

Antitumor benzothiazoles. 13. (Diacetoxy)iodobenzene (DAIB) oxidation of 2-(4-hydroxy-3-methoxyphenyl)benzothiazole and related compounds in the presence of dienophiles

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This paper is dedicated to Otto Meth-Cohn on the occasion of his 65th birthday in admiration of his cheerful efforts to keep the flag of heterocyclic chemistry flying high in bad times and good times

(received 13 May 00; accepted 03 Oct 00; published on the web 11 Oct 00)

Abstract

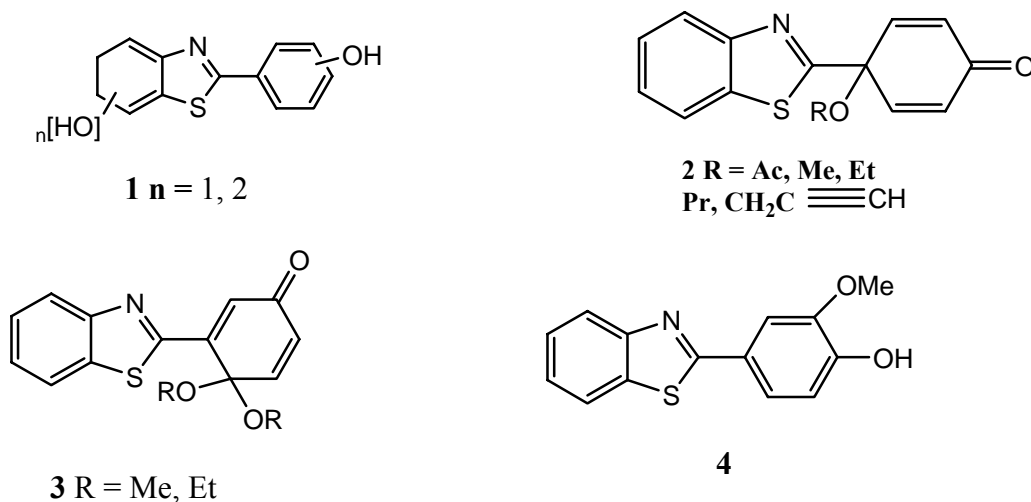
Oxidation of 2-methoxyphenols bearing an electron withdrawing group in the 4-position with (diacetoxy)iodobenzene (DAIB) in the presence of dienophiles affords bicyclo[2.2.2]octenones, 3-oxatricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-ones, tricyclo[6.2.2.0^{2,7}]dodeca-5,11-dien-9-ones, 5-methyl-5-(2-propenyl)bicyclo[2.2.2]oct-7-en-5-ones and derivatives thereof. When 2-(4-hydroxy-3-methoxyphenyl)benzothiazole is oxidised by DAIB in acetonitrile in the absence of a trapping partner the product is a benzothiazole-substituted 2,2'-dihydroxy-3,3'-dimethoxybiphenyl.

Keywords: Phenols, (diacetoxy)iodobenzene (DAIB), benzothiazoles, Diels Alder adducts

Introduction

It has been shown recently that phenolic protein tyrosine kinase (PTK) inhibitors which contain the catechol moiety decompose in buffer solution¹ and this reactivity is associated with a (delayed) increase in biological activity.² We have recently studied the oxidation of PTK inhibitors of the tyrphostin class with hypervalent iodine reagents and

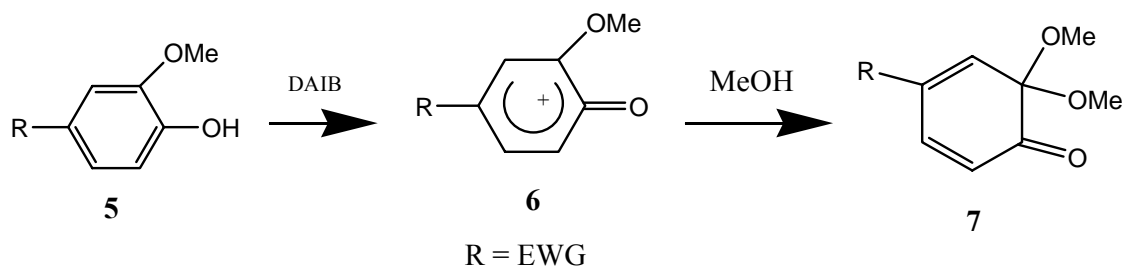
shown that certain oxidations furnish products of at least equal potency to the starting phenols as *in vitro* cell growth inhibitors.³ We have also explored the chemistry of polyhydroxylated 2-phenyl-benzothiazoles (1), designed originally as flavone (eg quercetin) and isoflavone (genistein) isosteres to inhibit PTK enzymes.⁴ Whilst these benzothiazoles are relatively ineffective as cell growth and PTK inhibitors their transformations by hypervalent iodine oxidants unveils promising antitumour activity. Thus, quinol esters and ethers (2) derived from the oxidation of 2-(4-hydroxyphenyl)benzothiazole and quinone monoketals (3) from the oxidation of 2-(3-hydroxyphenyl)benzothiazole, respectively, have significantly improved and extended antitumor potency *in vitro* against pairs of breast and colon human tumor cell lines.⁵ To augment our earlier work we were interested in studying the oxidation reactions of 2-(4-hydroxy-3-methoxyphenyl)benzothiazole (4).



The (diacetoxy)iodobenzene (DAIB) oxidation chemistry used to oxidise these benzothiazole substrates is relatively inefficient. Our earlier work has demonstrated that the nature of the additional substituents in the phenolic substrate, the solvent, and the reaction and purification conditions determines the nature of the product and yields in the presence of the oxidant.³ It is known that simple 2-methoxyphenols, substituted with an EWG in the 4- position (5), when oxidised using DAIB in methanol generate *p*-carbocation reactive intermediates (6) (Scheme 1) which react with the methanol to produce *ortho*-quinone monoketals (7) (OQMs).⁶ Although these compounds are often too unstable to isolate (in contrast to 2-acyloxy-2-alkoxy-3,5-cyclohexadione)s^{3,7} their presence in the reaction mixture may be inferred by the isolation of their Diels-Alder dimers.^{8,9} A number of recent publications have demonstrated that trapping OQMs,

generated from readily available 2-methoxyphenols, with dienophiles has value in the synthesis of bridged carbocycles with introduction of several new chiral centres in a regio and stereo-controlled manner.⁸⁻¹⁴ This approach has found use in the synthesis of natural products, for example, reserpine,¹¹ forsythide aglucone,¹² fused triquinanes,¹³ and pallescensin B.¹⁴

Our own interest in this chemistry stems from our efforts to understand both the role of oxidation of phenols in their biological activity and the routes by which they may be oxidised during bioactivating/deactivating processes. In this paper we have compared the DAIB oxidations of vanillin (5; R = CHO), and analogs with related EWG groups, with published information on similar oxidations of methyl vanillate (5; R = CO₂Me). These model oxidations have relevance to predictions the outcome of the oxidation of 2-(4-hydroxy-3-methoxyphenyl)benzothiazole (4).



Scheme 1. Oxidation of 2-methoxyphenols.

In particular we have used both electron rich and electron deficient dienophiles to trap the OQM intermediates: the products may be either bicyclo[2.2.2]octenones, 3-oxatricyclo-[5.2.2.0^{2,6}]undeca-4,10-dien-8-ones, tricyclo[6.2.2.0^{2,7}]dodeca-5,11-dien-9-ones, 5-methyl-5-(2-propenyl)bicyclo[2.2.2]oct-7-en-5-ones, or derivatives thereof, depending on the choice of dienophile and reaction conditions.

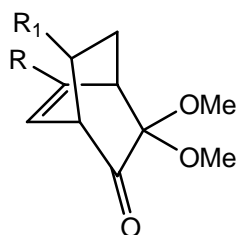
Results and Discussion

Oxidation of 2-methoxyphenols with DAIB in a nitromethane-methanol mixture in the presence of excess of the electron deficient dienophiles methylvinylketone, ethylvinylketone and methyl acrylate with the Lewis acid ZnCl₂ (0.1 mol. equiv.) to accelerate the Diels-Alder reaction, yielded the bicyclo[2.2.2]octenones (8a-e) (Scheme 2). The benzothiazole adducts (8c-e) were isolated in relatively low yields (35-40%) probably due to the bulky nature of the heterocycle in the 4-position of the intermediate

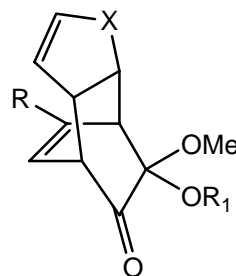
OQM (7; R = benzothiazol-2-yl). Steric and stability factors also appeared to be important in the dienophile, the reaction failing with *p*-nitrostyrene and acrolein. In these cases decomposition of the OQM preceded the detection of any cycloadduct.

