cis-3,5-Cyclohexadiene-1,2-diol derivatives: facial selectivity in their Diels–Alder reactions with ethylenic, acetylenic and azo dienophiles

Sunny M. Ogbomo\textsuperscript{a} and D. Jean Burnell*\textsuperscript{a,b}

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The Diels–Alder reactions of maleimide with the acetonide derivative (6a) of cis-3,5-cyclohexadiene-1,2-diol (1a) in various solvents showed facial selectivities ranging from 1 : 1 to 1 : 9. The same derivative 6a reacted in benzene with ethylenic dienophiles with generally modest facial selectivity, but acetylenic dienophiles added exclusively anti to the oxygen functions of 6a. Dimerization of cyclic acetics 6a and 7 was mainly, but for 6a not exclusively, by anti addition with respect to both the diene and the dienophile partners. Reactions of azo dienophiles with derivatives of 1a were predominantly by anti addition, but the diol itself (1a) gave the syn adduct as the major product.

Introduction

cis-3,5-Cyclohexadiene-1,2-diol 1a and its optically active variants 1b (Fig. 1) are available directly from aromatic precursors by the action of mutant strains of Pseudomonas putida.\textsuperscript{1,2} These cis-diols are now well established as compact, multifunctional starting materials,\textsuperscript{3} and there are many recent examples of their use in synthesis.\textsuperscript{4-10}

![Diene and Diol Structures](Image)

Fig. 1 The diene 1a with its 3-substituted analogue 1b and derivatives.

It is not surprising that the diols and their derivatives have served as Diels–Alder dienes in many instances. We assessed the facial selectivities of 1a and a number of diol-protected derivatives 2–8 in Diels–Alder reactions in chloroform with N-phenylmaleimide as the dienophile.\textsuperscript{11} What was most remarkable was that additions were very largely syn to the oxygen functions with 1a and with the noncyclic derivatives 2, 3 and 4a (from 88 : 12 with 4a up to exclusively syn with 2). This was corroborated recently by the reaction of 1a with a bromophenyl analog of N-phenylmaleimide,\textsuperscript{9} and, under high pressure, cyclic enones added to 1b (X = CH\textsubscript{3}) to provide the syn-addition products with isolated yields of approximately 70%.\textsuperscript{5,7,8} The reactions of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) with 1b (X = carbon and halogen) took place with at least 97% syn selectivity.\textsuperscript{12} Thus, the oxygen functions of 1a/b appear to impart a significant bias toward syn addition, just as syn addition is the preferred mode of reaction of some 5-heteroatom-substituted 1,3-cyclopentadienes.\textsuperscript{13-15} However, the structure of the adduct of a bromophenyl analog of PTAD with 4b (X = CH\textsubscript{3}) was determined by X-ray crystallography, and this was the anti adduct.\textsuperscript{16}

The facial selectivities in the additions of N-phenylmaleimide to the cyclic derivatives 6a, 7 and 8 ranged from 60 : 40, slightly favoring syn addition with 5 and 6a, to 4 : 96, strongly favoring anti addition with 8.\textsuperscript{14} It was postulated that these cyclic derivatives present steric interactions in the syn-transition state that cannot be avoided by conformational mobility of the protecting groups, so the cyclic protecting groups in 6a, 7 and 8 overcome the inherent tendency for syn addition. The result is that the anti-addition product either equals the amount of the syn adduct, or predominates.

The acetonide (6a/b) has been the derivative of 1a/b that has been utilized far more than any other. Experiments with 6a and 6b (X = alkyl, 7-norbornadienyl, CF\textsubscript{3}, and halogens) and N-phenyl- and N-ethylmaleimide resulted in additions with low facial selectivities,\textsuperscript{11,17-20} with the ratios being somewhat dependent on the solvent.\textsuperscript{19,20} However, for the reactions of 6b (X = carbon) with maleic anhydride, a dienophile that with 5-alkyl- and 5-halogen-substituted 1,3-cyclopentadienes was closely related to the maleimides in terms of reactivity and facial selectivity,\textsuperscript{14,21} only anti-addition products were reported,\textsuperscript{22,23} and the additions of substituted maleic anhydride derivatives to 6a gave the anti-addition products in roughly 75% yield.\textsuperscript{5} Quinones are also closely related to maleimides in terms of their Diels–Alder behavior,\textsuperscript{14,21} so it is curious that the reactions of benzoquinone...
and naphthoquinone with 6b (X = Cl, Br) gave only the anti adducts, although the yields were reported to be modest.\textsuperscript{23–25} All other reactions of 6b (X = carbon, halogens) with carbon-based dienophiles provided anti-addition products only.\textsuperscript{6b,17–20,24,26} Reactions of 6a and 6b (X = CF\textsubscript{3}, 7-norbornadienyl, halogen) with PTAD and with nitroso compounds gave the anti adducts exclusively.\textsuperscript{17,18,20,24,26,27} Also, addition of singlet oxygen to 6b (X = Cl) was only via anti addition.\textsuperscript{28}

