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A cascade thermal isomerisation of cyclobutane di-(carbomethoxy) Δ^2-1,2,3-triazolines with intramolecular 1,3-dipolar cycloreversion as the key step

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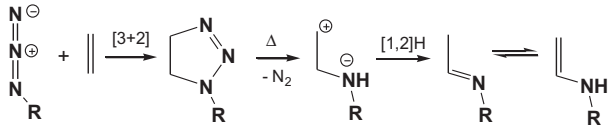
ABSTRACT

Unprecedented thermal isomerisation of the strained Δ^2-1,2,3-triazolines led to the formation of products possessing a novel 1,2,7-triaza-[3.3.0]octa-2-ene ring system incorporated in a norbornane framework. Experimental evidence and quantum chemical calculations have been used to support a postulated reaction mechanism involving as the first step, a rare example of intramolecular 1,3-dipolar cycloreversion. Subsequently, several steps involving 1,3-dipolar ring closure, hydrogen shifts and an intramolecular addition are postulated leading to the observed product of this deep-seated isomerisation. The influence of changing substituents on the product outcome of this novel reaction cascade was also studied.

1. Introduction

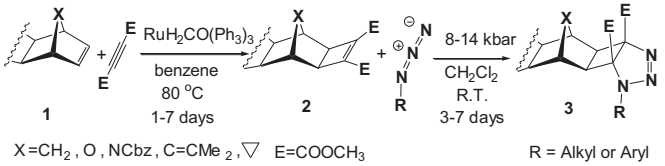
Standard Δ^2-1,2,3-triazoline chemistry involves formation of 1,2,3-triazolines by 1,3-dipolar addition of azides to alkenes. This reaction works best with electron-rich olefins (Scheme 1).[1] Thermolysis of 1,2,3-triazolines and imine formation with concomitant dinitrogen elimination is the standard chemical behaviour of this class of compounds.[2,3] However, unusual reaction products were formed in some cases, especially with substituted molecules.[4]



Scheme 1. Thermal rearrangement of Δ^2-1,2,3-triazolines.

In particular, fused-ring Δ^2-1,2,3-triazolines, readily cycloreverse when a small ring is annulated to the C–C subunit such as Dewar thiophene,[5] Dewar benzene[6] or 3,3-dimethylcyclopropene,[7] with molecular strain being a driving force for ring opening. This 1,3-dipolar cycloreversion of Δ^2-1,2,3-triazolines to a diazomethane gives an imine entity, which is involved in further molecular rearrangements.

Preparation of norbornene fused 2,3,4-triazabicyclo[3.2.0]hept-2-ene substrates required for our research was achieved employing the standard synthetic procedures developed in our laboratories. The first step was a ruthenium catalysed [2+2] cycloaddition reaction of norbornenes **1** and dimethylacetylene dicarboxylate (Mitsudo reaction)[8] to form the corresponding cyclobutene diesters **2** in high yields (Scheme 2).[9] These cyclobutene diesters were further subjected to high pressure azide additions[10] in dichloromethane to form 2,3,4-triazabicyclo[3.2.0]hept-2-enes **3**.[11]



Scheme 2. Preparation of 2,3,4-triazabicyclo[3.2.0]hept-2-enes.

This reaction sequence was used in our previous work to synthesise the corresponding aziridines and finally fused 7-azanorbornanes.[12,13] It was found during the work-up and handling that norbornene fused 2,3,4-triazabicyclo[3.2.0]hept-2-enes **3** are thermally unstable systems where substituents weaken the

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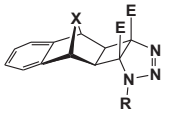
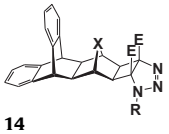
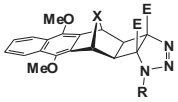
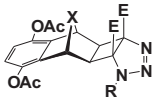
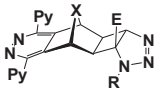
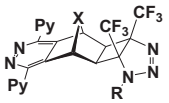
central cyclobutane C–C bond. These strained bicyclic systems possess several functionalities, which enhance their reactivity. The aim of this paper is to give detailed synthetic and mechanistic study in light of experimental evidence supporting the novel reaction cascade.[14]

2. Results and discussion

2.1. Preparation of triazolines

The 2,3,4-triazabicyclo[3.2.0]hept-2-enes **4**–**21** required for this study were prepared by high pressure azide additions[10] in dichloromethane (method B) or by stirring at room temperature without the presence of solvent (method A) (Table 1).

Table 1
Preparation of triazolines **4**–**21**

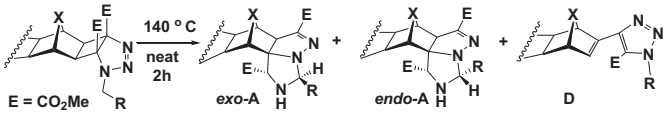
Triazoline	X	R	Method[a]	*p* (kbar)	*t* (d)	Yield (%)
						
4	CH_2	Bn	A		15	99[13]
5	CH_2	CH_2–4-$OMeC_6H_4$	B	14	3	61
6	CH_2	CH_2–4-$NO_2C_6H_4$	B	8	3	67
7	CH_2	CH_2COOCH_3	B	8	3	52[15]
8	CH_2	$CH_2CH{=}CH_2$	B	8	3	66
9	Δ[c]	Bn	A		23	98[13]
10	$C{=}CMe_2$	Bn	A		12	59[13]
11	NCBz[b]	Bn	A		12	80[16]
12	O	Bn	B	8	3	78[13]
13	O	CH_2–4-$OMeC_6H_4$	B	14	3	55
						
14	CH_2	CH_2–4-$OMeC_6H_4$	B	8	7	80
15	CH_2	CH_2–4-$SMeC_6H_4$	B	8	7	62
16	CH_2	4-Py	B	8	7	93
17	CH_2	3-Py	B	8	7	85
						
18	CH_2	Bn	A		3	74
						
19	CH_2	Ph	A		10	66[11]
						
20	CH_2	Bn	B	8	5	86[17]
						
21	CH_2	Bn	B	8	3	77

[a] Method A: neat, rt; method B: high pressure, CH_2Cl_2, rt.
[b] CBz=CO_2Bn; E=CO_2Me.
[c] Δ=cyclopropylidene.

2.2. Thermal isomerisations

Results of thermal isomerisation experiments of 2,3,4-triazabicyclo[3.2.0]hept-2-enes **4**–**21** are summarized in Tables 2 and 3. The effects of substitution changes and reaction conditions (at elevated temperature 140 °C, without the presence of solvent, Table 2, and at low temperature 60–80 °C in solvent, Table 3) on reaction outcomes were studied.

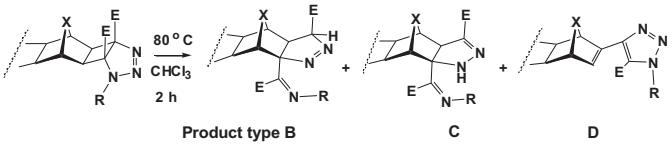
Table 2
Thermal isomerisations of triazolines **4**–**21** at 140 °C (isolated yields in %)



Triazoline	X	R	*t* (h)	*exo*-A	*endo*-A	D
4	CH_2	Ph	1	*exo*-**22** (24)	*endo*-**22** (18)	**23** (14)
5	CH_2	4-$OMeC_6H_4$	6	*exo*-**24** (24)	*endo*-**24** (13)	**26** (23)
6	CH_2	4-$NO_2C_6H_4$	1	*exo*-**27** (11)	*endo*-**27** (16)	**28** (11)
11	NCBz	Ph	1			[a]
12	O	Ph	1			[a]
13	O	4-$OMeC_6H_4$	1			[a]
18	CH_2	Ph	1	*exo*-**29** (23)	*endo*-**29**[b]	**30** (8)
21	CH_2	Ph	1			0[c]

[a] Other products isolated.
[b] Not isolated.
[c] At 100 °C, 2 h, or at 120 °C, 1 h no reaction, at 140 °C, 1 h decomposition.

Table 3
Thermal isomerisations of triazolines **4**–**20** at 80 °C (isolated yields in %)[e]

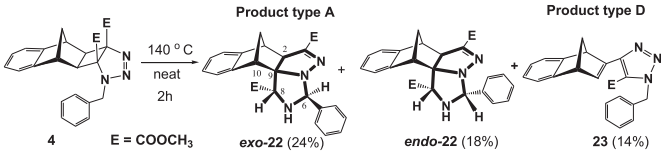


Triazoline	X	R	*t* (h)	B	C	D
4	CH_2	Bn	2		**31** (94)	
5	CH_2	CH_2–4-$OMeC_6H_4$	12	**32** (53)	**33** (35)	**26** (12)
7	CH_2	CH_2COOCH_3	2[a]		**34** (96)	
8	CH_2	$CH_2CH{=}CH_2$	12	**35** (87)		
9	Δ[f]	Bn	2		**36** (95)	
10	$C{=}CMe_2$	Bn	2			**37** (5)[c]
20	CH_2	Bn	2	**38** (93)		
14	CH_2	CH_2–4-$OMeC_6H_4$	12[b]		**39** (90)	
15	CH_2	CH_2–4-$SMeC_6H_4$	12[b]		**40** (80)	
16	CH_2	4-Py	72[b]	**41** (85)		
17	CH_2	3-Py	24[b]	**42** (60)		
19	CH_2	Ph	0.3[d]	**43** (58)		[c]

[a] 100 °C.
[b] 60 °C.
[c] Other products isolated.
[d] 140 °C, no solvent.
[e] E=CO_2Me.
[f] Δ=cyclopropylidene.

Our first observed thermal isomerisation of triazoline **4** (by heating at 140 °C for 2 h, without the presence of solvent in an open flask) led to the formation of mixture of isomeric polycycles (*exo*/*endo*)-**22** possessing a novel 1,2,7-triazabicyclo[3.3.0]octa-2-ene ring system, which is highlighted in bold (Scheme 3, product type A). In addition, a smaller amount of triazoline **23** (14%) was obtained (product type D).

NMR spectroscopy was employed for structural study of all new products and results obtained from ^{13}C and ^{1}H spectra, as well as 2D COSY and NOESY correlations were combined. For this purpose the ^{1}H NMR spectra were the most informative and show some interesting features. For instance, the ^{1}H NMR spectrum of *exo*-**22**



Scheme 3. Thermal rearrangement of triazoline **4** at 140 °C.

consists of 7 singlets (δ 2.84, 3.09, 3.13, 3.62, 3.74, 3.89 and 6.00), 3 doublets (δ 1.92, 2.07 and 7.72), and 2 aromatic multiplets (δ 7.04 and 7.38), while the ^{13}C NMR spectrum contains 22 carbon resonances. The key spectroscopic evidence for the product *exo*-**22** is a benzylic (C_6), two methyl and two bridgehead proton resonances and the molecular ion (^{1}H NMR: δ benzylic 6.00, δ OMe 3.13, 3.89, δ bridgehead 2.84, 3.74, HRMS-ESI: m/z=417.1685). Particularly indicative is the proton resonance of the C_8 methyl ester group positioned under the benzene ring, which is significantly affected by the aromatic ring current and shifted at higher magnetic field (δ 3.13). The strong NOESY correlation between the benzylic proton H_6 and the *endo* proton H_2 defines the outward orientation of the C_6 phenyl substituent (i.e., the *S*-configuration), whereas a NOESY correlation between proton H_8 and bridgehead proton H_{10} additionally supports the inward orientation of the C_8 ester group. At the highest magnetic field are the CH_2 bridge protons ($H_{17a,b}$) displaying a characteristic two-spin AB system[18] centred at δ 2.01. The structure of this novel compound was unambiguously confirmed by X-ray structural analysis (Fig. 1).

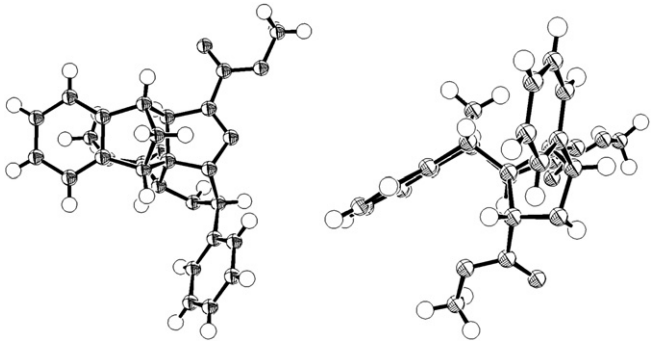


Fig. 1. An ORTEP view of the molecular structure of *exo*-**22** (top and side-view). Thermal ellipsoids are drawn at the 50% probability level.

The structure of the minor isomer *endo*-**22** was elucidated by the comparison of spectroscopic data with isomer *exo*-**22**. There are certain similarities with ^{1}H NMR spectra of two isomeric products (Fig. 2). In both isomers, one of the unsymmetrical C_8 ester signals is shielded by an aromatic ring and shifted towards higher magnetic field by ca. 1 ppm. Two bridgehead proton singlets are present in both structures indicating an unsymmetrical norbornane system. There is a significant difference in the chemical shifts of bridgehead protons H_{10}, mainly due to the orientation of the phenyl substituent. In the case of *endo*-**22** product, proton H_{10} is de-shielded as the phenyl ring is positioned inward (under the polycyclic framework). Finally, the change of configuration of C_6 causes the benzylic protons H_6 to be found at significantly different positions. Positive NOESY correlation between protons H_6 and H_8 in *endo*-**22** coupled with the lack of correlation between protons H_6 and H_2 defines without a doubt the inward orientation of the C_6 phenyl substituent (i.e., the *R*-configuration).

