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A novel and efficient stereo-controlled synthesis of hexahydroquinolinones via the diene-transmissive hetero-Diels–Alder reaction of cross-conjugated azatrienes with ketenes and electrophilic dienophiles

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ABSTRACT

The diene-transmissive hetero-Diels–Alder (DTHDA) reactions of cross-conjugated azatrienes (divinylimines or penta-1,4-dien-3-imines) having an *N*-aryl, *N*-alkyl, or *N*-dimethylamino substituent have been examined. The initial reaction of the azatrienes with diphenylketene at room temperature yielded β-lactams of [2+2] cycloadducts, which upon heating underwent [1,3]-sigmatropic rearrangement to produce the formal [4+2] cycloadducts. The reaction of *N*-phenylazatriene with dimethylketene or dichloroketene produced the [2+2] cycloadducts only, while the reaction of *N*-(dimethylamino)azatriene with dichloroketene gave the [4+2] cycloadduct without heating. When the [2+2] cycloadduct has two different vinyl substituents at C-4 of the β-lactam ring, the regioselectivity of the rearrangement depends on steric factors and the electronic demand of the substituents. The second Diels–Alder reaction of the initial [4+2] cycloadducts with electron-deficient dienophiles (TCNE, *N*-phenylmaleimide) stereoselectively yielded hexahydroquinolinone derivatives. Similarly, a tandem intermolecular–intramolecular mode of the aza-DTHDA reactions produced tetracyclic nitrogen-containing heterocycles in a regio- and stereoselective manner.

1. Introduction

The diene-transmissive Diels–Alder (DTDA) reaction is one of the sequential (so-called tandem, domino, cascade, etc.) transformation methodologies[1] and can usually be defined by two sequential cycloadditions that involve an initial Diels–Alder (DA) reaction of a cross-conjugated triene (n=1) (or its equivalents) with a dienophile, followed by a second DA cycloaddition on the newly formed, transmitted diene unit of the monoadduct with a dienophile to give a bis-adduct (first reaction in Chart 1), although the DTDA reaction is formally considered to be a set of multisequential DA reactions of α,ω-divinylpoly(vinylidene) in which the last two steps involve the above-defined DTDA process (e.g., n=2, 3, … in Chart 1). The diene-transmissive hetero-Diels–Alder (DTHDA) reaction is the special case of the DTDA reaction in which one or more heteroatoms are contained within either a triene/polyene framework or a dienophile skeleton or both in either DA process.

Since the early reports in 1955,[2] the utility of this attractive method has been shown by Tsuge, Kanemasa, Wada and others in an efficient synthesis of a variety of ring-fused oligocyclic compounds using cross-conjugated carbotrienes.[3] Recently, Fallis et al. reported an application of this method for the construction of a triterpenoid skeleton and tricyclic core of vinigrol.[4a–e] Sherburn et al. reported the formal total synthesis of triptolide, a diterpenoid natural product, using this methodology.[4f,g] Because the hetero-DA reaction is among the most powerful and attractive methods of obtaining six-membered heterocycles,[5] it is promising that the DTHDA methodology involving one or two hetero-DA reactions in the sequence offers an efficient and attractive method for stereoselective synthesis of ring-fused heterocyclic systems. In this context, our group previously reported the first example of the DTHDA reaction using divinyl thioketones as cross-conjugated thiatrienes.[6] Tsuge et al. reported the DTHDA reaction of divinyl ketones as cross-conjugated oxatrienes.[7] Spino et al. applied this oxatriene–DTHDA methodology to construct the picrasane framework by use of cyclic 2-formyl-1,3-diene.[8] Very recently, the first report on the DTHDA reaction using cross-conjugated dioxatrienes (1,1-diformylethenes) has appeared.[9] The DTHDA methodology involving aza-DA reactions would be a valuable and attractive synthetic tool for construction of a variety of ring-fused nitrogen-containing heterocyclic systems because nitrogen heterocycles are found in a wide range of natural and synthetic bioactive compounds.[5,10]

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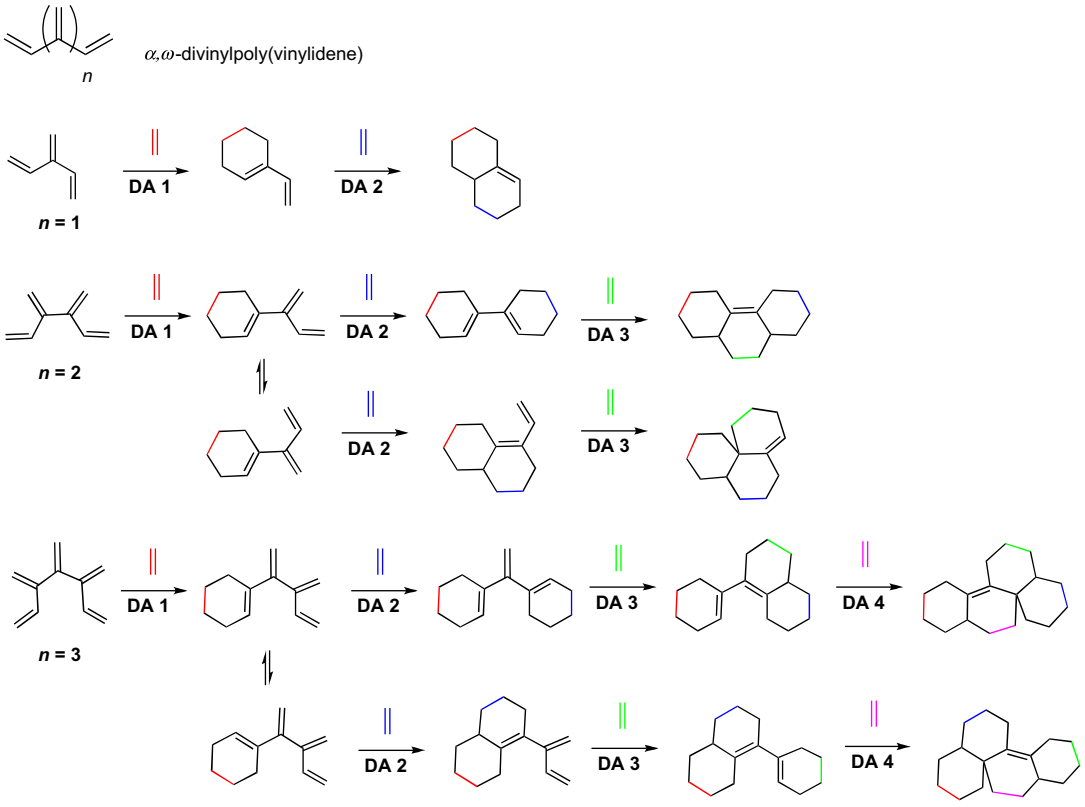


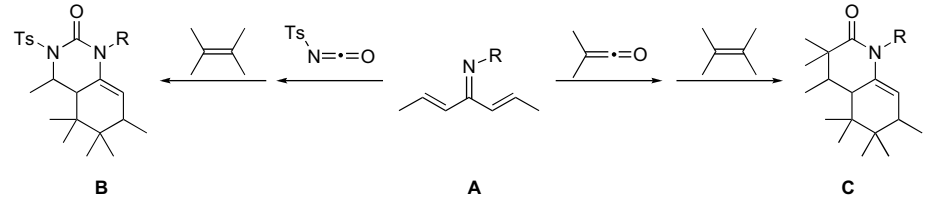
Chart 1. DTDA methodology of α,ω-divinylpoly(vinylidene).

Therefore, we started to investigate the DTHDA reaction using divinyl imines **A** as cross-conjugated azatrienes in the initial DA reaction with tosyl isocyanate and succeeded in stereoselective synthesis of hexahydroquinazolinones **B** by the DTHDA method for the first time (Scheme 1).[11,12] We also examined ketenes as an initial reactant with **A** to lead to hexahydroquinolinone derivatives **C**, the results of which were partly given in a preliminary communication.[13] Herein, we report this aza-DTHDA reaction with ketenes in detail and its application to an intramolecular version.

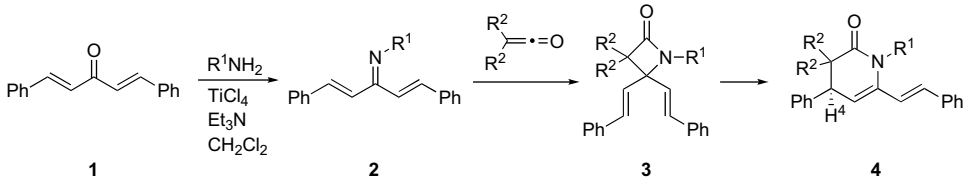
2. Results and discussion

2.1. Initial cycloaddition of azatrienes 2 with ketenes

Azatrienes **2** were prepared from the corresponding ketones **1** and a variety of primary amines by condensation using $TiCl_4$ and Et_3N at 0 °C for 1 h.[14,15] Azatrienes **2a–h** could be isolated,[16] but they were used without purification in the subsequent reaction with ketenes, while *N*,*N*-dimethylaminoazatriene **2i** is stable enough to allow isolation. *N*-Phenylazatriene **2a** reacted immediately (within 5 min) with diphenylketene[17] at room temperature to produce the [2+2] cycloadduct **3a** in 98% yield (Scheme 2, Table 1, entry 1).[18] Although **3a** is an isolable crystalline compound, it underwent [1,3]-sigmatropic rearrangement upon heating in toluene under reflux for 1 h to yield the thermodynamically more stable dihydropyridone **4a** quantitatively, which corresponds to the formal [4+2] (DA) cycloadduct of azatriene **2a** with diphenylketene (Table 1, entry 1).[19,20] Diphenylketene also reacted with azatrienes **2b–i** having various substituents R^1 (i.e., aryl, benzyl, alkyl, and dimethylamino groups on the nitrogen atom) to produce the [2+2] cycloadducts **3b–i** in good to excellent yields (entries 2–9). Similarly, thermal rearrangement of **3b–i** provided dihydropyridones



Scheme 1.



Scheme 2.

Table 1
Initial cycloaddition of azatrienes **2** with ketenes[a]

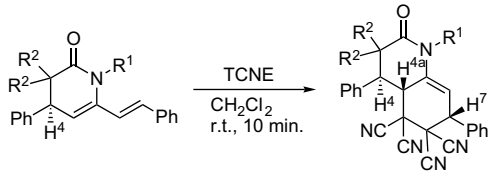
Entry	Azatriene	R^1	R^2	Product	Yield of **3** (%)	Product	Yield of **4** (%)
1	**2a**	Ph	Ph	**3a**	98	**4a**	99
2	**2b**	4-$MeOC_6H_4$	Ph	**3b**	84	**4b**	99
3	**2c**	4-MeC_6H_4	Ph	**3c**	80	**4c**	99
4	**2d**	4-ClC_6H_4	Ph	**3d**	96	**4d**	99
5	**2e**	4-$NO_2C_6H_4$	Ph	**3e**	96	**4e**	99
6	**2f**	Bn	Ph	**3f**	76	**4f**	99
7	**2g**	^{i}Pr	Ph	**3g**	90	**4g**	99
8	**2h**	^{n}Pr	Ph	**3h**	72	**4h**	98
9	**2i**	NMe_2	Ph	**3i**	91	**4i**	99
10	**2a**	Ph	Me	**3j**	16	**4j**	—[b]
11	**2a**	Ph	Cl	**3k**	20	**4k**	—[c]
12	**2i**	NMe_2	Me	**3l**	96	**4l**	99
13[d]	**2i**	NMe_2	Cl	**3m**	—[e]	**4m**	23

[a] Reaction of **2** with ketene was carried out in a one-pot procedure by generating **2** (**1** (1.0 equiv), R^1NH_2 (2.0 equiv), Et_3N (4.4 equiv), $TiCl_4$ (1.0 equiv)). In the case of R^1=NMe_2 (entries 9, 12, 13), isolated azatriene **2i** was used.
[b] Compound **3j** decomposed on heating to 200 °C.
[c] Compound **3k** decomposed on heating to 140 °C.
[d] THF was used as solvent.
[e] [2+2] cycloadduct **3m** was not obtained.

4b–i in excellent yields (entries 2–9). The reaction of **2a** with in situ generated dimethylketene and dichloroketene produced the [2+2] cycloadducts **3j** and **3k**, respectively, albeit in low yield (entries 10 and 11). Unfortunately, both adducts **3j**,**k** failed to give the expected rearrangement products **4j**,**k** under the thermal conditions tried (entries 10 and 11). Similarly, the [2+2] cycloadduct **3l** was obtained in 96% yield from the reaction of isolated azatriene **2i** (R^1=Me_2N) with dimethylketene, and the cycloadduct **3l** also underwent the [1,3]-sigmatropic rearrangement to give the formal [4+2] cycloadduct **4l** in 99% yield (entry 12). Meanwhile, the reaction of **2i** with dichloroketene directly gave the [4+2] cycloadduct **4m** (23%) instead of the corresponding [2+2] cycloadduct **3m** even at room temperature (entry 13).[18b,19c,d]

2.2. Second cycloaddition with tetracyanoethylene

With the monocycloadducts **4** in hand, we performed the second cycloaddition with some representative electron-deficient dienophiles, because normal electron-demand DA reactions were expected to proceed at the electron-rich 2-aminodiene moiety in **4**. Initially, the reaction of **4** with a symmetrical and reactive dienophile, tetracyanoethylene (TCNE) was carried out to examine the diastereo π-facial selectivity. The results are shown in Scheme 3 and Table 2. The reaction of **4a** with TCNE proceeded at room temperature for 10 min to produce [4+2] cycloadduct **5a** in 99% yield with complete diastereo π-facial selectivity (Table 2, entry 1). Similarly, the reactions of **4b–m** with TCNE proceeded smoothly within 10 min to produce **5b–m** in nearly quantitative yield (entries 2–11). In all reactions, the dienophile (TCNE) added from the less hindered back side (H^4) to the diene moiety of **4**, avoiding the more bulky axial phenyl substituent at the 4-position (vide infra, Fig. 2).



