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ORIGINAL PAPER

Synthesis of novel multi-functionalized pyrrolidines by [3 + 2] dipolar cycloaddition of azomethine ylides and vinyl ketones

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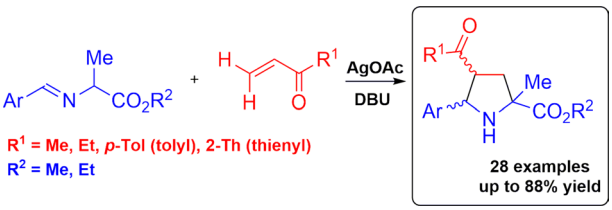
Abstract

An efficient and easy synthetic route to substituted pyrrolidine derivatives has been established through [3 + 2] dipolar cycloaddition of vinyl ketones and azomethine ylides. The reactions proceed smoothly, under mild conditions, affording moderate to high isolated yields (up to 88%) of the products, within a short reaction time (15–45 min), providing a series of novel potentially bioactive compounds. Mechanistic considerations revealed that this cycloaddition exclusively proceeds following *endo*-pathway which enables access to the *cis*-derivatives. The products that contain acetyl group at C4 easily undergo isomerization, as it was confirmed by monitoring of the reaction kinetics and DFT calculations.

Graphical abstract



Keywords Cycloadditions · Enones · Ylides · Heterocycles

Introduction

Pyrrolidine, as frequent structural motif in natural products, occupies significant place in organic, medicinal, and pharmaceutical chemistry [1–4]. It is widely present in biologically active molecules and pharmaceutical drug candidates, classifying pyrrolidine derivatives as a group of attractive synthetic targets. Consequently, these five-membered heterocycles are useful building blocks in the organic synthesis [5–13]. Pyrrolidine's ring is a key structural fragment of L-proline and other organocatalysts derived from it [14–17]. Pyrrolidine-containing compounds also exert the broad spectrum of potential therapeutic properties like analgesic [18], antibacterial [19–21], antitumor [22], anti-inflammatory [23, 24], and enzyme inhibiting [25].

Over the past 3 decades, several synthetic routes toward pyrrolidine core were developed [26–30], and pathways based on [3 + 2] dipolar cycloadditions prevail as the most suitable and used [31]. The leading species employed for this purpose are azomethine ylides acting as dipoles. Wide range of dipolarophiles like α,β-unsaturated carboxylic derivatives [32–50], nitroalkenes [51–57], alkenylsulfones [58–66], enones [67–70], and allenes [71–73] were examined,

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concluding that the cycloadditions of alkenes have been extremely versatile and economical processes [74–84].

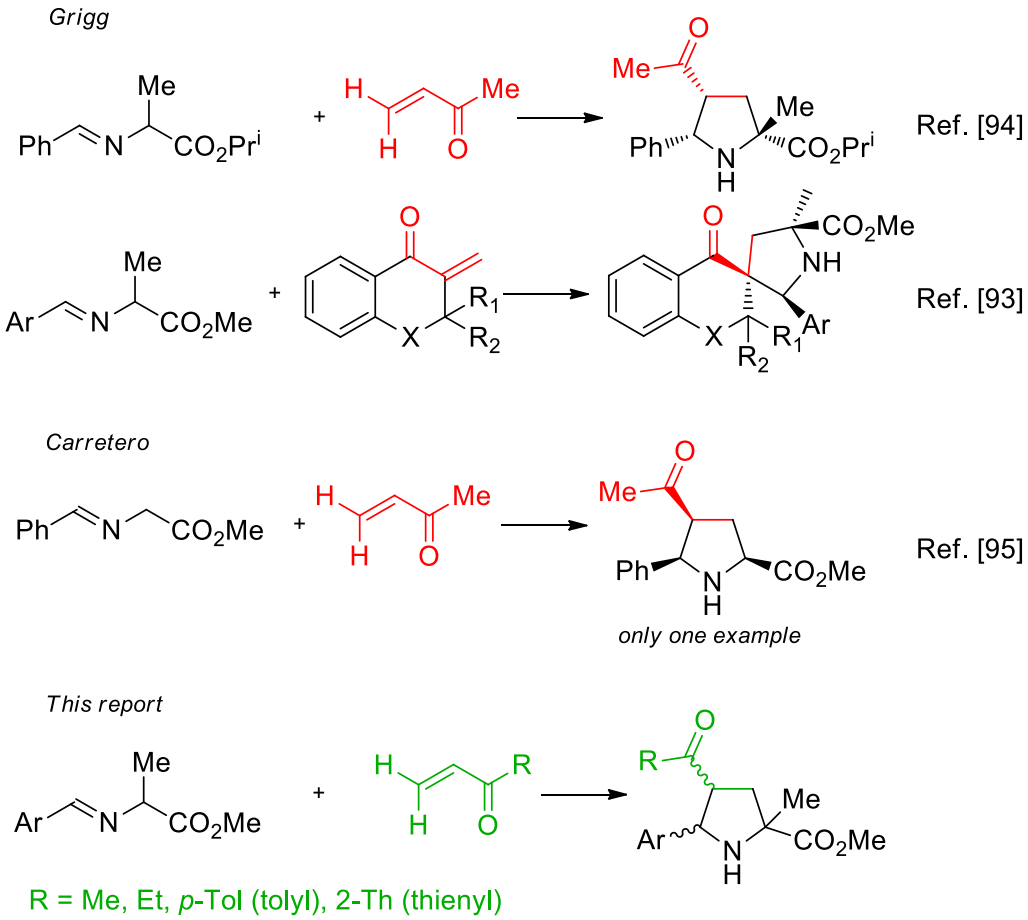
Our ongoing studies are directed toward enones comprising the exploration and the evaluation of their synthetic potential. Particularly, the focus is on the vinyl species and synthesis of novel compounds. In that context, we earlier reported several transformations of the ferrocene-containing enones, which resulted by the obtaining of numerous new compounds [85–90]. We also disclosed that vinyl ketones, despite their tendency toward polymerization, could provide easy access to aryltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-ones through the cycloaddition with *N*,*N*′-cyclic azomethine imines [89–91].

Accordingly, the reaction between azomethine ylides and vinyl ketones was excellent platform for continuation of research. Although the [3 + 2] cycloadditions of azomethine ylides to systems containing conjugated vinyl and C=O groups were studied [27, 74, 92–98], the attention was not dedicated to ylides having alkyl substituent on the carbon C2 (between nitrogen and ester group, Scheme 1). We found only Grigg's reports dealt with these dipoles [74, 93, 94]. In addition, the range of used vinyl α,β-unsaturated ketones is limited to but-3-en-2-one and series of chromenones utilized by Grigg [94]. Introducing of the acyl substituent into heterocyclic structure would increase the significance of the products as synthetic intermediates, since the transformability of carbonyl fragments provides multiply oriented approach to further derivatization. Bearing all previously mentioned in mind, we considered supplementing the field by the investigation of the reaction diversity and synthesis of new highly substituted pyrrolidine derivatives. Therefore, in this paper the dipolar cycloaddition between azomethine ylides and vinyl ketones is reported.

Results and discussion

The established route to the azomethine ylides includes a deprotonation of the imino ester obtained from carbonyl compound and ester of the amino acid, followed by coordination of the formed α-carbanion to metal ion [99]. Several metal salts proved to be useful, substantially influencing the stability of the ylide and stereoselectivity of the reaction [100]. Among them, silver acetate (AgOAc) is distinguished

Scheme 1



as the most efficient salt providing high yield of the one stereoisomer [32].

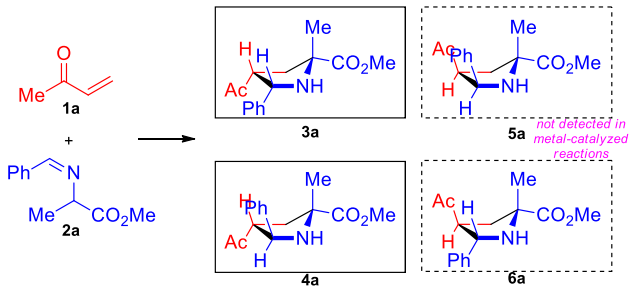
Our initial screening was oriented toward exploration of the potentially suitable solvents, catalysts, and bases. As a test reaction, the cycloaddition of but-3-en-2-one (**1a**) to azomethine ylide generated from methyl 2-(benzylideneamino)propanoate (**2a**) was selected (Table 1). At first, we screened solvents (Table 1, entries 2–10) among which the three—acetone, 1,4-dioxane, and acetonitrile provide high yields (Table 1, entries 2, 9, 10). However, we observed more than four products in acetone and 1,4-dioxane, unlike the products mixture in acetonitrile which contained only two diastereoisomers. Therefore, acetonitrile (MeCN) was considered as solvent of choice and we have continued initial investigation using it.

In the next segment of research, 13 salts along with AgOAc were examined as catalysts and data collected by analysis of ^{1}H NMR spectra of the crude reaction mixtures are inserted in Table 1 (entries 11–23). Only the Ag^+ and Cu^+ ions gave satisfactory results (Table 1, entries 2, 11, and 20), while all other examined metal cations were inactive, except Mn^{3+} which afforded products in yield of 18% (Table 1, entry 16). Furthermore, they expressed inhibiting activity, since the reaction took place in yield of 63% without the presence of salt (Table 1, entry 1). However, the procedures performed in the absence of metal cations suffered from low stereoselectivity. Surprisingly, Li^+ ion failed to provide products (Table 1, entries 22 and 23), despite it was mentioned earlier as a good catalyst [99–101]. The attempts to alter the initially used base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), with cheaper pyridine or triethylamine did not make any improvement (Table 1, entries 24 and 25), given that the reaction yields were particularly lower (65 and 29%, respectively). Therefore, we considered it was optimal to perform the further examinations in the presence of AgOAc and DBU.

The reaction between **1a** and **2a** might afford four products (**3a**, **4a**, **5a**, and **6a**, see scheme in Table 1). The results collected during initial investigations agreed with our expectations. It was predicted that the one cycloadduct will be favorably formed, with respect that the reaction conditions should exclude **5a** and **6a** (products of the *exo*-cycloaddition) [101]. Indeed, after stirring the reaction mixture of **1a** and **2a** for 45 min (Table 2, entry 2) we detected the presence of two diastereoisomers by analysis of ^{1}H NMR spectra of the crude reaction mixture. One, methyl 4-acetyl-2-methyl-5-phenylpyrrolidine-2-carboxylate (**4a**), was isolated by column chromatography (65%) and its structure was confirmed by spectroscopic methods. On the other hand, though the second diastereoisomer (**3a**) was spotted, we failed to isolate it.