The regiochemistry and relative stereochemistry of new adducts (8a, c-e) was assigned by comparison with 8b; analytical and spectral data are in close agreement with values reported for this compound.¹² In agreement with observations in the literature, we also found that bicyclo[2.2.2]octenones (8) readily lose CO when subject to EIMS analysis, precluding the detection of a molecular ion.

In the oxidative interaction of model 2-methoxyphenols with the cyclic, electron rich, dienophile furan the corresponding 3-oxatricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-ones (9a-d) were formed smoothly in 54 - 80% yield after chromatographic purification. The yields are similar to those described in the literature using a thermally rather than a Lewis acid mediated Diels-Alder reaction.¹⁵ The cycloaddition is relatively fast compared to that with electron deficient dienophiles, being complete in less than 15-20 minutes at 0 °C. Ethanol or propanol may replace methanol in the oxidation of vanillin generating mixed ketal intermediates. The products which result (9e, f) were a mixture of diastereomers (only one structure shown) in a roughly equal ratio, demonstrating that substitution at the ketal position in this case exerts little selective pressure on the Diels-Alder reaction. Replacement of furan with the bulkier 1,3-cyclohexadiene furnishes the tricyclo[6.2.2.0^{2,7}]dodeca-5,11-dien-9-one (9g) in lower yield (26%).



- 8a:** R = CHO, R₁ = COMe
b: R = CO₂Me, R₁ = CO₂Me
c: R = benzothiazol-2-yl, R₁ = COMe
d: R = benzothiazol-2-yl, R₁ = COEt
e: R = benzothiazol-2-yl, R₁ = CO₂Me



- 9a:** R = CHO, R₁ = Me, X = O
b: R = CO₂Me, R₁ = Me, X = O
c: R = COMe, R₁ = Me, X = O
d: R = CN, R₁ = Me, X = O
e: R = CHO, R₁ = Et, X = O
f: R = CHO, R₁ = Pr, X = O
g: R = CHO, R₁ = Me, X = (CH₂)₂

Compounds in series 9 have been characterised by a combination of infrared, mass and NMR (¹H, ¹³C, DEPT and 2D COSY) spectral analysis; the structure of 9a has also been corroborated by x-ray diffraction (Figure 1). This confirms the Diels-Alder adduct as being *endo* with respect to the OQM diene moiety and of the expected regiochemistry.

The structures of other bi- and tricycloadducts (10-14) derived from electron rich dienophiles were assigned by comparison with 9a, and were assumed to have an analogous relative stereochemistry. ^1H NMR spectra were assigned on the basis of proton-proton coupling patterns observed in the COSY spectrum. Protons derived from the original OQM ring were determined initially by the use of d_4 -furan in the synthesis of 9b.

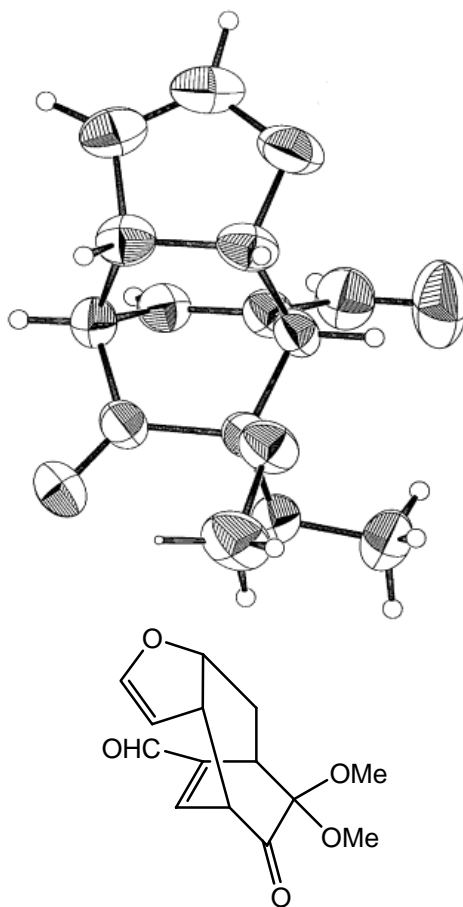
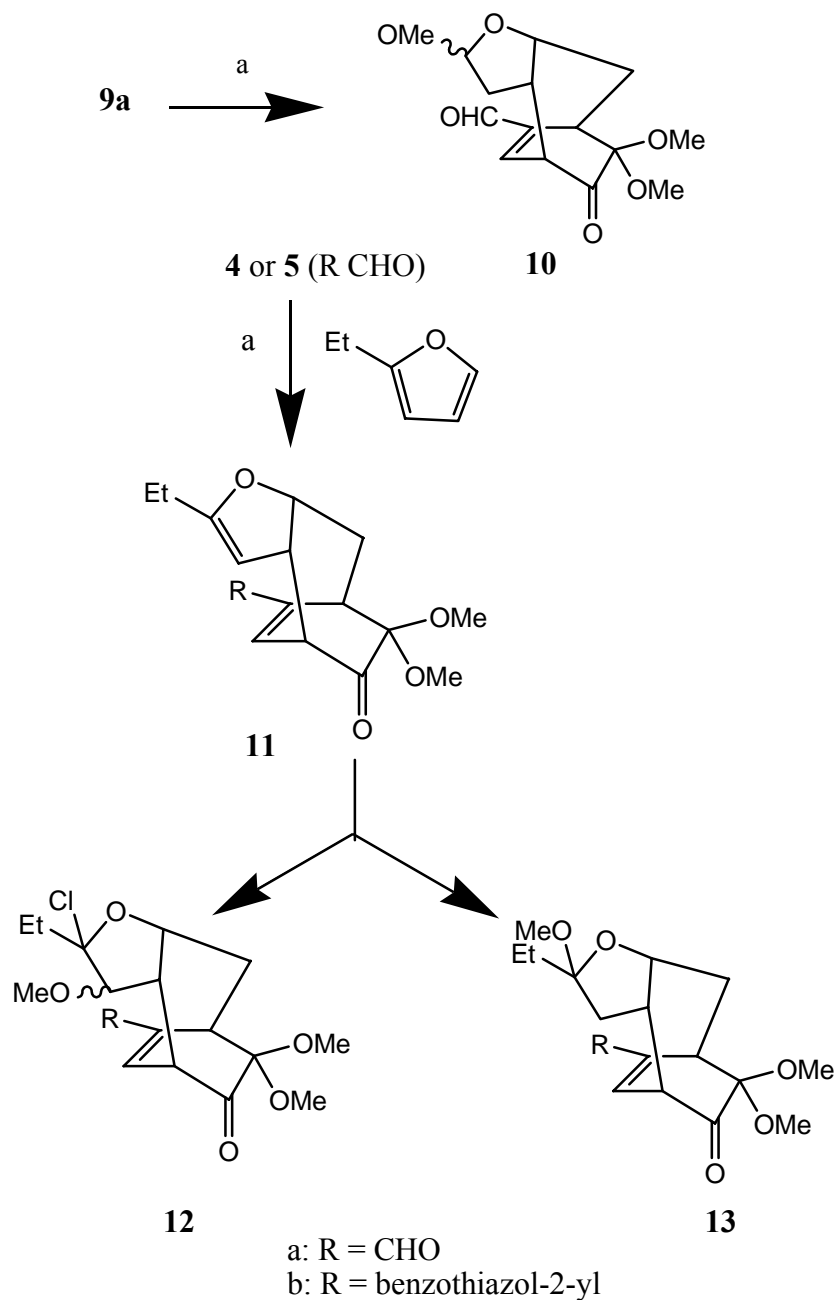


Figure 1. ORTEP diagram of the crystal structure of compound **9a**.

Adduct (9a) underwent a slow secondary transformation in 72 h involving methanol addition across the dihydrofuran double bond to form a tetrahydrofuran of tentative structure 10 (Scheme 2). Presumably this is an acid-catalysed process favoured by the prolonged exposure to the methanolic ZnCl_2 and acetic acid (liberated during the oxidation). Related additions were observed in the reactions between the benzothiazole (4) and vanillin (5; $\text{R} = \text{CHO}$) when carried out with 2-ethylfuran as dienophile. The

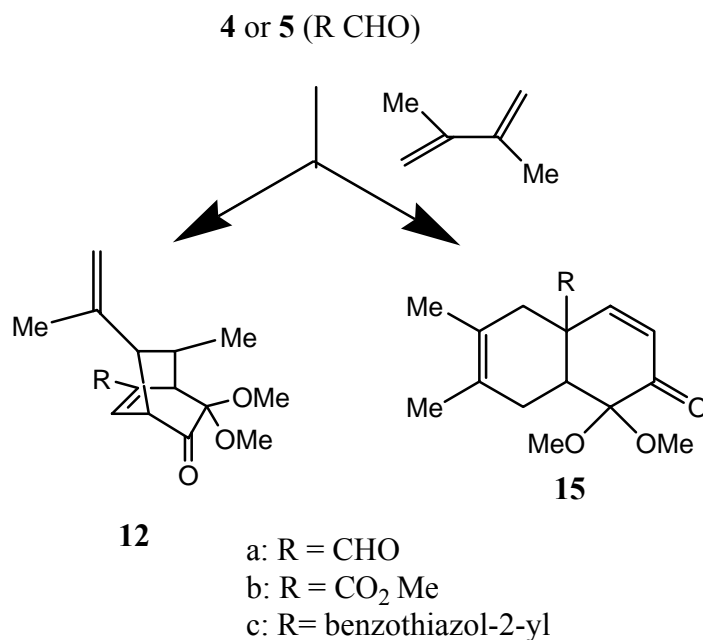
expected cycloadducts (11) analysed correctly for oxidative chloromethoxy addition across the tricyclic dihydrofuran double bond to form 12 (or 13) (Scheme 2); a reaction which warrants further investigation. The yields of these unexpected products were low, probably reflecting the substoichiometric concentration of chloride ion in the reaction.



