Explorations of an intramolecular route to pyrrolo[3,4-*b*]isoxazoles: an unexpected retro-Claisen reaction

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Abstract

Potential precursors have been prepared for intramolecular 1,3-dipolar cycloaddition to form a pyrrolo[3,4-*b*]isoxazole. The cycloaddition has not to date been accomplished, however an unexpected retro-Claisen reaction is reported.

Keywords: Acetoacetylation, nitro amine, aza-Henry reaction, retro-Claisen reaction, urea

Introduction

We have reported over a number of years on synthetic approaches to the 3-acyltetramic acid group of metabolites, which display an N-heterocyclic enolised tricarbonyl core, as illustrated in general structure **1** (Figure 1).[1] These metabolites show a range of biological activities, ranging through antibiotic, antitumour, antifungal and antiviral;[2] they also have a relationship to the inducers of bacterial quorum sensing.[3] Over recent years we have focussed on pyrroloisoxazoles **2** and **3** as providing masked forms of the polar enol functionality in the acyltetramic acids.[4-6]

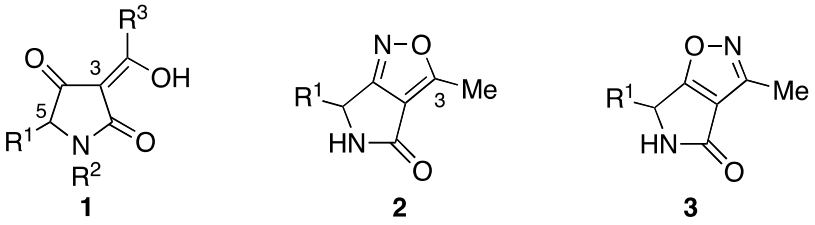
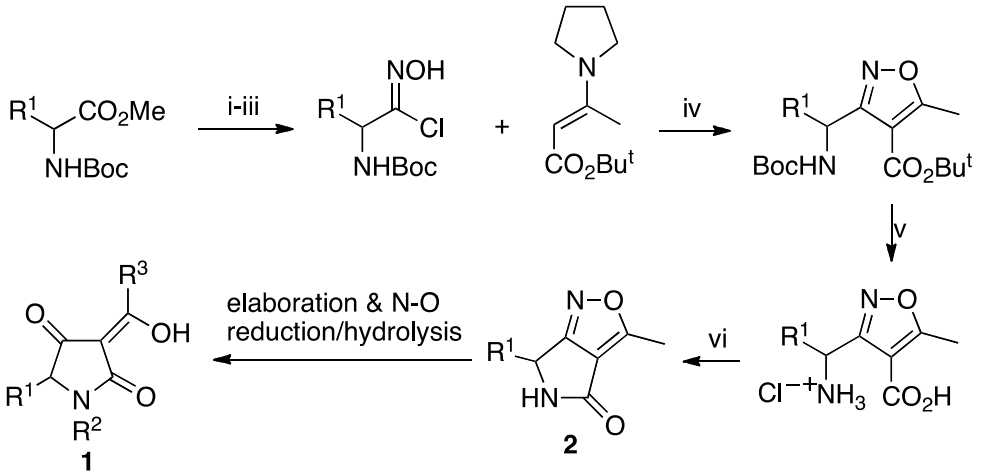


Figure 1. General structure of 3-acyltetramic acids **1**, and pyrroloisoxazole masked forms **2** & **3**.

Most recently we have reported on our 2nd generation approach that employs the 5,6-dihydropyrrolo[3,4-*b*]isoxazol-4-one building block **2** through the route shown in Scheme 1, which involves the 1,3-dipolar cycloaddition of an amino acid-derived nitrile oxide dipole with a β-ketoester enamine as dipolarophile.[5] One of the less efficient steps in this sequence is the ring

closure (lactam formation) of 3-(1-aminoalkyl)-5-methylisoxazole-4-carboxylates to complete the pyrroloisoxazole framework **2**. We were interested to investigate whether this sequence could be improved by reversing the order of N1-C2 bond formation and cycloaddition, making the amide bond first, which would also have the possible benefit of making the cycloaddition intramolecular. We report here our efforts to date, which generated an intermediate having a nitro group as dipole precursor and a β-keto amide as dipolarophile precursor, but revealed an unexpected retro-Claisen reaction on attempting to generate the dipolarophile.

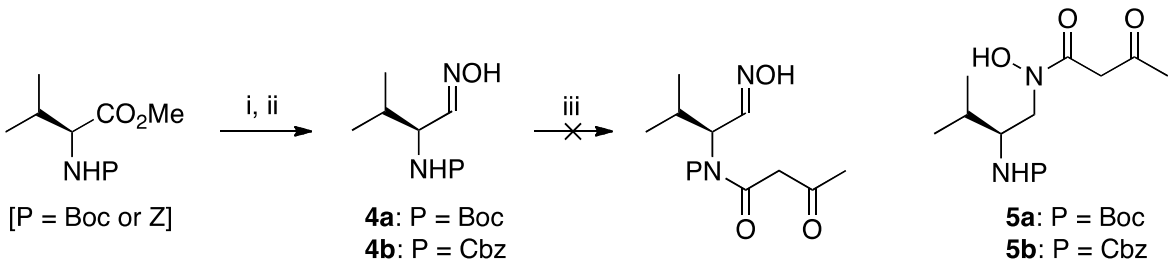


Scheme 1. 2nd Generation isoxazole route to acyltetramic acids. *Reagents*: i, DIBAL-H, toluene, –78 °C; ii, $NH_2OH.HCl$, NaOAc, EtOH aq., 70 °C; iii, *N*-chlorosuccinimide, $CHCl_3$, reflux; iv, Et_3N; v, TFA, 20 °C; 2M HCl; vi, EDCI, *N*-hydroxysuccinimide, DMF, 0→20 °C.

Results and Discussion

As the desired dipolarophile in the cycloaddition is an enamine prepared from a β-keto acid derivative, an obvious initial approach based on intermediates we had in hand was N-acetoacetylation of an amino acid-derived oxime. The nitrile oxide dipole would be prepared from the aldoxime via C-chlorination and 1,3-dehydrochlorination. Using valine as our test amino acid scaffold, the aldoxime **4a** was prepared from *N*-*tert*-butyloxycarbonyl-*S*-valine methyl ester (DIBAL-H, toluene, –78 °C, 2 h; then $NH_2OH.HCl$, NaOAc, EtOH aq, 70 °C, 10 min) in 89% yield as a 2:1 mixture of geometric isomers (Scheme 2). Acetoacetylation was attempted using 2,2,6-trimethyl-1,3-dioxin-4-one, the diketene-acetone adduct (PPTS, toluene reflux, 3 h).[7] The results were inconsistent, with product ^{1}H NMR spectra sometimes showing loss of the *tert*-butyloxycarbonyl group and sometimes not. Samples retaining the *tert*-butyloxycarbonyl group had ^{1}H NMR spectra that implied acylation of the oxime N-atom rather than the amine function, with a signal for the proton N*H*Boc being observed at δ 4.62 (1H, d, *J* 9.6 Hz). More surprisingly, the NMR spectra suggested the reduced structure **5a**, having an

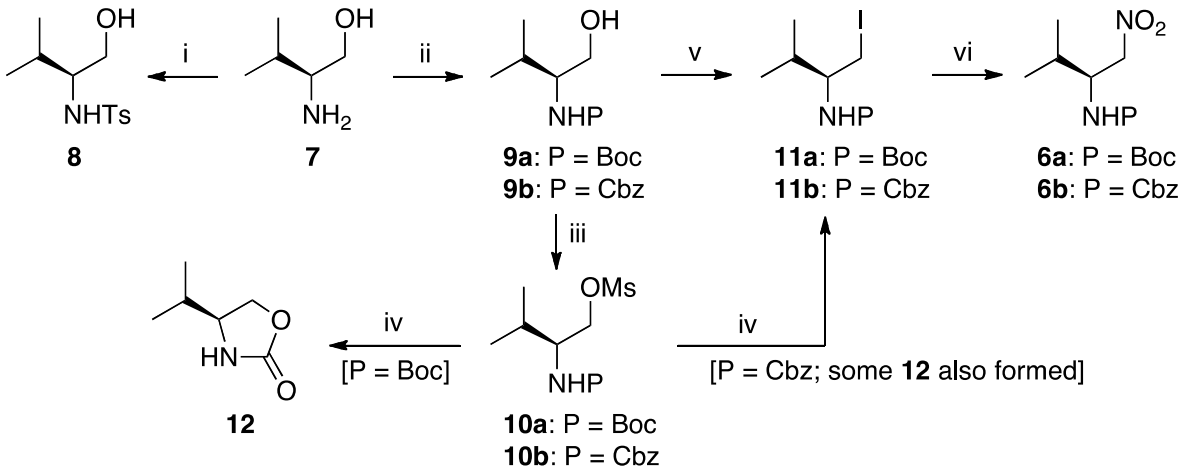
unexpected additional CH_2N signal (δ_H 4.11-4.24, 2H, m; δ_C 65.6) and no oxime sp^2-CHN signals, although we were unable to fully characterise this material. A test with $FeCl_3$ supported the assignment of a hydroxamate structure.[8] The capricious behaviour in the thermolysis led us to switch to the corresponding *N*-benzyloxycarbonyl aldoxime **4b**, prepared from *N*-benzyloxycarbonyl-*S*-valine methyl ester as outlined above for the *tert*-butyloxycarbonyl compound **4a**. Thermolysis with the diketene-acetone adduct, however, again gave a product assigned as the hydroxamate **5b**, showing δ_H 3.62-3.68 (1H, m, C*H*NHZ), 4.07-4.17 (2H, m, CHC*H*$_2$N), 4.62 (1H, d, *J* 9.6 Hz, CHN*H*Z), δ_C 67.0 (*C*H_2N), and no oxime CH signal. Again, full characterisation could not be accomplished. A redox process is clearly implicated alongside these acylations, but we are unable to identify the reducing agent. Changing the acetoacetylating agent to the more reactive diketene but omitting the acid (toluene reflux, 3 h) led to the same presumed hydroxamates **5a,b** from the aldoximes **4a,b**, respectively.



