High-Pressure-Promoted and Facially Selective Diels-Alder Reactions of Enzymatically Derived *cis*-1,2-Dihydrocatechols and their Acetonide Derivatives: Enantiodivergent Routes to Homochiral and Polyfunctionalized Bicyclo[2.2.2]octenes.

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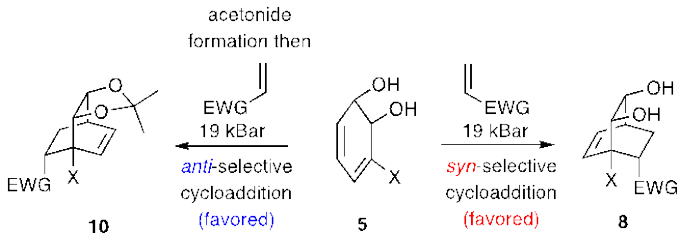
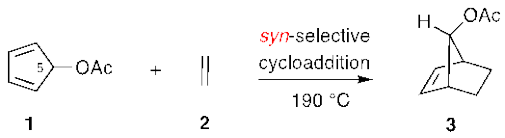


Abstract: *cis*-1,2-Dihydrocatechols **5** (X= Me and Cl), which are available in homochiral form through the whole-cell biotransformation of toluene and chlorobenzene, respectively, undergo Diels-Alder cycloaddition reactions with a range of electron-deficient dienophiles at 19 kbar (1.9 GPa). The favored products of such reactions are adducts of the general form **8** and that arise through the operation of a contrasteric or *syn*-addition pathway. In contrast, the acetonide derivatives of metabolites **5** undergo *anti*-selective addition reactions under the same conditions and so producing adducts of the general form **10**. Bicyclo[2.2.2]octenes **8** and **10**, which embody carbocyclic frameworks of opposite enantiomeric form, are useful scaffolds for chemical synthesis. Computational studies reveal that *syn*-adduct formation is kinetically and normally thermodynamically favored over *anti*-adduct formation when the free diols **5** are involved but the reverse is so when the corresponding acetonides participate as the 4π-addend. Furthermore, the reactions become more exothermic as pressure increases while, concurrently, the activation barrier diminishes and at 6 GPa (60 kbar) almost vanishes.

INTRODUCTION

An intriguing subset of the vast ensemble of Diels-Alder reactions is that in which certain allylic and hetero-atom based substituents associated with the participating diene facilitate the π-facially selective addition of dienophiles in a *syn* and, therefore, contrasteric manner.[1] One of the earliest (if not the first) reported examples of such a process is due to Woodward and Weinstein who reported (Scheme 1) the cycloaddition of 5-acetoxycyclopenta-1,3-diene (**1**) and ethylene (**2**) to form, via *syn*-addition, the 7-acetoxynorbornene **3**.[2]

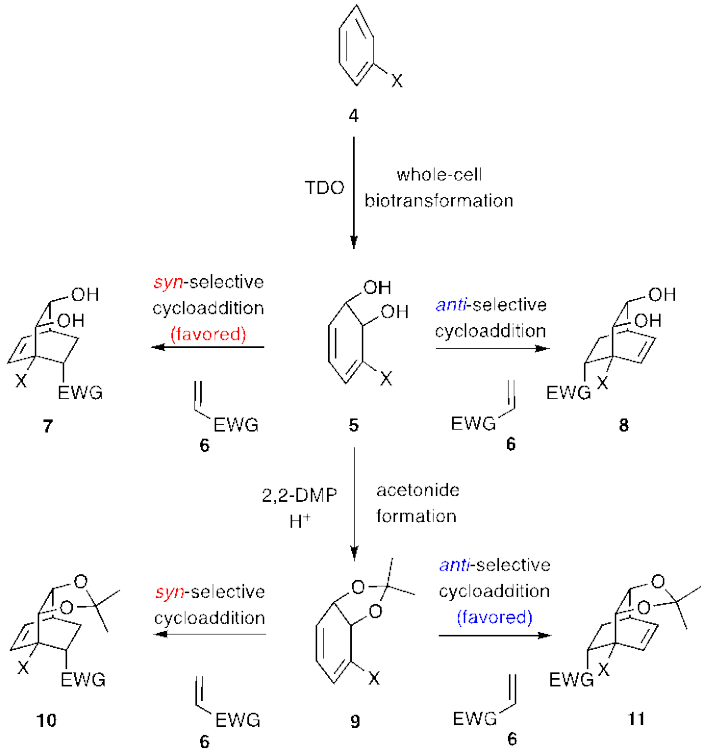
Scheme 1: The *syn*-selective cycloaddition of 5-acetoxycyclopentadiene (**1**) and ethylene (**2**) leading to adduct **3**.[2]



Since then numerous *syn*-addition variants involving C5-X substituted cyclopentadienes have been described[1,3] including ones that have been elegantly exploited in stereocontrolled total synthesis.[4] Rather extensive theoretical studies of these processes have also been conducted in efforts to identify the origins of the observed selectivities. In the most recent of these, Houk and co-workers have presented[3] a unified model rationalizing the observed selectivities and differing reaction rates as a function of the nature of C5-substituent on the cyclopentadiene. In essence, the π-facial selectivities are distortion controlled and such that, depending upon whether the C5-substituent is a σ-acceptor or σ-donor, the cyclopentadiene adopts an envelope conformation in either the *syn*- or *anti*-transition state, respectively. When the C5-substituent is a σ-acceptor then rapid *syn*-addition reactions tend to be observed.

Extending such intriguing processes to the next higher homologue of a diene such as **1** necessitates the involvement of the distinctly fragile benzene hydrate (viz. cyclohexa-2,4-dien-1-ol) and its derivatives[5] that are prone to dehydrative aromatization processes. This possibility is enhanced because cyclohexa-1,3-dienes are normally less effective participants in Diels-Alder cycloaddition reactions than cyclopenta-1,3-dienes.[6] They are also generally less accessible systems. That said, and as a result of pioneering work by Gibson, numerous *cis*-1,2-dihydrocatechols (viz. *cis*-cyclohexa-3,5-dien-1,2-diols) can now be obtained through the whole-cell biotransformation of many aromatics but perhaps most notably benzene and its mono-substituted derivatives.[7] So, for example, substrates such as **4** (X=H, Me, Cl, Br or I) can, as shown in Scheme 2, be converted, through the action of the enzyme toluene dioxygenase (TDO), into the metabolites **5** (X=H, Me, Cl, Br or I). Other than the parent system **5** (X=H), which is a meso compound, these products are obtained in enantiomerically pure form (>99.99% ee) and have been exploited in various ways for assembling a multitude of target compounds.[6,7]

Scheme 2: Formation of *cis*-1,2-dihydrocatechols **5** from benzenoid precursors **4** and the participation of them and the derived acetonides **9** in facially selective Diels-Alder reactions with the generalized dienophile **6** leading to adducts **7**, **8**, **10** and **11**.



One way to deploy these metabolites is as 4π-addends in [4+2]-cycloaddition reactions and the immediate issue is whether facially selective processes might be observed. Specifically, on reacting compound **5** with a generalized dienophile **6** in an *anti*-selective, *endo*-addition process that obeys the *ortho*-rule[8] would deliver adduct **7** while the alternative, contrasteric pathway would produce the *syn*-isomer **8**. Based on the outcomes involving C5-X substituted cyclopentadienes (e.g. Scheme 1), the latter pathway, leading to product **8**, should be favored. In contrast, conversion of metabolites of the general form **5** into the corresponding acetonides **9**, a well-defined process,[6,7] affords a diene to which *anti*-addition by dienophile **6** is now likely to be more facile because of the steric impacts of the *endo*-methyl group (of the acetonide) in such derivatives. Accordingly, a cycloaddition process leading to *anti*-adduct **10**, rather than *syn*-isomer **11**, might be anticipated.

The potential to control facial selectivity has considerable synthetic potential. Not least, this is because the *syn*- and *anti*-addition pathways deliver enantiomerically related bicyclo[2.2.2]octenes as shown in Figure 1. Thus, two-fold deoxygenation of the hypothetical *anti*-Diels-Alder adducts **7** and **10** would provide compound **12** while analogous manipulation of the *syn*-adducts **8** and **11** would deliver its enantiomer (*viz*. compound *ent*-**12**). As such, and as we have noted previously,[9] a single enantiomeric form of the starting metabolite **5** could thus be converted into either enantiomeric form of a given Diels-Alder adduct by controlling the facial selectivity of the cycloaddition process, including intramolecular variants.[9c]

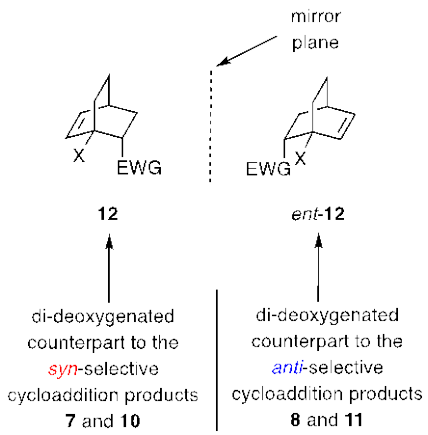


Figure 1: The enantiomeric relationship between bicyclo[2.2.2]octenes **12** derived from an *anti*-selective Diels-Alder reaction involving homochiral *cis*-1,2-dihydrocatechols **5** (X≠H) and those obtained through *syn*-selective ones.

The earliest reports[10] of the participation of enzymatically-derived *cis*-1,2-dihyrocatechols **5** in Diels-Alder cycloaddition reactions derived from attempts to form adducts with dienophiles that could be subject to X-ray analysis and thereby confirming structure (including absolute stereochemistry in one case[10a]) or providing stable derivatives for further manipulation.[10c] In such instances derivatives of **5** were employed and, as a result, only *anti*-addition products were reported to have been obtained. The first report of a *syn*-addition process was by Burnell in 1989[11] who

revealed that the parent system **5** (X=H) reacted, seemingly irreversibly, with *N*-phenylmaleimide in chloroform at ambient temperatures to give a 96:4 ratio of *syn*- and *anti*-adducts in good yield. Reduced preferences for *syn*-selective additions were observed when the bis-acetate, bis-trimethylsilyl, [1,3,2]dioxasilole and acetonide derivatives of compound **5** (X=H) were reacted with the same dienophile. Interestingly, the last two (bicyclic) derivatives were observed to react much more rapidly than the parent diene **5** (X=H). Many further examples of the selective *anti*-addition of various dienophiles to derivatives, e.g. **9**, of microbially-derived dienes have been reported[7,12] in the interim, including those wherein the acetonides dimerize.[13] However, reports of *syn*-selective processes are rare.[14]

Systematic extensions of Burnell's studies to the Diels-Alder reactions of homochiral metabolites such as **5b**-**e**, particularly with mono-activated dienophiles (*viz*. those containing only one electron-withdrawing group), have not been reported, a situation that undoubtedly reflects the larger HOMO-LUMO gaps between the reaction partners that would be involved in these potentially useful processes. Such conversions are also unlikely to be capable of catalysis by added Lewis acids because of the propensity of the starting dienes to undergo dehydrative aromatization.[15] Certainly all our attempts to effect such cycloadditions by this means have failed.

Given the capacity of high pressure[16] to facilitate normal electron-demand Diels-Alder reactions between otherwise recalcitrant reaction partners we were prompted to investigate the utility, or otherwise, of this technique to effect conversions of the general form **5** + **6** $\rightarrow$ **7** and/or **8** as well as the potentially enantio-complementary process **9** + **6** $\rightarrow$ **10** and/or **11** (Scheme 2). The results of our investigations of these possibilities are detailed below.[17]

RESULTS AND DISCUSSION

Synthetic and Spectroscopic Studies

Our initial studies of high-pressure promoted Diels-Alder reactions involved using the methyl-substituted and homochiral *cis*-1,2-dihydrocatechol **5** (X=Me), obtained through the biotransformation of toluene, or the derived acetonide **9** (X=Me) as the diene and furan-2(5*H*)-one (**12**) as the dienophile (Figure 2). Thus, a solution of equimolar quantities of the relevant diene and the dienophile **12** in dichloromethane was subjected, at ambient temperatures, to a pressure of 19 kbar for 24 h (see Experimental Section for details). The reaction between furan-2(5*H*)-one and diene **5** (X=Me) produced a *ca*. 6:1 mixture of the chromatographically separable and crystalline *syn*- and *anti*-adducts **13** (56%) and **14** (9%). The structure of the first of these adducts was established by single-crystal X-ray analysis, details of which are provided in the Supporting Information (SI) and Experimental Section. *syn*-Adduct **13** was readily converted into the corresponding acetonide **15** (90%) under standard conditions but the latter compound was not observed when acetonide **9** (X=Me) was reacted with furan-2(5*H*)-one under high pressure conditions. Thus, *anti*-adduct **16** (71%) was the exclusive product of this reaction and this compound could also be obtained in 86% yield by subjecting diol **14** to standard acetonide forming reaction conditions.

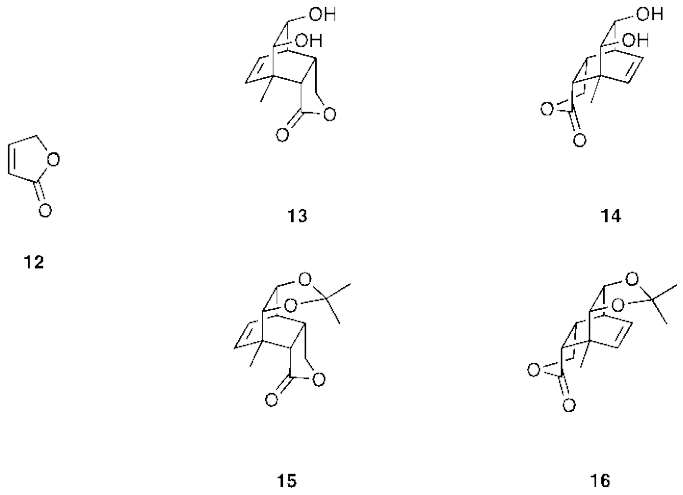


Figure 2: Dienophile **12**, the adducts, **13** and **14**, derived from its reaction with diene **5** (X=Me) and the corresponding acetonides, **15** and **16**, of these adducts.

An analogous series of experiments using cyclopent-2-en-1-one (**17**) (Figure 3) as the dienophile led to similar outcomes. Thus, the reaction of compound **17** with diene **5** (X=Me) under the same conditions as described above afforded the *syn*- and *anti*-adducts **18**[9a] (70%) and **19** (9%), respectively, and the structure of the first of these was again confirmed by single-crystal X-ray analysis (see SI and Experimental Section for details) .

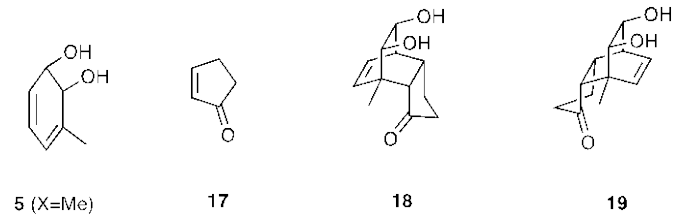


Figure 3: Dienophile **17** and the *syn*- and *anti*-adducts, **18** and **19** respectively, derived from its reaction at 19 kbar with diene **5** (X=Me)

When the acetonide **9** (X=Me) was reacted with dienophile **17** at 19 kbar (Figure 4) the *syn*-adduct **20** (7%) was the minor product of reaction and the corresponding *anti*-adduct **21** (53%) the major

one. The structure of compound **21** was also confirmed by single-crystal X-ray analysis (see Experimental Section and SI for details). As we have reported previously,[17d,e] an operationally simpler means of obtaining preparative quantities of compound **21** in higher yield (70%) involved subjecting a neat mixture of precursor **9** (X=Me) and five molar equivalents of dienophile **17** to microwave irradiation at 200 °C for 0.25 h. Under such conditions formation of small amounts of the *syn*-adduct **20** were still observed.

