isocyanate (163 mg, 1.37 mmol) and (4*R*,*E*)-4-ethyl-2-(2-phenylethenyl)-4,5-dihydro-1,3-oxazole (**13**) (138 mg, 0.69 mmol) was heated in a sealed tube at 150 °C for 1.5 hours. The residue was recrystallised from hot ethanol to afford the *title compound* (230 mg, 76%) as a colourless solid, mp 205–208 °C (Found: C, 73.70; H, 5.81; N, 9.51. $C_{27}H_{25}N_3O_3$ requires C, 73.78; H, 5.73; N, 9.56%); ν_{max} ($CHCl_3$)/cm^{-1} 3416, 1686, 1650, 1597 and 1541; δ_H (400 MHz; $CDCl_3$) 8.27 (1 H, s, N*H*), 7.40 (2 H, d, *J* 7.6, aromatic C*H*), 7.22–7.13 (10 H, m, aromatic C*H*), 6.99–6.95 (3 H, m, aromatic C*H*), 5.80 (1 H, s, PhC*H*), 4.67 (1 H, apparent t, *J* 8.2, one of OCH_2), 4.53 (1 H,

dd, *J* 8.5 and 1.9, one of OC*H*$_2$), 4.44 (1 H, m, *H*CEt), 2.06–1.91 (2 H, m, C*H*$_2$) and 0.93 (3 H, t, *J* 7.4, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 161.3, 151.3 (both C=O), 149.6 (alkene C), 141.4, 139.5, 137.8 (all aromatic C), 128.4, 128.3, 128.1, 127.6, 127.1, 126.7, 126.4, 123.0, 119.3 (all aromatic CH), 82.9 (alkene C), 73.3 (OCH_2), 57.8, 56.5 (both CH), 22.9 (CH_2) and 8.0 (CH_3); *m*/*z* (EI) 439 (M^+, 14%), 362 (7), 320 (12), 119 (100) and 77 (87).

(3*R*,7*R*)-*N*,6-Bis(4-bromophenyl)-3-ethyl-5-oxo-7-phenyl-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide (20b)

A mixture of 4-bromophenyl isocyanate (474 mg, 2.39 mmol) and (4*R*,*E*)-4-ethyl-2-(2-phenylethenyl)-4,5-dihydro-1,3-oxazole (**13**) (241 mg, 1.20 mmol) was stirred in a sealed tube at 150 °C for 1 hour. The resulting solid was filtered through a pad of silica (eluent 1:1 dichloromethane–hexane) to give the *title compound* (420 mg, 59%) as a colourless solid, mp 215–217 °C (Found: (FAB) $MH^+(^{79}Br^{81}Br)$, 598.0143. $C_{27}H_{23}Br_2N_3O_3$ requires MH, 598.0163); ν_{max} ($CHCl_3$)/cm^{-1} 3414, 1685, 1652, 1590 and 1529; δ_H (400 MHz; $CDCl_3$) 8.25 (1 H, s, N*H*), 7.34–7.27 (5 H, m, aromatic C*H*), 7.19–7.16 (6 H, m, aromatic C*H*), 6.85 (2 H, d, *J* 8.6, aromatic C*H*), 5.72 (1 H, s, PhC*H*), 4.51 (1 H, apparent t, *J* 8.1, one of OC*H*$_2$), 4.39 (1 H, dd, *J* 8.5 and 1.9, one of OC*H*$_2$), 4.43 (1 H, m, *H*CEt), 2.05–1.87 (2 H, m, C*H*$_2$) and 0.92 (3 H, t, *J* 7.4, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 162.1, 152.2 (both C=O), 150.2 (alkene C), 141.9, 139.5, 137.9 (all aromatic C), 132.6, 132.2, 129.7, 129.0, 128.5, 127.3, 121.7 (all aromatic CH), 121.4, 116.3 (both C-Br), 83.8 (alkene C), 74.3 (OCH_2), 63.4 (Ph*C*H), 57.4 (H*C*Et), 23.8 (CH_2) and 9.0 (CH_3); *m*/*z* (EI) 515 (1%), 397 (4), 325 (1), 197 (22) and 63 (100).