The epoxide compound 9 has some similarity to 1a, and its Diels–Alder reaction with \(N\)-phenylmaleimide took place exclusively anti to the oxygen.\textsuperscript{29} The same facial preference was reported for the addition of PTAD to 9.\textsuperscript{30} Calculations pointed to steric hindrance as the controlling factor.\textsuperscript{31}

In spite of the number of examples of Diels–Alder reactions of 1a and 1b in the literature, explanations for the facial selectivities are still lacking. The major drawback of using the published data for the development of hypotheses is that in most instances it appears that only the major adduct was isolated and characterized. Yields of less than 70\% are not uncommon—some are even less than 50\%—and so it is not known if the reactions of 1a/b are really highly facially selective with some important dienophiles. Therefore we undertook a reexamination of the facial selectivity in the Diels–Alder reactions of diol 1a and some of its derivatives. First, the acetonide 6a was reacted with a series of carbon-based dienophiles to determine if the maleimides are truly different from other dienophiles in that only they have been reported to have low facial selectivities. Second, 1a and a number of derivatives were reacted with azo-dienophiles in order to confirm whether large differences exist in facial selectivity between 1a and the derivatives. Our results are presented here.

### Results and discussion

#### The acetonide 6a with carbon-based dienophiles

The acetonide 6a was prepared from 10 by acetonization and double-elimination with base. The diol 10 had been synthesized from 1,4-cyclohexadiene (Scheme 1) by a previously described method.\textsuperscript{11}

![Scheme 1 Preparation of acetonide 6a.](image)

The reactant pair of diene 6a and maleimide provided an opportunity to assess the influence of the solvent on facial selectivity, because both addends might be expected to associate significantly with polar solvents. To the best of our knowledge, only three similar studies have been reported.\textsuperscript{11,19,32} The reactions of 6a with maleimide were carried out at room temperature in a variety of solvents (Table 1). In every instance two adducts (11 and 12, in Fig. 2) were obtained, in combined yields of over 80\%. As in all of the work described here, the relative amounts of the adducts were determined by careful integration of the well-dispersed signals for the olefinic hydrogens in the \(^1H\) NMR spectra of the reaction mixtures. (In this, and most subsequent reactions, the adducts were separable by flash chromatography, and the stereochemistry of each adduct was determined by measurement of NOE enhancements.)

The results in Table 1 show a much greater range of facial selectivities than the previous studies, from essentially no facial selectivity up to a 1 : 9 ratio. Whereas the three previous studies all used oxygen-substituted dienes (1a,\textsuperscript{11} 6a\textsuperscript{19} and 5-[(hydroxyimino)methyl]-1,2,3,4,5-pentamethylocyclopentadiene\textsuperscript{15}), in this work the dienophile bore an acidic hydrogen (in contrast with \(N\)-ethyl- and \(N\)-phenylmaleimide\textsuperscript{11,19,32}). The anti-addition product was generally more favored by a high solvent dielectric. (In Table 1, the solvents from benzene to water are given...
in the order of increasing dielectric constant.) Addition of salts (LiCl and LiClO₄) to the water resulted in slightly reduced facial selectivities. The facial selectivity in a solution of LiClO₄ in diethyl ether was better than in just diethyl ether. Thus, synthetically it would be advisable to use a solvent of high dielectric constant to maximize the yield of an anti adduct.

The facial selectivities of the reactions of N-methyl-, N-ethyl, and N-phenylmaleimide with 6a (leading to products 13–18) were similar to that of maleimide, i.e., low, when all the reactions were conducted in benzene (Table 2). The facial selectivity in the reaction of the unsymmetrical diol 1b (X = CF₃) with N-ethylmaleimide was consistent with the reactions of 1a: the ratio was 48 : 53 slightly favoring the anti adduct.¹⁸

