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Palladium-Catalysed Isomerisation of 2-Vinylidenehydrofurans to 1,3-Dienes and Some Aspects of Their Reactivity

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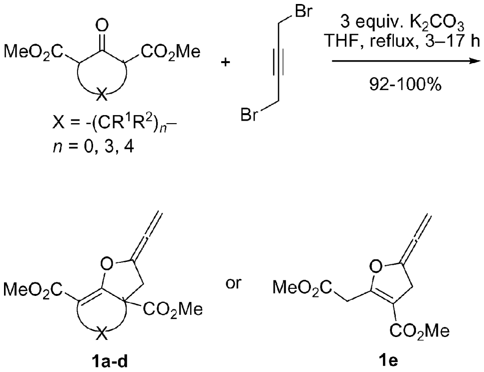
The transformation of easily accessible 2-vinylidenehydrofurans into stable 1,3-dienes has been achieved by using catalytic amounts of palladium(0). These valuable compounds were then engaged in subsequent Diels–Alder reactions giving access to complex heterocyclic cores found in numerous natural products. A rationale for the regioselectivity of the Diels–Alder reactions with vinylfurans has been provided by DFT calculations.

Introduction

The allene functionality possesses intriguing and unique reactivity and structural properties that make it an important building block in organic synthesis.[1] Consequently, this functionality is being widely investigated with a view to discovering new applications. Among them, alkoxyallenes have received particular attention and have been used in various transformations such as heterocyclisation, amidopalladation, cycloaddition, spiroannulation and cyclopentaannulation reactions.[2] The chemistry of cyclic versions of these important building blocks, namely 2-vinylidenehydrofurans and -pyrans, have, however, been much less explored, probably due to the lack of a general synthetic approach.[3]

Results and Discussion

We have previously reported the efficient and practical synthesis of 2-vinylidenehydrofurans **1** by a one-pot domino *C*,*O*-cycloalkylation sequence.[4] This reaction involves readily accessible cyclic or acyclic keto diesters that react smoothly in refluxing THF and in the presence of K_2CO_3 with 1,4-dibromobut-2-yne (Scheme 1).



Scheme 1. Synthesis of 2-vinylidenehydrofurans **1**.

Simple filtration through a short pad of Celite gives good yields of allenyl enol ethers **1a**–**e**. This transformation proved to be quite general and allowed the construction of previously unknown fused poly- and monocyclic heterocycles.

Having identified the conditions necessary to access these valuable alkoxyallenes **1a**–**e**, we then tried to exploit the reactivity of these molecules in subsequent transformations. One of our first ideas was the addition of various nucleophiles to the allene function. This would allow, after cyclisation, access to heterospirocyclic compounds such as the spiroketals found in numerous biologically active natural products (Scheme 2).[5]

As a first attempt in this direction we chose to study the acid-mediated addition of allylic alcohol as the nucleophile. Intramolecular nucleophilic addition of alcohols to an alkoxyallene to form dioxospiro compounds has been accomplished by Whitby and Kociensky.[6] Thus, in the case of

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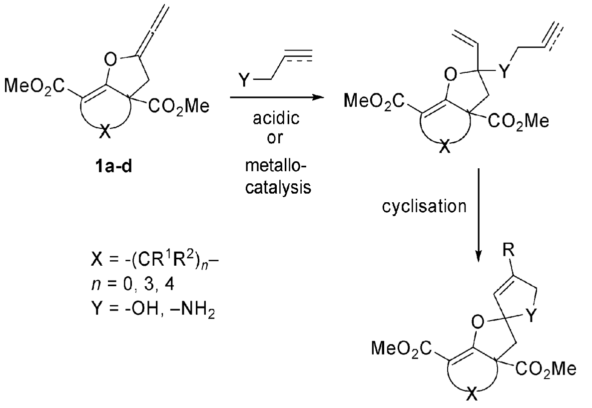
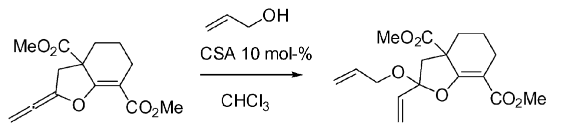


Scheme 2. Strategy to access spirocyclic compounds.

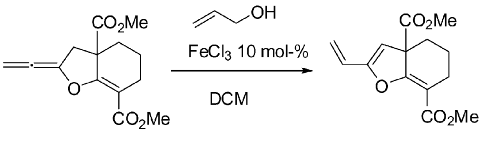
1a, various protic acidic catalysts (CSA, TFA) and reaction conditions (solvent, temperature) were screened. Although a total chemoselectivity was observed, only small amounts of the expected product **8a** could be isolated (yields <30%) as a 1:1 mixture of diastereomers (Scheme 3).[7]



1a **8a, 27 %**

Scheme 3. CSA-promoted synthesis of compound **8a**.

Alternatively, running the reaction in the presence of $FeCl_3$ as the Lewis acid catalyst (10 mol-%) in dichloromethane at room temperature furnished only the corresponding 1,3-diene **2a** in 23% yield (Scheme 4). No product resulting from the addition of allylic alcohol could be isolated.[8]

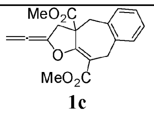
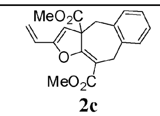
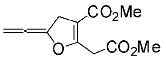
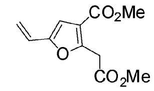


1a **2a, 23 %**

Scheme 4. Isomerisation of **1a**.

