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Oxabenzonorbornadiene (1a) reacted with various alkynes in the presence of Ni(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, PPh<sub>3</sub> and zinc powder in toluene to give two common products 2a and 2b regardless of the alkyne used. The formation of 2a and 2b are proposed to be from the Diels–Alder reaction of 1a and isobenzofuran. The latter is generated from the retro Diels–Alder reaction of [2 + 2 + 2] cycloadducts of 1a and alkynes catalyzed by the nickel system. A series of nickel-catalyzed [2 + 2 + 2] cycloadducts (4a–j and 5a–d) of oxa- and azabenzonorbornadienes (1a–d) with terminal alkynes were isolated at temperatures -5-18 °C. Similarly, hepta-1,6-diyne and octa-1,7-diyne reacted with 1a and 1d to give novel pentacyclic [2 + 2 + 2] cycloadducts 6a–d in 62–75% yields. These products are convenient isobenzofuran and isoindole precursors that react with various dienophiles to afford the corresponding Diels–Alder adducts. In addition, the [2 + 2 + 2] cycloadducts may be used as precursors for the synthesis of aromatic compounds. For example, the reaction of 1a with methyl but-2-ynoate catalyzed by the nickel system provided aromatic compound 3 in 94% yield. In this reaction, 1a is a 'masked acetylene' providing an acetylene moiety to 3.

# Introduction

Isobenzofuran and its derivatives have attracted considerable attention in recent years in organic synthesis. They have been widely used as dienes in the Diels-Alder reactions<sup>1</sup> to provide substituted 7-oxabicyclo[2.2.1]heptanes, which are key intermediates in natural products synthesis.<sup>2</sup> Recently, Padwa and co-workers have synthesised the Erythrinane alkaloid skeleton<sup>3</sup> and a variety of 1-hydroxy-4-aminonaphthalene derivatives<sup>4</sup> using isobenzofuran derivatives as key intermediates. In addition, isobenzofurans and isoindoles are important building blocks for the syntheses of a variety of fascinating polycyclic unnatural products.<sup>5,6</sup> However, isobenzofurans and isoindoles are generally highly reactive undergoing polymerization even at low temperature. Several precursors for isobenzofurans<sup>7</sup> and isoindoles<sup>8</sup> have been developed, but most are very unstable and difficult to handle. The search for new and viable precursors to conveniently generate isobenzofurans and isoindoles continues.

Transition metal-catalyzed [2 + 2 + 2] cocyclotrimerization is a powerful method for the construction of cyclic compounds in a chemo- and regioselective manner.9,10 Cocyclotrimerization of three acetylenes has been extensively studied by using different metal catalysts with different unsaturated compounds.11 The [2 + 2 + 2] cycloaddition of two acetylenes and an alkene has been less well explored.<sup>12</sup> In general, this cocyclotrimerization requires a high ratio of alkene to alkyne in order to suppress the competing trimerization of alkynes.<sup>13</sup> Recently, we reported a novel one step synthesis of cyclohexadiene derivatives of C<sub>60</sub> via a nickel-catalyzed cycloaddition of C<sub>60</sub> with diynes.<sup>14</sup> In addition, we<sup>15</sup> and Ikeda et al.<sup>16</sup> independently reported the [2 + 2 + 2] cocyclotrimerization of  $\alpha,\beta$ -unsaturated carbonyl compounds with mono alkynes and diynes mediated by nickel complexes. In the pursuit for new active alkenes for [2 + 2 + 2] cocyclotrimerization, we observed the cocyclotrimerization of oxa- and azabenzonorbornadienes

with alkynes. The cocyclotrimerization products may be used as convenient new precursors for isobenzofurans and isoindoles and for substituted aromatic compounds. Moreover, the reaction is an excellent method for constructing multiple fused rings by the cycloaddition of oxa- and azabenzonorbornadienes with diynes. Herein we report a detailed study of this nickel-catalyzed cocyclotrimerization reaction. Preliminary results of these studies have appeared in a communication.<sup>17</sup>

#### **Results and discussion**

#### Reaction of oxabenzonorbornadiene (1a) with alkynes

Compound **1a** reacted with various alkynes (see Table 1) at 25– 90 °C in the presence of Ni(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (5 mol%), PPh<sub>3</sub> and zinc powder in toluene to give two common products **2a** and **2b** (Scheme 1) regardless of the alkyne used. These two unusual



stereoisomers are readily distinguished in the <sup>1</sup>H and <sup>13</sup>C NMR spectra (see the Experimental section). A key difference between these two compounds is that **2a** exhibits a pair of resonances at 4.69 and 5.32 ppm for the four bridgehead protons, while **2b** shows only one resonance at 5.46 ppm for bridgehead protons. The symmetries of these two structures are

<sup>&</sup>lt;sup>†</sup> The IUPAC name for benzonorbornadiene is 1,4-dihydro-1,4methanonaphthalene.

Table 1 Formation of products 2a and 2b from oxabenzonorbornadiene (1a) and various alkynes catalyzed by NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>-PPh<sub>3</sub>-Zn<sup>a</sup>

					Product yield (%) <sup>b</sup>		
Entry	[ <b>1a</b> ]/M	[Acetylene]/M	[NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> -PPh <sub>3</sub> ]/M	Temp/°C	( <b>2a</b> )	( <b>2b</b> )	
1	0.40	$\begin{array}{c} \text{HC=C(CH_2)_4CH_3}\\ (0.40) \end{array}$	0.020/0.32	80	46	25	
2	0.40	HC≡CPh (0.80)	0.020/0.32	25	58	40	
3	0.50	MeCH=CHCOOMe (0.60)	0.025/0.40	30	65	31	
4	0.50	TMSCH≡CHCOOEt (0.60)	0.025/0.40	30	25	36	
5	0.50	$HC \equiv C(CH_2)_4 C \equiv CH$	0.025/0.0	90	52	26	
6	0.5	$N(H_2CC=CH)_3$ (0.50)	0.025/0.40	70	43	26	

<sup>*a*</sup> Each reaction was carried out in toluene solution (2.0 ml) in the presence of the reagents shown in Table 1 and Zn metal (2.75 mmol) at the temperature specified for 24 h. <sup>*b*</sup> The yields of **2a** and **2b** were determined by <sup>1</sup>H NMR integration using norbornene as internal standard.

primarily responsible for the number of NMR peaks observed. Although common products **2a** and **2b** were observed, the yields of these two species are different with different alkynes used. The results of these reactions are shown in Table 1. In addition to the common products, aromatic compounds were also observed in the reaction mixtures of **1a** and alkynes. As an example, the reaction of **1a** and methyl but-2-ynoate at 30 °C (entry 3) gave aromatic compound **3** in 92% yield in addition to products **2a** and **2b**.



The formation of **2a**, **2b** and aromatic compounds may be explained in terms of a nickel-catalyzed [2 + 2 + 2] cocyclotrimerization of **1a** and alkyne to give intermediate **I**. This cyclohexadiene intermediate is thermally unstable and readily undergoes retro Diels–Alder cycloaddition to give an aromatic product and isobenzofuran. Diels–Alder reaction of isobenzofuran with **1a** affords the observed products **2a** and **2b**. A summary of the reaction pathway is shown in Scheme 2. The driving force for the retro Diels–Alder reaction of intermediate **I** is the formation of a low energy aromatic product.