The thermolysis of triazolines **4**–**6** follows identical pattern. The *S*/*R* isomers were carefully separated for phenyl, *p*-methoxy and *p*-nitro substituted triazolines and experimental ^{1}H NMR ratios were determined: (*exo*/*endo*)-**22** (5:1), (*exo*/*endo*)-**24** (10:1), and (*exo*/*endo*)-**27** (6:1). In addition, thermolysis of triazoline **18** gave *exo*-**29**

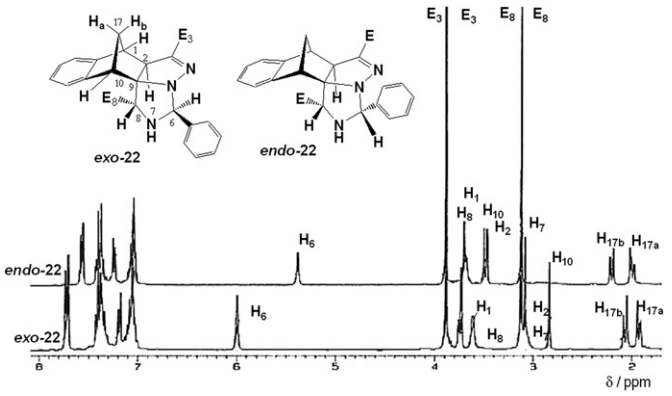
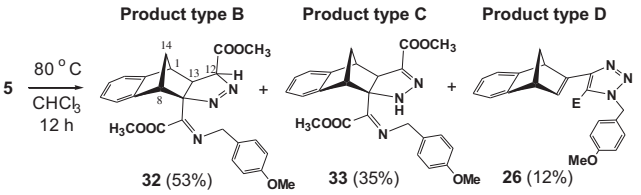


Fig. 2. 300 MHz ^{1}H NMR spectra of isomeric products *exo*-**22** and *endo*-**22** in $CDCl_3$.

as the major isomer. It was found that in all compounds investigated, the formation of the *exo*-isomer is favoured over the *endo*-isomer, *p*-methoxybenzyl substitution in **5** gave the highest *exo*/*endo*-ratio (10:1), which may be attributed to steric factors. This conclusion is supported by density functional theory calculations at the B3LYP/6-31G* level, which indicated that the *exo*-isomer, with inward positioned aryl substituent is thermodynamically less stable (*exo*/*endo*-difference is 4.2 kcal/mol).

It was found that the mixture of products formed by thermal reaction of cyclobutene triazolines **4**–**21** are highly influenced by reaction temperature. Entirely different products were formed when thermolysis experiments were carried at lower temperatures (Table 3). For instance, heating of *p*-methoxybenzyl triazoline **5** at 80 °C in chloroform gave as a main product dihydropyrazole *p*-methoxybenzylimine **32** (product type B). In addition, smaller amounts of products **33** and **26** were formed (products type C and D), which will be discussed in the following sections (Scheme 4). Structural elucidation of products (type B and C) was crucial for the mechanistic rationalization of the thermolysis process.

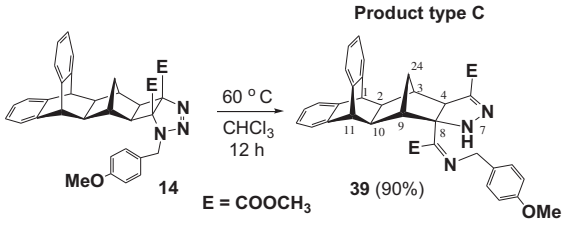


Scheme 4. Thermolysis of triazoline **5**.

The structural assignment of product **32** was based on the NMR spectroscopic evidence. For instance, the ^{1}H NMR of **32** contained a series of proton resonances, the most distinctive being a methylene bridge (AB spin system) δ 1.79, 2.18, *endo*-δ 2.96, the H_{12} δ 3.25, bridgehead (two lines) δ 3.27, 3.67, methoxy (three lines) δ 3.68, 3.74, 3.83, and benzylic methylene (AB spin system) δ 4.61, 4.75 (J=14.9 Hz), which is completely consistent with the assigned structure, and further supported by the 23-signal ^{13}C NMR spectrum, and high-resolution mass spectrometry (m/z=447.1802). Of particular importance are COSY and positive NOESY correlations between protons H_{12} and *endo*-H_{13}, which indicate their coupling, both signals appearing as doublets with coupling constant J=8.7 Hz.

Furthermore, thermal rearrangement of triazoline **14** at 60 °C in chloroform yielded rearranged dihydropyrazole benzylimine **39** (as a single product in 90% yield), product type C (Scheme 5). Identical products were formed by heating of other triazolines at 60–80 °C (Table 3). The ^{1}H NMR spectrum of **39** shows 6 singlets, 6 aliphatic doublets, 2 aromatic doublets and 2 aromatic multiplets, while a ^{13}C NMR spectrum contains 33 carbon resonances, HRMS $m/$

z=575.2420 calcd 575.2435. For **39** three methyl and four bridgehead resonances were found (^{1}H NMR: δ OMe 3.76, 3.77, 3.92, δ bridgehead 2.36, 2.44 (bicyclo[2.2.1] system) and 4.12, 4.27 (bicyclo[2.2.2] system). Methylene protons are distinctively shifted by aromatic ring current towards higher magnetic field (δ −0.21, 0.81), defining the spatial orientation of the bicyclo[2.2.2] system relative to the bicyclo[2.2.1] moiety. While *endo* protons H_2/H_{10} appear as an AB system (δ 2.03, 2.08), the *endo* proton H_4 is singlet, δ 3.71. The most characteristic feature of **39** was the proton resonance of the amino proton H_7 positioned at δ 6.52 (br s). The X-ray structure of this compound is given in Fig. 3.



Scheme 5. Thermolysis of triazoline **14**.

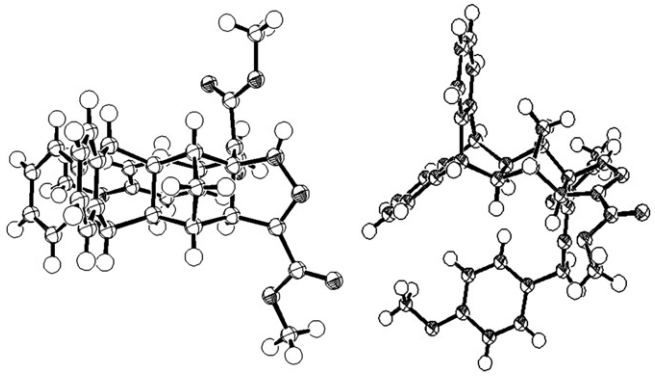


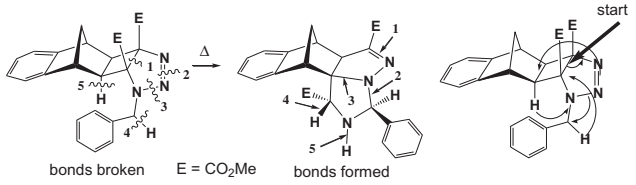
Fig. 3. An ORTEP view of the molecular structure of **39** (top and side-view). Thermal ellipsoids are drawn at the 50% probability level.

Structures of products type B (**32**) and type C (**33**) could be easily distinguished on the basis of their characteristic ^{1}H NMR chemical shifts and their coupling patterns. Therefore, protons H_{12} and *endo*-H_{13} are coupled in the case of 4,5-dihydro-3*H*-pyrazole (**32**), while this coupling is absent in 4,5-dihydro-1*H*-pyrazole (**33**). Furthermore, proton H_{12} appears at δ 2.95 in the case of **32**, while it is not present in 4,5-dihydro-1*H*-pyrazole **33**, instead, a new resonance for H_{10} appears at the lower field (δ 6.69). Accordingly, the change of magnetic environment around the *endo* protons H_{13} causes their appearance at different positions in the ^{1}H NMR spectra at δ 3.20 and 4.34 (in **32** and **33**, respectively). The resonances of the benzylic protons are much less affected.

The results summarized in Table 3 indicate that shorter heating times at lower temperatures led to the formation of product type B, which upon prolonged heating or temperature increases lead to the formation of product type C and other products.

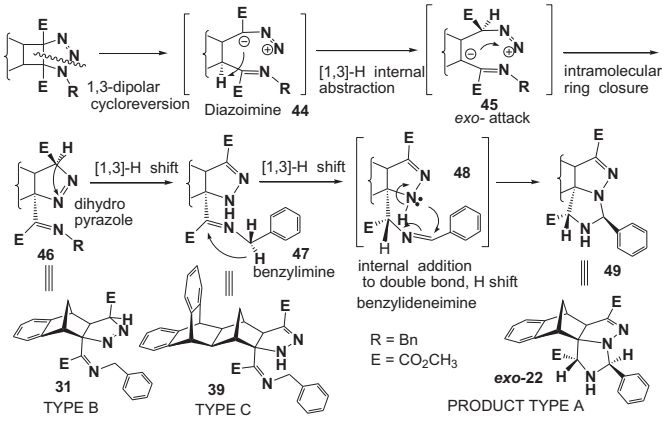
2.3. Mechanistic considerations

Elucidation of the structures of two key-intermediates, and of the final product (products of type A–C) was critical for completion of the overall reaction mechanism picture. An overall mechanistic picture of deep-seated rearrangement involving three H-shifts is depicted in Scheme 6. It involves five bonds to break, and also five new bonds to be formed in the process. We assume that rearrangement starts with breaking of the weakened central cyclobutane bond.



Scheme 6. An overall mechanistic picture of the rearrangement.

The proposed reaction mechanism starts with an intramolecular 1,3-dipolar cycloreversion and formation of the corresponding diazoimine **44** (Scheme 7).[19–21] The reaction mechanism proposed in Scheme 7 shows a series of highly stereoselective steps. This mechanistic proposal is based on the 1,3-dipolar cycloreversion of Δ^2-1,2,3-triazolines to diazomethane and imine entities, in particular when triazolines are annulated to the strained small ring systems.[5,6,7] In the next step, diazoimine **44** undergoes hydrogen migration and formation of zwitterion **45**, which is thermodynamically more stable 2-norbornenyl anion (by 26.2 kcal/mol, at the B3LYP level). Migration of the *endo*-C_2 hydrogen takes place from the *endo*-side resulting in the *S*-configuration on the ester/diazo substituted carbon. Intramolecular [1,5]-ring closure leads to benzylimino 4,5-dihydro-3*H*-pyrazole **46** (i.e., product type B), with norbornene C_2 possessing *R*-configuration. Selective formation of **46** results from the preferred *exo* attack of the terminal electrophilic diazo nitrogen onto the 2-norbornenyl anion.[22–24] After H-shift on the 4,5-dihydro-3*H*-pyrazole ring, a conjugated benzylimine 4,5-dihydro-1*H*-pyrazole **47** (product type C) is formed. Conjugation of the C=N bond with the carbonyl group makes **47** thermodynamically more stable than intermediate **46** (by 4.83 kcal/mol, as assessed by the B3LYP/6-31G* calculations). Consecutive H-shift within a benzylimine moiety gave an intermediate benzylideneimine **48**. This process is thermodynamically driven, since the conjugation with the aromatic π-system is more effective than conjugation of the C=N bond with the carbonyl group in **47**, making benzylideneimine **48** energetically more stable (by 5.70 kcal/mol, at the B3LYP/6-31G* level). Internal addition of the nitrogen lone pair to double bond and ring closure gave a final ring structure and a formal [1,3]-hydrogen shift completes the formation of **49** (product type A).



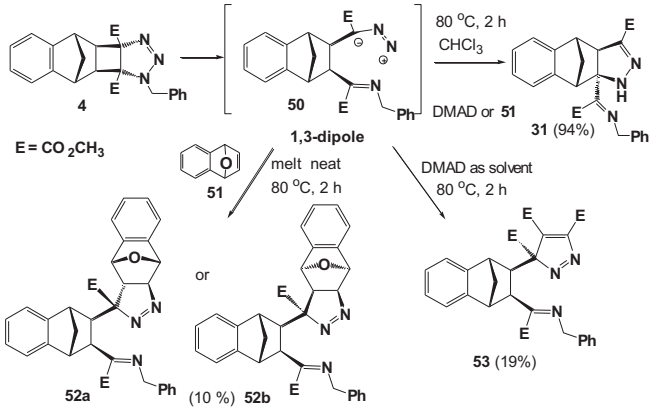
Scheme 7. Proposed reaction mechanism.

The alternative reaction path in which dihydropyrazole **46** firstly experiences H-shift within a benzylimine moiety to afford benzylideneimine intermediate is less likely to take place, since

spectroscopic evidence gathered so far supports the reaction path shown in Scheme 7 (i.e., the existence of intermediates **46** and **47**), while intermediate products for alternative reaction paths were not detected.

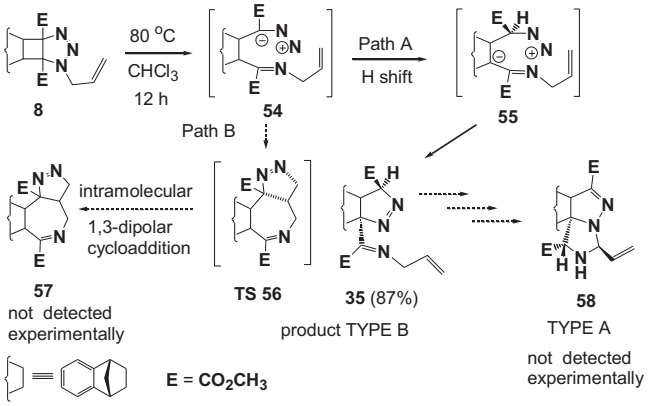
The nature of the formal [1,3]hydrogen shifts depicted in Scheme 7 deserves some comment. The most direct pathway for this reaction in 4,5-dihydro-3*H*-pyrazole **46** is a concerted sigmatropic [1,3]-H shift, occurring with suprafacial stereochemistry. According to Woodward–Hoffman selection rules, it is a thermally forbidden process and requires insurmountable E_a (which is further increased by locking of the allylic system in small five-membered ring). We carried out B3LYP/6-31G* calculations, which indicate that E_a for this process is 120.1 kcal/mol, thereby eliminating this possibility. Other reasonable mechanism involving unimolecular hydrogen shift would be a two-step process, consisting of intramolecular protonation of benzylimine nitrogen, and subsequent proton migration to 4,5-dihydro-1*H*-pyrazole. High basicity of the imino nitrogen[25] could serve as driving force for this pathway. For this process, B3LYP/6-31G* calculations predict significantly smaller E_a (41.2 kcal/mol). Recent calculations on the [1,3]-, [1,5]- and [1,7]-prototropic migrations indicate that a bimolecular multistep mechanism is often energetically more viable.[26–29] Calculated activation energy for prototropic migration in **46** by bimolecular mechanism is further reduced (E_a=34.9 kcal/mol), which indicates that a bimolecular mechanism of intermolecular [1,3]-H shift[30] is likely to be involved.

There is some experimental evidence in support of the proposed reaction mechanism shown in Scheme 7. Firstly, spectroscopic data for stable and isolated products type A–C. Secondly, heating of the intermediate dihydropyrazole **31** (product type B) at higher temperature (140 °C, solvent free, 2 h) led to its transformation into products (*S*/*R*)-**22** (product type A) in high yield. Furthermore, 1,3-dipole trapping experiments were conducted in order to prove the existence of initially formed diazoimine **50** (Scheme 8). Product **31** was obtained when trapping experiments were conducted using diluted samples of triazoline and trapping reagent (in chloroform). However, when trapping experiments were carried out in more concentrated solutions, in neat dipolarophile as solvent (7-oxabenzonorbornadiene and dimethylacetylene dicarboxylate), at 80 °C trapping products dihydropyrazoles **52** and **53** were formed in 10 and 19% yield, respectively. Even under these reaction conditions, major product was **31**, indicating a very low energy barrier of initial intramolecular hydrogen migration. Adduct **52** actually consisted of two isomeric products **52a** and **52b**, which were not separated and were not distinguishable by NMR spectroscopy. Spectral data are consistent with the structure of cycloadduct **52** showing, as the most informative, two methyl singlets δ 3.27, 4.00 and two sets of bridgehead singlets δ 3.66, 4.50 and 5.14, 5.22 in the ^{1}H NMR spectrum and molecular ion (HRMS m/z=561.2259). The most diagnostic peaks in the ^{1}H NMR spectrum of cycloadduct **53** are four methyl singlets δ 3.78, 3.87, 3.94, 3.95 and two bridgehead singlets δ 3.42, 3.76, as well as molecular ion in HRMS m/z=559.1957.



