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The preparation of 7-substituted norbornadiene-2,3-dicarboxylic anhydrides and an experimental and theoretical study of their reactivity

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Abstract—Four new substituted methano-bridged or heteroatom-bridged norbornadienomaleic anhydrides have been prepared and converted to sesquinorbornadiene anhydrides by reaction with cyclic 1,3-dienes. The versatility of parity reversal, in conjunction with *N*-substituent steric effects, has been used to produce all three possible stereoisomers of the *N*,*O*-sesquinorbornadiene anhydrides in separate, stereoselective cycloadditions. The anhydrides have been synthesized by cyclization of their diacids (in situ production) or by flash vacuum pyrolysis of their furan adducts (yielding crystalline products); further fragmentation occurs at these or higher temperatures to produce five-membered carbocyclic or heterocyclic anhydrides. Activation energies have been evaluated for the fragmentation and cycloaddition processes using DFT calculations (B3LYP/6-31G*) and these calculations correctly predict, which reaction can be intercepted at the norbornadienomaleic anhydride stage and preferred stereochemistry of cycloadducts.

1. Introduction

Alkene systems formed by sharing a common π-bond between two dienophiles have been found to yield a class of highly reactive dienophiles. This is particularly evident in those, which include maleic anhydride as one component, e.g., maleic anhydride with itself to give **1**,[1] maleic anhydride with *p*-benzoquinone to give **2**,[2] and maleic anhydride with norbornadiene or 7-oxanorbornadiene to give **3**[3,4] or **4**, respectively[5,6] (Fig. 1). In fact, the last mentioned compound **4** has been described in our previous paper where it is shown to be the most powerful C=C dienophile capable of isolation.[5,7] The ease with which **4** adds cyclic 1,3-dienes (cyclopentadiene and fulvenes) or five-membered heterocycles (furan and pyrrole) at room temperature has allowed rapid entry to a wide range of bridge-substituted oxasesquinorbornadienes, many for the first time. The fact that reaction of anhydride **4** can be achieved with thiophene under high pressure at room temperature has allowed production of the first sulfur-bridged sesquinorbornadiene.[8]

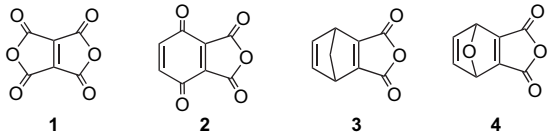

Figure 1. Superdienophiles **1**–**4**, formed by the formal fusion of two dienophiles at the π-bond.

2. Results and discussion

In this study, we discuss approaches to the synthesis of norbornadiene-2,3-dicarboxylic anhydrides **7a**–**f** modified at the 7-position (aza, oxa, thia, isopropylidene, and adamantylidene); reports on a high level computational and FVP study on the propensity of norbornadienes **7a**–**f** to undergo retro Diels–Alder fragmentation to form carbocyclic and heterocyclic anhydrides **8a**–**f** and to demonstrate the power of parity reversal and steric substituent control to form *N*,*O*-bridged sesquinorbornadiene anhydrides covering all geometrical types via individual, stereoselective cycloaddition reactions.

Our approach to the synthesis of norbornadiene-2,3-dicarbocyclic anhydrides **7a**–**f** was based on the flash vacuum pyrolysis (FVP)[9] of their respective furan adducts **5a**–**f** (Scheme 1). Preferential loss of furan rather than the alternative dienes in reaction **5**→**7** was predicted by smaller activation

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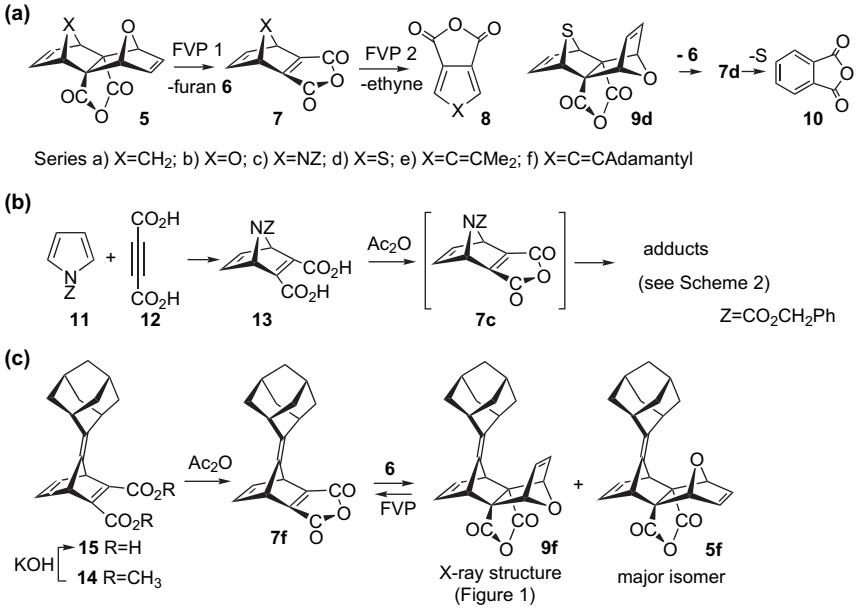


Scheme 1. Synthesis of norbornadiene-2,3-dicarboxylic anhydrides **7a–f**.

energies obtained from B3LYP/6-31G* calculations. Retro Diels–Alder reaction[10] led to the production of the parent anhydride **7a**, mp 85–85 °C (lit.[3] mp 88–89 °C) in 85% isolated yield by FVP (325 °C, 0.005 mbar) of the furan adduct **5a** in only the second method reported for the preparation and isolation of this compound. Given the simplicity of the process and the ready availability of the starting materials, this now constitutes the preferred route to **7a**. The ^{1}H NMR spectrum of **7a** (vinylic δ 7.14, bridgehead δ 4.08, and methylene δ 2.77) corresponded with that published,[3] while the ^{13}C NMR (not reported previously) exhibited five resonances (δ 47.7, 78.0, 142.6, 159.3, and 170.6) in accord with its C_2 symmetry. Reaction of **7a** with furan **6** regenerated the adduct **5a**, together with its isomers, in the same ratio as that observed in the in situ method (vide supra).[5]

Similar FVP of the furan adduct **5e** at 375 °C yielded 7-isopropylidene-norbornadiene-2,3-dicarboxylic anhydride **7e**,[11] mp 127–128 °C, in 57% isolated yield. The ^{1}H NMR of **7e** contained three proton resonances (vinylic δ 7.06, bridgehead δ 4.49, and methyl δ 1.52), which is completely consistent with the assigned structure, and further supported by the seven-line ^{13}C NMR (δ 19.5, 48,2, 103.5, 142.6, 159.1, 164.1, and 168.3). FVP pyrolysis of the extended-frame[12] furan adduct **5f**[13] in the adamantylidene series at 380 °C produced the corresponding anhydride **7f**, in quantitative yield. The ^{1}H NMR of **7f** contained five sets of proton resonances (vinylic δ 7.06, bridgehead δ 4.50, and adamantyl resonances: allylic δ 2.47, saturated δ 1.59–1.67, and 1.79–1.91). Similarly, FVP of *exo*,*endo*-furan adduct **9f** (X-ray, Fig. 2) produced anhydride **7f**. These experiments confirm that the stereochemistry of the adduct, e.g., *exo*,*endo*-adduct **9f** or *exo*,*exo*-adduct **5f**, is not critical for successful thermolysis.