Reactions of 6a with a number of additional carbon-based, ethylenic dienophiles were conducted in benzene (Table 2). Like maleimide, maleic anhydride, p-benzoquinone, and dimethyl maleate reacted with low facial selectivities, at best approximately 1 : 2, in favor of the anti adducts. The two adducts from the reaction of the quinone behaved very differently upon purification on silica. The syn adduct 21 was isolated in a straightforward way, but the anti adduct 22, while evident by ¹H NMR in the crude product mixture, was obtained as the aromatized compound 23. The unsymmetrical dienophile 3-buten-2-one was modestly more facially selective than maleimide, producing (endo) adducts in a ratio of 1 : 4 in favor of the anti adduct. In addition to the two endo adducts, the reaction with 3-buten-2-one yielded a small proportion of the anti-exo adduct 28. It was surprising that vinylene carbonate, which reacted sluggishly with 6a, produced adducts in a ratio of 4 : 1 in favor of the syn adduct. The reason for this difference in facial preference is not obvious.

Overall, none of these ethylenic dienophiles gave only one adduct with 6a. The many results for 6b suggest that it reacts with much higher facial selectivity than does 6a. A possible explanation is that an interaction between the annular substituent and the closer oxygen of 6b makes the difference in transition state energies of the syn and anti transition states larger with 6b than with 6a. The torsional angle from the annular substituent to the closer oxygen of 6b is very close to 60°. In the syn transition state, this angle would be compressed, whereas in the anti transition state this angle would become larger. While angular changes at the transition states would be similar with 6a, the size of a hydrogen on 6a, versus the substituent on 6b, would make the consequence of the angular change less pronounced.

Tetracyanoethylene presents sterically hindering carbon substituents in both the endo and exo regions of the Diels–Alder transition state. Thus, it would be reasonable to expect a significant barrier to syn addition with this dienophile,¹⁴,²¹ and, indeed, only its anti adduct 31 was observed. On the other hand, there is no steric reason to anticipate a significant barrier to syn addition with an acetylenic dienophile. With 5-alkyl-1,3-cyclopentadienes dimethyl acetylenedicarboxylate showed more syn adduct than did ethylenic dienophiles,²² and Paquette’s dodecahedrane synthesis relied on an initial syn addition of acetylenedicarboxylate to 9,10-dihydrofulvalene.³³ Nevertheless, both dimethyl acetylenedicarboxylate and ethyl propiolate reacted with 6a to provide only the anti adducts 32 and 33. Unsymmetrical dienes 1b (X = CF₃, 7-norbornadienyl, F) had shown the same selectivity.¹⁷,¹⁸,²⁰ It can be conjectured that the reluctance of the alkyne to add syn to the oxygen functions stems from a repulsive interaction in the syn transition state between the π-bond of the alkyne that is orthogonal to the plane of the developing σ-bonds and the lone pair(s) of the oxygen(s) on the diene. There is some computational evidence that a second factor can attenuate syn addition. A comparison of computed (HF/6-31G(d)) transition

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Total yield (11 and 12) (%)</th>
<th>Ratio of the syn adduct (11) to the anti adduct (12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No solvent</td>
<td>99</td>
<td>27 : 73</td>
</tr>
<tr>
<td>Benzene</td>
<td>83</td>
<td>42 : 58</td>
</tr>
<tr>
<td>Chloroform</td>
<td>99</td>
<td>46 : 54</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>90</td>
<td>45 : 55</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>99</td>
<td>39 : 61</td>
</tr>
<tr>
<td>Pyridine</td>
<td>97</td>
<td>29 : 71</td>
</tr>
<tr>
<td>Methanol</td>
<td>94</td>
<td>27 : 73</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>99</td>
<td>21 : 79</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>97</td>
<td>14 : 86</td>
</tr>
<tr>
<td>Water</td>
<td>89</td>
<td>10 : 90</td>
</tr>
<tr>
<td>1 M LiCl in water</td>
<td>81</td>
<td>14 : 86</td>
</tr>
<tr>
<td>1 M LiClO₄ in water</td>
<td>85</td>
<td>19 : 81</td>
</tr>
<tr>
<td>5 M LiClO₄ in diethyl ether</td>
<td>92</td>
<td>32 : 68</td>
</tr>
</tbody>
</table>

Table 2 Proportions of syn adduct and anti adduct from the Diels–Alder reactions of carbon-based dienophiles with the acetonide diene 6a in benzene