To support the pathway proposed in Scheme 2, an attempt was made to isolate the [2 + 2 + 2] cocyclotrimerization intermedi-

ates. In view of the fact that no such products were isolated at temperatures between 40–90 °C, the reactions of **1a** and alkynes were carried out at lower temperatures. Thus, treatment of **1a** with pent-1-yne in the presence of Ni(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (5 mol%), PPh<sub>3</sub> and zinc powder in toluene at 18 °C for 24 h gave a mixture of two cyclohexadiene derivatives **4a** and **5a** in 91% combined yield (Scheme 3). Mass spectral data show that these two





products are isomers having the same molecular weight. The structures of these two regioisomers are assigned based on the <sup>1</sup>H NMR coupling patterns. The individual yields of **4a** and **5a** were determined from the <sup>1</sup>H NMR spectrum of the mixture as 22% and 69% respectively. Control reactions revealed that no desired product was formed in the absence of either Ni(PPh<sub>3</sub>)<sub>2</sub>-Cl<sub>2</sub> or zinc metal. Additional PPh<sub>3</sub> was essential to stabilize Ni(0) and to achieve higher yields of products. Similarly, hex-1yne and hept-1-yne reacted with 1a to give 4b and 5b (1:2.1), and 4c and 5c (1:8.7) in 91 and 68% combined yields, respectively. In contrast, the reaction of phenylacetylene and ethyn-1ylcyclohex-1-ene with 1a afforded only 1,3-isomers 4e and 4g, in high yields, respectively (Table 2). It should be noted that temperature control is important for the success of isolation of cocyclotrimerization products. The reactions of pent-1-yne, hex-1-yne, hept-1-yne and ethyn-1-ylcyclohex-1-ene with 1a were controlled at 18 °C, while the reaction of phenylacetylene with **1a** was performed at -5 °C.

In the same manner, methoxy substituted oxabenzonor-

Table 2 Cocyclotrimerization of oxa- and azabenzonorbornadienes with terminal alkynes



	Entry	Alkene	Temp/°C	$R^{3}C\equiv CH(R^{3})$	Product yield (%) <sup><i>a</i></sup>
	1	1a	18	CH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub>	4a(22) + 5a(69)
	2	1a	18	$CH_{2}(CH_{2})_{2}$	4b(29) + 5b(62)
	3	1a	18	CH <sub>4</sub> (CH <sub>2</sub> ) <sub>4</sub>	4c(7) + 5c(61)
	4	1d	18	$CH_{4}(CH_{2})_{2}$	4d(26) + 5d(64)
	5	1a	-5	Ph	<b>4e</b> (95)
	6	1d	10	Ph	<b>4f</b> (93)
	7	1a	18	$-C_6H_9-$	<b>4g</b> (95)
	8	1d	10	$-C_6H_9-$	<b>4h</b> (90)
	9	1b	0	Ph	4i + 4i' (72)
	10	1c	0	Ph	<b>4j</b> (74)
<sup><i>a</i></sup> Yields are measured by <sup>1</sup> H	I NMR integr	ration method	using norborner	ne as internal standar	rd

bornadienes (1b, c) undergo cocyclotrimerization with alkynes in the presence of Ni(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, PPh<sub>3</sub>, and zinc powder. The reaction of 1b with phenylacetylene afforded two regio products 4i and 4i' in 72% combined yields, while treatment of 1c with phenylacetylene gave 4j in 74% yield. Similar to substrate 1a-c, azabenzonorbornadiene (1d) reacted with terminal alkynes hex-1-yne, phenylacetylene and ethyn-1-ylcyclohex-1ene under similar reaction conditions to afford cocyclotrimerization products 4d and 5d, 4f and 4h in fair to excellent yields (Table 2).

The nickel-catalyzed [2 + 2 + 2] cocyclotrimerization is successfully extended to bisalkynes. Thus, hepta-1,6-diyne and octa-1,7-diyne reacted with **1a** and **1d** to give novel pentacyclic adducts **6a–d** in 62–75% yields (Scheme 4). The facile formation



of products **6a–d** demonstrates that the present [2 + 2 + 2] cocyclotrimerization is a powerful method for the construction of multiple rings. Although methyl but-2-ynoate also undergoes

cocyclotrimerization with **1a** and **1e**, the [2 + 2 + 2] cycloaddition adducts cannot be isolated at temperatures above -10 °C due to thermal instability of these adducts (*vide infra*). Attempts to isolate tetrasubstituted [2 + 2 + 2] adducts from **1a** and disubstituted alkynes such as diphenylacetylene and methyl 3-phenylpropiolate did not succeed either.



In the present [2 + 2 + 2] cocyclotrimerization, the nickel system selectively catalyzes the cotrimerization of an oxa- or azabenzonorbornadiene and two alkyne moieties. Only a trace of the trimerization product of alkyne was observed in each reaction. The replacement of **1** by a less reactive olefin such as hex-1-ene, 2,3-dihydro-2*H*-pyran or cyclohexene did not give the expected [2 + 2 + 2] cotrimerization product.

All of the [2 + 2 + 2] cocyclotrimerization products of **1a–d** with terminal alkynes and bisalkynes are completely stereoselective giving only *exo* cyclohexadiene products. No corresponding *endo* products were observed in all of these reactions. The *exo* stereochemistry was established on the basis of the coupling constant of bridgehead proton and *endo* cyclohexadiene proton. It is well known that for norbornene and its derivatives, the coupling constant between an *endo* and a bridgehead proton is nearly zero, while the value between an *exo* and bridgehead proton is *ca*. 3 Hz and can be clearly observed.<sup>18</sup> In the present cyclohexadiene derivatives, all bridgehead protons appeared as singlets in the <sup>1</sup>H NMR spectra indicating these derivatives have *exo* stereochemistry.

As proposed in Scheme 2, the [2 + 2 + 2] cocyclotrimerization products **4–6** are thermally unstable and undergo retro Diels–Alder reaction to give isobenzofurans or isoindoles and aromatic compounds. The stability of the [2 + 2 + 2] cocyclotrimerization products depends greatly on the substituents

**Table 3** Effect of nickel catalysts on the [2+2+2] cocyclotrimerizationof oxabenzonorbornadiene with phenylacetylene "

		Products yield (%) <sup>b</sup>				
Entry	Ni catalyst/mmol	4e	2a	2b	7	
1	NiBr, (0.10), Zn (3.0)		_	_	41	
2	$Ni(COD)_{2}(0.10)$				14	
3	$Ni(PPh_{2})_{4}(0.050)$		58	40		
4	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (0.05), PPh <sub>3</sub> (0.8), Zn (3.0)	18	44	26		
5	$NiCl_{2}(P^{n}Bu_{3})_{2}(0.05), Zn(3.0)$	_			_	

<sup>*a*</sup> Reaction conditions: oxabenzonorbornadiene (0.50 mmol), phenylacetylene (1.0 mmol) and nickel catalyst (see Table 3) in toluene (1.25 ml) at ambient temperature. <sup>*b*</sup> Yields are based on oxabenzonorbornadiene.

present on the *exo* cyclohexadiene ring. The products with alkyl substituents on the *exo* cyclohexadiene ring are most stable and can be stored at room temperature for a few days in solution and in the solid state for a long time. Compounds **4g** and **4h** with a cyclohex-1-enyl substituent are stable in solution for only a few hours at room temperature. The products with phenyl substituents **4e** and **4f** can be observed only at temperatures below -5 °C. On the other hand, no [2 + 2 + 2] adduct was observed from methyl but-2-ynoate at -5-30 °C.

