CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200903454

[4+2] Cycloaddition Reactions Between 1,8-Disubstituted Cyclooctatetraenes and Diazo Dienophiles: Stereoelectronic Effects, Anticancer Properties and Application to the Synthesis of 7,8-Substituted Bicyclo[4.2.0]octa-2,4-dienes

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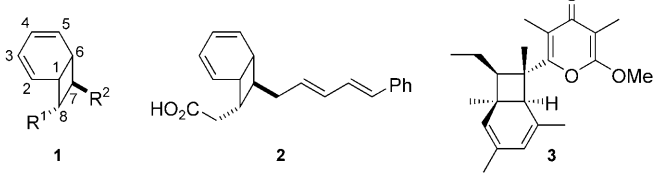
Abstract: A detailed examination of [4+2] cycloaddition reactions between 1,8-disubstituted cyclooctatetraenes and diazo compounds revealed that 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) reacts to form either 2,3- or 3,4-disubstituted adducts. The product distribution can be controlled by modulating the electron density of the cyclooctatetraene. Unprecedented [4+2] cycloadditions between diisopropyl azodicarboxylate (DIAD) and 1,8-disubstituted cyclooctatetraenes are also described and further manipulation of a resulting cycloadduct uncovered a new pathway to the synthetically challenging bicyclo-[4.2.0]octa-2,4-diene family. Variation of the substituents resulted in a range of compounds displaying selective action against different human tumour cell types.

Keywords: antitumor agents · bicyclo compounds · cycloaddition · cyclooctatetraene · diazo compounds · Diels–Alder reaction

Introduction

The 7,8-substituted bicyclo[4.2.0]octa-2,4-diene motif **1** appears in a number of natural products, most notably in the endiandric acids (e.g., endiandric acid D **2**),[1] synthesised by the Nicolaou group,[2] and the polyketide pyrone family (e.g., ocellapyrone A **3**),[3] synthesised by the Trauner,[4] Baldwin,[5] Moses[6] and Parker[7] groups. All of these groups masterfully accessed the requisite 7,8-substituted bicyclo-[4.2.0]octa-2,4-dienes **1** for their total syntheses through a biomimetically modelled 8π–6π electrocyclisation cascade from tetraenes **4**. These are typically[8] generated in situ by Lindlar reduction of enynes **5**, as demonstrated by Marvell,[9] Huisgen[10] and Nicolaou,[2,11] palladium(0)-mediated cross-coupling techniques (between **6** and **7**), as disclosed by the Trauner group,[4] and later by Parker,[7] or palladium(II)-mediated isomerisation, as reported by Baldwin[5] and Moses[6] (Scheme 1). Alternative methods to access this 7,8-substituted bicyclic system (i.e., **1**), however, are very few in number[12,13] and most give rise to symmetrical substitution patterns at these positions. Furthermore, efforts to convert derivatives, such as 7,8-dibromo-bicyclo[4.2.0]octa-2,4-diene, by using substitution reactions have generally failed,[14,15] giving little hope that other heteroatom substitution patterns (e.g., oxo)[16] will perform any better.

From a medicinal chemistry perspective, however, the 7,8-substituted bicyclo[4.2.0]octa-2,4-diene fragment **1** has the



1 **2** **3**

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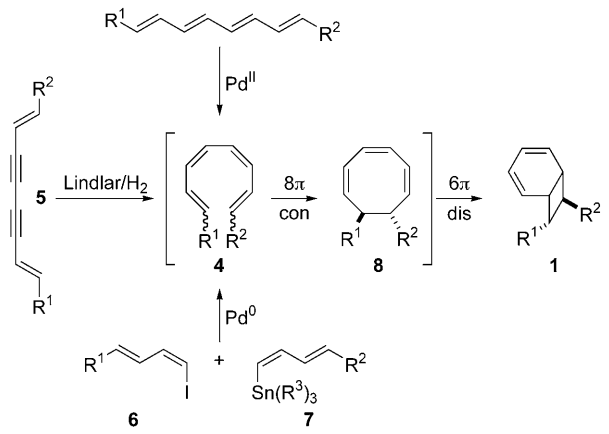
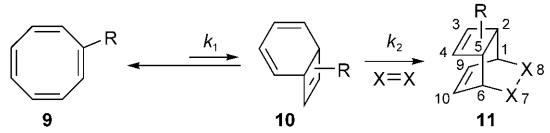
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200903454.



Scheme 1.

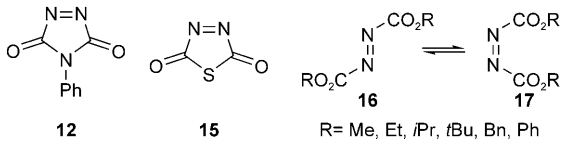
potential to act as a privileged structure, template or scaffold and, as such, is of interest for our drug discovery program. Hence, research into a new method for constructing asymmetric 7,8-substituted bicyclo[4.2.0]octa-2,4-dienes **1** was undertaken.

Since a cyclooctatriene ring (i.e., **8**) is formed in the 8π–6π electrocyclisation cascade from tetraenes **4** (Scheme 1), we wondered if a 1,8-substituted cyclooctatetraene could act as a vehicle to target bicycles **1**.[17] It is known that cyclooctatetraenes **9** react with dienophiles via their bicyclo-[4.2.0]octa-2,4,7-triene valence tautomers **10**,[18] which are present in the equilibrium in minute concentrations, to afford tetracycles **11** (Scheme 2).



Scheme 2.