<table>
<thead>
<tr>
<th>Dienophile</th>
<th>syn Adduct</th>
<th>anti Adduct</th>
<th>Proportions (%) of the syn and the anti adducts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maleimide</td>
<td>11</td>
<td>12</td>
<td>42 : 58</td>
</tr>
<tr>
<td>N-Methylmaleimide</td>
<td>13</td>
<td>14</td>
<td>47 : 53</td>
</tr>
<tr>
<td>N-Ethylmaleimide</td>
<td>15</td>
<td>16</td>
<td>39 : 61</td>
</tr>
<tr>
<td>N-Phenylmaleimide</td>
<td>17</td>
<td>18</td>
<td>52 : 48</td>
</tr>
<tr>
<td>Maleic anhydride</td>
<td>19</td>
<td>20</td>
<td>40 : 60</td>
</tr>
<tr>
<td>p-Benzoquinone</td>
<td>21</td>
<td>22</td>
<td>32 : 68</td>
</tr>
<tr>
<td>Dimethyl maleate</td>
<td>24</td>
<td>25</td>
<td>32 : 68</td>
</tr>
<tr>
<td>3-Buten-2-one</td>
<td>26</td>
<td>27</td>
<td>21 : 79</td>
</tr>
<tr>
<td>Vinylene carbonate</td>
<td>29</td>
<td>30</td>
<td>81 : 19</td>
</tr>
<tr>
<td>Tetracyanoethylene</td>
<td>—</td>
<td>31</td>
<td>0 : 100</td>
</tr>
<tr>
<td>Dimethyl acetylenedicarboxylate</td>
<td>—</td>
<td>32</td>
<td>0 : 100</td>
</tr>
<tr>
<td>Ethyl propiolate</td>
<td>—</td>
<td>33</td>
<td>0 : 100</td>
</tr>
</tbody>
</table>

* Data from ref. 19. ⁰ Ratio 60 : 40 for the reaction in chloroform, ref. 11. ¹ The adducts were not isolated. ² Reaction in toluene. ³ Only the endo adducts are given in the Table. The ratio of 25 : 26 : 27 was 21 : 79 : 14.
states for syn and anti additions of acetylene and of maleimide to 5-methyl-1,3-cyclopentadiene indicates that more syn addition should occur with acetylene (29% syn with acetylene versus 13% syn with maleimide). This is in accord with a simple steric rationalization. However, the corresponding comparisons with 5-chloro- and 5-bromo-1,3-cyclopentadiene reveal that much less syn addition should take place with acetylene compared to maleimide (for the chloro-diene, 14% syn with acetylene versus 88% syn with maleimide; and for the bromo-diene, 0.7% syn with acetylene versus 33% syn with maleimide). These results are not consistent with a simple steric argument, but do indicate another, very significant mechanism of inhibition of the syn addition. In the case of 6a/b, the geometry of this interaction is different from that in a 5-substituted 1,3-cyclopentadiene, and 6a/b has two, not just one, lone-pair-bearing plane-nonsymmetric atoms.

Dimerization

Dimerization of 1a or its derivatives would be a special case of the addition of a carbon-based dienophile, one in which the dienophile is also plane-nonsymmetric. Dienes 1a and 1b do not appear to dimerize spontaneously, but dimerization of 6b (X = CF3, Br, Cl, vinyl, CN, SiHMe3) is well known, and trans-benzylidene 8 (and the p-NO2-phenyl variant) also dimerizes readily giving 34 (Fig. 3). In every instance, the only dimer isolated was the result of anti addition of both the diene and the dienophile partners. That only one dimer was produced from 8 was in accord with the high facial selectivity witnessed in the reaction of 8 with N-phenylmaleimide. Prolonged storage of the cis-benzylidene 7, which was initially thought not to dimerize, also produced one dimer 35. This was once again the result of anti addition of both the diene and the dienophile partners.

Fig. 3 Dimeric products from acetonides.

Table 3 Proportions of syn adduct and anti adduct from the Diels–Alder reactions of 4-phenyl-1,2,4-triazoline-3,5-dione with 1a and derivatives in acetone

<table>
<thead>
<tr>
<th>Diene</th>
<th>syn Adduct</th>
<th>anti Adduct</th>
<th>Proportions (%) of syn and anti adducts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>38</td>
<td>39</td>
<td>76 : 24</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>40</td>
<td>0 : 100</td>
</tr>
<tr>
<td>4a</td>
<td>41</td>
<td>42</td>
<td>12 : 88</td>
</tr>
<tr>
<td>6a</td>
<td>—</td>
<td>43</td>
<td>0 : 100</td>
</tr>
<tr>
<td>7</td>
<td>—</td>
<td>44</td>
<td>0 : 100</td>
</tr>
<tr>
<td>8</td>
<td>—</td>
<td>45</td>
<td>0 : 100</td>
</tr>
</tbody>
</table>

produced from 6a indicates that 6a is more facially selective as a dienophile than as a diene.

