Tetrahedron 64 (2008) 9705–9716

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A novel and facile stereocontrolled synthetic method for polyhydro-quinolines and pyridopyridazines via a diene-transmissive Diels–Alder reaction involving inverse electron-demand hetero Diels–Alder cycloaddition of cross-conjugated azatrienes

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ARTICLE INFO

Article history:
Received 14 April 2008
Received in revised form 24 July 2008
Accepted 24 July 2008
Available online 29 July 2008

Keywords:
Diels–Alder
Cycloaddition
Diene-transmissive
Heterocycle
Tandem reaction

ABSTRACT

Cross-conjugated azatrienes bearing an electron-withdrawing sulfonyl or benzoyl group on the nitrogen atom underwent, on heating or in the presence of a Lewis acid (TMSOTf), an initial inverse electron-demand hetero Diels–Alder reaction with electron-rich dienophiles (vinyl ether, vinyl thioether, and allenyl ether) to produce 1:1 cycloadducts with high *endo* selectivity. The initial cycloadducts thus obtained underwent a second Diels–Alder reaction stereoselectively on the newly formed diene unit with electron-deficient dienophiles to give the crossed bis-cycloadducts, octahydroquinolines, with high diastereo-π-facial selectivity. The *N*-sulfonylazatrienes tethering an *ortho*-cinnamyloxyphenyl dienophile at the triene terminal underwent an initial intramolecular hetero Diels–Alder reaction of the inverse electron-demand type. The subsequent second Diels–Alder reaction of the formed mono-cycloadducts completed the diene-transmissive hetero Diels–Alder protocol to give benzopyrano[3,4-*c*]quinolines in a highly stereoselective manner.

1. Introduction

An efficient and convenient approach for the synthesis of complex organic molecules often includes sequential reactions in a set of multistep transformations, which is called a tandem, cascade, or domino reaction.[1] Any definition of these designations for multistep processes seems to include some ambiguity, some arbitrary choice, and limitation of their usage because of the large number of possible combinations of various transformations; however, the application of certain sequential reactions has emerged as one of the most effective and useful strategies in organic synthesis. The diene-transmissive Diels–Alder (DTDA) reaction represents one of these methodologies. Although the DTDA reaction is formally considered to be a set of multisequential Diels–Alder (DA) reactions of α,ω-divinylpoly(vinylidene), the DTDA reaction can usually be defined by the two final sequential cycloadditions that involve an initial DA reaction of a cross-conjugated triene (n=1) (or its equivalent) with a dienophile followed by a second DA cycloaddition with a dienophile on the newly formed, transmitted diene unit of the mono-adduct to give a bis-adduct (Chart 1). The research groups of Tsuge and Kanemasa, Fallis, Schreiber, Sherburn, and others have developed this DTDA methodology using cross-conjugated carbotrienes and equivalents.[2,3]

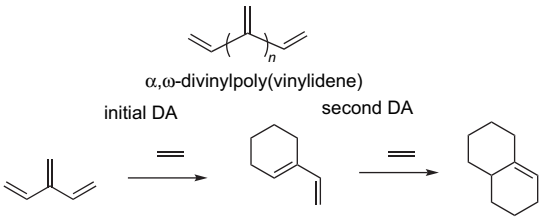

Chart 1. Diene-transmissive Diels–Alder methodology.

Fallis et al. reported the applications of the method for the construction of oxygenated nor-steroid and triterpenoid skeletons, and the tricyclic core of vinigrol.[3] On the other hand, the hetero Diels–Alder (HDA) methodology is among the most attractive and important tool for the synthesis of a wide range of six-membered heterocyclic compounds because of its potentially powerful and straightforward construction of heterocycles with high control of chemo-, regio-, and stereoselectivities.[4]

Therefore, the diene-transmissive hetero Diels–Alder (DTHDA) reaction, which is a special case of the DTDA reaction where one or more heteroatoms are contained within either a triene framework or a dienophile skeleton or both, should offer an efficient method

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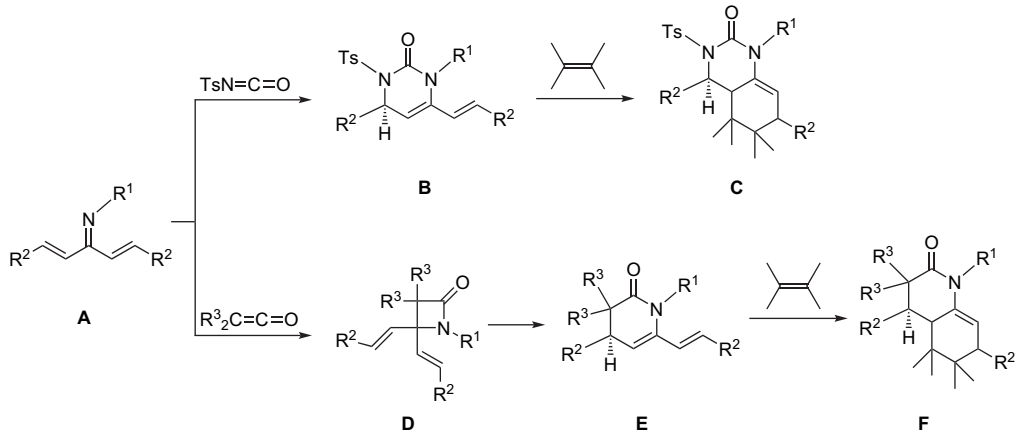
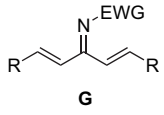
doi:10.1016/j.tet.2008.07.102



Scheme 1.

for the synthesis of, in particular, ring-fused heterocycles by performing tandem (hetero) DA reactions in a stereocontrolled manner. In this context, our group has previously reported the first examples of the DTHDA reaction,[5] which involved cross-conjugated thiatrienes.[5,6] Tsuge et al. reported a cross-conjugated oxatriene DTHDA reaction.[7] Spino et al. also used the DTHDA method of cross-conjugated oxatrienes for the construction of the picrasane skeleton.[8] The first representative of the DTHDA method using cross-conjugated azatrienes has been reported.[9] This process involved the initial aza DA cycloaddition of **A** with a reactive dienophile, tosyl isocyanate, followed by the second DA reaction of mono-adducts **B** with some representative electron-deficient dienophiles stereoselectively to give ring-fused pyrimidinone derivatives **C** as bis-adducts in good yields (Scheme 1).[9] The cross-conjugated azatrienes **A** also reacted with ketenes to furnish mono-adducts **E** via [2+2] adducts **D**.[10] The mono-adducts **E** also underwent the second DA reaction with electron-deficient dienophiles to give quinoline derivatives as bis-adducts with high regio- and stereoselectivities. In certain cases, the intermediary [2+2] adducts could be isolated. Unfortunately, the azatrienes **A** having an R^1 group on nitrogen, such as Ph, *p*-Tol, $PhCH_2$, *i*-Pr, and a quite effective electron-releasing Me_2N group, failed to undergo the initial cycloaddition with the representative reactive dienophiles such as tetracyanoethylene, *N*-phenylmaleimide, maleic anhydride, dimethyl fumarate, dimethyl acetylene dicarboxylate, ethyl vinyl ether, and styrene under, if necessary, harsh conditions and/or in the presence of a Lewis acid promoter.[9,10] To extend this DTHDA methodology, we decided to investigate the DTHDA reaction of cross-conjugated azatrienes **G** bearing an electron-withdrawing group (EWG) on nitrogen, which involved an inverse electron-demand aza Diels–Alder reaction in the initial cycloaddition. We report the results here.

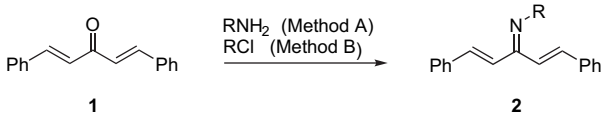


G

2. Results and discussion

2.1. Preparation of cross-conjugated azatrienes

The cross-conjugated *N*-sulfonylazatrienes **2a–c** were prepared in good yields by the condensation reaction between di-β-styryl ketone **1** and sulfonamides (method A), as shown in Scheme 2 and Table 1. *N*-Benzoylazatriene **2d** was synthesized via the aza-Peterson reaction of **1** with lithium hexamethyldisilazide, followed by acylation with benzoyl chloride (method B), because the application of method A to the preparation of **2d** failed. These *N*-sulfonyl- and acylazatrienes **2** could be readily purified through extraction work-up and/or silica gel column chromatography in contrast to labile *N*-alkyl analogs.



Scheme 2.

Table 1[a]

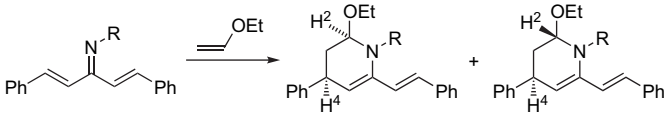
Entry	R	Method	Time (h)	Azatriene	Yield[b] (%)
1	$MeSO_2$	A	7	**2a**	82
2	$PhSO_2$	A	7	**2b**	87
3	*p*-$TolSO_2$	A	7	**2c**	65
4	PhCO	B	6 (5+1)	**2d**	46

[a] The reaction was carried out using method A or method B. Method A: **1** (1.0 equiv), RNH_2 (2.0 equiv), Et_3N (4.4 equiv), $TiCl_4$ (1.0 equiv) in CH_2Cl_2, 0 °Cto rt. Method B: **1** (1.0 equiv), LiHMDS (2.0 equiv) in THF, −78 °C to rt, then add RCl (3.0 equiv), −78 °C to rt.

[b] Isolated yield.

2.2. Initial cycloaddition of azatrienes 2 with ethyl vinyl ether

First, electron-deficient azatrienes **2** were allowed to react with an electron-rich dienophile, ethyl vinyl ether (Scheme 3, Table 2). Upon heating in toluene at 110 °C for 23 h, *N*-mesylazatriene **2a** reacted with ethyl vinyl ether to afford cycloadduct **3a** in 68% yield with an *endo*/*exo* ratio of 90:10 (entry 1), while the reactions of azatrienes **2b**,**c** gave exclusively *endo* adducts **3b**,**c** in 88% and 86% yields, respectively (entries 2 and 3). In contrast, *N*-benzoylazatriene **2d** did not react with ethyl vinyl ether under thermal reaction conditions (entry 4). Then, the reactions were carried out in the presence of a Lewis acid promoter. Common Lewis acids such as $AlCl_3$, $TiCl_4$, $SnCl_4$, $Yb(OTf)_3$, and $BF_3{\cdot}OEt_2$ did not effect the reactions of **2a–d** leading to cycloadducts **3a–d**, whereas the reaction



Scheme 3.