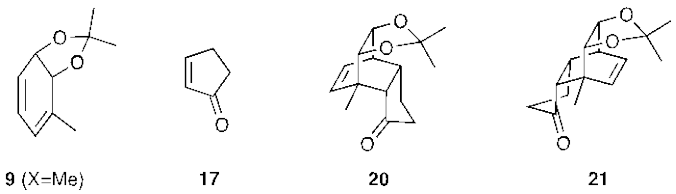
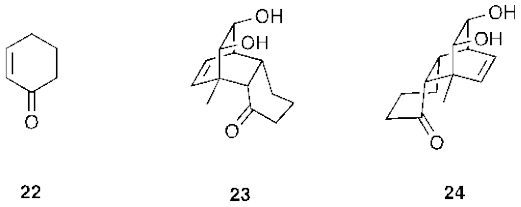


Figure 4: The *syn*- and *anti*-adducts **20** and **21**, respectively, obtained from the Diels-Alder reaction of acetonide **9** (X=Me) and dienophile **17** at 19 kbar.

Less satisfactory outcomes were observed when the next higher homologue, **22**, of dienophile **17** was subjected to analogous reaction with diene **5** (X=Me). Thus, under essentially the same conditions adducts **23** and **24** (Figure 5) were obtained in yields of 16% and 7%, respectively. These cycloaddition reactions were accompanied, as the predominat process, by those leading to aromatization of the diene substrate *cis*-1,2-dihydrocatechol **5** (X=Me). Satisfactory spectral data sets were obtained for each of adducts **23** and **24** but single-crystal X-ray analyses could not be conducted on either of them. However, various spectroscopic features of adducts **23** and **24**, as detailed below, were entirely consistent with the illustrated structural assignments.



22 23 24

Figure 5: Dienophile **22** and the *syn*- and *anti*-adducts **23** and **24**, respectively, derived from its reaction with diene **5** (X=Me) at 19 kbar.

As might be expected, efforts to engage unactivated dienophiles, including cyclopentene, in high-pressure promoted Diels-Alder reactions with diene **5** (X=Me) failed with the only characterizable product of such efforts being the dimer **25** (Figure 6) that was usually obtained in <20% yield. The illustrated structure for this dimer was assigned through nOe experiments, the key interactions observed by such means being shown. Clearly an *anti*-addition process is involved in the formation of this dimer.

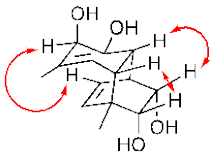


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Figure 6: The structure of the Diels-Alder dimer **25** obtained from diene **5** (X=Me) at 19 kbar and showing the key nOe interactions (in red) that led to the illustrated assignment of stereochemistry.

A study of acyclic, mono-activated dienophiles revealed, unsurprisingly perhaps, notable differences in outcomes depending upon the configuration about the C=C bond in such systems. Thus, when the *Z*-configured enone **26** (Figure 7) (see Experimental Section for details of the simple reaction sequence used to prepare this compound and its *E*-isomer) was reacted at 19 kbar with diene **5** (X=Me) then a mixture of the *syn*- and *anti*-adducts **27** (38%) and **28** (27%), respectively, was observed and the structure of the latter again confirmed by single-crystal X-ray analysis (see Experimental Section and SI for details). In contrast, when the *E*-configured dienophile **29** was

engaged in analogous reaction with the same diene, *viz*. *cis*-1,2-dihydrocatechol **5** (X=Me), then the *anti*-adduct **30** (37%) was obtained as the sole isolable product of reaction. On attempting to secure a single-crystal X-ray analysis of this last product the structure of the corresponding desilylated compound emerged (see SI and Experimental Section for details) and thus confirming that an anti-addition reaction had taken place.

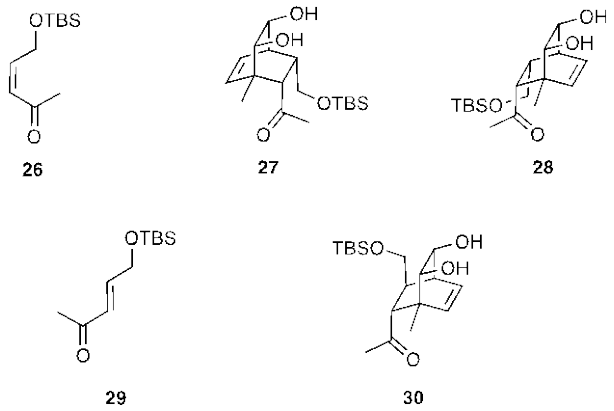

Figure 7: Dienophiles **26** and **29** and the Diels-Alder adducts **27**, **28** and **30** obtained from their reactions with diene **5** (X=Me) at 19 kbar.

Diene **5** (X=Me) is expected to be more reactive in normal electron-demand Diels-Alder cycloaddition reactions than its halogenated and thus less electron-rich counterparts **5** (X=Cl, Br or I) and this proved to be the case. In particular, when compound **5** (X=Cl) was reacted with dienophile **17** in dichloromethane at 19 kbar (Figure 8) then a chromatographically separable mixture of the *syn*-addition product **31** (11%), the *anti*-adduct **32** (3%) and a dimer (2%) of the diene was obtained. The structure of this last product is assigned as **33** by analogy with that established for dimer **25**. Spectral analyses of adducts **31** and **32**, most particularly comparisons between the two data sets, as well as those derived from other *syn*/*anti* pairs (details given below), support the illustrated assignments.

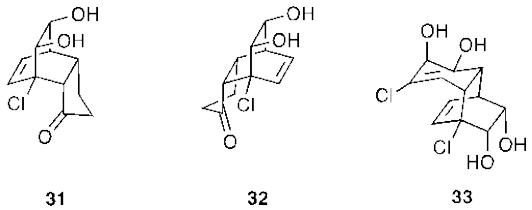

Figure 8: Products **31**-**33** obtained from the reaction of diene **5** (X=Cl) with cyclopent-2-en-1-one (**17**) at 19 kbar.

All efforts to effect Diels-Alder reactions between the brominated and iodinated analogues of compound **5** (X=Cl) and various dienophiles at 19 kbar failed. Only complex mixtures of products, including ones presumed to derive from aromatization of the starting diene, were observed.

Doubly activated dienophiles undergo *syn*-selective Diels-Alder cycloaddition reactions with diene **5** (X=Me) at 19 kbar as demonstrated (Figure 9) by its reaction with maleic anhydride (**34**) to give adduct **35** (48%). No evidence for the formation of the corresponding *anti*-adduct was obtained but the acetonide derivative of this can be prepared by reacting compound **9** (X=Me) with the same dienophile[18] in dichloromethane at ambient temperatures (no pressure applied). The rather modest yield observed in the conversion **5** (X=Me) + **34** $\rightarrow$ **35** may arise because of competing high-pressure promoted reactions between the two distinct electrophilic sites within dienophile **34** and the diol **5** (X=Me) although no products arising from these types of processes could be isolated from the reaction mixture. The *gem*-dimethylated dienophile **36** also reacted with the same diene, *viz*. **5** (X=Me), to give a chromatographically separable mixture of the anticipated *syn*-adduct **37** (73%) and *anti*-adduct **38** (9%), both of which were subject to single-crystal X-ray analysis (see SI and Experimental Section for details). The superior yields and impressive levels of facial selectivity observed in this reaction wherein a notionally rather sterically demanding dienophile (**34**) adds to

the diene **5** (X=Me) in a contrasteric fashion hint at the considerable potential of processes involving doubly-activated 2π-addends.

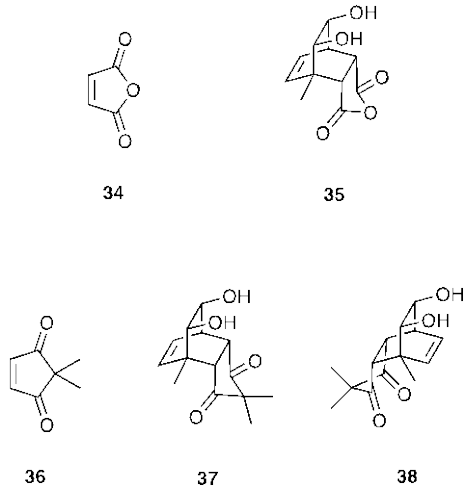

Figure 9: The adducts **35**, **37** and **39** derived from the reaction of diene **5** (X=Me) with the doubly-activated dienophiles **34** and **36** at 19 kbar.

As further testimony to the beneficial effects of two-fold activation of dienophiles in these high-pressure promoted cycloaddition reactions, when the mono-activated counterpart to compound **36**, namely the dimethylated cyclopent-2-en-1-one **39** (Figure 10), was used in its place then the *syn*-adduct **40** was obtained in just 2% yield (at 49% conversion) and accompanied by complex product mixtures with aromatic ones comprising the bulk of the material. The structure of compound **40** was confirmed by single-crystal X-ray analysis details of which will be reported elsewhere.

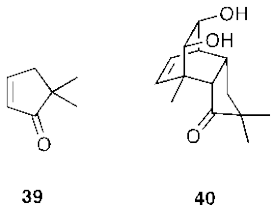

Figure 10: The *syn*-adduct **40** derived from reaction of the mono-activated dienophile **39** with diene **5** (X=Me) at 19 kbar.

In a single attempt to examine the capacities of elevated pressures to promote inverse electron-demand Diels-Alder reactions related to the ones detailed above, the known acetonide **9** (X=CN) derived from the metabolite **5** (X=CN) of benzonitrile and embodying an electron-deficient diene moiety was treated with an excess of the commercially available and electron-rich olefin **41** at 19 kbar (Figure 11). However, the hoped-for adduct was not observed. Rather, the crystalline and previously reported[13b] dimer **42**, formed through an *anti*-addition process, was obtained and its structure confirmed by single-crystal X-ray analysis (see SI and Experimental Section for details).

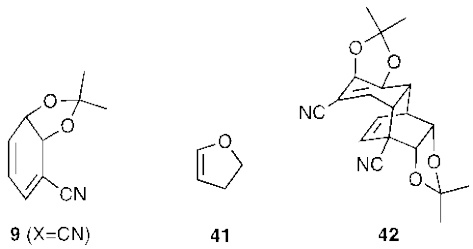

Figure 11: Substrates **9** (X=CN) and **41** used in attempts to effect an inverse-electron demand Diels-Alder reaction at 19 kbar and the observed product of diene dimerization **42**.

With eight pairs of isomeric *syn*- and *anti*-configured Diels-Alder adducts to hand, a detailed analysis of the derived spectral data sets was undertaken. Among the most useful features encountered were the differences in chemical shifts of the resonances due to the olefinic carbons in the ^{13}C NMR spectra of the isomeric pairs. So, for example, and as shown in Table 1, the resonances due to the double-bond carbons of the *syn*-isomer always appear at lower field than those due to their counterparts in the corresponding *anti*-isomer. Furthermore, the differences in chemical shift ($\Delta\delta$) between the olefinic resonances in the *syn*-isomers are invariably larger than

those associated with their *anti*-isomers. Such features are attributed to the shielding of olefinic carbons by the overhanging hydroxyl groups in the *anti*-isomers.

Table 1: The chemical shifts of the resonances due to the olefinic carbons of isomeric pairs of *syn*-and *anti*-Diels-Alder adducts[a]

Entry	Compound	Chemical Shift of Lower Field Olefinic Resonance	Chemical Shift of Higher Field Olefinic Resonance	Δδ
1	**13** (*syn*-isomer)	δ_C 139.7[b]	δ_C 132.2[b]	7.5
2	**14** (*anti*-isomer)	δ_C 137.4[b]	δ_C 131.3[b]	6.1
3	**15** (*syn*-isomer)	δ_C 138.8	δ_C 130.6	8.2
4	**16** (*anti*-isomer)	δ_C 136.2	δ_C 128.6	7.6
5	**18** (*syn*-isomer)	δ_C 137.5	δ_C 131.8	5.7
6	**19** (*anti*-isomer)	δ_C 136.3	δ_C 130.7	5.6
7	**20** (*syn*-isomer)	δ_C 138.5[c]	δ_C 132.1[c]	6.4
8	**21** (*anti*-isomer)	δ_C 135.8	δ_C 130.1	5.7
9	**23** (*syn*-isomer)	δ_C 139.0	δ_C 130.1	8.9
10	**24** (*anti*-isomer)	δ_C 138.4[b]	δ_C 131.0[b]	7.4
11	**27** (*syn*-isomer)	δ_C 137.8	δ_C 129.2	8.6
12	**28**(*anti*-isomer)	δ_C 135.9	δ_C 128.6	7.3
13	**31** (*syn*-isomer)	δ_C 136.0	δ_C 131.8	4.2
14	**32** (*anti*-isomer)	δ_C 133.8	δ_C 131.5	2.3
15	**37** (*syn*-isomer)	δ_C 138.7	δ_C 131.5	7.2
16	**38** (*anti*-isomer)	δ_C 137.0	δ_C 131.1	5.9

[a]unless otherwise specified, spectra were recorded in $CDCl_3$; [b]spectrum recorded in CD_3OD; [c]data taken from ref. 9a

In contrast to the trend highlighted immediately above, an analogous comparison of the chemical shifts of the resonances due to the carbons of the oxymethine residues revealed that those associated with the *anti*-isomer always appeared at lower field than those due to their counterparts in the corresponding *syn*-isomer (Table 2). This trend is attributed to shielding of the oxymethine carbons by the proximate olefin in the *syn*-isomers. The difference in chemical shifts between the two signals due to the oxymethine carbons was greater for the *syn*-isomer except in the case of the first pairing (see Entries 1 and 2) where there was none.

Table 2: The chemical shifts of the resonances due to the oxymethine carbons of isomeric pairs of *syn*-and *anti*-Diels-Alder adducts[a]

Entry	Compound	Chemical Shift of Lower Field Oxymethine Resonance	Chemical Shift of Higher Field Oxymethine Resonance	Δδ
1	**13** (*syn*-isomer)	δ_C 70.7[b]	δ_C 66.7[b]	4.0
2	**14** (*anti*-isomer)	δ_C 74.4[b]	δ_C 70.4[b]	4.0
3	**15** (*syn*-isomer)	δ_C 79.9	δ_C 75.0	4.9
4	**16** (*anti*-isomer)	δ_C 82.2	δ_C 77.8	4.4
5	**18** (*syn*-isomer)	δ_C 69.1	δ_C 65.4	3.7
6	**19** (*anti*-isomer)	δ_C 73.9	δ_C 70.3	3.6
7	**20** (*syn*-isomer)	δ_C 80.9[c]	δ_C 76.2[c]	4.7
8	**21** (*anti*-isomer)	δ_C 83.0	δ_C 79.2	3.8
9	**23** (*syn*-isomer)	δ_C 70.2	δ_C 65.9	4.3
10	**24** (*anti*-isomer)	δ_C 75.8[b]	δ_C 72.5[b]	3.3
11	**27** (*syn*-isomer)	δ_C 69.2	δ_C 64.1	5.1
12	**28**(*anti*-isomer)	δ_C 74.5	δ_C 70.8	3.7
13	**31** (*syn*-isomer)	δ_C 69.9	δ_C 65.5	4.4
14	**32** (*anti*-isomer)	δ_C 74.0	δ_C 69.9	4.1
15	**37** (*syn*-isomer)	δ_C 69.9	δ_C 64.9	5.0
16	**38** (*anti*-isomer)	δ_C 74.0	δ_C 69.8	4.2

[a]unless otherwise specified, spectra were recorded in $CDCl_3$; [b]spectrum recorded in CD_3OD; [c]data taken from ref. 9a

Another notable trend detected during analysis of the spectral data acquired on the reported Diels-Alder adducts concerned the specific rotations of these systems. Amongst those products obtained by reaction of cyclic and mono-activated dienophiles with dienes **5** (X=Me or Cl), the *syn*-isomer was invariably either laevorotatory or less dextrorotatory than the corresponding *anti*-isomer (see Entries 1-6, Table 3). This trend appears reversed (see Entries 7 and 8, Table 3) in those adducts arising from reactions involving acyclic or doubly-activated and cyclic dienophiles.

