Substituent effects in isoxazoles: identification of 4-substituted isoxazoles as Michael acceptors

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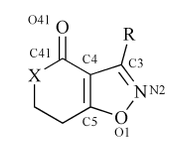
Crystallographic and theoretical studies have been used to investigate substituent effects, which are manifest in electrochemical and yeast-catalysed reactions of 4- and 5-acyl-, alkoxycarbonyl-, cyano- and phenyl-substituted isoxazoles. The results show that isoxazoles substituted at the 4-position with π-electron-withdrawing substituents have enhanced C4–C5 bond polarity and are structurally similar to Michael acceptors. As a consequence there is elongation and weakening of their N–O bonds. By contrast, their 5-substituted regioisomers and isoxazoles substituted at C4 with conjugating, but not π-electron-withdrawing, substituents have diminished C4–C5 bond polarity. This results in the selective electrochemical and yeast-catalysed reduction of 4-substituted isoxazoles, as well as their hydrogenolytic ring cleavage and conjugate reduction with sodium borohydride.

Introduction

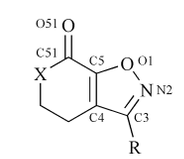
Isoxazoles are aromatic heterocycles but their aromatic rings are readily disrupted under reducing conditions.[1] This occurs *via* cleavage of their weak N–O bonds whereby the β-imino ketone functionality is revealed. Ring-opening is most commonly accomplished through hydrogenation with a suitable catalyst, such as palladium on carbon,[2] platinum black[3] or Raney nickel.[4] Other reducing agents known to effect ring-cleavage include samarium iodide,[5] molybdenum hexacarbonyl,[6] iron pentacarbonyl[7] and phenylmagnesium bromide.[8] Previously, we reported ring-opening reactions of isoxazoles *via* yeast catalysis[9] and electrolysis,[10] to give β-imino ketones as analogues of the herbicide Grasp®. Peculiar substituent effects were observed in these processes. Isoxazoles substituted at the 4-position with π-electron-withdrawing acyl, alkoxycarbonyl and cyano groups reacted smoothly and efficiently, while the 5-substituted regioisomers and 4- and 5-phenylisoxazoles were either inert or required more vigorous conditions to react, and then gave complex product mixtures. We have now examined the basis of these substituent effects, using crystallographic and theoretical methods, and found that 4-substituted isoxazoles are polarised in such a way that they behave as Michael acceptors.

Results and discussion

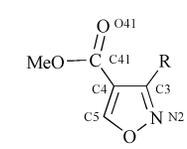
Our crystallographic studies involved analyses of bond lengths in regioisomeric pairs of 4- and 5-substituted isoxazoles. The solid-state structures of compounds **1a**,**b** and **2a**,**b** had been reported previously.[11–13] The latter two each comprise a unit cell with two crystallographically-independent molecules, while those of the former two each exhibit only one, and selected bond lengths for these structures are shown in Table 1. In attempts to make further comparisons between regioisomers and obtain data with lower standard errors, studies of compounds **3a**–**c** and **4a**–**c** were also carried out. The 4- and 5-methoxycarbonylisoxazoles **3a** and **4a** were synthesised *via* cycloaddition of 2,6-dichlorobenzonitrile oxide with methyl propiolate, while isoxazoles **3b** and **4b** were prepared through reaction of acetonitrile oxide and methyl (*Z*)-3-iodopropenoate. Isoxazoles **3c** and **4c** were obtained *via* reaction of 2,4,6-trimethylbenzonitrile oxide with methyl propiolate. However, as the 5-substituted regioisomer **4c** was found to be not crystalline, compounds **3c** and **4c** could not be used for structural studies.



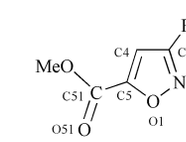
1a X = CH_2, R = 2,6-$Cl_2C_6H_3$
1b X = O, R = 2,6-$Cl_2C_6H_3$



2a X = CH_2, R = 2,6-$Cl_2C_6H_3$
2b X = O, R = 2,6-$Cl_2C_6H_3$



3a R = 2,6-$Cl_2C_6H_3$
3b R = Me
3c R = 2,4,6-$Me_3C_6H_2$
3d R = $(CH_2)_8Me$



4a R = 2,6-$Cl_2C_6H_3$
4b R = Me
4c R = 2,4,6-$Me_3C_6H_2$
4d R = $(CH_2)_8Me$

X-Ray crystallographic analysis showed four crystallographically-independent molecules in the unit cell of **3a** and only one in those of each of **3b** and **4a**,**b**. In each case the methoxycarbonyl group is coplanar with the isoxazole ring. The carbonyl groups of **3a**,**b** and **4a** are s-*trans* to the C4–C5 bond, while that of **4b** is s-*cis*. Key bond lengths derived from the crystallographic analyses of **3a**,**b** and **4a**,**b** are shown in Table 1. The data obtained for the 3-methylisoxazoles **3b** and **4b** have the lowest standard errors and are therefore the most reliable. They show that relative to the carbonyl group of **4b**, that of **3b** is more extensively conjugated to the ring. This is indicated by elongation of the C41–O41 bond of **3b**, compared with the C51–O51 bond of **4b**, and shortening of the C4–C41 bond of **3b**, compared with the C5–C51 bond of **4b**. This correlates with the more extensive conjugation of the isoxazole ring oxygen

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Table 1 Selected bond lengths (Å) of acyl- and alkoxycarbonyl-isoxazoles determined through X-ray crystallographic analysis

Compound	O1–N2	C5–O1	C4–C5	C4–C41	C41–O41	C5–C51	C51–O51
1a[a]	1.411(3)	1.324(4)	1.340(4)	1.445(4)	1.207(4)	—	—
1b[a]	1.426(2)	1.320(3)	1.330(3)	1.438(3)	1.188(3)	—	—
2a[a]	1.407(7)	1.349(8)	1.326(8)	—	—	1.45(1)	1.209(8)
	1.397(7)	1.329(8)	1.326(8)	—	—	1.461(9)	1.188(7)
2b[a]	1.391(7)	1.322(9)	1.32(1)	—	—	1.44(1)	1.19(3)
	1.398(7)	1.329(9)	1.32(1)	—	—	1.48(1)	1.18(1)
3a	1.422(5)	1.337(6)	1.345(7)	1.472(7)	1.196(5)	—	—
	1.422(5)	1.339(6)	1.354(7)	1.462(7)	1.211(5)	—	—
	1.423(5)	1.324(6)	1.350(7)	1.464(7)	1.198(6)	—	—
	1.419(5)	1.340(6)	1.338(7)	1.482(7)	1.204(5)	—	—
3b	1.427(2)	1.331(2)	1.345(2)	1.459(2)	1.211(2)	—	—
4a	1.400(2)	1.349(2)	1.337(3)	—	—	1.477(3)	1.203(2)
4b	1.416(2)	1.349(2)	1.347(2)	—	—	1.479(2)	1.203(2)

[a] Data from references 11–13.

