# A Simple Synthesis of Polysubstituted Pyrrolidines by an Organocatalytic Three-Component Approach Featuring a One-Pot Condensation and [3+2]-Cycloaddition Reaction in Aqueous Medium

Silvia Reboredo, Jose L. Vicario,* Luisa Carrillo, Efraím Reyes, Uxue Uria

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU), P.O. Box 644, 48080 Bilbao, Spain
Fax +34(94)6012748; E-mail: joseluis.vicario@ehu.es

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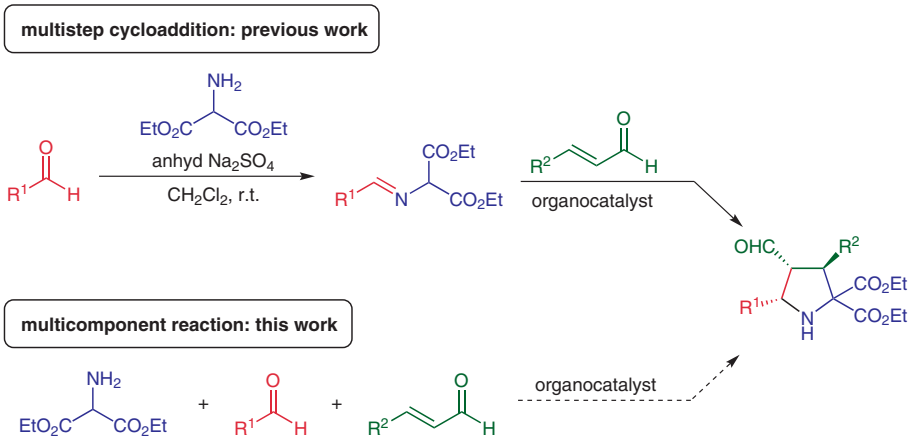
**Abstract:** A simple one-pot procedure was developed for [3+2]-cycloaddition reactions of α,β-unsaturated aldehydes, diethyl aminomalonate, and aromatic aldehydes in the presence of diphenyl[(2*S*)-pyrrolidin-2-yl]methanol as catalyst. This reaction converts simple, commercially available, starting materials into densely functionalized polysubstituted pyrrolidines under mild conditions and in a fully stereoselective fashion. Moreover, the use of brine as the reaction medium has remarkable beneficial effects in preventing the formation of self-condensation byproducts, cutting the reaction time, and reducing the production of wastes.

**Key words:** asymmetric catalysis, asymmetric synthesis, organocatalysis, cycloadditions , multicomponent reactions, heterocycles

During this century, enantioselective organocatalysis with chiral secondary amine catalysts has seen rapid growth as an environmentally benign and practical technique for asymmetric synthesis, and as a result it has become the subject of intensive research.[1] In particular, organocatalytic 1,3-dipolar cycloaddition reactions constitute a highly efficient approach to syntheses of many families of five-membered heterocyclic structures from simple and readily available starting materials.[2] In particular, when azomethine ylides are employed as 1,3-dipoles, an enantioselective organocatalytic version of this transformation provides a powerful method for the simple, rapid, and direct preparation of polysubstituted pyrrolidines.[3] Scaffolds such as these are present in numerous natural products, and they have a wide range of applications in the pharmaceutical industry.[4] The first organocatalytic [3+2] cycloaddition reaction to use azomethine ylides as 1,3-dipoles was developed by our group[5] and is based on the iminium activation approach. Imines derived from diethyl aminomalonate were treated with α,β-unsaturated aldehydes in the presence of cheap and commercially available diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (α,α-diphenylprolinol) as catalyst to give highly functionalized polysubstituted pyrrolidines in good yields and as single diastereoisomers of very high optical purity (Scheme 1). The key to this reaction was the use of arylideneaminomalonates as sources of azomethine ylides. The arylideneaminomalonates were prepared from commercially available diethyl aminomalonate and aromatic aldehydes. However, these imines had to be synthesized and purified in advance, and they were found to be unstable and could only be stored for a few days in a freezer.

With these precedents in mind, and in connection with our previous initial report, we decided to attempt the development of a modified version of the transformation that would allow us to prepare the same complex pyrrolidine




**Scheme 1** Organocatalytic enantioselective synthesis of pyrrolidines through [3+2] cycloaddition: multistep and multicomponent versions of the reaction

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adducts directly from commercially available reagents in a single step by means of a multicomponent approach relying on a one-pot condensation/organocatalytic enantioselective [3+2] process (Scheme 1).[6] This proposed alternative reaction design involved mixing an α,β-unsaturated aldehyde, diethyl aminomalonate, and a second aldehyde in the presence of a chiral catalyst, in the hope that the iminium ion produced by activation of the enal with the catalyst would undergo [3+2] cycloaddition with the azomethine ylide generated in situ by condensation of the second aldehyde with the aminomalonate reagent.

Asymmetric multicomponent reactions are very powerful tools for the construction of complex chiral molecular scaffolds from readily available starting materials through simple and efficient processes;[7] moreover, such reactions provide important benefits such as improved atom economy, reduction of operating times, and minimization of waste production. For these reasons, they are considered to meet several of the requirements of green chemistry, and can therefore help to solve several of the environmental problems that are emerging as important challenges for process chemists.

Importantly, for the projected multicomponent process to succeed, several issues relating to chemoselectivity have to be controlled to give the target pyrrolidines stereoselectively and in good yields. Because two aldehydes and two amines are present in the reaction mixture, several dynamic processes involving various combinations of these species could take place simultaneously within the reaction vessel. This implies that the role played by each reagent has to be efficiently controlled, that the chiral secondary amine catalyst must be involved exclusively in the activation of the α,β-unsaturated aldehyde through formation of the iminium ion, and that the diethyl aminomalonate must engage preferentially in a condensation reaction with the other aldehyde. Other possible combinations would lead to the formation of mixtures of products or to poor stereocontrol in the final pyrrolidine adducts.

We began by studying the reaction of commercially available diethyl aminomalonate (**2**), benzaldehyde (**1a**), and crotonaldehyde (**3a**) as a model reaction (Table 1). We decided to use diphenyl[(2*S*)-pyrrolidin-2-yl]methanol as the chiral amine catalyst, as we had previously identified this as this the most efficient promoter for a related [3+2] cycloaddition process. However, when we applied our optimized reaction conditions (tetrahydrofuran as solvent at 4 °C with four equivalents of water as an additive), we isolated pyrrolidine **4a** in a very poor yield along with a complex mixture of various byproducts, including pyrrolidine **5a**, which was isolated in 15% yield (entry 1). However, despite its low yield, cycloadduct **4a** was isolated as a single *endo*-diastereoisomer and in 98% ee. The formation of **5a** is likely to have been the result of initial formation of an azomethine ylide precursor through condensation of enal **3a** with diethyl aminomalonate, with subsequent cycloaddition of a second molecule of **3a**.[5c] The catalyst was shown to participate in the process, because byproduct **5a** was isolated as a single diastereoisomer with a very high ee. When we carried out the reaction in the absence of water (entry 2), we obtained an even poorer yield of **4a** together with larger quantities of the byproduct **5a**. With these results in mind, and taking into consideration that the presence of water appeared to assist the formation of the desired cycloadduct **4a** with respect to the undesired byproduct **5a**,[8] we decided to use a 1:1 mixture of tetrahydrofuran and water as the solvent (entry 3). As expected, the formation of the 2-alkenyl-substituted pyrrolidine **5a** was completely inhibited, and adduct **4a** was isolated in a higher, albeit still moderate, yield. We then examined the effect of a Brønsted acid as an additive to assist the formation of the activated iminium intermediate under these conditions (entry 4), but this resulted in a slight decrease in the yield. Other aqueous solvents (entries 5 and 6) and various protic solvents (entries 7–9) were also evaluated, but in all cases the reaction gave lower yields of adduct **4a**, although it should be stressed that the formation of byproduct **5a** was not observed in any of these cases. We then examined the effect of an increase in temperature, and we found that the yield of **4a** increased slightly at room temperature (entry 10). We also found that **4a** was obtained in 50% yield when we used a 1:1 mixture of tetrahydrofuran and brine as the solvent (entry 11). The use of the aqueous medium again resulted in complete inhibition of the side reaction that formed pyrrolidine **5a**. Finally, we were also able to reduce the amount of organic cosolvent to a very interesting 1:19 ratio of tetrahydrofuran to brine, and we obtained the required adduct **4a** in 54% yield after only one day of reaction, while preserving the excellent diastereo- and enantioselectivity (entry 12). A reaction using brine as the sole reaction medium gave **4a** in a slightly lower yield (entry 13). Several other conditions or combinations of solvents were tested, but in all cases these gave significantly lower yields than were obtained under the conditions shown in entry 12.

Therefore, after screening the reaction conditions we concluded that, despite not being able to improve on the moderate overall yield, the procedure shown in entry 12 gave the best results in preparing pyrrolidine **4a** directly from commercially available chemicals. Note that although this protocol is not superior to the multistep approach that we previously developed[5a] in terms of the overall yield, it is a competitive methodology for enantioselective synthesis of pyrrolidines because of its simplicity, lower reaction time, and the absence of operations to purify intermediates. Moreover, it involves the use of a mainly aqueous medium, requiring only small amounts of the organic cosolvent.

