JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

# Furanodendralenes

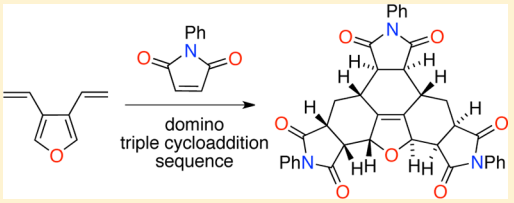
Thomas Fallon,[†] Anthony C. Willis,[†] Michael N. Paddon-Row,*[,‡] and Michael S. Sherburn*[,†]

[†]Research School of Chemistry, The Australian National University, Canberra, Australian Capital Territory 0200, Australia

[‡]School of Chemistry, The University of New South Wales, Sydney, New South Wales 2052, Australia

Supporting Information

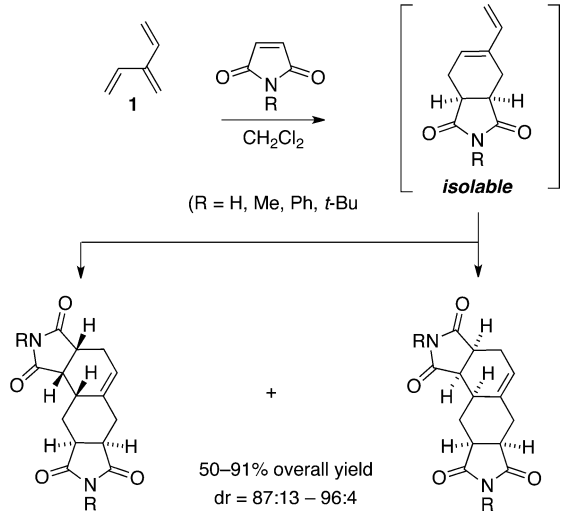
**ABSTRACT:** An examination of Diels–Alder reactions of furan-containing analogues of dendralenes has revealed complex and fascinating reaction sequences, which chart the inherent site and stereoselectivity of these processes and give rapid access to structures of high molecular complexity.




## INTRODUCTION

Growing interest in the dendralene family of branched unsaturated hydrocarbons[1] can be traced, in large part, to their significant synthetic potential. These compounds behave as multidienes, participating in *diene-transmissive* Diels–Alder[1,2] (DTDA) sequences that allow a rapid increase in structural complexity.[3] DTDA sequences of the simplest members, [3]dendralenes, have been studied the most intensively. The parent [3]dendralene (**1**), for example, has been shown to react as a diene in a selective single cycloaddition reaction with a range of electron-poor dienophiles[4] (Scheme 1). The resulting monocycloadduct carries a "transmitted" semicyclic diene that readily undergoes a second cycloaddition. Four new C–C bonds and a new decalin system are generated in this powerful double cycloaddition sequence, and moreover, the ability to employ two different dienophiles is of obvious value. Nevertheless, while [3]dendralene is manageable in the laboratory, it is not an ideal precursor since it readily dimerizes under normal laboratory conditions.

**Scheme 1. DTDA Sequence Between [3]Dendralene (1) and the Representative Dienophile *N*-Methylmaleimide (NMM)**




[4]Dendralene (**2**) is, in contrast, a bench stable compound, showing no sign of decomposition when stored neat in the laboratory. This compound undergoes DTDA sequences involving up to three cycloadditions (Scheme 2).[5] While significant progress is being made, there remains issues of selectivity in DTDA sequences involving [4]dendralene. First, uncatalyzed reactions generally give mixtures of products resulting from additions to the two different (*terminal* and *internal*) diene sites. Second, an initial addition to a *terminal* site produces a compound that is more reactive as a diene than the starting [4]dendralene, thereby leading to double DA adducts and precluding the possibility of two different dienophiles being employed in these two discrete cycloadditions.

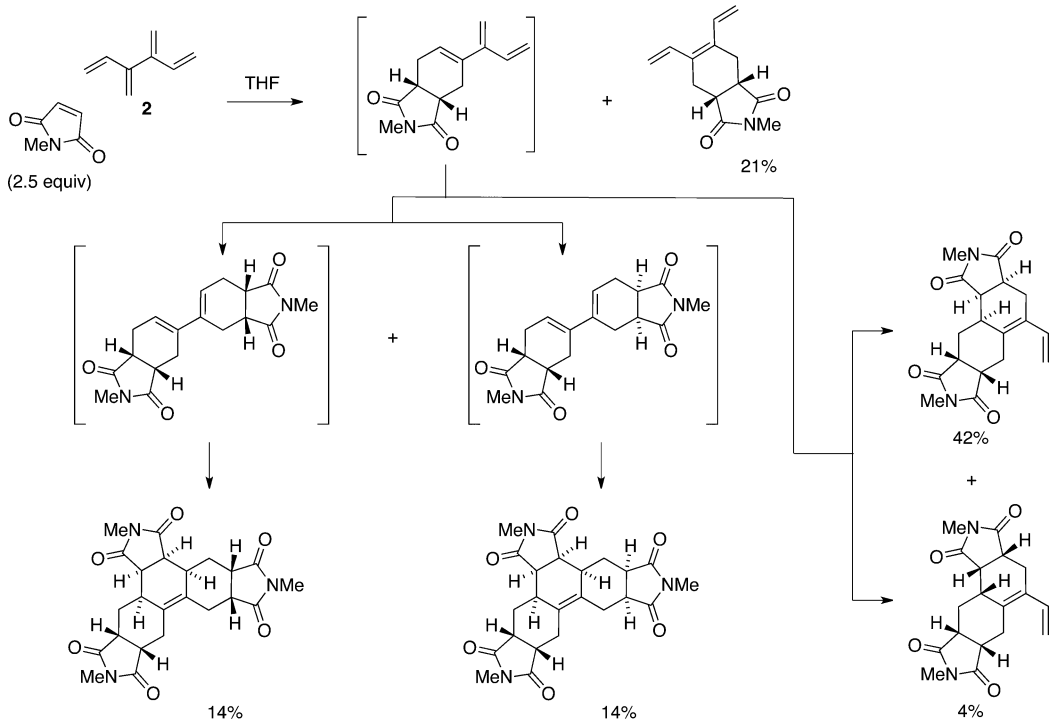
In addition to these reactivity problems, DTDA sequences involving the parent [3]dendralene and [4]dendralene produce compounds that lack the functionality to allow rapid elaboration into potential natural product targets. This study introduces a solution to the stability issue of [3]dendralene and generates more functionalized DTDA products. It also extends DTDA chemistry into the realm of thermodynamically controlled processes, thereby offering a potential solution to processes plagued by low levels of kinetic selectivity.

Furans are well-known as versatile dienes that permit the formation of oxygenated cyclohexene systems, through cycloadditions that are often found to be reversible on mild heating.[6] The purpose of this study was to unite the DTDA chemistry of dendralenes and the synthetic accessibility and versatility of furans. Depicted in Figure 1, are the four simplest furanodendralenes, structures **3**,[7] **4**, **5**,[8,9] and **6**, which are obtained by formal replacement of a pair of diene *inside* hydrogens of a dendralene with an oxygen.[10] In this study we report the Diels–Alder (DA) chemistry of furano[3]dendralene structure **3** and the three furano[4]dendralenes **4**, **5**, and **6** with maleimide dienophiles. We demonstrate that the incorporation

**Received:** February 25, 2014
**Published:** February 28, 2014

   dx.doi.org/10.1021/jo500458y | J. Org. Chem. 2014, 79, 3185–3193

**Scheme 2. DTDA Sequences Between [4]Dendralene (2) and *N*-Methylmaleimide (NMM)**



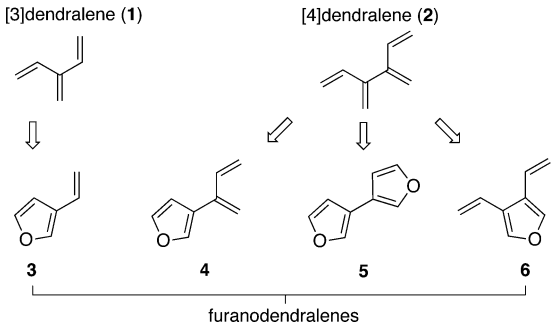




**Figure 1.** Dendralenes and furanodendralenes.

of furan rings into dendralene systems dramatically changes the reactivity and selectivity of DTDA sequences, and leads rapidly to oxygenated multicyclic structures, which should find application in efficient target synthesis.

DTDA reaction sequences involving a furofuran[11] and 3-alkenylfurans[12] have been reported, as have single additions of dienophiles to the semicyclic diene site of 3-alkenylfurans.[13] All prior work in this area involves furano[3]dendralenes, with two reports of DTDA reaction sequences previously published. Thus, Eberbach and co-workers reported a single example of a DTDA sequence involving a furofuran (Scheme 3a)[11] and Benítez and co-workers examined the DTDA reactivity of substituted 3-alkenyl furans (Scheme 3b).[12] Two separate reports of single cycloadditions of dienophiles to the semicyclic diene site of 3-alkenyl furans have also appeared, in reactions that represent key steps in total syntheses of natural products (Scheme 3c,d).[13] The goal of the present study was to develop a better understanding of the reactivity of these systems by preparing and studying a significantly broader range of substrates, and ones that lack extraneous substituents that might bias the outcomes of cycloaddition reactions.