With these disappointing results in hand, we therefore turned our attention to other strategies involving the use of palladium catalysis. A palladium(II)-mediated coupling of 1-methoxy-1,2-propadiene with secondary alcohols for the synthesis of α,α′-disubstituted dihydropyrans and tetrahydrooxepines has been accomplished by Rutjes et al.[9] This result along with others[1c,10] comforted us in the choice of this strategy for realising this transformation. The results are summarised in Table 1. In the case of allenes **1c** and **1e**, allylic alcohol was chosen as the nucleophile and the reaction was carried out in the presence of 5% palladium acetate, 5% dppp and triethylamine or K_2CO_3 in acetonitrile at 80 °C.

Table 1. Palladium-catalysed nucleophilic addition to vinylidenehydrofurans.

Entry	Allene	Base[a]	Time	Product	Yield[b]
1	 **1c**	Et_3N	5 h	 **2c**	58 %[c]
2	**1c**	Et_3N	23 h	**2c**	68 %[c]
3	**1c**	Et_3N	17 h	**2c**	72 %[d]
4	**1c**	K_2CO_3	4 h	**2c**	55 %[d]
5	 **1e**	Et_3N	21 h	 **2e**	26 %[d]

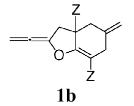
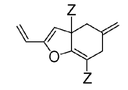
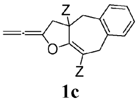
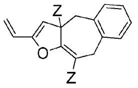
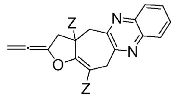
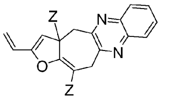
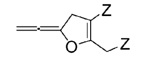
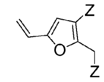
[a] 1.5 Equiv. of base was used. [b] Isolated yield after flash chromatography on silica gel. [c] 1.5 Equiv. of allylic alcohol was used. [d] 5 Equiv. of allylic alcohol were used.

However, regardless of the experimental conditions, no product resulting from the nucleophilic addition of the allylic alcohol to the allene function was isolated. Only the isomerised products **2c** and **2e** could be isolated from the reaction mixture in moderate-to-good yields even in the presence of a large excess of allylic alcohol (entries 3–5). A related transformation has been observed by Tsuji et al.[11] for the Pd^0-catalysed synthesis of propargyl carbonates to allenyl carboxylates, which in one case could be isomerised to the corresponding 2,4-dienyl carboxylate.

Clearly the presence of allylic alcohol is not necessary for the unexpected transformation of these highly sensitive allenes, which leads to stable and synthetically valuable 1,3-dienes. Moreover 1,3-dienes possess important synthetic potential.[12] Thus, we decided to optimise this reaction by varying different parameters such as the palladium source, the phosphane and the time (Table 2).[13] Interestingly, $[Pd(OAc)_2]$ or $[Pd(CH_3CN)_2Cl_2]$ alone did not catalyse the isomerisation; the starting material was degraded (entries 1 and 2), which indicates that Pd^{II} is not the active species. Alternatively, in situ generated Pd^0 using triphenylphosphane (entry 6) or tributylphosphane (entry 7) gave moderate yields relative to the use of 1,3-bis(diphenylphosphanyl)propane (dppp),[14] which was found to be by far the best ligand for clean conversion to the expected 3-oxa-1,3-dienes (entries 3–5, 8 and 9). This very useful transformation was revealed to be quite general, simple and a mild alternative to the well-known acid- or base-mediated isomerisation of allenes.[15] Note that under the reaction conditions, the exocyclic double bond in **2b** remained untouched and did not isomerise.

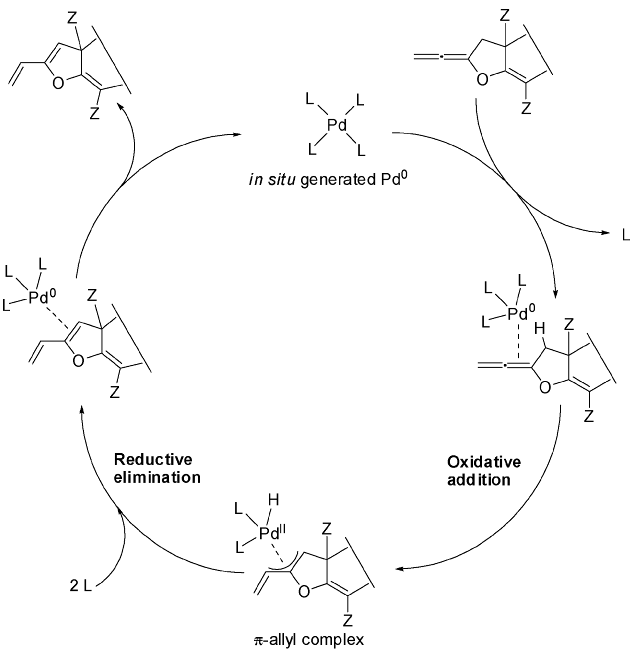
The results obtained during the optimisation of the reaction suggest that the mechanism involves an in situ generated Pd^0 as the active species (Scheme 5). The presence of

Table 2. Pd^0-catalysed isomerisation of 2-vinylidenehydrofurans **1** to 3-oxa-1,3-diene **2**.

