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Stereoselective Synthesis of Densely Functionalized Pyrrolidin-2-ones by a Conjugate Addition/Nitro-Mannich/Lactamization Reaction

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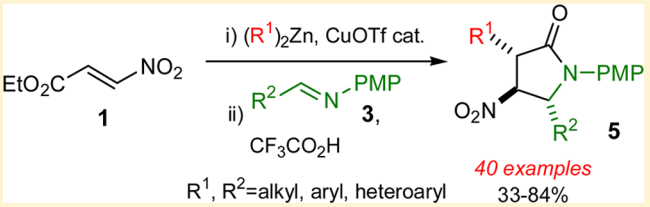
Supporting Information

ABSTRACT: Copper-catalyzed conjugate addition of diorgano zinc reagents to nitroacrylate **1** followed by a subsequent nitro-Mannich reaction and *in situ* lactamization leads to an efficient one-pot synthesis of 1,3,5-trisubstituted 4-nitropyrrolidin-2-ones (**5**). The versatility of the reaction is shown for a wide range of *N*-*p*-(methoxy)phenyl protected aldimines **3** derived from alkyl, aryl, and heteroaryl aldehydes. The densely functionalized pyrrolidin-2-ones **5** are isolated as single diastereoisomers (40 examples, 33−84% yield). An enantioselective copper-catalyzed conjugate addition of diethylzinc led to highly crystalline products that could be recrystallized to enantiopurity in high yield. A range of successful chemoselective transformations were investigated, which widens the applicability of the pyrrolidn-2-ones as stereochemically pure building blocks for further organic synthesis.



INTRODUCTION

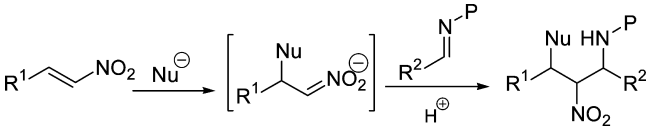
The nitro-Mannich (or aza-Henry) reaction has been developed extensively in recent years, with highly diastereoselective and enantioselective reactions being reported.[1] Direct reduction of the *β*-nitroamine products allows for an efficient synthesis of vicinal diamines,[2] found in many natural products and biologically active compounds,[3] as well as ligands for asymmetric catalysis.[4] In order to broaden the scope of the nitro-Mannich reaction we have been developing the conjugate addition of nucleophiles to nitroalkenes with *in situ* trapping of the nitronate anion with an imine (Scheme 1). This leads to a wider access to acyclic *β*-nitroamines and does not require a prerequisite synthesis of a nitroalkane (most often prepared from a nitroalkene).

We have recently reported an enantioselective conjugate addition nitro-Mannich protocol, initiated by asymmetric copper-catalyzed dialkyl zinc additions, which affords *anti*- or *syn*-*β*-nitroamines with exquisite control of stereochemistry over three contiguous centers.[5] The initial stereocenter from the conjugate addition reaction effectively controls the formation of the additional two new stereocenters from the nitro-Mannich reaction. In addition we have also investigated the addition of hydride nucleophiles in a similar protocol, which lays the foundation for an alternative method for the asymmetric synthesis of *β*-nitroamines.[6] In this paper we report a conjugate addition/nitro-Mannich/lactamization strategy that forms pyrrolidin-2-ones in one pot. We have found that conjugate addition of a diorgano zinc reagent to nitroacrylate **1** and subsequent trapping of the resultant nitronate anion **2** with an imine **3** leads to an intermediate *β*-nitroamine **4**, which cyclizes *in situ* to give a pyrrolidin-2-one **5** (Scheme 2).

The pyrrolidin-2-one structure is a significant heterocycle found in many complex natural products[7] and pharmaceutical compounds (Figure 1).[8] Currently, the synthesis of pyrrolidin-2-ones relies on methods involving cyclization of previously formed carbon skeletons such as cycloadditions,[9] amide bond formation,[10] radical cyclizations,[11] and expansion or contraction of a previously formed ring,[12] among many others.[13] These methods often involve toxic reagents and require a number of steps to obtain the desired heterocycle.

We are aware of only one other similar procedure specifically related to the work presented here, which has been reported by Dixon et al. (Scheme 2) and also generates densely substituted pyrrolidin-2-ones with three contiguous stereocenters.[14] Our

Scheme 1. Conjugate Addition Nitro-Mannich Reaction



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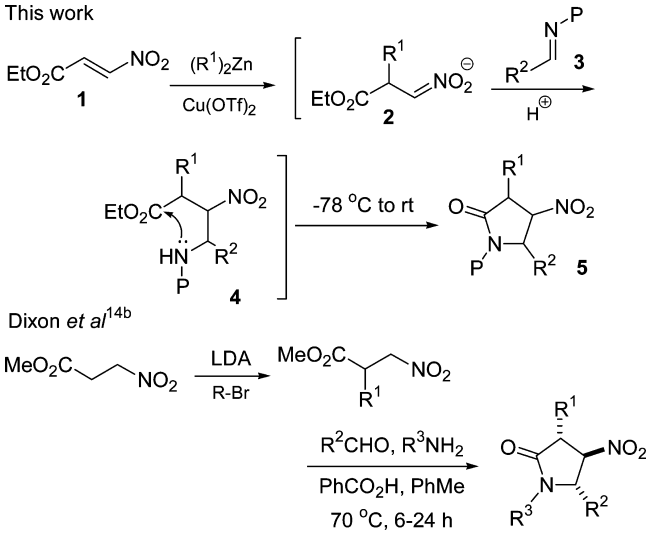
Scheme 2. Nitro-Mannich/Lactamization Strategies



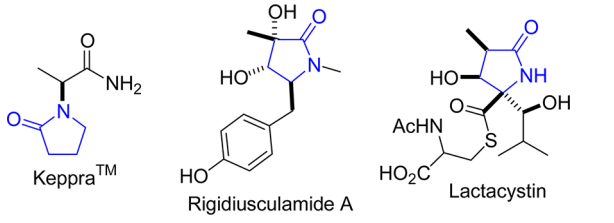


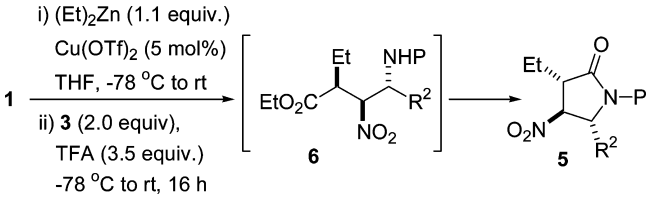
Figure 1. Pyrrolidinone-containing natural products and pharmaceutical compounds.

complementary results in contrast are made readily enantioselective by the use of chiral ligand copper complexes that control the asymmetry of the conjugate addition reaction. We have focused on the use of imines with a removable *N*-protecting group P, and the cyclization occurs spontaneously upon warming from −78 °C. With acyclic imines we isolate a single diastereoisomer, and we show that the product pyrrolidin-2-ones can be transformed into a number of different products by chemoselective reactions.

RESULTS AND DISCUSSION

As part of our studies into the enantioselective conjugate addition/nitro-Mannich protocol, initiated by asymmetric copper-catalyzed addition of dialkyl zincs,[5] we observed that treatment of **1** with diethyl zinc (1.1 equiv) at −78 °C gave the intermediate nitronate anion upon warming to rt. Recooling of the reaction to −78 °C, addition of *N*-*p*-methoxyphenyl (PMP) imine of benzaldehyde (2.0 equiv) and trifluoroacetic acid (TFA, 3.5 equiv), and allowing the reaction to warm to rt with an overnight stir gave pyrrolidinone **5a** (R^2 = Ph, P = PMP) in 67% yield as a single diastereoisomer (Scheme 3). A small solvent screen revealed that THF and diethyl ether were equally effective and superior to other less polar solvents. We have already seen that for this particular type of conjugate addition/nitro-Mannich reaction two distinct stereochemical outcomes are possible and are dependent upon the choice of solvent, which dictates whether the reaction is homogeneous or heterogeneous.[5] The polarity of nitroalkene **1** is such that in either THF or Et_2O the reaction is homogeneous. From our extensive studies, we would expect this reaction to form the *syn,anti*-*β*-nitroamine **6**, which in this reaction spontaneously

Scheme 3. General Procedure for Conjugate Addition/ Nitro-Mannich/Lactamization Reaction and Stereochemical Outcome



cyclizes to give **5**. This assumption was later confirmed by single crystal X-ray crystallography of two analogues of **5** (*vide infra*).

With the PMP group identified as the optimum imine N-protecting group, the scope of the reaction with respect to imine substituents was investigated (Table 1). All products were isolated as single diastereoisomers (except **5w**). The relative stereochemistry was confirmed by single crystal X-ray analysis[15] of **5r** and a derivative of **5q** (*vide infra*) and by analogy of coupling constants around the pyrrolidin-2-one ring (see Supporting Information).

With optimal conditions in hand, other N-protecting groups of the imine of benzaldehyde were briefly investigated. A similarly neutral *N*-*o*-methoxybenzyl (OMB) or *N*-butyl group afforded the desired pyrrolidin-2-ones **5b** and **5c** in 57% and 46% yield, respectively (R^2 = Ph, P = OMB and *n*-butyl, respectively). The more electron-withdrawing *N*-Boc group gave two acyclic, *β*-nitroamines **4** (R^1 = Et, R^2 = Ph, P = Boc) with a diastereomeric ratio of 7:1 (*syn,anti-*:*syn,syn-*) in 64% combined yield. We attribute that the lack of cyclization was due to the decreased availability of the nitrogen loan pair in the *β*-nitro-amine product.

Aromatic groups substituted in the *para* and *meta* positions consistently provided good yields (58−72%) across a range of electron-donating and -withdrawing functionalities (**5d−i**), with the exception of the *p*-methoxyphenyl analogue **5g** (49%). With *ortho* substituents the yields were reduced slightly to around 50%, perhaps due to steric interactions around the newly formed ring (**5j−l**). Two representative disubstituted aromatics (**5m**, **5n**) gave good to excellent yields. Heteroaromatic groups based on furan and thiophene gave good yields (**5o−q**, 64−70%). Pyridines gave moderate yields (**5r**, **5s**), but 2-pyrrole and 3-indene required *N*-tosyl protection (compare **5u** and **5w** with **5t** and **5v**). The *N*-Ts-2-pyrrole example (**5v**) gave the lowest yield (33%) of those investigated and was the only substrate that did not give a single diastereomer of pyrrolidin-2-one product, giving instead an 85:15 mixture of diastereoisomers presumably in favor of the diastereoisomer observed for all other examples. The thiooxazolene (**5x**) and oxazoline (**5y**) gave good yields of pyroolidin-2-one products (58% and 53% yield, respectively). The reaction conditions are also compatible with alkyl substituents (**5z**, **5aa−5cc**), to give the desired products in 38−62%. The lower yields for the primary alkyl chains (**5bb**, **5cc**) were due to the instability of the imine. A methoxy acetal (**5dd**) and an ethyl-ester substituent (**5ee**) gave good yields of desired products in 63% and 69% yield, respectively. To expand the scope further, the one-pot reaction was carried out using cyclic imine **7**[16] to give the densely substituted polycyclic pyrrolidin-2-one **8** in 60% yield in an unseparable dr of 5:1 (eq 1). The major isomer was assigned on the basis of NOESY data and by analogy of the

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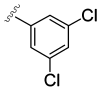
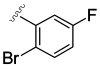
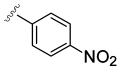
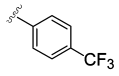
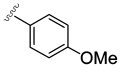
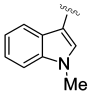
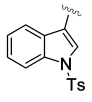
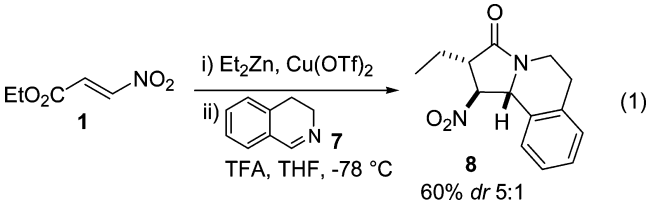
Table 1. Scope of Reaction with Respect to PMP Imine Partner[a]

Entry	R^2	Yield[b]/%	Entry	R^2	Yield[b]/%	Entry	R^2	Yield[b]/%
5a		67	**5m**		84	**5w**		33[c]
5d		60	**5n**		56	**5x**		58
5e		58	**5o**		68	**5y**		53
5f		70	**5p**		70	**5z**		62
5g		49	**5q**		64	**5aa**		56
5h		74	**5r**		50	**5bb**		38
5i		72	**5s**		42	**5cc**		40
5j		49	**5t**		-	**5dd**		63
5k		46	**5u**		56	**5ee**		69
5l		56	**5v**		-			

[a]Conditions as in Scheme 3 (P = PMP). [b]Isolated yield of single diastereoisomers. [c]Isolated as an 85:15 mixture of diastereoisomers.

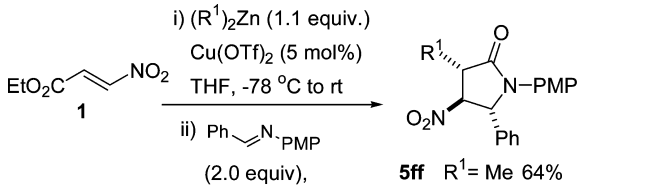


(1)

coupling constants around the pyrrolidinone ring compared to compounds **5** (see Supporting Information).

The reaction was also compatible with other diorgano zinc nucleophiles (Scheme 4). While the addition of alkyl groups was efficient, the one-pot reaction protocol using diphenyl zinc led to a complex mixture of unidentifiable products. A two -step procedure involving isolation of the phenyl conjugate addition product and then nitro Mannich reaction led to the isolation of **5hh** in 51% yield. Functionalized diorgano zinc reagents can be prepared using the tandem hydroboration/boron−zinc exchange method developed by Knochel,[17] and we have shown

Scheme 4. Use of Common Di-organo Zinc Nucleophiles



5ff R^1= Me 64%
5a R^1= Et 67%
5gg R^1= ^{i}Pr 57%
5hh R^1= Ph 51% (2 steps)

that they also participate in the conjugate addition nitro-Mannich reaction sequence,[5] which suggests they could also be compatible here.