4 **5**

Scheme 3. Second cycloaddition with TCNE.

Table 2
Second cycloaddition of **4** with TCNE

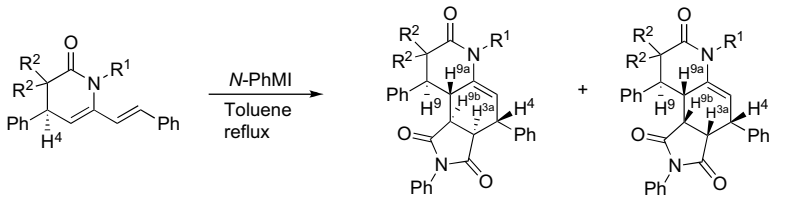
Entry	Diene	R^1	R^2	Product	Yield (%)
1	**4a**	Ph	Ph	**5a**	99
2	**4b**	4-$MeOC_6H_4$	Ph	**5b**	99
3	**4c**	4-MeC_6H_4	Ph	**5c**	99
4	**4d**	4-ClC_6H_4	Ph	**5d**	99
5	**4e**	4-$NO_2C_6H_4$	Ph	**5e**	98
6	**4f**	Bn	Ph	**5f**	99
7	**4g**	^{i}Pr	Ph	**5g**	99
8	**4h**	^{n}Pr	Ph	**5h**	99
9	**4i**	NMe_2	Ph	**5i**	99
10	**4l**	NMe_2	Me	**5l**	94
11	**4m**	NMe_2	Cl	**5m**	99

2.3. Second cycloaddition with *N*-phenylmaleimide

The reaction of **4** with *N*-phenylmaleimide (*N*-PhMI) was carried out to examine *endo*/*exo* selectivity as well as diastereo π-facial selectivity (Scheme 4 and Table 3). The reaction proceeded in refluxing toluene to produce the single diastereomer **6** nearly quantitatively. The sole exception is the case of **4l** giving **6l** (99%) in a 69:31 ratio of a separable diastereomeric mixture of the *exo*- and *endo*-isomers (entry 10). The π-facial selectivity of **4** for the *N*-PhMI dienophile agreed with that observed in the reaction with TCNE.

2.4. Determination of relative stereochemistry and proposed transition-state structures

The stereochemistry of bis-adducts **6** as well as **5** was determined by inspection of the vicinal coupling constants of H^{9a} using ^{1}H NMR spectroscopy (Fig. 1); a large vicinal coupling constant (*J*=ca. 12 Hz) between H^9 and H^{9a} indicated a trans diaxial relationship, and a relatively large vicinal coupling constant (*J*=ca. 8 Hz) between H^{9a} and H^{9b} suggested a pseudodiaxial relationship. Additionally, the nuclear Overhauser effect (NOE) was observed between H^9 and H^{9b}, and between H^{9a} and H^4 in a cis relationship. Thus, the stereochemical outcome implied that the dienophile attacked from the less hindered bottom H^4-side of monoadduct **4** in an *exo* mode (Fig. 2). The vicinal coupling constant between H^4 and the vinyl proton (H^5) on the pyridone ring of **4** was ca. 7 Hz, suggesting that H^4 orients in a quasi-equatorial position, and hence the



4 **6 *exo*** (H^{9a}-H^{9b} trans) **6 *endo*** (H^{9a}-H^{9b} cis)

Scheme 4. Second cycloaddition with *N*-phenylmaleimide.

Table 3
Second cycloaddition of **4** with *N*-phenylmaleimide

Entry	Diene	R^1	R^2	Time (h)	Product	Yield (%)	*exo*/*endo*[a]
1	**4a**	Ph	Ph	7.0	**6a**	99	>95/5
2	**4b**	4-$MeOC_6H_4$	Ph	8.0	**6b**	99	>95/5
3	**4c**	4-MeC_6H_4	Ph	7.0	**6c**	99	>95/5
4	**4d**	4-ClC_6H_4	Ph	7.0	**6d**	99	>95/5
5	**4e**	4-$NO_2C_6H_4$	Ph	8.0	**6e**	98	>95/5
6	**4f**	Bn	Ph	7.0	**6f**	99	>95/5
7	**4g**	^{i}Pr	Ph	13.0	**6g**	99	>95/5
8	**4h**	^{n}Pr	Ph	9.5	**6h**	99	>95/5
9	**4i**	NMe_2	Ph	6.0	**6i**	99	>95/5
10	**4l**	NMe_2	Me	40.0	**6l**	99	69/31
11	**4m**	NMe_2	Cl	7.0	**6m**	99	>95/5

[a] Ratio was determined by ^{1}H NMR spectroscopy. Ratio >95:5 denotes that no *endo*-isomer was detected.

phenyl group at C4 occupies a quasi-axial position. Therefore, the dienophiles attacked from the bottom H^4 side of the diene unit avoiding steric repulsion between the phenyl group at C4 and the dienophile. The observed *exo*-selectivity is explained in terms of the steric repulsion exerted between the bulky axial phenyl or chloro substituent at the C3 position and the imido moiety of the

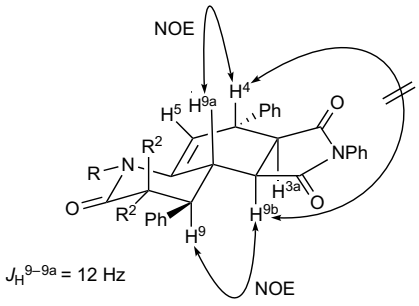


Figure 1. Stereochemistry of compound **6**.

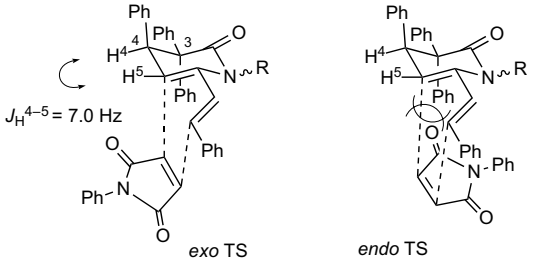


Figure 2. *exo* and *endo* transition-state models.

Table 4
Initial cycloaddition of azatrienes **8** with ketenes

Entry	Azatriene	R^1	R^2	Product	Yield of **9** (%)	Product	Yield of **10**+**11** (%)	Ratio (**10**/**11**)[a]
1	**8a**	Ph	Ph	**9a**	66	**10a**, **11a**	99	81/19
2	**8b**	4-$MeOC_6H_4$	Ph	**9b**	57	**10b**, **11b**	99	82/18
3	**8c**	Bn	Ph	**9c**	83	**10c**, **11c**	97	82/18
4	**8d**	^{i}Pr	Ph	**9d**	53	**10d**, **11d**	97	83/17
5	**8e**	NMe_2	Ph	**9e**	57	**10e**, **11e**	97	87/13
6[b]	**8e**	NMe_2	Me	**9f**	89	**10f**, **11f**	77	82/18

[a] Ratio was determined based on integration of the ^{1}H NMR signals of the methyl protons of the Et ester group.
[b] Reaction was carried out from isolated azatriene **8e**.

dienophile over the second orbital interaction in the *endo* transition-state. However, the *endo* addition was partially observed in the reaction of monoadduct **4l** bearing a relatively small methyl substituent at the C3 position (Table 3, entry 10).

2.5. DTHDA reaction of azatrienes 8, 14, and 15 bearing two different vinyl groups

2.5.1. *Initial cycloaddition of azatrienes **8**, **14**, and **15** with ketenes*

We performed the DTHDA reaction of cross-conjugated azatrienes (**8**, **14**, and **15**) bearing different substituents at the diene termini to examine electronic and/or steric effects in the DTHDA cycloaddition involving the [1,3]-sigmatropic rearrangement. Azatriene **8a** generated in situ from the corresponding ketone **7** and aniline also reacted with diphenylketene to afford the [2+2] cycloadduct **9a** in 66% yield (Scheme 5, Table 4, entry 1). The adduct **9a** underwent [1,3]-sigmatropic rearrangement upon heating in toluene for 2 h to afford the two formal [4+2] cycloadducts, dihydropyridones **10a** and **11a**, in 99% yield in a ratio of 81:19 (Table 4, entry 1). Similarly, azatrienes **8b–e** reacted with diphenylketene or dimethylketene to produce the [2+2] cycloadducts **9b–f** in 53–89% yields, and their thermal isomerization provided mixtures of pyridones **10b–f** and **11b–f** in good yields in ratios of 82–87:18–13. The predominant formation of **10** over **11** is attributed to the stabilizing ability difference due mainly to the substituents (Ph, CO_2Et) in the canonical resonance structures of the zwitterionic intermediates (Fig. 3).

Azatrienes **14** and **15** were also subjected to reaction with diphenylketene and dimethylketene to produce again the [2+2]

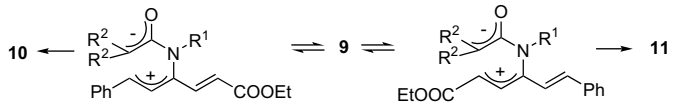
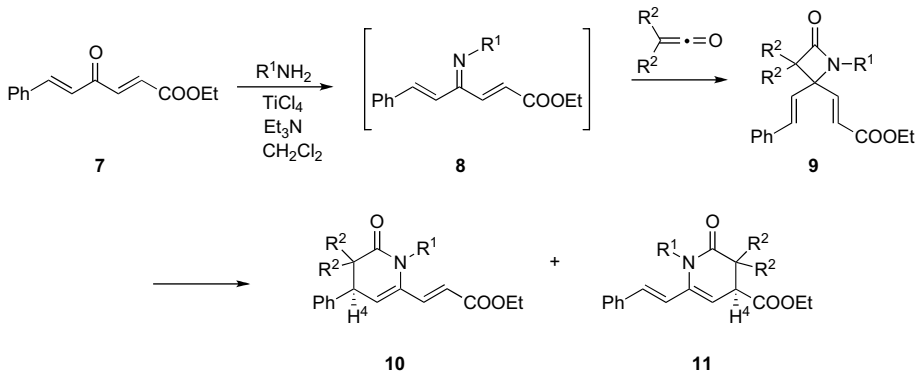
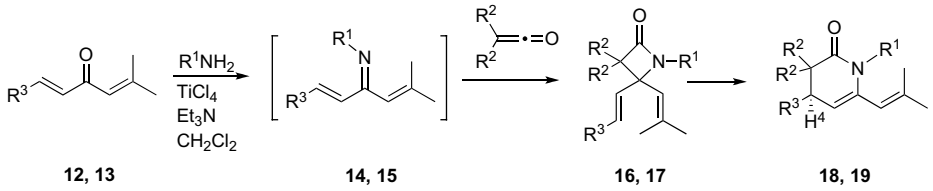


Figure 3.



Scheme 5.



Scheme 6.