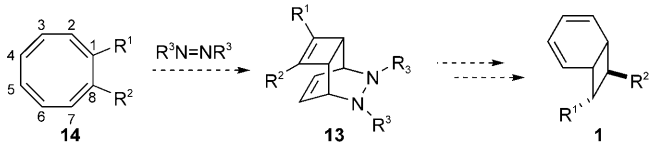
For the unsubstituted parent compound (**9**, R = H) the reaction proceeds in high yield with a range of dienophiles, including singlet oxygen,[19] maleic anhydride,[18,20,21] maleimides,[20,22] tetracyanoethylene,[23] dimethyl acetylenedicarboxylate (DMAD),[24] 4-phenyl-1,2,4-triazole-3,5-dione (PTAD, **12**),[25,26] benzoquinones,[27] benzodithiin tetraoxides[28] and 1,2-benzisothiazol-3-one 1,1-dioxides.[29] A [4+2] cycloaddition between a monosubstituted cyclooctatetraene (**9**, R ≠ H) and a symmetrical dienophile could, in principle, result in four regioisomeric products, as there are four different possible regioisomers for bicycle **10**. When R is electron donating the rate-determining step is the tautomerisation ($k_2 > k_1$) and, for all dienophiles previously investigated, 3-substituted products predominate.[30] In contrast, when R is electron withdrawing the reaction outcome depends upon the 2π component: tetracyanoethylene yields 3-substituted products,[31] whereas, the more reactive dienophile, PTAD (**12**, Scheme 3)[32] gives rise to mixtures of regioisomeric



Scheme 3.

products.[31,33] There are several reports of [4+2] cycloaddition reactions between electron-rich 1,8-disubstituted cyclooctatetraenes and tetracyanoethylene[30d,34,35] or maleic anhydride.[36] Although up to eight regioisomeric adducts are possible for these reactions, only 3,4-disubstituted products were observed in each case. Similarly, Paquette isolated solely 3,4-disubstituted adducts when PTAD (**12**) was reacted with a 1,2-bridged cyclooctatetraene[37] and 1,8-di-*tert*-butylcyclooctatetraene.[38,39]

However, cyclooctatetraenes bearing electron-withdrawing substituents remain untested, as do cases in which $R^1 \neq R^2$. Furthermore, a literature search failed to uncover any examples of [4+2] cycloadditions involving cyclooctatetraenes with other, less reactive, diazo dienophiles, such as DIAD (diisopropyl azodicarboxylate, **16**, R = *i*Pr, which must first be isomerised to **17**).[40,41] [4+2] Cycloadditions involving diazo dienophiles[42] are a powerful class of reactions, because the hydrazide adducts are readily converted into azo alkenes that subsequently undergo a cycloreversion reaction[43] which regenerates the 1,3-diene moiety.[44] In this capacity, PTAD (**12**) is often used as a protecting group for 1,3-dienes in natural product synthesis.[45] Inspired by this body of work, we postulated that reduction of a double bond in an appropriately substituted Diels–Alder adduct **13**—itself obtained from a [4+2] cycloaddition reaction between a 1,8-disubstituted cyclooctatetraene **14** and a diazo compound—followed by cycloreversion might constitute a novel route to 7,8-disubstituted bicyclo[4.2.0]octa-2,4-dienes **1** (Scheme 4).



Scheme 4.

The prospect that the adducts from [4+2] cycloaddition reactions between 1,8-disubstituted cyclooctatetraenes **14** and diazo compounds (e.g., **12**, **15**[29b,46] and **16**, Scheme 3) could find a niche synthetic application, coupled with the unanswered questions about the reaction itself, led us to undertake a comprehensive survey of the transformation. Such an investigation has the added advantage of generating an ordered array of novel nitrogen-containing compounds (i.e., **13**) for structure activity relationship studies. The results of this odyssey are reported herein, along with the conversion

of one of the major adducts to an, otherwise elusive, 7,8-disubstituted bicyclo[4.2.0]octa-2,4-diene.

Results and Discussion

A range of electron-poor and electron-rich 1,8-disubstituted cyclooctatetraenes were examined, that is, **18**,[47] **19**, **20**, **21**,[36b] **22**, **23** and **24** (Table 1). All of the substrates tested exist predominantly as the monocyclic tautomer and the equilibrium concentration of the bicyclic tautomer is less than 5%, as judged by ^{1}H NMR spectroscopy. This is in contrast to 1,8-di-*tert*-butylcylcooctatetraene, which has been investigated by Paquette, but is an atypical cyclooctatetraene, as its bicyclic tautomer predominates.[38] Since the results for the monosubstituted series depended, in part, upon the dienophile, both diisopropyl azodicarboxylate (DIAD, **16**, R = *i*Pr) and PTAD (**12**) were screened as the 2π component.

Table 1. The reaction of 1,8-disubstituted cyclooctatetraenes with diazo compounds **12** and **16**.[a]

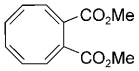
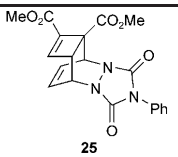
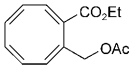
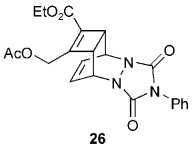
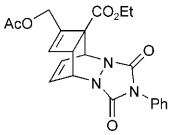
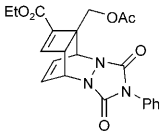
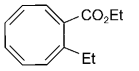
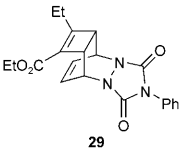
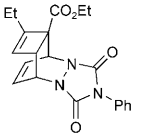
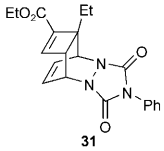
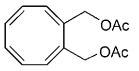
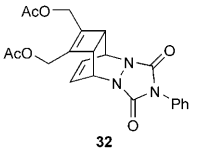
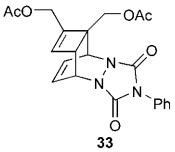
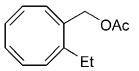
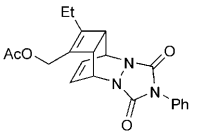
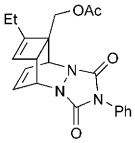
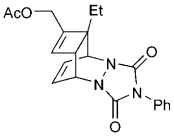
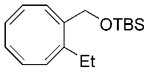
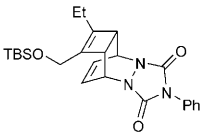
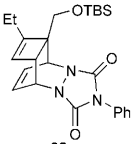
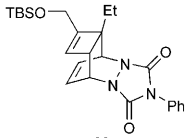
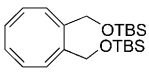
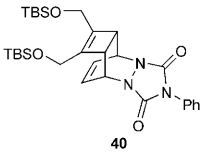
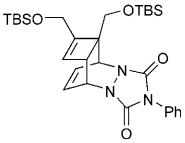
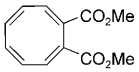
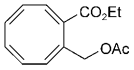
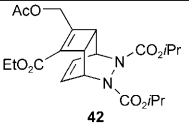
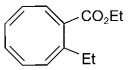
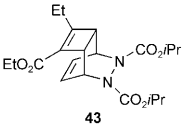
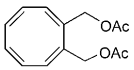
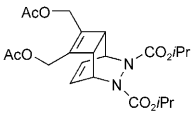
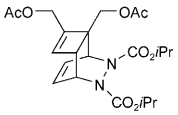
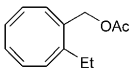
Entry	Cyclooctatetraene	Dienophile	Solvent	*t* [h]	*T* [°C]	Product(s)
1	 **18**	PTAD	EtOAc	1[b]	70	 **25** 58% (91%[c])
2	 **19**	PTAD	EtOAc	16	55	 **26** 15%;  **27** 13% (28%[d]);  **28** 3%
3	 **20**	PTAD	EtOAc	1[b]	70	 **29** 35%;  **30** 26%;  **31** 4%
4	 **21**	PTAD	EtOAc	68	55	 **32** 41%;  **33** 26%
5	 **22**	PTAD	EtOAc	2	55	 **34** 47%;  **35** 14%;  **36** 5%
6	 **23**	PTAD	EtOAc	1	55	 **37** 33%;  **38** 20%;  **39** 6%[e]
7	 **24**	PTAD	EtOAc	8	55	 **40** 10%[e];  **41** 20%[e]
8	 **18**	DIAD	EtOAc	16[f] 4[b]	35 70	No reaction No reaction