The 7-oxa derivative **7b** was prepared by FVP of **5b** as outlined in the previous paper[5] and the oily product so obtained was used immediately for cycloadditions with the 1,3-diene trapping agent. Attempts to prepare the 7-*N*-Z-derivative **7c** by FVP of the adduct **5c** were unsuccessful and led only to the *N*-Z-derivative of pyrrole-3,4-dicarboxylic anhydride **8c** and acetylene. In the case of the *S*-bridged system **7d**, pyrolysis of adduct **9d**[8] (370 °C, 0.005 mbar) gave no spectral support for the production of 7-thianorbornadiene anhydride **7d** in the crude pyrolyzate, however circumstantial evidence for its formation came from the isolation of phthalic anhydride **10** and spectral identification of furan from the cold trap. It is clear from this result that loss of sulfur from the 7-thianorbornadiene anhydride **7d** is preferred to retro Diels–Alder ejection of acetylene.

In seeking an explanation for these varied FVP results, we have conducted a quantum-chemical study using high level DFT calculations (B3LYP/6-31G*).[15] The transition states (TS1) involved in the production of the norbornadiene-2,3-dicarboxylic anhydrides **7a–c** from their furan adducts

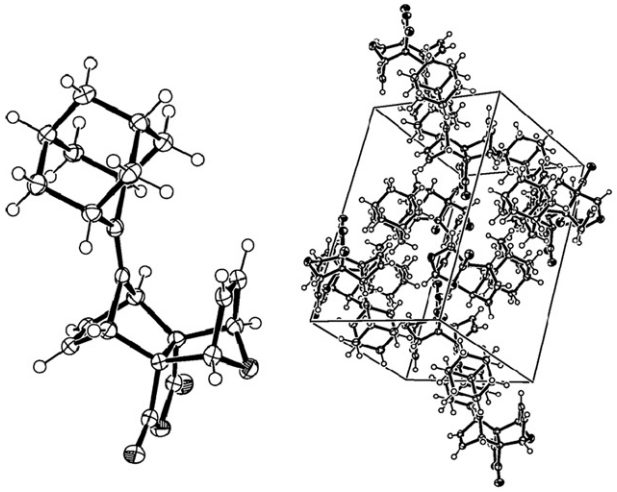
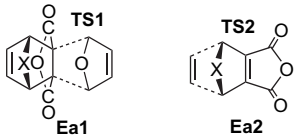


Figure 2. Structure and crystal packing of **9f** with 30% of anisotropic thermal probability.[14]

Table 1. Activation energies[a] for the retro Diels–Alder fragmentation reactions **5a–c** (and **9a–c**) to **7a–c** (Ea1) and **7a–c** to **8a–c** (Ea2) calculated using B3LYP/6-31G* method



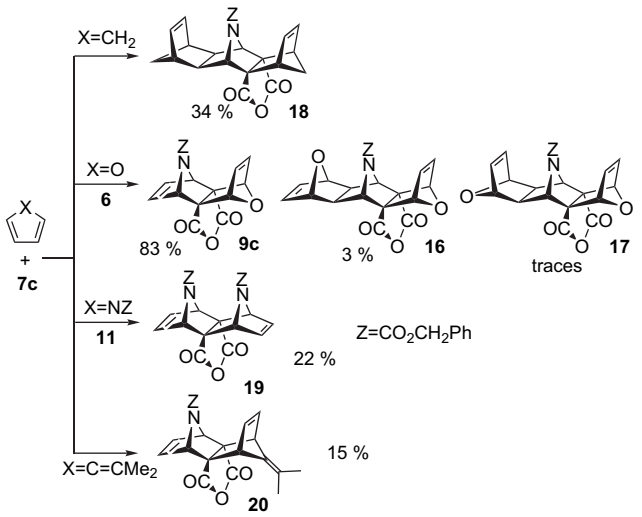
	5a–c	9a–c	7a–c
	exo,*exo*-isomer	*exo*,*endo*-isomer	
Series (a) X=CH_2	31.3	29.2	52.4
Series (b) X=O	31.2	30.6	37.9
Series (c) X=NCO_2Bn	33.2	31.1	32.3

[a] kcal mol^{-1}.

5a–c (or **9a–c**) and the related transition states (TS2) for the fragmentation of **7a–c** to their five-membered ring anhydrides **8a–c** were fully optimized. It is found that the activation energy for the retro Diels–Alder loss of furan (Ea1) remains very similar (29.2–33.2 kcal mol^{-1}) for all three substrates **5a–c** (see Table 1). In contrast, the activation energy (Ea2) for the loss of acetylene from the norbornadiene-anhydrides drops from 52.4 kcal mol^{-1} for the parent **7a** to 37.9 kcal mol^{-1} for the oxa-system **7b**, and further to 32.3 kcal mol^{-1} for the aza-system **7c**. As this activation energy (Ea2) for the aza-system is less than the activation (Ea1) for its formation from the *exo*,*exo*-fused stereoisomer **5c** by 1 kcal mol^{-1}, then the failure to intercept the intermediate anhydride **7c** is fully supported by the calculated energetics of the two sequential reactions.

An alternative route to adducts of norbornadiene anhydride, e.g., furan **5a** and **9a**, was reported by Williams et al.,[16] in which the related norbornadiene dicarboxylic acid was dehydrated to produce **7a** in situ and trapped by warming in acetic anhydride in the presence of cyclopentadiene. We have now used this technique to form adducts of 7-(*N*-benzyloxycarbonyl)norbornadienomaleic anhydride **7c** and 7-adamantylidene norbornadienomaleic anhydride **7f**. The required dicarboxylic acids were prepared from the addition of acetylene dicarboxylic acid to *N*-Z pyrrole (diethyl ether, sealed tube, 65 °C, 40%) to form **13** or hydrolysis of the adduct of DMAD with 6,6-adamantylidenefulvene **14** to access **15**. A selection of new azasesquinorbornadiene anhydrides formed by the generation and trapping of various pentacyclic dienes with norbornadienomaleic anhydride **7c** is presented in Scheme 2. All reactions are stereospecific giving a single product at the anhydride olefinic bond.

Dienophile **7c** reacted with excess cyclopentadiene at 60 °C to produce exclusive 2:1 adduct **18**. Formation of intermediate anhydride **9c** could be deduced from the structure of the final bis-adduct. The *exo*,*endo*-geometry on the unsubstituted part of **18** is revealed by the observation of the coupling between *endo*- and bridgehead protons but not on the anhydride side of molecule. The *exo*,*endo*-structure of the anhydride side of **18** can be envisaged by similar chemical shifts of the olefinic signals on both sides of adduct, and the lack of steric compression effects of nitrogen.[17] Owing to the steric hindrance on both sides, the rotation of the central carbamate N–CO bone is locked even at 60 °C, causing the loss of symmetry and the duplication of the ^1H and ^{13}C NMR signals.



