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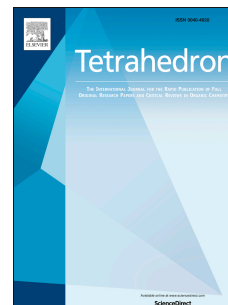
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1,3-Dipolar Cycloadditions with Azomethine Ylide Species Generated from Aminocyclopropanes

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Dedicated to the memory of Prof. Sir Derek Barton, one of the Chemistry greats of the 20th century.

Keywords

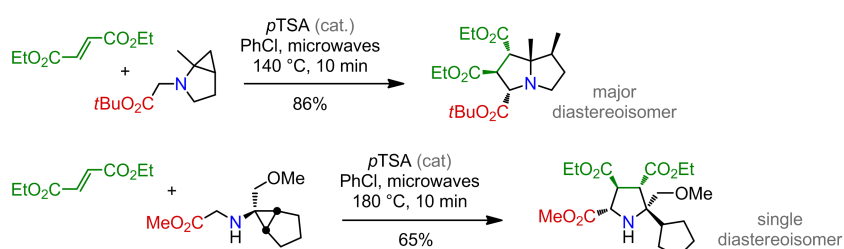
Cyclopropane; 1,3-Dipolar Cycloaddition; Azomethine Ylide; Microwave-assisted Synthesis; Pyrrolizidine; Titanium

Graphical Abstract

1,3-Dipolar Cycloadditions with Azomethine Ylide Species Generated from Aminocyclopropanes

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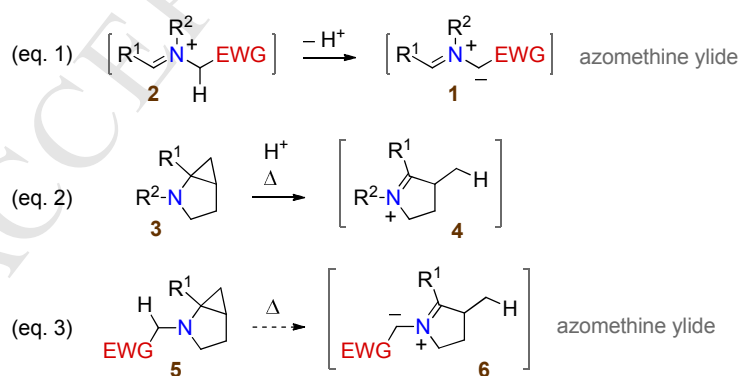


Abstract

Two types of bicyclic *N*-cyclopropyl glycine ester derivatives have been prepared and put under scrutiny as possible precursors of azomethine ylides. The results demonstrate that they can indeed participate in 1,3-dipolar cycloaddition reactions with dipolarophiles, as illustrated in the cases of phenyl vinyl sulfone, *N*-phenylmaleimide, diethyl fumarate and diethyl maleate. The relative configurations of the major diastereoisomers produced are consistent with the predicted generation of azomethine ylide species, reacting in concerted cycloaddition processes. This unprecedented way of generating such 1,3-dipoles provides access to functionalised pyrrolizidines and pyrrolidines, that would be difficult to make directly by more classic methods. It was also found that using phenyl vinyl sulfone or *N*-phenylmaleimide as the dipolarophile reactant, a domino nucleophilic conjugate addition / 1,3-dipolar cycloaddition process may operate competitively.

1. Introduction

1,3-Dipolar cycloaddition reactions constitute a general and versatile tool for the synthesis of five-membered ring heterocycles.¹ Among the various 1,3-dipoles that can be used, azomethine ylides **1** have led to a number of interesting applications, as they can provide access to diversely substituted pyrrolidines, as well as to oxazolidines and imidazolidines.² A number of methods have been developed for the generation of these dipoles, among which one of the most popular relies on the deprotonation of iminium species **2** featuring acidic hydrogens at the α position relative to the nitrogen atom (Scheme 1, equation 1).³ Since the protonation of bicyclic aminocyclopropanes **3** is an efficient and original route for the generation of iminium cations **4** (equation 2),⁴ we envisioned that the derivatives **5** could be suitable precursors to cyclic azomethine ylides **6** (equation 3).

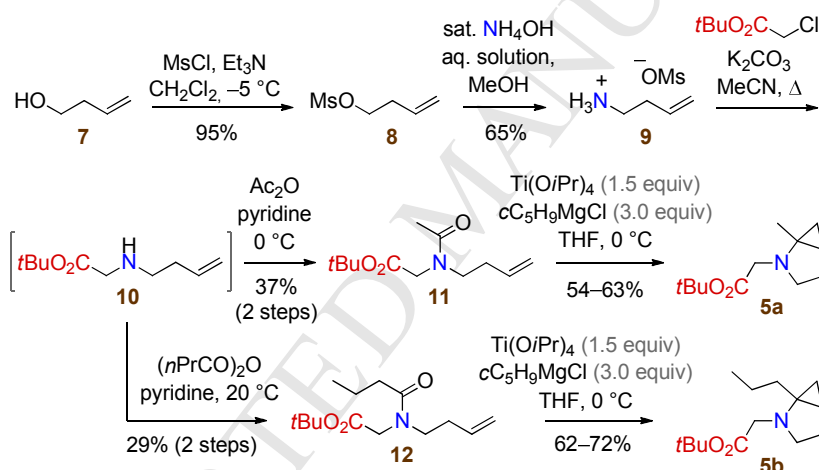


Scheme 1. Strategy for the generation of azomethine ylides from aminocyclopropanes. EWG = electron-withdrawing group.

2. Results and discussion

2.1. Synthesis of the substrates

For the purpose of this study, aminocyclopropanes **5a** and **5b** were readily prepared using an intramolecular Kulinkovich-de Meijere reaction as the key cyclopropanation step (Scheme 2).^{5,6,7} Although carboxylic esters are known to be more reactive than amides towards diisopropoxytitanacyclopropane complexes,⁸ this reaction proceeded with remarkably good chemoselectivity from **11** and **12** and no cyclopropanol resulting from an intramolecular Kulinkovich reaction was formed in significant amount. The steric effect exercised by the *tert*-butyl group, as well as a kinetic effect favouring the formation of a five-membered rather than a six-membered ring may reasonably account for this result.

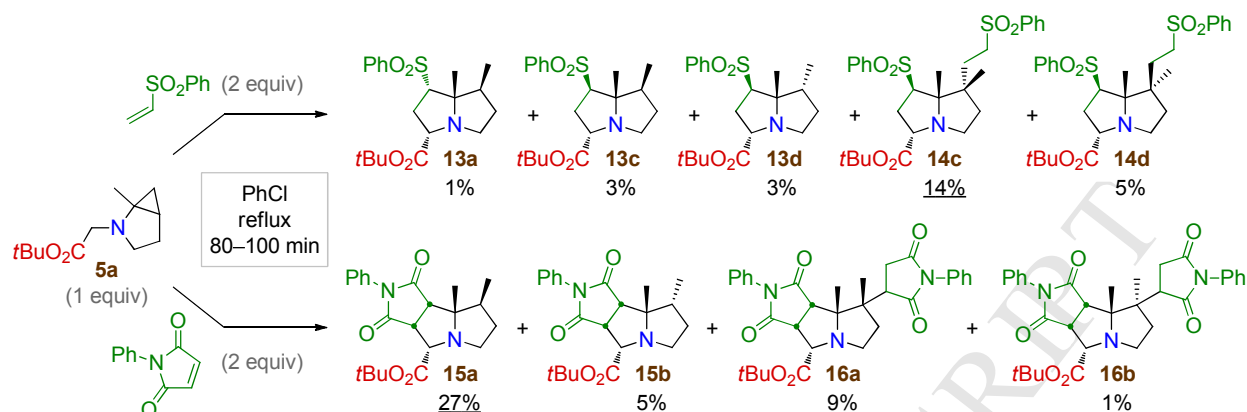


Scheme 2. Preparation of aminocyclopropanes substrates **5a** and **5b**.

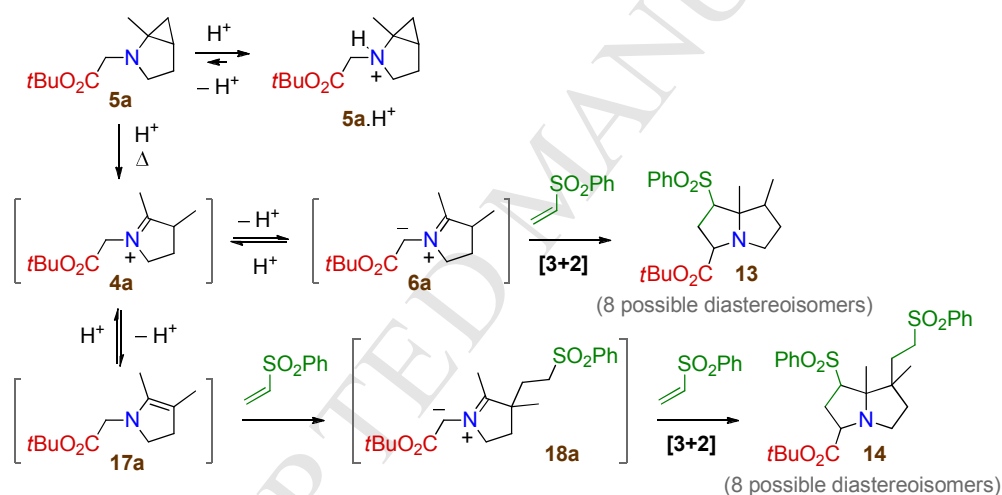
2.2. Cycloaddition reactions with phenyl vinyl sulfone and *N*-phenylmaleimide

Initial cycloaddition experiments were conducted with aminocyclopropane **5a** under standard thermal conditions, with two equivalents of phenyl vinyl sulfone or *N*-phenylmaleimide as the dipolarophile reactant. In both cases, rather complex mixtures of products were generated: the predicted cycloadducts **13** and **15** were formed with low to moderate diastereoselectivity, together with the unexpected by-products **14** and **16** having incorporated two molecules of the dipolarophile reactant (Scheme 3). The formation of these compounds, also formed as mixtures of diastereoisomers, can be rationalised by invoking an equilibrium between the azomethine ylide intermediate **6a** and an endocyclic enamine **17a**.⁹ The latter would undergo a conjugate addition

reaction / 1,3-dipolar cycloaddition sequence,¹⁰ as illustrated in Scheme 4 in the particular case of phenyl vinyl sulfone, with the generation of a highly substituted azomethine ylide **18a**.