Having identified the optimal conditions, we next examined the scope and limitations of the method with regard to the use of aromatic aldehydes other than benzaldehyde, together with other β-alkyl and β-aryl substituted α,β-unsaturated aldehydes with various electronic properties (Table 2). As can be seen from this table, the final cycloadducts **4a**–**n** were isolated in moderate yields in nearly all the cases, but the overall processes occurred with very high diastereoselectivities, giving the adducts in high de-

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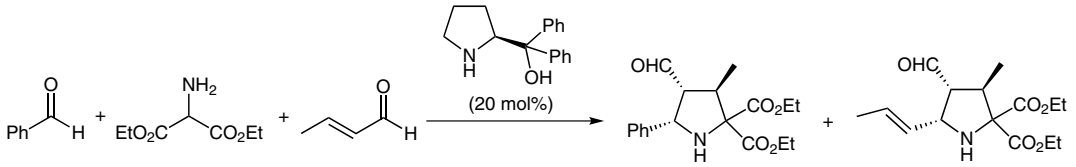
grees of enantiomeric enrichment. With regard to the role played by the substitution pattern on aldehyde **1** (entries 1–6), the yields and stereoselectivities did not appear to be directly related to the electronic nature of the β-substituent, and the yields obtained were similar to those achieved in the model reaction with benzaldehyde (**1a**). The only exception was that of 4-methoxybenzaldehyde (**1c**), which gave the final cycloadduct **4c** in yield that was markedly lower than those of other members of this series. It is significant that this aldehyde is a solid, whereas all the others are liquids, and we therefore ascribed the lower yield to the poorer miscibility/solubility of compound **1c** in the brine–tetrahydrofuran mixture; reagents that readily formed emulsions in the reaction medium gave higher yields of the final cycloadducts.[9] We also evaluated the effects on the overall process of β-substituents on the α,β-unsaturated aldehyde **3** (entries 7–14). The reactions proceeded in a similar manner to that observed with crotonaldehyde, affording the target polysubstituted pyrrolidines in moderate yields but excellent diastereo- and enantioselectivities. In a similar manner to that outlined above, no reaction took place when the solid enals **3e** and **3f** were used (entries 15 and 16).

In view of the performance of the reaction in an aqueous medium, we also decided to examine the possibility of carrying out the reaction with formaldehyde as the azomethine ylide precursor, which should have led to the formation of 4-unsubstituted pyrrolidines after the [3+2] cycloaddition, a substitution pattern that is not otherwise easily accessible by this type of cycloaddition reaction. When we stirred a mixture of aminomalonate **2**, crotonaldehyde, and aqueous formaldehyde under the optimized reaction conditions, we did not detect the expected cycloaddition product in the reaction mixture, but instead we obtained the bicyclic compound **7** (Scheme 2); this was presumably formed by Michael reaction of diethyl aminomalonate (**2**) with crotonaldehyde (**3a**), followed by intramolecular formation of a hemiaminal that subsequently condensed with two equivalents of formaldehyde. The stable bicyclic compound **7** was isolated, fully character-

**Table 1** Optimization of Experimental Conditions for the Multicomponent Reaction of Benzaldehyde (**1a**), Diethyl Aminomalonate (**2**), and Crotonaldehyde (**3a**)




**1a** **2** **3a** **4a** **5a**

| Entry[a] | Solvent | Additive (equiv) | Temp (°C) | Yield[b] (%) of **4a** | ee[c] (%) | Yield[b] (%) of **5a** |
|---|---|---|---|---|---|---|
| 1 | THF | $H_2O$ (4) | 4 | 11 | 98 | 15 |
| 2 | THF | – | 4 | 21 | n.d.[d] | 25 |
| 3 | THF–$H_2O$ (1:1) | – | 4 | 31 | 98 | <5 |
| 4 | THF–$H_2O$ (1:1) | BzOH (0.2) | 4 | 29 | n.d. | <5 |
| 5 | $CH_2Cl_2$–$H_2O$ (1:1) | – | 4 | 24 | n.d. | <5 |
| 6 | $Et_2O$–$H_2O$ (1:1) | – | 4 | 10 | n.d. | <5 |
| 7 | $F_3CCH_2OH$ | – | 4 | 20 | n.d. | <5 |
| 8 | EtOH | – | 4 | 27 | 97 | <5 |
| 9 | *i*-PrOH | – | 4 | 36 | 97 | <5 |
| 10 | THF–$H_2O$ (1:1) | – | r.t. | 47 | 98 | <5 |
| 11 | THF–brine (1:1) | – | r.t. | 50 | 97 | <5 |
| 12[e] | THF–brine (19:1) | – | r.t. | 54 | 98 | <5 |
| 13[e] | brine | – | r.t. | 45 | 98 | <5 |

[a] All reactions were performed on a 0.57 mmol scale for 72 h, except where indicated otherwise. In all the conditions tested, the *endo*/*exo* ratio for product **4a** was >95:5, as measured by $^1$H NMR spectroscopy on the crude reaction mixture.
[b] Yield of pure product after flash column chromatography.
[c] Determined by chiral HPLC after reduction to the corresponding alcohol **6a** (see experimental section).
[d] n.d. = not determined.
[e] Reaction time 24 h.

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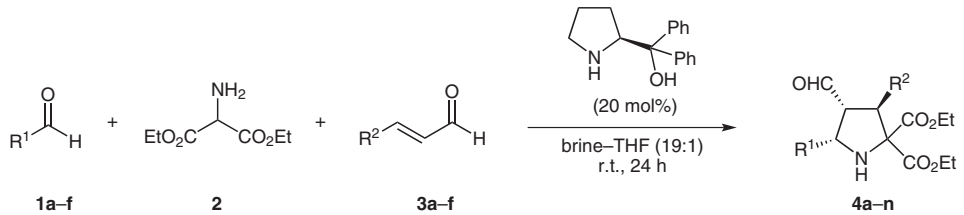
**Table 2** Reaction Scope

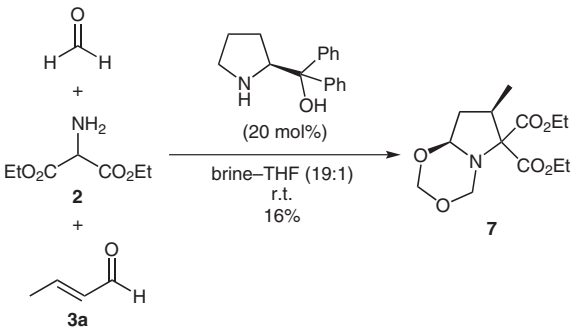



| Entry[a] | **1** | $R^1$ | **3** | $R^2$ | Product | Yield[b] (%) | *endo/exo*[c] | ee[d] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | Ph | **3a** | Me | **4a** | 54 | >95:5 | 99 |
| 2 | **1b** | 4-$FC_6H_4$ | **3a** | Me | **4b** | 40 | >95:5 | 99 |
| 3 | **1c** | 4-$MeOC_6H_4$ | **3a** | Me | **4c** | 15 | n.d.[e] | n.d. |
| 4 | **1d** | 2-$MeOC_6H_4$ | **3a** | Me | **4d** | 41 | 84:16 | >99 |
| 5 | **1e** | 2-$MeC_6H_4$ | **3a** | Me | **4e** | 58 | >95:5 | 99 |
| 6 | **1f** | 2-furyl | **3a** | Me | **4f** | 41 | >95:5 | 98 |
| 7 | **1e** | 2-$MeC_6H_4$ | **3b** | Bu | **4g** | 36 | >95:5 | 97 |
| 8 | **1e** | 2-$MeC_6H_4$ | **3c** | *i*-Pr | **4h** | 48 | >95:5 | 97 |
| 9 | **1e** | 2-$MeC_6H_4$ | **3d** | Ph | **4i** | 26 | >95:5 | 99 |
| 10 | **1b** | 4-$FC_6H_4$ | **3b** | Bu | **4j** | 43 | 92:8 | 96 |
| 11 | **1b** | 4-$FC_6H_4$ | **3c** | *i*-Pr | **4k** | 50 | >95:5 | 99 |
| 12 | **1f** | 2-furyl | **3b** | Bu | **4l** | 42 | 85:15 | 97 |
| 13 | **1f** | 2-furyl | **3c** | *i*-Pr | **4m** | 54 | >95:5 | 99 |
| 14 | **1f** | 2-furyl | **3d** | Ph | **4n** | 46 | 92:8 | 97 |
| 15 | **1a** | Ph | **3e** | 4-$MeOC_6H_4$ | – | <5 | – | – |
| 16 | **1a** | Ph | **3f** | 4-$O_2NC_6H_4$ | – | <5 | – | – |

[a] All the reactions were performed on a 0.57 mmol scale.
[b] Yield of pure product after flash column chromatography.
[c] Determined by $^1$H NMR spectroscopic analysis of the crude reaction mixture.
[d] Determined by chiral HPLC after reduction to the corresponding alcohol **6** (see experimental part).
[e] n.d. = not determined.

ized, and shown to be a single diastereoisomer, although, disappointingly, HPLC analysis on a chiral stationary phase under conditions previously optimized for the separation of the corresponding racemic standard indicated that **7** was present in a racemic form. This suggests that the amine catalyst may not have been involved in the formation of this product. The use of other conditions and/or catalysts always led to formation of **7** with no enantiocontrol.

Because the formylpyrrolidines **4a**–**n** were somewhat unstable compounds, to simplify their characterization we reduced the products after they had been isolated (Scheme 3). The resulting alcohols **6a**–**n** were stable and could be stored without decomposition for several weeks. These compounds could then be characterized and, in those cases where we could compare their spectral properties with those of previously prepared samples, we were able to confirm their absolute and relative configurations. These results could then be extrapolated to all the new adducts that we prepared. Comparisons of data showed that adducts **4** were identical to those obtained in the multistep version of this reaction that we previously reported.[5a]




**Scheme 2** Attempted condensation/cycloaddition sequence by using formaldehyde to form the azomethine ylide precursor

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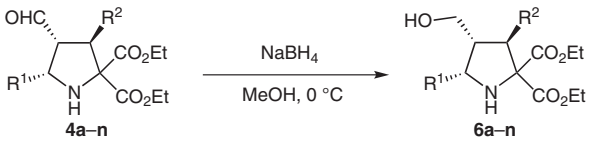


**Scheme 3** Reduction of pyrrolidine adducts **4a**–**n**

In conclusion, we have developed a simple and efficient organocatalytic procedure for the preparation of highly substituted pyrrolidines from commercially available aromatic aldehydes, diethyl malonate, and α,β-unsaturated aldehydes as starting materials. The process involves the condensation of the aromatic aldehyde with diethyl aminomalonate in situ in the presence of an iminium catalyst. This multicomponent transformation gives densely functionalized pyrrolidines in moderate yields and excellent diastereo- and enantioselectivities when the reaction is carried out in a mainly aqueous medium. The use of the aqueous environment was crucial for the reaction to proceed with high chemoselectivity without formation of undesirable cycloadducts through self-condensation side reactions. Although our protocol gives the final cycloadducts **4** in lower yields than those obtained in our previous multistep version of the reaction, the method has several benefits from the practical point of view, especially in terms of a lower reaction time, greater operational simplicity, and reduced production of waste, because there is no need to isolate and purify any synthetic intermediates.