Scheme 2. Reagents and conditions: a. DAIB, MeOH, MeNO₂, ZnCl₂, 0°C.

Open-chain dienes behave in two distinct ways (Scheme 3). With the OQMs generated from the phenols (4) and (5; R = CHO, CO₂Me), 2,3-dimethylbutadiene forms the expected bicyclo[2.2.2]octenone cycloadducts (14a-c). The cis-decalins (15a-c), arising from the reciprocal behaviour of the OQM as the dienophile and the butadiene as the diene, are also isolated, the ratio of the two products depending on the substituent in the 4-position of the OQMs. The smaller CHO and CO₂Me groups give an approximately 2.5 : 1 ratio of products in favour of the cis-decalins: the larger benzothiazole group however, gives a greater than 3 : 1 preference for the bicyclo[2.2.2]octenone (14c), presumably due to unfavourable steric interactions during the formation of the cis-decalin with the heterocycle at the bridgehead position. The overall yields are relatively consistent at around 60%.

The structures of the cis-decalins (15) were assigned largely on the basis of their NMR spectra. These structural assignments also compare well with those given for 15b in the literature.⁸

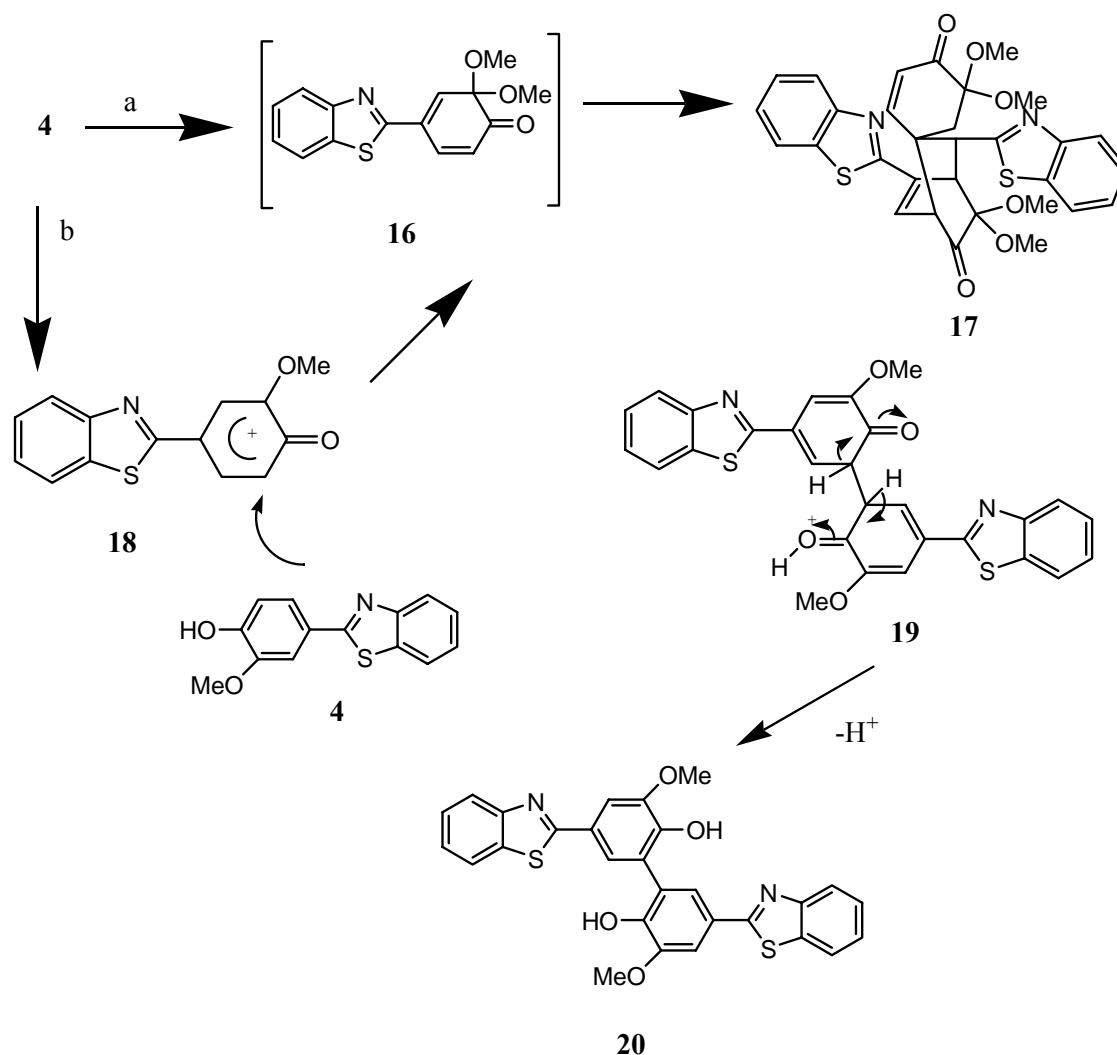


Scheme 3. Reagents and conditions: a. DAIB, MeOH, MeNO₂, ZnCl₂, 0°C.

When benzothiazole (4) was oxidised by DAIB at 0 °C in a mixture of methanol and nitromethane in the absence of a trapping partner, the OQM (16) was generated and isolated as its Diels-Alder dimer (17), albeit in poor yield (Scheme 4). In a non-nucleophilic solvent such as acetonitrile, benzothiazole (4), like other 2-methoxyphenols,³ undergoes an intermolecular oxidative coupling reaction in the presence of 0.5 equivalents of DAIB to form the corresponding 2,2'-dihydroxy-3,3'-dimethoxybiphenyl (20) in 32% yield. A possible mechanism for this coupling involves the intermediate p-carbocation (18) which is trapped by a molecule of unoxidised 4 to forge the 2,2'-biphenyl linkage (19). Loss of a proton then leads to the observed product (20) (Scheme 4).

Biological Results

In *in vitro* growth inhibition tests against the human breast cancer cell lines MCF-7 and MDA468 (over 7 and 10 days respectively) determined by MTT assay,¹⁶ the phenolic benzothiazole (4) gave IC₅₀ values (dose to inhibit cell growth by 50%) of 0.62 and 0.06 mM, respectively. The adducts (8c, 14c and 15c) were less inhibitory giving IC₅₀ values > 5 mM.



Scheme 4. Reagents and conditions: a. DAIB, MeOH, MeNO₂, 0°C, 2Hr; b. DAIB, MeCN, rt, 24Hrs:

Experimental Section

General Procedures. Melting points were obtained using a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 2020 Galaxy Series FT-IR spectrometer using KBr discs. ¹H and ¹³C NMR spectra were acquired using a Bruker ARX250 spectrometer at 250.13MHz and 62.9MHz respectively. Mass

spectra were recorded using a Micromass Platform Spectrometer or an AEI MS-902 Spectrometer using Electron Impact (EI), Electrospray (ES), Chemical Ionisation (CI), or Atmospheric Pressure CI (AP) techniques. Nominal mass spectra were obtained using an AP+ ionisation technique and accurate mass spectra using an EI+ technique unless otherwise stated. Flash column chromatography refers to medium pressure silica gel (C60 (40-60mm)) preparative column chromatography, unless otherwise stated. Petrol ether refers to the fraction which boils between 60 and 80 °C.

2-(4-Hydroxy-3-methoxyphenyl)benzothiazole (4). A mixture of vanillin(4.00 g, 26.3mmol) and 2-aminothiophenol (3.20 g, 25.6mmol) in toluene (50 mL) were heated at reflux in toluene (100 mL) overnight, under a Dean-Stark trap. After cooling to room temperature, the solvent was removed under reduced pressure and the residue recrystallised from ethanol / water to give white needles (4.43 g, 68%); mp 171 °C (lit. 173 °C¹⁷); ¹H NMR [DMSO-*d*₆] δ 9.90 (1H, bs, OH), 8.09 (1H, m, H-4/7), 8.04 (1H, m, H-4/7), 7.66 (1H, d, *J* 1.9Hz, H-2'), 7.51 (2H, m, H-5/6, H-6'), 7.41 (1H, m, H-5/6), 6.96 (1H, d, *J* 7.8Hz, H-5'), 3.92 (3H, s, OCH₃).