With these conditions in hand, we combined four enones (**1a**–**1d**) and 13 imino esters (**2a**–**2m**) intending to examine

Table 1 Screening studies of 1,3-dipolar cycloaddition of azomethine ylide obtained from **2a** to but-3-en-2-one (**1a**)



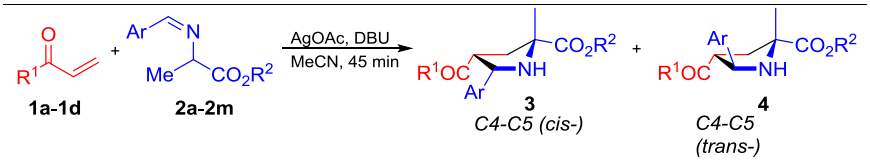
Entry	Catalyst	Solvent	Base	Yield/%[a]	*Cis/trans* ratio (**3a** + **5a**)/(**4a** + **6a**)[a]
1	–	MeCN	DBU	63	(5 + 2):(45 + 48)
2	AgOAc	MeCN	DBU	84	23:77
3	AgOAc	Hex	DBU	70	23:77
4	AgOAc	EtOAc	DBU	64	9:91
5	AgOAc	CH_2Cl_2	DBU	69	30:70
6	AgOAc	Et_2O	DBU	68	52:48
7	AgOAc	Tol	DBU	67	47:53
8	AgOAc	THF	DBU	78	39:61
9	AgOAc	1,4-Dioxane	DBU	92	33:67
10	AgOAc	Me_2CO	DBU	90	17:83
11	CuI	MeCN	DBU	43	71:29
12	$ZrCl_4$	MeCN	DBU	–	–
13	$Cu(OAc)_2$	MeCN	DBU	–	–
14	$Cu(acac)_2$	MeCN	DBU	–	–
15	$Co(OAc)_2$	MeCN	DBU	–	–
16	$Mn(OAc)_3$	MeCN	DBU	18	72:18
17	$Zn(OAc)_2$	MeCN	DBU	–	–
18	$Mn(OAc)_2$	MeCN	DBU	–	–
19	$Ni(OAc)_2$	MeCN	DBU	–	–
20	CuCl	MeCN	DBU	56	94:6
21	$Mg(NO_3)_2$	MeCN	DBU	–	–
22	LiI	MeCN	DBU	–	–
23	Li_2CO_3	MeCN	DBU	–	–
24	AgOAc	MeCN	Et_3N	29	50:50
25	AgOAc	MeCN	Py	65	83:17

Reactions were carried out with **1a** (1 mmol, 1 equiv.), **2a** (1 mmol, 1 equiv.), base (0.1 mmol, 0.1 equiv.), metal catalyst (0.3 mmol, 0.3 equiv.) in 2 cm^3 acetonitrile for 45 min at r.t

[a]Calculated on the basis of ^{1}H NMR spectral analysis of crude mixtures

the scope of the reaction. The data are summarized in Table 2. Interestingly, all enones containing substituent R^1 bigger than methyl (Table 2, entries 10–28) exclusively gave products with *cis*-orientation of aryl and acyl group. Contrary to these examples, methyl vinyl ketone afforded

Table 2 Substrate scope of reactions between vinyl ketones **1** and imino esters **2**



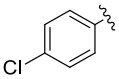
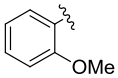
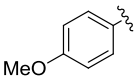
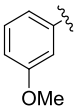
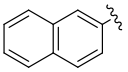
Entry	Enone	Imino ester	Product *C4-C5 configuration*	Yield of isolated product /%
1[a]	**1a** R^1 = Me	**2a** Ar =  R^2 = Me	**3a** *cis-*	51
2	**1a** R^1 = Me	**2a** Ar =  R^2 = Me	**4a** *trans-*	65
3[a]	**1a** R^1 = Me	**2b** Ar =  R^2 = Et	**3aa** *cis-*	59
4[b]	**1a** R^1 = Me	**2c** Ar =  R^2 = Me	**4b** *trans-*	63
5	**1a** R^1 = Me	**2d** Ar =  R^2 = Me	**3c** *cis-* **4c** *trans-*	45 37
6	**1a** R^1 = Me	**2e** Ar =  R^2 = Me	**3d** *cis-* **4d** *trans-*	34 30
7	**1a** R^1 = Me	**2f** Ar =  R^2 = Me	**4e** *trans-*	67
8	**1a** R^1 = Me	**2g** Ar =  R^2 = Me	**4f** *trans-*	68
9	**1a** R^1 = Me	**2h** Ar =  R^2 = Me	**34g** -	68
10	**1b** R^1 = Et	**2a** Ar =  R^2 = Me	**3h** *cis-*	73

Table 2 (continued)

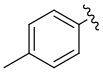
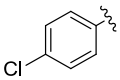
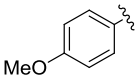
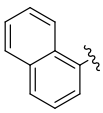
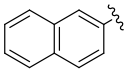
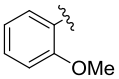
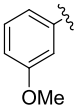
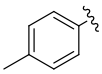
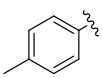
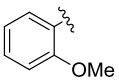
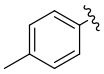
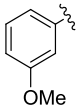
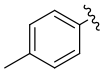
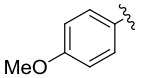
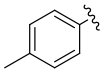
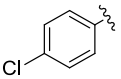
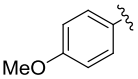
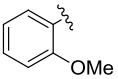
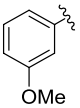
Entry	Enone	Imino ester	Product *C4-C5 configuration*	Yield of isolated product /%
11	**1b** R^1 = Et	**2i** Ar =  R^2 = Me	**3i** *cis-*	82
12	**1b** R^1 = Et	**2c** Ar =  R^2 = Me	**3j** *cis-*	64
13	**1b** R^1 = Et	**2e** Ar =  R^2 = Me	**3k** *cis-*	67
14	**1b** R^1 = Et	**2j** Ar =  R^2 = Me	**3l** *cis-*	88
15	**1b** R^1 = Et	**2g** Ar =  R^2 = Me	**3m** *cis-*	60
16	**1b** R^1 = Et	**2h** Ar =  R^2 = Me	**34n** -	82
17	**1b** R^1 = Et	**2d** Ar =  R^2 = Me	**3o** *cis-*	58
18	**1b** R^1 = Et	**2f** Ar =  R^2 = Me	**3p** *cis-*	64
19	**1b** R^1 = Et	**2k** Ar =  R^2 = Et	**3q** *cis-*	69
20	**1c** R^1 = 	**2a** Ar =  R^2 = Me	**3r** *cis-*	66
21	**1c** R^1 = 	**2d** Ar =  R^2 = Me	**3s** *cis-*	81

Table 2 (continued)

Entry	Enone	Imino ester	Product *C4-C5 configuration*	Yield of isolated product /%
22	**1c** R^1 = 	**2f** Ar =  OMe	R^2 = Me	**3t** *cis-*	78
23	**1c** R^1 = 	**2e** Ar =  MeO	R^2 = Me	**3u** *cis-*	57
24	**1c** R^1 = 	**2c** Ar =  Cl	R^2 = Me	**3v** *cis-*	63
25	**1d** R^1 = 	**2a** Ar = 	R^2 = Me	**3w** *cis-*	63
26	**1d** R^1 = 	**2e** Ar =  MeO	R^2 = Me	**3x** *cis-*	54
27	**1d** R^1 = 	**2l** Ar =  OMe	R^2 = Et	**3y** *cis-*	65
28	**1d** R^1 = 	**2m** Ar =  OMe	R^2 = Et	**3z** *cis-*	67

[a]Isolated yield after column chromatography and reaction performed within 15 min

[b]Yields calculated on the basis of ^{1}H NMR spectrum of mixture which contained only two diastereoisomers

mixtures of pyrrolidines with dominant *trans*-substituted (at C4 and C5) derivative (Table 2, entries 1–9). All cycloadditions ran smoothly with good overall yields, enabling isolation of one, main diastereoisomer. The other cycloadducts were detected using NMR spectroscopy, but they were present in negligible small quantities which made their isolation rather hard and almost impossible. The exception was **2d** which gave both successfully isolated diastereoisomers (**3c** and **4c**), as well as **2e** providing inseparable mixture of **3d** and **4d**.

The structural identification of the products was performed on the basis of their ^{1}H NMR spectra. We observed significant differences in the area between 4.3 and 5.3 ppm. In this range of chemical shifts, signals originated from hydrogen bonded to C5 appeared as well-defined doublets. Although they were characterized by similar coupling constants ($J = 7.2$–9.4 Hz), their chemical shifts differed by about 1 ppm. The diastereoisomers with *cis*-orientation (**3a**, **3aa**, **3c**, **3d**, **3h**–**3m**, and **3o**–**3z**) exhibited peaks at higher shifts ($\delta = 4.58$–5.29 ppm), while *trans*-derivatives' (**4a**–**4f**) signals appeared at somewhat lower values ($\delta = 4.39$–4.73 ppm). The values of the coupling constants assigned to these stereoisomers were close, whereby the one attributed to the derivative with *cis*-oriented substituents was always higher (ca. 0.5–1.0 Hz). We also noticed different shapes of signals of diastereotopic protons C3-H_a and C3-H_b depicted on the Fig. 1. However, the key role in the assignment of the correct molecular structure had acetyl groups of **3a** and **4a.** We noticed that the aryl substituent strongly influenced acetyl group in **3a**, shifting its singlet to values