The asymmetric catalytic addition of dialkyl zinc to nitroalkenes catalyzed by Cu-chiral ligand complexes is a well-known reaction, giving a range of products in high enantioselectivity.[18] To show that this protocol can be used to

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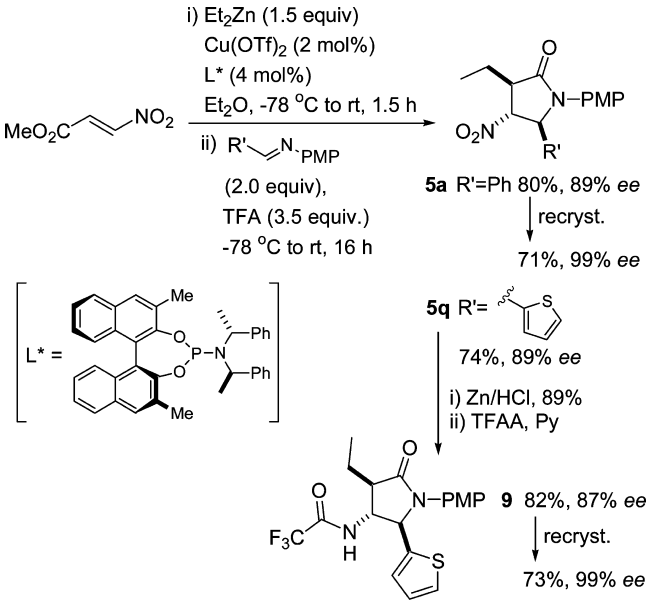
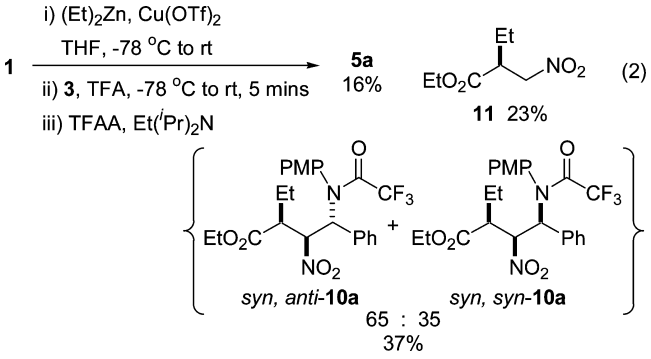
prepare enantiomerically enriched pyrolidin-2-ones we repeated the known asymmetric addition of diethyl zinc to methyl nitroacrylate[19] and intercepted the conjugate addition product with our nitro-Mannich/lactamization reaction (Scheme 5).

Scheme 5. Enantioselective Conjugate Addition/Nitro-Mannich/Lactamization Reactions



This gave enantioenriched **5a** and **5q** in high yield and 89% ee.[20] Pyrrolidin-2-one **5a** could be recrystallized from IPA/hexane to give **5a** in 71% yield and 99% ee. The absolute stereochemistry was not defined in the original publication of the asymmetric addition, so we attempted to grow suitable crystals of **5q** to use anomalous-dispersion effects in single crystal X-ray diffraction measurements. Suitable crystals were unfortunately not obtained, but reduction of **5q** to the 1,2-diamine and protection of the primary amine as the trifluoroacetamide gave **9** in high yield; **9** was highly crystalline and could be recrystallized to give a 73% yield of product with 99% ee. Anomalous-dispersion effects in the single crystal X-ray crystallographic analysis of **9** confirmed the absolute sense of chirality as depicted (Scheme 5).[15]

What is remarkable about this conjugate addition/nitro-Mannich/lactamization reaction is that for acyclic imines a single *trans,trans*-pyrrolidin-2-one diastereoisomer is isolated (except for the low yielding synthesis of **5w**). After addition of the imine and TFA at −78 °C the reaction is stirred for 1 h before the cooling bath is removed and the reaction is allowed to slowly equilibrate to room temperature and stirred for a nominal 16 h during which time both the nitro-Mannich and lactamization reactions take place. Repeat of the synthesis of **5a** (Scheme 3), but quenching the reaction with saturated $NaHCO_3$ solution 5 min after removing the −78 °C cooling bath, gave crude reaction material, which was trifluoroacetylated under our standard conditions.[5] Separation by column chromatography gave pyrrolidinone **5a** (16%), a mixture of *β*-nitrotrifluoroacetamides **10a** (37%) and the addition product **11** (23%, eq 2). The ratio of diastereoisomers of **10a** was 65:35 (*syn,anti*-:*syn,syn*-), and we assume **11** originates from degradation of other diastereoisomers of **10a** as we have previously seen during trifluoroacetamide protection of other *β*-nitroamines of this type.[5] The stereochemistry of **5a**



corresponds to the cyclization of the major *syn,anti*-**10a** diastereoisomer.

The synthesis of **5a** (Scheme 3) was repeated in d_8-THF, and aliquots were analyzed by ^{1}H NMR at time intervals directly after the removal of the −78 °C cooling bath (Table 2). After 5 min the spectrum showed only the formation of *syn,anti*-**10a** with a nearly equal quantity of the single pyrrolidin-2-one product **5a**, along with baseline traces of what we presume are other *β*-nitroamine diastereoisomers. Further analysis over 1.5 h revealed a gradual decrease in the proportion of *β*-nitroamine in favor of a single diastereoisomer of the cyclized product **5a**.

Table 2. ^{1}H NMR Studies[a]

entry	time (min)	ratio **5a**:*syn,anti*-**10a**
1	5	45:55
2	20	66:34
3	35	75:25
4	50	85:15
5	65	85:15
6	80	90:10

[a]Conditions as in Scheme 3 (P = PMP) in d_8-THF

These observations suggest that lactamization is the slowest step in this reaction sequence. We know from our previous studies concerning the conjugate addition of diethyl zinc to nitroalkenes and subsequent nitro-Mannich reaction that the *syn,anti*-diastereoisomer is by far the major diastereoisomer in homogeneous reactions.[5] In addition we have previously shown that *β*-nitroamines are susceptible to retro- and readdition.[5] The nitro Mannich reaction proceeds with high diastereoselectivity, but it seems, at ambient temperature at least, that only the *syn,anti*-*β*-nitroamine diastereoisomer cyclizes to give the all equatorial product. Any other *β*-nitroamine diastereoisomers formed could potentially equilibrate to the *syn,anti*-diastereoisomer to allow cyclization. This reaction scenario is also in line with Dixon's analysis of some relative kinetic data that also suggests the lactamization step is rate-determining in his closely related cascade reaction (Scheme 2).[14a] However, in the Dixon protocol they do see a minor pyrrolidin-2-one diastereoisomer in many cases. As they rule out any post cyclization epimerization, the minor diastereoisomer probably comes from the cyclization of a minor *β*-nitroamine diastereoisomer. This may be possible under their conditions of 70 °C in toluene, but generally not under our ambient reaction conditions.

To demonstrate the synthetic potential of these stereochemically pure building blocks, we investigated some chemoselective reactions (Scheme 6). Deprotection of the PMP group of **5a** proceeded smoothly using CAN, giving the lactam **12** in

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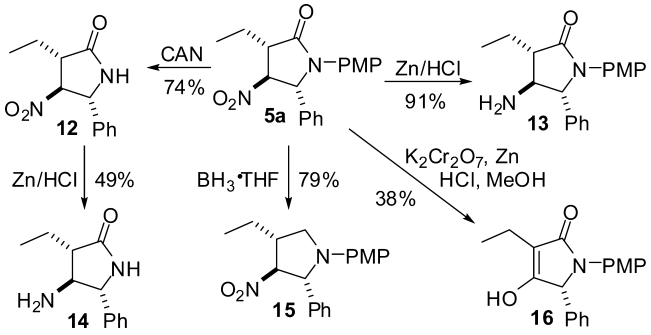
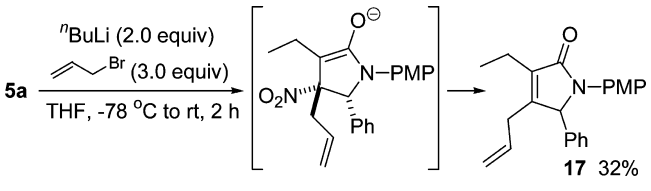
Scheme 6. Chemoselective Functional Group Interconversions



74% yield. Reduction of the nitro group to the primary amine **13** was achieved using standard Zn/HCl conditions to give a single compound in 91% crude yield as this material was unstable to chromatography. Attempted deprotection of the PMP group of **13** with CAN led to degradation under the oxidizing conditions. Fortunately reduction of the nitro function of **12** to give unprotected cyclic vicinal diamine **14** was possible in a moderate 49% yield. Removal of the carbonyl group was possible with BH_3·THF to give pyrrolidine **15** in 79% yield. Use of the Nef reaction to provide the corresponding dicarbonyl compound could provide another opportunity for further functional group addition. Attempts at using standard conditions with $TiCl_3$ led to no reaction under a variety of different conditions.[21] Treatment with chromium(II) dichloride, prepared *in situ* from reaction of potassium dichromate with 6 M HCl and zinc dust,[22] led to pyrrolone **16** in only 38% yield.[23] Unfortunately prolonged reaction did not improve the yield of this stubborn transformation.

Functionalization alpha to the carbonyl or nitro group would create more functionality in the pyrrolidin-2-one core. However treatment with a variety of bases and nucleophiles led to a mixture of unidentified products. An optimized procedure using ^{n}BuLi as base followed by the addition of allyl bromide led to the isolation of **17**, albeit in 32% yields (Scheme 7). A

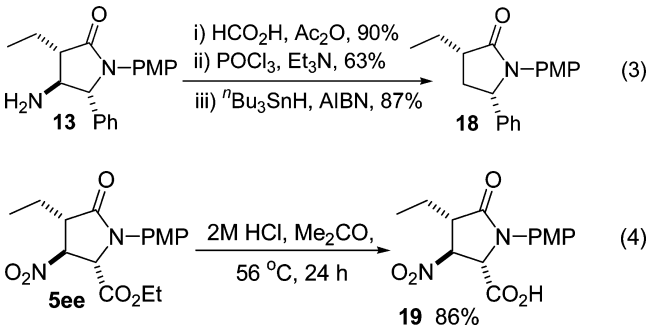
Scheme 7. Attempted α-Functionalization



reasonable mechanism to account for the formation of **17** is β-elimination of NO_2 to give the pyrrolidinone. The unexpected similarity in the acidic protons of the parent ring system **5a** seems to thwart selective functionalization in this manner.

Denitration with ^{n}Bu$_3$SnH and AIBN led to a complex mixture of products with some evidence for the formation of the oxime. A circuitous route involved formation of the formamide from the reduced product **13** (Scheme 6), followed by dehydration with $POCl_3$ to give the isocyanate[24] which was smoothly removed with ^{n}Bu$_3$SnH in refluxing toluene and AIBN to give **18** (eq 3).

A densely substituted proline like structure **19** could be accessed from the hydrolysis of ester **5ee** in high yield (eq 4).



CONCLUSION

In line with our previous work[5] the initial stereocenter formed from the copper-catalyzed conjugate addition of diorgano zinc reagents to nitroacrylate **1** controls the formation of two new stereogenic centers formed from an *in situ* nitro-Mannich reaction with added *N*-PMP protected imines. The major initial product, *syn,anti-β*-nitroamine **6**, exclusively cyclizes in a rate determining lactamization to give a range of densely functionalized pyrrolidin-2-ones **5** as single diastereoisomers. Any alternate acyclic diastereoisomers of **6**, formed in the reaction, can potentially equilibrate to allow cyclization to diastereoisomer **5**. Control of the absolute stereochemistry of the initial copper catalyzed conjugate addition reaction[19] can lead to the formation of highly crystalline, diastereomerically pure pyrrolidin-2-ones, which can be recrystallized to enantiopurity in high yield. The pyrrolidin-2-ones **5** and products generated from chemoselective reactions have the potential to be useful stereodefined building blocks for further asymmetric organic synthesis.

EXPERIMENTAL SECTION

General Procedure A for the Synthesis of Pyrrolidin-2-ones 5 (Table 1). To a solution of nitroalkene **1** (0.69 mmol) in THF (3 mL) under N_2 was added $Cu(OTf)_2$ (34.0 μmol, 5 mol %). The mixture was cooled to −78 °C, and diethyl zinc (0.76 mmol, of a 1.0 M solution in hexanes, 1.1 equiv) was added quickly dropwise. The orange mixture was stirred at this temperature for 10 min before being warmed to rt and stirred for a further 1.5 h. The dark mixture was recooled to −78 °C, and the corresponding imine (1.38 mmol, 2.0 equiv) in THF (2 mL) was added *via* cannula. The mixture was stirred for 20 min before TFA (2.41 mmol, 3.5 equiv) in THF (0.5 mL) was added *via* cannula. The mixture was stirred at this temperature for a further 1 h before being warmed to rt for 16 h. Saturated aq $NaHCO_3$ and Et_2O were then added, and the layers were separated. The aqueous phase was extracted with Et_2O, and the combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to leave crude pyrrolidinone. The pyrrolidinone was then purified further by column chromatography.

General Procedure B for the Asymmetric Synthesis of Pyrrolidinones 5a and 5q. A suspension of $Cu(OTf)_2$ (8 mg, 22.0 μmol, 5 mol %) and BINOL derived catalyst **L*** (Scheme 5, 14.7 mg, 27.0 μmol, 5 mol %) in Et_2O (3 mL) under N_2 was stirred at rt for 1 h. The mixture was cooled to −78 °C, and a solution of methyl nitroacrylate (76 mg, 580 μmol) in Et_2O (1 mL) was added, followed by diethyl zinc (640 μL, 640 μmol of a 1 M soln in hexanes, 1.1 equiv) quickly dropwise. The reaction then proceeded as for General procedure A.

General Procedure C for the Reduction of the Nitro Group. To a solution of pyrrolidinone (0.29 mmol) in EtOAc/MeOH (2:1, 6 mL) at 0 °C under N_2 was added HCl (1.47 mL of an aqueous 6 M sol, 8.82 mmol, 30.0 equiv). Zinc dust (1.15 g, 17.6 mmol, 60.0 equiv) was added portionwise over 20 min. The mixture was then warmed to rt and stirred for a further 15 h. $NaHCO_3$ was added carefully, followed by EtOAc. The layers were separated, the aqueous layer was

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extracted with EtOAc, and the combined organics werewashed with satd aq $NaHCO_3$ and brine. The pH of the aqueous layer was tested, and additional satd aq $NaHCO_3$ was added as necessary to reach pH 9. The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the product diamine.

5a. (3*R*,4*R*,5*S*)-3-Ethyl-1-(4-methoxy-phenyl)-4-nitro-5-phenyl-pyrrolidin-2-one (158 mg, 67%) as a pale yellow solid; prepared by general procedure A; mp 134−136 °C; R_f 0.28 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 3009, 2970, 1765, 1558, 1251 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (3H, t, J = 7.5), 1.83 (1H, ddq, J = 14.3, 8.2, 7.5), 2.13 (1H, dqd, J = 14.3, 7.5, 4.8), 3.32 (1H, ddd, J = 8.4, 6.8, 4.8), 3.73 (3H, s), 4.81 (1H, dd, J = 6.8, 5.2), 5.61 (1H, d, J = 5.3), 6.80 (2H, m), 7.20−7.27 (4H, m), 7.31−7.34 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (CH_3), 23.3 (CH_2), 49.2 (CH), 55.3 (CH_3), 65.8 (CH), 90.5 (CH), 114.2 (2 × *C*H), 124.9 (2 × *C*H), 126.6 (2 × *C*H), 129.2 (*C*H), 129.4 (2 × *C*H), 137.3 (Cq), 158.6 (Cq), 171.0 (*C*q), one quaternary carbon could not be distinguished; m/z (EI^+) 363 (M + Na^+, 100%); HRMS found 341.1484, $C_{19}H_{21}N_2O_4$ requires 341.1501. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05, H, 5.92, N, 8.23. Found C, 66.99, H, 5.91, N, 8.23%.