Diels-Alder cycloadducts - General method

To the 2-methoxy-4-(substituted)phenol (0.50 g) in nitromethane (15 mL) and alcohol (5 mL) was added the diene (2 mL) and zinc chloride (0.1 mol. equiv.). The reaction mixture was cooled to 0 °C, with stirring and DAIB (1.1 equivalents) was added as a solid. The reaction was followed to completion by thin layer chromatography. After 10-30 minutes (2hrs in the case of MVK, EVK and MA reactions) the solvents were removed *in vacuo* and the residual oil diluted with diethyl ether (30 mL), then washed with 5% sodium carbonate solution (2 x 50 mL) and water (2 x 50 mL). After drying the organic layer over magnesium sulphate the solvent was removed *in vacuo* and the product purified by flash column chromatography (eluted with ethyl acetate / hexane).

7-Acetyl-5-formyl-3,3-dimethoxybicyclo[2.2.2]oct-5-en-2-one (8a). A mixture of vanillin(0.50 g, 3.3 mmol), DAIB (1.17 g, 3.6 mmol) and MVK (2 mL) was reacted according to the general method, to give a pale yellow oil (0.35 g, 42%); ¹H NMR [CDCl₃] δ 9.54 (1H, s, CHO), 7.17 (1H, dd, *J* 2.0, 6.0Hz, H-6), 3.88 (1H, d, *J* 2.0Hz, H-4), 3.70 (1H, dd, *J* 1.8, 6.3Hz, H-1), 3.41 (3H, s, OCH₃), 3.35 (1H, m, H-7), 3.28 (3H, s, OCH₃), 2.50 (1H, m, H-8), 2.18 (3H, s, COCH₃), 1.41 (1H, m, H-8); ¹³C NMR [CDCl₃] δ 205.6 (C), 200.1 (C), 188.6 (CH), 146.1 (C), 144.6 (CH), 93.7 (C), 51.2 (CH), 50.7 (CH), 50.6 (CH), 48.7 (CH), 35.4 (CH), 28.6 (CH), 24.5 (CH₂); IR ν_{max} 2849, 1742, 1719, 1684, 1364, 1190, 1088, 1053cm⁻¹; TLC (ethyl acetate / hexane 2:8) R_F 0.13; MS (EI, *m/z*) 224 (M⁺-CO), 181 (-CH₃CO).

3,3-Dimethoxy-5,7-dimethoxycarbonylbicyclo[2.2.2]oct-5-en-2-one (8b). A mixture of methyl vanillate (0.50 g, 2.7 mmol), DAIB (0.97 g, 3.0 mmol) and MA (2 mL) was reacted according to the general method, to give a pale yellow oil (0.60 g, 76%); ^1H NMR [CDCl_3] δ 7.06 (1H, dd, J 2.0, 6.6 Hz, H-6), 3.77 (1H, d, J 2.8 Hz, H-4), 3.75 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.63 (1H, dd, J 1.7, 10.1 Hz, H-1), 3.32 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 3.08 (1H, m, H-7), 2.36 (1H, td, J 2.9, 10.3 Hz, H-8), 1.69 (1H, m, H-8); ^{13}C NMR [CDCl_3] δ 200.2 (C), 173.2 (C), 164.5 (C), 138.5 (C), 135.8 (CH), 93.6 (C), 52.9 (CH), 52.5 (CH), 51.2 (CH), 50.7 (CH), 50.5 (CH), 39.6 (CH), 38.7 (CH), 25.2 (CH_2); IR ν_{max} 2953, 1740, 1721, 1439, 1256, 1107, 1072, 774 cm^{-1} ; TLC (ethyl acetate / hexane 2:8) R_F 0.24; MS (EI, m/z) 270 ($\text{M}^+ - \text{CO}$), 211 ($-\text{CO}_2\text{CH}_3$), 151 ($-\text{HCO}_2\text{CH}_3$).

7-Acetyl-5-(benzothiazol-2-yl)-3,3-dimethoxybicyclo[2.2.2]oct-5-en-2-one (8c). Compound 4 (0.50 g, 1.9 mmol), DAIB (0.69 g, 2.1 mmol) and MVK (2 mL) was reacted according to the general method, to give an off white solid (0.25 g, 37%); mp 159 $^\circ\text{C}$; ^1H NMR [CDCl_3] δ 8.01 (1H, dd, J 1.0, 7.4 Hz, H-4'/7'), 7.83 (1H, dd, J 1.1, 7.2 Hz, H-4'/7'), 7.50-7.34 (2H, m, H-5',6'), 6.89 (1H, dd, J 1.7, 6.6 Hz, H-6), 4.40 (1H, dd, J 2.8, 5.1 Hz, H-4), 3.68 (1H, dd, J 1.7, 6.6 Hz, H-1), 3.45 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 3.27 (1H, m, H-7), 2.54 (1H, ddd, J 3.1, 10.4, 13.2 Hz, H-8), 2.17 (3H, s, COCH_3), 1.76 (1H, ddd, J 2.8, 6.8, 13.0 Hz, H-8); ^{13}C NMR [CDCl_3] δ 205.8 (C), 200.4 (C), 164.9 (C), 153.8 (C), 141.3 (C), 135.3 (C), 128.5 (CH), 126.7 (CH), 126.2 (CH), 123.8 (CH), 122.0 (CH), 94.3 (C), 51.0 (CH), 50.7 (CH), 50.6 (CH), 48.3 (CH), 40.6 (CH), 28.7 (CH), 24.8 (CH_2); IR ν_{max} 2944, 1730, 1709, 1433, 1360, 1096, 1071, 756 cm^{-1} ; MS (ES, m/z) 358 ($\text{M}^+ + 1$), 326 ($[\text{M}^+ + 1] - \text{CH}_3\text{OH}$); Anal. Calcd. for $\text{C}_{19}\text{H}_{19}\text{NO}_4\text{S}$: C, 63.85; H, 5.36; N, 3.92. Found: C, 63.59; H, 5.35; N, 3.91.

5-(Benzothiazol-2-yl)-3,3-dimethoxy-7-(propionyl)bicyclo[2.2.2]oct-5-en-2-one (8d). Compound 4 (0.50 g, 1.9 mmol), DAIB (0.69 g, 2.1 mmol) and EVK (2 mL) was reacted according to the general method, to give a white crystalline solid (0.25 g, 35%); mp 134 $^\circ\text{C}$; ^1H NMR [CDCl_3] δ 7.97 (1H, dd, J 1.4, 7.9 Hz, H-4'/7'), 7.81 (1H, dd, J 1.3, 8.1 Hz, H-4'/7'), 7.47-7.31 (2H, m, H-5',6'), 6.87 (1H, d, J 1.6, 6.2 Hz, H-6), 4.36 (1H, dd, J 2.8, 5.1 Hz, H-4), 3.62 (1H, dd, J 1.7, 6.6 Hz, H-1), 3.42 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 3.24 (1H, m, H-7), 2.51 (1H, m, H-8), 2.43 (2H, q, J 7.3 Hz, CH_2), 1.71 (1H, ddd, J 2.8, 6.8, 12.9 Hz, H-8), 1.02 (3H, t, J 7.3 Hz, CH_3); ^{13}C NMR [CDCl_3] δ 208.8 (C), 200.4 (C), 165.0 (C), 153.8 (C), 141.1 (C), 135.3 (C), 128.7 (CH), 126.6 (CH), 126.1 (CH), 123.8 (CH), 122.0 (CH), 94.3 (C), 51.0 (CH), 50.7 (CH), 47.3 (CH), 40.7 (CH), 34.7 (CH), 25.2 (CH_2), 8.2 (CH); IR ν_{max} 2980, 1740, 1715, 1485, 1317, 1092, 1055, 764 cm^{-1} ; MS (m/z) 372 ($\text{M}^+ + 1$), 340 ($[\text{M}^+ + 1] - \text{CH}_3\text{OH}$); Anal. Calcd. for $\text{C}_{20}\text{H}_{21}\text{NO}_4\text{S}$: C, 64.67; H, 5.70; N, 3.77. Found: C, 64.73; H, 5.69; N, 3.77.