NMR spectra were recorded in $CDCl_3$ at 20 °C on a Bruker AC-300 or Bruker AC-500 spectrometer operated at 300 or 500 MHz for $^1H$ and 75 MHz or 125.7 MHz for $^{13}C$. TMS was used as an internal standard unless otherwise stated. IR spectra were recorded for $CHCl_3$ solns on a PerkinElmer FT-IR 600 spectrophotometer; only the characteristic signals are reported. Mass spectra were recorded by EI (70 eV) or CI on a Waters Micromass GCT or Hewlett-Packard 5989B mass spectrometer. Optical rotations were determined on a PerkinElmer 241 polarimeter (λ = 589 nm, 1 dm cell). TLC was carried out on 0.2 mm thick plates of silica gel (Merck Kieselgel GF254), and visualization was performed by UV irradiation or by spraying with phosphomolybdic acid or 4-anisaldehyde soln. Flash column chromatography was performed on silica gel (Merck Kiesegel 60, 230–400 mesh). Enantiomeric excesses were determined by HPLC in a Waters 2695 chromatograph equipped with a Waters 2998 photodiode array UV detector and a Chiracel OJ, Chiralcel OD, or Chiralpak IA column. Chemicals were obtained from Acros, Sigma-Aldrich, or Alfa-Aesar. Solvents were purchased from Carlo-Erba SDS and used directly without further purification. Diphenyl[(2*S*)-pyrrolidin-2-yl]methanol, diethyl aminomalonate (**2**), aromatic aldehydes **1a**–**f**, and α,β-unsaturated aldehydes **3a**–**f**, employed as starting materials, were used as purchased. The racemic standards needed for optimization of the conditions for the separation of enantiomers were prepared by using DL-proline as a catalyst in each case.

**Diethyl 4-Formylpyrrolidine-2,2-dicarboxylates 4; General Procedure**

Aldehyde **1** (1.14 mmol) was added to a suspension of diethyl aminomalonate (**2**; 0.57 mmol) in a mixture of sat. brine (3.80 mL) and THF (0.20 mL) at r.t. The mixture was stirred for 30 min and then α,β-unsaturated aldehyde **3** (0.57 mmol) and diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (0.11 mmol) were added at once. The mixture was stirred at r.t. for the appropriate time and then $CH_2Cl_2$ (10 mL) was added. The phases were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The organic fractions were collected, combined, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography [silica gel, hexanes–EtOAc (19:1)] to give the corresponding cycloaddition product **4**.

**Diethyl 4-(Hydroxymethyl)pyrrolidine-2,2-dicarboxylates 6; General Procedure**

Because products **4** were somewhat unstable and to permit better characterization, they were reduced to the corresponding primary alcohols **6**. $NaBH_4$ (0.68 mmol) was added to a cooled (0 °C) soln of pyrrolidine **4** in MeOH (2.00 mL), and the mixture was stirring for 30 min at 0 °C. Sat. aq $NH_4Cl$ (3.00 mL) and $CH_2Cl_2$ (5.00 mL) were added and the mixture was stirred for a further 30 min at r.t. The mixture was then extracted with $CH_2Cl_2$ (3 × 10 mL) and the organic fractions were combined, collected, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography [silica gel, hexanes–EtOAc (1:1)].

**Diethyl (3*R*,4*R*,5*S*)-4-Formyl-3-methyl-5-phenylpyrrolidine-2,2-dicarboxylate (4a)**

The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (30 mg, 0.11 mmol), *trans*-crotonaldehyde (48 μL, 0.57 mmol), PhCHO (0.12 mL, 1.14 mmol), and diethyl aminomalonate (100 mg, 0.57 mmol) with reaction for 1 d gave a colorless oil; yield: 103 mg (0.31 mmol, 54%); *exo*/*endo* ($^1H$ NMR): >95:5.

**Diethyl (3*R*,4*R*,5*S*)-4-(Hydroxymethyl)-3-methyl-5-phenylpyrrolidine-2,2-dicarboxylate (6a)**

Reduction of **4a** (103 mg, 0.31 mmol) by the general procedure using $NaBH_4$ (14 mg, 0.37 mmol) gave a colorless oil; yield: 97 mg (0.29 mmol, 94%); 99% ee.

HPLC: Chiralcel OD, hexane–*i*-PrOH (95:05), flow rate: 1.00 mL/min; $t_R$ = 12.97 min (major, 3*R*,4*R*,5*S*-isomer), 15.17 min (minor, 3*S*,4*S*,5*R*-isomer).

All physical and spectroscopic data for compounds **4a** and **6a** agreed with the values reported in the literature.[5a]

**Diethyl (3*R*,4*R*,5*S*)-5-(4-Fluorophenyl)-4-formyl-3-methylpyrrolidine-2,2-dicarboxylate (4b)**

The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (30 mg, 0.11 mmol), *trans*-crotonaldehyde (48 μL, 0.57 mmol), 4-fluorobenzaldehyde (0.12 mL, 1.14 mmol), and diethyl aminomalonate (100 mg, 0.57 mmol) with reaction for 1 d gave a colorless oil; yield: 80 mg (0.23 mmol, 40%); *exo*/*endo* ($^1H$ NMR): >95:5.

**Diethyl (3*R*,4*R*,5*S*)-5-(4-Fluorophenyl)-4-(hydroxymethyl)-3-methylpyrrolidine-2,2-dicarboxylate (6b)**

Reduction of **4b** (80 mg, 0.23 mmol) by the general procedure using $NaBH_4$ (11 mg, 0.27 mmol) gave a colorless oil; yield: 72 mg (0.20 mmol, 87%).

HPLC: Chiralcel OJ, hexane–*i*-PrOH (98:02), flow rate: 1.00 mL/min; $t_R$ = 17.53 min (major, 3*R*,4*R*,5*S*-isomer), 22.95 min (minor, 3*S*,4*S*,5*R*-isomer); 99% ee.

All physical and spectroscopic data for compounds **4b** and **6b** agreed with the values reported in the literature.[5a]

**Diethyl (3*R*,4*R*,5*S*)-4-Formyl-5-(4-methoxyphenyl)-3-methylpyrrolidine-2,2-dicarboxylate (4c)**

The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (30 mg, 0.11 mmol), *trans*-crotonaldehyde (48 μL, 0.57 mmol), 4-methoxybenzaldehyde (0.12 mL, 1.14 mmol), and diethyl aminomalonate (100 mg, 0.57 mmol) with reaction for 3 d gave **4c** (27 mg, 0.08 mmol, 15%) as a colorless oil; *exo*/*endo* ($^1H$ NMR): 86:14.

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**Diethyl (3*R*,4*R*,5*S*)-4-(Hydroxymethyl)-5-(4-methoxyphenyl)-3-methylpyrrolidine-2,2-dicarboxylate (6c)**
Reduction of **4c** (27 mg, 0.08 mmol) by the general procedure using $NaBH_4$ (4 mg, 0.10 mmol) gave a colorless oil; yield: 22 mg (0.06 mmol, 75%).

All physical and spectroscopic data for compounds **4c** and **6c** agreed with the values reported in the literature.[5a]

**Diethyl (3*R*,4*R*,5*S*)-4-Formyl-5-(2-methoxyphenyl)-3-methylpyrrolidine-2,2-dicarboxylate (4d)**
The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (30 mg, 0.11 mmol), *trans*-crotonaldehyde (48 μL, 0.57 mmol), 2-methoxybenzaldehyde (0.12 mL, 1.14 mmol), and diethyl aminomalonate (100 mg, 0.57 mmol) with reaction for 3 d gave a colorless oil; yield: 76 mg (0.23 mmol, 41%); *exo*/*endo* ($^1$H NMR): 84:16.

**Diethyl (3*R*,4*R*,5*S*)-4-(Hydroxymethyl)-5-(2-methoxyphenyl)-3-methylpyrrolidine-2,2-dicarboxylate (6d)**
Reduction of **4d** (76 mg, 0.23 mmol) by the general procedure using $NaBH_4$ (11 mg, 0.28 mmol) gave a colorless oil; yield: 76 mg (0.21 mmol, 91%).

HPLC: Chiralcel OJ, hexane–*i*-PrOH (95:05), flow rate: 1.00 mL/min; $t_R$ = 15.91 min (major, 3*R*,4*R*,5*S*-isomer), 19.34 min (minor, 3*S*,4*S*,5*R*-isomer); >99% ee.

All physical and spectroscopic data for compounds **4d** and **6d** agreed with the values reported in the literature.[5a]

**Diethyl (3*R*,4*R*,5*S*)-4-Formyl-3-methyl-5-(2-tolyl)pyrrolidine-2,2-dicarboxylate (4e)**
The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (30 mg, 0.11 mmol), *trans*-crotonaldehyde (48 μL, 0.57 mmol), 2-methylbenzaldehyde (0.14 mL, 1.14 mmol), and diethyl aminomalonate (100 mg, 0.57 mmol) with reaction for 3 d gave a colorless oil: yield: 115 mg (0.33 mmol, 58%); *exo*/*endo* ($^1$H NMR): >95:5.

**Diethyl (3*R*,4*R*,5*S*)-4-(Hydroxymethyl)-3-methyl-5-(2-tolyl)pyrrolidine-2,2-dicarboxylate (6e)**
Reduction of **4e** (115 mg, 0.33 mmol) by the general procedure using $NaBH_4$ (15 mg, 0.40 mmol) gave a colorless oil; yield: 105 mg (0.30 mmol, 91%).