Table 1. (Continued)

Entry	Cyclooctatetraene	Dienophile	Solvent	t [h]	T [°C]	Product(s)
9	 **19**	DIAD	EtOAc	16[f]	35	 **42** 2%
10	 **20**	DIAD	cyclohexane	46[f]	35	 **43** 71%
11	 **21**	DIAD	cyclohexane/EtOAc, 1:1	8[f]	35	 **44** 39%  **45** 3%
12	 **22**	DIAD	cyclohexane	16[f]	35	No reaction

[a] 1.2 equivalents of the diazo compound, unless stated otherwise. PTAD = 4-phenyl-1,2,4-triazole-3,5-dione (**12**); DIAD = diisopropyl azodicarboxylate (**16**, R = *i*Pr); TBS = *tert*-butyldimethylsilyl. [b] Microwave irradiation (150 W). [c] 1.7 equivalents of PTAD. [d] Yield calculated by using the NMR spectrum. [e] Yield for the uncharacterised component was calculated by using the NMR spectrum. [f] UV irradiation (1000 W).

Unfortunately, the sulfur derivative **15** could not be generated in significant quantities and no reaction was observed with di-*tert*-butyl azodicarboxylate (**16**, R = *t*Bu). Reactions involving DIAD were performed in the presence of UV irradiation in order to isomerise the nitrogen–nitrogen double bond to the *cis* geometry (i.e., **16** to **17**, Scheme 3) as reported by Askani.[48] The results of these reactions are summarised in Table 1.

Moving through the PTAD (**12**) series (Table 1, entries 1–7), it is apparent that the ratio of 3,4-disubstitued adducts to 2,3-disubstituted adducts increases as the cyclooctatetraenes become more electron rich. The series begins with the exclusive formation of the 2,3-disubstituted adduct **25** from dimethyl cyclooctatetraene-1,8-dicarboxylate (**18**) (Table 1, entry 1) and culminates with the isolation of the 3,4-disubstituted adduct **34** as the major product from cyclooctatetraene **22** (Table 1, entry 5). When two regioisomeric 2,3-disubstituted adducts were possible (Table 1, entries 2, 3 and 5), adducts with the more electron-withdrawing substituent occupying the bridgehead position (compounds **27**, **30** and **35**) were isolated in higher yields than adducts with the less electron-withdrawing substituent at the bridgehead position (compounds **28**, **31** and **36**). The *tert*-butyldimethylsilyl-containing (TBS) substrate **23**, which was the most electron-rich cyclooctatetraene examined, generated results that deviate from these trends (Table 1, entry 6). It would appear that, in this instance, steric factors compete with the electronic effects to increase the formation of the 2,3-disubstituted adduct **38**, in which steric hindrance between the bulky TBS group and the ethyl group is now a considerable factor. An attempt to further extend the series by reacting the even more sterically demanding 1,8-bis[(*tert*-butyldimethylsilyl)-oxymethyl]cyclooctatetraene (**24**) with **12** was complicated by the formation of substantial quantities of an unidentified product that appeared to contain two PTAD moieties. It was, however, possible to ascertain that the 2,3-disubstituted isomer **41** is favoured to an even greater extent with this substrate.

Interestingly, no products arising from the 1,4-cycloaddition of **12** to the monocyclic cyclooctatetraene tautomer were observed with any of the substrates investigated. This is despite the propensity of **12** to give rise to such products when reacted with unsubstituted cyclooctatetraene[26a,30] and monosubstituted cyclooctatetraenes.[30d]

DIAD (**16**, R = *i*Pr) was less tolerant of highly electron-rich or -deficient cyclooctatetraenes than PTAD (**12**; compare entries 8 and 12 with entries 1 and 5, Table 1). For the three substrates that did react, the trend observed in the PTAD series appears to be inverted. Cyclooctatetraenes **19** and **20** produced only 3,4-disubstituted adducts (Table 1, entries 9 and 10), whereas a mixture of both possible regioisomers (**44** and **45**) was obtained from the more electron-rich 1,8-di(acetoxymethyl)cyclooctatetraene (**21**; Table 1, entry 11). To the best of our knowledge, these are the first examples of [4+2] cycloaddition reactions between cyclooctatetraenes and diazo dicarboxylates.

For a given cyclooctatetraene, **12** tended to give rise to higher ratios of 2,3-disubstituted adducts than **16** (R = *i*Pr; compare entries 2 and 3 with 9 and 10, Table 1). Particularly striking are the results for ethyl 8-ethylcyclooctatetraene-1-carboxylate (**20**); reaction with **12** yielded an almost 1:1 ratio of 2,3-disubstituted adducts to 3,4-disubstituted adduct, while addition to **16** (R = *i*Pr) led exclusively to the 3,4-disubstituted adduct **43** (Table 1, entries 3 and 10). This finding

parallels Huisgen's[31] observation that the reaction of monosubstituted cyclooctatetraenes with **12** results in a more diverse range of products than reactions with less reactive dienophiles. (Note: the standard protocol for PTAD reactions is to cease the reaction when the red colour has been discharged, which results in differing reaction times and temperatures.[31,33]) Although there are reports detailing the synthesis of 1-cyanocyclooctatetraene[33,49] and 1,2-dicyanocyclooctatetraene,[50] all attempts to synthesise nitrile-substituted cyclooctatetraenes to use in this reaction failed.