5-(Benzothiazol-2-yl)-3,3-dimethoxy-7-methoxycarbonylbicyclo[2.2.2]oct-5-en-2-one (8e). Compound 4 (0.50 g, 1.9 mmol), DAIB (0.69 g, 2.1 mmol) and MA (2 mL) was reacted according to the general method, to give a white solid (0.28 g, 39%); mp 153-4 °C; ¹H NMR [CDCl₃] δ 7.99 (1H, dd, *J* 1.3, 8.0Hz, H-4'/7'), 7.82 (1H, dd, *J* 1.4, 8.0Hz, H-4'/7'), 7.48-7.32 (2H, m, H-5',6'), 6.86 (1H, dd, *J* 2.1, 6.6Hz, H-6), 4.34 (1H, dd, *J* 2.7, 5.1Hz, H-4), 3.72 (1H, dd, *J* 2.0, 6.6Hz, H-1), 3.66 (3H, s, OCH₃), 3.40 (3H, s, OCH₃), 3.33 (3H, s, OCH₃), 3.19 (1H, m, H-7), 2.51 (1H, td, *J* 3.0, 10.3Hz, H-8), 1.89 (1H, m, H-8); ¹³C NMR [CDCl₃] δ 200.0 (C), 173.4 (C), 164.9 (C), 153.9 (C), 142.2 (C), 135.3 (C), 127.9 (CH), 126.7 (CH), 126.2 (CH), 123.9 (CH), 122.0 (CH), 94.1 (C), 52.9 (CH), 51.2 (CH), 51.0 (CH), 50.7 (CH), 40.7 (CH), 40.1 (CH), 25.5 (CH₂); IR ν_{max} 2951, 1732, 1439, 1339, 1211, 1088, 1042, 764cm⁻¹; MS (ES, *m/z*) 374 (M⁺+1), 342 ([M⁺+1]-CH₃OH); Anal. Calcd. for C₁₉H₁₉NO₅S: C, 61.11; H, 5.13; N, 3.75. Found: C, 61.14; H, 5.13; N, 3.65.

10-Formyl-9,9-dimethoxy-3-oxatricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-one (9a). A mixture of vanillin(0.50 g, 3.3 mmol), DAIB (1.17 g, 3.6 mmol), methanol (5 mL) and furan (2 mL) was reacted according to the general method, to give white needles (0.43 g, 69%); mp 102-3 °C; ¹H NMR [CDCl₃] δ 9.58 (1H, s, CHO), 7.05 (1H, m, H-11), 6.17 (1H, m, H-4), 5.17 (1H, dd, *J* 3.9, 9.4 Hz, H-2), 4.77 (1H, t, *J* 2.4Hz, H-5), 4.34 (1H, m, H-1), 3.55 (1H, m, H-6), 3.49 (1H, dd, *J* 2.4, 6.6Hz, H-7), 3.39 (3H, s, OCH₃), 3.27 (3H, s, OCH₃); ¹³C NMR [CDCl₃] δ 199.5 (C), 188.8 (CH), 148.8 (CH), 144.9 (CH), 143.0 (C), 100.4 (CH), 93.5 (C), 79.3 (CH), 54.1 (CH), 51.0 (CH), 50.5 (CH), 46.3 (CH), 40.8 (CH); IR ν_{max} 2837, 1738, 1678, 1610, 1086, 964, 855, 739cm⁻¹; MS (*m/z*) 251 (M⁺+1), 219 ([M⁺+1]-CH₃OH); Anal. Calcd. for C₁₃H₁₄O₅: C, 62.39; H, 5.64. Found: C, 62.20; H, 5.65.

9,9-Dimethoxy-10-methoxycarbonyl-3-oxatricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-one (9b). A mixture of methyl vanillate (0.5 g, 2.8 mmol), DAIB (0.98 g, 3.0 mmol), methanol (5 mL) and furan (2 mL) was reacted according to the general method, to give a white solid (0.49 g, 64%); mp 65 °C; ¹H NMR [CDCl₃] δ 7.13 (1H, dd, *J* 2.1, 6.8Hz, H-11), 6.22 (1H, dd, *J* 1.8, 2.8Hz, H-4), 5.21 (1H, dd, *J* 4.0, 9.5Hz, H-2), 4.78 (1H, t, *J* 2.1Hz, H-5), 4.34 (1H, m, H-1), 3.83 (3H, s, OCH₃), 3.53 (1H, m, H-6), 3.41 (3H, s, OCH₃), 3.38 (1H, d, *J* 6.8Hz, H-7), 3.36 (3H, s, OCH₃).¹⁵
2,4,5,6-Tetradeuterio-9,9-dimethoxy-10-methoxycarbonyl-3-oxatricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-one

A mixture of methyl vanillate(0.25 g, 1.4 mmol), DAIB (0.49 g, 1.5 mmol), methanol (5 mL) and *d*₄-furan (2 mL) was reacted according to the general method, to give a white solid (0.31 g, 80%); mp 74-5 °C; ¹H NMR [CDCl₃] δ 7.13 (1H, dd, *J* 2.1, 6.8Hz, H-11), 4.34 (1H, d, *J* 2.2Hz, H-1), 3.83 (3H, s, OCH₃), 3.42 (3H, s, OCH₃), 3.38

(1H, d, *J* 6.8Hz, H-7), 3.36 (3H, s, OCH₃); ¹³C NMR [CDCl₃] δ 200.6 (C), 164.7 (C), 136.7 (C), 135.5 (CH), 92.6 (C), 52.8 (CH), 52.6 (CH), 50.7 (CH), 50.5 (CH), 43.3 (CH); IR ν_{\max} 2951, 1742, 1719, 1441, 1248, 1067, 1049, 783cm⁻¹; *m/z* 285 (M⁺+1), 253 ([M⁺+1]-CH₃OH); TLC (ethyl acetate / hexane 2:8) R_F 0.23; HRMS (*m/z*) calcd for C₁₄D₄H₁₂O₆+NH₄ 302.1541, found 302.1530.

10-Acetyl-9,9-dimethoxy-3-oxatricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-one (9c). A mixture of acetovanillone(0.50 g, 3.0 mmol), DAIB (1.07 g, 3.3 mmol), methanol (5 mL) and furan (2 mL) was reacted according to the general method, to give a white solid (0.43 g, 54%); mp 90 °C; ¹H NMR [CDCl₃] δ 6.99 (1H, m, H-11), 6.16 (1H, m, H-4), 5.15 (1H, dd, *J* 4.0, 9.5Hz, H-2), 4.75 (1H, m, H-5), 4.44 (1H, m, H-1), 3.51 (1H, m, H-6), 3.36 (1H, dd, *J* 2.3, 6.7Hz, H-7), 3.27 (3H, s, OCH₃), 2.33 (3H, s, OCH₃); ¹³C NMR [CDCl₃] δ 200.4 (C), 194.7 (C), 148.7 (CH), 142.2 (C), 137.1 (CH), 100.5 (CH), 93.7 (C), 79.7 (CH), 53.6 (CH), 50.9 (CH), 50.6 (CH), 45.7 (CH), 41.8 (CH), 25.1 (CH); IR ν_{\max} 2989, 1738, 1674, 1238, 1130, 1055, 864, 721cm⁻¹; MS (*m/z*) 265 (M⁺+1), 233 ([M⁺+1]-CH₃OH); Anal. Calcd. for C₁₄H₁₆O₅: C, 63.63; H, 6.10. Found: C, 63.56; H, 6.12.

10-Cyano-9,9-dimethoxy-3-oxatricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-one (9d). A mixture of 4-hydroxy-3-methoxybenzoxonitrile (0.50 g, 3.4 mmol), DAIB (1.31 g, 4.0 mmol), methanol (5 mL) and furan (2 mL) was reacted according to the general method, to give a white solid (0.45 g, 54%); mp 88 °C; ¹H NMR [CDCl₃] δ 6.95 (1H, m, H-11), 6.30 (1H, m, H-4), 5.16 (1H, dd, *J* 3.9, 9.6Hz, H-2), 4.81 (1H, t, *J* 2.6Hz, H-5), 3.90 (1H, m, H-1), 3.54 (1H, m, H-6), 3.44 (1H, dd, *J* 2.4, 6.8Hz, H-7), 3.42 (3H, s, OCH₃), 3.39 (3H, s, OCH₃); ¹³C NMR [CDCl₃] δ 198.3 (C), 149.0 (CH), 143.6 (CH), 117.0 (C), 115.1 (C), 100.5 (CH), 92.9 (C), 78.8 (CH), 53.5 (CH), 50.9 (CH), 47.2 (CH), 46.1 (CH); IR ν_{\max} 2220, 1759, 1615, 1460, 1130, 1080, 870, 737cm⁻¹; TLC (ethyl acetate / hexane 2:8) R_F 0.23; MS (*m/z*) 248 (M⁺+1), 216 ([M⁺+1]-CH₃OH); HRMS (*m/z*) calcd for C₁₃H₁₃NO₄+NH₄ 265.1188, found 265.1183.

9-Ethoxy-10-formyl-9-methoxy-3-oxatricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-one (9e). A mixture of vanillin(0.50 g, 3.3 mmol), DAIB (1.17 g, 3.6 mmol), ethanol (5 mL) and furan (2 mL) was reacted according to the general method, to give a pale yellow crystalline solid (0.57 g, 65%); mp 66 °C; ¹H NMR [CDCl₃] δ 9.62 (1H, s, CHO), 7.07 (1H, m, H-11), 6.20 (1H, m, H-4), 5.23 (1H, m, H-2), 4.79 (1H, m, H-5), 4.38 (1H, m, H-1) 3.78-3.44 (4H, m, 6,7-H, CH₂), 3.43 (3H, s, OCH₃), 3.31 (3H, s, OCH₃), 1.22 (3H, t, *J* 7.1Hz, CH₃), 1.13 (3H, t, *J* 7.1Hz, CH₃); ¹³C NMR [CDCl₃] δ 199.7 (C), 188.8 (CH), 148.8 (CH), 148.7 (CH), 145.0 (CH), 144.9 (CH), 143.1 (C), 100.4 (CH), 93.6 (C), 79.5 (CH), 79.4 (CH), 59.0 (CH₂), 58.5 (CH₂), 54.1 (CH), 51.0 (CH), 50.4 (CH), 46.4 (CH), 46.2 (CH), 41.3 (CH), 41.0 (CH), 15.6 (CH), 15.2 (CH); IR ν_{\max} 2980, 1744,

1680, 1391, 1171, 1140, 1069, 743 cm^{-1} ; MS (m/z) 265 ($M^+ + 1$), 233 ($[M^+ + 1] - \text{CH}_3\text{OH}$); Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_5$: C, 63.87; H, 5.74. Found: C, 63.65; H, 6.23.