Entry	Allene	Catalyst (5 mol-%)	Time (h)	Product	Yield[a]
1	**1a**	$Pd(OAc)_2$	22	**2a**	–
2	**1a**	$Pd(CH_3CN)_2Cl_2$	3	**2a**	–
3	**1a**	$Pd(OAc)_2$, dppp	3	**2a**	72
4	 **1b**	$Pd(OAc)_2$, dppp	4	 **2b**	74
5	 **1c**	$Pd(OAc)_2$, dppp	10	 **2c**	72
6	**1c**	$Pd(OAc)_2$, PPh_3	24	**2c**	44
7	**1c**	$Pd(OAc)_2$, PBu_3	24	**2c**	51
8	 **1d**	$Pd(OAc)_2$, dppp	2.5	 **2d**	82
9	 **1e**	$Pd(OAc)_2$, dppp	2	 **2e**	92

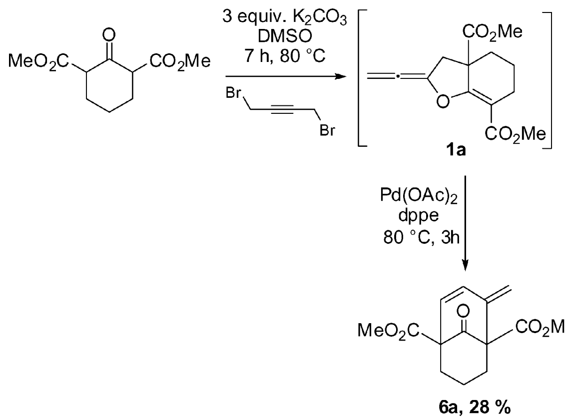
[a] Isolated yield after flash chromatography on silica gel. All reactions were conducted in MeCN at 80 °C by using 5 mol-% palladium catalyst and 5 mol-% phosphane (except for entries 1 and 2, Z = CO_2Me). In our case, a pseudo π-allyl-type intermediate is probably involved which rearranges to give the product (see Scheme 5).

hydrogen atoms at the allylic position makes possible the formation of a π-allyl complex formed by an oxidative addition. Irreversible reductive elimination, which gives rise to the stable 1,3-diene system, is probably the driving force of the reaction.



Scheme 5. Proposed mechanism for the allene isomerisation (Z = CO_2Me).

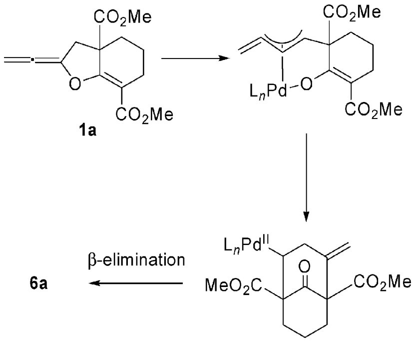
We then tried to perform the sequence *C,O*-cycloalkylation and isomerisation of the in situ formed vinylidenehydrofuran **1a** (Scheme 6). Surprisingly, only diene **6a**, resulting from an apparent *C,C*-dialkylation, was isolated in 28% yield.



Scheme 6. Unexpected formation of compound **6a**.

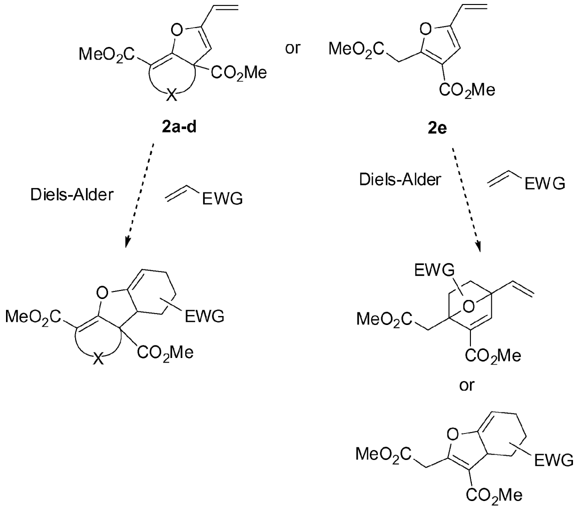
The mechanism to explain the formation of this compound (Scheme 7) is probably related to the known *C,O*/*C,C*-palladium-catalysed rearrangement first reported by Tsuji[16] and Trost[17] and their co-workers in the early 80s. This rearrangement has been exploited more recently by Langer and co-workers for the transformation of 2-alkylidene-5-vinyltetrahydrofurans into valuable bicyclo[3.2.1]octan-8-ones.[18]

This is the first example of such a transformation involving a 2-vinylidenehydrofuran and formally represents a *C,C*-dialkylation of keto diesters with 1,3-butadiene.



Scheme 7. Mechanism for the formation of **6a**.

We were next attracted by the synthetic potential of the 3-oxa-1,3-diene intermediates and their use in subsequent Diels–Alder reactions. Even if the furan ring system shows generally poor reactivity as a diene in cycloaddition reactions due to its inherent aromaticity[19] and facile retro-Diels–Alder reaction,[20] we believed that 2-vinylfurans or -hydrofurans would allow us to access complex heterocyclic cores (Scheme 8).

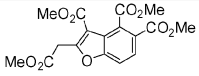
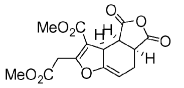
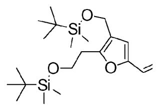
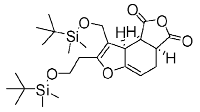
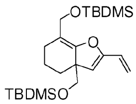


Scheme 8. DA reactions with 3-oxa-1,3-diene.