Table 2 Calculated bond lengths (Å) for the isoxazole **5**

Method	O1–N2	N2–C3	C3–C4	C4–C5	C5–O1
B3-LYP/6-31G*	1.400	1.313	1.424	1.360	1.345
B3-LYP/6-31+G*	1.401	1.313	1.425	1.362	1.345
B3-LYP/6-311+G(3df,2p)	1.394	1.305	1.420	1.354	1.339
MP2/6-31G*	1.392	1.328	1.414	1.364	1.354
CCSD/6-31G*	1.396	1.311	1.427	1.355	1.349
DRM microwave spectroscopy[a]	1.400	1.313	1.426	1.360	1.346

[a] Data from reference 18.

with the enoate moiety in **3b** than in **4b**, as reflected in the longer C5–O1 bond of **4b** relative to that of **3b**. In turn, this conjugation of the isoxazole ring oxygen increases the length of the N–O bond of **3b** relative to that of **4b**. The data for the regioisomeric pairs **1a** and **2a**, **1b** and **2b**, and **3a** and **4a**, are less accurate but seem to follow the same trends, particularly as regards the N2–O1 and O1–C5 bonds. Thus 4-acyl- and alkoxycarbonyl-substituted isoxazoles appear to display conjugation similar to that seen with α,β-unsaturated ketones and acrylates, and as a consequence their N–O bonds are elongated and presumably weakened.

In order to explore these observations, theoretical studies of variously substituted isoxazoles were also carried out. The theoretical calculations correspond to isolated gas-phase molecules, and are thus not affected by the intermolecular interactions that may distort crystallographic data. The calculations were carried out with standard *ab initio* and density functional procedures[14,15] using the GAUSSIAN 98 suite of programs.[16] The methods employed for structural predictions include the B3-LYP hybrid density functional theory approach, second-order Møller–Plesset perturbation theory (MP2) and coupled cluster theory (CCSD), with a variety of basis sets. Conformational energies and electron affinities were calculated using the high-level G3(MP2)//B3-LYP procedure unless otherwise noted, and refer to 0 K.[17]

The performance of the theoretical methods was first evaluated for the parent isoxazole **5**. Computed bond lengths for the minimum energy conformation were compared with those derived experimentally through double-resonance-modulated microwave spectroscopy[18] (Table 2). All the methods examined gave reasonable geometries, but particularly good performance was seen with the computationally efficient B3-LYP/6-31G* level of theory, where the maximum deviation from the experimental values was found to be 0.002 Å. This method was therefore used in further studies of the formyl-, cyano- and vinyl-substituted isoxazoles **6**–**11**. The formyl group was chosen as the simplest example of a carbonyl group. The cyano group was examined as another π-electron-withdrawing substituent. The vinyl group was investigated as a conjugating but not π-electron-withdrawing substituent, representative of alkenyl and aryl groups.

In the minimum energy conformations, the substituents of the isoxazoles **6**–**11** are coplanar with the isoxazole rings, due to conjugation. This gives rise to s-*trans* and s-*cis* forms (**a** and **b**) with the formyl- and vinyl-isoxazoles **6**, **7**, **10** and **11**. For 4-formylisoxazole **6**, the G3(MP2)//B3-LYP calculations show that the s-*trans* conformer **6a** is more stable than the s-*cis* form **6b** by 2.7 kJ mol^{-1}, while with the 5-formylisoxazole **7**, the calculated energy difference between the s-*trans* and s-*cis* conformers **7a** and **7b** is 6.4 kJ mol^{-1}, with the latter being of lower energy. For the 4- and 5-vinylisoxazoles **10** and **11**, the s-*trans* forms **10a** and **11a** are favoured over the s-*cis* isomers **10b** and **11b**, by 4.4 and 3.2 kJ mol^{-1}, respectively.

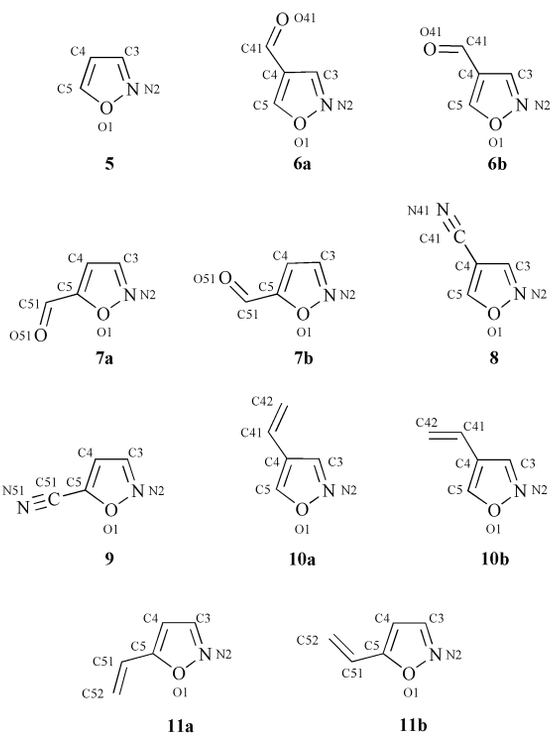
Bond lengths derived from the minimum energy conformations of the isoxazoles **5**–**11** are shown in Table 3. The observed trends are independent of the conformations in the cases of **6a**,**b**, **7a**,**b**, **10a**,**b** and **11a**,**b**. These trends for **6a**,**b** and **7a**,**b** are similar to those discussed above on the basis of the crystallographic results for **1a**,**b** and **2a**,**b**, and **3a**,**b** and **4a**,**b**. It is possible to make further comparisons by including the data for the unsubstituted isoxazole **5**. Conjugation of the carbonyl groups to the rings in **6a**,**b** and **7a**,**b** is reflected in the greater lengths of their C4–C5 bonds relative to that of **5**. This enhances conjugation between O1 and C4–C5 in **6a**,**b**, as indicated by the relative shortness of their C5–O1 bonds, but disrupts conjugation between O1 and C4–C5 in **7a**,**b**, as indicated by the relatively greater lengths of their C5–O1 bonds. As a result, the O1–N2 bonds of **6a**,**b** are longer than that of **5**, while those of **7a**,**b** are shorter. The cyano and vinyl substituents are also conjugated with the isoxazole rings of **8**–**11**, as indicated by the lengths of their C4–C5 bonds relative to that of **5**. Further analysis of bond lengths shows that when these groups are located at C5, in **9** and **11a**,**b**, they disrupt conjugation between O1 and C4–C5 and increase the O1–N2 interaction. The cyano group at C4 in **8** increases the extent of conjugation between O1 and C4–C5 and decreases the O1–N2 interaction, to a similar extent to that seen with the formyl substituent in **6a**,**b**. By comparison, the vinyl group at C4 of **10a**,**b** has little effect on either

Table 3 Selected bond lengths (Å) of the isoxazoles **5**–**11** derived for their minimum energy conformations using the B3-LYP/6-31G* method

Compound	O1–N2	C5–O1	C4–C5	C4–C41	C41–O41 C41–N41 C41–C42	C5–C51	C51–O51 C51–N51 C51–C52
5	1.400	1.345	1.360	—	—	—	—
6a	1.415	1.334	1.369	1.464	1.217	—	—
6b	1.412	1.332	1.371	1.466	1.217	—	—
7a	1.386	1.351	1.369	—	—	1.472	1.212
7b	1.387	1.355	1.368	—	—	1.471	1.215
8	1.405	1.334	1.370	1.419	1.163	—	—
9	1.387	1.356	1.367	—	—	1.419	1.163
10a	1.402	1.343	1.368	1.457	1.339	—	—
10b	1.401	1.341	1.370	1.460	1.339	—	—
11a	1.398	1.354	1.371	—	—	1.451	1.339
11b	1.394	1.356	1.372	—	—	1.453	1.339