HPLC: Chiralcel OD, hexane–*i*-PrOH (98:02), flow rate: 1.00 mL/min; $t_R$ = 16.64 min (major, 3*R*,4*R*,5*S*-isomer), 19.14 min (minor, 3*S*,4*S*,5*R*-isomer); 99% ee.

All physical and spectroscopic data for compounds **4e** and **6e** agreed with the values reported in the literature.[5a]

**Diethyl (3*R*,4*R*,5*S*)-4-Formyl-5-(2-furyl)-3-methylpyrrolidine-2,2-dicarboxylate (4f)**
The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (30 mg, 0.11 mmol), *trans*-crotonaldehyde (48 μL, 0.57 mmol), 2-furaldehyde (96 μL, 1.14 mmol), and diethyl aminomalonate (100 mg, 0.57 mmol) with reaction for 1 d gave a colorless oil; yield: 76 mg (0.23 mmol, 41%); *exo*/*endo* ($^1$H NMR): >95:5.

**Diethyl (3*R*,4*R*,5*S*)-5-(2-Furyl)-4-(hydroxymethyl)-3-methylpyrrolidine-2,2-dicarboxylate (6f)**
Reduction of **4f** (76 mg, 0.23 mmol) by the general procedure using $NaBH_4$ (11 mg, 0.27 mmol) gave a colorless oil; yield: 69 mg (0.21 mmol, 91%).

HPLC: Chiralcel OD, hexane–*i*-PrOH (85:15), flow rate: 1.00 mL/min; $t_R$ = 7.50 min (major, 3*R*,4*R*,5*S*-isomer), 11.93 min (minor, 3*S*,4*S*,5*R*-isomer); 98% ee.

All physical and spectroscopic data for compounds **4f** and **6f** agreed with the values reported in the literature.[5a]

**Diethyl (3*R*,4*R*,5*S*)-3-Butyl-4-formyl-5-(2-tolyl)pyrrolidine-2,2-dicarboxylate (4g)**
The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (30 mg, 0.11 mmol), (2*E*)-hept-2-enal (78 μL, 0.57 mmol), 2-methylbenzaldehyde (0.14 mL, 1.14 mmol), and diethyl aminomalonate (100 mg, 0.57 mmol) with reaction for 3 d gave a colorless oil; yield: 58 mg (0.15 mmol, 36%); *exo*/*endo* ($^1$H NMR): >95:5.

IR ($CHCl_3$): 3375 (NH), 1734 (CO) cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.86 [t, *J* = 6.7 Hz, 3 H, $(CH_2)_3CH_3$], 1.23–1.40 [m, 11 H, 2 × $CO_2CH_2CH_3$ + $(CH_2)_2CH_aH_bCH_3$], 1.71–1.82 [m, 1 H, $(CH_2)_2CH_aH_bCH_3$], 2.26 (s, 3 H, $ArCH_3$), 2.81 (d, *J* = 3.9 Hz, 1 H, NH), 2.89–3.00 (m, 1 H, CHCHO), 3.20–3.26 [m, 1 H, $CH(CH_2)_3CH_3$], 4.19–4.41 (m, 4 H, 2 × $CO_2CH_2CH_3$), 5.32 (d, *J* = 3.9 Hz, 1 H, CHAr), 7.06–7.22 (m, 3 H, C{Ar}H), 7.70 (d, *J* = 6.8 Hz, 1 H, C{Ar}H), 8.95 (d, *J* = 4.9 Hz, 1 H, CHO).

$^{13}$C NMR (75.4 MHz, $CDCl_3$): δ = 13.8 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 14.2 [$CH(CH_2)_3CH_3$], 19.4 ($ArCH_3$), 22.7 [$CH(CH_2)_3CH_3$], 30.1 [$CH(CH_2)_3CH_3$], 30.7 [$CH(CH_2)_3CH_3$], 44.3 [$CH(CH_2)_3CH_3$], 57.8 (CHCHO), 58.4 (CHAr), 61.7 ($CO_2CH_2CH_3$), 61.7 ($CO_2CH_2CH_3$), 75.0 [$C(CO_2Et)_2$], 126.0 (C{Ar}H), 126.3 (C{Ar}H), 127.4 (C{Ar}H), 130.5 (C{Ar}H), 134.9 (C{Ar}C), 136.7 (C{Ar}C), 169.6 ($CO_2Et$), 171.9 ($CO_2Et$), 201.6 (CHO).

MS (EI): *m*/*z* (%) = 389 (4) [M$^+$], 360 (2), 316 (100), 298 (4), 277 (8), 242 (8), 203 (15), 131 (19).

**Diethyl (3*R*,4*R*,5*S*)-3-Butyl-4-(hydroxymethyl)-5-(2-tolyl)pyrrolidine-2,2-dicarboxylate (6g)**
Reduction of **4g** (58 mg, 0.15 mmol) by the general procedure using $NaBH_4$ (10 mg, 0.25 mmol) gave alcohol **6g** as a colorless oil; yield: 52 mg (0.13 mmol, 87%); $[\alpha]_D^{20}$ –98.9 (*c* 1.0, $CH_2Cl_2$).

HPLC: Chiralpak IA, hexane–*i*-PrOH (98:02), flow rate: 1.00 mL/min; $t_R$ = 18.55 min (minor, 3*S*,4*S*,5*R*-isomer), 21.22 min (major, 3*R*,4*R*,5*S*-isomer); 97% ee.

IR ($CHCl_3$): 3352 (NH + OH), 1730 (CO) cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.91 [t, *J* = 6.9 Hz, 3 H, $(CH_2)_3CH_3$], 1.30 (t, *J* = 7.1, 1.0 Hz, 3 H, $CO_2CH_2CH_3$), 1.31 (t, *J* = 7.1, 1.0 Hz, 3 H, $CO_2CH_2CH_3$), 1.35–1.52 [m, 5 H, $CH(CH_2)_2CH_aH_bCH_3$], 1.62 [m, 1 H, $(CH_2)_2CH_aH_bCH_3$], 2.32 [s, 3 H, $ArCH_3$), 2.37 (m, 1 H, $CH(CH_2)_3CH_3$], 2.80 (br s, 1 H, OH or NH), 2.93 (m, 1 H, $CHCH_2OH$), 3.15–3.31 (m, 2 H, $CH_2OH$), 4.16–4.36 (m, 4 H, 2 × $CO_2CH_2CH_3$), 5.02 (d, *J* = 5.6 Hz, 1 H, CHAr), 7.09–7.24 (m, 3 H, C{Ar}H), 7.71 (d, *J* = 8.4 Hz, 1 H, C{Ar}H).

$^{13}$C NMR (75.4 MHz, $CDCl_3$): δ = 14.0 [$CH(CH_2)_3CH_3$], 14.0 ($CO_2CH_2CH_3$), 14.2 ($CO_2CH_2CH_3$), 19.3 ($ArCH_3$), 22.8 [$CH(CH_2)_3CH_3$], 30.6 [$CH(CH_2)_3CH_3$], 30.8 [$CH(CH_2)_3CH_3$], 45.4 [$CH(CH_2)_3CH_3$], 47.1 ($CHCH_2OH$), 58.9 (CHAr), 61.6 ($CHCH_2OH$), 62.9 ($CO_2CH_2CH_3$), 62.9 ($CO_2CH_2CH_3$), 74.2 [$C(CO_2Et)_2$], 126.0 (C{Ar}H), 126.1 (C{Ar}H), 127.0 (C{Ar}H), 130.3 (C{Ar}H), 135.3 (C{Ar}C), 138.1 (C{Ar}C), 170.9 ($CO_2Et$), 172.2 ($CO_2Et$).

MS (EI): *m*/*z* (%) = 345 (4) [M – EtOH]$^+$, 318 (100), 300 (8), 286 (9), 272 (19), 244 (55), 228 (56), 203 (29), 170 (36).

Anal. Calcd for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.50; N, 3.58. Found: C, 67.73; H, 8.21; N, 3.54.

**Diethyl (3*R*,4*R*,5*S*)-4-Formyl-3-isopropyl-5-(2-tolyl)pyrrolidine-2,2-dicarboxylate (4h)**
The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (30 mg, 0.11 mmol), (2*E*)-4-methylpent-2-enal (70 μL, 0.57 mmol), 2-methylbenzaldehyde (0.14 mL, 1.14 mmol), and diethyl aminomalonate (100 mg, 0.57 mmol) with reaction for 3 d gave a colorless oil; yield: 103 mg (0.27 mmol, 48%); *exo*/*endo* ($^1$H NMR): >95:5.

IR ($CHCl_3$): 3344 (NH), 1731 (CO) cm$^{-1}$.

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$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.82 [d, *J* = 6.7 Hz, 3 H, $CH(CH_3)_2$], 1.00 [d, *J* = 6.7 Hz, 3 H, $CH(CH_3)_2$], 1.20–1.40 (m, 6 H, 2 × $COCH_2CH_3$), 2.05–2.17 [m, 1 H, $CH(CH_3)_2$], 2.27 (s, 3 H, $ArCH_3$), 2.85 (d, *J* = 3.3 Hz, 1 H, NH), 3.03 (ddd, *J* = 8.8, 7.5, 5.0 Hz, 1 H, CHCHO), 3.31 [dd, *J* = 7.5, 5.0 Hz, 1 H, $CHCH(CH_3)_2$], 4.16–4.42 (m, 4 H, 2 × $CO_2CH_2CH_3$), 5.19 (dd, *J* = 8.8, 3.3 Hz, 1 H, ArCH), 7.08–7.21 (m, 3 H, C{Ar}H), 7.60–7.73 (m, 1 H, C{Ar}H), 8.99 (d, 1 H, *J* = 5.0 Hz, CHO).