Scheme 2. Azasesquinorbornadiene anhydrides formed by the generation and trapping of azanorbornadienomaleic anhydride **7c**.

This NMR analysis is further confirmed by determination of crystal structure (Fig. 3).

Reaction of **7c** with an excess of furan gives three adducts: *exo*,*endo*- 1:1 adduct **9c**, together with 2:1 *exo*,*endo*;*exo*,*exo*-bis-adduct **16** and *exo*,*endo*;*exo*,*endo*-bis-adduct **17**. At 30 °C, the olefinic proton resonances of the pyrrole side in the ^1H NMR spectrum of 1:1 adduct **9c** are broad and separated by 0.30 ppm; while on furan side by 0.06 ppm. This reflects their relative position in regard to the N–CO bond, which is undergoing slow rotation at this temperature. The coalescence of olefinic signals at the pyrrole side occurs at 63 °C, and the activation energy $\Delta G^{\ddagger}$ for the N–CO bond rotation has been calculated to be 67.8 kJ mol^{-1}. Structure of **9c** was unequivocally confirmed by X-ray crystallography (Fig. 3), while structures of adducts **16** and **17** are assigned by 1D and 2D NMR spectroscopy.

High stereospecificity was observed in the reaction of **7c** with 6,6-dimethylfulvene, where *exo*,*endo*-adduct **20** was formed as the single product in moderate yield (15%). Structure of **20** was deduced by NMR analysis and supported by similarity of its ^1H NMR spectrum to that of **9c**. The most indicative feature is the separation of olefinic protons of the pyrrole and fulvene sides (0.26 and 0.07 ppm, respectively). This result also indicated that cycloaddition of **7c**

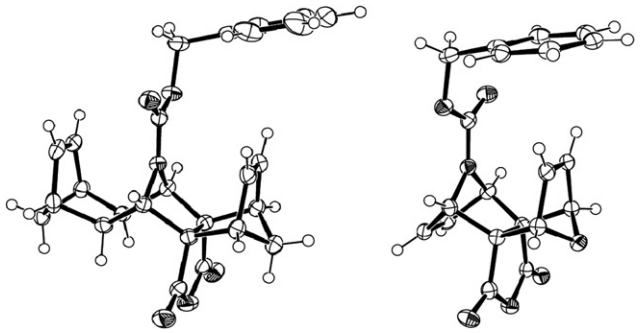
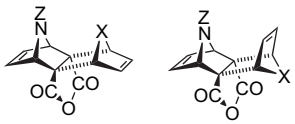


Figure 3. Crystal structures of **18** and **9c** with 30% of anisotropic thermal probability.

Table 2. B3LYP/6-31G* activation energies for Diels–Alder reactions of **7c** with cyclic dienes[a]



X	*exo,exo-*		*exo,endo-*	
CH_2	**5a**	11.4	**9a**	10.5
O	**5b**	16.7	**9b**	15.6
NZ	**5c**	20.2	**9c**	21.9
$C{=}CMe_2$	**5d**	11.5	**9e**	15.0

[a] kcal mol^{-1}; $Z{=}CO_2Me$.

with 6,6-dimethylfulvene, although predicted to be the most reactive (Table 2) is a less yielding reaction than with CPD and furan, presumably due to smaller efficiency of isolation process.

The opposite stereochemistry was obtained in the reaction of *N*-Z pyrrole **11** and diene **7c**. In this case, the *exo,exo*-product **19**, was formed exclusively (Scheme 2). The simplicity of the ^1H NMR spectra of **19** at 60 °C is indicative, possessing three non-benzenoid resonances, is in full agreement with its C_{2v} symmetry. At room temperature, the system suffers slow rotation about the bridge N–CO bond causing signal broadening. Again, the crystal analysis confirms the geometry of **19** (Fig. 4).

This difference and the stereochemical outcome could be easily predicted by DFT calculations at B3LYP/6-31G* level. Transition state geometries of Diels–Alder reactions of pentacyclic dienes (furan and 6,6-dimethylfulvene) with dienophile **7c** are illustrated in Figure 5. Calculated activation energies (Table 2) are in good agreement with experiment: *exo,endo*-addition is favored for CPD, furan and 6,6-dimethylfulvene, while *exo,exo*-addition is predicted for *N*-Z pyrrole reaction.

The availability of the new heterobridged dienophiles **7b** and **7c** has allowed a new set of parity reversal experiments[5] to be examined. As described above, the parity reversal reaction was conducted on the *N*-Z compound **7c**, which was

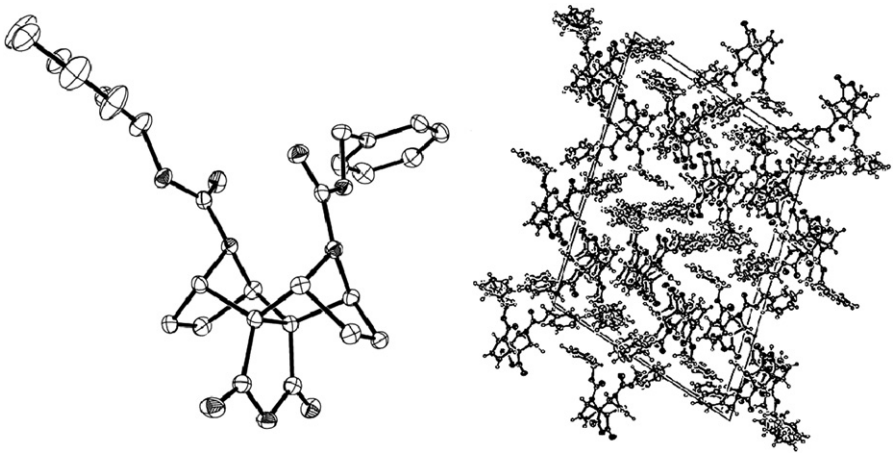


Figure 4. Structure and crystal packing of **19** with 30% of anisotropic thermal probability.