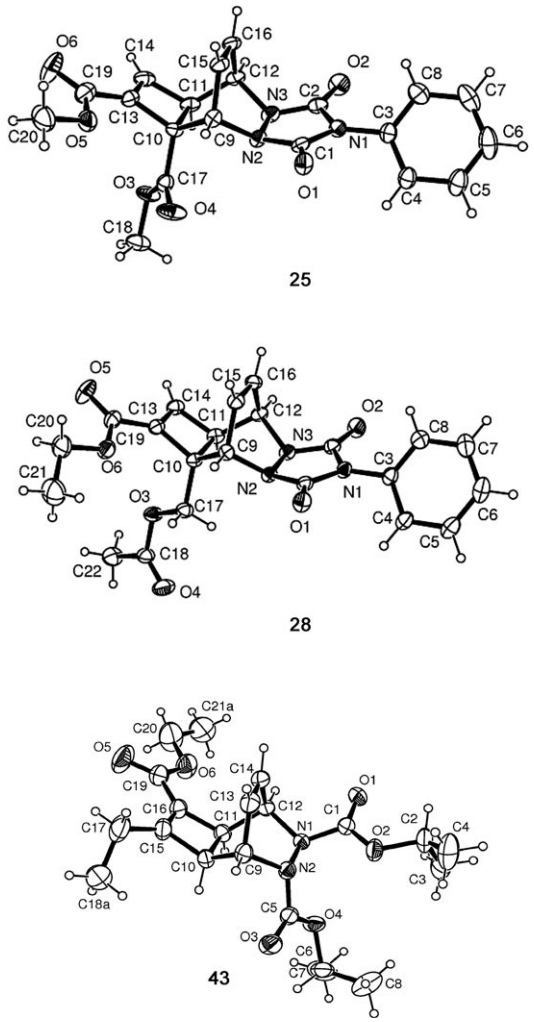
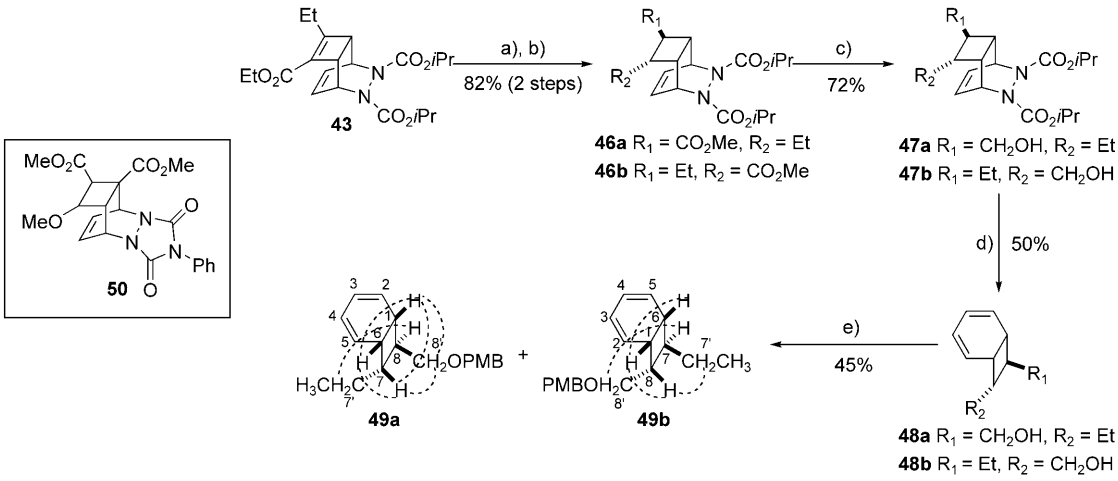


Figure 1. ORTEP diagrams of compounds **25**, **28** and **43** at the 30% probability level.

The structures of the adducts were determined by using a combination of 1D and 2D NMR experiments. If $R^1 = R^2$, the 2,3-disubstituted adducts could be unambiguously identified from the ^{1}H NMR spectra alone. For unsymmetrical substrates, COSY and NOESY spectra were needed for structure elucidation. COSY experiments were also used to confirm the structures of the 3,4-disubstituted adducts; cross peaks between the olefin protons and the bridgehead methine protons (H1 and H6) ruled out the possibility of 9,10-disubstituted adducts. Single-crystal X-ray diffraction analyses of several adducts [from both **12** and **16** (R = *i*Pr)] verified that the relative configurations at C1 and C6 are as depicted. As shown in Figure 1 for adducts **25**, **28** and **43** the dienophile adds to the less hindered face of the diene. Similar observations have been documented for the cyclooctatetraene–maleic anhydride adduct.[51]

With the survey of the key transformation complete, our focus shifted to converting one of the cycloadducts into a 7,8-disubstituted bicyclo[4.2.0]octa-2,4-diene **1**. Inspection of Table 1 reveals that adducts with the correct regiochemistry were isolated in good yields in two instances (Table 1, entries 5 and 10). Adduct **43**, which was isolated in high yield from ethyl 8-ethylcyclooctatetraene-1-carboxylate (**20**) and **16** (R = *i*Pr), without purification by preparative HPLC, was selected for further elaboration, mainly because its conjugated ester functionality should facilitate selective reduction of the desired double bond (Scheme 5). Reduction of the conjugated double bond in ester **43** was achieved by using magnesium in methanol.[52] Treatment with sodium methoxide completed epimerisation and furnished alkenes **46** as an in-



Scheme 5. a) Mg, MeOH, sonication, 3 h, RT; b) Na, MeOH, 4 h, 0–5 °C; c) $LiBEt_3H$, THF, 1 h −20–5 °C; d) KOH, EtOH, microwave irradiation (50 W), 80 °C, 5 psi, 5 h; e) NaH, PMB-Cl, Bu_4NI, THF, 0 °C–RT, overnight.