#### Effect of ligand on cocyclotrimerization

The [2 + 2 + 2] cocyclotrimerization depends greatly on the phosphine ligand <sup>19</sup> used (Table 3). Ni(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>–PPh<sub>3</sub>–Zn and Ni(PPh<sub>3</sub>)<sub>4</sub> were found to be the catalysts of choice for the present [2 + 2 + 2] cocyclotrimerization (Table 3, entries 3, 4). The highly basic ligand *n*-Bu<sub>3</sub>P strongly retards the reaction (entry 5). The replacement of Ni(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> and Ni(PPh<sub>3</sub>)<sub>4</sub> by Ni(COD)<sub>2</sub> and NiBr<sub>2</sub>–Zn (entries 1 and 2) led to no reaction between **1a** and phenylacetylene, but instead gave homo [2 + 2] dimerization of oxabenzonorbornadiene (**1a**) to yield 7 (Scheme 5).<sup>20</sup>



Mechanism of [2 + 2 + 2] cocyclotrimerization

Based on the well established organometallic chemistry of nickel complexes and observed regio- and stereoselectivity of cotrimerization products, a reasonable reaction mechanism for the Ni(0)-catalyzed [2 + 2 + 2] cocyclotrimerization of an oxabenzonorbornadiene and two alkynes is depicted in Scheme 6. The reduction of Ni(II) species to Ni(0) species is followed by coordination of two molecules of alkynes and oxidative cyclometallation to yield a nickelacyclopentadiene intermediate 8.21,22 Coordination of an oxabenzonorbornadiene (1a) and subsequent insertion into a Ni(II)-carbon bond produces nickelacycloheptadiene intermediate 9. Reductive elimination of 9 affording product 4 and regenerating Ni(0) completes the catalytic cycle. Alternatively, a mechanism which involves the coordination of an oxa- or azabenzonorbornadiene and an alkyne to Ni(0) to produce a nickelacyclopentene intermediate<sup>23</sup> 8' followed by insertion of another alkyne into the nickelcarbon bond to give nickelacycloheptadiene intermediate 9 can not be excluded.

It is clear from Scheme 6 that the stereochemistry of [2 + 2 + 2] cycloadducts is determined completely by the coordination of oxa- and azabenzonorbornadienes to the nickel center. The observation of only *exo* [2 + 2 + 2] cycloadducts



indicates that coordination of the carbon-carbon double bond of oxa- or azabenzonorbornadienes to the nickel center is exclusively via the exo face. Exo selectivity has been observed for palladium or nickel-catalyzed addition of aryl groups to oxa- and azabenzonorbornadienes.24 The regioselectivity of the diene moiety of [2 + 2 + 2] cycloadducts is determined at the formation of metallacycle 8 and is clearly affected by the substituent of the terminal alkynes used. Alkynes with a linear alkyl group favor the formation of 1,4-substituted metallacycle and thus 1,4-substituted cycloadducts, whereas for alkynes with a bulkier aryl or a cyclohexenyl substituent, 1,3-substituted metallacycle and cycloadducts predominate. The unfavorable formation of 1,4-substituted metallacycle for alkynes with an aryl or a cyclohexenyl substituent is likely due to steric congestion arising from these bulkier substituents with the nickel moiety.

#### Synthetic application of the [2 + 2 + 2] cycloadducts

In addition to an efficient method for constructing multiple fused rings (Scheme 4), the present [2 + 2 + 2] cycloaddition has two other synthetic applications. First, these products are convenient isobenzofuran and isoindole precursors. For example, heating **6c** and **6d** with **1a** led to the isolation of the Diels–Alder cycloadduct of isoindole **10** in 70% yield. Treatment of **6a** with cyclohex-2-en-1-one, dimethyl acetylenedicarboxylate and *N*-methoxycarbonyl-7-azabenzonorbornadiene, respectively, in toluene at 60 °C afforded the corresponding



**10**  $X = NSO_2 - p - CH_3C_6H_4$  (70 %)



be employed to synthesize aromatic compounds. The cycloaddition of **1a** and **1e** with methyl but-2-ynoate in the presence of the nickel catalyst demonstrates both applications. The reaction of **1a** with methyl but-2-ynoate produced aromatic compound **3** regioselectively and the Diels–Alder cycloadducts **2a** and **2b**. Whereas, the reaction of **1e** with methyl but-2-ynoate provided **3** and exclusively **16** in 94 and 72% yields, respectively. Compounds **1a** and **1e**, which provide an acetylene moiety to each aromatic compound, serve as 'masked acetylene' in the reactions. All new products were characterized by the <sup>1</sup>H, <sup>13</sup>C NMR, and low and high resolution mass spectral data (see the Experimental section).

In most of the regioselective cotrimerization of alkynes to arenes catalyzed by cobalt complexes, a diyne was used as one component and bistrimethylsilyl acetylene as the other. This generally led to the formation of a mixture of isomers when sterically less-hindered monoalkynes were used.<sup>25</sup> The present [2 + 2 + 2] cycloaddition reactions provide a highly regioselective, and *exo* selective new alternative method for the construction of arenes by employing masked acetylenes.



# Conclusion

We have observed unusual nickel-catalyzed reactions of oxaand azabenzonorbornadiene with various alkynes to give common products **2a**, **2b**, and aromatic compounds. These results may be rationalized based on a [2 + 2 + 2] cocyclotrimerization of two alkyne and one oxabenzonorbornadiene molecules. The [2 + 2 + 2] cycloadducts undergo retro Diels– Alder reaction to give aromatic products and isobenzofuran. The latter is then trapped by oxabenzonorbornadiene to give products **2a**, **2b**. We have isolated various [2 + 2 + 2] cycloadducts at low temperatures and have demonstrated that these nickel-catalyzed [2 + 2 + 2] cycloaddition reactions are very useful in the construction of multiple rings, synthesis of precursors of isobenzofurans and isoindoles and regioselective synthesis of substituted aromatic compounds.

# Experimental

All reactions were conducted under a nitrogen atmosphere on a dual-manifold Schlenck line by using purified deoxygenated solvents and standard inert atmosphere techniques, unless otherwise stated. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> using Me<sub>4</sub>Si as internal standard. Alkyl- and aryl-substituted alkynes were used as purchased without further purification. NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>,<sup>26</sup> oxabenzonorbornadienes **1a–c** *N*-methoxycarbonyl and *N-p*-tolylsulfonyl-7-azabenz-onorbornadienes<sup>27</sup> were synthesized according to the reported procedures.

# Reaction of methyl but-2-ynoate with oxabenzonorbornadiene (1a) to give 2a, 2b and 3

To a 50 ml round-bottomed side-arm flask was added **1a** (0.144 g, 1.00 mmol), NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.0325 g, 0.0500 mmol), PPh<sub>3</sub> (0.210 g, 0.801 mmol) and zinc powder (0.180 g, 2.75 mmol). The system was evacuated and purged with nitrogen gas three times. To the system was added freshly distilled toluene (2.0 ml) and methyl but-2-ynoate (0.118 g, 1.20 mmol). The reaction mixture was stirred at room temperature for 24 h. The solution was filtered through Celite and silica gel, and the filtrate was concentrated. The residue was separated on a silica gel column using hexanes–dichloromethane as eluent to afford **2a** (0.076 g), **2b** (0.052 g) and **3** (0.245 g) in 58, 40 and 92% yields, respectively. The TLC  $R_f$  values of **2a**, **2b** and **3** are 0.62, 0.50 and 0.45, respectively, using hexane–ethyl acetate (v/v = 4/1) as the eluent. Important spectral data of these products are listed below.