Scheme 3. Thermal reactions of **5a** with two equivalents of phenyl vinyl sulfone or *N*-phenylmaleimide (isolated yields).



Scheme 4. Proposed mechanism for the formation of compounds **13** and **14**.

For these experiments and the subsequent studies, analysis of the crude reaction products by HPLC/MS provided valuable information with respect to chemoselectivity: direct 1,3-dipolar cycloaddition *vs* conjugate addition-1,3-dipolar cycloaddition, as well as an assessment of the distribution of the diastereoisomers for both types of products.¹¹ A typical TIC chromatogram, in the case of the reactions of **5a** with *N*-phenylmaleimide, is presented in Figure 1. The major product **15a** is visible, at $t = 10.767$ minutes, along with 3 other diastereoisomers. Nine diastereoisomers of compound **16** also appear clearly on this chromatogram. The chemo- and diastereo-selectivity of the reaction is thus less than satisfactory.¹² Nonetheless, given the fact that 8 diastereoisomers of the adduct **15** and 16 diastereoisomers of the by-product **16** can in principle be formed, it is worth noting that **15a** was comparatively easy to purify and useful amounts of this compound could be isolated after a single flash chromatography.¹³ An X-ray structure of this cycloadduct is presented in Figure

2.¹⁴ The relative configuration of its chiral centres is consistent with a W-shaped conformation of the azomethine ylide **6a** and with an *endo* approach of the dipolarophile, if one assumes the cycloaddition to be a concerted process (*vide infra*).^{2d} The relative configurations of other purified individual diastereoisomers of compounds **13–16** were tentatively assigned on the basis of NOESY 2D NMR experiments.¹³

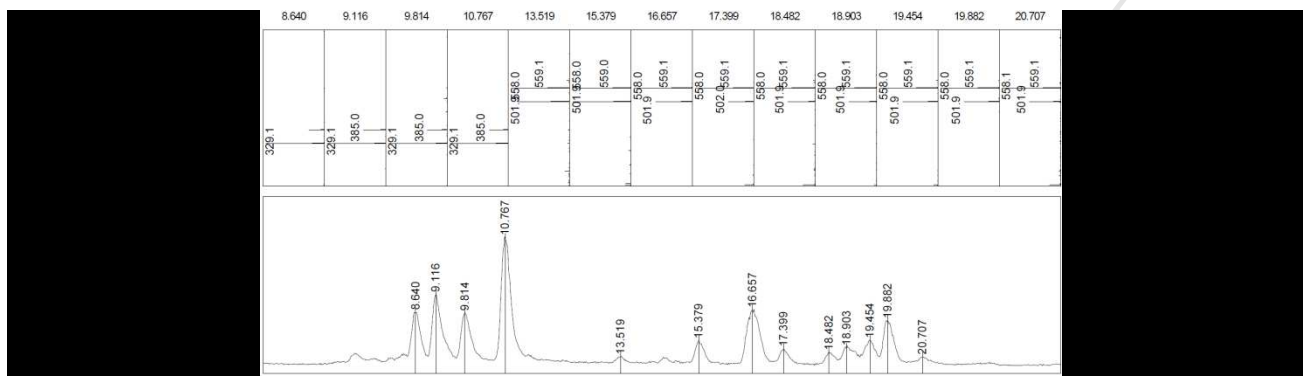


Figure 1. Typical HPLC/MS (ES⁺) TIC chromatogram of the crude product obtained after the thermal reaction of aminocyclopropane **5a** with a dipolarophile. The result shown here corresponds to the reaction with *N*-phenylmaleimide presented in Table 1, entry 8. Diastereoisomers of compounds **15** (M = 384 g / mol) and **16** (M = 557 g / mol) are clearly visible.

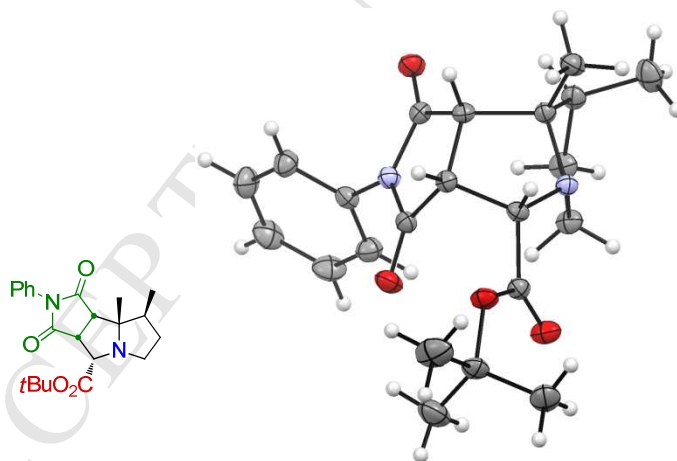


Figure 2. Ortep view of **15a**. Displacement ellipsoids are drawn at the 30% probability level.

The influence of several reaction parameters on the product distribution was briefly examined (Table 1). The results of this short study show that the use of only one equivalent of dipolarophile, rather than two, favour the formation of the simple 1,3-dipolar cycloaddition adducts (entry 3 *vs* entry 1 and entry 4 *vs* entry 2). However, introduction of phenyl vinyl sulfone in small portions of 0.1 equivalent did not result in the more selective production of the monosulfone adducts **13** (entries 5 and 6 *vs* entries 3 and 4). It is also interesting to note that the choice of *N*-phenylmaleimide as the dipolarophile led to the production of comparatively less by-product resulting from conjugate

addition-1,3-dipolar cycloaddition (entry 8 vs entry 4 and entry 9 vs entry 7). The use of *para*-toluenesulfonic acid (*p*TSA) reduced the reaction times by increasing the rate of the protonation of the substrate **5a**¹⁵ but also appeared to slightly favour the production of the by-products **14** and **16** (entry 2 vs entry 1, entry 4 vs entry 3, entry 6 vs entry 5 and entry 8 vs entry 9). With this respect, heating the reaction mixtures in a microwave reactor proved very interesting:¹⁵ the reactions were complete after 5 to 10 minutes only, with a better selectivity in favour of the simple cycloaddition adducts (entry 7 vs entries 3 and 4; entry 9 vs entry 8).

Table 1. Ratios of the 1,3-dipolar cycloaddition/conjugate addition-1,3-dipolar cycloaddition products, depending on several reaction parameters.

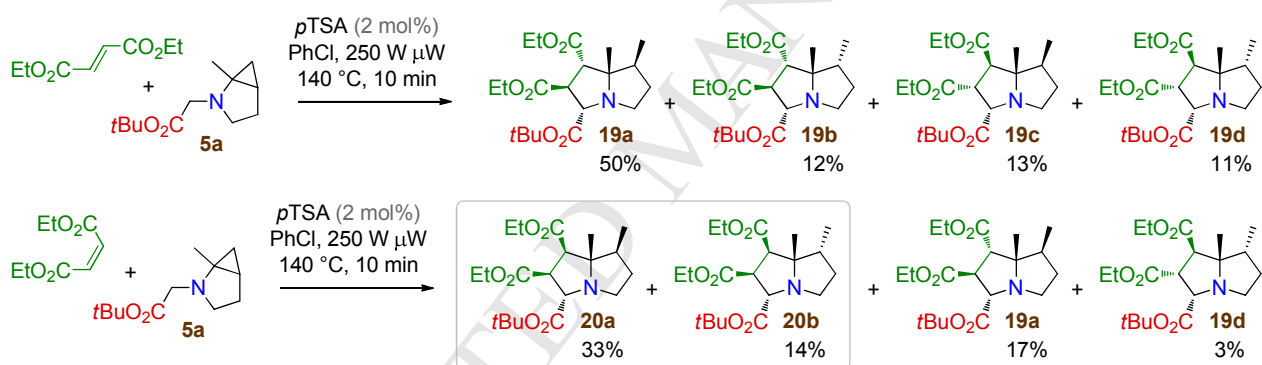
Entry	dipolarophile ^a (equiv)	<i>p</i> TSA (equiv)	method	time	ratio 13/14 (from PVS) or 15/16 (from NPM) ^a	Tentative yields
1	PVS (2)	0	conventional reflux	4 h	24 : 76	
2	PVS (2)	10%	conventional reflux	2 h	19 : 81	
3	PVS (1)	0	conventional reflux	3 h	53 : 47	
4	PVS (1)	10%	conventional reflux	2 h	52 : 48 ^b	13 (15%) ^c 14 (34%) ^c
5	PVS (1) ^c	0	conventional reflux	3 h	53 : 47	
6	PVS (1) ^d	10%	conventional reflux	2 h	40 : 60	
7	PVS (1)	0	microwave heating	10 minutes	56 : 44	13 + 14 (60%) ^e
8	NPM (1)	10%	conventional reflux	1 h	60 : 40	15 (28%) ^c 16 (28%) ^c
9	NPM (1)	0	microwave heating	5 minutes	73 : 27	

^a Estimated by HPLC/MS. PVS = phenyl vinyl sulfone; NPM = *N*-phenylmaleimide. ^b Two identical experiments were carried out. The ratios found were 54 : 46 and 50 : 50 respectively. The average value is displayed in the table. ^c Obtained as a mixture of diastereoisomers that were not separated. ^d Phenyl vinyl sulfone was introduced in portions of 0.1 equiv, at intervals of 10 minutes. ^e A mixture of both compounds was obtained. The diastereoisomers were not separated.