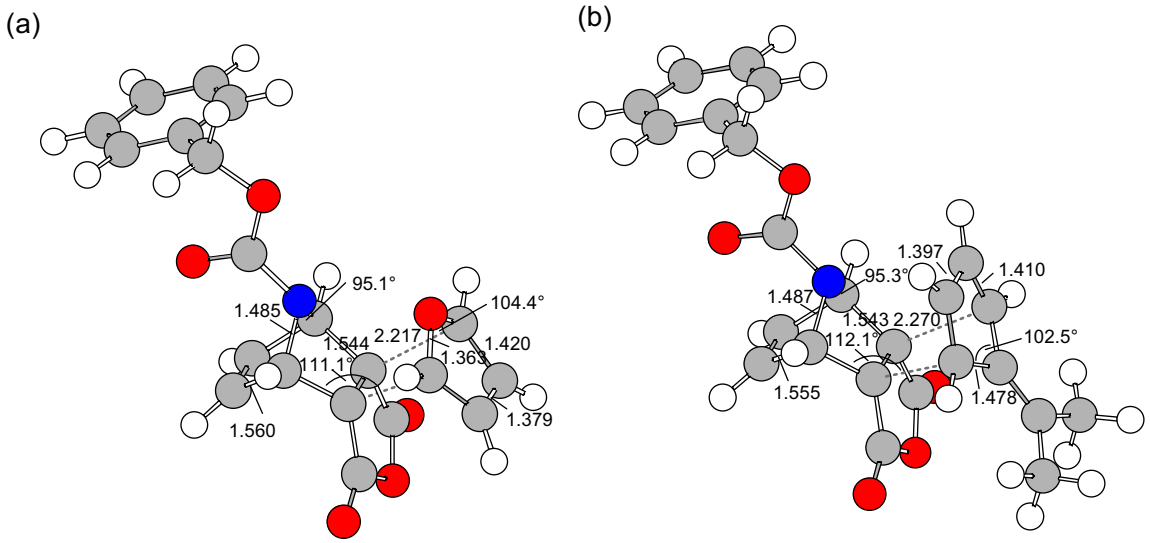
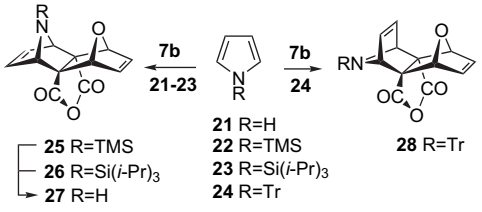


Figure 5. Transition state for: (a) *exo,exo*-Diels–Alder reaction of **7c** with furan, (b) *exo,endo*-Diels–Alder reaction of **7c** with 6,6-dimethylfulvene, calculated using B3LYP/6-31G* method.

generated in situ and reacted with furan **6** to form alternate turn-frame adduct **9c** as a major product (Scheme 2). Furthermore, reaction of pyrrole **21** with 7-oxanorbornadiene-maleic anhydride **7b** produced a single adduct **27** in which the heterobridges are *syn*-facially oriented (Scheme 3). The stereoselectivity of this reaction can be changed by attaching a bulky group onto the pyrrole nitrogen.[6] Thus, reaction of *N*-trityl pyrrole **24** with **7b** allowed entry to the isomeric turn-frame adduct **28**. Interestingly, reactions of *N*-TMS and *N*-*i*-Pr_3Si substituted pyrroles **22** and **23** with **7b** produced *exo*,*exo*-adduct **27**, indicating the removal of nitrogen protecting group from pyrroles in the course of cycloaddition. Cleavage of **22** and **23** could not be stopped by addition of bases such as triethylamine, potassium carbonate, and sodium hydrogencarbonate. The structures of these adducts were assigned on the basis of proton chemical shift data and comparisons with related model compounds of established structure (**27**: vinylic δ 6.81, 6.67, bridgehead δ 5.23, 4.48; **28**: vinylic δ 6.74, 6.56, bridgehead δ 5.29, 4.79). In each case, high stereoselectivity was observed, yet the combination of parity reversal methodology and steric control has allowed access to all three possible structures, some with frame geometry not available by either individual cycloaddition strategy. The ability to access adducts of formal *endo*-cycloaddition origin, a cycloaddition selectivity seldom observed in norbornene chemistry, makes the present methodology a powerful synthetic strategy.



Scheme 3. Cycloaddition reactions of pyrroles with anhydride **7b**.

The reactions described in Scheme 3 have demonstrated extremely high dienophilicity of anhydride **7b**, reacting with unsubstituted pyrrole at room temperature, within 10 min. It is known that pyrrole itself is very poor diene. To enhance its reactivity in Diels–Alder cycloadditions *N*-electron-withdrawing substituents are required, in conjunction with various physical and catalytic methods including high pressure, ultrasound, and Lewis acid catalysis.[18]

3. Conclusion

New heteroatom-bridged norbornadienomaleic anhydrides have been synthesized from their diacids or by flash vacuum pyrolysis of their furan adducts. Further fragmentation occurs at these or higher temperatures to produce five-membered carbocyclic or heterocyclic anhydrides. These heteronorbornadienomaleic anhydrides have been converted to sesquinorbornadiene anhydrides by reaction with (hetero)cyclic 1,3-dienes, showing high reactivity. The versatility of parity reversal, in conjunction with *N*-substituent steric effects, enabled the production of all three possible stereoisomers of the *N*,*O*-sesquinorbornadiene anhydrides. The structures of all new adducts were assigned on the basis of NMR spectroscopy and crystallographic analysis. In addition, density functional theory calculations (B3LYP/6-31G*) were successfully used to evaluate activation energies for the fragmentation processes and cycloaddition reactions. These calculations correctly predict, which reactions can be intercepted at the norbornadienomaleic anhydride stage and experimentally observed stereospecificities of Diels–Alder reactions with cyclic heterodienes.

4. Experimental details

4.1. General

Flash vacuum pyrolyses were conducted (100 mg scale) under very high vacuum (0.005 mbar)[19] in an unpacked 600×6 mm Pyrex tube heated by a horizontally-mounted 'Termolyne' model 21100 tube furnace (300–400 °C). The optimum pyrolysis temperature (calibrated using a thermocouple externally attached to the glass pyrolysis tube) was determined separately for each substrate.

NMR spectra were recorded on a Bruker AMX-300 or Bruker Avance DPX 400 NMR spectrometers. Spectra were measured in $CDCl_3$ with tetramethylsilane as an internal reference at 30 °C unless indicated otherwise. Mass spectrometry was conducted by Central Queensland University Analytical Laboratories using a Shimadzu QP200 mass spectrometer or a Micromass Autospec instrument. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Microanalyses were performed by CQUAL using a Fisons GSE EA 1108 microanalyser. Column chromatography was carried out on Merck silica gel 60 (180–230 mesh). Radial chromatography was performed on the Chromatotron model 7924T with Merck silica gel 60 PF_{254} as absorbent. Petroleum ether (bp range 40–60 °C), ethyl acetate, and diethyl ether p.a. grade were used as supplied. Substituted pyrroles, 6,6-adamantylidenefulvene,[13] and compounds **5a**,[5] **5e**,[5] **9d**,[8] and **9e**[5] were prepared according to literature. Other reagents are commercially available (Aldrich) and were used without further purification. Quantum-chemical calculations were performed using Spartan program on a Silicon Graphics R5000 workstation. For all structures, harmonic vibration frequency calculations were performed to confirm whether the obtained geometry represents a transition or minimum energy structure.