The behaviour of 2-vinylfuran towards various dienophiles has been studied and it was found that, in general, the conjugated system involving the exocyclic double bond is more reactive than the furan ring itself.[21] Li et al. have shown recently that under ultrasonic irradiation, reactive dienophiles such as DMAD regioselectively react with the furan ring to afford oxabicyclic alkenes in good yields.[22] Therefore, vinylfuran **2e** was engaged in Diels–Alder reactions with DMAD or maleic anhydride (Table 3).

Products **3a** and **3b** were obtained in good yields (63 and 72%, respectively) and total diastereoselectivity, both resulting from an expected reaction on the more reactive exocyclic double bond. When DMAD was employed, the cycloadduct intermediate was not isolated but oxidised directly under the reaction conditions to afford the benzofuran **3a**. The presence of an ester group on the furan ring of **2e**, partially decreasing its diene character, could explain this high chemoselectivity in favour of the exocyclic double bond. In order to validate this hypothesis, we synthesised the corresponding protected diol **2f**,[23] which was obtained by reduction of **2e** followed by protection of the resulting diol with the TBDMS group. Surprisingly, conducting the reaction with the free diol resulted in the decomposition of the starting material, but when **2f** was engaged in the cycloaddition reaction we isolated the protected tricyclic diol **3c** in good yield (79%). This shows that increasing the reactivity of the intracyclic diene did not change the chemoselectivity, which is still in favour of the exocyclic diene system. Interestingly, adducts **3b** and **3c** did not isomerise to the corresponding furans as observed by Kotsuki et al.[21a] and were both obtained as single diastereomers. Unfortunately and quite unexpectedly, in the case of dienes **2a** and **2c** only degradation occurred regardless of the nature of the dienophile (entries 4 and 5). Once again, arguing that the presence of the conjugated ester was unfavourable for the cycloaddition, we prepared the protected diol **2g**, which unfortunately also decomposed under the reaction conditions (entry 6).[24] The absence of the aromatic furan within the ring structure seems to affect the stability of the dienes, which decompose under reaction conditions that are probably too strong. Lewis acids such as $BF_3{\cdot}OEt_2$ and $SnCl_4$ were employed in order to catalyse the DA reaction at room temperature but either decomposition or no reaction was observed. Microwave experiments have also been conducted, but only resulted in the decomposition of the starting material.

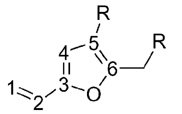
Table 3. Diels–Alder reactions between 2-vinylfurans **2** and various dienophiles.[a]

Entry	Diene	Dienophile	Yield[b] (%)	Product
1	**2e**	DMAD	63	 **3a**
2	**2e**	maleic anhydride	72	 **3b**
3	 **2f**	maleic anhydride	79[c]	 **3c**
4	**2a**	DMAD	–	–
5	**2c**	maleic anhydride	–	–
6	 **2g**	maleic anhydride	–	–

[a] Reaction conditions: dienophile (3.0 equiv.) was added to a solution of the diene (1.0 equiv.) in toluene under argon and the mixture was heated at reflux until TLC analysis indicated completion of the reaction (3–4 d). [b] Isolated yield after flash chromatography on silica gel. [c] The reaction was conducted in dichloromethane at reflux for 7 d.

DFT calculations have allowed us to rationalise the regioselectivity of the Diels–Alder reaction.[25] In a first step, the electronic properties of compounds **2e** and **2f** were compared in order to show the substituent effects on the HOMO (Table 4). As expected, the presence of an electron-donating substituent increases the HOMO energy and the coefficients of the $2p_z$ atomic orbitals on the reacting carbon atoms in the HOMO. The exocyclic diene in **2f** is therefore more reactive than the exocyclic diene in **2e**. This is in agreement with a Diels–Alder reaction under milder reaction conditions for compound **2f**. The reactivity of the intracyclic diene is enhanced too, but experimental results show that only the exocyclic diene leads to a Diels–Alder adduct.

Table 4. Effect of substituents on the HOMO of compounds **2e** and **2f**.



Diene	HOMO energy [eV]	Coefficients of the $2p_z$ atomic orbitals in the HOMO					
		C1	C2	C3	C4	C5	C6
2e	–0.214	0.209	0.099	–0.187	–0.175	0.121	0.177
2f	–0.199	0.219	0.085	–0.204	–0.162	0.140	0.225

In a second step, we investigated the Diels–Alder reaction profiles for dienes **2e** or **2f** with maleic anhydride as the dienophile. The region- and stereoselectivity were taken into account. We calculated the reaction profiles for both intracyclic and exocyclic dienes with both an *endo* and an *exo* approach. As expected, the Diels–Alder reaction between the exocyclic diene in the *endo* approach is the least energetic for both compounds **2e** and **2f**, which explains the total stereoselectivity observed in compounds **3b** and **3c** (Table 5).

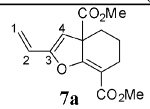
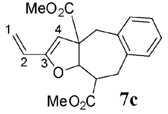
Table 5. Activation energies for the Diels–Alder reaction.

