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Scope of the reductive aldol reaction: application to aromatic carbocycles and heterocycles †

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The reductive aldol reaction of electron deficient aromatic compounds has been investigated and found to be a viable method for carbon–carbon bond formation. Reductions under ammonia and ammonia-free conditions were both capable of facilitating the aldol reaction although the latter showed more scope for reaction with enolisable aldehydes. Moreover, reduction under ammonia-free conditions allowed the addition of Lewis acids which improved stereoselectivity to favour the *anti* stereoisomer. Production of the *syn* diastereoisomer was possible through either one of two different protocols performed after partial reduction was complete. While the main emphasis of this paper concerns the reductive aldol reaction of electron deficient pyrroles, it was also shown that both benzenoid and furan aromatic compounds were amenable to such reducing conditions.

Introduction

The aldol reaction is a venerable method of C–C bond formation that has evolved into a highly sophisticated and powerful means of preparing β-hydroxy carbonyl compounds with significant control of both relative and absolute stereochemistry being possible.[1] Part of the reason for developing new methodology based around the aldol reaction is the preponderance of biologically active natural products that contain the β-hydroxy carbonyl motif, and this reaction has been used extensively in synthesis.[2]

It is fair to say that the most general method of forming an enolate for the aldol reaction involves deprotonation of a carbonyl compound with a base, usually in the presence of an activating Lewis acid. On the other hand, there are several procedures that generate an enolate by reduction and these usually involve the reaction of an α-halo (or equivalent) carbonyl compound with a reducing metal such as zinc or samarium.[3] We are currently investigating the partial reduction of aromatic compounds as another method of enolate generation that had not previously been used in conjunction with an aldehyde electrophile.[4] Our plan was to subject a range of aromatic heterocyclic (and carbocyclic) compounds to partial reduction using dissolving metal (Birch) conditions in ammonia[5] and also using our newly developed ammonia-free (AF) conditions.[6] Part of the chemistry described here has been communicated recently[4] and we now wish to present our methodology results in full.

In the longer term, we want to exploit the methodology described below in total synthesis and our choice of aromatic compounds and aldehyde electrophiles was governed by future application to the synthesis of lactacystin[7] and 16-methyloxazolomycin,[8] Fig. 1, both of which have interesting and potentially useful biological activity.

A retrosynthetic analysis of each compound shows that a reductive aldol reaction on an electron deficient pyrrole would be required to prepare the natural product core, and that it must be coupled to two different aliphatic aldehydes (isobutyraldehyde for lactacystin and acetaldehyde for 16-methyloxazolomycin). Moreover, we must develop methods of controlling the relative stereochemistry to be either *syn* (for methyloxazolomycin) or *anti* (for lactacystin) at will. Clearly, there is also a need to control the absolute stereochemistry of the aldol adducts: while we have presently been able to do this for reductive alkylation reactions by using a chiral auxiliary attached to the heterocycle,[9] this issue is beyond the remit of this paper.

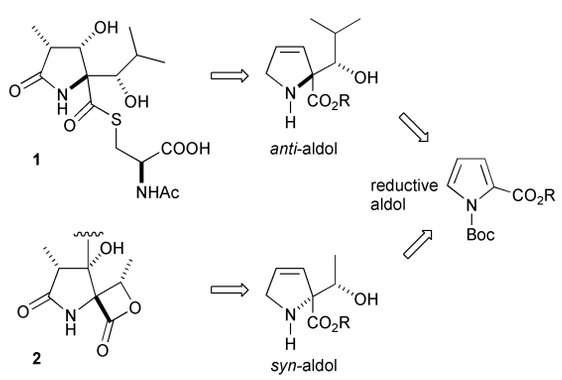

Fig. 1 lactacystin **1**; 16-methyloxazolomycin **2**.

Results and discussion

Reductive aldol reactions under Birch conditions

Our first experiments addressed the reductive aldol reaction under Birch type conditions, using electron deficient pyrrole heterocycles as a starting material. Therefore, readily available pyrroles **3** (R = Et) and **4** (R = *i*Pr) were reduced with lithium in ammonia, and the reaction quenched firstly with isoprene (to destroy any excess reducing agent and suppress pinacol by-products) and then with an aldehyde electrophile, Scheme 1. Pleasingly, the reaction worked as planned and furnished the reductive aldol adducts in excellent yield and with complete regioselectivity.

However, two problems arose with this methodology. Firstly, the use of enolisable aldehydes (such as isobutyraldehyde) led instantly to the formation of protonated compound **9**, which we presume is the result of proton transfer between the basic enolate and the methine proton α- to the aldehyde carbonyl group, Scheme 2. Attempts to transmetallate the enolate, with

† This is one of a number of contributions from the current members of the Dyson Perrins Laboratory to mark the end of almost 90 years of organic chemistry research in that building, as all its current academic staff move across South Parks Road to a new purpose-built laboratory.

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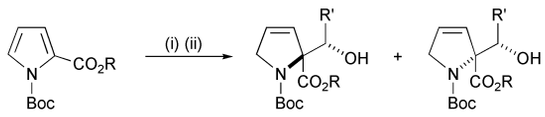
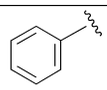
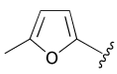
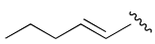
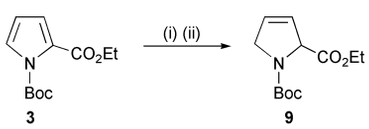


R'	Yield (%)	*anti:syn*	compound
	91	1:1	*anti/syn* **5**
	90	1:1	*anti/syn* **6**
	94	1:1	*anti/syn* **7**
	84	1:1	*anti/syn* **8**

Scheme 1 *Reagents*: (i) Li, NH_3, THF, −78 °C, then isoprene; (ii) R′CHO then NH_4Cl. R = *i*Pr except for *syn*/*anti*-**5** (R = Et).

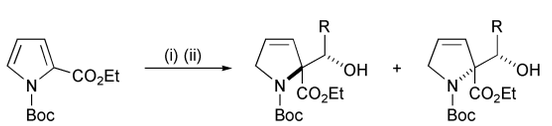


Scheme 2 *Reagents*: (i) Li, NH_3, THF, −78 °C, then isoprene; (ii) *i*PrCHO then NH_4Cl.

$CeCl_3$ for example,[10] were unsuccessful. Secondly, the aromatic and unsaturated aldehydes that did participate in the aldol reaction gave an equal mixture of both the *syn* and the *anti* diastereoisomers.

Reductive aldol reactions under ammonia-free conditions

Clearly, the limitations of the reductive aldol reaction in ammonia meant that application to the synthesis of complex natural products was not viable. In response to the challenge of using enolisable aldehydes as partners in the aldol, we decided to use the recently developed ammonia-free (AF) conditions for partial reduction of heterocycles.[6] In essence, the AF conditions generate the same type of enolate as that produced in ammonia: the main differences are the use of lithium di-*tert*-butylbiphenyl (LiDBB) as an electron transfer agent and bis-(methoxyethyl)amine (BMEA) as a proton source, Scheme 3. The enolate generated in THF was expected to have a significantly different aggregation state (and possibly enolate geometry) to that generated in ammonia which may manifest itself in reactivity differences.



R	Yield (%)	*anti:syn*	compound
Ph	73	1.8:1	*anti/syn* **5**
Me	69	1.8:1	*anti/syn* **10**
*i*Pr	74	8.0:1	*anti/syn* **11**
*t*Bu	71	5.3:1	*anti/syn* **12**

Scheme 3 *Reagents*: (i) LiDBB, BMEA, THF, −78 °C, then $Br(CH_2)_2Br$; (ii) RCHO then NH_4Cl.

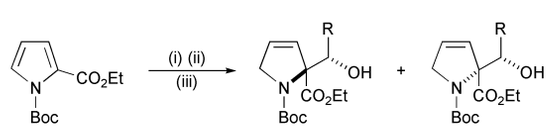
Therefore, pyrrole **3** was subjected to the ammonia-free reduction and then quenched with a variety of aromatic and aliphatic aldehydes, Scheme 3. Immediately, we discovered the aliphatic aldehydes that had failed to undergo the aldol reaction in ammonia were compatible with the ammonia-free conditions and gave good yields of the aldol adducts.

Moreover, in each case examined, the reaction gave a small, but useful, selectivity for the *anti* isomer, which could normally be separated from the *syn* diastereoisomer by chromatography on silica.

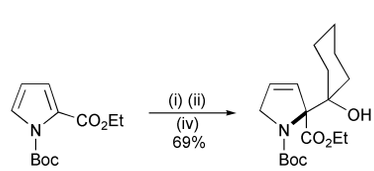
Our assignment of *syn* and *anti* relative stereochemistry has its foundations in X-ray crystallography and derivatives of *syn*-**5**, *syn*-**7** and *anti*-**11** have all had their structure proven unambiguously by this technique.[11] In addition, we have noticed two diagnostic differences in the spectroscopic data from such aldol adducts that have allowed us to assign stereochemistry without recourse to X-ray crystallography. Firstly, in each *syn* isomer, the O*H* resonance appears as a low field doublet in the ^1H NMR spectrum (~6–7 ppm) whereas the *anti* isomer has an OH signal that resonates at much higher field. Secondly, the IR spectrum of the *syn* isomers shows an OH stretch at around 3330 cm^{-1}, whereas their *anti* counterparts usually have an OH stretch at approximately 3500 cm^{-1}. Although these observations are used in a purely empirical sense, it should be noted that enhanced intramolecular hydrogen bonding in the *syn* isomers, relative to the *anti*, could be responsible for both effects.

It is worth noting here that both the ^1H and ^{13}C NMR spectra of the aldol adducts were complicated because of a doubling of some (sometimes all) signals. This has its origins in restricted rotation of the Boc group and this effect disappeared at high temperatures. Generally, the *anti* aldol compounds showed this doubling while their *syn* isomers did not.

As the ammonia-free conditions had overcome one of the limitations of the aldol reaction in ammonia, we then investigated methods for improving the stereoselectivity in favour of the *anti* aldol adduct. In this context we examined the role of the enolate counter-ion by performing transmetallation experiments on the lithium enolates generated in the ammonia-free reduction. Amongst the Lewis acids that we investigated ($ClTi(OiPr)_3$; Bu_2BOTf; $ZnBr_2$; $MgBr_2$) magnesium bromide was the most successful at improving the *anti*/*syn* ratio of diastereoisomers, and gave good to excellent levels of diastereoselection, Scheme 4. With the exception of aromatic aldehydes, which did not show any improvement in selectivity, there was a broad correlation between the size of the R group attached to the aldehyde and the stereoselectivity, which peaked when R = *i*Pr.