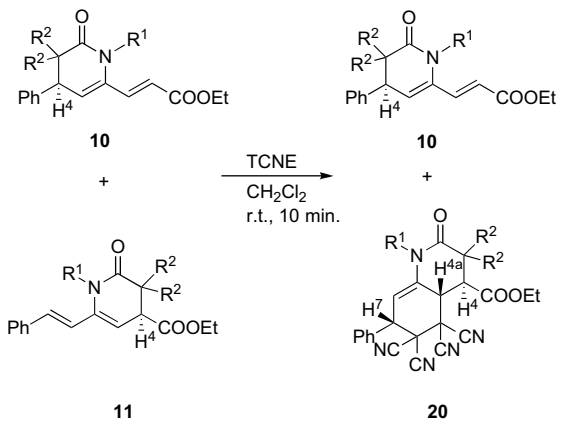
Table 5
Initial cycloaddition of azatrienes **14** and **15** with ketenes

Entry	Azatriene	R^1	R^2	R^3	Product	Yield of **16**/**17** (%)	Conditions (**16**/**17**→**18**/**19**)	Product	Yield of **18**/**19** (%)
1	**14a**	Ph	Ph	Ph	**16a**	43	Xylene, 140 °C, 5.0 h	**18a**	77
2	**14b**	4-$MeOC_6H_4$	Ph	Ph	**16b**	57	Xylene, 140 °C, 2.5 h	**18b**	90
3	**14c**	Bn	Ph	Ph	**16c**	71	Toluene, 110 °C, 1.0 h	**18c**	95
4	**14d**	^{i}Pr	Ph	Ph	**16d**	61	Toluene, 110 °C, 2.5 h	**18d**	50
5	**14e**	^{n}Pr	Ph	Ph	**16e**	89	Toluene, 110 °C, 1.0 h	**18e**	48
6	**14f**	NMe_2	Ph	Ph	**16f**	83	Toluene, 110 °C, 5.0 h	**18f**	57
7	**14f**	NMe_2	Me	Ph	**16g**	82	Toluene, 110 °C, 12 h	**18g**	70
8	**14f**	NMe_2	Cl	Ph	**16h**	—	rt, 5 min.	**18h**	70
9	**15a**	Ph	Ph	CO_2Et	**17a**	50	Xylene, 140 °C, 3.0 h	**19a**	88
10	**15b**	Bn	Ph	CO_2Et	**17b**	52	Toluene, 110 °C, 1.0 h	**19b**	91
11	**15c**	^{i}Pr	Ph	CO_2Et	**17c**	50	Xylene, 140 °C, 5.5 h	**19c**	93
12	**15d**	NMe_2	Ph	CO_2Et	**17d**	33	Toluene, 110 °C, 4.0 h	**19d**	94

cycloadducts **16** and **17**, respectively, both of which underwent [1,3]-sigmatropic rearrangement upon heating to give **18** and **19** as sole products, respectively (Scheme 6 and Table 5). The reaction of **14f** with dichloroketene proceeded at room temperature for 5 min to give the [4+2] cycloadduct **18h** instead of the [2+2] cycloadduct **16h** (entry 8). It is noteworthy to mention that although **18** and **19** were formed as the formal DA products of azatrienes with ketenes via the rearrangement, the reaction took place at the mono-substituted diene C-terminus, even for the case that the substituent is an electron-withdrawing ethoxycarbonyl group for **15**/**17** (Table 5). These results suggest that steric factors played the predominant role rather than electronic factors in the overall process ([2+2]+rearrangement). In fact, 1-dimethylamino-4,4-bis-(2-methyl-1-propenyl)-3,3-diphenylazetidin-2-one derived from 2,6-dimethyl-2,5-heptadien-4-one (phorone) did not undergo [1,3]-sigmatropic rearrangement even under the severe thermal conditions tried until its retro [2+2] reaction along with partial decomposition occurred.

2.5.2. *Second cycloaddition of monoadducts **10** and **11***

The monoadduct dienes **10** and **11** were inseparable by column chromatography. Thus, we attempted the second DA reaction with TCNE of **10** and **11** as a mixture (Scheme 7). When a mixture of **10a** and **11a** (ratio, 81:19) was treated with TCNE at room temperature for 10 min, we fortunately found that only **11a** reacted to provide bis-adduct **20a** in 95% yield along with **10a** in almost quantitative recovery yield (96%) (Table 6, entry 1). Similarly, bis-adducts **20b–f** and unreacted **10b–f** were both successfully obtained separately in good yields (entries 2–6). The trans relationship between H^4 and H^{4a} of **20** indicated that TCNE attacked from the less hindered H^4-side, avoiding the more bulky ester substituent at the 4-position of the pyridone ring of **11** in agreement with the reaction of **4** (vide supra).



Scheme 7. Second cycloaddition of **10**/**11** with tetracyanoethylene.

Thus, separated monoadduct **10a** reacted with an excess amount of methyl vinyl ketone (MVK) in refluxing xylene for 23 h to give hexahydroquinolinones **21a** and **22a** in 74% yield in a ratio of 17:83 (Scheme 8, Table 7, entry 1). The latter compound **22a** could be produced from the initially formed DA *endo*-adduct **21a** via [1,3]-H-migration under thermal reaction conditions because the separated compound **21d** (entry 3) was converted to **22d** by prolonged heating in xylene [**21d** (major isomer) was used instead of **21a**]. Similarly, the reactions of **10c–e** with MVK afforded **21c–e** and **22c–e** (entries 2–4). In the case of **10d**, the formation of small amounts of *exo* isomers was variably detected (*exo*-**21′d** and *exo*-**22′d**).

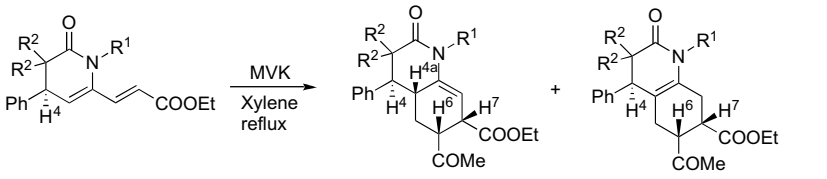
2.5.3. *Second cycloaddition of monoadducts **18** and **19***

Initially, the DA reaction with TCNE was carried out (Scheme 9 and Table 8). Monoadducts **18** and **19** were considered to be less reactive than monoadducts **4** and **11** because of steric hindrance between the two methyl substituents at the diene terminus and the attacking dienophile. Actually, these reactions required heating at a somewhat higher temperature and/or longer reaction time

Table 6
Second cycloaddition of **10**/**11** with tetracyanoethylene

Entry	Diene	R^1	R^2	Product	Yield of **20** (%)	Recovered **10** (%)
1	**10a**, **11a**	Ph	Ph	**20a**	95	96
2	**10b**, **11b**	4-$MeOC_6H_4$	Ph	**20b**	93	93
3	**10c**, **11c**	Bn	Ph	**20c**	91	97
4	**10d**, **11d**	^{i}Pr	Ph	**20d**	92	96
5	**10e**, **11e**	NMe_2	Ph	**20e**	94	97
6[a]	**10f**, **11f**	NMe_2	Me	**20f**	99	98

[a] Reaction was carried out for 3.5 h (monitored by ^{1}H NMR spectroscopy).



10 **21** ***endo*** (H^6-H^7 cis) **22** (*endo* isomer derivative)

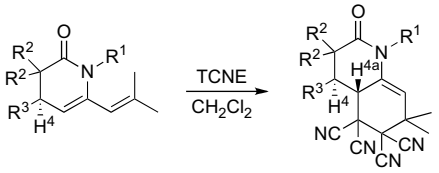
Scheme 8. Second cycloaddition of **10** with methyl vinyl ketone.

Table 7
Second cycloaddition of **10** with methyl vinyl ketone

Entry	Diene	R^1	R^2	Time (h)	Product	Yield (%)	Ratio (**21**/**22**)[a]
1	**10a**	Ph	Ph	23	**21a**, **22a**	74	17/83
2	**10c**	Bn	Ph	24	**21c**, **22c**	66	19/81
3	**10d**	^{i}Pr	Ph	26	**21d**, **22d**	65	80/20
4	**10e**	NMe_2	Ph	75	**21e**, **22e**	57	9/91

[a] Ratio was determined based on integration of the ^{1}H NMR signals of the methyl protons of the Et ester group.

compared with those of **4** and **11**; however, they provided clean reactions to give bis-adducts **23** and **24** in good to excellent yields with complete π-facial selectivity.



18, 19 **23, 24**

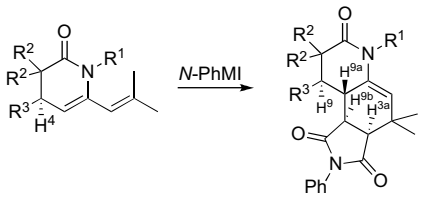
Scheme 9. Second cycloaddition of **18**/**19** with tetracyanoethylene.

Table 8
Second cycloaddition of **18**/**19** with tetracyanoethylene

Entry	Diene	R^1	R^2	R^3	Temp (°C)	Time (h)	Product	Yield of **23**/**24** (%)
1[a]	**18a**	Ph	Ph	Ph	83	6.5	**23a**	99
2[a]	**18b**	4-$MeOC_6H_4$	Ph	Ph	83	4.5	**23b**	99
3	**18c**	Bn	Ph	Ph	40	30	**23c**	99
4	**18d**	^{i}Pr	Ph	Ph	40	8.0	**23d**	98
5	**18e**	^{n}Pr	Ph	Ph	40	4.0	**23e**	99
6	**18f**	NMe_2	Ph	Ph	rt.	1.0	**23f**	99
7[a]	**18g**	NMe_2	Me	Ph	83	63	**23g**	99
8	**18h**	NMe_2	Cl	Ph	rt.	9.0	**23h**	62
9	**19a**	Ph	Ph	COOEt	40	0.5	**24a**	99
10	**19b**	Bn	Ph	COOEt	rt.	2.0	**24b**	91
11	**19c**	^{i}Pr	Ph	COOEt	rt.	2.0	**24c**	94
12	**19d**	NMe_2	Ph	COOEt	rt.	0.5	**24d**	99

[a] 1,2-Dichloroethane was used as solvent.

Next, the reaction with *N*-PhMI was performed to observe *endo*/*exo* selectivity and π-facial selectivity as well (Scheme 10, Table 9). The monoadduct **18f** reacted with *N*-PhMI in refluxing mesitylene for 30 h to produce a bis-adduct, hexahydroquinolinone **25f**, in 56% yield (entry 1), while the other compounds **18a**–**e** and **18g**,**h** only decomposed without giving any adducts under the reaction conditions. On the other hand, the reactions of monoadducts **19a**,**b**,**d** with *N*-PhMI proceeded under milder thermal conditions to give hexahydroquinolinones **26a**,**b**,**d** in excellent yields (entries 2–4). All of the reactions proceeded with complete π-facial and *endo*/*exo* selectivities to give single diastereomers. Namely, *N*-PhMI



18, 19 **25, 26** ***exo***

Scheme 10. Second cycloaddition of **18**/**19** with *N*-phenylmaleimide.

Table 9
Second cycloaddition of **18**/**19** with *N*-phenylmaleimide

Entry	Diene	R^1	R^2	R^3	Solvent	Temp (°C)	Time (h)	Product	Yield (%)
1	**18f**	NMe_2	Ph	Ph	Mesitylene	166	30	**25f**	56
2	**19a**	Ph	Ph	COOEt	Toluene	110	65	**26a**	98
3	**19b**	Bn	Ph	COOEt	Xylene	140	20	**26b**	93
4	**19d**	NMe_2	Ph	COOEt	Toluene	110	24	**26d**	98

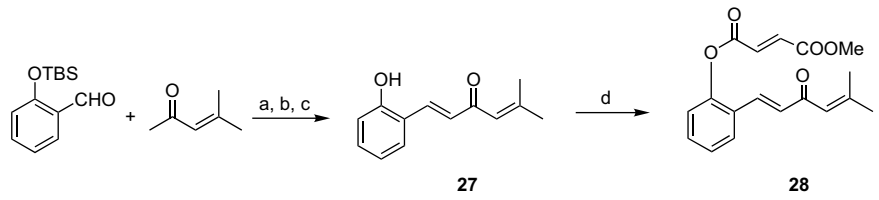
cycloadded from the less hindered back H^4-side to the diene (**18**, **19**) in the *exo* arrangement (cf. Fig. 2).

2.6. Intramolecular DTHDA reaction

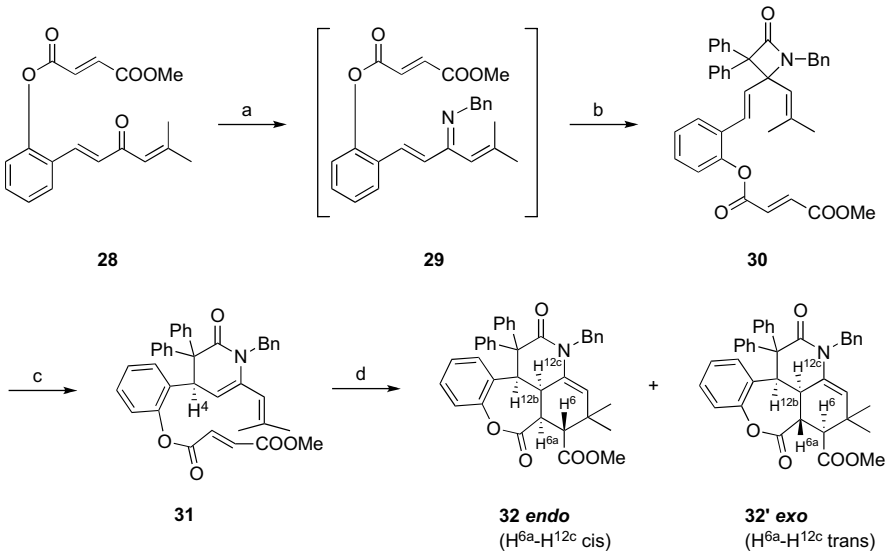
Synthesis of more highly ring-fused nitrogen heterocycles prompted us to incorporate an intramolecular mode in this DTHDA methodology, because we have succeeded in the intramolecular DTHDA reaction of *N*-sulfonyl azatrienes to give benzopyrano[3,4-*c*]quinolines with high regio- and stereoselectivities.[12b]

When an intramolecular version is used as the second DA reaction in this DTHDA methodology, the site selectivity in the initial cycloaddition with ketene is of particular importance for the second intramolecular DA reaction. Encouraged by the successful results in the intermolecular version (see azatrienes **14**, **15** in Scheme 6), we designed a new azatriene **29** to overcome these difficulties. Ketone **28**, the precursor of imine **29**, was synthesized as outlined in Scheme 11. Aldol reaction of mesityl oxide with TBS-protected salicylaldehyde (a) followed by dehydration with methanesulfonyl chloride/triethylamine (b) and deprotection of the TBS group by treatment with TBAF (c) gave ketone **27** in 86% yield in three steps (Scheme 11). Acylation of the hydroxyl group of **27** with fumaric acid monomethyl ester using DCC produced the tethered ketone **28** in 86% yield (d).