Scheme 8. 1,3-Dipole trapping experiments.

Intramolecular 1,3-dipole trapping[31] of the intermediate diazoalkane was also attempted with allyl triazoline **8** (Scheme 9). By thermal reaction conducted in chloroform at 80 °C for 12 h, intermediate diazoalkene **54** went through path A (following the general cascade mechanism outlined in Scheme 7) and formed dihydropyrazole **35** in 87% yield. Formation of product **57** arising from intramolecular 1,3-dipolar cycloaddition of the diazo group onto the C=C bond was not detected spectroscopically. When the experiment was conducted at higher temperature (solvent free, 140 °C, 2 h), only polymerized material was obtained. These results could be rationalized by the thermal instability of the intermediate dipole **54** and low dipolarophilicity of the alkene substituent. A comparison to the literature precedented rearrangement of triazolines to bicyclic systems involving intramolecular trapping of diazoalkene provides some information for the low reactivity of **8** towards intramolecular 1,3-cycloaddition.[32] Literature molecular systems are conformationally more flexible, as compared to substrate **8**, which induces larger molecular strain and steric congestion preventing reaction cascade to proceed via path B (this rationale is also indicated by molecular modelling).

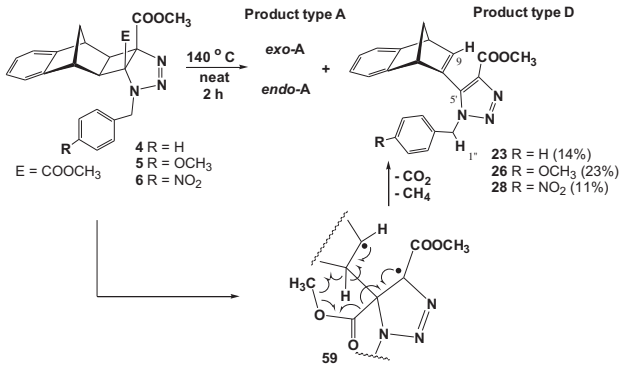


Scheme 9. Intramolecular 1,3-dipole trapping experiments of triazoline **8**.

2.4. Other thermolysis products

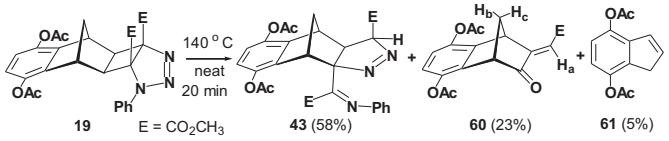
While the products type A–C described in previous sections are the major isolated products, thermal decomposition of certain cyclobutane diester triazolines led to the formation of new and unprecedented products. For instance, thermolysis of triazolines **4**–**6** and **18** at 140 °C besides products of type A yields significant amounts of triazoles **23**, **26**, **28** and **30** (product type D, Table 2, Scheme 10). High thermolysis temperature enhances the formation of product type D, while the experiments carried out at lower temperatures (60–80 °C) significantly reduce their formation (Table 3). It was not possible to determine by NMR spectroscopy, which of these two isomeric products has been formed. The ^{1}H NMR chemical shifts, the multiplicity of signals and the coupling constants with adjacent nuclei are consistent with proposed structure. The ^{1}H NMR spectrum of **23** is characterized by the presence of single methyl resonance δ 3.84, two bridgehead singlets, which are shifted towards lower field, δ 4.21, 4.31, and an olefinic singlet δ 6.66. In addition, the ^{13}C NMR spectrum consists of 20 carbons, while HRMS showed molecular ion (m/z): 386.1511.

Regioisomeric assignment of product **23** depicted in Scheme 10 was supported by HMBC correlations. Two three-bond HMBC correlations from H_9 and $H_{1''}$ to a common quaternary $C_{5'}$ are the most supportive. The tentative reaction mechanism is also proposed, involving cyclobutane carbon–carbon bond breaking, and formation of diradical **59**, followed by an eight-electron reorganization with concomitant loss of CO_2 and CH_4.

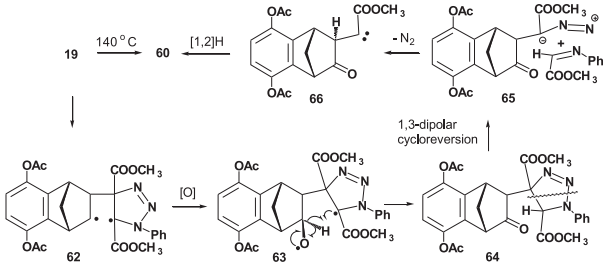


Scheme 10. Thermolysis of triazolines **4**–**6**.

An unprecedented thermolysis product was formed (23% yield) by heating phenyl substituted triazoline **19** in the standard manner (Scheme 11). The major product is **43** (product type B). Small amount of 4,7-diacetyloxyindene indene **61** was also isolated, as the result of a retro Diels–Alder reaction (details on this fragmentation are given in a further section and in Scheme 13). Indicative evidence for the formation of **60** is the presence of vinylic proton resonance in the ^{1}H NMR spectrum (H_a, δ 6.42) and two bridgehead proton resonances (singlets, δ 3.74, 5.16). The bridge protons appear as AB systems (H_b, δ 2.23, and the less shielded H_c, δ 2.71), and three methyl proton resonances appear at δ 2.32, 2.35 and 3.77. The assigned structure is further supported by the 17-signal ^{13}C NMR spectrum and high-resolution mass spectrometry (m/z=368.0896, calcd 368.0891). In addition, the structure of this novel product was unequivocally determined as ketone **60** by single crystal X-ray analysis (Fig. 4).

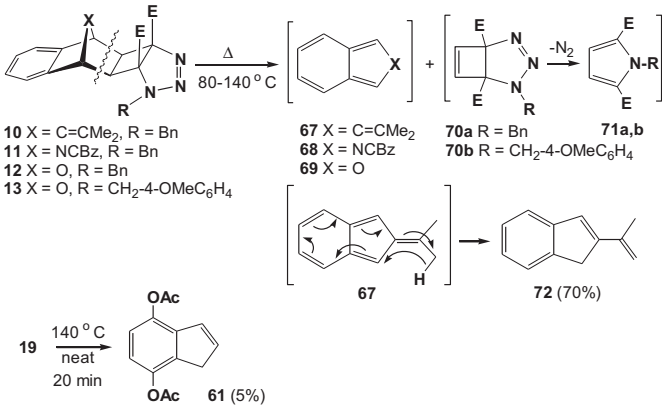


Scheme 11. Thermolysis of triazoline **19**.



Scheme 12. Thermolysis of triazoline **19**.

A plausible reaction mechanism leading to product **60** has been proposed involving cyclobutane C_2–C_3 bond cleavage as a first reaction step and formation of diradical **62** (Scheme 12). This homolytic bond cleavage is analogous to the one proposed for the thermolysis of triazolines **4**–**6** in Scheme 10. Ketone functionality is introduced by the air oxidation via an alkoxy radical intermediate **63**. The ethylene moiety of product **60** could be subsequently formed from ketone **64** by the 1,3-dipolar cycloreversion of the triazoline moiety, followed by dinitrogen elimination from 1,3-dipole **65** via carbene-like intermediate **66** and the subsequent formal [1,2]-hydrogen shift. The proposed **65**→**60** reaction sequence is well established in the literature on the thermolysis of diazo compounds,[33] especially those bearing electron-withdrawing substituents.[34]



Scheme 13. Thermal [8+4] cycloreversion of triazolines **10**–**13** and **19**.

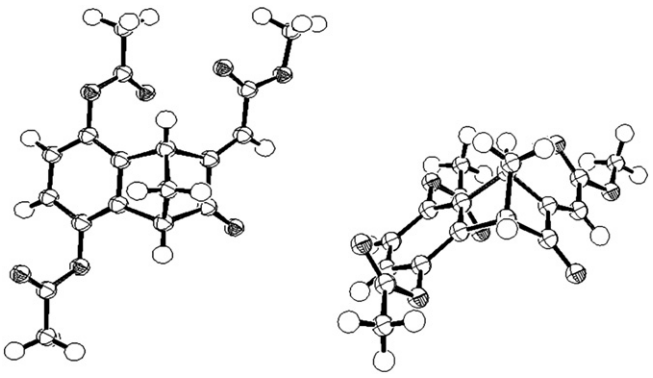
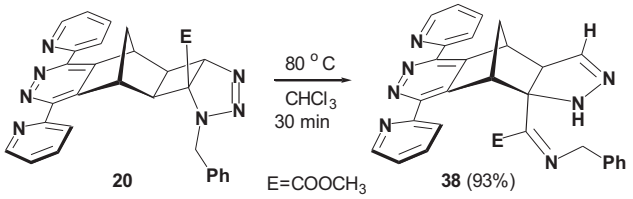


Fig. 4. An ORTEP view of the molecular structure of **60** (top and side-view). Thermal ellipsoids are drawn at the 50% probability level.

A different cycloreversion mechanism from that outlined in Scheme 7 operates in the case of 7-oxa, 7-aza- and 7-isopropylidene benzonorbornene triazolines **10**–**13** (as well as **19** to a smaller extent). Their thermal fragmentation at 80–140 °C via [8+4] cycloreversion forms reactive isobenzo species **67**–**69** and 1-substituted triazoles **70a**,**b**, which further decompose presumably via the corresponding pyrroles **71a**,**b** (Scheme 13). Within reaction conditions applied, isoindole **68** and isobenzofuran **69** quickly decompose, while the 2-(isopropylidene)isoindene **67** rearranges to the stable substituted indene **72**, by [1,11]-hydrogen shift through either a unimolecular or a bimolecular process.[26] This fragmentation pattern has been observed by us in related triazoline photochemistry[16] and aziridine cycloaddition chemistry.[35] A small amount of **37** (5%), product type D was also isolated from thermolysis of **10** at 80 °C.

It was found that variation of substituents could influence the reaction outcome (Tables 2 and 3). For instance, thermolysis of triazoline **20** possessing only one methyl ester group gave **38** as the

single product (product type C, Scheme 14), while, thermal cascade reaction of **19** stopped at the product type B stage.



Scheme 14. Thermolysis of triazoline **20**.

On the other hand, the replacement of the methyl ester substituents with trifluoromethyl in triazoline **21** does not sufficiently activate the cyclobutane ring to start cascade reaction in Scheme 7. Heating at lower temperatures (100–120 °C) showed no reaction, while thermolysis at 140 °C caused decomposition of substrate/products. While the variations of benzyl substituents at triazoline nitrogen does not influence reaction outcomes, preliminary results with *N*-phthalimidoethyl triazoline indicate that after the formation of product type B, elimination of *N*-phthalimidoethyl substituent takes place, which leads to further rearrangements.

2.5. Microwave reactions

It is known that rates of 1,3-dipolar cycloadditions and 1,3-dipolar cycloreversions are accelerated under microwave conditions.[36] Recent literature showed that classical thermal heating could be successfully replaced by microwave conditions for thermally promoted molecular rearrangements leading to unprecedented products.[37] Of particular interest is the example given by Wilson, where the initially formed triazoline intermediates undergo a thermal rearrangement and intermolecular cyclocondensation.[38] Therefore, we anticipated that both reactions (1,3-dipolar cycloadditions and 1,3-dipolar cycloreversions) involved in rearrangement of cyclobutane di-(carbomethoxy) triazolines will benefit from the rate enhancement by microwave irradiation, or even afford different products. Thus, the triazoline **4** was subjected to microwave heating in order to compare microwave and classical conditions. It was found that microwave induced rearrangements follow the same reaction mechanism as classical reaction leading to identical products. By heating of **4** in a closed-vial single mode microwave reactor at 50 °C for 30 min in chloroform (irradiation power 150 W), clean conversion (86% isolated yield) to **31**, product type C was achieved. When triazoline **4** was heated without the presence of solvent (70 °C, 5 min) full conversion to single product **23** was achieved (76% isolated yield), while increasing the temperature to 120 °C (solvent free, 20 min) yielded decomposition products.

3. Conclusion

In this study, unprecedented cascade thermal rearrangement of a series of cyclobutane di-(carbomethoxy) triazolines has been described. It was found that intramolecular 1,3-dipolar cycloreversion is a key step in isomerisation, followed by a series of hydrogen migrations and intramolecular cyclisations. The postulated reaction mechanism is in full accord with the experimental results and quantum chemical calculations. Although this reaction pattern is general in the series of cyclobutane triazolines, variations of reaction conditions and substituents of triazoline and cyclobutane rings lead in some cases to formation of unexpected products and various compositions of reaction mixtures.

4. Experimental section

4.1. General

Reagents were supplied by Aldrich and solvents were used without further purification. For chromatography petroleum ether fraction bp 40–60 °C was used. Thin layer chromatography (TLC) was performed on plastic sheets coated with Merck Kieselgel 60 F_{254}. Column chromatography on silica was carried out using Merck Silica Gel 60 (230–400 mesh). Preparative plates for the chromatotron were produced with Merck Silica Gel 60 PF_{254} containing gypsum. Melting points were determined on a Gallenkamp melting point apparatus and were uncorrected. The ^{1}H and ^{13}C NMR spectra were acquired using Bruker AMX300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) or Bruker Avance DPX400 (400 for ^{1}H NMR and 7100 MHz for ^{13}C NMR) spectrometers at 303 K. Chemical shifts (δ) are reported in parts per million relative to internal tetramethylsilane (TMS). ^{13}C spectra were referenced against residual solvent peaks. COSY and NOESY two-dimensional correlation NMR experiments employed the standard BRUKER parameters. FI-IR spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrometer. The high-resolution mass spectra were obtained by ESMS (electrospray mass spectrometry) on a Micromass Platform II single quadrupole mass spectrometer by Mr. Tom Frey. X-ray crystal structure determinations were carried out by Dr. John Fawcett at the University of Leicester. Microwave assisted reactions were conducted in CEM Discover®LabmateTH/ExplorerPLS® single mode microwave reactor using closed reaction vessel technique (power=125 W).