Azo dienophiles with 1a and derivatives

A survey of additions of 1a and derivatives 2, 4a, 6a, 7 and 8 with PTAD was carried out. The results are summarized in Table 3. The stereochemistry of the adducts could be determined by measurement of NOE enhancements, in most instances. This was not the case for 42 (Fig. 4), but acetylation of 39, the minor adduct from 1a, produced 42, the major adduct from 4a.

Fig. 4 Adducts derived from PTAD and DEAD.

The computational study with 5-substituted 1,3-cyclopentadienes had revealed inhibition of syn addition of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) to a diene with a lone-pair-bearing substituent. It was suggested that this interaction was a filled-orbital repulsion. The data in Table 3 suggest that such an interaction might exist with the derivatives of 1a as well. Whereas PTAD should be less sterically demanding than N-phenylmaleimide, the proportions of anti adduct with PTAD were much higher. What was again observed was that the simpler dienes 1a and 4a seemed to react with less facial selectivity than the substituted dienes 1b (X = wide variety of substituents), which had reacted with PTAD to give over 97% of the syn adduct, and 4b (X = CH3), for which only the anti adduct had been reported.
It is tempting to ascribe the syn selectivity of 1a/b to hydrogen bonding between the addends. The only products detected from the Diels–Alder reactions of PTAD with dienes 6a, 7 and 8 were the anti adducts 43, 44 and 45. The same facial selectivity was observed when diethyl azodicarboxylate (DEAD) was employed as an azo dienophile with 6a, 7 and 8. There are many examples of additions of heterodienophiles to 6b, and, in every instance, only the anti adducts were reported.17,18,20,24,26,27

Conclusions
The reactions of 6a with maleimide in various solvents showed a significant range of facial selectivities, from essentially 1 : 1 up to 1 : 9. Different ethylenic dienophiles added to 6a (in benzene) with modest facial selectivities, in contrast with reportedly high selectivities for the substituted dienes 6b. Acetylenic dienophiles added to 6a exclusively anti. There was also a marked tendency for azo dienophiles (PTAD and DEAD) to add anti to the oxygen functions of the diene, although the reaction of PTAD and 1a gave mainly the syn adduct.

Experimental
General
Melting points are uncorrected. NMR spectra are at 300 MHz for 1H and 74.5 MHz for 13C. Shifts are relative to internal tetramethylsilane. Nuclear Overhauser effect (NOE) measurements were made using difference spectra. Assignments are based on 2-D homo- and heterocorrelation experiments, APT spectra (for 13C) and the NOE measurements. 13C NMR shifts that are not assigned may be determined from the NOE and saturation at 1H NMR (in benzene)

Diels–Alder reactions of acetonide 6a with carbon-based dienophiles
Solutions of 6a and the dienophile in benzene were maintained at RT for a few hours. If TLC revealed some reaction progress, the mixture was stirred at RT until reaction was complete (by TLC). If TLC showed no reaction progress, the solution was heated at reflux until reaction was complete (by TLC). The crude reaction mixture was analysed by 1H NMR in order to obtain the proportions of the adducts by integration. Adducts were then purified by chromatography. Benzene solutions of some pure adducts (11–14, 24, 25, 29, 30, 31 and 33) were heated under reflux for 12 to 16 h. In no case was there evidence, by TLC or by 1H NMR, of equilibration to a mixture of adducts.