R	Yield (%)	*anti:syn*	compound
Ph	76	1.5:1	*anti/syn* **5**
Me	70	7.6:1	*anti/syn* **10**
*i*Pr	72	≥20:1	*anti/syn* **11**
*t*Bu	68	7.4:1	*anti/syn* **12**

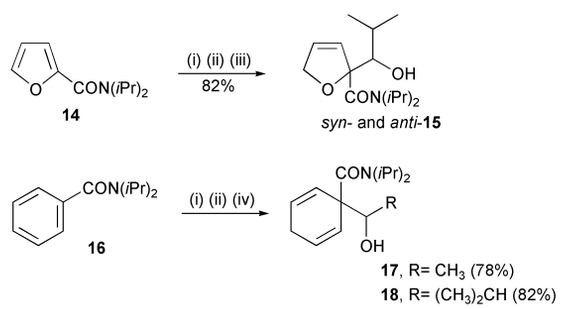


Scheme 4 *Reagents*: (i) LiDBB, BMEA, THF, −78 °C, then $Br(CH_2)_2Br$; (ii) $MgBr_2{\cdot}OEt_2$; (iii) RCHO then NH_4Cl; (iv) cyclohexanone then NH_4Cl.

In another development, we showed that the reductive aldol reaction was applicable to enolisable ketones as well as aldehydes as the reduction of **3** could be quenched successfully with cyclohexanone to give compound **13**, Scheme 4.

Reductive aldol reactions on furans and carbocycles

Because the reductive aldol reaction had worked so well on electron deficient pyrroles, we decided to examine some other aromatic systems to explore the scope of this new reaction, Scheme 5. We discovered that both electron deficient benzenoid systems and electron deficient furans are also compatible with the reductive aldol reaction and gave access to usefully functionalised material in good yields. Unfortunately, the aldol reaction of furan **14** resulted in the formation of a mixture (5 : 3) of diastereoisomers; based on our previous work in this area we suspect that this lack of selectivity has its origins in the non-selective formation of *E* and *Z* enolates from **14**, *vide infra*.[12]



Scheme 5 *Reagents*: (i) LiDBB, BMEA, THF, −78 °C, then $Br(CH_2)_2Br$; (ii) $MgBr_2{\cdot}OEt_2$; (iii) $(CH_3)_2CHCHO$ then NH_4Cl; (iv) RCHO then NH_4Cl

Mechanism of the reductive aldol reaction

The reduction of aromatic compounds by either Birch or ammonia-free conditions is simply a way of generating an (extended) enolate from an aromatic compound by the addition of two electrons and one proton, Fig. 2. Under Birch conditions, the metal provides the electrons and ammonia solvent the protons, whereas in the AF reaction, LiDBB is the reducing agent and BMEA a weak acid. In both cases, subsequent reaction of the extended enolate **A** with an aldehyde (or any other electrophile we have examined) always then takes place at the carbon adjacent to the heteroatom to furnish the functionalised dehydroproline products.

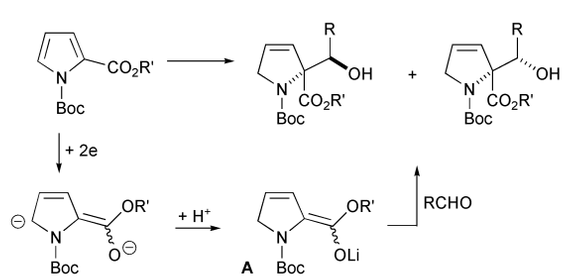
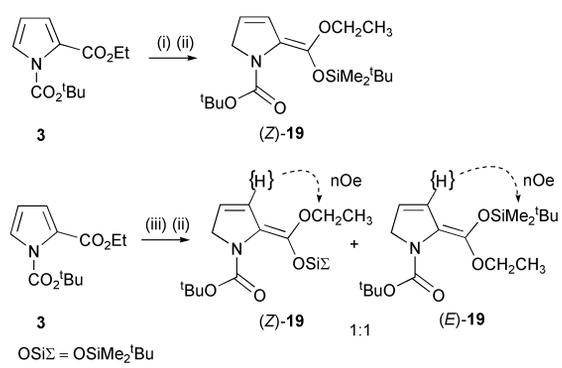


Fig. 2

The results obtained with aliphatic aldehydes as electrophiles show that there are significant differences in the reactivity of the enolate **A** depending upon its method of generation. We might expect the role of the solvent to be crucial in determining the aggregation state of the enolate and also (by affecting chelation) the enolate geometry. The most pronounced difference between the two sets of conditions is the marked protonation that occurs in ammonia with enolisable aldehydes whereas in THF a successful aldol reaction ensues. We suggest that the enolate generated in ammonia is more likely to exist as a monomer or dimer than that in THF (which will probably be part of a tetramer).[13] Consequently, the monomeric/dimeric enolate oxygen is less well stabilised by coordination to lithium than its tetrameric counterpart and is also less hindered. One might expect such 'naked' enolates to be significantly more reactive than their aggregated counterparts which could mean that deprotonation of the aldehyde (by the enolate oxygen) is faster than nucleophilic addition to the same C=O group.

Our next set of experiments were designed to test whether the aldol reactions were under kinetic or thermodynamic control and, to this end, we took *anti*-**12** and reacted it with LDA in THF at −78 °C so as to make the aldolate anion. This reaction was then quenched with ammonium chloride and no evidence was found either for epimerisation to the *syn* aldol diastereoisomer or for formation of the protonated material **9**: both of these might have been formed if the aldolate anion had undergone a retro-reaction to regenerate the enolate. Moreover, we repeated the LDA experiment in the presence of another, different, aldehyde (*i*PrCHO) and again saw no evidence for retro-aldol reaction as no crossover aldol product was observed at all. These control experiments all point to a reaction (at least under ammonia-free conditions) that is under kinetic rather than thermodynamic control.

As far as the aldol stereochemistry is concerned, we next sought to identify the particular enolate isomers that were being formed in the reduction by quenching the reaction with TBSOTf to generate silylketene acetals *E*- and *Z*-**19**, Scheme 6. Note that enolates generated in ammonia could not be trapped this way and we are currently unable to probe the enolate geometry in this solvent. However, quenching ammonia-free reductions with silyl electrophiles was most informative as it generated the desired compounds directly. Reaction of pyrrole **3** under ammonia-free conditions using LiDBB and quenching with TBSOTf gave a single silylketene acetal (as observed in the crude ^1H NMR spectra of the reaction). In order to try and generate the other stereoisomer we also performed the reduction with sodium/naphthalene under ammonia-free conditions. In this case, a 1 : 1 mixture of two isomers could be observed and the identity of each one proven by DPFGSE NOE experiments on the mixture (key enhancements are shown in Scheme 6). Comparison with the LiDBB experiment detailed earlier showed that such reducing conditions generated the *Z*-isomer exclusively.



Scheme 6 *Reagents*: (i) LiDBB, BMEA, THF, −78 °C, then $Br(CH_2)_2Br$; (ii) $^tBuMe_2SiOTf$, then pH 7 buffer; (iii) Na/naphthalene, BMEA, THF, −78 °C.

The rationale for formation of the *Z*-isomer of **A** under lithium AF conditions and the generation of a mixture under sodium AF conditions surely has its origins in chelation. Indeed, we suggest that Li^+ cation, which is always present in the reaction, may chelate to both the Boc group and the ester carbonyl throughout the reduction process (in fact this coordination may activate the heterocycle towards reduction). Such coordination inevitably leads to the formation of the *Z*-enolate isomer and, presumably, the analogous reduction with sodium involves little, or less, chelation than its lithium counterpart.

Next, we constructed some transition state models which would rationalise the observed stereoselectivity, Fig. 3. The key feature in these models is that the metal retains coordination to the enolate, aldehyde and Boc group; reaction *via* this array unavoidably means that a boat (or boat-like) conformation must be adopted by the six atoms in the cyclic transition structure. Examination of our model reveals that the R group attached to the aldehyde would prefer to sit in an axial position, where it can minimise steric repulsion with the pyrroline ring: we believe this factor to be responsible for the *anti* selectivity observed. Disruption of such three-point binding to the metal causes our model to break down and leads to transition structures which predict formation of the *syn* isomer *via* chair-like transition structures.[14] This factor explains the increased *anti*-selectivity observed with a more chelating (magnesium) enolate over the (less chelating) lithium enolate. One would predict that, if our model were correct, then a dialkyl boron enolate would give fundamentally different selectivity as boron is incapable of chelating to the enolate, Boc and carbonyl groups at the same time.[15] Frustratingly, we were not able to verify this prediction as the boronate aldol adducts could not be hydrolysed with base or oxidant to provide the aldol products in reliable yield.

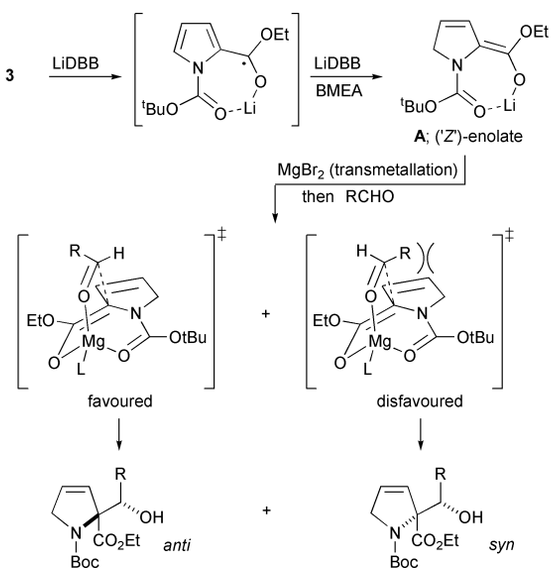


Fig. 3

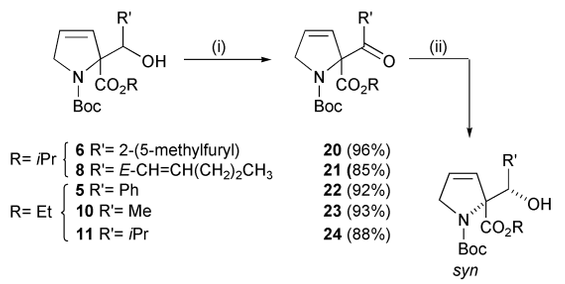
Although this model explains the increased *anti* selectivity observed as the R-group becomes larger from methyl to *i*Pr it does not rationalise the dip in *anti* selectivity seen when pivaldehyde (R = *t*Bu) was used. Moreover, the ammonia-free reductive aldol reactions with benzaldehyde were also anomalous because they gave poor *anti* selectivity. In this case, it may be that the flat aromatic portion of benzaldehyde can adopt the otherwise unfavourable equatorial position on the boat because of attractive π-stacking interactions with the C-3,4 alkene within the pyrroline ring. We cannot rule out the possibility that these, less reactive, aldehyde electrophiles are participating in a reversible aldol reaction.

We have not investigated the lack of stereoselectivity observed during the aldol reaction in ammonia, mostly because of the lack of synthetic utility of this reaction. Moreover, the reactive nature of the solvent means that we cannot trap the electrophile with sensitive electrophiles (such as TBSOTf) which means that we cannot probe enolate geometry or the role of more chelating Lewis acids during the Birch reduction. We intend to utilise the AF variant of the aldol reaction in future synthetic studies.

Control of stereochemistry post partial reduction

Our efforts to control the stereoselectivity of the aldol reaction have been successful in producing the *anti* diastereoisomer. However, we were not able to bias the reductive aldol reaction to give the *syn* isomer directly, despite extensive experimentation. Therefore, our efforts turned to using tactics which would convert the *anti* isomer into the *syn* after reduction.