Scheme 2. Attempted acetoacetylation of α-amino oximes. *Reagents*: i, DIBAL-H, toluene, –78 °C; ii, $NH_2OH.HCl$, NaOAc, EtOH aq., 70 °C; iii, 2,2,6-trimethyl-1,3-dioxen-4-one, $pyrH^+{}^-OTs$, toluene reflux; or diketene, toluene reflux.

These results led us to avoid the oxime as a precursor functional group for the nitrile oxide dipole. Instead we targeted the dehydration of a primary nitro group as the route to the nitrile oxide. Our target thus became an N-protected *S*-2-methyl-1-nitromethyl-1-propanamine **6a** or **6b** (Scheme 3), which could be N-acetoacetylated. Thus *S*-valinol **7** (prepared by reduction of *S*-valine: TMSCl, $NaBH_4$, THF, 0 °C, 24 h;[9] 78%) was selected as starting material. A good leaving group was now needed at the alcohol function for substitution to generate a primary nitro group, but attempted toluene-4-sulfonylation (TsCl, DCM, 0→20 °C, 17 h) unsurprisingly afforded the N-sulfonylated compound **8** (100%) rather than the desired O-sulfonylated compound. Thus *S*-valinol **7** was N-protected as the *tert*-butyloxycarbonyl derivative **9a** (Boc_2O, Et_3N, DCM, 0→20 °C, 17 h; 100%) and benzyloxycarbonyl derivative **9b** ($PhCH_2OCOCl$, $NaHCO_3$, EtOAc-H_2O, 0→20 °C, 17 h; 90%). The corresponding mesylate derivatives **10a** and **10b** were formed by a standard method (methanesulfonyl chloride, Et_3N, DCM, 0→20 °C, 4 h) in crude yields of over 90%. Attempts to use these crude materials in a nucleophilic substitution with nitrite were unsuccessful ($NaNO_2$, toluene or DMF, 0→60 °C, 17 h) with the alcohols **9a** and **9b** being recovered after aqueous workup. The mesylates were instead treated under Finkelstein conditions (NaI, acetone reflux, 17 h) in an attempt to generate the corresponding

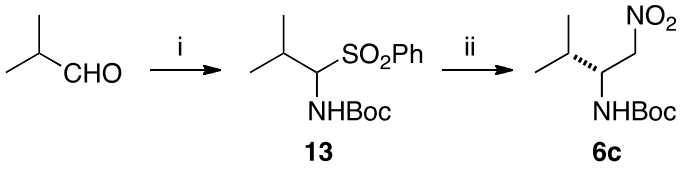
iodo compounds **11a** and **11b**, respectively. The *N*-*tert*-butyloxycarbonyl derivative **10a** however, underwent protecting group cleavage to afford the cyclic carbamate **12**; the N-benzyloxycarbonyl compound **10b** did give the iodo compound **11b** (42%) along with some cyclic carbamate **12** (7%). It is assumed that anchimeric assistance by the N-protecting group carbonyl oxygen atom is followed by loss of a carbenium ion (to afford the cyclic carbamate) competing with iodide nucleophilic attack. In an alternative direct iodination from alcohol **9a**, iodotriphenylphosphonium iodide was prepared (triphenylphosphine, iodine, DCM) to which imidazole and alcohol **9a** was added and the mixture heated under reflux for 17 h to afford the iodide **11a** (31% after chromatography). The yield and product purification was improved by replacing the triphenylphosphine with a polymer-supported triphenylphosphine,[10] to afford the iodides **11a** (43%) and **11b** (80%) from the corresponding alcohols **9a** and **9b**, respectively. Traces of the cyclised by-product **12** were sometimes observed in these reactions. The nitro substitution was undertaken with the iodo compounds, now using sodium nitrite in DMF (20 °C, 20 h) with the addition of phloroglucinol and urea to minimize the formation of nitrite ester.[11] The corresponding *N*-*tert*-butyloxycarbonyl and *N*-benzyloxycarbonyl *S*-2-methyl-1-nitromethylpropanamines **6a** (64%) and **6b** (70%) were isolated along with small recoveries of the corresponding alcohols **9a** or **9b**.



Scheme 3. Preparation of protected *S*-2-methyl-1-nitromethylpropanamines **6**. *Reagents*: i, TsCl, DCM, 0→20 °C; ii, For **9a**: Boc_2O, Et_3N, DCM, 0→20 °C. For **9b**: $PhCH_2OCOCl$, $NaHCO_3$, EtOAc-H_2O, 0→20 °C; iii, MsCl, Et_3N, DCM, 0→20 °C; iv, NaI, acetone reflux; v, PS-PPh_3, I_2; then imidazole; vi, $NaNO_2$, DMF, phloroglucinol, urea, 20 °C.

This route to optically active N-protected *S*-2-methyl-1-nitromethylpropanamines was complemented by a reported approach to the N-*tert*-butyloxycarbonyl *R*-compound **6c** via the aza-Henry reaction (Scheme 4).[12] Thus, sodium benzenesulfinate in water was added to *tert*-butyl carbamate (THF, 20 °C), followed by 2-methylpropanal and methanoic acid. After 17 h, the white precipitate was recrystallized to afford the sulfone **13** (75%). Reaction with

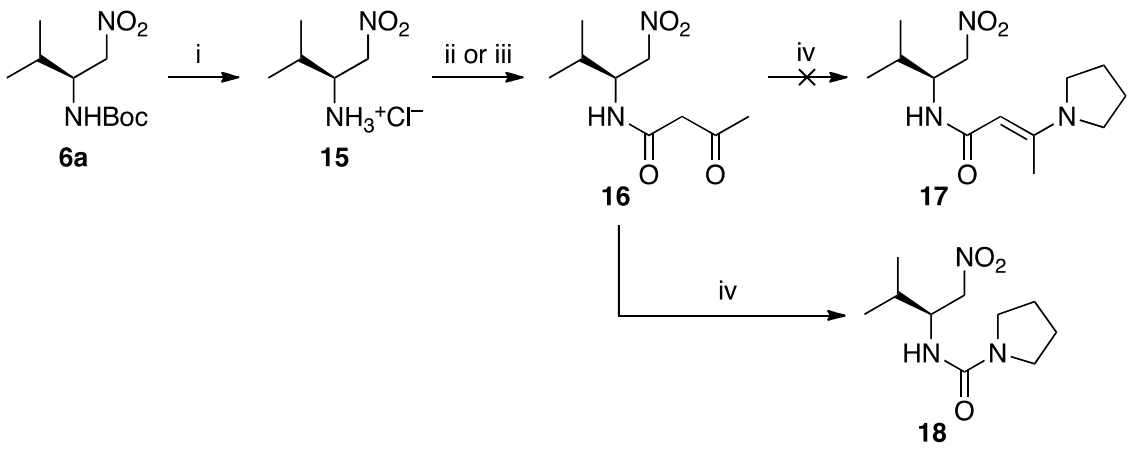
nitromethane in the presence of potassium hydroxide (toluene, –78→20 °C, 48 h) and catalytic benzylquininium chloride led to the nitro compound **6a** (72%). Replacing potassium by cesium hydroxide led to incomplete reaction after 48 h, in contrast to one of the earlier reports. The nitro compound prepared by this route was formed highly stereoselectively, whereas the route from *S*-valine was stereospecific.



13 **6c**

Scheme 4. Alternative preparation of *R*-nitromethylpropanamine **6a**. *Reagents*: i, $BocNH_2$, $PhSO_2Na$, THF aq., 20 °C; ii, $MeNO_2$, KOH, benzylquininium chloride (12 mol %), toluene, –78→20 °C, 48 h.