10-Formyl-9-methoxy-9-propyloxy-3-oxatricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-one (9f). A mixture of vanillin (0.50 g, 3.3 mmol), DAIB (1.17 g, 3.6 mmol), propanol (5 mL) and furan (2 mL) was reacted according to the general method, to give a pale yellow tarry solid (0.48 g, 52%); ^1H NMR [CDCl_3] δ 9.60 (1H, s, CHO), 7.06 (1H, dd, J 2.0, 6.5 Hz, H-11), 6.19 (1H, dd, J 2.5, 4.4 Hz, H-4), 5.21 (1H, m, H-2), 4.79 (1H, dd, J 2.7, 5.4 Hz, H-5), 4.38 (1H, dd, J 3.6, 5.7 Hz, H-1), 3.63-3.42 (4H, m, H-6, H-7, propyl-1- CH_2), 3.41 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 1.59 (2H, q, J 7.1 Hz, propyl-2- CH_2), 1.49 (2H, q, J 7.1 Hz, propyl-2- CH_2), 0.93 (3H, t, J 7.4 Hz, CH_3), 0.84 (3H, t, J 7.4 Hz, CH_3); ^{13}C NMR [CDCl_3] δ 199.7 (C), 199.6 (C), 188.8 (CH), 188.8 (CH), 148.8 (CH), 148.7 (CH), 145.0 (CH), 144.9 (CH), 143.1 (C), 100.4 (CH), 100.4 (CH), 93.5 (C), 79.5 (CH), 79.3 (CH), 64.9 (CH_2), 64.5 (CH_2), 54.2 (CH), 54.1 (CH), 50.9 (CH), 50.4 (CH), 46.5 (CH), 46.1 (CH), 41.4 (CH), 41.0 (CH), 23.3 (CH_2), 23.0 (CH_2), 11.1 (CH), 11.0 (CH); IR ν_{max} 2969, 1744, 1680, 1460, 1144, 1069, 868, 708 cm^{-1} ; MS (ES, m/z) 279 ($M^+ + 1$); Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_5$: C, 64.74; H, 6.52. Found: C, 64.58; H, 6.68.

11-Formyl-10,10-dimethoxytricyclo[6.2.2.0^{2,7}]dodeca-5,11-dien-9-one (9g). A mixture of vanillin (0.50 g, 3.3 mmol), DAIB (1.17 g, 3.6 mmol), methanol (5 mL) and cyclohexa-1,3-diene (2 mL) was reacted according to the general method, to give a white solid (0.22 g, 26%); mp 103 $^\circ\text{C}$; ^1H NMR [CDCl_3] δ 9.58 (1H, s, CHO), 7.03 (1H, dd, J 1.9, 6.5 Hz, H-12), 5.89 (1H, m, H-5), 5.48 (1H, d, J 8.8 Hz, H-6), 3.74 (1H, m, H-1), 3.35 (1H, m, H-8), 3.39 (3H, s, OCH_3), 3.24 (3H, s, OCH_3), 2.79 (1H, m, H-2), 2.70 (1H, m, H-4), 1.84 (2H, m, H-4, H-7), 1.69 (1H, m, H-3), 0.85 (1H, m, H-3); ^{13}C NMR [CDCl_3] δ 201.1 (C), 189.5 (CH), 147.0 (C), 144.7 (CH), 131.4 (CH), 127.6 (CH), 94.0 (C), 56.1 (CH), 50.6 (CH), 50.6 (CH), 42.2 (CH), 35.9 (CH), 32.3 (CH), 25.7 (CH_2), 23.3 (CH_2); IR ν_{max} 2931, 1742, 1672, 1177, 1140, 1080, 1049, 858 cm^{-1} ; MS (m/z) 263 ($M^+ + 1$), 231 ($[M^+ + 1] - \text{CH}_3\text{OH}$); Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_4$: C, 68.69; H, 6.92. Found: C, 68.67; H, 6.91.

10-Formyl-4,9,9-trimethoxy-3-oxatricyclo[5.2.2.0^{2,6}]undeca-10-en-8-one (10). To vanillin (0.50 g, 3.3 mmol), furan (2 mL) and zinc chloride (0.1 mol. equiv.) in nitromethane / methanol (15 mL/5 mL) was added DAIB (1.17 g, 3.6 mmol) at 0 $^\circ\text{C}$, with stirring. After 10 minutes the reaction was allowed to warm to room temperature and left to stand at room temperature for 3 days. Removal of the solvent *in vacuo* was followed by purification of the product by flash column chromatography (eluting with ethyl acetate / hexane 2:8), to give a white solid (0.29 g, 31%); mp 99 $^\circ\text{C}$; ^1H NMR [CDCl_3] δ 9.64 (1H, s, CHO), 7.04 (1H, m, H-11), 4.92 (1H, d, J 4.7 Hz, H-4), 4.73 (1H, dd, J 3.7, 7.9 Hz, H-2), 4.21 (1H, dd, J 2.0, 3.7 Hz, H-1), 3.50 (1H, dd, J 2.6, 6.5 Hz, H-

7), 3.42 (3H, s, OCH₃), 3.29 (6H, s, OCH₃), 2.99 (1H, m, H-6), 2.17 (1H, dd, *J* 6.9, 9.2Hz, H-5), 1.51 (1H, m, H-5); ¹³C NMR [CDCl₃] δ 200.1 (C), 189.0 (CH), 145.7 (C), 142.8 (CH), 105.4 (CH), 92.6 (C), 76.1 (CH), 54.7 (C), 53.5 (CH), 50.8 (CH), 50.5 (CH), 40.5 (CH), 39.5 (CH), 37.9 (CH₂); IR *v*_{max} 2959, 1744, 1682, 1211, 1169, 1101, 1049, 947cm⁻¹; MS (ES, *m/z*) 251 ([M⁺+1]-CH₂O); Anal. Calcd. for C₁₄H₁₇O₆: C, 59.78; H, 6.09. Found: C, 59.65; H, 6.45.

Cycloadduct 12/13a. A mixture of vanillin(0.50 g, 3.3 mmol), DAIB (1.17 g, 3.6 mmol), methanol (5 mL) and 2-ethylfuran (2 mL) was reacted according to the general method, to give a white solid (0.27 g, 30%); mp 137 °C; ¹H NMR [CDCl₃] δ 9.65 (1H, s, CHO), 7.11 (1H, qd, *J* 1.1, 2.0, 6.5Hz, H-11), 4.67 (1H, dd, *J* 3.6, 8.0Hz, H-2), 4.17 (1H, dd, *J* 2.0, 3.6Hz, H-1), 3.75 (1H, dd, *J* 2.7, 6.5Hz, H-7), 3.54 (1H, d, *J* 7.7Hz, H-5), 3.41 (3H, s, OCH₃), 3.29 (3H, s, OCH₃), 3.28 (3H, s, OCH₃), 3.05 (1H, m, H-6), 1.74 (2H, q, *J* 7.3Hz, CH₂), 0.81 (3H, t, *J* 7.6Hz, CH₃); ¹³C NMR [CDCl₃] δ 198.7 (C), 188.6 (CH), 146.3 (C), 142.6 (CH), 107.7 (C), 92.6 (C), 74.9 (CH), 61.1 (CH), 51.3 (CH), 50.9 (CH), 50.5 (CH), 49.5 (CH), 48.6 (CH), 40.3 (CH), 23.8 (CH₂), 8.3 (CH); IR *v*_{max} 2990, 1748, 1690, 1461, 1179, 1059, 858, 779cm⁻¹; MS (*m/z*) 313/315 (3:1) ([M⁺+1]-OCH₃); Anal. Calcd. for C₁₆H₂₂ClO₆: C, 55.70; H, 6.10. Found: C, 55.80; H, 6.10.