Table 4 π-Electron densities of the isoxazoles **5**–**11** derived for their minimum energy conformations using the B3-LYP/6-31G* method

Compound	O1	N2	C3	C4	C5	C41	O41	N41	C42	C51	O51	N51	C52
5	1.68	1.23	0.99	1.09	1.00	—	—	—	—	—	—	—	—
6a	1.68	1.22	0.95	1.09	0.96	0.79	1.31	—	—	—	—	—	—
6b	1.66	1.23	0.97	1.10	0.94	0.79	1.32	—	—	—	—	—	—
7a	1.67	1.19	0.99	1.05	1.01	—	—	—	—	0.80	1.29	—	—
7b	1.68	1.20	0.99	1.03	1.02	—	—	—	—	0.79	1.30	—	—
8	1.66	1.22	0.97	1.13	0.97	0.96	—	1.09	—	—	—	—	—
9	1.68	1.20	0.98	1.05	1.05	—	—	—	—	0.96	—	1.08	—
10a	1.68	1.22	0.99	1.06	1.02	1.00	—	—	1.02	—	—	—	—
10b	1.67	1.23	1.00	1.07	1.01	1.00	—	—	1.02	—	—	—	—
11a	1.70	1.23	0.99	1.10	0.99	—	—	—	—	1.02	—	—	0.97
11b	1.69	1.23	0.99	1.10	0.99	—	—	—	—	1.00	—	—	0.99



the O1–C4–C5 or O1–N2 interaction, presumably due to the non-polar nature of this substituent.

Through their conjugation with the isoxazole rings, the substituents of compounds **6**–**11** affect the π-electron distribution to various degrees (Table 4). The C4–C5 bond of **5** is polarised, and this is enhanced by the formyl substituent at C4 of **6a**,**b**, but diminished by that substituent at C5 of **7a**,**b**. The less polar cyano group has a similar but less marked effect in **8** and **9**, while the non-polar vinyl substituent of **10a**,**b** and **11a**,**b** has little impact on the electron distribution. It seems likely that this polarisation is the reason for the facile electrochemical and yeast-catalysed reduction of 4-carbonyl- and cyano-substituted isoxazoles, with their electron-deficient C5 centres. Presumably these reactions proceed *via* the corresponding radical anions, and properties of these species might also be expected to provide an indication of their ease of formation. However, analysis of bond lengths (Table 5) and π-electron distributions (Table 6) in the radical anions of **5**–**11**, and of the electron affinities of the isoxazoles **5**–**11** to give the corresponding radical anions (Table 7) gives no indication of other factors that might contribute to the observed pattern of reactivity. Indeed the electron affinities of the 5-formyl- and cyano-substituted isoxazoles **7a**,**b** and **9** are higher than those of the 4-substituted isomers **6a**,**b** and **8**, in contrast to the greater reactivity recorded for compounds of the latter types.

Thus the crystallographic and theoretical studies show a correlation between the structural effects of the substituents and the susceptibility of isoxazoles towards electrochemical and yeast-catalysed reduction. These processes result indirectly in ring-opening through N–O bond cleavage. To determine if there would also be a relationship between direct N–O bond cleavage and the elongation of bonds of this type in isoxazoles substituted at C4 with π-electron-withdrawing substituents, pairs of regioisomeric 4- and 5-substituted isoxazoles were subjected to catalytic hydrogenation. Each of the isoxazoles **1a**, **2a**, **3c** and **4c** underwent ring-opening on treatment with hydrogen over palladium on carbon, to give the corresponding imines **12**–**15**. However, in competitive experiments, the 4-carbonyl-substituted isoxazoles **1a** and **3c** were more reactive than their corresponding 5-substituted isomers **2a** and **4c**. Reaction of a 1 : 1 mixture of **1a** and **2a** when stopped part way afforded a 1 : 5 : 6 : 2 mixture of **1a**, **2a**, **12** and **13**, showing that **1a** had reacted approximately six times faster than **2a**. A 1 : 1 mixture of **3c** and **4c** gave a 10 : 11 : 1 mixture of **4c**, **14** and **15**, and there was no evidence of residual **3c**, demonstrating that **3c** is at least an order of magnitude more reactive than **4c**. It is therefore apparent that the elongation of N–O bonds of substituted isoxazoles results in their weakening and selective cleavage.

Another feature of 4-carbonyl- and cyano-substituted isoxazoles identified through the structural studies, and already mentioned above, is their similarity to Michael acceptors. To see

Table 5 Selected bond lengths (Å) of the radical anions of the isoxazoles **5**–**11**, determined using the B3-LYP/6-31G* method

Radical anion precursor	O1–N2	C5–O1	C4–C5	C4–C41	C5–C51	C41–O41 C41–N41 C41–C42	C51–O51 C51–N51 C51–C52
5[a]	1.470	1.422	1.432	—	—	—	—
5[b]	1.491	1.407	1.400	—	—	—	—
6a[a]	1.420	1.406	1.426	1.420	—	1.265	—
6a[b]	1.416	1.398	1.413	1.423	—	1.272	—
6b[a]	1.421	1.404	1.420	1.421	—	1.262	—
6b[b]	1.418	1.397	1.412	1.423	—	1.266	—
7a[b]	1.434	1.385	1.413	—	1.415	—	1.264
7b[b]	1.434	1.390	1.408	—	1.414	—	1.270
8[a]	1.442	1.415	1.453	1.396	—	1.179	—
8[b]	1.445	1.409	1.436	1.395	—	1.182	—
9[b]	1.445	1.408	1.419	—	1.382	—	1.189
10a[a]	1.427	1.417	1.442	1.424	—	1.378	—
10a[b]	1.418	1.404	1.423	1.423	—	1.392	—
10b[a]	1.431	1.414	1.432	1.423	—	1.376	—
10b[b]	1.426	1.404	1.416	1.423	—	1.384	—
11a[b]	1.448	1.390	1.416	—	1.403	—	1.395
11b[b]	1.444	1.396	1.416	—	1.402	—	1.399

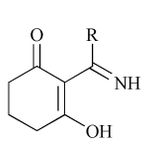
[a] Non-planar conformation (see footnote *c*). [b] Planar conformation. [c] The minimum energy conformations of the radical anions of **7a**,**b**, **9** and **11a**,**b** are all planar. Those of **5**, **6a**,**b**, **8** and **10a**,**b** are non-planar. The planar conformations of the anions of **5**, **6a**,**b**, **8** and **10a**,**b** are less stable than the non-planar forms, by 14.8, 1.7, 1.0, 14.7, 7.5 and 5.6 kJ mol^{-1}, respectively (B3-LYP/6-31G*, no ZPVE).