Table 2
Initial cycloaddition with ethyl vinyl ether

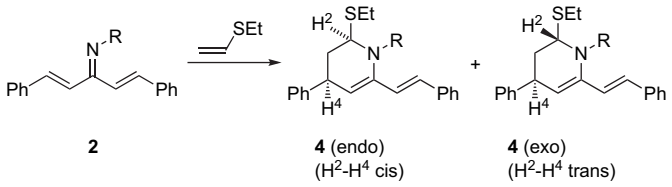
Entry	Azatriene	R	Solvent	Temp (°C)	TMSOTf (mol %)	Time (h)	Adduct	Yield[a] (%)	*endo*/*exo*[b]
1	**2a**	$MeSO_2$	Toluene	110	—	23	**3a**	68	90:10
2	**2b**	$PhSO_2$	Toluene	110	—	13	**3b**	88	>95:5
3	**2c**	*p*-$TolSO_2$	Toluene	110	—	15	**3c**	86	>95:5
4	**2d**	PhCO	Toluene	110	—	15	—	—	—
5	**2d**	PhCO	CH_2Cl_2	−60	100	2	**3d**	30	83:17
6	**2d**	PhCO	CH_2Cl_2	−60	75	2	**3d**	63	>95:5
7	**2d**	PhCO	CH_2Cl_2	−60	40	2	**3d**	72	>95:5
8	**2d**	PhCO	CH_2Cl_2	−60	25	1	**3d**	86	>95:5
9	**2d**	PhCO	CH_2Cl_2	−60	5	3	**3d**	37	>95:5

[a] Isolated yield.
[b] *endo*/*exo* Ratio determined based on ^{1}H NMR integration of the *endo*-cyclic olefinic proton of **3**. Ratio >95:5 denotes that no minor *exo*-isomer was detected.

of **2d** in the presence of $Me_3SiOSO_2CF_3$ (TMSOTf) at −60 °C in dichloromethane afforded cycloadduct **3d** in fair to good yield with high *endo* selectivity (entries 5–8). Reducing the amounts of the catalyst from 25 mol % to 5 mol % resulted in a decrease in the yield (from 86% to 37%) of **2d** (entries 8 and 9). It is noteworthy that *N*-benzoyl-1-azadiene **2d** underwent the TMSOTf-promoted [4+2]-cycloaddition with a vinyl ether, because reported examples of a Lewis acid-catalyzed 1-azadiene DA reaction with electron-rich dienophiles are rare.[4l,11]

2.3. Initial cycloaddition of azatrienes 2 with ethyl vinyl sulfide

Vinyl sulfide is also an electron-rich dienophile with a sufficiently high energy level of its HOMO to allow reaction with **2** (Scheme 4). In fact, *N*-sulfonylazatrienes **2a**,**c** reacted with ethyl vinyl sulfide in refluxing toluene to give cycloadducts **4a**,**c** in 68% and 51% yields, respectively, with high *endo* selectivity (Table 3, entries 1 and 2). Similar to the reaction with ethyl vinyl ether, *N*-benzoylazatriene **2d** did not react with ethyl vinyl sulfide under thermal conditions (entry 3); instead, the reaction of **2d** was promoted by TMSOTf at −60 °C in CH_2Cl_2, producing **4d** in good yield with *endo*/*exo* ratios of 69:31 to 82:18 (entries 4 and 5).



Scheme 4.

2.4. Initial cycloaddition of azatrienes 2 with allenyl methyl ether

There are precedents for the inverse electron-demand Diels–Alder reaction in which allenyl ethers react as an electron-rich dienophile as well.[12] Allenyl methyl ether[13] reacted with *N*-sulfonylazatrienes **2a**–**c** on heating at 110 °C to produce cycloadducts **5a**–**c** (Scheme 5, Table 4) having the *exo*-methylene dihydropyridine structure. The reaction was highly *exo* selective, in contrast to the reactions with ethyl vinyl ether and ethyl vinyl sulfide that were highly *endo* selective. It is worth mentioning that the reaction of *N*-sulfonyl-4-ethoxycarbonyl-1-azabuta-1,3-dienes with allenyl ethers was reported to give the corresponding *exo*-methylene cycloadducts with high *endo* selectivity.[12]

2.5. Second cycloaddition with tetracyanoethylene (TCNE)

The mono-cycloadducts **3**–**5** formed by the initial inverse electron-demand aza DA cycloaddition of **2** possess a newly formed amino diene unit, so that the dienes **3**–**5** are expected to undergo a second DA cycloaddition with electron-deficient dienophiles in a normal electron-demand mode. First, to examine the diastereo-π-facial selectivity of the second DA cycloaddition, a structurally simple and reactive dienophile, TCNE, was used (Scheme 6, Table 5).

In all cases, the reaction proceeded smoothly under mild reaction conditions to give the cycloadducts, octahydroquinolines **6**–**7** or **6′**–**8′**, in high yields with excellent diastereo-π-facial selectivity, regardless of the 2,4-*cis* (*endo*) or 2,4-*trans* (*exo*) isomers of dienes **3**–**5**. The stereochemical outcome would be ascribed to the mechanism whereby the dienophile (TCNE) attacked from the less hindered bottom H4 side of the diene (Scheme 6). A one-pot procedure for the diene-transmissive HDA methodology **2c**→**3c**→**6c** was proved effective (entry 13). A toluene solution of azatriene **2c** and ethyl vinyl ether was refluxed for 15 h (cf. Table 2, entry 3) and cooled to room temperature. Addition of TCNE to the resultant reaction mixture containing **3c** with stirring (cf. Table 5, entry 3) gave **6c** in 76% yield. Clearly, the one-pot procedure is viable and comparable to the stepwise procedure with regard to the total yield and handling.

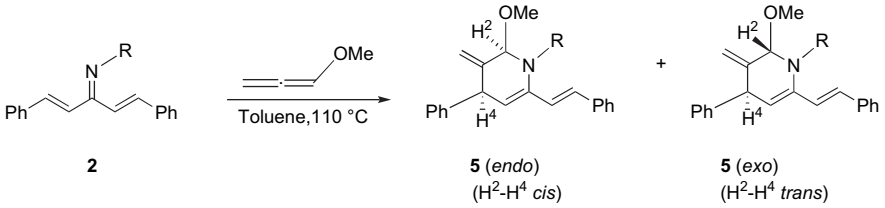
2.6. Second cycloaddition with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)

The reaction with an electrophilic dienophile, PTAD, was also examined (Scheme 7, Table 6). The reaction of dienes **3** and **4**

Table 3
Initial cycloaddition with ethyl vinyl sulfide

Entry	Azatriene	R	Solvent	Temp (°C)	TMSOTf (mol %)	Time (h)	Adduct	Yield[a] (%)	*endo*/*exo*[b]
1	**2a**	$MeSO_2$	Toluene	110	—	48	**4a**	68	>95:5
2	**2c**	*p*-$TolSO_2$	Toluene	110	—	37	**4c**	51	>95:5
3	**2d**	PhCO	Toluene	110	—	25	—	—	—
4	**2d**	PhCO	CH_2Cl_2	−60	100	1	**4d**	64	69:31
5	**2d**	PhCO	CH_2Cl_2	−60	25	1	**4d**	84	82:18

[a] Isolated yield.
[b] *endo*/*exo* Ratio determined based on ^{1}H NMR integration of the *endo*-cyclic olefinic proton of **4**. Ratio >95:5 denotes that no minor *exo*-isomer was detected.



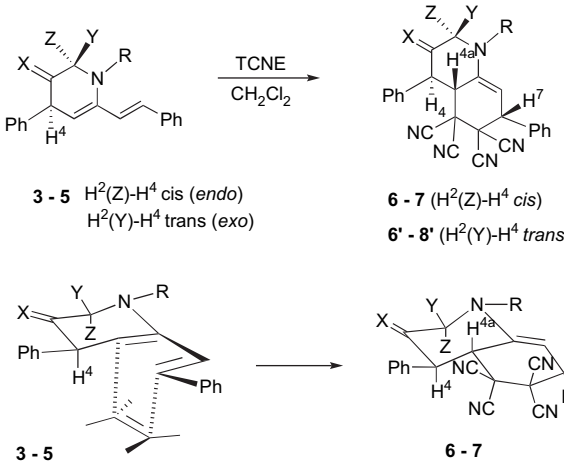
2 **5** (*endo*) (H^2-H^4 *cis*) **5** (*exo*) (H^2-H^4 *trans*)

Scheme 5.

Table 4
Initial cycloaddition with allenyl methyl ether

Entry	2	R	Time (h)	Adduct	Yield[a] (%)	*endo*/*exo*[b]
1	**2a**	$MeSO_2$	29	**5a**	30	<5:95
2	**2b**	$PhSO_2$	41	**5b**	39	<5:95
3	**2c**	*p*-$TolSO_2$	20	**5c**	28	<5:95

[a] Isolated yield.
[b] *endo*/*exo* Ratio determined based on ^{1}H NMR integration of the *endo*-cyclic olefinic proton of **5**. Ratio <5:95 denotes that no minor *endo*-isomer was detected.



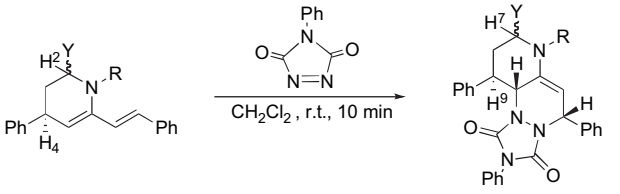
3 - 5 H^2(Z)-H^4 cis (*endo*) H^2(Y)-H^4 trans (*exo*)

6 - 7 (H^2(Z)-H^4 *cis*)
6' - 8' (H^2(Y)-H^4 *trans*)

3 - 5 **6 - 7**

Scheme 6.

proceeded rapidly within 10 min at room temperature to produce the cycloadducts **9**/**9′** and **10**/**10′**, respectively, in quantitative yield in all cases. The reaction was highly diastereo-π-facial selective, the dienophile (PTAD) having attacked from the less congested H4 side to the diene unit.



3 - 4 H^2-H^4 *cis* (*endo*) H^2-H^4 *trans* (*exo*)

9 - 10 (H^7-H^9 *cis*)
9' - 10' (H^7-H^9 *trans*)

Scheme 7.

Table 6
Second cycloaddition with PTAD

Entry	R	Y	Diene	Adduct[a]	Yield[b] (%)
1	$MeSO_2$	EtO	**3a** (*cis*)	**9a**	99
2	$PhSO_2$	EtO	**3b** (*cis*)	**9b**	99
3	*p*-$TolSO_2$	EtO	**3c** (*cis*)	**9c**	99
4	PhCO	EtO	**3d** (*cis*)	**9d**	99
5	PhCO	EtO	**3d** (*trans*)	**9′d**	99
6	$MeSO_2$	EtS	**4a** (*cis*)	**10a**	99
7	*p*-$TolSO_2$	EtS	**4c** (*cis*)	**10c**	92
8	PhCO	EtS	**4d** (*cis*)	**10d**	99
9	PhCO	EtS	**4d** (*trans*)	**10′d**	91

[a] A prime mark for the adducts (**9′**, **10′**) denotes an H7–H9 trans relationship.
[b] Isolated yield.