$^{13}$C NMR (75.4 MHz, $CDCl_3$): δ = 14.0 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 19.3 ($CH(CH_3)_2$), 19.4 ($CH(CH_3)_2$), 23.4 ($ArCH_3$), 27.8 [$CH(CH_3)_2$], 50.3 [$CHCH(CH_3)_2$], 53.8 (CHCHO), 59.2 (CHAr), 61.8 ($CO_2CH_2CH_3$), 61.9 ($CO_2CH_2CH_3$), 74.5 [$C(CO_2Et)_2$], 126.0 (C{Ar}H), 126.2 (C{Ar}H), 127.4 (C{Ar}H), 130.5 (C{Ar}H), 135.0 (C{Ar}C), 136.6 (C{Ar}C), 170.0 ($CO_2Et$), 172.2 ($CO_2Et$), 202.0 (CHO).

MS (EI): *m*/*z* (%) = 375 (1) [M$^+$], 346 (1), 302 (100), 277 (8), 256 (5), 228 (7), 203 (11), 131 (16).

**Diethyl (3*R*,4*R*,5*S*)-4-(Hydroxymethyl)-3-isopropyl-5-(2-tolyl)pyrrolidine-2,2-dicarboxylate (6h)**

Reduction of **4h** (103 mg, 0.27 mmol) by the general procedure using $NaBH_4$ (13 mg, 0.33 mmol) gave a colorless oil; yield: 96 mg (0.26 mmol, 96%); $[\alpha]_D^{20}$ –93.8 (*c* 1.0, $CH_2Cl_2$).

HPLC: Chiralpak IA, hexane–*i*-PrOH (98:02), flow rate: 1.00 mL/min; $t_R$ = 19.69 min (minor, 3*S*,4*S*,5*R*-isomer), 21.98 min (major, 3*R*,4*R*,5*S*-isomer); 97% ee.

IR ($CHCl_3$): 3570 (NH + OH), 1731 (CO) cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.92 [d, *J* = 6.7 Hz, 3 H, $CH(CH_3)_2$], 1.06 [d, *J* = 6.7 Hz, 3 H, $CH(CH_3)_2$], 1.22–1.37 (m, 6 H, $CO_2CH_2CH_3$), 2.19–2.37 [m, 4 H, $ArCH_3$ + $CH(CH_3)_2$], 2.46 (m, 1 H, $CHCH_2OH$), 2.86 (br s, 1 H, OH or NH), 3.00 [m, 1 H, $CHCH(CH_3)_2$], 3.14–3.42 (m, 2 H, $CH_2OH$), 4.15–4.37 (m, 4 H, 2 × $CO_2CH_2CH_3$), 4.85 (d, *J* = 6.5 Hz, 1 H, ArCH), 7.09–7.25 (m, 3 H, C{Ar}H), 7.71 (d, *J* = 7.8 Hz, 1 H, C{Ar}H).

$^{13}$C NMR (75.4 MHz, $CDCl_3$): δ = 14.0 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 17.7 [$CHCH(CH_3)_2$], 19.4 [$CHCH(CH_3)_2$], 23.6 ($ArCH_3$), 27.4 [$CHCH(CH_3)_2$], 42.4 [$CHCH(CH_3)_2$], 51.2 ($CHCH_2OH$), 60.4 (ArCH), 61.7 ($CO_2CH_2CH_3$), 61.9 ($CO_2CH_2CH_3$), 63.9 ($CH_2OH$), 73.5 [$C(CO_2Et)_2$], 125.6 (C{Ar}H), 126.1 (C{Ar}H), 127.1 (C{Ar}H), 130.3 (C{Ar}H), 135.3 (C{Ar}C), 138.1 (C{Ar}C), 170.6 ($CO_2Et$); 172.5 ($CO_2Et$).

MS (EI): *m*/*z* (%) = 331 (1) [M – EtOH]$^+$, 304 (100), 272 (7), 244 (45), 203 (15), 170 (23), 131 (24), 105 (14).

Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.42; H, 8.40; N, 3.39.

**Diethyl (3*R*,4*R*,5*S*)-4-Formyl-3-phenyl-5-(2-tolyl)pyrrolidine-2,2-dicarboxylate (4i)**

The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (30 mg, 0.11 mmol), *trans*-cinnamaldehyde (73 μL, 0.57 mmol), 2-methylbenzaldehyde (0.14 mL, 1.14 mmol), and diethyl aminomalonate (100 mg, 0.57 mmol) with reaction for 3 d gave a colorless oil; yield: 61 mg (0.15 mmol, 26%); *exo*/*endo* ($^1$H NMR): >95:5.

IR ($CHCl_3$): 3374 (NH), 1729 (CO) cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.78 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.29 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 2.39 (s, 3 H, $ArCH_3$), 3.09 (d, *J* = 4.8 Hz, 1 H, NH), 3.42–3.58 (m, 2 H, $CO_2CH_aH_bCH_3$ + CHCHO), 3.80–3.94 (m, 1 H, $CO_2CH_aH_bCH_3$), 4.20–4.43 (m, 2 H, $COCH_2CH_3$), 4.82 (d, *J* = 6.7 Hz, 1 H, CHPh), 5.59 (dd, *J* = 8.4, 4.8 Hz, 1 H, CHN), 7.09–7.40 (m, 8 H, C{Ar}H), 7.70 (d, *J* = 7.1 Hz, 1 H, C{Ar}H), 9.04 (d, *J* = 3.6 Hz, 1 H, CHO).

$^{13}$C NMR (75.4 MHz, $CDCl_3$): δ = 13.3 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 19.5 ($ArCH_3$), 48.6 (PhCH), 58.3 (CHCHO), 59.8 (CHN), 61.6 ($CO_2CH_2CH_3$), 61.9 ($CO_2CH_2CH_3$), 76.7 [$C(CO_2Et)_2$], 126.3 (C{Ar}H), 126.3 (C{Ar}H), 127.6 (C{Ar}H), 128.4 (C{Ar}H), 128.9 (C{Ar}H), 130.6 (C{Ar}H), 130.6 (C{Ar}H), 134.9 (C{Ar}C), 136.7 (C{Ar}C), 137.8 (C{Ar}C), 169.4 ($CO_2Et$), 171.6 ($CO_2Et$), 200.4 (CHO).

MS (EI): *m*/*z* (%) = 409 (1) [M+], 336 (100), 318 (9), 272 (8), 234 (10), 203 (12), 131 (35), 77 (10).

**Diethyl (3*R*,4*R*,5*S*)-4-(Hydroxymethyl)-3-phenyl-5-(2-tolyl)pyrrolidine-2,2-dicarboxylate (6i)**

Reduction of **4i** (61 mg, 0.15 mmol) by the general procedure using $NaBH_4$ (7 mg, 0.18 mmol) gave a colorless oil; yield: 45 mg (0.11 mmol, 73%); $[\alpha]_D^{20}$ –3.4 (*c* 0.5, $CH_2Cl_2$).

HPLC: Chiralcel OD, hexane–*i*-PrOH (98:02), flow rate: 1.00 mL/min; $t_R$ = 15.91 min (major, 3*R*,4*R*,5*S*-isomer), 19.34 min (minor, 3*S*,4*S*,5*R*-isomer); 99% ee.

IR ($CHCl_3$): 3395 (NH + OH), 1730 (CO) cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.75 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.25–1.32 (m, 4 H, $CO_2CH_2CH_3$ + OH), 2.40 (s, 3 H, $ArCH_3$), 2.80–2.99 (m, 1 H, $CHCH_2OH$), 3.03 (d, *J* = 4.2 Hz, 1 H, NH), 3.26–3.37 (m, 2 H, $CH_2OH$), 3.30–3.49 (m, 1 H, $CO_2CH_aH_bCH_3$), 3.71–3.87 (m, 1 H, $CO_2CH_aH_bCH_3$), 4.18–4.40 (m, 3 H, $COCH_2CH_3$ + CHPh), 5.42 (dd, *J* = 7.2, 4.2 Hz, 1 H, CHN), 7.14–7.38 (m, 6 H, C{Ar}H), 7.38 (d, *J* = 7.2 Hz, 2 H, C{Ar}H), 7.74 (d, *J* = 7.2 Hz, 1 H, C{Ar}H).

$^{13}$C NMR (75.4 MHz, $CDCl_3$): δ =13.3 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 19.5 ($ArCH_3$), 49.5 (PhCH), 51.7 ($CHCH_2OH$), 60.3 (NCH), 61.4 ($CO_2CH_2CH_3$), 61.7 ($CO_2CH_2CH_3$), 63.0 ($CH_2OH$), 76.2 [$C(CO_2Et)_2$], 126.0 (C{Ar}H), 126.2 (C{Ar}H), 127.1 (C{Ar}H), 127.2 (C{Ar}H), 128.4 (C{Ar}H), 128.8 (C{Ar}H), 130.4 (C{Ar}H), 135.3 (C{Ar}C), 138.3 (C{Ar}C), 140.5 (C{Ar}C), 170.0 ($CO_2Et$), 171.9 ($CO_2Et$).

MS (EI): *m*/*z* (%) = 365 (7) [M – EtOH]$^+$, 338 (60), 292 (14), 277 (10), 248 (25), 232 (56), 191 (60), 131 (100).

Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.38; H, 7.37; N, 3.20.

**Diethyl (3*R*,4*R*,5*S*)-3-Butyl-4-formyl-5-(4-fluorophenyl)pyrrolidine-2,2-dicarboxylate (4j)**

The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (30 mg, 0.11 mmol), (2*E*)-hept-2-enal (78 μL, 0.57 mmol), 4-fluorobenzaldehyde (0.12 mL, 1.14 mmol), and diethyl aminomalonate (100 mg, 0.57 mmol) with reaction for 1 d gave a colorless oil; yield: 97 mg (0.25 mmol, 43%); *exo*/*endo* ($^1$H NMR): 92:8.