4.1.1. (1α,2β,3α,6α,7β,8α)-11,12-dioxazatetracyclo-[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene-2,7-dicarboxylic anhydride (5b). A mixture containing (1α,2β,3α,6α,7β,8α)-11,12-dioxazatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene-2,7-dicarboxylic acid[20] (400 mg, 1.60 mmol), triethyl amine (0.5 mL), and acetic anhydride (5.0 mL) was stirred at 60 °C overnight. Volatiles were removed by evaporation in vacuo and brown colored residue purified by two-fold recrystallization from ethyl acetate. Anhydride **5b** was obtained as a yellow colored needles (270 mg, 73%), mp 183–184 °C, lit.[21] 184–185 °C. ^{1}H NMR ($CDCl_3$) δ 5.30 (4H, t, J=0.9 Hz, H1,3,6,8), 6.77 (4H, t, J=0.9 Hz, H4,5,9,10).

4.1.2. (1α,2β,3α,6α,7β,8α)-11-Isopropylidene-12-oxatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene-2,7-dicarboxylic

anhydride (5e). Mp 164–165 °C. ^{1}H NMR ($CDCl_3$) δ 1.61 (6H, s, CH_3), 3.78–3.80 (2H, m, H9,10), 4.99–5.01 (2H, m, H3,6), 6.56–6.60 (2H, m, H4,5), 6.71–6.73 (2H, m, H9,10). ^{13}C NMR ($CDCl_3$) δ 19.9, 46.7, 71.9, 81.7, 113.6, 139.5, 140.4, 145.1, 170.0. IR (KBr, cm^{-1}): 1760. HRMS(EI) (M^+) $C_{16}H_{14}O_4$ requires *m/z* 270.0892, found 270.0891.

4.1.3. 7-Oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic anhydride (7b). Anhydride **7b** was obtained by flash vacuum pyrolysis of anhydride **5b** (100 mg, 0.43 mmol) at 360±5 °C and 0.005 mbar. Product deposits at cooler parts of pyrolysis tube, as pale yellow oil (20 mg, 28%). It was washed from the tube with $CDCl_3$ and used immediately. ^{1}H NMR ($CDCl_3$) δ 5.80 (2H, s, H1,4), 7.30 (2H, s, H5,6).

4.1.4. (1α,2β,3α,6α,7β,8α)-11-Dibenzyloxycarbonyl-11-aza-12-oxatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene-2,7-dicarboxylic anhydride (5c). *N-Z* pyrrole **11** (50 mg, 0.25 mmol) was added to a solution of anhydride **7b** (20 mg, 0.12 mmol) in $CDCl_3$ (1 mL). The reaction was allowed to stand at room temperature for 5 min. Radial chromatography (Et_2O/petroleum ether) afforded the adduct **5c** (30 mg, 67%), which was crystallized from Et_2O/petroleum ether as colorless crystals. Mp 121–123 °C. ^{1}H NMR ($CDCl_3$) δ 5.04 (1H, d, *J*=12.0 Hz), 5.10 (1H, d, *J*=12.0 Hz) (C*H*$_2$Ph), 5.11 (1H, s, H1), 5.12 (1H, s, H1), 5.25 (1H, s, H3), 5.30 (1H, s, H6), 6.73–6.74 (4H, m, H4,5,9,10), 7.34–7.38 (5H, m, Ph). ^{13}C NMR ($CDCl_3$) δ 62.5, 62.5 (C1,8), 68.1 (*C*H$_2$Ph), 72.9, 73.3 (C2,7), 81.8, 82.0 (C3,6), 128.9, 129.0, 129.2 (C2′,3′,4′ of Ph), 140.6, 140.6, 140.8, 141.1 (C4,5,9,10), 152.9 (*C*O$_2$Bn), 168.1, 168.3 (*C*O of anhydride). IR (KBr, cm^{-1}): 1766 (C=OAnh), 1707 (C=OBn). HRMS $C_{20}H_{15}NO_6$ requires *m/z* 365.0899, found 365.0899.

4.1.5. 7-Adamantylidene-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic anhydride (7f). FVP of adduct **5f** (100 mg, 0.28 mmol) at 380 °C gave anhydride **7f** as a colorless solid (29 mg, 35%), which was used in the next reaction without purification. Mp 124–125 °C. ^{1}H NMR ($CDCl_3$) δ 1.59–1.67 (10H, m, AdH), 1.79–1.91 (2H, m, AdH), 2.47 (2H, s, AdH1,2), 4.50 (2H, s, H1,4), 7.06 (2H, s, H5,6). ^{13}C NMR ($CDCl_3$) δ 28.4, 28.5, 32.7, 37.2, 38.5, 38.6, 48.0, 119.0, 143.6, 158.3, 159.7, 169.1.

4.1.6. (1α,2β,3α,6α,7β,8α)-11-Adamantylidene-12-oxatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene-2,7-dicarboxylic anhydride (5f) and (1β,2β,3α,6α,7β,8β)-11-adamantylidene-12-oxatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene-2,7-dicarboxylic anhydride (9f). The dicarboxylic acid **14** (380 mg, 1.1 mmol) was dissolved in acetic anhydride, then furan (3.0 g, 44 mmol) was added. The mixture was placed in a sealed vessel, heated to 65–70 °C and left stirring for 4 h. Excess furan and acetic anhydride were removed in vacuo and the residue was then placed on a column of silica gel. Further separation by radial chromatography using 20:1 petroleum ether, with the solvent polarity gradually increased to ethyl acetate, gave two products, in order of elution **9f** (41 mg, 10%) and **5f** (186 mg, 46%). The products (both isomers) were white crystals. Compound **5f** mp 211–214 °C. ^{1}H NMR ($CDCl_3$) δ 1.60–1.95 (12H, m, AdH), 2.54–2.56 (2H, m, Ad H1,2), 3.77 (2H, s, H1,8), 4.98 (2H, s, H3,6), 6.58 (2H, t, *J*=1.5 Hz, H4,5), 6.72 (2H, s, H9,10). ^{13}C NMR ($CDCl_3$) δ 28.3, 28.4, 34.1, 37.1, 37.7, 38.3, 45.8, 72.0, 81.6, 128.4, 138.2, 139.6, 140.7, 170.2. IR (KBr, cm^{-1}): 1776 (C=O). HRMS(EI) (M^+) $C_{23}H_{22}O_4$ requires *m/z* 362.1518, found 362.1515. Compound **9f** mp 198–201 °C. ^{1}H NMR ($CDCl_3$) δ 1.60–2.00 (12H, m, AdH), 2.35–2.38 (2H, m, AdH1,2), 3.42 (2H, s, H1,8), 5.16 (2H, s, H3,6), 6.35 (2H, s, H4,5), 6.60 (2H, t, *J*=1.5 Hz, H9,10). ^{13}C NMR ($CDCl_3$) δ 18.8, 28.3, 33.8, 36.8, 37.2, 38.9, 42.8, 70.4, 82.7, 129.4, 138.7, 135.0, 141.0, 173.0. IR (KBr, cm^{-1}): 1770 (C=O). HRMS(EI) (M^+) $C_{23}H_{22}O_4$ requires *m/z* 362.1518, found 362.1516.