2.7. Second cycloaddition with dimethyl acetylene dicarboxylate (DMAD)

With DMAD, the reaction of dienes **3** proceeded on heating at 110 °C in toluene to produce compounds **12** in moderate yields (Scheme 8, Table 7). Compounds **12** would be formed by the elimination of ethanol and cis-stereoselective 1,3-H migration of the initially formed 1:1 cycloadducts (**11**), the result of which suggests that the H-migration would proceed in an ionic and stepwise manner. The cis-selectivity would be ascribed to the

Table 5
Second cycloaddition with TCNE

Entry	R	X	Y	Z	Diene	Conditions	Adduct[a]	Yield[b] (%)
1	$MeSO_2$	H_2	EtO	H	**3a** (*cis*)	rt, 10 min	**6a**	93
2	$PhSO_2$	H_2	EtO	H	**3b** (*cis*)	rt, 10 min	**6b**	99
3	*p*-$TolSO_2$	H_2	EtO	H	**3c** (*cis*)	rt, 10 min	**6c**	95
4	PhCO	H_2	EtO	H	**3d** (*cis*)	rt, 30 min	**6d**	99
5	PhCO	H_2	H	EtO	**3d** (*trans*)	rt, 60 min	**6′d**	85
6	$MeSO_2$	H_2	EtS	H	**4a** (*cis*)	40 °C, 30 min	**7a**	76
7	*p*-$TolSO_2$	H_2	EtS	H	**4c** (*cis*)	40 °C, 60 min	**7c**	93
8	PhCO	H_2	EtS	H	**4d** (*cis*)	rt, 30 min	**7d**	98
9	PhCO	H_2	H	EtS	**4d** (*trans*)	rt, 30 min	**7′d**	96
10	$MeSO_2$	H_2C	H	MeO	**5a** (*trans*)	rt, 40 min	**8′a**	90
11	$PhSO_2$	H_2C	H	MeO	**5b** (*trans*)	rt, 50 min	**8′b**	74
12	*p*-$TolSO_2$	H_2C	H	MeO	**5c** (*trans*)	rt, 55 min	**8′c**	92
13	*p*-$TolSO_2$	H_2	EtO	H	**3c** (*cis*)	110 °C, 15 h → rt, 2 days	**6c**	76

[a] A prime mark for the adducts (**6′**–**8′**) denotes an H2(Y)–H4 trans relationship. No minor isomer was detected by means of ^{1}H NMR spectroscopy.
[b] Isolated yield.

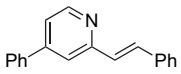
formation of the more stable cis-fused tetrahydroquinoline structure (**12**) having a planar cyclohexa-1,3-diene moiety rather than the less stable trans-fused one with a twisted planarity of the ring.

2.8. Second cycloaddition with *N*-phenylmaleimide (NPMI)

N-Sulfonylated dienes **3a–c** also reacted with *N*-phenylmaleimide (NPMI) in refluxing toluene to produce cycloadducts **14a** or **13b,c** as final products (Scheme 9, Table 8, entries 1–3). The reaction proceeded with high *endo*- and π-facial selectivities to give initially 1:1 cycloadducts **15a–c**, from which elimination of ethanol occurred to furnish compounds **13b,c** or the H-migration product **14a**. However, the reaction of dienes **4a–c** and **5a–c** with NPMI failed, no cycloadducts being obtained. In contrast to the reaction of *N*-sulfonylated dienes **3a–c**, the reaction of *N*-benzoylated dienes **3d** and **4d** produced the cycloadducts **15d**/**15′d** (entries 4 and 5) and a 1:1 mixture of **16d**+**17d**/**16′d**+**17′d** (entries 6 and 7), respectively. In fact, the *N*-benzoylated cycloadducts (**15d–17d**, **15′d–17′d**) are stable enough to allow isolation after being subjected to heating conditions.

2.9. By-product in the second thermal cycloaddition

The reactions of dienes **3–5** with TCNE and PTAD proceeded smoothly at room temperature to give the corresponding cycloadducts **6–10** quantitatively, whereas the reaction with DMAD and NPMI required a long heating time, which, particularly in the cases of sulfonylated dienes **3a–c**, resulted in the formation of by-product **18**, 4-phenyl-2-β-styrylpyridine, in 20–40% yield together with the cycloadducts (**12–14**). This is probably due to the thermal instability of **3** resulting from a cyclic N–O acetal structure in the competitive elimination–aromatization leading to the pyridine nucleus. In fact, when compound **3c** was independently treated with a base on heating, pyridine **18** was exclusively formed. Sulfinic acid and/or pyridine **18** formed would catalytically accelerate the ethanol elimination from **3**/**15a–c** to give **18**/**13** as well as the proton migration from **13** to give **14**.



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2.10. DTHDA methodology including an intramolecular aza DA cycloaddition

Because the DTHDA methodology of *N*-sulfonyl or *N*-acyl cross-conjugated azatrienes involving the inverse electron-demand aza DA reaction in the initial cycloaddition was successful, we envisaged that its intramolecular version would be viable. Scheme 10 illustrates the preparation of the cross-conjugated azatrienes tethering a dienophile.

The aldol reaction between TBS-protected salicylaldehyde and 4-phenylbut-3-en-2-one (a), dehydration (b), deprotection giving the phenol **19** (c), followed by the dienophile tether introduction (d), and imination of the carbonyl group in **20** (e) gave the desired substrates **21a,b** in total yields of 59% and 58%.

The azatriene **21** underwent an initial intramolecular aza DA reaction upon heating to produce the H4a–H10b trans cycloadducts **22** with retention of the trans configuration of the dienophile (H4–H4a). The stereochemical outcome of the adducts **22** suggests that the reaction proceeded in a highly *exo* selective manner with regard to the arrangement of the dienophile-connected tether relative to the diene moiety (Scheme 11, Table 9).

As shown in Scheme 6/Table 5 and Scheme 9/Table 8, the dienes **3–5** were shown to undergo the second cycloaddition smoothly with TCNE and NPMI. Unexpectedly, however, the dienes **22** did not react with these dienophiles at room temperature at all. The reactions with TCNE in refluxing dichloromethane and with NPMI in refluxing toluene resulted in complex mixtures of products, any adducts being obtained. It has previously been reported that *exo*-isomers (H4a–H10b trans) of structurally similar sulfur analogs to the dienes **22** (S instead of NR) are less reactive than the corresponding *endo*-isomers in the reactions with these dienophiles.[6] These facts suggest that relatively bulky dienophiles such as TCNE and NPMI, which are reactive enough, do not react with **22** under usual (thermal) conditions due to steric reasons encountered in the transition states. In fact, the relatively less congested dienophiles, DMAD and methyl acrylate, did react with the dienes **22**, the results of which are shown in Scheme 12/Table 10 and Scheme 13/Table 11.

The reaction of **22** with DMAD proceeded in refluxing toluene for 11–16 h to produce chromeno[3,4-*c*]quinolines **24** in fair to good yields with high stereoselectivity via 1,3-H migration of the initially formed cycloadducts **23**. DMAD probably attacked from the less congested bottom π-face (from the H10b side) of the diene **22** (see Fig. 1).

With methyl acrylate, the dienes **22** also underwent a DA reaction on heating to give single stereoisomers **25** of the 1:1 cycloadducts in good yields, no other isomers being detected in a crude mixture of the products. These facts suggest that the reaction proceeded with high regio-, *endo*, and diastereo-π-facial selectivities, as illustrated in Figure 1.

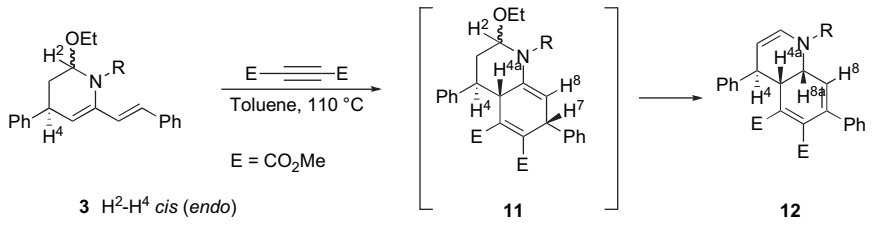
2.11. Structure determination

2.11.1. Selected mono-cycloadducts

The obtained mono- and bis-cycloadducts were all characterized with the help of analytical data and spectral evidence (see Section 4). Stereochemical assignments were mainly based on ^{1}H NMR spectroscopic studies and NOESY techniques, and X-ray crystallographic analysis of bis-cycloadduct **16′d**. Figure 2 and Table 12 show configurational structures of an *endo*-isomer and an *exo*-isomer with their most probable conformations of mono-cycloadducts (**3** and **4**) and observed vicinal coupling constants of H2–H5 around the tetrahydropyridine ring in the ^{1}H NMR spectra of **3** and **4**. For the *exo*-isomers, characteristic large vicinal coupling constants (J=11–14 Hz) were observed with $J_{3\text{–}4}$, suggesting a trans-diaxial relationship between H3 and H4. NOE was also observed between H4 and the EtX (CH_2) group. These facts confirm that H4 and the EtX group both occupy a quasi-axial 1,3-position. The preferred axial arrangement of the EtX group is ascribed to the anomeric effect between the oxygen or sulfur atom (X) and the nitrogen of the ring. As for the *endo*-isomers, large vicinal coupling constants were not observed as a whole, and it was deduced that H2 and H4 occupy a quasi-equatorial position and hence Ph and EtX groups are both in a quasi-axial arrangement. The fact that NOE was observed between the substituents (Ph and EtX) supports this arrangement. The twist chair form of the *endo*-isomers is somewhat deformed by the 1,3-diaxial repulsion between the substituents. The values of $J_{2\text{–}3}$, $J_{2\text{–}3'}$, $J_{3\text{–}4}$, $J_{3'\text{–}4}$, and $J_{4\text{–}5}$, listed in Table 12, agree well with these arrangements of the *exo*- and *endo*-isomer.

2.11.2. Selected bis-cycloadducts

The stereochemical arrangements and J values among H7, H8, H8′, and H9 of bis-cycloadducts **15d**/**16d** (*endo* for initial cycloaddition) and **15′d**/**16′d** (*exo* for initial cycloaddition) are very similar to those of the initial mono-cycloadducts, *endo*- and *exo*-**3d**/**4d**, respectively. The observed large coupling constant values (11.6–12.5 Hz) of $J_{9\text{–}9a}$ for all the cycloadducts (**13**, **15**, **15′**, **16**, and **16′**) (Fig. 3, Table 13) suggest a trans-diaxial relationship between H9 and H9a, and hence the stereochemistry is ascribed to attack the dienophile (NPMI) from the H4(9) side to the diene moiety of



Scheme 8.

Table 7
Second cycloaddition with DMAD

Entry	R	Diene	Time (h)	Adduct	Yield[a] (%)
1	$MeSO_2$	**3a** (*cis*)	5	**12a**	59
2	$PhSO_2$	**3b** (*cis*)	20	**12b**	31
3	*p*-$TolSO_2$	**3c** (*cis*)	21	**12c**	31

[a] Isolated yield.

mono-cycloadducts **3**/**4** (see Scheme 6). A characteristic feature is that the vicinal coupling constants J_{9a-9b} in a trans relationship for **15′d**/**16′d** were observed to be almost 0 Hz. X-ray crystallographic analysis of compound **16′d** (Fig. 4) showed that the stereochemistry of **16′d** as assigned in Figure 3 is correct and that the dihedral angle H9a–C9a–C9b–H9b equals 91.9°, which supports the observed J_{9a-9b} value of zero. Similarly, the dihedral angle H3a–C3a–C4–H4 equals 144.3°, which is consistent with J_{3a-4}=7.5 Hz. That the stereochemistry of **16′d** *in solution* (based on ^{1}H NMR) and *in crystals* (based on X-ray) is coincident with each other would be reasonable for such a rigid molecular structure.