Cycloadduct 12/13b. Compound 4 (0.50 g, 1.9 mmol), DAIB (0.69 g, 2.1 mmol), methanol (5 mL) and 2-ethylfuran (2 mL) was reacted according to the general method, to give a white solid (86 mg, 11%); mp 204 °C; ¹H NMR [CDCl₃] δ 8.06 (1H, dd, *J* 1.0, 7.2Hz, H-4'/7'), 7.85 (1H, dd, *J* 0.8, 7.6Hz, H-4'/7'), 7.48-7.34 (2H, m, H-5', H-6'), 6.92 (1H, ddd, *J* 0.9, 2.1, 6.6Hz, H-11), 4.77 (1H, dd, *J* 3.7, 8.0Hz, H-2), 4.64 (1H, dd, *J* 2.2, 3.7Hz, H-1), 3.72 (1H, d, *J* 7.7Hz, H-5), 3.65 (1H, dd, *J* 2.7, 6.7Hz, H-7), 3.43 (3H, s, OCH₃), 3.38 (3H, s, OCH₃), 3.29 (3H, s, OCH₃), 3.04 (1H, ddd, *J* 0.9, 2.7, 2.8Hz, H-6), 1.67 (2H, q, *J* 7.6Hz, CH₂), 1.26 (3H, t, *J* 7.2Hz, CH₃); ¹³C NMR [CDCl₃] δ 199.3 (C), 165.2 (C), 140.8 (C), 135.1 (C), 127.5 (C), 126.8 (CH), 126.4 (CH), 124.2 (CH), 122.0 (CH), 108.0 (CH), 93.2 (C), 77.6 (C), 75.6 (CH), 60.9 (CH), 51.0 (CH), 50.9 (CH), 50.7 (CH), 49.1 (CH), 48.6 (CH), 45.5 (CH), 23.7 (CH₂), 8.3 (CH); IR *v*_{max} 2941, 1740, 1458, 1223, 1146, 1065, 957, 764cm⁻¹; MS (ES, *m/z*) 450/452 (3:1) (M⁺+1), 418/420 (3:1) ([M⁺+1]-MeOH); Anal. Calcd. for C₂₂H₂₄ClNO₅S.½CH₂Cl₂: C, 54.88; H, 5.08; N, 2.85. Found: C, 55.32; H, 5.19; N, 2.82.

7-Formyl-2,2-dimethoxy-5-methyl-5-(2-propenyl)bicyclo[2.2.2]oct-7-ene-3-one

(14a). A mixture of vanillin(0.50 g, 3.3 mmol), DAIB (1.17 g, 3.6 mmol), methanol (5 mL) and 2,3-dimethylbutadiene (2 mL) was reacted according to the general method, to give a clear oil (0.13 g, 15%); ¹H NMR [CDCl₃] δ 9.55 (1H, s, CHO), 7.11 (1H, dd, *J* 1.9, 6.3Hz, H-8), 4.75 (1H, s, propenyl-CH₂), 4.63 (1H, s, propenyl-CH₂), 3.78 (1H, m,

H-1), 3.51 (1H, d, J 6.5Hz, H-4), 3.42 (3H, s, OCH₃), 3.28 (3H, s, OCH₃), 1.97 (1H, dd, J 2.5, 13.5Hz, H-6), 1.73 (3H, s, propenyl-CH₃/5-CH₃), 1.67 (1H, dd, J 3.5, 13.5Hz, H-6), 1.25 (3H, s, propenyl-CH₃/5-CH₃); ¹³C NMR [CDCl₃] δ 202.2 (C), 189.0 (CH), 150.2 (C), 146.4 (CH), 145.6 (C), 110.6 (CH₂), 93.9 (C), 59.9 (CH), 50.5 (CH), 50.3 (CH), 45.9 (C), 35.9 (CH), 32.3 (CH₂), 28.1 (CH), 20.3 (CH); IR ν_{\max} 2972, 1740, 1684, 1449, 1126, 1072, 1055, 897cm⁻¹; TLC (ethyl acetate / hexane 2:8) R_F 0.43; MS (m/z) 265 (M⁺+1).

Also isolated was *cis*-4a-formyl-1,1-dimethoxy-6,7-dimethyl-4a,5,8,8a-tetrahydro-1*H*-naphthalen-2-one 15a as a white solid (0.38 g, 43%); mp 126-7 °C; ¹H NMR [CDCl₃] δ 9.39 (1H, s, CHO), 6.67 (1H, dd, J 2.2, 10.2Hz, H-4), 6.09 (1H, d, J 10.2Hz, H-3), 3.32 (3H, s, OCH₃), 3.08 (3H, s, OCH₃), 2.90 (1H, td, J 2.2, 7.6Hz, H-8a), 2.41 (1H, bd, H-5), 2.05-1.70 (3H, m, H-8, H-5), 1.66 (3H, s, CH₃), 1.56 (3H, s, CH₃); ¹³C NMR [CDCl₃] δ 199.8 (CH), 192.0 (C), 151.9 (CH), 129.3 (CH), 125.0 (C), 122.2 (C), 99.6 (C), 52.5 (C), 51.0 (CH₃), 48.3 (CH₃), 39.9 (CH), 37.0 (CH₂), 28.9 (CH₂), 19.3 (CH), 19.0 (CH); IR ν_{\max} 2831, 1724, 1690, 1435, 1260, 1128, 1049, 845cm⁻¹; MS (m/z) 265 (M⁺+1), 233 ([M⁺+1]-CH₃OH), 205 (-CO); Anal. Calcd. for C₁₅H₂₀O₄: C, 68.16; H, 7.63. Found: C, 68.09; H, 7.65.

2,2-Dimethoxy-7-methoxycarbonyl-5-methyl-5-(2-propenyl)bicyclo[2.2.2]oct-7-en-5-one (14b). A mixture of methyl vanillate (0.50 g, 2.7 mmol), DAIB (0.97 g, 3.0 mmol), methanol (5 mL) and 2,3-dimethylbutadiene (2 mL) was reacted according to the general method, to give a white solid (0.15 g, 19%); mp 67 °C; ¹H NMR [CDCl₃] δ 7.11 (1H, dd, J 2.0, 6.5Hz, H-8), 4.73 (1H, d, J 6.5Hz, propenyl-CH₂), 4.63 (1H, s, propenyl-CH₂), 3.79 (3H, s, OCH₃), 3.70 (1H, m, H-1), 3.40 (3H, s, OCH₃), 3.37 (1H, d, J 6.5Hz, H-4), 3.32 (3H, s, OCH₃), 1.95 (1H, dd, J 2.7, 13.4Hz, H-6), 1.77 (1H, dd, J 3.4, 13.4Hz, H-6), 1.72 (3H, d, J 1.0Hz, propenyl-CH₃/5-CH₃), 1.21 (3H, s, propenyl-CH₃/5-CH₃); ¹³C NMR [CDCl₃] δ 202.9 (C), 165.0 (C), 150.4 (C), 138.4 (CH), 136.3 (C), 110.6 (CH₂), 94.0 (C), 59.4 (CH), 52.3 (CH), 50.5 (CH), 50.2 (CH), 45.1 (C), 39.1 (CH), 32.8 (CH₂), 28.1 (CH), 20.3 (CH); IR ν_{\max} 2969, 1740, 1709, 1437, 1240, 1090, 1047, 764cm⁻¹; MS (ES, m/z) 295 (M⁺+1), 263 ([M⁺+1]-CH₃OH); Anal. Calcd. for C₁₆H₂₂O₅: C, 65.29; H, 7.53. Found: C, 65.38; H, 7.56.

Also isolated was *cis*-1,1-dimethoxy-4a-methoxycarbonyl-6,7-dimethyl-4a,5,8,8a-tetrahydro-1*H*-naphthalen-2-one 15b as a white solid (0.33 g, 42%); mp 116 °C; ¹H NMR [CDCl₃] δ 6.61 (1H, dd, J 2.2, 10.2Hz, H-4), 6.01 (1H, d, J 10.1Hz, H-3), 3.74 (3H, s, OCH₃), 3.34 (3H, s, OCH₃), 3.23 (1H, td, J 2.1, 8.3Hz, H-8a), 3.11 (3H, s, OCH₃), 2.66 (1H, bd, H-5), 2.17-2.04 (2H, m, H-5, H-8), 1.71 (1H, bd, H-8), 1.66 (3H, s, CH₃), 1.58 (3H, s, CH₃); ¹³C NMR [CDCl₃] δ 192.5 (C), 176.3 (C), 151.3 (CH), 127.9 (CH), 124.7 (C), 122.8 (C), 99.8 (C), 52.7 (CH), 51.3 (CH), 48.5 (C), 48.3 (CH), 42.4

(CH₂), 40.7 (CH), 30.0 (CH₂), 19.4 (CH), 18.9 (CH); IR ν_{\max} 2942, 1730, 1694, 1441, 1244, 1130, 1053, 843cm⁻¹; MS (ES, m/z) 263 ([M⁺+1]-CH₃OH); Anal. Calcd. for C₁₆H₂₂O₅: C, 65.29; H, 7.53. Found: C, 65.11; H, 7.51.

