Multicomponent diastereoselective synthesis of indolizidines via 1,3-dipolar cycloadditions of azomethine ylides

Journal:	*SYNTHESIS*
Manuscript ID	SS-2016-07-0541-OP.R1
Manuscript Type:	Original Paper
Date Submitted by the Author:	n/a
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Keywords:	cycloaddition, fused-ring systems, heterocycles, multicomponent reaction, diastereoselectivity
Abstract:	The synthesis of polyfunctionalized indolizidines from pipecolinic acid alkyl ester derivatives, aldehydes and a wide range of dipolarophiles by a multicomponent 1,3-dipolar cycloadditions has been developed in a diastereselective manner. Reactions take place in toluene with short reaction times at 70 ºC, giving good yields. The synthesis of these fused heterocycles is also studied starting from the pipecolinic acid, generating the dipole through a decarboxylative route at 120 ºC. The relative configuration of the resulting products, as well as the mechanistic pathways are also explained.

SUPPORTING INFORMATION

Multicomponent diastereoselective synthesis of indolizidines via 1,3-dipolar cycloadditions of azomethine ylides

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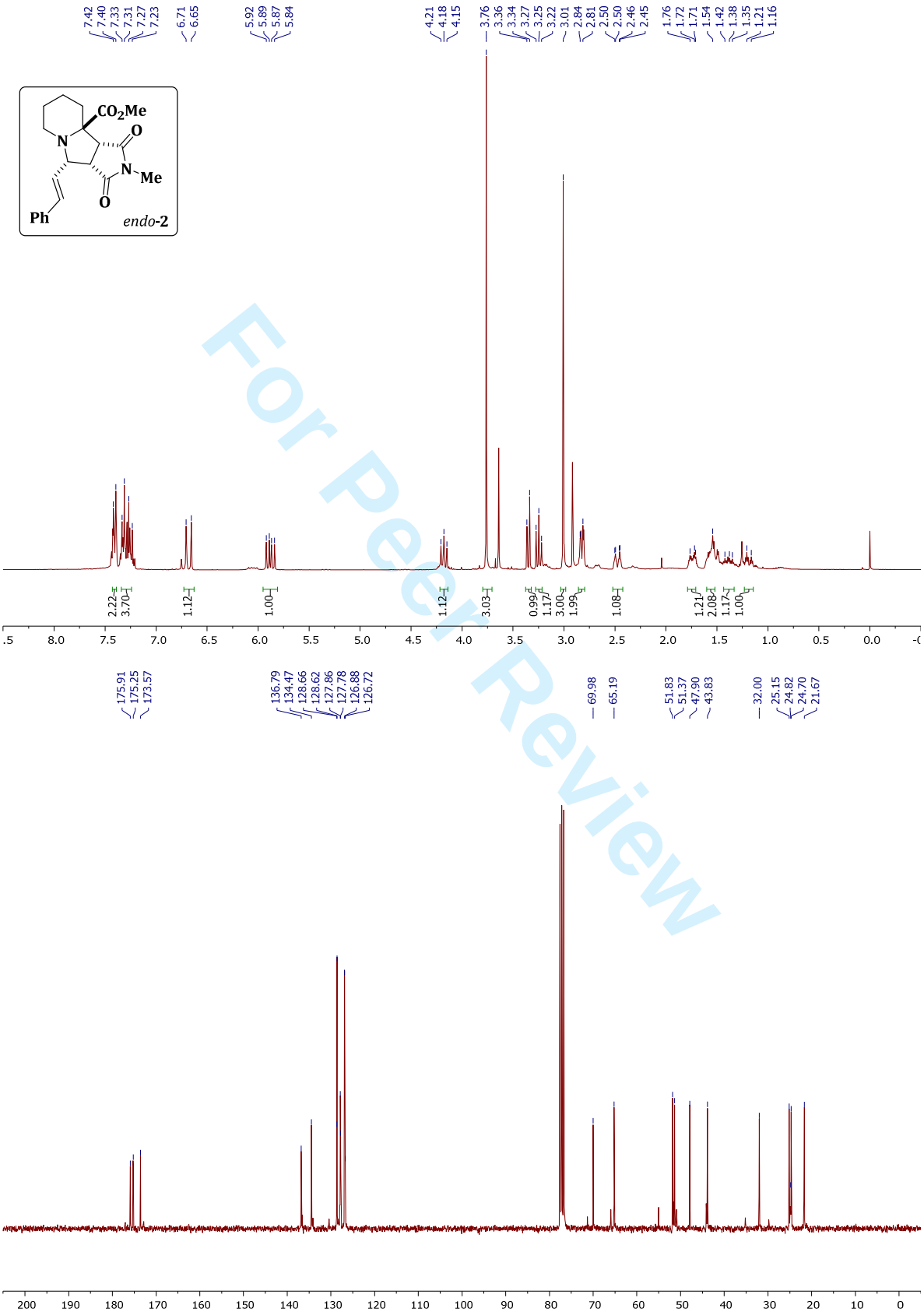
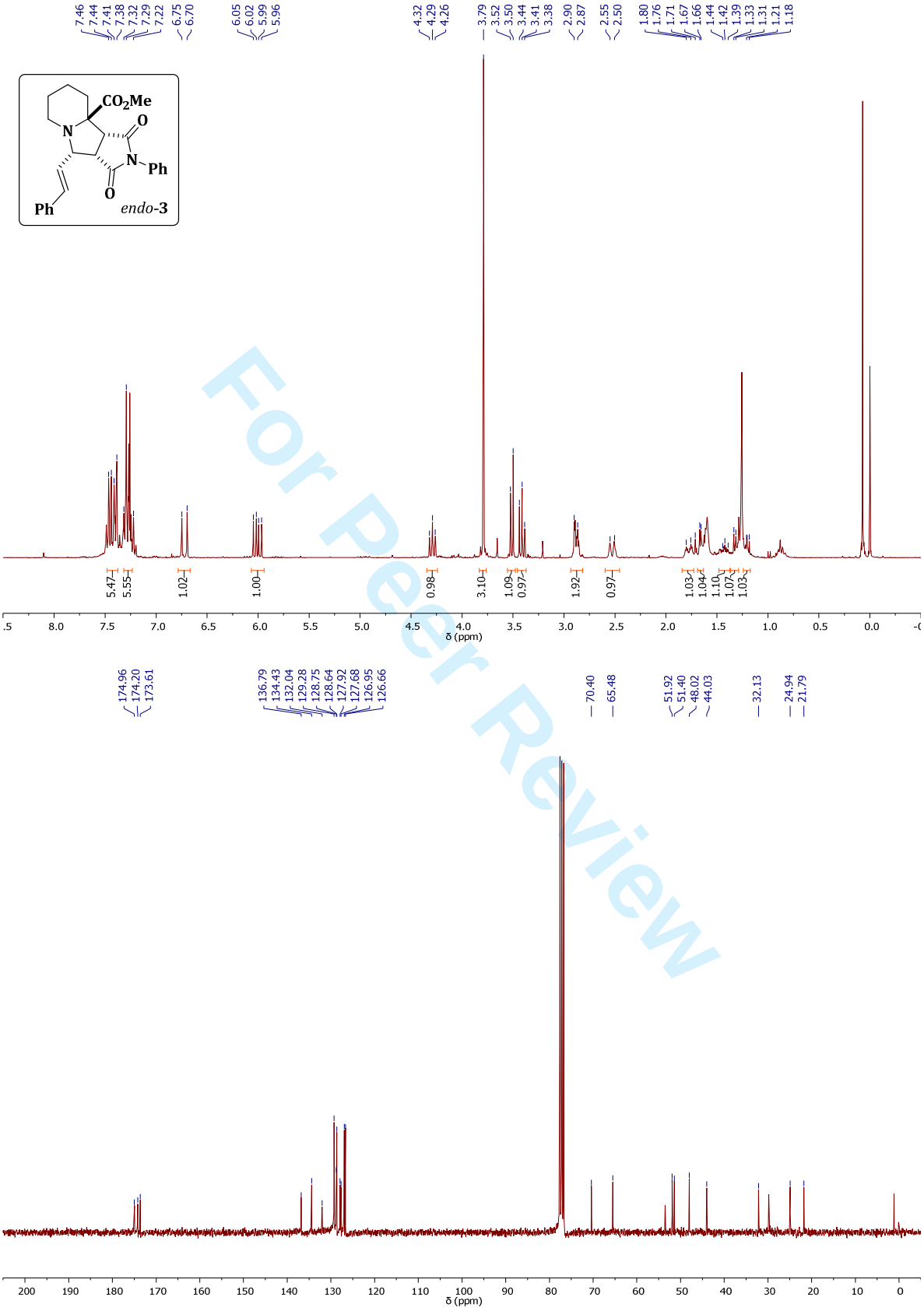
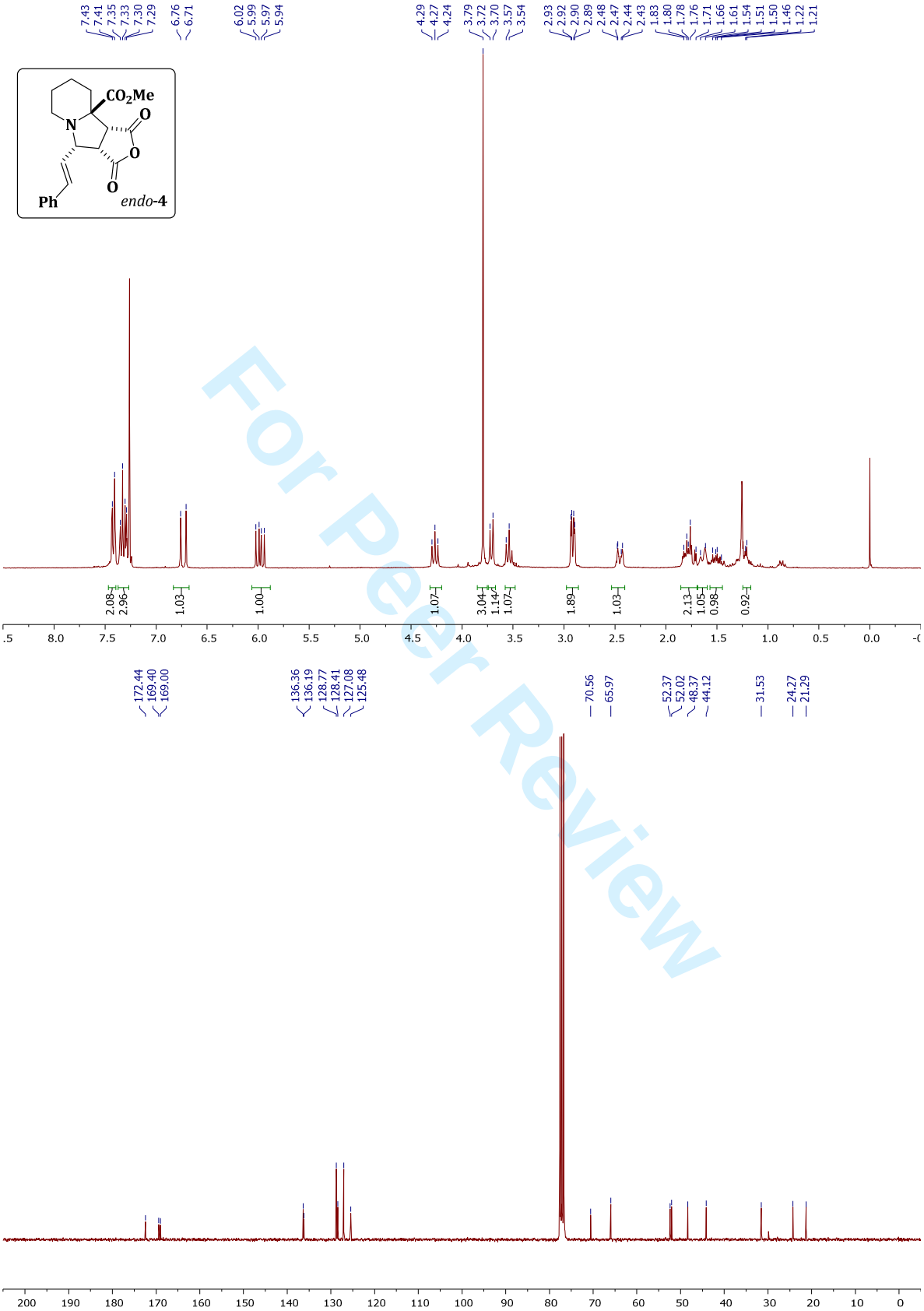
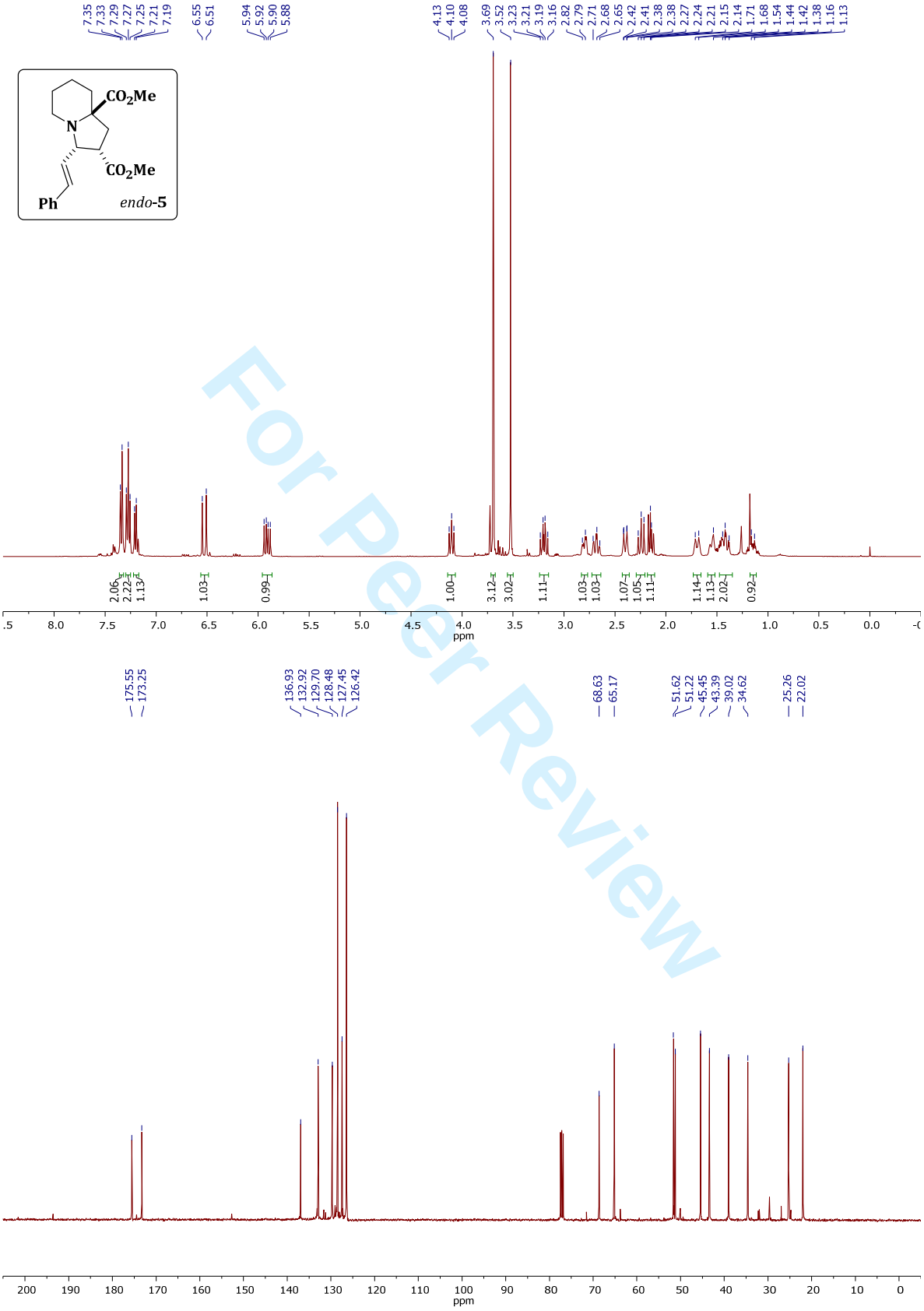
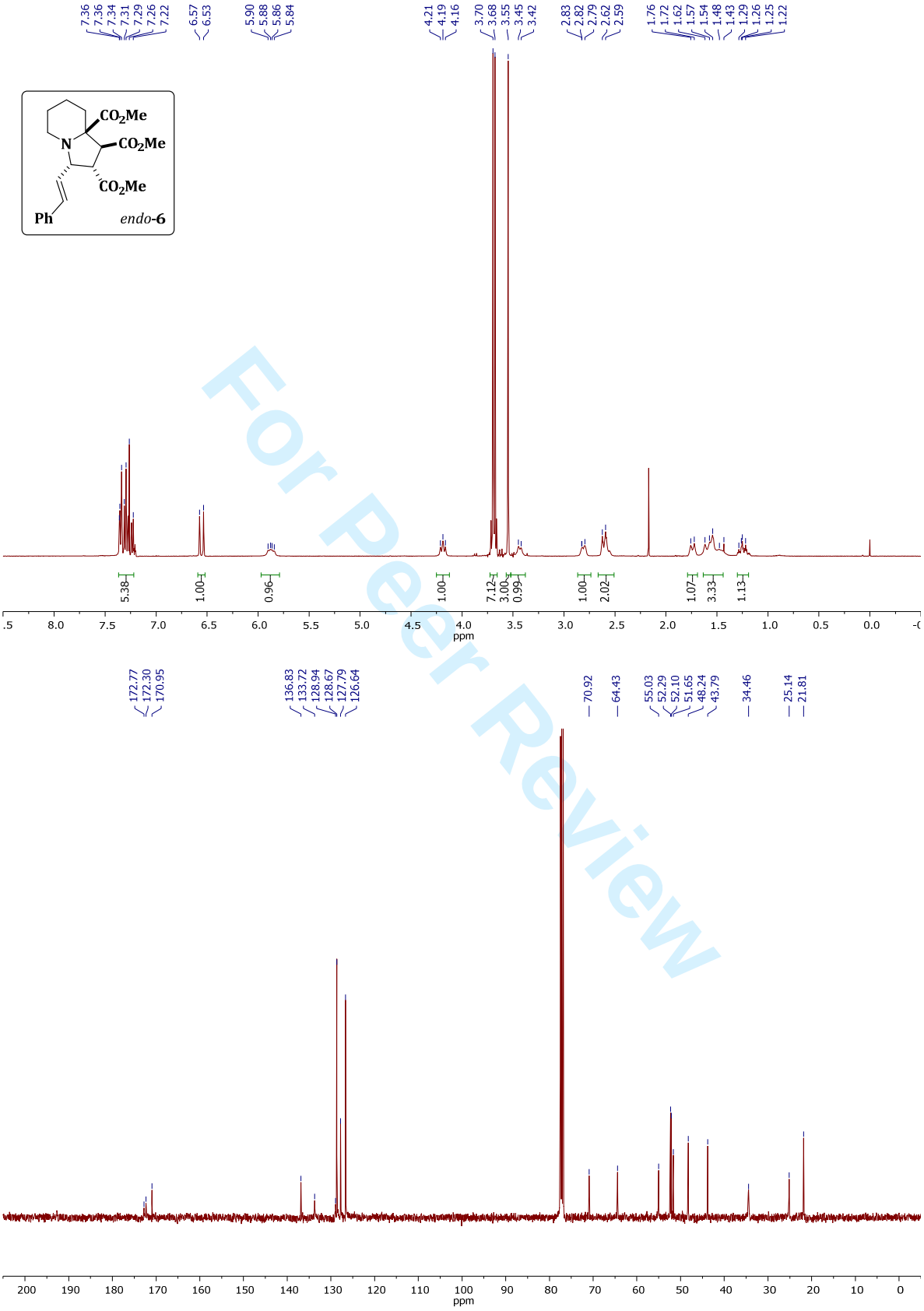
1. ^{1}H and ^{13}C NMR spectra