Initial attempts were made at oxidising the aldol stereoisomers to the corresponding ketones with wet Dess–Martin periodinane, Scheme 7.[16] This oxidising agent alone was capable of producing the ketones in high yield; others tried gave poor conversion during the oxidation of these hindered alcohols.



R'	Yield (%)	*syn*:*anti*	compound
2-(5-methylfuryl)	70	13:1	*syn* **6**
E-CH=CH(CH$_2$)$_2$CH$_3$	79	12:1	*syn* **8**
Ph	86	22:1	*syn* **5**
Me	89	≥20:1	*syn* **10**
*i*Pr	82	≥10:1	*syn* **11**

Scheme 7 *Reagents*: (i) Dess–Martin periodinane, wet CH_2Cl_2, Δ; (ii) $NaBH_4$, $CeCl_3$, *i*PrOH, −78 °C⟶RT.

Next, we reduced the ketones back to the aldol products to examine the level and sense of stereoselectivity that was feasible. Gratifyingly, each ketone gave a high yield of the alcohol with good to excellent stereoselectivity for the *syn* isomer with both aromatic and aliphatic sidechains, Scheme 7. The use of cerium trichloride was beneficial to the rate of reduction and allowed us to add the borohydride at low temperature, thus ensuring good stereoselectivity.[17]

The sense of reduction can be explained by using the Felkin–Anh model with the large (and electronegative) NBoc group orthogonal to the carbonyl π-system. Attack by the nucleophile would be expected to occur preferentially over the cyclic C=C unit rather than the exocyclic ester, Fig. 4. Although beneficial, the addition of cerium was not essential for obtaining *syn* selectivity, which points against a model based on chelation control.

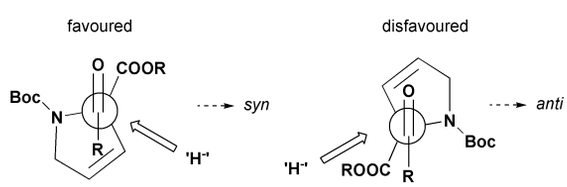
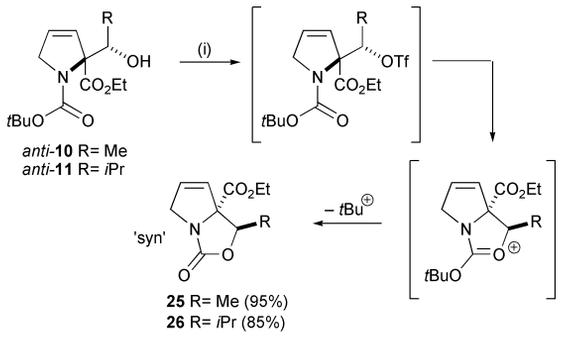


Fig. 4

As another shorter approach we examined direct inversion reactions of the *anti* isomers. Activation of the hydroxyl and intermolecular displacement with a nucleophile were not expected to be successful because of the neopentyl nature of the aldol hydroxyl group. Therefore, we chose to transform the *anti* aldol adduct into a reactive triflate and then promote intramolecular attack by the Boc carbonyl group (expecting subsequent loss of a *tert*-butyl cation). This strategy worked as planned and the *anti* isomers of **10** and **11** were transformed into the (*syn*) oxazolidinones in a one-pot procedure, Scheme 8. Proof of the stereochemical inversion was obtained by X-ray crystallography on a crystalline derivative of *syn*-**26**.[11] Although this inversion sequence adds an extra step in any



Scheme 8 *Reagents*: (i) Tf_2O, proton-sponge®, −78 °C⟶RT.

preparation of the *syn* compounds (with respect to the *anti* isomers) it does perform not only an inversion (with complete stereospecificity) but also generates a protected form of the aldol adduct *in situ*. This methodology, therefore, achieves our previously stated aim of being able to prepare the *syn* diastereoisomers in addition to the *anti* ones.

Conclusion

To conclude, we have demonstrated that the reductive aldol reaction of aromatic compounds is a viable and powerful method for the construction of complex hetero- and carbocyclic molecules. The basic reaction works well under both Birch and ammonia-free conditions although it is only the AF reduction that allows the use of enolisable aldehydes in the reaction. Moreover, only the AF conditions allow effective transmetallation and subsequent control of the stereochemistry of the aldol adducts, with a clear preference for the *anti* isomer being observed. Direct access to the *syn* diastereoisomer was not possible but could be achieved indirectly by either an oxidation/reduction sequence (two steps) or by an activation/displacement protocol (one step). Thus, the objectives of controlling the basic methodology have been met and this chemistry has proven itself to be both robust and reliable: application to the synthesis of complex natural products is currently underway.

Experimental

All solvents were distilled before use. Tetrahydrofuran was freshly distilled from sodium–benzophenone ketyl radical whilst dichloromethane was freshly distilled from calcium hydride. All non-aqueous reactions were carried out under argon using oven-dried glassware.

Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography was performed on commercially available pre-coated plates (Merck silica Kieselgel $60F_{254}$).

Proton and carbon NMR spectra were recorded on a Bruker DRX 400 Fourier transform spectrometer using an internal deuterium lock. Chemical shifts are quoted in parts per million (ppm) downfield of tetramethylsilane. Coupling constants *J* are quoted in Hz and are not rationalised. The symbol * after the proton NMR chemical shift indicates that the signal disappears after a D_2O "shake". Carbon NMR spectra were recorded with broad band proton decoupling and assignments were made possible using Attached Proton Test (APT) and HMQC spectra where appropriate. Many of the compounds reported exhibit a 'doubling' of some signals because of the restricted rotation of the Boc group.

Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. Positive ion chemical ionisation (CI) mass spectra and accurate mass data were recorded on a Micromass GCT instrument connected to an Agilent 6890 Series GC system.

General experimental procedures

Method A: General procedure for Birch reduction–aldol sequence

Lithium metal (38.1 mg, 5.57 mmol) was added to a freshly distilled solution of ammonia (50 ml) and THF (10 ml). The resulting dark blue solution was stirred at −78 °C for one hour under argon. The substrate (2.0 mmol) in THF (10 ml) was added and the solution stirred for 5 minutes before adding isoprene (5 drops). The aldehyde (7.2 mmol) was added and the solution left to stir for one hour at −78 °C before quenching with saturated ammonium chloride solution (5 ml) and warming to room temperature. Once the ammonia had evaporated the reaction mixture was poured into dilute hydrochloric acid (1 M, 50 ml) and diethyl ether (50 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 50 ml). The combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure to give a crude product. Purification by chromatography on silica gel, eluting with petrol followed by petrol–acetone (4%), gave the aldol products.

Method B: General procedure for *anti*-selective reductive aldol reaction

Small strips of lithium foil (28 mg, 4.0 mmol) were placed in a Schlenk tube containing 4,4′-di-*tert*-butylbiphenyl (DBB) (1.1 g, 4.0 mmol) and some glass 'anti-bumping' granules. The tube was evacuated and purged with argon several times. The contents were stirred until the lithium foil was completely reduced to powder. Freshly distilled tetrahydrofuran (25 ml) was added (giving a turquoise solution) and the tube was cooled to −78 °C under a positive pressure of argon. The substrate (1.0 mmol) and bis(methoxyethyl)amine (BMEA) (180 µl, 1.2 mmol) in freshly distilled THF (10 ml) were added dropwise over 5 minutes. (The turquoise colour persisted throughout the course of the substrate addition). The reaction mixture was stirred at −78 °C for a further 10 minutes and 1,2-dibromoethane (300 µl, 3.5 mmol) was added. After stirring for 15 minutes, magnesium bromide diethyl etherate (280 mg, 1.1 mmol) was added in one portion and the solution was stirred rapidly for 30 minutes. The aldehyde (2.2 mmol) was then added dropwise and after a further 10 minutes the reaction was quenched with saturated ammonium chloride solution (5 ml). The reaction mixture was warmed to room temperature and poured into dilute hydrochloric acid (1 M, 50 ml) and diethyl ether (50 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 50 ml). The combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure to give a crude product. Purification by chromatography on silica gel, eluting with petrol (to recover DBB) followed by petrol–acetone (4%), gave the aldol products.

Method C: Stereochemical inversion of *anti*-aldol products

The *anti*-aldol product (0.23 mmol) and proton-sponge® (98 mg, 0.46 mmol) were dissolved in dichloromethane (1.5 ml) and the reaction was cooled to −78 °C under an argon atmosphere. Trifluoromethanesulfonic anhydride (60 µl, 0.36 mmol) was added and the orange solution stirred for one hour before warming to room temperature. The mixture was poured into dilute hydrochloric acid (1 M, 50 ml) and extracted with diethyl ether (3 × 50 ml). The combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure to give a crude product. Purification by chromatography on silica gel, eluting with petrol–acetone (5%), gave the carbamate product.

Method D: Oxidation of aldol products with Dess–Martin periodinane

A mixture of *anti* and *syn* aldol products (1.75 mmol) was dissolved in wet dichloromethane (5 ml) and added to a suspen-

sion of Dess–Martin periodinane (850 mg, 2.00 mmol) in dichloromethane (15 ml). The suspension was heated at reflux for 6 hours and cooled to room temperature. Sodium hydroxide solution (1 M, 20 ml) was added and the aqueous layer was extracted with diethyl ether (2 × 50 ml). The combined organic extracts were dried over magnesium sulfate and evaporated to give a crude product that was purified by chromatography on silica gel, eluting with petrol–acetone (5%).

Method E: Stereocontrolled reduction of ketones with cerium(III) chloride and sodium borohydride

Cerium(III) chloride heptahydrate (4.5 g, 12 mmol) was suspended in isopropanol (30 ml) and the ketone (1.6 mmol) was added in one portion. The reaction mixture was cooled to −78 °C and sodium borohydride (151 mg, 4.0 mmol) was added in one portion. After stirring for ten minutes at this temperature, the dry-ice bath was removed and the reaction was allowed to warm to room temperature with stirring for six hours. Water (50 ml) was then added and the resulting white slurry was filtered through a pad of Celite®, washing with dichloromethane. The aqueous layer was extracted with dichloromethane (3 × 75 ml) and the combined organic extracts were dried over magnesium sulfate. The solvent was evaporated to give a crude product that was purified by chromatography on silica gel, eluting with petrol–acetone (5%).

(1″*RS*,2*RS*)-1-(1′,1′-Dimethylethyl) 2-ethyl 2-[1″-hydroxy-1″-phenylmethyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, *anti*-5 and (1″*RS*,2*SR*)-1-(1′,1′-dimethylethyl) 2-ethyl 2-[1″-hydroxy-1″-phenylmethyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, *syn*-5. By method B, pyrrole **3** (239 mg, 1.00 mmol) and benzaldehyde (203 µl, 2.00 mmol) gave the *aldol products anti*-**5** and *syn*-**5** as a 1.5 : 1 mixture (264 mg, 76%).