2.3. Cycloaddition reactions with diethyl fumarate and diethyl maleate, under microwave irradiation

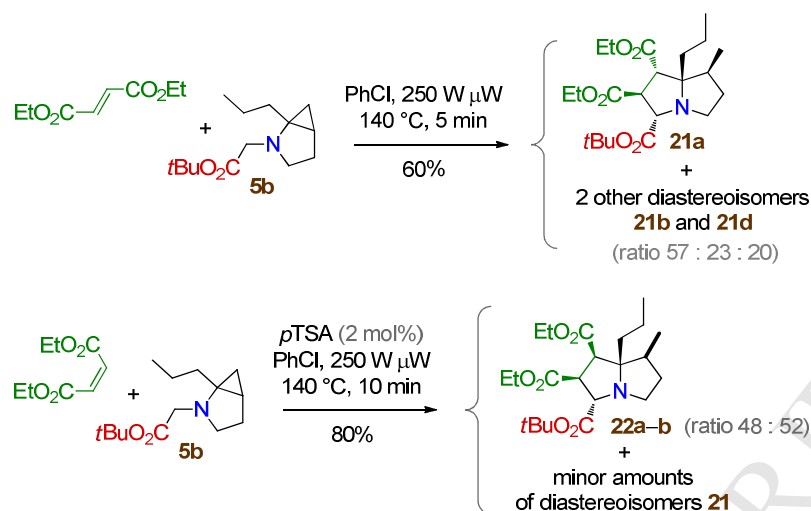
We next turned our attention to the use of diethyl fumarate and diethyl maleate as the dipolarophiles, with microwave heating. The corresponding reactions proved to be much more selective. Indeed, no

by-products arising from competitive Michael addition were observed and we thus elected reaction conditions involving the presence of 2 mol% of *p*TSA, ensuring full conversion of **5a** (Scheme 5). While all the diastereoisomers **19a–d** isolated after the reaction with diethyl fumarate had retained the *trans* relative configuration of the ethyl ester groups, the reaction with diethyl maleate led to the formation of the new diastereoisomers **20a** and **20b**, with a *cis* relative configuration of the same groups. This provides strong support for a concerted cycloaddition process. However, the fact that diastereoisomers **19a** and **19d**, which had been produced in the reaction with diethyl fumarate, were isolated in significant amounts after the reaction with diethyl maleate as well, did not rule out the possibility of a mechanism operating partly in a stepwise fashion. To get further insight into this problem, a reaction was run in the presence of excess amounts of geometrically pure diethyl maleate (two equivalents). Analysis of the crude product revealed the presence of a mixture of unreacted diethyl maleate and diethyl fumarate, thereby demonstrating partial isomerisation of diethyl maleate into diethyl fumarate under the reaction conditions, which is sufficient to explain the result observed.¹³ Accordingly, one can notice that once again, the relative configurations of all the products are consistent with a W-shaped conformation of the azomethine ylide **6a**, as drawn in Scheme 4.



Scheme 5. Cycloadditions of **5a** with diethyl fumarate and diethyl maleate.

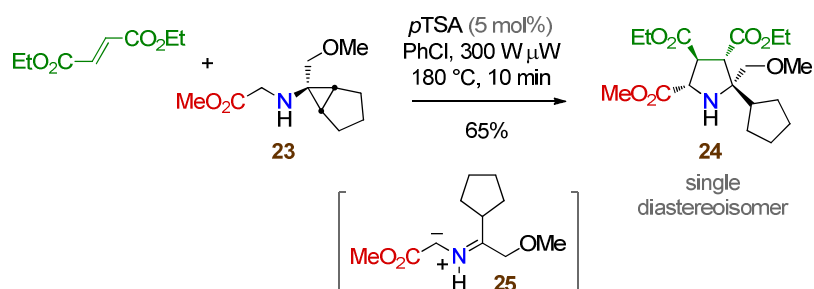
Further experiments were performed with the *n*-propyl aminocyclopropane derivative **5b**, leading to the production of compounds **21–22** with improved selectivities, as compared with the reactions of **5a** (Scheme 6).



Scheme 6. Cycloadditions of **5b** with diethyl fumarate and diethyl maleate.

2.4. Possibilities of extension

Finally, preliminary studies have been undertaken with a different kind of bicyclic aminocyclopropane substrate: compound **23**, synthesised by the method reported by P. Bertus and J. Szymoniak.¹⁶ This substrate reacted with diethyl fumarate to produce the expected substituted pyrrolidine **24** (Scheme 7), which is promising with respect to the generality of this new mode of generation of azomethine ylide species. Significant differences were observed, as compared with the results obtained with **5a** and **5b**: firstly, higher temperature (180 °C) had to be applied. Indeed, incomplete conversion of **23** was observed when microwave irradiation was carried out at 140 °C for 10 minutes. Secondly and more interestingly, the triester cycloadduct **24** was obtained as a single diastereoisomer. The relative configuration of its chiral centres, established by X-ray crystallography of the corresponding hydrochloride salt **24.HCl** (Figure 3),¹⁴ is again in agreement with a concerted 1,3-dipolar cycloaddition. Indeed, the two diethyl ester groups are in *trans* relative configuration and the relative configuration of the other chiral centres is consistent with the azomethine ylide intermediate **25** in the conformation displayed in Scheme 7. Moreover, it is interesting to note that the relative configuration of the three ester substituents is identical to the one observed with **19a** and **21a**, the major cycloadducts of **5a** and **5b** with diethyl fumarate (Schemes 5 and 6).



Scheme 7. Cycloaddition of **23** with diethyl fumarate.

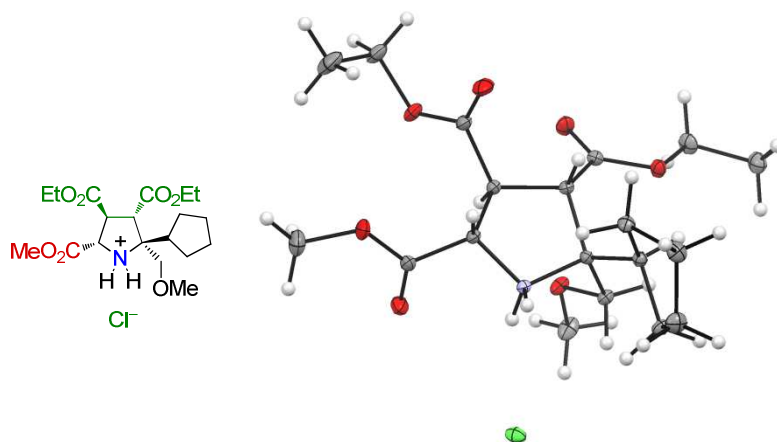


Figure 3. Ortep view of **24.HCl**. Displacement ellipsoids are drawn at the 30% probability level.

3. Conclusions

In summary, our results demonstrate that bicyclic aminocyclopropane derivatives that are substituted with a 2-alkoxy-2-oxoethyl group can undergo rearrangement into azomethine ylide species under thermal conditions. This represents an unprecedented route to these reactive 1,3-dipoles, complementary to classic methods, with an access to differently functionalised molecules. In particular, the substrates **5a**, **5b** and **23** can be used as precursors of the corresponding ylide species **6a**, **6b** and **25** and participate in 1,3-dipolar cycloaddition reactions with various dipolarophiles to produce highly substituted pyrrolizidine skeletons. Application of microwave heating conditions has allowed us to reduce the reaction times to a few minutes and to minimise a competitive process that is sometimes observed and that leads to more complex molecules having incorporated two units of the dipolarophile.

The potential of these cycloaddition reactions in synthetic applications is particularly relevant in the field of pyrrolizidine natural product synthesis.¹⁷ It is worthy of note that our method provides direct access to pyrrolizidine skeletons having an alkyl substituent at the ring junction carbon atom. In contrast, to the best of our knowledge, in all the other literature examples of pyrrolizidine cycloadducts, this substituent, if present, is an electron withdrawing group (typically an ester group).^{18,19} It is worth pointing out that several pyrrolizidine alkaloids of interest have an alkyl substituent at this position, for instance (+)-NP25302,²⁰ caldaphnidine M²¹ and (-)-penibruguieramine A²² (Figure 4).

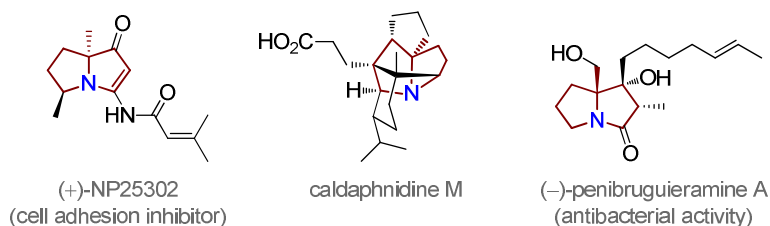


Figure 4. Examples of pyrrolizidine alkaloids having an alkyl substituent at the ring junction carbon atom.