As illustrated in Scheme 12, the azatriene **29** generated from ketone **28** and benzylamine (a) reacted with diphenylketene to produce the expected [2+2] cycloadduct **30** in 34% yield (b). The [1,3]-sigmatropic rearrangement worked cleanly upon heating **30** in toluene for 2 h to give diene **31** as the sole product in 88% yield (c). The intramolecular DA reaction of **31** required prolonged



Scheme 11. (a) LDA (1.1 equiv), THF, −78 °C, 1 h, 99%; (b) MsCl (1.2 equiv), Et_3N (2.4 equiv), CH_2Cl_2, rt, overnight, 93%; (c) TBAF (1.0 equiv), THF, rt, 1 h, 93%; (d) monomethylfumarate (1.1 equiv), DCC (2.0 equiv), DMAP (cat.), toluene, 10 min, 86%.



Scheme 12. (a) $BnNH_2$ (2.0 equiv), $TiCl_4$ (1.0 equiv), Et_3N (4.4 equiv), CH_2Cl_2, 0 °C, 1.5 h; (b) Ph_2CCO (2.0 equiv), rt, 2 h, 34%; (c) toluene, reflux, 2 h, 88%; (d) xylene, reflux, 31 h, 63% (48:52).

heating at a higher temperature (in refluxing xylene for 31 h) to proceed, giving a mixture of 8-oxa-3-azabenzo[4,5]cyclohepta[1,2,3-*de*]naphthalenes **32** (*endo*) and **32′** (*exo*) in 63% yield in a ratio of 48:52. Compound **32′** was assigned as an *exo*-cycloadduct, based on its vicinal coupling constant between H^{6a} and H^{12c} (J=10.5 Hz), which indicated a trans diaxial relationship between them. However, we could not clearly determine the *endo*/*exo* and π-facial selectivities of the cycloaddition by means of 2D NMR spectroscopy (NOESY) alone because of overlapping of several essential peaks. Finally, X-ray crystal structure analyses unequivocally established the structures of **32** and **32′** (Fig. 4), proving that both cycloadducts (**32** and **32′**) were formed by the tethered dienophile attacking from the β-face (anti to H^4) to the diene **31** in *endo* and *exo* modes with respect to the chain, respectively.

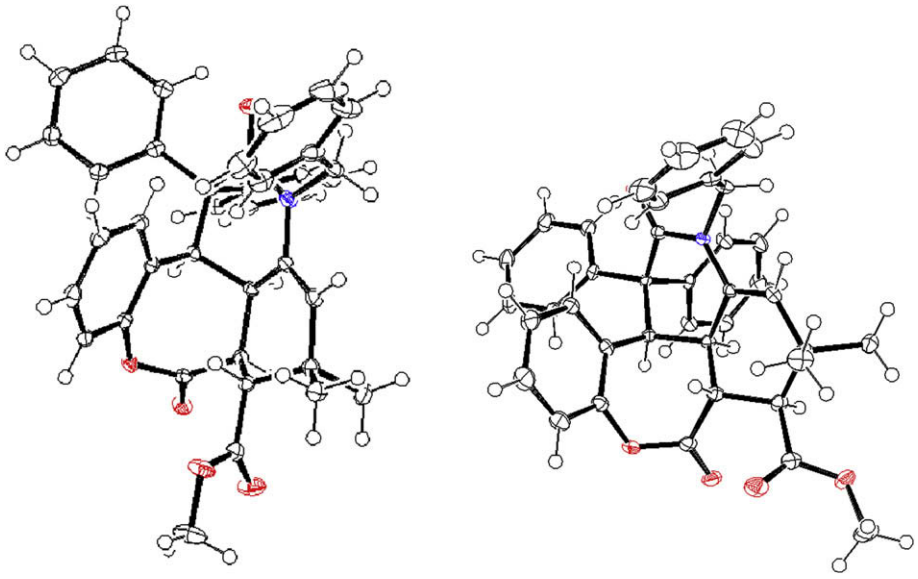


Figure 4. X-ray crystal structure analysis of **32** (left) and **32′** (right).

3. Conclusion

The DTHDA methodology of cross-conjugated azatrienes bearing electron-donating *N*-substituents reacting with ketenes followed by electrophilic dienophiles has been shown to be an efficient method for construction of hexahydroquinolinones with high regio- and stereoselectivities. The intermolecular–intramolecular DTHDA reaction mode was also successfully applied for the stereoselective synthesis of 8-oxa-3-azabenzo[4,5]cyclohepta[1,2,3-*de*]naphthalene. Further studies on the DTHDA reaction using cross-conjugated heterotrienes are currently under way in our laboratory.

4. Experimental

4.1. General

All melting points were determined on a Yanaco melting point apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270-30 or a Horiba FT-710 spectrophotometer. ^{1}H and ^{13}C NMR spectral data were obtained with a Bruker AV 600, a JEOL JNM-EX 500, a JEOL JNM-LA 400, a Bruker DPX 300, a JEOL JNM-EX 300, or a JEOL JNM-EX 270 instrument. Chemical shifts (δ) are quoted in parts per million using tetramethylsilane (δ=0) for ^{1}H NMR and $CDCl_3$ (δ=77.0) for ^{13}C NMR. Mass spectra were measured on a Bruker Daltonics microTOF, a Hitachi double-focusing M-80B, or a JEOL JMS-SX 102 spectrometer. Elemental analyses were performed with a YANACO CHN-CODER MT-6 model analyzer. Column chromatography was conducted on silica gel (Kanto Chemical Co. or Merck Co. Ltd). HPLC was performed on a JASCO UV-970 equipped with a detector (254 nm) using a Pegasil silica, 60–5, 20×250 mm column and EtOAc/hexane as eluent. All reactions were performed under argon.

4.2. Typical procedure for preparation of azatriene 2 and its sequential [2+2] cycloaddition with diphenylketene (Table 1, entry 1)

A mixture of 1,5-diphenyl-1,4-pentadiene-3-one (**1**) (234 mg, 1.0 mmol), Et_3N (0.612 mL, 4.4 mmol), and aniline (0.182 mL, 2.0 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C, and titanium tetrachloride (1.0 mL, 1.0 M solution in CH_2Cl_2, 1.0 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 30 min, then a solution of diphenylketene[12] (388 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 5 min, the reaction mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (10 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:4, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:4, v/v) yielded 1,3,3-triphenyl-4,4-di-β-styrylazetidin-2-one (**3a**) (494 mg, 98%) as colorless crystals. Mp 158–159 °C; IR (KBr): 1738, 1498, 1376, 752, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (d, *J*=16.3 Hz, 2H, α-H(styryl)), 6.58 (d, *J*=16.3 Hz, 2H, β-H (styryl)), 7.02–7.28 (m, 19H, Ar), 7.63 (d, *J*=7.4 Hz, 4H, Ar), 7.75 (d, *J*=7.7 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.8 (C), 77.9 (C), 118.4 (2CH), 124.0 (CH), 126.5 (4CH), 127.2 (2CH), 128.0 (3CH), 128.2 (4CH), 128.3 (3CH), 128.5 (4CH), 128.8 (4CH), 133.2 (2CH), 136.2 (2C), 137.6 (2C), 137.7 (C), 167.0 (C). HRMS-ESI *m*/*z* [M+Na]$^+$ calcd for $C_{37}H_{29}NNaO$: 526.2141, found: 526.2145.

4.3. Preparation of azatriene 2i and successive [2+2] cycloaddition with dimethylketene (Table 1, entry 12)

A mixture of 1,5-diphenyl-1,4-pentadiene-3-one (**1**) (234 mg, 1.0 mmol), Et_3N (0.612 mL, 4.4 mmol), and 1,1-dimethylhydrazine (0.152 mL, 2.0 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C, and titanium tetrachloride (1.0 mL, 1.0 M solution in CH_2Cl_2, 1.0 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 30 min, quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (10 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:9, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:9, v/v) yielded *N*,*N*-dimethyl-*N*′-(3-phenyl-1-β-styrylallylidene)hydrazine (**2i**) (214 mg, 77%) as orange crystals. Mp 122–123 °C; IR (KBr): 1738, 1498, 1376, 752, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68 (s, 6H, Me(NMe_2)), 6.96 (d, *J*=16.1 Hz, 1H, olefin), 7.00 (d, *J*=16.8 Hz, 1H, olefin), 7.16–7.55 (m, 12H, olefin, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.8 ($2CH_3$), 121.2 (CH), 125.8 (CH), 127.1 (4CH), 128.3 (CH), 128.6 (2CH), 128.8 (3CH), 134.8 (CH), 135.5 (CH), 136.4 (C), 136.6 (C), 159.1 (C). HRMS-ESI *m*/*z* [M+Na]$^+$ calcd for $C_{19}H_{21}N_2$: 277.1699, found: 277.1699.

Et_3N (0.033 mL, 0.24 mmol) was added to a solution of azatriene **2i** (55 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) at 0 °C followed by isobutyryl chloride (0.025 mL, 0.24 mmol). After 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (10 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:4, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:4, v/v) yielded 1-(*N*,*N*-dimethylamino)-3,3-dimethyl-4,4-di-β-styrylazetidin-2-one (**3l**) (67 mg, 96%) as colorless crystals. Mp 123–124 °C; IR (KBr): 1756, 1498, 1450, 1332, 976, 750, 698 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28 (s, 6H, 2Me), 2.98 (s, 6H, 2Me(NMe_2)), 6.44 (d, *J*=16.2 Hz, 2H, α-H(styryl)), 6.77 (d, *J*=16.2 Hz, 2H, β-H(styryl)), 7.23–7.45 (m, 10H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.8 ($2CH_3$), 46.6 ($2CH_3$), 56.1 (C), 72.8 (C), 126.5 (4CH), 127.6 (2CH), 127.9 (2CH), 128.6 (4CH), 133.6 (2CH), 136.5 (2C), 172.8 (C). HRMS-ESI *m*/*z* [M+Na]$^+$ calcd for $C_{23}H_{26}N_2NaO$: 369.1937, found: 369.1940.

4.4. Typical procedure for [1,3]-sigmatropic rearrangement of the [2+2] cycloadduct 3 (Table 1, entry 1)

A solution of **3a** (252 mg, 0.5 mmol) in toluene (20 mL) was heated at 110 °C for 2 h and then concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:4, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:4, v/v) yielded 1,3,3,4-tetraphenyl-6-β-styryl-3,4-dihydro-1*H*-pyridin-2-one (**4a**) (249 mg, 99%) as colorless crystals. Mp 216–217 °C; IR (KBr): 1682, 1496, 1336, 750, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (d, *J*=7.1 Hz, 1H, H-4), 5.85 (d, *J*=15.9 Hz, 1H, H-8), 6.10 (d, *J*=7.1 Hz, 1H, H-5), 6.59–6.61 (m, 2H, Ar), 6.65 (d, *J*=15.9 Hz, 1H, H-7), 6.86–6.97 (m, 5H, Ar), 7.03–7.45 (m, 16H, Ar), 7.69–7.72 (m, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 48.7 (CH), 60.7 (C), 109.1 (CH), 123.3 (CH), 125.8 (CH), 126.5 (4CH), 127.1 (CH), 127.55 (CH), 127.60 (CH), 127.9 (CH), 128.17 (2CH), 128.23 (2CH), 128.5 (4CH), 128.8 (2CH), 129.0 (2CH), 129.2 (2CH), 130.4 (CH), 130.5 (2CH), 136.4 (C), 138.3 (C), 138.79 (C), 138.81 (C), 141.2 (C), 142.0 (C), 170.8 (C). HRMS-ESI *m*/*z* [M+Na]$^+$ calcd for $C_{37}H_{29}NNaO$: 526.2141, found: 526.2152.

4.5. Typical procedure for the [4+2] cycloaddition of azatriene with dichloroketene (Table 1, entry 13)

Dichloroacetyl chloride (0.56 mL, 6.0 mmol) was added dropwise to a solution of Et_3N (0.84 mL 6.0 mmol) in THF (40 mL) at 0 °C followed by a solution of azatriene **2i** (552 mg, 2.0 mmol) in THF (15 mL), and the mixture was stirred for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc (30 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo.

Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:19, v/v)] yielded 3,3-dichloro-1-(*N*,*N*-dimethylamino)-4-phenyl-6-β-styryl-3,4-dihydro-1*H*-pyridin-2-one (**4m**) (178 mg, 23%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.94 (s, 3H, Me(NMe_2)), 2.97 (s, 3H, Me(NMe_2)), 4.27 (d, *J*=4.3 Hz, 1H, H-4), 5.64 (d, *J*=4.3 Hz, 1H, H-5), 6.87 (d, *J*=16.2 Hz, 1H, H-8), 6.94 (d, *J*=16.2 Hz, 1H, H-7), 7.27–7.47 (m, 10H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 42.5 (CH_3), 43.1 (CH_3), 54.4 (CH), 86.7 (C), 104.8 (CH), 121.4 (CH), 126.8 (2CH), 128.3 (3CH), 128.5 (CH), 128.7 (2CH), 130.0 (2CH), 131.2 (CH), 135.8 (C), 136.4 (C), 141.9 (C), 160.9 (C).

4.6. Typical procedure for the DA reaction of monoadducts 4 with tetracyanoethylene (Table 2, entry 1)

TCNE (29 mg, 0.225 mmol) was added to a solution of **4a** (75 mg, 0.15 mol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 10 min and then concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (3:7, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:3, v/v) yielded 2-oxo-1,3,3,4,7-pentaphenyl-1,2,3,4,4a,7-hexahydroquinoline-5,5,6,6-tetracarbonitrile (**5a**) (94 mg, 99%) as colorless crystals. Mp 195–197 °C; IR (KBr): 1696, 1650, 1496, 1280, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (ddd, *J*=1.9, 2.1, 10.9 Hz, 1H, H-4a), 4.29 (dd, *J*=1.9, 4.8 Hz, 1H, H-7), 4.92 (d, *J*=10.9 Hz, 1H, H-4), 5.10 (dd, *J*=2.1, 4.8 Hz, 1H, H-8), 6.67–7.74 (m, 25H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.9 (C), 43.8 (CH), 46.8 (CH), 48.7 (CH, C), 62.8 (C), 108.3 (CH), 109.1 (C), 109.8 (C), 110.0 (C), 111.5 (C), 127.5 (2CH), 127.8 (3CH), 128.0 (2CH), 128.2 (3CH), 128.8 (3CH), 128.9 (CH), 129.5 (CH), 129.8 (2CH), 130.2 (CH), 130.3 (3CH), 130.5 (2CH), 131.2 (2CH), 132.2 (C), 133.6 (C), 137.7 (C), 138.0 (C), 139.0 (C), 139.3 (C), 170.6 (C). LRMS-FAB *m*/*z* (ion, % relative intensity): 632 (M^++H, 6), 246 (17), 185 (60), 93 (100). HRMS-FAB *m*/*z* [M+H]$^+$ calcd for $C_{43}H_{30}N_5O$: 632.2450, found: 632.2443.

4.7. Typical procedure for DA reaction of monoadducts 4 with *N*-phenylmaleimide (Table 3, entry 1)

A mixture of **4a** (101 mg, 0.2 mmol) and *N*-phenylmaleimide (52 mg, 0.3 mmol) in toluene (20 mL) was heated at 110 °C for 7 h, and then concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (3:7, v/v)] followed by recrystallization CH_2Cl_2/hexane (1:3, v/v) yielded 2,4,6,8,8,9-hexaphenyl-4,6,8,9,9a,9b-hexahydro-3a*H*-pyrrolo[3,4-*f*]quinoline-1,3,7-trione (**6a**) (134 mg, 99%) as colorless crystals. Mp 198–200 °C; IR (KBr): 1710, 1628, 1496, 1382, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (br d, *J*=12.4 Hz, 1H, H-9a), 3.11 (dd, *J*=4.1, 8.2 Hz, 1H, H-9b), 3.23 (dd, *J*=8.1, 8.2 Hz, 1H, H-3a), 3.65 (dd, *J*=3.4, 8.1 Hz, 1H, H-4), 5.03 (dd, *J*=2.9, 3.4 Hz, 1H, H-5), 5.93 (d, *J*=12.4 Hz, 1H, H-9), 6.99 (d, *J*=7.1 Hz, 2H, Ar), 7.10–7.48 (m, 28H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.1 (CH), 42.3 (CH), 42.5 (CH), 44.5 (CH), 47.4 (CH), 63.4 (C), 106.9 (CH), 126.4 (3CH), 126.9 (CH), 127.25 (CH), 127.31 (2CH), 127.6 (CH), 127.66 (3CH), 127.69 (2CH), 127.9 (CH), 128.4 (4CH), 128.5 (CH), 128.8 (CH), 129.3 (3CH), 129.7 (2CH), 130.4 (2CH), 130.9 (2CH), 131.6 (CH), 131.7 (C), 136.17 (C), 136.23 (C), 138.49 (C), 138.52 (C), 141.1 (C), 142.8 (C), 172.3 (C), 174.1 (C), 176.3 (C). LRMS-EI *m*/*z* (ion, % relative intensity): 676 (M^+, 71), 503 (M^+−*N*-PhMI, 14), 481 (26), 309 (M^+−*N*-PhMI, Ph_2CCO, 100). HRMS-EI *m*/*z* [M]$^+$ calcd for $C_{47}H_{36}N_2O_3$: 676.2726, found: 676.2729.

4.8. Preparation of 4-oxo-6-phenylhexa-2,5-dienoic acid ethyl ester (7)

n-BuLi (38 mL, 1.6 M solution in hexane, 60 mmol) was added dropwise to a solution of dimethyl methylphosphonate (6.5 mL, 60 mmol) in THF (200 mL) at −65 °C, and the mixture was stirred for 30 min. A solution of methyl cinnamate (3.2 g, 20 mmol) in THF (30 mL) was added dropwise to the mixture. The reaction mixture was stirred for 5 min at the same temperature, quenched with saturated aqueous NH_4Cl and extracted with EtOAc (150 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (SiO_2: EtOAc) yielded (2-oxo-4-phenylbut-3-enyl)phosphonic acid dimethyl ester (4.9 g, 98%) as a colorless oil. IR (neat): 1736, 1690, 1658, 1610, 1262, 1048, 1030, 836, 800 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.31 (s, 1H, H-1), 3.38 (s, 1H, H-1′), 3.79 (d, *J*=0.8 Hz, 3H, Me(OMe)), 3.82 (d, *J*=0.8 Hz, 3H, Me(OMe)), 6.88 (d, *J*=16.1 Hz, 1H, H-3), 7.39–7.59 (m, 5H, Ar), 7.64 (d, *J*=16.1 Hz, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.7 (CH_2, d, *J*=129.1 Hz), 52.9 (CH_3), 53.1 (CH_3), 125.5 (CH), 128.5 (2CH), 128.9 (2CH), 130.9 (CH), 133.9 (C), 144.9 (CH), 190.7 (C, d, *J*=6.1 Hz).

A solution of (2-oxo-4-phenylbut-3-enyl)phosphonic acid dimethyl ester (1.3 g, 5.0 mmol) in DMF (50 mL) was added dropwise to a suspension of K_2CO_3 (1.1 g, 8.0 mmol) in DMF (200 mL) at −20 °C. After 5 min, a solution of ethyl glyoxylate (1.0 g, 10 mmol) in DMF (20 mL) was added dropwise at the same temperature, and the reaction mixture was stirred for an additional 5 min. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (50 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:9, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:8, v/v) yielded **7** (737 mg, 64%) as yellow crystals and its cis-isomer (**7′**) (334 mg, 29%) as a yellow oil, respectively.

4.8.1. (2E,5E)-4-Oxo-6-phenylhexa-2,5-dienoic acid ethyl ester (7)

Yellow crystals; mp 39 °C; IR (KBr): 1720, 1684 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, *J*=7.1 Hz, 3H, Me(COOEt)), 4.29 (q, *J*=7.1 Hz, 2H, CH_2(COOEt)), 6.83 (d, *J*=15.7 Hz, 1H, H-3), 6.98 (d, *J*=16.1 Hz, 1H, H-5), 7.39–7.45 (m, 3H, Ar), 7.49 (d, *J*=15.7 Hz, 1H, H-2), 7.57–7.62 (m, 2H, Ar), 7.72 (d, *J*=16.1 Hz, 1H, H-6); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.1 (CH_3), 61.3 (CH_2), 124.9 (CH), 128.5 (2CH), 129.0 (2CH), 131.1 (CH), 131.2 (CH), 134.1 (C), 138.4 (CH), 145.4 (CH), 165.6 (C), 188.3 (C). HRMS-ESI *m*/*z* [M+Na]$^+$ calcd for $C_{14}H_{14}NaO_3$: 253.0835, found: 253.0839.

4.8.2. (2Z,5E)-4-Oxo-6-phenyl-hexa-2,5-dienoic acid ethyl ester (7′)

Yellow oil; IR (neat): 1714, 1654, 1626 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, *J*=7.1 Hz, 3H, Me(COOEt)), 4.17 (q, *J*=7.1 Hz, 2H, CH_2(COOEt)), 6.22 (d, *J*=12.1 Hz, 1H, H-3), 6.70 (d, *J*=12.1 Hz, 1H, H-2), 6.84 (d, *J*=16.4 Hz, 1H, H-5), 7.27–7.56 (m, 6H, H-6, Ar); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.9 (CH_3), 61.1 (CH_2), 126.2 (CH), 126.3 (CH), 128.4 (2CH), 128.9 (2CH), 130.8 (CH), 134.2 (C), 140.3 (CH), 145.4 (CH), 165.0 (C), 193.6 (C). HRMS-ESI *m*/*z* [M+Na]$^+$ calcd for $C_{14}H_{14}NaO_3$: 253.0835, found: 253.0838.

4.9. Typical procedure for preparation of azatriene 8 and its sequential [2+2] cycloaddition with diphenylketene (Table 4, entry 1)

A mixture of **7** (230 mg, 1.0 mmol), Et_3N (0.612 mL, 4.4 mmol), and aniline (0.182 mL, 2.0 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C, and titanium tetrachloride (1.0 mL, 1.0 M solution in CH_2Cl_2, 1.0 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h, then a solution of diphenylketene (388 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 5 min, the reaction mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (10 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:4, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:4, v/v) yielded 3-(4-oxo-1,3,3-triphenyl-2-β-styrylazetidin-2-

yl)-acrylic acid ethyl ester (**9a**) (330 mg, 66%) as colorless crystals. Mp 169–171 °C; IR (KBr): 1750, 1708, 1500, 1376, 1308, 1188, 754, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, J=7.0 Hz, 3H, Me(COOEt)), 4.07 (dq, J=1.8, 7.0 Hz, 2H, CH_2(COOEt)), 5.81 (d, J=15.9 Hz, 1H, H-2), 6.08 (d, J=16.5 Hz, 1H, H-6), 6.63 (d, J=16.5 Hz, 1H, H-5), 7.06–7.10 (m, 3H, Ar), 7.18–7.31 (m, 11H, Ar), 7.29 (d, J=15.9 Hz, 1H, H-3), 7.50–7.52 (m, 2H, Ar), 7.63–7.66 (m, 4H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1 (CH_3), 60.6 (CH_2), 72.1 (C), 78.5 (C), 118.2 (2CH), 123.9 (CH), 124.3 (CH), 126.6 (2CH), 127.5 (2CH), 127.8 (CH), 128.3 (2CH), 128.4 (3CH), 128.5 (2CH), 128.6 (2CH), 128.8 (2CH), 129.0 (2CH), 134.0 (CH), 135.8 (C), 136.7 (C), 137.0 (C), 137.1 (C), 144.2 (CH), 165.1 (C), 166.4 (C). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{34}H_{29}NNaO_3$: 522.2040, found: 522.2040.

4.10. Typical procedure for [1,3]-sigmatropic rearrangement of [2+2] cycloadduct 9 (Table 4, entry 1)

A solution of **9a** (250 mg, 0.5 mmol) in toluene (20 mL) was heated at 110 °C for 2 h and then concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:4, v/v)] yielded a mixture of **10a** and **11a** (247 mg, 99%, 81:19) as a pale yellow solid.

4.11. Preparation of (*E*)-5-methyl-1-phenylhexa-1,4-dien-3-one (12)

n-BuLi (11.3 mL, 1.6 M in hexane, 18 mmol) was added dropwise to a solution of diisopropylamine (2.5 mL, 18 mmol) in THF (100 mL) at −65 °C, and the mixture was warmed to 0 °C and stirred for 1 h. The solution was recooled to −65 °C, and mesityl oxide (2.0 mL, 18 mmol) was added dropwise. After being stirred for 1 h, benzaldehyde (1.53 mL, 15 mmol) was added dropwise to the mixture. The reaction mixture was stirred for an additional 10 min at the same temperature, quenched with saturated aqueous NH_4Cl, and extracted with EtOAc (100 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:4, v/v)] yielded 1-hydroxy-5-methyl-1-phenylhex-4-en-3-one (2.72 g, 89%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.91 (d, J=1.2 Hz, 3H, Me), 2.19 (d, J=1.1 Hz, 3H, Me), 2.82 (d, J=5.7 Hz, 2H, H-2, H-2), 3.72 (d, J=2.7 Hz, 1H, OH), 5.13–5.20 (m, 1H, H-1), 6.03–6.05 (m, 1H, H-4), 7.28–7.41 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 (CH_3), 27.8 (CH_3), 52.1 (CH_2), 70.1 (CH), 123.6 (CH), 125.6 (2CH), 127.4 (CH), 128.4 (2CH), 143.0 (C), 157.6 (C), 200.6 (C).