4.1.7. 7-Benzyloxycarbonyl-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic acid (13). A solution of *N-Z* pyrrole **11** (2.00 g, 10 mmol) and acetylene dicarboxylic acid **12** (1.20 g, 11 mmol) in diethyl ether (10 mL) was heated at 60 °C in a sealed tube for 6 days. The adduct **13** was formed in 22% conversion yield determined by ^{1}H NMR and used in the next reaction step without isolation. ^{1}H NMR ($CDCl_3$) δ 5.09 (2H, s, PhC*H*$_2$), 5.73 (2H, t, *J*=1.3 Hz, H1,4), 7.18 (2H, br s, H5,6), 7.19–7.22 (5H, m, Ph).

4.1.8. Dimethyl-7-adamantylidene-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (14). A solution of 6,6-adamantylidenefulvene[13] (1.00 g, 5.05 mmol) and dimethyl dicarboxylate (2.99 g, 14.08 mmol) in chloroform (20 mL) was refluxed overnight. Solvent was removed in vacuo to afford dark colored oil. Flash column separation (silica, petroleum ether/ethyl acetate 5:1) afforded yellow colored oil. Compound **14** was obtained as a colorless solid by treatment with diethyl ether/petroleum ether (1.36 g, 80%) mp 156–158 °C. ^{1}H NMR ($CDCl_3$) δ 1.45–1.86 (12H, m, AdH), 2.46 (2H, s, AdH), 3.81 (6H, s, CH_3), 4.41 (2H, t, *J*=1.90 Hz, H1,4), 6.98 (2H, t, *J*=1.90 Hz, H4,5). ^{13}C NMR ($CDCl_3$) δ 28.3, 32.2, 37.1, 38.1, 38.2 (C3′), 51.9 (C1′), 52.0 (C1,4), 52.6 (CH_3), 115.2 (C7,2′), 142.5 (C5,6), 152.1 (C5,6), 155.5 (C2,3), 166.1 (C=O). IR (KBr, cm^{-1}): 1741 (C=O). HRMS $C_{21}H_{24}O_4$ requires *m/z* 340.1674, found 340.1675.

4.1.9. 7-Adamantylidene-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic acid (15). Diester **14** (2.63 g, 8 mmol) was dissolved in methanol (5 mL), and a solution of 10% aqueous potassium hydroxide (30 mL) was added. Reaction mixture was stirred for 12 h at room temperature. Solvent was removed in vacuo, residue taken up in water (20 mL) and acid **15** precipitated by careful addition of concentrated hydrochloric acid as a colorless solid (1.32 g, 53%), which was used in next reaction without further purification. Obtained from crude spectrum ^{1}H NMR ($CDCl_3$) δ 2.01–2.78 (16H, m, AdH, H1,4), 7.31 (2H, s, H5,6).

4.1.10. (1α,2β,3β,6β,7β,8α)-11-Benzyloxycarbonyl-11-aza-12-oxatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene-2,7-dicarboxylic anhydride (9c), (1α,2β,3β,6β,7β,8α,9β,10α,13α,14β)-15-benzyloxycarbonyl-15-aza-16,17-dioxahexacyclo[6.6.1.1^{3,6}.1^{10,13}.0^{2,7}.0^{9,14}]heptadeca-4,11-diene-2,7-dicarboxylic anhydride (16) and (1α,2β,3β,6β,7β,8α,9β,10β,13β,14β)-15-benzyloxycarbonyl-15-aza-16,17-dioxahexacyclo[6.6.1.1^{3,6}.1^{10,13}.0^{2,7}.0^{9,14}] and heptadeca-4,11-diene-2,7-dicarboxylic anhydride (17). Furan (2 mL, 29 mmol) was added to a mixture of

diacid **13** (300 mg, 0.52 mmol) and acetic anhydride (2.0 g, 19.6 mmol). The mixture was stirred at 60 °C overnight. The reaction was separated by column chromatography (Et_2O) to afford in the order of elution: mono-adduct **9c** (120 mg, 63%), *exo*,*endo*;*exo*,*exo*-bis-adduct **16** (10 mg, 4%) and a mixture of **16** and *exo*,*endo*;*exo*,*endo*-bis-adduct **17** (trace), all of which were crystallized from diethyl ether. Compound **9c** mp 147–148 °C. ^{1}H NMR ($CDCl_3$) δ 4.78 (1H, s, H1 or H8), 4.83 (1H, s, H8 or H1), 4.98 (1H, d, J=12.0 Hz, C*H*aHbPh), 5.15 (1H, d, J=12.0 Hz, CHa*H*bPh), 5.19 (1H, s, H3 or H6), 5.22 (1H, s, H6 or H3), 6.18 (1H, d, J=4.8 Hz, H4 or H5), 6.48 (1H, d, J=4.8 Hz, H5 or H4), 6.72 (1H, s, H9 or H10), 6.78 (1H, s, H10 or H9), 7.31–7.40 (5H, m, Ph). ^{13}C NMR ($CDCl_3$) δ 59.7, 59.8 (C1,8), 68.2 (CH_2Ph), 70.6, 71.5 (C2,7), 83.0, 83.1 (C3,6), 128.9, 129.3, 129.3 (C2′3′4′ of Ph), 136.4 (C1′ of Ph), 134.7, 135.0 (C4,5), 140.6, 141.8 (C9,10), 152.4 (*C*O_2Bn), 170.8 (carbonyl of anhydride). IR (KBr, cm^{-1}): 1758 (C=OAnh), 1706 (C=OBn). HRMS requires $C_{20}H_{15}NO_6$ *m*/*z* 365.0899, found 365.0904. Anal. calcd for $C_{20}H_{15}NO_6$: C, 65.74; H, 4.14; N, 3.84. Found C, 65.85; H, 4.15; N, 3.82%. Compound **16** mp 168–170 °C. ^{1}H NMR ($CDCl_3$) δ (1H, d, J=6.0 Hz, H9), 2.04 (1H, d, J=6.0 Hz, H14), 4.39 (1H, s, H1), 4.81 (1H, s, H8), 4.81 (1H, s, H10), 4.94 (1H, s, H13), 4.95 (1H, d, J=12.0 Hz, C*H*aHbPh), 5.12 (1H, d, J=12.0 Hz, CHa*H*bPh), 5.24 (1H, s, H3), 5.28 (1H, s, H6), 6.12 (1H, dd, J=5.8, 1.7 Hz, H4), 6.38 (1H, dd, J=5.8, 1.6 Hz, H12), 6.41 (1H, dd, J=5.8, 1.6 Hz, H11), 6.44 (1H, dd, J=5.8, 1.7 Hz, H5), 7.32–7.40 (5H, m, Ph). ^{13}C NMR ($CDCl_3$) δ 47.5, 47.7 (C9,14), 58.4, 58.7 (C1,8), 67.9 (CH_2Ph), 68.8, 69.8 (C2,7), 81.3, 81.4 (C10,13), 83.8, 83.9 (C3,6), 129.1, 129.1, 129.3 (C2′3′4′ of Ph), 134.9, 134.9 (C4,5), 136.9 (C1′ of Ph), 138.3, 138.6 (C11,12), 153.7 (*C*O_2Bn), 171.3 (carbonyl of anhydride). IR (KBr, cm^{-1}): 1756 (C=OAnh), 1701 (C=OBn). HRMS $C_{24}H_{19}NO_7$ requires *m*/*z* 433.1161, found 433.1162. Compound **17** obtained from crude spectrum. ^{1}H NMR ($CDCl_3$) δ 2.58 (1H, d, J=6.5 Hz, H9), 2.62 (1H, d, J=6.5 Hz, H14), 4.13 (1H, s, H1), 4.21 (1H, s, H8), 4.85 (1H, m, H10), 4.90 (1H, m, H13), 5.01 (1H, d, J=11.8 Hz, C*H*aHbPh), 5.08 (1H, d, J=11.8 Hz, CHa*H*bPh), 5.19 (1H, m, H3), 5.24 (1H, m, H6), 5.80 (1H, dd, J=5.8, 1.6 Hz), 5.92 (1H, dd, J=5.8, 1.7 Hz), 6.16 (1H, dd, J=5.8, 1.7 Hz), 6.35 (1H, dd, J=5.8, 1.7 Hz, H4,5,11,12), 7.30–7.40 (5H, m, Ph).