3. Conclusions

In conclusion, the diene-transmissive hetero Diels–Alder methodology including an inverse electron-demand aza Diels–Alder reaction in the initial cycloaddition has been developed. The protocol offers an attractive alternative to other methods for accessing ring-fused nitrogen-containing heterocycles with high regio- and stereoselectivities and atom efficiency, thus expanding the potential of the diene-transmissive hetero Diels–Alder methodology.

4. Experimental

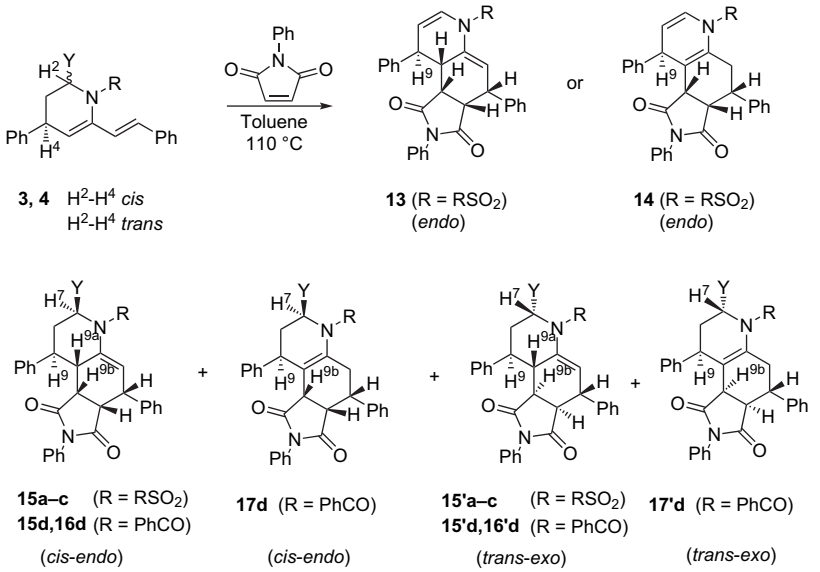
4.1. General

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

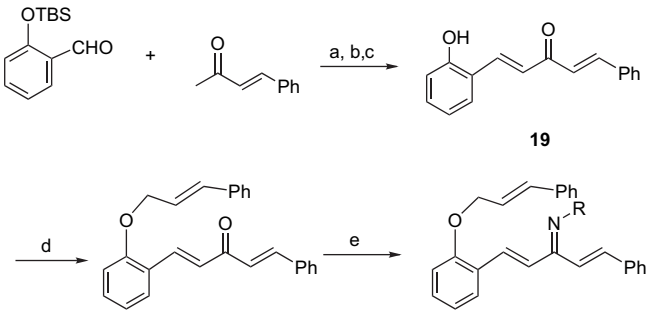
Table 8
Cycloaddition with NPMI

Entry	R	Y	Diene	Time (h)	Adduct[a]	Yield[b] (%)
1	$MeSO_2$	EtO	**3a** (*cis*)	3	**14a**	34
2	$PhSO_2$	EtO	**3b** (*cis*)	18	**13b**	21
3	*p*-$TolSO_2$	EtO	**3c** (*cis*)	18	**13c**	22
4	PhCO	EtO	**3d** (*cis*)	32	**15d**	83
5	PhCO	EtO	**3d** (*trans*)	75	**15′d**	66
6	PhCO	EtS	**4d** (*cis*)	53	**16d**+**17d**	93[c]
7	PhCO	EtS	**4d** (*trans*)	70	**16′d**+**17′d**	70[c]

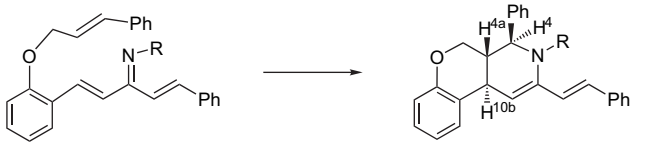
[a] A prime mark for the adducts (**15′**–**17′**) denotes an H7–H9 trans relationship.
[b] Isolated yield.
[c] 1:1 Ratio of adducts in a mixture.



Scheme 9.



Scheme 10. (a) LDA (1.2 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, 93%; (d) cinnamyl bromide (2.0 equiv), K_2CO_3 (2.0 equiv), acetone, reflux, 3 h, 95%; (e) RNH_2 (2.0 equiv), $TiCl_4$ (2.0 equiv), Et_3N (8.8 equiv), 0 °C, rt, overnight; **21a** (R=Ms): 72%, **21b** (R=Ts): 71%.

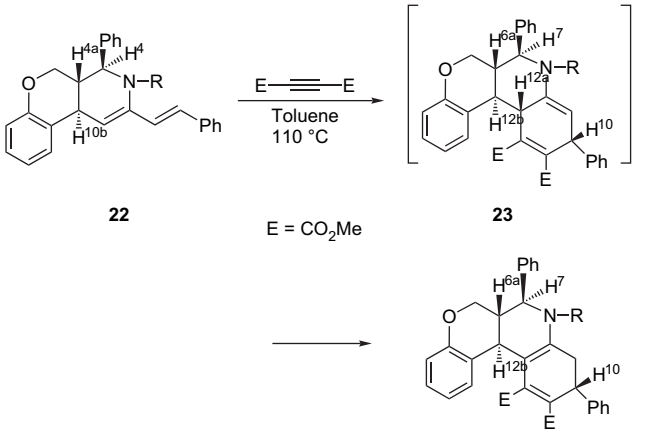


Scheme 11.

Table 9
Intramolecular aza DA reaction

Entry	R	Solvent	Temp (°C)	Time (h)	Adduct	Yield[a] (%)
1	$MeSO_2$	Xylene	140	3	**22a**	57
2	*p*-$TolSO_2$	Toluene	110	8	**22b**	60

[a] Isolated yield.

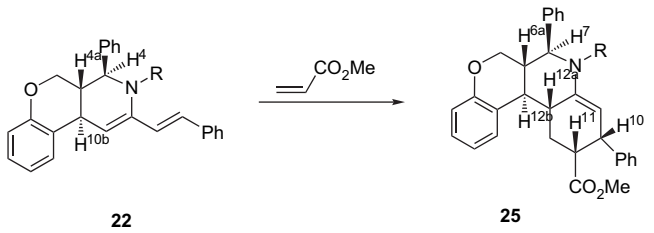


Scheme 12.

Table 10
Second cycloaddition with DMAD

Entry	Diene	R	Time (h)	Adduct	Yield[a] (%)
1	**23a**	$MeSO_2$	11	**24a**	62
2	**23b**	*p*-$TolSO_2$	16	**24b**	57

[a] Isolated yield.



Scheme 13.

Table 11
Second cycloaddition with methyl acrylate

Entry	Diene	Solvent	Temp (°C)	Time (h)	Adduct	Yield[a] (%)
1	**23a**	Toluene	110	9	**25a**	59
2	**23b**	Benzene	80	16	**25b**	54

[a] Isolated yield.

Merck Co. Ltd). PTLC was performed on Wakogel B5F. All reactions were performed under argon.

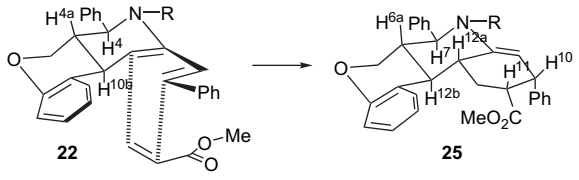


Figure 1.

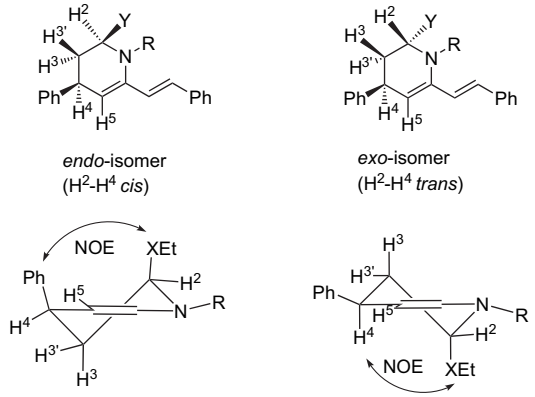
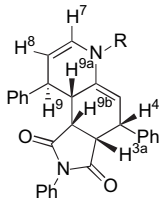


Figure 2.

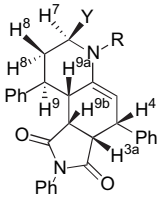
Table 12
Vicinal coupling constants

Diene	R	XEt	*J* (Hz)				
			2–3	2–3′	3–4	3′–4	4–5
3a (*endo*)	Ms	OEt	3.5	4.8	4.5	8.3	3.7
3a (*exo*)	Ms	OEt	2.4	2.4	12.6	6.6	1.5
3b (*endo*)	Bs[a]	OEt	3.7	5.5	6.5	7.8	3.6
3c (*endo*)	Ts	OEt	3.6	5.3	6.3	7.9	3.6
3d (*endo*)	Bz	OEt	7.0	3.4	7.0	7.5	3.6
3d (*exo*)	Bz	OEt	1.6	1.6	11.2	7.0	3.5
4a (*endo*)	Ms	SEt	4.2	7.0	6.0	7.4	3.7
4c (*endo*)	Ts	SEt	4.0	7.1	7.0	7.5	3.4
4d (*endo*)	Bz	SEt	8.0	5.7	6.5	10.0	3.8
4d (*exo*)	Bz	SEt	4.0	1.1	11.6	7.3	3.5

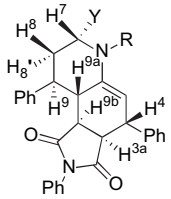
[a] Benzenesulfonyl.



13 (R = RSO_2)
(endo)



15d,16d (R = Bz)
(cis-endo)



15'd,16'd (R = Bz)
(trans-exo)

Figure 3.

Table 13
Vicinal coupling constants

Bis-adduct	R	Y	*J* (Hz)				
			9–9a	9a–9b	9b–3a	3a–4	4–5
13b	Bs	—	11.6	2.0	8.3	6.7	3.2
13c	Ts	—	11.6	2.0	8.3	6.5	3.2
15 (*endo*)	Bz	OEt	12.3	4.4	8.5	8.9	2.2
15′ (*exo*)	Bz	OEt	11.8	0	8.4	6.9	0
16 (*endo*)	Bz	SEt	12.6	2.5	8.8	4.6	0
16′ (*exo*)	Bz	SEt	12.2	0	8.0	7.5	0

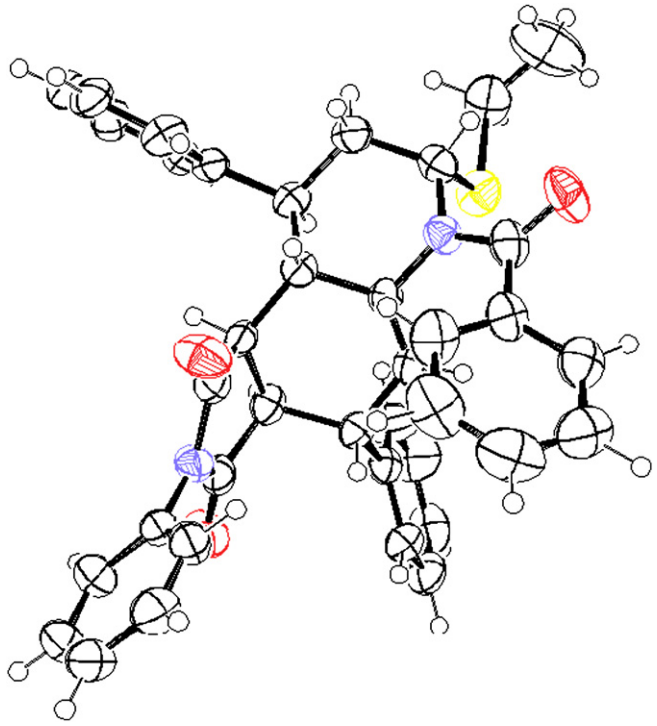


Figure 4. ORTEP drawing of **16′d**.