Diels–Alder reaction	Activation energy [kJ mol^{-1}]			
	exo/*endo*[a]	*exo*/*exo*[a]	intra/*endo*[a]	intra/*exo*[a]
2e + maleic anhydride	65	77	93	85
2f + maleic anhydride	65	76	92	84

[a] The first term refers to the exocyclic diene C1 to C4 or the intracyclic diene C3 to C6. The last term refers to the reactant approach.

We then tried to elucidate the reason for the non-reactivity of compounds **2a** and **2c** towards dienophiles (DMAD or maleic anhydride, Table 3, entries 4 and 5). Calculations (AMPAC) concerning the molecule geometric optimisation confirmed that orbital overlap is possible. Nevertheless, calculations of the orbital coefficients (semiempirical method AM1)[26] for compounds **2a** and **2c** show that the electron density distribution is not optimum, which may explain their lack of reactivity in the Diels–Alder reactions (Table 6) probably due to the presence of the conjugated double bond α to the ester function. Indeed, the distribution was greatly improved when this double bond was removed (compounds **7a** and **7c**).

Table 6. Orbital coefficients for compounds **2a**, **2c**, **7a** and **7c**.

C atom	Coefficient of orbitals ($\Sigma \epsilon_i^2$)			
	2a	**2c**	 **7a**	 **7c**
C1	0.072	0.063	0.147	0.137
C2	0.0378	0.0258	0.065	0.060
C3	0.0900	0.251	0.165	0.158
C4	0.2655	0.084	0.4138	0.391

Conclusions

We have shown that highly sensitive 2-vinylidenehydrofurans can be isomerised to stable dienes with a catalytic source of palladium(0). This procedure is general, mild and tolerates various functional groups. The simplicity of the procedure allows access to 3-oxa-1,3-dienes, which are precursors of benzofuran[27] and hydrobenzofuran[28] cores, by a cycloaddition reaction. Moreover, we have shown and confirmed by DFT calculations the enhanced reactivity of the exocyclic diene in this type of compound.

Experimental Section

General Information: Melting points were recorded by using a Büchi melting point apparatus. Mass spectra were obtained with a Nermag R 10–10 instrument by using electron spray (ES) or a MALDI-TOF-type instrument for the high-resolution mass spectra (HRMS). ^{1}H NMR spectra were recorded at 200 MHz with a Bruker AC-200 spectrometer or at 300 MHz with a Bruker AC-300 spectrometer. ^{13}C NMR spectra were similarly recorded at 75 MHz with a Bruker AC-300 spectrometer using a broad-band decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane. NMR experiments were carried out in deuteriochloroform ($CDCl_3$). Coupling constants (*J*) are reported in Hertz [Hz]. Infrared spectra were recorded with a Perkin–Elmer 1600 spectrometer. Flash chromatography was performed by using Merck 40–63 μm particle-sized silica gel (230–400 mesh). Visualization was achieved under a UVP mineralight UVGL-58 lamp and by developing the plates with *p*-anisaldehyde or phosphomolybdic acid reagent. All reagents were obtained from commercial suppliers unless otherwise stated.

Computational Details: All calculations were performed with the Gaussian 03 package.[29] The geometries of all the stationary points were optimized at the B3LYP/6-31G(d) level and characterized by the calculation of the vibrational frequencies. Starting from the transition-state structures, reaction profiles were determined by IRC calculations. The zero-point energy (ZPE) was added to energy values with vibrational frequencies scaled by 0.9806, as recommended by Scott and Radom.[30] In compound **2f**, TBDMSO moieties were replaced by OH groups in order to reduce the length of the calculations.

Experimental Procedures

General Procedure for the Pd-Catalysed Isomerisation of 2-Vinylidenehydrofurans to 1,3-Dienes: To a solution of 2-vinylidenehydrofuran (3.0 mmol, 1.0 equiv.) in anhydrous tetrahydrofuran (70 mL) under argon was added at room temperature 1,3-bis(diphenylphosphanyl)propane (dppp, 0.15 mmol, 0.05 equiv.) and then palladium acetate (0.15 mmol, 0.05 equiv.). The mixture was refluxed for 15 h, then cooled down to –20 °C, filtered through a pad of silica gel preimpregnated with diethyl ether and cooled to –30 °C. The crude solution was concentrated and purified by silica gel chromatography to provide the pure desired product.

Dimethyl 2-Vinyl-5,6-dihydro-4*H*-benzofuran-3a,7-dicarboxylate (2a): The product was obtained as a colourless oil (187 mg, 72%); R_f = 0.75 (diethyl ether/petroleum ether, 70:30). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.18 (dd, J = 17.3, 11.0 Hz, 1 H), 5.77 (dd, J = 17.3, 0.9 Hz, 1 H), 5.37 (dd, J = 11.0, 0.9 Hz, 1 H), 5.24 (s, 1 H), 3.74 (s, 3 H), 3.62 (s, 3 H), 2.63–2.47 (m, 2 H), 2.19 (dq, J = 14.2, 3.4 Hz, 1 H), 1.78–1.67 (m, 1 H), 1.56–1.33 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 171.2, 166.4, 163.6, 156.0, 123.9, 119.7, 105.4, 102.9, 59.1, 53.0, 51.6, 29.8, 22.8, 17.9 ppm.