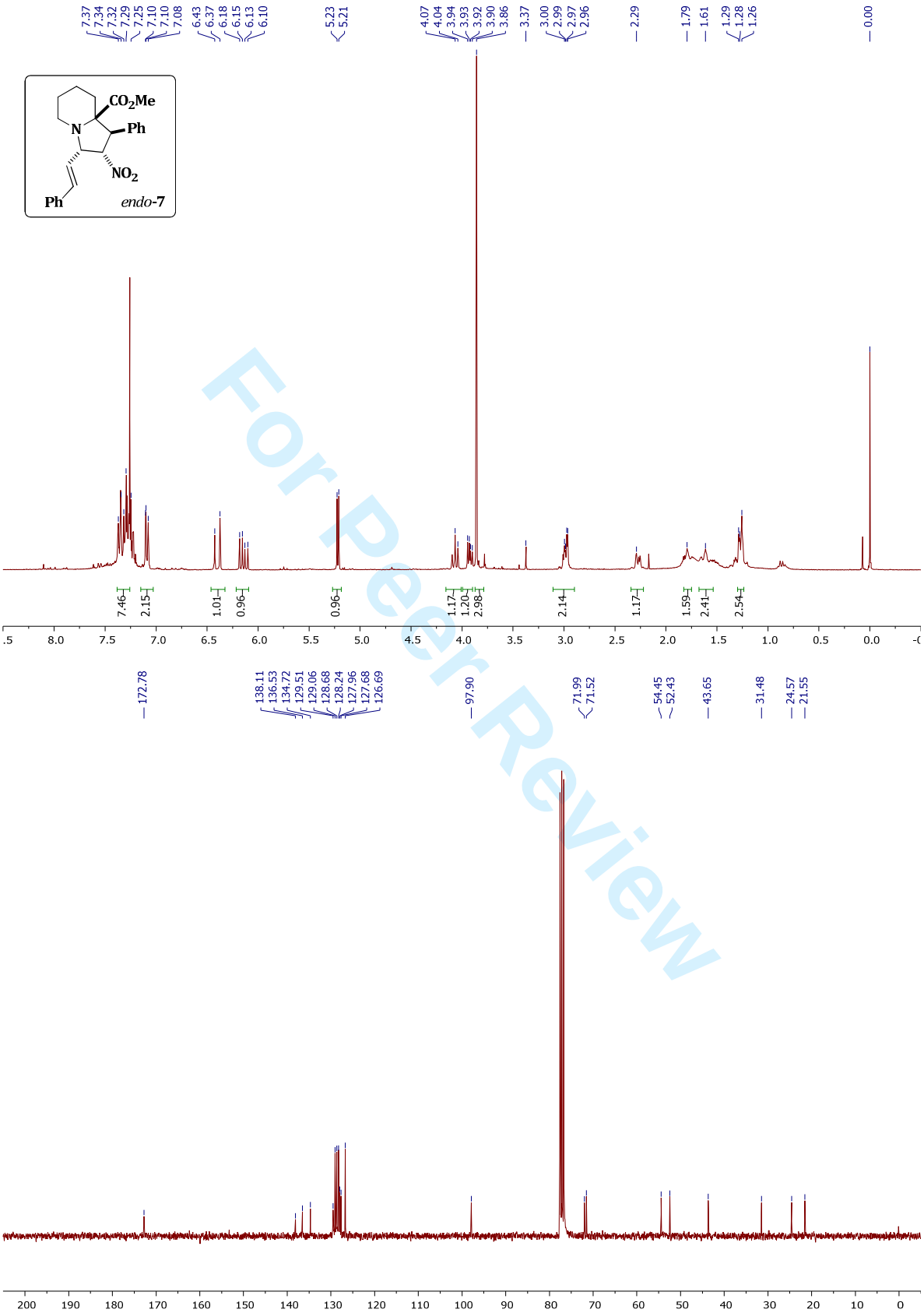












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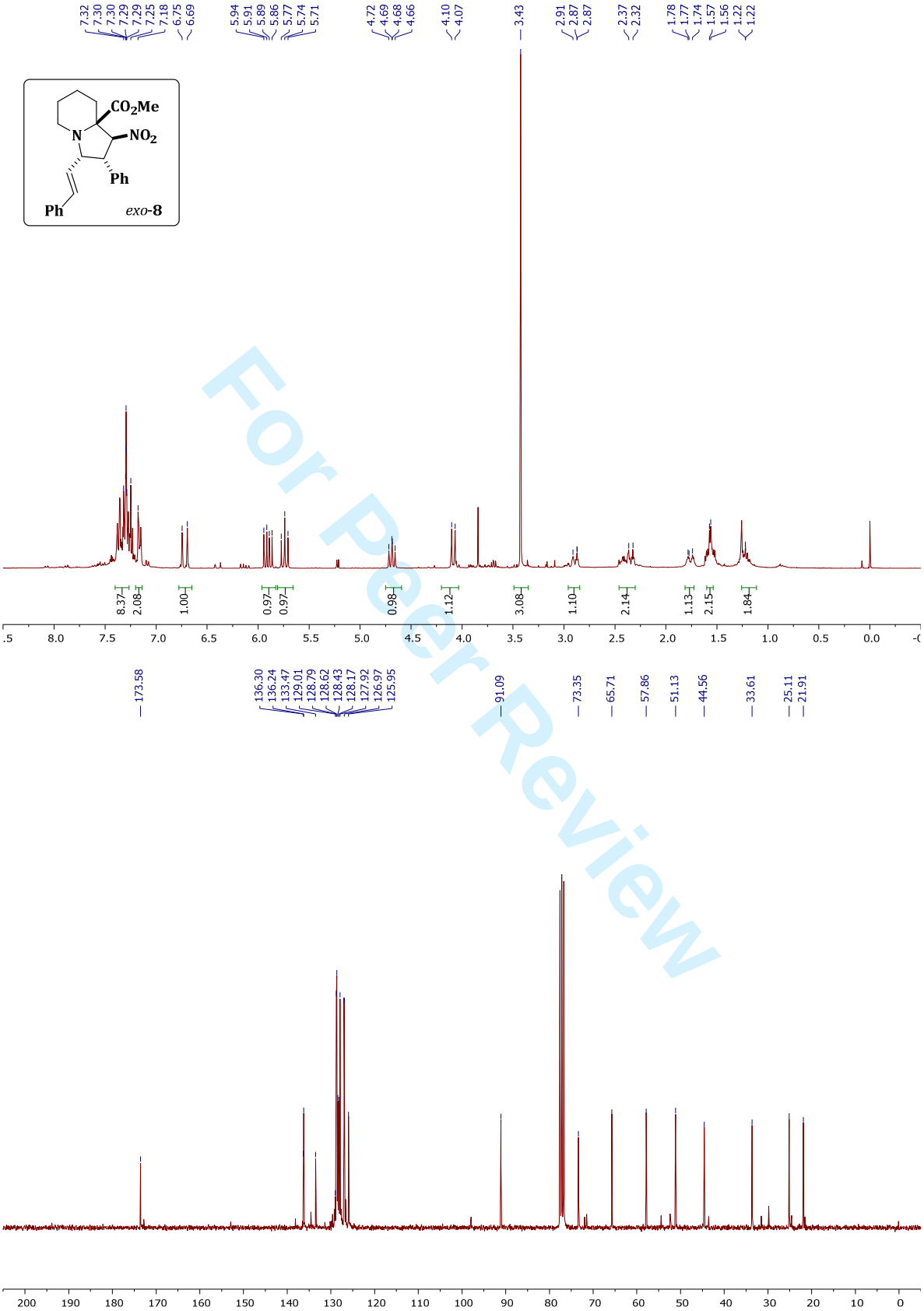