The next step was N-acetoacetylation of the amino-nitro compound **6a**, which was initially attempted as described earlier, using thermolysis of the diketene-acetone adduct (pyridinium toluene-4-sulfonate, toluene reflux, 3 h), but starting material was recovered. As an alternative acylating agent we employed S-*tert*-butyl 3-oxobutanthioate **14**, itself generated by base treatment of 2-methylpropane-2-thiol (NaH, THF, –15→0 °C) followed by addition of diketene to the thiolate at –5 °C.[13] Thus amino-nitro compound **6a** and the thioester **14** were reacted in the presence of silver(I) trifluoroacetate (THF in the dark) but starting carbamate **6a** was recovered.[14] We reasoned this was due to reduced nucleophilicity of the carbamate N-atom, so we removed the *tert*-butyloxycarbonyl group (TFA, followed by 2M hydrochloric acid) to afford the stable amine hydrochloride salt **15** (Scheme 5). Acylation was completed using both protocols described above, to afford the acetoacetamide **16** (68% from diketene-acetone adduct; just 19% from thioester **14**). The precursor functionality for generation of the required dipole (nitrile oxide from dehydration of the primary nitro group) and dipolarophile (enamine derived from the β-ketoamide) is present in the acetoacetamide **16**. The next step was planned to be the enamine formation, so the amide **16** was treated with pyrrolidine in toluene at reflux under Dean-Stark water removal conditions. After workup, a product was recovered (55%) but the ^1H NMR spectrum was missing the CH_3 and CH signals expected for the enamine **17**, although it did show signals for the pyrrolidine ring. The structure was revealed by an X-ray crystal structure determination to be the unexpected mixed urea **18** (Figure 2). The solid-state structure displays two independent molecules in the asymmetric unit, differing in the detailed conformation of the pyrrolidine sub-unit and linked via a strong N–H···O hydrogen bond.[15]



Scheme 5. Attempted enamine formation from acetoacetamide **16**. *Reagents*: i, TFA, 20 °C, 4.5 h, then 2M HCl aq., 20 °C, 0.5 h; ii, Et_3N, DCM, then 2,2,6-trimethyl-1,3-dioxin-4-one, $pyrH^{+}–OTs$, toluene reflux; iii, Et_3N, DCM, then $MeCOCH_2COSBu^t$ **14**, CF_3CO_2Ag, THF, –15 °C, 30 min; iv, pyrrolidine, toluene, Dean-Stark reflux.

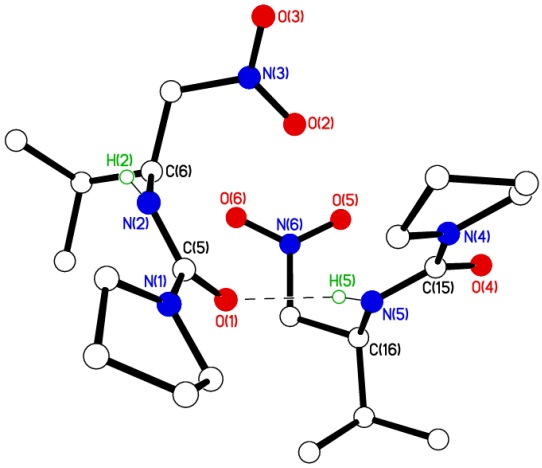
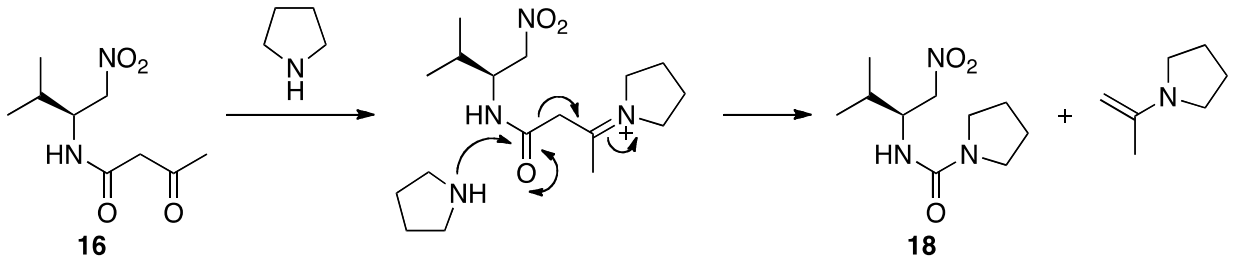


Figure 2. X-Ray crystal structure of mixed urea **18**. The structure comprises two independent molecules differing in conformation of the pyrrolidine unit. N(5)–H(5)···O(1): d(D...A) = 2.917(2) Å, <(DHA) = 155(2)°; N(2)–H(2)...O(4'): d(D...A) = 2.889(2) Å, <(DHA) = 160(2)°, generating chains parallel to *b;* ' = –x,y+1/2,–z+1/2.

We propose the mechanism shown in Scheme 6 wherein the iminium ion formed *en route* to the desired enamine **17**, or in equilibrium with it, is attacked by a second pyrrolidine molecule to promote a retro-Claisen reaction, affording the observed urea and presumably the pyrrolidine enamine of propanone as an unusual leaving group, although this was not isolated.



Scheme 6. Possible mechanism for formation of mixed urea **18**.

An alternative potential sequence towards an intramolecular dipolar cycloaddition would be nitrile oxide formation and then cycloaddition to the enol form of the β-keto amide. With this in mind we treated the nitro compound **16** under several reported dehydration conditions: di-*tert*-butyl dicarbonate[16] or ethyl chloroformate[17] (Et_3N, 0.1 mol equiv. 4-DMAP, in DCM, acetonitrile or toluene at reflux), but in all cases starting material was recovered unchanged. Likewise, an attempt to form a silyl nitronate as dipole (TMSCl, Et_3N, in THF or acetonitrile at reflux) returned starting nitro-amide **16**.

Conclusions

In conclusion, based on these explorations we have not been able to form the isoxazole building block **2** via an intramolecular approach , and continued to focus instead on developing the pyrroloisoxazole strategy towards masked acyltetramic acids via the previously reported intermolecular sequence.

Experimental Section

General. Commercial dry solvents were used in all reactions except for light petroleum and EtOAc, distilled from $CaCl_2$, and CH_2Cl_2 distilled over P_2O_5. THF was distilled from sodium and benzophenone. Light petroleum refers to the b.p. 40-60 °C fraction. Sodium hydride was obtained as 60% dispersion in oil and washed with light petroleum. Melting points were determined on a Leica Galen III hot stage apparatus. ^1H (250 MHz), ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on Bruker AC-250 or AC-400 spectrometers in $CDCl_3$ solutions with Me_4Si or $(CD_3)_2SO$ as internal standard unless otherwise specified. Chemical shifts δ are given in parts per million (ppm) and ^1H coupling constants *J* in Hz, with multiplicities: s (singlet), d (doublet), t (triplet) and m (multiplet). Mass spectra were recorded on a JEOL SX102 spectrometer, or carried out by the EPSRC National Mass Spectrometry Service Centre (Swansea) or on a ZQ2000 spectrometer with Waters 600 series liquid handling system, dual wavelength UV and ELS detectors at Novartis, Horsham UK. MicroMass LCT was detected

using a TOF spectrometer with Agilent 1100 series HPLC and Gilson 215 liquid handling; diode array and CAD detectors; Platform LC spectrometers with Agilent 1100 series HPLC diode array and ELS detectors; ThermoElectron LTQ Linear Quadrupole Ion Trap MS with ESI probe and APCI source were used for MS/MS; ThermoElectron DSQ MS with TRACE GC, at Novartis. GCMS was carried out on a Fisons 8000 series instrument using a 15 m x 0.25 mm DB-5 column and an EI low resolution MS at Novartis. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates, in the range 4000–600 cm^{-1}. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance, or on a LECO CHNS-932 Analyser, at Novartis. TLC using silica gel as absorbent was carried out on aluminium backed plates coated with silica gel (Merck Kieselgel 60 F_{254}), and TLC using alumina as absorbent was carried out on aluminium backed plates coated with neutral aluminium oxide (Merck 150 F_{254}, Type T). Silica gel (Merck Kieselgel 60 H silica) was used for column chromatography unless otherwise specified. Column chromatography using alumina was carried out with Aldrich aluminium oxide, activated neutral, Brockmann 1, STD Grade, 150 mesh sizes. Preparative TLC was carried out using aluminium oxide (Merck 60 F_{254}, Type E).

***S*-2-*tert*-Butyloxycarbonylamino-3-methylbutanaldoxime (4a).** DIBAL-H (1.0M in toluene, 22 mL, 21.73 mmol) was added dropwise over 1 h to a suspension of *N*-*tert*-butyloxycarbonylamino-*S*-valine methyl ester (2.0 g, 8.69 mmol) in dry toluene (10 mL) under nitrogen with stirring at –78 °C. After stirring the reaction mixture at –78 °C. for a further 30 min, MeOH (approx. 7 mL) was added to the mixture and it was poured into a solution of Rochelle salt (50 g) in water (100 mL) and stirred vigorously for 2 h. The aqueous phase was separated, extracted with EtOAc (3 x 50 mL), and the combined organic layers were washed with saturated brine (2 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield *S*-2-*tert*-butyloxycarbonylamino-3-methylbutanal (2.0 g, 100%) as a colourless oil that was used directly, IR (ν_{max}, $CHCl_3$/cm^{-1}), 3350, 2967, 2931, 1700, 1367, 1248, 1044, 1019. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 0.94-1.04 (6H, 2 x d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.45 (9H, s, C(CH_3)$_3$), 2.25-2.32 (1H, m, C*H*(CH_3)$_2$), 4.24-4.28 (1H, m, C*H*NH), 5.14-5.21 (1H, d, *J* 8, CHN*H*), 9.64 (1H, broad, CHO). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 17.6, 18.9 (CH(*C*H_3)$_2$), 28.4 (C(*C*H_3)$_3$), 29.0 (*C*H(CH_3)$_2$), 64.7 (CHNH), 78.9 (*C*(CH_3)$_3$), 155.9 (OCONH), 200.5 (CHO).