Dimethyl 5-Methylene-2-vinyl-5,6-dihydro-4*H*-benzofuran-3a,7-dicarboxylate (2b): The product was obtained as a colourless oil (192 mg, 74%); R_f = 0.75 (diethyl ether/petroleum ether, 70:30). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.18 (dd, J = 17.4, 11.0 Hz, 1 H), 5.77 (d, J = 17.4 Hz, 1 H), 5.37 (d, J = 11.0 Hz, 1 H), 5.24 (s, 1 H), 4.97 (s, 1 H), 4.93 (s, 1 H), 3.74 (s, 3 H), 3.62 (s, 3 H), 3.10–3.00 (m, 2 H), 2.23 (d, J = 13.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 170.2, 165.9, 163.3, 156.0, 138.3, 123.6, 119.9, 113.3, 104.4, 102.6, 60.5, 52.8, 51.6, 39.6, 30.9 ppm.

Dimethyl 1-Oxa-2-vinyl-4,9-dihydrobenzo[*f*]azulene-3a,10-dicarboxylate (2c): The product was obtained as a colourless oil (234 mg, 72%); R_f = 0.73 (diethyl ether/petroleum ether, 70:30). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.18–6.90 (m, 4 H), 6.17 (dd, J = 17.2, 11.0 Hz, 1 H), 5.78 (d, J = 17.2 Hz, 1 H), 5.37 (d, J = 11.0 Hz, 1 H), 5.20 (s, 1 H), 3.73 (s, 3 H), 3.55 (s, 3 H), 3.10 (s, 2 H), 3.00 (s, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 170.3, 166.6, 164.6, 155.0, 136.1, 134.7, 130.8, 130.3, 126.6, 123.5, 120.0, 106.6, 105.9, 61.1, 53.0, 51.8, 38.5, 32.2 ppm.

Dimethyl 2-Vinyl-4,11-dihydro-1-oxa-5,10-diazanaphtho[2,3-*f*]azulene-3a,12-dicarboxylate (2d): The product was obtained as a colourless oil (302 mg, 82%); R_f = 0.66 (diethyl ether/petroleum ether, 90:10). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.06–7.95 (m, 2 H), 7.74–7.65 (m, 2 H), 6.23 (dd, J = 17.4, 11.0 Hz, 1 H), 5.86 (d, J = 17.4 Hz, 1 H), 5.45 (d, J = 11.0 Hz, 1 H), 5.32 (s, 1 H), 4.39 (d, J = 17.6 Hz, 1 H), 4.11 (d, J = 17.6 Hz, 1 H), 3.76 (s, 3 H), 3.67 (d, J = 17.8 Hz, 1 H), 3.66 (s, 3 H), 3.33 (d, J = 17.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 170.1, 165.9, 151.6, 151.5, 141.4, 141.0, 129.6, 128.8, 128.3, 123.3, 120.8, 106.4, 102.8, 60.5, 53.7, 52.1, 42.1, 34.6 ppm.

Methyl 2-(Methoxycarbonylmethyl)-5-vinylfuran-3-carboxylate (2e): The product was obtained as a colourless oil (174 mg, 92%); R_f = 0.72 (diethyl ether/petroleum ether, 70:30). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.46 (s, 1 H), 6.36 (dd, J = 16.6, 11.3 Hz, 1 H), 5.62 (d, J = 16.6 Hz, 1 H), 5.16 (d, J = 11.3 Hz, 1 H), 4.05 (s, 2 H), 3.75 (s, 3 H), 3.66 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 169.0, 163.8, 153.5, 153.4, 124.3, 116.9, 114.1, 108.2, 51.6, 52.5, 33.3 ppm.

2-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-3-(*tert*-butyldimethylsilanyloxymethyl)-5-vinylfuran (2f): DMAP (2.40 mmol, 6.0 equiv.) and *tert*-butylchlorodimethylsilane (0.92 mmol, 2.3 equiv.) was added to a solution of diol **4e** (see below, 0.40 mmol, 1.0 equiv.) in distilled dichloromethane (8 mL). After 30 min of reaction, TLC analysis indicated completion of the reaction. The reaction mixture was diluted with DCM (30 mL) and washed with water (3 × 5 mL). The organic phase was then dried with MgSO$_4$, filtered and the solvent evaporated under reduced pressure. Purification by silica gel chromatography (diethyl ether/petroleum ether, 1:10) provided the pure desired product (117 mg, 74%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.42 (dd, J = 17.4, 11.1 Hz, 1 H), 6.20 (s, 1 H), 5.55 (d, J = 17.4 Hz, 1 H), 5.05 (d, J = 11.1 Hz, 1 H), 4.52 (s, 2 H), 3.82 (t, J = 6.9 Hz, 2 H), 2.82 (t, J = 6.9 Hz, 2 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.009 (s, 6 H), 0.004 (s, 6 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 151.3, 148.8, 125.2, 122.5, 111.0, 109.7, 61.9, 57.1, 30.5, 26.1, 26.0, 18.5, 18.4, –5.1, –5.4 ppm.