## RESULTS AND DISCUSSION

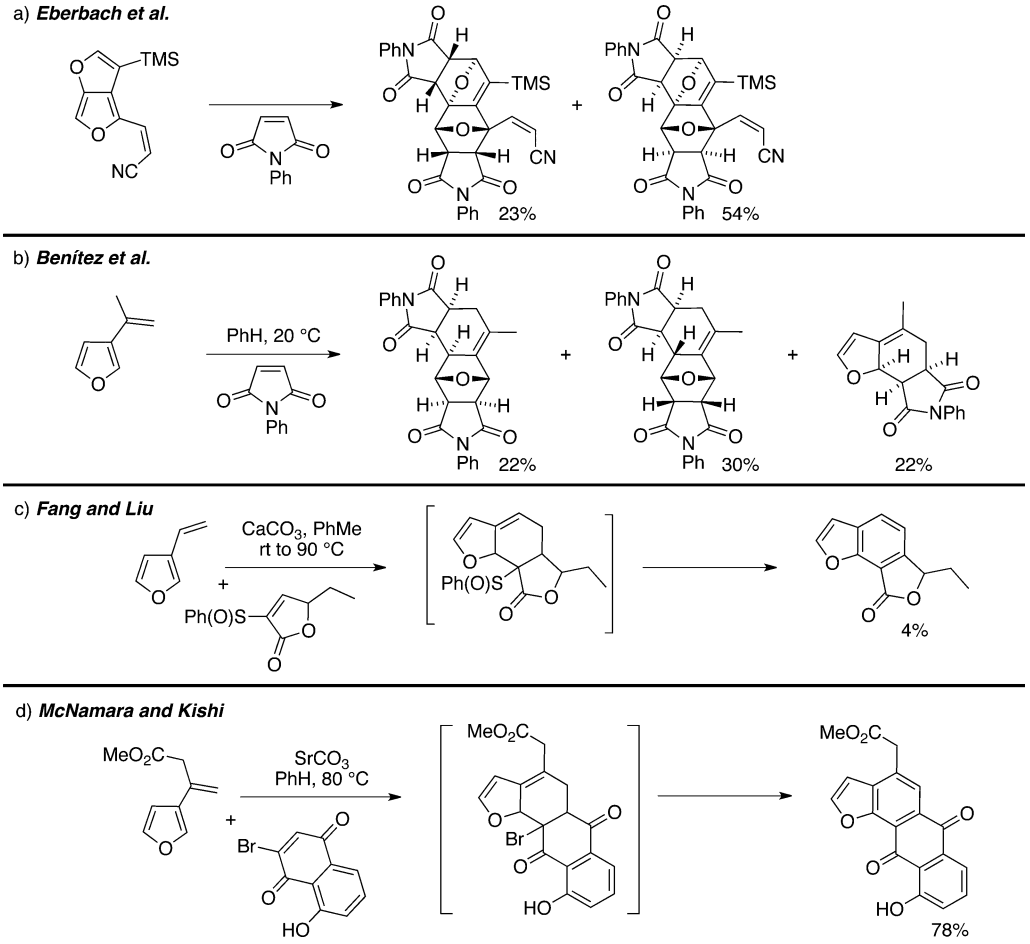
3-Vinylfuran **3** has been prepared several times, invariably by Peterson olefination of commercially available 3-furaldehyde.[7] We find that the volatility of 3-vinylfuran **3** (bp ca. 85 °C) renders these procedures challenging, at least to obtain the compound in pure, solvent-free form. We therefore developed a new approach employing the DBU elimination of 3-(2′-bromoethyl)furan (Scheme 4), with the product isolated in pure form by bulb-to-trap distillation from the reaction mixture. 2-(3-Furyl)-1,3-butadiene **4** was prepared via a Ni(0)-catalyzed Negishi cross-coupling reaction between chloroprene and the organozinc reagent derived from 3-bromofuran. We recently reported a synthesis of 3,3′-bifuran **5**,[8] using a modified version of previously reported protocols.[9] 3,4-Divinylfuran **6** was prepared through a double Kumada–Tamao–Corriu cross-coupling reaction between 3,4-dibromofuran and vinyl magnesium bromide.

3-Vinylfuran **3**[7] underwent a DA reaction with 1 mol equiv of *N*-methylmaleimide (NMM) in $CDCl_3$ at 50 °C to give predominantly a 1:1 mixture of *exo* and *endo* furan adducts **7** and **8** in 61% yield (Scheme 5). A small amount (4%) of the semicyclic diene addition product **9** was also isolated.[14] This distribution of products is significantly different from all previous reports of cycloadditions involving more highly substituted 3-alkenylfurans.[12,13] It is also different to the computationally predicted selectivities of the reaction of 3-vinylfuran with maleic anhydride by Sastry.[15] This result is, however, consistent with our M06-2X/6-311+G(2df,p)//B3LYP/6-31G(d) calculations, which predict a 1:1 ratio of *endo*:*exo* products and an 85:15 ratio of furan diene:semicyclic diene addition.

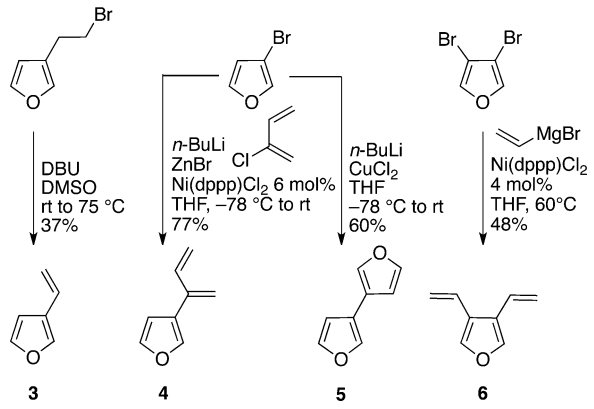
Upon exposure of 3-vinylfuran **3** to an excess of dienophile, no less than six products were obtained, in a high overall yield (Scheme 5). The four stereoisomeric DTDA products **10**, **11**, **12**, and **13** represented 90% of the mass balance from the


dx.doi.org/10.1021/jo500458y | J. Org. Chem. 2014, 79, 3185−3193

**Scheme 3. Published Examples of DA Reactions Involving 3-Alkenylfurans**




**Scheme 4. Synthesis of Furanodendralenes**



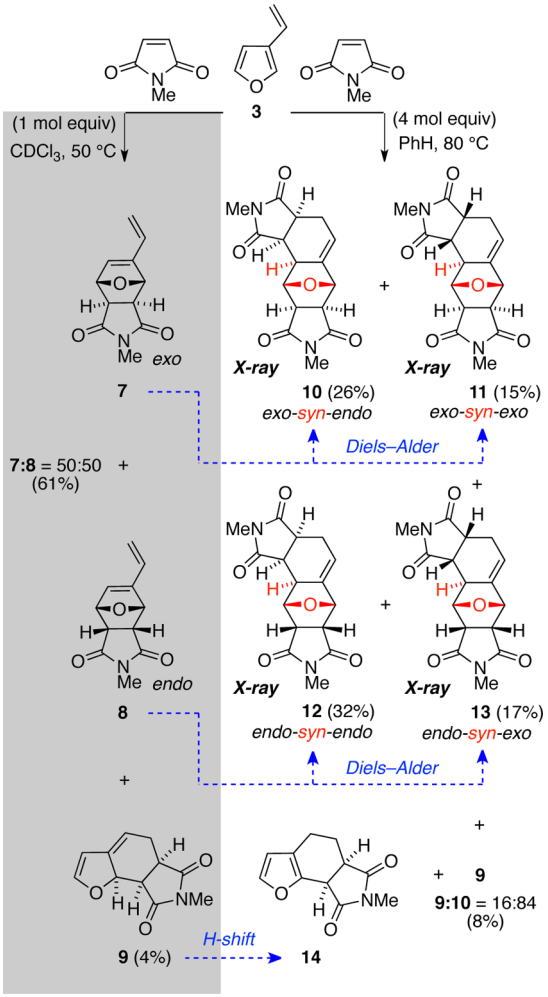

reaction. These structures were secured through single crystal X-ray analyses.[16] Double DA adducts **10** and **11** are derived from *exo*-monoadduct **7**, with double DA adducts **12** and **13** originating from *endo*-monoadduct **8**. It is evident that semicyclic dienes **7** and **8** undergo kinetically controlled cycloadditions with NMM with high $\pi$-diastereofacial selectivity, inasmuch as all four double cycloadducts are the result of addition *syn*- to the oxa bridge of the oxa-norbornene (as depicted in red in Scheme 5). Approach to the opposite face of vinyl-oxa-norbornenes **7** and **8** is evidently much more sterically challenging. Interestingly, the *endo*:*exo* ratio for each of the two cycloadditions is ca. 2:1. Presumably the presence of the oxa-bridge introduces a steric penalty toward *endo* approach, allowing the *exo* pathway to compete. In addition to these bis-adducts, small amounts of semicyclic monoadduct **9** and its isomer **14** were also isolated. Furan **14** is the product of aromatization of **9**, presumably through a stepwise mechanism.

The reactions of the three furano[4]dendralenes with maleimide dienophiles are summarized in Scheme 6. 2-(3-Furyl)-1,3-butadiene **4**[10] is an interesting substrate since it carries three distinct diene sites, namely the furan diene, an acyclic 1,3-butadiene, and a semicyclic diene. When treated with 1 mol equiv of NMM, the rapid and clean formation of monoadduct **15** is observed (Scheme 6a). This outcome reflects the higher reactivity of the acyclic 1,3-butadiene unit. Reaction at either of the other two sites would require a break in aromaticity, which is too high an energetic penalty. Our M06-2X/6-311+G(2df,p)//B3LYP/6-31G(d) calculations confirm that *endo* and *exo*-mode additions of NMM with 1,3-butadiene have significantly lower activation enthalpies and free energies than those between NMM and furan.

In stark contrast to this highly selective monoaddition, when furano[4]dendralene **4** was treated with an excess of NMM, a complex mixture of products was obtained. Upon the basis of the results with 3-vinylfuran **3**, we suspect a preference for the furan diene in the reaction between monoadduct **15** and NMM. This reaction would give four stereoisomeric double DA adducts, each of which would give at least two triple DA adducts.