In spite of the rather low diastereoselectivities that are often observed in the presently reported cycloaddition reactions, there are several instances where the major diastereoisomers of the products can be isolated in useful yields (up to 65%). It is anticipated that much more selective reactions can be designed on the basis of these first results, for instance by making the cycloaddition process intramolecular. Results of new studies carried out along this idea will be reported in due course.

4. Experimental

4.1. General information

THF was purified using a PureSolv solvent purification system (Innovative Technology Inc.). Analytical grade chlorobenzene was purchased from SDS and used as such. Cyclopentylmagnesium chloride solution in diethyl ether was purchased from Sigma-Aldrich or Fluka and titrated monthly according to a previously reported method.²³ Titanium (IV) *iso*-propoxide (VERTEC[®] TIPT) was purchased from Alfa Aesar, distilled under reduced pressure and stored under argon for several months. The microwave-promoted experiments were run using a CEM Discover Microwave Synthesis System with the temperature and time parameters indicated; the reaction vessels were not flushed with an inert gas. All other reactions were carried out under nitrogen or argon. The temperatures mentioned are the temperatures of the cold baths or the oil baths used. Concentration under reduced pressure was carried out using rotary evaporators at 40 °C. Flash column chromatography was performed on SDS Chromagel silica gel 60 (35–70 μm) or on VWR Chemicals or Merck silica gel 60 (40–63 μm). Petroleum ether refers to the 40–60 °C fraction. NMR spectra were recorded with AVANCE 300 (¹H at 300 MHz, ¹³C at 75.5 MHz) or AVANCE 400 (¹H at 400.2 MHz, ¹³C at 100.6 MHz) Bruker spectrometers. Chemical shifts δ are given in ppm, referenced to the peak of tetramethylsilane defined at $\delta = 0.00$ (¹H NMR), or the solvent peak of CDCl₃, defined at $\delta = 77.0$ (¹³C NMR). Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, sext = sextuplet, sept = septuplet, m = multiplet, br = broad. Coupling constants *J* are given in Hz and are rounded to the closest multiple of 0.5. Infrared spectra were recorded with a Perkin-Elmer BX or a Perkin-Elmer 2000 FT-IR spectrometer. Melting points were determined using a Büchi 535 apparatus and were not corrected. Mass spectra were obtained using

LC/MS Thermoquest Navigator (ES⁺), LCT Micromass (low- and high-resolution ES⁺), Hewlett-Packard Quad GC-MS engine spectrometer *via* direct injection (positive CI, NH₃) and JEOL GC-mate II (high-resolution EI) spectrometers. Underlined *m/z* values indicate the base peaks.

4.2. Procedures for the preparation of the substrates 5

4.2.1. Synthesis of 5a

A solution of but-3-en-1-yl methanesulfonate **8**²⁴ (1.00 equiv, 95.2 mmol, 14.3 g) in a mixture of MeOH (95 mL) and 32% NH₃ aqueous solution (95 mL) was vigorously stirred at 20 °C for 3.5 days. The solvents were then removed under reduced pressure to afford a white solid (14.7 g). Analysis of the crude product by ¹H NMR spectroscopy showed that it contained but-3-en-1-ammonium methanesulfonate **9** as the major component, in an estimated amount of 10.4 g (61.9 mmol, 65%).

9: ¹H NMR (CD₃OD, 300 MHz): δ 2.42 (2 H, tdt, *J* 7.5, 7.0, 1.5), 2.70 (3 H, s), 3.01 (2 H, t, *J* 7.5), 4.85 (3 H, br s), 5.14–5.29 (2 H, m), 5.82 (1 H, ddt, *J* 17.5, 10.0, 7.0).

Crude product of the previous step (1.14 equiv, assumed 47.4 mmol of mixture of ammonium salts, 7.32 g), *tert*-butyl 2-chloroacetate (1.00 equiv, 41.6 mmol, 5.95 mL) and potassium carbonate (2.00 equiv, 83.2 mmol, 11.5 g) were stirred in MeCN (0.20 L) at reflux for 1 h 30 min. After cooling, the inorganic salts were filtered off and rinsed with MeCN (50 mL) and Et₂O (50 mL). The combined organic solutions were concentrated under reduced pressure to give crude *tert*-butyl 2-(but-3-en-1-ylamino)acetate **10** as an oil (4.43 g) that was engaged in the next step without purification.

10: Pale yellow oil. IR (neat): ν 2977 (w), 2931 (w), 1731 (s, C=O), 1367 (m), 1223 (m), 1146 (s), 912 (m), 846 (w) cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 1.47 (9 H, s), 1.64 (1 H, br s, NH), 2.26 (2 H, qt, *J* 7.0, 1.5), 2.67 (2 H, t, *J* 7.0), 3.30 (2 H, s), 5.05 (1 H, dq, *J* 17.0, 1.5), 5.11 (1 H, dq, *J* 17.0, 1.5), 5.80 (1 H, ddt, *J* 17.0, 10.0, 7.0). ¹³C NMR (CDCl₃, 75.5 MHz): δ 28.0, 34.3, 48.3, 51.5, 80.9, 116.3, 136.1, 171.5. MS *m/z* (ES⁺) 130, 184, 186 (MH⁺), 240, 244, 300, 322. HRMS *m/z* (ES⁺) 186.1499 (MH⁺ C₁₀H₂₀NO₂ requires 186.1494).²⁵

Acetic anhydride (1.50 equiv, 36.0 mmol, 3.40 mL) was added dropwise, at 0 °C, to a solution of crude secondary amine **10** (1.00 equiv, assumed 23.9 mmol, 4.43 g) in pyridine (25 mL). The cold bath was removed. The mixture was stirred at 20 °C for 1 h, then poured in 1 M HCl aqueous solution (0.10 L). The pH was adjusted to 1 by adding concentrated HCl aqueous solution. The mixture was extracted with Et₂O (3 × 50 mL). The combined organic phases were washed with brine, then dried over MgSO₄, filtered and concentrated to afford a pale yellow oil (4.43 g). Purification by flash column chromatography on silica gel, (EtOAc/heptane, 40%) yielded pure *tert*-butyl 2-(*N*-(but-3-en-1-yl)acetamido)acetate **11** (3.52 g, 15.5 mmol, 37% over two steps from *tert*-butyl chloroacetate).

11: Colourless oil. C₁₂H₂₁NO₃ (227.30): calcd. C 63.41, H 9.31; found C 63.23, H 9.38. IR (neat): ν 3433 (br), 2979, 2931, 1742 (s), 1654 (s), 1428 (m), 1368 (m), 1225 (m), 1157 (s), 917 (w), 853 (w) cm⁻¹. ¹H NMR (CDCl₃, 300 MHz), 65 : 35 mixture of two rotamers. Major rotamer: δ 1.46 (9 H, s), 2.15 (3 H, s), 2.33 (2 H, tdt, *J* 7.5, 7.0, 1.5), 3.41 (2 H, t, *J* 7.5), 3.96 (2 H, s), 5.10 (1 H, dq, *J* 10.0,

1.5), 5.12 (1 H, dq, J 17.0, 1.0), 5.78 (1 H, ddt, J 17.0, 10.0, 7.0). Minor rotamer: δ 1.48 (9 H, s), 2.03 (3 H, s), 2.28 (2 H, tdt, J 7.5, 7.0, 1.5), 3.44 (2 H, t, J 7.5), 3.90 (2 H, s), 5.03 (1 H, dq, J 10.0, 1.5), 5.07 (1 H, dq, J 17.0, 1.5), 5.78 (1 H, ddt, J 17.0, 10.0, 7.0). ^{13}C NMR (CDCl_3 , 75.5 MHz), 65 : 35 mixture of two rotamers: δ 21.1, 21.5, 27.9, 28.0, 32.0, 32.9, 46.8, 48.2, 49.3, 51.7, 81.6, 82.4, 116.6, 117.6, 134.2, 135.2, 168.3, 168.4, 170.7, 170.8. MS (EI) m/z 126, 130, 145, 154, 162, 186, 227 ($[\text{M}]^+$). HRMS (EI) m/z 227.1519 (M^+ $\text{C}_{12}\text{H}_{21}\text{NO}_3^+$ requires 227.1516).

Cyclopentylmagnesium chloride (1.95 M in Et_2O , 3.00 equiv, 12.7 mmol, 6.52 mL) was added dropwise, over 10 min, to a cooled (0 °C), stirred solution of amide **11** (1.00 equiv 4.24 mmol, 963 mg) and titanium(IV) *isopropoxide* (1.50 equiv, 6.35 mmol, 1.88 mL) in THF (50 mL). After 30 min of stirring at 0 °C, H_2O (1.0 mL) was added, the cold bath was removed and the flask was exposed to air. Stirring was maintained until decolouration (1 h). The reaction mixture was filtered through a pad of celite (rinsing: Et_2O , 2 \times 50 mL). The combined organic solutions were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a yellow oil (834 mg). Purification by flash column chromatography on silica gel treated with a few drops of Et_3N (EtOAc /heptane 25%) yielded pure *tert*-butyl 2-(1-methyl-2-azabicyclo[3.1.0]hexan-2-yl)acetate **5a** (563 mg, 2.66 mmol, 63%).

Note : this reaction was repeated several times under identical conditions. Yields were in the range 54–63% (7 runs).