3a,7-Bis(*tert*-butyldimethylsilanyloxymethyl)-2-vinyl-3a,4,5,6-tetrahydrobenzofuran (2g): This compound was isolated by using the previous alcohol protection procedure starting from **4a** (see below) as the diol (154 mg, 75%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.22 (dd, J = 17.2, 11.0 Hz, 1 H), 5.57 (d, J = 17.2 Hz, 1 H), 5.26 (s, 1 H), 5.23 (d, J = 11.0 Hz, 1 H), 4.31 (d, J = 11.7 Hz, 1 H), 4.27 (d, J = 11.7 Hz, 1 H), 3.63 (d, J = 9.6 Hz, 1 H), 3.41 (d, J = 9.6 Hz Hz, 1 H), 2.23–2.13 (m, 4 H), 1.75–1.71 (m, 2 H), 0.95–0.83 (m, 18 H), 0.07–0.01 (m, 12 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 153.3, 152.4, 125.6, 115.9, 110.9, 68.0, 60.1, 49.9, 26.9, 25.9, 23.2, 18.4, 17.4, –5.1, –5.2, –5.3, –5.4 ppm.

(3a-Hydroxymethyl-2-vinyl-3a,4,5,6-tetrahydrobenzofuran-7-yl)methanol (4a): To a suspension of aluminium lithium hydride (3.57 mmol, 2.0 equiv.) in anhydrous THF (4 mL) under argon atmosphere at –40 °C was added dropwise a solution of the diester **2a** (1.78 mmol, 1.0 equiv.) in THF (3 mL). The reaction was warmed up to room temperature and stirred for 1 h when TLC analysis indicated completion of the reaction. Water (1 mL) was added to the reaction mixture. A solution of hydrochloric acid (1N) was added in order to dissolve the aluminium salts. The aqueous phase was extracted with diethyl ether (4 × 20 mL). The organic fractions were combined, washed with brine (50 mL), dried with anhydrous magnesium sulfate and evaporated to give the crude diol product **4a**. Analysis of the crude diol by ^{1}H NMR indicated a chemical purity superior to 95%. The product was used without further purification (417 mg, 87%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.24 (dd, J = 17.4, 10.9 Hz, 1 H), 5.61 (d, J = 17.4 Hz, 1 H), 5.27 (d, J = 10.9 Hz, 1 H), 5.16 (s, 1 H), 4.38 (d, J = 11.8 Hz, 1 H), 4.05 (d, J = 11.8 Hz, 1 H), 3.58 (d, J = 10.8 Hz, 1 H), 3.47 (d, J = 10.8 Hz, 1 H), 2.57 (br. s, 2 × OH), 2.22–2.11 (m, 1 H), 1.99–1.92 (m, 1 H), 1.83–1.64 (m, 3 H), 1.49–1.38 (m, 1 H) ppm. ^{13}C NMR(75 MHz, CDCl$_3$): δ = 153.9, 153.6, 124.7, 116.6, 109.5, 108.0, 67.4, 60.4, 49.7, 27.4, 23.4, 17.1 ppm.

2-(3-Hydroxymethyl-5-vinylfuran-2-yl)ethanol (4e): Diisobutylaluminium hydride (1.5 M solution in toluene, 5.54 mmol, 4.4 equiv.) was added to a solution of the diester **2e** (1.26 mmol, 1.0 equiv.) in anhydrous THF (25 mL) under argon at –20 °C. The reaction was warmed up to room temperature and stirred for 1 h. Water (5 mL) was added to the reaction mixture. A solution of 2 N hydrochloric acid was added in order to dissolve the previously formed aluminium salts. The aqueous phase was extracted with diethyl ether (4 × 20 mL). The organic fractions were combined, washed with brine (50 mL), dried with anhydrous magnesium sulfate and evaporated to give the crude diol product **4e**. Analysis of the crude diol by ^{1}H NMR indicated a chemical purity greater than 95%. The product was used without further purification (194 mg, 90%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.35 (dd, J = 17.4, 11.2 Hz, 1 H), 6.15 (s, 1 H), 5.52 (d, J = 17.4 Hz, 1 H), 5.03 (d, J = 11.2 Hz, 1 H), 4.00 (br. s, 2 H, OH), 3.73 (t, J = 5.6 Hz, 2 H), 2.80 (t, J = 5.6 Hz, 2 H), 2.28 (t, J = 5.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 151.4, 150.1, 124.9, 122.7, 111.5, 109.9, 60.2, 55.6, 29.7 ppm.

General Procedure for the Diels–Alder Cyclisation of Vinyl Enol Ethers: The dienophile (1.5 mmol, 3.0 equiv.) was added to a solution of diene (0.5 mmol, 1.0 equiv.) in freshly distilled toluene under argon and the mixture was heated at reflux. When TLC analysis indicated completion of the reaction, the mixture was filtered through a pad of Celite, the solvent evaporated in vacuo and the crude material purified by silica gel chromatography to provide the pure desired product.

Trimethyl 2-(Methoxycarbonylmethyl)benzofuran-3,4,5-tricarboxylate (3a): This compound was obtained as a colourless oil (55 mg, 63%) by using methyl 2-(methoxycarbonylmethyl)-5-vinylfuran-3-carboxylate (**2e**) as the diene and DMAD as the dienophile. $R_f = 0.26$ (diethyl ether/petroleum ether, 70:30). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.98 (d, J = 8.1 Hz, 1 H), 7.50 (d, J = 8.1 Hz, 1 H), 4.13 (s, 2 H), 3.95 (s, 3 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.67 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 168.1, 168.0, 166.1, 162.7, 159.7, 156.2, 127.7, 124.5, 130.4, 129.0, 122.6, 112.4, 52.8 (2 C), 52.1 (2 C), 34.9 ppm.