Enantioenriched sample was prepared by general procedure B to give (157 mg, 80%) as a pale yellow solid with identical spectral data to the racemic sample; HPLC (chiralcel AD 0.46 cm × 25 cm column, 90:10 hexane/IPA, 1 mL min^{-1}) 35.8 min (major), 45.0 min (minor) measured 89% ee. Recrystallization of the sample with IPA/hexane gave **5a** (140 mg, 71% overall yield, near racemic compound was isolated as solid, mother liquor contained enantiomerically enriched material) as an identical pale yellow solid; $[\alpha]_D$ −62.0 (*c* 0.98, $CHCl_3$, 20 °C); HPLC measured 99% ee.

5b. (3*S,4*S**,5*R**)-3-Ethyl-1-(2-methoxy-benzyl)-4-nitro-5-phenyl-pyrrolidin-2-one** (140 mg, 57%) as a pale yellow oil, prepared by general procedure A, except using Et_2O as the reaction solvent and 1.1 equiv of imine; R_f 0.35 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2976, 2938, 1697, 1553, 1245 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (3H, t, J = 7.5), 1.75 (1H, ddq, J = 14.4, 8.3, 7.5), 2.07 (1H, dqd, J = 14.2, 7.6, 4.6), 3.17 (1H, ddd, J = 8.4, 6.7, 4.7), 3.68 (3H, s), 3.78 (1H, d, J = 14.7), 4.67 (1H, dd, J = 6.6, 5.3), 4.80 (1H, d, J = 5.3), 5.03 (1H, d, J = 14.7), 6.76−6.89 (2H, m), 7.00 (1H, dd, J = 10.0, 2.4), 7.07−7.13 (2H, m), 7.21−7.29 (1H, m), 7.35−7.44 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9 (CH_3), 23.1 (CH_2), 40.6 (CH_2), 48.7 (CH), 55.0 (CH_3), 64.4 (CH), 90.8 (CH), 110.3 (CH), 120.6 (CH), 122.8 (Cq), 126.9 (CH), 129.1 (2 × CH), 129.2 (CH), 129.4 (CH), 129.5 (CH), 130.8 (CH), 137.5 (Cq), 157.6 (Cq), 171.8 (Cq); m/z (ESI^+) 355 (100%, MH^+); HRMS found 355.1651, $C_{20}H_{23}N_2O_4$ requires 355.1658.

5c. (3*S,4*R**,5*R**)-1-Butyl-3-ethyl-4-nitro-5-phenyl-pyrrolidin-2-one** (92 mg, 46%) as a pale yellow oil; prepared by general procedure A, except using Et_2O as the reaction solvent; R_f 0.44 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2963, 2933, 1696, 1557, 1458, 1421, 1368, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.2), 1.02 (3H, t, J = 7.4), 1.17−1.33 (2H, m), 1.35−1.44 (2H, m), 1.72 (1H, ddq, J = 14.4, 8.2, 7.4), 2.05 (1H, dqd, J = 14.0, 7.6, 4.8), 2.58 (1H, ddd, J = 13.2, 7.6, 6.0), 3.14 (1H, ddd, J = 8.4, 6.8, 4.8), 3.78 (1H, dt, J = 14.0, 8.0), 4.70 (1H, dd, J = 6.8, 5.4), 5.03 (1H, d, J = 5.4), 7.18−7.23 (2H, m), 7.38−7.46 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9 (CH_3), 13.7 (CH_3), 19.9 (CH_2), 23.1 (CH_2), 28.7 (CH_2), 40.7 (CH_2), 48.9 (CH), 64.3 (CH), 90.8 (CH), 126.9 (2 × CH), 129.5 (CH), 129.6 (2 × *C*H), 136.9 (Cq), 171.6 (Cq); m/z (ESI^+) 291 (M + H^+, 40%), 244 (M^+ − NO_2, 100%); HRMS found 291.1709, $C_{16}H_{23}N_2O_3$ requires 291.1712.

***syn,anti*-4 (R^1 = Et, R^2 = Ph, P = Boc). (2*S**,3*S**,4*R**)-Ethyl-4-(*tert*-butoxycarbonylamino)-2-ethyl-3-nitro-4-phenylbutanoate** (146 mg, 56%) as a white solid, prepared by general procedure A, except using Et_2O as the reaction solvent; mp 122−124 °C; R_f 0.28 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2977, 2934, 1705, 1555, 1367, 1241, 1161, 1018 cm^{-1}; NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.1), 1.33 (3H, t, J = 7.4), 1.42 (9H, s), 1.63 (2H, sept, J = 7.2), 2.99 (1H, app dt, J = 9.7, 6.7), 4.10−4.20 (1H, m), 4.24−4.31 (1H, m), 4.95 (1H, d, J = 9.4), 5.23 (1H, t, J = 9.4), 5.12 (1H, t, J = 9.2), 7.20−7.27 (2H, m), 7.30−7.38 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5 (CH_3), 13.9 (CH_3), 22.4 (CH_2), 28.0 (3 × CH_3), 47.4 (CH), 56.2 (CH), 61.1 (CH_2), 80.3 (Cq), 91.7 (CH), 126.7 (2 × CH), 128.5 (CH), 128.7 (CH), 129.4 (CH), 136.6 (Cq), 154.3 (Cq), 171.8 (Cq); m/z (CI^+) 381 (47%, M + H^+), 234 (100%, M + H^+ − $CO_2{}^tBu$ − NO_2); HRMS found 381.2034, $C_{19}H_{29}N_2O_6$ requires 381.2026. Anal. Calcd for $C_{19}H_{28}N_2O_6$: C, 59.98, H, 7.42, N, 7.36. Found C, 59.90, H, 7.42, N 7.27%.

***syn,syn*-4 (R^1 = Et, R^2 = Ph, P = Boc). (2*S**,3*S**,4*S**)-Ethyl-4-(*tert*-butoxycarbonylamino)-2-ethyl-3-nitro-4-phenyl-butanoate** (23 mg, 8%) as a white solid; prepared by general procedure A, except using Et_2O as the reaction solvent; mp 84−86 °C; R_f 0.33 (20% Me_2CO/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.4), 1.32 (3H, t, J = 7.2), 1.47 (9H, s), 1.60−1.67 (2H, m), 3.20 (1H, ddd, J = 11.3, 7.4, 5.4), 4.13−4.23 (1H, m), 4.24−4.33 (1H, m), 5.12 (1H, dd, J = 11.0, 3.8), 5.35 (1H, dd, J = 10.4, 3.6), 5.91 (1H, d, J = 10.4), 7.20−7.38 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2 (CH_3), 13.8 (CH_3), 23.8 (CH_2), 27.9 (3 × CH_3), 46.8 (CH), 53.3 (CH), 61.3 (CH_2), 80.0 (Cq), 92.4 (CH), 125.5 (2 × CH), 128.0 (CH), 128.6 (2 × CH), 136.7 (Cq), 154.6 (Cq), 170.8 (Cq); m/z (CI^+) 381 (17%, M + H^+), 234 (100%, M + H^+ − Boc − NO_2); HRMS found 381.2032, $C_{19}H_{29}N_2O_6$ requires 381.2026.

5d. (3*S,4*S**,5*R**)-3-Ethyl-1-(4-methoxy-phenyl)-4-nitro-5-*p*-tolyl-pyrrolidin-2-one** (23 mg, 8%) as a white solid; prepared by general procedure A; mp 104−106 °C; R_f 0.27 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2966, 1706, 1555, 1513, 1366, 1249 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 7.5), 1.83 (1H, app tq, J = 14.4, 7.5), 2.14 (1H, dqd, J = 14.2, 7.5, 4.8), 2.31 (3H, s), 3.32 (1H, ddd, J = 8.5, 6.8, 4.8), 3.74 (3H, s), 4.79 (1H, dd, J = 6.8, 5.3), 5.57 (1H, d, J = 5.3), 6.79−6.81 (2H, m), 7.09−7.15 (2H, m), 7.24−7.28 (2H, m), 7.29−7.34 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.5 (CH_3), 20.8 ($ArCH_3$), 23.0 (CH_2), 48.9 (CH), 55.0 (CH_3), 65.4 (CH), 90.3 (CH), 113.8 (2 × CH), 124.6 (2 × CH), 126.2 (2 × CH), 129.2 (Cq), 129.7 (2 × CH), 133.9 (Cq), 138.8 (Cq), 157.2 (Cq), 170.6 (Cq); m/z (ESI^-) 353 (70%, M − H^+); HRMS found 353.1513, $C_{20}H_{21}N_2O_4$ requires 353.1501. Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78, H, 6.26, N, 7.90. Found C, 67.95, H, 6.18, N, 7.56%.

5e. (3*S,4*S**,5*R**)-3-Ethyl-1-(4-methoxy-phenyl)-4-nitro-5-(4-nitro-phenyl)-pyrrolidin-2-one** (143 mg, 54%) as an off white solid; prepared by general procedure A; mp 167−169 °C; R_f 0.16 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2968, 2950, 1701, 1610, 1555, 1510, 1343, 1246, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 7.6), 1.85 (1H, app dquint, J = 14.6, 7.4), 2.13 (1H, dqd, J = 14.4. 7.6, 4.8), 3.38 (1H, app td, J = 7.8, 4.8), 3.72 (3H, s), 4.76 (1H, dd, J = 7.1, 5.8), 5.76 (1H, d, J = 5.8), 6.77−6.81 (2H, m), 7.20−7.24 (2H, m), 7.42−7.44 (2H, m), 8.61−8.20 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.7 (CH_3), 23.2 (CH_2), 48.7 (CH), 55.4 (CH_3), 64.7 (CH), 89.6 (CH), 114.6 (2 × CH), 124.7 (2 × CH), 124.9 (2 × CH), 127.0 (2 × CH), 128.8 (Cq), 144.4 (Cq), 148.4 (Cq), 157.9 (Cq), 170.7 (Cq); m/z (ES^-) 384 (30%, M − H^+), 366 (100%, M − H^+ − H_2O); HRMS found 384.1178, $C_{19}H_{18}N_3O_6$ requires 384.1196. Anal. Calcd for $C_{19}H_{19}N_3O_6$: C, 59.22, H, 4.97, N, 10.90. Found C, 58.88, H, 4.94, N, 10.75%.

5f. (3*S,4*S**,5*R**)-3-Ethyl-1-(4-methoxy-phenyl)-4-nitro-5-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one** (196 mg, 70%) as a pale yellow solid; prepared by general procedure A; mp 140−142 °C; R_f 0.20 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2969, 2939, 1704, 1555, 1512, 1323, 1248, 1166, 1122, 1112, 1067 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 7.5), 1.83 (1H, app tq, J = 14.4, 7.5), 2.12 (1H, dqd, J = 14.3, 7.5, 4.8), 3.36 (1H, app td, J = 7.6, 4.7), 3.73 (3H, s), 4.76 (1H, dd, J = 6.6, 5.5), 5.71 (1H, d, J = 5.7), 6.80 (2H, d, J = 9.0), 7.24 (2H, d, J = 9.0), 7.34 (2H, d, J = 8.4), 7.60 (2H, d, J = 7.8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.8 (CH_3), 23.3 (CH_2), 49.0 (CH), 55.4 (CH_3), 65.1 (CH), 90.0 (CH), 114.5 (3 × CH), 123.7 (1C, q, J = 270.9, CF_3), 124.7 (2 × CH). 126.6 (CH), 127.2 (2 × CH), 129.1 (Cq), 131.4 (1C, q, J = 32.4, CCF_3), 141.5 (Cq), 157.8 (Cq), 170.9 (Cq); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.2 (3F, s, CF_3); m/z (FAB^+) 409 (100%, M + H^+), 363 (35%, M + H^+ − NO_2); HRMS found 409.1385, $C_{20}H_{20}F_3N_2O_4$ requires 409.1375. Anal. Calcd for

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$C_{20}H_{19}F_3N_2O_4$: C, 58.82, H, 4.69, N, 6.86. Found C, 58.92, H, 4.65, N, 6.66%.

5g. (3*S,4*S**,5*R**)-3-Ethyl-1,5-bis(4-methoxy-phenyl)-4-nitro-pyrrolidin-2-one** (121 mg, 47%) as an off white solid; prepared by general procedure A; mp 88−90 °C; R_f 0.23 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2966, 2936, 2838, 1704, 1553, 1512, 1366, 1248, 1177, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 7.5), 1.83 (1H, app dquint, J = 14.8, 7.5), 2.13 (1H, dqd, J = 14.2, 7.5, 4.7), 3.31 (1H, ddd, J = 8.2, 7.1, 4.7), 3.73 (3H, s), 3.76 (3H, s), 4.79 (1H, dd, J = 7.0, 5.5), 5.53 (1H, d, J = 5.4), 6.78−6.80 (2H, m), 6.82−6.85 (2H, m), 7.11−7.13 (2H, m), 7.21−7.27 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9 (CH_3), 23.3 (CH_2), 49.2 (*C*H), 55.3 (CH_3), 55.4 (CH_3), 65.6 (*C*H), 90.9 (*C*H), 114.2 (2 × *C*H), 114.8 (2 × *C*H), 125.2 (2 × *C*H), 128.0 (2 × *C*H), 129.0 (*C*q), 129.5 (*C*q), 157.6 (*C*q), 160.1 (*C*q), 170.9 (*C*q); m/z (FAB^+) 371 (100% MH^+), 324 (30%, $M^+ - NO_2$); HRMS found 371.1598, $C_{20}H_{23}N_2O_5$ requires 371.1607.

5h. (3*S,4*S**,5*R**)-5-(4-Chloro-phenyl)-3-ethyl-1-(4-methoxy-phenyl)-4-nitro-pyrrolidin-2-one** (191 mg, 74%) as an off-white solid; prepared by general procedure A; mp 136−138 °C; R_f 0.34 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2967, 2936, 1702, 1554, 1510, 1246, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 7.4), 1.84 (1H, app dquint, J = 14.9, 7.5), 2.12 (1H, dqd, J = 14.3, 7.5, 4.7), 3.33 (1H, ddd, J = 8.1, 7.1, 4.7), 3.74 (3H, s), 4.77 (1H, dd, J = 7.0, 5.5), 5.59 (1H, d, J = 5.5), 6.78−6.82 (2H, m), 7.15−7.17 (2H, m), 7.20−7.23 (2H, m), 7.29−7.34 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.4 (CH_3), 22.9 (CH_2), 48.6 (*C*H), 55.2 (CH_3), 64.8 (*C*H), 89.9 (*C*H), 113.9 (2 × *C*H), 124.6 (2 × *C*H), 127.7 (2 × *C*H), 128.7 (*C*q), 129.4 (2 × *C*H), 134.8 (*C*q), 135.4 (*C*q), 157.4 (*C*q), 170.5 (*C*q); m/z (ESI^-) 373 (78%, M-H^+). Anal. Calcd for $C_{19}H_{19}N_2O_4Cl$: C, 60.88, H, 5.11, N, 7.47. Found C, 60.76, H, 5.07, N, 7.20%.