Data for *anti*-aldol **5**: δ_H (400 MHz; $CDCl_3$) 7.33–7.21 (10 H, m, Ph), 5.95 (1 H, dt, *J* 6.8 and 2.0 Hz, CH_A=CH_B), 5.92 (1 H, dt, *J* 6.8 and 2.0 Hz, CH_A=CH_B), 5.84 (1 H, dt, *J* 6.8 and 2.0 Hz, CH$_A$=CH_B), 5.81 (1 H, dt, *J* 6.8 and 2.4 Hz, CH$_A$=CH_B), 5.76 (1 H, d, *J* 0.8 Hz, C*H*OH), 5.61 (1 H, d, *J* 1.2 Hz, C*H*OH), 4.39 (1 H, dq, *J* 10.8 and 7.2 Hz, CH_AH$_B$O), 4.37–4.28 (2 H, m, OH), 4.30 (1 H, dq, *J* 10.8 and 6.8 Hz, CH_AH$_B$O), 4.18 (1 H, dq, *J* 10.8 and 7.2 Hz, CH$_A$$H_B$O), 4.14 (1 H, dq, *J* 10.8 and 7.2 Hz, CH$_A$$H_B$O), 4.08 (1 H, dt, *J* 15.6 and 2.0 Hz, CH_AH$_B$N), 3.99 (1 H, dt, *J* 15.6 and 2.4 Hz, CH_AH$_B$N), 3.17 (1 H, dt, *J* 15.6 and 2.4 Hz, CH$_A$$H_B$N), 3.12 (1 H, dt, *J* 15.6 and 2.4 Hz, CH$_A$$H_B$N), 1.56 (9 H, s, C$Me_3$), 1.49 (9 H, s, C$Me_3$), 1.30 (3 H, t, *J* 7.2 Hz, CH$_2$CH_3) and 1.28 (3 H, t, *J* 7.2 Hz, CH$_2$CH_3); δ_C (100.6 MHz) 174.7 (C=O), 173.6 (C=O), 153.6 (C=O), 152.5 (C=O), 138.3 (C, Ph), 137.9 (C, Ph), 130.5 (CH=CH), 130.4 (CH=CH), 127.7 (Ph), 127.6 (Ph), 127.6 (Ph), 127.5 (Ph), 127.3 (Ph), 127.1 (Ph), 125.9 (CH=CH), 125.8 (CH=CH), 81.1 (C), 80.1 (C), 78.2 (C), 77.8 (C), 74.5 (CHOH), 74.1 (CHOH), 62.0 (CH$_2$O), 61.8 (CH$_2$O), 54.6 (CH$_2$N), 54.5 (CH$_2$N), 28.5 (CMe_3), 28.3 (CMe_3), 14.1 (CH$_2$*C*H$_3$) and 14.0 (CH$_2$*C*H$_3$); ν_{max}/cm^{-1} (film) 3522 (O–H), 2978, 1698 (C=O), 1394, 1368, 1159, 1099 and 1048; *m*/*z* (CI) 370 (100%, MNa$^+$), 292 (46) and 274 (34); $C_{19}H_{25}NO_5Na$ requires *M*, 370.1630. Found MNa$^+$, 370.1633.

Data for *syn*-aldol **5**: δ_H (400 MHz; $CDCl_3$) 7.31–7.19 (5 H, m, Ph), 7.11 (1 H, d, *J* 10.4 Hz, OH), 5.76 (1 H, dt, *J* 6.4 and 2.0 Hz, CH_A=CH_B), 5.66 (1 H, br. d, *J* 6.4 Hz), 5.33 (1 H, d, *J* 10.4 Hz, C*H*OH), 4.38 (1 H, dq, *J* 10.8 and 7.2 Hz, CH_ACH_BO), 4.28 (1 H, dq, *J* 10.8 and 7.6 Hz, CH_ACH_BO), 4.06 (1 H, dt, *J* 16.0 and 1.6 Hz, CH_AH$_B$N), 3.36 (1 H, dt, *J* 15.6 and 2.0 Hz, CH_AH$_B$N), 1.52 (9 H, s, CMe_3) and 1.34 (3 H, t, *J* 7.2 Hz, CH$_2$CH_3); δ_C (100.6 MHz) 169.3 (C=O), 156.5 (C=O), 139.8 (C), 128.7, 128.2, 127.7, 127.6, 81.9 (*C*Me$_3$), 81.3 (CN), 77.1 (CHO), 61.9 (CH$_2$O), 55.6 (CH$_2$N), 28.3 (CMe_3) and 14.2 (CH$_2$*C*H$_3$); ν_{max}/cm^{-1} (film) 3305 (O–H), 2980, 2934, 2871, 1748 (C=O), 1675 (C=O), 1402, 1369, 1246, 1205 and 1164; *m*/*z* (CI) 370 (63%, MNa$^+$), 348 (100, MH$^+$), 292 (92) and 274 (43); $C_{19}H_{25}NO_5Na$ requires *M*, 370.1630. Found MNa$^+$, 370.1631.

(1″*RS*,2*RS*)-1-(1′,1′-Dimethylethyl) 2-(1-methylethyl) 2-[hydroxy(5″-methyl-2″-furanyl)methyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, *syn*-6 and (1″*RS*,2*SR*)-1-(1′,1′-dimethylethyl) 2-(1-methylethyl) 2-[hydroxy(5″-methyl-2″-furanyl)methyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, *anti*-6. By general method A, pyrrole **4** (219 mg, 0.87 mmol) and 5-methylfurfural (190 µl, 2.59 mmol) gave an inseparable 1 : 1 mixture of *aldol products anti*-**6** and *syn*-**6** (284 mg, 90%); δ_H (300 MHz; $CDCl_3$) 6.98 (1 H, d, *J* 10.0 Hz, CHO*H* of *syn* isomer), 6.13–5.67 (9 H, m), 5.27 (1 H, d, *J* 10.0 Hz, C*H*OH of *syn* isomer), 5.20–5.15 (2 H, m, 2 × C*H*Me$_2$), 4.40–3.57 (5 H, m, CH$_2$N, CHO*H*), 2.27–2.23 (6 H, m, ArCH$_3$), 1.58–1.47 (18 H, m, 2 × CMe_3) and 1.36–1.24 (12 H, m, CHMe_2); ν_{max}/cm^{-1} (film) 3518 (O–H of *anti* isomer), 3292 (O–H of *syn* isomer), 2978, 2933, 2924, 1746 (C=O), 1704 (C=O), 1686 (C=O), 1455, 1400, 1254 and 1161.

(1″*RS*,2*RS*)-1-(1′,1′-Dimethylethyl) 2-(1-methylethyl) 2-[hydroxy(1″-methyl-1*H*-pyrrol-2″-yl)methyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, *anti*-7 and (1″*RS*,2*SR*)-1-(1′,1′-dimethylethyl) 2-(1-methylethyl) 2-[hydroxy(1″-methyl-1*H*-pyrrol-2″-yl)methyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, *syn*-7. By general method A, pyrrole **4** (300 mg, 1.19 mmol) and 1-methyl-2-pyrrolecarboxaldehyde (509 µl, 4.74 mmol) gave the *aldol products anti*-**7** and *syn*-**7** as a 1 : 1 mixture (406 mg, 94%).

Data for *anti*-aldol **7**: δ_H (300 MHz; $CDCl_3$) 6.51–6.46 (2 H, m), 6.12–6.07 (1 H, m), 6.06–5.95 (7 H, m), 5.81 (1 H, s, C*H*OH), 5.69 (1 H, s, C*H*OH), 5.12 (1 H, sp, *J* 6.3 Hz, C*H*Me$_2$), 5.03 (1 H, sp, *J* 6.2 Hz, C*H*Me$_2$), 4.36–4.16 (3 H, m, 2 × OH and CH_AH$_B$N), 4.10 (1 H, dt, *J* 15.3 and 1.9 Hz, CH_AH$_B$N), 3.74–3.41 (1 H, m, CH$_A$$H_B$N), 3.65 (3 H, s, NMe), 3.60 (3 H, s, NMe), 3.53 (1 H, dt, *J* 15.3 and 1.9 Hz, CH$_A$$H_B$N), 1.48 (9 H, s, C$Me_3$), 1.43 (9 H, s, C$Me_3$) and 1.34–1.12 (12 H, m, 4 × CH$_3$); δ_C (75.4 MHz, major rotomer only) 173.0 (C=O), 154.0 (C=O), 130.3, 126.2, 122.1, 108.2, 106.7, 80.0 (C–O), 69.3 (CH–O), 67.4 (CH–O), 54.7 (CH$_2$N), 34.0 (Ar-Me), 28.4 (CMe_3), 28.2 (CMe_3) and 21.5 (Me); ν_{max}/cm^{-1} (film) 3517 (O–H), 2978, 2867, 1703, 1395, 1368, 1259 and 1169; *m*/*z* (CI) 365 (6%, MH$^+$), 347 (90), 291 (100), 247 (30) and 110 (94); $C_{19}H_{28}N_2O_5$ requires *M*, 365.2076. Found MH$^+$, 365.2075.

Data for *syn*-aldol **7**: δ_H (300 MHz; $CDCl_3$) 6.65 (1 H, d, *J* 9.9 Hz, OH), 6.51 (1 H, m, Ar-H), 6.07–5.92 (2 H, m, Ar-H), 5.74 (1 H, dt, *J* 6.2 and 2.1 Hz, CH_A=H$_B$), 5.61 (1 H, dt, *J* 6.2 and 2.2 Hz, CH$_A$=H_B), 5.40 (1 H, d, *J* 9.9 Hz, C*H*OH), 5.13 (1 H, sp, *J* 6.3 Hz, C*H*Me$_2$), 4.28 (1 H, dt, *J* 16.1 and 2.1 Hz, CH_AH$_B$N), 3.99 (1 H, dt, *J* 15.9 and 2.1 Hz, CH$_A$$H_B$N), 3.62 (3 H, s, N*Me*), 1.53 (9 H, s, CMe_3) and 1.29 (6 H, t, *J* 6.0 Hz, 2 × CH$_3$); δ_C (75.4 MHz) 168.9 (C=O), 156.2 (C=O), 131.1 (C, Ar), 128.2, 127.9, 122.1, 106.8, 106.3, 81.3 (C), 81.2 (C), 69.5 (CH–O), 68.5 (CH–O), 55.9 (CH$_2$N), 34.3 (Ar-Me), 28.4 (CMe_3) and 21.7 (CHMe_2); ν_{max}/cm^{-1} (film) 3307 (O–H), 2978, 2869, 1742 (C=O), 1678 (C=O), 1400, 1369, 1252 and 1170; *m*/*z* (CI) 365 (1%, MH$^+$), 291 (15), 156 (25) and 110 (100); $C_{19}H_{28}N_2O_5$ requires *M*, 365.2076. Found MH$^+$, 365.2071.