 $(1R^*, 3R^*, 10S^*, 12S^*)$ -19,20-Dioxahexacyclo[10.6.1.1<sup>3,10</sup>.-0<sup>2,11</sup>.0<sup>4.9</sup>.0<sup>13,18</sup>]icosa-4,6,8,13,15,17-hexaene 2a. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.27 (m, 4 H, benzo), 7.08 (m, 4 H, benzo), 5.32 (dd, J = 3.4 Hz, J = 1.8 Hz, 2 H, bridgehead), 4.69 (s, 2 H, bridgehead), 2.80 (dd, J = 3.4 Hz, J = 1.8 Hz, 2 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  146.97 (s), 143.64 (s), 127.03 (d), 126.42 (d), 119.93 (d), 119.35 (d), 80.21 (d, O-C, bridgehead), 51.00 (d), 50.10 (d); MS: [m/z, (%)] 262 (M<sup>+</sup>, 59.0), 233 (91.1), 215 (91.0), 118 [(C<sub>8</sub>H<sub>6</sub>O)<sup>+</sup>, 100]; HRMS: calcd for C<sub>18</sub>H<sub>14</sub>O<sub>2</sub> 262.0995, found 262.0970.

(1*R*\*,3*S*\*,10*R*\*,12*S*\*)-19,20-Dioxahexacyclo[10.6.1.1<sup>3,10</sup>.-0<sup>2,11</sup>.0<sup>4.9</sup>.0<sup>13,18</sup>]icosa-4,6,8,13,15,17-hexaene 2b. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.21 (dd, *J* = 5.2 Hz, *J* = 3.0 Hz, 4 H, benzo), 7.67 (dd, *J* = 5.3 Hz, *J* = 3.0 Hz, 4 H, benzo), 5.46 (s, 4 H, bridgehead), 2.06 (s, 2 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 146.48 (s), 126.57 (d), 119.08 (d), 81.31 (d, O-C, bridgehead), 51.22 (d); MS: [*m*/*z*, (%)] 262 (M<sup>+</sup>, 7.2), 233 (5.5), 215 (29.0), 202 (22.7), 189 (8.2), 165 (6.9), 118 [(C<sub>8</sub>H<sub>6</sub>O)<sup>+</sup>, 100]; HRMS: calcd for C<sub>18</sub>H<sub>14</sub>O<sub>2</sub> 262.0995, found 262.000.

**Dimethyl 2,4-dimethylisophthaloate 3.** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.78 (d, J = 8.0 Hz, 1 H, aromatic H), 7.06 (d, J = 8.0 Hz, 1 H, aromatic H), 3.90 (s, 3 H, COOCH<sub>3</sub>), 3.85 (s, 3 H, COOCH<sub>3</sub>), 2.47 (s, 3 H, CH<sub>3</sub>), 2.28 (s, 3 H, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  171.56 (C=O), 170.11 (C=O), 167.63 (s), 138.72 (s), 136.31 (d), 136.22 (d), 128.04 (s), 127.34 (d), 52.11 (q), 51.88 (q) 19.71 (q), 17.98 (q); MS: [m/z, (%)] 222 (M<sup>+</sup>, 47.2), 207 [(M - CH<sub>3</sub>)<sup>+</sup>, 79.7], 191 [(M - OCH<sub>3</sub>)<sup>+</sup>, 100], 162 [(M - COOCH<sub>3</sub>)<sup>+</sup>, 45.5]; HRMS: calcd for C<sub>12</sub>H<sub>14</sub>O<sub>4</sub> 222.0893, found 222.0897.

The reaction of 1a and various alkynes in the presence of NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, PPh<sub>3</sub> and zinc powder also led to the formation

of **2a** and **2b**. The reaction conditions and the yields are listed in Table 1.

A similar procedure was employed for the reaction of **1e** with methyl but-2-ynoate to give **3** and **16** in 94 and 72% yields, respectively. The spectral data of compound **16** follow.

# (1*R*\*,3*R*\*,10*S*\*,12*S*\*)-5,8,14,17-Tetramethyl-19,20-dioxa-

hexacyclo[10.6.1.1<sup>3,10</sup>.0<sup>2,11</sup>.0<sup>49</sup>.0<sup>13,18</sup>]icosa-4,6,8,13,15,17-hexaene 16. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  6.91 (s, 2 H, benzo), 6.77 (s, 2 H, benzo), 5.40 (dd, J = 2.97 Hz, J = 1.8 Hz, 2 H, bridgehead), 4.67 (s, 2 H, bridgehead), 2.76 (dd, J = 3.01 Hz, J = 1.7 Hz, 2 H), 2.39 (s, 6 H, 2 × CH<sub>3</sub>), 2.23 (s, 6 H, 2 × CH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  144.99 (s), 141.89 (s), 128.28 (d), 127.77 (d), 126.29 (s), 125.81 (s), 78.98 (d, O–C, bridgehead), 76.04 (d, O–C, bridgehead), 49.61 (d), 18.20 (q), 17.95 (q); MS (FAB): [m/z, (%)] 319 (M + 1, 10.1), 173 (C<sub>12</sub>H<sub>13</sub>O, 88.3), 146 (C<sub>10</sub>H<sub>10</sub>O, 100); HRMS (M + 1): calcd for C<sub>22</sub>H<sub>23</sub>O<sub>2</sub> 319.1698, found 319.1674.

General procedure for the isolation of [2 + 2 + 2] cocyclotrimerization products. To a 50 ml round-bottomed side-arm flask was added an oxa- or azabenzonorbornadiene (1.00 mmol), NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.0325 g, 0.0500 mmol), PPh<sub>3</sub> (0.210 g, 0.801 mmol) and zinc powder (0.180 g, 2.75 mmol). The system was evacuated and purged with nitrogen gas three times. To the system was added freshly distilled toluene (2.0 ml) and an alkyne (mono alkyne, 2.0 mmol; bisalkyne, 1.0 mmol). The reaction mixture was stirred for 24 h at a specified temperature as shown in Table 2. The solution was filtered through Celite and silica gel, and the filtrate was concentrated. The residue was separated on a silica gel column using hexanes-dichloromethane as eluent to afford the [2 + 2 + 2] products. Compounds **5a**-**d** were thus prepared following the above procedure. The corresponding minor isomers 4a-d cannot be separated from 5a-d completely. Due to thermal instability, no purifications on silica gel column were carried out for 4e, 4i-j. The residues from concentration of the filtrates were used directly for spectral analysis. For compounds 6a-d, the reaction temperature was 18 °C and the reaction time was 48 h. Selected spectral data are listed below:

# (1*R*\*,8*S*\*,9*R*\*,14*S*\*)-10,13-Dipropyl-15-oxatetracyclo-

**[6.6.1.0<sup>2,7</sup>.0<sup>9,14</sup>]pentadeca-2,4,6,10,12-pentaene 5a.** Yield 69%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.24 (m, 2 H, benzo), 7.14 (m, 2 H, benzo), 5.47 (br s, 2 H, cyclohexadiene), 5.17 (s, 2 H, O–CH, bridgehead), 2.62 (br s, 2 H, =CH, *endo* cyclohexadiene), 2.08 (t, J = 8.0 Hz, 4 H, CH<sub>2</sub>, propyl), 1.46 (m, 4 H, CH<sub>2</sub>, propyl), 0.96 (t, J = 9.0 Hz, 6 H, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 146.12 (s), 135.64 (s), 126.53 (d), 121.28 (d), 118.88 (d), 86.80 (d, O–C, bridgehead), 41.08 (d), 34.45 (t), 22.26 (t), 13.85 (q); MS: [*m*/*z*, (%)] 280 (M<sup>+</sup>, 0.5), 237 [(M – C<sub>3</sub>H<sub>7</sub>)<sup>+</sup>, 3.5], 162 [(M – C<sub>8</sub>H<sub>6</sub>O)<sup>+</sup>, 17.5], 133 (54.4), 118 (C<sub>8</sub>H<sub>6</sub>O<sup>+</sup>, 100); HRMS: calcd for C<sub>20</sub>H<sub>24</sub>O 280.1828, found 280.1802.