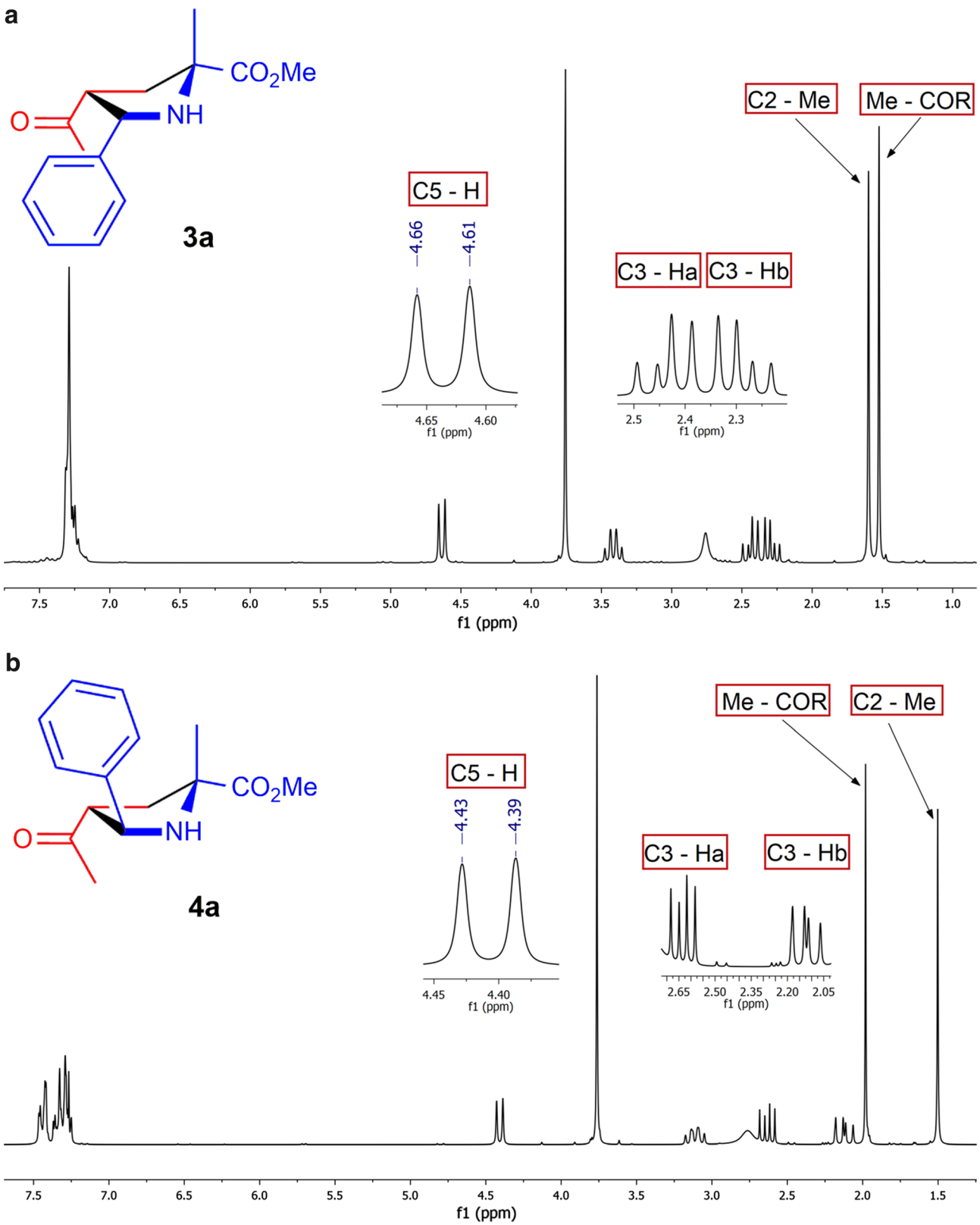
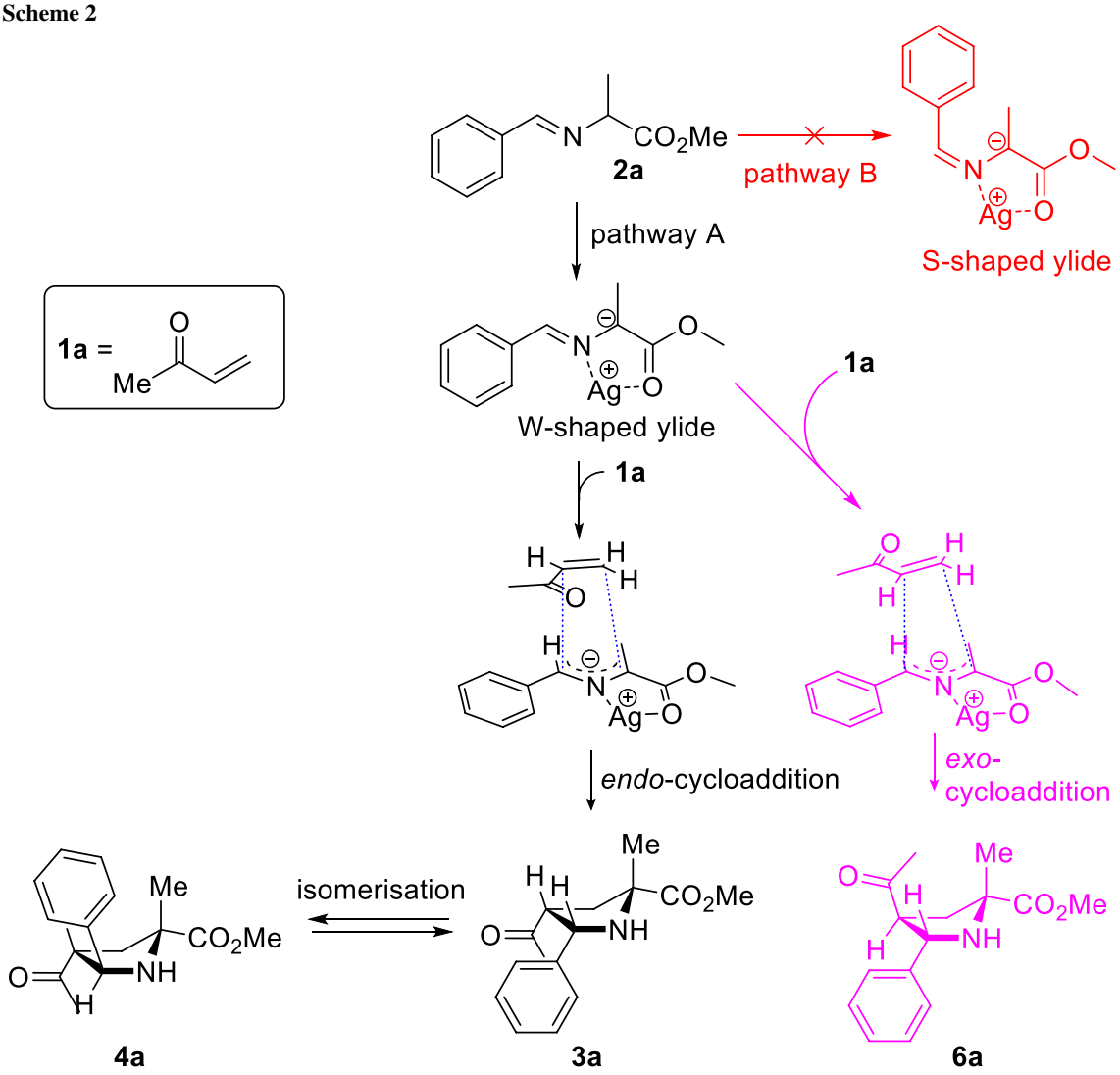


Fig. 1 ^{1}H NMR spectral differences of **3a** and **4a**; **a** ^{1}H NMR spectrum of **3a**; **b** ^{1}H NMR spectrum of **4a**

Scheme 2



about 1.50 ppm. The magnetic anisotropy of aryl group was also spotted in ^{1}H NMR spectra of **4a** where C4-H moiety was detected at 3.11 ppm (instead of 3.42 ppm) and the peak of the alanine originated methyl group was moved from 1.60 to 1.50 ppm. The spatial arrangement of substituents in **3a** and **4a**, after all, were approved by observing their noticeable interactions in NOESY spectra. The anisotropy influence, as expected, was absent in ^{1}H NMR spectra **34g** and **34n**, limiting structural identification of these two pyrrolidine derivatives.

The stereochemical outcome of the cycloadditions suggests that reaction has proceeded following the *endo*-mechanism. We proposed models for the intermediates. This is illustrated in Scheme 2, where the plausible reaction mechanism between **1a** and **2a** is presented. Azomethine ylide is capable to adopt W- or S-shaped conformation [101]. The presence of Ag^+ ion (0.3 equiv), DBU (0.1 equiv), along with acetonitrile as solvent, favors formation of the W-shaped dipole, wherefore there was not possibility for reaction to follow the pathway B. We assume that cycloadduct **3a** was formed primarily and easily underwent isomerization affording product **4a** with *trans*-orientation of substituents at C4 and C5. To confirm the proceeding of the isomerization process, we submitted again **1a** to the reaction with **2a** in a significantly shorter period. To our surprise, overall reaction yield was satisfactory high after only 15 min (82%) with preferably formed *cis*-derivate **3a** (**3a**/**4a** ratio was 66:34) which was isolated after usual work up (Table 2, entry 1). Otherwise, the reaction mixture after 3 h contained almost pure **4a** (yield 65%). Epimerization of similar systems has already been reported [101, 102], but we observed that the spontaneous process occurs in cases when methyl vinyl ketone (**1a**) was reactant. Additionally, the reaction in shorter time (15 min) was performed employing **1a** and **2b**

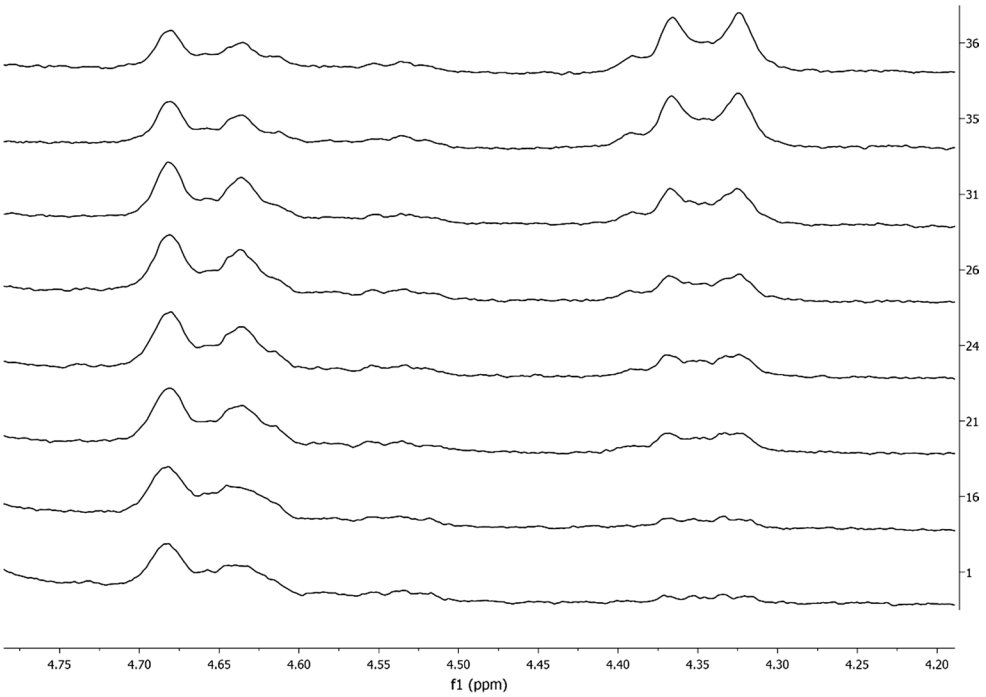


Fig. 2 ^{1}H NMR spectra of the monitored reaction between **1a** and **2a** in CD_3CN