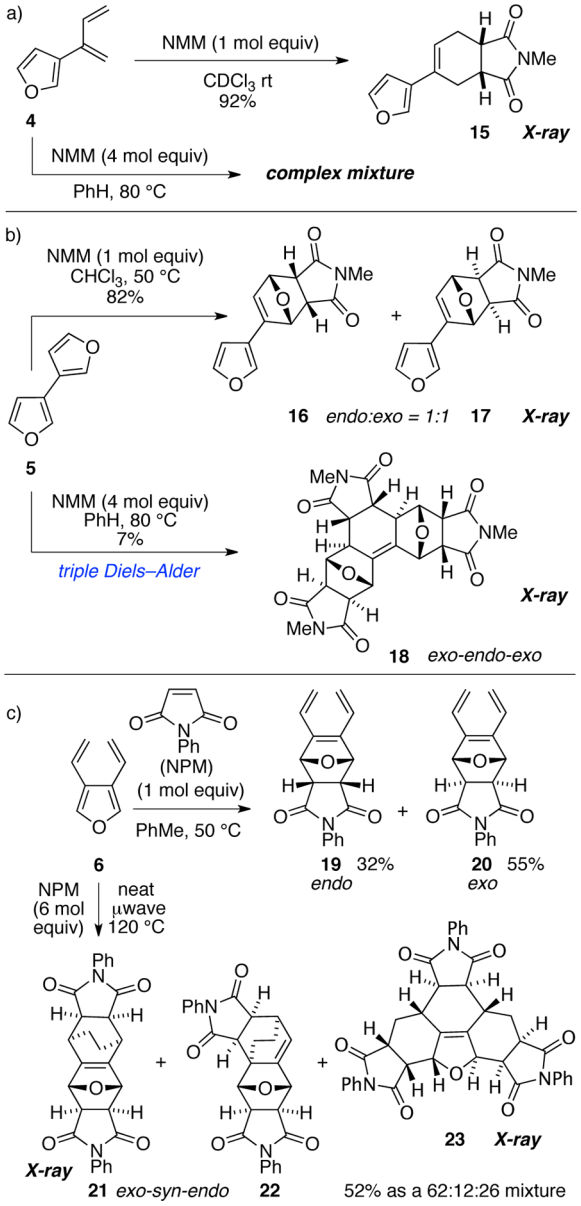

dx.doi.org/10.1021/jo500458y | J. Org. Chem. 2014, 79, 3185−3193

**Scheme 5. Reaction of 3-Vinylfuran 3 with *N*-Methyl Maleimide (NMM)[a]**




[a]Products from the 1 mol equiv of NMM reaction are depicted in the shaded box, products from the 4 mol equiv of NMM reaction are unshaded.

**Scheme 6. Reaction of Furano[4]dendralenes 4, 5, and 6 with Maleimide Dienophiles**



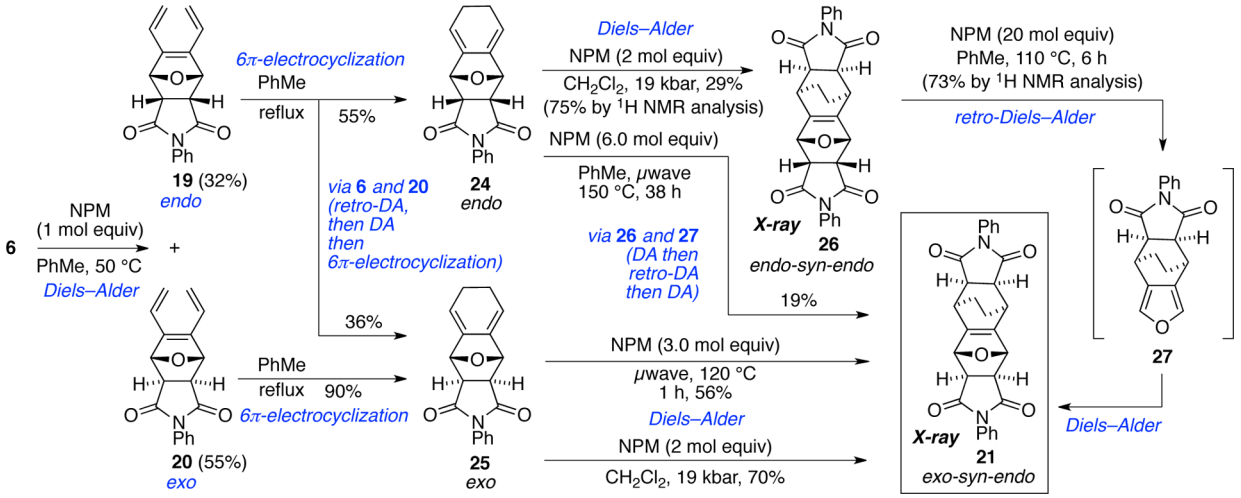

The reaction of 3,3′-bifuran **5**[8] with 1 mol equiv of NMM is highly site selective for one of the two equivalent furan dienes, giving a 1:1 mixture of *exo* and *endo* monoadducts **16** and **17** in 82% yield (Scheme 6b). The chemoselectivity of this reaction is interesting: the high yielding formation of monoadducts **16** and **17** demonstrates that these 3-alkenylfurans are significantly less reactive toward NMM than is the starting bifuran **5**. Presumably, the furan diene units of the monoadducts are both sterically more shielded and electronically less activated than in the bifuran precursor. The apparently exclusive site selection witnessed in this reaction, specifically for the furan diene rather than the internal diene, is predicted by our M06-2X/6-311+G(2df,p)//B3LYP/6-31G(d) calculations and is also consistent with simple aromaticity arguments: addition at a furan diene breaks the aromaticity of only one ring, whereas addition at the internal diene site of bifuran would break the aromaticity of two furan rings.

Treatment of 3,3′-bifuran **5** with an excess of NMM gave a complex mixture of products from which triple DA adduct **18** could be isolated after HPLC purification (Scheme 6b). The structure of this multicyclic system was unambiguously established using single crystal X-ray analysis.[16] This reaction's lack of selectivity is offset by a noteworthy boost in molecular complexity, with 6 new C−C bonds and 12 contiguous stereogenic centers generated in one simple synthetic operation. We remain cautious on the matter of the pathway to this product and its implications; the characterization of stereoisomer **18** is probably related to its ease of isolation rather than its ease of formation.

When 3,4-divinylfuran **6** was treated with *N*-phenylmaleimide (NPM; this compound was used in place of NMM in this series to produce more highly crystalline products to facilitate structure elucidation through single crystal X-ray analysis)[16] at 50 °C, a ca. 2:3 mixture of *endo* and *exo* adducts **19** and **20** was produced (Scheme 6c). The observation of addition to the furan diene instead of the semicyclic diene, and the formation of both *endo* and *exo* isomers in roughly the same amounts, is consistent with the DA reactions of the other furanodendralenes reported in this study.


dx.doi.org/10.1021/jo500458y | J. Org. Chem. 2014, 79, 3185−3193

**Scheme 7. Domino Pericyclic Reactions Involving 3,4-Divinylfuran 6 and *N*-Phenyl Maleimide**




When 3,4-divinylfuran **6** was treated with an excess of NPM at 120 °C, double DA adduct **21** was the major product. Under these conditions, isomeric double DA product **22** and triple DA adduct **23** were also isolated. Tris-adduct **23** was isolated as a single stereoisomer and is the result of an initial DA reaction by NPM at the semicyclic diene site of divinylfuran **6**, followed by a second addition to the other semicyclic diene site and finally an addition to the resulting transmitted diene. Evidently, following the first addition, the subsequent two additions are highly selective. If a method can be developed to steer the initial site selectivity to the semicyclic diene, a high yield of a single diastereomeric product can be anticipated.

A final set of experiments were conducted to identify the origins of double DA adducts **21** and **22** (Scheme 7). Heating the *exo* adduct **20** in refluxing toluene induced 6π-electrocyclization and the formation of 1,3-cyclohexadiene **25** in 90% yield. When *endo* adduct **19** was exposed to the same conditions, a mixture of 6π-electrocyclization products **24** and **25** was obtained. The formation of ***exo*** electrocyclization product **25** from ***endo*** *Z*-triene precursor **19** can be explained by a heat-promoted retro-DA reaction to give **6** and NPM, followed by an *exo* DA reaction to give **20** and, finally, a 6π-electrocyclization to give **25**.

DA reactions of 6π-electrocyclization products **24** and **25** were examined under both thermal and high pressure conditions. *exo*-1,3-Cyclohexadiene **25** reacted with NPM to give *exo-syn-endo*[17] compound **21** as the only isolable product. Isomer **22** (Scheme 6c) must arise through a 1,5-hydrogen shift of intermediate **25** followed by DA addition to the rearranged 1,3-cyclohexadiene intermediate.

When *endo*-1,3-cyclohexadiene **24** was treated with NPM at 19 kbar pressure, the corresponding double DA adduct **26** was isolated in 29% yield (the yield was estimated at 75% by $^1$H NMR analysis of the crude product mixture).[18] When treated with excess NPM at 150 °C, however, ***endo***-1,3-cyclohexadiene **24** gave rise to ***exo-syn-endo*** adduct **21** as the only observed product in 19% yield (this reaction was accompanied by significant decomposition). The formation of **21** in this reaction is notable and must arise first by initial DA reaction to give **26** followed by retro DA reaction to furan intermediate **27** then *exo* DA reaction to **21**. In effect, the minor product from the initial cycloaddition to the furano[4]dendralene **6**, namely, *endo* adduct **19**, is reunited with the major *exo* adduct **20** at the end of the sequence, specifically hexacycle **21**.

## CONCLUSION

To summarize, this exploratory study has demonstrated that the readily accessible furanodendralenes represent a fascinating platform for cascade pericyclic processes that contain multiple reversible and irreversible events. The DA reactions of the three furano[4]dendralene systems investigated here, namely, **4**, **5**, and **6**, have significantly expanded upon previous efforts in this field. Our work has revealed a rich and diverse chemistry and the rapid formation of complex multicyclic systems. Importantly, the outcomes of DA reactions of the furanodendralenes can now be rationalized through computational studies and an appreciation of the behaviors of different classes of diene systems. Evidently, challenges remain. In particular, methods to control the outcome of these domino sequences must be developed. The investigation described herein paves the way for such studies, which will ultimately set the scene for applications in target synthesis.