separable mixture of diastereomers (Scheme 5). The ester functionality was then smoothly reduced with Super-Hydride® ($LiBEt_3H$) to provide alcohols **47** in good yield. When alcohols **47** were subjected to microwave irradiation in the presence of potassium hydroxide, the hitherto unknown bicyclo[4.2.0]octa-2,4-dienes **48** were formed cleanly in yields of up to 50%. Elaboration of alcohols **48** to *para*-methoxybenzyl ethers (PMBO) **49** enabled separation of the diastereomers through careful flash column chromatography. The relative stereo configurations were determined from the NOESY spectra of PMB ethers **49** (key correlations shown in Scheme 5). It is important to note that substantial efforts to generate a suitable precursor for bicycles **48**, either through the dienediyne or cross-coupling[53] approaches, failed. Also, when the conjugate reduction was performed on cyclooctatetraene **20** a complex mixture was obtained and the expected [4.2.0] bicycle was not isolated, even after preparative HPLC. This indicates that protection of the 1,3-diene unit in **20** through a [4+2] cycloaddition reaction with **16** (R = *i*Pr) is a crucial step in the sequence. An attempt was made to extend the protocol to access a 1,8-disubstituted bicyclo[4.2.0]octa-2,4-diene from PTAD adduct **25** (Table 1, entry 1). However, when compound **25** was exposed to magnesium in methanol, conjugate addition of methoxide was observed instead of double bond reduction and the trisubstituted product **50** was deemed to be incompatible with the basic[45a] or reducing[45h,i] conditions that are typically required for PTAD deprotection.

Since our recent focus has been on cancer treatments,[54] a range of cell lines were treated with the compounds listed in Table 2. The responses of different cell types varied considerably. The most notable feature was the sensitivity of the melanoma cell line MM96 L to **25**, **28**, **29**, **36**, and **43**, followed by moderate sensitivity of the breast cancer cell line MCF7 to compound **25**. The nature of the diimide substituents appears to be irrelevant to potency, which seems to depend on the identity and location of substituents in the unsaturated butane ring. Since MM96 L is susceptible to oxidative stress,[55] these compounds may inhibit a relevant cellular defence mechanism. The leukaemia cell line K562 and normal fibroblasts NFF tended to be insensitive to these structures. To determine whether potency would increase with pure enantiomers as opposed to racemates **25** was resolved by using chiral chromatography, however, neither enantiomer improved potency.

Table 2. Inhibition of the growth of cultured human cells (IC_{50} μg mL^{-1}).

Compound[a]	MCF7	MM96 L	NFF	K562
27	12	27	>100	19
26	20	28	38	68
46	>100	69	>100	>100
44	>100	67	>100	>100
34	21	57	>100	91
32	48	>100	>100	>100
47	>100	>100	>100	>100
42	41	69	>100	>100
45	>100	>100	>100	>100
30	12	13	>100	>100
33	5	>100	>100	>100
29	6	9	49	29
43	32	1.8	79	61
28	5.5	0.64	11	11
36	12	12	>100	>100
25[b]	2.1	1.7	5	4.8

[a] Dissolved in ethanol, unless specified otherwise. [b] Dissolved in acetone.

Conclusion

In summary, a survey of the [4+2] cycloaddition reaction between 1,8-disubstituted cyclooctatetraenes and diazo dienophiles revealed that if PTAD (**12**) is the dienophile, 3,4-disubstituted products predominate for electron-rich cyclooctatetraenes, while electron-deficient cyclooctatetraenes are mainly converted into 2,3-disubstituted adducts. The reactions between 1,8-disubstituted cyclooctatetraenes and DIAD (**16**, R = *i*Pr), which are reported here for the first time, lead predominantly to 3,4-disubstituted adducts. Also detailed is a novel protocol for the preparation of 7,8-disubstituted bicyclo[4.2.0]octa-2,4-dienes that utilises one of the [4+2] cycloaddition products as a key intermediate. This structure class may constitute a platform for achieving varying potencies against a range of human tumour types.

Experimental Section

Representative procedure: the reaction of cyclooctatetraenes with PTAD (12): Compound **12** (13.6 mg, 0.08 mmol) was added to a solution of **22** (13.6 mg, 0.067 mmol) in ethyl acetate (0.8 mL) and the mixture was stirred at 55 °C until thin-layer chromatography (TLC) indicated complete consumption of the starting material (~2 h). The solution was concentrated in vacuo and the residue was subjected to flash column chromatography (petroleum ether/Et_2O, 1:3 then Et_2O). The resulting mixture of regioisomeric adducts was further purified by preparative HPLC in the following order:

*2-(Acetoxymethyl)-3-ethyl-7,8-diazatricyclo[4.2.2.0^{2,5}]deca-3,9-diene-7,8-dicarboxylic acid phenylimide (**35**)*: White solid, 14% yield; m.p. 80–81 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 (t, J = 7.5 Hz, 3H), 1.84–1.92 (m, 1H), 2.01–2.09 (m, 1H), 2.09 (s, 3H), 2.82–2.83 (m, 1H), 4.38 (d, J = 11.2 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.97–5.01 (m, 2H), 5.62–5.63 (m, 1H), 6.16–6.19 (m, 1H), 6.27–6.30 (m, 1H), 7.32–7.35 (m, 1H), 7.41–7.45 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 10.3, 20.9, 22.3, 40.0, 48.7, 54.7, 55.2, 64.3, 125.6, 126.9, 127.0, 127.5, 128.3, 129.1, 131.4, 156.45, 156.54, 156.7, 170.8 ppm; MS (ESI): m/z: 402 [M+Na]$^+$; HRMS (ESI): m/z: calcd for $C_{21}H_{21}N_3O_4Na$ [M+Na]$^+$: 402.1424; found: 402.1425.

*3-(Acetoxymethyl)-4-ethyl-7,8-diazatricyclo[4.2.2.0^{2,5}]deca-3,9-diene-7,8-dicarboxylic acid phenylimide (**34**)*: Colourless oil, 47% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, J = 7.6 Hz, 3H), 2.01–2.07 (m, 2H), 2.07 (s, 3H), 3.13–3.14 (m, 2H), 4.40 (d, J = 13.3 Hz, 1H), 4.50 (d, J = 13.3 Hz, 1H), 5.01–5.04 (m, 2H), 6.15–6.18 (m, 2H), 7.32–7.35 (m, 1H), 7.40–7.43 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 11.6, 20.8, 21.1, 37.0, 38.0, 54.2, 54.4, 58.7, 125.6, 126.5, 128.2, 129.1, 131.4, 136.5, 150.1, 156.05, 156.13, 170.6 ppm; MS (ESI): m/z: 402 [M+Na]$^+$; HRMS (ESI): m/z: calcd for $C_{21}H_{21}N_3O_4Na$ [M+Na]$^+$: 402.1424; found: 402.1424.