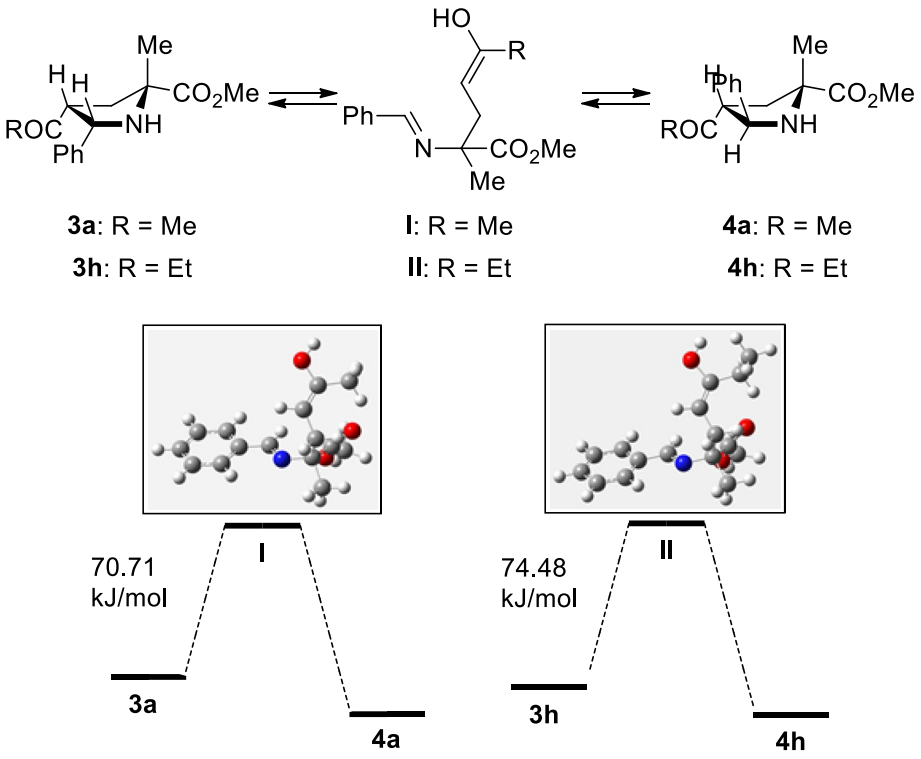


Fig. 3 Differences in free energy values for the diastereoisomers **3a**, **3h**, **4a**, **4h**, and corresponding intermediates **I** and **II**

to give **3aa**, also the product with *cis*-orientation of substituents (Table 2, entry 3).

Also, we monitored the reaction between **1a** and **2a** in CD_3CN recording ^{1}H NMR spectra. The results presented in Fig. 2 confirmed the isomerization process. At the beginning of the monitoring (Fig. 2, spectrum 1) doublet at ca. 4.35 ppm originated by C5-H from **4a** was absent and it has become stronger with time (Fig. 2, spectra 31, 35, and 36). Simultaneously, signal assigned to **3a** (doublet at ca. 4.65 ppm) remains almost unchanged.

In contrast to **1a**, all other enones (**1b**–**1d**) predominantly gave products with *cis*-orientation of substituents

at C4–C5 pyrolidine's fragment. These products did not undergo isomerization, confirming the proposed *endo*-mechanism of the cycloaddition.

The mechanism of isomerization was also studied by A. Sarotti et al. [102] who proved that it takes place through retro-Mannich//Mannich cascade under acidic conditions. Following this pathway, we proposed intermediates which participate in epimerization processes of **3a** and **3h**. To gain insight, the calculations at DFT level of theory were performed in Gaussian 09 software [103], using B3LYP density functional theory method (6-31G basis set) for the diastereoisomers **3a**, **3h**, **4a**, **4h**, and correspondingintermediates **I** and **II** (Fig. 3). Both *trans*-derivatives **4a** and **4h** are characterized by lower free energy values. The free energy difference of **I** and **3a** is 70.71 kJ/mol, while the same one in the case of **II** and **3h** is 74.48 kJ/mol. This might be a significant difference, since it was not observed the epimerization of **3h**.

Conclusion

Vinyl ketones have been employed in the reaction with azomethine ylides providing easy access to the first time synthesized (2*R*)-methyl 4-acyl-5-aryl-2-methylpyrrolidine-2-carboxylates in a moderate chemical yields (up to 88%). Products were easily isolated as pure diastereoisomers. But-3-en-2-one (**1a**), as example of vinyl ketones which contains small group, predominantly afforded pure products **4a**–**4f**, unlike other vinyl substrates those dominantly gave diastereoisomers **3h**–**3m**, **3o**–**3z** with the different orientation of substituents. Using quite simple and fast procedure, 28 pyrrolidine derivatives, which could be of interest for the studies of organocatalysis and bioactivity, were synthesized and isolated.

Experimental

All reagents were purchased from commercial suppliers (Sigma–Aldrich, Merck, Fluka) and used without further purification, except the solvents which were purified by distillation and dried. α-Imino esters **2** were prepared according to literature [101]. Enones **1c** and **1d** were prepared using synthetic strategy consisting of (1) Friedel–Crafts acylation with 3-chloropropanoyl chloride, and (2) dehydrohalogenation of the obtained chloroketones, which were carried out according to the literature procedures [104, 105]. Spectral characteristics of obtained enones agreed with literature data [106–108].

All reactions were monitored by thin-layer chromatography (TLC) on Silica gel 60 F254 precoated Al foils (200 µm layer thickness, Sigma–Aldrich). The spots on TLC were visualized by fluorescence quenching with UV light at 254 nm and I_2, when necessary. Column chromatography was performed using silica gel 0.060–0.200 mm, 60 A (Acros Organics).

Infrared spectra were recorded using a Perkin-Elmer Spectrum One FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian Gemini 2000 as indicated. Chemical shifts (δ, ppm) are relative to tetramethylsilane (TMS) with the resonance of the undeuterated solvent or TMS as internal standard. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, q = quartet, dq = doublet of quartets, m = multiplet), coupling constants (J, Hz), integration, and assignation. Data for ^{13}C NMR spectra are presented in terms of chemical shifts. Microanalyses of carbon, hydrogen, and nitrogen were carried out with a Carlo Erba 1106 microanalyzer; these results agreed favorably with the calculated values.

General procedure for the syntheses of *α*-imino esters

The α-imino esters **2** were prepared by a slight modification of the reported procedure [101]. Anhydrous sodium sulfate (284 mg, 2 mmol, 2 equiv.) and 111 mg Et_3N (1.1 mmol, 1.1 equiv.) were added to the solution of the methyl/ethyl ester hydrochloride of the L-alanine (154/168 mg, 1.1 mmol, 1.1 equiv.) in 5 cm^3 anhydrous dichloromethane. The suspension was stirred at room temperature for 1 h, and the corresponding aldehyde (benzaldehyde, *p*-methoxybenzaldehyde, *o*-methoxybenzaldehyde, *m*-methoxybenzaldehyde, *p*-chlorobenzaldehyde, *p*-tolylaldehyde, *o*-tolylaldehyde, cyclohexanecarbaldehyde, 1-naphtylaldehyde, or 2-naphtylaldehyde, 1 mmol, 1 equiv.) was added. The mixture was stirred overnight and then sodium sulfate was filtered off. The organic solution was washed with aq. $NaHCO_3$, dried (Na_2SO_4 anh.), and concentrated in vacuo to afford the crude α-imino esters **2**; these were used for the cycloaddition reactions without further purification.

General procedure for the syntheses of enones

The enones **1c** and **1d** were synthesized by the following procedure: a mixture of 700 mg 3-chloropropanoyl chloride (5.5 mmol, 1.1 equiv.) and 801 mg $AlCl_3$ (6 mmol, 1.2 equiv.) in 40 cm^3 dichloromethane was cooled to 0 °C. An aromatic compound (toluene or thiophene, 5 mmol, 1 equiv.) was added dropwise and the mixture was left to stir overnight at ambient temperature. The reaction mixture was poured out into an ice water, extracted with dichloromethane, and dried over anhydrous Na_2SO_4. The solvent was then removed by distillation and the crude product was diluted with 20 cm^3 diethyl ether and 2 cm^3 triethylamine. This mixture was stirred at room temperature for 60 h, afterwards

extracted with diethyl ether and dried (Na_2SO_4 anh.). Evaporation of the solvent afforded the crude enones **1c** and **1d**, which was used in further reactions without purification.

General procedure for the [3 + 2] cycloaddition reactions

In a 10 cm^3 flask, the corresponding enone (1.1 mmol, 1.1 equiv.) and the α-imino ester (1 mmol, 1 equiv.) were dissolved in the anhydrous acetonitrile to afford a final α-imino ester's concentration of 0.5 M. In the absence of light, 52 mg silver acetate (0.3 mmol, 0.3 equiv.) and 15 mg DBU (0.1 mmol, 0.1 equiv.) were added. The mixture was stirred at room temperature for 45 min and afterwards the precipitated silver acetate was filtered off and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, *n*–hexane:ethyl acetate = 4:1). The purity of the products was checked by TLC (20%, v:v, ethyl acetate in *n*-hexane), ^{1}H and ^{13}C NMR spectroscopy, and elemental analyses.

Methyl (2*R*,4*R*,5*S*)-4-acetyl-2-methyl-5-phenylpyrrolidine-2-carboxylate (3a, $C_{15}H_{19}NO_3$) Pale yellow liquid; 67 mg, yield 51%; $R_f = 0.4$ (*n*-Hex : EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.38–7.15$ (m, 5H, Ph), 4.64 (d, $J = 8.9$ Hz, 1H, C5-H), 3.76 (s, 3H, RCOOMe), 3.42 (ddd, $J = 8.9$, 7.9, 7.2 Hz, 1H, C4-H), 2.76 (bs, 1H, N–H), 2.44 (dd, $J = 13.4$, 7.9 Hz, 1H, C3-H_a), 2.28 (dd, $J = 13.4$, 7.2 Hz, 1H, C3-H_b), 1.60 (s, 3H, C2-Me), 1.52 (s, 3H, MeCOR) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 208.1$, 177.7, 140.1, 128.4, 127.8, 127.5, 65.5, 64.0, 56.6, 52.5, 37.7, 30.8, 25.5 ppm; IR (neat): $\bar{\nu} = 3322$, 3041, 2980, 1725, 1704, 1459, 1193, 1160, 851, 713 cm^{-1}.