## EXPERIMENTAL SECTION

**General Methods.** $^1$H NMR spectra were recorded at 800, 600, 400, and 300 MHz. Residual chloroform (δ 7.26 ppm) was used as the internal reference for $^1$H NMR spectra recorded in this solvent. Coupling constants (*J*) are quoted to the nearest 0.1 Hz. $^{13}$C NMR spectra were recorded at 200, 150, 100, or 75 MHz. The central line of the deuterochloroform signal (δ 77.1 ppm) was used as an internal reference for $^{13}$C NMR spectra recorded in this solvent. Assignment of carbon signals was assisted by DEPT or HSQC experiments. IR spectra were recorded as thin films on sodium chloride plates for oils or as potassium bromide discs for solid products. Mass spectra were recorded using electron impact ($EI^+$) ionization mode at 70 eV for low-resolution mass spectra. High-resolution mass spectra were recorded employing a magnetic sector analyzer at 70 eV. Melting points are uncorrected. Analytical thin layer chromatography was performed using silica gel plates, precoated with silica gel 60 F243 (0.2 mm). Flash chromatography employed 230−400 mesh silica gel. Reactions were conducted under a positive pressure of dry argon or nitrogen in oven-dried glassware. Diethyl ether ($Et_2O$) and tetrahydrofuran (THF) were dried over sodium wire and distilled from sodium benzophenone ketyl. Petrol refers to 40−60 °C petroleum spirits unless otherwise stated. Commercially available chemicals were purified by standard procedures or used as purchased.


dx.doi.org/10.1021/jo500458y | J. Org. Chem. 2014, 79, 3185−3193

**3-Vinylfuran (3).** 3-(2-Bromoethyl)furan[19] (2.0 g, 11.4 mmol) was dissolved in DMSO (10 mL) in a 100 mL three-neck round-bottomed flask equipped with a short *vigreux* column connected to a liquid nitrogen cooled trap. The solution was stirred at rt, and 1,8-diazabicyclo[5.4.0]undec-7-ene (3.42 mL, 22.85 mmol, 2.0 mol equiv) was added dropwise. The solution was stirred at rt for two hours, and then the system was carefully evacuated (double manifold) keeping the pressure above 10 mbar. The solution was then slowly heated to 75 °C and stirred for 30 min, after which time the distillation was deemed complete. 3-Vinylfuran (**3**) was collected in the trap in pure form as a colorless, volatile oil (396 mg, 37%). $^1$H NMR and $^{13}$C NMR spectra were consistent with those reported in the literature.[20]

**3-(Buta-1,3-dien-2-yl)furan (4).** 3-Bromofuran (1.35 mL, 15.0 mmol) was dissolved in THF (30 mL), and the solution was cooled to −70 °C. *n*-BuLi in hexanes (1.6 M, 9.4 mL, 15.0 mmol, 1.0 mol equiv) was slowly added over 15 min, and the solution was stirred for 30 min. A solution of $ZnBr_2$ (3.72 g, 16.5 mmol, 1.1 mol equiv) in THF (12 mL) was slowly added over 15 min. The solution was allowed to warm to 0 °C, after which Ni(dppp)$Cl_2$ (490 mg, 0.9 mmol, 6 mol %) was added followed by chloroprene (1.40 g, 15.8 mmol, 1.05 equiv). The solution was allowed to warm to rt and stirred for 2 h. The solution was then poured onto a mixture of pentane (150 mL) and water (150 mL). The organic phase was washed with water (8 × 100 mL) and then brine (100 mL). The organic phase was dried over $MgSO_4$, and the solvent was carefully removed under reduced pressure (100 mbar/0 °C) to give the title compound **4** as a colorless, volatile oil (1.38 g, 77%): $^1$H NMR (300 MHz; $CDCl_3$) $\delta$/ppm 7.48 (1H, *br*. s) 7.41 (1H, dd, $J$ = 2.1 and 1.8 Hz) 6.54 (1H, ddd, $J$ = 17.4, 10.5, and 0.6 Hz) 6.49 (1H, ddd, $J$ = 1.5, 0.6, and 0.3 Hz) 5.45 (1H, dd, $J$ = 17.4, and 1.5 Hz) 5.22 (3H, m); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$/ppm 142.8 (CH), 139.8 (CH), 138.5 (CH), 137.2 (C), 124.2 (C), 116.4 ($CH_2$), 115.0 ($CH_2$), 101.0 (CH); $\nu_{max}$ (film)/cm$^{-1}$ 2977, 1840, 1796, 1632, 1599, 1575, 1556 and 1507; GCMS (75 eV) $m/z$ 120 (58, [M]$^+$), 91 (100); HREIMS calcd for $C_8H_8O$ [M]$^+$ 120.0575, found 120.0576.

**3,4-Divinylfuran (6).** 3,4-Dibromofuran[21] (12.07 g, 53.4 mmol) was dissolved in THF (25 mL), and Ni(dppp)$Cl_2$ (1.16 g, 2.14 mmol, 4 mol %) was added. The solution was stirred, and a solution of vinyl magnesium bromide in hexanes (1.0 M, 134 mL, 133.6 mmol) was slowly added such that the temperature did not exceed 60 °C. The solution was then heated at 60 °C for 2 h and cooled to rt, and 1 M HCl (200 mL) was added. The mixture was extracted with pentane (300 mL), and the organic phase washed with water (6 × 200 mL) and then brine. The organic phase was then dried over $MgSO_4$, and the solvent carefully removed under reduced pressure (40 mbar/0 °C). The residue was subjected to flash chromatography on silica gel eluting with pentane to give, after careful evaporation of the solvent (40 mbar/0 °C), the title compound **6** as a colorless oil (3.10g, 48%): $R_f$ 0.47 (pentane); $^1$H NMR (300 MHz; $CDCl_3$) $\delta$/ppm 7.44 (2H, s), 6.57 (2H, dd, $J$ = 17.7 and 11.1 Hz), 5.49 (2H, dd, $J$ = 17.7 and 1.5 Hz), 5.21 (2H, dd, $J$ = 11.1 and 1.5 Hz); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$/ppm 140.5 (CH), 126.5 (CH), 123.4 (C), 155.5 ($CH_2$); $\nu_{max}$ (film)/cm$^{-1}$ 2926, 1640, and 1528; EIMS (75 eV) $m/z$ 120.1 (35, [M]$^+$), 91.1 (100, [M − CO]$^+$); HREIMS calcd for $C_8H_8O$ [M]$^+$ 120.0575, found 120.0575.

**Compounds 7, 8, and 9.** Durene (16.5 mg, 0.123 mmol) was weighed into a valve-appended NMR tube and dissolved in $CDCl_3$ (0.5 mL). To this was added 3-vinylfuran **3** (0.35 mmol, as determined by subsequent quantitative $^1$H NMR analysis against durene), *N*-methylmaleimide (39 mg, 0.35 mmol, 1.0 mol equiv) and then $CDCl_3$ (0.3 mL). The tube was sealed and heated at 50 °C for 2.5 h. The solvent was removed in vacuo, and the residue was subjected to flash chromatography on silica gel using gradient elution with 1:1 diethyl ether:pentane to 100% diethyl ether to give the title compounds **7** and **8** as a 1:1 mixture (44 mg, 61%) and compound **9** as a white powder (3 mg, 4%). Analytical samples of **7** and **8** were obtained by preparative HPLC (Waters SunFire column, 1:1 EtOAc:hexane, 8.5 mL/min; **7**, $t_R$ 9.0 min; **8**, $t_R$ 10.5 min). Compounds **7** and **8** were obtained as colorless oils.

**7**: $R_f$ 0.20 (1:1 ether:pentane); $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 6.40 (1H, dd, $J$ = 17.7 and 10.8 Hz), 6.25 (1H, s) 5.44, (1H, d, $J$ = 17.7 Hz), 5.40 (1H, s), 5.31 (1H, d, $J$ = 10.8 Hz), 5.27 (1H, s), 2.98 (3H, s), 2.96 (1H, d, $J$ = 6.5 Hz), 2.86 (1H, d, $J$ = 6.5 Hz); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 176.4 (C), 176.1 (C), 148.9 (C), 131.6 (CH), 127.7 (CH), 118.1 ($CH_2$), 82.1 (CH), 80.4 (CH), 49.9 (CH), 47.5 (CH), 25.1 ($CH_3$); $\nu_{max}$ (film)/cm$^{-1}$ 3006, 2950, 1772, 1698, 1573, and 1436; EIMS (70 eV) $m/z$ (%) 205.1 (13, [M]$^+$), 149.0 (11), 120.0 (28), 94.0 (100); HREIMS calcd for $C_{11}H_{11}NO_3$ [M]$^+$ 205.0739, found 205.0744.

**8**: $R_f$ 0.20 (1:1 ether:pentane); $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 6.34 (1H, dd, $J$ = 17.6 and 10.8 Hz), 5.47 (1H, d, $J$ = 5.44 Hz), 5.48 (1H, d, 17.6 Hz), 5.32−5.30 (2H, m), 3.63 (1H, dd, $J$ = 7.5 and 5.8 Hz), 3.58 (1H, dd, $J$ = 7.2 and 5.5 Hz), 2.78 (3H, s); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 175.1 (C), 173.9 (C), 147.0 (C), 129.2 (CH), 127.7 (CH), 120.0 ($CH_2$), 80.4 (CH), 79.6 (C), 48.5 (CH), 46.4 (CH), 24.6 ($CH_3$); $\nu_{max}$ (film)/cm$^{-1}$ 2955, 2924, 1776, 1699, 1571 and 1433; EIMS (70 eV) $m/z$ (%) 205.1 (14, [M]$^+$), 149.0 (15), 120.0 (23), 94.0 (100); HREIMS calcd for $C_{11}H_{11}NO_3$ [M]$^+$ 205.0739, found 205.0740.