To the crude aldehyde (1.5 g, 6.94 mmol) in EtOH (10 mL) was added hydroxylamine hydrochloride (0.96 g, 13.88 mmol) and NaOAc (2.28 g, 27.76 mmol) in water (10 mL). A few drops of EtOH were added to dissolve the precipitate and the solution was warmed to 70 °C for 10 min, cooled and stored in a refrigerator overnight. The white precipitate formed was filtered. The remaining mixture was extracted with EtOAc (3 x 70 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to yield the *title compound* **4a** (1.34 g, 89%) as a white solid, *syn*:*anti* 2:1, m.p. 117-124 °C, $[\alpha]_D^{20}$ +23.4 (*c* 12.8, MeOH), IR (ν_{max} Nujol/cm^{-1}), 3342, 2955, 1722, 1682, 1459, 1376, 1312, 1016. ^{1}H NMR (400 MHz; (CD_3)$_2$SO), δ_H 0.77-.0.83 (6H, 2 x d, *J* 7.2, CH(C*H*$_3$)$_2$), 1.37 (9H, s, C(CH_3)$_3$), 1.72-1.78 (1H, m,

C*H*(CH_3)$_2$), 4.50-4.58 (1H, dd, *J* 8, 14, C*H*NH), 6.50-6.52 (1H, d, *J* 8, C*H*NOH), 6.98-7.01 (1H, d, *J* 14, CHN*H*), 10.9 (1H, s, OH). ^{13}C NMR (100 MHz; (CD_3)$_2$SO), δ_C 18.6, 18.7 (CH(*C*H_3)$_2$), 28.2 (C(*C*H_3)$_3$), 39.4 (*C*H(CH_3)$_2$), 50.2 (*C*HNH), 79.0 (*C*(CH_3)$_3$), 149.9 (CHN), 155.2 (OCONH). HRMS: Calcd for $C_{10}H_{20}N_2O_3$: MH^+ 215.1547; found: MH^+, 217.1557. Anal. Calcd for $C_{10}H_{20}N_2O_3$: C, 55.53; H, 9.32; N, 12.95%, Found: C, 55.51; H, 9.14; N, 13.01%.

***S*-2-Benzyloxycarbonylamino-3-methylbutanaldoxime (4b).** Prepared by the same method as oxime **4a** but using *N*-benzyloxycarbonylamino-*S*-valine methyl ester (18.3 g, 68.98 mmol) in dry toluene (100 mL) and DIBAL-H (1.0M in toluene, 173 ml, 172.4 mmol), and worked-up using MeOH (15 mL), Rochelle salt (150 g) in water (300 mL) to afford 2-benzyloxycarbonylamino-3-methylbutanal (17.0 g, 100%) as a colourless oil that was used directly. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 0.92-1.03 (6H, 2 x d, *J* 6.8, CH(C*H*$_3$)$_2$), 2.27-2.35 (1H, m, C*H*(CH_3)$_2$), 4.31-4.34 (1H, dd, *J* 4.4, 7.8, C*H*NH), 5.11 (2H, s, C*H*$_2$Ph), 5.46-5.47 (1H, d, *J* 7.8, CHN*H*), 7.26-7.36 (5H, m, Ar-H), 9.62 (1H, s, CHO). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 17.5, 18.9 (CH(*C*H_3)$_2$), 29.0 (*C*H(CH_3)$_2$), 65.0 (CHNH), 65.8 (*C*H_2Ph), 128.2, 128.4, 128.5 (Ar-CH), 136.1 (Ar-C), 156.4 (OCONH), 199.9 (CHO).

The crude aldehyde (16.2 g, 68.85 mmol) was treated with hydroxylamine hydrochloride (9.57 g, 137.71 mmol), NaOAc (22.59 g, 275.41 mmol) in water (50 mL) and worked up to afford the *title compound* **4b** (16.8 g, 97%) as a white solid, *syn*:*anti* 2:1, mp 124-126 °C, $[\alpha]_D^{20}$ +26 (*c* 10, MeOH). ^{1}H NMR (400 MHz; (CD_3)$_2$SO), δ_H 0.83-0.87 (6H, 2 x d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.73-1.82 (1H, m, C*H*(CH_3)$_2$), 4.58-4.63 (1H, ddd, *J* 7.0, 8.8, 15.6, C*H*NH), 5.02 (2H, s, C*H*$_2$Ph), 6.53-6.55 (1H, d, *J* 7.0, CHN*H*), 7.31-7.39 (5H, m, Ar-H), 7.45-7.48 (1H, d, *J* 8.8, C*H*NH), 10.98 (1H, s, OH). ^{13}C NMR (100 MHz; (CD_3)$_2$SO), δ_C 18.2, 18.7 (CH(*C*H_3)$_2$), 30.5 (*C*H(CH_3)$_2$), 50.7 (CHNH), 65.3 (*C*H_2Ph), 127.7, 127.8 128.3 (Ar-CH), 137.1 (Ar-C), 149.6 (CHN), 156.0 (OCONH). HRMS: Calcd for $C_{13}H_{18}N_2O_3$: M^+ 250.1317; found: M^+ 250.1310.

Attempted N-acylation of *S*-2-*tert*-butyloxycarbonylamino-3-methylbutanaldoxime (4a). *S*-2-*tert*-Butyloxycarbonylamino-3-methylbutanaldoxime (0.2 g, 0.93 mmol) **4a** was added to 2,2,6-trimethyl-1,3-dioxin-4-one (145 mg, 133 μL, 1.02 mmol) in dry toluene (20 mL) and followed by PPTS (256 mg, 1.02 mmol). The mixture was heated under reflux for 3 h and then concentrated under reduced pressure. The residue was partitioned between EtOAc (30 mL) and water (30 mL) and the aqueous phase extracted with EtOAc (2 x 30 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was subjected to column chromatography eluting with light petroleum : EtOAc (1:3 v/v) to yield an orange oil (94.4 mg) identified as *S*-(1-hydroxy-3-oxobutanoylaminomethyl-2-methylpropyl)carbamic acid *tert*-butyl ester **5a** based on its ^{1}H NMR spectrum. A test with $FeCl_3$ supported the assignment of a hydroxamate structure, but complete characterization was not possible. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 0.93-0.97 (6H, 2 x d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.44 (9H, s, C(CH_3)$_3$), 1.77-1.82 (1H, m, C*H*(CH_3)$_2$), 2.28 (3H, s, CH_3CO), 3.49 (2H, s, CH_2), 3.66-3.68 (1H, m, C*H*NH), 4.11-4.24 (2H, m, CHC*H*$_2$), 4.59-4.64 (1H, d, *J* 9.6 Hz, CHN*H*). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 18.4, 19.4 (CH(*C*H_3)$_2$), 28.4 (C(*C*H_3)$_3$), 30.1 (*C*H(*C*H_3)$_2$), 30.2 (*C*H_3CO), 49.9 (CH_2), 54.6 (CHNH), 65.6 (CH_2), 79.9 (*C*(CH_3)$_3$), 155.8 (OCONH), 167.1 (CONOH), 200.6 (CH_3*C*O).