5i. (3*S,4*S**,5*R**)-3-Ethyl-1-(4-methoxy-phenyl)-4-nitro-5-*m*-tolyl-pyrrolidin-2-one** (175 mg, 72%) as an off white solid; prepared by general procedure A; mp 109−111 °C; R_f 0.32 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2966, 2938, 1704, 1556, 1517, 1367, 1248, 1182, 1032, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 7.4), 1.82 (1H, app dquint, J = 14.3, 7.5), 2.13 (1H, dqd, J = 14.2, 7.5, 4.8), 2.31 (3H, s), 3.31 (1H, ddd, J = 8.4, 6.8, 4.7), 3.74 (3H, s), 4.79 (1H, dd, J = 6.8, 5.4), 5.56 (1H, d, J = 5.4), 6.78−6.82 (2H, m), 7.08−7.15 (4H, m), 7.23−7.27 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.5 (CH_3), 20.8 (CH_3), 23.0 (CH_2), 48.9 (*C*H), 55.0 (CH_3), 65.4 (*C*H), 90.3 (*C*H), 113.8 (2 × *C*H), 124.6 (2 × *C*H), 126.2 (2 × *C*H), 129.2 (*C*q), 129.7 (2 × *C*H), 133.9 (*C*q), 138.8 (*C*q), 157.2 (*C*q), 170.6 (*C*q); m/z (ESI^+) 355 (10%, M + H^+), 308 (100%, M − NO_2); HRMS found 377.1471, $C_{20}H_{22}N_2O_4Na$ requires 377.1477.

5j. (3*S,4*S**,5*R**)-3-Ethyl-1-(4-methoxy-phenyl)-5 (2-methoxy-phenyl)-4-nitro-pyrrolidin-2-one** (125 mg, 49%) as an off white solid; prepared by general procedure A; mp 114−116 °C; R_f 0.27 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2967, 2937, 2838, 1701, 1553, 1512, 1244, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, t, J = 7.5), 1.69 (1H, ddq, J = 14.2, 9.1, 7.3), 2.09 (1H, dqd, J = 14.1, 7.8, 4.7), 3.15 (1H, app dt, J = 9.4, 4.9), 3.73 (3H, s), 3.84 (3H, s), 4.89 (1H, app t, J = 4.4), 5.92 (1H, d, J = 4.0), 6.78−6.82 (2H, m), 6.89 (2H, d, J = 8.0), 7.05 (1H, dd, J = 7.6, 1.6), 7.25−7.29 (1H, m), 7.33−7.37 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4 (CH_3), 24.0 (CH_2), 50.6 (*C*H), 55.5 (CH_3), 55.5 (CH_3), 62.3 (*C*H), 77.4 (*C*q), 88.8 (*C*H), 111.0 (2 × *C*H), 114.2 (2 × *C*H), 120.9 (*C*H), 124.4 (*C*H), 124.9 (*C*q), 128.5 (*C*H), 130.2 (*C*H), 156.7 (*C*q), 157.4 (*C*q), 171.7 (*C*q); m/z (CI^+) 370 (100%, M^+), 370 (20%, M + H^+); HRMS found 370.1515, $C_{20}H_{22}N_2O_5$ requires 370.1523.

5k. (3*S,4*S**,5*R**)-3-Ethyl-1-(4-methoxy-phenyl)-4-nitro-5-*o*-tolyl-pyrrolidin-2-one** (112 mg, 46%) as an off white solid; prepared by general procedure A; mp 102−104 °C; R_f 0.38 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2968, 2935, 1705, 1555, 1513, 1367, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 60 °C, signals at rt appear broad due to atropisomerism) δ 1.08 (3H, t, J = 7.4), 1.77 (1H, ddq, J = 14.3, 8.6, 7.3), 2.15 (1H, dqd, J = 14.3, 7.6, 5.2), 2.36 (3H, s), 3.25 (1H, app Dt, J = 8.7, 5.2), 3.75 (3H, s), 4.81 (1H, dd, J = 5.3, 4.3), 5.91 (1H, d, J = 4.3), 6.78−6.80 (2H, m), 7.11 (1H, d, J = 4.8), 7.14−7.21 (3H, m), 7.26−7.28 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4 (CH_3), 19.3 (CH_3), 23.9 (CH_2), 50.3 (*C*H), 55.4 (CH_3), 62.6 (*C*H), 89.6 (*C*H), 114.3 (2 × *C*H), 124.4 (3 × *C*H), 125.7 (*C*q), 127.0 (*C*H), 128.9 (*C*H), 129.8 (*C*q), 131.6 (*C*H), 135.7 (*C*q), 157.6 (*C*q), 171.5 (*C*q); m/z (FAB^+) 377 (15%, M + Na^+), 176 (100%); HRMS found 377.1464, $C_{20}H_{22}N_2O_4Na$ requires 377.1472.

5l. (3*S,4*S**,5*R**)-5-(2-Bromo-phenyl)-3-ethyl-1-(4-methoxy-phenyl)-4-nitro-pyrrolidin-2-one** (162 mg, 56%) as an off white solid; prepared by general procedure A, except using 1.1 equiv of imine; mp 132−134 °C; R_f 0.23 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2967, 2936, 2879, 2838, 1704, 1554, 1511, 1365, 1247, 1177, 1027 cm^{-1}; ^1H NMR (400 MHz, DMSO, 100 °C, signals at rt appear broad due to atropisomerism) δ 1.00 (3H, t, J = 7.2), 1.73 (1H, app dquint, J = 14.8, 7.6), 1.92 (1H, dqd, J = 12.0, 7.2, 5.6), 3.28 (1H, ddd, J = 12.0, 8.0, 6.4), 3.63 (3H, s), 5.11 (1H, app t, J = 5.6), 6.00 (1H, d, J = 5.2), 6.76−6.80 (2H, m), 7.14−7.23 (2H, m), 7.23−7.34 (2H, m), 7.53 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.6 (CH_3), 24.4 (CH_2), 51.2 (*C*H), 55.5 (CH_3), 64.7 (*C*H), 88.5 (*C*H), 114.4 (2 × *C*H), 123.18 (*C*q), 124.0 (*C*H), 127.5 (*C*q), 128.3 (*C*q), 129.7 (2 × *C*H), 130.6 (*C*H), 133.9 (*C*H), 136.3 (*C*H), 157.6 (*C*q), 171.7 (*C*q); m/z (ESI^+) 419 (5% M + H^+), 372 (100%, $M^+ - NO_2$); HRMS found 419.0624, $C_{19}H_{20}N_2O_4Br$ requires 419.0606. Anal. Calcd for $C_{19}H_{19}BrN_2O_4$: C, 54.43, H, 4.57, N, 6.68. Found C, 54.67, H, 4.56, N 6.65%.

5m. (3*S,4*S**,5*R**)-5-(3,5-Dichloro-phenyl)-3-ethyl-1-(4-methyoxy-phenyl)-4-nitro-pyrrolidin-2-one** (232 mg, 83%) as a white solid; prepared by general procedure A; mp 70−72 °C, R_f 0.14 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2968, 2838, 1707, 1557, 1513, 1440, 1386, 1366, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, t, J = 7.4), 1.83 (1H, app dquint, J = 14.8, 7.4), 2.15 (1H, dqd, J = 15.1, 7.6, 4.9), 3.33 (1H, ddd, J = 8.2, 7.0, 4.8), 3.77 (3H, s), 4.74 (1H, dd, J = 7.0, 5.4), 5.56 (1H, d, J = 5.5), 6.82−6.86 (2H, m), 7.11 (2H, d, J = 2.0), 7.20−7.24 (2H, m), 7.31 (1H, t, J = 2.0); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9 (CH_3), 23.4 (CH_2), 48.9 (*C*H), 55.5 (CH_3), 64.7 (*C*H), 89.8 (*C*H), 114.6 (2 × *C*H), 124.9 (2 × *C*H), 125.3 (2 × *C*H), 128.8 (*C*q), 129.7 (*C*H), 136.3 (2 × *C*q), 140.9 (*C*q), 158.0 (*C*q), 170.8 (*C*q); m/z (ESI^+) 408 (100%, M^+), 363 (78%, $M^+ - NO_2$); HRMS found 408.0636, $C_{19}H_{18}N_2O_4Cl_2$ requires 408.0638. Anal. Calcd for $C_{19}H_{18}N_2O_4Cl_2$: C, 55.76, H, 4.43, N, 6.84. Found C, 55.44, H, 4.36, N, 6.74%.

5n. (3*S,4*S**,5*R**)-5-(2-Bromo-5-fluoro-phenyl)-3-ethyl-1-(4-methyoxy-phenyl)-4-nitro-pyrrolidin-2-one** (169 mg, 56%) as a white solid; prepared by general procedure A; mp 150−152 °C; R_f 0.20 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2968, 2838, 1709, 1558, 1513, 1466, 1387, 1367, 1250, 1031, 831 cm^{-1}; ^1H NMR (400 MHz, D_6C_2SO, 100 °C, at rt signals appeared broad due to atropisomerism) δ 0.68 (3H, t, J = 7.5), 1.43 (1H, app dquint, J = 14.8, 7.4), 1.61 (1H, app dquint, J = 13.2, 6.5), 2.97 (1H app q, J = 6.8), 3.32 (3H, s), 4.87 (1H, app t, J = 6.3), 5.66 (1H, d, J = 5.5), 6.46 (2H, d, J = 8.8), 6.69−6.74 (1H, m), 6.87 (3H, d, J = 8.8), 7.24 (1H, dd, J = 8.4, 5.2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.6 (CH_3), 24.5 (CH_2), 51.0 (*C*H), 55.5 (CH_3), 64.5 (*C*H), 88.3 (*C*H), 114.5 (2 × *C*H), 117.2 (*C*q), 118.1 (2C, d, J = 22.0, *C*HCF), 124.0 (2 × *C*H), 129.3 (*C*q), 135.3 (*C*H), 138.7 (*C*q), 157.8 (*C*q), 162.3 (1C, d, J = 248.5, *C*F), 171.5 (*C*q); ^{19}F NMR (282 MHz, $CDCl_3$) δ −111.8 (1F, s, C*F*); m/z (ESI^+) 437 (100%, M + H^+), 391 (86%, $MH^+ - NO_2$); HRMS found 436.0424, $C_{19}H_{18}N_2O_4BrF$ requires 436.0429, Anal. Calcd for $C_{19}H_{18}N_2O_4BrF$: C, 52.19, H, 4.15, N, 6.41. Found C, 52.00, H, 4.11, N, 6.25%.

5o. (3*S,4*S**,5*S**)-3-Ethyl-5-(furan-2-yl)-1-(4-methoxyphenyl)-4-nitropyrrolidin-2-one** (155 mg, 68%) as an off white solid; prepared by general procedure A; mp 87−88 °C; R_f 0.33 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2967, 2937, 1703, 1556, 1513, 1385, 1369, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (3H, t, J = 7.6), 1.93 (1H, ddq, J = 14.4, 8.5, 7.4), 2.17 (1H, dqd, J = 14.2, 7.6, 4.9), 3.24 (1H, ddd, J = 8.7, 5.9, 4.9), 3.77 (3H, s), 5.12 (1H, dd, J = 5.9, 4.9), 5.55 (1H, d, J = 4.7), 6.27−6.30 (2H, m), 6.83−6.85 (2H, m), 7.07−7.10 (2H, m), 7.46 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0 (CH_3), 23.3 (CH_2), 49.3 (*C*H), 55.5 (CH_3), 60.3 (*C*H), 86.7 (*C*H), 110.9 (*C*H), 111.5 (*C*H), 114.4 (2 × *C*H), 126.6 (2 × *C*H),

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128.8 (Cq), 143.8 (CH), 148.1 (Cq), 158.6 (Cq), 170.8 (Cq); *m/z* (ESI$^+$) 353 (100%, M + Na$^+$), 331 (81%, M + H$^+$), 284 (78%, M − NO_2); HRMS found 353.1125, $C_{17}H_{18}N_2O_5Na$ requires 353.1113.

5p. (3*S,4*S**,5*R**)-3-Ethyl-5-furan-3-yl-1-(4-methoxy-phenyl)-4-nitro-pyrrolidin-2-one** (143 mg, 70%) as an orange solid; prepared by general procedure A; mp 116−118 °C; R_f 0.25 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2968, 2938, 2884, 1702, 1555, 1512, 1366, 1248, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, t, *J* = 7.5), 1.85 (1H, app dquint, *J* = 14.8, 7.4), 2.13 (1H, dqd, *J* = 14.2, 7.4, 4.7), 3.29 (1H ddd, *J* = 8.2, 7.1, 4.8), 3.76 (3H, s), 4.84 (1H, dd, *J* = 7.0, 5.6), 5.55 (1H, d, *J* = 5.5), 6.25 (1H, m), 6.81−6.86 (2H, m), 7.14−7.21 (2H, m), 7.33 (1H, s), 7.38 (1H, t, *J* = 1.6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.8 (CH_3), 23.3 (CH_2), 49.0 (CH), 55.5 (CH_3), 58.4 (CH), 89.5 (CH), 107.8 (CH), 114.6 (2 × CH), 122.4 (Cq), 125.8 (2 × CH), 129.0 (Cq), 141.4 (CH), 144.8 (CH), 158.1 (Cq), 170.6 (Cq); *m/z* (CI$^+$) 331 (100%, M + H$^+$); HRMS found 331.1294, $C_{17}H_{19}N_2O_5$ requires 331.1291. Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81, H, 5.49, N, 8.48. Found C, 61.62, H, 5.41, N, 8.35%.

5q. (3*R*,4*R*,5*R*)-3-Ethyl-1-(4-methoxy-phenyl)-4-nitro-5-thiophen-2-yl-pyrrolidin-2-one (152 mg, 64%) as an off white solid; prepared by general procedure A; mp 90−92 °C; R_f 0.32 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2967, 2936, 1701, 1553, 1511, 1362, 1246, 1030, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, t, *J* = 7.4), 1.91 (1H, app dquint, *J* = 15.0, 7.4), 2.16 (1H, dqd, *J* = 14.2, 7.5, 5.2), 3.29 (1H, ddd, *J* = 8.1, 6.8, 4.9), 3.75 (3H, s), 4.94 (1H, dd, *J* = 6.4, 5.4), 5.89 (1H, d, *J* = 5.1), 6.83 (2H, app d, *J* = 8.8), 6.91 (1H, dd, *J* = 4.0, 1.4), 7.01 (1H, d, *J* = 2.8), 7.23 (2H, app d, *J* = 9.2), 7.27 (1H, d, *J* = 4.4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.8 (CH_3), 23.5 (CH_2), 49.2 (CH), 55.4 (CH_3), 62.0 (CH), 90.6 (CH), 114.6 (2 × CH), 125.9 (2 × CH), 127.0 (CH), 127.3 (CH), 127.8 (CH), 129.0 (Cq), 140.6 (Cq), 158.1 (Cq), 170.5 (Cq); *m/z* (ESI$^+$) 369 (90%, M + Na$^+$), 300 (100%, M$^+$ − NO_2); HRMS found 369.0888, $C_{17}H_{18}N_2O_4NaS$ requires 369.0885. Anal. Calcd for $C_{17}H_{18}N_2O_4S$: C, 58.94, H, 5.24, N, 8.09. Found C, 58.84, H, 5.19, N, 8.04%.