**9**: $R_f$ 0.08 (1:1 ether:pentane), mp 240−243 °C ($CH_2Cl_2$/hexane); $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 6.91 (1H, s), 5.64 (1H, d, $J$ = 2.3 Hz), 5.42 (1H, dd, $J$ = 7.4 and 3.7 Hz), 4.93 (1H, dt, $J$ = 8.2 and 3.3 Hz), 3.68 (1H, dd, $J$ = 8.4 and 8.4 Hz), 3.05 (1H, t, $J$ = 7.0 Hz), 2.97−2.94 (1H, m), 2.90 (3H, s), 2.02−1.99 (1H, m); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 179.0 (C), 174.3 (C), 155.5 (H), 142.9 (C), 106.7 (CH), 103.9 (CH), 79.1 (CH), 42.5 (CH), 38.5 (CH), 25.4 ($CH_2$), 25.1 ($CH_3$); $\nu_{max}$ (KBr)/cm$^{-1}$ 2952, 2923, 1775, 1697, 1566, and 1435; EIMS (70 eV) $m/z$ (%) 205.1 (100, [M]$^+$), 120.0 (97), 94.0 (66), 91 (64); HREIMS calcd for $C_{11}H_{11}NO_3$ [M]$^+$ 205.0739, found 205.0734.

**Compounds 10, 11, 12, 13, 9, and 14.** Durene (19 mg, 0.142 mmol) was weighed into a valve-appended NMR tube and dissolved in benzene-$d_6$ (0.5 mL). 3-Vinylfuran **3** (0.285 mmol, as determined by quantitative $^1$H NMR analysis against durene) was added followed by *N*-methylmaleimide (126 mg, 1.138 mmol, 4.0 mol equiv), and an additional aliquot of benzene-$d_6$ (0.7 mL) was added. The tube was sealed and heated at 80 °C for 1 h. The solution was cooled, and the solvent was removed in vacuo. The residue was subjected to flash chromatography on silica gel using gradient elution with diethyl ether to ethyl acetate:diethyl ether 2:1 to give the title compounds as white solids (compound **9** and **14**; 5 mg, 8% as a 16:84 **9**:**14** mixture, compounds **11**, **12**, and **13**; 58 mg, 64% as a 50:27:23 mixture **11**:**12**:**13** and compound **10**; 23 mg, 26%). Analytical samples of compounds **11**, **12**, and **13** were obtained by preparative HPLC (SunFire preparative column, ethyl acetate:hexane 1:1, 8.5 mL/min; **13**, $t_R$ 27 min; **11**, $t_R$ 32 min; **12**, $t_R$ 35 min). Recrystallization of compound **10** from chloroform/hexane gave crystals suitable for single crystal X-ray analysis. Recrystallization of compound **11** from dichloromethane/heptane gave crystals suitable for single crystal X-ray analysis. Recrystallization of compounds **12** and **13** from dichloromethane/hexane gave crystals suitable for single crystal X-ray analysis.

**14**: $R_f$ 0.30 (ether), mp 122−123 °C ($CH_2Cl_2$/hexane); $^1$H NMR (400 MHz; $CDCl_3$) $\delta$/ppm 7.38 (1H, d, $J$ = 2.0 Hz), 6.23 (1H, d, $J$ = 2.0 Hz), 4.08 (1H, d, $J$ = 8.4 Hz), 3.36 (1H, ddd, $J$ = 8.4, 4.4, and 4.0 Hz), 2.97 (3H, s), 2.56−2.47 (1H, m), 2.44−2.35 (2H, m), 1.91−1.82 (1H, m); $^{13}$C NMR (100 MHz; $CDCl_3$) $\delta$/ppm 178.4 (C), 174.7 (C), 143.2 (CH), 142.7 (C), 119.6 (C), 110.4 (CH), 41.1 (CH), 40.3 (CH), 25.1 ($CH_3$), 22.0 ($CH_2$), 19.2 ($CH_2$); $\nu_{max}$ (KBr)/cm$^{-1}$ 2935, 2853, 1771, 1700, 1500 and 1439; EIMS (70 eV) $m/z$ (%) 205.1 (55, [M]$^+$), 120.1 (100), 91.0 (49); HREIMS calcd for $C_{11}H_{11}NO_3$ [M]$^+$ 205.0739, found 205.0744.

**10**: $R_f$ 0.19 (ethyl acetate:diethyl ether 2:1); mp 247−255 °C ($CHCl_3$/hexane); $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 5.92−5.92 (1H, m), 5.49 (1H, s), 4.92 (1H, s), 3.36 (1H, dd, $J$ = 8.7 and 8.7 Hz), 3.10 (1H, t, $J$ = 7.0 Hz), 3.05 (1H, d, $J$ = 6.9 Hz), 2.96 (1H, d, $J$ = 6.8 Hz), 2.92 (3H, s), 2.86 (3H, s), 2.85 (1H, dd, $J$ = 14.1 and 7.4 Hz), 2.27 (1H, d, $J$ = 8.7 Hz), 2.04 (1H, d, $J$ = 15.2 Hz); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 178.8 (C), 176.4 (C), 176.2 (C), 176.0 (C), 141.8 (C), 118.1 (CH), 79.6 (CH), 79.5 (CH), 49.6 (CH), 48.9 (CH), 42.3 (CH), 40.2 (CH), 39.2 (CH), 25.2 ($CH_3$), 25.1 ($CH_3$),


dx.doi.org/10.1021/jo500458y | J. Org. Chem. 2014, 79, 3185−3193

23.5 ($CH_2$); $\nu_{max}$ (KBr)/cm$^{-1}$ 2961, 2933, 1767, 1692, and 1435; EIMS (70 eV) $m/z$ (%) 316.1 (100, $[M]^+$), 120.1 (77), 91.1 (93); HREIMS calcd for $C_{16}H_{16}N_2O_5$ $[M]^+$ 316.1059, found 316.1063.

**11**: $R_f$ 0.36 (ethyl acetate:diethyl ether 2:1); $t_R$ 35 min (ethyl acetate:hexane 1:1, 8.5 mL/min, SunFire prep column); mp 220−222 °C ($CH_2Cl_2$/hexane); $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 5.94−5.93 (1H, m), 5.51 (1H, d, $J$ = 6.4 HZ), 4.96 (1H, d, $J$ = 6.1 Hz), 3.63 (1H, dd, $J$ = 9.3 and 6.5 Hz), 3.56 (1H, dd, $J$ = 9.3 and 6.2 Hz), 3.32 (1H, t, $J$ = 8.6 Hz), 3.08 (1H, t, $J$ = 6.8 Hz), 2.91 (1H, s), 2.89 (1H, s) 2.86 (1H, ddd, $J$ = 15.4, 7.4, and 1.7 Hz), 2.14 (1H, d, $J$ = 8.6 Hz), 1.96 (1H, d, $J$ = 15.3 Hz); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 78.7 (C), 176.3 (C), 175.2 (C), 174.2 (C), 139.9 (C), 120.3 (CH), 78.6 (CH), 78.3 (CH), 51.2 (CH), 50.6 (CH), 40.2 (CH), 39.8 (CH), 39.0 (CH), 25.1 ($CH_3$), 24.7 ($CH_3$), 23.5 ($CH_2$); $\nu_{max}$ (KBr)/cm$^{-1}$ 2961, 2933, 1767, 1692 and 1435; EIMS (70 eV) $m/z$ (%) 316.1 (100, $[M]^+$), 120.1 (97), 91.1 (98); HREIMS calcd for $C_{16}H_{16}N_2O_5$ $[M]^+$ 316.1059, found 316.1050.

**12**: $R_f$ 0.36 (ethyl acetate:diethyl ether 2:1); $t_R$ 32 min (ethyl acetate:hexane 1:1, 8.5 mL/min, SunFire prep column); mp 267−268 °C ($CH_2Cl_2$/heptane); $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 6.04−6.03 (1H, m), 5.25 (1H, m) 5111 (1H, m), 3.06 (1H, m, $J$ = 7.0 Hz), 3.03 (1H, d, $J$ = 8.4 Hz), 3.01 (3H, s), 2.99 (3H, S), 2.85−2.80 (2H, m), 2.64 (1H, t, $J$ = 10.0 Hz) 1.95 (1H, d, $J$ = 10.4 Hz), 1.92−1.91 (1H, m); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 178.5 (C), 178.0 (C), 176.1 (C), 175.9 (C), 143.1 (C), 118.7 (CH), 81.3 (CH), 80.8 (CH), 49.5 (CH), 48.7 (CH), 44.4 (CH), 43.0 (CH), 39.0 (CH), 25.4 ($CH_3$), 24.8 ($CH_3$), 24.3 ($CH_2$); $\nu_{max}$ (KBr)/cm$^{-1}$ 2922, 1770, 1693, 1435 and 1388; EIMS (70 eV) $m/z$ (%) 316.1 (100, $[M]^+$), 120.1 (60), 91.1 (56); HREIMS calcd for $C_{16}H_{16}N_2O_5$ $[M]^+$ 316.1059, found 316.1063.

**13**: $R_f$ 0.36 (ethyl acetate:diethyl ether 2:1); $t_R$ 27 min (ethyl acetate:hexane 1:1, 8.5 mL/min, SunFire prep column); mp 245 °C ($CH_2Cl_2$/hexane); $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 6.05−6.05 (1H, m), 5.28 (1H, d, $J$ = 6.2 Hz), 5.15 (1H, d, $J$ = 6.1 Hz), 3.67 (1H, dd, $J$ = 9.3 and 6.3 Hz), 3.61 (1H, dd, $J$ = 9.3 and 6.2 Hz), 3.00 (3H, s), 2.87 (3H, s), 2.81−2.78 (28, m), 2.62 (1H, t, $J$ = 9.8 Hz), 1.82−1.80 (2H, m); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 178.4 (C), 177.5 (C), 174.7 (C), 174.1 (C), 141.5 (C), 121.2 (CH), 80.1 (CH), 79.9 (CH), 51.1 (CH), 50.7 (CH), 43.2 (CH), 42.3 (CH), 38.9 (CH), 24.9 ($CH_3$), 24.9 ($CH_3$), 24.4 ($CH_2$); $\nu_{max}$ (KBr)/cm$^{-1}$ 2953, 2892, 1782, 1766, 1698 and 1436; EIMS (70 eV) $m/z$ (%) 316.1 (15, $[M]^+$), 120.1 (10), 91.1 (11), 85.0 (65) 83.0 (100); HREIMS calcd for $C_{16}H_{16}N_2O_5$ $[M]^+$ 316.1059, found 316.1059.