IR ($CHCl_3$): 3352 (NH), 1731 (CO) cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.86 [t, *J* = 6.8 Hz, 3 H, $CH(CH_2)_3CH_3$], 1.18–1.38 [m, 11 H, 2 × $CO_2CH_2CH_3$ + $CH(CH_2)_2CH_aH_bCH_3$], 1.70–1.78 [m, 1 H, $CH(CH_2)_2CH_aH_bCH_3$], 2.77–2.82 (m, 1 H, CHCHO), 2.98 (d, *J* = 4.5 Hz, 1 H, NH), 3.20–3.30 [m, 1 H, $CH(CH_2)_3CH_3$], 4.17–4.41 (m, 4 H, 2 × $COCH_2CH_3$), 5.13 (dd, *J* = 8.7, 4.5 Hz, 1 H, ArCH), 6.93–7.05 (m, 2 H, C{Ar}H), 7.27–7.37 (m, 2 H, C{Ar}H), 9.04 (d, *J* = 4.3 Hz, 1 H, CHO).

$^{13}$C NMR (75.4 MHz, $CDCl_3$): δ = 13.8 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 14.2 [$CH(CH_2)_3CH_3$], 22.7 [$CH(CH_2)_3CH_3$], 30.2 [$CH(CH_2)_3CH_3$], 30.4 [$CH(CH_2)_3CH_3$], 43.9 [$CH(CH_2)_3CH_3$], 59.5 (CHCHO), 61.3 (ArCH), 61.8 ($CO_2CH_2CH_3$), 61.8 ($CO_2CH_2CH_3$), 75.1 [$C(CO_2Et)_2$], 115.5 (d, $J_{C-F}$ = 21.4 Hz, C{Ar}H), 128.7 (d, $J_{C-F}$ = 8.0 Hz, C{Ar}H), 134.7 (C{Ar}C), 162.0 (d, $J_{C-F}$ = 190.5 Hz, C{Ar}F), 170.0 ($CO_2Et$), 171.8 ($CO_2Et$), 202.0 (CHO).

MS (EI): *m*/*z* (%) = 393 (4) [M+], 364 (4), 320 (100), 302 (6), 274 (12), 246 (13), 207 (12), 135 (16).

**Diethyl (3*R*,4*R*,5*S*)-3-Butyl-5-(4-fluorophenyl)-4-(hydroxymethyl)pyrrolidine-2,2-dicarboxylate (6j)**

Reduction of **4j** (97 mg, 0.25 mmol) by the general procedure using $NaBH_4$ (11 mg, 0.29 mmol) gave a colorless oil; yield: 52 mg (0.13 mmol, 52%); $[\alpha]_D^{20}$ –81.2 (*c* 1.0, $CH_2Cl_2$).

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HPLC: Chiralpak IA, hexane–*i*-PrOH (95:05), flow rate: 1.00 mL/min; $t_R$ = 15.42 min (minor, 3*S*,4*S*,5*R*-isomer), 17.88 min (major, 3*R*,4*R*,5*S*-isomer); 96% ee.

IR ($CHCl_3$): 3354 (NH + OH), 1729 (CO) $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.92 [t, *J* = 6.9 Hz, 3 H, $CH(CH_2)_3CH_3$], 1.29 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.30 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.23–1.45 [m, 6 H, $CH(CH_2)_3CH_3$], 2.23–2.32 (m, 1 H, $CHCH_2OH$), 2.87–3.01 [m, 2 H, $CH(CH_2)_3CH_3$ + OH or NH], 3.20–3.42 (m, 2 H, $CH_2OH$), 4.15–4.36 (m, 4 H, 2 × $COCH_2CH_3$), 4.78–4.85 (m, 1 H, ArCH), 7.02 (t, *J* = 8.6 Hz, 2 H, C{Ar}H), 7.37 (dd, *J* = 8.6, 5.3 Hz, 2 H, C{Ar}H).

$^{13}C$ NMR (75.4 MHz, $CDCl_3$): δ = 14.0 [$CH(CH_2)_3CH_3$], 14.0 ($CO_2CH_2CH_3$), 14.1 ($CO_2CH_2CH_3$), 22.8 [$CH(CH_2)_3CH_3$], 30.3 [$CH(CH_2)_3CH_3$], 30.5 [$CH(CH_2)_3CH_3$], 45.0 [$CH(CH_2)_3CH_3$], 49.7 ($CHCH_2OH$), 61.6 (ArCH), 61.7 ($CO_2CH_2CH_3$), 61.7 ($CO_2CH_2CH_3$), 62.2 ($CH_2OH$), 74.8 [$C(CO_2Et)_2$], 115.2 (d, $J_{C–F}$ = 21.3 Hz, C{Ar}H), 128.4 (d, $J_{C–F}$ = 7.8 Hz, C{Ar}H), 136.1 (d, $J_{C–F}$ = 2.9 Hz, C{Ar}C), 162.0 (d, $J_{C–F}$ = 245.6 Hz, C{Ar}F), 170.9 ($CO_2Et$), 172.1 ($CO_2Et$).

MS (EI): *m*/*z* (%) = 349 (4) $[M – EtOH]^+$, 322 (100), 305 (13), 276 (24), 248 (75), 232 (86), 174 (42), 135 (88).

Anal. Calcd for $C_{21}H_{30}NO_5F$: C, 63.78; H, 7.65; N, 3.54. Found: C, 63.64; H, 7.93; N, 3.56.

**Diethyl (3*R*,4*R*,5*S*)-5-(4-Fluorophenyl)-4-formyl-3-isopropylpyrrolidine-2,2-dicarboxylate (4k)**

The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (30 mg, 0.11 mmol), (2*E*)-4-methylpent-2-enal (70 μL, 0.57 mmol), 4-fluorobenzaldehyde (0.12 mL, 1.14 mmol), and diethyl aminomalonate (100 mg, 0.57 mmol) with reaction for 1 d gave a colorless oil; yield: 108 mg (0.28 mmol, 50%); *exo*/*endo* ($^1H$ NMR): >95:5.

IR ($CHCl_3$): 3347 (NH), 1731 (CO) $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.78 [d, *J* = 6.7 Hz, 3 H, $CH(CH_3)_2$], 0.98 [d, *J* = 6.7 Hz, 3 H, $CH(CH_3)_2$], 1.29 (t, *J* = 7.1 Hz, 3 H, $COCH_2CH_3$), 1.29 (t, *J* = 7.1 Hz, 3 H, $COCH_2CH_3$), 2.01–2.15 [m, 1 H, $CHCH(CH_3)_2$], 2.94–3.07 (m, 2 H, CHCHO + NH), 3.32 [dd, *J* = 7.8, 5.2 Hz, 1 H, $CHCH(CH_3)_2$], 4.13–4.46 (m, 4 H, 2 × $CO_2CH_2CH_3$), 5.04 (d, *J* = 9.2 Hz, 1 H, ArCH), 6.92–7.04 (m, 2 H, C{Ar}H), 7.26–7.41 (m, 2 H, C{Ar}H), 9.03 (d, *J* = 4.6 Hz, 1 H, CHO).

$^{13}C$ NMR (75.4 MHz, $CDCl_3$): δ = 14.0 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 19.2 [$CH(CH_3)_2$], 23.6 [$CH(CH_3)_2$], 27.6 [$CH(CH_3)_2$], 49.9 [$CHCH(CH_3)_2$], 55.7 (CHCHO), 61.8 ($CO_2CH_2CH_3$), 61.9 (ArCH), 62.0 ($CO_2CH_2CH_3$), 74.6 [$C(CO_2Et)_2$], 115.4 (d, $J_{C–F}$ = 21.4 Hz, C{Ar}H), 128.8 (d, $J_{C–F}$ = 8.1 Hz, C{Ar}H), 134.6 (C{Ar}C), 162.2 (d, $J_{C–F}$ = 190.5 Hz, C{Ar}F), 169.6 ($CO_2Et$), 172.1 ($CO_2Et$), 202.5 (CHO).

MS (EI): *m*/*z* (%) = 379 (2) [M+], 350 (4), 306 (100), 281 (6), 260 (8), 232 (10), 207 (10), 190 (7), 162 (15), 135 (17).

**Diethyl (3*R*,4*R*,5*S*)-5-(4-Fluorophenyl)-4-(hydroxymethyl)-3-isopropylpyrrolidine-2,2-dicarboxylate (6k)**

Reduction of **4k** (108 mg, 0.28 mmol) by the general procedure using $NaBH_4$ (13 mg, 0.34 mmol) gave a colorless oil; yield: 78 mg (0.20 mmol, 72%); $[\alpha]_D^{20}$ –74.2 (*c* 1.0, $CH_2Cl_2$).

HPLC: Chiralcel OJ, hexane–*i*-PrOH (99:01), flow rate: 1.00 mL/min; $t_R$ = 21.42 min (major, 3*R*,4*R*,5*S*-isomer), 32.33 min (minor, 3*S*,4*S*,5*R*-isomer); >99% ee.

IR ($CHCl_3$): 3325 (NH + OH), 1730 (CO) $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.88 [d, *J* = 6.8 Hz, 3 H, $CH(CH_3)_2$], 1.03 [d, *J* = 6.8 Hz, 3 H, $CH(CH_3)_2$], 1.22–1.35 (m, 6 H, 2 × $COCH_2CH_3$), 1.75 (br s, 1 H, OH or NH), 2.20–2.26 [m, 1 H, $CHCH(CH_3)_2$], 2.26–2.42 [m, 1 H, $CHCH(CH_3)_2$], 2.96–3.04 (m, 2 H, $CHCH_2OH$ + OH or NH), 3.17–3.37 (m, 2 H, $CH_2OH$), 4.13–4.38 (m, 4 H, 2 × $CO_2CH_2CH_3$), 4.76 (d, *J* = 7.1 Hz, 1 H, ArCH), 6.95–7.07 (m, 2 H, C{Ar}H), 7.32–7.42 (m, 2 H, C{Ar}H).