Table 3: Specific rotations of paired *syn*- and *anti*-Diels-Alder adducts[a]

Entry	*syn*-adduct	$[\alpha]_D$	*anti*-adduct	$[\alpha]_D$
1	**13**	–42[b]	**14**	+74
2	**15**	–47	**16**	+90

3	**18**	–196	**19**	+222
4	**20**	–122[c]	**21**	+218
5	**23**	+2	**24**	+29
6	**31**	–74	**32**	+103
7	**27**	+49	**28**	–16
8	**37**	+34	**38**	–2

[a]unless otherwise specified, optical rotations were recorded in spectroscopic grade $CHCl_3$ at 20-25 °C; [b]optical rotation measured in CH_3OH; [c]measurement taken from ref. 9a

Another aspect of our studies of the title reactions involved efforts to establish the impact of varying pressures on *syn*/*anti*-product distributions. To that end the reaction between diene **5** (X=Me) and furan-2(5*H*)-one (**12**) was conducted at 9, 14 and 19 kbar. At the lowest of these pressures no reaction was observed and on increasing this to 14 kbar low yields of a *ca*. 5:1 mixture of the *syn*- and *anti*-adducts **13** and **14**, respectively, was observed. At 19 kbar, and as noted previously, a *ca*. 6:1 ratio of the same products was observed but now in a combined yield of 65% yield. Accordingly, we conclude that effective cycloaddition reactions involving dienes **5** (X=Me and Cl) and mono-activated dienophiles only appear to take place at close to the operating limits of the pressure reactor available to us.

While the work reported above provides a means for controlling facial selectivity in the Diels-Alder reactions of the homochiral metabolites **5** (X=Me or Cl) and the corresponding acetonides **9** (X=Me or Cl), the operational complexities of needing to apply extreme pressures detract from the routine use of such protocols. Since we have observed[17d] that microwave irradiation can, in certain instances, effectively promote Diels-Alder reactions of the diene **9** (X=Me) with dienophiles where conventional thermal activation does not work, investigations of the capacity of the former technique to promote *syn*-selective Diels-Alder reactions of homochiral *cis*-1,2-dihydrocatechols such as **5** (X=Me) are now underway. Results will be reported in due course.

Theoretical Studies

While the *syn*-selective Diels-Alder reactions of C5-functionalized cyclopentadienes and related systems have been the subject of rather extensive experimental and theoretical studies, most recently by Houk and co-workers,[3] much less attention has been paid to the corresponding studies of homologues such as **5**. Indeed, the single such study we are aware of is due to Pye, Burnell and co-workers[19] who described, inter alia, an inverse relationship between the size of the barrier to ring inversion of 1,3-cyclohexadiene, the corresponding *cis*-1,2-dihydrocatechol and the associated 1,3-dioxolane-like derivative and their rates of Diels-Alder cycloaddition. Specifically, and unsurprisingly, those 1,3-cyclohexadienes already in a planar or near-planar conformation (such as the acetonides **9**) react more readily with dienophiles while those systems bearing two free hydroxyl groups, as seen in compounds of the general form **5,** have much higher barriers to ring inversion between the two non-planar conformations. Interestingly, these workers did not discern a relationship between orbital energies, as measured by photoelectron spectroscopy (PES), and the facial selectivity (*syn*- vs *anti*-) of the Diels-Alder reactions of these systems. Such observations and a lack of understanding of how the applications of pressure might impact on the cycloaddition reactions reported above prompted the computational studies now described.

Chen, Hoffmann and Cammi have predicted[20] that the Diels-Alder reaction of cyclopentadiene with ethylene becomes barrierless at around 50 kbar. In the present work, their recently developed computational method, the XP-PCM (extreme pressure polarizable continuum model) protocol,[21] capable of executing quantum mechanical modeling of molecules under pressure, has been used to investigate the *syn*-/*anti*-selectivity of the addition reactions shown in Figures 2-4 and 8 at high (20 kbar or 2 GPa) pressure. Activation and reaction energies were calculated by such means and these are presented in Table 4. Consistent with experimental observations, at 20 kbar the *syn*-addition pathway is favored over its *anti*-counterpart for those processes involving the free diol **5** (Figures 2, 3 and 8) while for those in which the corresponding acetonide **9** is the 4π-addend (Figure 4) then

anti-addition is preferred. Furthermore, the impacts of varying pressures on product distributions for the Diels-Alder reaction **5** (X=Me) + **12** → **13** + **14** (Figure 2) have been studied and the changes in the Gibbs free energy profiles as a function of pressures ranging between 1 atm (1.01 bar) and 5.8 GPa (58 kbar) are shown in Figure 12. So, at 1 atm reactions barriers up to 30 kcal/mol are calculated both for the *syn*- and *anti*-addition pathways but these decrease with increasing pressure and, in keeping with experimental observations, the reactions also become more exothermic albeit at slightly differing rates.

Table 4. The activation ($\Delta G_{tot}^{\ddagger}$) and reaction ($\Delta G_{tot}^{rxn}$) energies (in kcal/mol), at ~20 kbar, of the potential energy surface obtained for reactions shown in Figures 2–4 and 8.

Reaction	***syn*-addition**		***anti*-addition**	
	$\Delta G_{tot}^{\ddagger}$	ΔG_{tot}^{rxn}	$\Delta G_{tot}^{\ddagger}$	ΔG_{tot}^{rxn}
5(X=Me) + **12** → **13** + **14**	15.7	–62.4	16.0	–62.0
5 (X=Me) + **17** → **18** + **19**	13.1	–60.2	14.5	–59.7
5 (X=Cl) + **17** → **31** + **32**	14.9	–60.2	17.1	–60.6
9 + **17** → **20** + **21**	14.9	–61.5	13.8	–59.5

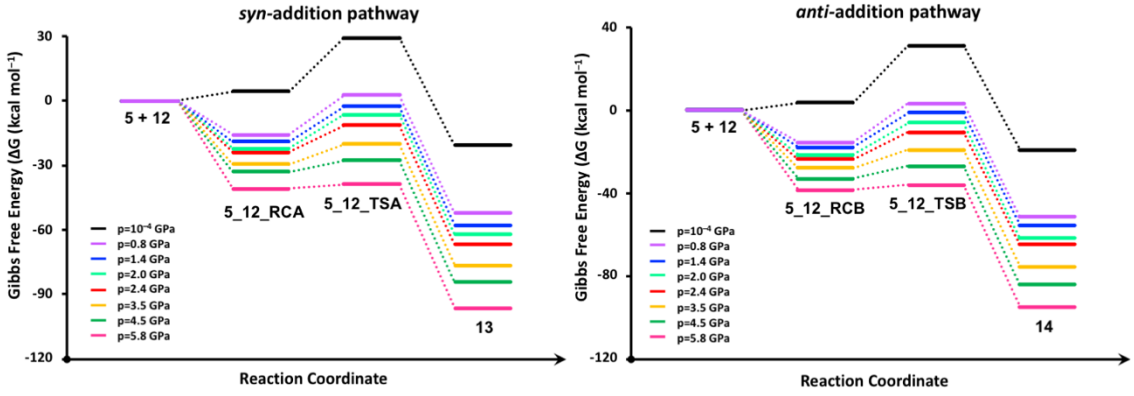

Figure 12. The calculated Gibbs free energy profiles for the reaction of diene **5** (X=Me) and dienophile **12** at varying pressures and leading to the *syn*- and *anti*-adducts **13** and **14**, respectively (RC = reaction complex and TS = transition state).

CONCLUSIONS

The present study establishes that the *syn*-selective Diels-Alder cycloaddition reactions of microbially-derived and homochiral *cis*-1,2-dihydrocatechols **5** (X=Me and Cl) with certain cyclic or *Z*-configured dienophiles can be achieved at elevated pressure. Conversely, the derived acetonides **9** (X=Me and Cl) engage in *anti*-selective reactions with the same suite of dienophiles and so providing a means of obtaining either enantiomeric form of the product bicyclo[2.2.2]octenes. As demonstrated in multiple studies,[22] such adducts embody particularly valuable frameworks for chemical synthesis. While the suite of *cis*-1,2-dihydrocatechols that can engage in the title reactions is modest at the present time, there is little reason to doubt that heterodienophiles could be engaged in analogous, facially selective cycloaddition reactions and so potentially significantly expanding the range adducts available by such means. Such possibilities will be the subject of future studies, as will alternative and operationally simpler means of promoting them. The outcomes of such work will be reported in due course. Computational studies reveal that the *syn*-adduct formation is favored thermodynamically when the unprotected diol **5** is involved but *anti*-adduct formation is favored when the corresponding acetonide **9** is involved as the 4π-addend. Investigations also reveal that both the *syn*- and *anti*-addition processes become more exothermic as pressure increases, while the associated reaction barriers decrease and, indeed, almost vanish at 6 GPa (60 kbar).

EXPERIMENTAL SECTION

General experimental procedures have been described previously.[17] Unless otherwise specified, NMR spectra were recorded using either deuteriochloroform or deuteriomethanol as solvent while optical rotations were measured, unless otherwise specified, in spectroscopic grade chloroform that had been filtered through a plug of anhydrous K_2CO_3 immediately

prior to use. A 20 kbar high pressure reactor purchased from PSIKA® Pressure Systems Ltd (U.K.) was used for the reactions described herein. This reactor was comprised of an electro-hydraulic station controlling two hydraulic presses each driving pistons exerting force on opposing ends of a central hollow chamber containing the reaction vessel suspended in 15:85 v/v methanol/castor oil. All reactions were run at ambient temperatures and once complete pressure was released *via* the control station, then the reaction vessel was removed from the main chamber and wiped clean of any castor oil. Teflon® reaction vessels for containing the reaction mixtures and that could be placed in the main reaction chamber of the PSIKA® reactor were constructed by workshop staff in Research School of Chemistry at the Australian National University. These vessels consisted of a hollow Teflon® cylindrical base/chamber (24 mm i.d./26 mm o.d.) and a solid Teflon® cap/plunger fitted two rubber O-rings that could be inserted into the open end of the cylindrical base/chamber then pushed down below the opening and such that the lower end of the cap came into contact with the upper surface of the solution contained in the vessel. This ensured that almost all the air in the reaction chamber was expelled prior to pressurization. Cylindrical bases of varying lengths were constructed such that reactions volumes of 1, 9 and 18 mL (at STP) could be accommodated. The so-called light solvent CH_2Cl_2 was used in all high-pressure experiments because it does not freeze under such conditions (CAUTION: the reactions described above and below involve extreme pressures and must be conducted with particular care. Operation of the reactor and its contents was carried out in a thick-walled bunker with an open end covered by a meshed blast shield made from multi-stranded steel rope. The pressurization and depressurization steps were carried out remotely and monitored by CCTV).

General Procedure for Conducting High-Pressure Diels-Alder Cycloaddition Reactions. The appropriate dienophile (2 mol equiv) was added, in one portion, to the Teflon® reaction base/chamber containing a solution of the appropriate *cis*-1,2-dihydrocatechol **5**[7] (1 mol

equiv) or the corresponding acetonide **9** in CH_2Cl_2 (~0.5 mL per 100 mg of the substrate diene) maintained at room temperature under an atmosphere of nitrogen. The Teflon® cap/plunger fitted with O-rings (see above) was placed into the opening of the reaction chamber and pushed home as far as possible before the entire assembly was placed in the cavity of the PSIKA® High Pressure Reactor. The system was then pressurized to 19 kbar and maintained at around this pressure (some depressurization of the system was often observed over prolonged periods) and ambient temperature. The system was then depressurized and the Teflon® cap/plunger slowly removed from the Teflon® reaction chamber. The mixture so revealed was concentrated under reduced pressure and the residue then filtered to remove any solids. The filtrate was subjected to flash chromatography (details of which are given below for each individual reaction) and concentration of the appropriate fractions then gave the reaction product(s).

(3a*S*,4*R*,5*S*,6*R*,7*S*,7a*S*)-5,6-Dihydroxy-7-methyl-3a,4,7,7a-tetrahydroethanoisobenzo-furan-(3*H*)-one (13) and (3a*S*,4*R*,5*R*,6*S*,7*S*,7a*S*)-5,6-Dihydroxy-7-methyl-3a,4,7,7a-tetra-hydro-4,7-ethanoisobenzofuran-(3*H*)-one (14). A high-pressure promoted Diels-Alder cycloaddition reaction between furan-2(5*H*)-one (**12**) (3.19 g, 0.038 mol, ex ALDRICH) and *cis*-1,2-dihydrocatechol **5** (X=Me) (2.39 g, 0.019 mol) was carried out as described in the general procedure. The resulting brown oil was subject to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution) and so providing two fractions, A and B.

Concentration of fraction A (R_f = 0.3) afforded a colorless solid. Recrystallisation (methanol) of this material afforded the title adduct **13**[17c] (2.15 g, 56%) as colorless, crystalline prisms, m.p. = 186-187 °C, $[\alpha]_D$ = –44 (*c* 1.0, CH_3OH). ^{1}H NMR (300 MHz, CD_3OD) δ 6.31 (app t, *J* = 8.2 Hz, 1H), 6.08 (d, *J* = 8.2 Hz, 1H), 4.44 (t, *J* = 9.2 Hz, 1H), 3.94 (dd, *J* = 9.2 and 4.1 Hz, 1H), 3.70 (dd, *J* = 8.7 and 3.2 Hz, 1H), 3.37 (d, *J* = 8.7 Hz, 1H), 3.29-

3.24 (complex m, 1H), 2.96 (d, *J* = 10.0 Hz, 1H), 2.85-2.81 (complex m, 1H), 1.58 (s, 3H) (OH proton resonances not observed due to D exchange); $^{13}C\{^{1}H\}$ NMR (75 MHz, CD_3OD, APT) δ 182.4 (C), 139.7 (CH), 132.2 (CH), 73.1 (CH_2), 70.7 (CH) 66.7 (CH), 44.6 (CH), 43.6 (C), 43.5 (CH), 33.3 (CH), 20.1 (CH_3); IR ν_{max} (KBr) 3262, 1746, 1392, 1182, 1081, 1061, 1034, 1015, 1001, 702 cm^{-1}; MS (EI, 70 eV) *m/z* 211 [$(M+H)^+$, 2%], 151 (95), 106 (50), 91(100); HRMS (EI, 70 eV): calcd for $C_{11}H_{15}O_4$ $(M+H)^+$, 211.0970; found 211.0970. Anal. Calcd for $C_{11}H_{14}O_4$ C, 62.85; H, 6.71. Found C, 62.63; H, 6.71%.

Concentration of fraction B (R_f = 0.1) afforded a colorless solid that was recrystallized (methanol) to give the title adduct **14**[17c] (365 mg, 9%) as clear, colorless prisms, m.p. = 167-169 °C, $[\alpha]_D$ = +74 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, CD_3OD) δ 6.27 (app t, *J* = 8.0 Hz, 1H), 6.01 (d, *J* = 8.0 Hz, 1H), 4.41 (t, *J* = 9.2 Hz, 1H), 4.02 (dd, *J* = 7.5 and 2.7 Hz, 1H), 3.93 (dd, *J* = 9.2 and 3.9 Hz, 1H), 3.61 (d, *J* = 7.5 Hz, 1H), 2.97-2.95 (complex m, 1H), 2.90-2.82 (complex m, 1H), 2.55 (d, *J* = 9.9 Hz, 1H), 1.60 (s, 3H) (2 x OH proton resonances not observed due to H/D exchange); $^{13}C\{^{1}H\}$ NMR (75 MHz, CD_3OD, APT) δ 179.9 (C), 137.4 (CH), 131.3 (CH), 74.4 (CH), 72.2 (CH_2), 70.4 (CH), 47.4 (CH), 43.1 (C), 42.5 (CH), 36.8 (CH), 18.6 (CH_3); IR ν_{max} (KBr) 3411, 3271, 2942, 2929, 2912, 1752, 1391, 1379, 1322, 1179, 1073, 1013, 802 cm^{-1}; MS (EI, 70 eV) *m/z* 211 [$(M+H)^+$, 5%], 151 (60), 106 (61), 91(100); HRMS (EI, 70 eV): calcd for $C_{11}H_{15}O_4$ $(M+H)^+$, 211.0970; found 211.0965. Anal. Calcd for $C_{11}H_{14}O_4$ C, 62.85; H, 6.71. Found C, 62.96; H, 6.53%.