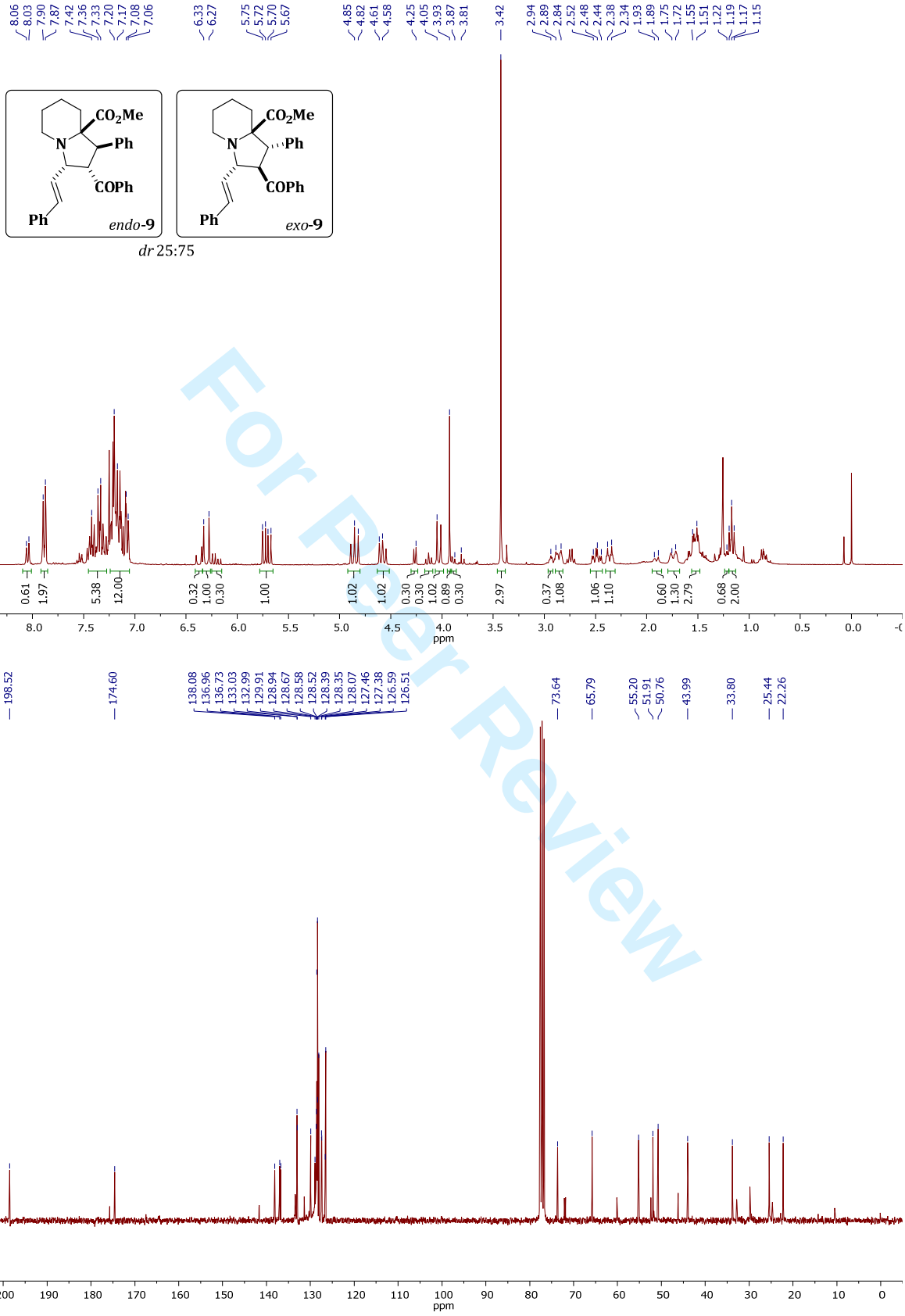

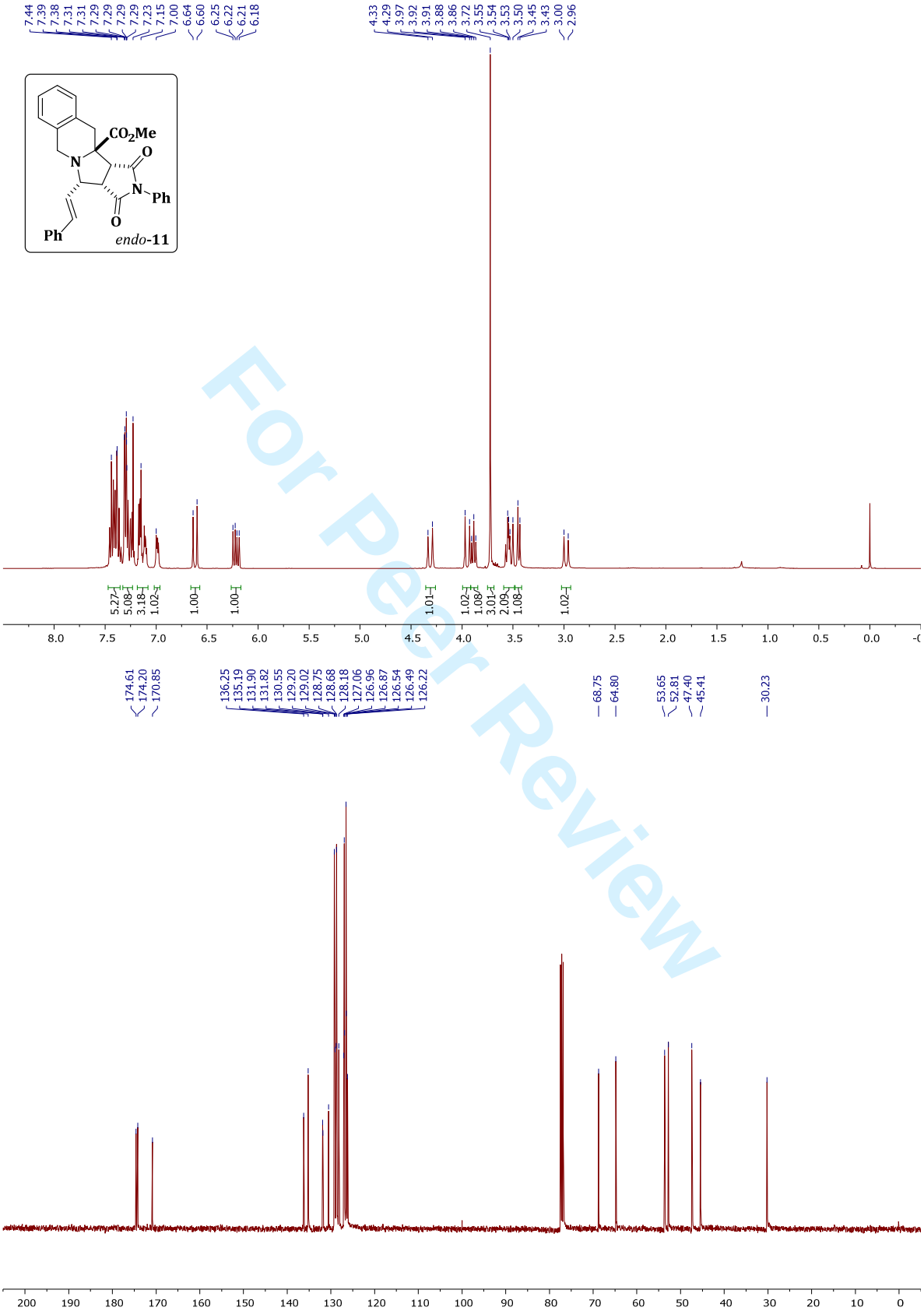

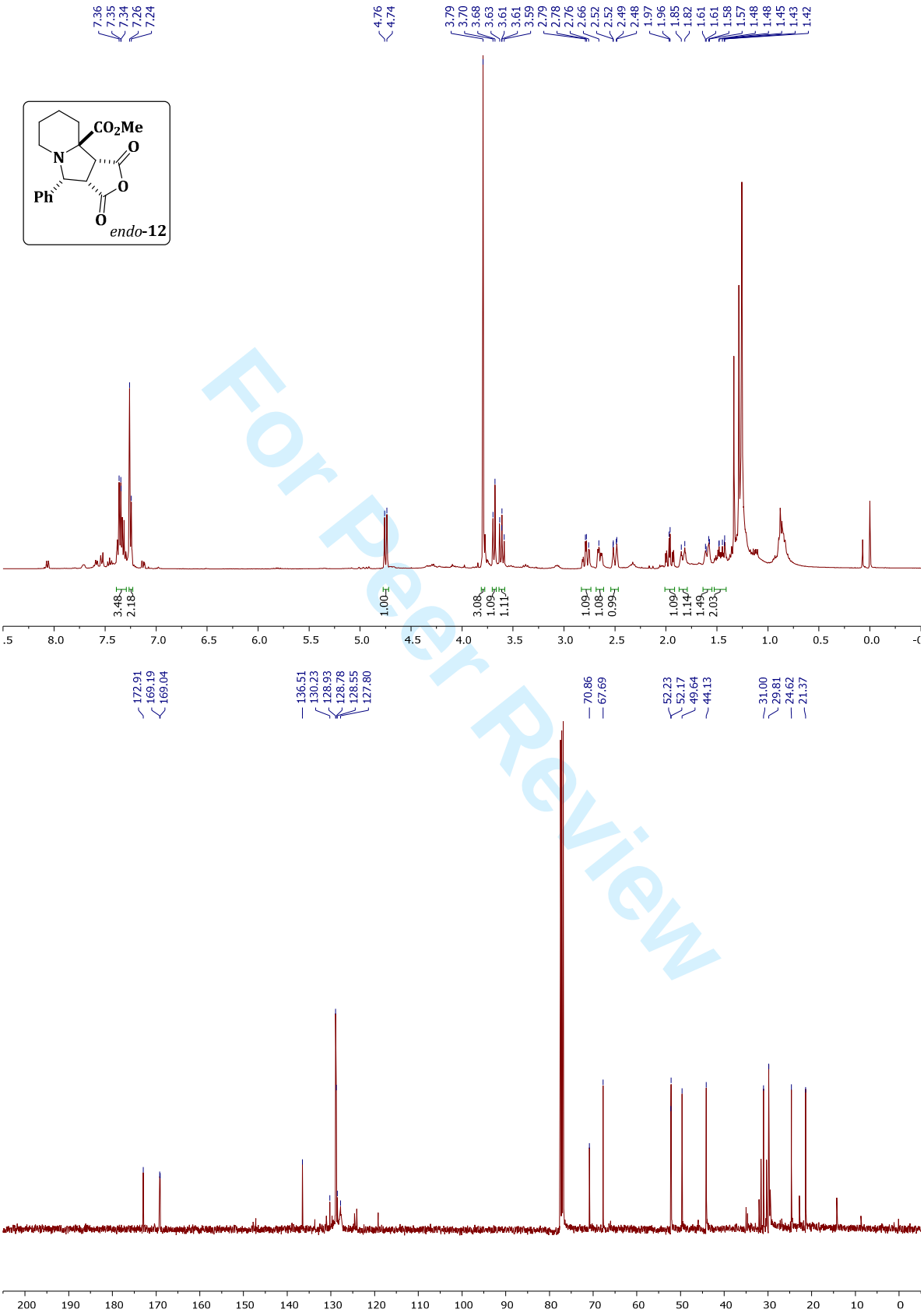

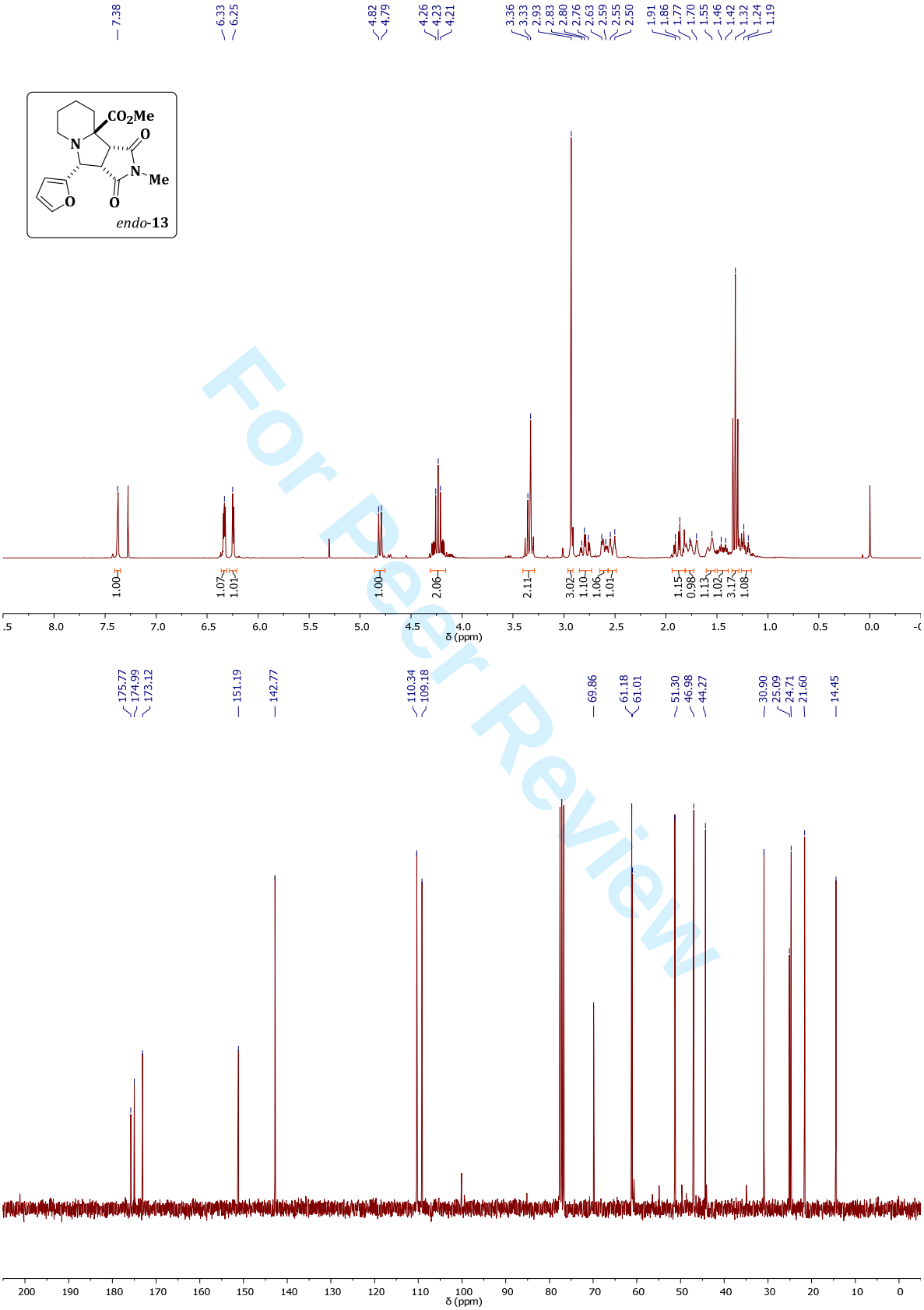

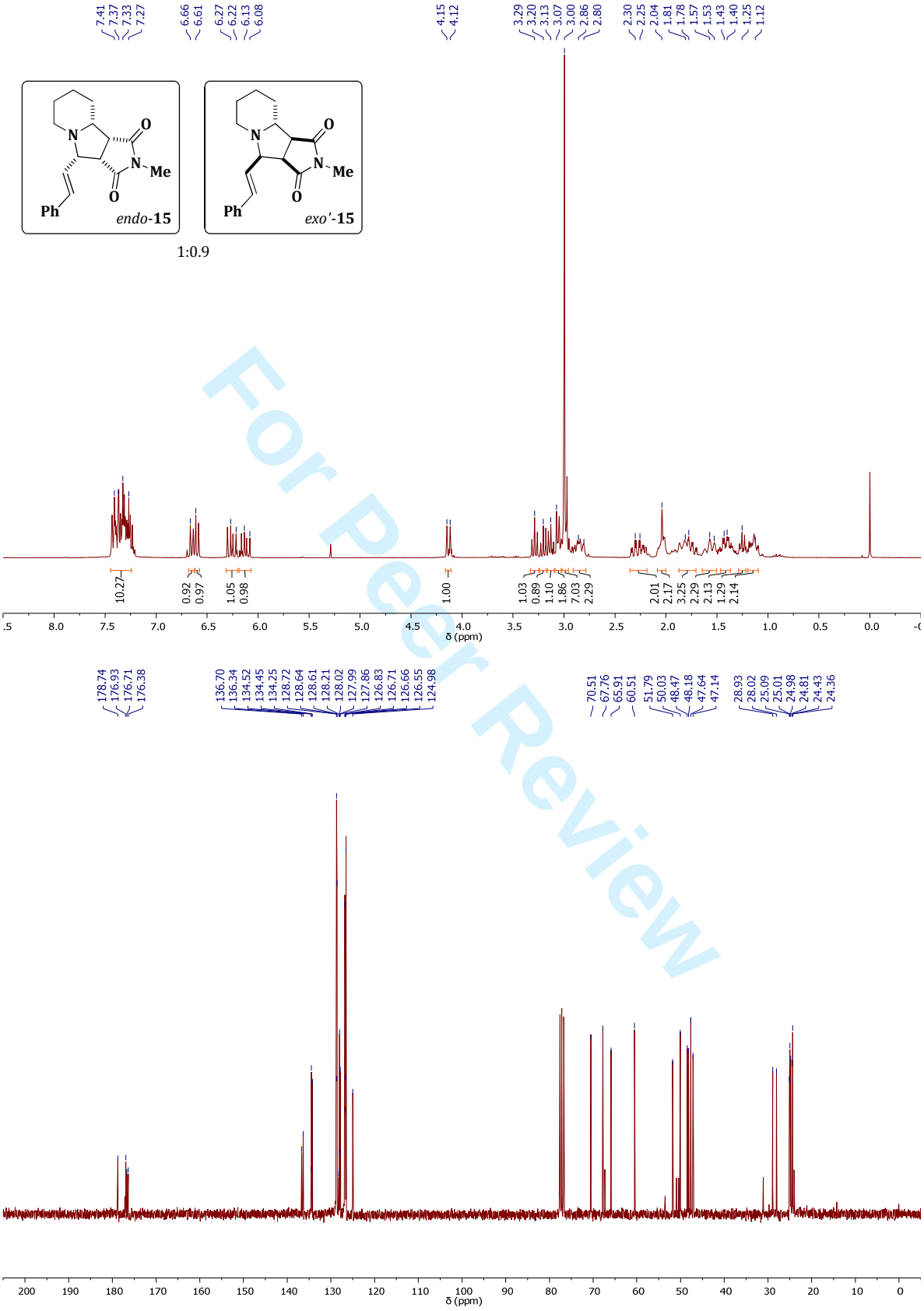

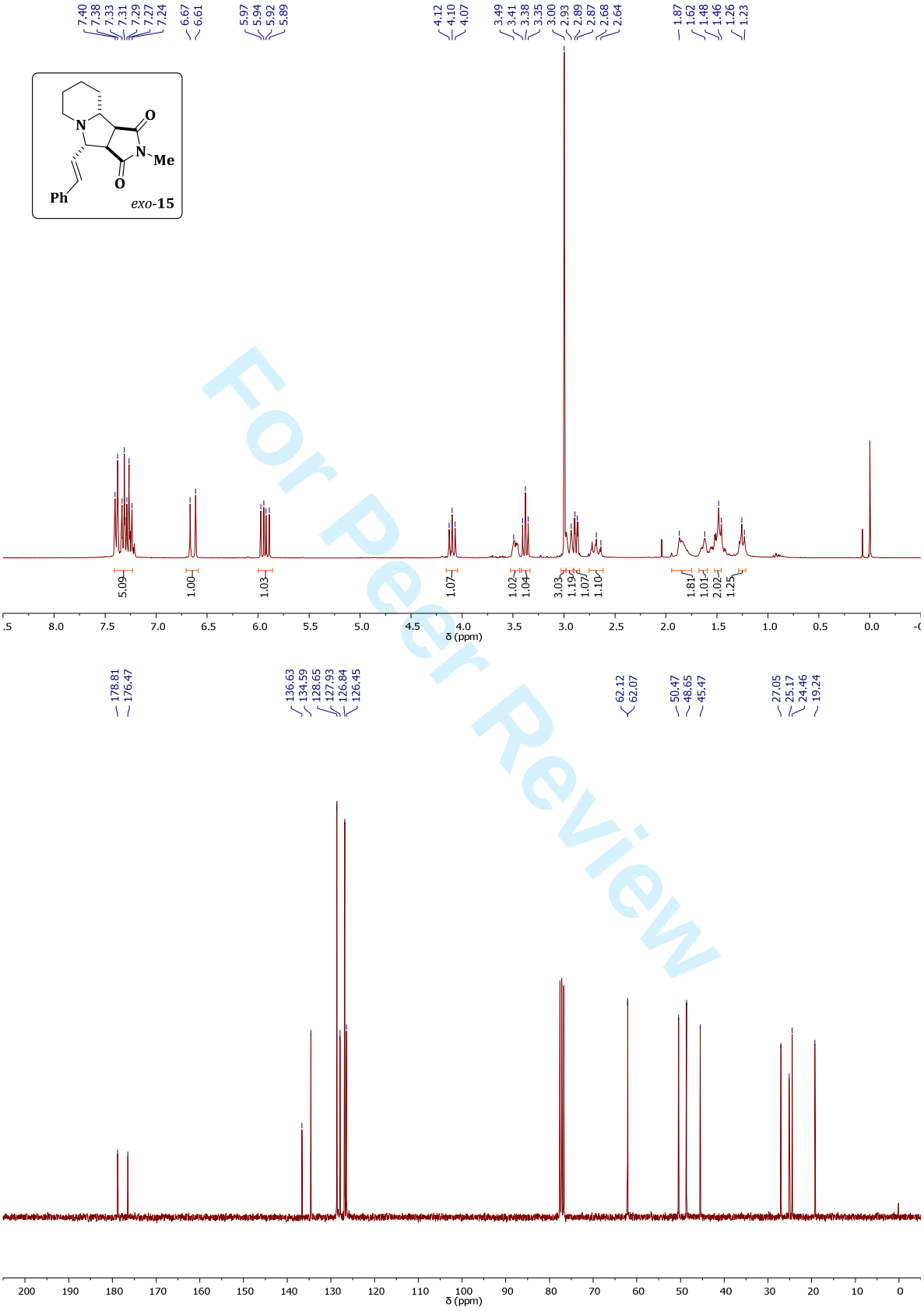

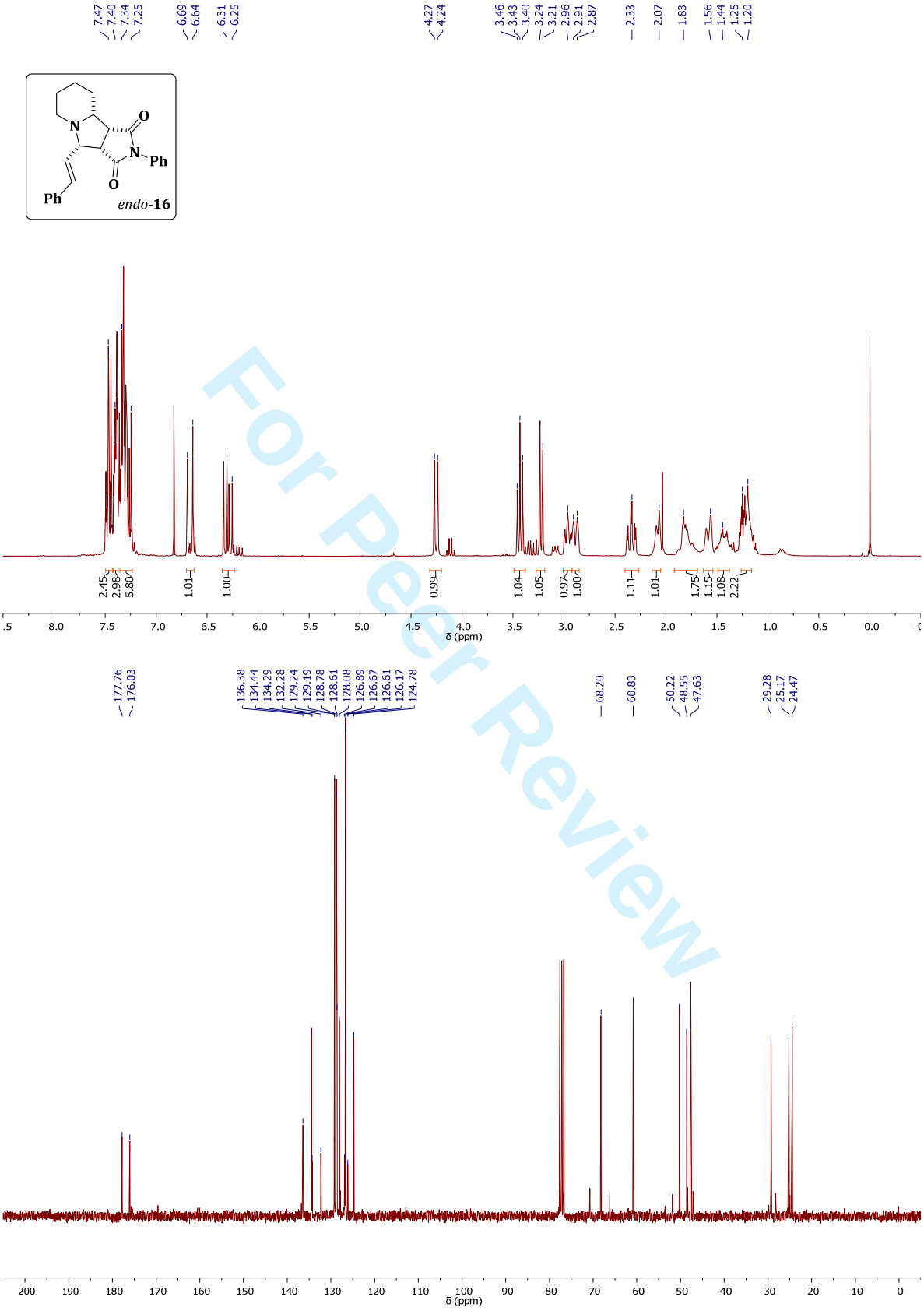

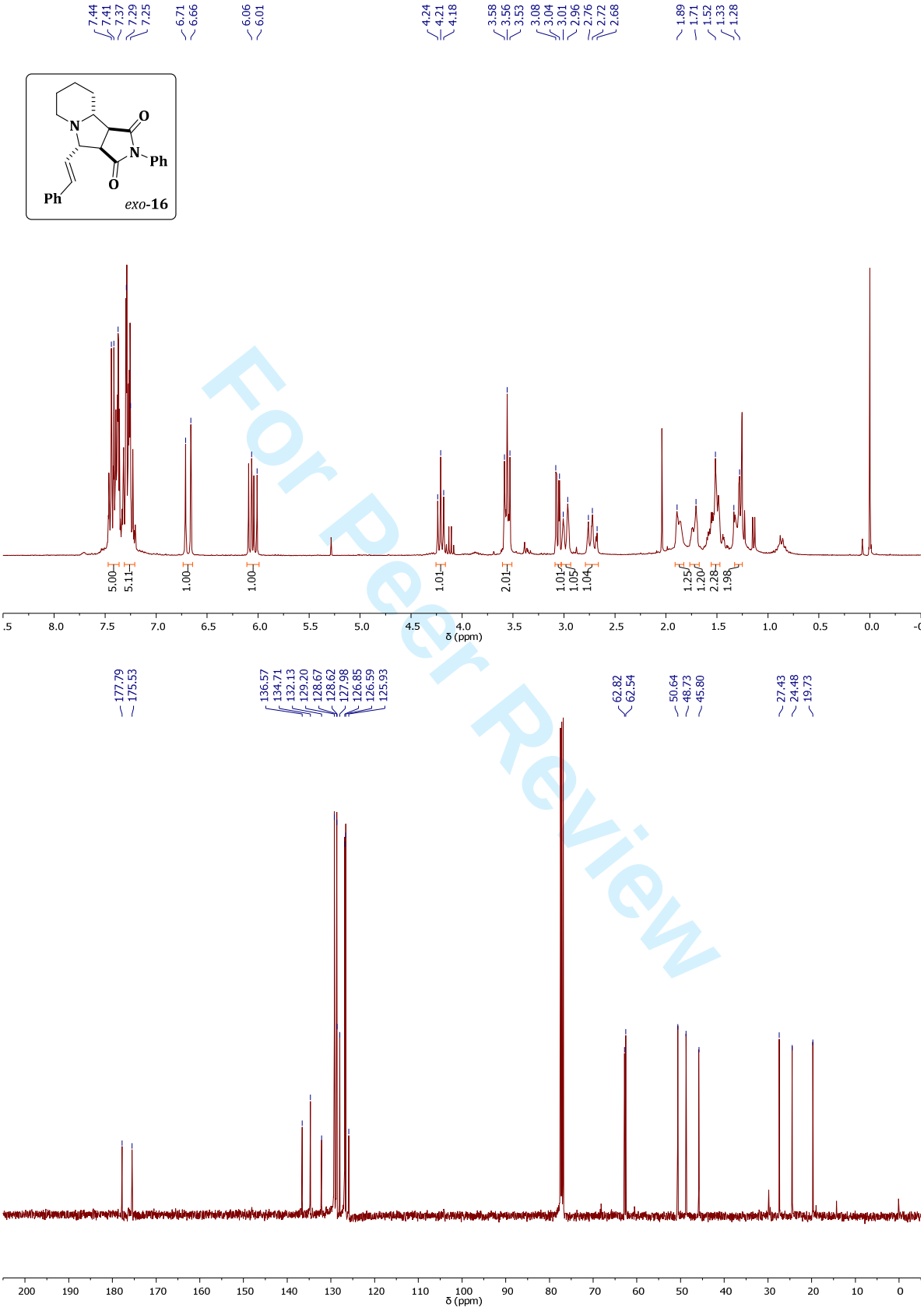

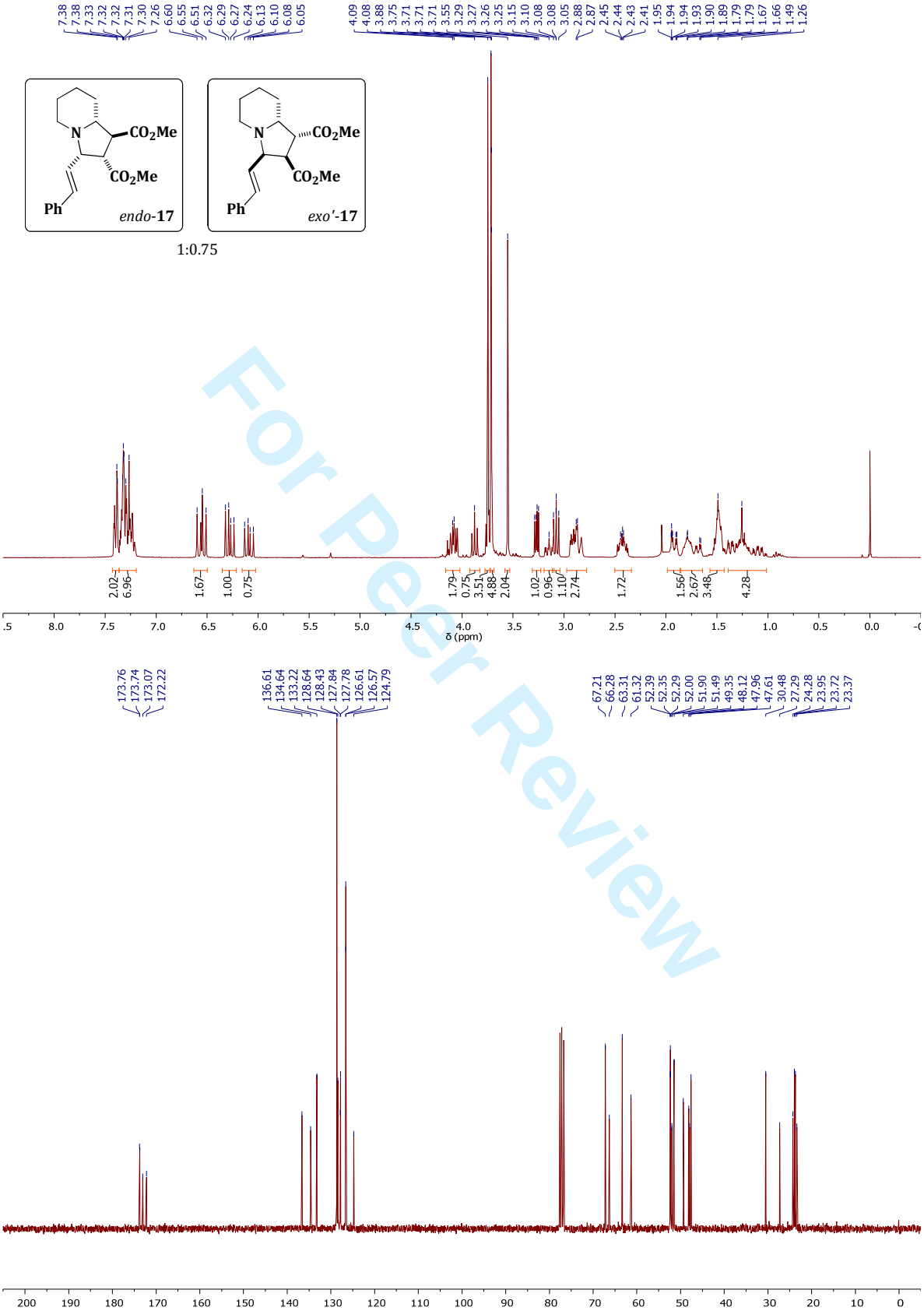

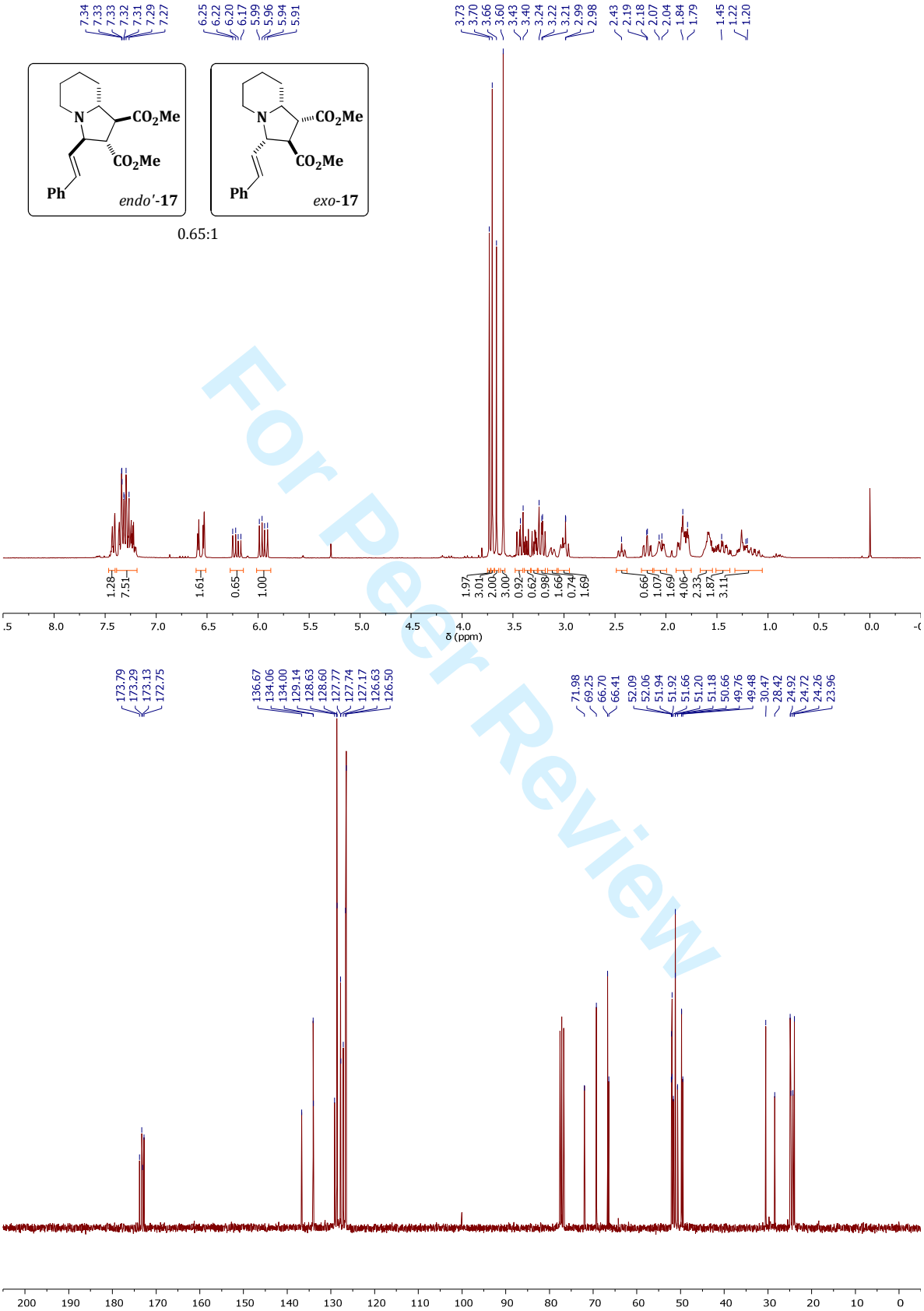

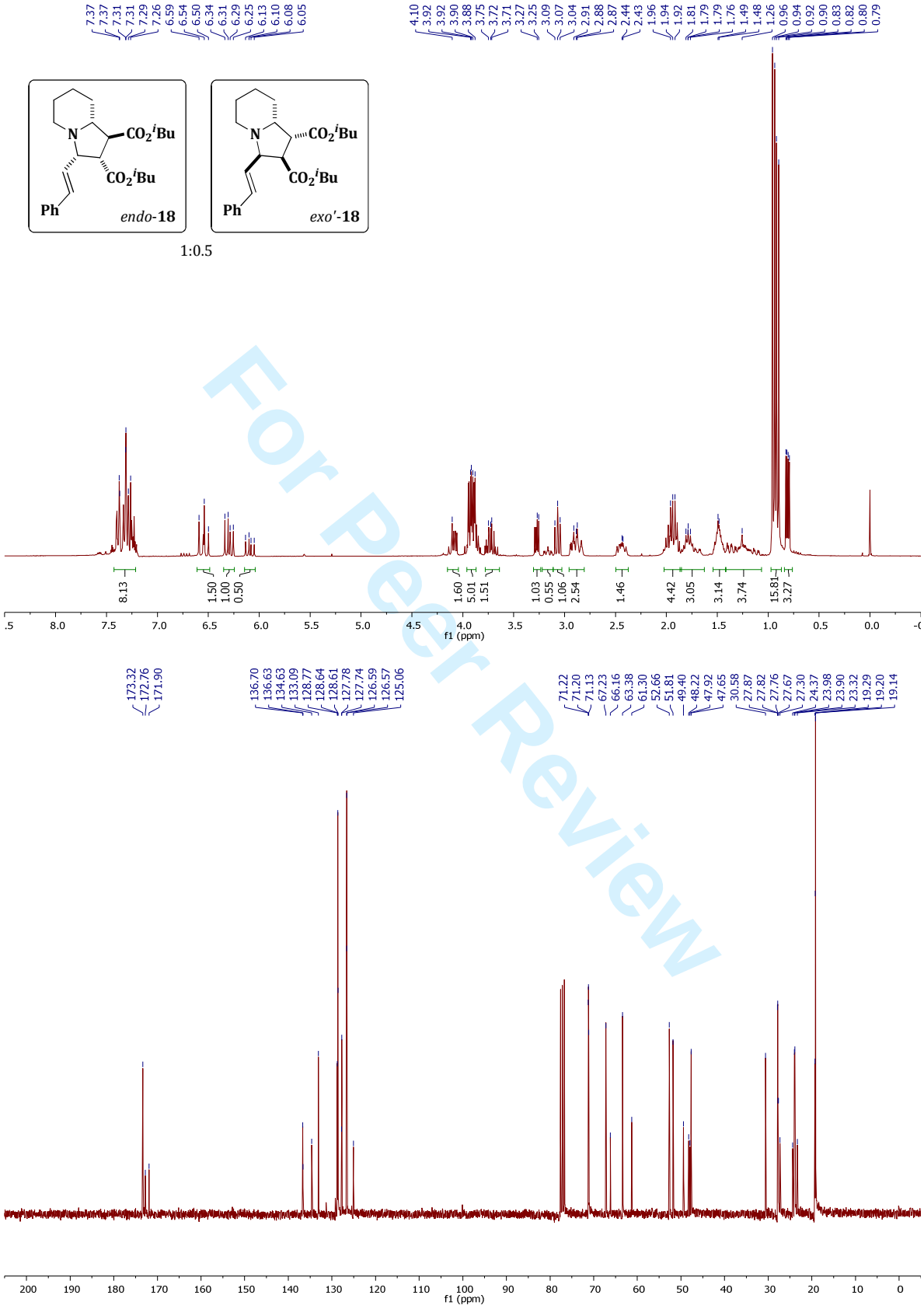

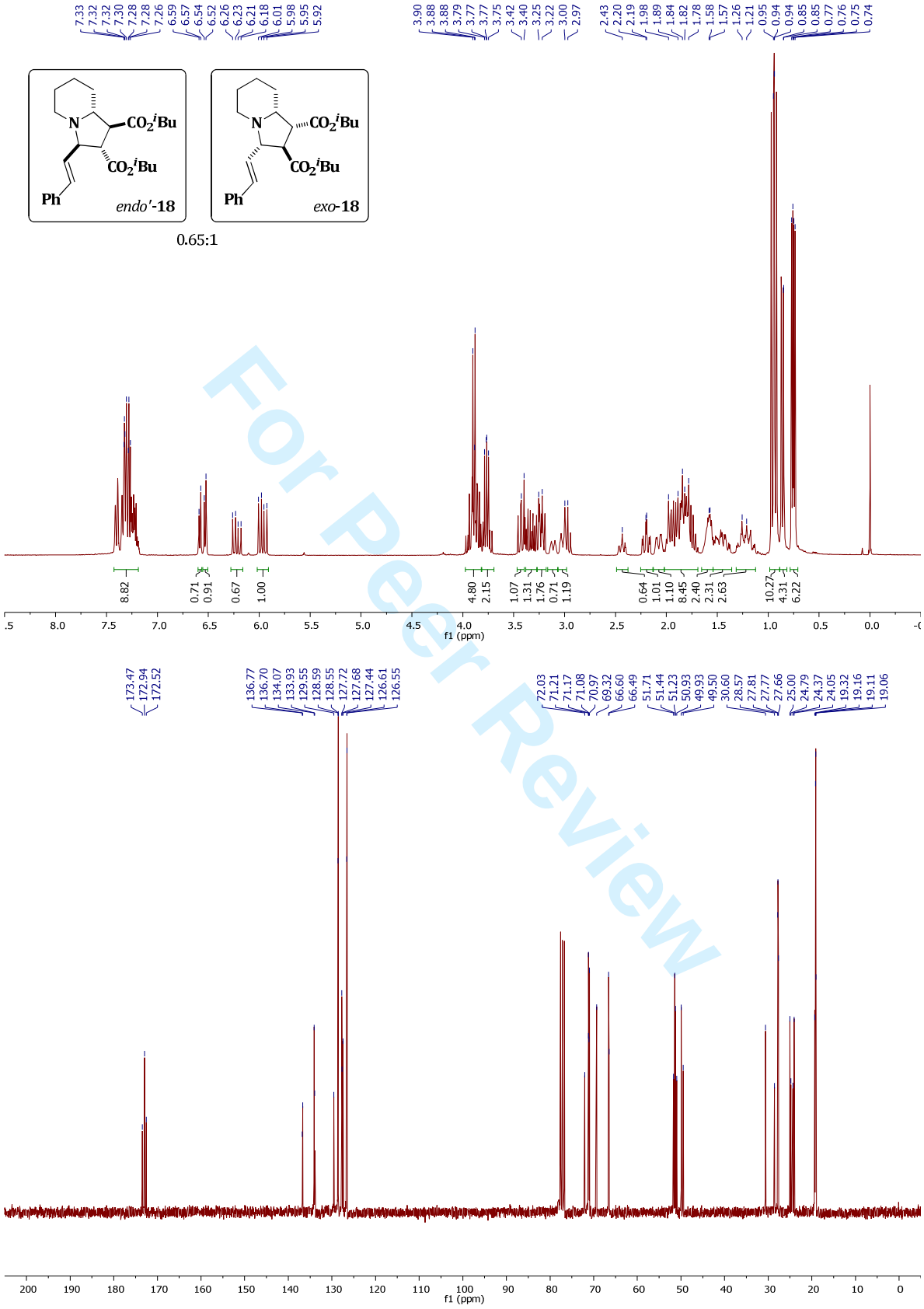

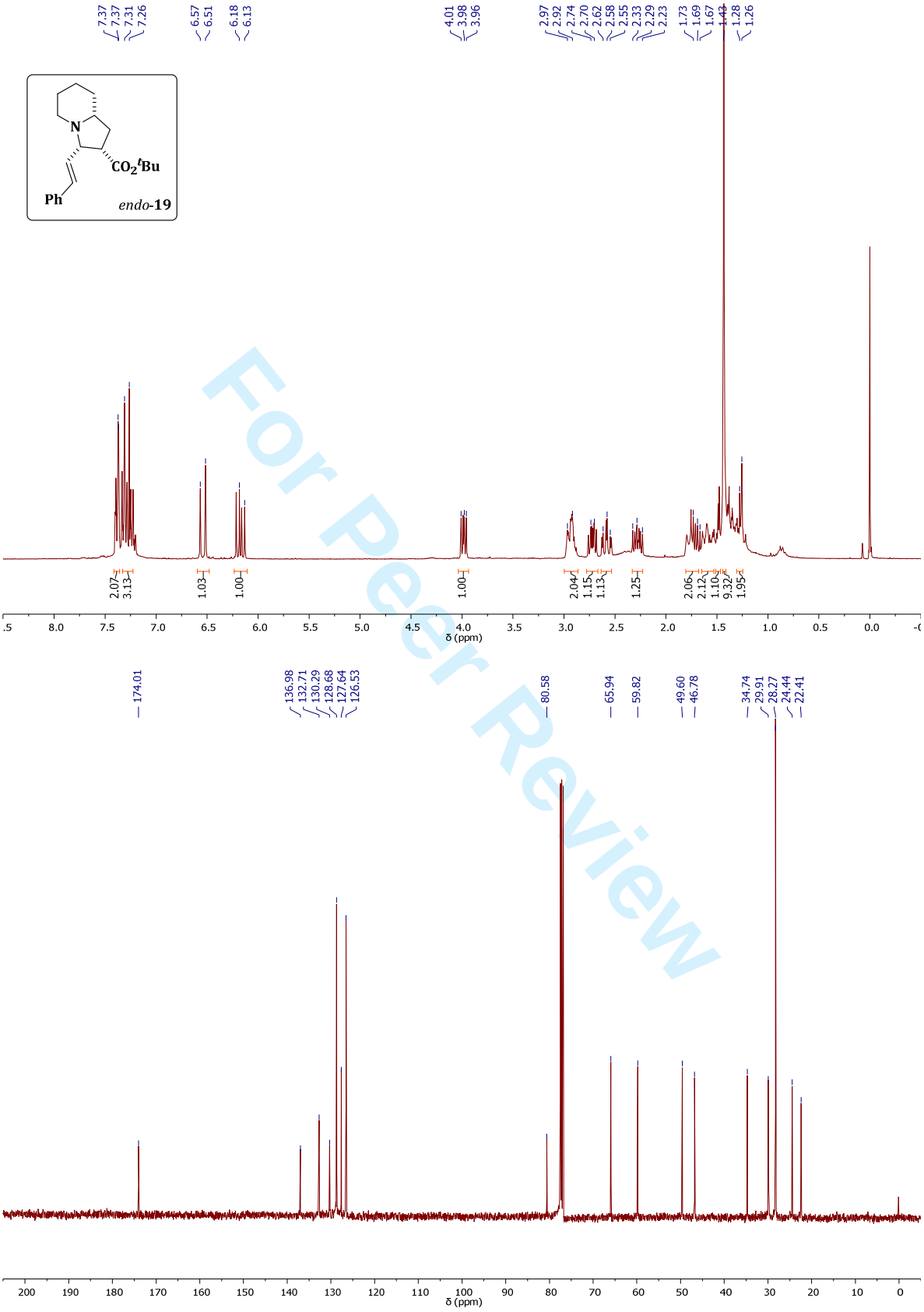

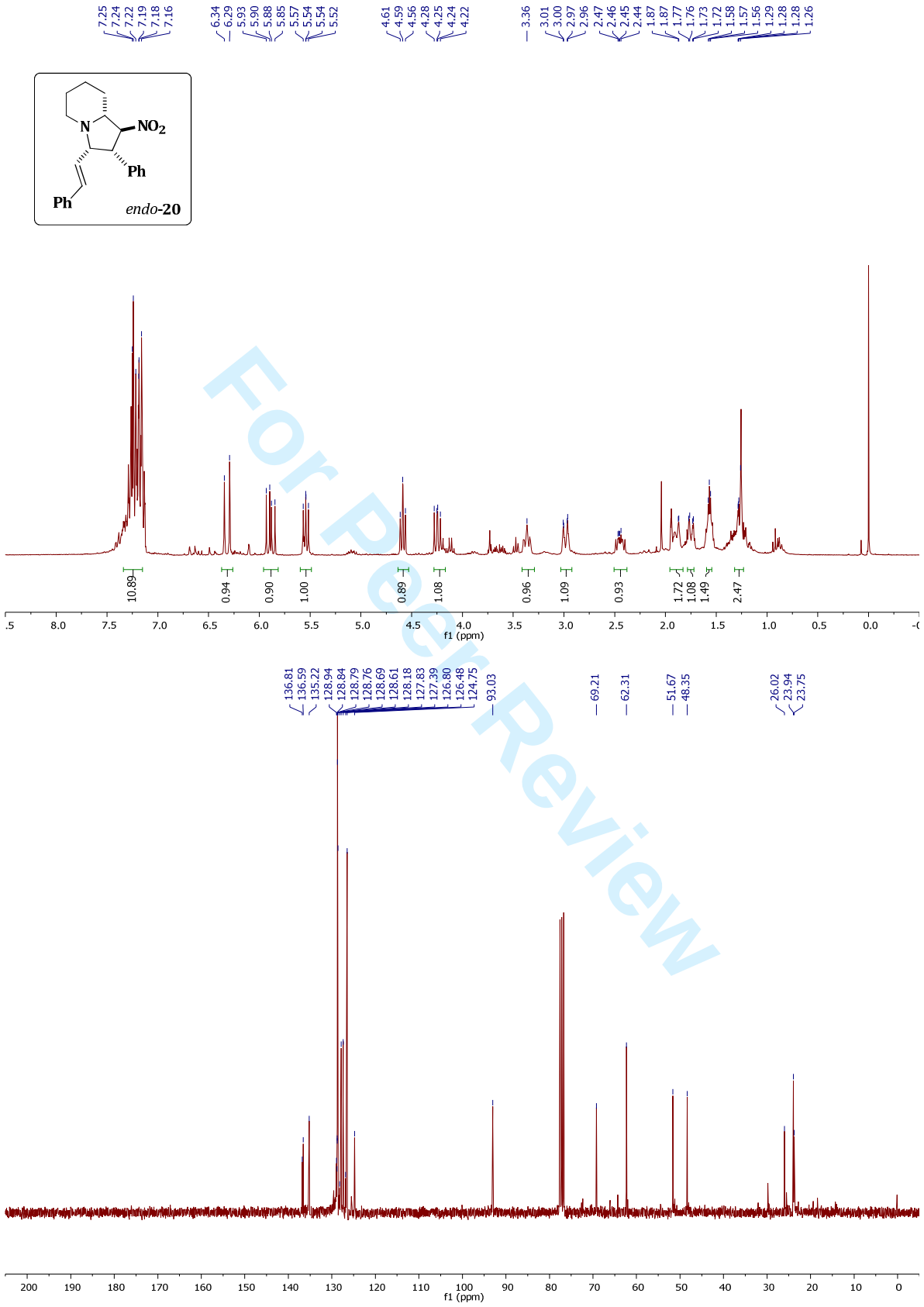

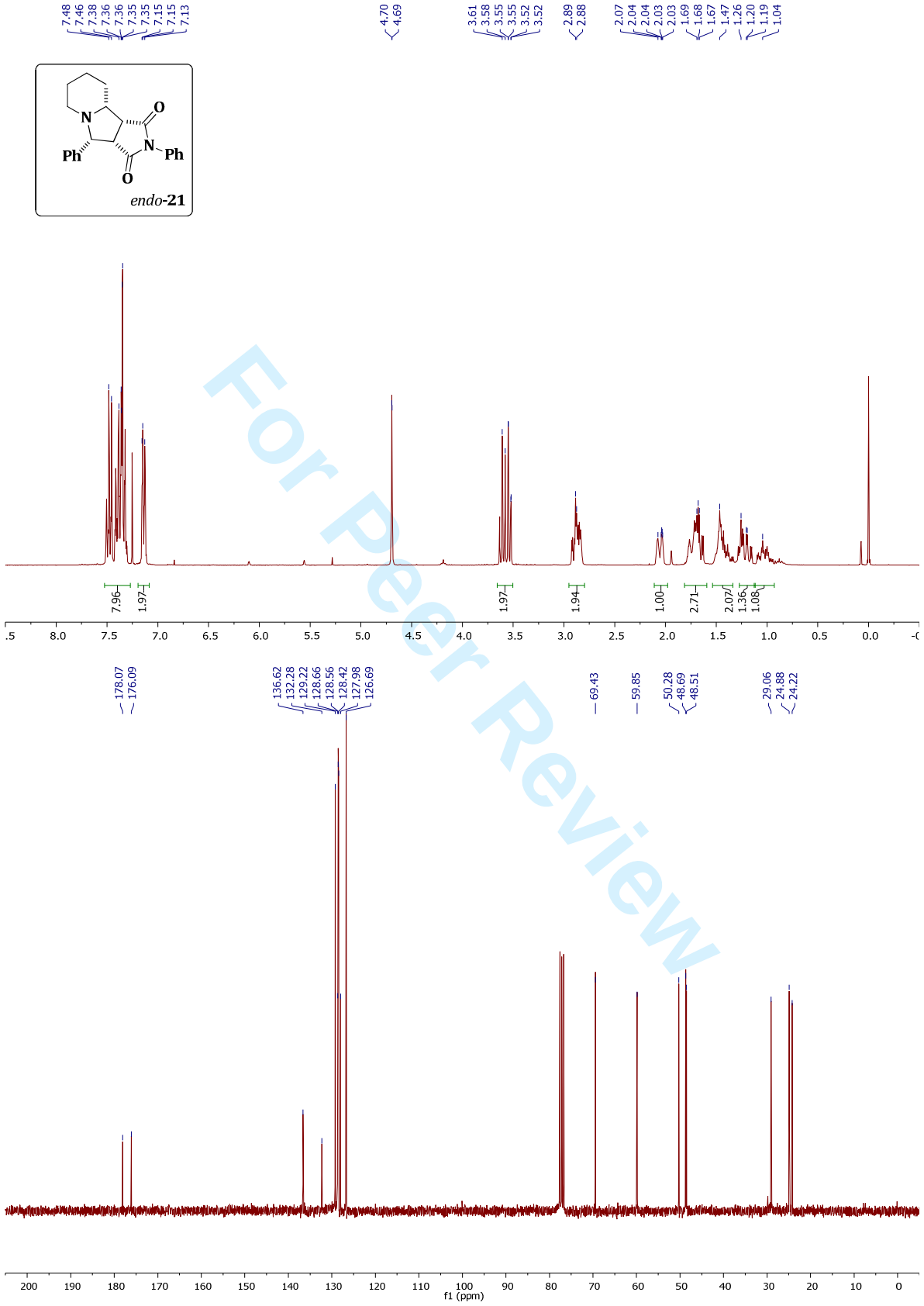

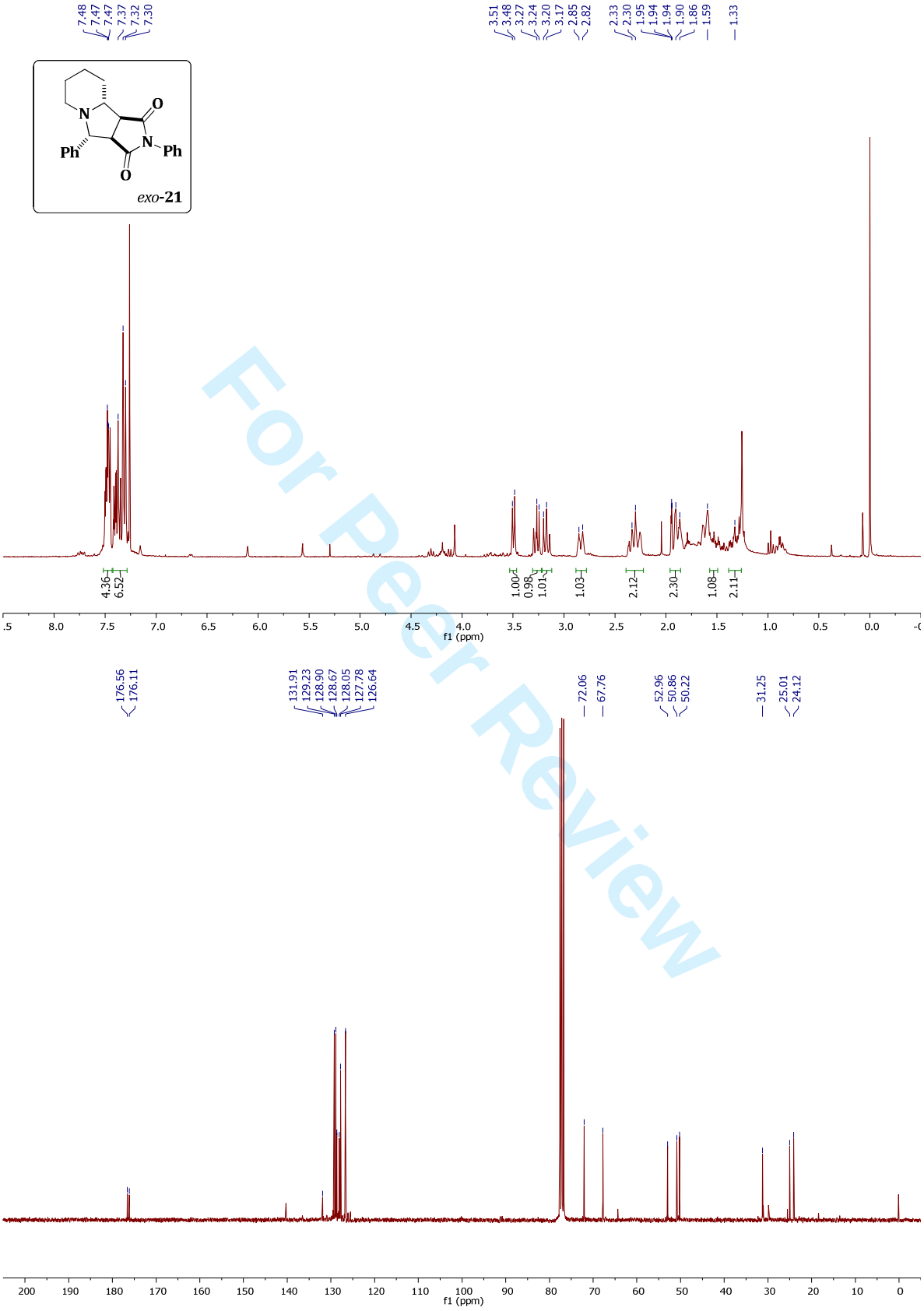

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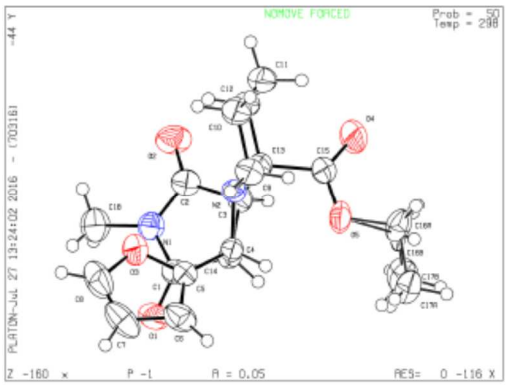

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Multicomponent diastereoselective synthesis of indolizidines via 1,3-dipolar cycloadditions of azomethine ylides

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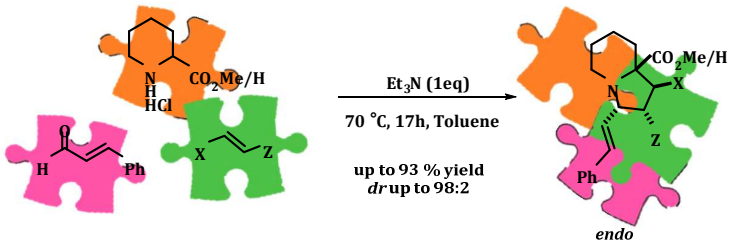
Dedicated to Prof. Dieter Enders



Received:
Accepted:
Published online:
DOI:

Abstract The synthesis of polyfunctionalized indolizidines from pipecolinic acid alkyl ester derivatives, aldehydes and a wide range of dipolarophiles by a multicomponent 1,3-dipolar cycloadditions has been developed in a diastereselective manner. Reactions take place in toluene with short reaction times at 70 °C, giving good yields. The synthesis of these fused heterocycles is also studied starting from the pipecolinic acid, generating the dipole through a decarboxylative route at 120 °C. The relative configuration of the resulting products, as well as the mechanistic pathways are also explained.