4.2. Synthesis of cyclobutene triazolines

General method. Mixture of corresponding cyclobutene diester (100 mg, 0.3–0.7 mmol) and an azide (5–10 equiv) in CH_2Cl_2 (1 mL) was pressurized at 14 kbar for 3 days. Products were isolated by radial chromatography (petroleum ether/ethyl acetate), or by treatment with cold methanol and filtration.

*4.2.1. Dimethyl-4-(p-methoxybenzyl)-4,5,6-triaza-1α,2β,8β,9α-pentacyclo[7.6.1.0^{2,8}0^{3,7}0^{10,15}]hexadeca-6,10,12,14-tetraene-3,7-dicarboxylate (**5**).* Mixture of corresponding cyclobutene diester (100 mg, 0.352 mmol) and *p*-methoxybenzyl azide (200 mg, 1.23 mmol) in CH_2Cl_2 (1 mL) was pressurized at 14 kbar for 3 days. Radial chromatography (petroleum ether/ethyl acetate 20:1, R_f=0.45), followed by treatment with cold methanol afforded triazoline as yellow oil (96 mg, 61%); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.69 (td, *J*=11.1, 1.6 Hz, 1H, H16a), 2.00 (d, *J*=11.1 Hz, 1H, H16b), 2.03 (d, *J*=6.9 Hz, 1H, H2), 2.29 (d, *J*=6.9 Hz, 1H, H8), 3.45 (s, 3H, OCH_3), 3.67 (s, 1H, H1), 3.79 (3H, s, OCH_3), 3.82 (s, 1H, H9), 3.86 (3H, s, $COOCH_3$), 4.69 (d, *J*=15.0 Hz, 1H, NCH_2Ph), 4.86 (d, *J*=15.0 Hz, 1H, NCH_2Ph), 6.85–6.86 (m, 2H, Ar), 7.05–7.08 (m, 2H, Ar), 7.19 (d, *J*=9.5 Hz, 2H, Ar), 7.27 (d, *J*=9.5 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm 43.9, 44.6, 48.4, 50.2, 50.5, 51.9, 52.2, 55.3, 64.7, 66.0, 91.9, 113.9, 114.0, 121.1, 121.3, 126.3, 126.4, 130.0, 145.8, 145.9, 159.0, 166.2, 166.8; HRMS (ES): M^+, found 447.1798. $C_{25}H_{27}N_3O_5$ requires 447.1798. Anal. Calcd for $C_{25}H_{27}N_3O_5$: C, 66.80; H, 6.05; N, 9.35. Found: C, 66.82; H, 6.09; N, 9.31%.

*4.2.2. Dimethyl-4-(p-nitrobenzyl)-4,5,6-triaza-1α,2β,8β,9α-pentacyclo[7.6.1.0^{2,8}0^{3,7}0^{10,15}]hexadeca-6,10,12,14-tetraene-3,7-dicarboxylate (**6**).* A solution of corresponding cyclobutene diester (200 mg, 0.700 mmol) and *p*-nitrobenzyl azide (500 mg, 2.65 mmol) in CH_2Cl_2 (1 mL) was pressurized at 8 kbar for 3 days. Solvent was removed in vacuo at room temperature and the residue was treated with cold methanol to afford a yellow oil. It was taken up in $CHCl_3$, washed with H_2O, dried ($MgSO_4$) and evaporated in vacuo at room

temperature to afford a brown coloured oil (215 mg, 67%); R_f=0.6 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.75 (d, J=10.4 Hz, 1H, H16a), 2.03 (d, J=10.4 Hz, 1H, H16b), 2.12 (d, J=6.7 Hz, 1H, H2), 2.36 (d, J=6.7 Hz, 1H, H8), 3.58 (s, 3H, OCH_3), 3.75 (s, 1H, H1), 3.82 (s, 1H, H9), 3.84 (s, 3H, OCH_3), 4.81 (s, 2H, NCH_2Ph), 7.07–7.18 (m, 4H, Ar), 7.50 (d, J=8.7 Hz, 2H, Ar), 8.20 (d, J=8.7 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$), δ/ppm 44.0, 44.6, 45.1, 48.4, 49.8, 49.9, 52.4, 52.7, 66.6, 91.7, 121.2, 121.4, 123.7, 126.5, 129.0, 145.6, 143.7, 145.6, 147.6, 143.7, 165.9, 166.5; HRMS (ES): M^+, found 462.1533. $C_{24}H_{22}N_4O_6$ requires 462.1539. Anal. Calcd for $C_{24}H_{22}N_4O_6$: C, 62.33; H, 4.79; N, 12.12. Found: C, 62.29; H, 4.78; N, 12.14%.

*4.2.3. Dimethyl-4-carbmethoxymethyl-4,5,6-triaza-1α,2β,8β,9α-pentacyclo[7.6.1.0^{2,8}0^{3,7}0^{10,15}]hexadeca-6,10,12,14-tetraene-3,7-dicarboxylate (**7**).* To a solution of corresponding cyclobutene diester (200 mg, 0.704 mmol) in CH_2Cl_2 (1 mL) was added carbmethoxymethyl azide (300 mg, 260 mmol), and pressurized at 8 kbar for 3 days. Evaporation of the solution gave a yellow oil, which was subjected to radial chromatography (eluent 10:1 petroleum ether/methanol) to afford triazoline **7** as yellow oil (146 mg, 52%); R_f=0.5 (petroleum ether/ethyl acetate 20:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.77 (td, J=10.8, 1.3 Hz, 1H, H16a), 2.09 (td, J=10.8, 1.3 Hz, 1H, H16b), 2.39 (td, J=6.9, 1.1 Hz, 1H, H2), 2.48 (td, J=6.9, 1.1 Hz, 1H, H8), 3.74 (s, 3H, OCH_3), 3.78 (s, 1H, H1), 3.80 (s, 3H, OCH_3), 3.84 (s, 1H, H9), 3.85 (s, 3H, OCH_3), 4.33 (d, J=17.9 Hz, 1H, NCH_2Ph), 4.66 (d, J=17.9 Hz, 1H, NCH_2Ph), 7.07 (dd, J=5.3, 3.1 Hz, 2H, Ar), 7.16–7.19 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm 44.1, 44.7, 45.1, 48.2, 48.3, 50.7, 52.4, 52.6, 54.8, 66.9, 92.1, 121.0, 121.4, 126.1, 126.4, 146.1, 146.3, 166.5, 166.8, 169.4; HRMS (ES): M^+, found 399.1432. $C_{20}H_{21}N_3O_6$ requires 399.1430. Anal. Calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52. Found: C, 60.18; H, 5.31; N, 10.49%.

*4.2.4. Dimethyl-4-allyl-4,5,6-triaza-1α,2β,8β,9α-pentacyclo[7.6.1.0^{2,8}0^{3,7}0^{10,15}]hexadeca-6,10,12,14-tetraene-3,7-dicarboxylate (**8**).* To a solution of corresponding cyclobutene diester (200 mg, 0.704 mmol) in CH_2Cl_2 (1 mL) was added allyl azide (400 mg, 4.80 mmol), and pressurized at 8 kbar for 3 days. Evaporation of the solution gave a yellow oil, which was treated with cold methanol. The solid was collected by filtration and washed with a small amount of cold methanol to afford triazoline **8** as colourless solid (170 mg, 66%); mp 116–118 °C; R_f=0.35 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.70 (td, J=10.7, 1.6 Hz, 1H, H16a), 2.05 (td, J=10.7, 1.6 Hz, 1H, H16b), 2.21 (td, J=6.7, 1.3 Hz, 1H, H2), 2.34 (td, J=6.7, 1.3 Hz, 1H, H8), 3.67 (s, 1H, H1), 3.78 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.95 (s, 1H, H9), 4.15 (ddd, J=10.2, 7.5, 1.3 Hz, 1H), 4.36 (ddd, J=10.2, 7.5, 1.3 Hz, 1H), 5.21 (td, J=16.9, 1.3 Hz, 1H, NCH_2Ph), 5.24 (td, J=16.9, 1.3 Hz, 1H, NCH_2Ph), 5.92–5.94 (m, 1H), 5.89–5.91 (m, 1H, Ar), 5.94–5.95 (m, 1H, Ar), 7.07–7.10 (m, 1H, Ar), 7.15–7.19 (m, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm 44.4, 44.7, 45.1, 49.0, 50.4, 51.2, 52.7, 52.8, 66.5, 92.4, 119.4, 121.6, 121.7, 126.8 (2C), 133.1, 146.1, 146.3, 166.7, 167.3; IR (KBr): 1450, 1720, 1742 cm^{-1}; HRMS (ES): M^+, found 367.1537. $C_{20}H_{21}N_3O_4$ requires 367.1532. Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.35; H, 5.81; N, 11.37%.

*4.2.5. Dimethyl-4-(p-methoxybenzyl)-16-oxa-4,5,6-triaza-1α,2β,8β,9α-pentacyclo[7.6.1.0^{2,8}0^{3,7}0^{10,15}]hexadeca-6,10,12,14-tetraene-3,7-dicarboxylate (**13**).* A solution of corresponding cyclobutene diester (100 mg, 0.349 mmol) and *p*-methoxybenzyl azide (200 mg, 1.23 mmol) in CH_2Cl_2 (1 mL) was pressurized at 14 kbar for 3 days. Radial chromatography (petroleum ether/ethyl acetate 20:1; R_f=0.35), followed by treatment with cold methanol afforded triazoline **13** as colourless solid (86 mg, 55%); mp 117–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.07 (d, J=6.4 Hz, 1H, H2), 2.48 (d, J=6.4 Hz, 1H, H8), 3.65 (s, 3H, $COOCH_3$), 3.74 (s, 3H, OCH_3), 3,82 (s, 3H, $COOCH_3$), 4.63 (d, J=15.0 Hz, 1H, NCH_2Ph), 4.98 (d, J=15.0 Hz, 1H, NCH_2Ph), 5.75 (s, 1H, H1), 5.96 (s, 1H, H9), 6.85 (d, J=8.6 Hz, 2H, Ar), 7.24–7.26 (m, 4H, Ar), 7.28–7.30 (d, J=8.6 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm 47.5, 49.5, 50.9, 52.4, 52.6, 53.3, 66.2, 78.6, 78.7, 91.0, 114.1, 119.6, 119.8, 127.3, 127.4, 127.7, 129.9, 142.5, 143.2, 159.6, 165.6, 166.4; HRMS (ES): M^+, found 449.1596. $C_{24}H_{23}N_3O_6$ requires 449.1586. Anal. Calcd for $C_{24}H_{23}N_3O_6$: C, 64.13; H, 5.16; N, 9.35. Found: C, 64.17; H, 5.01; N, 9.31%.

*4.2.6. Dimethyl-6,7,8-triaza-8-(p-methoxybenzyl)-1α,2β,3α,4β,10-β,11α,12β,13α-octatacyclo[11.6.6.1^{3,11}0^{2,12}0^{4,10}0^{5,9}0^{14,19}0^{20,25}]-hexacosa-6,14,16,18,20,22,24-heptaene-5,9-dicarboxylate (**14**).* To a solution of corresponding cyclobutene diester (100 mg, 0.240 mmol) in CH_2Cl_2 (1 mL) was added *p*-methoxylbenzyl azide (200 mg, 1.22 mmol), and pressurized at 8 kbar for 1 week. The solution was evaporated to give a yellow oil, which was subjected to column chromatography (CH_2Cl_2/petroleum ether=1:1; R_f=0.55) to afford product **14** as a white powder (110 mg, 80%); mp 96–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm −0.22 (d, J=12.6 Hz, 1H, H25a), 0.93 (d, J=12.6 Hz, 1H, H25b), 1.43 (d, J=2.2 Hz, 1H, H2), 1.55 (d, J=2.2 Hz, 1H, H12), 1.97 (d, J=2.5 Hz, 1H, H4), 2.20 (d, J=2.5 Hz, 1H, H10), 2.51 (s, 1H, H3), 2.30 (s, 1H, H11), 3.63 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.13 (d, J=2.7 Hz, 1H, H13), 4.15 (d, J=2.7 Hz, 1H, H1), 4.54 (d, J=15.1 Hz, 1H, NCH_2Ph), 4.79 (d, J=15.1 Hz, 1H, NCH_2Ph), 6.81 (d, J=8.6 Hz, 2H, Ar), 7.02–7.06 (m, 4H, Ar), 7.13–7.18 (m, 6H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm 29.7, 40.9, 41.2, 47.6, 47.7, 48.1, 48.2, 48.7, 50.7, 52.4, 52.7, 52.8, 54.8, 55.6, 67.2, 92.8, 114.4, 123.4, 123.7, 124.8, 126.0, 126.1, 126.6, 128.4, 130.2, 142.0 (overlap two carbons), 144.6, 144.7 (overlap two carbons), 159.8, 166.4, 166.9; HRMS (ES): M^+, found 575.2436. $C_{35}H_{33}N_3O_5$ requires 575.2420. Anal. Calcd for $C_{35}H_{33}N_3O_5$: C, 73.03; H, 5.78; N, 7.30. Found: C, 73.12; H, 5.77; N, 7.24%.

*4.2.7. Dimethyl-6,7,8-triaza-8-(p-methylthiobenzyl)-1α,2β,3α,4β,10-β,11α,12β,13α-octatacyclo[11.6.6.1^{3,11}0^{2,12}0^{4,10}0^{5,9}0^{14,19}0^{20,25}]-hexacosa-6,14,16,18,20,22,24-heptaene-5,9-dicarboxylate (**15**).* To a solution of corresponding cyclobutene diester (150 mg, 0.360 mmol) in CH_2Cl_2 (1 mL) was added *p*-methylthiobenzyl azide (300 mg, 1.67 mmol), and pressurized at 8 kbar for 1 week. Evaporation of the solution gave a yellow oil, which was subjected to radial chromatography (ethyl acetate/petroleum ether=1:5; R_f=0.4) to afford triazoline **15** as white powder (130 mg, 62%); mp 104–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm −0.19 (d, J=12.6 Hz, 1H, H25a), 0.94 (d, J=12.6 Hz, 1H, H25b), 1.47 (dd, J=2.3, 6.4 Hz, 1H, H2), 1.64 (dd, J=2.3, 6.4 Hz, 1H, H12), 1.99 (d, J=6.4 Hz, 1H, H4), 2.25 (d, J=6.4 Hz, 1H, H10), 2.26 (s, 1H, H3), 2.45 (s, 1H, H11), 2.47 (s, 3H, SCH_3), 3.48 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.18 (d, J=2.6 Hz, 1H, H1), 4.20 (d, J=2.6 Hz, 1H, H13), 4.58 (d, J=15.2 Hz, 1H, NCH_2Ph), 4.82 (d, J=15.2 Hz, 1H, NCH_2Ph), 7.04–7.07 (m, 2H, Ar), 7.08–7.11 (m, 2H, Ar), 7.18–7.24 (m, 8H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm 16.5, 30.0, 41.2, 41.5, 47.9, 48.0, 48.5, 48.5, 48.6, 51.0, 52.7, 53.0, 53.1, 55.1, 67.6, 93.1, 123.8, 123.9, 125.0, 125.1, 126.3, 126.8, 126.9, 127.4, 127.5, 128.5, 129.5, 133.5, 139.1, 142.3, 144.9, 166.6, 167.1; HRMS (ES): M^+, found 591.2196. $C_{35}H_{33}N_3O_4S$ requires 591.2192. Anal. Calcd for $C_{35}H_{33}N_3O_4S$: C, 71.04; H, 5.62; N, 7.10. Found: C, 71.01; H, 5.60; N, 7.02%.