5a: Colourless oil. $\text{C}_{12}\text{H}_{21}\text{NO}_2$ (211.30): calcd. C 68.21, H 9.91; found C 68.39, H 9.91. IR (neat): ν 3409 (br), 2975, 2932, 2869, 2817 (w), 1747 (s), 1727 (m), 1453 (w), 1391 (w), 1367 (m), 1257 (w), 1223 (w), 1150 (s) cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ 0.09 (1 H, dd, J 8.0, 5.5), 0.73 (1 H, t, J 5.5), 1.15 (1 H, dt, J 8.0, 4.0), 1.34 (3 H, s), 1.47 (9 H, s), 1.74 (1 H, dd, J 11.0, 7.0), 1.93 (1 H, m), 2.03 (1 H, ddd, J 11.0, 7.0, 4.0), 3.16 (2 H, AB system, δ_{A} 2.80, δ_{B} 3.53, J_{AB} 16.0), 3.32 (1 H, t, J 8.0). ^{13}C NMR (CDCl_3 , 75.5 MHz): δ 7.9, 19.3, 22.2, 26.0, 28.0, 46.1, 50.3, 54.6, 80.5, 170.5. MS (positive CI, NH_3) m/z 110, 156, 210, 212 (MH^+), 213. MS (EI) m/z 110, 111, 155, 211 ($[\text{M}]^+$). HRMS (EI) m/z 211.1577 (M^+ $\text{C}_{12}\text{H}_{21}\text{NO}_2^+$ requires 211.1567).

4.2.2. Synthesis of **5b**

Butyric anhydride (1.21 equiv, 24.0 mmol, 3.93 mL) was added dropwise, at 20 °C, to a solution of crude secondary amine **10** (prepared as described above for the synthesis of **5a**, 1.00 equiv, assumed 19.9 mmol, 3.68 g) in pyridine (20 mL). The mixture was stirred at 20 °C for 2 h, then poured in 1 M HCl aqueous solution (50 L). The pH was adjusted to 1 by adding concentrated HCl aqueous solution. The mixture was extracted with Et_2O (3 \times 50 mL). The combined organic phases were washed with 2 M NaOH aqueous solution (3 \times 20 mL), then dried over MgSO_4 , filtered and concentrated to afford a pale yellow oil (3.97 g). Purification by flash column chromatography on silica gel, (EtOAc /heptane, 30%) yielded pure *tert*-butyl 2-(*N*-(but-3-en-1-yl)butyramido)acetate **12** (3.28 g, 12.8 mmol, 29% over two steps from *tert*-butyl chloroacetate).

12: Colourless oil. IR (neat): ν 2974, 2933, 1741 (m), 1650 (s), 1644 (s), 1455, 1366 (m), 1225 (m), 1152 (s), 914, 853, 748 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz), 67 : 33 mixture of two rotamers. Major rotamer: δ 0.95 (3 H, t, J 7.5), 1.44 (9 H, s), 1.68 (2 H, sext, J 7.5), 2.21–2.38 (4 H, m), 3.38 (2 H, t, J 7.5), 3.94 (2 H, s), 5.07 (1 H, br d, J 10.0), 5.09 (1 H, ddq, J 17.0, 1.0), 5.76 (1 H, ddt, J 17.0, 10.0, 7.0). Minor rotamer: 0.92 (3 H, t, J 7.5), 1.46 (9 H, s), 1.67 (2 H, sext, J 7.5), 2.16 (2 H, t, J 7.5), 2.21–2.38 (2 H, m), 3.42 (2 H, t, J 7.5), 3.89 (2 H, s), 5.00 (1 H, br d, J 10.0), 5.04 (1 H, br d, J

17.0), 5.76 (1 H, ddt, J 17.0, 10.0, 7.0). ^{13}C NMR (CDCl_3 , 75.5 MHz), 67 : 33 mixture of two rotamers: δ 13.9, 13.9, 18.4, 18.6, 28.0, 28.0, 32.1, 33.2, 34.7, 35.0, 47.0, 48.4, 48.5, 51.0, 81.5, 82.4, 116.5, 117.5, 134.3, 135.4, 168.5, 168.6, 173.1, 173.2. MS m/z (ES^+) 222, 223, 254, 278 (MNa^+), 279. HRMS m/z (ES^+) 278.1744 (MNa^+ $\text{C}_{14}\text{H}_{25}\text{NNaO}_3$ requires 278.1732).

Cyclopentylmagnesium chloride (1.99 M in Et_2O , 3.00 equiv, 15.0 mmol, 7.54 mL) was added dropwise, at 0 °C, over 10 min, to a stirred solution of amide **12** (1.00 equiv, 5.00 mmol, 1.28 g) and titanium(IV) *iso*-propoxide (1.50 equiv, 7.50 mmol, 2.22 mL) in THF (0.10 L). After 30 min of stirring at 0 °C, H_2O (5.0 mL) was added, the cold bath was removed and the flask was exposed to air. Stirring was maintained until decolouration (1 h). The reaction mixture was filtered through a pad of celite (rinsing: Et_2O , 2 \times 50 mL). The combined organic solutions were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a yellow oil (1.80 g). Purification by flash column chromatography on silica gel (EtOAc /heptane, gradient from 10 to 20%) yielded pure *tert*-butyl 2-(1-propyl-2-azabicyclo[3.1.0]hexan-2-yl)acetate **5b** (866 mg, 3.62 mmol, 72%).

Note : another run performed on 12.7 mmol scale gave **5b** in 62% yield.

5b: Colourless oil. IR (neat): ν 2930, 2869, 1747 (m), 1726 (m), 1455 (w), 1366 (m), 1256 (w), 1223 (w), 1145 (s), 958, 917, 849 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ 0.10 (1 H, dd, J 8.0, 5.5), 0.68 (1 H, dd, J 5.5, 4.5), 0.90 (3 H, t, J 7.0), 1.20 (1 H, ddd, J 8.5, 8.0, 4.5), 1.22–1.51 (3 H, m), 1.46 (9 H, s), 1.76 (1 H, m), 1.91 (1 H, m), 1.97 (1 H, m), 1.99 (1 H, m), 3.14 (2 H, AB system, δ_{A} 2.80, δ_{B} 3.47, J_{AB} 16.0), 3.28 (1 H, m). ^{13}C NMR (CDCl_3 , 75.5 MHz): δ 6.9, 14.3, 19.3, 20.8, 26.3, 28.1, 34.3, 49.8, 50.2, 54.8, 80.5, 170.8. MS m/z (ES^+) 184, 185, 206, 262 (MNa^+). HRMS m/z (ES^+) 262.1789 (MNa^+ $\text{C}_{14}\text{H}_{25}\text{NNaO}_2$ requires 262.1783).

4.3. Typical procedures for the cycloaddition reactions under standard thermal conditions

4.3.1. Reaction of **5a** with phenyl vinyl sulfone

A solution of **5a** (1.00 equiv, 1.70 mmol, 360 mg) and phenyl vinyl sulfone (2.00 equiv, 3.41 mmol, 573 mg) in PhCl (17 mL) was stirred at reflux for 100 minutes. After cooling, the mixture was concentrated under reduced pressure to give the crude product (orange oil, 988 mg). Analysis by ^1H NMR spectroscopy revealed the presence of **14c** as the major product, with an 18% estimated yield. Several purification operations, by flash column chromatography on silica gel (EtOAc /heptane, gradient from 5% to 100% or $\text{EtOAc}/\text{CH}_2\text{Cl}_2$, gradient from 0% to 50%) or by preparative TLC yielded pure samples of several adducts of the reaction: **14c** (129 mg, 235 μmol , 14%), **14d** (total amount 50.5 mg, 92.1 μmol , 5%), **13c** (total amount 16.8 mg, 44.2 μmol , 3%), **13d** (total amount 16.7 mg, 44.0 μmol , 3%) and **13a** (total amount 9.4 mg, 24.7 μmol , 1%). Some unreacted **5a** was recovered as well (39.6 mg, 187 μmol , 11%).

Major product 14c: Colourless crystals. IR (neat): ν 2976 (w), 2937 (w), 2881 (w), 1721 (m, C=O), 1446 (w), 1367 (w), 1299 (m), 1287 (m), 1247 (w), 1142 (s), 1084 (m), 914 (w), 843 (w), 757 (w), 723 (m), 688 (m) cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ 1.09 (3 H, s), 1.41 (9 H, s), 1.46 (3 H, s), 1.68 (2 H, m with the aspect of a dd, J 8.0, 7.0), 2.00 (1 H, ddd, J 13.5, 12.0, 5.5), 2.10 (1 H, ddd, J 13.5, 12.0, 4.0), 2.11 (1 H, ddd, J 13.5, 9.5, 7.5), 2.52 (1 H, ddd, J 10.0, 8.0, 6.5), 2.62 (1 H, ddd, J 13.5, 7.5, 7.0), 2.96 (1 H, ddd, J 10.0, 8.0, 7.0), 3.13 (1 H, ddd, J 14.0, 12.0, 4.0), 3.43 (1 H, ddd, J 14.0,

12.0, 5.5), 3.46 (1 H, dd, J 9.5, 7.0), 3.90 (1 H, t, J 7.5), 7.57 (2 H, br t, J 7.5), 7.59 (2 H, br t, J 7.5), 7.66 (1 H, br t, J 7.5), 7.69 (1 H, br t, J 7.5), 7.81 (2 H, br d, J 7.5), 8.02 (2 H, br d, J 7.5). ^{13}C NMR (CDCl_3 , 75.5 MHz): δ 18.4, 21.6, 28.0, 30.5, 32.7, 36.8, 44.5, 45.3, 53.2, 62.0, 65.5, 79.7, 81.9, 127.9, 128.4, 129.3, 129.4, 133.5, 133.6, 139.0, 141.2, 170.5.