# (1R\*,8S\*,9R\*,14S\*)-10,13-Dibutyl-15-oxatetracyclo-

**[6.6.1.0<sup>27</sup>.0**<sup>9,14</sup>**]pentadeca-2,4,6,10,12-pentaene 5b.** Yield 62%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.24 (m, 2 H, benzo), 7.16 (m, 2 H, benzo), 5.47 (br s, 2 H, cyclohexadiene), 5.16 (s, 2 H, O–CH, bridgehead), 2.62 (br s, 2 H, =CH, *endo* cyclohexadiene), 2.11 (t, *J* = 8.0 Hz, 4 H, CH<sub>2</sub>, butyl), 1.39 (m, 8 H, CH<sub>2</sub>, butyl), 0.93 (t, *J* = 9.0 Hz, 6 H, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  146.09 (s), 135.90 (s), 126.53 (d), 121.10 (d), 118.90 (d), 86.79 (d, O–C, bridgehead), 41.05 (d), 31.99 (t), 31.49 (t), 22.60 (t), 14.06 (q); MS: [*m*/*z*, (%)] 308 (M<sup>+</sup>, 0.6), 190 [(M − C<sub>8</sub>H<sub>6</sub>O)<sup>+</sup>, 29.5], 147 (16.8), 118 (C<sub>8</sub>H<sub>6</sub>O<sup>+</sup>, 100), 105 (68.4); HRMS: calcd for C<sub>22</sub>H<sub>28</sub>O 308.2142, found 308.2143.

# (1R\*,8S\*,9R\*,14S\*)-10,13-Dipentyl-15-oxatetracyclo-

**[6.6.1.0<sup>2,7</sup>.0<sup>9,14</sup>]pentadeca-2,4,6,10,12-pentaene 5c.** Yield 61%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.25 (m, 2 H, benzo), 7.16 (m, 2 H,

benzo), 5.46 (br s, 2 H, cyclohexadiene), 5.16 (s, 2 H, O–CH, bridgehead), 2.61 (br s, 2 H, =CH, *endo* cyclohexadiene), 2.11 (t, J = 8.0 Hz, 4 H, CH<sub>2</sub>, pentyl), 1.35 (m, 12 H, CH<sub>2</sub>), 0.9 (t, 6 H, J = 9.0 Hz, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  146.00 (s), 135.97 (s), 125.55 (d), 121.08 (d), 118.92 (d), 86.80 (d, O–C, bridgehead), 41.05 (d), 32.29 (t), 31.89 (t), 29.00 (t), 22.61 (t), 14.11 (q); MS: [m/z, (%)] 336 (M<sup>+</sup>, 0.8), 279 [(M – C<sub>4</sub>H<sub>8</sub>)<sup>+</sup>, 16.0], 218 [(M – C<sub>8</sub>H<sub>6</sub>O)<sup>+</sup>, 27], 118 (C<sub>8</sub>H<sub>6</sub>O<sup>+</sup>, 100); HRMS: calcd for C<sub>24</sub>H<sub>32</sub>O 336.2455, found 336.2451.

# (1*R*\*,8*S*\*,9*R*\*,14*S*\*)-10,13-Dipropyl-15-[(4-methylphenyl)sulfonyl]-15-azatetracyclo[6.6.1.0<sup>2,7</sup>.0<sup>9,14</sup>]pentadeca-2,4,6,10,12pentaene 5d. Yield 64%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): $\delta$ 7.39 (d,

J = 6.0 Hz, 2 H, tosyl), 6.97–6.90 (m, 6 H, benzo tosyl), 5.38 (br s, 2 H, cyclohexadiene), 4.79 (s, 2 H, N–CH, bridgehead), 2.55 (br s, 2 H, =CH, *endo* cyclohexadiene), 2.26 (s, 3 H, CH<sub>3</sub>), 2.05 (m, 4 H, CH<sub>2</sub>, propyl), 1.43 (m, 4 H, CH<sub>2</sub>, propyl), 0.94 (t, J = 9.0 Hz, 6 H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  144.13 (s), 143.79 (s), 136.42 (s), 135.96 (s), 128.71 (d), 127.74 (d), 126.46 (d), 122.82 (d), 119.94 (d), 71.39 (d, N–C, bridgehead), 43.19 (d), 34.51 (t), 22.47 (t), 21.28 (q), 13.88 (q); MS (FAB): [*m*/*z*, (%)] 334 (M + 1, 3.6), 271 (C<sub>15</sub>H<sub>13</sub>NSO<sub>2</sub><sup>+</sup>, 100), 231 (24.8), 91 (46.1); HRMS (M+1): calcd for C<sub>27</sub>H<sub>32</sub>NSO<sub>2</sub> 434.2154, found 434.2155.

### (1*R*\*,8*S*\*,9*R*\*,14*S*\*)-10,12-Diphenyl-15-oxatetracyclo-[6.6.1.0<sup>2,7</sup>.0<sup>9,14</sup>]pentadeca-2,4,6,10,12-pentaene 4e. Yield 95%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.40 (m, 10 H, phenyl), 7.25 (m, 4 H, benzo), 6.70 (br s, 1 H, cyclohexadiene), 6.05 (d, *J* = 3.6 Hz, 1 H, cyclohexadiene), 5.41 (s, 1 H, O–CH, bridgehead), 5.22 (s, 1 H, O–CH, bridgehead), 3.36 (d, *J* = 11 Hz, 1 H, *endo* cyclohexadiene), 3.10 (dd, *J* = 11 Hz, *J* = 3.6 Hz, 1 H, =CH, *endo* cyclohexadiene); <sup>13</sup>C {<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>): δ 146.10 (s), 145.20 (s), 140.80 (s), 135.52 (s), 132.50 (s), 132.48 (s), 129.10 (d), 128.71 (d), 128.25 (d), 128.24 (d), 127.51 (d), 127.48 (d), 127.00 (d), 126.10 (d), 125.90 (d), 125.20 (d), 122.26 (d), 122.10 (d), 118.75 (d), 118.31 (d), 86.62 (d, O–C, bridgehead), 85.52 (d, O–C, bridgehead), 42.60 (d), 42.25 (d); MS: *[m/z*, (%)] 262 [(M – C<sub>18</sub>H<sub>14</sub>)<sup>+</sup>, 57.9], 230 [(M – C<sub>8</sub>H<sub>6</sub>O)<sup>+</sup>, 100], 183 (28.2), 152 (20.9), 118 (C<sub>8</sub>H<sub>6</sub>O<sup>+</sup>, 53.2).