**Compound 15.** 2-(3-Furyl)-1,3-butadiene **4** (70 mg, 0.582 mmol) was dissolved in chloroform (1.2 mL), and *N*-methylmaleimide (65 mg, 0.582 mmol, 1.0 equiv) was added. The solution was allowed to stand at rt for 2 h. The solvent was removed in vacuo, and the residue was subjected to flash chromatography on silica gel eluting with 2:3 diethyl ether:petroleum spirits to give the title compound **15** as a white solid (132 mg, 92%). A sample was recrystallized from dichloromethane to give crystals suitable for single crystal X-ray analysis: $R_f$ 0.07 (2:3 diethyl ether:petroleum spirits); mp 83−84 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz; $CDCl_3$) $\delta$/ppm 7.42 (1H, *br.* s), 7.32 (1H, dd, $J$ = 1.8 and 1.5 Hz), 6.42 (1H, dd, $J$ = 1.8 and 0.9 Hz), 6.00 (1H, ddd, $J$ = 6.6, 3.6, 2.7 Hz), 3.20−3.08 (2H, m), 2.89 (3H, s), 2.84 (1H, dd, $J$ = 12.3 and 2.7 Hz), 2.71 (1H, ddd, $J$ = 15.6, 9.6, and 2.7 Hz), 2.50−2.42 (1H, m), 2.39−2.31 (1H, m); $^{13}$C NMR (100 MHz; $CDCl_3$) $\delta$/ppm 180.1 (C), 197.7 (C), 143.7 (CH), 138.5 (CH), 130.6 (C), 126.2 (C), 120.4 (CH), 107.3 (CH), 39.4 (CH), 39.2 (CH), 26.3 ($CH_2$), 25.1 ($CH_3$), 24.2 ($CH_2$); $\nu_{max}$ (film)/cm$^{-1}$ 2951, 2902, 2849, 1774 and 1694; EIMS (70 eV) $m/z$ (%) 232.1 (56, $[M + H]^+$), 231.1 (87, $[M]^+$), 216.1 (9, $[M - CH_3]^+$) 146.1 (100, $[M - C_3H_3NO_2]^+$); HREIMS calcd for $C_{13}H_{13}NO_3$ $[M]^+$ 231.0895, found 231.0896.

**Compounds 16 and 17.** 3,3′-Bifuran **5** (134 mg 1.0 mmol) was dissolved in chloroform (2 mL), and *N*-methylmaleimide (111 mg, 1.0 mmol, 1.0 mol equiv) was added. The solution was stirred at 50 °C for 2.5 h. The solvent was removed in vacuo, and the residue was subjected to flash chromatography on silica gel eluting with 7:3 diethyl ether:hexane to give the title compounds **16** and **17** as a 1:1 mixture (202 mg, 82%). Analytical samples of both isomers were obtained by flash chromatography on silica gel eluting with $CH_2Cl_2$:MeOH 99.5:0.5 to give both compounds as white solids. A sample of *exo*-adduct **17** was recrystallized from $CH_2Cl_2$/heptane to give crystals suitable for single crystal X-ray analysis.

**16**: $R_f$ 0.19 (7:3 diethyl ether:hexane), 0.08 ($CH_2Cl_2$:MeOH 99.5:0.5); mp 48−51 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz; $CDCl_3$) $\delta$/ppm 7.49 (1H, *br.* s), 7.36 (1H, dd, $J$ = 1.8 and 1.5 Hz,) 6.35 (1H, dd, $J$ = 2.1 and 0.9 Hz), 6.26 (1H, d, $J$ = 1.8 Hz), 5.41 (1H, d, $J$ = 4.2 Hz), 5.37 (1H, d, $J$ = 5.3 Hz), 3.67−3.57 (2H, m), 2.66 (3H, s); $^{13}$C NMR (100 MHz; $CDCl_3$) $\delta$/ppm 175.2 (C), 174.0 (C), 144.0 (CH), 141.1 (CH), 139.4 (C), 124.9 (CH), 117.8 (C), 108.1 (CH), 81.1 (CH), 80.4 (CH), 48.4 (CH), 46.5 (CH), 24.5 ($CH_3$); $\nu_{max}$ (film)/cm$^{-1}$ 2919, 1775, 1698, and 1434; EIMS (70 eV) $m/z$ (%) 245.1 (60, $[M]^+$), 160.1 (28) 134.0 (100); HREIMS calcd for $C_{13}H_{11}NO_4$ $[M]^+$ 245.0688, found 245.0689.

**17**: $R_f$ 0.19 (7:3 diethyl ether:hexane), 0.13 ($CH_2Cl_2$:MeOH 99.5:0.5); mp 157−158 °C ($CH_2Cl_2$/heptane); $^1$H NMR (400 MHz; $CDCl_3$) $\delta$/ppm 7.62 (1H, *br.* s), 7.45 (1H, dd, $J$ = 2.1 and 1.5 Hz), 6.46 (1H, dd, $J$ = 1.8 and 0.9 Hz), 6.38 (1H, d, $J$ = 2.1 Hz), 5.35 (1H, s), 5.33 (1H, d, $J$ = 1.5 Hz), 3.00 (1H, d, $J$ = 6.6 Hz), 2.99 (3H, s), 2.89 (1H, d, $J$ = 6.6 Hz); $^{13}$C NMR (100 MHz; $CDCl_3$) $\delta$/ppm 176.3 (C), 176.1 (C), 144.4 (CH), 141.3 (C), 140.0 (CH), 127.0 (CH), 117.5 (C), 108.4 (CH), 82.0 (CH), 77.3 (CH), 49.9 (CH), 47.6 (CH), 25.1 ($CH_3$); $\nu_{max}$ (film)/cm$^{-1}$ 2928, 1772, 1698, and 1435; EIMS (70 eV) $m/z$ (%) 245.1 (32, $[M]^+$), 134.1 (100); HREIMS calcd for $C_{13}H_{11}NO_4$ $[M]^+$ 245.0688, found 245.0689.

**Tris-Adduct 18.** 3,3′-Bifuran **5** (72 mg, 0.537 mmol) and *N*-methylmaleimide (239 mg, 2.15 mmol, 4.0 mol equiv) were dissolved in benzene (1 mL), and the resulting mixture was heated in a microwave reactor at 80 °C for 2 h. The solvent was evaporated, and the residue was subjected to flash chromatography on silica gel eluting with ethyl acetate to give a mixture that was further purified using preparative HPLC (Altech SemiPrep column eluting with ethyl acetate at 4.5 mL/min, $t_R$ 7.4 min) to give the title compound **18** as a white crystalline solid (34 mg, 7% yield). A sample was recrystallized from acetone/water and gave crystals suitable for single crystal X-ray analysis: $R_f$ 0.54 (ethyl acetate), mp >300 °C (acetone/water); $^1$H NMR (600 MHz; $CDCl_3$) $\delta$/ppm 5.28−5.27 (1H, m), 5.21 (1H, s), 5.19 (1H, s), 3.73−3.69 (2H, m), 3.03 (1H, d, $J$ = 7.1 Hz), 2.98 (1H, d, $J$ = 7.1 Hz), 2.98 (3H, s), 2.98 (3H, s), 2.83 (3H, s), 2.61−2.57 (2H, m), 2.00−1.96 (1H, m), 1.89−1.85 (1H, m); $^{13}$C NMR (150 MHz; $CDCl_3$) $\delta$/ppm 177.2 (C), 176.7 (C), 175.6 (C), 175.3 (C), 174.2 (C), 174.1 (C), 134.5 (C), 131.1 (C), 81.4 (CH), 79.8 (CH), 78.8 (CH), 78.2 (CH), 51.0 (CH) 50.6 (CH), 49.1 (CH), 48.4 (CH), 44.8 (CH), 42.7 (CH), 42.3 (CH), 42.0 (CH), 25.4 ($CH_3$) two coincident signals, 25.0 ($CH_3$); $\nu_{max}$ (film)/cm$^{-1}$ 2952, 1777, 1701, 1436 and 1382; EIMS (70 eV) $m/z$ (%) 467.1 (100, $[M]^+$), 113.2 (72); HREIMS calcd for $C_{23}H_{21}N_3O_8$ $[M]^+$ 467.1329, found 467.1322.

**Compounds 19 and 20.** 3,4-Divinylfuran **6** (601 mg, 5.0 mmol) was dissolved in PhMe (20 mL), and *N*-phenylmaleimide (866 mg, 5.0 mmol, 1.0 mol equiv) was added. The solution was stirred at 50 °C for 1 h. The solvent was removed in vacuo, and the residue was subjected to flash chromatography on silica gel eluting with 2:3 diethyl ether:hexane to give the title compounds **19** and **20** as white solids (*endo*-adduct **19**; 474 mg, 32%, *exo*-adduct **20**; 804 mg, 55%).

**19**: $R_f$ 0.08 (2:3 diethyl ether:hexane); mp >200 °C (diethyl ether:hexane); $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 7.39 (2H, t, $J$ = 7.7 Hz), 7.34 (1H, t, $J$ = 7.4 Hz), 7.02 (2H, d, $J$ = 7.7 Hz), 6.62 (2H, dd, $J$ = 17.5 and 11.0 Hz), 5.64 (2H, s), 5.46 (2H, d, $J$ = 17.7 Hz), 5.39 (2H, d, $J$ = 11.0 Hz), 3.84 (2H, d, $J$ = 1.4 Hz); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 172.6 (C), 140.1 (C), 131.5 (C), 129.2 (CH), 128.8 (CH), 126.6 (CH), 125.2 (CH), 120.2 ($CH_2$), 81.3 (CH), 48.3 (CH), $\nu_{max}$ (KBr)/cm$^{-1}$ 2986, 2959, 1777, 1709, 1312, 1598 and 1495; EIMS (70 eV) $m/z$ (%) 293.1 (45, $[M]^+$), 173.0 (42), 146.1 (30),119.0 (42), 91.0 (100); HREIMS calcd for $C_{18}H_{15}NO_3$ $[M]^+$ 293.1052, found 293.1055.