4.2. Typical procedure for the preparation of cross-conjugated azatriene 2: method A (Table 1, entry 3)

A mixture of 1,5-diphenyl-1,4-pentadien-3-one (**1**) (2.34 g, 10 mmol), Et_3N (6.13 mL, 44 mmol), and *p*-toluenesulfonamide (3.4 g, 20 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C, and titanium tetrachloride (10 mL, 1.0 M solution in CH_2Cl_2, 10 mmol) was added dropwise. The reaction mixture was warmed to room temperature with stirring for 7 h, after which the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was 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. Recrystallization from CH_2Cl_2/hexane (1:2, v/v) yielded *N*-(3-phenyl-1-β-styryl-2-propenylidene)-4-*p*-toluenesulfonamide (**2c**) (2.53 g, 65%) as yellow needles; mp 184–185 °C; IR (KBr): 1632, 1512, 1340, 1282, 1146, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 3H, Ts), 7.26–7.59 (m, 16H, Ar, olefin), 7.93 (d, *J*=8.2 Hz, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5 (CH_3), 123.3 (C), 127.1 (3CH), 128.5 (4CH), 129.0 (4CH), 129.4 (3CH), 130.7 (2CH), 134.7 (C), 138.9 (C), 143.3 (C), 144.2 (2CH), 172.6 (C). LRMS-EI *m*/*z* (%): 387 (M^+, 1), 232 (M^+–Ts, 100). Anal. Calcd for $C_{24}H_{21}NO_2S$: C, 74.39; H, 5.46; N, 3.61. Found: C, 74.53; H, 5.63; N, 3.60.

4.3. Preparation of cross-conjugated azatriene 2d: method B (Table 1, entry 4)

A solution of **1** (234 mg, 1.0 mmol) in THF (10 mL) was cooled to −78 °C and lithium bis(trimethylsilyl)amide (2.0 mL, 1.0 M solution in THF, 2.0 mmol) was added dropwise. The reaction mixture was gradually warmed to room temperature with stirring for 5 h and then cooled to −78 °C again. After the addition of benzoyl chloride (0.348 mL, 3.0 mmol), the reaction mixture was warmed to room temperature with stirring for 1 h, after which the reaction was quenched with 10% aqueous K_2CO_3 and the mixture was extracted with EtOAc (10 mL×2). The combined extracts were washed with 10% aqueous K_2CO_3 and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography [SiO_2: EtOAc/hexane (1:9, v/v)] followed by recrystallization from CH_2Cl_2/Et_2O (1:4, v/v) yielded *N*-(3-phenyl-1-β-styryl-2-propenylidene)benzamide (**2d**) (155 mg, 46%) as pale yellow crystals; mp 162–163 °C; IR (KBr): 1643, 1581 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 7.18 (d, *J*=16.1 Hz, 2H, olefin), 7.39–7.45 (m, 6H, Ar), 7.54 (t, *J*=7.6 Hz, 2H, Ar), 7.65 (t, *J*=7.4 Hz, 1H, Ar), 7.70–7.71 (m, 4H, Ar), 7.75 (d, *J*=16.1 Hz, 2H, olefin), 7.92 (d, *J*=7.6 Hz, 2H, Ar); ^{13}C NMR (151 MHz, DMSO-d_6) δ 122.2 (2CH), 128.1 (4CH), 128.86 (2CH), 128.91 (2CH), 128.93 (4CH), 130.0 (2CH), 133.2 (CH), 133.3 (C), 135.0 (2C), 140.6 (2CH), 161.1 (C), 179.6 (C). Anal. Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15. Found: C, 85.22; H, 5.71; N, 4.21.

4.4. Typical procedure for the initial [4+2] cycloaddition reaction of cross-conjugated azatriene 2 with ethyl vinyl ether under thermal conditions (Table 2, entry 3)

A mixture of **2c** (388 mg, 1.0 mmol) and ethyl vinyl ether (1.0 mL, 10 mmol) in toluene (30 mL) was heated at 110 °C for 15 h, additional ethyl vinyl ether (1.0 mL, 10 mmol) being added every 2 h during that time. After being cooled to room temperature, the reaction mixture was concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:9, v/v)] yielded 2-ethoxy-4-phenyl-6-β-styryl-1-*p*-toluenesulfonyl-1,2,3,4-tetrahydropyridine (**3c** (*endo*), H2–H4 cis) (395 mg, 86%) as a yellow oil; IR (neat): 1354, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 1.91 (ddd, *J*=3.6, 6.3, 14.0 Hz, 1H, H-3), 2.09 (ddd, *J*=5.3, 7.9, 14.0 Hz, 1H, H-3′), 2.46 (s, 3H, Ts), 2.65 (ddd, *J*=3.6, 6.3, 7.9 Hz, 1H, H-4), 3.60 (dq, *J*=7.1, 9.6 Hz, 1H, OCH_2CH_3), 3.90 (dq, *J*=7.1, 9.6 Hz, 1H, OCH_2CH_3), 5.54 (dd, *J*=3.6, 5.3 Hz, 1H, H-2), 5.96 (d, *J*=3.6 Hz, 1H, H-5), 6.84 (s, 2H, H-7, H-8), 7.06–7.08 (m, 2H, Ar), 7.14–7.18 (m, 1H, Ar), 7.21–7.34 (m, 7H, Ar), 7.43–7.45 (m, 2H, Ar), 7.72 (d, *J*=8.3 Hz, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.9 (CH_3), 21.6 (CH_3), 37.0 (CH), 38.0 (CH_2), 63.4 (CH_2), 84.4 (CH), 125.3 (CH), 126.5 (CH), 126.8 (2CH), 127.3 (CH), 127.5 (2CH), 127.7 (CH), 128.0 (2CH), 128.3 (2CH), 128.6 (2CH), 129.3 (CH), 129.7 (2CH), 135.0 (C), 136.7 (C), 136.9 (C), 143.9 (C), 144.4 (C). LRMS-EI *m*/*z* (%): 459 (M^+, 2), 304 (13), 258 (61), 256 (100). HRMS-EI *m*/*z* $[M]^+$ calcd for $C_{28}H_{29}O_3NS$: 459.1868, found: 459.1860.

4.5. Typical procedure for the initial [4+2] cycloaddition reaction of cross-conjugated azatriene 2d with ethyl vinyl ether promoted by TMSOTf (Table 2, entry 8)

A mixture of **2d** (675 mg, 2.0 mmol) and ethyl vinyl ether (0.57 mL, 6.0 mmol) in CH_2Cl_2 (30 mL) was cooled to −60 °C. Trimethylsilyltrifluoromethanesulfonate (1.0 M solution in CH_2Cl_2, 0.5 mL, 0.5 mmol) was added dropwise to the mixture at a rate of 0.5 mL/h by syringe pump with stirring. After the addition was completed, the reaction mixture was diluted with MeOH and water, and then extracted with CH_2Cl_2 (10 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)] followed by recrystallization from CH_2Cl_2/Et_2O (1:4, v/v) yielded (2-ethoxy-4-phenyl-6-β-styryl-3,4-dihydro-2*H*-pyridin-1-yl)phenylmethanone (**3d** (*endo*), H2–H4 cis) (702 mg, 86%) as colorless crystals; mp 133–134 °C; IR (KBr): 1635, 1358, 1065, 1026, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, J=7.0 Hz, 1H, OCH_2CH_3), 2.13 (ddd, J=3.4, 7.5, 13.9 Hz, 1H, H-3′), 2.75 (ddd, J=7.0, 7.0, 13.9 Hz, 1H, H-3), 3.62 (ddd, J=3.6, 7.0, 7.5 Hz, 1H, H-4), 3.78 (m, 2H, OCH_2CH_3), 6.01 (d, J=3.6 Hz, 1H, H-5), 6.11 (br s, 1H, H-2), 6.28 (d, J=16.0 Hz, 1H, H-8), 6.41 (d, J=16.0 Hz, 1H, H-7), 7.11 (d, J=7.4 Hz, 2H, Ar), 7.14–7.39 (m, 11H, Ar), 7.58–7.61 (m, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1 (CH_3), 38.7 (CH), 40.6 (CH_2), 64.0 (CH_2), 81.1 (CH), 125.0 (CH), 126.1 (CH), 126.3 (2CH), 126.6 (CH), 127.5 (CH), 127.6 (2CH), 128.1 (4CH), 128.4 (2CH), 128.5 (2CH), 128.8 (CH), 130.8 (CH), 136.6 (C), 136.8 (C), 137.2 (C), 144.2 (C), 170.5 (C). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{28}H_{27}NNaO_2$: 432.1934, found: 432.1954. Anal. Calcd for $C_{28}H_{27}NO_2$: C, 82.12; H, 6.65; N, 3.42. Found: C, 82.20; H, 6.94; N, 3.40.