(1R\*,8S\*,9R\*,14S\*)-10,12-Diphenyl-15-[(4-methylphenyl)sulfonyl]-15-azatetracyclo[6.6.10<sup>2,7</sup>.0<sup>9,14</sup>]pentadeca-2,4,6,10,12pentaene 4f. Yield 93%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ 7.57-7.31 (m, 12 H, phenyl tosyl), 7.15-6.93 (m, 4 H, benzo), 6.92 (d, J = 8.14 Hz, 2 H, tosyl), 6.57 (s, 1 H, cyclohexadiene), 5.94 (d, J = 4.21 Hz, 1 H, cyclohexadiene), 5.04 (s, 1 H, N-CH,bridgehead), 4.87 (s, 1 H, N-CH, bridgehead), 3.24 (d, J = 11.31 Hz, 1 H, endo cyclohexadiene), 3.02 (dd, J = 11.35 Hz, J = 4.25 Hz, 1 H, =CH, endo cyclohexadiene), 2.26 (s, 3 H, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 144.67 (s), 143.88 (s), 142.75 (s), 140.66 (s), 140.15 (s), 136.35 (s), 136.01 (s), 135.96 (s), 129.15 (d), 128.85 (d), 128.80 (d), 128.76 (d), 128.49 (d), 128.41 (d), 127.79 (d), 127.73 (d), 127.39 (d), 127.22 (d), 126.90 (d), 126.08 (d), 125.87 (d), 125.66 (d), 123.61 (d), 121.32 (d), 120.43 (d), 120.21 (d), 119.60 (d), 71.46 (d, N-C, bridgehead), 69.40 (d, N-C, bridgehead), 43.81 (d), 43.64 (d), 21.33 (q); MS (FAB): [m/z, (%)] 502  $[(M + 1)^+, 4.8]$ , 271  $(C_{15}H_{13}NSO_2^+, 100)$ , 231 (32.9), 91  $(C_7H_7^+, 45.4)$ ; HRMS (M + 1): calcd for  $C_{33}H_{28}$ NSO<sub>2</sub> 502.1841, found 502.1815.

 $(1R^*,8S^*,9R^*,14S^*)$ -10,12-Di(cyclohex-1-enyl)-15-oxatetracyclo[6.6.1.0<sup>2,7</sup>.0<sup>9,14</sup>]pentadeca-2,4,6,10,12-pentaene 4g. Yield 95%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.32 (m, 2 H, benzo), 7.18 (m, 2 H, benzo), 6.30 (br s, 1 H, cyclohexadiene), 6.01 (br t, J = 3.9 Hz, 1 H, cyclohexenyl), 5.92 (br t, J = 3.9 Hz, 1 H, cyclohexenyl), 5.74 (d, J = 2.8 Hz, 1 H, cyclohexadiene), 5.33 (s, 1 H, O–CH, bridgehead), 5.28 (s, 1 H, O–CH, bridgehead), 2.89 (s, 1 H, endo cyclohexadiene), 2.88 (d, J = 2.8 Hz, 1 H, =CH, endo cyclohexadiene), 2.25 (m, 8 H, –CH<sub>2</sub>–, cyclohexenyl), 1.66

# $(1R^*, 8S^*, 9R^*, 14S^*)$ -10,12-Di(cyclohex-1-enyl)-15-[(4-meth-ylphenyl)sulfonyl]-15-azatetracyclo[6.6.1.0<sup>2,7</sup>.0<sup>9,14</sup>]pentadeca-

**2,4,6,10,12-pentaene 4h.** Yield 90%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.42 (d, J = 8.1 Hz, 2 H, tosyl), 7.11–6.85 (m, 6 H, benzo tosyl), 6.24 (s, 1 H, cyclohexadiene), 5.99 (br s, 1 H, cyclohexenyl), 5.81 (br s, 1 H, cyclohexenyl), 5.58 (br s, 1 H, cyclohexenyl), 4.84 (s, 1 H, N–CH, bridgehead), 4.76 (s, 1 H, N–CH, bridgehead), 2.82 (br s, 2 H, =CH, *endo* cyclohexadiene), 2.28 (s, 3 H, CH<sub>3</sub>), 2.23 (m, 8 H, –CH<sub>2</sub>–, cyclohexenyl), 1.66 (m, 8 H, CH<sub>2</sub>, cyclohexenyl); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  145.20 (s), 138.18 (s), 136.92 (s), 135.98 (s), 135.55 (s), 134.45 (s), 128.77 (d), 127.91 (d), 126.72 (d), 124.22 (d), 123.08 (d), 120.31 (d), 119.14 (d), 118.36 (d), 117.51 (d), 71.55 (d, N–C, bridgehead), 70.26 (d, N–C, bridgehead), 43.17 (d), 41.87 (d), 26.32 (t), 26.21 (t), 25.81 (t), 22.93 (t), 22.88 (t), 22.30 (t), 22.27 (t), 21.38 (q); MS (FAB): [*m*/*z*, (%)] 509 (M<sup>+</sup>, 2.1), 271 (C<sub>15</sub>H<sub>13</sub>NSO<sub>2</sub><sup>+</sup>, 91.6), 91 (C<sub>7</sub>H<sub>7</sub>)<sup>+</sup>; HRMS (FAB): calcd for C<sub>33</sub>H<sub>35</sub>NSO<sub>2</sub> 509.2388, found 509.2398.

# $(15^*, 8R^*, 9S^*, 14R^*)$ -10,12-Diphenyl-3-methoxy-15-oxatetracyclo[6.6.1.0<sup>2,7</sup>.0<sup>9,14</sup>]pentadeca-2,4,6,10,12-pentaene 4i and $(15^*, 8R^*, 9S^*, 14R^*)$ -10,12-diphenyl-6-methoxy-15-oxatetra-

cyclo[6.6.1.0<sup>2,7</sup>.0<sup>9,14</sup>]pentadeca-2,4,6,10,12-pentaene 4i'. Combined yield 72%. The following two sets of spectral data are for compounds 4i and 4i'. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.50–6.80 (m, 13 H, phenyl, benzo), 6.70 (s, 1 H, cyclohexadiene), 6.02 (d, J = 4.5 Hz, 1 H, cyclohexadiene), 5.60 (s, 1 H, O–CH, bridgehead), 5.24 (s, 1 H, O–CH, bridgehead), 3.86 (s, 3 H, OCH<sub>3</sub>), 3.31 (d, J = 11.5 Hz, 1 H, endo cyclohexadiene), 3.11 (dd, J = 11.5 Hz, J = 4.5 Hz, 1 H, =CH, endo cyclohexadiene); MS (FAB): [m/z, (%)] 337 [(M + 1)<sup>+</sup>, 15.0], 361 [(M - O)<sup>+</sup>, 16.8], 307 (13.63).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.50–6.80 (m, 13 H, phenyl, benzo), 6.75 (s, 1 H, cyclohexadiene), 6.10 (d, J = 4.5 Hz, 1 H, cyclohexadiene), 5.52 (s, 1 H, O–CH, bridgehead), 5.38 (s, 1 H, O–CH, bridgehead), 3.86 (s, 3 H, OCH<sub>3</sub>), 3.31 (d, J = 11.5 Hz, 1 H, *endo* cyclohexadiene), 3.04 (dd, J = 11.5 Hz, 1 H, =CH, *endo* cyclohexadiene); MS (FAB): [*m*/*z*, (%)] 337 [(M + 1)<sup>+</sup>, 15.0], 361 [(M – O)<sup>+</sup>, 16.8], 307 (13.63).