**20**: $R_f$ 0.15 (2:3 diethyl ether:hexane); mp 191−193 °C (diethyl ether:hexane); $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 7.48 (2H, t, $J$ = 7.7 Hz), 7.40 (1H, t, $J$ = 7.4 Hz), 7.29 (2H, d, $J$ = 7.4 Hz), 6.58 (2H, dd, $J$ = 17.5 and 10.9 Hz) 5.58 (2H, s) 5.50 (2H, d, $J$ = 17.6 Hz), 5.38


dx.doi.org/10.1021/jo500458y | *J. Org. Chem.* 2014, 79, 3185−3193

(28, d, $J$ = 10.9 Hz), 3.09 (2H, s); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 175.2 (C), 141.9 (C), 131.9 (C), 129.3 (CH), 128.9 (CH), 126.7 (CH), 125.3 (CH), 118.1 (CH2), 82.4 (CH), 49.4 (CH); $\nu_{max}$ (KBr)/$cm^{-1}$ 3011, 1776, 1713, 1611, 1598 and 1497; EIMS (70 eV) $m/z$ (%) 293.1 (100, $[M]^+$), 175.0 (61), 173.0 (63), 118.0 (92), 91.0 (59); HREIMS calcd for $C_{18}H_{15}NO_3$ $[M]^+$ 293.1052, found 293.1050.

**Compounds 21, 22, and 23.** 3,4-Divinylfuran **6** (120 mg, 1.0 mmol) and *N*-phenylmaleimide (1.04 g, 6.0 mmol, 6.0 mol equiv) were combined in a microwave tube and heated at 120 °C for 1 h. The gummy residue was subjected to flash chromatography on silica gel eluting with 3:1 ethyl acetate:hexane to give a mixture of compounds **21**, **22**, and **23** in a 62:12:26 ratio (244 mg 52%, ratio determined by quantitative $^1$H NMR). Analytical samples were obtained by preparative HPLC (SunFire prep column, ethyl acetate:hexane 70:30, 8.5 mL/min; **23**, $t_R$ 4.0 min; **27**, $t_R$ 6.5 min; **21**, $t_R$ 16.0 min). Samples of compounds **21** and **23** were recrystallized from chloroform/hexane, respectively, to give crystals suitable for single crystal X-ray analysis.

**21**: $R_f$ 0.38 (ethyl acetate); mp 184−185 °C ($CHCl_3$/hexane); $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 7.39 (2H, dd, $J$ = 7.6 and 7.6 Hz), 7.35 (2H, dd, $J$ = 7.6 and 7.6 Hz), 7.33−7.29 (2H, m), 7.19 (2H, d, $J$ = 6.6 Hz), 7.04 (2H, d, $J$ = 7.4 Hz), 5.32 (2H, s), 3.65 (2H, s), 3.04 (2H, s), 2.87 (2H, s), 1.73 (2H, d, $J$ = 8.4 Hz), 1.09 (2H, d, $J$ = 8.6 Hz); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 176.9 (C), 174.7 (C), 148.3 (C), 131.8 (C), 131.6 (C), 129.3 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 126.9 (CH), 126.6 (CH), 82.6 (CH), 48.7 (CH), 44.2 (CH), 33.2 (CH), 24.8 ($CH_2$); $\nu_{max}$ (KBr)/$cm^{-1}$ 2954, 2873, 1776, 1710, 1597 and 1499; EIMS (70 eV) $m/z$ (%) 466.1 (1, $[M]^+$), 293.1 (100), 173.0 (90), 118.0 (82), 91.0 (57); HREIMS calcd for $C_{28}H_{22}N_2O_5$ $[M]^+$ 466.1529, found 466.1528.

**22**: mp 166−167 °C (benzene); $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 7.47 (2H, dd, $J$ = 7.7 and 7.7 Hz), 7.42 (2H, dd, $J$ = 7.7 and 7.7 Hz), 7.40 (1H, dd, $J$ = 7.5 and 7.5 Hz), 7.35 (1H, dd, $J$ = 7.4 and 7.4 Hz), 7.29 (2H, d, $J$ = 7.5 Hz), 7.18 (2H, d, $J$ = 7.4 Hz), 6.21 (1H, d, $J$ = 6.2 Hz), 5.55 (1H, s), 5.20 (1H, s), 3.47 (1H, d, $J$ = 7.0 Hz), 3.40 (1H, s), 3.22 (1H, dd, $J$ = 8.2 and 4.0 Hz), 3.20 (1H, d, $J$ = 7.0 Hz), 3.04 (1H, d, $J$ = 8.2 Hz), 1.87−1.82 (2H, m), 1.79−1.77 (1H, m), 2.23 (1H, dd, $J$ = 12.1, 12.1, and 4.8 Hz); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 176.3 (C), 176.0 (C), 175.7 (C), 175.0 (C), 145.4 (C), 131.8 (C, two coincident signals), 129.3 (CH), 129.2 (CH), 129.0 (CH), 128.7 (CH), 126.6 (CH), 126.3 (CH), 120.8 (CH), 83.1 (CH), 79.1 (CH), 50.2 (C), 49.9 (CH), 46.2 (CH), 45.0 (CH), 45.0 (CH), 31.5 (CH), 28.6 ($CH_2$), 26.7 ($CH_2$); $\nu_{max}$ (KBr)/$cm^{-1}$ 2960, 2923, 2851, 1776, 1713, 1631, 1598 and 1498; EIMS (70 eV) $m/z$ (%) 466.2 (33, $[M]^+$), 173.1 (32), 85.1 (50), 71 (70), 56 (100); HREIMS calcd for $C_{28}H_{22}N_2O_5$ $[M]^+$ 466.1529, found 466.1527.

The structure and stereochemistry of compound **22** was established by two-dimensional NMR analysis. From the $^1$H, $^{13}$C, COSY, and HSQC NMR spectra, the atom connectivity of the structure was established. The stereochemistry was assigned on the basis of the NOE enhancements, as shown in the Supporting Information.

**23**: mp 190−193 °C ($CHCl_3$/hexane); $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 7.49 (2H, dd, $J$ = 7.6 and 7.6 Hz), 7.45−7.42 (5H, m), 7.38 (1H, d, $J$ = 7.9 Hz), 7.36 (1H, d, $J$ = 7.7 Hz), 7.24 (2H, d, $J$ = 7.8 Hz), 7.21 (2H, d, $J$ = 7.8 Hz), 7.20 (2H, d, $J$ = 7.8 Hz), 3.77−3.73 (2H, m), 3.49 (1H, dd, $J$ = 9.2 and 5.3 Hz), 3.46−3.45 (1H, m), 3.31−3.29 (1H, m), 2.95 (1H, d, $J$ = 11.2 Hz), 2.74−2.70 (2H, m), 2.43−2.39 (1H, m), 2.15 (1H, s), 1.89 (1H, ddd, $J$ = 13.6, 5.1, and 5.1 Hz); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 178.0 (C), 177.0 (C), 176.9 (C), 174.8 (C), 173.6 (C), 173.2 (C), 134.5 (C), 134.4 (C), 131.6 (C), 131.5 (C), 131.3 (C), 129.5 (CH), 129.1 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.7 (CH), 126.4 (CH), 126.1 (CH), 125.7 (CH), 82.9 (CH), 80.9 (CH), 47.4 (CH), 46.4 (CH), 44.7 (CH), 42.1 (CH), 41.2 (CH), 41.0 (CH), 31.8 (CH), 30.3 (CH), 27.0 ($CH_2$), 26.3 ($CH_2$); $\nu_{max}$ (KBr)/$cm^{-1}$ 2962, 2926, 2854, 1778, 1710, 1586 and 1498; EIMS (70 eV) $m/z$ (%) 639.2 (100, $[M]^+$), 491.1 (12), 318.1 (15), 175.1 (60); HREIMS calcd for $C_{38}H_{29}N_3O_7$ $[M]^+$ 639.2006, found 639.2004.

**Compound 25.** Compound **20** (80 mg, 0.273 mmol) was dissolved in toluene, and the solution was stirred at reflux for 12 h. The solution was then passed through a short pad of silica eluting with diethyl ether:hexane 1:1. The solvent was removed in vacuo to give the title compound **25** as a white solid (72 mg, 90%): $R_f$ 0.17 (2:3 diethyl ether/hexane); mp 154−156 °C (diethyl ether/hexane): $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 7.44 (2H, dd, $J$ = 6.9, 6.9 Hz), 7.37 (1H, dd, $J$ = 7.0, 7.0 Hz), 7.25 (2H, dd, $J$ = 7.3, 7.3 Hz), 5.67 (2H, s) 5.23 (2H, s) 3.16 (2H, s), 2.26 (4H, s); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 175.7 (C), 136.7 (C), 131.9 (C), 129.3 (CH), 128.9 (CH), 126.6 (CH), 114.8 (CH), 81.2 (CH), 50.2 (CH), 22.1 ($CH_2$); $\nu_{max}$ (KBr)/$cm^{-1}$ 2961, 2915, 1778, 1708, 1595, 1501 and 1494; EIMS (70 eV) $m/z$ (%) 293.1 (70, $[M]^+$), 146.1 (39), 120.1 (100), 91.1 (46), HREIMS calcd for $C_{18}H_{15}NO_3$ $[M]^+$ 293.1052, found 293.1055.

**Compounds 24 and 25.** Compound **19** (105 mg, 0.358 mmol) was dissolved in toluene (2.5 mL), and the solution was stirred at reflux for 12 h. The solvent was removed in vacuo, and the residue was subjected to flash chromatography on silica gel using a gradient elution from 2:3 diethyl ether:hexane to 3:2 diethyl ether:hexane to give the title compounds **24** and **25** as white solids (*endo*-adduct **24**; 58 mg, 55%, *exo*-adduct **25**; 38 mg, 36%).