Table 6 π-Electron densities of the planar conformations of the radical anions of the isoxazoles **5**–**11**, determined using the B3-LYP/6-31G* method

Radical anion percursor	O1	N2	C3	C4	C5	C41	C51	O41	O51	N41	N51	C42	C52
5	1.81	1.49	1.18	1.20	1.32	—	—	—	—	—	—	—	—
6a	1.77	1.28	0.99	1.11	1.27	1.05	—	1.53	—	—	—	—	—
6b	1.77	1.29	1.02	1.11	1.25	1.05	—	1.51	—	—	—	—	—
7a	1.75	1.35	1.06	1.22	1.07	—	1.05	—	1.49	—	—	—	—
7b	1.76	1.36	1.05	1.20	1.07	—	1.05	—	1.50	—	—	—	—
8	1.80	1.34	1.03	1.23	1.22	1.00	—	—	—	1.28	—	—	—
9	1.79	1.39	1.07	1.22	1.20	—	1.03	—	—	—	1.30	—	—
10a	1.78	1.30	1.02	1.12	1.32	1.12	—	—	—	—	—	1.34	—
10b	1.78	1.32	1.05	1.11	1.28	1.11	—	—	—	—	—	1.31	—
11a	1.78	1.39	1.06	1.25	1.06	—	1.16	—	—	—	—	—	1.29
11b	1.78	1.39	1.05	1.25	1.07	—	1.15	—	—	—	—	—	1.31

Table 7 Electron affinities (eV) of the isoxazoles **5**–**11**, determined using the G3(MP2)/B3-LYP method

Compound	Electron affinity (eV)
5	−1.02
6a	0.15
6b	0.35
7a	0.74
7b	0.75
8	0.10
9	0.41
10a	−0.55
10b	−0.28
11a	−0.02
11b	−0.02



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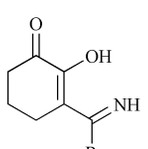

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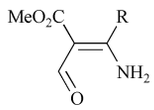
R = 2,6-$Cl_2C_6H_3$

if this would be reflected in their reactivity, the isoxazoles **3c** and **4c** were treated with an excess of sodium borohydride. With the 5-methoxycarbonylisoxazole **4c**, reaction afforded only the hydroxymethylisoxazole **17a**, which was isolated in 93% yield. By contrast, the 4-methoxycarbonylisoxazole **3c** underwent conjugate reduction to give the isoxazoline **16a**, in 91% yield. The generality of these processes was explored using the isoxazoles **3d** and **4d**, which were obtained by treatment of methyl (*Z*)-3-iodopropenoate with decanenitrile oxide. On reaction with borohydride, **4d** gave the isoxazole **17b** in 92% yield, while **3d** produced the isoxazoline **16b** and the isoxazole **18**, in yields of 73 and 18%, respectively. Clearly the 4-substituted isoxazoles **3c**,**d** behave as masked acrylates but this is not observed with the 5-substituted regioisomers **4c**,**d**. To the best or our knowledge, there is only one other report of hydride reduction of isoxazoles to give isoxazolines,[19] and in that case it was shown that 4-carbonyl-substituted isoxazoles did not react in this manner. This inconsistency may be attributed to the use of at least a ten-fold excess of sodium borohydride in the present study, but only stoichiometric quantities in the earlier work. Brown and Rapoport[20] have shown that a large excess of reducing agent is required for conjugate reduction of α,β-unsaturated esters.

In summary, the present studies show that a conjugating, π-electron-withdrawing substituent at the 4-position of an isoxazole elongates the N–O bond, and enhances the C4–C5 bond polarity to a similar extent to that seen with Michael acceptors. As a result these isoxazoles are susceptible to electrochemical and yeast-catalysed reduction and hydrogenolytic ring cleavage, and they undergo conjugate reduction with borohydride. The latter observation is probably the most important in terms of synthetic potential, given the versatile functionality of isoxazoles and their rigidity, which should make them suitable for exploitation in asymmetric synthesis. To this end



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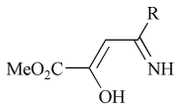

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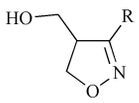

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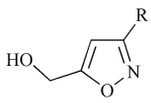

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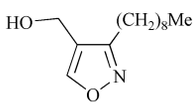
a R = 2,4,6-$Me_3C_6H_2$
b R = $(CH_2)_8Me$



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we intend to investigate reductions and nucleophilic addition reactions of isoxazoles that are substituted at C4 with chiral auxiliaries attached *via* ester linkages.

Experimental

Melting points were determined on a Kofler hot-stage apparatus under a Reichert microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian Gemini 300 or a Varian Mercury 300 spectrometer, as dilute solutions in $CDCl_3$. Electron impact mass spectra were recorded on either a VG Micromass 7070F or an AEI MS-30 spectrometer, operating at an ionisation potential of 70 eV. IR spectra were recorded on KBr discs using a Perkin-Elmer 1800 Fourier Transform Infrared Spectrometer. Elemental analyses were performed by the Microanalytical Laboratory, Research School of Chemistry, Australian National University. Chromatography was performed using Merck-Keiselgel 60 (230–400 mesh ASTM). The ketoisoxazoles **1a** and **2a** were prepared as reported.[10]

Single crystal X-ray diffraction data were obtained for **3a**,**b** and **4a**,**b**. A Nonius Kappa CCD diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71069 Å) was used for all crystals. Intensity data were collected at 200 K to $2\theta_{max}$ = 55° in each case. The structures were solved by direct methods[21] and refined on F by full-matrix least-squares.[22] Non-hydrogen atoms were refined with anisotropic displacement parameters. Further specific details are given under the individual compounds.

3-(2,6-Dichlorophenyl)isoxazole-4-carboxylic acid methyl ester 3a and 3-(2,6-dichlorophenyl)isoxazole-5-carboxylic acid methyl ester 4a

Triethylamine (0.70 mL, 5.0 mmol) was added dropwise over 15 min to a stirred mixture of 2,6-dichlorobenzohydroximoyl chloride[23] (1.0 g, 4.5 mmol) and methyl propiolate (0.47 g, 5.6 mmol) in THF (20 mL) at 18 °C. After heating the mixture at reflux for 2 days, the solvent was removed under reduced pressure. The residue was taken up in Et_2O (100 mL) and the solution was washed with H_2O (2 × 75 mL). The aqueous solutions were extracted with Et_2O (3 × 75 mL). The combined organic solutions were washed with brine (1 × 50 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes–EtOAc (4 : 1) afforded the *title compounds* **3a** (233 mg, 19%) as colourless needles, after recrystallization through vapour diffusion from hexanes and Et_2O at 18 °C, mp 85–87 °C; ν_{max} 1732, 1576, 1561, 1433, 1395, 1306, 1196, 1148, 1128, 1105, 1075, 1017, 861, 775, 730 cm^{-1}; δ_H 3.76 (3H, s, CH_3O), 7.34–7.45 (3H, m, 3 × PhH), 9.08 (1H, s, H5); δ_C 52.1 (CH_3O), 114.2 (C4), 126.8 (C), 127.9 (2 × CH), 132.0 (CH), 135.4 (2 × C), 154.9 (C3), 158.7 (C=O), 163.2 (C5); *m*/*z* 238, 236 ($M^{+\bullet}$ − Cl, 51 and 100%), 212 (22), 198 (13), 184 (8), 171 (6), 157 (5), 148 (8), 136 (4), 109 (7), 100 (3), 75 (5); Found 238.0085. $C_{11}H_7{}^{37}ClNO_3$ ($M^{+\bullet}$ − Cl) requires 238.0085; Found, 236.0112. $C_{11}H_7{}^{35}ClNO_3$ ($M^{+\bullet}$ − Cl) requires 236.0111; and **4a** (700 mg, 57%) as a colourless solid, mp 114–116 °C (lit.[10] mp 114–116 °C); ν_{max} 1736, 1593, 1581, 1459, 1377, 1307, 1232, 1198, 1152, 1100, 1079, 1001, 953, 915, 851, 807, 789, 772, 730, 710 cm^{-1}; δ_H 4.03 (3H, s, CH_3O), 7.08 (1H, s, H4), 7.27–7.50 (3H, m, 3 × PhH); *m*/*z* 277, 275, 273 ($M^{+\bullet}$, 5, 23 and 46%), 216 (29), 214 (75), 212 (100), 186 (38), 184 (46); the ^{1}H NMR spectral data of the isoxazole **4a** are consistent with reported values.[10]