7-(Benzothiazol-2-yl)-2,2-dimethoxy-5-methyl-5-(2-propenyl)bicyclo[2.2.2]oct-7-

en-3-one (14c). Compound 4 (0.50 g, 1.9 mmol), DAIB (0.72 g, 2.2 mmol), methanol (5 mL) and 2,3-dimethylbutadiene (2 mL) was reacted according to the general method, to give an off white solid (0.33 g, 45%); mp 98-9 °C; ¹H NMR [CDCl₃] δ 8.02 (1H, dd, J 1.2, 7.6Hz, H-4'/7'), 7.84 (1H, dd, J 1.6, 7.7Hz, H-4'/7'), 7.47 (2H, m, H-5', H-6'), 6.88 (1H, dd, J 2.0, 6.5Hz, H-8), 4.75 (1H, s, propenyl-CH₂), 4.68 (1H, s, propenyl-CH₂), 4.26 (1H, dd, J 3.0, 5.3Hz, H-1), 3.47 (3H, s, OCH₃), 3.42 (1H, d, J 6.5Hz, H-4), 3.35 (3H, s, OCH₃), 2.04 (2H, qd, J 3.4, 13.5Hz, H-6), 1.74 (3H, s, propenyl-CH₃/5-CH₃), 1.27 (3H, s, propenyl-CH₃/5-CH₃); ¹³C NMR [CDCl₃] δ 202.8 (C), 165.5 (C), 153.9 (C), 150.5 (C), 139.9 (C), 135.2 (C), 130.9 (CH), 126.6 (CH), 126.0 (CH), 123.7 (CH), 121.9 (CH), 110.8 (CH₂), 94.4 (C), 59.3 (CH), 50.9 (CH), 50.3 (CH), 45.5 (C), 41.3 (CH), 33.0 (CH₂), 28.1 (CH), 20.4 (CH), 14.6 (CH); IR ν_{\max} 2943, 1731, 1435, 1200, 1125, 1067, 889, 758cm⁻¹; MS (m/z) 370 (M⁺+1), 338 ([M⁺+1]-CH₃OH); Anal. Calcd. for C₂₁H₂₃NO₃S: C, 68.27; H, 6.27; N, 3.79. C, 68.24; H, 6.27; N, 3.72.

cis-4a-(benzothiazol-2-yl)-1,1-dimethoxy-6,7-dimethyl-4a,5,8,8a-tetrahydro-1H-

naphthalen-2-one (15c). Also isolated was as an off white solid (94 mg, 13%); mp 144-5 °C; ¹H NMR [CDCl₃] δ 7.99 (1H, dd, J 0.7, 7.5Hz, H-4'/7'), 7.85 (1H, dd, J 1.4, 7.8Hz, H-4'/7'), 7.43 (1H, td, J 1.3, 7.3Hz, H-5'/6'), 7.35 (1H, td, J 1.2, 7.3Hz, H-5'/6'), 6.92 (1H, dd, J 2.0, 10.1Hz, H-4), 6.22 (1H, d, J 10.1Hz, H-3), 3.43 (1H, td, J 2.0, 9.0Hz, H-8a), 3.29 (3H, s, OCH₃), 2.99 (1H, bd, H-5), 2.78 (3H, s, OCH₃), 2.33-2.17 (2H, m, H-5, H-8), 1.89 (1H, bdd, H-8), 1.67 (3H, s, CH₃), 1.62 (3H, s, CH₃); ¹³C NMR [CDCl₃] δ 192.9 (C), 151.8 (CH), 129.9 (CH), 126.3 (CH), 125.2 (C), 125.1 (CH), 123.9 (C), 123.0 (CH), 121.8 (CH), 99.9 (C), 50.9 (CH), 48.7 (CH), 47.5 (C), 46.5 (CH₂), 44.1 (CH), 31.0 (CH₂), 19.5 (CH), 18.9 (CH); IR ν_{\max} 2930, 1692, 1495, 1437, 1119, 1059, 847, 772cm⁻¹; MS (ES, m/z) 370 (M⁺+1), 338 ([M⁺+1]-CH₃OH); Anal. Calcd. for C₂₁H₂₃NO₃S: C, 68.27; H, 6.27; N, 3.79. C, 67.82; H, 6.28; N, 3.70.

2,11-Di(benzothiazol-2-yl)-6,6,10,10-tetramethoxytricyclo[6.2.2.0^{2,7}]dodeca-3,11-

dien-5,9-dione (17). Compound 4 (0.50 g, 1.9 mmol) and DAIB (0.69 g, 2.1 mmol) was reacted according to the general method, to give a white solid (56 mg, 10%); mp 241 °C (blackens and sublimes); ¹H NMR [CDCl₃] δ 8.05 (2H, d, J 7.4Hz, H-4'/4''/7'/7''), 7.92 (1H, dd, J 1.1, 7.5Hz, H-4'/4''/7'/7''), 7.84 (1H, dd, J 1.1, 7.8Hz, H-4'/4''/7'/7''), 7.56-7.36 (4H, m, H-5', H-5'', H-6', H-6''), 6.85 (1H, dd, J 2.2, 6.8Hz, H-12), 6.81 (1H, d, J 11.0Hz, H-3), 6.17 (1H, d, J 10.2Hz, H-4), 4.33 (1H, t, J 2.0Hz, H-8), 4.17 (1H, t, J 1.4Hz, H-7), 3.98 (1H, d, J 6.8Hz, H-1), 3.55 (3H, s, OCH₃), 3.50 (3H, s,

OCH₃), 3.42 (3H, s, OCH₃), 3.09 (3H, s, OCH₃); ¹³C NMR [CDCl₃] δ 197.7 (C), 192.1 (C), 172.5 (C), 163.7 (C), 153.9 (C), 153.1 (C), 146.8 (CH), 139.7 (C), 135.9 (C), 135.4 (C), 130.3 (CH), 128.9 (CH), 126.7 (CH), 126.6 (CH), 126.3 (CH), 125.9 (CH), 124.5 (CH), 123.9 (CH), 122.0 (CH), 121.9 (CH), 98.4 (C), 94.8 (C), 60.2 (CH), 53.5 (C), 51.7 (CH), 50.5 (CH), 50.4 (CH), 49.2 (CH), 47.3 (CH), 43.4 (CH); IR ν_{max} 2957, 1741, 1711, 1435, 1115, 1055, 910, 762cm⁻¹; MS (*m/z*) 575 (M⁺+1), 543 ([M⁺+1]-CH₃OH), 511 (-CH₃OH); Anal. Calcd. for: C₃₀H₂₆N₂O₆S₂: C, 62.70; H, 4.56; N, 4.87. Found: C, 62.70; H, 4.62; N, 4.80.

5,5'-Di(benzothiazol-2-yl)-2,2'-dihydroxy-3,3'-dimethoxybiphenyl (20). To 4 (0.50 g, 1.9 mmol) in acetonitrile (120 mL) was added DAIB (0.32 g, 1.0 mmol), after mixing the reaction mixture was allowed to stand for 24 hours. The precipitated biphenyl was collected by filtration, washed with acetonitrile and dried under vacuum, to give a red solid (0.16 g, 32%); mp 219-20 °C; ¹H NMR [DMSO-*d*₆] δ 9.48 (2H, bs, OH), 8.07 (2H, m, H-4,4'/7,7'), 8.01 (2H, m, H-4,4'/7,7'), 7.67 (2H, d, *J* 2.1Hz, H-6, H-6'), 7.55 (2H, d, *J* 2.1Hz, H-4, H-4'), 7.51 (2H, m, H-5,5'/6,6'), 7.40 (2H, m, H-5,5'/6,6'), 4.01 (6H, s, OCH₃); ¹³C NMR [DMSO-*d*₆] δ 168.3 (C), 154.5 (C), 149.1 (C), 148.3 (C), 135.1 (C), 127.4 (CH), 126.0 (C), 125.9 (CH), 124.4 (C), 124.0 (CH), 123.2 (CH), 123.0 (CH), 109.7 (CH), 57.0 (CH₃); IR ν_{max} 2361, 1593, 1470, 1416, 1271, 1198, 1088, 756cm⁻¹; MS (*m/z*) 513 (M⁺+1), 258 (C₁₄H₁₀NO₂S⁺); Anal. Calcd. for: C₂₈H₂₀N₂O₄S₂: C, 65.61; H, 3.93; N, 5.46. Found: C, 65.12; H, 3.88; N, 5.41.

Biological Methods

Cell growth inhibitory assay

Growth of breast cancer cells was quantitated using the MTT assay¹⁶, in which enzymes in the mitochondria of living cells reduce MTT to a purple formazan product. Briefly, cells were seeded into 96 well microtitre plates at a density of 3500 cells/well and allowed to adhere overnight. Plates were incubated for 7 days (MCF-7) or 10 days (MDA468) following treatment with a range of final test reagent concentrations between 1 nM and 100 mM (n=8). MTT (Sigma) was added (final conc. 400 mg/mL) and the plates incubated for a further 4 hours. The MTT was aspirated and the formazan product solubilised by the addition of DMSO:glycine buffer (4:1, 125 mL). Absorbance was read on an Anthos Labtec Instruments 2001 plate reader at 550 nm. IC₅₀ values were calculated by interpolation.

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