(3a*R*,4*S*,4a*S*,7a*S*,8*R*,8a*S*)-2,2,4-Trimethyl-3a,4,4a,5,7,7a,8,8a-octahydro-4,8-etheneofuro-[3,4-*f*]-1,3-benzodioxol-5-one (15). *p*-Toluenesulfonic acid (42 mg, 0.22 mmol) was added, in one portion, to a magnetically stirred solution of diol **13** (500 mg, 2.38 mmol) in 2,2-dimethoxypropane (9.3 mL) maintained at –10 °C under an atmosphere of nitrogen. Stirring was continued for 3 h before the reaction mixture was warmed to ambient temperatures and

stirred for a further 12 h. The resulting yellow solution was treated dropwise with triethylamine (5 mL) and stirred for a further 0.5 h then transferred to a separating funnel containing NaOH (20 mL of a 1 M aqueous solution) and extracted with diethyl ether (3 × 60 mL). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a colorless solid. Subjection of this material to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) then furnished a solid, recrystallization (diethyl ether/hexane) of which gave acetonide **15** (534 mg, 90%) as a colorless, crystalline solid, m.p. = 147-149 °C, $[\alpha]_D$ = –47 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (app t, *J* = 8.0 Hz, 1H), 6.00 (d, *J* = 8.0 Hz, 1H), 4.33 (t, *J* = 9.4 Hz, 1H), 4.10 (dd, *J* = 8.0 and 3.8 Hz, 1H), 3.81 (m, 2H), 3.27-3.23 (complex m, 1H), 2.91-2.87 (complex m, 2H), 1.56 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, APT) δ 178.5 (C), 138.8 (CH), 130.6 (CH), 112.0 (CH_2), 79.9 (CH), 75.0 (CH), 70.2 (C), 42.4 (CH), 40.8 (C), 38.7 (CH), 31.5 (CH), 26.1 (CH_3), 24.1 (CH_3), 18.8 (CH_3); IR ν_{max} (KBr) 2977, 2930, 1758, 1386, 1262, 1063, 1043, 751 cm^{-1}; MS (EI, 70 eV) *m/z* 251 [$(M+H)^+$, 2%], 250 ($M^{+\bullet}$, 1) 235 [$(M-H_3C\bullet)^+$, 42], 192 (78), 147 (55), 119 (100), 100 (92), 91 (62); MS (EI, 70 eV) *m/z* 211 [$(M+H)^+$, 5%], 151 (60), 106 (61), 91(100); HRMS (EI, 70 eV): calcd for $C_{14}H_{18}O_4$ ($M^{+\bullet}$), 250.1205; found 250.1207. Anal. Calcd for $C_{14}H_{18}O_4$ C, 67.18; H, 7.25. Found C, 66.88; H, 7.08%.

(3a*S*,4*S*,4a*S*,7a*S*,8*R*,8a*R*)-2,2,4-Trimethyl-3a,4,4a,5,7,7a,8,8a-octahydro-4,8-etheneofuro-[3,4-*f*]-1,3-benzodioxol-5-one (16). *Method A*: A high-pressure promoted Diels-Alder cycloaddition reaction between furan-2(5*H*)-one (**12**) (0.19 mL, 2.18 mmol) and acetonide **9** (X=Me)[23] (182 mg, 1.09 mmol) was carried out as described in the general procedure. The crude reaction mixture was concentrated under reduced pressure to afford a brown oil that was subjected to flash chromatography (3:7 v/v ethyl acetate/hexane elution). Concentration of the

appropriate fractions (R_f = 0.3) afforded a colorless solid which was recrystallized (CH_2Cl_2) to give adduct **16** (194 mg, 71%) as a colorless needles, m.p. = 163-165 °C, $[\alpha]_D$ = +90 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (app t, *J* = 8.7 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 4.34 (t, *J* = 9.4 Hz, 1H), 4.26 (dd, *J* = 7.1 and 3.3 Hz, 1H), 3.92-3.85 (complex m, 2H), 2.98 (m, 1H), 2.68 (m, 1H), 2.32 (d, *J* = 9.4 Hz, 1H), 1.59 (s, 3H), 1.33 (s, 3H), 1.29 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, APT) δ 176.4 (C), 136.2 (CH), 128.6 (CH), 109.4 (CH_2), 82.2 (CH), 82.1 (CH), 77.8 (CH), 70.1 (C), 40.9 (C), 38.3 (CH), 35.4 (CH), 25.3 (CH_3), 24.8 (CH_3), 18.2 (CH_3); IR ν_{max} (KBr) 2977, 1763, 1370, 1267, 1205, 1070, 1045, 1017, 746 cm^{-1}; MS (EI, 70 eV) *m/z* 251 [$(M+H)^+$, 2%], 235 [$(M-H_3C\bullet)^+$, 54], 192 (94), 147 (69), 119 (100), 100 (81); HRMS (EI, 70 eV): calcd for $C_{14}H_{19}O_4$ $(M + H)^+$, 251.1283; found 251.1281. Anal. Calcd for $C_{14}H_{18}O_4$ C, 67.18; H, 7.25. Found C, 67.32; H, 7.26%.

Method B: *p*-Toluenesulfonic acid (12 mg, 0.06 mmol) was added, in one portion, to a magnetically stirred solution of diol **14** (150 mg, 0.71 mmol) in 2,2-dimethoxypropane (2.3 mL) maintained at –10 °C under an atmosphere of nitrogen. Stirring was continued for 1 h before the reaction mixture was warmed to ambient temperatures and then stirred for a further 24 h. The resulting yellow solution was treated dropwise with triethylamine (3 mL) and stirred for another 0.5 h then transferred to a separating funnel containing NaOH (10 mL of a 1 M aqueous solution) and extracted with diethyl ether (4 × 40 mL). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a colorless powder. Recrystallisation (CH_2Cl_2) of this material provided an analytically pure sample of compound **16** (154 mg, 86%) as colorless needles, m.p. = 163-165 °C. This material was identical, in all respects, with that obtained *via* Method A.

(3a*S*,7a*S*,7*S*,8*R*,9*S*)-8,9-Dihydroxy-7-methyl-2,3,3a,4,7,7a-hexahydro-4,7-ethano-1*H*-inden-1-one (18) and (3a*R*,7a*R*,7*R*,8*S*,9*R*)-8,9-Dihydroxy-7-methyl-2,3,3a,4,7,7a-hexa-

hydro-4,7-ethano-1*H*-inden-1-one (19). The high-pressure promoted Diels-Alder cycloaddition reaction between cyclopent-2-en-1-one (**17**) (1.55 mL, 18.6 mmol) and *cis*-1,2-dihydrocatechol **5** (X=Me) (1.18 g, 9.32 mmol) was carried out as described in the general procedure. The crude reaction mixture was concentrated under reduced pressure to afford a yellow oil that was subjected to flash chromatography (1:1 v/v ethyl acetate/hexane elution) and thereby providing two fractions, A and B.

Concentration of fraction A (R_f = 0.3) afforded a colorless solid that was recrystallized (ether/hexane) to give the title diol **18**[17a] (1.36 g, 70%) as colorless prisms, m.p. = 93-94 °C, $[\alpha]_D$ = –196 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (broadened, *J* = 8.0 Hz, 1H), 5.80 (d, *J* = 8.0 Hz, 1H), 3.68 (m, 1H), 3.28 (dd, *J* = 8.7 and 5.0 Hz, 1H), 3.15 (m, 1H), 3.01-2.96 (complex m, 2H), 2.76 (m, 1H), 2.48 (d, *J* = 9.9 Hz, 1H), 2.10-1.96 (complex m, 3H), 1.59 (m, 1H), 1.45 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, APT) δ 223.7 (C), 137.5 (CH), 131.8 (CH), 69.1 (CH), 65.4 (CH), 49.4 (CH), 43.3 (CH), 42.7 (C), 39.3 (CH_2), 31.3 (CH), 25.0 (CH_2), 19.2 (CH_3); IR ν_{max} (KBr) 3408, 3304, 2942, 2903, 1716, 1454, 1399, 1370, 1080, 702 cm^{-1}; MS (EI, 70 eV) *m/z* 208 ($M^{+\bullet}$, 2%), 148 [$(M-C_2H_4O_2)^{+\bullet}$, 100], 120 (36), 106 (76), 92 (69); HRMS (EI, 70 eV): calcd for $C_{12}H_{16}O_3$ ($M^{+\bullet}$), 208.1099; found 208.1104. Anal. Calcd for $C_{12}H_{16}O_3$ C, 69.21; H, 7.74. Found C, 69.27; H, 7.59%.

Concentration of fraction B (R_f = 0.1) afforded compound **19** (182 mg, 9%) as a clear, colorless and viscous oil, $[\alpha]_D$ = +222 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (broadened t, *J* = 8.0 Hz, 1H), 5.90 (d, *J* = 8.0 Hz, 1H), 3.95 (m, 1H), 3.47 (t, *J* = 7.1 Hz, 1H), 2.92 (m, 1H), 2.61 (dd, *J* = 11.3 and 6.5 Hz, 2H), 2.52 (m, 1H), 2.09-2.00 (complex m, 3H), 1.97 (d, *J* = 9.4 Hz, 1H), 1.65 (m, 1H), 1.47 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, CD_3OD, APT) δ 223.0 (C), 137.1 (CH), 132.5 (CH), 75.2 (CH), 71.7 (CH), 55.8 (CH), 45.3 (CH), 40.7 (C), 38.3 (CH_2), 26.5 (CH), 19.3 (CH_3) (one signal obscured or overlapping); IR ν_{max} (KBr) 3399,

2962, 2932, 2908, 2879, 1727, 1403, 1171, 1099, 1058, 728 cm^{-1}; MS (EI, 70 eV) *m/z* 208 ($M^{+\bullet}$, 1%), 148 [$(M-C_2H_4O_2)^{+\bullet}$, 100], 120 (45), 106 (81), 105 (65), 92 (83), 91 (60), 56 (57); HRMS (EI, 70 eV): calcd for $C_{12}H_{16}O_3$ ($M^{+\bullet}$), 208.1099; found 208.1099.

(3a*R*,4*S*,4a*S*,7a*S*,8*R*,8a*S*)-2,2,4-trimethyl-3a,4,4a,6,7,7a,8,8a-octahydro-5*H*-4,8-ethenoind-eno[5,6-*d*][1,3]dioxol-5-one (20) and (3a*R*,4*R*,4a*R*,7a*R*,8*S*,8a*S*)-2,2,4-trimethyl-3a,4,4a,6,7,7a,8,8a-octahydro-5*H*-4,8-ethenoindeno[5,6-*d*][1,3]dioxol-5-one (21). *Method A:* A solution of freshly prepared diene **9** (X=Me) (1.54 g, 9.3 mmol) and cyclopent-2-en-1-one (**17**) (1.28 mL, 15.8 mmol) in dichloromethane (9 mL) was pressurized according to the general proceedure detailed above. Subjection of the ensuing brown oil to flash chromatography (silica, 1:19 $\rightarrow$ 1:4 v/v ethyl acetate/hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.6 in 1:1 v/v ethyl acetate/hexane, phosphomolybdic acid visualisation) afforded the title acetonide **20** (290 mg, 13%) as a clear, colorless oil, the spectral data for which were identical, in all respects, with those reported earlier[9a] for this compound.

Concentration of fraction B (R_f = 0.5 in 1:1 v/v ethyl acetate/hexane, phosphomolybdic acid visualisation) afforded the title compound **21**[17d,23] (1.22 g, 53%) as a white, crystalline solid, m.p. = 80-81˚C, $[\alpha]_D$ +218 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 6.12 (dd, *J* = 8.4 and 6.3 Hz, 1H), 5.77 (d, *J* = 8.4 Hz, 1H), 4.25 (ddd, *J* = 7.2, 3.3 and 1.2 Hz, 1H), 3.81 (dd, *J* = 7.2 and 1.2 Hz, 1H), 2.93 (m, 1H), 2.50-2.42 (complex m, 1H), 2.13-1.97 (complex m, 3H), 1.91 (d, *J* = 9.6 Hz, 1H), 1.74-1.62 (complex m, 1H), 1.45 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 220.1, 135.8, 130.1, 109.2, 83.0, 79.2, 52.6, 42.2, 41.0, 39.8, 36.6, 25.8, 25.4, 25.3, 19.0; IR ν_{max} 2983, 2939, 1733, 1456, 1381, 1372, 1264, 1207, 1166, 1093, 1074, 1053, 890, 873, 728 cm^{-1}; MS (EI, 70 eV) *m/z* 248

($M^{+\bullet}$, 4%), 233 {[M – $CH_3\bullet$]$^+$, 30}, 190 {[M – $(CH_3)_2CO$]$^{+\bullet}$, 100}, 161 (48), 134 (52), 105 (92), 100 (91), 91 (52), 43 (92); HRMS (EI, 70 eV): calcd for $C_{15}H_{20}O_3$ [$M^{+\bullet}$] 248.1412; found 248.1413. Anal. Calcd for $C_{15}H_{20}O_3$ C, 72.55; H, 8.12. Found C, 72.64; H, 8.06%.

Method B: 2,2-Dimethoxypropane (10 mL, 81.3 mmol) was added to a magnetically stirred solution of diol **18** (2.38 g, 11.5 mmol) and *p*-TsOH•H_2O (24.6 mg, 0.1 mmol) in dichloromethane (20 mL) maintained at 0 °C. After 3 h the reaction mixture was warmed to ambient temperatures and after a further 72 h it was concentrated under reduced pressure and the ensuing deep-red oil subjected to flash chromatography (silica, 1:4 → 3:7 v/v ethyl acetate/hexane gradient elution). Concentration of the appropriate fractions (R_f = 0.7 in 1:1 v/v ethyl acetate/hexane elution, phosphomolybdic acid visualisation) afforded acetonide **20** (2.80 g, 98%) as a clear, colorless oil and identical in all respects with the material obtained by Method A.

(1*S*,4*R*,4a*S*,9*S*,10*R*)-9,10-Dihydroxy-1-methyl-1,4a,5,6,7,8a-hexahydro-1,4-ethanonaphthalen-8(4*H*)-one (23) and (1*R*,4*S*,4a*R*,8a*R*,9*S*,10*R*)-9,10-Dihydroxy-1-methyl-1,4a,5,6,-7,8a-hexahydro-1,4-ethanonaphthalen-8(4*H*)-one (24). A high-pressure promoted Diels-Alder cycloaddition reaction between cyclohex-2-en-1-one (**22**) (17) (1.55 mL, 18.6 mmol) and *cis*-1,2-dihydrocatechol **5** (X=Me) (300 mg, 9.32 mmol) was carried out as described in the general procedure. The crude reaction mixture was concentrated under reduced pressure to afford a yellow oil that was subjected to flash chromatography (silica, 4:6 → 9:1 v/v ethyl acetate/40-60 petroleum spirit gradient elution) and thereby providing two fractions, A and B.

Concentration of fraction A (R_f = 0.7 in 7:3 v/v ethyl acetate/40-60 petroleum spirit elution) afforded *syn*-adduct **23** (83 mg, 16%) as a clear, colorless oil, $[\alpha]_D$ = +2 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07-5.99 (complex m, 2H), 3.65 (m, 1H), 3.28 (dd, *J* = 8.7 and 4.7 Hz, 1H), 3.11 (d, *J* = 5.3 Hz, 1H), 2.96-2.89 (complex m, 3H), 2.52 (m, 1H),

2.37 (m, 1H), 2.11 (m, 1H), 1.91-1.81 (complex m, 2H), 1.67 (m, 1H), 1.40 (s, 3H), 1.00 (m, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$, APT) δ 214.5 (C), 139.0 (CH), 130.1 (CH), 70.2 (CH), 65.9 (CH), 51.9 (CH), 43.3 (CH), 41.2 (C), 39.4 (CH_2), 34.9 (CH), 28.2 (CH_2), 21.5 (CH_2), 20.8 (CH_3); IR ν_{max} (KBr) 3380, 3043, 2929, 2874, 1695, 1452, 1396, 1364, 1290, 1239, 1121, 1062, 1039, 1005, 836, 718, 680 cm^{-1}; MS (EI, 70 eV) *m/z* 222 ($M^{+\bullet}$, 1%), 204 (2), 186 (2), 163 (4), 162 (4), 134 (25), 118 (100) 105 (55), 91 (45); HRMS (EI, 70 eV): calcd for $C_{13}H_{18}O_3$ [$M^{+\bullet}$] 222.1256; found 222.1257.