X-Ray data for 3a. $C_{11}H_7Cl_2NO_3$, primitive orthorombic, space group $Pna2_1$ (no. 33), a = 14.7870(2) Å, b = 22.7232(3) Å, c = 14.1751(2) Å, V = 4763.0(1) Å^3, Z = 16, D_{calc} = 1.518 g cm^{-3}, μ = 5.38 cm^{-1}. A total of 69227 reflections were measured, corrected for absorption[24] and merged to yield 5676 unique reflections (R_{int} = 0.065). Hydrogen atoms were included at geometrically determined positions. The compound is present as a racemate within the crystal structure. There are four independent molecules of $C_{11}H_7Cl_2NO_3$ in the crystallographic asymmetric unit. The absolute structure of the crystal was determined by relative refinement. Final agreement factors for 3287 reflections with $I > 2\sigma(I)$ and 612 parameters were R = 0.038, wR = 0.037 and gof = 0.97. CCDC reference number 191571. See http://www.rsc.org/suppdata/p2/b2/b207808b/ for crystallographic files in .cif or other electronic format.

X-Ray data for 4a. $C_{11}H_7Cl_2NO_3$, primitive monoclinic, space group $P2_1/a$ (no. 14), a = 10.4382(3) Å, b = 10.2875(4) Å, c = 11.4036(5) Å, β = 109.859(2)°, V = 1151.73(7) Å^3, Z = 4, D_{calc} = 1.569 g cm^{-3}, μ = 5.56 cm^{-1}. A total of 20168 reflections were measured, corrected for absorption[24] and merged to yield 2631 unique reflections (R_{int} = 0.058). Hydrogen atom coordinates were refined. Final agreement factors for 1685 reflections with $I > 2\sigma(I)$ and 175 parameters were R = 0.033, wR = 0.038 and gof = 0.93. CCDC reference number 191572. See http://www.rsc.org/suppdata/p2/b2/b207808b/ for crystallographic files in .cif or other electronic format.

3-Methylisoxazole-4-carboxylic acid methyl ester 3b and 3-methylisoxazole-5-carboxylic acid methyl ester 4b

To a stirred mixture of (*Z*)-3-iodopropenoic acid methyl ester (11.3 g, 53.4 mmol) and acetohydroximoyl chloride[25] (620 mg, 6.67 mmol) at 18 °C was added over 16 h a solution of triethylamine (1.02 mL, 7.34 mmol) in dry Et_2O (4 mL). After stirring at 18 °C for a further 24 h, the mixture was poured into H_2O (75 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 75 mL) and the combined organic solutions were washed with brine (1 × 75 mL) and then dried (anhydrous $MgSO_4$). The ethereal solvent was distilled off at atmospheric pressure and flash column chromatography of the residue, eluting with hexanes–EtOAc (4 : 1) afforded the *title compounds* **3b** (197 mg, 21%) as colourless blocks, after recrystallization from hexanes and Et_2O at 0 °C; mp 24–25 °C ν_{max} 1734, 1592, 1491, 1435, 1405, 1299, 1249, 1133, 1109, 805, 772 cm^{-1}; δ_H 2.50 (3H, s, CH_3), 3.86 (3H, s, CH_3O), 8.84 (1H, s, H5); δ_C 10.1 (CH_3), 51.2 (CH_3O), 112.7 (C4), 158.2 (C3), 161.3 (C=O), 162.5 (C5); Found 141.0425. $C_6H_7NO_3$ ($M^{+\bullet}$) requires 141.0426; and **4b** (508 mg, 54%) as colourless plates, after recrystallization from hexanes and Et_2O at 0 °C, mp 94–95 °C; ν_{max} 1731, 1444, 1382, 1299, 1233, 1093, 1004, 932, 900, 851, 771 cm^{-1}; δ_H 2.38 (3H, s, CH_3), 3.96 (3H, s, CH_3O), 6.80 (1H, s, H4); δ_C 11.3 (CH_3), 52.7 (CH_3O), 110.0 (C4), 157.2 (C3), 159.7 (C5), 160.4 (C=O); *m*/*z* 141 ($M^{+\bullet}$, 76%), 115 (6), 110 (23), 102 (10), 91 (3), 82 (100), 77 (3), 73 (10), 63 (2), 59 (8), 54 (23).

X-Ray data for 3b. $C_6H_7NO_3$, primitive monoclinic, space group $P2_1/c$ (no. 14), a = 7.8027(3) Å, b = 11.2422(5) Å, c = 8.4806(4) Å, β = 111.428(2)°, V = 692.49(5) Å^3, Z = 4, D_{calc} = 1.354 g cm^{-3}, μ = 1.10 cm^{-1}. A total of 14023 reflections were measured, corrected for absorption[24] and merged to yield 1573 unique reflections (R_{int} = 0.059). Hydrogen atom coordinates and isotropic displacement factors were refined. Final agreement factors for 904 reflections with $I > 2\sigma(I)$ and 115 parameters were R = 0.036, wR = 0.040 and gof = 1.01. CCDC reference number 191573. See http://www.rsc.org/suppdata/p2/b2/b207808b/ for crystallographic files in .cif or other electronic format.

X-Ray data for 4b. $C_6H_7NO_3$, primitive monoclinic, space group $P2_1/m$ (no. 11), a = 5.8086(2) Å, b = 6.3238(3) Å, c = 8.8391(4) Å, β = 92.435(2)°, V = 324.39(2) Å^3, Z = 2, D_{calc} = 1.445 g cm^{-3}, μ = 1.17 cm^{-1}. A total of 9358 reflections were measured, corrected for absorption[26] and merged to yield 752 unique reflections (R_{int} = 0.045). Hydrogen atom coordinates and isotropic displacement parameters were refined. All non-hydrogen atoms lie on a crystallographic mirror plane. Final agreement factors for 693 reflections with $I > 2\sigma(I)$ and 76 parameters were R = 0.035, wR = 0.053 and gof = 2.12. CCDC reference number 191574. See http://www.rsc.org/suppdata/p2/b2/b207808b/ for crystallographic files in .cif or other electronic format.