Key words cycloaddition, multicomponent, indolizidine, azomethine ylides, iminium route, decarboxylative route

Introduction

The indolizidine structure can be found in many alkaloid families being the most important moiety in the molecule.[1] These alkaloids, which can be isolated from plant or animal sources, have shown important biological properties and medicinal applications.[2] As representative examples, pharmaceutically interesting tetrahydroxyalkaloids such as castanospermine and 6-epicastanospermine are possible lead compounds in the search for anti-AIDS drugs, and the most simple structure of tashiromine has multiple interesting biological activities (Figure 1).

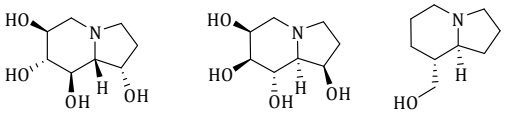
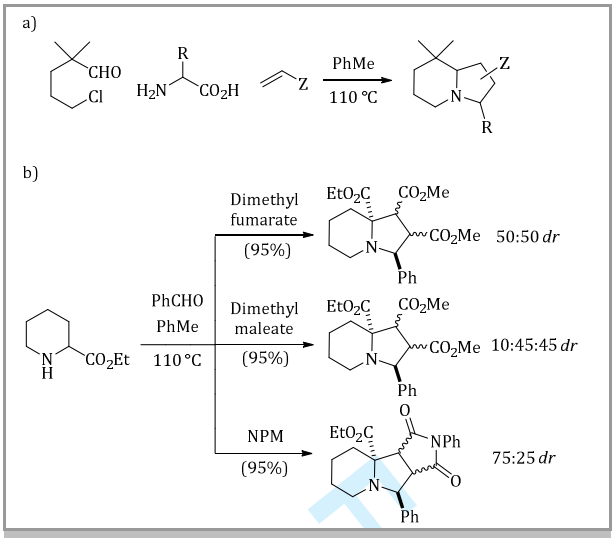


Figure 1. Representative natural indolizidine alkaloids.

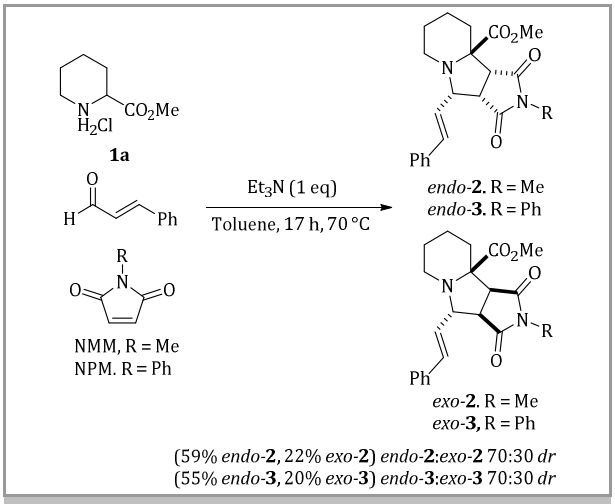
Many synthetic approaches have been successfully developed to prepare this fused heterocyclic skeleton. Most of them can be classified according to the cyclization order, that means, five-member ring followed by six-membered ring construction (5→6) and *vice versa* (6→5).[3] The most common used access is the 5→6 pathway, and the reason is the high availability of both natural or synthetic polifunctionalized pyrrolidines or proline derivatives.[4,5] In addition, interesting 6→5 sequences have been published.[6]

Such as it has been extensively demonstrated, 1,3-dipolar cycloaddition (1,3-DC) involving azomethine ylides is a potential tool for the construction of complex alkaloid structures.[7,8,9] Focusing on 6→5 sequences mediated by these type of cycloadditions generating the intermediate azomethine ylides via decarboxylation route,[10] intramolecular 1,3-DC between δ-chloroaldehydes, glycine and electrophilic alkenes, gave indolizidines in very high yields (Scheme 1a).[11] Another decarboxylations underwent by tetrahydroisoquinoline-3-carboxylic acid and by tetrahydro-β-carboline-3-carboxylic acid also gave polycycles in good yields.[12]

The generation of the azomethine ylide through the iminium route, where a decarboxylation do not occur, has also been explored.[13,14,15] Ethyl pipecolinate was used as starting material in the generation of the corresponding iminium salt only with benzaldehyde at 120 °C yielding mixture of stereoisomers when *N*-methylmaleimide, dimethyl fumarate and maleate were used (Scheme 1b).[16] In all these examples the chemical yield was almost quantitative (95%) and the mixture of diastereoisomers was notable. In the case of dimethyl fumarate and *N*-phenylmaleimide (NPM) a 50:50 and a 75:25 mixture of *endo*:*exo* adducts was obtained, respectively. The intrinsic thermal isomerization of dimethyl maleate also promoted the generation of a third diastereoisomer (Scheme 1b).



Scheme 1. Precedents of the thermal preparation of indolizidines by 1,3-DC with azomethine ylides



Scheme 2. Synthesis of indolizidines **2** and **3** through multicomponent cycloaddition of pipecolinic acid methyl ester, with cinnamaldehyde and maleimides.

Following with the multicomponent 1,3-dipolar cycloaddition strategy designed for the synthesis of pyrrolizidines[17] using proline ester hydrochlorides, aldehydes and dipolarophiles, at room temperature, we will survey in this work the general scope of this cycloaddition employing six-membered ring templates for the construction of the fleeting azomethine ylide with aldehydes, and further capture with dipolarophiles. We will study the generation of these intermediates through the iminium route, or through the decarboxylation way. All these reactions will be designed with the idea of increasing the functionality of the resulting polysubstituted indolizidines improving the diastereomeric ratio at the end of the processes. A comparison between both methodologies will be also stablished.

Results and discussion

Following the optimized reaction conditions described by our group in the synthesis of pyrrolizidines,[17a,c] the first attempt to run 1,3-DC between the iminium salt, generated from methyl pipecolinate hydrochloride **1a** and cinnamaldehyde, and further cyclization with *N*-substituted maleimides as dipolarophiles was performed at 25 °C in toluene. The reaction did not take place neither using these reaction conditions nor employing the silver catalyzed-process at room temperature. When increasing the temperature to 70 °C in toluene and in the absence of silver salts the reaction succeeded. Indolizidines **2** and **3** were isolated with high *endo*-diastereoselectivity when methyl pipecolinate and one equivalent of triethylamine were allowed to react with *N*-methylmaleimide (NMM) or with *N*-phenylmaleimide (NPM). No differences were observed concerning both of the yield the diastereoselectivity (70:30 *dr*). Compound **2** was isolated in 81% overall yield (*endo*-**2** 59%, and *exo*-**2** 22%) and **3** in 75% overall yield (*endo*-**3** 55%, and *exo*-**3** 20%) (Scheme 2). In contrast, when maleic anhydride was tested higher yield and complete *endo*-diastereoselectivity was achieved for compound **4** (Figure 2).

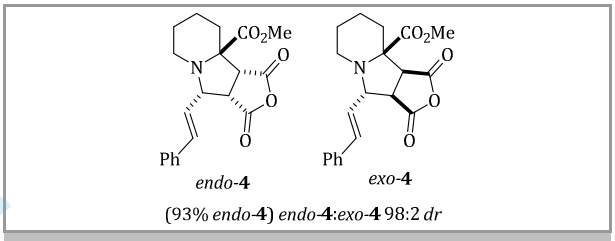
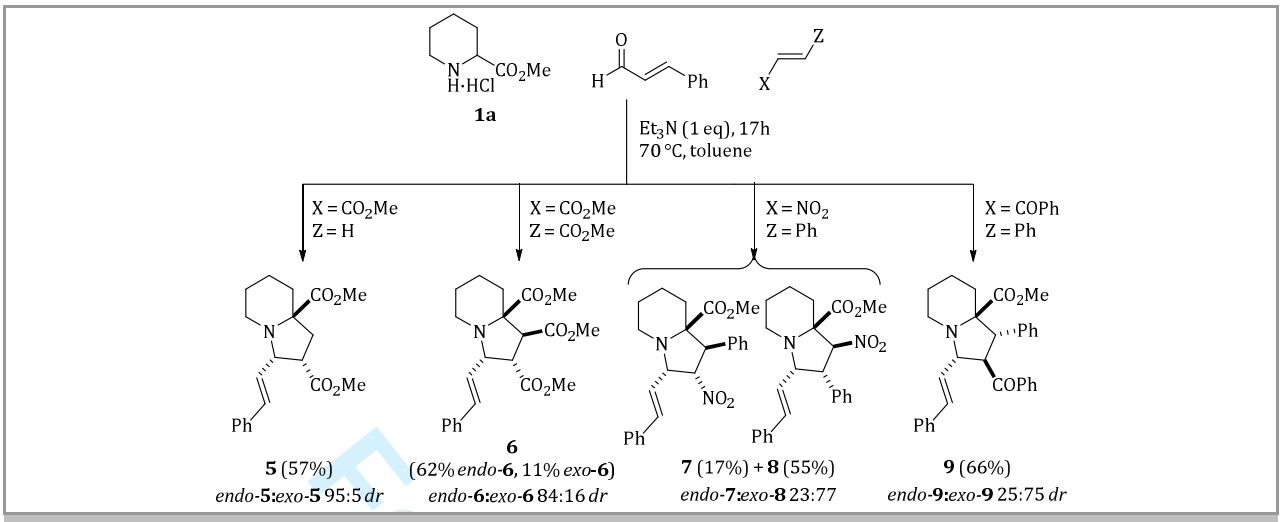


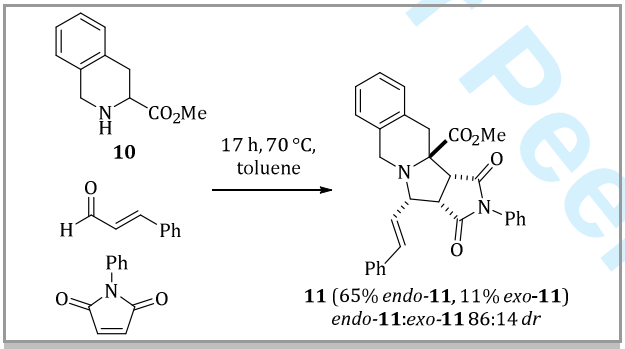
Figure 2. Chemical yield and distereoselection of the reaction of the Scheme 2 using maleic anhydride as dipolarophile.

Following with the study of the general scope several dipolarophiles maintaining the aldehyde structure were tested. The highest *endo*-diastereselection was achieved when the less sterically hindered methyl acrylate was employed as dipolarophile (Scheme 3) yielding *endo*-**5** (57%) in a 95:5 *dr*. When methyl fumarate was used as dipolarophile, the diastereoselectivity observed for compound *endo*-**6** (84:16 *dr*) was slightly lower than the obtained one for the methyl acrylate but higher than with NMM (Scheme 3). *trans*-β-Nitrostyrene and chalcone were suitable dipolarophiles for this thermal multicomponent reaction affording indolizidines **7**, **8** and **9**, respectively. With the conjugated ketone the chemical yield was lower (66% overall yield) than the analogous obtained in the example run with the nitroalkene (72% overall yield). However, apart from the *endo*-**7** cycloadduct (17% yield), the regioisomer *exo*-**8** (55% yield) was also identified in high proportions. In the case of chalcone the unexpected cycloadduct *exo*-**9** was obtained as major product (75:25 *dr*) (Scheme 3).

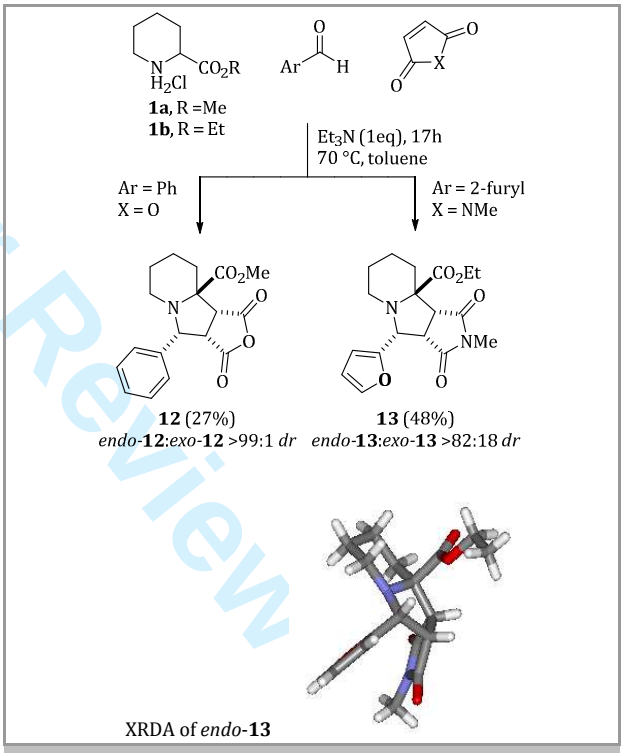
Methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate **10**, prepared from phenyl alanine methyl ester[18] was also tested in this multicomponent process. Cinnamaldehyde, **10** and NPM were mixed and the reaction was warmed at 70 °C for 17 h. Tetracyclic complex skeleton *endo*-**11** was obtained as major compound in 65% yield, and *exo*-**11** in 11% yield with a 86:14 *dr* (Scheme 4).



Scheme 3. Multicomponent cycloaddition of pipecolinic acid methyl ester hydrochloride **1a**, cinnamaldehyde and different dipolarophiles.



Scheme 4. Synthesis of indolizidine **11** through the multicomponent cycloaddition of **10** and cinnamaldehyde, with NPM.



Scheme 5. Synthesis of indolizidines *endo*-**12** and *endo*-**13** through multicomponent cycloaddition of pipecolinic acid alkyl esters **1**, with aromatic aldehydes and different dipolarophiles.

A comparison with the thermal 1,3-DC reported in the literature by Joucla and coworkers (Scheme 1b),[16] where benzaldehyde was employed, was done. The reaction with *N*-methylmaleimide did not work under our reaction conditions, and a complex mixture of inseparable products was detected after performing the reaction at 110 °C. However, the reaction involving maleic anhydride, benzaldehyde, and **1a** at 70 °C gave a modest isolated chemical yield (27%) of cycloadduct *endo*-**12** as unique diastereoisomer (Scheme 5). Furfural was also tested together with ethyl pipecolinate **1b** and NMM affording *endo*-cycloadduct **13** as major compound in 82:18 *dr* and 48% overall yield (Scheme 5).

Nevertheless, crotonaldehyde, isovaleraldehyde and (2*E*,4*E*)-hexa-2,4-dienal showed very poor reactivity. According to our studies, reactions run with all type of aldehydes, but specially unsaturated aldehydes, were very sensitive to high temperatures (>70 °C) affording decomposition products (detected in crude ^{1}H-NMR spectra).

After careful analysis of ^{1}H-NMR of the reaction crudes, only a mixture of two diastereoisomers was identified. At this point, we can assume that the reaction mechanism proceeds with relative high to excellent diastereocontrol as consequence of the S-type dipole generated by iminium route which attacks preferentially by its α-position to carbon atom of dipolarophile with partial positive charge (Figure 3a). This S-dipole, through the most favorable *endo*-approach allows the 2,4-*trans*-2,5-*trans* arrangement of the five-membered ring (Figure 3b). This

preferential trend was observed in compounds **2**, **3**, **4**, **5**, **6**, **11**, **12** and **13**. Only in the example run with the chalcone the *exo*-diasteroselectivity was preferentially observed presumably due to the high steric interaction between the phenyl group closer to ketone group and the substituents of the cyclic dipole.[19] In this example a 2,4-*cis*-2,5-*trans* arrangement was generated. On the other hand, the cycloadduct resulting from the *γ*-attack of the S-dipole was preferred in the reaction performed with *trans*-β-nitrostyrene, which is an excellent Michael acceptor able to trap whatever type of resonance forms. In this case, the new compound **8** was formed by a more feasible *exo*-attack of the dipolarophile. This identical behavior was described during the multicomponent synthesis of pyrrolizidines because of steroelectronic effects of the nitroalkene.[17]

The relative configuration of the major *endo*-cycoadducts **2**-**6** and **11**-**13** was proposed according to unambiguous nOe experiments. A representative example of these analyses is shown in Figure 4. The most stable conformations of *endo*-**5** and *endo*-**6** have been represented with the corresponding nOe effects detected. It is noteworthy to indicate that a small, but definitive, increment of electronic population in the signal of methyl group was produced when the hydrogen atom bonded to the C3 position was irradiated. In addition, this configuration was identical to the obtained by Joucla *et al.* after X-ray diffraction analysis,[16] and also with the same structural arrangement of pyrrolicidines obtained after multicomponent 1,3-DC involving prolinates.[17] At the end of the experimental work an X-ray diffraction analysis of crystalline major diastereoisomer *endo*-**13**[20] could be performed confirming all these stereochemical results obtained by NMR experiments (Scheme 5).

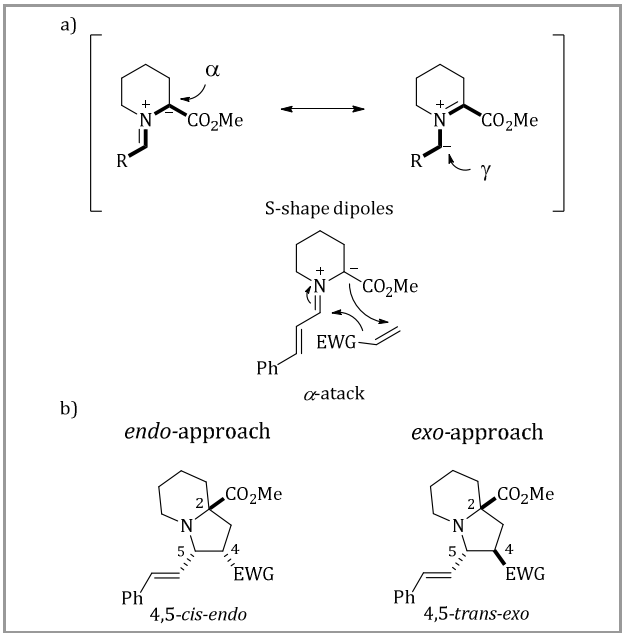


Figure 3. Mechanistic details of the synthesis of indolizidines by the iminium route.

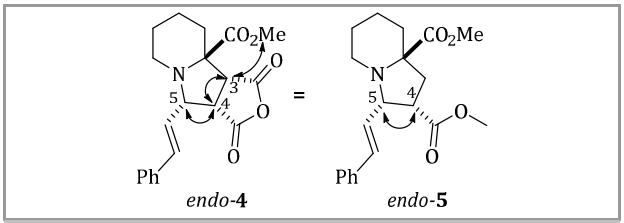


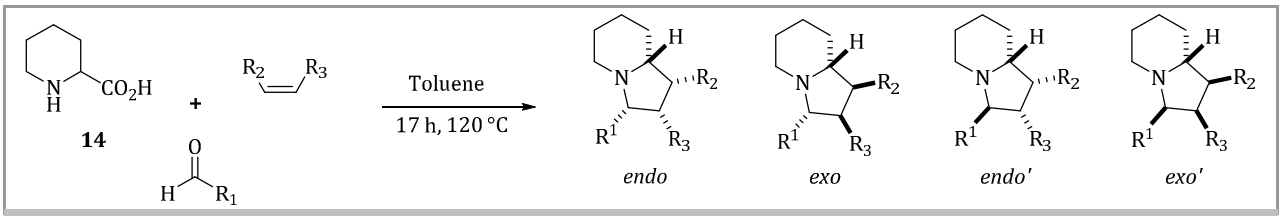
Figure 4. Representative nOe detected for major *endo*-adducts (**4** and **5**) of this series of reactions.

Next, we study the availability of performing the corresponding 1,3-DC starting from pipecolinic acid **14**, aldehydes and dipolarophiles. In this reaction, the necessary decarboxylation of the iminium salt generated in situ occurred at higher temperatures (refluxing toluene) (Scheme 6). To the best of our knowledge, this type of cycloaddition of **14** has not been reported yet.[21] Thus, compound **14**, cinnamaldehyde, and NMM were diluted in toluene and the mixture was heated in a sealed tube at 120 °C (bath temperature) obtaining a mixture of four different stereosiomers **15** in 89% overall yield (Table 1, entry 1). In all cases the diastereomeric ratio observed in the crude ^{1}H-NMR spectra was identical to the analogous one determined after separation of each isomers by column chromatography. With NPM chemical yield of **16** was lower (78%) but the *endo*-diastereoselection was the highest of all this series of decarboxylative reactions using cinnamaldehyde (Table 1, entry 2). Dimethyl and diisobutyl fumarates gave both identical chemical yields (75%) and mixtures of diastereoisomers of products **17** and **18** (Table 1, entries 3 and 4). Non-symmetrical dipolarophiles such as *tert*-butyl acrylate and *trans*-β-nitrostyrene were next evaluated. Compounds **19** and **20** were isolated in 52 and 40% overall yields, respectively (Table 1, entries 5 and 6). Finally, benzaldehyde was tested with **14** and NPM affording a very high yield (95%) of compound **21** as mixture of four stereoisomers (Table 1, entry 7). However, the reaction with NMM or *tert*-butyl acrylate only afforded decomposition products at the end of the reaction. Other aldehydes such as crotonaldehyde, isovaleraldehyde and furfural also failed as starting materials in the multicomponent reaction employing NMM.