4.6. Typical procedure for the initial [4+2] cycloaddition reaction of cross-conjugated azatriene 2 with ethyl vinyl sulfide under thermal conditions (Table 3, entry 2)

Ethyl vinyl sulfide (0.5 mL, 5.0 mmol) and 4 Å MS (1.0 g, 100 wt %) were added to a solution of **2c** (1.0 g, 2.6 mmol) in toluene (30 mL). The reaction mixture was heated at 110 °C for 37 h in a sealed tube, during which time additional ethyl vinyl sulfide (0.1 mL, 1.0 mmol) was added every 2 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 (1:9, v/v)] followed by recrystallization from CH_2Cl_2/Et_2O (1:4, v/v) yielded 2-ethylthio-4-phenyl-6-β-styryl-1-*p*-toluenesulfonyl-1,2,3,4-tetrahydropyridine (**4c** (*endo*), H2–H4 cis) (635 mg, 51%) as colorless crystals; mp 157–158 °C; IR (KBr): 2924, 1358, 1165, 1088 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.35 (t, J=7.5 Hz, 3H, SCH_2CH_3), 1.69 (ddd, J=4.5, 7.0, 13.6 Hz, 1H, H-3), 2.38 (ddd, J=7.1, 7.5, 13.6 Hz, 1H, H-3′), 2.42 (ddd, J=3.4, 7.0, 7.5 Hz, 1H, H-4), 2.47 (s, 3H, Ts), 2.72 (dq, J=7.5, 13.4 Hz, 1H, SCH_2CH_3), 2.93 (dq, J=7.5, 13.4 Hz, 1H, SCH_2CH_3), 5.57 (dd, J=4.5, 7.1 Hz, 1H, H-2), 6.11 (d, J=3.4 Hz, 1H, H-5), 6.86 (d, J=16.1 Hz, 1H, H-8), 6.91 (d, J=16.1 Hz, 1H, H-7), 6.99 (d, J=7.2 Hz, 2H, Ar), 7.17–7.20 (m, 1H, Ar), 7.23–7.26 (m, 3H, Ar), 7.32–7.34 (m, 4H, Ar), 7.47 (d, J=7.2 Hz, 2H, Ar), 7.76 (d, J=8.2 Hz, 2H, Ar); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.6 (CH_3), 21.6 (CH_3), 26.2 (CH_2), 37.4 (CH), 39.7 (CH_2), 59.6 (CH), 126.5 (CH), 126.7 (CH), 126.8 (2CH), 127.2 (CH), 127.6 (2CH), 127.7 (2CH), 127.8 (CH), 128.5 (2CH), 128.6 (2CH), 129.8 (2CH), 129.9 (CH), 136.3 (C), 136.5 (C), 136.8 (C), 143.6 (C), 144.1 (C). HRMS-ESI m/z $[M+H]^+$ calcd for $C_{28}H_{30}NO_2S_2$: 476.1712, found: 476.1710.

4.7. Typical procedure for the first [4+2] cycloaddition reaction of cross-conjugated azatriene 2d with ethyl vinyl sulfide promoted by TMSOTf (Table 3, entry 5)

Ethyl vinyl sulfide (0.081 mL, 0.8 mmol) was added to a solution of **2d** (135 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) and the mixture was cooled to −60 °C. Trimethylsilyltrifluoromethanesulfonate (1.0 M solution in CH_2Cl_2, 0.1 mL, 0.1 mmol) was added dropwise to the mixture at a rate of 0.6 mL/h by syringe pump. After the addition, the reaction mixture was stirred at the same temperature for 50 min and then diluted with MeOH and water and extracted with CH_2Cl_2 (10 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-ethylthio-4-phenyl-6-β-styryl-3,4-dihydro-2*H*-pyridin-1-yl)phenylmethanones (**4d** (*endo*) and **4d** (*exo*)) as a mixture (143 mg, 84%). Further purification performed by PTLC [SiO_2: EtOAc/hexane (1:9, v/v)] followed by recrystallization from CH_2Cl_2/Et_2O (1:4, v/v) yielded pure **4d** (*endo*) and **4d** (*exo*), respectively. Compound **4d** (*endo*): colorless crystals; mp 150–151 °C; IR (KBr): 1635, 1350, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.38 (t, J=7.4 Hz, 3H, SCH_2CH_3), 1.90 (ddd, J=5.7, 10.0, 13.7 Hz, 1H, H-3′), 2.76 (dq, J=7.4, 12.9 Hz, 1H, SCH_2CH_3), 2.99–3.07 (m, 2H, H-3, SCH_2CH_3), 3.60 (ddd, J=3.8, 6.5, 10.0 Hz, 1H, H-4), 6.16 (d, J=3.8 Hz, 1H, H-5), 6.26 (dd, J=5.7, 8.0 Hz, 1H, H-2), 6.30 (d, J=16.0 Hz, 1H, H-8), 6.39 (d, J=16.0 Hz, 1H, H-7), 7.10–7.11 (m, 2H, Ar), 7.15–7.31 (m, 7H, Ar), 7.34–7.40 (m, 4H, Ar), 7.54–7.55 (m, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1 (CH_3), 26.2 (CH_2), 39.9 (CH), 43.2 (CH_2), 56.1 (CH), 125.7 (CH), 126.3 (2CH), 126.6 (CH), 126.8 (CH), 127.4 (2CH), 127.6 (CH), 127.7 (2CH), 127.9 (2CH), 128.3 (2CH), 128.7 (2CH), 129.7 (CH), 130.6 (CH), 136.3 (C), 136.8 (C), 138.9 (C), 143.0 (C), 169.7 (C). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{28}H_{27}NNaOS$: 448.1706, found: 448.1702. Anal. Calcd for $C_{28}H_{27}NOS$: C, 79.02; H, 6.39; N, 3.29. Found: C, 79.26; H, 6.52; N, 3.27. Compound **4d** (*exo*): colorless crystals; mp 110–111 °C; IR (KBr): 1635, 1350, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (t, J=7.5 Hz, 3H, SCH_2CH_3), 2.35 (ddd, J=4.0, 11.6, 13.9 Hz, 1H, H-3), 2.47 (ddd, J=1.1, 7.3, 13.9 Hz, 1H, H-3′), 2.83 (dq, J=7.5, 12.8 Hz, 1H, SCH_2CH_3), 2.99 (dq, J=7.5, 12.8 Hz, 1H, SCH_2CH_3), 3.96 (ddd, J=3.5, 7.3, 11.6 Hz, 1H, H-4), 5.67 (d, J=3.5 Hz, 1H, H-5), 6.08 (d, J=15.7 Hz, 1H, H-8), 6.23 (br s, 1H, H-2), 6.38 (d, J=15.7 Hz, 1H, H-7), 7.00 (d, J=7.1 Hz, 2H, Ar), 7.12–7.19 (m, 3H, Ar), 7.31–7.36 (m, 6H, Ar), 7.40–7.43 (m, 2H, Ar), 7.67–7.68 (m, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.3 (CH_3), 25.6 (CH_2), 39.1 (CH_2), 39.2 (CH), 59.4 (CH), 117.8 (CH), 126.1 (2CH), 127.0 (CH), 127.3 (CH), 127.47 (CH), 127.54 (2CH), 128.1 (2CH), 128.2 (2CH), 128.3 (2CH), 128.8 (CH), 128.9 (2CH), 130.9 (CH), 136.1 (C), 136.5 (C), 136.8 (C), 143.5 (C), 170.2 (C). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{28}H_{27}NNaOS$: 448.1706, found: 448.1706. Anal. Calcd for $C_{28}H_{27}NOS$: C, 79.02; H, 6.39; N, 3.29. Found: C, 79.12; H, 6.60; N, 3.24.

4.8. Typical procedure for the initial [4+2] cycloaddition reaction of cross-conjugated azatriene 2 with methyl allenyl ether (Table 4, entry 3)

A mixture of **2c** (194 mg, 0.5 mmol) and methyl allenyl ether[13] (350 mg, 5.0 mmol) was heated in toluene (15 mL) at 110 °C for 20 h; additional methyl allenyl ether (70 mg, 1.0 mmol) being added every 2 h during this time. After being cooled, the reaction mixture was 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 2-methoxy-3-methylene-4-phenyl-6-β-styryl-1-*p*-toluenesulfonyl-1,2,3,4-tetrahydropyridine (**5c**) (64 mg, 28%) as colorless crystals; mp 142–144 °C; IR (KBr): 1356, 1168 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.87 (s, 3H, Ts), 3.43 (s, 3H, OMe), 4.20 (br s, 1H, H-4), 5.29 (s, 1H, H-10), 5.38 (s, 1H, H-9), 5.52 (s, 1H, H-2), 5.98 (d, J=2.8 Hz, 1H, H-5), 6.95 (d, J=15.9 Hz, 1H, H-8), 6.83 (d, J=15.9 Hz, 1H, H-7), 7.16–7.36 (m, 12H, Ar), 7.43 (d, J=7.9 Hz, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6 (CH_3), 44.5 (CH), 55.7 (CH_3), 89.5 (CH), 117.3 (CH_2), 122.8 (CH), 126.7 (CH), 126.8 (3CH), 127.8 (CH), 128.0 (2CH), 128.3 (2CH), 128.5 (2CH), 128.6 (2CH), 129.2 (2CH), 130.0 (CH), 134.1 (C), 135.5 (C), 136.8 (C), 143.4 (CH), 143.8 (C), 144.2 (C). LRMS-EI m/z (%) 457 (M^+,

14), 426 (5). HRMS-EI *m*/*z* [M]$^+$ calcd for $C_{28}H_{27}NO_3S$: 457.1712, found: 457.1710.

4.9. Typical procedure for the second [4+2] cycloaddition reaction of mono-adduct 3 with TCNE (Table 5, entry 3)

TCNE (56 mg, 0.44 mmol) was added to a solution of **3c** (*endo*) (101 mg, 0.22 mmol) in CH_2Cl_2 (5 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 (1:2, v/v)] followed by recrystallization from CH_2Cl_2/diethyl ether (1:4, v/v) yielded 2-ethoxy-4,7-diphenyl-1-*p*-toluenesulfonyl-1,2,3,4,4a,7-hexahydroquinoline-5,5,6,6-tetracarbonitrile (**6c**) (123 mg, 95%) as colorless crystals; mp 198–199 °C; IR (KBr): 1342, 1165 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 2.28 (ddd, *J*=1.8, 6.1, 15.0 Hz, 1H, H-3′), 2.51 (s, 3H, Ts), 2.56 (ddd, *J*=4.9, 9.2, 15.0 Hz, 1H, H-3), 3.28 (ddd, *J*=6.1, 9.2, 11.6 Hz, 1H, H-4), 3.44 (dq, *J*=7.0, 9.2 Hz, 1H, OCH_2CH_3), 3.67 (dq, *J*=7.0, 9.2 Hz, 1H, OCH_2CH_3), 3.80 (ddd, *J*=2.1, 2.1, 11.6 Hz, 1H, H-4a), 4.38 (dd, *J*=2.1, 3.6 Hz, 1H, H-7), 5.64 (dd, *J*=1.8, 4.9 Hz, 1H, H-2), 6.38 (dd, *J*=2.1, 3.6 Hz, 1H, H-8), 7.31–7.49 (m, 12H, Ar), 7.86 (ddd, *J*=1.8, 1.8, 8.6 Hz, 2H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.8 (CH_3), 21.7 (CH_3), 36.7 (CH_2), 39.7 (CH), 40.5 (C), 42.6 (CH), 44.5 (C), 46.8 (CH), 64.1 (CH_2), 83.9 (CH), 108.4 (C), 109.7 (C), 110.1 (C), 111.3 (C), 112.9 (CH), 127.8 (3CH), 128.8 (2CH), 129.0 (2CH), 129.3 (2CH), 130.17 (2CH), 130.21 (CH), 130.6 (2CH), 131.7 (C), 132.5 (C), 135.8 (C), 138.2 (C), 145.3 (C). LRMS-FAB *m*/*z* (%): 610 (M$^+$+Na, 29), 482 (17), 176 (100). HRMS-FAB *m*/*z* [M+Na]$^+$ calcd for $C_{34}H_{29}N_5O_3SNa$: 610.1889, found: 610.1900.