Methanesulfonyl chloride (0.84 mL, 10.9 mmol) was added to a solution of 1-hydroxy-5-methyl-1-phenyl-hex-4-en-3-one (1.85 g, 9.08 mmol) and Et_3N (3.1 mL, 21.8 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was warmed to room temperature with stirring overnight, diluted with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (30 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:4, v/v)] afforded **12** (1.44 g, 85%) as a yellow oil. IR (neat): 1658, 1628, 1600, 1450, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.97 (d, J=1.2 Hz, 3H, Me), 2.22 (d, J=1.1 Hz, 3H, Me), 6.34–6.36 (m, 1H, H-4), 6.78 (d, J=16.1 Hz, 1H, H-2), 7.34–7.41 (m, 3H, Ar), 7.50–7.60 (m, 3H, Ar, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 27.9 (CH_3), 123.6 (CH), 128.2 (2CH), 128.3 (CH), 128.9 (2CH), 130.1 (CH), 135.0 (C), 142.0 (CH), 156.4 (C), 190.2 (C).

4.12. Preparation of (*E*)-6-methyl-4-oxo-hepta-2,5-dienoic acid ethyl ester (13)

n-BuLi (11.3 mL, 1.6 M in hexane, 18 mmol) was added dropwise to a solution of diisopropylamine (2.5 mL, 18 mmol) in THF (100 mL) at −65 °C, and the mixture was warmed to 0 °C and stirred for 1 h. The solution was cooled to −65 °C, before mesityl oxide (2.0 mL, 18 mmol) was added dropwise, and the reaction mixture was stirred for an additional 1 h. A solution of ethyl glyoxylate (3.6 g, 36 mmol) in THF (10 mL) was added dropwise to the mixture at −65 °C, and the resulting mixture was stirred for an additional 1 h at the same temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (100 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:4, v/v)] yielded 2-hydroxy-6-methyl-4-oxo-hept-5-enoic acid ethyl ester (2.0 g, 54%) as a colorless oil. IR (neat): 3448, 1736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (t, J=7.0 Hz, 3H, Me(COOEt)), 1.91 (d, J=1.2 Hz, 3H, Me), 2.16 (d, J=1.2 Hz, 3H, Me), 2.90 (dd, J=6.1, 17.1 Hz, 1H, H-3), 2.96 (dd, J=4.0, 17.1 Hz, 1H, H-3), 3.39 (d, J=5.8 Hz, 1H, OH), 4.25 (dq, J=1.8, 7.3 Hz, 2H, CH_2(COOEt)), 4.49 (ddd, J=4.0, 5.8, 6.1 Hz, 1H, H-2), 6.07 (dd, J=1.2, 1.2 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.2 (CH_3), 19.9 (CH_3), 26.7 (CH_3), 46.6 (CH_2), 60.5 (CH_2), 66.5 (CH), 122.8 (CH), 155.8 (C), 173.1 (C), 196.6 (C). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{10}H_{16}NaO_4$: 223.0941, found: 223.0935.

Methanesulfonyl chloride (0.88 mL, 11.4 mmol) was added to a solution of 2-hydroxy-6-methyl-4-oxo-hept-5-enoic acid ethyl ester (1.9 g, 9.5 mmol) and Et_3N (3.2 mL, 22.8 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight, diluted with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (30 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:4, v/v)] yielded **13** (1.6 g, 94%) as a yellow oil. IR (neat): 1720, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J=7.1 Hz, 3H, Me(COOEt)), 1.90 (d, J=1.1 Hz, 3H, Me), 2.14 (d, J=1.0 Hz, 3H, Me), 4.18 (q, J=7.1 Hz, 2H, CH_2(COOEt)), 6.24 (dd, J=1.0, 1.1 Hz, 1H, H-5), 6.60 (d, J=15.9 Hz, 1H, H-3), 7.05 (d, J=15.9 Hz, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (CH_3), 21.3 (CH_3), 28.0 (CH_3), 61.1 (CH_2), 122.6 (CH), 130.0 (CH), 141.7 (CH), 160.0 (C), 165.8 (C), 188.5 (C). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{10}H_{14}NaO_3$: 205.0835, found: 205.0829.

4.13. Typical procedure for preparation of azatriene 14 and its sequential [2+2] cycloaddition with diphenylketene (Table 5, entry 1)

A mixture of **12** (559 mg, 3.0 mmol), Et_3N (1.8 mL, 13 mmol), and aniline (0.55 mL, 6.0 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C, and titanium tetrachloride (3.0 mL, 1.0 M solution in CH_2Cl_2, 3.0 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 h, then cooled to 0 °C. A solution of diphenylketene (1.2 g, 6.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After 5 min, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (30 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:9, v/v)] yielded 4-(2-methylpropenyl)-1,3,3-triphenyl-4-β-styrylazetidin-2-one (**16a**) (589 mg, 43%) as a yellow oil. IR (neat): 1748, 1664, 1600, 1380 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 3H, Me), 1.58 (s, 3H, Me), 5.59 (d, J=1.2 Hz, 1H, H-3), 6.03 (d, J=16.1 Hz, 1H, H-6), 6.56 (d, J=16.1 Hz, 1H, H-5), 7.04–7.08 (m, 3H, Ar), 7.17–7.37 (m, 11H, Ar), 7.47 (dd, J=1.2, 7.1 Hz, 2H, Ar), 7.66–7.71 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7 (CH_3), 27.3 (CH_3), 72.7 (C), 78.1 (C), 118.2 (3CH), 120.4 (CH), 124.0 (CH), 126.6 (3CH), 126.8 (CH), 127.1 (CH), 127.3 (CH), 127.8 (CH), 128.2 (2CH), 128.5 (2CH), 128.9 (CH), 129.1 (2CH), 129.3 (2CH), 131.0 (CH), 132.2 (CH), 136.5 (C), 137.4 (C), 137.5 (C), 138.6 (C), 139.6 (C), 167.5 (C). LRMS-FAB m/z (ion, % relative intensity): 456

(M^++H, 68), 455 (M^+, 22), 261 (100), 170 (44), 167 (33), 77 (Ph, 35). HRMS-EI *m*/*z* $[M]^+$ calcd for $C_{33}H_{29}NO$: 455.2249, found: 455.2250.

4.14. Typical procedure for [1,3]-sigmatropic rearrangement of [2+2] cycloadduct 16 (Table 5, entry 1)

A solution of **16a** (300 mg, 0.66 mmol) in xylene (30 mL) was heated 140 °C for 5 h, and then concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:4, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:4, v/v) yielded 6-(2-methyl-propenyl)-1,3,3,4-tetraphenyl-3,4-dihydro-1*H*-pyridin-2-one (**18a**) (231 mg, 77%) as colorless crystals. Mp 192–193 °C; IR (KBr): 3032, 2360, 1634, 1496, 1327, 1265, 756, 694 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.45 (d, *J*=1.1 Hz, 3H, Me), 1.55 (d, *J*=1.1 Hz, 3H, Me), 4.22 (d, *J*=6.8 Hz, 1H, H-4), 4.94–4.96 (m, 1H, H-7), 5.57 (dd, *J*=1.1, 6.8 Hz, 1H, H-5), 5.58–6.61 (m, 2H, Ar), 6.85–6.90 (m, 2H, Ar), 6.93–6.97 (m, 3H, Ar), 7.05–7.15 (m, 5H, Ar), 7.24–7.29 (m, 1H, Ar), 7.33–7.38 (m, 3H, Ar), 7.40–7.43 (m, 2H, Ar), 7.67–7.77 (m, 2H, Ar); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.5 (CH_3), 25.6 (CH_3), 48.9 (CH), 60.7 (C), 111.0 (CH), 120.1 (CH), 125.6 (CH), 126.4 (2CH), 127.0 (CH), 127.3 (CH), 127.4 (CH), 128.08 (2CH), 128.09 (2CH), 128.3 (2CH), 128.6 (2CH), 128.9 (2CH), 129.2 (2CH), 130.5 (2CH), 137.0 (C), 138.0 (C), 138.6 (C), 139.1 (C), 141.3 (C), 142.0 (C), 170.9 (C). LRMS-EI *m*/*z* (ion, % relative intensity): 455 (M^+, 42), 261 (100), 170 (54), 165 (22), 77 (Ph, 11). HRMS-ESI *m*/*z* $[M+Na]^+$ calcd for $C_{33}H_{29}NNaO$: 478.2141, found: 478.2141. Anal. Calcd for $C_{33}H_{29}NO$: C, 87.00; H, 6.42; N, 3.07. Found: C, 87.12; H, 6.66; N, 3.05.

4.15. Typical procedure for the second cycloaddition of monoadduct 11 with tetracyanoethylene (Table 6, entry 1)

TCNE (10 mg, 0.08 mmol) was added to a solution of a mixture of **10a** and **11a** (175 mg, 0.35 mol, 81:19) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 10 min and then concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (3:7, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:3, v/v) yielded 5,5,6,6-tetracyano-2-oxo-1,3,3,7-tetraphenyl-1,2,3,4,4a,5,6,7-octahydroquinoline-4-carboxylic acid ethyl ester (**20a**) (40 mg, 95% yield based on **11a**) as colorless crystals along with 3-(6-oxo-1,4,5,5-tetraphenyl-1,4,5,6-tetrahydropyridin-2-yl)-acrylic acid ethyl ester (**10a**) (136 mg, 96% recovery) as colorless crystals.

Compound **20a**: colorless crystals; mp 115–117 °C; IR (KBr): 1732, 1706, 1670, 1496, 1322, 1280, 1250, 1196, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.0 Hz, 3H, Me(COOEt)), 3.62 (dq, *J*=7.0, 10.7 Hz, 1H, CH_2(COOEt)), 3.94 (dq, *J*=7.0, 10.7 Hz, 1H, CH_2(COOEt)), 4.17 (dd, *J*=1.8, 3.4 Hz, 1H, H-7), 4.49 (ddd, *J*=1.8, 1.8, 11.0 Hz, 1H, H-4a), 4.54 (d, *J*=11.0 Hz, 1H, H-4), 4.94 (dd, *J*=1.8, 3.4 Hz, 1H, H-8), 7.07–7.08 (d, *J*=7.3 Hz, 2H, Ar), 7.19–7.21 (d, *J*=7.3 Hz, 2H, Ar), 7.26–7.48 (m, 14H, Ar), 7.53–7.54 (d, *J*=7.3 Hz, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.2 (CH_3), 42.9 (CH), 43.5 (C), 46.4 (C), 46.9 (CH), 50.8 (CH), 61.1 (C), 62.8 (CH_2), 109.4 (C), 109.8 (C), 109.9 (CH), 110.4 (C), 110.9 (C), 127.4 (2CH), 128.1 (2CH), 128.2 (CH), 128.3 (CH), 128.5 (2CH), 128.9 (CH), 129.3 (2CH), 129.4 (2CH), 129.5 (2CH), 130.20 (2CH), 130.26 (2CH), 130.30 (CH), 132.7 (C), 137.4 (C), 137.5 (C), 138.6 (C), 138.7 (C), 169.3 (C), 169.9 (C). LRMS-FAB *m*/*z* (ion, % relative intensity): 628 (M^++H, 100), 500 (M^++H−TCNE, 37), 499 (M^+−TCNE, 29), 165 (32). HRMS-FAB *m*/*z* $[M+H]^+$ calcd for $C_{40}H_{30}N_5O_3$: 628.2348, found: 628.2359.

Compound **10a**: colorless crystals; mp 171–173 °C; IR (KBr): 1714, 1680, 1496, 1182, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, *J*=7.1 Hz, 3H, Me(COOEt)), 4.05 (q, *J*=7.1 Hz, 2H, CH_2(COOEt)), 4.28 (d, *J*=7.1 Hz, 1H, H-4), 5.73 (d, *J*=15.9 Hz, 1H, H-2), 6.26 (d, *J*=7.1 Hz, 1H, H-3), 6.57–6.61 (m, 3H, Ar), 6.66–6.99 (m, 5H, Ar), 7.08–7.29 (m, 4H, Ar), 7.13 (d, *J*=15.9 Hz, 1H, H-3), 7.32–7.43 (m, 6H, Ar), 7.60–7.63 (m, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1 (CH_3), 48.7 (CH), 60.47 (CH_2), 60.53 (C), 115.7 (CH), 120.1 (CH), 125.9 (CH), 126.5 (2CH), 127.4 (CH), 127.7 (CH), 127.9 (CH), 128.30 (2CH), 128.32 (4CH), 128.5 (2CH), 129.1 (2CH), 129.2 (2CH), 130.4 (2CH), 136.9 (C), 137.2 (C), 138.2 (C), 138.6 (CH), 140.7 (C), 141.4 (C), 166.0 (C), 170.6 (C). HRMS-ESI *m*/*z* $[M+Na]^+$ calcd for $C_{34}H_{29}NNaO_3$: 522.2040, found: 522.2045.