*4.2.8. Dimethyl-6,7,8-triaza-8-(4′-pyridyl)-1α,2β,3α,4β,10-β,11α,12β,13α-octatacyclo[11.6.6.1^{3,11}0^{2,12}0^{4,10}0^{5,9}0^{14,19}0^{20,25}]-hexacosa-6,14,16,18,20,22,24-heptaene-5,9-dicarboxylate (**16**).* To a solution of corresponding cyclobutene diester (100 mg, 0.240 mmol) in CH_2Cl_2 (1 mL) was added 4-pyridyl azide (200 mg, 1.70 mmol), and pressurized at 8 kbar for 1 week. Evaporation of the solution gave yellow oil, which was subjected to radial chromatography (ethyl acetate and CH_2Cl_2 1:4; R_f=0.2), to afford

product **16** as a white powder (120 mg, 93%); mp 128–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm −0.03 (d, J=12.9 Hz, 1H, H25a), 1.08 (d, J=12.9 Hz, 1H, H25b), 1.62 (dd, J=8.6, 2.5 Hz, 1H, H2), 1.67 (dd, J=8.6, 1.9 Hz, 1H, H12), 2.28 (d, J=6.8 Hz, 1H, H4), 2.33 (s, 1H, H3), 2.34 (d, J=6.8 Hz, 1H, H10), 2.96 (s, 1H, H11), 3.55 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.17 (s, 1H, H1), 4.21 (s, 1H, H13), 6.96 (d, J=6.3 Hz, 2H, Ar), 7.03–7.07 (m, 2H, Ar), 7.12–7.14 (m, 2H, Ar), 7.19–7.22 (m, 4H, Ar), 8.46 (d, J=5.4 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 30.2, 41.3, 41.4, 47.8, 48.0, 48.4, 48.5, 52.5, 53.4, 53.6, 53.8, 54.3, 63.8, 96.1, 109.6, 123.9, 125.0, 125.2, 126.4, 126.5, 127.0, 127.1, 142.1, 142.2, 144.5, 144.6, 144.7, 151.5, 165.5, 167.0; HRMS (ES): M^+, found 532.2107. $C_{32}H_{28}N_4O_4$ requires 532.2111. Anal. Calcd for $C_{32}H_{28}N_4O_4$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.11; H, 5.33; N, 10.56%.

*4.2.9. Dimethyl-6,7,8-triaza-8-(3′-pyridyl)-1α,2β,3α,4β,10-β,11α,12β,13α-octatacyclo[11.6.6.1^{3,11}0^{2,12}0^{4,10}0^{5,9}0^{14,19}0^{20,25}]-hexacosa-6,14,16,18,20,22,24-heptaene-5,9-dicarboxylate (**17**).* To a solution of cyclobutene diester **14p** (100 mg, 0.240 mmol) in CH_2Cl_2 (1 mL) was added 3-pyridyl azide (200 mg, 1.70 mmol), and pressurized at 8 kbar for 1 week. Evaporation of the solution gave a yellow oil, which was subjected to radial chromatography (ethyl acetate/petroleum ether=1:2; R_f=0.4). Purified material was then recrystallized from CH_2Cl_2/petroleum ether to afford product **17** as a white powder (110 mg, 85%); mp 120–122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm −0.05 (d, J=12.8 Hz, 1H, H25a), 1.09 (d, J=12.8 Hz, 1H, H25b), 1.59 (d, J=8.4 Hz, 1H, H2), 1.64 (d, J=8.4 Hz, 1H, H12), 2.33 (s, 3H, H3, H4, H10), 2.93 (s, 1H, H3), 3.54 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.21 (s, 1H, H1), 4.25 (s, 1H, H13), 7.03–7.08 (m, 2H, Ar), 7.13–7.15 (m, 2H, Ar), 7.19–7.22 (m, 4H, Ar), 7.28–7.31 (m, 1H, Ar), 7.55–7.59 (m, 1H, Ar), 8.33–8.34 (m, 1H, Ar), 8.35–8.38 (m, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm 30.1, 41.2, 41.3, 47.7, 47.8, 48.4, 48.5, 52.6, 54.4, 53.6, 53.2, 64.4, 95.6, 122.5, 123.8, 123.9, 124.9, 125.1, 126.2, 126.3, 126.8, 127.0, 136.4, 142.0, 142.1, 144.5, 144.7, 145.0, 165.7, 167.0; HRMS (ES): M^+, found 532.2108. $C_{32}H_{28}N_4O_4$ requires 532.2111. Anal. Calcd for $C_{32}H_{28}N_4O_4$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.11; H, 5.36; N, 10.56%.

*4.2.10. Dimethyl-17-benzyl-3,10-dimethoxy-15,16,17-triaza-1α,12α,13β,19β-hexacyclo[10.7.1.0^{2,11}0^{4,9}0^{13,19}0^{14,18}]dodeca-2,4,6,8,10,15-heptaene-14,18-dicarboxylate (**18**).* To a solution of corresponding cyclobutene diester (200 mg, 0.500 mmol) in CH_2Cl_2 (1 mL) was added benzyl azide (300 mg, 1.67 mmol), and pressurized at 8 kbar for 3 days. Evaporation of the solution gave a brownish coloured oil, which was treated with cold methanol. The solid was collected by filtration and washed with a small amount of cold methanol to afford triazoline **18** as a white powder (190 mg, 74%); mp 104–106 °C; %); R_f=0.7 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.74 (d, J=6.1 Hz, 1H, H20a), 2.18 (d, J=6.1 Hz, 1H, H20b), 2.20 (d, J=6.7 Hz, 1H, H13), 2.56 (d, J=6.7 Hz, 1H, H19), 3.66 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.04 (s, 1H, H1), 4.20 (s, 1H, H12), 4.64 (d, J=15.0 Hz, 1H, NCH_2Ph), 5.14 (d, J=15.0 Hz, 1H, NCH_2Ph), 7.26–7.31 (m, 5H, Ar), 7.42–7.45 (m, 2H, Ar), 8.02–8.04 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$), δ/ppm 29.7, 42.1, 42.4, 43.5, 49.7, 52.0, 53.2, 54.3, 56.5, 65.8, 79.1, 93.3, 122.5, 122.6, 125.9, 126.0, 127.6, 128.6, 128.7, 128.8, 129.3, 132.7, 133.1, 137.7, 145.3, 145.4, 166.3, 167.1; IR (KBr): 1456, 1732, 1749 cm^{-1}; HRMS (ES): M^+, found 527.2056. $C_{30}H_{29}N_3O_6$ requires 527.2062. Anal. Calcd for $C_{30}H_{29}N_3O_6$: C, 68.30; H, 5.54; N, 7.96. Found: C, 68.45; H, 5.61; N, 7.65 %.

*4.2.11. 4-Benzyl-11,14-di(2′-pyridyl)-3,7-di(trifluoromethyl)-4,5,6,12,13-pentaaza-1α ,2β,8β,9α-pentacyclo[7.6.1.0^{2,8}0^{3,7}0^{10,15}]hexadeca-6,10,12,14-tetraene (**21**).* Solution of cyclobutene **21p** (Supplementary data) (150 mg, 0.326 mmol) and benzyl azide (200 mg, 1.304 mmol) in CH_2Cl_2 (1 mL) was pressurized for 3 days at 8 kbar. The solvent was removed in vacuo at room temperature and the residue treated with cold methanol. The precipitate was collected by filtration as colourless crystals (149 mg, 77%); mp 223–224 °C; %); R_f=0.4 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.76 (d, J=12.4 Hz, 1H, H16a), 2.30 (d, J=7.1 Hz, 1H, H8), 2.52 (d, J=7.1 Hz, 1H, H2), 2.74 (d, J=12.4 Hz, 1H, H16b), 4.68 (d, J=15.5 Hz, 1H, NCH_2Ph), 4.88 (s, 1H, H1), 4.97 (s, 1H, H9), 5.09 (d, J=15.5 Hz, 1H, NCH_2Ph), 7.05–7.09 (m, 3H, Ar), 7.29–7.32 (m, 2H, Ar), 7.43–7.44 (m, 2H, Ar), 7.91–7.95 (m, 2H, Ar), 8.60 (t, J=6.6 Hz, 2H, Ar), 8.77 (t, J=4.2 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm 40.2, 42.2, 44.6, 45.5, 47.0, 51.5, 67.4 (q, J=31.2 Hz), 88.7 (q, J=29.8 Hz), 122.1, 122.9 (q, J=276.7 Hz), 124.9 (q, J=284.6 Hz), 123.3, 123.9, 128.6, 129.0, 135.8, 137.8, 146.7, 149.5, 149.7, 152.2, 152.7, 154.7, 154.8; HRMS (ES): M^+, found 593.1770. $C_{30}H_{21}N_7F_6$ requires 593.1763. Anal. Calcd for $C_{30}H_{21}N_7F_6$: C, 60.71; H, 3.57; N, 16.52. Found: C, 60.77; H, 3.51; N, 16.45%.

4.3. Thermal rearrangement of triazolines

General method A: sample of triazoline (100–200 mg) in a round-bottomed flask was heated at 140 °C for 1 h. After cooling, reaction mixture was separated by radial chromatography and all new products fully characterized by ^{1}H, ^{13}C NMR spectroscopy and high-resolution mass spectrometry.

General method B: sample of triazoline (100–200 mg) was dissolved in $CDCl_3$ (0.5 mL) in an NMR tube and heated at 80 °C for 2–12 h, the products were separated by radial chromatography.

*4.3.1. (6S,8S,9R)-Dimethyl-6-phenyl-4,5,7-triaza-1α,2β,10α-hexacyclo[8.6.1.0^{2,9}0^{5,9}0^{11,16}]heptadeca-3,11,13,15-tetraene-3,8-dicarboxylate (exo-**22**), (6R,8S,9R)-dimethyl-6-phenyl-4,5,7-triaza-1α,2β,10α-hexacyclo[8.6.1.0^{2,9}0^{5,9}0^{11,16}]heptadeca-3,11,13,15-tetraene-3,8-dicarboxylate (endo-**22**) and 1α,8α-10-(3′-benzyl-4′-carbmethoxy-1,2,3-triazolyl)bicyclo[6.2.1.0^{2,7}]undeca-2,4,6,9-tetraene (**23**).* A sample of triazoline **4** (200 mg, 0.479 mmol) was heated at 140 °C for 1 h in round-bottomed flask. Resulting brown coloured oil was subjected to radial chromatography (petroleum ether/ethyl acetate 10:1, then the solvent polarity was gradually increased to ethyl acetate) to afford several products. Single crystals suitable for X-ray analysis were obtained by slow diffusion of petroleum ether in dichloromethane solution of compound *exo*-**22**.

Compound *exo*-**22** (colourless solid, 48 mg, 24%); mp 164–166 °C; %); R_f=0.8; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.92 (d, J=9.6 Hz, 1H, H17a), 2.07 (d, J=9.6 Hz, 1H, H17b), 2.84 (s, 1H, H10), 3.09 (s, 1H, H2), 3.13 (s, 3H, OCH_3), 3.62 (br s, 1H, H1), 3.74 (s, 1H, H8), 3.89 (s, 3H, OCH_3), 6.00 (s, 1H, NH), 7.04–7.06 (m, 4H, Ar), 7.38–7.41 (m, 3H, Ar), 7.72 (d, J=7.5 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 47.0, 49.0, 52.2, 52.4, 55.9, 61.4, 65.6, 81.5, 88.5, 121.7, 124.4, 126.8, 127.4, 127.5, 128.5, 128.8, 139.3, 143.4, 146.4, 148.3, 162.9, 171.7; HRMS (ES): M^+, found 417.1685. $C_{24}H_{23}N_3O_4$ requires 417.1689. Anal. Calcd for $C_{24}H_{23}N_3O_4$: C, 69.05; H, 5.55; N, 10.07. Found: C, 69.01; H, 5.49; N, 10.01%.

Compound *endo*-**22** (colourless solid, 31 mg, 18%); mp 156–159 °C; R_f=0.75; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.99 (dt, J=9.6, 1.4 Hz, 1H, H17a), 2.23 (dt, J=9.6, 1.4 Hz, 1H, H17b), 2.89 (t, J=11.5 Hz, 1H, H7), 3.13 (s, 3H, OCH_3), 3.48 (s, 1H, H2), 3.51 (d, J=1.4 Hz, 1H, H10), 3.69 (d, J=11.5 Hz, 1H, H8), 3.72 (s, 1H, H1), 3.90 (s, 3H, OCH_3), 5.39 (d, J=11.5 Hz, 1H, H6), 7.04–7.06 (m, 4H, Ar), 7.24–7.25 (m, 1H, Ar), 7.38–7.41 (m, 2H, Ar), 7.57 (d, J=6.5 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 44.7, 45.4, 51.4, 52.7, 52.8, 58.2, 62.5, 81.6, 87.9, 121.5, 125.9, 126.9, 127.1, 129.0, 129.1, 125.5, 139.2, 143.4, 146.8, 148.6, 162.9, 169.1; HRMS (ES): M^+, found 417.1694. $C_{24}H_{23}N_3O_4$ requires 417.1689.

Compound **23** (colourless solid, 21 mg, 14%); mp 124–126 °C; R_f=0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm 2.33 (d, J=8.7 Hz, 1H, H11a), 2.39 (d, J=8.7 Hz, 1H, H11b), 3.81 (s, 3H, OCH_3), 3.98 (s, 1H,

H1), 4.22 (s, 1H, H8), 5.32 (d, J=15.0 Hz, 1H, NCH_2Ph), 5.43 (d, J=15.0 Hz, 1H, NCH_2Ph), 6.68 (s, 1H, C=CH), 7.06–7.11 (m, 4H, Ar), 7.21–7.24 (m, 4H, Ar), 7.30–7.33 (m, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 47.4, 48.9, 50.9, 52.9, 60.2, 115.9, 122.3, 122.8, 126.7, 126.9, 127.6, 127.9, 128.8, 132.6, 137.9, 146.7, 147.6, 160.9, 162.4, 163.2; IR (KBr): 1440, 1606, 1734 cm^{-1}; HRMS (ES): M^+, found 357.1476. $C_{22}H_{19}N_3O_2$ requires 357.1477.