4.3.2. Reaction of **5a** with *N*-phenylmaleimide

A solution of **5a** (1.00 equiv, 1.13 mmol, 238 mg) and *N*-phenylmaleimide (2.00 equiv, 2.26 mmol, 391 mg) in PhCl (10 mL) was stirred at reflux for 80 minutes. After cooling, the mixture was concentrated under reduced pressure to give the crude product (orange oil, 704 mg). Analysis by ^1H NMR spectroscopy revealed the presence of **15a** as the major product. Purification by flash column chromatography on silica gel (EtOAc/heptane, gradient from 10% to 100%) afforded pure **15a** (101 mg, 263 μmol , 23%). Several other purifications by flash column chromatography on silica gel (EtOAc/heptane, gradient from 10% to 100% or EtOAc/ CH_2Cl_2 , gradient from 0% to 30%) or by recrystallisation (EtOAc) yielded pure samples of several adducts of the reaction: **15a** (total amount 116 mg, 302 μmol , 27%), **15b** (total amount 21.8 mg, 56.6 μmol , 5%), **16b** (total amount 8.1 mg, 14.5 μmol , 1%) and **16a** (total amount 56 mg, 100 μmol , 9%).

Major product 15a: Colourless crystals. M.p. 156.3–157.3 °C (EtOAc). $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_4$ (384.48): calcd. C 68.73, H 7.34; found C 68.52, H 7.53. IR (neat): ν 2966 (m), 2933 (w), 2875 (w), 1779 (w), 1746 (m), 1711 (s, C=O), 1496 (m), 1377 (m), 1366 (m), 1184 (m), 1174 (m), 1164 (m), 1156 (m), 1147 (m), 1128 (m), 1106 (m), 757 (m) cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ 1.09 (3 H, d, J 7.0), 1.15 (3 H, s), 1.51 (9 H, s), 1.59 (1 H, dddd, J 13.0, 9.0, 8.5, 7.0), 2.12 (1 H, dddd, J 13.0, 8.5, 8.0, 4.0), 2.46 (1 H, ddq, J 8.5, 8.0, 7.0), 2.82 (1 H, ddd, J 10.0, 8.5, 7.0), 3.07 (1 H, d, J 8.5), 3.10 (1 H, ddd, J 10.0, 9.0, 4.0), 3.83 (1 H, dd, J 8.5, 8.0), 4.04 (1 H, d, J 8.0), 7.25 (2 H, br d, J 7.5), 7.37 (1 H, br t, J 7.0), 7.45 (2 H, br dd, J 7.5, 7.0). ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 16.1, 21.1, 28.1, 34.4, 37.3, 45.6, 51.2, 53.8, 63.6, 75.7, 82.2, 126.4, 128.6, 129.1, 131.9, 168.6, 175.5, 175.5. MS m/z (positive CI, NH_3) 283 ($[\text{M}-(\text{CO}_2t\text{Bu})]^+$), 284, 329, 330, 385 (MH^+), 386. MS m/z (IE) 94, 136, 282, 283 ($[\text{M}-(\text{CO}_2t\text{Bu})]^+$), 284, 384 (M^+). HRMS m/z (EI) 384.2049 (M^+ $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_4$ requires 384.2049).

Second major product 16a: Colourless crystals. M.p. 198–199 °C (dec.). IR (neat): ν 2979 (w), 1776 (w), 1738 (m), 1712 (s), 1598 (w), 1500 (m), 1456 (w), 1385 (m), 1190 (m), 1154 (m), 753 (w), 735 (w) cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ 1.28 (3 H, s), 1.54 (9 H, s), 1.56 (3 H, s), 1.76 (1 H, ddd, J 13.0, 9.5, 4.5), 1.92 (1 H, ddd, J 13.0, 11.5, 6.5), 2.87 (2 H, AB part of an ABX system, δ_A 2.70, δ_B 3.03, J_{AB} 18.5, J_{AX} 5.0, J_{BX} 9.5), 3.04 (1 H, ddd, J 12.0, 11.5, 4.5), 3.39 (1 H, ddd, J 12.0, 9.5, 6.5), 3.59 (1 H, d, J 8.0), 3.83 (1 H, dd, J 9.0, 8.0), 4.34 (1 H, d, J 9.0), 5.00 (1 H, dd, J 9.5, 5.0), 7.23 (2 H, br d, J 8.0), 7.27 (2 H, br d, J 8.0), 7.40 (1 H, br t, J 8.0), 7.41 (1 H, br t, J 8.0), 7.48 (2 H, br t, J 8.0), 7.49 (1 H, br t, J 8.0). ^{13}C NMR (CDCl_3 , 75.5 MHz): δ 21.4, 23.2, 28.1, 33.3, 36.2, 44.9, 46.1, 47.5, 50.3, 55.4, 64.9, 82.7, 83.2, 126.2, 126.6, 128.7, 128.9, 129.2, 129.4, 131.9, 131.9, 167.6, 175.0, 175.5, 177.6, 178.1. MS m/z (positive CI, NH_3) 271, 272, 385, 386, 558 (MH^+). HRMS m/z (EI) 557.2518 (M^+ $\text{C}_{32}\text{H}_{35}\text{N}_3\text{O}_6$ requires 557.2526).

4.4. Typical procedures for the cycloaddition reactions under microwave conditions

4.4.1. Reaction of **5a** with diethyl fumarate

p-Toluenesulfonic acid monohydrate (2% equiv, 20.0 μ mol, 3.8 mg) was added to a solution of **5a** (1.00 equiv, 1.00 mmol, 211 mg) and diethyl fumarate (1.00 equiv, 1.00 mmol, 164 μ L) in PhCl (1.0 mL). The mixture was heated using a microwave apparatus (power: 250 W, temperature: 140 $^{\circ}$ C, ramp time: 2 min, hold time: 10 min, max. pressure: 10 bars). After cooling, saturated aqueous NaHCO₃ solution (20 mL) was added and the mixture was extracted with EtOAc (2 \times 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product (378 mg). Purification by flash column chromatography on silica gel (EtOAc/heptane, gradient from 20 to 30%) afforded pure **19c** (41.4 mg, 108 μ mol, 11%), a 60 : 40 mixture of **19c** and **19d** (14.8 mg, 38.5 μ mol, 4%), pure **19d** (21.6 mg, 56.3 μ mol, 6%), a 50 : 50 mixture **19d** and **19a** (30.9 mg, 80.5 μ mol, 8%), pure **19a** (126 mg, 328 μ mol, 32%), a 65 : 35 mixture of **19a** and **19b** (78.1 mg, 204 μ mol, 20%) and pure **19b** (20.5 mg, 53.4 μ mol, 5%). These amounts correspond to a total of 333 mg of cycloaddition diastereoisomers **19a–d** (869 μ mol, 87%).

Major product 19a: Colourless oil. IR (neat): ν 2975, 2934, 2876, 1726 (s), 1367 (m), 1280, 1231 (m), 1147 (s), 1096, 1031 (m), 846 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 0.89 (3 H, d, *J* 7.0), 1.23 (3 H, t, *J* 7.0), 1.25 (3 H, s), 1.28 (3 H, t, *J* 7.0), 1.45 (1 H, dddd, *J* 12.0, 11.5, 11.5, 6.5), 1.48 (9 H, s), 1.83 (1 H, ddd, *J* 12.0, 6.0, 5.0), 1.96 (1 H, dqd, *J* 11.5, 7.0, 6.0), 2.59 (1 H, ddd, *J* 11.5, 8.5, 5.0), 2.86 (1 H, d, *J* 12.0), 2.95 (1 H, dd, *J* 8.5, 6.5), 3.63 (1 H, dd, *J* 12.0, 11.5), 3.93 (1 H, d, *J* 11.5), 4.03–4.29 (4 H, m). ¹³C NMR (CDCl₃, 75.5 MHz): δ 14.1, 14.2, 14.5, 25.4, 28.0, 33.3, 39.2, 47.6, 49.0, 58.8, 60.8, 60.9, 66.6, 73.0, 82.0, 168.2, 171.1, 172.1. MS *m/z* (EI) 136, 208, 209, 236, 282, 310, 383 (M⁺). MS *m/z* (ES⁺) 282, 306, 328, 329, 350, 384 (MH⁺), 406 (MNa⁺), 407. HRMS *m/z* (ES⁺) 406.2216 (MNa⁺ C₂₀H₃₃NNaO₆ requires 406.2206).

19b: Colourless oil. IR (neat): ν 2975, 1726 (s), 1454, 1367, 1231, 1146, 1096, 1031, 846, 737 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 0.92 (3 H, d, *J* 7.5), 1.24 (3 H, t, *J* 7.0), 1.26 (3 H, t, *J* 7.0), 1.41 (3 H, s, H₆), 1.48 (9 H, s), 1.58 (1 H, dddd, *J* 12.5, 9.0, 7.5, 5.0), 1.95 (1 H, dddd, *J* 12.5, 8.5, 8.0, 6.0), 2.18 (1 H, dqd, *J* 9.0, 7.5, 6.0), 2.86 (1 H, ddd, *J* 10.0, 8.5, 7.5), 2.92 (1 H, d, *J* 10.5), 3.09 (1 H, ddd, *J* 10.0, 8.0, 5.0), 3.60 (1 H, t, *J* 10.5), 4.02 (1 H, d, *J* 10.5), 4.02–4.26 (4 H, m). ¹³C NMR (CDCl₃, 75.5 MHz): δ 13.9, 14.1, 14.2, 28.0, 30.8, 31.7, 42.8, 48.6, 50.3, 56.5, 60.8, 60.9, 67.3, 77.2, 82.1, 168.5, 172.6, 172.6. MS *m/z* (ES⁺) 236, 282, 326, 328, 329, 330, 350, 384 (MH⁺), 406 (MNa⁺). HRMS *m/z* (ES⁺) 406.2216 (MNa⁺ C₂₀H₃₃NNaO₆ requires 406.2206).