Asymmetric sample prepared by general procedure B to give **5q** (149 mg, 74%) as a pale yellow solid identical to the racemic sample; $[\alpha]_D$ −48.1 (*c* 1, $CHCl_3$, 20 °C); HPLC (chiralcel AD 0.46 × 25 cm column, 90:10 hexane/IPA, 1 mL min^{-1}) 38.8 min (major), 46.4 min (minor) measured 89% ee.

5r. (3*S,4*S**,5*S**)-3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-(pyridin-2-yl)pyrrolidin-2-one** (118 mg, 50%) as a white solid; prepared by general procedure A; mp 115−117 °C (Et_2O/pentane); R_f 0.08 (20% Me_2CO/hexane); IR ν_{max} (thin film) 3026, 2975, 1691, 1550, 1517, 1393, 1366, 1292, 1252, 1224, 1206, 1029, 755, cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.11 (3H, t, *J* = 7.35), 1.89 (1H, ddq, 14.7, 9.0, 7.4), 2.15 (1H, dqd, *J* = 14.3, 7.6, 4.8), 3.27 (1H, ddd, *J* = 9.0, 5.8, 4.8), 3.73 (3H, s), 5.26 (1H, dd, *J* = 5.8, 4.4), 5.64 (1H, d, *J* = 4.4), 6.78 (2H, d, *J* = 9.1), 7.11 (1H, d, *J* = 7.8), 7.14 (2H, d, *J* = 9.1), 7.23 (1H, ddd, *J* = 7.5, 4.5, 0.7), 7.60 (1H, td, *J* = 7.7, 1.7), 8.63 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.3 (CH_3), 23.6 (CH_2), 49.5 (CH), 55.5 (CH_3), 67.2 (CH), 87.9 (CH), 114.4 (2 × CH), 123.2 (2 × CH), 123.9 (CH), 126.0 (CH), 129.4 (Cq), 137.1 (CH), 150.7 (CH), 155.8 (CH), 158.1 (Cq), 171.6 (Cq).; *m/z* (CI$^+$) 342 (100%, M + H$^+$); HRMS found 342.1450, $C_{18}H_{20}N_3O_4$ requires 342.1448. Anal. Calcd for $C_{18}H_{19}N_3O_4$: C, 63.33, H, 5.61, N, 12.31. Found C, 63.04, H, 5.56, N, 12.11%.

5s. (3*S,4*S**,5*R**)-3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-(pyridin-3-yl)pyrrolidin-2-one** (99 mg, 42%) as a white solid; prepared by general procedure A; mp 91−93 °C; R_f 0.05 (20% Me_2CO/hexane); IR ν_{max} (thin film) 2963, 1709, 1550, 1511, 1362, 1252, 1184, 1035, 1025, 832, 712, cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.11 (3H, t, *J* = 7.7), 1.88 (1H, ddq, *J* = 14.4, 8.0, 4.9), 2.15 (1H, dqd, *J* = 14.1, 7.5, 4.8), 3.38 (1H, ddd, *J* = 8.0, 7.3, 4.7), 3.74 (3H, s), 4.80 (1H, dd, *J* = 7.2, 5.7), 5.65 (1H, d, *J* = 5.9), 6.80 (2H, d, *J* = 9.2), 7.20 (2H, m), 7.28 (1H, d, *J* = 9.2), 7.53 (1H, dt, *J* = 7.9, 1.9), 8.54 (1H, d, *J* = 2.1), 8.57 (1H, dd, *J* = 4.8, 1.4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.7 (CH_3), 23.2 (CH_2), 48.8 (CH), 55.5 (CH_3), 63.6 (CH), 89.9 (CH), 114.6 (2 × CH), 124.2 (2 × CH), 125.3 (CH), 128.7 (CH), 133.0 (Cq), 134.4 (CH), 148.8 (CH), 150.8 (CH), 158.0 (Cq), 170.7 (Cq).; *m/z* (CI$^+$) 342 (100%, M + H$^+$), 295 (10%); HRMS found 342.1461, $C_{18}H_{20}N_3O_4$ requires 342.1458. Anal. Calcd for $C_{18}H_{19}N_3O_4$: C, 63.33, H, 5.61, N, 12.31. Found C, 63.36, H, 5.62, N, 12.24%.

5u. (3*S,4*S**,5*R**)-3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-(1-tosyl-1*H*-indol-3-yl)pyrrolidin-2-one** (206 mg, 56%) as a yellow solid; mp 131−132 °C; R_f 0.08 (20% Me_2CO/hexane); IR ν_{max} (thin film) 3104, 2935, 1709, 1553, 1511, 1445, 1363, 1350, 1244, 1174, 828, 746, 678 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.08 (3H, t, *J* = 7.4), 1.82 (1H, ddq, *J* = 14.2, 8.5, 7.2), 2.15 (1H, dqd, *J* = 14.2, 7.6, 4.8), 2.43 (3H, s), 3.38 (1H, ddd, *J* = 8.5, 6.7, 4.8), 3.76 (3H, s), 4.97 (1H, dd, *J* = 6.7, 5.2), 5.83 (1H, d, *J* = 5.3), 6.76 (2H, d, *J* = 9.0), 7.13 (2H, d, *J* = 8.4), 7.25 (2H, d, *J* = 9.0), 7.29 (1H, m), 7.35 (1H, m), 7.46 (4H, m), 7.93 (1H, d, *J* = 8.4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.1 (CH_3), 21.7 (CH_3), 23.6 (CH_2), 49.2 (CH), 55.5 (CH_3), 59.5 (CH), 88.2 (CH), 114.3 (2 × CH), 114.4 (CH), 118.3 (Cq), 119.2 (CH), 124.2 (CH), 124.8 (2 × CH), 125.8 (CH), 126.1 (CH), 126.8 (2 × CH), 127.5 (Cq), 129.3 (Cq), 130.0 (2 × CH), 134.5 (Cq), 135.7 (Cq), 145.4 (Cq), 157.8 (Cq), 170.7 (Cq).; *m/z* (ESI$^+$) 534 (100%, M + H$^+$); HRMS found 534.1674, $C_{28}H_{28}N_3O_6S$ requires 534.1699.

5w. (3*S,4*S**,5*S**)-3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-(1-tosyl-1H-pyrrol-2-yl)pyrrolidin-2-one** (110 mg, 33%), as a yellow solid; inseparable 85:15 mixture of diastereoisomers (diastereoisomer ratio calculated by C*H*Et signal, δ major = 2.86, δ minor = 3.01); prepared by general procedure A; mp 147−148 °C; R_f 0.18 (20% Me_2CO/hexane); IR ν_{max} (thin film) 3004, 2994, 2878, 1699, 1550, 1512, 1368, 1248, 1172, 1154, 833, 816, 736, 703, 671 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.13 (3H, t, *J* = 7.4), 1.59 (1H, m), 2.12 (1H, dqd, *J* = 14.8, 7.4, 4.8), 2.50 (3H, s), 2.86 (1H, m), 3.74 (3H, s), 4.94 (1H, s), 6.02 (1H, s), 6.10 (1H, s), 6.22 (1H, t, *J* = 3.4), 6.58 (2H, d, *J* = 9.1), 6.91 (2H, d, *J* = 9.2), 7.38 (3H, m), 7.63 (2H, d, *J* = 8.2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.0 (CH_3), 21.7 (CH_3), 25.5 (CH_2), 52.3 (CH), 55.3 (CH_3), 59.4 (CH), 86.4 (CH), 111.7 (2 × CH), 113.9 (2 × CH), 114.9 (CH), 123.2 (2 × CH), 124.0 (CH), 126.9 (CH), 128.3 (CH), 129.8 (CH), 130.5 (2 × CH), 135.3 (Cq), 145.9 (Cq), 157.1 (Cq), 171.6 (Cq); *m/z* (EI$^+$) 483 (20%, M$^+$), 281 (24%), 155 (22%, Ts$^+$), 91 (100%, $PhCH_2^+$); HRMS found 483.1451, $C_{24}H_{25}N_3O_6S$ requires 483.1464. Anal. Calcd for $C_{24}H_{25}N_3O_6S$: C, 59.61, H, 5.21, N, 8.69. Found C, 59.52, H, 5.20, N, 8.61.

Minor diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.12 (3H, t, *J* = 7.4), 1.33 (1H, m), 2.12 (1H, m), 2.47 (3H, s), 3.01 (1H, ddd, J = 9.6, 7.3, 4.6), 3.74 (3H, s), 5.73 (1H, s), 6.20 (1H, s), 6.22 (1H, s), 6.27 (1H, t, *J* = 3.4), 6.61 (2H, d, *J* = 9.1), 6.98 (2H, d, *J* = 9.0), 7.38 (3H, m), 7.60 (2H, d, *J* = 8.2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.2(CH_3), 18.9 (CH), 21.7 (CH_3), 45.8 (CH), 55.3 (CH_3), 60.0 (CH), 86.6 (CH), 112.0 (2 × CH), 113.9 (2 × CH), 114.6 (CH), 123.2 (CH), 124.4 (CH), 126.7 (2 × CH), 129.6 (CH), 130.3 (CH), 171.0 (Cq), 4 carbons missing.

5x. (3*S,4*S**,5*S**)-3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-(thiazol-2-yl)pyrrolidin-2-one** (139 mg, 58%) as a yellow solid; prepared by general procedure A; mp 121−122 °C; R_f 0.31 (30% EtOAc/hexane); IR ν_{max} (thin film) 2961, 1716, 1558, 1512, 1440, 1390, 1363, 1248, 1187, 1029, 833, 782, 752 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.14 (3H, t, *J* = 7.1), 1.90 (1H, ddq, *J* = 14.3, 8.9, 7.1), 2.15 (1H, dqd, *J* = 14.0, 7.6, 4.9), 3.25 (1H, dt, *J* = 9.0, 5.0), 3.78 (3H, s), 5.36 (1H, dd, *J* = 5.1, 3.8), 6.02 (1H, d, *J* = 4.2), 6.87 (2H, d, *J* = 9.2), 7.25 (2H, d, *J* = 9.2), 7.31 (1H, d, *J* = 3.0), 7.80 (1H, d, *J* = 3.4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.2 (CH_3), 23.7 (CH_2), 49.7 (CH), 55.5 (CH_3), 63.3 (CH), 87.4 (CH), 114.6 (2 × CH), 121.0 (CH), 126.4 (2 × CH), 128.7 (Cq), 143.6 (CH), 158.6 (Cq), 165.7 (Cq), 171.1 (Cq).; *m/z* (EI$^+$) 347 (100%, M$^+$), 300 (55%, M$^+$ − HNO_2); HRMS found 347.0940, $C_{16}H_{17}N_3O_4S$ requires 347.0934. Anal. Calcd for $C_{16}H_{17}N_3O_4S$: C, 55.32, H, 4.93, N, 12.10. Found C, 55.23, H, 4.89, N, 12.02%.

5y. (3*S,4*S**,5*S**)-3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-(oxazol-2-yl)pyrrolidin-2-one** (121 mg, 53%) as a white solid; prepared by general procedure A; mp 97−98 °C; R_f 0.15 (20% Me_2CO/hexane); IR ν_{max} (thin film) 3128, 2964, 1706, 1562, 1509, 1387, 1243, 1179, 1115, 1031, 834, 779.5 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.17 (3H, t, *J* = 7.5), 1.96 (1H, ddq, *J* = 14.3, 8.7, 7.4), 2.19 (1H, dqd, *J* = 14.3, 7.6, 4.9), 3.25 (1H, ddd, *J* = 8.7, 5.7, 4.9), 3.78 (3H, s), 5.28 (1H, dd, *J* = 5.6, 4.4), 5.79 (1H, d, *J* = 4.4), 6.86 (2H, d, *J* = 9.0), 7.11

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(1H, s), 7.19 (2H, d, J = 9.0), 7.62 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.1 (CH_3), 23.4 (CH_2), 49.2 (CH), 55.5 (CH_3), 59.6 (CH), 85.6 (CH), 114.6 (2 × CH), 126.4 (2 × CH), 128.2 (CH), 128.6 (Cq), 140.5 (CH), 158.8 (Cq), 159.3 (Cq), 170.8 (Cq); m/z (EI$^+$) 331 (100%, M$^+$), 284 (72%, M$^+$ − HNO_2); HRMS found 331.1155, $C_{16}H_{17}N_3O_5$ requires 331.1163. Anal. Calcd for $C_{16}H_{17}N_3O_5$: C, 58.00, H, 5.17, N, 12.68. Found C, 57.97, H, 5.09, N, 12.64%.

5z. (3*S,4*S**,5*R**)-5-Cyclohexyl-3-ethyl-1-(4-methoxy-phenyl)-4-nitro-pyrrolidin-2-one** (147 mg, 62%) as an off white solid; prepared by general procedure A; mp 122−124 °C; R_f 0.35 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2929, 2855, 1698, 1555, 1512, 1450, 1366, 1248, 1033 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.81 (1H, dq, J = 12.4, 3.3), 0.98 (1H, q, J = 12.6, 3.2), 1.10 (3H, t, J = 7.4), 1.05−1.20 (3H, m), 1.51 (2H, d, J = 8.0), 1.64−1.74 (5H, m), 2.10 (1H, dqd, J = 9.5, 7.6, 4.8), 3.11 (1H, ddd, J = 9.4, 6.0, 4.8), 3.83 (3H, s), 4.51 (1H, app t, J = 4.2), 4.81 (1H, app t, J = 5.4), 6.94 (2H, m), 7.23 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2 (CH_3), 23.4 (CH_2), 25.6 (CH_2), 25.8 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 28.5 (CH_2), 38.1 (CH), 50.0 (CH), 55.6 (CH_3), 66.8 (CH), 84.4 (CH), 114.7 (2 × CH), 126.6 (2 × CH), 129.0 (Cq), 158.4 (Cq), 171.0 (Cq); m/z (FAB$^+$) 369 (100% MNa$^+$); HRMS found 369.1794, $C_{19}H_{26}N_2O_4Na$ requires 369.1790.

5aa. (3*S,4*S**,5*R**)-3-Ethyl-5-isopropyl-1-(4-methoxy-phenyl)-4-nitro-pyrrolidin-2-one** (119 mg, 56%) as a white solid; prepared by general procedure A; mp 116−118 °C; R_f 0.29 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2966, 2937, 2878, 1702, 1557, 1513, 1368, 1249, 1033, 836 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (3H, d, J = 6.8), 0.96 (3H, d, J = 6.8), 1.12 (3H, t, J = 7.3), 1.73 (1H, ddq, J = 14.2, 9.0, 7.4), 2.04−2.18 (2H, m), 3.15 (1H, ddd, J = 9.1, 6.3, 4.6), 3.82 (3H, s), 4.56 (1H, dd, J = 5.1, 3.8), 4.76 (1H, dd, J = 6.3, 5.1), 6.93−6.96 (2H, m), 7.22−7.27 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.1 (CH_3), 14.9 (CH_3), 17.7 (CH_3), 23.3 (CH_2), 27.7 (CH), 49.9 (CH), 55.6 (CH_3), 66.9 (CH), 83.7 (CH), 114.2 (2 × CH), 126.3 (2 × CH), 128.8 (Cq), 158.4 (Cq), 170.9 (Cq); m/z (CI$^+$) 307 (100%, MH$^+$); HRMS found 307.1659, $C_{16}H_{23}N_2O_4$ requires 307.1658.