3-(2,4,6-Trimethylphenyl)isoxazole-4-carboxylic acid methyl ester 3c and 3-(2,4,6-trimethylphenyl)isoxazole-5-carboxylic acid methyl ester 4c

A mixture of 2,4,6-trimethylbenzonitrile oxide[23] (400 mg, 2.48 mmol) and methyl propiolate (208 mg, 2.48 mmol) in THF (65 mL) was heated at reflux for 2 days. After the solvent was removed under reduced pressure, the residue was taken up in Et_2O (100 mL) and the solution was washed with H_2O (1 × 75 mL). The aqueous phase was separated and extracted with Et_2O (3 × 75 mL). The combined organic solutions were washed with brine (1 × 75 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes–Et_2O (7 : 3) afforded the *title compounds* **3c** (425 mg, 70%) as colourless blocks, after recrystallization through vapour diffusion from hexanes and Et_2O at 18 °C, mp 75–77 °C (Found: C, 68.22; H, 6.03; N, 5.60. $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16; N, 5.71%); ν_{max} 1724, 1610, 1573, 1457, 1394, 1306, 1136, 1018, 839, 407 cm^{-1}; δ_H 2.05 (6H, s, *o*,*o*′-MesCH$_3$), 2.33 (3H, s, *p*-MesCH$_3$), 3.73 (3H, s, CH$_3$O), 6.94 (2H, s, 2 × MesH), 9.06 (1H, s, H5); δ_C 19.8 (2 × CH$_3$), 21.1 (CH$_3$), 51.7 (CH$_3$O), 113.7 (C4), 123.7 (C), 128.1 (2 × CH), 136.8 (2 × C), 138.9 (C), 160.8 (C3 and C=O), 163.2 (C5); *m*/*z* 245 (M$^{+\bullet}$, 100%), 228 (20), 214 (21), 198 (6), 186 (58), 170 (29), 158 (84), 149 (6), 142 (23), 130 (26), 115 (28), 103 (16), 91 (36), 84 (15), 77 (28), 65 (13), 57 (15); Found 245.1053. $C_{14}H_{15}NO_3$ (M$^{+\bullet}$) requires 245.1052; and **4c** (164 mg, 27%) as a colourless oil (Found: C, 68.46; H, 6.25; N, 5.58. $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16; N, 5.71%); ν_{max} 2955, 1749, 1653, 1613, 1585, 1505, 1457, 1384, 1305, 1286, 1235, 1221, 1171, 1123, 1002, 852, 770 cm^{-1}; δ_H 2.13 (6H, s, *o*,*o*′-MesCH$_3$), 2.38 (3H, s, *p*-MesCH$_3$), 4.01 (3H, s, CH$_3$O), 6.90 (1H, s, H4), 6.96 (2H, s, 2 × MesH); δ_C 20.1 (2 × CH$_3$), 21.0 (CH$_3$), 52.7 (CH$_3$O), 110.9 (C4), 124.7 (C), 128.4 (2 × CH), 137.0 (C), 139.2 (2 × C), 157.2 (C3), 159.9 (C=O), 162.6 (C5); *m*/*z* 245 (M$^{+\bullet}$, 59%), 214 (5), 186 (100), 171 (12), 158 (70), 143 (26), 133 (18), 119 (20), 115 (24), 103 (15), 91 (30), 77 (22), 62 (9), 57 (8); Found 245.1056. $C_{14}H_{15}NO_3$ (M$^{+\bullet}$) requires 245.1052.

3-Nonylisoxazole-4-carboxylic acid methyl ester 3d and 3-nonylisoxazole-5-carboxylic acid methyl ester 4d

A solution of triethylamine (0.37 mL, 2.60 mmol) in Et_2O (10 mL) was added over 18 h to a stirred solution of (*Z*)-3-iodopropenoic acid methyl ester (4.00 g, 18.9 mmol) and decylhydroximoyl chloride (prepared from decanaldoxime and *N*-chlorosuccinimide) (485 mg, 2.36 mmol) in dry Et_2O (100 mL) at 18 °C. After stirring at 18 °C for a further 24 h, the mixture was poured into H_2O (50 mL). The aqueous layer was separated and extracted with Et_2O (3 × 100 mL). The combined organic solutions were washed with brine (1 × 75 mL), dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes–CH_2Cl_2 (1 : 1) afforded the *title compounds* **3d** (102 mg, 17%) as a colourless oil (Found: C, 66.62; H, 9.39; N, 5.74. $C_{14}H_{23}NO_3$ requires C, 66.37; H, 9.15; N, 5.53%); ν_{max} 2926, 2855, 1735, 1586, 1436, 1297, 1245, 1134, 1103, 806, 778 cm^{-1}; δ_H 0.89 (3H, t, J 6.7, C*H*$_3$CH$_2$), 1.20–1.45 (12H, m, 6 × CH$_2$), 1.72 (2H, quintet, J 7.7, CH$_2$), 2.92 (2H, t, J 7.7, CH$_2$), 3.87 (3H, s, CH$_3$O), 8.85 (1H, s, H5); δ_C 14.1 (CH$_3$), 22.6 (CH$_2$), 25.2 (CH$_2$), 27.6 (CH$_2$), 29.24 (CH$_2$), 29.2 (CH$_2$), 29.3 (CH$_2$), 29.4 (CH$_2$), 31.8 (CH$_2$), 51.8 (CH$_3$O), 112.7 (C4), 161.7 (C3), 162.5 (C=O), 163.0 (C5); *m*/*z* 253 (M$^{+\bullet}$, 25%), 238 (7), 222 (18), 210 (12), 194 (14), 182 (17), 168 (13), 154 (49), 141 (100), 122 (26), 110 (7), 96 (16), 83 (19), 68 (19); Found 253.1675. $C_{14}H_{23}NO_3$ (M$^{+\bullet}$) requires 253.1678; and **4d** (258 mg, 43%) as a colourless solid, mp 50–52 °C (Found: C, 66.28; H, 8.72; N, 5.37. $C_{14}H_{23}NO_3$ requires C, 66.37; H, 9.15; N, 5.53%); ν_{max} 2953, 2914, 2848, 1731, 1470, 1291, 1274, 1088, 1007, 908, 851, 770, 717 cm^{-1}; δ_H 0.88 (3H, t, J 7.0, C*H*$_3$CH$_2$), 1.28–1.43 (12H, m, 6 × CH$_2$), 1.67 (2H, quintet, J 7.5, CH$_2$), 2.72 (2H, t, J 7.5, CH$_2$), 3.96 (3H, s, CH$_3$O), 6.81 (1H, s, H4); δ_C 14.0 (CH$_3$), 22.6 (CH$_2$), 25.9 (CH$_2$), 28.1 (CH$_2$), 29.0 (CH$_2$), 29.2 (2 × CH$_2$), 29.4 (CH$_2$), 31.8 (CH$_2$), 52.7 (CH$_3$O), 109.2 (C4), 157.3 (C3), 159.3 (C=O), 164.7 (C5); *m*/*z* 253 (M$^{+\bullet}$, 11%), 238 (6), 224 (3), 210 (5), 194 (58), 182 (4), 166 (21), 154 (43), 141 (100), 122 (7), 108 (6), 96 (11), 82 (16), 68 (16); Found 253.1676. $C_{14}H_{23}NO_3$ (M$^{+\bullet}$) requires 253.1678.

(*E*)-3-Amino-2-formyl-3-(2,4,6-trimethylphenyl)acrylic acid methyl ester 14

A solution of 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **3c** (100 mg, 0.408 mmol) in MeOH (1 mL) was added to a suspension of 10% palladium on carbon (10 mg) in MeOH (5 mL) under an atmosphere of hydrogen. After stirring at 18 °C for 24 h, the mixture was filtered through a pad of Celite®. The filter cake was washed with MeOH (5 × 10 mL) and the combined filtrates were concentrated under reduced pressure. Flash column chromatography of the residue, eluting with hexanes–EtOAc (4 : 1) afforded the *title compound* **14** (99 mg, 98%) as a colourless oil (Found: C, 67.96; H, 6.90; N, 5.62. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66%); ν_{max} 3440, 3319, 2948, 2924, 1731, 1600, 1535, 1436, 1270, 1186, 1125 cm^{-1}; δ_H 2.22 (6H, s, *o*,*o*′-MesCH$_3$), 2.30 (3H, s, *p*-MesCH$_3$), 3.76 (3H, s, CH$_3$O), 5.81 (2H, br s, NH$_2$), 6.89 (2H, s, 2 × MesH), 10.2 (1H, s, CHO); δ_C 19.0 (2 × CH$_3$), 21.1 (CH$_3$), 50.8 (CH$_3$O), 101.9 (*C*CO$_2$CH$_3$), 128.1 (2 × CH), 133.4 (2 × C), 133.9 (C), 138.4 (C), 166.6 (CNH$_2$), 170.8 (C=O), 191.9 (CHO); *m*/*z* 247 (M$^{+\bullet}$, 8%), 232 (100), 217 (60), 202 (66), 186 (25), 172 (50), 158 (40), 146 (85), 130 (21), 115 (17), 88 (11), 77 (14); Found 247.1207. $C_{14}H_{17}NO_3$ (M$^{+\bullet}$) requires 247.1208.