After careful analyses of selective nOe experiments of each isolated product/mixture, and by comparison of the analogous chemical shifts and coupling constants we could identify each structure. *Endo*-cycloadduct was always the most abundant stereoisomer, followed by the *exo*-adduct and a couple of similar diastereoisomers with different olefinic chemical shifts. nOe experiments revealed clear *all-cis*-arrangement in C2, C3, C4, and C5, for the *endo*-cycloadduct **15** (Figure 5). Apart from *cis*-maleimide ring junction nOe, a very small one was observed between hydrogens bonded to C2 and C5 positions (Figure 5). A crucial nOe between hydrogens placed at C2 and the closer olefinic one was observed in both *endo'*- and *exo'*-**15** (Figure 5).

With all these stereochemical information, we can propose that the reaction, once produced the decarboxylation, operated through the most stable S-shape dipole interacting with the electrophilic alkene by its α-position. S-Shape dipole underwent thermal steromutation in the iminium salt affording unstable U-shape dipole, which is the responsible of the generation of

endo'- and *exo'*-diastereoisomers. Besides, the regioselectivity of this cycloaddition was very high because we could not detect any stereoisomer due to the attack of the dipole by its γ-position (Figure 6).



Scheme 6. Multicomponent 1,3-DC via decarboxylative route employing **14**, aldehydes, and dipolarophiles

Table 1. Multicomponent 1,3-DC by mixing amino acid **14**, aldehydes, and dipolarophiles at 120 °C.

Entry	R^1	Dipolarophile	Product	Yield (%)[a]	*dr*[b] (*endo*:*exo*:*endo'*:*exo'*)
1	(*E*)-PhCH=CH-	NMM	**15**	89	35:22:20:23
2	(*E*)-PhCH=CH-	NPM	**16**	78	45:17:18:20
3	(*E*)-PhCH=CH-	Dimethyl fumarate	**17**	75	33:29:18:20
4	(*E*)-PhCH=CH-	Diisobutyl fumarate	**18**	75	35:30:19:17
5	(*E*)-PhCH=CH-	*tert*-Butyl acrylate	**19**	52	39:28:17:16
6	(*E*)-PhCH=CH-	*trans*-β-Nitrostyrene	**20**	40	43:25:11:21
7	Ph	NPM	**21**	95	57:25:13:5

[a] Overall chemical yield isolated after flash chromatography.
[b] Mixture of diastereoisomers detected by ^{1}H-NMR of the crude mixture and after the separation of all of the corresponding diastereoisomers.

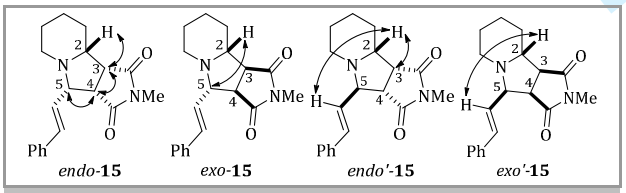


Figure 5. Representative nOe effects detected for adducts **15** derived from pipecolinic acid **14** and NMM.

As conclusion, we have prepared indolizidines from methyl pipecolinate and methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate in a multicomponent 1,3-DC using functionalized conjugate aldehydes as cinnamaldehyde and different dipolarophiles at 70 °C. The major isomers resulted from the attack of the reactive S-shape dipole, prepared via the iminium route, by its α-position affording *all cis*-endo diasteroisomers. Under these reaction conditions, the diasteroselection was notably higher than the analogous ones reported in the literature at 110 °C. In other side, the appearance of the U-shape dipole at 120 °C allowed to obtain two more diastereoisomers (*endo'* and *exo'*) when the multicomponent sequence dealt with a dipole generated by a decarboxylative route. Here, *endo*-cycloadduct was the major isomer, especially when a bulky substituent in the dipolaophile was bonded (Ph, Bu^t, Bu^i) but with very significant amounts of the corresponding *exo*-adduct. In all these examples, the diasteromeric ratio was very low. No regioisomeric adducts controlled by a γ-attack were obtained in any case.

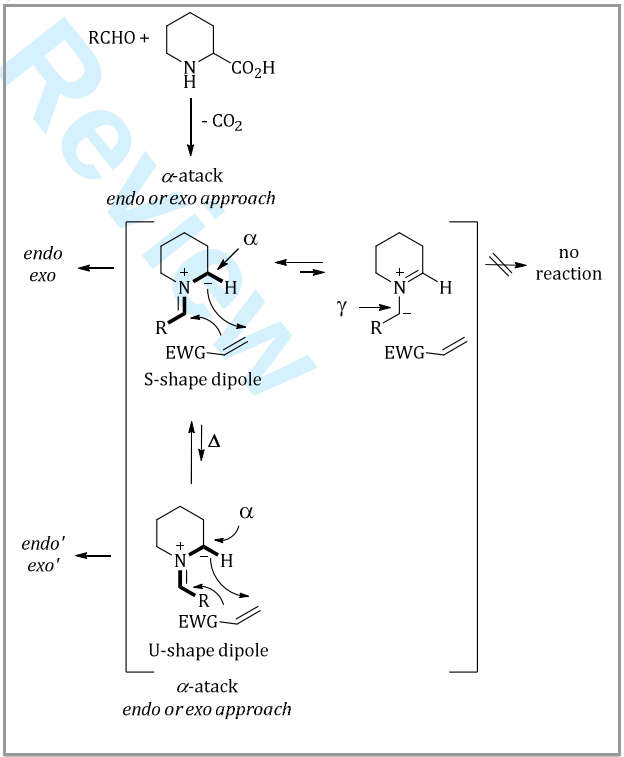


Figure 6. Mechanistic details of the synthesis of indolizidines by the decarboxylative route.

Experimental part

Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. Only the structurally most important peaks of the IR spectra, recorded on a Nicolet 510 P-FT, are listed. For solid samples ATR device was employed. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were obtained on a Bruker AC-300 using $CDCl_3$ as solvent and TMS as internal standard.

Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on a Shimadzu QP-5000 and high-resolution mass spectra were obtained on a Finnigan VG Platform. HRMS (EI) were recorded on a Finnigan MAT 95S. Analytical TLC was performed on Schleicher & Schuell F1400/LS silicagel plates and the spots were visualized under UV light (λ = 254 nm). Flash chromatography was done using Merck silica gel 60 (0.040–0.063 mm).

General procedure for the synthesis of indolizidines 3-9

To a solution of the pipecolic acid methyl ester hydrochloride **1** (40 mg, 0.22 mmol) in toluene (1 mL), Et_3N (1 equiv, 30.5 µL, 0.22 mmol), the corresponding aldehyde (1 equiv, 0.22 mmol) and the dipolarophile (1 equiv, 0.22 mmol) were added. The resulting mixture was stirred at 70 °C for 17 h. EtOAc (5mL) and H_2O (5 mL) were added and the organic phase was separated, dried ($MgSO_4$), and evaporated to obtain the crude heterocycle, which was purified by flash chromatography (silica-gel) in chemical yields reported along the text.

Methyl (3a*S,4*S**,9a*R**,9b*R**)-2-methyl-1,3-dioxo-4-[(*E*)-styryl]decahydro-9a*H*-pyrrolo[3,4-*a*]indolizine-9a-carboxylate (*endo*-2)**

Yield: 36 mg (59%), colorless prims, mp 134-135 °C (Et_2O).

IR (neat): 1734, 1698, 1213 cm^{-1}.

^{1}H-NMR: δ = 1.18 (dt, *J* = 13.3, 3.5 Hz, 1H, $NCH_2CH_2CH_2$), 1.27–1.48 (m, 1H, $NCH_2CH_2CH_2$), 1.45–1.63 (m, 2H, NCH_2CH_2), 1.74 (dt, *J* = 13.2, 3.4 Hz, 1H, CCH_2), 2.48 (ddd, *J* = 13.2, 2.9, 1.4 Hz, 1H, CCH_2), 2.81, 2.84 (2xd, *J* = 2.7 Hz, 2H, NCH_2), 3.01 (s, 3H, NCH_3), 3.25 (dd, *J* = 8.0, 7.9 Hz, 1H, NCHCH), 3.35 (d, *J* = 7.9 Hz, 1H, CCH), 3.76 (s, 3H, OCH_3), 4.18 (dd, *J* = 9.2, 8.0, Hz, 1H, NCH), 5.88 (dd, *J* = 15.6, 9.2 Hz, 1H, PhCHCH), 6.68 (d, *J* = 15.6 Hz, 1H, PhCH), 7.22–7.35 (m, 3H, ArH), 7.36–7.45 (m, 2H, ArH).

^{13}C-NMR: δ = 21.7 ($NCH_2CH_2CH_2$), 24.7 (NCH_2CH_2), 25.1 (NCH_3), 32.0 (CCH_2), 43.8 (NCH_2), 47.9 (NCHCHCO), 51.4 (CCHCO), 51.8 (OCH_3), 65.2 (NCH), 69.9 (CCO_2Me), 126.7, 127.8, 128.6, 128.7, 134.5, 136.8 (ArC, C=C), 173.6, 175.3 (2xNCO), 175.9 (CO_2Me).

MS (EI): *m/z* = 368 (M^+, 3%), 310 (20), 309 (100), 224 (3).

HRMS (DIP) calcd. for $C_{21}H_{24}N_2O_4$: 368.1746; found 368.1750.

Methyl (3a*S,4*S**,9a*R**,9b*R**)-1,3-dioxo-2-phenyl-4-[(*E*)-styryl]decahydro-9a*H*-pyrrolo[3,4-*a*]indolizine-9a-carboxylate (*endo*-3)**

Yield: 52 mg (55%), pale yellow oil.

IR (neat): 2933, 1710, 1498, 1448, 1375, 1179, 1309, 1192 cm^{-1}.

^{1}H-NMR: δ = 1.17–1.23 (m, 1H, $NCH_2CH_2CH_2$), 1.28–1.35 (m, 1H, $NCH_2CH_2CH_2$), 1.38–1.48 (m, 1H, NCH_2CH_2), 1.62–1.68 (m, 1H, NCH_2CH_2), 1.78 (dt, *J* = 13.1, 3.2 Hz, 1H, CCH_2), 2.53 (dd, *J* = 13.1, 1.5 Hz, 1H, CCH_2), 2.82–2.93 (m, 2H, NCH_2), 3.41 (t, *J* = 8.0, Hz, 1H, NCHCH), 3.51 (d, *J* = 8.0 Hz, 1H, CCH), 3.79 (s, 3H, OCH_3), 4.29 (dd, *J* = 8.9, 8.0, Hz, 1H, NCH), 6.01 (dd, *J* = 15.7, 8.9 Hz, 1H, PhCHCH), 6.72 (d, *J* = 15.7 Hz, 1H, PhCH), 7.16–7.35 (m, 5H, ArH), 7.37–7.50 (m, 5H, ArH).

^{13}C-NMR: δ = 21.8 ($NCH_2CH_2CH_2$), 24.9 (NCH_2CH_2), 32.1 (CCH_2), 44.0 (NCH_2), 48.0 (NCHCHCO), 51.4 (CCHCO), 51.9 (OCH_3), 65.5 (NCH), 70.4 (CCO_2Me), 126.7, 126.9, 127.7, 127.9, 128.6, 128.8, 129.3, 132.0, 134.4, 136.8 (ArC, C=C), 173.6 (CO), 174.2 (CO), 175.0 (CO_2Me).

MS (EI): *m/z* = 430 (M^+, 3%), 372 (26), 371 (100), 224 (6).

HRMS (DIP) calcd. for $C_{26}H_{26}N_2O_4$: 430.1893; found 430.1911.

Methyl (3a*S,4*S**,9a*R**,9b*R**)-1,3-dioxo-4-[(*E*)-styryl]octahydro-3*H*,9a*H*-furo[3,4-*a*]indolizine-9a-carboxylate (*endo*-4)**

Yield: 72 mg (93%), colorless prisms, mp 146-148 °C (Et_2O).

IR (neat): 1774, 1734, 1226 cm^{-1}.

^{1}H-NMR: δ = 1.15–1.25 (m, 1H, $NCH_2CH_2CH_2$), 1.50 (ddt, *J* = 12.9, 8.4, 3.9 Hz, 1H, $NCH_2CH_2CH_2$), 1.58–1.69 (m, 1H, NCH_2CH_2), 1.67–1.85 (m, 2H, CCH_2, NCH_2CH_2), 2.45 (ddd, *J* = 12.7, 4.5, 1.9 Hz, 1H, CCH_2), 2.90 (d, *J* = 2.7 Hz, 1H, NCH_2), 2.93 (d, *J* = 2.7 Hz, 1H, NCH_2), 3.54 (dd, *J* = 8.5, 8.3 Hz, 1H, NCHCH), 3.71 (d, *J* = 8.5 Hz, 1H, CCH), 3.79 (s, 3H, OCH_3), 4.27 (dd, *J* = 9.3, 8.3 Hz, 1H, NCH), 5.98 (dd, *J* = 15.7, 9.3 Hz, 1H, PhCHCH), 6.73 (d, *J* = 15.7 Hz, 1H, PhCH), 7.26–7.36 (m, 3H, ArH), 7.39–7.44 (m, 2H, ArH).

^{13}C-NMR: δ = 21.3 ($NCH_2CH_2CH_2$), 24.3 (NCH_2CH_2), 31.5 (CCH_2), 44.1 (NCH_2), 48.4 (NCHCHCO), 52.0 (CCHCO), 52.4 (OCH_3), 66.0 (NCH), 70.6 (CCO_2Me), 125.5, 127.1, 128.4, 128.8, 136.2, 136.4 (ArC, C=C), 169.0, 169.4 (2xNCO), 172.4 (CO_2Me).

MS (EI): *m/z* = 355 (M^+, 5%), 297 (20), 296 (100), 225 (10), 224 (50).

HRMS (DIP) calcd. for $C_{20}H_{21}NO_5$: 355.1420; found 355.1426.

Dimethyl (2*S,3*S**,8a*R**)-3-[(*E*)-styryl]hexahydroindolizine-2,8a(1*H*)-dicarboxylate (*endo*-5)**

Yield: 43 mg (57%), yellow solid, mp 189-190 °C (Et_2O).

IR (neat): 2977, 2946, 1745, 1474 cm^{-1}.

^{1}H-NMR: δ = 1.11–1.17 (m, 1H, $NCH_2CH_2CH_2$), 1.33–1.51 (m, 2H, NCH_2CH_2, $NCH_2CH_2CH_2$), 1.52–1.60 (m, 1H, NCH_2CH_2), 1.65 – 1.75 (m, 1H, CCH_2), 2.15 (dd, *J* = 12.4, 8.0, Hz, 1H, $CHCH_2$), 2.24 (dd, *J* = 12.4, 10.8, Hz, 1H, $CHCH_2$), 2.40 (dtd, *J* = 12.4, 3.3, 1.2 Hz, 1H, CCH_2), 2.68 (td, *J* = 11.7, 3.3 Hz, 1H, NCH_2), 2.80 (dd, *J* = 11.7, 3.9 Hz, 1H, NCH_2), 3.20 (td, *J* = 10.5, 8.0 Hz, 1H, NCHCH), 3.53 (s, 3H, $CHCO_2CH_3$), 3.70 (s, 3H, CCO_2CH_3), 4.10 (ddd, *J* = 10.8, 8.8, 8.0 Hz, 1H, NCH), 5.91 (dd, *J* = 15.8, 8.8 Hz, 1H, PhCHCH), 6.53 (d, *J* = 15.8 Hz, 1H, PhCH), 7.15–7.21 (m, 1H, ArH), 7.23–7.30 (m, 2H, ArH), 7.31–7.38 (m, 2H, ArH).

^{13}C-NMR: δ = 22.0 ($NCH_2CH_2CH_2$), 25.3 (NCH_2CH_2), 34.6 (CCH_2CH_2), 39.0 (CCH_2CH), 43.4 (NCH_2), 45.5 ($CHCO_2Me$), 51.2 (OCH_3), 51.6 (OCH_3), 65.2 (NCH), 68.6 (CCO_2Me), 126.4, 127.5, 128.5, 129.7, 132.9, 136.9 (ArC, C=C), 173.3 (CO_2Me), 175.6 (CO_2Me).

MS (EI): *m/z* = 343 (M^+, 2%), 285 (20), 284 (100), 224 (12).

HRMS (DIP) calcd. for $C_{20}H_{25}NO_4$: 343.1784; found: 343.1800.

Trimethyl (1*S,2*S**,3*S**,8a*R**)-3-[(*E*)-styryl]hexahydroindolizine-1,2,8a(1*H*)-tricarboxylate (*endo*-6)**

Yield: 62 mg (70%), pale yellow oil.

IR (neat): 1732, 1201, 1167 cm^{-1}.

^{1}H-NMR: δ = 1.24 (tdd, *J* = 13.5, 8.8, 3.9 Hz, 1H, $NCH_2CH_2CH_2$), 1.46–1.65 (m, 3H, NCH_2CH_2, $NCH_2CH_2CH_2$), 1.68–1.79 (m, 1H, CCH_2), 2.40–2.72 (m, 2H, NCH_2, CCH_2), 2.76–2.85 (m, 1H, NCH_2), 3.43 (d, *J* = 10.8 Hz, 1H, CCH), 3.55 (s, 3H, $CHCO_2CH_3$), 3.68 (s, 3H, $CHCO_2CH_3$), 3.69 (dd, *J* = 10.8, 10.5 Hz, 1H, NCHCH), 3.70 (s, 3H, CCO_2CH_3), 4.19 (dd, *J* = 10.5, 9.1 Hz, 1H, NCH), 5.87 (dd, = 15.8, 9.1 Hz, 1H, PhCHCH), 6.55 (d, *J* = 15.8 Hz, 1H, PhCH), 7.19–7.37 (m, 5H, ArH).

^{13}C-NMR: δ = 21.8 ($NCH_2CH_2CH_2$), 25.1 (NCH_2CH_2), 34.5 (CCH_2), 43.8 (NCH_2), 48.2 (CCH), 51.7 (NCHCH), 52.1 (OCH_3), 52.3 (OCH_3), 55.0 (OCH_3), 64.4 (NCH), 70.9 (CCO_2Me), 126.6, 127.8, 128.7, 128.9, 133.7, 136.8 (ArC, C=C), 171.0 (CCO_2Me), 172.3 ($CHCO_2Me$), 172.8 ($CHCO_2Me$).

MS (EI): *m/z* = 401 (M^+, 5%), 343 (21), 342 (100), 310 (13), 282 (38), 250 (23).

HRMS (DIP) calcd. for $C_{22}H_{27}NO_6$: 401.1838; found 401.1849.

Methyl (1*S,2*S**,3*S**,8a*R**)-2-nitro-1-phenyl-3-[(*E*)-styryl]hexahydroindolizine-8a(1*H*)-carboxylate (*endo*-7)**

Yield: 15 mg (17%), brown sticky oil.

IR (neat): 1734, 1556, 1223 cm^{-1}.

^{1}H-NMR: δ = 1.21–1.38 (m, 2H, $NCH_2CH_2CH_2$), 1.50–1.70 (m, 2H, NCH_2CH_2), 1.74–1.87 (m, 1H, CCH_2), 2.24–2.31 (m, 1H, CCH_2), 2.96–3.02 (m, 2H, NCH_2), 3.86 (s, 3H, OCH_3), 3.93 (dd, *J* = 8.4, 5.2 Hz, 1H, NCHCHPh), 4.08 (t, *J* = 8.4 Hz, 1H, NCH), 5.22 (d, *J* = 5.2, 1H, $CHNO_2$), 6.15 (dd, *J* = 15.8, 8.4 Hz, 1H, PhCHCH), 6.40 (d, *J* = 15.8 Hz, 1H, PhCH), 7.06–7.12 (m, 2H, ArH), 7.22–7.39 (m, 8H, ArH).

^{13}C-NMR: δ = 21.6 (NCH$_2$CH$_2$*C*H$_2$), 24.6 (NCH$_2$*C*H$_2$), 31.5 (*C*CH$_2$), 43.7 (NCH*C*HPh), 52.4 (N*C*H$_2$), 54.5 (O*C*H$_3$), 71.5 (N*C*H), 72.0 (*C*CO$_2$Me), 97.9 (*C*HNO$_2$), 126.7, 127.7, 128.0, 128.2, 128.7, 129.1, 129.5, 134.7, 136.5, 138.1 (Ar*C*, *C*=*C*), 172.8 (*C*O$_2$Me).

MS (EI): *m/z* = 360 (M$^+$-NO$_2$, 91%), 348 (13), 347 (51), 302 (25), 301 (100), 300 (39), 224 (18), 210 (45), 198 (13).

HRMS (DIP) calcd. for $C_{24}H_{26}N_2O_4$(-NO$_2$): 360.1983; found: 360.1974.

Methyl (1*S,2*R**,3*S**,8a*R**)-1-nitro-2-phenyl-3-[(*E*)-styryl]hexahydroindolizine-8a(1*H*)-carboxylate (*exo*-8)**

Yield: 62 mg (55%), colorless prisms, mp 146-148 °C (Et$_2$O).

IR (neat): 1543, 1354 cm^{-1}.

^{1}H-NMR: δ = 1.08–1.32 (m, 2H, NCH$_2$CH$_2$C*H*$_2$), 1.47–1.65 (m, 2H, NCH$_2$C*H*$_2$), 1.69–1.82 (m, 1H, CC*H*$_2$), 2.21–2.56 (m, 2H, NC*H*$_2$, CC*H*$_2$), 2.86–2.93 (m, 1H, NC*H*$_2$), 3.43 (s, 3H, OC*H*$_3$), 4.09 (d, *J* = 10.0 Hz, 1H, CC*H*Ph), 4.69 (dd, *J* = 9.6, 8.4 Hz, 1H, NC*H*), 5.74 (dd, *J* = 10.0, 9.6 Hz, 1H, C*H*NO$_2$), 5.90 (dd, *J* = 15.8, 8.4 Hz, 1H, PhCHC*H*), 6.72 (d, *J* = 15.8 Hz, 1H, PhC*H*), 7.08–7.21 (m, 2H, Ar*H*), 7.27–7.34 (m, 6H, Ar*H*), 7.35–7.42 (m, 2H, Ar*H*).