5bb. (3*S,4*S**,5*R**)-3-Ethyl-1-(4-methoxy-phenyl)-4-nitro-5-pentyl-pyrrolidin-2-one** (88 mg, 38%) as an orange oil; prepared by general procedure A; R_f 0.29 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2958, 2861, 1699, 1552, 1511 1247, 1032 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.82 (3H, t, J = 6.9), 1.10 (3H, t, J = 7.4), 1.16−1.30 (6H, m), 1.44−1.50 (1H, m), 1.73−1.81 (2H, m), 2.09 (1H, dqd, J = 15.0, 7.6, 4.8), 3.19 (1H ddd, J = 8.7, 6.0, 5.0), 3.81 (3H, s), 4.48 (1H, ddd, J = 8.5, 4.5, 3.5), 4.71 (1H, dd, J = 5.9, 5.2), 6.92−6.94 (2H, m), 7.20−7.21 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0 (CH_3), 13.9 (CH_3) 22.4 (CH_2), 23.6 (CH_2), 23.7 (CH_2), 31.4 (CH_2), 32.5 (CH_2), 49.5 (CH), 55.6 (CH_3), 62.5 (CH), 87.4 (CH), 114.7 (2 × CH), 126.6 (2 × CH), 128.9 (Cq), 158.5 (Cq), 170.8 (Cq), m/z (CI$^+$) 335 (100%, MH$^+$); HRMS found 335.1962, $C_{18}H_{27}N_2O_4$ requires 335.1971. Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 58.00, H, 5.17, N, 12.68. Found C, 57.97, H, 5.09, N, 12.64%.

5cc. (3*S,4*S**,5*R**)-3-Ethyl-1-(4-methoxyphenyl)-5-methyl-4-nitropyrrolidin-2-one** (78 mg, 40%) as a colorless oil. Prepared by general procedure A, with the exception that acetaldehyde imine was formed and used *in situ*. To a solution of acetaldehyde (77 μL, 1.38 mmol) in THF (3 mL) were added under N_2 dried 4 Å molecular sieves (1.4 g) and the mixture cooled at −78 °C. Then a solution of *p*-anisidine (170 mg, 1.38 mmol) in THF (1 mL) was added and the mixture stirred at this temperature for 1.5 h. The solution was then transferred into the reaction *via* cannula while kept cold. R_f 0.22 (20% EtOAc/hexanes); IR ν_{max} (thin film) 2967, 1702, 1554, 1513, 1368, 1248, 1033, 834 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.07 (3H, t, J = 7.4), 1.35 (3H, d, J = 6.3), 1.79 (1H, m), 2.08 (1H, m), 3.26 (1H, ddd, J = 8.3, 7.3, 4.7), 3.81 (3H, s), 4.49 (1H, app q, J = 6.2), 4.60 (1H, dd, J = 7.2, 5.7), 6.93 (2H, app d, J = 8.9), 7.18 (2H, app d, J = 8.9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.6 (CH_3), 19.3 (CH_3), 23.1 (CH_2),48.5 (CH), 55.4 (CH_3), 58.0 (CH), 89.3 (CH), 114.5 (2 × CH), 126.6 (2 × CH), 128.4 (Cq), 158.4 (Cq), 170.4 (Cq), m/z (EI$^+$) 278 (5%, M$^+$), 91 (100%); HRMS found 278.12631, $C_{14}H_{18}N_2O_4$ requires 278.12611. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42, H, 6.52, N, 10.07. Found C, 60.31, H, 6.61, N, 9.77%.

5dd. (2*S,3*S**,4*S**)-3-Ethyl-5-(dimethoxymethyl)-1-(4-methoxy-phenyl)-4-nitropyrrolidin-2-one** (147 mg, 63%) as a white solid; Prepared by general procedure A; mp 112−113 °C; R_f 0.41 (30% EtOAc/hexanes); IR ν_{max} (thin film) 2939, 1698, 1548, 1510, 1370, 1249, 1069, 1034, 834, 754 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.14 (3H, t, J = 7.4), 1.81 (1H, ddq, J = 14.0, 9.7, 7.2), 2.09 (1H, dqd, J = 14.0, 7.4, 4.3), 2.97 (1H, dt, J = 9.8, 4.6), 3.38 (3H, s), 3.40 (3H, s), 3.84 (3H, s), 4.24 (1H, d, J = 2.4), 4.76 (1H, dd, J = 3.2, 2.6), 5.07 (1H, dd, J = 4.9, 3.4), 6.97 (2H, d, J = 8.9), 7.30 (2H, d, J = 9.0); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.3 (CH_3), 23.1 (CH_2), 50.2 (CH), 55.5 (CH_3), 56.9 (CH_3), 57.9 (CH_3), 64.3 (CH), 82.1 (CH), 102.3 (CH), 114.7 (2 × CH), 126.2 (2 × CH), 128.8 (Cq), 158.3 (Cq), 171.7 (Cq).; m/z (EI$^+$) 338 (75%, M$^+$), 217 (85%, M$^+$ − NO_2 −CH(OMe)$_2$), 114 (100%); HRMS found 338.1472, $C_{16}H_{22}N_2O_6$ requires 338.1478. Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80, H, 6.55, N, 8.28. Found C, 56.70, H, 6.51, N, 8.11%.

5ee. (2*S,3*S**,4*S**)-4-Ethyl-1-(4-methoxy-phenyl)-3-nitro-5-oxo-pyrrolidine-2-carboxylic Acid Ethyl Ester** (160 mg, 69%) as an orange oil; Prepared by general procedure A; R_f 0.35 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2970, 2938, 2839, 1743, 1708, 1555, 1511, 1369, 1245, 1194, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (3H, t, J = 7.5), 1.21 (3H, t, J = 7.3), 1.79 (1H, ddq, J = 14.7, 8.8, 7.3), 2.11 (1H, dqd, J = 15.2, 7.6, 5.1), 3.14 (1H, ddd, J = 9.2, 5.0, 4.3), 3.73 (3H, s), 4.21 (2H, dq, J = 7.1, 1.9), 4.99 (1H, dd, J = 4.2, 3.4), 5.21 (1H, d, J = 3.3), 6.93 (2H, m), 7.33 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2 (CH_3), 14.0 (CH_3), 23.5 (CH_2), 49.5 (CH), 55.5 (CH_3), 61.5 (CH_2), 62.9 (CH), 84.5 (CH), 114.5 (2 × CH), 125.9 (2 × CH), 129.2 (Cq), 158.6 (Cq), 168.5 (Cq), 171.3 (Cq); m/z (FAB$^+$) 359 (100%, M + Na$^+$); HRMS found 359.1223, $C_{16}H_{20}N_2O_6Na$ requires 359.1219.

5ff. (3*S,4*R**, 5*R**)-1-(4-Methoxy-phenyl)-3-methyl-4-nitro-5-phenyl-pyrrolidin-2-one** (143 mg, 64%) as a white solid; prepared by general procedure A, except dimethylzinc was used; mp 114−116 °C; R_f 0.23 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2938, 2837, 1702, 1552, 1500, 1244, 1779, 1031, 831 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (3H, d, J = 7.3), 3.38 (1H, quint, J = 7.3), 3.73 (3H, s), 4.73 (1H, dd, J = 7.3, 5.8), 5.63 (1H, d, J = 5.9), 6.77−6.81 (2H, m), 7.22−7.37 (7H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1 (CH_3), 42.6 (CH), 55.0 (CH_3), 65.1 (CH), 92.4 (CH), 113.9 (2 × CH), 124.6 (2 × CH), 126.4 (2 × CH), 128.8 (CH), 129.0 (Cq), 129.1 (2 × CH), 136.6 (Cq), 157.2 (Cq), 171.0 (Cq); m/z (ESI$^+$) 326 (100%, M$^+$); HRMS found 326.1255, $C_{18}H_{18}N_2O_4$ requires 326.1261. Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25, H, 5.56, N, 8.58. Found C, 66.07, H, 5.54, N, 8.38%.

5gg. (3*S,4*S**,5*R**)-3-Isopropyl-1-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidin-2-one** (125 mg, 51%) as a white solid; prepared by general procedure A, except diisopropylzinc was used; mp 140−141 °C; R_f 0.50 (20% EtAc/hexanes); IR ν_{max} (thin film) 2962, 1708, 1557, 1513, 1369, 1249, 1032, 700 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.07 (6H, dd, J = 8.3, 7.0), 2.55 (1H, m), 3.43 (1H, dd, J = 7.6, 4.5), 3.73 (3H, s), 4.88 (1H, dd, J = 7.6, 5.9), 5.52 (1H, d, J = 5.9), 6.79 (2H, app d, J = 9.1), 7.19 (2H, m), 7.23 (2H, app d, J = 9.1), 7.28−7.35 (3H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.3 (CH_3), 19.6 (CH_3), 28.0 (CH), 53.3 (CH), 55.3 (CH_3), 65.9 (CH), 88.4 (CH), 114.1 (2 × CH), 125.0 (2 × CH), 126.6 (2 × CH), 129.1 (CH), 129.2 (Cq), 129.3 (2 × CH), 137.2 (Cq), 157.5 (Cq), 170.5 (Cq).; m/z (ESI$^+$) 355 (M + H$^+$, 20%), 308 (M$^+$ − NO_2, 100%); HRMS found 355.1647, $C_{20}H_{23}N_2O_4$ requires 355.1658. Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78, H, 6.26, N, 7.90. Found C, 67.70, H, 6.22, N, 7.84%.

5hh. (3*S,4*S**,5*R**)-1-(4-Methoxyphenyl)-4-nitro-3,5-diphenyl-pyrrolidin-2-one.** To a solution of nitroalkene **1** (100 mg, 0.69 mmol) in THF (3 mL) under N_2 was added Cu(OTf)$_2$ (12 mg, 34.0 μmol, 5 mol %). The mixture was cooled to −78 °C, and the diphenylzinc solution (0.76 mmol, 1.1 equiv) was added quickly dropwise. The orange mixture was stirred at this temperature for 10 min before being warmed to rt and stirred for a further 1.5 h. Saturated aq NH_4Cl and Et_2O were then added, and the layers were separated.

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The aqueous phase was extracted with Et_2O, and the combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to leave crude nitroalkane. Purification by flash column chromatography (10% Et_2O/hexanes) gave ethyl 3-nitro-2-phenylpropanoate (92 mg, 60%) as a colorless oil; R_f 0.35 (10% Et_2O/hexanes); ^1H NMR was in agreement with the literature.[25]

A solution of ethyl 3-nitro-2-phenylpropanoate (121 mg, 0.54 mmol) in THF (3 mL), under N_2 was cooled to −78 °C, and a solution of ^{n}BuLi (0.32 mL, 0.54 mmol, 1.0 equiv, 1.7 M solution in hexanes) was added dropwise. The orange mixture was stirred at this temperature for 10 min before being warmed to rt and stirred for a further 30 min. The mixture was recooled to −78 °C, and the PMP-protected imine (228 mg, 1.08 mmol, 2.0 equiv) in THF (2 mL) was added *via* cannula. The mixture was stirred for 20 min before TFA (104 μL, 1.35 mmol, 2.5 equiv) in THF (0.5 mL) was added *via* cannula. The mixture was stirred at this temperature for a further 1 h before being warmed to rt for 16 h. Saturated aq $NaHCO_3$ (20 mL) and Et_2O (20 mL) were then added, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to leave crude pyrrolidinone **5hh**. Purification by flash column chromatography (20% EtOAc/hexanes) gave **5hh** (106 mg, 51%) as a white solid; mp 136−137 °C; R_f 0.24 (20% EtOAc/hexanes); IR ν_{max} (thin film) 1721, 1553, 1510, 1247, 1177, 1036, 847, 753, 714, 696 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.73 (3H, s), 4.69 (1H, d, J = 8.0), 5.15 (1H, dd, J = 8.0, 6.3), 5.68 (1H, d, J = 6.2), 6.81 (2H, app d, J = 6.2), 7.23−7.45 (12H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 53.3 (*C*H), 55.3 (CH_3), 65.5 (CH), 93.0 (CH), 114.2 (2 × *C*H), 125.2 (2 × *C*H), 126.9 (2 × CH), 128.2 (2 × CH), 128.5 (CH), 129.1 (Cq), 129.3 (3 × CH), 129.4 (2 × CH), 134.9 (Cq), 157.7 (Cq), 169.1 (Cq).; m/z (CI^+) 389 (M + H^+, 6%), 342 (100%, M − NO_2); HRMS found 389.15036, $C_{23}H_{21}N_2O_4$ requires 389.15013. Anal. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12, H, 5.19, N, 7.21. Found C, 70.91, H, 5.17, N, 7.15%.

8. (1*S,2*S**,10b*R**)-2-Ethyl-1-nitro-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one** (107 mg, 60%) as a yellow oil; prepared by general procedure A and isolated as a 5:1 mixture of diastereoisomers (diastereoisomer ratio calculated by C*H*NO_2 signal, δ major = 4.83, δ minor = 5.24). Major diastereoisomer, (91 mg, 51%) as a yellow oil; R_f 0.37 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2967, 2937, 2878, 1700, 1552, 1459, 1428, 1367; ^1H NMR (600 MHz, $CDCl_3$) δ (0.91 (3H, t, J = 7.2), 1.68 (2H, app dquint, J = 14.4, 7.2), 1.94 (1H, dqd, J = 14.4, 7.8, 4.8), 2.77 (1H, dq, J = 16.2, 2.4), 2.92 (1H, ddd, J = 16.8, 11.4, 4.8), 3.14 (1H, dddd, J = 12.9, 10.2, 4.8, 1.8), 3.26 (1H, tdd, J = 8.4, 4.8, 1.2), 4.34 (1H, ddd, J = 8.4, 6.0, 2.4), 4.81 (1H, dd, J = 8.4, 6.6), 5.25, (1H, dd, J = 6.6), 7.12−7.17 (2H, m), 7.25−7.29 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.3 (CH_3), 22.4 (CH_2), 28.3 (CH_2), 37.5 (CH_2), 49.8 (CH), 58.9 (CH), 90.5 (CH), 124.8 (CH), 127.6 (CH), 128.3 (CH), 129.8 (CH), 133.6 (Cq), 134.0 (Cq), 169.3 (Cq); m/z (CI^+) 261 (100%, MH^+); HRMS found 261.1238, $C_{14}H_{17}N_2O_3$, requires 261.1239. Minor diastereoisomer peaks: ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, t, J = 7.2), 1.58−1.65 (1H, m), 1.85−1.92 (1H, m), 2.78 (1H, dd, J = 4.4, 2.4), 2.89−3.03 (1H, m), 3.13−3.22 (1H, m), 3.30 (1H, dddd, J = 12.8, 8.0, 4.8, 1.2), 4.37 (1H, ddd, J = 13.2, 6.0, 2.4), 5.24 (1H, dd, J = 9.2, 6.0), 5.47 (1H, d, J = 6.0), 7.11−7.20 (2H, m), 7.26−7.33 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7 (CH_3), 20.3 (CH_2), 28.1 (CH_2), 37.5 (CH_2), 47.3 (CH), 58.3 (CH), 88.5 (CH), 124.7 (CH), 124.8 (CH), 128.6 (CH), 129.9 (CH), 133.2 (Cq), 134.3 (Cq), 170.0 (Cq).