4.16. Typical procedure for the second cycloaddition of monoadducts 10 with methyl vinyl ketone (Table 7, entry 1)

Methyl vinyl ketone (0.06 mL, 0.7 mmol) was added to a xylene (10 mL) solution of **10a** (72 mg, 0.15 mmol) and heated at 140 °C for 14 h. After being cooled to room temperature, the reaction mixture was concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:4, v/v)] yielded a mixture of **21a** and **22a** (61 mg, 74%, 17:83) as a colorless solid. Analytically pure **22a** was obtained by preparative HPLC [EtOAc/hexane (1:4, v/v)].

6-Acetyl-2-oxo-1,3,3,4-tetraphenyl-1,2,3,4,5,6,7,8-octahydroquinoline-7-carboxylic acid ethyl ester (**22a**): colorless crystals; mp 202–204 °C; IR (KBr): 1732, 1716, 1680, 1496, 1346, 700 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 0.70 (t, *J*=7.2 Hz, 3H, Me(COOEt)), 1.73–1.78 (m, 2H, H-6, H-8), 1.80 (s, 3H, Me(COMe)), 2.02 (d, *J*=17.4 Hz, 1H, H-8), 2.24 (dd, *J*=6.1, 17.4 Hz, 1H, H-5), 2.82 (ddd, *J*=2.6, 2.6, 6.2 Hz, 1H, H-7), 2.86–2.92 (m, 1H, H-5), 3.66 (dq, *J*=7.2, 10.5 Hz, 1H, CH_2(COOEt)), 3.74 (dq, *J*=7.2, 10.5 Hz, 1H, CH_2(COOEt)), 3.75 (s, 1H, H-4), 6.84–6.88 (m, 3H, Ar), 6.94–7.09 (m, 11H, Ar), 7.21–7.24 (m, 3H, Ar), 7.29–7.34 (m, 1H, Ar), 7.62 (d, *J*=7.7 Hz, 2H, Ar); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.8 (CH_3), 26.6 (CH_2), 27.4 (CH_3), 29.3 (CH_2), 39.5 (CH), 47.2 (CH), 53.8 (CH), 60.66 (C), 60.70 (CH_2), 115.2 (C), 125.7 (CH), 126.4 (2CH), 127.2 (CH), 127.3 (CH), 127.8 (CH), 128.0 (CH), 128.1 (2CH), 128.2 (4CH), 129.1 (3CH), 129.3 (CH), 129.6 (CH), 130.0 (C), 130.3 (2CH), 138.0 (C), 138.3 (C), 141.2 (C), 141.9 (C), 170.5 (C), 171.4 (C), 207.6 (C). HRMS-ESI *m*/*z*: $[M+Na]^+$ calcd for $C_{38}H_{35}NNaO_4$: 592.2458, found: 592.2457.

Compound **21a**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, *J*=7.1 Hz, 3H, Me(COOEt)).

4.17. Typical procedure for the second cycloaddition of monoadduct 18 with tetracyanoethylene (Table 8, entry 1)

TCNE (17 mg, 0.13 mmol) was added to a solution of **18a** (50 mg, 0.11 mmol) in 1,2-dichloroethane (5 mL). The reaction mixture was heated at 83 °C for 6.5 h, and then concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (3:7, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:4, v/v) yielded 7,7-dimethyl-2-oxo-1,3,3,4-tetraphenyl-1,2,3,4,4a,7-hexahydroquinoline-5,5,6,6-tetracarbonitrile (**23a**) (64 mg, 99%) as colorless crystals. Mp 200–201 °C; IR (KBr): 3024, 1689, 1651, 1311, 748, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 3H, Me), 1.59 (s, 3H, Me), 4.15 (dd, *J*=1.8, 10.8 Hz, 1H, H-4a), 4.63 (d, *J*=1.8 Hz, 1H, H-8), 4.81 (d, *J*=10.8 Hz, 1H, H-4), 6.44 (d, *J*=6.4 Hz, 1H, Ar), 6.99 (d, *J*=7.7 Hz, 2H, Ar), 7.04–7.12 (m, 1H, Ar), 7.16–7.23 (m, 5H, Ar), 7.23–7.32 (m, 4H, Ar), 7.35 (dd, *J*=7.2, 7.9 Hz, 2H, Ar), 7.40 (dd, *J*=7.4, 7.5 Hz, 1H, Ar), 7.49 (dd, *J*=7.6, 7.9 Hz, 2H, Ar), 7.69 (d, *J*=7.6 Hz, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.0 (CH_3), 30.1 (CH_3), 39.7 (C), 43.1 (CH), 43.2 (C), 49.1 (CH), 51.4 (C), 62.4 (C), 109.7 (C), 110.2 (C), 110.46 (C), 110.53 (C), 115.1 (CH), 127.5 (3CH), 127.85 (3CH), 127.90 (CH), 127.93 (3CH), 128.0 (CH), 128.7 (CH), 129.6 (CH), 129.7 (2CH), 130.2 (3CH), 131.4 (2CH), 132.9 (C), 134.1 (C), 139.0 (C), 139.4 (C), 139.7 (C), 170.5 (C). LRMS-EI *m*/*z* (ion, % relative intensity): 583 (M^+, 28), 455 (M^+−TCNE, 5), 284 (41), 261 (25), 194 (Ph_2CCO, 100), 166 (30), 165 (29), 77 (Ph, 10). HRMS-ESI *m*/*z* $[M+Na]^+$ calcd for $C_{39}H_{29}N_5NaO$: 606.2264, found: 606.2236.

4.18. Typical procedure for the second cycloaddition of monoadduct 19 with *N*-phenylmaleimide (Table 9, entry 2)

A mixture of **19a** (80 mg, 0.19 mmol) and *N*-phenylmaleimide (66 mg, 0.38 mmol) in toluene (30 mL) was heated at 110 °C for 65 h, and then concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (3:7, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:3, v/v) yielded 4,4-dimethyl-1,3,7-trioxo-2,6,8,8-tetraphenyl-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1*H*-pyrrolo[3,4-*f*]quinoline-9-carboxylic acid ethyl ester (**26a**) (116 mg, 98%) as a colorless solid. Mp 60–62 °C; IR (KBr): 1724, 1708, 1394, 1196, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, J=7.3 Hz, 3H, Me(COOEt)), 0.96 (s, 3H, Me), 1.07 (s, 3H, Me), 2.94 (d, J=7.9 Hz, 1H, H-3a), 3.52 (ddd, J=2.1, 4.0, 12.2 Hz, 1H, H-9a), 3.63 (dd, J=4.0, 7.9 Hz, 1H, H-9b), 3.88 (dq, J=7.3, 10.7 Hz, 1H, CH_2(COOEt)), 3.96 (dq, J=7.3, 10.7 Hz, 1H, CH_2(COOEt)), 4.33 (d, J=2.1 Hz, 1H, H-5), 5.23 (d, J=12.2 Hz, 1H, H-9), 7.10–7.21 (m, 9H, Ar), 7.33–7.50 (m, 9H, Ar), 7.55 (d, J=7.6 Hz, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.3 (CH_3), 29.8 (CH_3), 29.9 (CH_3), 33.8 (CH), 34.4 (C), 45.0 (CH), 46.9 (CH), 51.6 (CH), 61.1 (CH_2), 61.3 (C), 115.8 (CH), 126.5 (2CH), 126.9 (CH), 127.0 (2CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 128.5 (3CH), 128.8 (CH), 129.2 (3CH), 129.3 (2CH), 129.6 (CH), 130.2 (2CH), 131.6 (C), 136.2 (C), 138.7 (C), 139.7 (C), 140.6 (C), 170.8 (C), 171.9 (C), 175.7 (C), 177.0 (C). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{40}H_{36}N_2NaO_5$: 647.2516, found: 647.2506.

4.19. Preparation of methyl 2-((*E*)-5-methyl-3-oxohexa-1,4-dienyl)phenyl fumarate (28)

A mixture of salicylaldehyde (0.533 mL, 5.0 mmol), Et_3N (0.835 mL, 6.0 mmol), and 4-(dimethylamino)pyridine (10 mg, 0.08 mmol) in CH_2Cl_2 (40 mL) was cooled to 0 °C, and a solution of *tert*-butyldimethylsilyl chloride (904 mg, 6.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 h, quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (20 mL×2). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:9, v/v)] yielded 2-(*tert*-butyldimethylsilanyloxy)-benzaldehyde as a colorless oil (1.18 g, quant.).

Mesityl oxide (3.2 mL, 27.6 mmol) was added dropwise to a solution of lithium diisopropylamide (15.3 mL, 1.8 M in THF, 27.6 mmol) in THF (250 mL) at −65 °C. The reaction mixture was stirred for 1 h, and a solution of 2-(*tert*-butyldimethylsilanyloxy)-benzaldehyde (5.5 g, 23.0 mmol) in THF (30 mL) was added dropwise. The reaction mixture was stirred for an additional 50 min, quenched with saturated aqueous NH_4Cl and extracted with EtOAc (100 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (3:97, v/v)] yielded 1-[2-(*tert*-butyldimethylsilanyloxy)-phenyl]-1-hydroxy-5-methylhex-4-en-3-one (6.9 g, 90%) as a pale yellow oil. IR (neat): 3479, 2939, 2900, 2862, 1736, 1682, 1619, 1481, 1450, 1381, 1257, 1111, 1049, 918, 833, 771, 447 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.23 (s, 3H, Me(OTBS)), 0.27 (s, 3H, Me(OTBS)), 0.98 (s, 9H, 3Me(OTBS, ^{t}Bu)), 1.89 (d, J=1.1 Hz, 3H, Me), 2.17 (d, J=1.0 Hz, 3H, Me), 2.66 (dd, J=9.5, 17.3 Hz, 1H, H-2), 2.95 (dd, J=2.4, 17.3 Hz, 1H, H-2), 3.77 (d, J=3.2 Hz, 1H, OH), 5.44 (dt, J=2.8, 9.5 Hz, 1H, H-1), 6.02–6.04 (m, 1H, H-4), 6.77 (dd, J=1.0, 8.0 Hz, 1H, Ar), 6.98 (ddd, J=0.9, 7.5, 7.5 Hz, 1H, Ar), 7.13 (ddd, J=1.8, 7.7, 7.7 Hz, 1H, Ar), 7.50 (dd, J=1.7, 7.6 Hz, 1H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.4 (CH_3), −4.0 (CH_3), 18.1 (C), 20.9 (CH_3), 25.7 ($3CH_3$), 27.7 (CH_3), 50.6 (CH_2), 65.4 (CH), 117.9 (CH), 121.3 (CH), 123.7 (CH), 126.5 (CH), 127.8 (CH), 133.5 (C), 151.7 (C), 156.6 (C), 201.1 (C). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{19}H_{30}NaO_3Si$: 357.1856, found: 357.1864.

Methanesulfonyl chloride (0.34 mL, 4.4 mmol) was added to a solution of 1-[2-(*tert*-butyldimethylsilanyloxy)phenyl]-1-hydroxy-5-methylhex-4-en-3-one (1.2 g, 3.7 mmol) and Et_3N (1.2 mL, 8.9 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was warmed to room temperature with stirring overnight, diluted with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (20 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:9, v/v)] yielded (*E*)-1-[2-(*tert*-butyldimethylsilyloxy)-phenyl]-5-methylhexa-1,4-dien-3-one (860 mg, 74%) as a yellow oil. IR (neat): 2939, 2862, 1658, 1620, 1481, 1304, 1257, 1111, 1049, 987, 918, 841, 779, 447 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.24 (s, 6H, 2Me(OTBS)), 1.06 (s, 9H, 3Me(OTBS, ^{t}Bu)), 1.95 (d, J=1.1 Hz, 3H, Me), 2.18 (d, J=1.1 Hz, 3H, Me), 6.40–6.42 (m, 1H, H-4), 6.71 (d, J=16.4 Hz, 1H, H-2), 6.84 (dd, J=1.0, 8.1 Hz, 1H, Ar), 6.99 (dd, J=7.5, 7.5 Hz, 1H, Ar), 7.22–7.26 (m, 1H, Ar), 7.58 (dd, J=1.6, 7.8 Hz, 1H, Ar), 7.96 (d, J=16.4 Hz, 1H, H-1); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.3 ($2CH_3$), 18.3 (C), 20.9 (CH_3), 25.8 ($3CH_3$), 27.7 (CH_3), 119.9 (CH), 121.6 (CH), 122.8 (CH), 126.4 (C), 127.3 (CH), 128.6 (CH), 131.2 (CH), 137.5 (CH), 154.7 (C), 154.7 (C), 191.2 (C). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{19}H_{28}NaO_2Si$: 339.1751, found: 339.1759.