(3*R*,7*R*)-*N*,6-Bis(4-nitrophenyl)-3-ethyl-5-oxo-7-phenyl-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide (20c)

A mixture of 4-nitrophenyl isocyanate (235 mg, 1.43 mmol) and (4*R*,*E*)-4-ethyl-2-(2-phenylethenyl)-4,5-dihydro-1,3-oxazole (**13**) (144 mg, 0.72 mmol) was stirred in a sealed tube at 150 °C for 1 hour. The resulting solid recrystallised from ethanol to afford the *title compound* (280 mg, 74%) as a yellow solid, mp 209–212 °C (Found: C, 61.24; H, 4.36; N, 13.53. $C_{27}H_{23}N_5O_7$ requires C, 61.24; H, 4.38; N, 13.23%); ν_{max} ($CHCl_3$)/cm^{-1} 3406, 1681, 1546 and 1509; δ_H (400 MHz; $CDCl_3$) 8.56 (1 H, s, N*H*), 8.12–8.08 (4 H, m, aromatic C*H*), 7.59 (2 H, dd, *J* 7.2 and 2.0, aromatic C*H*), 7.24–7.19 (7 H, m, aromatic C*H*), 5.90 (1 H, s, PhC*H*), 4.71 (1 H, apparent t, *J* 8.3, one of OC*H*$_2$), 4.71 (1 H, dd, *J* 8.6 and 2.1, one of OC*H*$_2$), 4.50 (1 H, m, *H*CEt), 2.08–2.03 (1 H, m, one of C*H*$_2$), 1.99–1.93 (1 H, m, one of C*H*$_2$) and 0.96 (3 H, t, *J* 7.3, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 160.4, 151.1 (both C=O), 148.3 (alkene C), 144.7, 144.5, 143.1, 141.6, 139.7 (all aromatic C), 127.8, 127.3, 126.2, 125.1, 123.8, 123.2, 117.6 (all aromatic CH), 82.5 (alkene C), 73.1 (OCH_2), 61.1 (Ph*C*H), 56.1 (H*C*Et), 22.2 (CH_2) and 7.4 (CH_3); *m*/*z* (EI) 365 (51%), 102 (74) and 55 (100).

(3*R*,7*R*)-*N*,6-Bis(4-methoxyphenyl)-3-ethyl-5-oxo-7-phenyl-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide (20d)

A mixture of 4-methoxyphenyl isocyanate (246 mg, 1.65 mmol) and (4*R*,*E*)-4-ethyl-2-(2-phenylethenyl)-4,5-dihydro-1,3-oxazole (**13**) (166 mg, 0.83 mmol) was stirred in a sealed tube at 150 °C for 1 hour. After cooling, the resulting solid was recrystallised from ethanol to give the *title compound* (40 mg, 10%) as a slightly impure colourless waxy solid; ν_{max} ($CHCl_3$)/cm^{-1} 3418, 1685, 1646, 1598 and 1511; δ_C (100 MHz; $CDCl_3$) 162.2, 158.8 (both C=O), 156.2 (alkene C), 152.0, 151.0, 141.8, 141.7, 133.2 (all aromatic C), 129.4, 128.8, 128.2, 127.5, 122.0, 114.6, 114.4 (all aromatic CH), 83.7 (alkene C), 74.1 (OCH_2), 63.9 (Ph*C*H), 57.3 (H*C*Et), 55.9, 55.8 (both OCH_3), 23.9 (CH_2) and 9.0 (CH_3); *m*/*z* (EI) 499 (M^+, 1%), 422 (1), 349 (1), 200 (1), 149 (100) and 55 (32).