19c: Colourless oil. IR (neat): ν 2974, 1730 (s), 1367 (m), 1212 (m), 1150 (s), 1030 (m) cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 0.87 (3 H, s), 1.02 (3 H, d, *J* 7.0), 1.23 (3 H, t, *J* 7.0), 1.27 (3 H, t, *J* 7.0), 1.43 (9 H, s), 1.72 (1 H, dddd, *J* 12.5, 12.0, 10.5, 8.5), 2.08 (1 H, dddd, *J* 12.5, 7.0, 6.5, 1.0), 2.28 (1 H, dqd, *J* 12.0, 7.0, 6.5), 2.70 (1 H, ddd, *J* 10.5, 9.5, 7.0), 2.95 (1 H, ddd, *J* 9.5, 8.5, 1.0), 3.53 (1 H, d, *J* 11.5), 3.96 (1 H, dd, *J* 11.5, 7.5), 3.98–4.26 (4 H, m), 4.03 (1 H, d, *J* 7.5). ¹³C NMR (CDCl₃, 75.5 MHz): δ 14.0, 14.1, 14.2, 20.6, 28.0, 36.3, 43.8, 46.3, 51.7, 53.8, 60.6, 60.9, 65.3, 73.0, 81.7, 170.7, 171.4, 171.8. MS *m/z* (ES⁺) 282, 306, 328, 329, 350, 406 (MNa⁺). HRMS *m/z* (ES⁺) 406.2217 (MNa⁺ C₂₀H₃₃NNaO₆ requires 406.2206).

19d: Colourless oil. IR (neat): ν 2976, 2935, 2907, 2876, 1727 (s), 1367 (m), 1251, 1216 (m), 1150 (s), 1096, 1031 (m) cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 1.08 (3 H, s), 1.16 (3 H, d, *J* 7.0), 1.23 (3 H, t, *J* 7.0), 1.26 (3 H, t, *J* 7.0), 1.44 (9 H, s), 1.58 (1 H, ddt, *J* 12.5, 6.5, 5.5), 1.96 (1 H, dddd, *J* 12.5,

8.0, 7.5, 6.5), 2.08 (1 H, qdd, J 7.0, 6.5, 5.5), 2.83–3.00 (2 H, m), 3.52 (1 H, d, J 11.0), 3.88 (1 H, dd, J 11.0, 8.0), 3.95–4.22 (2 H, m), 4.11 (1 H, d, J 8.0), 4.16 (2 H, q, J 7.0). ^{13}C NMR (CDCl_3 , 75.5 MHz): δ 14.0, 14.2, 16.1, 26.6, 28.0, 34.3, 42.1, 46.7, 48.6, 51.5, 60.5, 60.9, 64.8, 74.7, 81.8, 170.7, 171.5, 171.9. MS m/z (ES^+) 282, 306, 328, 329, 350, 406 (MNa^+), 578. HRMS m/z (ES^+) 406.2199 (MNa^+ $\text{C}_{20}\text{H}_{33}\text{NNaO}_6$ requires 406.2206).

4.4.2. Reaction of 5a with diethyl maleate

p-Toluenesulfonic acid monohydrate (2% equiv, 20.0 μmol , 3.8 mg) was added to a solution of **5a** (1.00 equiv, 1.00 mmol, 211 mg) and diethyl maleate (1.00 equiv, 1.00 mmol, 162 μL) in PhCl (1.0 mL). The mixture was heated using a microwave apparatus (power: 250 W, temperature: 140 $^\circ\text{C}$, ramp time: 2 min, hold time: 10 min, max. pressure: 10 bars). After cooling, saturated aqueous NaHCO_3 solution (20 mL) was added and the mixture was extracted with EtOAc (2 \times 20 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give the crude product (383 mg). Purification by flash column chromatography on silica gel (EtOAc/heptane 30%) afforded pure **19d** (7.1 mg, 18.5 μmol , 2%), a 43 : 57 mixture of **19d** and **19a** (15.6 mg, 40.6 μmol , 4%), pure **19a** (17.8 mg, 46.4 μmol , 5%), a 41 : 59 mixture of **19a** and **20a** (91.1 mg, 237 μmol , 24%), pure **20a** (68.3 mg, 178 μmol , 18%), a 56 : 44 mixture of **20a** and **20b** (9.1 mg, 23.7 μmol , 2%) and pure **20b** (49.9 mg, 130 μmol , 13%). These amounts correspond to a total of 259 mg of cycloaddition diastereoisomers **19** and **20** (675 μmol , 67%).

Major product 20a: Colourless oil. IR (neat): ν 2975, 2933, 2874 (w), 1727 (s), 1367 (m), 1245, 1207 (m), 1151 (s), 1097 (m), 1064, 1046, 1030, 1015, 846, 836 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ 1.03 (3 H, d, J 6.5), 1.04 (3 H, s), 1.20 (3 H, t, J 7.0), 1.25 (3 H, t, J 7.0), 1.50 (9 H, s), 1.52 (1 H, m), 1.85 (1 H, m), 1.86 (1 H, m), 2.71 (1 H, ddd, J 11.0, 9.5, 5.5), 2.90 (1 H, m), 3.13 (1 H, d, J 9.0), 3.53 (1 H, dd, J 10.5, 9.0), 4.03–4.23 (2 H, m), 4.12 (2 H, q, J 7.0), 4.41 (1 H, d, J 10.5). ^{13}C NMR (CDCl_3 , 75.5 MHz): δ 14.0, 14.2, 14.2, 20.0, 28.0, 32.5, 45.3, 47.9, 48.5, 55.5, 60.5, 60.7, 66.0, 77.2, 81.7, 169.3, 171.2, 171.9. MS m/z (ES^+) 282, 306, 328, 329, 350, 384 (MH^+), 406 (MNa^+). HRMS m/z (ES^+) 406.2194 (MNa^+ $\text{C}_{20}\text{H}_{33}\text{NNaO}_6$ requires 406.2206).

20b: Colourless oil. IR (neat): ν 2976, 2935, 2879 (w), 1726 (s), 1367, (m), 1256, 1220, 1200 (m), 1147 (s), 1097 (m), 1065 (m), 1042, 1029, 1015, 847 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ 1.09 (3 H, d, J 7.0), 1.21 (3 H, t, J 7.0), 1.24 (3 H, t, J 7.0), 1.25 (3 H, s), 1.43 (1 H, dddd, J 12.0, 11.0, 10.0, 8.0), 1.49 (9 H, s), 1.91 (1 H, dddd, J 12.0, 8.5, 7.0, 3.5), 2.17 (1 H, dq, J 11.0, 7.0), 2.72 (1 H, ddd, J 11.0, 10.0, 3.5), 2.94 (1 H, ddd, J 11.0, 8.5, 8.0), 3.19 (1 H, d, J 11.0), 3.41 (1 H, dd, J 11.0, 10.5), 4.09 (2 H, q, J 7.0), 4.10 (2 H, q, J 7.0), 4.29 (1 H, d, J 10.5). ^{13}C NMR (CDCl_3 , 75.5 MHz): δ 14.0, 14.1, 15.0, 22.7, 28.0, 31.5, 44.3, 47.0, 48.8, 49.1, 60.5, 60.7, 66.3, 77.3, 81.9, 169.5, 171.2, 171.7. MS m/z (ES^+) 282, 306, 328, 329, 350, 384 (MH^+), 406 (MNa^+). HRMS m/z (ES^+) 406.2208 (MNa^+ $\text{C}_{20}\text{H}_{33}\text{NNaO}_6$ requires 406.2206).

4.4.3. Reaction of 5b with diethyl fumarate

p-Toluenesulfonic acid monohydrate (4.0% equiv, 33.4 μmol , 6.4 mg) was added to a solution of **5b** (1.00 equiv, 835 μmol , 200 mg) and diethyl fumarate (1.00 equiv, 835 μmol , 137 μL) in PhCl (1.0 mL). The mixture was heated using a microwave apparatus (power: 250 W, temperature: 140 $^\circ\text{C}$, ramp time: 2 min, hold time: 10 min, max. pressure: 10 bars). After cooling, saturated aqueous

NaHCO₃ solution (20 mL) was added and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product (355 mg). Analysis by ¹H NMR spectroscopy revealed the presence of 3-*tert*-butyl 1,2-diethyl 7-methyl-7a-propylhexahydro-1*H*-pyrrolizine-1,2,3-tricarboxylate, mainly as the diastereoisomer **21a**. Purification by flash column chromatography on silica gel (EtOAc/heptane 10%) afforded pure **21c** (8.6 mg, 20.8 μmol, 2%), a 50 : 50 mixture of **21c** and **21d** (6.5 mg, 15.7 μmol, 2%), pure **21d** (26.9 mg, 65.3 μmol, 8%), a 33 : 67 mixture of **21d** and **21a** (28.1 mg, 68.2 μmol, 8%) and a 70 : 30 mixture of **21a** and **21b** (110 mg, 267 μmol, 32%). These amounts correspond to a total of 180 mg of cycloaddition diastereoisomers **21** (438 μmol, 52%).