TBAF (2.7 mL, 1.0 M solution in THF, 2.7 mmol) was added to a solution of (*E*)-1-[2-(*tert*-butyldimethylsilanyloxy)phenyl]-5-methylhexa-1,4-dien-3-one (850 mg, 2.7 mmol) in THF (60 mL) at 0 °C. The reaction mixture was stirred for 25 min, diluted with saturated aqueous NH_4Cl, and extracted with EtOAc (20 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:4, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:9, v/v) yielded (*E*)-1-(2-hydroxyphenyl)-5-methylhexa-1,4-dien-3-one (**27**) (495 mg, 91%) as yellow needles. Mp 142–143 °C; IR (KBr): 3132, 1620, 1566, 1450, 1373, 1257, 1126, 979, 748, 455 cm^{-1}; ^1H NMR (500 MHz, DMSO) δ 1.93 (s, 3H, Me), 2.13 (s, 3H, Me), 6.43 (s, 1H, H-4), 6.83 (dd, J=7.6, 7.6 Hz, 1H, Ar), 6.90 (d, J=8.4 Hz, 1H, Ar), 6.95 (d, J=16.1 Hz, 1H, H-2), 7.23 (dt, J=1.6, 7.8 Hz, 1H, Ar), 7.60 (dd, J=1.5, 7.7 Hz, 1H, Ar), 7.77 (d, J=16.1 Hz, 1H, H-1), 10.18 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.2 (CH_3), 28.0 (CH_3), 116.7 (CH), 120.4 (CH), 122.1 (C), 123.3 (CH), 128.5 (CH), 129.2 (CH), 131.5 (CH), 139.2 (CH), 156.3 (C), 156.8 (C), 192.4 (C). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{13}H_{14}NaO_2$: 225.0886, found: 225.0890.

Dicyclohexyl carbodiimide (2.7 g, 12.9 mmol) was added to a solution of **27** (1.3 g, 6.4 mmol), fumaric acid monomethyl ester (920 mg, 7.1 mmol) and 4-dimethylaminopyridine (64 mg, 0.52 mmol) in toluene (200 mL). The reaction mixture was stirred for 3 h, quenched with water and extracted with EtOAc (50 mL×2). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:4, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:9, v/v) yielded methyl 2-((*E*)-5-methyl-3-oxohexa-1,4-dienyl)phenyl fumarate (**28**) (1.59 g, 78%) as pale yellow needles. Mp 73–75 °C; IR (KBr): 2908, 1728, 1628, 1257, 1173, 980, 756 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.96 (d, J=1.1 Hz, 3H, Me), 2.22 (d, J=1.1 Hz, 3H, Me), 3.87 (s, 3H, Me(COOMe)), 6.26–6.29 (m, 1H, H-3), 6.79 (d, J=16.1 Hz, 1H, H-2), 7.08 (d, J=15.9 Hz, 1H, H-4 or H-5), 7.12 (d, J=15.9 Hz, 1H, H-4 or H-5), 7.17 (dd, J=1.1, 8.2 Hz, 1H, Ar), 7.30 (dd, J=7.5, 7.5 Hz, 1H, Ar), 7.42 (ddd, J=1.5, 7.7, 7.7 Hz, 1H, Ar), 7.61 (d, J=16.1 Hz, 1H, H-1), 7.70 (dd, J=1.5, 7.8 Hz, 1H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.1 (CH_3), 27.9 (CH_3), 52.4 (CH_3), 122.7 (CH), 123.7 (CH), 126.7 (CH), 127.5 (CH), 127.6 (C), 130.1 (CH), 130.9 (CH), 132.3 (CH), 134.5 (CH), 135.4 (CH), 148.9 (C), 157.4 (C), 163.1 (C), 164.9 (C), 189.3 (C). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{18}H_{18}NaO_5$: 337.1046, found: 337.1046.

4.20. Preparation of the azatriene 29 and its sequential [2+2]-cycloaddition with diphenylketene

A mixture of **28** (285 mg, 0.9 mmol), Et_3N (0.56 mL, 4.0 mmol), and benzylamine (0.25 mL, 1.8 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C, and titanium tetrachloride (0.9 mL, 1.0 M solution in CH_2Cl_2, 0.9 mmol) was added dropwise. The reaction mixture was stirred at the same temperature for 1.5 h, then a solution of diphenylketene (353 mg, 1.8 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 2 h, the reaction mixture was quenched with water and passed through a short Celite® pad eluting with CH_2Cl_2. The filtrate was extracted with CH_2Cl_2 (10 mL×2), and the combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:4, v/v)] afforded 2-{(*E*)-2-[1-benzyl-2-(2-methylprop-1-enyl)-4-oxo-3,3-diphenylazetidin-2-yl]vinyl}phenyl methyl fumarate (**30**) (183 mg, 34%) as a yellow oil. IR (neat): 3023, 1743, 1142, 1295, 1211, 1180, 1142, 980, 756, 702, 524, 478 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H, Me), 1.41 (d, *J*=1.0 Hz, 3H, Me), 3.85 (s, 3H, Me(COOMe)), 4.32 (d, *J*=15.1 Hz, 1H, benzyl), 4.47 (d, *J*=15.1 Hz, 1H, benzyl), 5.06–5.09 (m, 1H, H-3), 5.80 (d, *J*=16.2 Hz, 1H, H-2), 6.41 (d, *J*=16.2 Hz, 1H, H-1), 6.85 (dd, *J*=1.4, 7.8 Hz, 1H, Ar), 6.98 (s, 2H, H-4, H-5), 7.00–7.39 (m, 16H, Ar), 7.69 (dd, *J*=1.4, 7.3 Hz, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.5 (CH_3), 26.4 (CH_3), 43.8 (CH_2), 52.4 (CH_3), 73.0 (C), 78.0 (C), 121.3 (CH), 121.9 (CH), 125.2 (CH), 126.4 (CH), 126.7 (CH), 126.9 (CH), 127.0 (CH), 127.28 (2CH), 127.31 (2CH), 128.2 (2CH), 128.5 (2CH), 128.6 (2CH), 128.8 (C), 129.1 (2CH), 129.2 (2CH), 132.4 (CH), 132.9 (CH), 134.8 (CH), 137.05 (C), 137.10 (C), 138.6 (C), 138.8 (C), 147.3 (C), 162.9 (C), 164.8 (C), 169.6 (C). HRMS-EI *m*/*z* $[M]^+$ calcd for $C_{39}H_{35}NO_5$: 597.2515, found: 597.2517.

4.21. [1,3]-Sigmatropic rearrangement of the [2+2] cycloadduct 30

A solution of **30** (180 mg, 0.3 mmol) in toluene (20 mL) was heated at 110 °C for 2 h, and then concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:9, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:8, v/v) yielded 2-[1-benzyl-6-(2-methylprop-1-enyl)-2-oxo-3,3-diphenyl-1,2,3,4-tetrahydropyridin-4-yl]phenyl methyl fumarate (**31**) (158 mg, 88%) as pale yellow crystals. Mp 84–85 °C; IR (KBr): 2962, 2924, 2360, 1736, 1658, 1442, 1304, 1242, 1173, 756, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.42 (d, *J*=0.8 Hz, 3H, Me), 1.71 (d, *J*=0.8 Hz, 3H, Me), 3.82 (s, 3H, Me(COOMe)), 4.41 (d, *J*=6.9 Hz, 1H, H-1), 4.71 (d, *J*=14.7 Hz, 1H, benzyl), 5.03 (d, *J*=14.7 Hz, 1H, benzyl), 5.32 (d, *J*=6.9 Hz, 1H, H-2), 5.49 (br s, 1H, H-3), 6.54 (d, *J*=7.9 Hz, 2H, Ar), 6.75 (s, 2H, H-4, H-5), 6.77 (dd, *J*=1.1, 8.2 Hz, 1H, Ar), 6.88–7.03 (m, 4H, Ar), 7.10–7.29 (m, 7H, Ar), 7.30–7.37 (m, 3H, Ar), 7.46–7.52 (m, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.3 (CH_3), 25.6 (CH_3), 40.0 (CH), 46.9 (CH_2), 52.4 (CH_3), 60.2 (C), 110.4 (CH), 119.1 (CH), 121.3 (CH), 126.0 (CH), 126.1 (CH), 126.3 (2CH), 127.1 (CH), 127.4 (CH), 128.0 (2CH), 128.1 (CH), 128.2 (2CH), 128.3 (2CH), 128.8 (2CH), 129.9 (CH), 130.2 (C), 130.4 (2CH), 132.7 (CH), 134.7 (CH), 137.5 (C), 138.0 (C), 140.2 (C), 140.9 (C), 141.9 (C), 148.2 (C), 162.4 (C), 165.1 (C), 170.6 (C). HRMS-ESI *m*/*z* $[M+Na]^+$ calcd for $C_{39}H_{35}NNaO_5$: 620.2407, found: 620.2415.

4.22. Intramolecular DA reaction of monoadduct 31

A solution of **31** (156 mg, 0.26 mmol) in xylene (30 mL) was heated at 140 °C for 31 h and then concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:10, v/v)] yielded an inseparable mixture of 3-benzyl-5,5-dimethyl-2,7-dioxo-1,1-diphenyl-2,3,5,6,6a,7,12b,12c-octahydro-1*H*-8-oxa-3-azabenzo[4,5]cyclohepta[1,2,3-*de*]naphthalene-6-carboxylic acid methyl ester (**32** and **32′**) (99 mg, 63%) in a ratio of 48:52. Analytically pure **32** and **32′** were obtained by preparative HPLC [SiO_2: EtOAc/hexane (1:19 to 1:8, v/v)].

Compound **32**: colorless crystals; mp 217–219 °C; IR (KBr): 2924, 1751, 1660, 1643, 1173, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.76 (s, 3H, Me), 0.81 (s, 3H, Me), 2.00 (d, *J*=14.0 Hz, 1H, H-6), 3.44 (ddd, *J*=2.2, 3.5, 10.6 Hz, 1H, H-12c), 3.70 (dd, *J*=10.6, 14.0 Hz, 1H, H-6a), 3.71 (s, 3H, Me(COOMe)), 4.60 (d, *J*=3.5 Hz, 1H, H-12b), 5.03 (d, *J*=2.2 Hz, 1H, H-4), 5.04 (d, *J*=13.6 Hz, 1H, benzyl), 5.22 (d, *J*=13.6 Hz, 1H, benzyl), 6.89–6.95 (m, 2H, Ar), 7.02–7.10 (m, 3H, Ar), 7.17–7.25 (m, 7H, Ar), 7.26–7.33 (m, 5H, Ar), 7.34–7.38 (m, 2H, Ar); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.3 (CH_3), 30.0 (CH_3), 33.9 (C), 36.4 (CH), 44.5 (CH), 46.2 (CH), 48.5 (CH_2), 48.7 (CH), 52.0 (CH_3), 56.8 (C), 119.0 (CH), 119.2 (CH), 125.0 (CH), 126.4 (CH), 126.7 (2CH), 127.0 (CH), 127.09 (2CH), 127.17 (2CH), 127.24 (CH), 128.1 (C), 128.4 (2CH), 129.2 (CH), 129.3 (2CH), 129.4 (CH), 130.8 (2CH), 133.1 (C), 137.1 (C), 140.0 (C), 145.3 (C), 150.4 (C), 169.46 (C), 169.51 (C), 171.4 (C). HRMS-ESI *m*/*z*: $[M+Na]^+$ calcd for $C_{39}H_{35}NNaO_5$: 620.2407, found: 620.2408.

Compound **32′**: colorless crystals; mp 152–154 °C; IR (KBr): 2924, 1774, 1736, 1450, 1219, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.56 (s, 3H, Me), 1.10 (s, 3H, Me), 2.74 (d, *J*=10.7 Hz, 1H, H-6), 2.78 (dd, *J*=10.5, 10.7 Hz, 1H, H-6a), 2.80–2.84 (m, 1H, H-12c), 3.67 (s, 3H, Me(COOMe)), 4.51 (d, *J*=6.1 Hz, 1H, H-12b), 4.67 (d, *J*=1.8 Hz, 1H, H-4), 4.91 (d, *J*=16.1 Hz, 1H, benzyl), 5.42 (d, *J*=16.1 Hz, 1H, benzyl), 6.99 (ddd, *J*=0.9, 7.4, 7.7 Hz, 1H, Ar), 7.01–7.11 (m, 6H, Ar), 7.15–7.37 (m, 12H, Ar); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.9 (CH_3), 30.2 (CH_3), 35.3 (C), 41.6 (CH), 41.9 (CH), 43.4 (CH), 47.0 (CH_2), 51.8 (CH), 51.9 (CH_3), 56.4 (C), 116.6 (CH), 120.2 (CH), 126.0 (CH), 126.3 (2CH), 126.4 (CH), 127.05 (2CH), 127.07 (CH), 127.2 (CH), 127.4 (2CH), 128.4 (2CH), 128.5 (C), 129.06 (CH), 129.07 (CH), 129.3 (2CH), 130.8 (2CH), 133.2 (C), 136.6 (C), 139.8 (C), 144.0 (C), 150.9 (C), 169.7 (C), 170.8 (C), 172.5 (C). HRMS-ESI *m*/*z*: $[M+Na]^+$ calcd for $C_{39}H_{35}NNaO_5$: 620.2407, found: 620.2386.

4.23. X-ray crystallographic data for compounds 32 and 32′

Crystallographic data (excluding structure factors) for **32** and **32′** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 701491 and 682526, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.10.090.

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