Attempted N-acylation of *S*-2-benzyloxycarbonylamino-3-methylbutanaldoxime (4b).
Method A. Performed by the same method as for *S*-2-*tert*-butyloxycarbonylamino-3-methylbutanaldoxime **4a** but using 2-benzyloxycarbonylamino-3-methylbutanaldoxime **4b** (200 mg, 0.80 mmol), 2,2,6-trimethyl-1,3-dioxin-4-one (125 mg, 115 μL, 0.88 mmol), dry toluene (20 mL) and PPTS (221 mg, 0.88 mmol) to yield an orange oil (53.8 mg) identified as *S*-(1-hydroxy-3-oxobutanoylaminomethyl-2-methylpropyl)carbamic acid benzyl ester **5b** based on its ^{1}H NMR spectrum. A test with $FeCl_3$ supported the assignment of a hydroxamate structure, but complete characterization was not possible. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 0.83-0.87 (6H, 2 x d, *J* 7.2, CH(C*H*$_3$)$_2$), 1.69-1.76 (1H, m, C*H*(CH$_3$)$_2$), 2.14 (3H, s, CH$_3$CO), 3.34 (2H, s, CH$_2$), 3.62-3.68 (1H, m, C*H*NH), 4.07-4.17 (2H, m, CHC*H*$_2$), 4.94-4.96 (1H, d, *J* 9.6, CHN*H*), 5.02 (2H, s, C*H*$_2$Ph), 7.22-7.29 (5H, m, Ar-H). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 18.5, 19.4 (CH(*C*H$_3$)$_2$), 29.6 (*C*H(CH$_3$)$_2$), 30.4 (CH$_3$), 49.9 (CH$_2$), 55.4 (CHNH), 67.0 (CH$_2$), 68.1 (*C*H$_2$Ph), 128.3, 128.5, 128.8 (Ar-CH), 136.6 (Ar-C), 156.4 (OCONH), 172.4 (CONOH), 200.6 (CH$_3$*C*O).
Method B. Performed as Method A but using 2-benzyloxycarbonylamino-3-methylbutanaldoxime **4b** (500 mg, 2.00 mmol) and diketene (180 mg, 160 μL, 2.10 mmol) in dry toluene (20 mL) to yield a yellow oil (94.6 mg) whose NMR data were identical to a sample prepared by Method A above.
***S*-(1-Hydroxymethyl-2-methylpropyl)carbamic acid *tert*-butyl ester (9a).** Di-*tert*-butyl dicarbonate (2.22 g, 10.18 mmol) in CH_2Cl_2 (10 mL) was added dropwise to *S*-valinol **7** (1.0 g, 9.69 mmol) in CH_2Cl_2 (25 mL) at 0 °C. Et_3N (1.03 g, 1.42 mL, 10.18 mmol) was then added dropwise to the reaction mixture. The mixture was stirred at 20 °C for 17 h, washed with citric acid solution (1M, 50 mL) and saturated brine (2 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a colourless oil that was purified by column chromatography eluting with light petroleum : EtOAc (2:1 v/v) to yield the *title compound* **9a** (1.31 g, 66%) as a colourless oil, $[\alpha]_D^{20}$ –24.8 (c 10, $CHCl_3$), lit.[10] $[\alpha]_D^{20}$ –17 (*c* 1.68, $CHCl_3$), IR (ν_{max} $CHCl_3$/cm^{-1}), 3337, 3032, 2962, 1714, 1315, 1234, 1150. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 0.88-0.92 (6H, 2 x d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.40 (9H, s, C(C*H*$_3$)$_3$), 1.75-1.86 (1H, m, C*H*(CH$_3$)$_2$), 3.01 (1H, br, OH), 3.33-3.41 (1H, m, C*H*NH), 3.51-3.68 (1H, m, CHC*H*$_2$), 4.80-4.89 (1H, broad, CHN*H*). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 18.5, 19.5 (CH(*C*H$_3$)$_2$), 28.4 (C(*C*H$_3$)$_3$), 29.2 (*C*H(CH$_3$)$_2$), 59.2 (*C*HNH), 63.2 (CH*C*H$_2$), 79.4 (*C*(CH$_3$)$_3$), 156.8 (OCONH). HRMS: Calcd for $C_{10}H_{21}NO_3$: MH^+ 204.1594; found: MH^+ 204.1589.
***S*-(1-Hydroxymethyl-2-methylpropyl)carbamic acid benzyl ester (9b).** Benzyl chloroformate (1.82 g, 1.52 ml, 10.66 mmol) was added dropwise to a bi-phase solution of *S*-valinol **7** (1 g, 9.69 mmol) and $NaHCO_3$ (3.42 g, 40.71 mmol) in water (50 mL) and CH_2Cl_2 (50 mL) at 0 °C. The mixture was stirred for 17 h and the aqueous phase was then acidified to pH 1 with 2M hydrochloric acid and extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were washed with saturated brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a colourless oil that was purified by column chromatography eluting with light petroleum : EtOAc (2:1 v/v) to yield the *title compound* **9b** (2.06 g, 90%) as a white solid, mp 50-52 °C, $[\alpha]_D^{20}$ –20.67 (*c* 12, $CHCl_3$), IR (ν_{max} $CHCl_3$/cm^{-1}), 3322, 3031, 2963, 2875, 1700, 1541, 1235, 1177. ^{1}H

NMR (400 MHz; $CDCl_3$), δ_H 0.89-0.94 (6H, 2 x d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.80-1.87 (1H, m, C*H*(CH$_3$)$_2$), 2.96 (1H, br, OH), 2.45-2.51 (1H, m, C*H*NH), 3.58-3.68 (2H, m, CHC*H*$_2$), 5.07-5.11 (1H, m, C*H*$_2$), 5.16-5.18 (1H, d, *J* 8.8, CHN*H*), 7.27-7.36 (5H, m, Ar-H). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 18.5, 19.5 (CH(*C*H$_3$)$_2$), 29.3 (*C*H(CH$_3$)$_2$), 58.6 (*C*HNH), 63.6 (CH$_2$OH), 66.9 (*C*H$_2$Ph), 127.8, 128.2, 128.5 (Ar-CH), 136.5 (Ar-C), 157.2 (OCONH). HRMS: Calcd for $C_{13}H_{19}NO_3$: MH^+ 238.1438; found: MH^+ 238.1447.

***S*-2-*tert*-Butoxycarbonylamino-3-methylbutyl methanesulfonate (10a).** Et_3N (305 mg, 420 μL, 3.01 mmol) was added to *S*-(1-hydroxymethyl-2-methylpropyl)carbamic acid *tert*-butyl ester **9a** (510 mg, 2.51 mmol) in CH_2Cl_2 (20 mL) at 0 °C under nitrogen followed by methanesulfonyl chloride (345 mg, 233 μl, 3.01 mmol). The mixture was stirred at 20 °C for 4 h, then washed with water (30 mL), citric acid solution (1M, 30 mL) and saturated brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the *title compound* **10a** (735.1 mg, 100%) as a white solid that was used directly. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 0.93-0.99 (6H, 2 x d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.44 (9H, s, (C(C*H*$_3$)$_3$), 1.83-1.88 (1H, m, C*H*(CH$_3$)$_2$), 3.02 (3H, s, SCH$_3$), 3.59-3.63 (1H, m, C*H*NH), 4.24-4.27 (2H, m, CHC*H*$_2$), 4.64-4.65 (1H, br, CHN*H*). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 18.5, 19.4 (CH(*C*H$_3$)$_2$), 28.4 (C(*C*H$_3$)$_3$), 29.1 (*C*H(CH$_3$)$_2$), 37.4 (SCH$_3$), 58.2 (CHNH), 69.7 (CH$_2$), 79.8 (*C*(CH$_3$)$_3$), 155.6 (OCONH).

***S*-2-Benzyloxycarbonylamino-3-methylbutyl methanesulfonate (10b).** Prepared as for *S*-2-*tert*-Butoxycarbonylamino-3-methylbutyl methanesulfonate **10a** but using Et_3N (0.24 g, 0.32 mL, 2.32 mmol), *S*-(1-hydroxymethyl-2-methylpropyl)carbamic acid benzyl ester **9b** (0.5 g, 2.11 mmol) in CH_2Cl_2 (20 mL) and methanesulfonyl chloride (0.27 g, 2.32 mmol) to yield the *title compound* **10b** (0.62 g, 93%) as a white solid that was used directly. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 0.96-1.03 (6H, 2 x d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.85-1.92 (1H, m, C*H*(CH$_3$)$_2$), 2.96 (3H, s, SCH$_3$), 3.69-3.75 (1H, m, C*H*NH), 4.28-4.29 (2H, d, *J* 4.4, CHC*H*$_2$), 4.85-4.88 (1H, d, *J* 9.2, CHN*H*), 5.11-5.12 (2H, s, C*H*$_2$Ph), 7.30-7.37 (5H, m, Ar-H). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 18.5, 19.4 (CH(*C*H$_3$)$_2$), 29.1 (*C*H(CH$_3$)$_2$), 37.4 (SCH$_3$), 56.0 (CHNH), 67.0 (CH$_2$), 69.4 (*C*H$_2$Ph), 128.2, 128.3, 128.6 (Ar-C), 136.4 (Ar-C), 156.1 (OCONH).

4-(2-Propyl)oxazolidin-2-one (12). *Method A.* NaI (339 mg, 2.26 mmol) was added to *S*-2-*tert*-butoxycarbonylamino-3-methylbutyl methanesulfonate **10a** (199 mg, 0.71 mmol) in acetone (20 mL). The mixture was heated under reflux for 17 h and then concentrated under reduced pressure to leave a residue that was partitioned between EtOAc (30 mL) and water (30 mL) and the aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with sodium thiosulfate solution (10 % w/v, 30 mL), water (30 mL) and saturated brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the *title compound* **12** (162 mg, 100%) as a white solid, mp 63-65 °C (lit.[18] 67-70 °C), $[\alpha]_D^{20}$ +17.1 (*c* 12, $CHCl_3$) [lit.[18] $[\alpha]_D^{26}$ +16.5 (*c* 10.4, $CHCl_3$)]. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 0.83-0.91 (6H, 2 x d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.63-1.71 (1H, m, C*H*(CH$_3$)$_2$), 3.52-3.58 (1H, dd, *J* 6.4, 16.0, C*H*NH), 4.02-4.06 (1H, dd, *J* 6.4, 8.7, C*H*$_2$), 4.36-4.40 (1H, t, *J* 8.7, 16.0, CH$_2$), 6.26 (1H, br, CHN*H*). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 18.1, 18.5 (CH(*C*H$_3$)$_2$), 33.1 (*C*H(CH$_3$)$_2$), 58.8 (CHNH), 69.0 (CH*C*H$_2$), 160.6 (OCONH).