Diels–Alder reaction of 6a with maleimide
A solution of 6a (124 mg, 0.817 mmol) and maleimide (158 mg, 1.63 mmol) in benzene (4.0 ml) at RT for 16 h gave 11 (182 mg, 45% after recrystallization from benzene) and 12 (152 mg, 38% after recrystallization from benzene) as colourless crystals. For \((3a,4a,4aβ,7αβ,8aα-4a,7a,8,8a-tetrahydro-2,2,6,6-tetramethyl-4,8-etheno-4H-1,3-dioxolo[4,5-f]isoindole-5,7(3aH,6f)]\)dione 11: \(mp 172–174 °C; \nu_{max}/cm^{-1} 1754; \delta_{H} (CDCl_3) 8.40 (1 \ H, \ \text{very br, N-H}), 6.20 (2 \ H, \ m, \ 9-H \ and \ 10-H), 4.15 (2 \ H, \ dd, \ J 1.6 \ and \ 2.2, 3a-H \ and \ 8a-H), 3.39 (2 \ H, \ m, \ 4-H \ and \ 8-H), 3.36 (2 \ H, \ narrow m, \ 4a-H \ and \ 7a-H), 1.49 (3 \ H, \ s, \ 2-Me_2O) \) and 1.35 (3 \ H, \ s, \ 2-Me_2O); saturation at \(\delta 6.20 \) led to NOEs at \(\delta 4.15 (1%)\) and 3.39 (9%), saturation at \(\delta 4.15 \) led to NOEs at \(\delta 6.20 (1.5%)\), 3.39 (14%) and 1.35 (2%), saturation at \(\delta 3.39 \) led to NOEs at \(\delta 3.36 \) led to NOE at \(\delta 0.149 \) (1%), saturation at \(\delta 1.49 \) led to NOE at \(\delta 3.36 (5%)\) and saturation at \(\delta 3.35 \) led to NOE at \(\delta 4.15 (8%)\); \(\delta_{C} (CDCl_3) 179.7 \) (C-5 and C-7), 131.6 (C-9 and C-10), 112.5 (C-2), 73.7 (C-3a and C-8a), 39.0 (C-4a and C-7a), 36.5 (C-4 and C-8), 26.3 (2-Me_2O) and 24.2 (2-Me_2O); \(m/z 250 (5\%, \text{M}^+ + 1), 234.0773 (64, \text{M}^+ - \text{CH}_2, \text{C}_3\text{H}_3\text{NO}) \) requires 234.0766, 192 (51), 191 (63), 163 (40), 162 (35), 146 (36), 135 (48), 120 (64), 119 (32), 118 (48), 117 (39), 100 (74), 92 (78), 91 (82), 85 (53), 78 (49), 65 (55) and 43 (100).

For \((3a,4a,4aα,7αβ,8aα-4a,7a,8,8a-tetrahydro-2,2,6,6-tetramethyl-4,8-etheno-4H-1,3-dioxolo[4,5-f]isoindole-5,7(3aH,6f)]\)dione 12: \(mp 218–220 °C; \nu_{max}/cm^{-1} 1730, 1689, 1682; \delta_{C} (CDCl_3) 178.7 \) (1H, \ very br, N-H), 6.13 (2 \ H, m, 9-H and 10-H), 4.28 (2 \ H, narrow m, 3a-H and 8a-H), 3.44 (2 \ H, br m, 4-H and 8-H), 2.81 (2 \ H, t, J 1.4, 4a-H and 7a-H), 1.34 (3 \ H, s, 2-Me_2O) and 1.29 (3 \ H, s, 2-Me_2O); saturation at \(\delta 6.13 \) led to NOE at \(\delta 6.14 (7%)\), saturation at \(\delta 4.28 \) led to NOEs at \(\delta 3.44 (9\%)\), 2.81 (13%) and 1.29 (2%); saturation at \(\delta 3.44 \) led to NOEs at \(\delta 6.13 (8\%)\), 4.28 (4%) and 2.81 (5%); saturation at \(\delta 2.81 \) led to NOEs at \(\delta 3.48 (11\%)\) and 3.44 (8%); saturation at \(\delta 1.34 \) led to NOE at \(\delta 6.13 (1.5\%)\) and saturation at \(\delta 1.29 \) led to NOE at \(\delta 4.28 (7\%)\); \(\delta_{C} (CDCl_3) 177.3 \) (C-5 and C-7), 129.7 (C-9 and C-10), 109.8 (C-2), 77.2 (C-3a and C-8a), 41.7 (C-4a and C-7a), 36.3 (C-4 and C-8), 25.3 (2-Me_2O) and 24.9 (2-Me_2O); \(m/z 250 (0.7\%, \text{M}^+ + 1), 234.0773 (30, \text{M}^+ - \text{CH}_2, \text{C}_3\text{H}_3\text{NO}) \) requires 234.0766, 192 (17), 191 (23), 163 (14), 162 (12), 146 (12), 135 (15), 120 (23), 100 (32), 92 (55), 91 (72) and 43 (100).