The relative configuration of compound **14** is assumed to be *E*, based on the structure of the precursor isoxazole **3c**.

(*Z*)-2-Hydroxy-4-imino-4-(2,4,6-trimethylphenyl)but-2-enoic acid methyl ester 15

A solution of 3-(2,4,6-trimethylphenyl)isoxazole-5-carboxylic acid methyl ester **4c** (100 mg, 0.408 mmol) in MeOH (1 mL) was added to a suspension of 10% palladium on carbon (10 mg) in MeOH (3 mL) under an atmosphere of hydrogen. After stirring at 18 °C for 10 days, the mixture was filtered through a pad of Celite®. The filter cake was washed with MeOH (5 × 10 mL)

and the combined filtrates were concentrated under reduced pressure. Flash column chromatography of the residue, eluting with hexanes–EtOAc (4 : 1) afforded the *title compound* **15** (99 mg, 98%) as a colourless oil (Found: C, 67.92; H, 6.91; N, 5.63. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66%); δ_H 2.26 (s, 6H, *o*,*o*′-MesCH$_3$), 2.30 (s, 3H, *p*-MesCH$_3$), 3.85 (s, 3H, CH$_3$O), 5.76 (br s, 1H, NH or OH), 5.90 (s, 1H, CH), 6.90 (s, 2H, 2 × MesH), 10.5 (br s, 1H, NH or OH); δ_C 19.2 (2 × CH$_3$), 21.0 (CH$_3$), 52.6 (CH$_3$O), 94.4 (CH), 128.3 (2 × CH), 133.5 (C), 134.7 (2 × C), 139.0 (C), 164.0 (*C*CO$_2$Me), 168.0 (C=NH), 178.4 (C=O); *m*/*z* 247 (M$^{+\bullet}$, 14%), 188 (100), 158 (7), 145 (36), 130 (23), 115 (9), 105 (6), 91 (8), 77 (6); Found 247.1210. $C_{14}H_{17}NO_3$ (M$^{+\bullet}$) requires 247.1208.

The relative configuration of compound **15** is assumed to be *Z*, based on the structure of the precursor isoxazole **4c**.

Competitive hydrogenation of 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester 3c and 3-(2,4,6-trimethylphenyl)isoxazole-5-carboxylic acid methyl ester 4c

To a mixture of 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **3c** (50.0 mg, 0.204 mmol) and 3-(2,4,6-trimethylphenyl)isoxazole-5-carboxylic acid methyl ester **4c** (50.0 mg, 0.204 mmol) in MeOH (5 mL) was added 10% palladium on carbon (10 mg) under an atmosphere of hydrogen. After the suspension was stirred at 18 °C for 2 days, the mixture was filtered through a pad of Celite®. The filter cake was washed with MeOH (5 × 10 mL), and the combined filtrates were concentrated under reduced pressure. ^{1}H NMR analysis indicated the mixture was composed of (*E*)-3-amino-2-formyl-3-(2,4,6-trimethylphenyl)acrylic acid methyl ester **14** (described above), 3-(2,4,6-trimethylphenyl)isoxazole-5-carboxylic acid methyl ester **4c** (described above) and (*Z*)-2-hydroxy-4-imino-4-(2,4,6-trimethylphenyl)but-2-enoic acid methyl ester **15** (described above) in a ratio of 11 : 10 : 1.

4-Hydroxymethyl-3-(2,4,6-trimethylphenyl)-2-isoxazoline 16a

Sodium borohydride (185 mg, 4.89 mmol) was added over 15 min to a stirred solution of 3-(2,4,6-trimethylphenyl)isoxazole-4-carboxylic acid methyl ester **3c** (80.0 mg, 0.326 mmol) in dry EtOH (5 mL) at 0–5 °C (ice bath). After heating at reflux for 24 h, the mixture was cooled to 0–5 °C (ice bath) and quenched by dropwise addition of 1 M HCl (to pH 2). The solvent was evaporated *in vacuo*, the residue was taken up in Et$_2$O (10 mL) and the solution was washed with H$_2$O (1 × 7 mL). The aqueous layer was extracted with Et$_2$O (3 × 7 mL). The combined organic solutions were washed with H$_2$O (1 × 7 mL), aq. NaHCO$_3$ (1 × 7 mL) and brine (1 × 7 mL), dried (anhydrous MgSO$_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes–EtOAc (4 : 1) afforded the *title compound* **16a** (65 mg, 91%) as a colourless oil (Found: C, 71.11; H, 7.71; N, 6.12. $C_{13}H_{17}NO_2$ requires C, 71.21; H, 7.81; N, 6.39%); ν_{max} 3369, 2962, 2922, 2208, 2088, 1612, 1453, 1378, 1313, 1261, 1140, 1102, 975, 852, 733, 573 cm^{-1}; δ_H 1.55 (1H, br s, OH), 2.28 (6H, s, *o*,*o*′-MesCH$_3$), 2.30 (3H, s, *p*-MesCH$_3$), 3.69 (2H, m, CH$_2$O), 3.75 (1H, m, H4), 4.50 (2H, m, H5 and H5′), 6.91 (2H, s, 2 × MesH); δ_C 20.0 (2 × CH$_3$), 21.1 (CH$_3$), 54.5 (C4), 61.0 (CH$_2$O), 71.8 (C5), 124.9 (C), 128.7 (2 × CH), 136.7 (2 × C), 138.8 (C), 158.3 (C3); *m*/*z* 219 (M$^{+\bullet}$, 100%), 202 (51), 188 (47), 172 (90), 164 (4), 158 (55), 146 (76), 130 (48), 121 (20), 115 (42), 103 (26), 91 (55), 77 (4), 65 (22), 57 (4); Found 219.1258. $C_{13}H_{17}NO_2$ (M$^{+\bullet}$) requires 219.1259.