*4.3.2. (6S,8S,9R)-Dimethyl-6-(p-methoxyphenyl)-4,5,7-triaza-1α,2β,10α-hexacyclo[8.6.1.0^{2,9}0^{5,9}0^{11,16}]heptadeca-3,11,13,15-tetraene-3,8-dicarboxylate (exo-**24**), (6R,8S,9R)-dimethyl-6-(p-methoxyphenyl)-4,5,7-triaza-1α,2β,10α-hexacyclo[8.6.1.0^{2,9}0^{5,9}0^{11,16}]heptadeca-3,11,13,15-tetraene-3,8-dicarboxylate (endo-**24**) and 1α,8α-10-(1′-p-methoxybenzyl-4′-carbmethoxy-1,2,3-triazolyl)bicyclo[6.2.1.0^{2,7}]undeca-2,4,6,9-tetraene (**26**).* A sample of triazoline **5** (38 mg, 0.100 mmol) was heated in a test tube at 140 °C for 6 h. The yellow coloured oily residue was subjected to radial chromatography (starting with petroleum ether/ethyl acetate 20:1, then the solvent polarity was gradually increased to ethyl acetate) to afford three products, in order of elution: *exo*-**24** (yellow solid, 11 mg, 25%); mp 262–263 °C; R_f=0.75; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.95 (d, J=9.8 Hz, 1H, H17a), 2.06 (d, J=9.8 Hz, 1H, H17b), 2.86 (s, 1H, H10), 3.08 (s, 1H, H2), 3.14 (s, 3H, OCH_3), 3.74 (s, 1H, H1), 3.81 (s, 1H, H8), 3.90 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 5.97 (s, 1H, NH), 6.93 (d, J=8.8 Hz, 2H, Ar), 7.05–7.24 (m, 4H, Ar), 7.63 (d, J=8.8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 47.0, 47.7, 49.3, 55.2, 61.8, 65.6, 75.3, 84.9, 88.5, 113.5, 121.6, 124.5, 126.5, 127.4, 130.2, 132.6, 143.4, 146.3, 148.1, 159.9, 162.5, 171.8; HRMS (ES): M^+, found 447.1791. $C_{25}H_{25}N_3O_5$ requires 447.1794.

Compound *endo*-**24** (yellow solid, 6 mg, 13%); mp 242–243 °C; R_f=0.7; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.93 (d, J=9.8 Hz, 1H, H17a), 2.04 (d, J=9.8 Hz, 1H, H17b), 2.84 (s, 1H, H7), 3.07 (s, 1H, H2), 3.11 (s, 3H, OCH_3), 3.77 (s, 1H, H1), 3.78 (s, 1H, H8), 3.91 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 5.45 (s, 1H, NH), 6.91 (d, J=8.8 Hz, 2H, Ar), 7.07–7.22 (m, 4H, Ar), 7.64 (d, J=8.8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 44.9, 45.7, 52.4, 52.7, 52.8, 57.2, 61.5, 82.6, 87.9, 122.5, 125.9, 126.7, 127.3, 128.0, 129.4, 135.5, 137.2, 143.7, 144.8, 148.6, 163.9, 168.5; HRMS (ES): M^+, found 447.1788. $C_{25}H_{25}N_3O_5$ requires 447.1794.

Compound **26** (yellow oil, 9 mg, 23%); R_f=0.6; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.31 (td, J=8.6, 1.6 Hz, 1H, H11a), 2.36 (td, J=8.6, 1.6 Hz, 1H, H11b), 3.75 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.21 (s, 1H, H1), 4.31 (s, 1H, H8), 5.26 (d, J=14.8 Hz, 1H, NCH_2Ph), 5.34 (d, J=14.8 Hz, 1H, NCH_2Ph), 6.66 (s, 1H, C=CH), 7.07 (d, J=8.6 Hz, 4H, Ar), 6.77–7.31 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 30.1, 46.9, 48.9, 51.6, 55.6, 60.2, 114.2, 115.9, 122.3, 122.8, 126.5, 126.6, 129.6, 130.0, 130.4, 146.6, 146.7, 147.6, 159.2, 160.8, 162.4; HRMS (ES): M^+, found 387.1580. $C_{23}H_{21}N_3O_3$ requires 387.1583.

*4.3.3. (6S,8S,9R)-Dimethyl-6-(p-nitrophenyl)-4,5,7-triaza-1α,2β,10α-hexacyclo[8.6.1.0^{2,9}0^{5,9}0^{11,16}]heptadeca-3,11,13,15-tetraene-3,8-dicarboxylate (exo-**27**), (6R,8S,9R)-dimethyl-6-(p-nitrophenyl)-4,5,7-triaza-1α,2β,10α-hexacyclo[8.6.1.0^{2,9}0^{5,9}0^{11,16}]heptadeca-3,11,13,15-tetraene-3,8-dicarboxylate (endo-**27**) and 1α,8α-10-(1′-p-nitrobenzyl-4′-carbmethoxy-1,2,3-triazolyl)bicyclo[6.2.1.0^{2,7}]undeca-2,4,6,9-tetraene (**28**).* A sample of triazoline **6** (100 mg, 0.216 mmol) was heated at 140 °C for 1 h. The brown coloured oily residue was subjected to radial chromatography (starting with petroleum ether/ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate) to afford several products: *exo*-**27** (colourless solid, 11 mg, 11%); mp 163–164 °C; R_f=0.7; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.98 (dq, J=9.7, 1.8 Hz, 1H, H17a), 2.06 (dt, J=9.7, 1.3 Hz, 1H, H17b), 2.76 (s, 1H, H1), 3.06 (s, 1H, H2), 3.15 (s, 3H, OCH_3), 3.23 (br s, 1H, NH), 3.57 (br s, 1H, H8), 3.76 (s, 1H, H10), 3.93 (s, 3H, OCH_3), 6.03 (s, 1H, H6), 7.08–7.20 (m, 4H, Ar), 7.95 (d, J=8.9 Hz, 2H, p-NO_2–C_6H_4), 8.27 (d, J=8.9 Hz, 2H, p-NO_2–C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 47.6, 49.1, 52.7, 52.9, 55.3, 62.3, 65.6, 79.6, 91.2, 121.7, 124.3, 124.5, 126.6, 127.3, 128.1, 136.9, 149.0, 149.2, 149.3, 149.9, 162.2, 171.5; HRMS (ES): M^+, found $C_{24}H_{22}N_4O_6$: 462.1529, requires 462.1539.

Compound *endo*-**27** (colourless solid, 16 mg, 16%); mp 161–162 °C; R_f=0.65; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.04 (d, J=9.7 Hz, 1H, H17a), 2.19 (d, J=9.7 Hz, 1H, H17b), 2.88 (t, J=2.1 Hz, 1H, NH), 3.17 (s, 3H, OCH_3), 3.42 (s, 1H, H10), 3.54 (d, J=1.6 Hz, 1H, H2), 3.73 (d, J=1.6 Hz, 1H, H1), 3.74 (s, 1H, H8), 4.01 (s, 3H, OCH_3), 5.43 (d, J=9.1 Hz, 1H, H6), 7.04–7.11 (m, 4H, Ar), 7.81 (d, J=8.4 Hz, 2H, p-NO_2–C_6H_4), 8.28 (d, J=8.4 Hz, 2H, p-NO_2–C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 49.2, 49.4, 51.1, 52.8, 53.0, 58.6, 60.8, 62.7, 80.8, 88.2, 121.6, 124.4, 126.1, 127.3, 128.0, 143.1, 146.1, 148.0, 148.4, 148.6, 162.6, 168.9; HRMS (ES): M^+, found 462.1531. $C_{24}H_{22}N_4O_6$ requires 462.1534.

Compound **28** (yellow solid, 11 mg, 11%); mp 203–205 °C; R_f=0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.14 (td, J=8.3, 1.5 Hz, 1H, H11a), 2.16 (td, J=8.2, 1.5 Hz, 1H, H11b), 3.55 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.12 (s, 1H, H1), 4.13 (s, 1H, H8), 5.20 (d, J=15.2 Hz, 1H, NCH_2Ph), 5.31 (d, J=15.2 Hz, 1H, NCH_2Ph), 6.46 (s, 1H, C=CH), 6.77–7.31 (m, 4H, Ar), 7.95 (d, J=8.9 Hz, 2H, Ar), 8.27 (d, J=8.9 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 33.1, 46.9, 47.9, 52.6, 57.6, 60.7, 109.2, 116.6, 122.5, 122.9, 127.5, 127.6, 128.8, 130.1, 131.4, 143.4, 145.5, 146.6, 158.1, 161.1, 162.1; HRMS (ES): M^+, found 402.1329. $C_{22}H_{18}N_4O_4$ requires 402.1327.

*4.3.4. (6S,8S,9R)-Dimethyl-12,19-dimethoxy-6-phenyl-4,5,7-triaza-1α,2β,10α-heptacyclo[10.8.1.0^{2,9}0^{5,9}0^{11,20}]henicosa-3,11,13,15,17,19-hexaene-3,8-dicarboxylate (exo-**29**), 6R,8S,9R-dimethyl-12,19-dimethoxy-6-phenyl-4,5,7-triaza-1α,2β,10α-heptacyclo[10.8.1.0^{2,9}0^{5,9}0^{11,20}]henicosa-3,11,13,15,17,19-hexaene-3,8-dicarboxylate (endo-**29**) and 1α,12α-3,10-dimethoxy-13-(3′-benzyl-4′-carbmethoxy-1,2,3-triazolyl)bicyclo[10.2.1.0^{2,11}0^{4,9}]pentadeca-2,4,6,8,10,13-hexaene (**30**).* A sample of triazoline **18** (100 mg, 0.190 mmol) was heated at 140 °C for 1 h. The brown coloured oily residue was subjected to radial chromatography (starting with petroleum ether/ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate) to afford three products: *exo*-**29** (colourless solid, 23 mg, 23%); mp 141–143 °C; R_f=0.7; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.97 (dt, J=1.6, 9.8 Hz, 1H, H21a), 2.13 (dt, J=16.0, 9.8 Hz, 1H, H21b), 2.61 (s, 3H, OCH_3), 3.09 (br s, 1H, H10), 3.15 (s, 1H, H2), 3.21 (s, 1H, H1), 3.67 (s, 3H, OCH_3), 3.86 (s, 1H, H8), 3.93 (s, 3H, OCH_3), 3.93 (s, 1H), 4.06 (s, 3H, OCH_3), 4.21 (s, 1H), 6.07 (s, 1H, NH), 7.42–7.47 (m, 3H, Ar), 7.80 (d, J=7.2 Hz, 2H, Ar), 8.02 (dd, J=3.4, 5.2 Hz, 2H, Ar), 8.10 (dd, J=3.4, 5.2 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 45.2, 46.5, 51.7, 52.1, 52.9, 61.7, 61.9, 62.2, 65.4, 81.4, 88.9, 122.4, 122.5, 126.0, 126.2, 127.7, 128.5, 128.8, 128.9, 129.1, 130.1, 133.9, 138.5, 145.1, 145.9, 147.9, 162.4, 171.7; HRMS (ES): M^+, found 527.2057. $C_{30}H_{29}N_3O_6$ requires 527.2056.

Compound *endo*-**29** (obtained from crude spectrum); R_f=0.68; ^{1}H NMR ($CDCl_3$) δ/ppm 5.56 (s, 1H, NH); HRMS (m/z): calcd for $C_{30}H_{29}N_3O_6$: 527.2056, found: 527.2059.

Compound **30** (colourless solid, 7 mg, 8%); mp 166–167 °C; R_f=0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm 2.37 (d, J=8.9 Hz, 1H, H13a), 2.39 (d, J=8.9 Hz, 1H, H13b), 3.81 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.66 (s, 1H, H1), 4.82 (s, 1H, H22), 5.22 (d, J=15.2 Hz, 1H, NCH_2Ph), 5.59 (d, J=15.2 Hz, 1H, NCH_2Ph), 6.78 (s, 1H, H14), 7.12–7.13 (m, 2H), 7.22–7.25 (m, 3H, Ar), 7.48 (dd, J=3.3, 6.4 Hz, 2H, Ar), 8.03 (dd, J=3.3, 6.4 Hz, 1H, Ar), 8.06 (dd, J=3.3, 6.4 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 45.3, 47.6, 47.7, 52.9, 57.9, 62.4, 62.5, 115.7, 122.6, 122.7, 126.4, 126.5, 127.8, 128.1, 128.8, 128.7, 129.3, 131.2, 131.8, 132.9, 137.7, 145.9, 146.7, 159.9, 162.4, 163.1; HRMS (ES): M^+, found 467.1833. $C_{28}H_{25}N_3O_4$ requires 467.1845.

4.3.5. (9R)-Methyl-10,11-diaza-9-(imino-1′-carbmethoxy-2′-benzyl)-1α,8α,9β,13β-tetracyclo[6.5.1.0^{2,7}0^{9,13}]tetradeca-2,4,6,11-

*tetraene-12-carboxylate (**31**).* A solution of triazoline **4** (70 mg, 0.168 mmol) was heated in $CDCl_3$ (0.5 mL) at 80 °C for 2 h. The solvent was removed in vacuo to afford the product as a yellow coloured oil (66 mg, 94%); R_f=0.35 (petroleum ether/ethyl acetate 20:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.97 (td, J=9.8, 1.4 Hz, 1H, H14a), 2.08 (td, J=9.8, 1.4 Hz, 1H, H14b), 3.81 (s, 1H, H13), 3.86 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.98 (s, 1H, H8), 4.09 (s, 1H, H1), 4.42 (q, J=8.9 Hz, 1H, NCH_2Ph), 4.47 (q, J=8.9 Hz, 1H, NCH_2Ph), 6.82–7.39 (m, 9H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 40.7, 40.8, 48.2, 52.4, 56.2, 56.7, 57.7, 84.3, 121.5, 122.8, 126.4, 127.2, 127.5, 127.8, 128.4, 138.5, 142.9, 143.0, 147.5, 158.9, 163.4, 163.8; IR (KBr): 1458, 1674, 1728, 1732, 2952 cm^{-1}; HRMS (ES): M^+, found 417.1686. $C_{24}H_{23}N_3O_4$ requires 417.1689.