Methyl (2*R*,4*R*,5*R*)-4-acetyl-2-methyl-5-phenylpyrrolidine-2-carboxylate (4a, $C_{15}H_{19}NO_3$) Pale yellow liquid; 85 mg, yield 65%; $R_f = 0.4$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.49–7.24$ (m, 5H, Ph), 4.41 (d, $J = 8.3$ Hz, 1H, C5-H), 3.76 (s, 3H, RCOOMe), 3.11 (ddd, $J = 9.9$, 8.3, 6.9 Hz, 1H, C4-H), 2.76 (bs, 1H, N–H), 2.63 (dd, $J = 13.2$, 6.9 Hz, 1H, C3-H_a), 2.12 (dd, $J = 13.2$, 9.9 Hz, 1H, C3-H_b), 1.98 (s, 3H, MeCOR), 1.50 (s, 3H, C2-Me) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 207.5$, 177.2, 142.4, 128.4, 127.5, 127.0, 65.2, 64.1, 59.5, 52.4, 38.8, 30.1, 26.9 ppm; IR (neat): $\bar{\nu} = 3345$, 3028, 2952, 1731, 1713, 1456, 1361, 1266, 1176, 1106, 702 cm^{-1}.

Ethyl (2*R*,4*R*,5*S*)-4-acetyl-2-methyl-5-phenylpyrrolidine-2-carboxylate (3aa, $C_{16}H_{21}NO_3$) Pale yellow liquid; 76 mg, yield 59%; $R_f = 0.5$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.38–7.16$ (m, 5H, Ph), 4.63 (d, $J = 9.0$ Hz, 1H, C5-H), 4.21 (q, $J = 7.1$ Hz, 2H, RCOOCH_2CH_3), 3.40 (ddd, $J = 9.0$, 8.0, 7.3 Hz, 1H, C4-H), 2.68 (bs, 1H, N–H), 2.44 (dd, $J = 13.3$, 8.0 Hz, 1H, C3-H_a), 2.27 (dd, $J = 13.3$, 7.3 Hz, 1H, C3-H_b), 1.59 (s, 3H, C2-Me), 1.52 (s, 3H, MeCOR), 1.29 (t, $J = 7.1$ Hz, 3H, RCOOCH$_2$$CH_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 208.1$, 177.3, 140.3, 128.5, 128.3, 127.7, 127.5, 127.1, 65.4, 63.9, 61.3, 56.6, 37.5, 30.7, 25.4, 14.4 ppm; IR (neat): $\bar{\nu} = 3351$, 3031, 2978, 1724, 1456, 1371, 1265, 1184, 1106, 1022, 702 cm^{-1}.

Methyl (2*R*,4*R*,5*R*)-4-acetyl-5-(4-chlorophenyl)-2-methylpyrrolidine-2-carboxylate (4b, $C_{15}H_{18}ClNO_3$) Pale yellow liquid; 78 mg, yield 63%; $R_f = 0.5$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.44–7.34$ (m, 2H, *p*-ClPh), 7.32–7.24 (m, 2H, *p*-ClPh), 4.41 (d, $J = 8.1$ Hz, 1H, C5-H), 3.75 (s, 3H, RCOOMe), 3.13–2.91 (m, 1H, C4-H), 2.82 (bs, 1H, N–H), 2.58 (dd, $J = 13.2$, 6.9 Hz, 1H, C3-H_a), 2.12 (dd, $J = 13.2$, 9.9 Hz, 1H, C3-H_b), 2.00 (s, 3H, MeCOR), 1.49 (s, 3H, C2-Me) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 207.4$, 177.3, 141.6, 133.1, 128.6, 128.4, 65.1, 63.1, 59.8, 52.5, 39.0, 30.1, 27.1 ppm; IR (neat): $\bar{\nu} = 3339$, 2954, 1730, 1713, 1490, 1361, 1267, 1176, 1103, 1015, 831 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-4-acetyl-5-(2-methoxyphenyl)-2-methylpyrrolidine-2-carboxylate (3c, $C_{16}H_{21}NO_4$) Pale yellow liquid; 39 mg, yield 55%; $R_f = 0.2$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.41$ (dd, $J = 7.5$, 1.2 Hz, 1H, *o*-MeOPh), 7.27–7.17 (m, 1H, *o*-MeOPh), 6.92 (t, $J = 7.5$ Hz, 1H, *o*-MeOPh), 6.83 (d, $J = 8.2$ Hz, 1H, *o*-MeOPh), 4.81 (d, $J = 8.2$ Hz, 1H, C5-H), 3.84 (s, 3H, *o*-MeOPh), 3.76 (s, 3H, RCOOMe), 3.58 (ddd, $J = 8.3$, 8.2, 5.9 Hz, 1H, C4-H), 2.68 (bs, 1H, N–H), 2.50 (dd, $J = 13.4$, 8.3 Hz, 1H, C3-H_a), 2.19 (dd, $J = 13.4$, 5.9 Hz, 1H, C3-H_b), 1.62 (s, 3H, C2-Me), 1.58 (s, 3H, MeCOR) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 208.9$, 177.8, 156.5, 128.5, 127.8, 127.6, 120.8, 110.0, 65.3, 58.6, 55.3, 54.7, 52.5, 38.3, 30.2, 25.6 ppm; IR (neat): $\bar{\nu} = 3334$, 2953, 2838, 1728, 1601, 1490, 1463, 1244, 1162, 1110, 758 cm^{-1}.

Methyl (2*R*,4*R*,5*R*)-4-acetyl-5-(2-methoxyphenyl)-2-methylpyrrolidine-2-carboxylate (4c, $C_{16}H_{21}NO_4$) Pale yellow liquid; 33 mg, yield 68%; $R_f = 0.1$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.62$ (dd, $J = 7.5$, 1.4 Hz, 1H, *o*-MeOPh), 7.24 (dt, $J = 8.0$, 1.9 Hz, 1H, *o*-MeOPh), 6.96 (td, $J = 7.5$, 0.9 Hz, 1H, *o*-MeOPh), 6.84 (d, $J = 8.0$ Hz, 1H, *o*-MeOPh), 4.73 (d, $J = 7.2$ Hz, 1H, C5-H), 3.77 (s, 6H, *o*-MeOPh, RCOOMe), 3.09 (ddd, $J = 9.6$, 7.2, 5.7 Hz, 1H, C4-H), 2.86 (bs, 1H, N–H), 2.61 (dd, $J = 13.2$, 5.7 Hz, 1H, C3-H_a), 2.08 (s, 3H, MeCOR), 2.03 (dd, $J = 13.2$, 9.6 Hz, 1H, C3-H_b), 1.50 (s, 3H, C2-Me) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 208.3$, 177.5, 156.7, 131.1, 128.3, 127.5, 120.8, 110.3, 65.8, 59.3, 58.1, 55.1, 52.6, 39.2, 29.4, 27.1 ppm; IR (neat): $\bar{\nu} = 3361$, 2952, 1731, 1489, 1464, 1362, 1244, 757 cm^{-1}.

Methyl (2*R*,4*R*)-4-acetyl-5-(4-methoxyphenyl)-2-methylpyrrolidine-2-carboxylate (3d, 4d, $C_{16}H_{21}NO_4$) Pale yellow liquid; 93 mg, yield 64%; $R_f = 0.4$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) *cis*: $\delta = 7.25–7.18$ (m, 2H, *p*-MeOPh), 6.84–6.78 (m, 2H, *p*-MeOPh), 4.59 (d, $J = 9.0$ Hz, 1H, C5-H), 3.79 (s, 3H, *p*-MeOPh), 3.76 (s, 3H, RCOOMe), 3.38 (ddd, $J = 9.0$, 8.0, 7.5 Hz, 1H, C4-H), 2.85 (bs, 1H, N–H), 2.41 (dd, $J = 13.4$, 8.0 Hz, 1H, C3-H_a), 2.27 (dd, $J = 13.4$, 7.5 Hz, 1H, C3-H_b), 1.58 (s, 3H, C2-Me), 1.55 (s, 3H, MeCOR); *trans*: $\delta = 7.40–7.32$ (m, 2H, *p*-MeOPh), 6.91–6.84 (m, 2H, *p*-MeOPh), 4.32 (d, $J = 8.5$ Hz, 1H, C5-H), 3.77 (s, 3H, *p*-MeOPh), 3.75 (s, 3H, RCOOMe), 3.17–3.00 (m, 1H, C4-H), 2.85 (bs, 1H, N–H), 2.63 (dd, $J = 13.3$, 7.1 Hz, 1H, C3-H_a), 2.10 (dd, $J = 13.3$, 9.8 Hz, 1H, C3-H_b), 1.96 (s, 3H, MeCOR), 1.49 (s, 3H, C2-Me) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 208.4$, 207.8, 177.8, 177.4, 159.2, 159.1, 134.3, 132.2, 128.6, 128.3, 113.9, 113.8, 65.4, 65.1, 64.1, 63.4, 59.6, 56.6, 55.4, 55.3, 52.6, 52.5, 38.9, 37.6, 31.0, 30.3, 27.1, 25.5 ppm.

Methyl (2*R*,4*R*,5*R*)-4-acetyl-5-(3-methoxyphenyl)-2-methylpyrrolidine-2-carboxylate (4e, $C_{16}H_{21}NO_4$) Pale yellow liquid; 48 mg, yield 67%; $R_f = 0.3$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.22$ (d, $J = 7.8$, Hz, 1H, *m*-MeOPh), 7.09–6.95 (m, 2H, *m*-MeOPh), 6.84–6.75 (m, 1H, *m*-MeOPh), 4.39 (d, $J = 8.1$ Hz, 1H, C5-H), 3.81 (s, 3H, *m*-MeOPh), 3.76 (s, 3H, RCOOMe), 3.16–3.01 (m, 1H, C4-H), 2.64 (bs, 1H, N–H), 2.62 (dd, $J = 13.2$, 6.7 Hz, 1H, C3-H_a), 2.10 (dd, $J = 13.2$, 9.9 Hz, 1H, C3-H_b), 2.00 (s, 3H, MeCOR), 1.50 (s, 3H, C2-Me) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 207.7$, 177.5, 159.9, 144.7, 129.5, 119.4, 113.1, 112.7, 65.3, 64.1, 59.8, 55.4, 52.6, 39.1, 30.2, 27.1 ppm; IR (neat): $\bar{\nu} = 3336$, 2953, 2838, 1732, 1713, 1601, 1488, 1456, 1436, 1265, 1166, 1107, 1045, 785 cm^{-1}.