(3*R*,7*R*)-*N*,6-Bis((4-methylphenyl)sulfonyl)-3-ethyl-5-oxo-7-phenyl-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine-8-carboxamide (20e)

A mixture of toluene-4-sulfonyl isocyanate (310 mg, 1.57 mmol) and (4*R*,*E*)-4-ethyl-2-(2-phenylethenyl)-4,5-dihydro-1,3-oxazole (**13**) (158 mg, 0.79 mmol) was stirred in a sealed tube overnight, during which time the product solidified. The resulting solid was then recrystallised from ethanol to give the *title compound* (440 mg, 94%) as a colourless solid, mp 88–92 °C (Found: C, 58.50; H, 5.06; N, 7.07. $C_{29}H_{29}N_3O_7S_2$ requires C, 58.47; H, 4.91; N, 7.05%); ν_{max} ($CHCl_3$)/cm^{-1} 3360, 1712, 1672, 1598 and 1043; δ_H (400 MHz; $CDCl_3$) 8.67 (1 H, s, N*H*), 7.88 (2 H, d, *J* 8.3, aromatic C*H*), 7.26 (2 H, d, *J* 8.2, aromatic C*H*), 7.19–7.10 (7 H, m, aromatic C*H*), 6.94 (2 H, d, *J* 8.3, aromatic C*H*), 6.34 (1 H, s, PhC*H*), 4.58 (1 H, apparent t, *J* 8.6, one of OC*H*$_2$), 4.47 (1 H, dd, *J* 8.7 and 2.6, one of OC*H*$_2$), 4.28 (1 H, m, *H*CEt), 2.38 (3 H, s, C*H*$_3$), 2.25 (3 H, s, C*H*$_3$), 2.02–1.96 (1 H, m, one of C*H*$_2$), 1.84–1.77 (1 H, m, one of C*H*$_2$) and 0.82 (3 H, t, *J* 7.4, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 160.1, 154.4 (both C=O), 147.4 (alkene C), 145.2, 145.1, 140.9, 136.4, 135.5 (all aromatic C), 129.9, 129.3, 129.2, 129.1, 129.0, 128.6, 127.7 (all aromatic CH), 83.5 (alkene C), 75.3 (OCH_2), 57.7 (CH), 57.4 (CH), 23.4 (CH_2), 22.0 (CH_3), 21.9 (CH_3) and 8.5 (CH_3); *m*/*z* (EI) 105 (35), 91 (65), 89 (90) and 65 (100).

(3*R*,7*R*)-6,7-Diphenyl-3-ethyl-8-methyl-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine (21)

A mixture of phenyl isocyanate (511 mg, 4.3 mmol) and (4*R*,*E*)-4-ethyl-2-(2-phenylpropen-2-yl)-4,5-dihydro-1,3-oxazole (**15**) (924 mg, 4.3 mmol) was heated in a sealed tube at 60 °C for 30 hours. The residue was purified by column chromatography (eluent 2:1 diethyl ether–hexane) to afford the *title compound* (883 mg, 62%) as a yellow solid, mp 58–60 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3066, 1758, 1710 and 1655; δ_H (400 MHz; $CDCl_3$) 7.38–7.17 (5 H, m, aromatic C*H*), 7.11 (3 H, m, aromatic C*H*), 6.98 (2 H, m, aromatic C*H*), 5.05 (1 H, s, *H*CPh), 4.33 (1 H, poorly resolved dd, *J* 7.9 and 6.9, one of OC*H*$_2$), 4.26 (1 H, m, *H*CEt), 4.17 (1 H, dd, *J* 8.2 and 2.1, one of OC*H*$_2$), 2.04–1.98 (1 H, m, one of C*H*$_2$), 1.86–1.77 (1 H, m, one of C*H*$_2$), 1.41 (3 H, s, C*H*$_3$) and 0.93 (3 H, t, *J* 7.5, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 152.1 (C=O), 143.9 (alkene C), 142.8, 142.2 (both aromatic C), 130.2, 129.8, 129.6, 129.2, 129.0, 128.2 (all aromatic CH), 78.5 (alkene C), 72.5 (OCH_2), 70.6, 57.9 (both CH), 25.2 (CH_2), 12.5 and 10.4 (both CH_3); *m*/*z* (APCI) 335 (MH^+, 100%).