(1″*RS*,2*RS*,2″*E*)-1-(1′,1′-Dimethylethyl) 2-(1-methylethyl) 2-[1″-hydroxy-2″-hexen-1″-yl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, *anti*-8 and (1″*RS*,2*SR*,2″*E*)-1-(1′,1′-dimethylethyl) 2-(1-methylethyl) 2-[1″-hydroxy-2″-hexen-1″-yl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, *syn*-8. By general method A, pyrrole **4** (219 mg, 1.30 mmol) and *trans*-2-hexenal (41 µl, 2.59 mmol) gave an inseparable mixture of *aldol products*: *anti*-**8** and *syn*-**8** (317 mg, 84%); δ_H (300 MHz; $CDCl_3$) 6.10 (1 H, d, *J* 10.0 Hz, CHO*H*), 6.13–5.63 (3 H, m, 3 × HC=CH), 5.45–5.25 (1 H, m, HC=CH), 5.19–4.95 (1 H, m, C*H*Me$_2$), 4.69–4.60 (1 H, m, C*H*OH), 4.40–3.93 (2 H, m, CH$_2$N), 2.09–1.94 (2 H, m, HC=CHCH_2), 1.55–1.21 (17 H, m, CMe_3, CH$_2$ and CHMe_2) and 0.95–0.85 (3 H, m, CH$_3$); ν_{max}/cm^{-1} (film) 3529 (O–H of *anti*

isomer), 3329 (O–H of *syn* isomer), 2977, 2932, 2871, 1745 (C=O), 1704 (C=O), 1683 (C=O), 1455, 1399, 1248 and 1164.

(1″*RS*,2*RS*)-1-(1′,1′-Dimethylethyl) 2-ethyl 2-[1″-hydroxyethyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, *anti*-10 and (1″*RS*,2*SR*)-1-(1′,1′-dimethylethyl) 2-ethyl 2-[1″-hydroxyethyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, *syn*-10. By method B, pyrrole **3** (239 mg, 1.00 mmol) and acetaldehyde (112 µl, 2.00 mmol) gave the *aldol products anti*-**10** and *syn*-**10** as a 7.6 : 1 mixture (200 mg, 70%).

Data for *anti*-aldol **10**: δ_H (400 MHz, $CDCl_3$) 6.12 (1 H, dt, *J* 6.4 and 2.0 Hz, C*H*$_A$=CH$_B$), 6.04 (1 H, dt, *J* 6.4 and 1.6 Hz, C*H*$_A$=CH$_B$), 5.83 (1 H, dt, *J* 6.4 and 2.0 Hz, CH$_A$=C*H*$_B$), 5.81 (1 H, dt, *J* 6.4 and 2.4 Hz, CH$_A$=C*H*$_B$), 4.74 (1 H, qd, *J* 6.4 and 2.4 Hz, C*H*Me), 4.68 (1 H, qd, *J* 6.4 and 2.4 Hz, C*H*Me), 4.36 (1 H, dt, *J* 15.6 and 2.0 Hz, C*H*$_A$H$_B$N), 4.33–4.06 (7 H, m, 2 × CH$_2$O, C*H*$_A$H$_B$N and 2 × CH$_A$*H*$_B$N), 1.46 (9 H, s, CMe$_3$), 1.43 (9 H, s, CMe$_3$), 1.27 (3 H, t, *J* 7.2 Hz, CH$_2$C*H*$_3$), 1.24 (3 H, t, *J* 7.2 Hz, CH$_2$C*H*$_3$), 1.06 (3 H, dd, *J* 6.4 and 0.8 Hz, CH*Me*) and 1.02 (3 H, dd, *J* 6.4 and 0.8 Hz, CH*Me*); δ_C (100.6 MHz) 174.1 (C=O), 173.7 (C=O), 153.8 (C=O), 152.8 (C=O), 129.9 (C=C), 129.6 (C=C), 126.5 (C=C), 126.2 (C=C), 80.8 (C), 80.3 (C), 78.2 (C), 77.5 (C), 69.0 (CHOH), 68.8 (CHOH), 61.7 (CH$_2$O), 61.5 (CH$_2$O), 55.3 (2 × CH$_2$N), 28.3 (C*Me*$_3$), 28.3 (C*Me*$_3$), 16.2 (*C*H$_3$CH), 15.6 (*C*H$_3$CH), 14.0 (*C*H$_3$CH$_2$) and 14.0 (*C*H$_3$CH$_2$); ν_{max}/cm^{-1} (film) 3540 (O–H), 2980, 2936, 2869, 1705 (C=O), 1393, 1368, 1258, 1156, 1107 and 1038; *m*/*z* (CI) 308 (100%, MNa$^+$), 230 (40) and 186 (37); $C_{14}H_{23}NO_5Na$ requires *M*, 308.1474. Found MNa$^+$, 308.1465.

Data for *syn*-aldol **10**: δ_H (400 MHz, $CDCl_3$) 5.87 (1 H, dt, *J* 6.3 and 2.0 Hz, C*H*$_A$=CH$_B$), 5.83 (1 H, d, *J* 10.7 Hz, OH), 5.62 (1 H, dt, *J* 6.3 and 2.2 Hz, CH$_A$=C*H*$_B$), 4.37–4.13 (5 H, m, C*H*Me, CH$_2$N and CH$_2$O), 1.51 (9 H, s, CMe$_3$), 1.27 (3 H, t, *J* 7.2 Hz, CH$_2$C*H*$_3$) and 1.08 (3 H, d, *J* 6.5 Hz, CH*Me*); δ_C (100.6 MHz) 169.7 (C=O), 156.1 (C=O), 129.3 (C=C), 127.6 (C=C), 81.9 (C), 81.1 (C), 70.2 (CHOH), 61.5 (CH$_2$O), 56.0 (CH$_2$N), 28.3 (C*Me*$_3$), 17.7 (CH*C*H$_3$) and 14.1 (CH$_2$*C*H$_3$); ν_{max}/cm^{-1} (film) 3348 (O–H), 2978, 2933, 2871, 1748 (C=O), 1681 (C=O), 1401, 1369, 1253, 1209 and 1169; *m*/*z* (CI) 308 (78%, MNa$^+$), 230 (100) and 186 (34); $C_{14}H_{23}NO_5Na$ requires *M*, 308.1474. Found MNa$^+$, 308.1474.

(1″*RS*,2*RS*)-1-(1′,1′-Dimethylethyl) 2-ethyl 2-[1″-hydroxy-2″-methylpropyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, *anti*-11 and (1″*RS*,2*SR*)-1-(1′,1′-dimethylethyl) 2-ethyl 2-[1″-hydroxy-2″-methylpropyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, *syn*-11. By method B, pyrrole **3** (239 mg, 1.00 mmol) and isobutyraldehyde (180 µl, 2.00 mmol) gave the *aldol products anti*-**11** and *syn*-**11** as a > 20 : 1 mixture (205 mg, 72%).

Data for *anti*-aldol **11**: δ_H (400 MHz, $CDCl_3$) 6.01 (1 H, dt, *J* 6.4 and 2.0 Hz, HC=CH), 5.96 (2 H, s, HC=CH), 5.93 (1 H, dt, *J* 6.4 and 2.0 Hz, HC=CH), 4.46–4.03 (10 H, m, C*H*$_2$N, C*H*$_2$O and C*H*OH), 3.90 (1 H, br. d, *J* 2.0 Hz, OH), 3.63 (1 H, br. d, *J* 2.4 Hz, OH), 1.87–1.74 (2 H, m, C*H*Me$_2$), 1.47 (9 H, s, ^{t}Bu), 1.44 (9 H, s, ^{t}Bu), 1.27 (3 H, t, *J* 7.2 Hz, OCH$_2$*Me*), 1.23 (3 H, t, *J* 6.8 Hz, CH$_2$*Me*), 1.00 (3 H, d, *J* 7.2 Hz, Me), 0.98 (3 H, d, *J* 6.4 Hz, Me), 0.90 (3 H, d, *J* 6.8 Hz, Me) and 0.87 (3 H, d, *J* 6.8 Hz, Me); δ_C (100.6 MHz) 174.3, 174.1, 153.8, 153.0, 129.0, 128.5, 128.6, 80.7, 80.1, 78.3, 77.9, 76.2, 75.6, 61.6, 61.4, 55.5, 55.4, 28.9, 28.6, 28.3, 22.2, 21.8, 17.2, 16.6, 14.0 and 13.9; ν_{max}/cm^{-1} (film) 3539 (O–H), 2975, 2871, 1706 (C=O), 1393, 1367, 1246, 1155, 1109 and 1041; *m*/*z* (CI) 336 (100%, MNa$^+$), 258 (47) and 213 (67); $C_{16}H_{27}NO_5Na$ requires *M*, 336.1787. Found MNa$^+$, 336.1784.

Data for *syn*-aldol **11**: δ_H (400 MHz, $CDCl_3$) 5.85 (1 H, d, *J* 10.7 Hz, OH), 5.82 (1 H, dt, *J* 6.3 and 2.2 Hz, C*H*$_A$=CH$_B$), 5.68 (1 H, dt, *J* 6.3 and 2.2 Hz, CH$_A$=C*H*$_B$), 4.33–4.13 (4 H, m, CH$_2$N and CH$_2$O), 3.98 (1 H, dd, *J* 10.7 and 4.9 Hz, CHOH), 1.75 (1 H, spd, *J* 6.7 and 4.9 Hz, C*H*Me$_2$), 1.51 (9 H, C*Me*$_3$), 1.28 (3 H, t, *J* 7.1 Hz, CH$_2$C*H*$_3$), 0.93 (3 H, d, *J* 6.9 Hz, CH*Me*$_A$Me$_B$) and 0.93 (3 H, d, *J* 6.7 Hz, CHMe$_A$*Me*$_B$); δ_C (100.6 MHz) 130.1 (CH=CH), 126.8 (CH=CH), 81.8 (C), 81.1 (C), 77.6 (CHOH), 61.6 (CH$_2$O), 55.8 (CH$_2$N), 30.5 (*C*HMe$_2$), 28.3 (C*Me*$_3$), 22.0 (CH*Me*$_A$Me$_B$), 17.4 (CHMe$_A$*Me*$_B$) and 14.1 (CH$_2$*C*H$_3$) [2 C=O resonance absent]; ν_{max}/cm^{-1} (film) 3340 (O–H), 2978, 2872, 1747 (C=O), 1681 (C=O), 1398, 1368, 1247, 1206 and 1170; *m*/*z* (CI) 336 (23%, MNa$^+$), 314 (50, MH$^+$), 258 (100) and 214 (44); $C_{16}H_{27}NO_5Na$ requires *M*, 336.1787. Found MNa$^+$, 336.1783.

(1″*RS*,2*RS*)-1-(1′,1′-Dimethylethyl) 2-ethyl 2-[1″-hydroxy-2″,2″-dimethylpropyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, *anti*-12 and (1″*RS*,2*SR*)-1-(1′,1′-dimethylethyl) 2-ethyl 2-[1″-hydroxy-2″,2″-dimethylpropyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate, *syn*-12. By general method B, pyrrole **3** (239 mg, 1.00 mmol) and pivaldehyde (276 µl, 2.50 mmol) gave the *aldol products anti*-**12** and *syn*-**12** as a 7.4 : 1 mixture (222 mg, 68%).