When the same procedure was applied to *S*-2-benzyloxycarbonylamino-3-methylbutyl methanesulfonate **10b** (64 mg, 0.2 mmol) using NaI (97 mg, 0.65 mmol) in acetone (10 mL), the *title compound* **12** (5mg, 7%) was isolated along with *S*-(1-iodomethyl-2-methylpropyl)carbamic acid benzyl ester **11b** (29.6 mg, 42%), data as reported below.

***S*-(1-Iodomethyl-2-methylpropyl)carbamic acid *tert*-butyl ester (11a).** *Method A.* Iodine (2.75 g, 10.82 mmol) was added to a suspension of polystyrene-triphenylphosphine (5.19 g, 10.33 mmol) in CH_2Cl_2 (100 mL) and the mixture stirred at 20 °C under nitrogen for 15 min. Imidazole (827 mg, 12.30 mmol) was then added and the mixture stirred for 15 min before *S*-(1-hydroxymethyl-2-methylpropyl)carbamic acid *tert*-butyl ester **9a** (1.0 g, 4.92 mmol) was added and the mixture heated under reflux for 20 h, then cooled and filtered. The filtrate was washed with sodium thiosulfate solution (10% w/v, 70 mL), water (70 mL) and saturated brine (70 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford a yellow solid (897 mg) that was purified by column chromatography eluting with light petroleum : EtOAc (2:1 v/v) to yield the *title compound* **11a** (668 mg, 43%) as a yellow solid, mp 62-65 °C (lit.[10] mp 48-51 °C), $[\alpha]_D^{20}$ –20.8 (*c* 12.5, $CHCl_3$) [lit.[10] $[\alpha]_D^{20}$ –18.7 (*c* 2.1, $CHCl_3$)], IR (ν_{max} $CHCl_3$/cm^{-1}), 3292, 2962, 2870, 1691, 1365, 1258, 1168. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 0.92-0.97 (6H, 2 x d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.45 (9H, s, C(CH$_3$)$_3$), 1.75-1.80 (1H, m, C*H*(CH$_3$)$_2$), 3.09-3.13 (1H, m, C*H*NH), 3.31-3.35 (1H, dd, *J* 4.8, 10.4, CHC*H*H), 3.40-3.43 (1H, dd, *J* 3.6, 10.4, CHCH*H*), 4.53-4.58 (1H, br, CHN*H*). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 12.5 (CH*C*H$_2$), 17.9, 18.3 (CH(*C*H$_3$)$_2$), 27.3 (C(*C*H$_3$)$_3$), 31.3 (*C*H(CH$_3$)$_2$), 54.4 (CHNH), 78.9 (*C*(CH$_3$)$_3$), 159.1 (OCONH). HRMS: Calcd for $C_{10}H_{20}INO_2$: MH^+ 314.0613; found: MH^+ 314.0627. Anal. Calcd for $C_{10}H_{20}INO_2$: C, 38.35; H, 6.44; N, 4.47%, Found: C, 38.67; H, 6.41; N, 4.73%.

Method B. Iodine (2.75 g, 10.82 mmol) was added to triphenylphosphine (2.84 g, 10.82 mmol) in CH_2Cl_2 (100 mL) and the mixture stirred at 20 °C under nitrogen for 15 min. Imidazole (827 mg, 12.30 mmol) was then added and the mixture stirred for 15 min before *S*-1-(hydroxymethyl-2-methylpropyl)carbamic acid *tert*-butyl ester **9a** (1 g, 4.92 mmol) was added and the mixture heated under reflux for 20 h, then worked up as method A to afford a yellow solid (3.74 g) that was purified by column chromatography eluting with light petroleum : EtOAc (2:1 v/v) to yield the *title compound* **11a** as a yellow solid (471 mg, 31%) whose data were identical to those reported above.

***S*-(1-Iodomethyl-2-methylpropyl)carbamic acid benzyl ester (11b).** Prepared as in method A for *S*-(1-iodomethyl-2-methylpropyl)carbamic acid *tert*-butyl ester **11a** but using iodine (2.35 g, 8.85 mmol), polystyrene-triphenylphosphine (4.45 g, 8.85 mmol), imidazole (0.72 g, 10.54 mmol) and *S*-(1-hydroxymethyl-2-methylpropyl)carbamic acid benzyl ester **9b** (1 g, 4.21 mmol) to afford a yellow solid (1.26 g) that was purified by column chromatography eluting with light petroleum : EtOAc (2:1 v/v) to yield the *title compound* **11b** (1.17 g, 80 %) as a light yellow solid, mp 76-77.5 °C, $[\alpha]_D^{20}$ –22.5 (*c* 10.3, $CHCl_3$), IR (ν_{max} $CHCl_3$/cm^{-1}), 3338, 2960, 2872, 1689, 1532, 1239, 1182. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 0.86-0.91 (6H, 2 x d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.68-1.77 (1H, m, C*H*(CH$_3$)$_2$), 3.08-3.15 (1H, m, C*H*NH), 3.26-3.30 (1H, dd, *J* 5.9, 10.4, CHC*H*$_2$), 3.34-3.38 (1H, dd, *J* 4, 10.4, CHC*H*$_2$), 4.72-4.75 (1H, d, *J* 8.4, CHN*H*), 5.04 (2H, s,

C*H*$_2$Ph), 7.24-7.31 (5H, m, Ar-H). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 12.0 (CH_2), 17.3, 18.2 (CH(CH_3)$_2$), 31.3 (*C*H(CH_3)$_2$), 55.1 (CHNH), 65.9 (*C*H$_2$Ph), 127.1, 127.2, 127.5 (Ar-CH), 136.4 (Ar-C), 157.1 (OCONH). HRMS: Calcd for $C_{13}H_{18}INO_2$: MH^+ 348.0457; found: MH^+ 348.0465.

***S*-(2-Methyl-1-nitromethylpropyl)carbamic acid *tert*-butyl ester (6a).** $NaNO_2$ (490 mg, 7.09 mmol), phloroglucinol (447 mg, 3.55 mmol) and urea (490 mg, 7.09 mmol) were added to *S*-(1-iodomethyl-2-methylpropyl)carbamic acid *tert*-butyl ester **11a** (1.01 g, 3.22 mmol) in dry DMF under nitrogen, the mixture was stirred at 20 °C for 20 h and washed with water (30 mL), sodium thiosulfate solution (10% w/v, 30 mL), water (30 mL), $KHCO_3$ solution (10% w/v, 30 mL) and saturated brine (30 ml). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford a yellow solid (998 mg) that was purified by column chromatography eluting with light petroleum : EtOAc (2:1 v/v) to yield the *title compound* **6a** (487 mg, 64%) as a light yellow solid, mp 84-86.5 °C (lit.[12a] 80-83 °C for *R*-isomer), $[\alpha]_D^{20}$ –24 (*c* 10, $CHCl_3$) [lit.[12a] $[\alpha]_D^{25}$ +34.8 (*c* 1.0, CH_2Cl_2) for *R*-isomer], IR (ν_{max} $CHCl_3$/cm^{-1}), 3349, 2979, 1681, 1536, 1369, 1248, 1163. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 0.89-0.94 (6H, 2 x d, *J* 7.2, CH(C*H*$_3$)$_2$), 1.37 (9H, s, C(CH_3)$_3$), 1.78-1.87 (1H, m, C*H*(CH_3)$_2$), 3.87-3.90 (1H, m, C*H*NH), 4.54-4.57 (2H, m, CHC*H*$_2$), 4.73-4.76 (1H, br, CHN*H*). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 18.5, 19.5 (CH(*C*H$_3$)$_2$), 28.3 (C(*C*H$_3$)$_3$), 30.0 (*C*H(CH_3)$_2$, 55.0 (CHNH), 74.5 (CH*C*H$_2$), 79.8 (*C*(CH_3)$_3$), 155.6 (OCONH). HRMS: Calcd for $C_{10}H_{20}N_2O_4$: MH^+ 233.1496; found: MH^+ 233.1504.