4.10. Typical procedure for the second [4+2] cycloaddition reaction of mono-adduct 3 with 4-phenyl-1,2,4-triazoline-3,5-dione (Table 6, entry 3)

4-Phenyl-1,2,4-triazoline-3,5-dione (110 mg, 0.65 mmol) was added to a solution of **3c** (*endo*) (250 mg, 0.54 mmol) 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 (1:2, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:6, v/v) yielded 7-ethoxy-2,4,9-triphenyl-6-*p*-toluenesulfonyl-4,6,7,8,9,9a-hexahydro-2,3a,6,9b-tetraazacyclopenta[*a*]naphthalene-1,3-dione (**9c**) (341 mg, 99%) as colorless crystals; mp 222–223 °C; IR (KBr): 1720, 1350, 1165 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.40 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 2.39 (ddd, *J*=2.6, 3.1, 15.2 Hz, 1H, H-8′), 2.44 (s, 3H, Ts), 2.48 (m, 1H, H-8), 3.41 (ddd, *J*=3.1, 11.0, 11.0 Hz, 1H, H-9), 3.82 (dq, *J*=7.0, 9.3 Hz, 1H, OCH_2CH_3), 3.99 (dq, *J*=7.0, 9.3 Hz, 1H, OCH_2CH_3), 5.24 (dd, *J*=2.0, 2.0 Hz, 1H, H-4), 5.36 (ddd, *J*=0.8, 2.0, 11.0 Hz, 1H, H-9a), 5.71 (dd, *J*=2.6, 3.2 Hz, 1H, H-7), 5.89 (dd, *J*=0.8, 2.0 Hz, 1H, H-5), 7.14–7.15 (m, 2H, Ar), 7.22–7.24 (m, 3H, Ar), 7.25–7.30 (m, 5H, Ar), 7.33–7.39 (m, 7H, Ar), 7.69–7.70 (m, 2H, Ar); ^{13}C NMR (151 MHz, $CDCl_3$) δ 15.1 (CH_3), 21.6 (CH_3), 35.2 (CH_2), 44.4 (CH), 54.2 (CH), 61.4 (CH), 64.8 (CH_2), 85.8 (CH), 110.0 (CH), 125.1 (2CH), 127.57 (2CH), 127.60 (2CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 128.6 (2CH), 128.72 (2CH), 128.73 (2CH), 128.8 (2CH), 129.8 (2CH), 131.0 (C), 131.8 (C), 135.7 (C), 138.5 (C), 141.4 (C), 144.5 (C), 148.5 (C), 155.0 (C). HRMS-ESI *m*/*z* [M+Na]$^+$ calcd for $C_{36}H_{34}N_4NaO_5S$: 657.2142, found: 657.2175. Anal. Calcd for $C_{36}H_{34}N_4O_5S$: C, 68.12; H, 5.40; N, 8.83. Found: C, 67.76; H, 5.53; N, 8.77.

4.11. Typical procedure for the second [4+2] cycloaddition reaction of mono-adduct 3 with dimethyl acetylene dicarboxylate (Table 7, entry 3)

A mixture of **3c** (162 mg, 0.35 mmol) and dimethyl acetylene dicarboxylate (99 mg, 0.70 mmol) in toluene (5 mL) was heated at 110 °C for 21 h and then concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:2, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:9, v/v) yielded dimethyl-4,7-diphenyl-1-*p*-toluenesulfonyl-1,4,4a,8a-tetrahydroquinoline-5,6-dicarboxylate (**12c**) (60 mg, 31%) as colorless crystals; mp 185–186 °C; IR (KBr): 1728, 1257, 1358, 1165 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.49 (s, 3H, Ts), 2.69 (dd, *J*=5.3, 10.8 Hz, 1H, H-4a), 2.86 (s, 3H, COOMe), 3.44 (ddd, *J*=2.0, 2.0, 10.8 Hz, 1H, H-4), 3.52 (s, 3H, COOMe), 4.51 (dd, *J*=5.3, 5.3 Hz, 1H, H-8a), 4.93 (dd, *J*=2.0, 7.9 Hz, 1H, H-3), 6.23 (d, *J*=5.3 Hz, 1H, H-8), 6.73 (dd, *J*=2.0, 7.9 Hz, 1H, H-2), 6.83 (d, *J*=6.1 Hz, 2H, Ar), 7.17–7.29 (m, 6H, Ar), 7.37 (t, *J*=7.6 Hz, 2H, Ar), 7.42 (d, *J*=8.2 Hz, 2H, Ar), 7.76 (d, *J*=8.2 Hz, 2H, Ar); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.6 (CH_3), 39.1 (CH), 44.7 (CH), 50.0 (CH), 51.4 (CH_3), 52.1 (CH_3), 115.1 (CH), 125.2 (CH), 125.5 (CH), 127.3 (CH), 127.4 (3CH), 128.1 (2CH), 128.2 (4CH), 128.9 (2CH), 129.9 (2CH), 130.2 (C), 133.9 (C), 134.6 (C), 136.5 (C), 140.1 (C), 140.2 (C), 144.5 (C), 166.80 (C), 166.82 (C). HRMS-ESI *m*/*z* [M+Na]$^+$ calcd for $C_{32}H_{29}NNaO_6S$: 578.1608, found: 578.1630.

4.12. Typical procedure for the second [4+2] cycloaddition reaction of mono-adduct 3 with *N*-phenylmaleimide (Table 8, entry 3)

A mixture of **3c** (151 mg, 0.33 mmol) and *N*-phenylmaleimide (114 mg, 0.66 mmol) in toluene (5 mL) was heated at 110 °C for 18 h and then concentrated in vacuo. Purification of the residue by flash chromatography [SiO_2: EtOAc/hexane (1:2, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:9, v/v) yielded 2,4,9-triphenyl-6-*p*-toluenesulfonyl-3a,4,6,9,9a,9b-hexahydropyrrolo[3,4-*f*]quinoline-1,3-dione (**13c**) (43 mg, 22%) as a colorless crystals; mp 246–247 °C; IR (KBr): 1713, 1381, 1350, 1173 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (br dd, *J*=1.9, 11.6 Hz, 1H, H-9), 2.40 (s, 3H, Ts), 2.88 (dd, *J*=2.0, 8.3 Hz, 1H, H-9b), 3.02 (dd, *J*=6.5, 8.3 Hz, 1H, H-3a), 3.30 (ddd, *J*=1.5, 2.0, 11.6 Hz, 1H, H-9a), 3.92 (br dd, *J*=3.2, 6.5 Hz, 1H, H-4), 5.06 (dd, *J*=1.9, 8.0 Hz, 1H, H-8), 6.36 (dd, *J*=1.5, 3.2 Hz, 1H, H-5), 6.81 (dd, *J*=2.2, 8.0 Hz, 1H, H-7), 6.90 (dd, *J*=2.1, 7.8 Hz, 2H, Ar), 7.20–7.50 (m, 15H, Ar), 7.68 (d, *J*=8.3 Hz, 2H, Ar); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.6 (CH_3), 33.1 (CH), 41.7 (CH), 42.0 (CH), 43.7 (CH), 48.6 (CH), 114.4 (CH), 125.2 (CH), 125.4 (CH), 125.8 (2CH), 127.3 (2CH), 127.7 (CH), 127.7 (CH), 127.9 (2CH), 128.1 (2CH), 128.3 (CH), 129.0 (2CH), 129.0 (4CH), 130.0 (2CH), 131.7 (C), 133.3 (C), 134.2 (C), 140.0 (C), 141.8 (C), 144.6 (C), 175.3 (C), 176.1 (C). HRMS-ESI *m*/*z* [M+Na]$^+$ calcd for $C_{36}H_{30}N_2NaO_4S$: 609.1818, found: 609.1789.

4.13. Preparation of ketone 20

A solution of *tert*-butyldimethylsilyl chloride (904 mg, 6.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise at 0 °C to a solution 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). The reaction mixture was warmed to room temperature with stirring for an additional 1 h and then diluted 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.).

n-Butyllithium (1.5 M solution in hexane, 2.4 mL, 3.6 mmol) was added dropwise to a solution of diisopropylamine (0.63 mL, 3.6 mmol) in THF (40 mL) at −65 °C, and the mixture was warmed to room temperature and stirred for an additional 1 h. The solution was cooled to −65 °C before a solution of benzalacetone (526 mg, 3.6 mmol) in THF (15 mL) was added dropwise and the reaction mixture was stirred for 1 h at the same temperature. A solution of 2-(*tert*-butyldimethylsilanyloxy)benzaldehyde (709 mg, 3.0 mmol)

in THF (10 mL) was added dropwise to the mixture at −65 °C and the reaction mixture was stirred for an additional 10 min. The reaction mixture was 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)] yielded 1-[2-(*tert*-butyldimethylsilanyloxy)phenyl]-1-hydroxy-5-phenylpent-4-en-3-one as a colorless oil (1.14 g, 99%).

Methane sulfonyl chloride (0.23 mL, 3.0 mmol) was added to a solution of 1-[2-(*tert*-butyldimethylsilanyloxy)phenyl]-1-hydroxy-5-phenylpent-4-en-3-one (957 mg, 2.5 mmol) and Et_3N (0.84 mL, 6.0 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The reaction mixture was warmed to room temperature with stirring overnight, diluted with saturated aqueous $NaHCO_3$, 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 (1:9, v/v)] yielded 1-[2-(*tert*-butyldimethylsilanyloxy)phenyl]-5-phenylpenta-1,4-dien-3-one as a yellow oil (838 mg, 93%).

TBAF (1.0 M solution in THF, 1.0 mL, 1.0 mmol) was added to a solution of 1-[2-(*tert*-butyldimethylsilanyloxy)phenyl]-5-phenylpent-1,4-dien-3-one (365 mg, 1.0 mmol) in THF (30 mL) at 0 °C. The reaction mixture was stirred for 10 min and then 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 (1:2, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:9, v/v) yielded 1-(2-hydroxyphenyl)-5-phenylpent-1,4-dien-3-one (**19**) (233 mg, 93%) as yellow needles.

K_2CO_3 (276 mg, 2.0 mmol) and cinnamyl bromide (0.30 mL, 2.0 mmol) were added to a solution of **19** (250 mg, 1.0 mmol) in acetone (40 mL). The mixture was heated under reflux for 2 h. After being cooled to room temperature, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc (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)] followed by recrystallization from CH_2Cl_2/hexane (1:9, v/v) yielded 1-phenyl-5-[2-(3-phenyl-2-propenoxy)phenyl]penta-1,4-dien-3-one (**20**) (273 mg, 94%) as yellow needles; mp 100–101 °C; IR (KBr): 1652, 1588, 1572, 996, 688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.79 (d, J=5.5 Hz, 2H, H-5, H-6), 6.47 (dt, J=5.5, 15.9 Hz, 1H, H-7), 6.78 (d, J=15.9 Hz, 1H, H-8), 6.98 (d, J=7.9 Hz, 1H, Ar), 7.01 (d, J=7.9 Hz, 1H, Ar), 7.08 (d, J=16.2 Hz, 1H, H-2), 7.24 (d, J=15.9 Hz, 1H, H-3), 7.24–7.36 (m, 7H, Ar), 7.42 (d, J=7.3 Hz, 2H, Ar), 7.51 (d, J=6.7 Hz, 2H, Ar), 7.62 (d, J=7.3 Hz, 1H, Ar), 7.69 (d, J=15.9 Hz, 1H, H-4), 8.12 (d, J=16.2 Hz, 1H, H-1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 69.0 (CH_2), 112.6 (CH), 121.0 (CH), 123.9 (CH), 124.0 (C), 125.6 (CH), 126.1 (CH), 126.6 (2CH), 128.0 (CH), 128.3 (2CH), 128.6 (2CH), 128.8 (2CH), 129.3 (CH), 130.2 (CH), 131.6 (CH), 133.3 (CH), 134.8 (C), 136.2 (C), 138.8 (CH), 142.8 (CH), 157.7 (C), 189.5 (C). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{26}H_{22}NaO_2$: 389.1512, found: 389.1513.