*4.3.6. (9R,12R)-Methyl-11,12-diaza-9-(imino-1′-carbmethoxy-2′-(p-methoxybenzyl))-1α,8α, 13β-tetracyclo[6.5.1.0^{2,7}0^{9,13}]tetradeca-2,4,6,10-tetraene-12-carboxylate (**32**), (9R)-methyl-11,12-diaza-9-(imino-1′-carbmethoxy-2′-(p-methoxybenzyl))-1α,8α,13β-tetracyclo[6.5.1.0^{2,7}0^{9,13}]tetradeca-2,4,6,11-tetraene-12-carboxylate (**33**) and 1α,8α-10-(1′-p-methoxybenzyl-4′-carbmethoxy-1,2,3-triazolyl)bicyclo[6.2.1.0^{2,7}]undeca-2,4,6,9-tetraene (**26**).* A solution of triazoline **5** (49 mg, 0.109 mmol) was heated in $CDCl_3$ (0.5 mL) at 80 °C overnight. The solvent was removed in vacuo to afford yellow coloured oily residue. Radial chromatography (starting with petroleum ether/ethyl acetate 20:1, then solvent polarity was gradually increased to ethyl acetate) afforded three products in order of elution:

Compound **32** (yellow oil, 26 mg, 53%); R_f=0.8; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.79 (td, J=9.6, 1.5 Hz, 1H, H14a), 2.18 (d, J=9.6 Hz, 1H, H14b), 2.96 (d, J=8.7 Hz, 1H, H13), 3.25 (d, J=8.7 Hz, 1H, H1), 3.27 (s, 1H, H12), 3.67 (s, 1H, H8), 3.68 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.61 (d, J=14.9 Hz, 1H, NCH_2Ph), 4.75 (d, J=14.9 Hz, 1H, NCH_2Ph), 6.89 (d, J=8.5 Hz, 2H, Ar), 7.10–7.12 (m, 2H, Ar), 7.21–7.22 (m, 2H, Ar), 7.29 (d, J=8.5 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 38.9, 45.3, 47.6, 48.7, 49.1, 51.2, 52.2, 52.4, 55.7, 57.9, 114.2, 121.4, 126.8, 127.2, 129.9, 131.9, 148.4, 148.9, 159.0, 161.9, 163.9, 165.4, 168.1; HRMS (ES): M^+, found 447.1802. $C_{25}H_{25}N_3O_5$ requires 447.1794.

Compound **33** (yellow oil, 17 mg, 35%); R_f=0.75; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.97 (qd, J=10.3, 1.2 Hz, 1H, H14a), 2.05 (td, J=10.3, 1.2 Hz, 1H, H14b), 3.67 (s, 1H, H13), 3.75 (s, 1H, H8), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.05 (s, 1H, H1), 4.38 (d, J=14.3 Hz, 1H, NCH_2Ph), 4.41 (d, J=14.3 Hz, 1H, NCH_2Ph), 6.74 (s, 2H, Ar), 7.01–7.26 (m, 6H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 46.2, 46.7, 47.7, 51.6, 52.4, 55.7, 56.0, 57.9, 58.0, 84.2, 114.1, 121.6, 122.9, 124.2, 127.1, 128.4, 130.2, 130.7, 142.9, 143.0, 147.6, 158.8, 158.9, 163.4, 163.9; HRMS (ES): M^+, found 447.1799. $C_{25}H_{25}N_3O_5$ requires 447.1794. Compound **26** (yellow oil, 5 mg, 12%); R_f=0.6.

*4.3.7. (9R)-Methyl-11,12-diaza-9-(imino-1′,3′-dicarbmethoxy)-1α,8α,13β-tetracyclo[6.5.1.0^{2,7}0^{9,13}]tetradeca-2,4,6,11-tetraene-12-carboxylate (**34**).* A solution of triazoline **7** (98 mg, 0.241 mmol) in $CDCl_3$ (0.5 mL) was heated at 100 °C for 2 h in a sealed glass tube. Solvent was removed in vacuo to afford product **34** as yellow solid (94 mg, 96%); mp 128–129 °C). R_f=0.3 (petroleum ether/ethyl acetate 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm 1.85 (qd, J=10.2, 1.8 Hz, 1H, H14a), 2.18 (td, J=10.2, 1.8 Hz, 1H, H14b), 2.98 (dd, J=8.9, 1.6 Hz, 1H, NCH_2E), 3.29 (s, 1H, H13), 3.32 (d, J=9.0 Hz, 1H, NCH_2E), 3.69 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.75 (s, 1H, H1), 3.77 (s, 3H, OCH_3), 3.80 (s, 1H, H8), 7.09–7.23 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 38.9, 46.7, 47.5, 49.2, 50.6, 51.5, 52.7, 54.8, 55.7, 58.4, 122.1, 122.5, 127.1, 127.9, 148.3, 148.9, 162.4, 165.2, 167.9, 170.5; HRMS (ES): M^+, found 399.1428. $C_{20}H_{21}N_3O_6$ requires 399.1430.

*4.3.8. (9R)-Methyl-10,11-diaza-9-(imino-1′-carbmethoxy-2′-allyl)-1α,8α,13β-tetracyclo[6.5.1.0^{2,7}0^{9,13}]tetradeca-2,4,6,10-tetraene-12-carboxylate (**35**).* A sample of triazoline **8** (100 mg, 0.272 mmol) was heated in a test tube at 80 °C overnight. Radial chromatography (starting with petroleum ether/ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate) afforded **35** as yellow coloured oil (87 mg, 87%); R_f=0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm 1.85 (td, J=9.8, 1.5 Hz, 1H, H14a), 2.17 (td, J=9.8, 1.5 Hz, 1H, H14b), 2.95 (d, J=8.7 Hz, 1H, H13), 3.17 (d, J=8.7 Hz, 1H, H12), 3.29 (s, 1H, H1), 3.71 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.84 (s, 1H, H8), 4.17 (dd, J=15.6, 5.1 Hz, 1H, NCH_2Ph), 4.23 (dd, J=15.6, 5.1 Hz, 1H, NCH_2Ph), 5.14 (td, J=10.4, 1.6 Hz, 1H, $CH_2CH{=}CH_2$), 5.27 (td, J=10.4, 1.6 Hz, 1H, $CH_2CH{=}CH_2$), 5.93–6.08 (m, 1H, $CH_2CH{=}CH_2$), 7.09–7.11 (m, 2H, Ar), 7.21–7.26 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 38.8, 46.2, 47.5, 47.9, 49.1, 52.1, 52.4, 57.2, 98.4, 116.3, 121.4, 121.6, 126.5, 126.8, 135.9, 148.4, 148.9, 162.1, 163.9, 168.1; HRMS (ES): M^+, found 367.1537. $C_{20}H_{21}N_3O_4$ requires 367.1532.

*4.3.9. (9R)-Methyl-10,11-diaza-9-(imino-1′-carbmethoxy-2′-benzyl)-1α,8α,13β-tetracyclo[6.5.1.0^{2,7}0^{9,13}]tetradeca-spiro(14:1′-cyclopropane)-2,4,6,11-tetraene-12-carboxylate (**36**).* A solution of triazoline **9** (79 mg, 0.183 mmol) was heated in $CDCl_3$ (0.5 mL) at 80 °C for 2 h. The solvent was removed in vacuo to afford product **36** as yellow coloured solid (75 mg, 95%); mp 101–104 °C); R_f=0.55 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.29 (t, J=7.7 Hz, 2H, H16), 0.81 (dt, J=7.9, 2.9 Hz, 1H, H15a), 1.00 (dt, J=7.9, 1.9 Hz, 1H, H15b), 3.13 (s, 1H, H13), 3.21 (s, 1H, H1), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.96 (s, 1H, H8), 4.43 (d, J=15.5 Hz, 1H, NCH_2Ph), 4.47 (d, J=15.5 Hz, 1H, NCH_2Ph), 6.79 (dd, J=7.3, 3.5 Hz, 2H, Ar), 6.98–7.35 (m, 7H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 2.1, 9.2, 43.6, 51.9, 52.1, 53.2, 57.3, 58.6, 59.5, 84.6, 121.7, 123.6, 125.7, 126.7, 126.8, 128.0, 128.5, 138.2, 140.4, 143.4, 147.4, 158.4, 163.2, 163.4; HRMS (ES): M^+, found 443.1841. $C_{26}H_{25}N_3O_4$ requires 443.1845.

*4.3.10. 1α,8-10-(1′-Benzyl-4′-carbmethoxy-1,2,3-triazolyl)-11-isopropylidene-bicyclo[6.2.1.0^{2,7}]undeca-2,4,6,9-tetraene (**37**) and 2-isopropylidylene-indene (**72**).* A solution of triazoline **10** (71 mg, 0.156 mmol) was heated in $CDCl_3$ (0.5 mL) at 80 °C for 2 h. The solvent was removed in vacuo to give yellow coloured oil. Radial chromatography (starting with petroleum ether/ethyl acetate 20:1, then solvent polarity was gradually increased to 5:1) afforded products **37** and **72**.

Compound **72** (colourless oil, 17 mg, 70%); R_f=0.95; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.05 (s, 3H, CH_3), 3.54 (s, 2H, CH_2), 5.02 (s, 1H, C=CH), 5.26 (s, 1H, C=CH), 6.78 (s, 1H, H1), 7.16 (t, J=7.3 Hz, 2H, Ar–H), 7.21 (d, J=7.3 Hz, 1H, Ar–H), 7.40 (d, J=7.3 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 20.8, 38.7, 113.3, 121.4, 123.9, 125.3, 126.8, 128.2, 128.3, 140.0, 143.4, 145.7, 148.7; HRMS (ES): M^+, found 156.0935. $C_{12}H_{12}$ requires 156.0939.

Compound **37** (colourless oil, 4 mg, 5%, obtained from crude spectrum); R_f=0.6; ^{1}H NMR ($CDCl_3$) δ/ppm 1.55 (s, 6H, CH_3), 3.82 (s, 3H, OCH_3), 4.70 (s, 1H), 4.77 (s, 1H), 5.38 (d, J=14.1 Hz, 1H, NCH_2Ph), 5.39 (d, J=14.1 Hz, 1H, NCH_2Ph), 6.76 (s, 1H, C=CH), 7.07–7.34 (m, 9H, Ar); HRMS (ES): M^+, found 397.17833. $C_{25}H_{23}N_3O_2$ requires 397.1790.

*4.3.11. (9R)-3,6-Di(2′-pyridyl)-9-(imino-1′-carbmethoxy-2′-benzyl)-4,5,10,11-tetraaza-1α,8α,9β,13β-tetracyclo[6.5.1.0^{2,7}0^{9,13}]tetradeca-2,4,6,11-tetraene (**38**).* A solution of triazoline **20** (92 mg, 0.173 mmol) in $CDCl_3$ (0.5 mL) was heated in NMR tube at 80 °C for 2 h. Radial chromatography (starting with petroleum ether/ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate) afforded **38** as yellow coloured solid (85 mg, 93%); mp 175–176 °C); R_f=0.35; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 2.02 (dt, J=10.6, 1.6 Hz, 1H, H14a), 2.16 (dt, J=10.6, 1.6 Hz, 1H, H14b), 3.73 (s, 1H, H13), 3.93 (s, 3H, OCH_3), 4.25 (d, J=13.9 Hz, 1H, NCH_2Ph), 4.37 (d, J=13.9 Hz, 1H, NCH_2Ph), 4.69 (s, 1H, H1), 4.97 (s, 1H, H8),

6.99–7.00 (m, 2H, Ar), 7.01 (s, 1H, H12), 7.20–7.26 (m, 2H, Ar), 7.31–7.35 (m, 1H, Ar), 7.43 (dd, J=4.8, 2.3 Hz, 1H, Ar), 7.61 (s, 1H, Ar), 7.86 (dt, J=7.5, 1.7 Hz, 1H, Ar), 7.93 (dt, J=7.5, 1.7 Hz, 1H, Ar), 8.46 (d, J=4.2 Hz, 1H, Ar), 8.62 (d, J=7.5 Hz, 1H, Ar), 8.64 (d, J=7.5 Hz, 1H, Ar), 8.88 (d, J=5.1 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 45.9, 49.2, 52.5, 55.3, 59.1, 63.9, 81.9, 123.0, 123.2, 124.4, 124.5, 127.4, 128.8, 128.9, 137.3, 138.9, 143.2, 145.2, 148.5, 149.4, 149.8, 153.2, 153.7, 155.1, 155.2, 152.9, 154.2, 162.9, 164.1, 164.2; HRMS (ES): M^+, found 515.2072. $C_{30}H_{25}N_7O_2$ requires 515.2070.

*4.3.12. (8R)-Methyl-6,7-diaza-8-(imino-1′-carbmethoxy-2″-(p-methoxybenzyl))-1α,2β,3α,4β,9α,10β,11α-heptacyclo[7.6.6.1^{3,9}0^{2,10}0^{4,8}0^{12,17}0^{18,23}]tetracosa-5,12,14,16,18,20,22-heptaene-5-carboxylate (**39**).* A solution of *p*-methoxybenzyl triazoline **14** (100 mg, 0.18 mmol) in $CDCl_3$ (0.5 mL) was heated at 60 °C for 12 h. The reaction was followed by ^{1}H NMR spectroscopy and stopped upon completion. Product **39** was isolated by radial chromatography (petroleum ether/ethyl acetate 5:1) as colourless solid (90 mg, 90%); mp 138–140 °C; R_f=0.8; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm −0.21 (d, J=11.8 Hz, 1H, H24a), 0.81 (d, J=11.8 Hz, 1H, H24b), 2.03 (dd, J=7.8, 2.0 Hz, 1H, H2), 2.08 (dd, J=7.8, 2.0 Hz, 1H, H10), 2.36 (m, 1H, H9), 2.44 (m, 1H, H3), 3.71 (m, 1H, H4), 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.12 (m, 1H, H11), 4.27 (m, 1H, H1), 4.49 (d, J=14.8 Hz, 1H, NCH_2Ph), 4.60 (d, J=14.8 Hz, 1H, NCH_2Ph), 6.52 (br s, 1H, NH), 6.63 (d, J=8.7 Hz, 2H, Ar), 6.89 (d, J=8.7 Hz, 2H, Ar), 7.09–7.11 (m, 4H, Ar), 7.16–7.18 (m, 2H, Ar), 7.25–7.27 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 30.4, 43.7, 46.3, 48.1, 48.4, 48.7, 51.2, 52.6, 53.1, 55.9, 57.8, 58.2, 83.1, 114.5, 123.9, 124.1, 124.9, 125.2, 126.4, 126.5, 126.9, 127.0, 129.2, 131.0, 137.1, 140.4, 142.6, 142.7, 144.9, 145.0, 159.2, 163.6, 165.2; HRMS (ES): M^+, found 575.2435. $C_{35}H_{33}N_3O_5$ requires 575.2420. Anal. Calcd for $C_{35}H_{33}N_3O_5$: C, 73.03; H, 5.78; N, 7.30. Found: C, 73.09; H, 5.73; N, 7.23%. Slow evaporation of mixed petrol ether/ethyl acetate solution gave a colourless single crystal suitable for X-ray analysis.