9. *N*-((2*R*,3*R*,4*R*)-4-Ethyl-1-(4-methoxyphenyl)-5-oxo-2-(thiophen-2-yl)pyrrolidin-3-yl)-2,2,2-trifluoroacetamide. Reduction of **5q** (0.40 mmol, 89% ee) by general procedure C gave diamine (3*R*,4*R*,5*R*)-4-amino-3-ethyl-1-(4-methoxyphenyl)-5-(thiophen-2-yl)-pyrrolidin-2-one (113 mg, 89%) as a yellow oil; R_f 0.25 (30% Me_2CO/hexanes); $[\alpha]_D$ −22.2 (c 1.00, $CHCl_3$, 20 °C); IR ν_{max} (thin film) 3363, 2962, 1687, 1509, 1367, 1295, 1244, 1029, 830, 699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.11 (3H, t, J = 7.5), 1.82 (1H, m), 1.96 (1H, dqd, J = 14.1, 7.6, 5.2), 2.17 (2H, br), 2.38 (1H, ddd, J = 9.4, 6.7, 5.1), 3.32 (1H, dd, J = 9.3, 7.2), 3.70 (3H, s), 4.88 (1H, d, J = 7.2), 6.76 (2H, app d, J = 9.0), 6.85 (1H, dd, J = 5.1, 3.6), 6.95 (1H, dd, J = 3.6, 1.3), 7.12 (2H, app d, J = 8.9), 7.18 (1H, d, J = 5.0); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.0 (CH_3), 22.9 (CH_2), 51.2 (CH), 55.1 (CH_3), 61.1 (*C*H), 67.1 (CH), 113.7 (2 × CH), 125.6 (2 × CH), 125.8 (CH), 126.6 (CH), 126.8 (*C*H), 130.0 (Cq), 142.4 (Cq), 157.2 (Cq), 173.9 (Cq); m/z (ESI^+) 317 (71%, M + H^+), 206 (100%); HRMS found 317.1321, $C_{17}H_{21}N_2O_2S$ requires 317.1324. Anal. Calcd for $C_{17}H_{20}N_2O_2S$: C, 64.53, H, 6.37, N, 8.85. Found C, 64.68, H, 6.56, N, 8.77%.

To a solution of the diamine (3*R*, 4*R*, 5*R*)-4-amino-3-ethyl-1-(4-methoxyphenyl)-5-(thiophen-2-yl)pyrrolidin-2-one (127 mg, 0.41 mmol) in DCM (4 mL) under N_2 at 0 °C, was added trifluoroacetic anhydride (0.28 mL, 2.05 mmol, 5 equiv) followed by pyridine (0.16 mL, 2.05 mmol, 5 equiv). The mixture was then warmed to rt and stirred for a further 2 h. Then 2 M aq HCl and CH_2Cl_2 were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organics washed with satd aq $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give crude trifluoroacetamide **9**. Purification by flash column chromatography (30% Me_2CO/hexanes) gave trifluoroacetamide **9** (136 mg, 82%) as a white solid; mp 139−140 °C; R_f 0.46 (30% Me_2CO/hexanes); HPLC (chiralcel AD 0.46 × 25 cm column, 90:10 hexane/IPA, 1 mL min^{-1}) 10.9 min (major), 20.4 min (minor) measured 87% ee; IR ν_{max} (thin film) 3257, 3089, 1720, 1672, 1515, 1254, 1212, 1168, 1030, 845, 693 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.4), 1.65 (1H, m), 1.87 (1H, m), 2.25 (1H, dt, J = 8.7, 5.5), 3.74 (3H, s), 4.36 (1H, app dt, J = 8.7, 5.3), 5.18 (1H, d, J = 4.7), 6.81 (2H, app d, J = 8.9), 6.85 (1H, m), 6.89 (1H, m), 7.15 (2H, app d, J = 8.9), 7.19 (1H, d, J = 5.0), 8.26 (1H, d, J = 8.7); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.2 (CH_3), 23.7 (CH_2), 49.4 (CH), 55.3 (CH_3), 56.9 (CH), 65.0 (CH), 114.1 (2 × CH), 125.6 (CH), 115.7 (q, J = 288, CF_3), 126.0 (2 × CH), 126.5 (CH), 126.9 (CH), 129.2 (Cq), 141.3 (Cq), 157.0 (q, J = 38, CF_3C═O), 157.9 (Cq), 173.6 (Cq); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.0 (3F, s, *C*F_3); m/z (ESI^+) 413 (100%, M + H^+), 300 (30%, M^+-NHTFA); HRMS found 413.1139, $C_{19}H_{20}F_3N_2O_3S$ requires 413.1147. Anal. Calcd for $C_{19}H_{19}F_3N_2O_3S$: C, 55.33, H, 4.64, N, 6.79. Found C, 55.24, H, 4.59, N, 6.69%. Recrystallization of the sample with Et_2O/hexane gave **9** (111 mg, 73% overall yield) as an identical white solid; $[\alpha]_D$ +14.7 (c 1.00, $CHCl_3$, 20 °C); HPLC measured 99% ee.

***syn,anti*-10a (2*S**,3*R**,4*S**)-2-Ethyl-4[(4-methoxyphenyl-(2,2,2-trifluoro-acetyl)-amino]-3-nitro-4-phenyl-butyric Acid Ethyl Ester** and ***syn,syn*-10a (2*S**,3*R**,4*R**)-2-Ethyl-4[(4-methoxyphenyl-(2,2,2-trifluoro-acetyl)-amino]-3-nitro-4-phenyl-butyric Acid Ethyl Ester.** According to general procedure A but quenching the reaction with saturated $NaHCO_3$ solution 5 min after removing the −78 °C cooling bath. After workup the crude mixture was dissolved in CH_2Cl_2 (10 mL) and cooled to −78 °C, and DIPEA (1.48 mmol, 0.25 mL) and TFAA (1.48 mmol, 0.20 mL) were added. The reaction was warmed to rt and stirred for 30 min. The organic solution was then washed with 2 M HCl, H_2O, dried ($MgSO_4$), filtered, and evaporated to dryness. Purification by column chromatography gave an inseparable 65:35 mixture of *syn,anti*-**10a** and *syn,syn*-**10a** as a yellow oil (120 mg, 37%). Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 60:30:10:0. R_f 0.14 (10% acetone/petrol); IR νmax (thin film) 2974, 2938, 2842, 1730, 1698, 1557, 1510, 1254, 1205, 1180, 1156, 734, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *syn,anti*-10a δ 1.08 (3H, t, J = 7.4,), 1.29 (3H, t, J = 7.2), 1.78 (1H, dqd, J = 13.2, 7.4, 5.8), 2.02 (1H, ddq, J = 14.1, 9.1, 7.4), 3.01 (1H, ddd, J = 9.1, 5.6, 3.6), 3.79 (3H, s), 4.20−4.35 (2H, m), 5.61 (1H, m), 6.01 (1H, dd, J = 10.6, 3.2), 6.49−6.78 (2H, m), 6.91- 7.06 (2H, m), 7.18−7.32 (5H, m); *syn,syn*-**10a** δ 1.03 (3H, t, J = 7.3), 1.37 (3H, t, J = 7.2), 1.70 (1H, dqd, J = 11.3, 7.1, 4.2), 1.96 (1H, m), 2.96 (1H, m), 3.79, (3H, s), 4.20−4.35 (2H, m), 5.59 (1H, m), 6.04 (1H, d, J = 9.5) remaining signals could not be distinguished; ^{13}C NMR (125 MHz, $CDCl_3$) *syn,anti*-10a δ 11.9 (CH_3), 14.1 (CH_3), 22.8 (CH_2), 47.7 (CH), 55.5 (CH_3), 61.8 (CH_2), 66.0 (CH), 88.3 (CH), 113.5 (CH), 113.8 (CH), 113.9 (CH), 116.2 (q, J = 288.7, CF_3), 128.9 (CH), 129.4 (CH × 2), 129.7 (CH), 130.6 (CH), 131.6 (CH), 136.1 (Cq), 138.1 (Cq), 158.1 (q, J = 35.7, C═O), 160.4 (Cq), 171.4 (Cq); *syn, syn*-**10a** δ 12.4 (CH_3), 14.1 (CH_3), 20.1 (CH_2), 48.0 (CH), 61.9 (CH_2), 87.1 (CH), 116.4 (q, J = 288.7, CF_3), 130.7 (CH) remaining

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signals could not be distinguished; ^{19}F (282 MHz, $CDCl_3$) δ − 67.7 (3F, s, CF_3); m/z (EI^+) 482 (M+, 8%); HRMS $C_{23}H_{25}F_3N_2O_6$ calcd. 482.16592 found 482.16656.

12. (3*S,4*S**,5*R**)- 3-Ethyl-4-nitro-5-phenyl-pyrrolidin-2-one.** To a solution of pyrrolidinone **5a** (100 mg, 0.29 mmol) in MeCN (4 mL) at 0 °C under N_2 was added CAN (0.71 g, 1.18 mmol, 4.0 equiv) as a solution in H_2O (4 mL) dropwise over 3 min. The solution turned dark orange. The mixture was stirred at 0 °C for a further 2 h over which time the solution became light orange. H_2O was added, and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organics washed with satd aq $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash column chromatography (30% Me_2CO/hexanes) gave pyrrolidinone **12** (50 mg, 74%) as a brown oil; R_f 0.44 (30% Me_2CO/hexanes); IR ν_{max} (thin film) 2968, 2926, 2878, 1703, 1552, 1457, 1367, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.4), 1.71 (1H, app d quint, J = 14.5, 7.5), 1.96 (1H, dqd, J = 14.4, 7.5, 4.9), 3.17 (1H, app td, J = 7.7, 4.8), 4.73 (1H, dd, J = 7.5, 6.0), 5.16 (1H, d, J = 5.9), 6.99 (1H, br, s), 7.31−7.33 (2H, m), 7.40−7.47 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2 (CH_3), 22.0 (CH_2), 44.3 (*C*H), 56.4 (*C*H), 91.8 (*C*H), 125.6 (3 × *C*H), 128.8 (2 × *C*H), 139 (*C*q), 174 (*C*q); m/z (FAB) 257 (45%, M + Na^+), 235 (30%, M + H^+), HRMS: found 257.0905, $C_{12}H_{14}N_2O_3Na$ requires 257.0902. Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53, H, 6.02, N, 11.96. Found C, 61.12, H, 5.99, N 11.86%.

13. (3*S,4*S**,5*R**)-4-Amino-3-ethyl-1-(4-methyoxy-phenyl)-5-phenyl-pyrrolidin-2-one** (83 mg, 91%) as an off white solid; prepared by general procedure C from pyrrolidinone **5a** (0.29 mmol); mp >250 °C; R_f 0.22 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2961, 2932, 2876, 1689, 1510, 1456, 1370, 1246, 1031; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, t, J = 7.4), 1.72 (2H, s, br), 1.82 (1H, app d quint, J = 14.5, 7.3), 1.97 (1H, dqd, J = 14.9, 7.4, 5.2), 2.43 (1H, ddd, J = 11.8, 6.7, 5.3), 3.20 (1H, dd, J = 9.2, 7.1), 3.70 (3H, s), 4.66 (1H, d, J = 7.0), 6.71−6.75 (2H, m), 7.15−7.19 (2H, m), 7.20−7.24 (2H, m), 7.26−7.31 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2 (CH_3), 22.2 (CH_2), 51.8 (*C*H), 55.3 (CH_3), 60.9 (*C*H), 71.3 (*C*H), 113.9 (2 × *C*H), 124.9 (2 × *C*H), 127.1 (2 × *C*H), 128.1 (*C*H), 128.9 (2 × *C*H), 130.6 (*C*q), 139.0 (*C*q), 156.9 (*C*q), 174.5 (*C*q); m/z (FAB^+) 333 (20%, M + Na^+), HRMS found 333.1567, $C_{19}H_{22}N_2O_2Na$ requires 333.1579.

14. (3*S,4*S**,5*R**)-4-Amino-3-ethyl-5-phenyl-pyrrolidin-2-one** (16 mg, 49%) as an off white solid; prepared by general procedure C from pyrrolidinone **12** (0.16 mmol); mp 149−151 °C; R_f 0.27 (50% Me_2CO/hexanes); IR ν_{max} (thin film) 3230, 2963, 2927, 2876, 1689, 1630, 1456, 1278 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, t, J = 7.5), 1.71 (1H, ddq, J = 14.4, 7.6, 7.4), 1.84 (1H, ddq, J = 14.2, 7.5, 5.4), 2.06 (2H, br s), 2.30 (1H, ddd, J = 9.3, 6.3, 5.5), 3.15 (1H, app t, J = 8.6), 4.24 (1H, d, J = 7.2), 6.03 (1H, br s), 7.32−7.42 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0 (CH_3), 22.2 (CH_2), 51.8 (*C*H), 62.2 (*C*H), 65.5 (*C*H), 127.6 (2 × *C*H), 129.4 (*C*H), 129.9 (2 × *C*H), 141.5 (*C*q), 179.2 (*C*q); m/z (CI^+) 205 (100%, MH^+); HRMS found 205.1338, $C_{12}H_{17}N_2O$ requires 205.1341.

15. (2*R,3*S**,4*R**)-4-Ethyl-1-(4-methoxy-phenyl)-3-nitro-2-phenyl-pyrrolidine.** To a solution of pyrrolidinone **5a** (70 mg, 0.21 mmol) in THF (5 mL) under N_2 at 0 °C was added BH_3−THF complex (0.72 mL, of a 1.0 M sol. in THF, 0.72 mmol, 3.5 equiv) dropwise. The mixture was stirred at 0 °C until no more effervescence was observed before being heated to reflux for 15 h. The mixture was cooled to rt, and MeOH was added before being concentrated *in vacuo* to give crude pyrrolidine **15**. Purification by flash column chromatography (20%Me_2CO/hexanes) gave pyrrolidine **15** (53 mg, 79%) as a yellow solid; mp 50−52 °C; R_f 0.21 (20% Me_2CO/hexanes); IR δ_{max} (thin film) 2964, 2932, 1548, 1510, 1358, 1241, 1180, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.4), 1.58 (2H, app quintd, J = 7.4, 2.6), 2.85 (1H, m), 3.67 (1H, dd, J = 9.2, 5.6), 3.72 (3H, s), 3.85 (1H, dd, J = 9.2, 8.0), 4.76 (1H, app t, J = 5.3), 5.13 (1H, d, J = 4.8), 6.46−6.50 (2H, m), 6.74−6.78 (2H, m), 7.28−7.34 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.1 (CH_3), 25.6 (CH_2), 45.2 (*C*H), 54.9 (CH_2), 55.7 (CH_3), 68.5 (*C*H), 97.8 (*C*H), 114.7 (2 × *C*H), 114.9 (2 × *C*H), 126.1 (2 × *C*H), 128.2 (*C*H), 129.2 (2 × *C*H), 140.0 (*C*q), 141.1 (*C*q), 152.2 (*C*q); m/z (ESI^+) 326 (54%, M^+), 250 (100%, M + H^+ − Ph); HRMS found 326.1626, $C_{19}H_{22}N_2O_3$ requires 326.1625. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92, H, 6.79, N, 8.58. Found C, 70.20, H, 6.86, N, 8.54%.