Methyl 7-(Methoxycarbonylmethyl)-1,3-dioxo-1,3,3a,4,8a,8b-hexahydrobenzo[1,2-*b*;3,4-*c*′]difuran-8-carboxylate (3b): This compound was obtained as a white solid (54 mg, 72%) by using methyl 2-(methoxycarbonylmethyl)-5-vinylfuran-3-carboxylate (**2e**) as the diene and maleic anhydride as the dienophile. $R_f = 0.10$ (diethyl ether/petroleum ether, 70:30). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.32 (dt, J = 7.9, 3.6 Hz, 1 H), 4.06–3.98 (m, 1 H), 3.96 (d, J = 1.3 Hz, 1 H), 3.78 (d, J = 16.6 Hz, 1 H), 3.75 (s, 3 H), 3.66 (s, 3 H), 3.58 (d, J = 16.6 Hz, 1 H), 3.35 (m, 1 H), 2.98 (m, 1 H), 2.1 (m, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 173.6, 169.6, 167.9, 164.1, 161.9, 155.5, 108.9, 95.7, 52.7, 51.9, 43.1, 41.8, 38.8, 33.7, 24.6 ppm.

8-(*tert*-Butyldimethylsilanyloxymethyl)-7-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-1,3,3a,4,8a,8b-hexahydrobenzo[1,2-*b*;3,4-*c*′]difuran-1,3-dione (3c): This compound was obtained as an oil (62 mg, 79%) by using 2-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-3-(*tert*-butyldimethylsilanyloxymethyl)-5-vinylfuran (**2f**) as the diene and maleic anhydride as the dienophile. $R_f = 0.55$ (ethyl acetate/petroleum ether, 50/50). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.16–5.11 (m, 1 H), 4.57 (d, J = 12.5 Hz, 1 H), 4.42 (d, J = 12.5 Hz, 1 H), 3.77–3.60 (m, 4 H), 3.37–3.31 (m, 1 H), 2.50–2.44 (t, J = 7.0 Hz, 1 H), 2.94–2.85 (m, 1 H), 2.15–2.04 (m, 1 H), 0.91 (s, 9 H), 0.82 (s, 9 H), 0.08 (s, 6 H), 0.05 (s, 6 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 173.8, 169.7, 157.1, 151.4, 112.7, 91.6, 60.3, 57.1, 43.1, 42.8, 39.5, 30.0, 25.9, 25.8, 25.6, 24.7, 18.4, 18.3, –3.6, –5.3, –5.4, –5.5 ppm.

Dimethyl 4-Methylene-9-oxobicyclo[3.3.1]non-2-ene-1,5-dicarboxylate (6a): Potassium carbonate (830 mg, 6.0 mmol, 3.0 equiv.) followed by the dropwise addition of 1,4-dibromobut-2-yne (424 mg, 2.0 mmol, 1.0 equiv.) were added to a solution of dimethyl 2-oxocyclohexane-1,3-dicarboxylate (430 mg, 2.0 mmol, 1.0 equiv.) in DMSO (10 mL) under argon . The reaction was then heated at 80 °C. After stirring for 7 h, TLC analysis indicated completion of the reaction and formation of the 2-vinylidenehydrofuran. Palladium acetate (22.5 mg, 0.1 mmol, 0.05 equiv.) and diphenylphosphanylethane (dppe) (80 mg, 0.2 mmol, 0.10 equiv.) were then added to the reaction mixture, which instantly turned red. The mixture was filtered through a pad of Celite and the solvent was removed in vacuo. The resulting residue was then purified by silica gel chromatography to provide the pure desired product **6a** (151 mg, 28%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.60 (d, J = 9.9 Hz, 1 H), 5.86 (d, J = 9.9 Hz, 1 H), 5.20 (s, 1 H), 4.76 (s, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 2.44–2.20 (m, 2 H), 2.17–1.90 (m, 2 H), 1.80–1.70 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 203.1, 170.7, 170.6, 146.0, 132.5, 126.5, 115.3, 64.6, 59.9, 52.7, 52.4, 41.0, 35.8, 17.5 ppm.

Dimethyl 2-(Allyloxy)-2-vinyl-2,3,3a,4,5,6-hexahydrobenzofuran-3a,7-dicarboxylate (8a): Allylic alcohol (0.118 mL, 5.8 mmol, 5 equiv.) followed by a 0.1 M solution of CSA (1.16 mL, 0.1 equiv.) in chloroform were added to a cooled (–10 °C) solution of the allene **1a** (1.16 mmol, 1.0 equiv.) in chloroform (23 mL, 0.05 M). When TLC analysis indicated completion of the reaction, the reaction was quenched with a 10% aqueous solution of Na$_2$CO$_3$ (10 mL). The aqueous fraction was extracted with chloroform (2 × 5 mL). The organic fractions were combined, washed with brine (10 mL), dried (MgSO$_4$) and the solvents evaporated. The residue was purified by flash chromatography to afford the product **8a** as a 1:1 mixture of diastereomers (101 mg, 27%). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 173.9, 173.8, 167.1, 167.0, 162.9, 161.9, 134.8, 134.6, 134.5, 134.4, 118.8, 118.6, 116.6, 116.1, 110.0, 108.8, 101.7, 100.6, 65.4, 64.1, 54.0, 53.9, 52.5, 52.4, 51.1, 51.08, 47.8, 46.8, 32.5, 32.3, 25.3, 23.4, 19.0, 18.9 ppm.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for compounds **2a–2e**, **3a–c**, **6a**, **8a**.

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