^{13}C-NMR: δ = 21.9 (NCH$_2$CH$_2$*C*H$_2$), 25.1 (NCH$_2$*C*H$_2$), 33.6 (*C*CH$_2$), 44.6 (*C*CHPh), 51.1 (N*C*H$_2$), 57.9 (O*C*H$_3$), 65.7 (N*C*H), 73.4 (*C*CO$_2$Me), 91.1 (*C*HNO$_2$), 126.0, 127.0, 127.9, 127.9, 128.2, 128.4, 128.6, 128.8, 133.5, 136.3 (Ar*C*, *C*=*C*), 173.6 (*C*O$_2$Me).

MS (EI): *m/z* = 360 (M$^+$-NO$_2$, 57%), 348 (19), 347 (80), 301 (33), 300 (100).

HRMS (DIP) calcd. for $C_{24}H_{26}N_2O_4$(-NO$_2$): 360.1983; found: 360.1974.

Methyl (1*R,2*S**,3*S**,8a*R**)-2-benzoyl-1-phenyl-3-[(*E*)-styryl]hexahydroindolizine-8a(1*H*)-carboxylate (*endo*-9) and Methyl (1*S**,2*R**,3*S**,8a*R**)-2-benzoyl-1-phenyl-3-[(*E*)-styryl]hexahydroindolizine-8a(1*H*)-carboxylate (*exo*-9)**

Yield: 68 mg (66%), colorless sticky oil.

IR (neat): 1718, 1682, 1447, 1207 cm^{-1}.

^{1}H-NMR: δ (mixture of *endo*:*exo* 0.33:1) = 1.13–1.19 (m, *exo*-2H, NCHCHC*H*$_2$), 1.20–1.24 (m, *endo*-2H, NCHCHC*H*$_2$), 1.49–1.56 (m, *endo*-2H, NCHC*H*$_2$, *exo*-2H, NCHC*H*$_2$), 1.68–1.81 (m, *endo*-1H, CC*H*$_2$, *exo*-1H, CC*H*$_2$), 1.88–1.93 (m, *endo*-2H, NC*H*$_2$, CC*H*$_2$), 2.36 (dt, *J* = 12.3, 3.4 Hz, *exo*-1H, CC*H*$_2$), 2.49 (td, *J* = 11.4, 4.0 Hz, *exo*-1H, NC*H*$_2$), 2.87 (dd, *J* = 15.3, 3.8 Hz, *exo*-1H, NC*H*$_2$), 2.96–2.92 (m, *endo*-1H, NC*H*$_2$), 3.42 (s, *exo*-3H, OC*H*$_3$), 3.90 (dd, *J* = 8.5, 6.3 Hz, *endo*-1H, NCHC*H*), 3.93 (s, *endo*-3H, OC*H*$_3$), 4.03 (d, *J* = 11.2 Hz, *exo*-1H, CC*H*), 4.13 (dd, *J* = 8.5, 8.3 Hz, *endo*-1H, NC*H*), 4.26 (d, *J* = 6.3 Hz, *endo*-1H, CC*H*), 4.58 (dd, *J* = 10.2, 8.8 Hz, *exo*-1H, NC*H*), 4.85 (dd, *J* = 11.2, 10.2 Hz, *exo*-1H, NCHC*H*), 5.71 (dd, *J* = 15.7, 8.8 Hz, *exo*-1H, PhCHC*H*), 6.20 (dd, *J* = 15.9, 8.3 Hz, *endo*-1H, PhCHC*H*), 6.30 (d, *J* = 15.7 Hz, *exo*-1H, PhC*H*), 6.37 (d, *J* = 15.9 Hz, *endo*-1H, PhC*H*), 7.04–7.23 (m, *endo*-9H, *exo*-9H, Ar*H*), 7.28–7.46 (m, *endo*-4H, *exo*-4H, Ar*H*), 7.83–7.92 (m, *exo*-2H, Ar*H*), 8.01–8.08 (m, *endo*-2H, Ar*H*).

^{13}C-NMR: δ (major diastereoisomer) = 22.3 (NCH$_2$CH$_2$*C*H$_2$), 25.4 (NCH$_2$*C*H$_2$), 33.8 (*C*CH$_2$), 44.0 (N*C*H$_2$), 50.8 (*C*CHPh), 51.9 (*C*HCO), 55.2 (O*C*H$_3$), 65.8 (N*C*H), 73.6 (*C*CO$_2$Me), 126.5, 126.6, 127.4, 127.5, 128.1, 128.1, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6, 128.7, 128.9, 129.9, 133.0, 133.0, 136.7, 137.0, 138.1 (Ar*C*, *C*=*C*), 174.6 (*C*O$_2$Me), 198.5 (*C*O).

MS (EI): *m/z* = 465 (M$^+$, 3%), 407 (30), 406 (100), 360 (8).

HRMS (DIP) calcd. for $C_{31}H_{31}NO_3$: 465.2324; found 465.2334.

General procedure for the synthesis of indolizidine 11

To a solution of the amine **10** (40 mg, 0.21 mmol) in toluene (1 mL), the corresponding aldehyde (1 equiv, 0.21 mmol) and the dipolarophile (1 equiv, 0.21 mmol) were added. The resulting mixture was stirred at 70 °C for 17 h. The solvent was evaporated and the heterocycles were separated by flash chromatography (silica-gel) in good chemical yields (see text).

Methyl (3a*S,4*S**,11a*R**,11b*R**)-1,3-dioxo-2-phenyl-4-[(*E*)-styryl]-1,2,3,3a,4,6,11,11b-octahydro-11a*H*-pyrrolo[3',4':3,4]pyrrolo[1,2-*b*]isoquinoline-11a-carboxylate (*endo*-11)**

Yield: 68 mg (65%), white solid, mp 209-212 °C (Et$_2$O).

IR (neat): 1703, 1494, 1396, 1203 cm^{-1}.

^{1}H-NMR: δ = 2.98 (d, *J* = 16.8 Hz, 1H, CC*H*$_2$), 3.44 (d, *J* = 8.0 Hz, 1H, CC*H*CO), 3.52 (d, *J* = 16.8 Hz, 1H, CC*H*$_2$), 3.55 (dd, *J* = 8.2, 8.0 Hz, 1H, NCHC*H*), 3.72 (s, 3H, OC*H*$_3$), 3.88 (dd, *J* = 8.6, 8.2 Hz, 1H, NC*H*), 3.95 (d, *J* = 18.1 Hz, 1H, NC*H*$_2$), 4.31 (d, *J* = 18.1 Hz, 1H, NC*H*$_2$), 6.22 (dd, *J* = 15.7, 8.6 Hz, 1H, PhCHC*H*), 6.62 (d, *J* = 15.7 Hz, 1H, PhC*H*), 6.94–7.06 (m, 1H, Ar*H*), 7.09–7.21 (m, 3H, Ar*H*), 7.23–7.32 (m, 5H, Ar*H*), 7.37–7.48 (m, 5H, Ar*H*).

^{13}C-NMR: δ = 30.2 (*C*CH$_2$), 45.4 (N*C*H$_2$), 47.4 (NCH*C*HCO), 52.8 (*C*CHCO), 53.7 (O*C*H$_3$), 64.8 (N*C*H), 68.8 (*C*CO$_2$Me), 126.2, 126.5, 126.6, 126.9, 127.1, 128.2, 128.7, 128.8, 129.0, 129.2, 130.6, 131.9, 135.2, 136.3 (Ar*C*, *C*=*C*), 170.9 (*C*O), 174.2 (*C*O), 174.6 (*C*O$_2$Me).

MS (EI): *m/z* = 478 (M$^+$, <1%), 420 (31), 419 (100), 180 (4).

HRMS (DIP) calcd. for $C_{30}H_{26}N_2O_4$: 478.1893; found 478.1883.

General procedure for the synthesis of indolizidines 12-13

To a solution of the pipecolic acid alkyl ester hydrochloride **1** (0.22 mmol) in toluene (1 mL), Et$_3$N (1 equiv, 30.5 µL, 0.22 mmol), the corresponding aldehyde (1 equiv, 0.22 mmol) and the dipolarophile (1 equiv, 0.22 mmol) were added. The resulting mixture was stirred at 70 °C for 17 h. EtOAc (5mL) and H$_2$O (5 mL) were added and the organic phase was separated, dried (MgSO$_4$), and evaporated to obtain the crude product which was purified by flash chromatography (silica-gel) in good chemical yields (see text).

Methyl (3a*S,4*R**,9a*R**,9b*R**)-1,3-dioxo-4-phenyloctahydro-3*H*,9a*H*-furo[3,4-*a*]indolizine-9a-carboxylate (*endo*-12)**

Yield: 20 mg (27%), yellow sticky oil.

IR (neat): 2927, 2856, 1781, 1733, 1209, 922, 734 cm^{-1}.

^{1}H-NMR: δ = 1.53–1.39 (m, 2H, NCHCHC*H*$_2$), 1.55–1.65 (m, 1H, NCH$_2$C*H*$_2$), 1.83 (dt, *J* = 13.8, 3.5 Hz, 1H, NCH$_2$C*H*$_2$), 1.96 (td, *J* = 13.4, 3.9 Hz, 1H, CC*H*$_2$), 2.45–2.55 (m, 1H, CC*H*$_2$), 2.65 (dd, *J* = 11.9, 4.3 Hz, 1H, NC*H*$_2$), 2.78 (td, *J* = 11.9, 3.3 Hz, 1H, NC*H*$_2$), 3.61 (dd, *J* = 9.4, 8.3 Hz, 1H, PhCHC*H*), 3.69 (d, *J* = 8.3 Hz, 1H, CC*H*CO), 3.79 (s, 3H, OC*H*$_3$), 4.75 (d, *J* = 9.4 Hz, 1H, PhC*H*), 7.22–7.28 (m, 2H, Ar*H*), 7.29–7.40 (m, 3H, Ar*H*).

^{13}C-NMR: δ = 21.4 (NCH$_2$CH$_2$*C*H$_2$), 24.6 (NCH$_2$*C*H$_2$), 31.0 (*C*CH$_2$), 44.1 (N*C*H$_2$), 49.6 (NCH*C*HCO), 52.2 (O*C*H$_3$), 52.1 (*C*CHCO), 67.7 (N*C*H), 70.9 (*C*CO$_2$Me), 127.8, 128.6, 128.8, 128.9, 130.2, 136.5 (Ar*C*, *C*=*C*), 169.0, 169.2 (2xN*C*O), 172.9 (*C*O$_2$Me).

MS (EI): *m/z* = 329 (M$^+$, <1%), 271 (18), 270 (100), 220 (8), 198 (67).

HRMS (DIP) calcd. for $C_{18}H_{19}NO_5$(-CO$_2$Me): 270.1130; found 270.1132.

Ethyl (3a*S,4*R**,9a*R**,9b*R**)-4-(furan-2-yl)-2-methyl-1,3-dioxodecahydro-9a*H*-pyrrolo[3,4-*a*]indolizine-9a-carboxylate (*endo*-13)**

Yield: 30 mg (39%), white prisms, mp 121-124 °C (Et$_2$O).

IR (neat): 2936, 1699, 1432, 1377, 1281, 1230, 1148, 1006, 755 cm^{-1}.

^{1}H-NMR: δ = 1.21 (dt, *J* = 13.3, 3.8 Hz, 1H, NCH$_2$CH$_2$C*H*$_2$), 1.32 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$), 1.44 (ddd, *J* = 12.4, 5.3, 4.1 Hz, 1H, NCH$_2$CH$_2$C*H*$_2$), 1.51–1.61 (m, 1H, NCH$_2$C*H*$_2$), 1.78 (dd, *J* = 13.9, 6.0 Hz, 1H, NCH$_2$C*H*$_2$), 1.87 (td, *J* = 13.2, 3.7 Hz, 1H, CC*H*$_2$), 2.53 (ddt, *J* = 13.2, 4.6, 2.1 Hz, 1H, CC*H*$_2$), 2.56–2.65 (m, 1H, NC*H*$_2$), 2.79 (td, *J* = 11.7, 3.5 Hz, 1H, NC*H*$_2$), 2.93 (s, 3H, NC*H*$_3$), 3.28–3.40 (m, 2H, NCHC*H*, CC*H*), 4.23 (q, *J* = 7.2 Hz, 2H, C*H*$_2$CH$_3$), 4.80 (d, *J* = 8.2 Hz, 1H, NC*H*), 6.24 (dd, *J* = 3.2, 0.8 Hz, 1H, OCHCHC*H*), 6.33 (dd, *J* = 3.2, 1.9 Hz, 1H, OCHC*H*), 7.38 (dd, *J* = 1.9, 0.8 Hz, 1H, OC*H*).

^{13}C-NMR: δ = 14.5 (CH$_2$*C*H$_3$), 21.6 (NCH$_2$CH$_2$*C*H$_2$), 24.7 (NCH$_2$*C*H$_2$), 25.1 (NC*H*$_3$), 30.9 (*C*CH$_2$), 44.3 (N*C*H$_2$), 47.0 (NCH*C*HCO), 51.3 (*C*CHCO), 61.0 (*C*H$_2$CH$_3$), 61.2 (N*C*H), 69.9 (*C*CO$_2$Et), 109.2 (OCH*C*H), 110.3 (O*C*CH), 142.8 (O*C*H), 151.1 (O*C*CH), 173.1, 175.0 (2xN*C*O), 175.8 (*C*O$_2$Et).

MS (EI): *m/z* = 346 (M$^+$, <1%), 274 (16), 273 (100).

HRMS (DIP) calcd. for $C_{18}H_{22}N_2O_5$: 346.1529; found: 346.1519.

General procedure for the synthesis of indolizidines 15-21

To a solution of the pipecolinic acid **13** (40 mg, 0.31 mmol) in toluene (1 mL), the corresponding aldehyde (1 equiv, 0.31 mmol) and the dipolarophile (1 equiv, 0.31 mmol) were added. The resulting mixture was stirred in a pressure tube at 120 °C for 17 h. The solvent was evaporated and the mixture was separated by flash chromatography affording the corresponding cycloadducts.

(3a*S,4*S**,9a*R**,9b*R**)-2-Methyl-4-[(*E*)-styryl]octahydro-1*H*-pyrrolo[3,4-*a*]indolizine-1,3(2*H*)-dione (*endo*-15) and (3a*R**,4*R**,9a*R**,9b*S**)-2-Methyl-4-[(*E*)-styryl]octahydro-1*H*-pyrrolo[3,4-*a*]indolizine-1,3(2*H*)-dione (*exo'*-15)**

Yield: 57 mg (59%), brown sticky oil.

IR (neat): 2938, 1697, 1433, 1382, 1281, 1239, 1138, 1039, 965, 749, 694 cm^{-1}.

^{1}H-NMR: δ (mixture of *endo*:*exo'* 1:0.9) = 1.11–1.28 (m, *endo*-2H, NCHCH_2, *exo'*-1H, NCHCH_2), 1.34–1.45 (m, *endo*-1H, NCH$_2$CH_2, *exo'*-1H, NCHCH_2), 1.50–1.66 (m, *endo*-1H, NCH$_2$CH_2, *exo'*-1H, NCH$_2$CH_2), 1.69–1.90 (m, *endo*-1H, NCH$_2$CH$_2$CH_2, *exo'*-2H, NCH$_2$CH$_2$CH_2, CH$_2$CH_2), 1.97–2.12 (m, *endo*-1H, NCH$_2$CH$_2$CH_2, *exo'*-1H, NCH$_2$CH$_2$CH_2), 2.18–2.36 (m, *J* = m, *endo*-1H, NCH_2, *exo'*-1H, NCH_2), 2.79–2.93 (m, *endo*-2H, NC*H*CH$_2$, NCH_2, *exo'*-1H, NC*H*CH$_2$), 2.98–3.02 (m, *endo*-3H, NCH_3, *exo'*-4H, NCH_3, NC*H*CH), 3.03–3.08 (m, *endo*-1H, NCHC*H*, *exo'*-1H, NCH_2), 3.10–3.32 (m, *endo*-1H, CH$_2$CHC*H*, *exo'*-2H, NCHC*H*, CH$_2$CHC*H*), 4.13 (d, *J* = 9.6 Hz, *endo*-1H, NC*H*CH), 6.12 (dd, *J* = 15.7, 9.2 Hz, *exo'*-1H, PhCHC*H*), 6.26 (dd, *J* = 15.7, 9.6 Hz, *endo*-1H, PhCHC*H*), 6.61 (d, *J* = 15.7 Hz, *exo'*-1H, PhC*H*), 6.64 (d, *J* = 15.7 Hz, *endo*-1H, PhC*H*), 7.46 – 7.21 (m, *endo*-5H, *exo'*-5H, Ar*H*).

^{13}C-NMR: δ (mixture of *endo*:*exo'*) = 24.4, 24.4 (2xNCH$_2$CH$_2$CH$_2$), 24.8, 25.0 (2xNCH$_2$CH_2), 25.0, 25.1 (2xNCH_3), 28.0, 28.9 (2xNCHCH_2), 47.1, 47.6, 48.2 (3xCHCO), 48.5 (NCH_2), 50.0 (CHCO), 51.8 (NCH_2), 60.5, 65.9, 67.8, 70.5 (4xNC*H*), 125.0, 126.5, 126.8, 127.9, 128.0, 128.2, 128.6, 128.7, 134.3, 134.5, 136.3, 136.7 (Ar*C*, 2x*C*=*C*), 176.4, 176.7, 176.9, 178.7 (4x*C*O).

MS (EI): *m/z* = 310 (M^+, 18%), 309 (17), 220 (14), 219 (100), 199 (20), 198 (17), 115 (10).

HRMS (DIP) calcd. for $C_{19}H_{22}N_2O_2$: 310.1681; found: 310.1668.

(3a*R,4*S**,9a*R**,9b*S**)-2-Methyl-4-[(*E*)-styryl]octahydro-1*H*-pyrrolo[3,4-*a*]indolizine-1,3(2*H*)-dione (*exo*-15)**

Yield: 21 mg (22%), yellow sticky oil.

IR (neat): 2919, 2850, 1698, 1435, 1283, 1122, 1074, 1010, 966, 732, 694 cm^{-1}.

^{1}H-NMR: δ = 1.21–1.30 (m, 1H, NCHCH_2), 1.44–1.53 (m, 4H, NCH$_2$CH_2, NCHCH_2), 1.55–1.69 (m, 1H, NCH$_2$CH_2), 1.78–1.89 (m, 2H, NCH$_2$CH$_2$CH_2), 2.62–2.75 (m, 1H, NCH_2), 2.88 (dd, *J* = 8.2, 2.1 Hz, 1H, CH$_2$CHC*H*), 2.91–2.98 (m, 1H, NCH_2), 3.00 (s, 1H, NCH_3), 3.38 (dd, *J* = 8.2, 8.0 Hz, 1H, NCHC*H*CO), 3.44–3.51 (m, 1H, NCH_2), 4.10 (dd, *J* = 9.5, 8.0 Hz, 1H, NC*H*CHCO), 5.93 (dd, *J* = 15.7, 9.5 Hz, 1H, PhCHC*H*), 6.64 (d, *J* = 15.7 Hz, 1H, PhC*H*), 7.23–7.42 (m, 5H, Ar*H*).

^{13}C-NMR: δ = 19.2 (NCH$_2$CH$_2$CH_2), 24.5 (NCH$_2$CH_2), 25.2 (NCH_3), 27.0 (NCHCH_2), 45.5 (NCH_2), 48.7 (NCHCHCO), 50.5 (NCHCHCO), 62.1, 62.1 (2xNC*H*), 126.5, 126.8, 127.9, 128.6, 134.6, 136.6 (Ar*C*, *C*=*C*), 176.5, 178.8 (2xN*C*O).

MS (EI): *m/z* = 310 (M^+, 18%), 309 (16), 220 (14), 219 (100), 199 (9), 198 (12), 115 (9).

HRMS (DIP) calcd for $C_{19}H_{22}N_2O_2$: 310.1681; found: 310.1668.

(3a*S,4*S**,9a*R**,9b*R**)-2-Phenyl-4-[(*E*)-styryl]octahydro-1*H*-pyrrolo[3,4-*a*]indolizine-1,3(2*H*)-dione (*endo*-16)**

Yield: 31 mg (27%), yellow sticky oil.

IR (neat): 2941, 1708, 1498, 1381, 1185, 968, 849, 734 cm^{-1}.

^{1}H-NMR: δ = 1.15–1.29 (m, 2H, NCHCH_2CH$_2$), 1.38–1.47 (m, 1H, NCH$_2$CH_2), 1.54–1.63 (m, 1H, NCH$_2$CH_2), 1.77–1.85 (m, 1H, NCH$_2$CH$_2$CH_2), 2.02–2.13 (m, 1H, NCH$_2$CH$_2$CH_2), 2.34 (td, *J* = 11.5, 3.0 Hz, 1H, NCH_2), 2.85–2.92 (m, 1H, NCH_2), 2.96 (ddd, *J* = 10.8, 8.4, 2.7 Hz, 1H, NC*H*CH$_2$), 3.22 (dd, *J* = 7.9, 0.8 Hz, 1H, NCHC*H*CO), 3.43 (dd, *J* = 8.4, 7.9 Hz, 1H, CH$_2$CHC*H*), 4.25 (d, *J* = 9.5 Hz, 1H, NC*H*CHCO), 6.30 (dd, *J* = 15.7, 9.5 Hz, 1H, PhCHC*H*), 6.67 (d, *J* = 15.7 Hz, 1H, PhC*H*), 7.19–7.52 (m, 10H, Ar*H*).

^{13}C-NMR: δ = 24.5 (NCH$_2$CH$_2$CH_2), 25.2 (NCH$_2$CH_2), 29.3 (NCHCH_2), 47.6 (NCHCHCO), 48.6 (NCH_2), 50.2 (NCHCHCO), 60.8 (NC*H*), 68.2 (NC*H*), 124.8, 126.2, 126.9, 128.1, 128.6, 128.8, 129.1, 132.3, 134.4, 136.4 (Ar*C*, *C*=*C*), 176.0, 177.8 (2xN*C*O).

MS (EI): *m/z* = 372 (M^+, 23%), 371 (16), 282 (19), 281 (100), 199 (32), 198 (18), 115 (10).