4.1.11. (1α,2β,3β,6β,7β,8α,9β,10β,13β,14β)-15-Benzyloxycarbonyl-15-azahexacyclo[6.6.1.1^{3,6}.1^{10,13}.0^{2,7}.0^{9,14}]heptadeca-4,11-diene-2,7-dicarboxylic anhydride (18). A mixture of diacid **13** (114 mg, 0.38 mmol) and cyclopentadiene (1.0 g, 15.2 mmol) in acetic anhydride (2.0 g, 19.6 mmol) was stirred at 65 °C overnight. Column chromatography (Et_2O/petroleum ether 1:1) afforded the bis-adduct **18** (56 mg, 34%), which crystallized from Et_2O/petroleum ether as colorless crystals, mp 173–174 °C. ^{1}H NMR ($CDCl_3$) δ 1.19 (1H, d, J=8.4 Hz, Hc), 1.36 (1H, d, J=8.4 Hz, Hd), 1.47 (1H, d, J=10.3 Hz, Ha), 1.56 (1H, d, J=10.3 Hz, Hb), 2.41 (1H, d, J=1.5 Hz, H9), 2.42 (1H, d, J=1.5 Hz, H14), 2.88 (1H, s, H10), 2.92 (1H, s, H13), 3.30 (1H, s, H3), 3.35 (1H, s, H6), 4.17 (1H, s, H1), 4.22 (1H, s, H8), 4.99 (1H, d, J=11.9 Hz, C*H*aHbPh), 5.06 (1H, d, J=11.9 Hz, CHa*H*bPh), 5.55 (1H, dd, J=5.6, 3.1 Hz, H11), 5.87 (1H, dd, J=5.6, 3.1 Hz, H12), 5.70 (1H, dd, J=5.5, 3.2 Hz, H4), 6.08 (1H, dd, J=5.5, 3.2 Hz, H5), 7.36–7.39 (5H, m, Ph). ^{13}C NMR ($CDCl_3$) δ 46.3, 46.4 (C10,13), 47.1, 48.0 (C9,14), 49.8, 49.9, 50.0, 52.4 (C3,6,16,17), 59.6, 60.0 (C1,8), 67.5 (CH_2Ph), 69.75, 70.5 (C2,7), 129.3, 129.3, 129.6 (C2′3′4′ of Ph), 132.8, 133.2, 134.1, 134.4 (C4,5,11,12), 136.9 (C1′ of Ph), 152.5 (*C*O_2Bn), 173.1, 173.2 (carbonyl of anhydride). IR (KBr, cm^{-1}): 1761 (C=OAnh), 1703 (C=OBn). HRMS $C_{26}H_{23}NO_5$ requires *m*/*z* 429.1576, found 429.1576 (91.5%), 338.1 (7.5), 294.1 (61.0), 272.1 (32.0), 228.1 (100), 184.1 (60.0), 156.1 (21.8), 128.1 (10.0). Anal. calcd for $C_{26}H_{23}NO_5$: C, 72.7; H, 5.40; N, 3.26. Found C, 72.61; H, 5.39, N, 3.25%.

4.1.12. (1α,2β,3α,6α,7β,8α)-11,12-Dibenzyloxycarbonyl-11,12-diazatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene-2,7-dicarboxylic anhydride (19). A mixture containing diacid **13** (200 mg, 0.64 mmol) and *N*-Z pyrrole **11** (260 mg, 1.3 mmol) in acetic anhydride (2.2 g, 21.6 mmol) was stirred at 80 °C overnight. The reaction was purified by column chromatography (Et_2O/petroleum ether 1:1) to afford the product **19**, which was crystallized from benzene (70 mg, 22%), mp 147 °C (colorless crystals). ^{1}H NMR ($CDCl_3$) δ 4.84 (2H, br s, two of CH_2Ph×2), 5.02 (2H, br s, two of CH_2Ph×2), 5.20 (4H, s, H1,3,6,8), 6.71 (2H, s, two of H4,5,9,10), 6.76 (2H, s, two of H4,5,9,10), 7.33–7.36 (10H, m, Ph×2). ^{1}H NMR ($CDCl_3$, 60 °C) δ 4.94 (4H, br s, CH_2Ph×2), 5.18 (4H, s, H1,3,6,8), 6.72 (4H, s, H4,5,9,10), 7.24–7.31 (10H, m, Ph×2). ^{13}C NMR ($CDCl_3$, 30 °C) δ 63.3 (C1,3,6,8), 68.5 (CH_2Ph), 71.2 (C3,7), 129.1, 129.2 (C2′3′4′ of Ph, two overlapped), 136.3 (C1′ of Ph), 141.2, 141.9 (C4,5,9,10), 154.2 (*C*O_2Bn), 168.4 (carbonyl of anhydride). IR (KBr, cm^{-1}): 1771 (C=OAnh), 1711 (C=OBn). LRMS (*m*/*z*) 499 (M+H, 13.2%), 319 (15.0), 297 (21.9), 201 (76.2), 157 (100). Anal. calcd for $C_{28}H_{22}N_2O_7$: C, 67.45; H, 4.45; N, 5.62. Found C, 67.15; H, 4.42; N, 5.61%.