*3-(Acetoxymethyl)-2-ethyl-7,8-diazatricyclo[4.2.2.0^{2,5}]deca-3,9-diene-7,8-dicarboxylic acid phenylimide (**36**)*: Colourless oil, 5% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00 (t, J = 7.5 Hz, 3H), 1.81–1.88 (m, 1H), 1.98–2.05 (m, 1H), 2.08 (s, 3H), 2.86–2.87 (m, 1H), 4.42 (dt, J = 2.0, 14.2 Hz, 1H), 4.50 (dt, J = 1.3, 14.2 Hz, 1H), 4.76 (dd, J = 1.6, 5.9 Hz, 1H), 4.98–

5.00 (m, 1H), 5.86 (s, 1H), 6.10–6.13 (m, 1H), 6.28–6.31 (m, 1H), 7.33–7.35 (m, 1H), 7.42–7.43 ppm (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 9.6, 20.7, 22.9, 41.3, 50.4, 54.8, 58.3, 60.1, 125.6, 125.9, 128.19, 128.22, 129.1, 131.5, 131.6, 148.3, 156.3, 156.5, 170.3 ppm; MS (ESI): *m/z*: 402 $[M+Na]^+$; HRMS (ESI): *m/z*: calcd for $C_{21}H_{21}N_3O_4Na$ $[M+Na]^+$: 402.1424; found: 402.1424.

Representative procedure: the reaction of cyclooctatetraenes with PTAD under microwave irradiation: A solution of compounds **20** (20 mg, 0.098 mmol) and **12** (18 mg, 0.10 mmol) in ethyl acetate (1.2 mL) was subjected to microwave irradiation (70 °C, 150 W, 1 h) and then concentrated in vacuo. Flash column chromatography (petroleum ether/Et_2O, 10:1 then Et_2O) furnished a mixture of regioisomers. The resulting mixture of regioisomeric adducts was further purified by preparative HPLC in the following order:

*2-Carboethoxy-3-ethyl-7,8-diazatricyclo[4.2.2.0^{2,5}]deca-3,9-diene-7,8-dicarboxylic acid phenylimide (**30**)*: Yellow oil, 26% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (t, J = 7.5 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.86–2.06 (m, 2H), 3.56–3.58 (m, 1H), 4.27 (qd, J = 1.1, 7.1 Hz, 2H), 4.99–5.03 (m, 1H), 5.38 (dd, J = 1.8, 5.8 Hz, 1H), 5.81–5.83 (m, 1H), 6.18–6.30 (m, 2H), 7.29–7.37 (m, 1H), 7.41 ppm (d, J = 4.5 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 10.2, 14.3, 22.2, 39.7, 54.6, 55.4, 56.5, 61.6, 125.6, 126.3, 127.3, 128.2, 129.1, 131.0, 131.4, 154.2, 156.2, 170.6 ppm; MS (ESI): *m/z*: 402 $[M+Na]^+$; HRMS (ESI): *m/z*: calcd for $C_{21}H_{21}N_3O_4Na$ $[M+Na]^+$: 402.1424; found: 402.1424.

*3-Carboethoxy-2-ethyl-7,8-diazatricyclo[4.2.2.0^{2,5}]deca-3,9-diene-7,8-dicarboxylic acid phenylimide (**31**)*: Yellow oil, 4% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99 (t, J = 7.5 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 2.02 (q, J = 7.5 Hz, 2H), 2.96 (d, J = 4.6 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.94 (dd, J = 1.6, 5.5 Hz, 1H), 5.06–5.08 (m, 1H), 6.09–6.12 (m, 1H), 6.32–6.35 (m, 1H), 6.59 (d, J = 0.6 Hz, 1H), 7.33–7.36 (m, 1H), 7.41–7.45 ppm (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.2, 23.0, 29.7, 41.7, 50.5, 54.5, 58.0, 60.6, 125.6, 125.7, 128.3, 128.9, 129.1, 131.4, 143.5, 144.3, 156.4, 156.5, 161.2 ppm; MS (ESI): *m/z*: 402 $[M+Na]^+$; HRMS (ESI): *m/z*: calcd for $C_{21}H_{21}N_3O_4Na$ $[M+Na]^+$: 402.1424; found: 402.1421.

*3-Carboethoxy-4-ethyl-7,8-diazatricyclo[4.2.2.0^{2,5}]deca-3,9-diene-7,8-dicarboxylic acid phenylimide (**29**)*: White solid, 35% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, J = 7.7 Hz, 3H), 1.27 (t, J = 6.9 Hz, 3H), 2.32–2.48 (m, 2H), 3.22 (t, J = 4.2 Hz, 1H), 3.31–3.34 (m, 1H), 4.16 (qd, J = 1.5, 6.9 Hz, 2H). 5.08–5.12 (m, 1H), 5.17–5.21 (m, 1H), 6.13–6.25 (m, 2H), 7.31–7.36 (m, 1H), 7.40–7.43 ppm (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 11.0, 14.3, 22.5, 36.1, 38.4, 53.8, 60.2, 125.5, 125.6, 127.1, 128.3, 129.1, 131.4, 131.9, 156.0, 156.2, 161.9, 164.9 ppm; MS (ESI): *m/z*: 402 $[M+Na]^+$; HRMS (ESI): *m/z*: calcd for $C_{21}H_{21}N_3O_4Na$ $[M+Na]^+$: 402.1424; found: 402.1421.