HRMS (DIP) calcd. for $C_{24}H_{24}N_2O_2$: 372.1838; found: 372.1828.

(3a*R,4*S**,9a*R**,9b*S**)-2-Phenyl-4-[(*E*)-styryl]octahydro-1*H*-pyrrolo[3,4-*a*]indolizine-1,3(2*H*)-dione (*exo*-16)**

Yield: 17 mg (15%), prisms, mp 133-137 °C (Et_2O).

IR (neat): 2930, 1705, 1498, 1384, 1189, 974, 749 cm^{-1}.

^{1}H-NMR: δ = 1.25–1.34 (m, 2H, NCHCH_2), 1.46–1.62 (m, 2H, NCH$_2$CH_2), 1.69–1.76 (m, 1H, NCH$_2$CH$_2$CH_2), 1.79–1.95 (m, 1H, NCH$_2$CH$_2$CH_2), 2.66–2.79 (m, 1H, NCH_2), 2.93–3.02 (m, 1H, NC*H*CH$_2$), 3.06 (dd, *J* = 8.4, 2.4 Hz, 1H, CH$_2$CHC*H*), 3.56 (dd, *J* = 8.4, 8.2 Hz, 1H, NCHC*H*CO), 3.53–3.59 (m, 1H, NCH_2), 4.21 (dd, *J* = 9.1, 8.2 Hz, 1H, NC*H*CHCO), 6.05 (dd, *J* = 15.7, 9.1 Hz, 1H, PhCHC*H*), 6.69 (d, *J* = 15.7 Hz, 1H, PhC*H*), 7.23–7.46 (m, 10H, Ar*H*).

^{13}C-NMR: δ = 19.7 (NCH$_2$CH$_2$CH_2), 24.5 (NCH$_2$CH_2), 27.4 (NCHCH_2), 45.8 (NCH_2), 48.7 (NCHCHCO), 50.6 (NCHCHCO), 62.5 (NC*H*), 62.8 (NC*H*), 125.9, 126.6, 126.9, 128.0, 128.6, 128.7, 129.2, 132.1, 134.7, 136.6 (Ar*C*, *C*=*C*), 175.5, 177.8 (2xN*C*O).

MS (EI): *m/z* = 372 (M^+, 23%), 371 (13), 282 (19), 281 (100), 199 (15), 198 (14).

HRMS (DIP) calcd. for $C_{24}H_{24}N_2O_2$: 372.1838; found: 372.1828.

Dimethyl (1*S,2*S**,3*S**,8a*R**)-3-[(*E*)-styryl]octahydroindolizine-1,2-dicarboxylate (*endo*-17) and dimethyl (1*R**,2*R**,3*R**,8a*R**)-3-[(*E*)-styryl]octahydroindolizine-1,2-dicarboxylate (*exo'*-17)**

Yield: 37 mg (35%), yellow oil.

IR (neat): 2934, 2853, 1733, 1436, 1300, 1196, 1168, 1011, 968, 749, 693 cm^{-1}.

^{1}H-NMR: δ (mixture of *endo*:*exo'* 1:0.75, difficult assignment) = 1.04–1.41 (m, 4H), 1.49 (tt, *J* = 7.1, 3.6 Hz, 3H), 1.64–1.71 (m, 1H), 1.78 (td, *J* = 9.2, 7.4, 4.2 Hz, 2H), 1.87–1.96 (m, 1H), 2.36–2.50 (m, 2H), 2.80–2.96 (m, 3H), 3.08 (dd, *J* = 7.8, 7.1 Hz, 1H), 3.15 (ddd, *J* = 11.5, 8.9, 2.9 Hz, 1H), 3.27 (dd, *J* = 7.1, 4.2 Hz, 1H), 3.55 (s, 2H), 3.71 (s, *J* = 1.0 Hz, 5H), 3.75 (s, 2H), 3.88 (t, *J* = 8.1 Hz, 1H), 4.03–4.15 (m, 2H), 6.09 (dd, *J* = 15.7, 9.8 Hz, 1H), 6.28 (dd, *J* = 15.7, 9.5 Hz, 1H), 6.54 (d, *J* = 15.7 Hz, 1H), 6.57 (d, *J* = 15.7 Hz, 1H), 7.22–7.35 (m, 7H), 7.36–7.42 (m, 2H).

^{13}C-NMR: δ (mixture of *endo*:*exo'*, difficult assignment) = 23.4, 23.7, 24.0, 24.3, 27.3, 30.5, 47.6, 48.0, 48.1, 49.4, 51.5, 51.9, 52.0, 52.3, 52.3, 61.3, 63.3, 66.3, 67.2, 124.8, 126.6, 127.8, 127.8, 128.4, 132.2, 134.7, 136.6, 172.2, 173.1, 173.7, 173.8.

MS (EI): *m/z* = 343 (M^+, 33%), 284 (35), 282 (19), 253 (15), 252 (100), 250 (17), 199 (39), 198 (24), 115 (17).

HRMS (DIP) calcd. for $C_{20}H_{25}NO_4$: 343.1784; found: 343.1785.

Dimethyl (1*S,2*S**,3*R**,8a*R**)-3-((*E*)-styryl)octahydroindolizine-1,2-dicarboxylate (*endo'*-17) and Dimethyl (1*R*,2*R*,3*S*,8a*R*)-3-[(*E*)-styryl]octahydroindolizine-1,2-dicarboxylate (*exo*-17)**

Yield: 43 mg (40%), yellow oil.

IR (neat): 2944, 2854, 1733, 1436, 1196, 1167, 1005, 969, 746, 693 cm^{-1}.

^{1}H-NMR: δ (mixture of *endo'*:*exo* 0.65:1, difficult assignment) = 1.06–1.25 (m, 2H), 1.43 (tdd, *J* = 12.4, 10.8, 3.6 Hz, 2H), 1.58 (q, *J* = 3.4 Hz, 2H), 1.76–1.91 (m, 4H), 1.98–2.07 (m, 1H), 2.19 (td, *J* = 10.4, 2.5 Hz, 1H), 2.43 (ddd, *J* = 10.8, 8.3, 2.3 Hz, 1H), 2.95–3.05 (m, 1H), 3.12 (d, *J* = 10.9 Hz, 1H), 3.18–3.32 (m, 3H), 3.37 (dd, *J* = 8.5, 4.9 Hz, 1H), 3.43 (dd, *J* = 10.0, 7.8 Hz, 1H), 3.59 (s, 3H), 3.66 (s, 2H), 3.70 (s, 3H), 3.73 (s, 2H), 5.95 (dd, *J* = 15.8, 8.6 Hz, 1H), 6.21 (dd, *J* = 15.8, 8.5 Hz, 1H), 6.55 (dd, *J* = 15.8 Hz, 1H), 6.57 (dd, *J* = 15.8 Hz, 1H), 7.16–7.45 (m, 9H).

^{13}C-NMR: δ (mixture of *endo'*:*exo*, difficult assignment) = 24.0, 24.3, 24.7, 24.9, 28.4, 30.5, 49.5, 49.8, 50.7, 51.2, 51.2, 51.7, 51.9, 51.9, 52.0, 52.1, 66.4, 66.7, 69.3, 72.0, 126.5, 126.6, 127.2, 127.7, 127.8, 128.6, 128.6, 129.1, 134.0, 134.1, 136.7, 173.8, 173.1, 173.3, 173.8.

MS (EI): *m/z* = 343 (M^+, 34%), 284 (36), 253 (15), 252 (100), 199 (66), 198 (36), 192 (12), 157 (13), 156 (13), 122 (13), 115 (18).

HRMS (DIP) calcd. for $C_{20}H_{25}NO_4$: 343.1784; found: 343.1785.

Diisobutyl (1*S,2*S**,3*S**,8a*R**)-3-[(*E*)-styryl]octahydroindolizine-1,2-dicarboxylate (*endo*-18) and diisobutyl (1*R**,2*R**,3*R**,8a*R**)-3-[(*E*)-styryl]octahydroindolizine-1,2-dicarboxylate (*exo'*-18)**

Yield: 49 mg (37%), yellow oil.

IR (neat): 2961, 2935, 1731, 1469, 1379, 1169, 1002, 967, 748, 693 cm^{-1}.

^{1}H-NMR: δ (mixture of *endo*:*exo'* 1:0.5, difficult assignment) = 0.79 (s, 1H), 0.80 (s, 1H), 0.82 (s, 1H), 0.83 (s, 1H), 0.90 (s, 3H), 0.92 (s, 3H), 0.94 (s, 3H), 0.96 (s, 3H), 1.07–1.15 (m, 1H), 1.16–1.29 (m, 2H), 1.41–1.31 (m, 1H), 1.48 (dtt, *J* = 9.2, 6.3, 3.6 Hz, 2H), 1.69 (dd, *J* = 12.1, 3.3 Hz, 0H), 1.73–1.87 (m, 1H), 1.89–2.03 (m, 2H), 2.36–2.53 (m, 1H), 2.78–2.96 (m, 2H), 3.07 (t, *J* = 7.7 Hz, 1H), 3.16 (ddd, *J* = 11.3, 8.8, 2.8 Hz, 1H), 3.27 (dd, *J* = 7.4, 4.3 Hz, 1H), 3.62–3.81 (m, 1H), 3.82–3.99 (m, 4H), 4.03–4.19 (m, 1H), 6.09 (dd, *J* = 15.7, 9.8 Hz, 1H), 6.30 (dd, *J* = 15.7, 9.5 Hz, 1H), 6.52 (d, *J* = 15.6, Hz, 1H), 6.57 (d, *J* = 15.7, Hz, 1H), 7.16–7.47 (m, 8H).

^{13}C-NMR: δ (mixture of *endo*:*exo'* 1:0.5, difficult assignement) = 19.1, 19.2, 19.3, 23.9, 24.0, 24.4, 27.3, 27.7, 27.8, 27.9, 30.6, 47.7, 47.9, 48.2, 49.4, 51.8, 52.7, 61.3, 63.4, 66.2, 67.2, 71.1, 71.2, 125.1, 126.6, 127.7, 127.8, 128.6, 128.8, 129.2, 133.1, 134.6, 136.6, 136.7, 171.9, 172.8, 173.3.

MS (EI): *m/z* = 427 (M^+, 27%), 354 (15), 337 (22), 336 (100), 326 (39), 324 (13), 224 (22), 199 (38), 198 (21), 122 (15).

HRMS (DIP) calcd. for $C_{26}H_{37}NO_4$: 427.2723; found: 427.2720.

Diisobutyl (1*S,2*S**,3*R**,8a*R**)-3-[(*E*)-styryl]octahydroindolizine-1,2-dicarboxylate (*endo'*-18) and diisobutyl (1*R**,2*R**,3*S**,8a*R**)-3-[(*E*)-styryl]octahydroindolizine-1,2-dicarboxylate (*exo*-18)**

Yield: 50 mg (38%), yellow oil.

IR (neat): 2960, 1729, 1469, 1383, 1168, 1002, 968, 738, 692 cm^{-1}.

^{1}H-NMR: δ (mixture of *endo'*:*exo* 0.65:1 difficult assignment) = 0.74 (s, 1H), 0.75 (s, 1H), 0.76 (s, 1H), 0.77 (s, 1H), 0.85 (d, *J* = 0.8 Hz, 2H), 0.87 (d, *J* = 0.8 Hz, 2H), 0.92 (d, *J* = 0.6 Hz, 3H), 0.94 (d, *J* = 0.6 Hz, 3H), 0.95 (s, 2H), 0.97 (s, 2H), 1.12–1.31 (m, 2H), 1.37–1.67 (m, 3H), 1.71–2.03 (m, 7H), 2.04–2.11 (m, 1H), 2.20 (td, *J* = 10.4, 2.5 Hz, 1H), 2.43 (ddd, *J* = 10.7, 8.2, 2.4 Hz, 1H), 2.92–3.07 (m, 1H), 3.11 (d, *J* = 10.9 Hz, 1H), 3.18–3.48 (m, 4H), 3.69–3.82 (m, 2H), 3.84–3.95 (m, 4H), 5.97 (dd, *J* = 15.8, 8.7 Hz, 1H), 6.22 (dd, *J* = 15.8, 8.5 Hz, 1H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.56 (d, *J* = 15.8 Hz, 1H), 7.20–7.43 (m, 8H).

^{13}C-NMR: δ (mixture of *endo'*:*exo*, 0.65:1 difficult assignment) = 19.1, 19.2, 19.3, 24.1, 24.4, 24.8, 25.0, 27.6, 27.7, 27.8, 28.6, 30.6, 49.5, 49.9, 50.9, 51.2, 51.4, 51.7, 66.5, 66.6, 69.3, 71.0, 71.1, 71.2, 72.0, 126.6, 127.4, 127.7, 128.6, 129.6, 133.9, 134.1, 136.7, 136.8, 172.5, 172.9, 173.5.

MS (EI): *m/z* = 427 (M^+, 34%), 354 (23), 337 (22), 336 (100), 326 (47), 252 (17), 224 (24), 199 (80), 198 (35), 122 (17).

HRMS (DIP) calcd. for $C_{26}H_{37}NO_4$: 427.2723; found: 427.2720.

***tert*-Butyl (2*S**,3*S**,8a*R**)-3-[(*E*)-styryl]octahydroindolizine-2-carboxylate (*endo*-19)**

Yield: 20 mg (19%), yellow sticky oil.

IR (neat): 2931, 1723, 1366, 1148, 966 cm^{-1}.

^{1}H-NMR: δ = 1.23–1.39 (m, 2H, NCHC*H*$_2$CH$_2$), 1.43 (s, 9H, *t*-Bu), 1.47–1.78 (m, 5H, C*H*$_2$CHCO$_2$, NCH$_2$C*H*$_2$, NCH$_2$CH$_2$C*H*$_2$), 2.28 (ddd, *J* = 12.5, 10.3, 6.3 Hz, 1H, C*H*$_2$CHCO$_2$), 2.58 (td, *J* = 12.3, 3.3 Hz, 1H, NC*H*$_2$), 2.72 (ddd, *J* = 10.3, 7.4, 5.9 Hz, 1H, C*H*CO$_2$), 2.86–3.01 (m, 2H, NC*H*CH$_2$, NC*H*$_2$), 3.98 (dd, *J* = 9.2, 5.9 Hz, 1H, NC*H*), 6.17 (dd, *J* = 15.7, 9.2 Hz, 1H, PhCHC*H*), 6.54 (d, *J* = 15.7 Hz, 1H, PhC*H*), 7.18–7.43 (m, 5H, Ar*H*).

^{13}C-NMR: δ = 22.4 (NCH$_2$CH$_2$*C*H$_2$), 24.4 (NCH$_2$*C*H$_2$), 28.3 (*C*H$_3$), 29.9 (NCH*C*H$_2$CH$_2$), 34.7 (*C*H$_2$CHCO$_2$*t*-Bu), 46.8 (N*C*H$_2$), 49.6 (*C*HCO$_2$*t*-Bu), 59.8 (N*C*H), 66.0 (N*C*H), 80.6 (*C*Me$_3$), 126.5, 127.6, 128.7, 130.3, 132.7, 137.0 (Ar*C*, *C*=*C*), 174.0 (*C*O).

MS (EI): *m/z* = 327 (M^+, 18%), 271 (27), 270 (100), 254 (16), 226 (18), 180 (74).

HRMS (DIP) calcd. for $C_{21}H_{29}NO_2$: 327.2198; found: 327.2199.

(1*S,2*R**,3*S**,8a*R**)-1-Nitro-2-phenyl-3-[(*E*)-styryl]octahydroindolizine (*endo*-20)**

Yield: 19 mg (18%), brown sticky oil.

IR (neat): 2938, 2855, 1717, 1549, 1496, 1449, 1362, 1264, 1144, 967, 736, 694 cm^{-1}.

^{1}H-NMR: δ = 1.25–1.36 (m, 2H, NCHC*H*$_2$), 1.51–1.62 (m, 1H, NCHCHC*H*$_2$), 1.70–1.78 (m, 1H, NCHCHC*H*$_2$), 1.84–1.93 (m, 2H, NCHCHC*H*$_2$), 2.44 (ddd, *J* = 11.9, 8.9, 6.5 Hz, 1H, NC*H*$_2$), 2.90–3.03 (m, 1H, NC*H*$_2$), 3.30–3.42 (m, 1H, NC*H*CH$_2$), 4.25 (dd, *J* = 10.1, 7.8 Hz, 1H, NC*H*CHPh), 4.59 (dd, *J* = 7.8, 7.2 Hz, 1H, NCHC*H*Ph), 5.54 (dd, *J* = 8.4, 7.2 Hz, 1H, C*H*NO$_2$), 5.89 (dd, *J* = 15.6, 10.1 Hz, 1H, PhCHC*H*), 6.32 (d, *J* = 15.6 Hz, 1H, PhC*H*), 7.06–7.38 (m, 10H, Ar*H*).

^{13}C-NMR: δ = 23.8 (NCH$_2$CH$_2$*C*H$_2$), 23.9 (NCH$_2$*C*H$_2$), 26.0 (NCH*C*H$_2$), 48.4 (N*C*H$_2$), 51.7 (NCH*C*H), 62.3 (N*C*H), 69.2 (N*C*H), 93.0 (*C*NO$_2$), 124.8, 126.5, 127.4, 127.8, 128.6, 128.7, 128.8, 135.2, 136.6, 136.8 (Ar*C*, *C*=*C*).

MS (EI): *m/z* = 348 (M^+, 1%), 303 (25), 302 (100), 300 (11), 257 (10), 219 (15), 143 (11), 117 (20), 115 (21).

HRMS (DIP) calcd. for $C_{22}H_{24}N_2O_2$: 348.1838; found: 348.1825.

(3a*S,4*R**,9a*R**,9b*R**)-2,4-Diphenyloctahydro-1H-pyrrolo[3,4-*a*]indolizine-1,3(2*H*)-dione (*endo*-21)**

Yield: 58 mg (54%), white solid, mp 151-154 °C (Et_2O).

IR (neat): 2943, 2850, 1701, 1497, 1393, 1189, 848, 755, 693 cm^{-1}.

^{1}H-NMR: δ = 0.89–1.12 (m, 1H, NCH$_2$CH$_2$C*H*$_2$), 1.11–1.29 (m, 1H, NCH$_2$CH$_2$C*H*$_2$), 1.33–1.56 (m, 2H, NCHC*H*$_2$), 1.60–1.84 (m, 2H, NCH$_2$C*H*$_2$), 1.97–2.20 (m, 1H, NC*H*$_2$), 2.87 (ddt, *J* = 14.5, 6.4, 2.7 Hz, 2H, N*H*$_2$, NC*H*CH$_2$), 3.35–3.73 (m, 2H, PhCHC*H*, CH$_2$CHC*H*), 4.69 (d, *J* = 0.9 Hz, 1H, NC*H*Ph), 7.07–7.19 (m, 2H, Ar*H*), 7.30–7.54 (m, 8H, Ar*H*).

^{13}C-NMR: δ = 24.2 (NCH$_2$CH$_2$*C*H$_2$), 24.9 (NCH$_2$*C*H$_2$), 29.1 (NCH*C*H$_2$), 48.5 (N*C*H$_2$), 48.7 (NCH*C*HCO), 50.3 (NCH*C*HCO), 59.9 (N*C*H), 69.4 (N*C*H), 126.7, 128.0, 128.4, 128.6, 128.6, 128.7, 132.3, 136.6 (Ar*C*), 176.1, 178.1 (2xN*C*O).

MS (EI): *m/z* = 346 (M^+, 61%), 345 (48), 269 (22), 198 (12), 173 (57), 172 (100), 115 (14).

HRMS (DIP) calcd. for $C_{22}H_{22}N_2O_2$: 346.1681; found: 346.1668.

(3a*R,4*R**,9a*R**,9b*S**)-2,4-Diphenyloctahydro-1H-pyrrolo[3,4-*a*]indolizine-1,3(2*H*)-dione (*exo*-21)**

Yield: 26 mg (24%), yellow oil.

IR (neat): 2934, 2854, 1712, 1496, 1376, 1173, 734, 698 cm^{-1}.

^{1}H-NMR: δ = 1.29–1.39 (m, 2H, NCH$_2$CH$_2$C*H*$_2$), 1.58–1.64 (m, 1H, NCHC*H*$_2$), 1.82–1.97 (m, 2H, NCH$_2$C*H*$_2$), 2.22–2.41 (m, 2H, NC*H*CH$_2$, N*H*$_2$), 2.84 (d, *J* = 11 Hz, 1H, N*H*$_2$), 3.35–3.73 (m, 1H, NCHC*H*), 3.17 (dd, *J* = 9.3, 8.5 Hz, 1H, CH$_2$CHC*H*), 3.27 (dd, *J* = 9.3, 6.9 Hz, 1H, PhCHC*H*), 3.49 (d, *J* = 6.9 Hz, 1H, NC*H*Ph), 7.28–7.42 (m, 6H, Ar*H*), 7.44–7.53 (m, 4H, Ar*H*).

^{13}C-NMR: δ = 24.1 (NCH$_2$CH$_2$*C*H$_2$), 25.0 (NCH$_2$*C*H$_2$), 31.3 (NCH*C*H$_2$), 50.2 (NCH*C*HCO), 50.9 (N*C*H$_2$), 53.0 (NCH*C*HCO), 67.8 (N*C*H), 72.0 (N*C*H), 126.6, 127.8, 127.9, 128.1, 128.7, 128.9, 129.2, 131.9 (Ar*C*), 176.1, 176.6 (2xN*C*O).

MS (EI): *m/z* = 346 (M^+, 73%), 345 (56), 269 (23), 198 (20), 173 (55), 172 (100), 115 (15).

HRMS (DIP) calcd. for $C_{22}H_{22}N_2O_2$: 346.1681; found: 346.1668.

Acknowledgments

The Spanish Ministerio de Ciencia e Innovación (MICINN) (projects CTQ2010-20387, and Consolider Ingenio 2010, CSD2007-00006), the Spanish Ministerio de Economia y Competitividad (MINECO) (projects CTQ2013-43446-P and CTQ2014-51912-REDC), FEDER, the Generalitat Valenciana (PROMETEO 2009/039 and PROMETEOII/2014/017), and the University of Alicante. L. C. M. thanks Spanish Government for a fellowship.

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