Data for *anti*-aldol **12**: δ_H (400 MHz; $CDCl_3$) 6.02 (1 H, dt, *J* 6.4 and 2.0 Hz, C*H*$_A$=CH$_B$), 5.98 (1 H, dt, *J* 6.4 and 2.0 Hz, C*H*$_A$=CH$_B$), 5.94 (1 H, dt, *J* 6.4 and 1.6 Hz, CH$_A$=C*H*$_B$), 5.89 (1 H, dt, *J* 6.4 and 2.0 Hz, CH$_A$=C*H*$_B$), 4.43 (1 H, dt, *J* 15.6 and 2.4 Hz, C*H*$_A$H$_B$N), 4.38–3.99 (10 H, m, CH$_2$N, C*H*OH, and C*H*$_2$O), 4.34 (1 H, dt, *J* 15.6 and 2.4 Hz, C*H*$_A$H$_B$N), 1.45 (9 H, s, COCMe$_3$), 1.44 (9 H, s, COCMe$_3$), 1.24 (3 H, t, *J* 7.2 Hz, CH$_2$C*H*$_3$), 1.22 (3 H, t, *J* 7.2 Hz, CH$_2$C*H*$_3$), 0.97 (9 H, s, CMe$_3$) and 0.96 (9 H, s, CMe$_3$); δ_C (100.6 MHz) 174.9 (C=O), 174.8 (C=O), 154.0 (C=O), 153.2 (C=O), 129.2 (CH=CH), 129.1 (CH=CH), 127.7 (CH=CH), 127.6 (CH=CH), 80.8 (C–O), 80.0 (C–O), 78.5 (CH$_2$O), 78.3 (CH$_2$O), 77.2 (CHOH), 76.5 (CHOH), 61.7, 61.5, 55.4 (CH$_2$N), 55.2 (CH$_2$N), 35.7 (C–N), 35.7 (C–N), 28.3 (COC*Me*$_3$), 28.3 (COC*Me*$_3$), 27.8 (C*Me*$_3$), 27.5 (C*Me*$_3$), 14.0 (CH$_2$*C*H$_3$) and 13.8 (CH$_2$*C*H$_3$); ν_{max}/cm^{-1} (film) 3535 (O–H), 2983, 2907, 2868, 1714 (C=O), 1392, 1368, 1160, 1102 and 1045; *m*/*z* (CI) 350 (100%, MNa$^+$), 272 (18) and 228 (26); $C_{17}H_{29}NO_5Na$ requires *M*, 350.1943. Found MNa$^+$, 350.1942.

Data for *syn*-aldol **12**: δ_H (400 MHz; $CDCl_3$) 6.40 (1 H, d, *J* 10.8 Hz, OH), 5.77 (1 H, dt, *J* 6.3 and 2.1 Hz, C*H*$_A$=CH$_B$), 5.71 (1 H, dt, *J* 6.2 and 1.8 Hz, CH$_A$=C*H*$_B$), 4.39–4.08 (4 H, m, CH$_2$N and CH$_2$O), 3.99 (1 H, d, *J* 10.7 Hz, C*H*OH), 1.49 (9 H, s, CMe$_3$, Boc), 1.27 (3 H, t, *J* 7.1 Hz, CH$_2$C*H*$_3$) and 0.96 (9 H, s, CMe$_3$); δ_C (100.6 MHz) 131.4 (CH=CH), 125.0 (CH=CH), 82.0 (C), 81.2 (C), 79.2 (CHOH), 61.7 (CH$_2$O), 55.7 (CH$_2$N), 37.2 (*C*Me$_3$), 28.3 (C*Me*$_3$), 27.7 (C*Me*$_3$) and 14.1 (CH$_2$*C*H$_3$) [2 × C=O resonances absent]; ν_{max}/cm^{-1} (film) 3317 (O–H), 2981, 2907, 2871, 1748 (C=O), 1709 (C=O), 1682 (C=O), 1393, 1368, 1253, 1194 and 1163; *m*/*z* (CI) 350 (53%, MNa$^+$), 328 (56, MH$^+$), 272 (100) and 228 (26); $C_{17}H_{29}NO_5Na$ requires *M*, 350.1943. Found MNa$^+$, 350.1941.

(2*RS*)-1-(1′,1′-Dimethylethyl) 2-ethyl 2-(1-hydroxycyclohexyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate 13. By general method B, pyrrole **3** (239 mg, 1.00 mmol) and cyclohexanone (208 µl, 2.00 mmol) gave the *aldol product* **13** (235 mg, 69%); δ_H (400 MHz; $CDCl_3$) 5.88 (1 H, dt, *J* 6.0 and 1.6 Hz, C*H*$_A$=CH$_B$), 5.84 (1 H, dt, *J* 6.4 and 2.0 Hz, CH$_A$=C*H*$_B$), 5.73* (1 H, br. s, OH), 4.28 (1 H, dt, *J* 16.0 and 1.6 Hz, C*H*$_A$H$_B$N), 4.25 (1 H, dq, *J* 10.8 and 7.2 Hz, C*H*$_A$H$_B$O), 4.13 (1 H, dq, *J* 10.8 and 7.2 Hz, CH$_A$*H*$_B$O), 4.08 (1 H, dt, *J* 16.0 and 2.0 Hz, CH$_A$*H*$_B$N), 2.50 (1 H, br. d, CH of CH$_2$), 1.82–0.95 (9 H, m, CH$_2$), 1.51 (9 H, s, C*Me*$_3$) and 1.26 (3 H, t, *J* 7.2 Hz, CH$_2$C*H*$_3$); δ_C (100.6 MHz) 169.8 (C=O), 155.8 (C=O), 129.0 (C=C), 127.2 (C=C), 84.6, 80.6, 76.1, 61.2, 55.7, 34.1 (CH$_2$), 32.1 (CH$_2$), 28.4 (C*Me*$_3$), 25.9 (CH$_2$), 21.7 (CH$_2$), 21.6 (CH$_2$) and 14.1 (CH$_3$); ν_{max}/cm^{-1} (film) 3334 (O–H), 2977, 2935, 2861, 1740 (C=O), 1681 (C=O), 1392, 1245 and 1170; *m*/*z* (CI) 362 (38%, MNa$^+$), 340 (100, MH$^+$) and 284 (46); $C_{18}H_{30}NO_5$ requires *M*, 340.2124. Found MH$^+$, 340.2134.

(1′*RS*,2*RS*)-2-(1′-Hydroxy-2′-methylpropyl)-*N*,*N*-bis(1-methylethyl)-2,5-dihydro-2-furancarboxamide, *anti*-15 and (1′*RS*,2*SR*)-2-(1′-hydroxy-2′-methylpropyl)-*N*,*N*-bis(1-methylethyl)-2,5-dihydro-2-furancarboxamide, *syn*-15. By general method B, *N*,*N*-diisopropyl-2-furancarboxamide **14** (195 mg, 1.00 mmol) and isobutyraldehyde (180 μl, 2.00 mmol) gave the *syn-aldol product* **15** (135 mg, 50%); δ_H (400 MHz, $CDCl_3$) 6.20 (1 H, dt, *J* 6.1, 2.5 Hz, CH_A=CH$_B$), 6.01 (1 H, dt, *J* 6.3, 1.8 Hz, CH$_A$=CH_B), 4.87 (1 H, sp, *J* 6.6 Hz, Me$_2$CH_AN), 4.80–4.63 (2 H, m, C$H_A H_B$O), 3.53 (1 H, dd, *J* 6.8, 4.5 Hz, C*H*OH), 3.38 (1 H, sp, *J* 6.8 Hz, Me$_2$CH_BN), 2.95 (1 H, d, *J* 7.1 Hz, O*H*), 1.91 (1 H, spd, *J* 6.8, 4.5 Hz, C*H*Me$_2$), 1.40 (3 H, d, *J* 6.8 Hz, *i*-PrN), 1.36 (3 H, d, *J* 6.8 Hz, *i*-PrN), 1.18 (3 H, d, *J* 6.8 Hz, *i*-PrN), 1.14 (3 H, d, *J* 6.8 Hz, *i*-PrN), 1.14 (3 H, d, *J* 7.1 Hz, CH*Me*$_2$) and 0.99 (3 H, d, *J* 7.1 Hz, CH*Me*$_2$); δ_C (100.6 MHz, $CDCl_3$) 171.6, 130.4, 126.8, 98.6, 80.7, 76.0, 47.7, 46.7, 30.1, 21.5, 20.9, 20.5, 20.2, 17.4; ν_{max}/cm^{-1} (film) 3440, 2964, 2929, 2873, 2850, 1606; *m*/*z* (ESI) 270 (100%, MH$^+$); and the *anti-aldol product* **15** (85 mg, 32%); δ_H (400 MHz, $CDCl_3$) 6.18 (1 H, dt, *J* 6.0, 2.5 Hz, CH_A=CH$_B$), 6.00 (1 H, dt, *J* 6.0, 1.8 Hz, CH$_A$=CH_B), 4.93 (1 H, sp, *J* 6.6 Hz, Me$_2$CH_AN), 4.79–4.67 (2 H, m, C$H_A H_B$O), 3.79 (1 H, br s, C*H*OH), 3.48 (1 H, sp, *J* 6.8 Hz, Me$_2$CH_BN), 2.51 (1 H, d, *J* 6.0 Hz, O*H*), 1.89 (1 H, spd, *J* 6.8, 4.5 Hz, C*H*Me$_2$), 1.43 (3 H, d, *J* 7 Hz, *i*-PrN), 1.38 (3 H, d, *J* 7 Hz, *i*-PrN), 1.21 (3 H, d, *J* 7 Hz, *i*-PrN), 1.14 (3 H, d, *J* 6.8 Hz, *i*-PrN), 1.04 (3 H, d, *J* 7 Hz, CH*Me*$_2$) and 0.97 (3 H, d, *J* 7 Hz, CH*Me*$_2$); δ_C (100.6 MHz) 171.4, 131.0, 126.4, 99.0, 79.3, 76.5, 47.5, 46.7, 29.5, 21.9, 21.0, 20.6, 20.5, 20.5, and 17.1; ν_{max}/cm^{-1} (film) 3325 (O–H), 2954, 2866, 1606 (C=O) and 1060; *m*/*z* (CI) 270 (100%, MH$^+$) and 198 (14); $C_{15}H_{28}NO_3$ requires *M*, 270.2069. Found MH$^+$, 270.2068.