Representative procedure: the reaction of cyclooctatetraenes with DIAD (16, R = *i*Pr): A solution of **20** (1.96 g, 9.60 mmol) and **16** (R = *i*Pr; 2.25 mL, 11.4 mmol) in cyclohexane (100 mL) in a pyrex reaction vessel was exposed to UV irradiation (Hanovia high pressure mercury–xenon vapour lamp, 1000 W; note: the light was passed through a 30 cm long ≈5 °C water filter) for 46 h. The solvent was removed in vacuo and the residue was purified by flash column chromatography (petroleum ether/Et_2O, 1:1 then Et_2O) to yield compound **43**[60] as a colourless oil (2.75 g, 71%) that solidified into a crystalline solid (m.p. 70–72 °C) suitable for X-ray crystallography when stored at −20 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.92 (t, J = 7.6 Hz, 3H), 0.97 (t, J = 7.6 Hz, 3H), 1.15–1.21 (m, 30H), 2.21–2.36 (m, 4H), 2.85–3.20 (m, 4H), 4.03–4.11 (m, 4H), 4.74–4.82 (m, 4H), 4.93 (brs, 2H), 5.04 (brs, 2H), 6.10–6.16 (m, 2H), 6.31–6.35 ppm (m, 2H); GC/MS (EI): *m/z* (%): 406 (5) $[M]^+$, 320 (12), 131 (21), 81 (86), 43 (100), 41 (52); HRMS (EI): *m/z*: calcd for $C_{21}H_{30}N_2O_6$ $[M]^+$: 406.2098; found: 406.2086.

Magnesium reduction of compound 43: Magnesium turnings, in three equal portions, (0.742 g, 30.5 mmol in total) were added to a solution of diene **43** (1.48 g, 3.64 mmol) in anhydrous methanol (63 mL) under an argon atmosphere. After each addition the suspension was briefly heated to reflux (heat gun) and then sonicated until all of the metal had dissolved (ca. 1 h each time). The reaction was quenched with 10% citric acid solution (100 mL) and the product was extracted into diethyl ether (3×70 mL). The combined organic phase was washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was subjected to flash column chromatography (petroleum ether/Et_2O, 1:1 then Et_2O) and the resulting mixture of methyl and ethyl esters was taken up in anhydrous methanol (59 mL). Sodium (0.421 g, 18.3 mmol) was added at 0 °C under argon. The mixture was stirred at 0–5 °C for 4 h and then quenched with saturated ammonium chloride (75 mL). The product was extracted into diethyl ether (3×50 mL) and the combined organic phase was washed with water (75 mL) and brine (75 mL). Drying ($MgSO_4$) followed by concentration in vacuo afforded compounds **46a** and **46b** as a white foam (1.17 g, 82%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.74 (t, J = 7.3 Hz, 3H), 1.14–1.19 (m, 12H), 1.27–1.40 (m, 2H), 2.46–2.27 (m, 2H), 2.69 (brs, 1H), 3.13 (brs, 1H), 3.57 (s, 3H), 4.79–4.91 (m, 4H), 6.37–6.73 ppm (m, 2H); GC/MS (EI): *m/z* (%): 394 (7) $[M]^+$, 308 (17), 266 (21), 115 (35), 91 (25), 83 (22), 81 (59), 79 (34), 78 (84), 44 (29), 43 (100), 41 (58); HRMS (EI): *m/z*: calcd for $C_{20}H_{30}N_2O_6$ $[M]^+$: 394.2098; found: 394.2111.

Super hydride® reduction of compounds 46a and 46b: Super hydride ($LiBHEt_3$; 1.0 M in tetrahydrofuran, 2.04 mL, 2.04 mmol) was added to a solution of the esters **46a** and **46b** (0.361 g, 0.916 mmol) in anhydrous tetrahydrofuran (6.4 mL) at −20 °C under an argon atmosphere. The reaction was stirred at 0 °C for 1 h and then poured into ice-cold hydrochloric acid (2 N, 10 mL). The product was extracted into ethyl acetate (2×10 mL). The aqueous phase was treated with brine (10 mL) and additional product was extracted into ethyl acetate (2×10 mL). The combined organic phase was washed with brine (20 mL) and dried ($MgSO_4$). Concentration in vacuo followed by flash column chromatography (petroleum ether/Et_2O, 1:1 then Et_2O) furnished alcohols **47a** and **47b** as a white foam (0.241 g, 72%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.71 (t, J = 7.4 Hz, 3H), 1.10–1.18 (m, 12H), 1.23–1.35 (m, 2H), 1.87 (quint, J = 6.8 Hz, 1H), 2.02 (quint, J = 8.5 Hz, 1H), 2.67 (brs, 2H), 3.40–3.44 (m, 2H), 4.78–4.87 (m, 4H), 6.34–6.69 ppm (m, 2H); GC/MS (EI): *m/z* (%): 366 (4) $[M]^+$, 280 (8), 86 (33), 81 (43), 57 (22), 43 (100), 41 (47); HRMS (EI): *m/z*: calcd for $C_{19}H_{30}N_2O_5$ $[M]^+$: 366.2149; found: 366.2162;

Diene deprotection of alcohols 47a and 47b: Potassium hydroxide (0.742 g, 13.2 mmol) was added to a solution of alcohols **47a** and **47b** (0.445 g, 1.21 mmol) in anhydrous ethanol (10 mL) and the mixture was heated in a microwave reactor (5 psi, 80 °C, 50 W) for 5 h. On cooling, water (30 mL) was added and the product was extracted into diethyl ether (3×20 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (petroleum ether/Et_2O/NEt_3, 50:50:0.5) afforded dienes **48a** and **48b** as a colourless oil (0.099 g, 50%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78–0.86 (m, 6H), 1.23–1.29 (m, 2H), 1.42–1.65 (m, 4H), 2.17–2.22 (m, 1H), 2.41–2.47 (m, 2H), 2.52–2.58 (m, 2H), 2.65–2.72 (m, 1H), 3.11–3.13 (m, 1H), 3.19–3.21 (m, 1H), 3.53–3.66 (m, 2H), 3.74–3.83 (m, 2H), 5.54–5.68 (m, 6H), 5.82–5.86 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 12.2, 12.6, 23.4, 29.0, 32.3, 33.1, 33.9, 36.2, 48.6, 50.6, 51.9, 53.8, 63.7, 65.8, 121.2, 121.8, 124.0, 124.4, 125.3, 126.4, 126.8, 127.9 ppm; GC/MS (EI): *m/z* (%): 164 (3) $[M]^+$, 133 (1), 80 (20), 78 (65), 57 (100); HRMS (EI): *m/z*: calcd for $C_{11}H_{16}O$ $[M]^+$: 164.1196; found: 164.1200;

PMB derivatisation of dienes 48a and 48b: Sodium hydride (60% suspension in mineral oil, 14 mg, 0.35 mmol), 4-methoxybenzyl chloride (30 μL, 0.22 mmol) and tetrabutylammonium iodide (8.1 mg, 0.022 mmol) were added to a solution of dienes **48a** and **48b** (22 mg, 0.14 mmol) in anhydrous tetrahydrofuran at 0 °C under an argon atmosphere. The mixture was warmed to room temperature overnight and then diluted with diethyl ether (5 mL). The solution was then washed with water (5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (petroleum ether/Et_2O, 19:1) provided ethers **49a** and **49b** as a mixture of diastereomers (17 mg, 45%). Careful flash column chromatography of this mixture (petroleum ether/Et_2O, 39:1, no pressure) provided analytically pure samples of each diastereomer. Significant decomposition occurred during separation of the diastereomers.