Methyl (2*R*,4*R*,5*R*)-4-acetyl-2-methyl-5-(naphthalen-2-yl)pyrrolidine-2-carboxylate (4f, $C_{19}H_{21}NO_3$) Pale yellow liquid; 63 mg, yield 68%; $R_f = 0.4$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.88–7.73$ (m, 4H, Nph), 7.58 (dd, $J = 8.6$, 1.7 Hz, 1H, Nph), 7.50–7.40 (m, 2H, Nph), 4.58 (d, $J = 8.2$ Hz, 1H, C5-H), 3.77 (s, 3H, RCOOMe), 3.18 (ddd, $J = 9.8$, 8.2, 6.9 Hz, 1H, C4-H), 2.94 (bs, 1H, N–H), 2.67 (dd, $J = 13.2$, 6.9 Hz, 1H, C3-H_a), 2.15 (dd, $J = 13.2$, 9.8 Hz, 1H, C3-H_b), 1.96 (s, 3H, MeCOR), 1.53 (s, 3H, C2-Me) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 207.7$, 177.5, 140.2, 133.4, 133.2, 128.4, 127.9, 127.7, 126.1, 126.0, 125.8, 125.0, 65.4, 64.4, 59.6, 52.6, 39.1, 30.3, 27.1 ppm; IR (neat): $\bar{\nu} = 3342$, 3058, 2951, 1729, 1712, 1361, 1268, 1194, 1169, 1105, 860, 820, 751 cm^{-1}.

Methyl 4-acetyl-5-cyclohexyl-2-methylpyrrolidine-2-carboxylate (34g, $C_{15}H_{25}NO_3$) Pale yellow liquid; 70 mg, yield 62%; $R_f = 0.5$ (*n*-Hex:EtOAc = 4:1, v/v, I_2); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.73$ (s, 3H, RCOOMe), 3.11 (ddd, $J = 9.0$, 6.7, 4.1 Hz, 1H, C4-H), 2.92 (dd, $J = 9.1$, 6.7 Hz, 1H, C5-H), 2.55 (dd, $J = 14.0$, 9.0 Hz, 1H, C3-H_a), 2.49 (bs, 1H, N–H), 2.24 (s, 3H, MeCOR), 1.96–1.53 (m, 5H), 1.82 (dd, $J = 14.0$, 4.1 Hz, 1H, C3-H_b), 1.49 (s, 3H, C2-Me), 1.46–0.85 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 211.1$, 177.7, 68.1, 65.3, 53.0, 52.5, 39.5, 39.0, 31.2, 31.08, 31.06, 26.4, 25.9, 25.8, 25.7 ppm; IR (neat): $\bar{\nu} = 3361$, 2926, 2852, 1732, 1700, 1450, 1354, 1192, 1160, 1105 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-2-methyl-5-phenyl-4-propionylpyrrolidine-2-carboxylate (3h, $C_{16}H_{21}NO_3$) Pale yellow liquid; 100 mg, yield 73%; $R_f = 0.5$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.42–7.15$ (m, 5H, Ph), 4.62 (d, $J = 8.8$ Hz, 1H, C5-H), 3.76 (s, 3H, RCOOMe), 3.42 (ddd, $J = 8.8$, 8.0, 7.1 Hz, 1H, C4-H), 2.73 (bs, 1H, N–H), 2.43 (dd, $J = 13.3$, 8.0 Hz, 1H, C3-H_a), 2.29 (dd, $J = 13.3$, 7.1 Hz, 1H, C3-H_b), 1.92 (dq, $J = 18.0$, 7.2 Hz, 1H, CH_3CH_2COR), 1.72 (dq, $J = 18.0$, 7.2 Hz, 1H, CH_3CH_2COR), 1.61 (s, 3H, C2-Me), 0.51 (t, $J = 7.2$ Hz, 3H, CH_3CH_2COR) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 210.6$, 177.6, 139.8, 128.1, 127.5, 127.4, 65.4, 64.1, 55.5, 52.3, 37.7, 37.0, 25.2, 7.0 ppm; IR (neat): $\bar{\nu} = 3333$, 3031, 2973, 1728, 1705, 1449, 1273, 1114, 756 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-2-methyl-4-propionyl-5-(*p*-tolyl)pyrrolidine-2-carboxylate (3i, $C_{17}H_{23}NO_3$) Pale yellow liquid; 117 mg, yield 82%; $R_f = 0.5$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.21–7.02$ (m, 4H, *p*-MePh), 4.58 (d, $J = 8.8$ Hz, 1H, C5-H), 3.75 (s, 3H, RCOOMe), 3.40 (ddd, $J = 8.8$, 7.8, 7.2 Hz, 1H, C4-H), 2.69 (bs, 1H, N–H), 2.42 (dd, $J = 13.3$, 7.8 Hz, 1H, C3-H_a), 2.30 (s, 3H, *p*-MePh), 2.29 (dd, $J = 13.3$, 7.2 Hz, 1H, C3-H_b), 1.93 (dq, $J = 17.9$, 7.2 Hz, 1H, CH_3CH_2COR), 1.73 (dq, $J = 17.9$, 7.2 Hz, 1H, CH_3CH_2COR), 1.60 (s, 3H, C2-Me), 0.54 (t, $J = 7.2$ Hz, 3H, CH_3CH_2COR) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 210.8$, 177.7, 137.1, 136.8, 128.8, 127.2, 65.4, 64.0, 55.6, 52.3, 37.7, 37.1, 25.2, 21.0, 7.1 ppm; IR (neat): $\bar{\nu} = 3335$, 2976, 2951, 1729, 1458, 1267, 1194, 1111, 817 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-5-(4-chlorophenyl)-2-methyl-4-propionylpyrrolidine-2-carboxylate (3j, $C_{16}H_{20}ClNO_3$) Pale yellow liquid; 93 mg, yield 64%; $R_f = 0.4$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.42–7.11$ (m, 4H, *p*-ClPh), 4.59 (d, $J = 9.0$ Hz, 1H, C5-H), 3.75 (s, 3H, RCOOMe), 3.40 (ddd, $J = 9.0$, 8.0, 7.5 Hz, 1H, C4-H), 2.82 (bs, 1H, N–H), 2.41 (dd, $J = 13.4$, 8.0 Hz, 1H, C3-H_a), 2.28 (dd, $J = 13.4$, 7.5 Hz, 1H, C3-H_b), 1.96 (dq, $J = 18.3$, 7.2 Hz, 1H, CH_3CH_2COR), 1.75 (dq, $J = 18.3$, 7.2 Hz, 1H, CH_3CH_2COR), 1.59 (s, 3H, C2-Me), 0.56 (t, $J = 7.2$ Hz, 3H, CH_3CH_2COR) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 210.2$, 177.6, 138.7, 133.2, 128.9, 128.3, 65.4, 63.2, 55.2, 52.4,

37.6, 37.3, 25.2, 7.1 ppm; IR (neat): $\bar{\nu}$ = 3342, 2975, 2952, 1729, 1490, 1273, 1195, 1110, 1015 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-5-(4-methoxyphenyl)-2-methyl-4-propionylpyrrolidine-2-carboxylate (3k, $C_{17}H_{23}NO_4$) Pale yellow liquid; 102 mg, yield 67%; R_f = 0.2 (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.25–7.08 (m, 2H, *p*-MeOPh), 6.90–6.75 (m, 2H, *p*-MeOPh), 4.58 (d, *J* = 8.9 Hz, 1H, C5-H), 3.77 (s, 3H, *p*-MeOPh), 3.76 (s, 3H, RCOOMe), 3.42 (ddd, *J* = 8.9, 7.9, 7.2 Hz, 1H, C4-H), 2.41 (dd, *J* = 13.4, 7.9 Hz, 1H, C3-H_a), 2.29 (dd, *J* = 13.4, 7.2 Hz, 1H, C3-H_b), 1.95 (dq, *J* = 18.2, 7.2 Hz, 1H, CH_3CH_2COR), 1.74 (dq, *J* = 18.2, 7.2 Hz, 1H, CH_3CH_2COR), 1.60 (s, 3H, C2-Me), 0.56 (t, *J* = 7.2 Hz, 3H, CH_3CH_2COR) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 210.8, 177.6, 158.9, 131.8, 128.5, 113.6, 65.4, 63.6, 55.4, 55.2, 52.3, 37.6, 37.2, 25.2, 7.2 ppm; IR (neat): $\bar{\nu}$ = 3342, 2973, 2954, 1728, 1610, 1512, 1248, 1180, 1111 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-2-methyl-5-(naphthalen-1-yl)-4-propionylpyrrolidine-2-carboxylate (3l, $C_{20}H_{23}NO_3$) Pale yellow liquid; 64 mg, yield 88%; R_f = 0.5 (*n*-Hex: EtOAc = 4:1, v/v);^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.9 Hz, 1H, Nph), 7.90–7.35 (m, 6H, Nph), 5.29 (d, *J* = 7.7 Hz, 1H, C5-H), 3.78 (s, 3H, RCOOMe), 3.70 (ddd, *J* = 8.2, 7.7, 4.5 Hz, 1H, C4-H), 2.74 (bs, 1H, N–H), 2.61 (dd, *J* = 13.5, 8.2 Hz, 1H, C3-H_a), 2.32 (dd, *J* = 13.5, 4.5 Hz, 1H, C3-H_b), 1.80 - 1.51 (m, 1H, CH_3CH_2COR), 1.70 (s, 3H, C2-Me), 2.21 (dq, *J* = 18.0, 7.2 Hz, 1H, CH_3CH_2COR), 0.27 (t, *J* = 7.2 Hz, 3H, CH_3CH_2COR) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 211.4, 178.1, 134.6, 133.6, 131.1, 129.1, 128.0, 126.3, 125.6 (2C), 124.4, 122.7, 65.0, 60.6, 54.6, 52.6, 38.4, 36.7, 25.7, 7.0 ppm; IR (neat): $\bar{\nu}$ = 3332, 3052, 2974, 2937, 1728, 1457, 1270, 1195, 1111, 802, 778 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-2-methyl-5-(naphthalen-2-yl)-4-propionylpyrrolidine-2-carboxylate (3m, $C_{20}H_{23}NO_3$) Pale yellow liquid; 51 mg, yield 60%; R_f = 0.4 (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.84–7.72 (m, 4H, Nph), 7.49–7.41 (m, 2H, Nph), 7.38 (dd, *J* = 8.7, 1.2 Hz, 1H, Nph), 4.79 (d, *J* = 8.7 Hz, 1H, C5-H), 3.78 (s, 3H, RCOOMe), 3.50 (ddd, *J* = 8.7, 7.9, 6.9 Hz, 1H, C4-H), 2.82 (bs, 1H, N–H), 2.49 (dd, *J* = 13.4, 7.9 Hz, 1H, C3-H_a), 2.36 (dd, *J* = 13.4, 6.9 Hz, 1H, C3-H_b), 1.92 (dq, *J* = 18.0, 7.2 Hz, 1H, CH_3CH_2COR), 1.68 (dq, *J* = 18.0, 7.2 Hz, 1H, CH_3CH_2COR), 1.66 (s, 3H, C2-Me), 0.41 (t, *J* = 7.2 Hz, 3H, CH_3CH_2COR) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 210.8, 177.8, 137.4, 133.2, 133.0, 128.1, 128.0, 127.7, 126.3, 126.2, 125.9, 125.7, 65.8, 64.6, 55.7, 52.6, 38.1, 37.3, 25.4, 7.3 ppm; IR (neat): $\bar{\nu}$ = 3460, 3059, 2976, 1728, 1458, 1270, 1193, 1112, 859, 821, 751 cm^{-1}.