Concentration of fraction B (R_f = 0.1) afforded compound **24** (182 mg, 9%) as a clear, colorless and viscous oil, $[\alpha]_D$ = +29 (*c* = 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (m, 2H), 3.97 (m, 1H), 3.46 (t, *J* = 6.9 Hz, 1H), 2.74 (m, 1H), 2.60 (d, *J* = 6.5 Hz, 1H), 2.45 (d, *J* = 6.5 Hz, 1H), 2.41-2.29 (complex m, 3H), 2.09 (m, 1H), 1.89-1.68 (complex m, 3H), 1.37 (s, 3H), 1.11 (m, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, CD_3OD, APT) δ 216.1 (C), 138.4 (CH), 131.0 (CH), 75.8 (CH), 72.5 (CH), 57.1 (CH), 45.4 (CH), 43.3 (C), 41.8 (CH), 40.7 (CH_2), 29.7 (CH_2), 23.2 (CH_2), 20.4 (CH_3); IR ν_{max} (KBr) 3384, 2831, 1704, 1406, 1087, 1060, 1014, 727 cm^{-1}; MS (EI, 70 eV) *m/z* 222 ($M^{+\bullet}$, 1%), 204 (1), 163 (42), 162 (48), 118 (100), 105 (57), 91 (42); HRMS (EI, 70 eV): calcd for $C_{13}H_{18}O_3$ [$M^{+\bullet}$] 222.1256; found 222.1256.

(1*S*,2*S*,3*R*,4*R*,4a*R*,7*R*,8*S*,8a*R*)-2,3,7,8-Tetrahydroxy-4,6-dimethyl-1,2,3,4,7,8-hexahydro-1,4-ethenonapthalene (25). An attempted high-pressure promoted Diels-Alder reaction between cyclopentene (540 mg, 7.93 mmol) and *cis*-1,2-dihydrocatechol **5** (X=Me) (500 mg, 3.96 mmol) was carried out as described in the general procedure. The crude reaction mixture was concentrated under reduced pressure to afford a brown semi-solid. Filtration of this material and washing of the retained solids with cold $CHCl_3$ (10 mL) then furnished the title dimer **25** (81 mg, 16%) as colorless prisms, m.p. = 182-183 °C. ^{1}H NMR (300 MHz, CD_3OD) 6.16 (broadened t, *J* = 8.2 Hz, 1H), 5.87 (d, *J* = 8.2 Hz, 1H), 5.62 (s, 1H), 4.07 (dd, *J* = 7.7

and 2.7 Hz, 1H), 3.84 (d, *J* = 3.1 Hz, 1H), 3.53 (d, *J* = 7.7 Hz, 1H), 3.34 (m, 1H), 3.07 (m, 1H), 2.17 (m, 2H), 1.85 (broadened s, 3H), 1.39 (s, 3H) (resonances due to OH group protons not observed); $^{13}C\{^{1}H\}$ NMR (75 MHz, CD_3OD, APT) δ□137.0 (CH), 136.2 (C), 132.1 (CH), 125.1 (CH), 76.1 (CH), 72.2 (CH), 72.1 (CH), 71.7 (CH), 43.1 (CH), 41.7 (CH), 36.2 (CH), 22.1 (CH_3), 16.7 (CH_3) (signal due to quaternary carbon not observed); IR ν_{max} (KBr) 3337, 2964, 2910, 1448, 1395, 1118, 1043, 1001, 888, 724 cm^{-1}; MS (EI, 70 eV) *m/z* 252 ($M^{+\bullet}$, <1%), 234 [$(M - H_2O)^{+\bullet}$, 1], 192 (45), 174 (40), 159 (100), 124 (85), 108 (80), 91 (45), 80 (85); HRMS (EI, 70 eV): calcd for $C_{14}H_{18}O_3$ [$(M - H_2O)^{+\bullet}$] 234.1256; found 234.1259.

(*Z*)-5-((*tert*-Butyldimethylsilyl)oxy)pent-3-en-2-one (26). *Step i:* Commercially-derived *Z*-2-butene-1,4-diol (20.0 g, 0.23 mol) was added dropwise to a magnetically stirred suspension of sodium hydride (5.7 g, 0.25 mol) in THF (160 mL) maintained at 0 °C under a atmosphere of nitrogen. After 1 h the resulting mixture was treated, in ten equal portions, with *tert*-butyldimethylsilyl chloride (34.4 g, 0.23 mol) over 0.5 h and the mixture thus obtained stirred at ambient temperatures for 12 h then slowly quenched with water (100 mL) (CAUTION POSSIBILITY OF HYDROGEN EVOLUTION) before being extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with K_2CO_3 (3 × 100 mL of a saturated aqueous solution) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a clear, yellow oil. This material was subjected to flash chromatography (silica gel, 1:9 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f = 0.3) gave (*Z*)-4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-ol[1] (36.0 g, 78%) and a clear, colorless oil. The spectral data derived from this material were identical, in all respects, with those reported[24] in the literature.

Step ii: The Dess-Martin periodinane (10.0 g, 0.024 mol) was added to a magnetically stirred solution of (*Z*)-4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-ol (3.90 g, 0.019 mol) in dichloromethane (160 mL) maintained at 0 °C under an atmosphere of nitrogen for 2 h. The resulting mixture was

warmed to ambient temperatures and stirring continued for a further 1 h after which the now cloudy mixture was treated with $NaHCO_3$ (100 mL of a saturated aqueous solution) then $Na_2S_2O_3$ (100 mL of a 1 M aqueous solution) and stirring continue for another 1 h. The resulting clear solution was extracted with diethyl ether (4 x 100 mL) and the combined organic phases washed with $NaHCO_3$ (1 × 50 mL of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a cloudy oil. Subjection of this material to flash chromatograpghy (silica gel, 1:19 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.7) afforded aldehyde (*Z*)-4-((*tert*-butyldimethylsilyl)oxy)but-2-enal[25] (3.10 g, 80%) as a viscous, clear, colorless and unstable oil. Due to its sensitivity this material was used directly in *Step iii* of the reaction sequence as detailed immediately below.

Step iii. Methyl lithium (12.7 mL of a 1.4 M solution in THF, 0.018 mol) was added dropwise to a magnetically stirred solution of (*Z*)-4-((*tert*-butyldimethylsilyl)oxy)but-2-enal (2.97 g, 0.015 mol) in THF (300 mL) maintained at –78 °C under an atmosphere of nitrogen. Stirring was then continued for a further 2 h and then the now dark-yellow reaction mixture treated, dropwise, with acetic acid (6 mL of a 2.8 M solution in THF, 0.017 mol). The ensuing mixture was warmed to ambient temperatures then treated with water (100 mL) and extracted with diethyl ether (3 × 200 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this materials to flash chromatography (silica gel, 1:9 v/v ethyl acetate/hexane elution) afforded two major fractions, A and B.

Concentration of fraction A (R_f = 0.3) afforded (*Z*)-5-((*tert*-butyldimethylsilyl)oxy)pent-3-en-2-ol (1.42 g, 44%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58-5.54 (complex m, 2H), 4.62 (qn, *J* = 6.5 Hz, 1H), 4.31 (dd, *J* = 12.2 and 5.0 Hz, 1H), 4.21 (dd, *J* = 12.2 amd 4.3 Hz, 1H), 2.25 (broad s, 1H), 1.25 (d, *J* = 6.5 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 135.4 (CH), 128.8 (CH), 63.9 (CH), 58.4 (CH_2), 25.8 (CH_3), 23.2 (CH_3), 18.1 (C), –0.1,

–5.3 (CH_3); IR (KBr) ν_{max} 3350, 2955, 2930, 2858, 1472, 1463, 1255, 1082, 838, 776 cm^{-1}; MS (EI, 70 eV) *m/z* 215 [$(M\text{-}H\bullet)^+$, <1%], 199 (5), 171 (24), 159 (39), 141 (25), 75 (100); HRMS (EI, 70 eV): calcd for $C_{11}H_{23}O_2Si$ [$(M\text{-}H\bullet)^+$], 215.1467; found 215.1466.

Concentration of fraction B (R_f = 0.2) afforded compound (*E*)-5-((*tert*-butyldimethylsilyl)oxy) -pent-3-en-2-ol (1.20 g, 37%) as a clear, colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (m, 2H), 4.29-4.26 (complex m, 1H), 4.13 (m, 2H), 2.32 (broad s, 1H), 1.21 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$) δ 134.0 (CH), 128.8 (CH), 67.9 (CH), 63.0 (CH_2), 25.8 (CH_3), 23.0 (CH_3), 18.2 (C), –5.4 (CH_3) (one signal obscured or overlapping); IR (KBr) ν_{max} 3358, 2930, 2858, 1255, 1123, 1085, 777 cm^{-1}; MS (EI, 70 eV) *m/z* 216 [$M^{+\bullet}$, <1%], 215 (<1), 201 (2), 199 (2), 171 (28), 159 (33), 141 (2), 75 (100); HRMS (EI, 70 eV): calcd for $C_{11}H_{23}O_2Si$ [$(M\text{-}H\bullet)^+$], 215.1467; found 215.1466. The (–)-enantiomeric form of (*E*)-5-((*tert*-butyldimethylsilyl)oxy) -pent-3-en-2-ol has been reported previously.[26]

Step iv: Dess-Martin periodinane (1.36 g, 3.22 mmol) was added to a magnetically stirred solution of (*Z*)-5-((*tert*-Butyldimethylsilyl)oxy)pent-3-en-2-ol (675 mg, 3.12 mol) in dichloromethane (20 mL) maintained at ambient temperatures under a nitrogen atmosphere. The resulting mixture was stirred a a further 1 h then treated with $NaHCO_3$ (40 mL of a saturated aqueous solution) and $Na_2S_2O_3$ (40 mL of a 1 M aqueous solution). Stirring was continued for a further 1 h then the resulting clear solution was extracted with dichloromethane (3 × 40 mL). The combined organic phases were washed with $NaHCO_3$ (1 × 30 mL of a saturated aqueous solution) before being dried, filtered and concentrated under reduced pressure to afford a cloudy oil. Subjection of this material to flash chromatography (silica gel, 1:19 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.6) then afforded the *Z*-configured dienophile **26** (610 mg, 91%) as a clear, colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.25 (dt, *J* = 11.5 and 4.4 Hz, 1H), 6.14 (dt, *J* = 11.5 and 2.4 Hz, 1H), 4.70 (dd, *J* = 4.4 and 2.4 Hz, 2H), 2.21 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); MS

(EI, 70 eV) *m/z* 214 ($M^{+\bullet}$, 11%), 213 (46%), 171 (53), 157 (26), 143 (42), 75 (100). This rather unstable material was used immediately in the Diels-Alder reactions described herein.

(1*S*,2*R*,3*S*,4*R*,7*R*,8*S*)-2,3-Dihydroxy-7-ethanone-8-[(1',1'-dimethylethyl)dimethylsilyloxy -methyl-1-methylbicyclo[2.2.2]oct-5-ene (27) and (1*R*,2*R*,3*S*,4*S*,7*S*,8*R*)-2,3-Dihydroxy-7-ethanone-8-[(1',1'-dimethylethyl)dimethylsilyloxymethyl-1-methylbicyclo[2.2.2]oct-5-ene (28). The high-pressure promoted Diels-Alder cycloaddition reaction between α,β-unsaturated ketone **26** (600 mg, 2.8 mmol) and *cis*-1,2-dihydrocatechol **5** (X=Me) (300 mg, 2.3 mmol) was carried out as described in the general procedure. The crude reaction mixture was concentrated under reduced pressure to afford a brown oil that was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane →□1:1 v/v ethyl acetate/hexanegradient elution) and thereby affording two fractions, A and B.

Concentration of fraction A (R_f = 0.4, 1:4 v/v ethyl acetate/hexane elution) furnished the *syn*-adduct **27** (310 mg, 38%) as a clear, colorless oil, $[\alpha]_D$ = +49 (*c* = 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ□6.02 (app t, *J* = 8.2 Hz, 1H), 5.93 (d, *J* = 8.2 Hz, 1H), 3.68 (m, 1H), 3.38 (d, *J* = 5.2 Hz, 1H), 3.34-3.27 (complex m, 4H), 3.20 (dd, *J* = 8.8 and 5.2 Hz, 1H), 2.80 (m, 1H), 2.64 (m, 1H), 2.17 (s, 3H), 1.14 (s, 3H), 0.84 (s, 9H), –0.02 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, APT) δ 211.0 (C), 137.8 (CH), 129.2 (CH), 69.2 (CH), 64.1 (CH), 64.0 (CH_2), 49.0 (CH), 41.8 (C), 40.2 (CH), 39.8 (CH), 35.4 (CH_3), 25.7 (CH_3), 19.2 (CH_3), 18.2 (C), –5.7 (CH_3) (one signal obscured or overlapping); IR ν_{max} (KBr) 3389, 2955, 2930, 2883, 2857, 1712, 1471, 1463, 1389, 1361, 1256, 1107, 1074, 1037, 837, 778, 694 cm^{-1}; MS (EI, 70 eV) *m/z* 339 [$(M - H\bullet)^+$, <1%], 325 [$(M - H_3C\bullet)^+$, <1], 283 [$(M - C_4H_9\bullet)^+$, 12], 157 (100), 75 (45); HRMS (EI, 70 eV): calcd for $C_{14}H_{23}O_4Si$ [$(M - C_4H_9\bullet)^+$] 283.1366; found 283.1366. Anal. Calcd for $C_{18}H_{32}O_4Si$ C, 63.49; H, 9.47. Found C, 63.20; H, 9.44%.

Concentration of fraction B (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane) afforded the *anti*-adduct **28** (220 mg, 27%) as a clear, colorless solid, m.p. = 93-94 °C, $[\alpha]_D$ = –16 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (app t, *J* = 8.0 Hz, 1H), 6.03 (d, *J* = 8.0 Hz, 1H), 3.97 (m, 1H), 3.49 (d, *J* = 7.6 Hz, 1H), 3.36-3.27 (complex m, 2H), 2.82 (m, 1H), 2.76 (d, *J* = 10.2 Hz, 1H), 2.40-2.31 (complex m, 2H), 2.19 (s, 3H), 1.60 (broad s, 1H), 1.25 (s, 3H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, APT) δ 208.4 (C), 135.9 (CH), 128.6 (CH), 74.5 (CH), 70.8 (CH), 63.5 (CH_2), 54.5 (CH), 44.6 (CH), 42.7 (C), 40.4 (CH), 35.3 (CH_3), 25.7 (CH_3), 18.8 (CH_3), 18.2 (C), –5.6(5) (CH_3), –5.7(0) (CH_3); IR ν_{max} (KBr) 3401, 2928, 1713, 1470, 1361 1256, 1174, 1062, 1006, 836, 776, 729 cm^{-1}; MS (70 eV) *m/z* 283 [(M – C_4H_9•)$^+$, 14%], 223 (23), 157 (100), 89 (53), 75 (68), 73 (55); HRMS (EI, 70 eV): calcd for $C_{14}H_{23}O_4Si$ [(M – C_4H_9•)$^+$] 283.1366; found 283.1369. Anal. Calcd for $C_{18}H_{32}O_4Si$ C, 63.49; H, 9.47. Found C, 63.40; H, 9.43%.