#### (1S\*,8R\*,9S\*,14R\*)-3,6-Dimethoxy-10,12-diphenyl-15-oxatetracyclo[6.6.1.0<sup>2,7</sup>.0<sup>9,14</sup>]pentadeca-2,4,6,10,12-pentaene 4i. Yield 74%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.40 (m, 10 H, phenyl), 6.79 (s, 1 H, cyclohexadiene), 6.71 (br s, 2 H, dimethoxybenzo), 6.09 (d, J = 4.4 Hz, 1 H, cyclohexadiene), 5.58 (s, 1 H, O-CH, bridgehead), 5.50 (s, 1 H, O-CH, bridgehead), 3.83 (s, 3 H, OCH<sub>3</sub>), 3.80 (s, 3 H, OCH<sub>3</sub>), 3.32 (d, J = 11.6 Hz, 1 H, endo cyclohexadiene), 3.11 (dd, J = 11.6 Hz, J = 4.4 Hz, 1 H, =CH, endo cyclohexadiene); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): $\delta$ 146.69 (s), 146.46 (s), 141.72 (s), 141.11 (s), 139.42 (s), 135.67 (s), 135.47 (s), 134.98 (s), 128.74 (d), 128.52 (d), 128.35 (d), 127.34 (d), 127.19 (d), 126.05 (d), 125.82 (d), 125.49 (d), 122.52 (d), 121.89 (d), 85.15 (d, O-C, bridgehead), 84.08 (d, O-C, bridgehead), 56.16 (q, OCH<sub>3</sub>), 56.01 (q, OCH<sub>3</sub>), 42.84 (d), 41.96 (d); MS: [m/z, (%)] 408 (M<sup>+</sup>, 0.1), 230 [(M - C<sub>18</sub>H<sub>14</sub>)<sup>+</sup>, 100], 178 $[(C_{10}H_{10}O_3)^+, 1.16];$ HRMS: calcd for $C_{28}H_{24}O_3$ 408.1725, found 408.1717.

(1*S*\*,2*R*\*,10*S*\*,11*R*\*)-18-Oxapentacyclo[9.6.1.0<sup>2,10</sup>.0<sup>4,8</sup>.0<sup>12,17</sup>]octadeca-3,8,12,14,16-pentaene 6a. Yield 62%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.26 (m, 2 H, benzo), 7.15 (m, 2 H, benzo), 5.52 (br s, 2 H, =CH, cyclohexadiene), 5.16 (s, 2 H, O–CH, bridgehead), 2.69 (br s, 2 H, *endo* cyclohexadiene), 2.34 (m, 4 H, 2 × CH<sub>2</sub>), 1.77 (m, 1 H), 1.62 (m, 1 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  146.22 (s), 139.65 (s), 126.54 (d), 118.89 (d), 115.37 (d), 86.62 (d, O–C, bridgehead), 42.03 (d), 31.38 (t), 24.48 (t); MS (FAB): [*m*/*z*, (%)] 236 (M<sup>+</sup>, 5.1), 154 (16.6), 136 (15.1), 118 [(C<sub>8</sub>H<sub>6</sub>O)<sup>+</sup>, (C<sub>9</sub>H<sub>10</sub>)<sup>+</sup>, 100]; HRMS: calcd for C<sub>17</sub>H<sub>16</sub>O 236.1201, found 236.1198.

### (1S\*,2R\*,11S\*,12R\*)-19-Oxapentacyclo[10.6.1.0<sup>2,11</sup>.0<sup>4,9</sup>.-

**0**<sup>13,18</sup>**]nonadeca-3,9,13,15,17-pentaene 6b.** Yield 70%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.22 (m, 2 H, benzo), 7.13 (m, 2 H, benzo), 5.39 (br s, 2 H, =CH, cyclohexadiene), 5.15 (s, 2 H, O-CH, bridgehead), 2.62 (br s, 2 H, *endo* cyclohexadiene), 2.26 (m, 4 H, 2 × CH<sub>2</sub>), 1.57 (m, 4 H, 2 × CH<sub>2</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  146.09 (s), 133.59 (s), 126.54 (d), 119.95 (d), 118.89 (d), 86.63 (d, O-C, bridgehead), 41.28 (d), 29.83 (t), 23.13 (t); MS (FAB): [*m*/*z*, (%)] 250 (M<sup>+</sup>, 9.4), 233 (22.3), 132 [(M - C<sub>8</sub>H<sub>6</sub>O)<sup>+</sup>, 8.2], 118 [(C<sub>8</sub>H<sub>6</sub>O)<sup>+</sup>, 100]; HRMS: calcd for C<sub>18</sub>H<sub>18</sub>O 250.1357, found 250.1363.

#### (1*S*\*,2*R*\*,10*S*\*,11*R*\*)-18-[(4-Methylphenyl)sulfonyl]-18azapentacyclo[9.6.1.0<sup>2,10</sup>.0<sup>4,8</sup>.0<sup>12,17</sup>]octadeca-3,8,12,14,16-

**pentaene 6c.** Yield 71%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.40 (d, J = 8.23 Hz, 2 H, tosyl H), 6.99–6.91 (m, 6 H, aromatic), 5.43 (br s, 2 H, =CH, cyclohexadiene), 4.78 (s, 2 H, N–CH, bridgehead), 2.61 (br s, 2 H, *endo* cyclohexadiene H), 2.31 (m, 4 H, 2 × CH<sub>2</sub>), 2.27 (s, 3 H, CH<sub>3</sub>), 1.76 (m, 1 H), 1.64 (m, 1 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  144.39 (s), 142.64 (s), 140.43 (s), 136.05 (s), 128.75 (d), 127.82 (d), 126.56 (d), 119.86 (d), 114.59 (d), 70.90 (d, N–C, bridgehead), 42.87 (d), 31.41 (t), 24.54 (t), 21.36 (q); MS (FAB): [*m*/*z*, (%)] 390 (M + 1, 6.7), 271 (C<sub>15</sub>H<sub>13</sub>NSO<sub>2</sub><sup>+</sup>, 100), 155 (25.4), 91 (45.4); HRMS (M+1): calcd for C<sub>24</sub>H<sub>24</sub>NSO<sub>2</sub> 390.1528, found 390.1518.

(1*S*\*,2*R*\*,11*S*\*,12*R*\*)-19-[(4-Methylphenyl)sulfonyl]-19-azapentacyclo[10.6.1.0<sup>2,11</sup>.0<sup>4,9</sup>.0<sup>13,18</sup>]nonadeca-3,9,13,15,17-pentaene 6d. Yield 75%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.43 (d, *J* = 8.27 Hz, 2 H, tosyl H), 7.01–6.92 (m, 6 H, aromatic), 5.32 (br s, 2 H, =CH, cyclohexadiene), 4.79 (s, 2 H, N–CH, bridgehead), 2.57 (br s, 2 H, *endo* cyclohexadiene H), 2.28 (s, 3 H, CH<sub>3</sub>), 2.25 (m, 4 H, 2 × CH<sub>2</sub>), 1.59 (m, 4 H, 2 × CH<sub>2</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  144.62 (s), 142.65 (s), 135.61 (s), 134.38 (s), 128.76 (d), 127.76 (d), 126.54 (d), 119.83 (d), 119.06 (d), 70.88 (d, N–C, bridgehead), 42.08 (d), 29.77 (t), 23.03 (t), 21.34 (q); MS (FAB): [*m*/*z*, %)] 404 (M + 1, 3.3), 271 (C<sub>15</sub>H<sub>13</sub>NSO<sub>2</sub><sup>+</sup>, 100), 155 (23.5), 91 (47.7); HRMS (M+1): calcd for C<sub>25</sub>H<sub>26</sub>NSO<sub>2</sub> 404.1684, found 404.1675.