4.1.13. (1α,2β,3β,6β,7β,8α)-11-Benzyloxycarbonyl-12-isopropylidene-11-azatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene-2,7-dicarboxylic anhydride (20). 6,6-Dimethylfulvene (200 mg, 1.9 mmol) was added to a mixture of diacid **13** (248 mg, 0.83 mmol) and acetic anhydride (3.0 g, 39.0 mmol). The mixture was stirred at 60 °C overnight. Column chromatography (CH_2Cl_2) afforded mono-adduct **20**, which was crystallized from CH_2Cl_2/petroleum ether as colorless crystals (50 mg, 15%), mp 124–125 °C. ^{1}H NMR ($CDCl_3$) δ 1.51 (6H, s, CH_3), 3.80 (1H, s, H3), 3.83 (1H, s, H6), 4.84 (1H, s, H1), 4.89 (1H, s, H9), 4.98 (1H, d, J=12.1 Hz, C*H*aHbPh), 5.14 (1H, d, J=12.1 Hz, CHa*H*bPh), 5.98 (1H, s, H4), 6.26 (1H, s, H5), 6.66 (1H, s, H9), 6.73 (1H, s, H10), 7.31–7.39 (5H, m, Ph). ^{13}C NMR ($CDCl_3$) δ 19.8 (CH_3), 48.2 (C3,6), 61.2, 61.2 (C1,8), 67.7 (CH_2Ph), 128.7, 128.9, 129.0 (C2′3′4′ of Ph), 133. 7, 133.9 (C4,5), 136.5 (C1′ of Ph), 140.3, 141.5 (C9,10), 115.8 (C13), 145.4 (C12), 151.6 (*C*O_2Bn), 171.5 (carbonyl of anhydride). IR (KBr, cm^{-1}): 1768 (C=OAnh), 1709 (C=OBn). HRMS $C_{24}H_{21}NO_5$ requires *m*/*z* 403.1420, found 403.1425.

4.1.14. (1α,2β,3α,6α,7β,8α)-11-Aza-12-oxatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene-2,7-dicarboxylic anhydride (27). *Method A*. To a solution of anhydride **7b**

obtained by FVP of **5b** (100 mg, 0.43 mmol) in $CDCl_3$ (0.5 mL) pyrrole was added (160 mg, 2.86 mmol) and kept at room temperature for 10 min. The reaction mixture was subjected to radial chromatography (petroleum ether/ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate) to afford the product **27**, as a colorless solid (17 mg, 16%), mp 168–169 °C. ^{1}H NMR ($CDCl_3$) δ 4.32 (1H, br s, NH), 4.48 (2H, t, J=1.5 Hz, H1,7), 5.23 (2H, t, J=0.8 Hz, H3,6), 6.67 (2H, t, J=1.5 Hz, H9,10), 6.81 (2H, t, J=0.8 Hz, H4,5). ^{13}C NMR ($CDCl_3$) δ 63.5 (C2,7), 71.9 (C1,8), 81.2 (C3,6), 138.2, 142.2, 164.9 (CO). IR (KBr, cm^{-1}): 1778 (C=O). HRMS $C_{12}H_9NO_5$ requires m/z 247.0481, found 247.0492.

Method B. To a solution of anhydride **7b** obtained by FVP of **5b** (68 mg, 0.29 mmol) in $CDCl_3$ (0.5 mL) *N*-TMS substituted pyrrole **22** was added (152 mg, 1.10 mmol) and kept at room temperature for 30 min. The reaction mixture was subjected to radial chromatography (petroleum ether/ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate) to afford **27** (23 mg, 22%).

Method C. To a solution of anhydride **7b** obtained by FVP of **5b** (76 mg, 0.33 mmol) in $CDCl_3$ (0.5 mL) *N*-*i*-Pr_3Si pyrrole **23** was added (268 mg, 1.20 mmol) and kept at room temperature for 30 min. The reaction mixture was subjected to radial chromatography (petroleum ether/ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate) to afford **27** (14 mg, 13%).

4.1.15. (1α,2β,3α,6α,7β,8α)-11-(Triphenylmethyl)-11-aza-12-oxatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene-2,7-dicarboxylic anhydride (28). To a solution of anhydride **7b** obtained by FVP of **5b** (100 mg, 0.43 mmol) in $CDCl_3$ (0.5 mL) *N*-Tr-pyrrole **24** was added (390 mg, 1.17 mmol) and kept at room temperature for 10 min. The reaction mixture was subjected to radial chromatography (petroleum ether/ethyl acetate 10:1, then solvent polarity was gradually increased to ethyl acetate) to afford the product **28**, as a colorless solid (25 mg, 12%), mp 192–193 °C. ^{1}H NMR ($CDCl_3$) δ 4.79 (2H, t, J=0.9 Hz, H1,8), 5.29 (2H, t, J=0.9 Hz, H3,6), 6.56 (2H, t, J=0.9 Hz, H9,10), 6.74 (2H, t, J=0.9 Hz, H4,5), 7.01–7.28 (15H, m, Ph). ^{13}C NMR ($CDCl_3$) δ 64.2 (C2,7), 70.8 (C1,8), 80.4 (C3,6), 136.7, 140.1, 144.2, 146.8, 150.2, 152.7, 165.1 (CO). IR (KBr, cm^{-1}): 1772 (C=O). HRMS $C_{31}H_{23}NO_5$ requires m/z 489.1576, found 489.1551.

4.1.16. X-ray data: compound 9f. $C_{23}H_{22}O_4$; monoclinic, space group $P2(1)/n$, a=10.2110(8), b=15.985(2), c=10.6753(13) Å, α=90, β=91.034(6), γ=90°, V=1742.2(4) Å^3, Z=4, D_x=1.382 Mg m^{-3}, l=0.71073 Å, T=100 K, R=0.059 for 3299 unique reflections; **9c**: ($C_{20}H_{15}NO_6$); monoclinic, space group $P2(1)/c$, a=7.0114(3), b=16.4247(5), c=14.0029(7) Å, α=90, β=101.756(2), γ=90°, V=1578.75(11) Å^3, Z=4, D_x=1.537 Mg m^{-3}, l=0.71073 Å, T=100 K, R=0.059 for 3592 unique reflections; **18**: ($C_{26}H_{23}NO_5$); triclinic, space group P-1, a=10.2470(3), b=11.0605(4), c=11.4148(5) Å, α=104.893(2), β=103.557(2), γ=116.008(2)°, V=1030.01(7) Å^3, Z=2, D_x=1.385 Mg m^{-3}, l=0.71073 Å, T=100 K, R=0.059 for 3592 unique reflections; **19**: ($C_{28}H_{22}N_2O_7$); monoclinic, space group $P2(1)/n$, a=22.3696(7), b=7.4256(2), c=29.9342(6) Å, α=90, β=106.724(2), γ=90°, V=4762.0(2) Å^3, Z=8, D_x=1.391 Mg m^{-3}, l=0.71073 Å, T=150 K, R=0.027 for 10,869 unique reflections.

4.2. Supplementary material

Full crystallographic data for compounds **9c**, **9f**, **18**, and **19** have been deposited with the Cambridge Crystallographic Data Centre, deposition numbers CCDC 624019—624022. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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