(*E*)-5-((*tert*-Butyldimethylsilyl)oxy)pent-3-en-2-one (29). Dess-Martin periodinane (200 mg, 0.05 mmol) was added to a magnetically stirred solution of (*E*)-5-((*tert*-butyldimethylsilyl)oxy)-pent-3-en-2-ol (100 mg, 0.05 mol) (prepared as described above at *Step iii* of the synthesis of compound **26**) in dichloromethane (2 mL) maintained at ambient temperatures under a nitrogen atmosphere. The resulting mixture was stirred for a further 0.2 h then treated with $NaHCO_3$ (3 mL of a saturated aqueous solution) and $Na_2S_2O_3$ (3 mL of a 1 M aqueous solution). Stirring was continued for a further 1 h then the resulting clear solution extracted with dichloromethane (3 × 5 mL). The combined organic phases were washed with $NaHCO_3$ (1 × 4 mL of a saturated aqueous solution) before being dried, filtered and concentrated under reduced pressure to afford a cloudy oil. Subjection of this material to flash chromatography (silica gel, 1:19 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.5) then afforded the *E*-configured dienophile **29**[27] (95 mg, 96%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (dt, *J* =

15.7 and 3.5 Hz, 1H), 6.34 (dt, *J* = 15.7 and 2.1 Hz, 1H), 4.36 (m, 2H), 2.27 (s, 3H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 198.3 (C), 146.1 (CH), 128.7 (CH), 62.1 (CH_2), 27.2 (CH_3), 25.7 (CH_3), 18.2 (C), –0.1 (CH_3); IR (KBr) ν_{max} 2955, 2929, 2857, 1676, 1360, 1284, 1255, 1134, 966, 837, 778 cm^{-1}; MS (EI, 70 eV) *m/z* 196 [$(M\text{-}H_2O)^{+\bullet}$, 3%], 157 [$(M\text{-}C_4H_9\bullet)^{+}$, 33%], 149 (48), 75 (100); HRMS (EI, 70 eV): calcd for $C_7H_{13}O_2Si$ [$(M\text{-}C_4H_9\bullet)^{+}$], 157.0684; found 157.0684.

(1*R*,2*R*,3*S*,4*S*,7*R*,8*S*)-2,3-Dihydroxy-7-ethanone-8-[(1',1'-dimethylethyl)dimethylsilyloxy -methyl-1-methylbicyclo[2.2.2]oct-5-ene (30). The high-pressure promoted Diels-Alder cycloaddition reaction between α,β-unsaturated ketone **29** (600 mg, 2.8 mmol) and *cis*-1,2-dihydrocatechol **5** (X=Me) (176 mg, 1.4 mmol) was carried out as described in the general procedure. The crude reaction mixture was concentrated under reduced pressure to afford a brown oil. Subjection of this material to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) then afforded *anti*-adduct **30** (175 mg, 37%) as a colorless, crystalline solid, m.p. = 59-60 °C, $[\alpha]_D$ = –6 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (app t, *J* = 7.8 Hz, 1H), 5.90 (d, *J* = 7.8 Hz, 1H), 4.19 (m, 1H), 3.58 (dd, *J* = 8.1 and 1.5 Hz, 1H), 3.45 (t, *J* = 7.1 Hz, 1H), 2.88 (m, 1H), 2.50 (d, *J* = 7.1 Hz, 1H), 2.19 (m, 2H), 2.12 (s, 3H), 1.87 (m, 1H), 1.27 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H) (resonance due to an OH proton not observed); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, APT) δ 210.4 (C), 134.6 (CH), 132.8 (CH), 75.1 (CH), 67.1 (CH), 64.5 (CH_2), 56.7 (CH), 45.1 (CH), 42.6 (C), 40.0 (CH), 30.8 (CH_3), 25.7 (CH_3), 18.8 (CH_3), 18.1 (C), –5.6 (CH_3), –5.7 (CH_3); IR ν_{max} (KBr) 3389, 2954, 2929, 2885, 2857, 1698, 1361, 1254, 1099, 1042, 837, 777, 667 cm^{-1}; MS (EI, 70 eV) *m/z* 340 ($M^{+\bullet}$, 4%), 283 [$(M - C_4H_9\bullet)^{+}$, 52], 223 (42), 157 (100), 135 (55), 105 (53), 89 (76), 75 (91), 73 (83); HRMS (EI, 70 eV): calcd for $C_{18}H_{32}O_4Si$

($M^{+\bullet}$) 340.2070; found 340.2065. Anal. Calcd for $C_{18}H_{32}O_4Si$ C, 63.49; H, 9.47. Found C, 63.38; H, 9.63%.

(3a*S*,4*R*,7*R*,7a*R*,8*S*,9*S*)-7-chloro-8,9-dihydroxy-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-ethano-inden-1-one (31), (3a*R*,4*S*,7*S*,7a*S*,8*S*,9*S*)-7-chloro-8,9-dihydroxy-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-ethanoinden-1-one (32) and (1*S*,4*S*,4a*S*,7*S*,8*S*,8a*R*,10*S*)-4,6-dichloro-1,4,4a,7,8,8a-hexahydro-1,4-ethanonaphthalene-7,8,9,10-tetraol (33). A solution of diene **5** (X=Cl) (1.00 g, 6.83 mmol) and cyclopent-2-en-1-one (**17**) (465 mg, 4.74 mol) in dichloromethane (6 mL) was subjected, at ambient temperatures, to 19 kbar pressure for 72 h. The reaction mixture thus obtained was subjected to flash chromatography (silica, 1:1 → 1:0 v/v ethyl acetate/40-60 petroleum ether gradient elution) to afford three fractions, A, B and C.

Concentration of fraction A (R_f = 0.5 in 7:3 v/v ethyl acetate/40-60 petroleum ether) gave a white solid, recrystallization (chloroform/hexane) of which afforded compound **31** (175 mg, 11%) as a colorless needles, m.p. = 119-121 °C, $[\alpha]_D$ = –74 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25-6.05 (complex m, 2H), 3.78 (m, 1H), 3.68 (m, 1H), 3.35 (d, *J* = 6.0 Hz, 1H), 3.23 (d, *J* = 3.0 Hz, 1H), 3.15 (m, 1H), 2.90 (m, 1H), 2.30-2.00 (complex m, 4H), 1.55 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, APT) δ 218.9 (C), 136.0 (CH), 131.8 (CH), 71.2 (C), 69.9 (CH), 65.5 (CH), 50.5 (CH), 42.6 (CH), 39.2 (CH_2), 33.0 (CH), 24.6 (CH_2); IR ν_{max} (KBr) 3271, 2947, 1730, 1401, 1261, 1174, 1086, 1052, 994, 836, 800, 699 cm^{-1}; MS (EI, 70 eV) *m/z* 230 and 228 ($M^{+\bullet}$, 3 and 10%), 170 (55), 169 (65), 168 (88), 126 (100), 112 (61), 105 (53), 91 (69), 77 (57); HRMS (EI, 70 eV): calcd for $C_{11}H_{13}{}^{35}ClO_3$ ($M^{+\bullet}$) 228.0553; found 228.0553. Anal. Calcd for $C_{11}H_{13}ClO_3$ C, 57.78; H, 5.73. Found C, 57.91; H, 5.76%.

Concentration of fraction B (R_f = 0.2 in 7:3 v/v ethyl acetate/40-60 petroleum ether) gave a white solid recrystallization (chloroform/hexane) of which afforded compound **32** (43

mg, 3%) as a colorless needles, m.p. = 121-123 °C, $[\alpha]_D$ = +103 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3/D_2O$) δ 6.25 (m, 1H), 6.10 (d, *J* = 8.0 Hz, 1H), 4.05 (m, 1H), 3.80 (d, *J* = 8.0 Hz, 1H), 2.97 (m, 1H), 2.65-2.55 (complex m, 1H), 2.45 (d, *J* = 9.0 Hz, 1H), 2.20-2.00 (complex m, 3H), 1.60 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, APT) δ 215.9 (C), 133.8 (CH), 131.5 (CH), 74.0 (CH), 71.2 (C), 69.9 (CH), 53.7 (CH), 42.5 (CH), 39.2 (CH_2), 36.3 (CH), 24.6 (CH_2); IR ν_{max} (KBr) 3392, 2945, 1736, 1403, 1261, 1167, 1112, 1066, 993, 810, 717 cm^{-1}; MS (EI, 70 eV) *m/z* 231 and 229 {$(M + H)^+$, both <%}, 170 (62), 169 (68), 168 (73), 126 (100), 112 (65), 105 (45), 91 (70), 56 (82); HRMS (EI, 70 eV): calcd for $C_{11}H_{13}{}^{35}ClO_3$ ($M^{+\bullet}$) 228.0551; Found 228.0553.

Concentration of fraction C (R_f = 0.1 in 7:3 v/v ethyl acetate/40-60 petroleum ether) gave dimer **33** (35 mg, 2%) as a white, crystalline solid, m.p. = 138-140 °C, $[\alpha]_D$ = –112 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, CD_3OD) δ 6.23 (d, *J* = 2.7 Hz, 1H), 6.15 (m, 1H), 6.03 (d, *J* = 9.3 Hz, 1H), 4.05 (m, 1H), 3.98 (d, *J* = 3.3 Hz, 1H), 3.83 (d, *J* = 7.8 Hz, 1H), 3.40 (m, 1H), 3.03 (m, 1H), 2.66 (dd, *J* = 9.9 and 2.7 Hz, 1H), 2.15 (m, 1H) (signals due to OH group protons not observed due to H/D exchange); $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD, APT) δ 134.9 (CH), 133.9 (C), 133.1 (CH), 127.2 (CH), 76.6 (CH), 75.7 (C), 73.6 (CH), 72.0 (CH), 71.4 (CH), 45.8 (CH). 40.9 (CH), 38.4 (CH); IR ν_{max} (KBr) 3353, 2916, 1649, 1401, 1256, 1123, 1040, 996, 898, 835, 706 cm^{-1}; MS (EI, 70 eV) *m/z* 294 and 292 ($M^{+\bullet}$, <1 and 1%), 181 and 179 (20 and 60), 146 and 144 (50 and 100), 115 (50); HRMS (EI, 70 eV): calcd for $C_{12}H_{14}{}^{35}Cl_2O_4$ ($M^{+\bullet}$) 292.0269; found 292.0278. Anal. Calcd for $C_{12}H_{14}Cl_2O_4$ C, 49.17; H, 4.81. Found C, 48.84; H, 4.93%.

On conducting out the above-mentioned reaction with diol **5** (X=Cl) alone then dimer **33** was obtained in 26% yield.

(3a*S*,4*S*,7*R*,7a*S*,8*S*,9*R*)-8,9-dihydroxy-4-methyl-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1,3-dione (35). A solution of diene **5** (X=Me) (300 mg, 2.37 mmol) and maleic anhydride (**34**) (465 mg, 4.74 mol) in dichloromethane (1 mL) was subjected to 19 kbar pressure at ambient temperatures for 24 h. The crude reaction mixture was subjected to flash chromatography (silica, 1:1 → 7:3 v/v ethyl acetate/40-60 petroleum ether gradient elution) to afford, after concentration of the relevant fractions (R_f = 0.6 in 7:3 v/v ethyl acetate/40-60 petroleum ether), compound **35** (256 mg, 48%) as a white, crystalline solid, m.p. = 161-163 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 6.22 (apt. t, *J* = 8.4 Hz, 1H), 5.98 (d, *J* = 8.4 Hz, 1H), 3.75 (dd, *J* = 8.7 and 3.6 Hz, 1H), 3.62 (dd, *J* = 8.7 and 3.3 Hz, 1H), 3.35-3.25 (complex m, 2H), 3.17 (m, 1H), 1.52 (s, 3H) (signals due to OH group protons not observed due to H/D exchange); ^{13}C{^{1}H} NMR (75 MHz, CD_3OD, APT) δ 176.2 (C), 175.0 (C), 139.1 (CH), 132.4 (CH), 69.6 (CH), 65.2 (CH), 44.6 (CH), 43.5 (C), 41.5 (CH), 41.3 (CH), 19.8 (CH_3); IR ν_{max} (KBr) 3349, 2969, 1837, 1773, 1389, 1236, 1136, 1080, 1025, 929, 778, 703 cm^{-1}; MS (EI, 70 eV) *m/z* 224 ($M^{+\bullet}$, <1%), 206 [$(M - H_2O)^{+\bullet}$, 1%), 138 (96), 137 (67), 94 (78), 93 (63), 92 (100), 91 (90), 62 (83), 61 (88); HRMS (EI, 70 eV): calcd for $C_{11}H_{10}O_4$ [$(M - H_2O)^{+\bullet}$] 206.0579; found 206.0581. Anal. Calcd for $C_{11}H_{12}O_5$ C, 58.93; H, 5.39. Found C, 58.87; H, 5.23%.

(3a*S*,4*S*,7*R*,7a*S*,8*S*,9*R*)-8,9-dihydroxy-2,2,4-trimethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-ethano-indene-1,3(2*H*)-dione (37) and (3a*R*,4*R*,7*S*,7a*R*,8*S*,9*R*)-8,9-dihydroxy-2,2,4-trimethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-ethanoindene-1,3(2*H*)-dione (38). A solution of diol **5** (X=Me) (1.01 g, 8.0 mmol) and 2,2-dimethyl-4-cyclopenten-1,3-dione (**36**) (2.00 g, 16.2 mmol) in dichloromethane (9 mL) was subjected to 19 kbar pressure at ambient temperatures for 24 h. The ensuing reaction mixture, a brown oil, was subjected to flash chromatography

(silica, 3:7 → 4:1 v/v ethyl acetate/hexane gradient elution) and so affording two fractions, A and B.

Concentration of fraction A (R_f = 0.2 in 1:1 v/v ethyl acetate/hexane, phosphomolybdic acid visualisation) gave the *syn*-adduct **37**[9a] (1.47 g, 73%) as a white, crystalline solid, m.p. = 119-121˚C, $[\alpha]_D$ = +34 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (dd, *J* = 8.4 and 6.3 Hz, 1H), 5.83 (dd, *J* = 8.4 and 1.2 Hz, 1H), 3.77 (dd, *J* = 9.0 and 3.6 Hz, 1H), 3.70 – 3.34 (broad, 2H), 3.51 (dd, *J* = 10.2 and 3.0 Hz, 1H), 3.29 (d, *J* = 8.7 Hz, 1H), 3.30 – 3.26 (partially obscured m, 1H), 3.21 (d, *J* = 10.2 Hz, 1H), 1.58 (s, 3H), 1.06 (s, 3H), 0.92 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, APT) δ 220.8 (C), 219.7 (C), 138.7 (CH), 131.5 (CH), 69.9 (CH), 64.9 (CH), 54.7 (C), 47.6 (CH), 45.0 (CH), 42.8 (C), 39.8 (CH), 23.5 (CH_3), 20.3 (CH_3), 16.8 (CH_3); IR ν_{max} 3442, 2970, 2930, 2874, 1757, 1718, 1462, 1379, 1360, 1286, 1204, 1143, 1113, 1051, 1021, 701 cm^{-1}; MS (EI, 70 eV) *m/z* 250 ($M^{+\bullet}$, 8%), 190 {[M – (HOCHCHOH)]$^{+\bullet}$, 59}, 162 (4), 119 (14), 105 (10), 91 (23), 70 (100); HRMS (EI, 70 eV): calcd for $C_{11}H_{10}O_4$ ($M^{+\bullet}$) 250.1205; found 250.1203. Anal. Calcd for $C_{14}H_{18}O_4$ C, 67.18; H, 7.25. Found C, 66.79; H, 6.93%.

Concentration of fraction B (R_f 0.1 in 1:1 v/v ethyl acetate–hexane, phosphomolybdic acid visualisation) gave the *anti*-adduct **38** (190 mg, 9%) as a white, crystalline solid, m.p. = 124-125˚C, $[\alpha]_D$ = –2 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (t, *J* = ~8.4 Hz, 1H), 5.87 (d, *J* = 8.4 Hz, 1H), 4.04 (m, 1H), 3.54 (d, *J* = 7.5 Hz, 1H), 3.42-3.38 (complex m, 1H), 3.24-2.76 (broad s, 2H), 3.02 (dd, *J* = 10.2 and 3.0 Hz, 1H), 2.65 (d, *J* = 10.2 Hz, 1H), 1.61 (s, 3H), 1.03 (s, 3H), 0.93 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, APT) δ 217.8 (C), 216.8 (C), 137.0 (CH), 131.1 (CH), 74.0 (CH), 69.8 (CH), 54.4 (C), 51.4 (CH), 48.2 (CH), 43.1 (C), 39.1 (CH), 23.4 (CH_3), 19.3 (CH_3), 17.0 (CH_3); IR ν_{max} 3494, 2987, 2954, 2937, 2889, 1715, 1453, 1408, 1374, 1334, 1286, 1199, 1143, 1123, 1081, 1055, 1010, 1029, 829,

732 cm^{-1}; MS (EI, 70 eV) *m/z* 250 ($M^{+\bullet}$, 1%), 190 {[M – (HOCHCHOH)]$^{+\bullet}$, 81}, 119 (13), 91 (11), 70 (100); HRMS (EI, 70 eV): calcd for $C_{14}H_{18}O_4$ ($M^{+\bullet}$) 250.1205; found 250.1205. Anal. Calcd for $C_{14}H_{18}O_4$ C, 67.18; H, 7.25. Found C, 67.22; H, 6.99%.