Major product 21a: ¹H NMR (CDCl₃, 300 MHz): δ 0.89 (3 H, d, *J* 7.0), 0.95 (3 H, m), 1.23 (3 H, t, *J* 7.0), 1.27 (3 H, t, *J* 7.0), 1.36–1.64 (4 H, m), 1.46 (1 H, dddd, *J* 12.0, 11.5, 6.0, 4.5), 1.47 (9 H, s), 1.78 (1 H, ddd, *J* 12.0, 6.0, 5.5), 1.98 (1 H, qdd, *J* 7.0, 6.0, 5.0), 2.59 (1 H, ddd, *J* 11.5, 9.0, 5.5), 2.95 (1 H, dd, *J* 9.0, 6.0), 3.13 (1 H, d, *J* 12.0), 3.59 (1 H, dd, *J* 12.0, 11.5), 3.81 (1 H, d, *J* 11.5), 4.03–4.27 (4 H, m). ¹³C NMR (CDCl₃, 75.5 MHz): δ 14.0, 14.1, 14.2, 14.6, 16.7, 27.9, 33.1, 39.1, 40.0, 47.4, 49.3, 53.8, 60.7, 60.8, 68.0, 75.1, 81.8, 168.2, 171.4, 172.3.

4.4.4. Reaction of **5b** with diethyl maleate

p-Toluenesulfonic acid monohydrate (2% equiv, 20.0 μmol, 3.8 mg) was added to a solution of **5b** (1.00 equiv, 1.00 mmol, 239 mg) and diethyl maleate (1.00 equiv, 1.00 mmol, 162 μL) in PhCl (1.0 mL). The mixture was heated using a microwave apparatus (power: 250 W, temperature: 140 °C, ramp time: 2 min, hold time: 10 min, max. pressure: 10 bars). After cooling, saturated aqueous NaHCO₃ solution (20 mL) was added and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product (400 mg). Analysis by GC/MS and NMR spectroscopy showed full conversion of **5b** and the production of 3-*tert*-butyl 1,2-diethyl 7-methyl-7a-propylhexahydro-1*H*-pyrrolizine-1,2,3-tricarboxylate, mainly as the diastereoisomers **22a** and **22b** (ratio 48 : 52). The diastereoisomers **21** were also observed, in minor amounts. Purification by flash column chromatography on silica gel (EtOAc/heptane 20%) afforded various mixtures of diastereoisomers of 3-*tert*-butyl 1,2-diethyl 7-methyl-7a-propylhexahydro-1*H*-pyrrolizine-1,2,3-tricarboxylate (total amount 331 mg, 804 μmol, 80%). After a second flash column chromatography, **22a** was isolated [contaminated with a minor amount of **21a**] (44.9 mg, 109 μmol, 11%), as well as pure **22b** (36.5 mg, 88.6 μmol, 9%).

22a: Colourless oil. ¹H NMR (CDCl₃, 300 MHz): δ 0.83 (3 H, t, *J* 7.0), 1.09 (3 H, d, *J* 6.5), 1.20 (3 H, t, *J* 7.0), 1.20–1.60 (2 H, m), 1.25 (3 H, t, *J* 7.0), 1.38 (2 H, m), 1.50 (9 H, s), 1.52 (1 H, m), 1.78 (1 H, m), 1.82 (1 H, m), 2.70 (1 H, ddd, *J* 10.0, 9.0, 6.0), 2.85 (1 H, ddd, *J* 10.0, 6.0, 2.0), 3.09 (1 H, d, *J* 9.0), 3.43 (1 H, dd, *J* 10.5, 9.0), 4.00–4.21 (4 H, m), 4.25 (1 H, d, *J* 10.5). ¹³C NMR (CDCl₃, 75.5 MHz): δ 13.7, 14.1, 14.1, 14.9, 18.1, 28.0, 32.8, 36.1, 46.8, 47.2, 48.6, 56.2, 60.5, 60.5, 66.5, 77.2, 81.3, 169.4, 171.4, 172.1. MS *m/z* (ES⁺) 334, 356, 357, 378, 412 (MH⁺), 434 (MNa⁺), 435. HRMS *m/z* (ES⁺) 434.2509 (MNa⁺ C₂₂H₃₇NNaO₆ requires 434.2519).

22b: Colourless solid. M.p. 77.5–78 °C. IR (neat): ν 2959, 2934, 2873 (w), 1745 (m), 1721 (s), 1365 (m), 1333 (m), 1205 (m), 1156 (s), 1141 (m), 1102 (m), 1069 (m), 1018 (m), 845 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 0.88 (3 H, t, *J* 7.0), 1.06 (3 H, d, *J* 7.0), 1.21 (3 H, t, *J* 7.0), 1.24 (3 H, t, *J* 7.0),

1.26 (1 H, m), 1.40 (1 H, dddd, J 12.0, 11.0, 9.5, 8.0), 1.48 (9 H, s), 1.50 (1 H, m), 1.53–1.70 (2 H, m), 1.85 (1 H, dddd, J 12.0, 8.5, 7.0, 3.5), 2.33 (1 H, dq, J 11.0, 7.0), 2.66 (1 H, ddd, J 11.0, 9.5, 3.5), 2.87 (1 H, ddd, J 11.0, 8.5, 8.0), 3.24 (1 H, d, J 11.0), 3.36 (1 H, dd, J 11.0, 10.5), 4.09 (2 H, q, J 7.0), 4.10 (2 H, q, J 7.0), 4.20 (1 H, d, J 10.5). ^{13}C NMR (CDCl_3 , 75.5 MHz): δ 14.1, 14.1, 14.7, 15.2, 16.9, 28.0, 31.9, 35.2, 39.0, 47.4, 48.6, 50.1, 60.4, 60.6, 66.7, 79.8, 81.4, 169.7, 171.4, 171.8. MS m/z (ES^+) 206, 334, 356, 357, 378, 412 (MH^+), 434 (MNa^+), 435. HRMS m/z (ES^+) 434.2505 (MNa^+ $\text{C}_{22}\text{H}_{37}\text{NNaO}_6$ requires 434.2519).

4.5. Cycloaddition of **23** with diethyl fumarate

p-Toluenesulfonic acid monohydrate (5.0% equiv, 12.5 μmol , 2.4 mg) was added to a solution of **23** (1.00 equiv, 250 μmol , 53.3 mg) and diethyl fumarate (1.00 equiv, 250 μmol , 43.0 mg) in PhCl (0.25 mL). The mixture was heated using a microwave apparatus (power: 300 W, temperature: 180 $^\circ\text{C}$, ramp time: 2 min, hold time: 10 min, max. pressure: 10 bars). After cooling, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 1 M NaOH aqueous solution (2.0 mL) and H_2O (5.0 mL), then dried over Na_2SO_4 , filtered and concentrated to afford the crude product (162 mg). Purification by flash column chromatography on silica gel (EtOAc/heptane 20%) afforded pure 3,4-diethyl 2-methyl 5-cyclopentyl-5-(methoxymethyl)pyrrolidine-2,3,4-tricarboxylate **24** (63.0 mg, 163 μmol , 65%).

24: Thick pale yellow oil. ^1H NMR (CDCl_3 , 300 MHz): δ 1.24 (3 H, t, J 7.0), 1.25 (3 H, t, J 7.0), 1.28–1.88 (8 H, m), 2.26 (1 H, m), 2.39 (1 H, br s, NH), 3.19 (3 H, s), 3.30 (1 H, d, J 11.0), 3.32 (2 H, AB system, δ_A 3.23, δ_B 3.41, J_{AB} 9.5), 3.50 (1 H, dd, J 11.0, 10.0), 3.74 (3 H, s), 3.83 (1 H, d, J 10.0), 4.12 (2 H, q, J 7.0), 4.17 (2 H, AB part of an ABX_3 system, δ_A 4.13, δ_B 4.21, J_{AB} 18.0, J_{AX} 7.0, J_{BX} 7.0). ^{13}C NMR (CDCl_3 , 75.5 MHz): δ 14.1, 14.2, 24.7, 25.5, 26.8, 27.5, 46.5, 52.0, 52.3, 54.3, 58.6, 60.6, 60.9, 62.6, 69.1, 76.0, 170.8, 172.2, 172.8.

10 M HCl aqueous solution (about 0.1 mL) was added into a solution of a sample of **24** (1.00 equiv, 186 μmol , 71.8 mg) in EtOAc (1.0 mL). The mixture was concentrated under reduced pressure to give a viscous pale yellow oil (82.4 mg). This crude product had turned solid after a few days. Recrystallisation from EtOAc afforded pure **24.HCl** as colourless crystals that were suitable for X-ray diffraction (53.8 mg, 126 μmol , 69%).

24.HCl: Colourless crystals. M.p. 145.6–148.6 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz): δ 1.28 (3 H, t, J 7.0), 1.29 (3 H, t, J 7.0), 1.47–1.67 (8 H, m), 2.64 (1 H, tt, J 10.0, 8.0), 3.34 (3 H, s), 3.59 (1 H, d, J 11.0), 3.77 (2 H, AB system, δ_A 3.76, δ_B 3.78, J_{AB} 10.5), 3.85 (1 H, dd, J 11.0, 10.0), 3.88 (3 H, s), 4.20 (2 H, br q, J 7.0), 4.25 (2 H, AB part of an ABX_3 system, δ_A 4.23, δ_B 4.27, J_{AB} 11.0, J_{AX} 7.0, J_{BX} 7.0), 4.75 (1 H, d, J 10.0), 7.56 (1 H, br s, NH), 12.55 (1 H, br s, NH). ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 13.98, 14.04, 24.5, 25.2, 27.7, 27.8, 45.0, 52.1, 53.8, 58.9, 59.6, 62.0, 62.3, 71.8, 74.4, 77.2, 167.6, 168.1, 168.9.

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Supplementary data

Supplementary data related to this article can be found at <http://xx.xx>.

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