Diels–Alder reaction of 6a with N-methylmaleimide
A solution of 6a (108 mg, 0.712 mmol) and N-methylmaleimide (79 mg, 0.71 mmol) in benzene (1.0 ml), stirred at RT for 17 h, yielded 13 (74 mg, 40%) and 14 (71 mg, 38%) as colourless crystals. For \((3aα,4aα,4aβ,7βα,8αα-4a,7a,8,8a-tetrahydro-2,2,6,6-trimethyl-4,8-etheno-4H-1,3-dioxolo[4,5-f]isoindole-5,7(3aH,6f)]\)dione 13: \(mp 218–220 °C; \nu_{max}/cm^{-1} 1689; \delta_{C} (CDCl_3) 6.12 (2 \ H, \ dd, \ J 3.0 \ and \ 4.5, 9-H \ and \ 10-H), 4.15 (2 \ H, \ dd, \ J 1.7 \ and \ 2.2, 3a-H \ and \ 8a-H), 3.41 (2 \ H, m, 4-H \ and \ 8-H), 3.32 (2 \ H, narrow m, 4a-H \ and \ 7a-H), 2.91 (3 \ H, s, \ N-Me) \), 1.48 (3 \ H, s, 2-Me_2O) and 1.35 (3 \ H, s, 2-Me_2O); saturation at \(\delta 4.15 \) led to NOEs at \(\delta 6.12 (2%)\),
3.41 (10%), and 1.35 (2%) and saturation at δ 1.48 led to NOE at δ 3.32 (5%); δC (CDCl3) 179.4 (C-5 and C-7), 131.5 (C-9 and C-10), 112.4 (C-2), 73.9 (C-3a and C-8a), 37.7 (C-4a and C-7a), 36.6 (C-4 and C-8), 26.3 (2-Me); 24.7 (N–H) and 24.2 (2-Meβ); m/z 264 (2%, M+ + 1), 248.0913 (35, M– CH3, C8H8NO requires 248.0922), 206 (51), 205 (47), 204 (16), 177 (32), 176 (25), 160 (21), 146 (37), 120 (43), 119 (21), 118 (22), 100 (73), 92 (100), 91 (100), 85 (39), 78 (29), 77 (22), 65 (33) and 43 (100).

For (3aa,4aβ, 8aβ, 9aα)-4a, 9a, 9a-tetrahydro-2,2-dimethyl-4,9-etheno-1,3-dioxolo[4,5-b]napthalene-5,8(4aH,8aH)-dione 21: mp 122–123°; νmax/cm–1 1703; δH (CDCl3) 6.69 (2 H, s, 6-H and 7-H), 6.17 (2H, dd, J 2.9 and 4.4, 10-H and 11-H), 4.10 (2 H, apparent t, J 1.9, 3a-H and 9a-H), 3.15 (4 H, apparent br s, 4-H, 4a-H, 8a-H and 9-H), 1.51 (3 H, s, 2-Meβ) and 1.36 (3 H, s, 2-Meα); saturation at δ 6.17 led to NOEs at δ 4.10 (1%) and 3.51 (2%), saturation at δ 4.10 led to NOEs at δ 6.17 (2%) and 3.51 (4%), saturation at δ 1.51 led to NOE at δ 3.51 (3%) and saturation at δ 1.36 led to NOE at δ 4.10 (8%); δC (CDCl3) 199.4 (C-5 and C-8), 141.8 (C-6 and C-7), 132.8 (C-10 and C-11), 122.2 (C-2), 73.9 (C-3a and C-9a), 42.0, 39.2, 26.5 (2-Meβ) and 24.3 (2-Meα); m/z 260 (7%, M+), 245.0815 (50, M– CH3, C11H10O requires 245.0812), 231 (8), 203 (11), 202 (13), 185 (18), 173 (23), 157 (13), 145 (16), 129 (17), 120 (9), 100 (46), 91 (44), 82 (54), 53 (33) and 40 (100).

For (3aa,4aβ, 8aβ, 9aα)-3a, 4a, 9a, 9a-tetrahydro-2,2-dimethyl-4,9-etheno-1,3-dioxolo[4,5-b]napthalene-5,8(4aH,8aH)-dione 24: mp 151–152°; νmax/cm–1 157 (13), 145 (16), 129 (17), 120 (9), 100 (46), 91 (44), 82 (54), 53 (33) and 40 (100).

Diels–Alder reaction of 6a with maleic anhydride

A solution of 6a (124 mg, 0.817 mmol) and maleic anhydride (159 mg, 1.62 mmol) in benzene (4.0 ml) was stirred at RT for 16 h. After a 1H NMR spectrum was taken, the product was passed through a very short silica gel column in order to remove less polar impurities. A mixture of adducts (334 mg, 83%) was obtained. Attempts to separate the adducts by chromatography led to hydrolysis. Assignment of the structures was based on similarity of the NMR spectra to other adduct mixtures. In the 1H NMR spectra, the olefinic signal was always slightly downfield in the syn adduct, the carbinolic signal was always slightly downfield in the anti adduct, and the signal for the hydrogens α to the carbinols was always at least 0.5 ppm downfield for the syn adduct.