Methyl 5-cyclohexyl-2-methyl-4-propionylpyrrolidine-2-carboxylate (34n, $C_{16}H_{27}NO_3$) Pale yellow liquid; 115 mg, yield 82%; R_f = 0.4 (*n*-Hex:EtOAc = 4:1, v/v, I_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.72 (s, 3H, RCOOMe), 3.15 (ddd, *J* = 8.7, 6.5, 4.1 Hz, 1H, C4-H), 2.93 (dd, *J* = 9.0, 6.5 Hz, 1H, C5-H), 2.54 (q, *J* = 7.2 Hz, 2H, CH_3CH_2COR), 2.52 (dd, *J* = 13.7, 8.7 Hz, 1H, C3-H_a), 2.46 (bs, 1H, N–H), 1.97 - 1.52 (m, 5H), 1.80 (dd, *J* = 13.7, 4.1 Hz, 1H, C3-H_b), 1.49 (s, 3H, C2-Me), 1.46–0.86 (m, 6H), 1.05 (t, *J* = 7.2 Hz, 3H, CH_3CH_2COR) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 213.8, 177.7, 68.5, 65.5, 52.4, 52.1, 40.2, 39.0, 37.2, 31.4, 31.0, 26.4, 26.0, 25.8, 25.5, 7.9 ppm; IR (neat): $\bar{\nu}$ = 3363, 2926, 2852, 1732, 1700, 1449, 1267, 1196, 1107 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-5-(2-methoxyphenyl)-2-methyl-4-propionylpyrrolidine-2-carboxylate (3o, $C_{17}H_{23}NO_4$) Pale yellow liquid; 76 mg, yield 58%; R_f = 0.2 (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 7.7, 1.5 Hz, 1H, *o*-MeOPh), 7.20 (td, *J* = 7.9, 1.5 Hz, 1H, *o*-MeOPh), 6.89 (t, *J* = 7.9 Hz, 1H, *o*-MeOPh), 6.81 (d, *J* = 8.2 Hz, 1H, *o*-MeOPh), 4.79 (d, *J* = 8.2 Hz, 1H, C5-H), 3.84 (s, 3H, *o*-MeOPh), 3.75 (s, 3H, RCOOMe), 3.57 (ddd, *J* = 8.3, 8.2, 5.6 Hz, 1H, C4-H), 2.61 (bs, 1H, N–H), 2.49 (dd, *J* = 13.4, 8.3 Hz, 1H, C3-H_a), 2.18 (dd, *J* = 13.4, 5.6 Hz, 1H, C3-H_b), 1.97 (dq, *J* = 17.9, 7.3 Hz, 1H, CH_3CH_2COR), 1.79 (dq, *J* = 17.9, 7.3 Hz, 1H, CH_3CH_2COR), 1.63 (s, 3H, C2-Me), 0.50 (t, *J* = 7.2 Hz, 3H, CH_3CH_2COR) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 211.7, 177.9, 156.4, 128.2, 127.7, 127.5, 120.6, 109.8, 65.3, 58.6, 55.2, 53.7, 52.4, 38.4, 36.5, 25.5, 7.2 ppm; IR (neat): $\bar{\nu}$ = 3426, 2972, 2941, 1728, 1490, 1463, 1243, 1113, 757 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-5-(3-methoxyphenyl)-2-methyl-4-propionylpyrrolidine-2-carboxylate (3p, $C_{17}H_{23}NO_4$) Pale yellow liquid; 45 mg, yield 64%; R_f = 0.3 (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.0, Hz, 1H, *m*-MeOPh), 6.90–6.81 (m, 2H, *m*-MeOPh), 6.80–6.72 (m, 1H, *m*-MeOPh), 4.58 (d, *J* = 8.8 Hz, 1H, C5-H), 3.78 (s, 3H, *o*-MeOPh), 3.75 (s, 3H, RCOOMe), 3.39 (ddd, *J* = 8.8, 7.8, 6.9 Hz, 1H, C4-H), 2.63 (bs, 1H, N–H), 2.42 (dd, *J* = 13.4, 7.8 Hz, 1H, C3-H_a), 2.28 (dd, *J* = 13.4, 6.9 Hz, 1H, C3-H_b), 1.94 (dq, *J* = 17.8, 7.1 Hz, 1H, CH_3CH_2COR), 1.75 (dq, *J* = 17.8, 7.2 Hz, 1H, CH_3CH_2COR), 1.61 (s, 3H, C2-Me), 0.57 (t, *J* = 7.2 Hz, 3H, CH_3CH_2COR) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 210.7, 177.8, 159.7, 141.8, 129.3, 119.9, 113.4, 113.1, 65.6, 64.3, 55.7, 55.4, 52.5, 37.8, 37.2, 25.4, 7.4 ppm; IR (neat): $\bar{\nu}$ = 3345, 2972, 2941, 1729, 1601, 1488, 1457, 1271, 1046, 786, 704 cm^{-1}.

Ethyl (2*R*,4*R*,5*S*)-2-methyl-4-propionyl-5-(o-tolyl)pyrrolidine-2-carboxylate (3q, $C_{18}H_{25}NO_3$) Pale yellow liquid; 54 mg, yield 69%; R_f = 0.5 (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.52–7.38 (m, 1H, *o*-MePh),