$^{13}C$ NMR (75.4 MHz, $CDCl_3$): δ = 14.0 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 17.6 [$CH(CH_3)_2$], 23.6 [$CH(CH_3)_2$], 27.0 [$CH(CH_3)_2$], 45.2 [$CHCH(CH_3)_2$], 50.8 ($CHCH_2OH$), 61.7 ($CO_2CH_2CH_3$), 62.0 ($CO_2CH_2CH_3$), 62.8 (ArCH), 63.3 ($CH_2OH$), 74.0 [$C(CO_2Et)_2$], 115.2 (d, $J_{C–F}$ = 21.2 Hz, C{Ar}H), 128.4 (d, $J_{C–F}$ = 7.8 Hz, C{Ar}H), 136.0 (d, $J_{C–F}$ = 3.1 Hz, C{Ar}C), 162.0 (d, $J_{C–F}$ = 255.5 Hz, C{Ar}F), 170.5 ($CO_2Et$), 172.5 ($CO_2Et$).

MS (EI): *m*/*z* (%) = 335 (2) $[M – EtOH]^+$, 308 (65), 291 (10), 248 (100), 234 (12), 174 (33), 135 (43), 109 (25).

**Diethyl (3*R*,4*R*,5*S*)-3-Butyl-4-formyl-5-(2-furyl)pyrrolidine-2,2-dicarboxylate (4l)**

The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (30 mg, 0.11 mmol), (2*E*)-hept-2-enal (78 μL, 0.57 mmol), 2-furaldehyde (96 μL, 1.14 mmol), and diethyl aminomalonate (100 mg, 0.57 mmol) with reaction for 1 d gave a colorless oil; yield: 88 mg (0.24 mmol, 42%); *exo*/*endo* ($^1H$ NMR): 85:15.

IR ($CHCl_3$): 3355 (NH), 1728 (CO) $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.83 [t, *J* = 6.8 Hz, 3 H, $CH(CH_2)_3CH_3$], 1.15–1.35 [m, 11 H, 2 × $CO_2CH_2CH_3$ + $CH(CH_2)_2CH_aH_bCH_3$], 1.61–1.77 [m, 1 H, $CH(CH_2)_2CH_aH_bCH_3$], 2.90–2.96 (m, 1 H, CHCHO), 3.08 (br s, 1 H, NH), 3.25–3.32 [m, 1 H, $CH(CH_2)_3CH_3$], 4.13–4.33 (m, 4 H, 2 × $CO_2CH_2CH_3$), 4.99 (d, *J* = 8.7 Hz, 1 H, CHfuryl), 6.18–6.30 (m, 2 H, C{HetAr}H), 7.25–7.32 (m, 1 H, C{HetAr}H), 9.21 (d, *J* = 4.1 Hz, 1 H, CHO).

$^{13}C$ NMR (75.4 MHz, $CDCl_3$): δ = 13.8 ($CO_2CH_2CH_3$), 13.9 ($CO_2CH_2CH_3$), 14.1 [$CH(CH_2)_3CH_3$], 22.7 [$CH(CH_2)_3CH_3$], 30.2 [$CH(CH_2)_3CH_3$], 30.3 [$CH(CH_2)_3CH_3$], 44.4 [$CH(CH_2)_3CH_3$], 56.2 (CHCHO), 59.6 (CHfuryl), 61.8 ($CO_2CH_2CH_3$), 61.9 ($CO_2CH_2CH_3$), 75.0 [$C(CO_2Et)_2$], 108.0 (C{HetAr}H), 110.3 (C{HetAr}H), 142.4 (C{HetAr}H), 152.8 (C{HetAr}C), 169.7 ($CO_2Et$), 171.4 ($CO_2Et$), 201.1 (CHO).

MS (EI): *m*/*z* (%) = 365 (7) [M+], 336 (4), 308 (1); 292 (100), 274 (7), 246 (17), 218 (24), 179 (21), 137 (25).

**Diethyl (3*R*,4*R*,5*S*)-3-Butyl-5-(2-furyl)-4-(hydroxymethyl)pyrrolidine-2,2-dicarboxylate (6l)**

Reduction of **4l** (88 mg, 0.24 mmol) by the general procedure using $NaBH_4$ (12 mg, 0.29 mmol) gave a colorless oil; yield: 62 mg (0.17 mmol, 71%); $[\alpha]_D^{20}$ –33.7 (*c* 1.0, $CH_2Cl_2$).

HPLC: Chiralpak IA, hexane–*i*-PrOH (95:05), flow rate: 1.00 mL/min; $t_R$ = 17.80 min (minor, 3*S*,4*S*,5*R*-isomer), 22.89 min (major, 3*R*,4*R*,5*S*-isomer); 97% ee.

IR ($CHCl_3$): 3375 (NH + OH), 1730 (CO) $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.87 [t, *J* = 7.0 Hz, 3 H, $CH(CH_2)_3CH_3$], 1.22–1.43 [m, 11 H, 2 × $CO_2CH_2CH_3$ + $CH(CH_2)_2CH_aH_bCH_3$], 1.47–1.63 [m, 1 H, $CH(CH_2)_2CH_aH_bCH_3$], 1.82 (br s, 1 H, OH or NH), 2.30–2.42 (m, 1 H, $CHCH_2OH$), 2.62–2.80 [m, 1 H, $CH(CH_2)_3CH_3$], 3.06 (br s, 1 H, OH or NH), 3.23–3.33 (m, 1 H, $CH_aH_bOH$), 3.45–3.56 (m, 1 H, $CH_aH_bOH$), 4.13–4.34 (m, 4 H, 2 × $CO_2CH_2CH_3$), 4.80 (d, *J* = 7.4 Hz, 1 H, furylCH), 6.23–6.27 (m, 1 H, C{HetAr}H), 6.28–6.33 (m, 1 H, C{HetAr}H), 7.32–7.36 (m, 1 H, C{HetAr}H).

$^{13}C$ NMR (75.4 MHz, $CDCl_3$): δ = 13.9 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 14.1 [$CH(CH_2)_3CH_3$], 22.9 [$CH(CH_2)_3CH_3$], 30.1 [$CH(CH_2)_3CH_3$], 30.5 [$CH(CH_2)_3CH_3$], 44.8 [$CH(CH_2)_3CH_3$], 49.9 ($CHCH_2OH$), 57.0 (furylCH), 61.6 ($CO_2CH_2CH_3$), 61.7 ($CO_2CH_2CH_3$), 62.6 ($CH_2OH$), 74.8 [$C(CO_2Et)_2$], 107.2 (C{HetAr}H), 110.4 (C{HetAr}H), 141.9 (C{HetAr}H), 155.3 (C{HetAr}C), 170.8 ($CO_2Et$), 171.9 ($CO_2Et$).

MS (EI): *m*/*z* (%) = 367 (2) [M+], 321 (11), 294 (100), 277 (18), 248 (23), 220 (84), 204 (75), 139 (45), 107 (98).

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Anal. Calcd for $C_{19}H_{29}NO_6$: C, 62.11; H, 7.96; N, 3.81. Found: C, 62.54; H, 7.10; N, 3.88.

**Diethyl (3*R*,4*R*,5*S*)-4-Formyl-5-(2-furyl)-3-isopropylpyrrolidine-2,2-dicarboxylate (6m)**

The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (30 mg, 0.11 mmol), (2*E*)-4-methylpent-2-enal (70 μL, 0.57 mmol), 2-furaldehyde (96 μL, 1.14 mmol), and diethyl aminomalonate (100 mg, 0.57 mmol) with reaction for 1 d gave a colorless oil; yield: 108 mg (0.31 mmol, 54%); *exo*/*endo* ($^1$H NMR): >95:5.

IR ($CHCl_3$): 3351 (NH), 1725 (CO) cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.75 [d, *J* = 6.8 Hz, 3 H, $CH(CH_3)_2$], 0.97 [d, *J* = 6.8 Hz, 3 H, $CH(CH_3)_2$], 1.19–1.36 (m, 6 H, 2 × $CO_2CH_2CH_3$), 2.00–2.10 [m, 1 H, $CH(CH_3)_2$], 2.97–3.16 (m, 2 H, CHCHO + NH), 3.33 [dd, *J* = 8.7, 4.9 Hz, 1 H, $CHCH(CH_3)_2$], 4.10–4.36 (m, 4 H, 2 × $COCH_2CH_3$), 4.90–5.01 (m, 1 H, furylCH), 6.14–6.32 (m, 2 H, C{HetAr}H), 7.25–7.32 (m, 1 H, C{HetAr}H), 9.21 (d, *J* = 4.3 Hz, 1 H, CHO).

$^{13}$C NMR (75.4 MHz, $CDCl_3$): δ = 13.9 ($CO_2CH_2CH_3$), 19.1 [$CH(CH_3)_2$], 23.4 [$CH(CH_3)_2$], 27.4 [$CH(CH_3)_2$], 50.2 [$CHCH(CH_3)_2$], 55.7 (CHCHO), 56.7 (furylCH), 61.8 ($CO_2CH_2CH_3$), 62.1 ($CO_2CH_2CH_3$), 74.6 [$C(CO_2Et)_2$], 108.0 (C{HetAr}H), 110.3 (C{HetAr}H), 142.4 (C{HetAr}H), 152.7 (C{HetAr}C), 170.0 ($CO_2Et$), 171.7 ($CO_2Et$), 201.5 (CHO).

MS (EI): *m*/*z* (%) = 351 (2) [M+], 322 (2), 308 (2), 278 (100), 253 (6), 232 (11), 204 (13), 179 (16), 137 (20).

**Diethyl (3*R*,4*R*,5*S*)-5-(2-Furyl)-4-(hydroxymethyl)-3-isopropylpyrrolidine-2,2-dicarboxylate (6m)**

Reduction of **4m** (108 mg, 0.31 mmol) by the general procedure using $NaBH_4$ (14 mg, 0.37 mmol) gave a colorless oil; yield: 89 mg (0.25 mmol, 81%); $[\alpha]_D^{20}$ –55.6 (*c* 1.0, $CH_2Cl_2$).

HPLC: Chiralcel OD, hexane–*i*-PrOH (95:05), flow rate: 1.00 mL/min; $t_R$ = 8.38 min (major, 3*R*,4*R*,5*S*-isomer), 10.02 min (minor, 3*S*,4*S*,5*R*-isomer); 99% ee.