(1′*RS*)-1-(1′-Hydroxyethyl)-*N*,*N*-bis(1″-methylethyl)-2,5-cyclohexadiene-1-carboxamide 17. By general method B, *N*,*N*-diisopropylbenzamide **16** (205 mg, 1.00 mmol) and acetaldehyde (112 μl, 2.00 mmol) gave the *aldol product* **17** (196 mg, 78%); δ_H 5.99 (1 H, dtd, *J* 10.0, 3.2 and 1.2 Hz, CH_A=CH$_B$), 5.89 (1 H, dq, *J* 10.4 and 2.0 Hz, CH$_A$=CH_B), 5.86 (1 H, dtd, *J* 10.0, 3.2 and 1.2 Hz, CH$_A$=CH_B), 5.57 (1 H, dq, *J* 10.4 and 2.4 Hz, CH_A=CH$_B$), 4.64 (1 H, sp, *J* 6.8 Hz, NCH_AMe$_2$), 4.17 (1 H, d, *J* 2.4 Hz, C*H*OH), 3.26 (1 H, sp, *J* 6.8 Hz, NCH_BMe$_2$), 2.77 (1 H, dtt, *J* 23.6, 3.2 and 2.4 Hz, CH$_A H_B$), 2.65 (1 H, dsp, *J* 23.6 and 1.6 Hz, CH$_A H_B$), 1.40 (3 H, d, *J* 6.8 Hz, Me), 1.39 (3 H, d, *J* 6.8 Hz, Me), 1.05 (3 H, d, *J* 6.4 Hz, Me), 1.04 (3 H, d, *J* 6.8 Hz, Me) and 1.03 (3 H, d, *J* 6.4 Hz, Me); δ_C (100.6 MHz) 173.2 (C=O), 127.1 (C=C), 125.6 (C=C), 125.6 (C=C), 125.3 (C=C), 72.5 (CHOH), 54.4 (C), 47.3 (CHN), 47.0 (CHN), 26.7 (CH$_2$), 20.7 (CH$_3$), 20.3 (CH$_3$), 20.1 (2 × CH$_3$) and 16.5 (CH$_3$); ν_{max}/cm^{-1} (film) 3423 (O–H), 2972, 2878, 1598 (C=O), 1439, 1368, 1280, 1211, 1126 and 1047; *m*/*z* (CI) 252 (100%, MH$^+$); $C_{15}H_{26}NO_2$ requires *M*, 252.1964. Found MH$^+$, 252.1958.

(1′*RS*)-1-(1′-Hydroxy-2′-methylpropyl)-*N*,*N*-bis(1″-methylethyl)-2,5-cyclohexadiene-1-carboxamide 18. By general method B, *N*,*N*-diisopropylbenzamide **16** (205 mg, 1.00 mmol) and isobutyraldehyde (180 μl, 1.2 mmol) gave the *aldol product* **18** (230 mg, 82%); δ_H 6.01 (1 H, dq, *J* 10.4 and 2.0 Hz, CH_A=CH$_B$), 5.91–5.86 (2 H, m, CH$_A$=CH_B), 5.62 (1 H, dq, *J* 10.4 and 2.0 Hz, CH_A=CH$_B$), 4.64 (1 H, sp, *J* 6.4 Hz, NCH_AMe$_2$), 3.83 (1 H, d, *J* 2.4 Hz, C*H*OH), 3.25 (1 H, sp, *J* 6.8 Hz, NCH_BMe$_2$), 2.83 (1 H, dtt, *J* 23.6, 3.2 and 2.4 Hz, CH$_A H_B$), 2.66 (1 H, dsp, *J* 23.6 and 1.6 Hz, CH$_A H_B$), 1.89 (1 H, spd, *J* 6.8 and 2.4 Hz, CHC*H*Me$_2$), 1.40 (3 H, d, *J* 6.8 Hz, Me), 1.37 (3 H, d, *J* 7.2 Hz, Me), 1.04 (6 H, d, *J* 6.8 Hz, 2 × Me), 0.97 (3 H, d, *J* 6.8 Hz, Me) and 1.82 (3 H, d, *J* 7.2 Hz, Me); δ_C (100.6 MHz) 173.2 (C=O), 127.4 (C=C), 126.9 (C=C), 125.4 (C=C), 124.8 (C=C), 80.6 (CHO), 54.8 (C), 47.1 (CHN), 28.3 (CHN), 26.7 (CH$_2$), 23.8 (CH*Me*), 20.8 (CH*Me*), 20.2 (CH*Me*), 20.2 (CH*Me*), 20.1 (CH*Me*) and 17.3 (CH*Me*); ν_{max}/ cm^{-1} (film) 3445 (O–H), 2962, 2874, 1597 (C=O), 1420, 1365, 1317, 1250, 1210, 1135 and 1015; *m*/*z* (CI) 280 (100%, MH$^+$); $C_{17}H_{30}NO_2$ requires *M*, 280.2277. Found MH$^+$, 280.2275.

(2*RS*)-1-(1′,1′-Dimethylethyl) 2-(1-methylethyl) 2-[(5″-methyl-2″-furanyl)carbonyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate 20. By method D, a mixture of the aldol products **6** (100 mg, 0.27 mmol) and Dess–Martin periodinane (1.16 g, 2.73 mmol) gave the *ketone* **20** (91 mg, 96%); δ_H [300 MHz, $(CD_3)_2SO$, 160 °C] 7.02 (1 H, d, *J* 3.3 Hz, ArH), 6.26 (1 H, d, *J* 3.3 Hz, ArH), 6.19 (1 H, dt, *J* 6.3 and 2.1 Hz, CH=CH), 5.96 (1 H, dt, *J* 6.3 and 2.1 Hz, CH=CH), 4.97 (1 H, sp, *J* 6.6 Hz, C*H*Me$_2$), 4.31 (1 H, dt, *J* 16.0 and 2.1 Hz, CH_AH$_B$N), 4.20 (1 H, dt, *J* 16.0 and 2.1 Hz, CH$_A H_B$N), 2.23 (3 H, s, CH$_3$), 1.29 (9 H, s, C*Me*$_3$), 1.24 (3 H, d, *J* 6.6 Hz, CH*Me*$_A$Me$_B$) and 1.24 (3 H, d, *J* 6.6 Hz, CHMe$_A$*Me*$_B$); δ_C (75.4 MHz) 167.5, 157.1, 153.2, 129.9, 129.5, 128.1, 127.5, 119.7, 108.7, 81.5, 80.9, 69.5, 54.0, 28.2, 27.7, 21.5 and 13.8; ν_{max}/cm^{-1} (film) 2979, 2931, 2869, 1744 (C=O), 1705 (C=O), 1680 (C=O), 1511, 1389, 1257 and 1108; *m*/*z* (CI) 364 (25%, MH$^+$) and 264 (100); $C_{19}H_{25}NO_6$ requires *M*, 363.1681. Found M$^+$, 363.1681.

(*RS*,2*RS*)-1-(1′,1′-Dimethylethyl) 2-(1-methylethyl) 2-[hydroxy(5″-methyl-2″-furanyl)methyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate *syn*-6. By method E, ketone **20** (85 mg, 0.23 mmol) gave the *syn-aldol* **6** (60 mg, 70%); δ_H (300 MHz, $CDCl_3$) 6.93 (1 H, d, *J* 10.0 Hz, CHO*H*), 6.04 (1 H, d, *J* 3.0 Hz, ArH), 5.86–5.83 (1 H, dt, *J* 6 and 2 Hz, ArH), 5.74 (1 H, dt, *J* 6.3 and 1.9 Hz, CH=CH), 5.65 (1 H, dt, *J* 6.3 and 1.9 Hz, CH=CH), 5.24 (1 H, d, *J* 10.0 Hz, *CH*OH), 5.13 (1 H, sp, *J* 6.3 Hz, C*H*Me$_2$), 4.19 (1 H, dt, *J* 16.0 and 2.0 Hz, CH_AH$_B$N), 3.81 (1 H, dt, *J* 16.0 and 2.0 Hz, CH$_A H_B$N), 2.20 (3 H, s, CH$_3$), 1.52 (9 H, s, C*Me*$_3$), 1.31 (3 H, d, *J* 6.3 Hz, CH*Me*$_A$Me$_B$) and 1.27 (3 H, d, *J* 6.3 Hz, CHMe$_A$*Me*$_B$); *m*/*z* (CI) 366 (5%, MH$^+$), 348 (42), 309 (80), 292 (39) and 248 (100); $C_{19}H_{28}NO_6$ requires *M*, 366.2047. Found MH$^+$, 366.2047.

(2*RS*,2″*E*)-1-(1′,1′-Dimethylethyl) 2-(1-methylethyl) 2-(2″-hexenoyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate 21. By method D, a mixture of the aldol products **8** (135 mg, 0.27 mmol) and Dess–Martin periodinane (1.60 g, 3.80 mmol) gave the *ketone* **21** (113 mg, 85%); δ_H [300 MHz, $(CD_3)_2SO$, 160 °C] 6.82 (1 H, dt, *J* 16.0 and 7.4 Hz, COCH=C*H*), 6.43 (1 H, dt, *J* 16.0 and 1.4 Hz, COC*H*=CH), 6.17 (1 H, dt, *J* 6.2 and 1.9 Hz, HC=CH), 5.77 (1 H, dt, 1 H, *J* 6.2 and 1.9 Hz, HC=CH), 4.97 (1 H, sp, *J* 6.5 Hz, CH*Me*$_2$), 4.23–4.19 (2 H, m, CH$_2$N), 2.18 (2 H, qd, *J* 6.0 and 1.4 Hz, COCH=CHCH_2), 1.51–1.37 (11 H, m, C*Me*$_3$ and CH$_2$), 1.24 (3 H, d, *J* 6.5 Hz, CH*Me*$_A$Me$_B$), 1.22 (3 H, d, *J* 6.5 Hz, CHMe$_A$*Me*$_B$) and 0.91 (3 H, t, *J* 7.2 Hz, CH$_2$CH_3); δ_C (75.4 MHz) 190.4, 167.8, 153.1, 148.9, 130.5, 127.3, 123.9, 81.1, 69.3, 54.1, 34.5, 28.2, 27.9, 21.7, 21.3 and 13.6; ν_{max}/cm^{-1} (film) 2977, 2932, 2871, 1744 (C=O), 1705 (C=O), 1630, 1389, 1259, 1159 and 1106; *m*/*z* (CI) 352 (63%, MH$^+$) and 252 (100); $C_{19}H_{30}NO_5$ requires *M*, 352.2124. Found MH$^+$, 352.2117.

(1″*RS*,2*SR*,2″*E*)-1-(1′,1′-Dimethylethyl) 2-(1-methylethyl) 2-[1″-hydroxy-2″-hexen-1″-yl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate *syn*-8. By method E, ketone **21** (85 mg, 0.25 mmol) gave the *syn-aldol* **8** (78 mg, 79%); δ_H (300 MHz, $CDCl_3$) 6.08 (1 H, d, *J* 10.0 Hz, OH), 5.77 (1 H, dt, *J* 6.3 and 1.9 Hz, HC=CH), 5.65 (1 H, dtd, *J* 15.0, 6.9 and 1.2 Hz, CH=CH), 5.57 (1 H, dt, *J* 6.3 and 1.9 Hz, CH=CH), 5.26 (1 H, dd, *J* 15.0 and 5.6 Hz, CH=CH), 5.03 (1 H, sp, *J* 6.2 Hz, CH*Me*$_2$), 4.54 (1 H, dd, *J* 10.0 and 5.6 Hz, C*H*OH), 4.18 (1 H, dt, *J* 16.0 and 2.2 Hz, CH_AH$_B$N), 3.98 (1 H, dt, *J* 16.0 and 2.2 Hz, CH$_A H_B$N), 1.86 (2 H, q, *J* 7.2 Hz, CH=CHCH_2), 1.44–1.38 (9 H, br. s, C*Me*$_3$), 1.33–1.23 (2 H, m, CH$_2$), 1.21 (3 H, d, *J* 6.2 Hz, CH*Me*$_A$Me$_B$), 1.17 (3 H, d, *J* 6.2 Hz, CHMe$_A$*Me*$_B$) and 0.78 (3 H, t, *J* 7.2 Hz, CH$_2$CH_3); δ_C (75.4 MHz) 169.0, 156.0, 132.8, 128.9, 127.5, 127.1, 81.2, 80.8, 74.7, 69.1, 55.9, 34.4, 34.3, 28.2, 22.2, 21.7 and

13.5; ν_{max}/cm^{-1} (film) 3331 (O–H), 2976, 2930, 2871, 1744 (C=O), 1681 (C=O), 1456, 1401, 1250, 1165 and 1109; *m*/*z* (CI) 354 (100%, MH$^+$), 254 (15) and 200 (24); $C_{19}H_{32}NO_5$ requires *M*, 354.2280. Found MH$^+$, 354.2279.