(3*R*,7*R*,7a*R*,9a*R*)-3-Ethyl-7a-methyl-6,7,9-biphenyl-2,3,5,6,7,7a,8,9-octahydroazeto[2,3-*d*][1,3]oxazolo[3,2-*c*]pyrimidine-5,8-dione (22)

A mixture of phenyl isocyanate (414 mg, 3.48 mmol) and (4*R*,*E*)-4-ethyl-2-(2-phenylpropen-2-yl)-4,5-dihydro-1,3-oxazole (**15**) (374 mg, 1.74 mmol) was heated in a sealed tube at 150 °C for 24 hours. The reaction mixture was allowed to cool, and the resulting solid purified by column chromatography over neutral alumina (eluent 2:1 diethyl ether–hexane) to afford the *title compound* (204 mg, 26%) as a slightly impure off-white solid, mp 82–84 °C (Found MH^+, 454.2124. $C_{28}H_{28}N_3O_3$ requires M, 454.2131); ν_{max} ($CHCl_3$)/cm^{-1} 3019, 1728 and 1684; δ_H (400 MHz; $CDCl_3$) 7.58–7.11 (15 H, m, aromatic C*H*), 4.80 (1 H, s, C*H*Ph), 4.16 (1 H, dd, *J* 9.4 and 8.3, one of OC*H*$_2$), 3.95 (1 H, m, *H*CEt), 3.20 (1 H, apparent t, *J* 8.6, one of OC*H*$_2$), 2.08 (3 H, s, C*H*$_3$), 1.61 (1 H, m, one of C*H*$_2$), 1.39–1.32 (1 H, m, one of C*H*$_2$) and 0.89 (3 H, t, *J* 7.5, C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 169.5, 164.5 (both C=O), 152.4 (C-9a), 141.1, 137.0, 135.7 (all aromatic C), 129.8, 129.5, 129.5,

129.4, 129.1, 129.0, 128.9, 128.8, 128.2, 127.9, 127.5 (all aromatic CH), 73.3 (OCH_2), 69.9, 67.8 (both CH), 50.8 (C-7a), 32.0 (CH_2), 24.1 and 10.9 (both CH_3); *m/z* (APCI) 454 (MH^+, 100%).

(3*R*)-3-Ethyl-8-methyl-6-((4-methylphenyl)sulfonyl)-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine (23)

Toluene-4-sulfonyl isocyanate (728 mg, 3.70 mmol) and (4*R*)-4-ethyl-2-propen-2-yl-4,5-dihydro-1,3-oxazole **(14)** (257 mg, 1.85 mmol) were dissolved in toluene (15 ml) and stirred for 1 h. After this time the solvent was removed *in vacuo*, and the resulting solid transferred to a sintered glass funnel and washed with diethyl ether (10 ml) and dried *in vacuo* to give the *title compound* (971 mg, 98%) as an impure white solid still containing some toluene; ν_{max} ($CHCl_3$)/cm^{-1} 1765 and 1693; δ_H (400 MHz; $CDCl_3$) 7.89 (2 H, d, *J* 8.2, aromatic C*H*), 7.30 (2 H, d, *J* 8.2, aromatic C*H*), 4.43 (1 H, d, *J* 13.3, one of CH_2N), 4.23 (1 H, *d, J* 13.3, one of CH_2N), 4.17 (1 H, apparent t, *J* 7.6, one of OCH_2), 4.09 (1 H, m, C*H*Et), 4.00 (1 H, dd, *J* 8.1 and 2.6, one of OCH_2), 2.36 (3 H, s, CH_3), 1.75–1.72 (1 H, m, one of CH_2), 1.65 (3 H, s, CH_3), 1.57–1.51 (1 H, m, one of CH_2) and 0.75 (3 H, t, *J* 7.5, CH_3); *m/z* (APCI) 337 (MH^+, 100%).