16. 3-Ethyl-4-hydroxy-1-(4-methoxy-phenyl)-5-phenyl-1,5-dihydro-pyrrol-2-one and **4-Ethyl-5-hydroxy-1-(4-methoxy-phenyl)-2-phenyl-1,2-dihydro-pyrrol-3-one.** To a solution of potassium dichromate (0.26 g, 0.88 mmol, 6.0 equiv) in 6 M HCl (6.40 mL, 26.5 mmol, 180.0 equiv) at 0 °C under N_2 was added Zn dust (480 mg, 7.35 mmol, 50.0 equiv) portionwise over 20 min. During the addition, the solution turned from orange to dark blue. After complete dissolution of the zinc the resulting $CrCl_2$ solution was transferred to a refluxing solution of pyrrolidinone **5a** (50 mg, 0.15 mmol) in MeOH/EtOAc (2.5:1, 7 mL). The solution was refluxed for 1 h before satd aq $NaHCO_3$ and CH_2Cl_2 were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organics washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give crude pyrrolones **16**. Purification by flash column chromatography (30% Me_2CO/hexanes) gave pyrrolones **16** as an inseparable 1:1 mixture of tautomers, (14 mg, 30%) as a yellow oil; R_f 0.09 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 3367, 2971, 2937, 2839, 1776, 1689, 1512, 1250, 1031 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.5), 1.07 (3H, t, J = 7.5), 1.77 (1H, app quint, J = 7.2), 1.96 (1H, tq. J = 14.8, 7.5), 2.05−2.11 (2H, tq, J = 14.8, 7.5), 3.74 (3H, s), 3.77 (3H, s), 5.39 (1H, s), 5.52 (1H, s), 6.80−6.82 (2H, m), 6.84−6.86 (2H, m), 7.22−7.23 (2H, m), 7.29−7.35 (10H), 7.48−7.49 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.9 (CH_3), 7.4 (CH_3), 30.1 (CH_2), 30.6 (CH_2), 55.5 (2 × CH_3), 69.2 (*C*H), 70.3 (*C*H), 75.7 (*C*q), 75.9 (*C*q), 114.3 (2 × *C*H), 114.5 (2 × *C*H), 123.4 (2 × *C*H), 125.2 (2 × *C*H), 126.2 (2 × *C*H), 128.0 (2 × *C*H), 128.9 (2 × *C*H), 128.9 (*C*q), 129.2 (2 × *C*H), 129.3 (2 × *C*H), 129.7 (*C*q), 132.6 (*C*q), 133.6 (*C*q), 157.5 (*C*q), 157.9 (*C*q), 171.7 (*C*q), 172.1 (*C*q), 203.6 (*C*q), 205.5 (*C*q); m/z (ESI^+) 309 (20%, M^+); HRMS found 309.1368, $C_{19}H_{19}NO_3$ requires 309.1368.

17. 4-Allyl-3-ethyl-1-(4-methoxyphenyl)-5-phenyl-1,5-dihydro-pyrrol-2-one. A solution of pyrrolidinone **5a** (84 mg, 0.25 mmol) in THF (5 mL) was cooled to −78 °C and *n*-butyl lithium (200 μL, of a 2.5 M soln in THF, 0.50 mmol, 2.0 equiv) was added dropwise *via* cannula under N_2. The mixture was stirred at this temperature for 10 min before allyl bromide (65 μL, 0.75 mmol, 3.0 equiv) was added *via* cannula. The mixture was warmed to rt and stirred for a further 2 h before satd aq NH_4Cl and Et_2O were added, and the layers were separated. The aqueous layer was extracted with Et_2O, and the combined organics washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give crude pyrrolone **17**. Purification by flash column chromatography gave pyrrolone **17** (27 mg, 32%) as a yellow oil; Rf 0.50 (20% Me_2CO/hexanes); IR ν_{max} 2928, 1720, 1512, 1446, 1370, 1292, 1249, 1168 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.91 (3H, t, J = 7.2), 1.74 (1H, dq, J = 15.2, 7.6), 1.87 (1H, dq, J = 14.8, 7.6), 2.44−2.55 (2H, m), 3.77 (3H, s), 5.06 (1H, app dt, J = 10.0, 1.0), 5.16 (1H, dd, J = 17.2, 2.0), 5.42 (1H, s), 5.77 (1H, ddt, J = 16.8, 10.0, 7.4), 6.78−6.82 (2H, m), 6.92−6.96 (2H, m), 7.12−7.15 (2H, m), 7.20−7.26 (3H, m); ^{13}C NMR (125 MHz) δ 9.1 (CH_3), 29.5 (CH_2), 41.3 (CH_2), 55.2 (CH_3), 55.4 (*C*q), 111.7 (*C*H), 114.0 (2 × *C*H), 118.3 (CH_2), 127.8 (2 × *C*H), 128.2 (2 × *C*H), 128.3 (2 × *C*H), 128.5 (*C*H), 128.7 (*C*q), 131.4 (*C*q), 133.4 (*C*H), 144.5 (*C*q), 158.3 (*C*q), 181.8 (*C*q); m/z (CI+) 334 (100%, MH+); HRMS found 334.1799, $C_{22}H_{24}NO_2$ requires 334.1807.

18. (3*S,5*S**)-3-Ethyl-1-(4-methoxyphenyl)-5-phenylpyrrolidin-2-one**. To a solution of diamine **13** (250 mg, 0.81 mmol) in formic acid (5 mL) at 0 °C was added dropwise acetic anhydride (0.81 mL, 8.06 mmol, 10 equiv). The mixture was then stirred at rt for 2 h. Then water (20 mL) was added, and the mixture was extracted with DCM (3 × 20 mL). The combined organics were washed with satd aq $NaHCO_3$ (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give crude formamide. Purification by flash column chromatography (30%Me_2CO/hexanes) gave *N*-((2*R**,3*S**,4*S**)-4-ethyl-1-(4-methoxyphenyl)-5-oxo-2-phenylpyrrolidin-3-yl)formamide (246 mg, 90%) as a white crystalline solid, which was found to be a 4:1 mixture of rotamers (rotamer ratio calculated by

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CHNH signal, δ major = 4.24, δ minor = 3.67); mp 130−131 °C; R_f 0.16 (30% Me_2CO/hexanes). Major rotamer: IR ν_{max} (thin film) 3239, 3059, 2961, 1704, 1644, 1510, 1374, 1246, 1180, 1026, 834, 749, 737, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.03 (3H, t, J = 7.5), 1.62 (1H, m), 1.91 (1H, m), 2.53 (1H, m), 3.73 (3H, s), 4.24 (1H, dt, J = 7.8, 5.7), 5.05 (1H, d, J = 4.9), 6.37 (1H, d, J = 8.4), 6.75 (2H, app d, J = 9.2), 7.10−7.31 (7H, m), 8.18 (1H, d, J = 1.2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.5 (CH_3), 23.4 (CH_2), 50.3 (CH), 55.3 (CH_3), 56.0 (CH), 68.6 (CH), 114.0 (2 × CH), 124.3 (2 × CH), 126.7 (2 × CH), 128.2 (CH), 128.9 (2 × CH), 130.4 (Cq), 138.3 (Cq), 157.0 (Cq), 160.9 (CH), 174.1 (Cq); m/z (CI^+) 339 (M + H^+, 30%), 294 (100%, M^+ − NHCOH); HRMS found 339.1699, $C_{20}H_{23}N_2O_3$ requires 339.1709. Minor rotamer: ^1H NMR (600 MHz, $CDCl_3$) δ 1.10 (3H, t, J = 7.4), 1.62 (1H, m), 1.91 (1H, m), 2.53 (1H, m), 3.67 (1H, m), 3.71 (3H, s), 4.76 (1H, d, J = 7.7), 6.30 (1H, t, J = 10.8), 6.78 (2H, app d, J = 9.2), 7.10−7.31 (7H, m), 7.62 (1H, d, J = 11.5); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.8 (CH_3), 21.6 (CH_2), 48.8 (CH), 55.3 (CH_3), 60.9 (CH), 68.4 (CH), 113.9 (2 × CH), 124.9 (2 × CH), 127.0 (2 × CH), 128.7 (CH), 129.2 (2 × CH), 129.7 (Cq), 136.7 (Cq), 157.2 (Cq), 163.7 (CH), 172.5 (Cq).

To a solution of the formamide formed above (441 mg, 1.31 mmol) in THF (4 mL) under N_2 at −78 °C was added Et_3N (0.92 mL, 6.53 mmol, 5 equiv) followed by a solution of $POCl_3$ (0.16 mL, 1.55 mmol, 1.18 equiv) in THF (1 mL) dropwise. The mixture was then warmed to 0 °C and stirred for a further 1 h. Then ice−water (20 mL) was added, and the mixture extracted with EtOAc (4 × 30 mL). The combined organics were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give crude isocyanide. Purification by flash column chromatography (20%Me_2CO/hexanes) gave (3*S**,4*S**,5*R**)-3-ethyl-4-isocyano-1-(4-methoxyphenyl)-5-phenylpyrrolidin-2-one (261 mg, 63%) as a white crystalline solid; mp 168−169 °C; R_f 0.26 (20% Me_2CO/hexanes); IR ν_{max} (thin film) 2970, 2141, 1707, 1509, 1458, 1365, 1247, 1223, 1193, 1179, 1039, 830, 78, 742, 700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.16 (3H, t, J = 7.5), 1.83 (1H, m), 2.12 (1H, dqd, J = 12.4, 7.6, 4.7), 2.92 (1H, ddd, J = 9.4, 7.9, 4.7), 3.71 (3H, s), 3.79 (1H, dd, J = 9.4, 7.6), 5.10 (1H, d, J = 7.6), 6.77 (2H, app d, J = 9.0), 7.15 (2H, app d, J = 9.0), 7.22−7.35 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.7 (CH_3), 22.5 (CH_2), 50.0 (CH), 55.2 (CH_3), 59.9 (CH), 67.4 (CH), 114.0 (2 × CH), 125.0 (2 × CH), 126.8 (2 × CH), 129.0 (CH), 129.2 (2 × CH), 129.2 (Cq), 136.4 (Cq), 157.3 (Cq), 160.2 (Cq), 171.2 (Cq); m/z (EI^+) 320 (M^+, 100%); HRMS found 320.15222, $C_{20}H_{20}N_2O_2$ requires 320.15193. Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98, H, 6.29, N, 8.74. Found C, 74.94, H, 6.27, N, 8.68%.

To a solution of isocyanide formed above (56 mg, 0.18 mmol) in toluene (1 mL) under N_2 was added $^nBu_3SnH$ (0.10 mL, 0.32 mmol, 2 equiv). The mixture was degassed with N_2, then AIBN (6 mg, 0.036 mmol, 20 mol %) was added, and the mixture refluxed for 3 h. Then the volatiles were removed *in vacuo* to give crude pyrrolidine. Purification by flash column chromatography (50% Et_2O/hexane) gave pyrrolidine **18** (45 mg, 87%) as a white solid; mp 97−98 °C; R_f 0.19 (50% Et_2O/hexane); IR ν_{max} (thin film) 2956, 1689, 1511, 1380, 1361, 1298, 1249, 1175, 1034, 829, 761, 699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.03 (3H, t, J = 7.5), 1.59 (1H, ddq, J = 14.0, 9.2, 7.3), 1.67 (1H, ddd, J = 12.9, 10.5, 8.9), 2.10 (1H, dqd, J = 14.1, 7.5, 4.1), 2.62 (1H, ddd, J = 10.4, 9.0, 4.1), 2.76 (1H, ddd, J = 12.9, 8.8, 7.1), 3.71 (3H, s), 5.10 (1H, dd, J = 8.8, 7.1), 6.75 (2H, app d, J = 8.9), 7.17−7.29 (7H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.5 (CH_3), 24.5 (CH_2), 36.2 (CH_2), 44.0 (CH), 55.2 (CH_3), 62.2 (CH), 113.7 (2 × CH), 124.7 (2 × CH), 126.6 (2 × CH), 127.6 (2 × CH), 128.7 (CH), 130.9 (Cq), 141.4 (Cq), 156.7 (Cq), 176.5 (Cq); m/z (EI^+) 295 (M^+, 100%); HRMS found 295.15751, $C_{19}H_{21}NO_2$ requires 295.15667. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26, H, 7.17, N, 4.74. Found C, 77.19, H, 7.21, N, 4.79%.

19. (2*S,3*S**,4*S**)-4-Ethyl-1-(4-methoxyphenyl)-3-nitro-5-oxopyrrolidine-2-carboxylic Acid.** To a solution of ethyl ester **5ee** (336 mg, 1.00 mmol) in acetone (11 mL) under N_2 was added an aqueous solution of HCl (2M, 10 mL, 20 equiv), and the mixture was refluxed for 24 h. The mixture was then cooled, EtOAc (20 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organics were extracted with satd aq $NaHCO_3$ (2 × 10 mL). The combined aqueous extracts were then acidified to pH = 1 with addition of 2 M HCl and then extracted with EtOAc (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give carboxylic acid 19 (265 mg, 86%) as a white solid; mp 155−156 °C; R_f 0.34 (10% MeOH/DCM); IR ν_{max} (thin film) 2967, 2463, 1739, 1634, 1604, 1560, 1604, 1369, 1248, 1222, 1203, 1183, 1021, 792 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 1.13 (3H, t, J = 7.4), 1.80 (1H, ddq, J = 14.2, 8.7, 7.4), 2.00 (1H, dqd, J = 14.1, 7.4, 5.5), 3.17 (1H, ddd, J = 8.9, 5.5, 3.7), 3.79 (3H, s), 5.29 (1H, t, J = 3.3), 5.34 (1H, d, J = 2.8), 6.95 (2H, app d, J = 8.9), 7.36 (2H, app d, J = 8.9); ^{13}C NMR (150 MHz, CD_3OD) δ 11.5 (CH_3), 24.5 (CH_2), 51.0 (CH), 55.9 (CH_3), 66.1 (CH), 85.4 (CH), 115.3 (2 × CH), 127.1 (2 × CH), 130.9 (Cq), 160.0 (Cq), 171.4 (Cq), 174.4 (Cq); m/z (CI^+) 309 (100%, M + H^+), 218 (40%, M^+ −CO_2 − NO_2); HRMS found 309.10666, $C_{14}H_{17}N_2O_6$ requires 309.10872. Anal. Calcd for $C_{14}H_{16}N_2O_6$: C, 54.54, H, 5.23, N, 9.09. Found C, 54.21, H, 5.19, N, 8.96%.

■ ASSOCIATED CONTENT

Supporting Information

General experimental details, X-ray representations, copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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