***S*-(2-Methyl-1-nitromethylpropyl)carbamic acid benzyl ester (6b).** Prepared as for *S*-(2-methyl-1-nitromethylpropyl)carbamic acid *tert*-butyl ester **6a** but using $NaNO_2$ (430 mg, 6.24 mmol), phloroglucinol (393 mg, 3.12 mmol), urea (374 mg, 6.24 mmol) and *S*-(1-iodomethyl-2-methylpropyl)carbamic acid benzyl ester **11b** (984 mg, 2.83 mmol) to afford a yellow solid (862 mg) that was purified by column chromatography eluting with light petroleum : EtOAc (2:1 v/v) to yield the *title compound* **6b** (628 mg, 70%) as a light yellow solid, mp 66 °C, $[\alpha]_D^{20}$ –32.4 (*c* 10, $CHCl_3$), IR (ν_{max} $CHCl_3$/cm^{-1}), 3324, 2964, 1696, 1554, 1381, 1244. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 0.91-0.95 (6H, 2 x d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.82-1.87 (1H, m, C*H*(CH_3)$_2$), 3.91-4.00 (1H, m, C*H*NH), 4.46-4.52 (2H, m, CHC*H*$_2$), 4.98-5.02 (1H, br, CHN*H*), 5.04 (2H, s, C*H*$_2$Ph), 7.24-7.32 (5H, m, Ar-H). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 19.1, 19.8 (CH(*C*H$_3$)$_2$), 30.4 (*C*H(CH_3)$_2$), 55.6 (CHNH), 67.6 (*C*H$_2$Ph), 78.9 (CH*C*H$_2$), 128.6, 128.7, 129.0 (Ar-CH), 136.4 (Ar-C), 156.2 (OCONH). HRMS: Calcd for $C_{13}H_{18}N_2O_4$: MH^+ 267.1339; found: MH^+ 267.1338.

(1-Benzenesulfonyl-2-methylpropyl)carbamic acid *tert*-butyl ester (13). To *tert*-butyl carbamate (1.32 g, 11.27 mmol) in THF (4 mL) at 20 °C was added benzenesulfinic acid sodium salt (2.03 g, 12.39 mmol) in water (10 mL), followed by 2-methylpropanal (0.89 g, 1.13 mL, 12.39 mmol) and then formic acid (2.5 mL). The mixture was stirred for 17 h and the white precipitate formed (3.68 g) was filtered and recrystallised from 2-methylpentane : EtOAc (4:1 v/v) to yield the *title compound* **13** (2.64 g, 75%) as a white solid, mp 122.5-123.5 °C, IR (ν_{max} $CHCl_3$/cm^{-1}), 3353, 2974, 1703, 1644, 1367, 1307, 1168, 1142, 1082. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 1.00-1.08 (6H, 2 x d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.16 (9H, s, C(CH_3)$_3$), 2.68-2.76 (1H, m, C*H*(CH_3)$_2$), 4.66-4.69 (1H, dd, *J* 3.4, 11.2, C*H*NH), 5.04-5.07 (1H, d, *J* 11.2, CHN*H*), 7.48-7.57 (3H, m, Ar-H), 7.82-7.84 (2H, d, *J* 7.4, Ar-H). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 17.3, 21.0

(CH(*C*H$_3$)$_2$), 27.3 (*C*H(CH$_3$)$_2$), 28.4 (C(*C*H$_3$)$_3$), 74.7 (*C*HNH), 81.2 (*C*(CH$_3$)$_3$), 129.3, 129.6, 134.1 (Ar-CH), 138.5 (Ar-C), 154.5 (OCONH). HRMS: Calcd for $C_{15}H_{23}NO_4S$: MH^+ 314.1420; found: MH^+ 314.1434. Anal. Calcd for $C_{15}H_{23}NO_4S$: C, 57.48; H, 7.40; N, 4.47, S, 10.23%, Found: C, 57.28; H, 7.69; N, 4.71; S, 9.93%.

***R*-(2-Methyl-1-nitromethylpropyl)carbamic acid *tert*-butyl ester (6c).** *N*-Benzylquininium chloride (35 mg, 0.08 mmol, 12 mol %) was added to (1-benzenesulfonyl-2-methylpropyl)carbamic acid *tert*-butyl ester **13** (200 mg, 0.64 mmol) and KOH (186 mg, 3.32 mmol) in toluene (5 mL) at –78 °C under nitrogen. Nitromethane (203 mg, 180 μL, 3.32 mmol) was added dropwise and the mixture allowed to reach 20 °C and stirred for 48 h. The mixture was concentrated under reduced pressure, the residue partitioned between EtOAc (30 mL) and water (30 mL) and the aqueous layer extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with water (30 mL) and saturated brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield a yellow oil (151 mg) that was purified by column chromatography eluting with EtOAc : 2-methylpentane (2:3 v/v) to yield the *title compound* **6c** (107 mg, 72%) as a light yellow solid, data identical to those reported above for *S*-isomer **6a** with the exception of an opposite sign of optical rotation, $[\alpha]_D^{20}$ +25 (*c* 10, $CHCl_3$) [lit.[12a] $[\alpha]_D^{25}$ +34.8 (*c* 1.0, CH_2Cl_2)].

***S*-2-Methyl-1-nitromethylpropylamine hydrochloride (15).** TFA (14.82 g, 9.66 mL, 130.01 mmol) was added to *S*-(2-methyl-1-nitromethylpropyl)carbamic acid *tert*-butyl ester **6a** (1.51 mg, 6.50 mmol), the mixture was stirred at 20 °C for 4.5 h and then concentrated under reduced pressure. Hydrochloric acid (2M, 65 mL, 130.01 mmol) was added to the residue and the mixture was stirred at 20 °C for 0.5 h and then concentrated under reduced pressure to leave a residue that was dissolved in water (30 mL) and washed with EtOAc (2 x 30 mL). The aqueous phase was evaporated to dryness to yield the *title compound* **15** (0.99 g, 90%) as a light yellow solid, mp 137-141 °C, $[\alpha]_D^{20}$ –11.2 (*c* 10, MeOH), IR (ν_{max} $CHCl_3$/cm^{-1}), 3424, 2974, 1558. ^{1}H NMR (400 MHz; (CD$_3$)$_2$SO), δ_H 0.94-0.98 (6H, 2 x d, *J* 6.8, CH(C*H*$_3$)$_2$), 2.00-2.05 (1H, m, *CH*(CH$_3$)$_2$), 3.67-3.71 (1H, m, C*H*NH), 4.77-4.79 (1H, dd, *J* 8, 15.4, CHC*H*H), 4.96-4.97 (1H, dd, *J* 3.2, 15.4, CHCH*H*), 8.48 (3H, br, NH_3). ^{13}C NMR (100 MHz; (CD$_3$)$_2$SO), δ_C 17.4, 18.1 (CH(*C*H$_3$)$_2$), 28.2 (*C*H(CH$_3$)$_2$), 52.9 (CHNH), 74.3 (CH*C*H$_2$). HRMS: Calcd for $C_5H_{12}N_2O_2$: MH^+ 133.0971; found: MH^+ 133.0977.

***N*-(*S*-2-Methyl-1-nitromethylpropyl)-3-oxobutanamide (16).** Et_3N (937 mg, 1.29 mL, 9.26 mmol) was added to *S*-2-methyl-1-nitromethylpropylamine hydrochloride **15** (1.42 g, 8.42 mmol) in CH_2Cl_2 (20 mL), the mixture stirred at 20 °C for 30 min then concentrated under reduced pressure to afford a residue that was dissolved in toluene (25 mL) and 2,2,6-trimethyl-1,3-dioxin-4-one (1.32 g, 1.21 mL, 9.26 mmol) and PPTS (2.33 g, 9.26 mmol, 1.1 eq) were added. The mixture was heated at reflux under Dean-Stark conditions for 3 h and then concentrated under reduced pressure to leave a residue that was partitioned between water (30 mL) and EtOAc (30 mL) and the aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (30 mL) and saturated brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a brown oil

(2.38 g) that was purified by column chromatography eluting with light petroleum : EtOAc (1:2 v/v) to yield the *title compound* **16** (1.23 g, 68%) as a brown oil, $[\alpha]_D^{20}$ –36 (*c* 10, $CHCl_3$), IR (ν_{max} $CHCl_3$/cm^{-1}), 3299, 3073, 2966, 1716, 1556, 1382. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 0.99-1.03 (6H, 2 x d, *J* 7.2, $CH(CH_3)_2$), 1.92-1.98 (1H, m, $CH(CH_3)_2$), 2.28 (3H, s, CH_3CO), 3.42 (2H, s, $COCH_2$), 4.32-4.39 (1H, m, CHNH), 4.52-4.56 (1H, dd, *J* 4.8, 12.6, CHCHH), 4.56-4.61 (1H, dd, *J* 6.8, 12.6, CHCHH), 7.44-7.46 (1H, d, *J* 7.6, CHNH). ^{13}C NMR (100 MHz; $CDCl_3$), δ_C 18.5, 19.4 ($CH(CH_3)_2$), 29.7 ($CH(CH_3)_2$), 31.2 (CH_3CO), 48.9 ($CHCH_2$), 53.2 (CHNH), 76.5 ($COCH_2$), 165.6 (CONH), 204.8 (CO). HRMS: Calcd for $C_9H_{16}N_2O_4$: MH^+ 217.1183; found: MH^+ 217.1188.