(3a*S*,4*S*,7*R*,7a*S*,8*S*,9*R*)-8,9-dihydroxy-2,2,4-trimethyl-1,2,3a,4,7,7a-hexahydro-3*H*-4,7-ethanoinden-3-one (40). *Method A*: A solution of diene **5** (X=Me) (100 mg, 0.79 mmol) and 5,5-dimethyl-2-cyclopentenone (**39**) (178 mg, 1.62 mol) in dichloromethane (1 mL) was subjected to 19 kbar pressure at ambient temperatures for 24 h. The crude reaction product, a brown oil, was subjected to flash chromatography (silica, 1:1 → 1:0 v/v ethyl acetate/hexane gradient elution) and so affording two fractions, A and B.

Concentration of fraction A (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane) gave the compound **40** (2 mg, 2% at 49% conversion) as a white, crystalline solid, m.p. = 80-82˚C, $[\alpha]_D$ = –96 (*c* = 0.04, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (t, *J* = 8.5 Hz, 1H), 5.87 (d, *J* = 8.5 Hz, 1H), 3.78 (m, 1H), 3.26 (dd, *J* = 9.0 and 5.0 Hz, 1H), 3.01 (m, 1H), 2.85 (d, *J* = 4.5 Hz, 1H), 2.77-2.74 (complex m, 2H), 2.72 (d, *J* = 5.0 Hz, 1H), 1.87 (dd, *J* = 13.0 and 9.0 Hz, 1H), 1.55 (s, 3H), 1.26 (dd, *J* = 13.0 and 9.0 Hz, 1H), 1.00 (s, 3H), 0.91 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz) δ 224.3 (C), 138.8 (CH), 131.9 (CH), 71.0 (CH), 66.0 (CH), 46.7 (CH), 46.1 (C), 42.6 (CH), 42.2 (C), 40.7 (CH_2), 29.0 (CH), 26.7 (CH_3), 22.5 (CH_3), 19.6 (CH_3); IR ν_{max} 3401, 2961, 2928, 2868, 1732, 1454, 1381, 1364, 1274, 1251, 1112, 1054, 1008, 937, 897, 833, 733, 704 cm^{-1}; MS (EI, 70 eV) *m/z* 236 ($M^{+\bullet}$, 3%), 218 {[M – H_2O]$^{+\bullet}$, 1%}, 176 {[M – (HOCHCHOH)]$^{+\bullet}$, 100}, 161 (20), 148 (26), 133 (17), 119 (10), 105 (60), 92 (77), 91(28) 77 (28), 56 (32); HRMS (EI, 70 eV): calcd for $C_{14}H_{20}O_3$ ($M^{+\bullet}$) 236.1412; found 236.1405. Anal. Calcd for $C_{14}H_{20}O_3$ C, 71.16; H, 8.53. Found C, 71.22; H, 8.76%.

Concentration of fraction B gave diene **5** (X=Me) (51 mg, 51% recovery) as a white, crystalline solid that was identical, in all respects, with an authentic sample.

Method B: A solution of (3a*R*,4*S*,4a*S*,7a*S*,8*R*,8a*S*)-2,2,4,6,6-pentamethyl-3a,4,4a,6,7,7a,8,8a-octahydro-5*H*-4,8-ethenoindeno[5,6-*d*][1,3]dioxol-5-one[9a] (8.6 mg, 0.03 mmol) dissolved in THF (2.5 mL) was treated with aqueous HCl (2.5 mL of a 2 mol/L solution in water, 5.00 mmol) and the ensuing mixture allowed to stand at ambient temperatures for 20 h. After this time, the reaction mixture was concentrated under reduced pressure and the resulting light-yellow oil subjected to flash chromatography (silica, 3:7 → 1:1 v/v ethyl acetate/hexane gradient elution) and thereby affording two fractions, A and B.

Concentration of fraction A (R_f = 0.7 in 1:1 v/v ethyl acetate/hexane) gave a white, crystalline solid (0.3 mg, 3% recovery) that proved identical, in all respects, with the starting material.

Concentration of fraction B (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane) gave compound **40** (6.2 mg, 87% at 97% conversion) a white, crystalline solid. This material was identical, in all respects, with that obtained by Method A.

(3a*R*,5a*R*,6*R*,9a*S*,10*S*,10a*S*,10b*S*)-2,2,8,8-tetramethyl-3a,6a,9a,10,10a,10b-hexahydro-6,10-ethenonaphtho[1,2-*d*:6,7-*d'*]bis([1,3]dioxole)-4,6(5a*H*)-dicarbonitrile (42). A solution of diene **9** (X=CN) (500 mg, 2.82 mmol) and 2,3-dihydrofuran (**41**) (426 mg, 5.64 mmol) in dichloromethane (1 mL) was placed in a Teflon® high-pressure reaction vessel under a nitrogen atmosphere and subsequently subjected to 19 kbar pressure at ambient temperature for 24 h. The system was then restored to atmospheric pressure and concentrated under reduced pressure. The resulting white solid was suspended in diethyl ether and the ensuing mixture filtered and the solid thus retained washed with diethyl ether then 40-60 petroleum ether to give, after drying, compound **42**[13b] (437 mg, 87%). A sample of this material was recrystallized (chloroform/hexane) to afford an analytically pure sample of dimer **42** as clear, colorless crystals, m.p. = 225-230 °C (lit.[13b] m.p.= 211 °C), $[\alpha]_D$ = +76 (*c* 0.6,

CH_3OH) (R_f = 0.7 in 1:1 v/v ethyl acetate/40-60 petroleum ether). ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (m, 1H), 6.13 (dd, *J* = 8.2 and 6.5 Hz, 1H), 6.00 (d, *J* = 8.2 Hz, 1H), 4.43 (m, 2H), 4.23-4.17 (complex m, 2H), 3.04 (m, 1H), 2.84 (m, 1H), 2.42 (d, *J* = 8.8 Hz, 1H), 1.40 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, APT) δ 141.3 (CH), 131.0 (CH), 129.1 (CH), 120.1 (C), 117.6 (C), 116.9 (C), 111.1 (C), 109.8 (C), 79.7 (CH), 77.9 (CH), 76.7 (CH), 69.2 (CH), 44.1 (C), 39.5 (CH), 37.9 (CH), 33.1 (CH), 28.1 (CH_3), 26.7 (CH_3), 25.5 (CH_3), 25.3 (CH_3); IR ν_{max} (KBr) 2987, 2936, 2905, 2251, 2221, 1382, 1373, 1241, 1225, 1210, 1074, 917, 876, 729 cm^{-1}; MS (EI, 70 eV) *m/z* 354 ($M^{+\bullet}$, 1%), 339 (90), 281 (100), 238 (51), 221 (80), 209 (54), 193 (56), 120 (72%), 100 (85); HRMS (EI, 70 eV): calcd for $C_{20}H_{22}N_2O_4$ ($M^{+\bullet}$) 354.1580; found 354.1580. Anal. Calcd for $C_{20}H_{22}N_2O_4$ C, 67.78; H, 6.26; N, 7.90. Found C, 67.96; H, 6.52; N, 8.22%.

Crystallographic Studies. *Crystallographic Data for Compound **13***. $C_{11}H_{14}O_4$, *M* = 210.23, *T* = 296 K, monoclinic, space group $P2_1$, *Z* = 2, *a* = 7.9645(8) Å, *b* = 7.661(1) Å, *c* = 8.4030(7) Å; β = 101.737(7)°; *V* = 501.98 (9) $Å^3$, D_x = 1.391 Mg m^{-3}, 816 unique data ($2\theta_{max}$ = 120.14°), *R* = 0.036 [for 773 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.048 (all data), *S* = 2.024.

*Crystallographic Data for Compound **18***. $C_{12}H_{16}O_3$, *M* = 208.26, *T* = 298 K, orthorhombic, space group $P2_12_12_1$, *Z* = 4, *a* = 8.061(1) Å, *b* = 9.4760(7) Å, *c* = 13.8309(9) Å; *V* = 1056.5(2) $Å^3$, D_x = 1.309 Mg m^{-3}, 923 unique data ($2\theta_{max}$ = 119.8°), *R* = 0.038 [for 890 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.053 (all data), *S* = 1.919.

*Crystallographic Data for Compound **21***. $C_{15}H_{20}O_3$, *M* = 248.31, *T* = 200 K, orthorhombic, space group $P2_12_12_1$, *Z* = 4, *a* = 7.6438 (1) Å, *b* = 8.6599(2) Å, *c* = 19.9512(3) Å; *V* = 1320.66(4) $Å^3$, D_x = 1.249 Mg m^{-3}, 1736 unique data ($2\theta_{max}$ = 55.032°), *R* = 0.0316 [for 1487 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.0385 (all data), *S* = 0.910.

Crystallographic Data for Compound ***28***. $C_{18}H_{32}O_4Si$, M = 340.54, T = 200 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 6.2032(6) Å, b = 9.3477(10) Å, c = 34.405(4) Å; V = 1995.0(4) Å^3, D_x = 1.134 Mg m^{-3}, 2625 unique data ($2\theta_{max}$ = 55.8°), R = 0.034 [for 1469 reflections with $I > 3.0\sigma(I)$]; Rw = 0.051 (all data), S = 1.06.

Crystallographic Data for Alcohol Arising from Desilylation of Compound ***30***. $C_{12}H_{18}O_4$, M = 226.26, T = 200 K, orthorhombic, space group $C222_1$, Z = 8, a = 8.5915(2) Å, b = 11.1420(2) Å, c = 23.4743(4) Å; V = 2247.11(8) Å^3, D_x = 1.338 Mg m^{-3}, 1470 unique data ($2\theta_{max}$ = 54.934°), R = 0.0332 [for 1263 reflections with $I > 2.0\sigma(I)$]; Rw = 0.0387 (all data), S = 1.077.

Crystallographic Data for Compound ***37***. $C_{14}H_{18}O_4$, M = 250.28, T = 200 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 8.8953(2) Å, b = 10.5661(3) Å, c = 13.6736(3) Å; V = 1285.16(5) Å^3, D_x = 1.294 Mg m^{-3}, 1700 unique data ($2\theta_{max}$ = 54.944°), R = 0.0290 [for 1344 reflections with $I > 2.0\sigma(I)$]; Rw = 0.0400 (all data), S = 1.095.

Crystallographic Data for Compound ***38***. $C_{14}H_{18}O_4$, M = 250.28, T = 200 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 8.7557(3) Å, b = 8.9604(3) Å, c = 15.5281(6) Å; V = 1218.25(7) Å^3, D_x = 1.365 Mg m^{-3}, 1625 unique data ($2\theta_{max}$ = 54.948°), R = 0.0284 [for 1289 reflections with $I > 2.0\sigma(I)$]; Rw = 0.0366 (all data), S = 1.146.

Crystallographic Data for Compound ***42***. $C_{20}H_{22}N_2O_4$, M = 354.40, T = 200 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 8.4308(2) Å, b = 8.6710(2) Å, c = 25.4210(7) Å; V = 1858.36(8) Å^3, D_x = 1.267 Mg m^{-3}, 2425 unique data ($2\theta_{max}$ = 54.934°), R = 0.0323 [for 1907 reflections with $I > 2.0\sigma(I)$]; Rw = 0.0387 (all data), S = 1.136.

Structure Determination. Images for all compounds were recorded on a Nonius CCD diffractometer (Mo Kα, graphite monochromator, λ = 0.71073 Å) and data extracted using the DENZO package.[28] Structure solution was by direct methods (SIR97)[29] and refinement was by full matrix least-squares on F using the CRYSTALS program package.[30] Atomic co-ordinates, bond lengths and angles, an

displacement parameters have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication numbers 2011871, 2011873-2011878 and 2018805. Copies of the data can be obtained, free-of-charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (e-mail: deposit@ccdc.ac.uk).

THEORETICAL STUDIES

Methodologies. Geometries optimizations and frequency calculations were calculated at the M062X/6-31+G(d) level of theory[31] in the gas phase. The M062X method has been found to accurately reproduce experimental trends in the reactivity and selectivity of Diels-Alder reactions.[3,32] All the geometries were verified either as local minima (possessing no imaginary frequencies) or transition states (possessing only one imaginary frequency) which were confirmed via intrinsic reaction coordinate (IRC) calculations.[33] Entropies, thermal corrections, and zero-point vibrational energies were scaled using the recommended scaling factors.[34] The PCM solvent model was used to correct for implicit solvent effects in dichloromethane based on the gas phase geometries. The effects of high-pressure were evaluated using the XP-PCM protocol.[20,21] As an extension of the basic polarizable continuum model (PCM),[35] which deals with solvation energy of molecules at standard pressure, the XP-PCM protocol aims to introduce, explicitly, the effect of pressure into quantum chemical calculations. Cyclohexane has been used as the external medium (ε_0=2.0165, ρ=0.78 g/cm^3), at standard thermodynamic conditions as, at the present time, there are only a limited number of external media parametrized in the XP-PCM protocol. All standard density functional theory (DFT) calculations and XP-PCM calculations were carried out using the Gaussian 16 software package.[36]

ASSOCIATED CONTENT

Supporting Information.

The Supporting information is available free-of-charge at https://pubs.acs.org/doi/10.1021/acs.jocXXXXX.

Synthetic schemes and procedures for preparing dienophiles **26** and **29**; plots derived from the X-ray analyses of compounds **13**, **18**, **21**, **28**, alcohol derived from the desilylation of ether **30**, **37**, **38** and **42**; ^{1}H and ^{13}C NMR spectra of compounds **13-16**, **18**, **19**, **21**, **23-33**, **35**, **37**, **38**, **40** and **42** as well as those of the synthetic precursors to dienophiles **26** and **29**; raw computational data and xyz coordinates of all optimized geometries in the gas phase. CCDC depositions 2011871, 2011873-2011878 and 2018805 contain the supplementary crystallographic data for this paper. These data can be obtained free-of-charge via www.ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: + 44 1223 336033.

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The manuscript was written through contributions from all of the authors. All of the authors

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Notes

The authors declare no competing financial interest.

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REFERENCES

1. For useful points of entry into the literature on this topic, see: (a) Macaulay, J. B.; Fallis, A. G. π-Facial Selectivity: Heteroatom Directed Syn/Anti Stereoselection in Diels-Alder Cycloadditions of Plane-Nonsymmetric Cyclopentadienes. *J. Am. Chem. Soc*. **1988**, *110*, 4074-4076; (b) Mehta, G.; Uma, R. Stereoelectronic Control in Diels-Alder Reaction of Dissymmetric 1,3-Dienes. *Acc. Chem. Res*. **2000**, *33*, 278-286; (c) Ishida, M.; Inagaki, S. π-Facial Selectivity of Diels-Alder Reactions. *Top. Curr. Chem*. **2009**, *289*, 183-219; (d) Liu, P.-Y.; Wu, Y.-J.; Pye, C. C.; Thornton, P. D.; Poirier, R. A.; Burnell, D. J. Facial Selectivity in the Diels-Alder Reactions of 2,2-Disubstituted Cyclopent-4-ene-1,3-dione Derivatives and a Computational Examination of the Facial Selectivity of the Diels-Alder Reactions of Structurally Related Dienes and Dienophiles. *Eur. J. Org. Chem*.

2012, 1186-1194; (e) Levandowski, B. J.; Herath, D.; Gallup, N. M.; Houk, K. N. Origins of π-Facial Stereoselectivity in Thiophene 1-Oxide Cycloadditions. *J. Org. Chem*. **2018**, *83*, 2611-2616.

2. Winstein, S.; Shatavsky, M.; Norton, C.; Woodward, R. B. 7-Norbornenyl and 7-Norbornyl Cations. *J. Am. Chem. Soc*. **1955**, *77*, 4183-4184.