(1″*RS*,2*SR*)-1-(1′,1′-Dimethylethyl) 2-ethyl 2-[1″-hydroxy-1″-phenylmethyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate *syn*-5. By method E, ketone **22** (90 mg, 0.25 mmol) gave the *syn*-aldol product **5** (79 mg, 86%), spectroscopically identical to an authentic sample.

(2*RS*)-1-(1′,1′-Dimethylethyl) 2-ethyl 2-acetyl-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate 23. By method D, a mixture of aldols **10** (500 mg, 1.75 mmol) and Dess–Martin periodinane (850 mg, 2.00 mmol) gave the *ketone* **23** (463 mg, 93%); δ_H (400 MHz, $CDCl_3$) 6.14 (1 H, dt, *J* 6.4 and 2.0 Hz, CH_A=CH$_B$), 6.07 (1 H, dt, *J* 6.0 and 2.0 Hz, CH$_A$=CH_B), 5.80 (1 H, dt, *J* 6.0 and 2.0 Hz, CH$_A$=CH_B), 5.78 (1 H, dt, *J* 5.6 and 2.0 Hz, CH$_A$=CH_B), 4.36 (2 H, t, *J* 2.4 Hz, CH$_2$N), 4.31–4.16 (4 H, m, CH$_2$N and CH$_2$O), 4.24 (2 H, q, *J* 7.2 Hz, OCH$_2$), 2.28 (3 H, s, Me), 2.21 (3 H, s, Me), 1.49 (9 H, s, CMe$_3$), 1.41 (9 H, s, CMe$_3$), 1.30 (3 H, t, *J* 7.6 Hz, CH$_2$CH_3) and 1.28 (3 H, t, *J* 7.2 Hz, CH$_2$CH_3); δ_C (100.6 MHz) 201.0 (C=O), 200.1 (C=O), 167.9 (C=O), 167.6 (C=O), 153.6 (C=O), 153.1 (C=O), 131.0 (C=C), 130.7 (C=C), 130.0 (C=C), 126.9 (C=C), 83.0 (C), 82.8 (C), 81.4 (C), 80.7 (C), 61.8 (CH$_2$O), 61.8 (CH$_2$O), 54.3 (CH$_2$N), 54.1 (CH$_2$N), 28.3 (C*C*H$_3$), 28.0 (C*C*H$_3$), 26.2 (CH$_3$), 25.2 (CH$_3$), 14.1 (CH$_3$) and 14.1 (CH$_3$); ν_{max}/cm^{-1} (film) 2979, 2934, 2870, 1731 (C=O), 1705 (C=O), 1391, 1367, 1259, 1219 and 1172; *m*/*z* (CI) 306 (100%, MNa$^+$), 284 (19, MH$^+$), 250 (16) and 228 (33); $C_{14}H_{21}NO_5Na$ requires *M*, 306.1317. Found MNa$^+$, 306.1320.

(1″*RS*,2*SR*)-1-(1′,1′-Dimethylethyl) 2-ethyl 2-[1″-hydroxyethyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate *syn*-10. By method E, ketone **23** (463 mg, 1.64 mmol) gave the *syn*-aldol product **10** (415 mg, 89%), spectroscopically identical to an authentic sample.

(2*RS*)-1-(1′,1′-Dimethylethyl) 2-ethyl 2-(2″-methylpropanoyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate 24. By method D, a mixture of aldols **11** (495 mg, 1.58 mmol) and Dess–Martin periodinane (850 mg, 2.00 mmol) gave the *ketone* **24** (433 mg, 88%); δ_H (400 MHz, $CDCl_3$) 6.13 (1 H, dt, *J* 6.4 and 2.0 Hz, CH_A=CH$_B$), 6.07 (1 H, dt, *J* 6.0 and 2.0 Hz, CH_A=CH$_B$), 5.84 (1 H, dt, *J* 6.4 and 2.0 Hz, CH$_A$=CH_B), 5.81 (1 H, dt, *J* 6.4 and 2.0 Hz, CH$_A$=CH_B), 4.39 (1 H, dt, *J* 16.0 and 2.4 Hz, CH_AH$_B$N), 4.33 (1 H, dt, *J* 16.4 and 2.4 Hz, CH$_A$H$_B$N), 4.32–4.13 (6 H, m, CH$_2$N and CH$_2$O), 3.04 (1 H, sp, *J* 6.8 Hz, C*H*Me$_2$), 3.03 (1 H, sp, *J* 6.4 Hz, C*H*Me$_2$), 1.49 (9 H, s, CMe$_3$), 1.40 (9 H, s, CMe$_3$), 1.30 (3 H, t, *J* 7.2 Hz, CH$_2$CH_3), 1.29 (3 H, t, *J* 7.6 Hz, CH$_2$CH_3), 1.10 (6 H, d, *J* 6.8 Hz, CH*Me*$_2$) and 1.10 (6 H, d, *J* 6.8 Hz, CH*Me*$_2$); δ_C (100.6 MHz) 207.5 (C=O), 206.3 (C=O), 168.0 (C=O), 167.8 (C=O), 153.4 (C=O), 153.3 (C=O), 130.8 (CH=CH), 130.4 (CH=CH), 126.9 (CH=CH), 126.6 (CH=CH), 83.2, 83.1, 81.3, 80.6, 61.7, 54.3, 54.2, 35.9, 35.5, 28.3 (C*Me*$_3$), 28.0 (C*Me*$_3$), 20.7, 20.5, 19.9, 19.5, 14.2 and 14.1; ν_{max}/cm^{-1} (film) 2978, 2935, 2873, 1732 (C=O), 1706 (C=O), 1392, 1367, 1258, 1213 and 1173; *m*/*z* (CI) 334 (100%, MNa$^+$), 312 (36, MH$^+$), 256 (41) and 212 (35); $C_{16}H_{25}NO_5Na$ requires *M*, 334.1630. Found MNa$^+$, 334.1633.

(1″*RS*,2*SR*)-1-(1′,1′-Dimethylethyl) 2-ethyl 2-[1″-hydroxy-2″-methylpropyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate *syn*-11. By method E, ketone **24** (433 mg, 1.39 mmol) gave the *syn*-aldol **11** (357 mg, 82%), spectroscopically identical to an authentic sample.

(1*RS*,7a*SR*)-Ethyl 1-methyl-3-oxo-1*H*-pyrrolo[1,2-*c*][1,3]-oxazole-7a(5*H*)-carboxylate 25. By general method C, *anti*-**10** (50 mg, 175 μmol) gave the *carbamate* **25** (35 mg, 95%); δ_H (400 MHz, $CDCl_3$) 6.20 (1 H, dt, *J* 6.0 and 2.0 Hz, H_AC=CH$_B$), 5.87 (1 H, dt, *J* 6.4 and 2.8 Hz, H$_A$C=CH_B), 5.01 (1 H, q, *J* 6.8 Hz, C*H*Me), 4.50 (1 H, dt, *J* 16.0 and 2.0 Hz, CH_AH$_B$N), 4.23 (2 H, q, *J* 7.2 Hz, OCH$_2$), 4.02 (1 H, ddd, *J* 15.6, 2.8 and 1.6 Hz, CH$_A$$H_B$N), 1.41 (3 H, d, *J* 6.8 Hz, CH*Me*) and 1.29 (3 H, t, *J* 7.2 Hz, CH$_2$CH_3); δ_C (100.6 MHz) 170.6 (C=O), 161.0 (C=O), 133.9 (C=C), 126.3 (C=C), 80.3 (C), 77.4, 62.1 (CH$_2$O), 55.4 (CH$_2$N), 17.9 (CH*Me*) and 14.0 (CH$_2$*Me*); ν_{max}/cm^{-1} (film) 2984, 2936, 2880, 1760 (C=O), 1732 (C=O), 1462, 1365, 1290, 1260, 1212, 1181, 1068 and 1043; *m*/*z* (CI) 229 (62%, MNH$_4^+$), 212 (100, MH$^+$), 140 (64) and 94 (43); $C_{10}H_{14}NO_4$ requires *M*, 212.0923. Found MH$^+$, 212.0927.

(1*RS*,7a*SR*)-Ethyl 1-(1′-methylethyl)-3-oxo-1*H*-pyrrolo[1,2-*c*][1,3]oxazole-7a(5*H*)-carboxylate 26. By general method C, *anti*-**11** (30 mg, 96 μmol) gave the *carbamate* **26** (20 mg, 85%); δ_H (400 MHz, $CDCl_3$) 6.18 (1 H, dt, *J* 6.0 and 1.6 Hz, H_AC=CH$_B$), 5.99 (1 H, ddd, *J* 6.0, 2.4 and 2.0 Hz, H$_A$C=CH_B), 4.52 (1 H, d, *J* 8.4 Hz, C*H*^{i}Pr), 4.46 (1 H, dt, *J* 15.6 and 2.0 Hz, CH_AH$_B$N), 4.21 (2 H, q, *J* 6.8 Hz, OCH_2CH$_3$), 3.97 (1 H, ddd, *J* 15.6, 2.8 and 1.6 Hz, CH$_A$$H_B$N), 1.86 (1 H, dsp, *J* 8.4 and 6.8 Hz, C*H*Me$_A$Me$_B$), 1.28 (3 H, t, *J* 7.2 Hz, OCH$_2$CH_3), 1.07 (3 H, d, *J* 6.8 Hz, CH*Me*$_A$Me$_B$) and 1.03 (3 H, d, *J* 6.4 Hz, CHMe$_A$*Me*$_B$); δ_C (100.6 MHz) 170.9 (C=O), 160.8 (C=O), 133.5 (C=C), 126.6 (C=C), 85.9 (CHO), 80.1 (C), 62.2 (CH$_2$O), 54.8 (CH$_2$N), 30.6 (*C*HMe$_2$), 19.2 (CH*Me*$_A$Me$_B$), 18.1 (CHMe$_A$-*Me*$_B$) and 14.0 (CH$_2$CH$_3$); ν_{max}/cm^{-1} (film) 2969, 2939, 2880, 1775 (C=O), 1738 (C=O), 1463, 1366, 1289, 1255, 1210, 1169, 1073 and 1029; *m*/*z* (CI) 257 (40%, MNH$_4^+$), 240 (100, MH$^+$), 140 (39) and 122 (33); $C_{10}H_{14}NO_4$ requires *M*, 240.1236. Found MH$^+$, 240.1235.

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