***N*-(*S*-2-Methyl-1-nitromethylpropyl)-*N*'-(tetramethylenyl)urea (18).** To *N*-(*S*-2-methyl-1-nitromethylpropyl)-3-oxobutanamide **16** (48 mg, 0.22 mmol) in toluene (20 mL) was added pyrrolidine (18 mg, 20 µl, 0.24 mmol) dropwise and the mixture heated to reflux under Dean-Stark conditions for 3 h, then cooled and the solvent removed under reduced pressure. The residue was partitioned between water (30 mL) and EtOAc (30 mL), the aqueous phase extracted with EtOAc (2 x 30 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to leave a dark brown oil (163 mg) that was purified by column chromatography eluting with light petroleum : EtOAc (1:2 v/v) to yield the *title compound* **18** (28 mg, 55%) as a brown oil, recrystallised from Et_2O–hexane to afford colourless crystals, $[\alpha]_D^{20}$ –6.96 (*c* 10, $CHCl_3$), IR (ν_{max} $CHCl_3$/cm^{-1}), 3423, 2964, 2872, 1635, 1552. ^{1}H NMR (400 MHz; $CDCl_3$), δ_H 0.99-1.04 (6H, 2 x d, *J* 6.8, $CH(CH_3)_2$), 1.86-1.94 (5H, m, $CH(CH_3)_2$ & 2 x CH_2), 3.33-3.36 (4H, m, 2 x NCH_2), 4.06-4.13 (1H, m, CHNH), 4.56-4.60 (2H, dd & br, *J* 4, 12.4, CHCHH & CHNH), 4.65-4.69 (1H, dd, *J* 5.6, 12.4, CHCHH). ^{1}H NMR (100 MHz; $CDCl_3$), δ_C 19.3, 19.6 ($CH(CH_3)_2$), 25.5 (CH_2), 30.0 ($CH(CH_3)_2$), 45.5 (NCH_2), 54.5 (CHNH), 76.7 ($CHCH_2$), 155.8 (NCON). HRMS: Calcd for $C_{10}H_{19}N_3O_3$: MH^+ 230.1499; found: MH^+ 230.1499.

Crystal data for urea (18). $C_{10}H_{19}N_3O_3$, *M* = 229.28, orthorhombic, *a* = 9.3464(17), *b* = 14.504(3), *c* = 18.094(3) Å, *U* = 2453.0(8) $Å^3$, *T* = 150(2) K, space group $P2_12_12_1$, Mo-Kα radiation, λ = 0.71073 Å, *Z* = 8, D_c = 1.242 Mg m^{-3}, *F*(000) = 992, crystal dimensions 0.47 × 0.15 × 0.09 mm, μ(Mo-Kα) = 0.092 mm^{-1}, 3.60 < 2θ < 56.66°, 25509 reflections measured,[19] 3449 unique reflections. Solved by direct methods and refined by full-matrix least-squares on F^2.[20] The final cycle (for 299 parameters) converged with *wR*2 = 0.0969 (for all data) and *R*1 = 0.0393 [$F^2 > 2\sigma$]. Friedel pairs were merged due to the absence of any significant anomalous scattering. The enantiomer was assigned from an unchanging chiral centre {C(6) & C(15)}.

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References

PMid:19917748 PMCid:2812153 4. Jones, R. C. F.; Bhalay, G.; Carter, P. A.; Duller, K. A. M.; Dunn, S. H. J. Chem. Soc., Perkin Trans. 1 1999, 765. 5. Jones, R. C. F.; Dawson, C. E.; O'Mahony, M. J. Synlett 1999, 873. 6. Jones, R. C. F.; Pillainayagam, T. A. Synlett 2004, 2815. http://dx.doi.org/10.1055/s-2004-835640

1. For leading references to our early pre-isoxazole work: (a) Jones, R. C. F.; Tankard, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 240.
   (b) Jones, R. C. F.; Bhalay, G.; Patience, J. M.; Patel, P. *J. Chem. Res. (S)* **1999**, 250.
2. (a) Royles, B. J. L. *Chem. Rev.* **1995**, *95*, 1981. http://dx.doi.org/10.1021/cr00038a009
   (b) Schobert, R.; Schlenk, A. *Bioorg. Med. Chem.* **2008**, *16*, 4203. http://dx.doi.org/10.1016/j.bmc.2008.02.069
   (c) Jeong, Y.-C.; Moloney, M. *J. Org. Chem.* **2011**, *76*, 1343. http://dx.doi.org/10.1021/jo102304y; PMid:21250713.
3. (a) Kaufmann, G. F.; Sartorio, R.; Lee, S.-H.; Rogers, C. J.; Meijler, M. M.; Moss, J. A.; Clapham, B.; Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 309. PMid:15623555 PMCid:544315.
   (b) Lowery, C. A.; Park, J.; Gloeckner, C.; Meijler, M. M.; Mueller, R. S.; Boshoff, H. I.; Ulrich, R. L.; Barry, C. E.; Bartlett, D. H.; Kravchenko, V. V.; Kaufmann, G. F.; Janda, K. D. *J. Am. Chem. Soc.* **2009**, *131*, 14473. http://dx.doi.org/10.1021/ja9056079; PMid:19807189 PMCid:2760024.
   (c) Ueda, C.; Tateda, K.; Horikawa, M.; Kimura, S.; Ishii, Y.; Nomura, K.; Yamada, K.; Suematsu, T.; Inoue, Y.; Ishiguro, M.; Miyairi, S.; Yamaguchi, K. *Antimicrob. Agents Chemother.* **2010**, *54*, 683. http://dx.doi.org/10.1128/AAC.00702-09; PMid:19917748 PMCid:2812153.
4. For our 1st generation approach: Jones, R. C. F.; Bhalay, G.; Carter, P. A.; Duller, K. A. M.; Dunn, S. H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 765, and refs. therein.
5. For our 2nd generation approach: (a) Jones, R. C. F.; Dawson, C. E.; O'Mahony, M. J. *Synlett* **1999**, 873.
   (b) Jones, R. C. F.; Pillainayagam, T. A. *Synlett* **2004**, 2815. http://dx.doi.org/10.1055/s-2004-835640
6. For our related work on the 3-acyl-4-hydroxypyridin-2-one series: Jones, R.C.F.; Choudhury, A. K.; Iley, J. N.; Light, M. E.; Loizou, G.; Pillainayagam, T. A. *Beilstein J. Org. Chem.* **2012**, *8*, 308, and refs. therein. http://dx.doi.org/10.3762/bjoc.8.33; PMid:22423299 PMCid:3302094.
7. For leading references to the recent application of 6-substituted 2,2-dimethyl-1,3-dioxin-4-ones as acetoacylating agents: (a) Patel, B. H.; Mason, A. M.; Barrett, A. G. M. *Org. Lett.* **2011**, *13*, 5156. http://dx.doi.org/10.1021/ol202028t; PMid:21879703.
   (b) Patel, B. H.; Heath, S. F. A.; Mason, A. M.; Barrett, A. G. M. *Tetrahedron Lett.* **2011**,

52, 2258. http://dx.doi.org/10.1016/j.tetlet.2011.01.100
8. Agrawal, Y. K. *Russian Chem. Rev.* **1979**, *48*, 948. http://dx.doi.org/10.1070/RC1979v048n10ABEH002422
9. Giannis, A.; Sandhoff, K. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 218. http://dx.doi.org/10.1002/anie.198902181
10. Caputo, R.; Cassano, E.; Longobardo, L.; Palumbo, G. *Tetrahedron* **1995**, *51*, 12337. http://dx.doi.org/10.1016/0040-4020(95)00778-7
11. Kornblum, N.; Larson, H. O.; Blackwood, R. K.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E. *J. Am. Chem. Soc.* **1956**, *78*, 1497. http://dx.doi.org/10.1021/ja01588a059
12. (a) Palomo, C.; Oiarbide, M.; Laso, A.; Lopez, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622. http://dx.doi.org/10.1021/ja056594t; PMid:16351089.
(b) Fini, F.; Sgarzani, V.; Petterson, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7975. http://dx.doi.org/10.1002/anie.200502646; PMid:16287160.
13. Fox, C. M. J.; Ley, S. V. *Org. Synth.* **1987**, *66*, 108.
14. Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145. http://dx.doi.org/10.1016/S0040-4020(01)88210-7
15. Crystal data for urea **18** are given in the Experimental Section. Complete crystallographic data (including structure factors) have been deposited at the Cambridge Crystallographic Data Centre, deposition number CCDC 893686. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
16. Basel, Y.; Hassner, A. *Synthesis* **1997**, 309. http://dx.doi.org/10.1055/s-1997-1181.
17. Shimizu, T.; Hayashi, Y.; Shibafuchi, H.; Teramura, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2827. http://dx.doi.org/10.1246/bcsj.59.2827.
18. Benoit, D.; Coulbeck, E.; Eames, J.; Motevalli, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1068. http://dx.doi.org/10.1016/j.tetasy.2008.03.032.
19. SAINT (2006), and APEX 2 (2006) software for CCD diffractometers. Bruker AXS Inc., Madison, USA.
20. Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112.