*7-Ethyl-8-[(4-methoxybenzyloxy)methyl]bicyclo[4.2.0]octa-2,4-diene (**49a**)*: R_f = 0.32; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (t, J = 7.4 Hz, 3H), 1.49–1.62 (m, 2H), 2.42 (quint, J = 8.1 Hz, 1H), 2.50–2.57 (m, 1H), 2.68 (ddd, J = 5.2, 8.3, 10.7 Hz, 1H), 3.07–3.13 (m, 1H), 3.36 (dd, J = 6.6, 9.8 Hz, 1H), 3.43 (dd, J = 5.3, 9.8 Hz, 1H), 3.79 (s, 3H), 4.39 (d, J = 11.7 Hz, 1H),

4.43 (d, $J=11.8$ Hz, 1H), 5.53–5.61 (m, 2H), 5.65 (dd, $J=5.2$, 9.4 Hz, 1H), 5.80–5.84 (m, 1H), 6.86 (d, $J=8.7$ Hz, 2H), 7.22 ppm (d, $J=8.7$ Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=12.6$, 23.4, 33.7, 34.0, 49.2, 51.4, 55.3, 72.4, 73.0, 113.7, 121.6, 123.9, 126.5, 127.0, 129.0, 130.9, 159.0 ppm; GC/MS (EI): *m/z* (%): 284 (1) $[M]^+$, 175 (2), 162 (1), 145 (1), 136 (24), 121 (100) 78 (20); HRMS (EI): *m/z*: calcd for $C_{19}H_{24}O_2$ $[M]^+$: 284.1771; found: 284.1776.

*7-Ethyl-8-[(4-methoxybenzyloxy)methyl]bicyclo[4.2.0]octa-2,4-diene (**49b**)*: $R_f=0.21$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.80$ (t, $J=7.4$ Hz, 3H), 1.38–1.48 (m, 2H), 2.09–2.19 (m, 1H), 2.52 (ddd, $J=5.0$, 8.0, 11.1 Hz, 1H), 2.67 (ddd, $J=5.5$, 9.0, 17.9 Hz, 1H), 3.13–3.17 (m, 1H), 3.61 (dd, $J=5.5$, 9.0 Hz, 1H), 3.62 (t, $J=9.0$ Hz, 1H), 3.79 (s, 3H), 4.40 (s, 2H), 5.54–5.64 (m, 3H), 5.77–5.82 (m, 1H), 6.85 (d, $J=8.8$ Hz, 2H), 7.24 ppm (d, $J=8.8$ Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=12.3$, 28.9, 32.7, 36.4, 49.5, 51.3, 55.3, 70.9, 72.7, 113.7, 121.3, 123.9, 126.1, 127.4, 129.3, 130.7, 159.1 ppm; GC/MS (EI): *m/z* (%): 284 (1) $[M]^+$, 255 (1), 175 (3), 162 (1), 145 (1), 136 (23), 121 (100); HRMS (EI): *m/z*: calcd for $C_{19}H_{24}O_2$ $[M]^+$: 284.1771; found: 284.1767.

Biological testing: Cells were cultured at 3000 cells per well in 96 well plates by using 10% FCS (fetal calf serum) in RPMI (Roswell Park Memorial Institute) media and incubated for 24 h at 37°C. Cells were treated with the following concentrations of drug: 100 $\mu g\,mL^{-1}$, 30 $\mu g\,mL^{-1}$, 10 $\mu g\,mL^{-1}$, 3 $\mu g\,mL^{-1}$, 1 $\mu g\,mL^{-1}$, 0.3 $\mu g\,mL^{-1}$, 0.1 $\mu g\,mL^{-1}$ (solvent as indicated in Table 2), allowed to grow until 90–95% confluent and fixed with ethanol. Attached cell lines (NFF, MCF7, MM96 L) were stained with 0.4% sulforhodamine B solution and read at 560 nm on a VERSAmax microplate reader. The non-adherent cell line K562 was treated by using [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium] (MTS) assay, Promega's Celltiter 96 AQ One solution cell proliferation assay, and read at 490 nm.

Acknowledgements

We thank EcoBiotics Ltd and the University of Queensland for financial support. Dr. L. Lambert is acknowledged for assistance with NMR experiments and the University of Queensland Enantioselective Chromatography Facility for assistance with *ee* determinations and preparative separations.

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[40] DIAD (**16**, R = *i*Pr) is a less reactive dienophile than PTAD (**12**) as the nitrogen–nitrogen double bond in DIAD has a *trans* configuration while in PTAD it is constrained to a *cis* configuration (see ref. [32])

[41] Several compounds formally corresponding to the Diels–Alder adducts of cyclooctatetraene and an azo dicarboxylate are known. However, these compounds were prepared indirectly through a protocol involving [4+2] cycloadditions between the azo compound and 7,8-dibromobicyclo[4.2.0]octa-2,4-diene, see: a) V. Mascitti, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 15664–15665. Debromination then provides compounds of type **10** ($R^1 = R^2 = H$). See, for example: b) R. Askani, *Chem. Ber.* **1969**, *102*, 3304–3309; c) R. Askani, H. Eichenauer, J. Köhler, *Chem. Ber.* **1982**, *115*, 748–753; d) W. P. Lay, K. Mackenzie, A. S. Miller, D. L. Williams-Smith, *Tetrahedron* **1980**, *36*, 3021–3031.

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[60] Adducts from reactions between cyclooctatetraenes and DIAD exhibited complex ^{1}H and ^{13}C NMR spectra due to the presence of multiple rotamers. For other examples, see: references [42a] and [42d]. Attempts at deconvolution by using high or low temperatures or more polar deuterated solvents failed. Only ^{1}H NMR data is reported.

Received: December 17, 2009
Published online: June 22, 2010