IR ($CHCl_3$): 3412 (NH + OH), 1729 (CO) cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.83 [t, *J* = 6.9 Hz, 3 H, $CH(CH_3)_2$], 0.99 [t, *J* = 6.9 Hz, 3 H, $CH(CH_3)_2$], 1.18–1.31 (m, 6 H, 2 × $CO_2CH_2CH_3$), 1.94 (br s, 1 H, OH or NH), 2.15–2.25 [m, 1 H, $CH(CH_3)_2$], 2.40–2.53 (m, 1 H, $CHCH_2OH$), 2.86 [dd, *J* = 6.9, 2.9 Hz, 1 H, $CHCH(CH_3)_2$], 3.23–3.28 (m, 1 H, $CH_aH_bOH$), 3.40–3.52 (m, 1 H, $CH_aH_bOH$), 4.09–4.34 (m, 5 H, 2 × $COCH_2CH_3$ + OH or NH), 4.74 (d, *J* = 7.4 Hz, 1 H, furylCH), 6.24 (d, *J* = 3.2 Hz, 1 H, C{HetAr}H), 6.30–6.32 (m, 1 H, C{HetAr}H), 7.33–7.36 (m, 1 H, C{HetAr}H).

$^{13}$C NMR (75.4 MHz, $CDCl_3$): δ = 14.0 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 17.4 [$CH(CH_3)_2$], 23.7 [$CH(CH_3)_2$], 26.4 [$CH(CH_3)_2$], 45.3 [$CHCH(CH_3)_2$], 50.3 ($CHCH_2OH$), 57.6 (furylCH), 61.6 ($CO_2CH_2CH_3$), 62.0 ($CO_2CH_2CH_3$), 63.5 ($CH_2OH$), 74.1 [$C(CO_2Et)_2$], 107.1 (C{Ar}H), 110.4 (C{Ar}H), 141.8 (C{Ar}H), 155.1 (C{Ar}C), 170.5 ($CO_2Et$), 172.3 ($CO_2Et$).

MS (EI): *m*/*z* (%) = 353 (2) [M$^+$], 307 (3), 280 (96), 263 (12), 234 (12), 220 (100), 174 (15), 107 (44).

Anal. Calcd for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.70; N, 3.96. Found: C, 61.47; H, 7.56; N, 3.57.

**Diethyl (3*R*,4*R*,5*S*)-4-Formyl-5-(2-furyl)-3-phenylpyrrolidine-2,2-dicarboxylate (4n)**

The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (30 mg, 0.11 mmol), *trans*-cinnamaldehyde (73 μL, 0.57 mmol), 2-furaldehyde (96 μL, 1.14 mmol), and diethyl aminomalonate (100 mg, 0.57 mmol) with reaction for 1 d gave a colorless oil; yield: 101 mg (0.26 mmol, 46%); *exo*/*endo* ($^1$H NMR): 92:8.

IR ($CHCl_3$): 3351 (NH), 1728 (CO) cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.75 (t, *J* = 7.1 Hz, 3 H, $COCH_2CH_3$), 1.26 (t, *J* = 7.1 Hz, 3 H, $COCH_2CH_3$), 3.35–3.61 (m, 2 H, $CO_2CH_aH_bCH_3$ + NH), 3.62–3.73 (m, 1 H, CHCHO), 3.78–3.88 (m, 1 H, $CO_2CH_aH_bCH_3$), 4.15–4.38 (m, 2 H, $CO_2CH_2CH_3$), 4.85 (d, *J* = 10.1 Hz, 1 H, PhCH), 5.22 (d, *J* = 8.5 Hz, 1 H, furylCH), 6.25–6.35 (m, 2 H, C{HetAr}H), 7.18–7.40 (m, 6 H, C{Ar}H + C{HetAr}H), 9.29 (d, *J* = 3.1 Hz, 1 H, CHO).

$^{13}$C NMR (75.4 MHz, $CDCl_3$): δ = 13.3 ($CO_2CH_2CH_3$), 13.9 ($CO_2CH_2CH_3$), 48.8 (PhCH), 56.5 (CHCHO), 59.5 (furylCH), 61.8 ($CO_2CH_2CH_3$), 61.9 ($CO_2CH_2CH_3$), 76.6 [$C(CO_2Et)_2$], 108.4 (C{HetAr}H), 110.4 (C{HetAr}H), 127.6 (C{Ar}H), 128.3 (C{Ar}H), 128.7 (C{Ar}H), 136.4 (C{Ar}C), 142.4 (C{HetAr}H), 153.1 (C{HetAr}C), 169.8 ($CO_2Et$), 170.9 ($CO_2Et$), 199.3 (CHO).

MS (EI): *m*/*z* (%) = 385 (2) [M$^+$], 312 (100), 294 (3), 266 (13), 238 (27), 210 (15), 180 (17), 131 (17).

**Diethyl (3*R*,4*R*,5*S*)-5-(2-Furyl)-4-(hydroxymethyl)-3-phenylpyrrolidine-2,2-dicarboxylate (6n)**

Reduction of **4n** (101 mg, 0.26 mmol) by the general procedure using $NaBH_4$ (15 mg, 0.32 mmol) gave a colorless oil; yield: 37 mg (0.09 mmol, 35%); $[\alpha]_D^{20}$ +30.8 (*c* 1.0, $CH_2Cl_2$).

IR ($CHCl_3$): 3372 (NH + OH), 1728 (CO) cm$^{-1}$.

HPLC: Chiralpak IA, hexane–*i*-PrOH (80:20), flow rate: 1.00 mL/min; $t_R$ = 12.70 min (minor, 3*S*,4*S*,5*R*-isomer), 22.29 min (major, 3*R*,4*R*,5*S*-isomer); 97% ee.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.74 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.25 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 3.06–3.23 (m, 2 H, $CH_2OH$), 3.34–3.55 (m, 2 H, $CHCH_2OH$ + $CO_2CH_aH_bCH_3$), 3.75–3.89 (m, 1 H, $CO_2CH_aH_bCH_3$), 4.12 (d, *J* = 11.1 Hz, 1 H, PhCH), 4.17–4.37 (m, 2 H, $COCH_2CH_3$), 4.99 (d, *J* = 6.9 Hz, 1 H, furylCH), 6.26 (d, *J* = 3.2 Hz, 1 H, C{HetAr}H), 6.32–6.36 (m, 1 H, C{HetAr}H), 7.20–7.44 (m, 6 H, C{Ar}H + C{HetAr}H).

$^{13}$C NMR (75.4 MHz, $CDCl_3$): δ = 13.3 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 50.2 (PhCH), 50.3 ($CHCH_2OH$), 57.1 (furylCH), 61.7 ($CO_2CH_2CH_3$), 61.7 ($CO_2CH_2CH_3$), 62.0 ($CH_2OH$), 76.8 [$C(CO_2Et)_2$], 107.5 (C{HetAr}H), 110.5 (C{HetAr}H), 127.4 (C{Ar}H), 128.3 (C{Ar}H), 128.8 (C{Ar}H), 137.1 (C{Ar}C), 141.9 (C{HetAr}H), 155.7 (C{HetAr}C), 170.7 ($CO_2Et$), 171.4 ($CO_2Et$).

MS (EI): *m*/*z* (%) = 387 (1) [M$^+$], 341 (6), 314 (34), 297 (24), 268 (6), 224 (18), 139 (24), 107 (100).

Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.10, H, 6.50; N, 3.62. Found: C, 65.39; H, 6.39; N, 3.69.

**Diethyl (7*R*,8a*S*)-7-Methyldihydro-4*H*-pyrrolo[2,1-*d*][1,3,5]dioxazine-6,6(7*H*)-dicarboxylate (7)**

The general procedure using diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (59 mg, 0.23 mmol), *trans*-crotonaldehyde (96 μL, 1.14 mmol), HCHO (0.10 mL, 1.37 mmol), and diethyl aminomalonate (200 mg, 1.14 mmol) with reaction for 1 d gave a colorless oil; yield: 52 mg (0.18 mmol, 16%).

IR ($CHCl_3$): 1725 (CO) cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.2 Hz, 3 H, $CHCH_3$), 1.23 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.26 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.41–1.52 (m, 1 H, $CHCH_aH_bCH$), 1.62–1.69 (m, 1 H, $CHCH_aH_bCH$), 3.40–3.60 (m, 1 H, $CHCH_3$), 4.10 (d, *J* = 8.3 Hz, 1 H, $NCH_aH_bO$), 4.15–4.30 (m, 4 H, 2 × $CO_2CH_2CH_3$), 4.54 (d, *J* = 11.3 Hz, 1 H, $OCH_aH_bO$), 4.77 (d, *J* = 8.8 Hz, 1 H, $NCH_aH_bO$), 4.91 (dd, *J* = 9.9, 4.3 Hz, 1 H, OCHN), 5.07 (d, *J* = 11.3 Hz, 1 H, $OCH_aH_bO$).

$^{13}$C NMR (75.4 MHz, $CDCl_3$): δ = 13.8 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 21.5 ($CHCH_3$), 37.1 ($CHCH_2CH$), 61.9 ($CO_2CH_2CH_3$), 62.5 ($CO_2CH_2CH_3$), 69.4 [$C(CO_2CH_2CH_3)_2$], 70.8 ($CHCH_3$), 72.0 ($NCH_2O$), 76.0 ($OCH_2O$), 90.0 ($CHOCH_2$), 169.2 ($CO_2CH_2CH_3$), 169.6 ($CO_2CH_2CH_3$).

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MS (EI): *m*/*z* (%) = 286 (4) $[M - H]^+$, 272 (4), 230 (6), 214 (100), 184 (7), 170 (9), 142 (85), 127 (6), 96 (10), 70 (35).

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**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(9) This behavior was also observed in other cases in which one of the reactants (either the aromatic aldehyde **1** or the enal **3**) was a solid. In particular, when we examined the use of 3,4-dimethoxybenzaldehyde, 3,5-dimethoxybenzaldehyde, 3,4-methylenedioxybenzaldehyde, or 3-(2-furyl)acrylaldehyde in combination with other liquid aromatic aldehydes or enals, we obtained the cycloaddition products in trace amounts only.

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