Diels–Alder cycloaddition of *in situ* generated isobenzofuran or isoindole with 1a. To a 50 ml round-bottomed side-arm flask consisting of 6c (or 6d) (0.0720 mmol) and 1a (0.0104 g, 0.0720 mmol) was added freshly distilled xylene (5.0 ml). The system was evacuated and purged with nitrogen gas three times. The reaction mixture was then heated at 90 °C for 7.5 h. The solvent was removed under vacuum and the resulting solid was purified by silica gel column using a mixture of hexanes–ethyl acetate (v/v = 7/3) as eluent to give 10 in 70% yield.

(1*S*\*,3*S*\*,10*R*\*,12*R*\*)-20-[(4-Methylphenyl)sulfonyl]-19-oxa-20-azahexacyclo[10.6.1.1<sup>3,10</sup>.0<sup>2,11</sup>.0<sup>4,9</sup>.0<sup>13,18</sup>]icosa-4,6,8,13,15,17hexaene 10. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.34 (d, *J* = 7.6 Hz, 2 H, tosyl H), 7.12 (m, 4 H, benzo), 7.07 (m, 4 H, benzo), 6.94 (d, *J* = 6.4 Hz, 2 H, tosyl H), 5.07 (br s, 2 H, O–CH, bridgehead), 4.66 (s, 2 H, N–CH, bridgehead), 2.95 (br s, 2 H), 2.27 (s, 3 H, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  146.13 (s), 142.84 (s), 141.24 (s), 136.26 (s), 129.85 (d), 128.92 (d), 127.82 (d), 127.35 (d), 126.87 (d), 126.67 (d), 120.43 (d), 118.94 (d), 77.69 (d, C–O, bridgehead), 65.42 (d, N-C, bridgehead), 49.26 (d), 21.33 (q); MS (FAB): [m/z, (%)] 416  $[(M + 1)^+, 28.8]$ , 272 (85.9), 271 (100), 245 (72.5), 91(75.2); HRMS (M + 1): calcd for C25H22NSO3 416.1320, found 416.1352.

Similarly, 11 and 12, 13 and 14 and 15 were prepared by reacting 6a with cyclohex-2-en-1-one, dimethyl acetylenedicarboxylate and N-methoxycarbonyl-7-azabenzonorborndiene at 60 °C in toluene for 3 h. The combined yields of these products is 77, 60 and 68%. Selected spectral data of these products follow.

# (1S\*,2S\*,7R\*,8R\*)-15-Oxatetracyclo[6.6.1.0<sup>2,7</sup>.0<sup>9,14</sup>]-

pentadeca-9,11,13-trien-3-one 11. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.29 (m, 2 H, benzo), 7.17 (m, 2 H, benzo), 5.75 (s, 1 H, O-CH, bridgehead), 5.12 (br s, 1 H, O-CH, bridgehead), 2.44-2.27 (m, 4 H, CH & CH<sub>2</sub>), 2.19 (m, 1 H), 2.00 (m, 1 H), 1.72 (m, 1 H), 1.56 (m, 1 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 189.53 (C=O, s), 145.33 (s), 144.43 (s), 126.86 (d), 126.77 (d), 119.27 (d), 118.99 (d), 84.27 (d, C-O, bridgehead), 81.91 (d, C-O, bridgehead), 51.97 (d), 42.38 (d), 38.98 (t), 27.92 (t), 20.59 (t).

#### (1S\*,2R\*,7S\*,8R\*)-15-Oxatetracyclo[6.6.1.0<sup>2,7</sup>.0<sup>9,14</sup>]penta-

deca-9,11,13-trien-3-one 12. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.26–7.15 (m, 4 H, benzo), 5.59 (d, J = 5.5 Hz, 1 H, O–CH, bridgehead), 5.33 (d, 1 H, J = 4.9 Hz, O-CH, bridgehead), 3.15 (m, 1 H, CH), 2.99 (m, 1 H, CH), 2.06 (m, 1 H, CH), 2.00 (m, 1 H), 1.49–1.29 (m, 2 H, CH<sub>2</sub>), 0.91 (m, 1 H), 0.67 (m, 1 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 189.5 (C=O, s), 143.75 (s), 143.19 (s), 127.05 (d), 126.68 (d), 121.81 (d), 120.98 (d), 83.24 (d, C-O, bridgehead), 80.77 (d, C-O, bridgehead), 50.69 (d), 39.92 (t), 38.49 (d), 24.38 (t), 20.24 (t).

11-oxatricyclo[6.2.1.0<sup>2,7</sup>]undeca-2,4,6,9-tetraene-Dimethyl **9,10-dicarboxylate 13.** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.43 (m, 2 H, benzo), 7.07 (m, 2 H, benzo), 5.97 (s, 2 H, O-CH, bridgehead), 3.81 (s, 6 H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  162.78 (C=O, s), 151.19 (s), 146.12 (s), 126.12 (d), 121.48 (d), 84.79 (d, C-O, bridgehead), 52.38 (d).

Methyl (1S\*,2S\*,3S\*,10R\*,11R\*,12R\*)-19-oxa-20-azahexacyclo[10.6.1.1<sup>3,10</sup>.0<sup>2,11</sup>.0<sup>4,9</sup>.0<sup>13,18</sup>]icosa-4,6,8,13,15,17-hexaene-20carboxylate 14. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.20 (m, 4 H, benzo), 7.04 (m, 4 H, benzo), 5.38 (dd, J = 3.5 Hz, J = 1.9 Hz, 2 H, O-CH, bridgehead), 4.67 (s, 2 H, N-CH, bridgehead), 3.68  $(s, 3 H, OCH_3), 2.69 (dd, J = 3.4 Hz, J = 1.9 Hz, 2 H); {}^{13}C NMR$ (75 MHz, CDCl<sub>3</sub>): δ 154.68 (C=O, s), 147.27 (s), 145.72 (s), 127.40 (d), 126.63 (d), 119.65 (d), 119.32 (d), 81.09 (d, C-O, bridgehead), 62.58 (d, C-N, bridgehead), 52.12 (d), 51.82 (q); MS (FAB): [m/z, (%)] 319 (M<sup>+</sup>, 8.3), 320 (M + 1, 68.3), 245 (41.8), 175 (100), 118 (C<sub>8</sub>H<sub>6</sub>O, 40.8); HRMS (M + 1): calcd for C<sub>20</sub>H<sub>18</sub>NO<sub>3</sub> 320.1286, found 320.1273.

Methyl (1R\*,2S\*,3S\*,10R\*,11R\*,12S\*)-19-oxa-20-azahexacyclo[10.6.1.1<sup>3,10</sup>.0<sup>2,11</sup>.0<sup>4,9</sup>.0<sup>13,18</sup>]icosa-4,6,8,13,15,17-hexaene-20carboxylate 15. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.23 (m, 4 H, benzo), 7.03 (m, 4 H, benzo), 5.25 (s, 2 H, O-CH, bridgehead), 4.57 (s, 2 H, N-CH, bridgehead), 3.19 (s, 3 H, OCH<sub>3</sub>), 1.97 (s, 2 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 153.64 (C=O, s), 146.20 (s), 145.48 (s), 127.22 (d), 126.42 (d), 120.23 (d), 119.49 (d), 80.21 (d, C-O, bridgehead), 50.72 (d, C-N, bridgehead), 51.03 (q), 49.62 (d); MS (FAB): [m/z, (%)] 320 (M + 1, 68.3), 176 (96.40), 175 (100), 118 ( $C_8H_6O$ , 40.5); HRMS (M + 1): calcd for C<sub>20</sub>H<sub>18</sub>NO<sub>3</sub> 320.1286, found 320.1268.

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