3. Levandowski, B. J.; Zou, L.; Houk, K. N. Hyperconjugative Aromaticity and Antiaromaticity Control the Reactivities and π-Facial Stereoselectivities of 5-Substituted Cyclopentadiene Diels-Alder Cycloadditions. *J. Org. Chem*. **2018**, *83*, 14658-14666 and references cited therein.

4. Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. Total Synthesis, Relay Synthesis, and Structural Confirmation of the C18-Norditerpenoid Alkaloid Neofinaconitine. *J. Am. Chem. Soc*. **2013**, *135*, 14313-14320.

5. For a useful point of entry into the literature on arene hydrates and related systems, see: Boyd, D. R.; Sharma, N. D.; Ljubez, V.; McGeehin, P. K. M.; Stevenson, P. J.; Blain, M.; Allen, C. C. R. Chemoenzymatic synthesis of monocyclic arene oxides and arene hydrates from substituted benzene substrates. *Org. Biomol. Chem*. **2013**, *11*, 3020-3029.

6. Levandowski, B. J.; Houk, K. N. Theoretical Analysis of Reactivity Patterns in Diels-Alder Reactions of Cyclopentadiene, Cyclohexadiene, and Cycloheptadiene with Symmetrical and Unsymmetrical Dienophiles. *J. Org. Chem*. **2015**, *80*, 3530-3537.

7. For recent reviews on the microbial production and the chemical utilization of *cis*-1,2-dihydrocatechols see: (a) Lewis, S. E., Asymmetric Desymmetrization under Enzymatic Conditions. In *Asymmetric Desymmetrization Reactions*; You, S.-L., Ed.; Wiley VCH Verlag GmbH & Co. KGaA.: Weinheim, 2016; (b) Hudlicky, S. E. Benefits of Unconventional Methods in the Total Synthesis of Natural Products. *ACS Omega* **2018**, *3*, 17326-17340; (c) Lan, P.; Ye, S.; Banwell, M. G. The Application of Dioxygenase-Based Chemoenzymatic Processes to the Total Synthesis of Natural Products. *Chem. Asian J*. **2019**, *14*, 4001-4012.

8. Grimblat, N.; Sarotti, A. M. Looking at the big picture in activation strain/energy decomposition analysis: the case of the *ortho-para* regioselectivity rule in Diels-Alder reactions. *Org. Biomol. Chem*. **2020**, *18*, 1104-1111 and references cited therein.

9. (a) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A. A chemoenzymatic synthesis of the linear triquinane (–)-hirsutene and identification of possible precursors to the naturally occurring (+)-enantiomer. *Tetrahedron*, **2004**, *60*, 535-547; (b) Dietinger, C. E.; Banwell, M. G.; Garson, M. J. and Willis, A. C. Chemoenzymatic and Enantioselective Assembly of the (1 -Octahydro-1,6-methano-1*H*-indene Framework Associated with 2-Isocyano-allopupukeanane: Validation of a New Synthetic Strategy and the Identification of Enantiomeric Switching Regimes. *Tetrahedron*, **2010**, *66*, 5250–5261; (c) Austin, K. A. B.; Elsworth, J. D.; Banwell, M. G.; Willis, A. C. Chemoenzymatic and enantiodivergent routes to 1,2-ring-fused bicyclo[2.2.2]octanone and related tricyclic frameworks. *Org. Biomol. Chem*. **2010**, *8*, 751-754.

10. (a) Kobal, V. M.; Gibson, D. T.; Davis, R. E.; Garza, A. X-Ray Determination of the Absolute Stereochemistry of the Initial Oxidation Product Formed from Toluene by *Pseudomonas putida* 39/D. *J. Am. Chem. Soc*., **1973**, *95*, 4420-4421; (b) Gibson, D. T.; Gschwendt, B.; Yeh, W. K.; Kobal, V. M. Initial Reactions in the Oxidation of Ethylbenzene by *Pseudomonas putida*. *Biochem*. **1973**, *12*, 1520-1528; (c) Cotterill, I. C.; Roberts, S. M.; Williams, J. O. Diels-Alder Reactions involving *cis*-1,2-Isopropylidenedioxycyclohexa-3,5-diene and Enzymatic Resolution of One of the Adducts. *J. Chem. Soc., Chem. Commun*. **1988**, 1628-1629.

11. (a) Gillard, J. R.; Burnell, D. J., Facial Selectivity in the Diels-Alder Reactions of *cis*-Cyclohexa-3,5-diene-1,2-diol and Derivatives with *N*-Phenylmaleimide. *J. Chem. Soc., Chem. Commun*. **1989**, 1439-1440; (b) Ogbomo, S. M.; Burnell, D. J. *cis*-3,5-Cyclohexadiene-1,2-diol derivatives: facial selectivity in their Diels-Alder reactions with ethylenic, acetylenic and azo dienophiles. *Org. Biomol. Chem*. **2006**, *4*, 3838-3848.

12. (a) Pilgrim, S.; Kociok-Köhn, G.; Lloyd, M. D.; Lewis, S. E. “Inosaminoacids”: novel inositol-amino acid hybrid structures accessed by microbial arene oxidation. *Chem. Commun*. **2011**, *47*, 4799-4801; (b) Griffen, J. A.; White, J. C.; Kociok-Köhn, G.; Lloyd, M. D.; Wells, A.; Arnot, T. C.; Lewis, S. E. New aminocyclitols with quaternary stereocentres via acylnitroso cycloaddition with an *ipso*, *ortho* arene dihydrodiol. *Tetrahedron* **2013**, *69*, 5989-5997; (c) Pazos, M.; Martínez, S.; Vila, M. A.; Rodríguez, P.; Veiga, N.; Seoane, G.; Carrera, I. Aza and oxo Diels-Alder reactions using *cis*-cyclohexadienediols of microbial origin: chemoenzymatic preparation of synthetically valuable heterocyclic scaffolds. *Tetrahedron: Asymm*. **2015**, *26*, 1436-1447.

13. (a) Hudlicky, T.; Boros, E. E.; Olivo, H. F.; Merola, J. S. Stereoselective Dimerization of Arene-*cis*-diol Acetonides Derived from the Oxidation of Halobenzenes by *Pseudomonas putida*: Absolute Configuration of the Adducts by X-ray Crystallography. *J. Org. Chem*. **1992**, *57*, 1026-1028; (b) Tran, C. H.; Crout, D. H. G.; Errington, W.; Whited, G. M. Synthesis of (–)-6-Hydroxyshikimic Acid from ((5*S*,6*R*)-5,6-Dihydroxy-1,3-cyclohexadienyl)methanenitrile. *Tetrahedron: Asymm*. **1996**, *7*, 691-698.

14. Baran, A.; Günel, A.; Balci, M. Synthesis of Bicyclo[2.2.2]octane-2,3,5,6,7,8-hexols (Bishomoinositols) as Glycoside Inhibitors. *J. Org. Chem*. **2008**, *73*, 4370-4375.

15. Boyd, D. R.; Balcker, J.; Dalton, H.; Kelly, S. C.; More O’Ferral, R. A.; Rao, A. N.; Sharma, N. D.; Sheldrake, G. N. *J. Chem. Soc., Chem. Commun*. **1994**, 313-314.

16. (a) Tietze, L. F.; Henrich, M.; Niklaus, A.; Buback, M. The Effect of High Pressure on the Diastereoselectivity of Intermolecular All-Carbon Diels-Alder Reactions. *Chem. Eur. J*. **1999**, *5*, 297-304 and references cited therein; (b) Rogachev, V., Metz, P. Thermal and high pressure intramolecular Diels–Alder reaction of vinylsulfonamides. *Nat. Protoc.* **2006**, *1*, 3076–3087.

17. Some preliminary aspects of our studies of this topic have been reported as parts of campaigns to establish total syntheses of natural products, see: (a) Banwell, M. G.; Edwards, A. J.; Harfoot, G.

J.; Jolliffe, K. A. A chemoenzymatic synthesis of (–)-hirsutene from toluene. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2439-2441; (b) Banwell, M. G.; Harfoot, G. J. A Chemoenzymatic and Enantioselective Route to the Tricyclic Frameworks Associated with the Protoilludane and Marasmane Classes of Sesquiterpene. *Aust. J. Chem*. **2004**, *57*, 895-897; (c) Banwell, M. G.; Edwards, A. J.; M. D.; Stewart, S. G. A Chemoenzymatic Synthesis of the *cis*-Decalin Core Associated with the Novel Anti-Mitotic Agent Phomopsidin: Some Observations Concerning a High-Pressure-Promoted Diels–Alder Cycloaddition Reaction of (1*S*,2*R*)-3-Methyl-*cis*-1,2-dihydrocatechol and the Anionic Oxy–Cope Rearrangement of Compounds Derived from the Adduct. *Aust. J. Chem.*, **2004**, *57*, 641–644; (d) Reekie, T. A.; Austin, K. A. B.; Banwell, M. G.; Willis, A. C. The Chemoenzymatic Total Synthesis of Phellodonic Acid, a Biologically Active and Highly Functionalized Hirsutene Derivative Isolated from the Tasmanian Fungus *Phellodon melaleucus*. *Aust. J. Chem*. **2008**, *61*, 94-106; (e) Bon, D. J.-Y. D.; Banwell, M. G.; Willis, A. C. A chemoenzymatic total synthesis of the hirsutene-type sesquiterpene (+)-connatusin B from toluene. *Tetrahedron*, **2010**, *66*, 7807-7814; (f) Schwartz, B. D.; Matousova, E.; White, R.; Banwell, M. G.; Willis, A. C. A Chemoenzymatic Total Synthesis of the Protoilludane Aryl Ester (±)-Armillarivin. *Org. Lett*. **2013**, *15*, 1934-2937.

18. Banwell, M. G.; Dupuche, J. R. Synthesis of enantiopure *cis*-decalins from microbially-derived *cis*-1,2-dihydrocatechols. *Chem. Comm*. **1996**, 869-870.

19. Pye, C. C.; Poirier, R. A.; Burnell, D. J.; Kalpstein, D. An ab initio study of 5,6-disubstituted 1,3-cyclohexadienes. *J. Mol. Structure: THEOCHEM*, **2009**, *909*, 66-74.

20. Chen, B.; Hoffmann, R.; Cammi, R. The effect of pressure on organic reactions in fluids – a new theoretical perspective. *Angew. Chem. Int. Ed.* **2017,** *56*, 11126-11142.

21. Cammi, R., A new extension of the polarizable continuum model: Toward a quantum chemical description of chemical reactions at extreme high pressure. *J. Comput. Chem*. **2015**, *36*, 2246-2259.

22. For selected examples of the exploitation of bicyclo[2.2.2]octenes in synthesis, see: (a) Minger, T. L.; Phillips, A. J. Ring-opening-ring-closing metathesis of bicyclo[2.2.2]octenes: a novel synthesis of decalins and hydrindanes. *Tetrahedron Lett*. **2002**, *43*, 5357-5359; (b) Liao, C.-C.; Peddinti, R. K. Masked *o*-Benzoquinones in Organic Synthesis. *Acc. Chem. Res*. **2002**, *35*, 856-866; (c) Hren, J.; Polanc, S.; Kocevar, M. The synthesis and transformations of fused bicyclco[2.2.2]octenes. ARKIVOC, **2008**, *(i)*, 209-231; (d) Kotha, S.; Pulletikurti, S. Synthesis of propellanes containing a bicyclo[2.2.2]octane unit *via* the Diels-Alder reaction and ring-closing metathesis as key steps. *RSC Adv*. **2018**, *8*, 14906-14915.

23. (a) Banwell, M. G.; Dupuche, J. R.; Gable, R. W. A Caveat Concerning Anionic Oxy-Cope Rearrangements within Bicyclo[2.2.2]octenyl Frameworks. *Aust. J. Chem*. **1996**, *49*, 639-645; (b) Banwell, M. G.; Austin, K. A. B.; Willis, A. C. Chemoenzymatic total syntheses of the linear triquinane-type natural products (+)-hirsutic acid and (–)-complicatic acid from toluene. *Tetrahedron*, **2007**, *63*, 6388-6403.

24. Sun, M.; Deng, Y.; Batyreva, E.; Sha, W.; Salomon, R. G. Novel Bioactive Phospholipids: Practical Total Syntheses of Products from the Oxidation of Arachidonic and Linoleic Esters of 2-Lysophosphatidylcholine. *J. Org. Chem*. **2002**, *67*, 3575-3584.

25. Sodeoka, M.; Yamada, H.; Shibasaki, M. A New Method for the Stereocontrolled Synthesis of Silyl Dienol Ethers Using (Naphthalene)chromium Tricarbonyl Catalyzed Isomerization. *J. Am. Chem. Soc.* **1990**, *112*, 4906-4911.

26. Song, L.; Yao, H.; Zhu, L.; Tong, R. Asymmetric Total Syntheses of (–)-Penicipyrone and (–)-Tenuipyrone via Biomimetic Cascade Intermolecular Michael Addition/Cycloketalization. *Org. Lett*. **2013**, *15*, 6-9.

27. Dischmann, M.; Frassetto, T.; Breuning, M. A.; Koert, U. Total Synthesis of Isoquinocyclinone. *Chem. Eur. J*. **2014**, *20*, 11300-11302.

28. Otwinowski, Z.; Minor, W. DENZO-SMN. Processing of X-ray diffraction data collected in oscillation mode. In *Methods in Enzymology. Macromolecular Crystallography, Part A*. Carter, C. W. Jr., Sweet R. M. Eds., Academic: New York, **1997**, Vol. *276*, pp. 307-326.

29. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *SIR*97: a new tool for crystal structure determination and refinement. *J. Appl. Crystallogr*. **1999**, *32*, 115-119.

30. Watkin, D. J.; Prout, C. K.; Carruthers, J. R.; Betteridge, P. W.; Cooper, R. I. CRYSTALS *Issue 11*: Chemical Crystallography Laboratory: Oxford, 2001.

31. Y. Zhao, D. G. Truhlar, The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovelant interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Account* **2008,** *120*, 215-241.

32. (a) Aragonès, A. C.; Haworth, N. L.; Darwish, N.; Ciampi, S.; Bloomfield, N. J.; Wallace, G. G.; Diez-Perez, I.; Coote, M. L., Electrostatic catalysis of a Diels–Alder reaction. *Nature* **2016,** *531*, 88; (b) Levandowski, B. J.; Hamlin, T. A.; Helgeson, R. C.; Bickelhaupt, F. M.; Houk, K., Origins of the *Endo* and *Exo* Selectivities in Cyclopropenone, Iminocyclopropene, and Triafulvene Diels–Alder Cycloadditions. *J. Org. Chem.* **2018,** *83*, 3164-3170; (c) Levandowski, B. J.; Hamlin, T. A.; Bickelhaupt, F. M.; Houk, K. Role of Orbital Interactions and Activation Strain (Distortion Energies) on Reactivities in the Normal

and Inverse Electron-Demand Cycloadditions of Strained and Unstrained Cycloalkenes. *J. Org. Chem* **2017,** *82*, 8668-8675; (d) Lan, Y.; Zou, L.; Cao, Y.; Houk, K., Computational Methods to Calculate Accurate Activation and Reaction Energies of 1,3-Dipolar Cycloadditions of 24 1,3-Dipoles. *J. Phys. Chem. A* **2011,** *115*, 13906-13920.

33. (a) Fukui, K. The Path of Chemical Reactions - The IRC Approach. *Acc. Chem. Res*. **1981**, *14* 363-68; (b) Hratchian, H. P.; Schlegel, H. B. in *Theory and Applications of Computational Chemistry: The First 40 Years*, Ed. Dykstra, C. E.; Frenking, G.; Kim, K. S.; Scuseria, G. Elsevier, Amsterdam, **2005**, 195-249.

34. Alecu, I.; Zheng, J.; Zhao, Y.; Truhlar, D. G. Computational Thermochemistry: Scale Factor Databases and Scale Factors for Vibrational Frquencies Obtained from Electronic Model Chemistries. *J. Chem. Theory Comput.* **2010,** *6*, 2872-2887.

35. Tomasi, J.; Mennucci, B.; Cammi, R. Quantum Mechanical Solvation Models. *Chem. Rev*. **2005**, *105*, 2999-3094.

36. Gaussian 16, Revision C.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H. *et al* Gaussian Inc., Wallingford CT, USA **2016**.