The ^{1}H NMR data of the 2-isoxazoline **16a** are fully consistent with reported values.[27]

5-Hydroxymethyl-3-(2,4,6-trimethylphenyl)isoxazole 17a

Sodium borohydride (185 mg, 4.89 mmol) was added over 15 min to a stirred solution of 3-(2,4,6-trimethylphenyl)isoxazole-5-carboxylic acid methyl ester **4c** (80.0 mg, 0.326 mmol) in dry EtOH (6 mL) at 0–5 °C (ice bath). After heating at reflux for 24 h, the mixture was cooled to 0–5 °C (ice bath) and quenched by dropwise addition of 1 M HCl (to pH 2). The solvent was removed under reduced pressure, the residue was taken up in Et$_2$O (10 mL) and the solution was washed with H$_2$O (1 × 7 mL). The aqueous layer was extracted with Et$_2$O (3 × 10 mL). The combined organic solutions were washed with H$_2$O (1 × 7 mL), aq. NaHCO$_3$ (1 × 7 mL) and brine (1 × 7 mL), dried (anhydrous MgSO$_4$) and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes–EtOAc (4 : 1) afforded the *title compound* **17a** (66 mg, 93%) as a colourless oil (Found: C, 71.63; H, 6.91; N, 6.56. $C_{13}H_{15}NO_2$ requires C, 71.87; H, 6.96; N, 6.45%); ν_{max} 3382, 2923, 2860, 1612, 1457, 1393, 1363, 1173, 1142, 1076, 1036, 996, 888, 852, 813, 575 cm^{-1}; δ_H 1.20 (1H, br s, OH), 2.15 (6H, s, *o*′,*o*′-MesCH$_3$), 2.33 (3H, s, *p*-MesCH$_3$), 4.87 (2H, s, CH$_2$O), 6.21 (1H, s, H4), 6.95 (2H, s, 2 × MesH); δ_C 20.1 (2 × CH$_3$), 21.0 (CH$_3$), 56.3 (CH$_2$O), 103.2 (C4), 125.7 (C), 128.3 (2 × CH), 137.0 (2 × C), 138.9 (C), 162.1 (C3), 171.7 (C5); *m*/*z* 217 (M$^{+\bullet}$, 64%), 205 (3), 186 (100), 171 (13), 143 (26), 131 (17), 119 (22), 115 (21), 103 (12), 91 (30), 77 (19), 65 (9), 53 (6); Found 217.0658. $C_{13}H_{15}NO_2$ (M$^{+\bullet}$) requires 217.0653.

4-Hydroxymethyl-3-nonyl-2-isoxazoline 16b and 4-hydroxymethyl-3-nonylisoxazole 18

Sodium borohydride (186 mg, 4.92 mmol) was added over 15 min to a solution of the isoxazole **3d** (83.0 mg, 0.328 mmol) in dry EtOH (17 mL) at 0–5 °C (ice bath). After heating at reflux for 24 h, the reaction mixture was cooled to 0–5 °C (ice bath) and quenched by dropwise addition of 1 M HCl (to pH 2). The solvent was evaporated under reduced pressure, the residue was taken up in Et$_2$O (10 mL) and the solution was washed with H$_2$O (7 mL). The aqueous phase was extracted with Et$_2$O (3 × 10 mL). The combined organic solutions were washed with H$_2$O (2 × 7 mL) and brine (1 × 7 mL), dried (anhydrous MgSO$_4$) and evaporated *in vacuo*. Flash column chromatography of the residue, eluting with hexanes–EtOAc (7 : 3) afforded the *title compounds* **16b** (54 mg, 73%) as a colourless oil (Found: C, 68.67; H, 11.38; N, 5.85. $C_{13}H_{25}NO_2$ requires C, 68.68; H, 11.08; N, 6.16%); ν_{max} 3400, 2926, 2854, 1466, 1378, 1095, 1043, 929, 873, 722 cm^{-1}; δ_H 0.88 (3H, t, *J* 6.7, C*H*$_3$CH$_2$), 1.20–1.40 (10H, m, 5 × CH$_2$), 1.50–1.71 (5H, m, 2 × CH$_2$ and OH), 2.26 (1H, m, CH$_2$), 2.45 (1H, m, CH$_2$), 3.39 (1H, m, H4), 3.78 (2H, m, CH$_2$O), 4.26 (2H, m, H5 and H5′); δ_C 14.1 (CH$_3$), 22.6 (CH$_2$), 26.1 (CH$_2$), 26.5 (CH$_2$), 29.1 (CH$_2$), 29.2 (CH$_2$), 29.3 (CH$_2$), 29.4 (CH$_2$), 31.8 (CH$_2$), 52.4 (C4), 61.0 (CH$_2$O), 71.0 (C5), 159.9 (C3); *m*/*z* 227 (M$^{+\bullet}$, 26%), 210 (5), 196 (16), 180 (13), 156 (5), 140 (6), 128 (61), 115 (100), 108 (9), 98 (15), 85 (25), 69 (20), 55 (29); Found 227.1882. $C_{13}H_{25}NO_2$ (M$^{+\bullet}$) requires 227.1885; and **18** (13 mg, 18%) as a colourless oil (Found: C, 69.68; H, 10.54; N, 6.15. $C_{13}H_{23}NO_2$ requires C, 69.29; H, 10.29; N, 6.22%; ν_{max} 3400, 2926, 2854, 1609, 1465, 1417, 1117, 1020, 873 cm^{-1}; δ_H 0.88 (3H, t, *J* 7.0, C*H*$_3$CH$_2$), 1.18 (13H, m, 6 × CH$_2$ and OH), 1.71 (2H, quintet, *J* 7.7, CH$_2$), 2.71 (2H, t, *J* 7.7, CH$_2$), 4.58 (2H, s, CH$_2$O), 8.30 (1H, s, H5); δ_C 14.1 (CH$_3$), 22.7 (CH$_2$), 24.9 (CH$_2$), 27.7 (CH$_2$), 29.2 (CH$_2$), 29.3 (CH$_2$), 29.5 (CH$_2$), 29.7 (CH$_2$), 31.9 (CH$_2$), 53.9 (CH$_2$O), 118.4 (C4), 156.1 (C5), 162.0 (C3); *m*/*z* 225 (M$^{+\bullet}$, 4%), 208 (9), 196 (6), 182 (7), 154 (8), 136 (14), 126 (57), 113 (100), 98 (8), 85 (11), 69 (8), 55 (19); Found 225.1727. $C_{13}H_{23}NO_2$ (M$^{+\bullet}$) requires 225.1729.

5-Hydroxymethyl-3-nonylisoxazole 17b

Using the procedure described above for the reduction of the isoxazole **3d**, reaction of sodium borohydride (224 mg, 5.93 mmol) and 3-nonylisoxazole-5-carboxylic acid methyl ester **4d** (100 mg, 0.395 mmol) followed by flash column chromatography of the residue, eluting with hexanes–EtOAc

(7 : 3) afforded the *title compound* **17b** (82 mg, 92%) as a colourless solid, mp 34–35 °C (Found: C, 69.35; H, 10.01; N, 6.08. $C_{13}H_{23}NO_2$ requires C, 69.29; H, 10.29; N, 6.22%); ν_{max} 3368, 2928, 2856, 1669, 1134, 1071, 999, 802 cm^{-1}; δ_H 0.89 (3H, t, *J* 6.8, CH_3CH_2), 1.38–1.42 (12H, m, 6 × CH_2), 1.50–1.75 (3H, m, CH_2 and OH), 2.67 (2H, t, *J* 7.3, CH_2), 4.76 (2H, s, CH_2O), 6.11 (1H, s, H4); δ_C 14.0 (CH_3), 22.6 (CH_2), 25.9 (CH_2), 28.2 (CH_2), 29.1 (CH_2), 29.2 (2 × CH_2), 29.4 (CH_2), 31.8 (CH_2), 56.1 (CH_2O), 101.4 (C4), 164.2 (C3), 171.3 (C5); *m/z* 225 ($M^{+\bullet}$, 4%), 194 (34), 182 (6), 168 (7), 154 (3), 140 (5), 126 (44), 96 (13), 82 (11), 68 (11), 55 (20); Found 225.1727. $C_{13}H_{23}NO_2$ ($M^{+\bullet}$) requires 225.1729.

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