**24**: $R_f$ 0.06 (diethyl ether/hexane 2:3); mp 150−151 °C (diethyl ether/hexane); $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 7.44 (2H, dd, $J$ = 7.6 and 7.6 Hz), 7.36 (1H, dd, $J$ = 6.7 and 6.7 Hz), 7.19 (2H, d, $J$ = 8.4 Hz), 5.68 (2H, s), 5.26 (2H, dd, $J$ = 3.8 and 2.2 Hz), 3.73 (2H, dd, $J$ = 4.0 and 2.4 Hz), 2.27−2.20 (4H, m); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 173.6 (C), 134.9 (C), 131.6 (C), 129.2 (CH), 128.7 (CH), 126.1 (CH), 116.5 (CH), 79.9 (CH), 51.2 (CH), 22.2 ($CH_2$); $\nu_{max}$ (KBr)/$cm^{-1}$ 2928, 2828, 1776, 1713, 1598 and 1499; EIMS (70 eV) $m/z$ (%) 293.1 (25, $[M]^+$), 175.1 (69), 146.1 (42), 120.1 (100), 91.1 (78); HREIMS calcd for $C_{18}H_{15}NO_3$ $[M]^+$ 293.1052, found 293.1055.

**Compound 21.** *Thermal Conditions.* Compound **25** (147 mg, 0.5 mmol), *N*-methylmaleimide (346 mg, 1.59, 3.0 mol equiv), and BHT (10 mg) were combined and heated in a microwave reactor at 120 °C for 1 h. The residue was subjected to flash chromatography on silica gel using a gradient elution from 3:1 ethyl acetate:hexane to ethyl acetate to give the title compound **21** as a light yellow solid (130 mg, 56%).

*High Pressure Conditions.* Compound **25** (131 mg, 0.447 mmol) and *N*-phenylmaleimide (155 mg, 0.895 mmol, 2.0 equiv) were dissolved in dichloromethane (6 mL), and the solution was placed into a high pressure Teflon vessel. The vessel was placed into a hydraulic press and compressed at 19 kbar overnight. The solvent was removed in vacuo, and the residue was subjected to flash chromatography on silica gel eluting with ethyl acetate to give the title compound **21** as a light yellow solid (145 mg, 70%).

**Compound 26.** Compound **24** (27.7 mg, 0.0944 mmol) and *N*-phenylmaleimide (32.7 mg, 0.189 mmol, 2.0 mol equiv) were dissolved in dichloromethane (0.5 mL) in a Teflon high pressure vessel. The vessel was placed into a hydraulic press and compressed at 19 kbar overnight. The solution was then passed through a short pad of silica eluting with chloroform after which the solvent was removed in vacuo. The residue was then subjected to preparative HPLC (SunFire prep column eluting with ethyl acetate:hexane 1:1, 8.5 mL/min, $t_R$ 12.0 min) to give the title compound **26** as a white solid (12 mg, 29%,). The poor isolated yield reflects difficulties in isolation. In a separate run the crude material was analyzed by $^1$H NMR spectroscopy against an internal standard, which revealed a clean conversion to the product in 75% yield.

**26**: mp 181−182 °C ($CHCl_3$/hexane); $^1$H NMR (800 MHz; $CDCl_3$) $\delta$/ppm 7.39 (2H, t, $J$ = 7.7 Hz), 7.35 (2H, t, $J$ = 7.6 Hz), 7.33−7.29 (2H, m), 7.19 (2H, d, $J$ = 6.6 Hz), 7.04 (2H, d, $J$ = 7.4 Hz), 5.32 (2H, s), 3.65 (2H, s), 3.04 (2H, s), 2.87 (2H, s), 1.73 (2H, d, $J$ = 8.4 Hz), 1.09 (2H, d, $J$ = 8.6 Hz); $^{13}$C NMR (200 MHz; $CDCl_3$) $\delta$/ppm 176.9 (C), 174.7 (C), 148.3 (C), 131.8 (C), 131.6 (C), 129.3 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 126.9 (CH), 126.6 (CH), 82.6 (CH), 48.7 (CH), 44.2 (CH), 32.2 (CH), 24.8 ($CH_2$); $\nu_{max}$ (KBr)/$cm^{-1}$ 2955, 2872, 1778, 1703, 1595 and 1494; EIMS (70 eV) $m/z$ (%) 466.1 (2, $[M]^+$), 293.1 (100), 173.0 (83), 118.0 (80), 91.0 (55); HREIMS calcd for $C_{28}H_{22}N_2O_5$ $[M]^+$ 466.1529, found 466.1529.


dx.doi.org/10.1021/jo500458y | J. Org. Chem. 2014, 79, 3185−3193

**Compound 21.** Compound **24** (37.1 mg, 0.126 mmol) and *N*-phenylmaleimide (131 mg, 0.759 mmol, 6.0 mol equiv) were dissolved in toluene (0.5 mL), and the resulting solution was heated in microwave reactor at 150 °C for 38 h. The solvent was removed in vacuo, and the residue was subjected to flash chromatography on silica gel eluting with ethyl acetate to give the title compound **21** (11 mg, 19%).

**Isomerization of 26 to 21.** A solution of compound **26** (3.4 mg, 0.00729 mmol) and *N*-phenylmaleimide (25 mg, 0.146 mmol, 20 mol equiv) in toluene (0.2 mL) was heated at reflux for 6 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in $CDCl_3$ containing tetrachloroethylene (10 μL). Analysis of the sample by $^1H$ NMR spectroscopy revealed clean conversion to the *exo*-adduct **21** in 73% yield.

## ■ ASSOCIATED CONTENT

### Supporting Information

Selected NOE enhancements of compound **22**; a discussion of the potential for thermodynamic control in the Diels–Alder reaction between NMM and **3**, and implications for other members of the series; CIFs and anisotropic displacement ellipsoid plots for compounds **10**–**13**, **15**, **17**, **18**, **21**, **23**, and **26** (CCDC Nos. 966665–966674, respectively); computational details; $^1H$ and $^{13}C$ NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Authors

*E-mail: michael.sherburn@anu.edu.au (synthetic).
*E-mail: m.paddonrow@unsw.edu.au (computational).


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the Australian Research Council. MNP-R acknowledges that the computational component of this research was undertaken with the assistance of resources provided at the NCI National Facility through the National Computational Merit Allocation Scheme supported by the Australian Government. We thank Dr. Ian Cade (ANU) for a preliminary X-ray analysis of compound **23**.

## ■ REFERENCES


(1) For recent reviews, see: (a) Mackay, E. G.; Sherburn, M. S. *Pure Appl. Chem.* **2013**, *85*, 1227. (b) Hopf, H.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 2298.

(2) Professor Tsuge coined the term *diene-transmissive*: Tsuge, O.; Wada, E.; Kanemasa, S. *Chem. Lett.* **1983**, 239.

(3) For a recent review, see: Green, N. J.; Sherburn, M. S. *Aust. J. Chem.* **2013**, *66*, 267.

(4) Bradford, T. A.; Payne, A. D.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *J. Org. Chem.* **2010**, *75*, 491.

(5) Payne, A. D.; Willis, A. C.; Sherburn, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12188.

(6) (a) Boutelle, R. C.; Northrop, B. H. *J. Org. Chem.* **2011**, *76*, 7994. (b) For a review, see: Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179.

(7) (a) Tanaka, R.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2007**, *72*, 8671. (b) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693.

(8) Fallon, T.; Willis, A. C.; Rae, A. D.; Paddon-Row, M. N.; Sherburn, M. S. *Chem. Sci.* **2012**, *3*, 2133.

(9) (a) Kabir, S. M. H.; Miura, M.; Sasaki, S.; Harada, G.; Kuwatani, Y.; Yoshida, M.; Iyoda, M. *Heterocycles* **2000**, *52*, 761. (b) Kauffmann, T.; Lexy, H.; Kriegesmann, R. *Chem. Ber.* **1981**, *114*, 3667.

(10) See ref 8 for a multigram scale synthesis of compound **5**.

(11) Eberbach, W.; Fritz, H.; Laber, N. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 568.

(12) Benítez, A.; Herrera, F. R.; Romero, M.; Talamás, F. X.; Muchowski, J. M. *J. Org. Chem.* **1996**, *61*, 1487.

(13) (a) Fang, L.-Z.; Liu, J.-K. *Heterocycles* **2009**, *78*, 2107. (b) McNamara, J. M.; Kishi, Y. *Tetrahedron* **1984**, *40*, 4685.

(14) The mass balance for this reaction was unreacted **3** and a mixture of the double DA products **10**, **11**, **12**, and **13**. Interestingly, the 1:1 ratio of *exo* and *endo* furan diene adducts **7** and **8** remained constant throughout this reaction, while the amount of precursor declined and that of the double DA adducts increased. The implications of these observations on the reversibility of DA reactions involving **3** and related observations with **4**, **5**, and **6** are discussed in the Supporting Information.

(15) Gayatri, G.; Sastry, G. N. *J. Phys. Chem. A* **2009**, *113*, 12013.

(16) See the Supporting Information for details.

(17) This product is the result of NPM docking in an *endo*-manner to the 1,3-cyclohexadiene group of *exo*-adduct **21** with a *syn*-disposition relative to the oxa-bridge.

(18) The low yield in this case likely reflects losses encountered during purification on HPLC.

(19) (a) Sperry, J. B.; Whitehead, C. R.; Ghiviriga, I.; Walczak, R. M.; Wright, D. L. *J. Org. Chem.* **2004**, *69*, 3726. (b) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1985**, *50*, 3988.

(20) Hersel, U.; Steck, M.; Seifert, K. *Eur. J. Org. Chem.* **2000**, 1609.

(21) Prepared according to the procedure: Mee, S. P. H.; Lee, V.; Baldwin, J. E.; Cowley, A. *Tetrahedron* **2004**, *60*, 3695.