4.14. Typical procedure for the preparation of cross-conjugated azatriene 21

Titanium tetrachloride (1.0 M solution in CH_2Cl_2, 4.0 mL, 4.0 mmol) was added dropwise at 0 °C to a solution of **20** (733 mg, 2.0 mmol), Et_3N (2.45 mL, 17.6 mmol), and *p*-toluenesulfonamide (685 mg, 4.0 mmol) in CH_2Cl_2 (40 mL). The mixture was warmed to room temperature with stirring overnight, diluted with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (40 mL×2). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Recrystallization from CH_2Cl_2/hexane (1:9, v/v) yielded 4-methyl-*N*-(3-phenyl-1-{2-[2-(3-phenyl-2-propenoxy)phenyl]vinyl}allylidene)benzenesulfonamide (**21b**) (738 mg, 71%) as yellow needles; mp 156–157 °C; IR (KBr): 1622, 1344, 1284, 1152 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.38 (s, 3H, Ts), 4.77 (d, J=5.8 Hz, 2H, H-5, H-6), 6.34 (dt, J=5.8, 15.9 Hz, 1H, H-7), 6.73 (d, J=15.9 Hz, 1H, H8), 6.97 (d, J=8.3 Hz, 1H, Ar), 7.01 (t, J=7.6 Hz, 1H, Ar), 7.11–7.43 (m, 13H, olefin, Ar), 7.50 (d, J=7.3 Hz, 2H, Ar), 7.63 (br s, 1H, olefin), 7.89–7.99 (m, 4H, olefin, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5 (CH_3), 69.2 (CH_2), 112.5 (CH), 121.2 (2CH), 123.6 (CH), 123.8 (CH), 124.1 (C), 126.6 (2CH), 127.0 (2CH), 128.0 (CH), 128.4 (2CH), 128.6 (2CH), 128.9 (2CH), 129.3 (2CH), 130.44 (2CH), 132.0 (CH), 133.3 (CH), 134.9 (C), 136.2 (C), 139.1 (C), 140.0 (CH), 143.1 (C), 144.0 (CH), 157.6 (C), 173.3 (C). LRMS-EI m/z (%): 519 (M^+, 1), 455 (44), 363 (100), 91 (92). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{33}H_{29}NNaO_3S$: 542.1760, found: 542.1771.

4.15. Typical procedure for the intramolecular aza Diels–Alder reaction (Table 9, entry 2)

A toluene (30 mL) solution of **21b** (520 mg, 1.0 mmol) was heated at 110 °C for 8.0 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 (1:9, v/v)] yielded 4-phenyl-2-β-styryl-3-*p*-toluenesulfonyl-3,4,4a,10b-tetrahydro-2*H*-chromeno[3,4-*c*]pyridine (**22b**) (312 mg, 60%) as an orange oil; IR (neat): 1319, 1142 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.21 (dddd, J=3.4, 10.4, 10.7, 11.0 Hz, 1H, H-4a), 2.37 (s, 3H, Ts), 2.60 (dd, J=4.0, 11.0 Hz, 1H, H-10b), 3.81 (dd, J=10.4, 10.4 Hz, 1H, H-5′), 4.06 (dd, J=3.4, 10.4 Hz, 1H, H-5), 4.72 (d, J=10.7 Hz, 1H, H-4), 6.63 (d, J=4.0 Hz, 1H, H-1), 6.74 (dd, J=7.9, 7.9 Hz, 1H, Ar), 6.77 (d, J=15.9 Hz, 1H, H-12), 6.86 (d, J=15.9 Hz, 1H, H-11), 6.92 (dd, J=7.3, 7.3 Hz, 1H, Ar), 7.09–7.38 (m, 14H, Ar), 7.62 (d, J=8.2 Hz, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6 (CH_3), 35.7 (CH), 48.5 (CH), 63.5 (CH), 67.6 (CH_2), 116.8 (CH), 121.1 (CH), 122.3 (C), 125.8 (CH), 126.8 (2CH), 127.0 (3CH), 127.5 (CH), 127.5 (2CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.6 (2CH), 128.9 (2CH), 129.5 (2CH), 130.8 (C), 136.3 (C), 136.6 (C), 140.4 (C), 141.9 (C), 143.9 (C), 154.0 (C). LRMS-EI m/z (%): 519 (M^+, 1), 455 (22), 360 (97), 91 (100). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{33}H_{29}NNaO_3S$: 542.1760, found: 542.1759.

4.16. Typical procedure for the second [4+2] cycloaddition reaction of mono-adduct 23 with dimethyl acetylene dicarboxylate (Table 10, entry 2)

A toluene (10 mL) solution of **22b** (104 mg, 0.2 mmol) and dimethyl acetylene dicarboxylate (0.049 mL, 0.4 mmol) was heated at 110 °C for 16 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)] followed by recrystallization from CH_2Cl_2/hexane (1:5, v/v) yielded dimethyl 7,10-diphenyl-8-*p*-toluenesulfonyl-6a,7,8,9,10,12b-hexahydro-6*H*-chromeno[3,4-*c*]quinoline-11,12-carboxylate (**24b**) (75 mg, 57%) as colorless crystals; mp 230–232 °C; IR (KBr): 1732, 1362, 1166 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.11 (br dd, J=3.1, 11.3 Hz, 1H, H-12b), 2.24 (s, 3H, Ts), 2.61 (dddd, J=4.0, 10.1, 11.0, 11.3 Hz, 1H, H-6a), 2.92 (ddd, J=3.1, 6.7, 18.3 Hz, 1H, H-9′), 3.02 (s, 3H, COOMe), 3.41 (dd, J=10.7, 11.0 Hz, 1H, H-6′), 3.69 (s, 3H, COOMe), 4.02 (dd, J=4.0, 10.7 Hz, 1H, H-6), 4.10 (dd, J=1.2, 18.3 Hz, 1H, H-9), 4.18 (br d, J=6.7 Hz, 1H, H-10), 4.41 (d, J=10.1 Hz, 1H, H-7), 6.69–6.76 (m, 4H, Ar), 6.85 (dd, J=7.3, 7.3 Hz, 1H, Ar), 6.95 (d, J=8.2 Hz, 2H, Ar), 7.07 (dd, J=6.7, 8.2 Hz, 1H, Ar), 7.24–7.43 (m, 6H, Ar), 7.51–7.56 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (CH_3), 37.2 (CH), 37.6 (CH_2), 39.0 (CH), 50.0 (CH), 51.6 (CH_3), 52.3 (CH_3), 65.7 (CH), 67.9 (CH_2), 117.1 (CH), 120.0 (C), 121.0 (CH), 126.3 (2CH), 126.8 (2CH), 127.2 (CH), 127.9 (CH), 127.9 (2CH), 128.1 (CH), 128.6 (2CH), 128.9 (2CH), 129.1 (C), 129.3 (CH), 129.4 (C), 129.7 (2CH), 135.5 (C), 137.6 (C), 138.7 (C),

141.0 (C), 141.4 (C), 143.8 (C), 155.1 (C), 166.3 (C), 167.0 (C). LRMS-EI *m*/*z* (%): 661 (M^+, 59), 595 (19), 506 (M^+−Ts, 94), 505 (M^+−Ts, H, 89), 474 (73), 117 (93), 91 (100). HRMS-EI *m*/*z* $[M]^+$ calcd for $C_{39}H_{35}NO_7S$: 661.2134, found: 661.2145.

4.17. Typical procedure for the second [4+2] cycloaddition reaction of mono-adduct 23 with methyl acrylate (Table 11, entry 2)

Methyl acrylate (0.14 mL, 1.54 mmol) was added to a benzene (10 mL) solution of **22b** (40 mg, 0.077 mmol) and heated at 80 °C for 16 h. After being cooled to room temperature, the reaction mixture was concentrated in vacuo. Purification of the residue by PTLC [SiO_2: EtOAc/hexane (1:2, v/v)] followed by recrystallization from CH_2Cl_2/hexane (1:5, v/v) yielded 7,10-diphenyl-8-*p*-toluenesulfonyl-6a,7,8,10,11,12,12a,12b-octahydro-6*H*-5-oxa-8-aza-benzo[*c*]-phenanthrene-11-carboxylic acid methyl ester (**25b**) (31 mg, 54%) as colorless crystals; mp 99–101 °C; IR (KBr): 1738, 1494, 1338, 1164 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.54 (ddd, *J*=9.5, 13.1, 13.1 Hz, 1H, H-12′), 2.29 (dddd, *J*=3.7, 10.7, 10.7, 11.3 Hz, 1H, H-6a), 2.38 (s, 3H, Ts), 2.47 (ddd, *J*=4.9, 9.2, 9.5 Hz, 1H, H-11), 2.51–2.55 (m, 2H, H-12, H-12a), 2.59 (dd, *J*=10.7, 10.7 Hz, 1H, H-12b), 3.47 (s, 3H, COOMe), 3.54 (dd, *J*=3.7, 9.2 Hz, 1H, H-10), 3.72 (dd, *J*=10.7, 10.7 Hz, 1H, H-6′), 4.09 (dd, *J*=3.7, 10.7 Hz, 1H, H-6), 4.91 (d, *J*=11.3 Hz, 1H, H-7), 6.09 (dd, *J*=1.2, 3.7 Hz, 1H, H-9), 6.85 (d, *J*=7.9 Hz, 1H, Ar), 6.90 (dd, *J*=7.6, 7.6 Hz, 1H, Ar), 7.14 (dd, *J*=7.9, 7.9 Hz, 1H, Ar), 7.19–7.37 (m, 13H, Ar), 7.52 (d, *J*=7.9 Hz, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5 (CH_3), 31.6 (CH_2), 37.9 (CH), 43.7 (CH), 44.0 (CH), 45.3 (CH), 48.9 (CH), 51.7 (CH_3), 63.0 (CH), 67.4 (CH_2), 117.7 (CH), 120.9 (CH), 123.5 (C), 125.5 (CH), 127.0 (CH), 127.2 (2CH), 127.7 (2CH), 128.0 (CH), 128.1 (2CH), 128.2 (CH), 128.6 (2CH), 128.7 (2CH), 129.0 (CH), 129.4 (2CH), 137.8 (C), 138.1 (C), 141.2 (C), 142.8 (C), 143.8 (C), 155.7 (C), 175.5 (C). LRMS-EI *m*/*z* (%): 605 (M^+, 9), 541 (30), 540 (18), 450 (100), 221 (43), 117 (51), 91 (81). HRMS-EI *m*/*z* $[M]^+$ calcd for $C_{37}H_{35}NO_5S$: 605.2236, found: 605.2220.

4.18. X-ray data for compound 16′d

Crystallographic data (excluding structure factors) for **16′d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 679645. 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.2008.07.102.

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