(3*R*,7*R*)-3-Ethyl-8-methyl-6-((4-methylphenyl)sulfonyl)-7-phenyl-5-oxo-2,3,6,7-tetrahydro-5*H*-[1,3]oxazolo[3,2-*c*]pyrimidine (24)

A mixture of toluene-4-sulfonyl isocyanate (321 mg, 1.63 mmol) and (4*R*,*E*)-4-ethyl-2-(1-phenylpropen-2-yl)-4,5-dihydro-1,3-oxazole **(15)** (350 mg, 1.63 mmol) was dissolved in dry toluene (10 ml) and stirred for 1 hour. After removing the toluene *in vacuo*, the resulting solid was washed with diethyl ether and dried *in vacuo* to afford the *title compound* (501 mg, 75%) as an off-white solid, mp 155–157 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2971, 1761 and 1691; δ_H (400 MHz; $CDCl_3$) 7.34–7.24 (5 H, m, aromatic C*H*), 7.17 (2 H, d, *J* 8.3, aromatic C*H*), 7.00 (2 H, d, *J* 8.3, aromatic C*H*), 5.71 (1 H, s, C*H*Ph), 4.25 (1 H, apparent t, *J* 7.3, one of OCH_2), 4.16–4.11 (2 H, m, C*H*Et and one of OCH_2), 2.30 (3 H, s, CH_3), 2.05–1.99 (1 H, m, one of CH_2), 1.81–1.73 (1 H, m, one of CH_2), 1.49 (3 H, s, CH_3) and 0.90 (3 H, t, *J* 7.5, CH_3); δ_C (100 MHz; $CDCl_3$) 148.0 (C=O), 144.3, 141.5, 141.4, 136.8 (C-8a and 3 aromatic C), 129.2 (aromatic CH), 129.0 (broad, 2 aromatic CH), 128.7, 128.1 (both aromatic CH), 80.9 (alkene C), 71.6 (OCH_2), 64.0, 57.0 (both CH), 23.7 (CH_2), 21.9, 11.5 and 9.3 (all CH_3); *m/z* (APCI) 412 (M^+, 100%).

2-Propen-2-yl-4,4-dimethyl-4,5-dihydro-1,3-oxazole (25)

2-Amino-2-methylpropanol (14.03 g, 0.16 mol) in dichloromethane (100 ml) was added to $Na_2CO_3 \cdot 10H_2O$ (16 g, 56 mmol) in water (60 ml). Methacryloyl chloride (18.01 g, 0.17 mol) was added, and the resulting suspension stirred overnight. The aqueous layer was saturated with sodium chloride, extracted three times with dichloromethane (50 ml), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give *N*-(2-hydroxy-1,1-dimethylethyl)-2-methylprop-2-enamide (23.23 g, 94%) as a colourless oil. A portion of this compound (7.34 g, 47 mmol) in dichloromethane (100 ml) was cooled to 5 °C. Triethylamine (9.45 g, 93 mmol) and methanesulfonyl chloride (5.35 g, 47 mmol) were added and the solution was stirred overnight. The solution was washed twice with saturated $NaHCO_3$ (35 ml) and quickly dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by short path distillation to afford the *title compound* (3.65 g, 56%) as a colourless oil, bp 125 °C, water pump; ν_{max} (neat)/cm^{-1} 2969, 2929, 2892, 1657, and 1619; δ_H (400 MHz; $CDCl_3$) 5.63 (1 H, s, alkene C*H*), 5.24 (1 H, s, alkene C*H*), 3.80 (2 H, s, OCH_2), 1.85 (3 H, s, CH_3) and 1.17 (6 H, s, 2 × CH_3); δ_C (100 MHz; $CDCl_3$) 163.0 (C=N), 133.3 (alkene C), 121.6 (alkene CH_2), 79.0 (OCH_2), 67.7 (C), 28.7 (2 × CH_3) and 19.7 (CH_3); *m/z* (EI) 140 (MH^+, 100%), 124 (93), 109 (60) and 68 (75).

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