7.20–7.04 (m, 3H, *o*-MePh), 4.68 (d, $J = 8.2$ Hz, 1H, C5-H), 4.21 (q, $J = 7.1$ Hz, 2H, RCOOCH_2CH_3), 3.43 (ddd, $J = 8.3$, 8.2, 5.3 Hz, 1H, C4-H), 2.56 (bs, 1H, N–H), 2.51 (dd, $J = 13.5$, 8.3 Hz, 1H, C3-H_a), 2.37 (s, 3H, *o*-MePh), 2.26 (dd, $J = 13.5$, 5.3 Hz, 1H, C3-H_b), 1.92 (dq, $J = 17.6$, 7.2 Hz, 1H, CH_3CH_2COR), 1.63 (s, 3H, C2-Me), 1.57 (dq, $J = 17.6$, 7.2 Hz, 1H, CH_3CH_2COR), 1.29 (t, $J = 7.1$ Hz, 3H, RCOOCH_2CH_3), 0.47 (t, $J = 7.2$ Hz, 3H, CH_3CH_2COR) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 211.1$, 177.4, 137.5, 135.2, 130.2, 127.3, 126.6, 126.2, 65.0, 61.3, 60.7, 53.8, 37.9, 36.3, 25.6, 19.7, 14.4, 7.2 ppm; IR (neat): $\bar{\nu} = 3338$, 2977, 2938, 1719, 1461, 1374, 1267, 1187, 1108, 761 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-2-methyl-4-(4-methylbenzoyl)-5-phenylpyrrolidine-2-carboxylate (3r, $C_{21}H_{23}NO_3$) Pale yellow liquid; 103 mg, yield 66%; $R_f = 0.4$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.55$–7.40 (m, 2H, *p*-MePh), 7.15–6.89 (m, 7H, Ph, *p*-MePh), 4.80 (d, $J = 8.8$ Hz, 1H, C5-H), 4.28 (pseudo q, $J = 8.6$ Hz, 1H, C4-H), 3.78 (s, 3H, RCOOMe), 2.87 (bs, 1H, N–H), 2.62–2.40 (m, 2H, C3-H_a, C3-H_b), 2.30 (s, 3H, *p*-MePh), 1.66 (s, 3H, C2-Me) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 199.0$, 177.9, 143.2, 140.3, 135.3, 128.8, 128.2, 127.8, 127.6, 127.1, 65.8, 64.8, 52.5, 50.7, 38.4, 25.3, 21.6 ppm; IR (neat): $\bar{\nu} = 3347$, 3029, 2948, 2924, 1719, 1671, 1607, 1455, 1256, 1194, 1161 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-5-(2-methoxyphenyl)-2-methyl-4-(4-methylbenzoyl)pyrrolidine-2-carboxylate (3s, $C_{22}H_{25}NO_4$) Pale yellow liquid; 59 mg, yield 81%; $R_f = 0.3$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.46$ (d, $J = 8.0$ Hz, 2H, *p*-MePh), 7.32 (dd, $J = 7.7$, 1.8 Hz, 1H, *o*-MeOPh), 7.01 (d, $J = 8.1$ Hz, 2H, *p*-MePh), 7.02–6.91 (m, 1H, *o*-MeOPh), 6.83–6.72 (m, 1H, *o*-MeOPh), 6.37 (d, $J = 8.3$ Hz, 1H, *o*-MeOPh), 4.94 (d, $J = 8.4$ Hz, 1H, C5-H), 4.45 (ddd, $J = 8.4$, 8.1, 6.7 Hz, 1H, C4-H), 3.79 (s, 3H, RCOOMe), 3.46 (s, 3H, *o*-MeOPh), 2.62 (dd, $J = 13.2$, 8.1 Hz, 1H, C3-H_a), 2.57 (bs, 1H, N–H), 2.37 (dd, $J = 13.2$, 6.7 Hz, 1H, C3-H_b), 2.30 (s, 3H, *p*-MePh), 1.69 (s, 3H, C2-Me) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 200.7$, 178.0, 155.9, 142.7, 129.1, 128.6, 128.4, 128.1, 127.9, 127.7, 120.2, 109.1, 65.9, 59.3, 54.4, 52.5, 48.9, 39.5, 25.5, 21.7 ppm; IR (neat): $\bar{\nu} = 3435$, 2952, 2840, 1730, 1678, 1606, 1490, 1464, 1245, 1181, 1107, 1028, 756 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-5-(3-methoxyphenyl)-2-methyl-4-(4-methylbenzoyl)pyrrolidine-2-carboxylate (3t, $C_{22}H_{25}NO_4$) Pale yellow liquid; 72 mg, yield 78%; $R_f = 0.2$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.49$ (d, $J = 8.1$ Hz, 2H, *p*-MePh), 7.06 (d, $J = 8.1$ Hz, 2H, *p*-MePh), 6.98–6.86 (m, 1H, *m*-MeOPh), 6.65 (d, $J = 7.7$ Hz, 1H, *m*-MeOPh), 6.58 - 6.48 (m, 2H, *o*-MeOPh), 4.78 (d, $J = 9.3$ Hz, 1H, C5-H), 4.27 (pseudo q, $J = 8.5$, 1H, C4-H), 3.79 (s, 3H, RCOOMe), 3.56 (s, 3H, *m*-MeOPh), 2.63 (bs, 1H, N–H), 2.51 (m, 2H, C3-H_a, C3-H_b), 2.32 (s, 3H, *p*-MePh), 1.66 (s, 3H, C2-Me) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 199.0$, 177.9, 159.0, 143.2, 142.0, 135.4, 128.8, 128.7, 128.3, 120.1, 113.3, 113.1, 65.8, 64.8, 55.0, 52.5, 50.7, 38.3, 25.3, 21.6 ppm; IR (neat): $\bar{\nu} = 3352$, 2952, 2836, 1728, 1678, 1607, 1456, 1258, 1181, 1110, 1043, 788, 702 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-5-(4-methoxyphenyl)-2-methyl-4-(4-methylbenzoyl)pyrrolidine-2-carboxylate (3u, $C_{22}H_{25}NO_4$) Pale yellow liquid; 86 mg, yield 57%; $R_f = 0.1$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.58$–7.42 (m, 2H, *p*-MePh), 7.14–7.02 (m, 2H, *p*-MePh), 6.98–6.87(m, 2H, *p*-MeOPh), 6.62–6.48 (m, 2H, *p*-MeOPh), 4.77 (d, $J = 9.3$ Hz, 1H, C5-H), 4.25 (ddd, $J = 9.3$, 8.7, 7.8 Hz, 1H, C4-H), 3.79 (s, 3H, RCOOMe), 3.64 (s, 3H, *p*-MeOPh), 2.83 (bs, 1H, N–H), 2.55 (dd, $J = 13.2$, 8.7 Hz, 1H, C3-H_a), 2.48 (dd, $J = 13.2$, 7.8 Hz, 1H, C3-H_b), 2.32 (s, 3H, *p*-MePh), 1.65 (s, 3H, C2-Me) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 199.2$, 177.9, 158.6, 143.1, 135.3, 132.6, 128.8, 128.8, 128.3, 113.1, 65.7, 64.2, 55.2, 52.5, 50.8, 38.3, 25.3, 21.7 ppm; IR (neat): $\bar{\nu} = 3435$, 2952, 1728, 1677, 1608, 1512, 1250, 1181, 1110, 1034, 823 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-5-(4-chlorophenyl)-2-methyl-4-(4-methylbenzoyl)pyrrolidine-2-carboxylate (3v, $C_{21}H_{22}ClNO_3$) Pale yellow liquid; 109 mg, yield 63%; $R_f = 0.4$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.54$–7.40 (m, 2H, *p*-MePh), 7.18–7.04 (m, 2H, *p*-MePh), 6.96 (s, 4H, *p*-ClPh), 4.78 (d, $J = 9.4$ Hz, 1H, C5-H), 4.26 (ddd, $J = 9.4$, 8.8, 8.3 Hz, 1H, C4-H), 3.79 (s, 3H, RCOOMe), 2.88 (bs, 1H, N–H), 2.55 (dd, $J = 13.1$, 8.8 Hz, 1H, C3-H_a), 2.45 (dd, $J = 13.1$, 8.3 Hz, 1H, C3-H_b), 2.33 (s, 3H, *p*-MePh), 1.64 (s, 3H, C2-Me) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 198.5$, 177.7, 143.4, 139.0, 135.0, 132.6, 129.0, 128.8, 128.1, 127.6, 65.6, 63.7, 52.4, 50.3, 38.0, 25.2, 21.5 ppm; IR (neat): $\bar{\nu} = 3435$, 2952, 1729, 1678, 1607, 1281, 1182, 1110, 1015, 821 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-2-methyl-5-phenyl-4-(thiophene-2-carbonyl)pyrrolidine-2-carboxylate (3w, $C_{18}H_{19}NO_3S$) Yellow liquid; 103 mg, yield 63%; $R_f = 0.3$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.46$–7.34 (m, 2H, Th), 7.18–6.84 (m, 8H, Ph, Th), 4.76 (d, $J = 8.8$ Hz, 1H, C5-H), 4.12 (ddd, $J = 8.8$, 7.8, 7.6 Hz, 1H, C4-H), 3.77 (s, 3H, RCOOMe), 2.83 (bs, 1H, N–H), 2.57 (dd, $J = 13.2$, 7.8 Hz, 1H, C3-H_a), 2.49 (dd, $J = 13.2$, 7.6 Hz, 1H, C3-H_b), 1.67 (s, 3H, C2-Me) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 192.1$, 177.6, 145.0, 139.4, 133.4, 131.7, 127.6, 127.5, 127.5, 127.2, 65.7, 65.4, 52.4, 52.3, 38.2, 25.2 ppm; IR (neat): $\bar{\nu} = 3420$, 3348, 3090, 2949, 2926, 1716, 1648, 1416, 1112, 731 cm^{-1}.

Methyl (2*R*,4*R*,5*S*)-5-(4-methoxyphenyl)-2-methyl-4-(thiophene-2-carbonyl)pyrrolidine-2-carboxylate (3x, $C_{19}H_{21}NO_4S$) Yellow liquid; 88 mg, yield 54%; $R_f = 0.1$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.45$ (d, $J = 4.9$ Hz, 1H, Th), 7.41 (d, $J = 3.6$ Hz, 1H, Th), 7.14–7.00 (m, 2H, *p*-MeOPh), 6.94 (dd, $J = 4.9$, 3.6 Hz, 1H, Th), 6.73–6.47 (m, 2H, *p*-MeOPh), 4.76 (d, $J = 8.8$ Hz, 1H, C5-H), 4.09 (pseudo q, $J = 8.8$ Hz, 1H, C4-H), 3.79 (s, 3H, RCOOMe), 3.66 (s, 3H, *p*-MeOPh), 2.99 (bs, 1H, N–H), 2.66–2.38 (m, 2H, C3-H_a, C3-H_b), 1.67 (s, 3H, C2-Me) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 192.3$, 177.5, 158.9, 145.2, 133.5, 131.9, 131.4, 128.9, 127.7, 113.3, 65.9, 65.1, 55.3, 52.7, 52.5, 38.4, 25.2 ppm; IR (neat): $\bar{\nu} = 3432$, 3095, 2954, 2936, 1727, 1655, 1512, 1416, 1245, 839, 728 cm^{-1}.

Ethyl (2*R*,4*R*,5*S*)-5-(2-methoxyphenyl)-2-methyl-4-(thiophene-2-carbonyl)pyrrolidine-2-carboxylate (3y, $C_{20}H_{23}NO_4S$) Yellow liquid; 44 mg, yield 65%; $R_f = 0.3$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.48$ (dd, $J = 3.9$, 1.0 Hz, 1H, Th), 7.43–7.34 (m, 2H, Th, *o*-MeOPh), 6.98 (dd, $J = 8.0$, 1.8 Hz, 1H, *o*-MeOPh), 6.91 (ddd, $J = 4.9$, 3.9, 0.6 Hz, 1H, Th), 6.85–6.73 (m, 1H, *o*-MeOPh), 6.48 (dd, $J = 8.2$, 1.1 Hz, 1H, *o*-MeOPh), 4.95 (d, $J = 8.1$ Hz, 1H, C5-H), 4.35–4.20 (m, 1H, C4-H), 4.24 (q, $J = 7.1$ Hz, 2H, RCOOCH_2CH_3), 3.60 (s, 3H, *o*-MeOPh), 2.64 (dd, $J = 13.3$, 8.2 Hz, 1H, C3-H_a), 2.62 (bs, 1H, N–H), 2.34 (dd, $J = 13.3$, 5.9 Hz, 1H, C3-H_b), 1.68 (s, 3H, C2-Me), 1.31 (t, $J = 7.1$ Hz, 3H, RCOOCH$_2$CH$_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 193.5$, 177.4, 155.9, 145.2, 133.3, 131.4, 128.0, 127.6, 127.4, 127.2, 120.3, 109.1, 65.7, 61.3, 59.5, 54.6, 50.6, 39.2, 25.3, 14.4 ppm; IR (neat): $\bar{\nu} = 3336$, 3077, 2978, 2937, 1723, 1660, 1490, 1464, 1417, 1244, 1184, 1106, 1026, 755, 727 cm^{-1}.

Ethyl (2*R*,4*R*,5*S*)-5-(3-methoxyphenyl)-2-methyl-4-(thiophene-2-carbonyl)pyrrolidine-2-carboxylate (3z, $C_{20}H_{23}NO_4S$) Yellow liquid; 62 mg, yield 67%; $R_f = 0.3$ (*n*-Hex:EtOAc = 4:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.45$ (dd, $J = 4.9$, 1.1 Hz, 1H, Th), 7.41 (dd, $J = 3.8$, 1.1 Hz, 1H, Th), 7.02–6.85 (m, 2H, Th, *m*-MeOPh), 6.79–6.65 (m, 2H, *m*-MeOPh), 6.57 (ddd, $J = 8.2$, 2.6, 1.0 Hz, 1H, *m*-MeOPh), 4.75 (d, $J = 8.8$ Hz, 1H, C5-H), 4.24 (q, $J = 7.1$ Hz, 2H, RCOOCH_2CH_3), 4.09 (ddd, $J = 8.9$, 7.8, 7.7 Hz, 1H, C4-H), 3.63 (s, 3H, *m*-MeOPh), 2.73 (bs, 1H, N-H), 2.51 (dd, $J = 13.3$, 7.7 Hz, 1H, C3-H_a), 2.47 (dd, $J = 13.3$, 7.8 Hz, 1H, C3-H_b), 1.66 (s, 3H, C2-Me), 1.32 (t, $J = 7.1$ Hz, 3H, RCOOCH$_2$CH$_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 192.1$, 177.3, 159.1, 145.3, 141.4, 133.4, 131.7, 128.7, 127.6, 120.1, 113.4, 113.0, 65.7, 65.4, 61.3, 55.2, 52.4, 38.1, 25.3, 14.4 ppm; IR (neat): $\bar{\nu} = 3345$, 3077, 2978, 2937, 1723, 1659, 1602, 1466, 1417, 1263, 1182, 1155, 1108, 1043, 855, 791, 728 cm^{-1}.

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