*4.3.13. (8R)-Methyl-6,7-diaza-8-(imino-1′-carbmethoxy-2′-(p-methylthiobenzyl))-1α,2β,3α, 4β,9α,10β,11α-heptacyclo[7.6.6.1^{3,9}0^{2,10}0^{4,8}0^{12,17}0^{18,23}]tetracosa-5,12,14,16,18,20,22-heptaene-5-carboxylate (**40**).* A solution of *p*-methylthiobenzyl triazoline **15** (50 mg, 0.09 mmol) in $CDCl_3$ (0.5 mL) in an NMR tube was heated at 60 °C for 12 h. The reaction was followed by ^{1}H NMR spectroscopy and stopped upon completion. Product **40** was isolated by radial chromatography (petroleum ether/ethyl acetate 2:1) (40 mg, 80%); mp 106–108 °C; R_f=0.85; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm −0.21 (d, J=11.8 Hz, 1H, H24a), 0.81 (d, J=11.8 Hz, 1H, H24b), 2.02 (dd, J=8.0, 2.7 Hz, 1H, H2), 2.09 (dd, J=8.0, 2.7 Hz, 1H, H10), 2.37 (m, 1H, H9), 2.44 (m, 1H, H3), 2.45 (s, 3H, SCH_3), 3.72 (s, 1H, H4), 3.77 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.12 (d, J=2.8 Hz, 1H, NCH_2Ph), 4.28 (d, J=2.8 Hz, 1H, NCH_2Ph), 4.52 (d, J=15.2 Hz, 1H, H11), 4.62 (d, J=15.2 Hz, 1H, H1), 6.55 (br s, 1H, NH), 6.89 (d, J=8.4 Hz, 2H, Ar), 6.98 (d, J=8.4 Hz, 2H, Ar), 7.09–7.11 (m, 4H, Ar), 7.15–7.18 (m, 2H, Ar), 7.25–7.28 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 16.7, 30.4, 43.7, 46.3, 48.1, 48.4, 48.7, 51.3, 52.6, 53.1, 57.9, 58.2, 83.1, 123.6, 123.8, 123.9, 124.6, 124.9, 126.2, 126.4, 126.6, 126.7, 126.9, 127.2, 128.2, 135.6, 137.3, 142.3, 142.4, 144.5, 144.6, 163.6, 165.0; HRMS (ES): M^+, found 591.2197. $C_{35}H_{33}N_3O_4S$ requires 591.2192.

*4.3.14. (8R)-Methyl-6,7-diaza-8-(imino-1′-carbmethoxy-2′-(4″-pyridyl))-1α,2β,3α, 4β,9α,10β,11α-heptacyclo[7.6.6.1^{3,9}0^{2,10}0^{4,8}0^{12,17}0^{18,23}]tetracosa-6,12,14,16,18,20,22-heptaene-5-carboxylate (**41**).* A solution of 4-pyridyl triazoline **17** (100 mg, 0.18 mmol) in $CDCl_3$ (0.5 mL) in an NMR tube was heated at 60 °C for 72 h. The reaction was followed by ^{1}H NMR spectroscopy and stopped upon completion. Product **41** was isolated by radial chromatography (petroleum ether/ethyl acetate 5:1). Evaporation of the solvent gave a light-yellow powder (85 mg, 85%); mp 106–108 °C; R_f=0.25; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm −0.25 (d, J=12.0 Hz, 1H, H24a), 1.02 (d, J=12.0 Hz, 1H, H24b), 2.10 (d, J=8.6 Hz, 1H, H10), 2.12 (s, 1H, H3), 2.19 (d, J=8.6 Hz, 1H, H2), 2.53 (s, 1H, H9), 2.87 (d, J=8.6 Hz, 1H, H4), 3.22 (d, J=8.2 Hz, 1H, H5), 3.42 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 4.29 (d, J=2.7 Hz, 1H, H1), 4.32 (d, J=2.7 Hz, 1H, H11), 6.49 (d, J=4.6 Hz, 2H, Ar–py), 7.10–7.12 (m, 4H, Ar), 7.19–7.20 (m, 2H, Ar), 7.24–7.28 (m, 2H, Ar), 8.41 (br s, 2H, Ar–py); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 31.7 (C24), 42.4, 44.3, 45.0, 48.8 (overlap, C1,C11), 49.4, 50.5, 52.7 (overlap 2×OCH_3), 55.5, 77.9, 113.6, 124.0, 125.0, 125.2, 126.5, 127.0, 127.1, 142.2, 142.3, 144.7, 144.8, 150.8 (overlap, 2×C_{Ar}), 157.8 (overlap, 2×C_{Ar}), 163.4, 164.2, 168.2; HRMS (ES): M^+, found 532.2111. $C_{32}H_{28}N_4O_4$ requires 532.2111.

*4.3.15. (8R)-Methyl-6,7-diaza-8-(imino-1′-carbmethoxy-2′-(3″-pyridyl))-1α,2β,3α,4β,9α,10β,11α-heptacyclo[7.6.6.1^{3,9}0^{2,10}0^{4,8}0^{12,17}0^{18,23}]tetracosa-5,12,14,16,18,20,22-heptaene-5-carboxylate (**42**).* A solution of 3-pyridyl triazoline **17** (50 mg, 0.09 mmol) in $CDCl_3$ (0.5 mL) in an NMR tube was heated at 60 °C for 24 h. The reaction was followed by ^{1}H NMR spectroscopy and stopped upon completion. Product **42** was isolated by radial chromatography (petroleum ether/ethyl acetate 4:1). Evaporation of the solvent gave a light-yellow powder (42 mg, 84%); mp 84–86 °C; R_f=0.4; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm −0.24 (d, J=12.0 Hz, 1H, H24a), 1.07 (d, J=12.0 Hz, 1H, H24b), 2.11 (dd, J=8.7, 2.4 Hz, 1H, H10), 2.13 (s, 1H, H3), 2.19 (dd, J=8.7, 2.4 Hz, 1H, H2), 2.56 (s, 1H, H9), 2.88 (d, J=8.7 Hz, 1H, H4), 3.23 (d, J=8.3 Hz, 1H, H5), 3.45 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 4.30 (d, J=2.7 Hz, 1H, H1), 4.33 (d, J=2.7 Hz, 1H, H11), 7.01 (d, J=8.8 Hz, 1H, Ar), 7.09–7.12 (m, 4H, Ar), 7.20–7.22 (m, 3H, Ar), 7.25–7.28 (m, 2H, Ar), 7.90 (br s, 1H, Ar), 8.30 (br s, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 31.7, 42.4, 44.4, 45.0, 48.7, 48.8, 49.5, 50.5, 52.7, 52.9, 55.8, 77.9, 123.9, 124.0, 124.1, 125.0, 125.1, 125.2, 126.5, 126.6, 126.7, 127.0, 127.1, 134.6, 139.5, 142.2, 142.3, 144.7, 144.8, 145.9, 165.5, 165.8; HRMS (ES): M^+, found 532.2125. $C_{32}H_{28}N_4O_4$ requires 532.2111.

*4.3.16. (9R)-Methyl-10,11-diaza-3,6-diacetyloxy-9-(imino-1′-carbmethoxy-2′-phenyl)-1α,8α,13β-tetracyclo[6.5.1.0^{2,7}0^{9,13}]tetradeca-2,4,6,10-tetraene-12-carboxylate (**43**), 3,6-diacetyloxy-10-(methylidene-1′-carbmethoxy)-1α,8α-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6,10-triene-9-one (**60**) and 4,7-diacetyloxyindene (**61**).* A sample of triazoline **19** (200 mg, 0.387 mmol) was heated at 140 °C for 20 min. The product was purified by radial chromatography (petroleum ether/ethyl acetate 10:1). The solvent was removed in vacuo to afford the product as a yellow coloured oil, which was treated with cold methanol to give product **43**, which was collected by filtration. Radial chromatography of other fractions (petroleum ether/ethyl acetate 10:1) afforded two additional products, **60** and **61**. Single crystals suitable for X-ray analysis were obtained by slow diffusion of petroleum ether in dichloromethane solution of compound **60**.

Compound **43** (colourless solid, 115 mg, 58%); mp 128–129 °C; R_f=0.65 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm 1.92 (td, J=10.3, 1.4 Hz, 1H, H14a), 2.32 (s, 3H, OAc), 2.33 (s, 3H, OAc), 2.37 (d, J=10.3 Hz, 1H, H14b), 3.23 (d, J=8.6 Hz, 1H, H13), 3.31 (s, 1H, H1), 3.47 (overlapped, d, J=8.6 Hz, 1H, H12), 3.47 (s, 3H, OCH_3), 3.47 (overlapped, s, 1H, H8), 3.66 (s, 3H, OCH_3); 6.77 (d, J=8.5 Hz, 2H, Ar), 6.87 (s, 2H, Ar), 7.09 (t, J=7.6 Hz, 1H, Ar), 7.29 (d, J=8.5 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 21.3, 38.5, 45.6, 45.8, 46.0, 46.2, 46.8, 49.7, 52.2, 52.5, 118.9, 121.1, 121.3, 125.0, 129.1, 141.1, 141.6, 142.0, 142.3, 142.5, 150.5, 154.3, 163.6, 169.2, 169.4; HRMS (ES): M^+, found 517.1483. $C_{27}H_{25}N_3O_8$ requires 517.1486.

Compound **60** (yellow solid, 46 mg, 23%); mp 153–155 °C; R_f=0.75 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm 2.23 (td, J=10.2, 1.7 Hz, 1H, H11a), 2.32 (s, 3H, OAc), 2.35 (s, 3H, OAc), 2.71 (td, 1H, J=10.2, 1.7 Hz, H11b), 3.74 (s, 1H, H1), 3.77 (s, 3H, OCH_3), 5.16 (s, 1H, H8), 6.42 (s, 1H, C=CH), 6.89 (d,

J=8.9 Hz, 1H, Ar), 6.93 (d, J=8.9 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 21.2, 43.7, 46.8, 48.9, 52.2, 53.4, 53.5, 117.1, 122.6, 123.2, 139.8, 142.6, 143.1, 143.9, 149.7, 166.4, 169.1, 169.6, 199.6; HRMS (ES): M^+, found 368.0891. $C_{18}H_{16}O_7$ requires 368.0896. Anal. Calcd for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68; O, 32.53. Found: C, 65.14; H, 4.44; O, 30.29%.

Compound **61** (yellow oil, 9 mg, 5%); R_f=0.85 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm 1.75 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.93 (s, 1H, H1a), 3.13 (s, 1H, H1b), 7.03–4.48 (m, 4H, Ar, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 29.5, 55.2, 60.3, 82.3, 86.8, 118.0, 118.6, 120.1, 122.8, 127.8, 127.9, 149.9, 151.6; HRMS (ES): M^+, found 232.0738. $C_{13}H_{12}O_4$ requires 232.0736.

4.4. Trapping experiments

*4.4.1. Methyl-10,11-diaza-12-(1′α,8′α,9′β,10′β-tricyclo[6.2.1.0^{2,7}]undeca-2′,4′,6′-triene-9′-(imino-1″-carbmethoxy-2″-benzyl))-1α,8α,9β,13β-14-oxatetracyclo[6.5.1.0^{2,7}0^{9,13}]tetradeca-2,4,6,10-tetraene-12-carboxylate (**52**).* A mixture of triazoline **4** (60 mg, 0.144 mmol) and 7-oxabenzonorbornadiene (200 mg, 1.44 mmol) was heated in a test tube at 80 °C for 2 h. Radial chromatography (starting with petroleum ether/ethyl acetate 20:1, then solvent polarity was gradually increased to ethyl acetate) afforded adduct **52** as brown coloured solid (8 mg, 10%); mp 139–142 °C; R_f=0.3; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.90 (d, J=9.7 Hz, 1H, H11a′), 2.23 (d, J=6.1 Hz, 1H, H9), 2.71 (d, J=6.1 Hz, 1H, H11b′), 2.74 (td, J=9.1, 1.9 Hz, 1H, H10′), 3.23 (d, J=6.1 Hz, 1H, H13), 3.27 (s, 3H, OCH_3), 3.66 (s, 1H, H1′), 4.00 (s, 3H, OCH_3), 4.45 (d, J=14.4 Hz, 1H, NCH_2Ph), 4.50 (d, J=14.4 Hz, 1H, NCH_2Ph), 4.59 (s, 1H, H8′), 5.14 (s, 1H, H1), 5.22 (d, J=6.1 Hz, 1H, H9′), 5.75 (s, 1H, H8), 7.08–7.38 (m, 13H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 46.3, 47.1, 47.9, 49.0, 49.5, 50.1, 50.5, 51.4, 51.7, 57.8, 80.9, 81.2, 98.8, 120.2, 120.7, 121.4, 121.5, 126.2, 127.1, 127.6, 127.7, 127.9, 128.3, 128.8, 138.4, 142.9, 146.0, 147.2, 151.3, 164.2, 168.6, 171.3; HRMS (ES): M^+, found 561.2259. $C_{34}H_{31}N_3O_5$ requires 561.2264.

*4.4.2. 9-(5′-(3′,4′,5′-Tricarbmethoxy-1′,2′-diazolyl))-10-(imino-1″-carbmethoxy-2″-benzyl)-1α,8α,9β,10β-tricyclo[6.2.1.0^{2,7}]undeca-2′,4′,6′-triene (**53**).* A mixture of triazoline **4** (50 mg, 0.199 mmol) and DMAD (300 mg, 2.11 mmol, large excess) was heated in a test tube at 80 °C for 3 h. Radial chromatography (starting with petroleum ether/ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate) afforded adduct **53** as a yellow solid (21 mg, 19%); mp 64–65 °C; R_f=0.4; ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.56 (d, J=10.4 Hz, 1H, H11a), 1.70 (dt, J=10.4, 1.3 Hz, 1H, H11b), 3.18 (s, 2H, H9), 3.42 (s, 1H, H10), 3.78 (s, 3H, OCH_3), 3.84 (1H, s, H9), 3.87 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.28 (d, J=17.5 Hz, 1H, NCH_2Ph), 4.60 (d, J=17.5 Hz, 1H, NCH_2Ph), 6.97–7.19 (m, 9H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm 45.6, 46.9, 47.5, 48.6, 52.1, 52.9, 53.7, 54.1, 59.6, 84.3, 106.8, 121.7, 122.2, 126.1, 127.1, 128.2, 137.2, 147.0, 147.2, 150.4, 153.7, 157.2, 160.7, 162.4, 163.1, 165.9, 166.4; HRMS (ES): M^+, found 559.1957. $C_{30}H_{29}N_3O_8$ requires 559.1955.

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Supplementary data

Supplementary data contain synthetic, crystallographic and computational details associated with this article. CCDC 829014–829016 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data related to this article can be found in the online version, at doi:10.1016/j.tet.2012.02.073.

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