For (3aa,4aβ, 8aβ, 9aα)-3a, 4a, 9a, 9a-tetrahydro-2,2-dimethyl-4,8-etheno[3,4-j]-1,3-benzodioxole-5,7-dione 19: δH (CDCl3) (data from the adduct mixture) 6.20 (2H, dd, J 2.9 and 4.3), 4.15 (2H, narrow m), 3.40 (2H, m), 3.38 (2H, narrow m), 1.49 (3H, s) and 1.35 (3H, s).

For (3aa,4aβ, 8aβ, 9aα)-3a, 4a, 9a, 9a-tetrahydro-2,2-dimethyl-4,8-etheno[3,4-j]-1,3-benzodioxole-5,7-dione 20: δH (CDCl3) (data from the adduct mixture) 6.13 (2H, dd, J 3.0 and 4.5), 4.28 (2H, narrow m), 3.44 (2H, m), 2.82 (2H, apparent t, J 1.4), 1.34 (3H, s) and 1.29 (3H, s).

Diels–Alder reaction of 6a with p-benzoquinone

A solution of 6a (358 mg, 2.34 mmol) and p-benzoquinone (385 mg, 3.53 mmol) in benzene (2.0 ml) was stirred at RT for 72 h. Chromatography (20% EtOAc in hexanes) could not separate the adducts cleanly. Compound 21 (84 mg, 9%) was obtained as colourless crystals following recrystallization four times from EtOAc–hexanes and hexanes. The other adduct was isolated as the aromatized compound 23 (511 mg, 56%) after recrystallization three times from EtOAc–hexanes and hexanes.
For (3aR*,4R*,7R*,7aS*,8R*)-8-acetyl-3a,4,7,7a-tetraydro-2,2-dimethyI-4,7-ethano-1,3-benzoxazole 28: δH (CDCl3) (data from a mixture with 26) 6.13–6.26 (2 H, m), 4.17 (1 H, br dd, J 3.0 and 7.2), 4.1 (1 H, overlapped), 3.8 (1 H, overlapped, 7-H), 2.94 (1 H, m, 4-H), 2.53 (1 H, dd, J 2.7, 5.5 and 10.8, 8-H), 2.23 (3 H, s, COCH3), 1.86 (1 H, dd, J 2.1, 5.5 and 13.5, 9-H), 1.37 (1 H, overlapped, 9-H), 1.32 (3 H, s, 2-Me) and 1.23 (3 H, s, 2-Me).

Diels–Alder reaction of 6a with vinylene carbonate

A solution of 6a (152 mg, 1.00 mmol) and vinylene carbonate (0.12 ml, 2.0 mmol) heated under reflux for 8 days, gave 29 (182 mg, 38%) and 30 (43 mg, 9%) as colourless solids after recrystallization from hexane.

For (3aR*,4R*,7R*,7aS*,8R*)-8-acetyl-3a,4,7,7a-tetraydro-2,2-dimethyI-4,7-ethano-1,3-benzoxazole 28: mp 218–220 °C; vmax/cm−1 1772; δH (CDCl3) 6.16 (2 H, dd, J 4.2 and 9-H and 10-H), 4.67 (2 H, br s, 3a-H and 8a-H), 4.20 (2 H, br, s, 4a-H and 7a-H), 3.47 (2 H, m, 4-H and 8-H), 1.46 (3 H, s, 6-Me) and 1.30 (3 H, s, 6-Me); saturation at δ 4.62 led to NOEs at δ 4.21 (1%) and 3.47 (5%), saturation at δ 3.47 led to NOEs at δ 4.21 (5%) and 3.47 (4%), (3aR*,4R*,7R*,7aS*,8R*)-8-acetyl-3a,4,7,7a-tetraydro-2,2-dimethyI-4,7-ethano-1,3-benzoxazole 28: δH (CDCl3) (data from a mixture with 26) 6.13–6.26 (2 H, m), 4.17 (1 H, br dd, J 3.0 and 7.2), 4.1 (1 H, overlapped), 3.8 (1 H, overlapped, 7-H), 2.94 (1 H, m, 4-H), 2.53 (1 H, dd, J 2.7, 5.5 and 10.8, 8-H), 2.23 (3 H, s, COCH3), 1.86 (1 H, dd, J 2.1, 5.5 and 13.5, 9-H), 1.37 (1 H, overlapped, 9-H), 1.32 (3 H, s, 2-Me) and 1.23 (3 H, s, 2-Me).
Dimerization of 7

Diene 7 dimerized to 35 spontaneously during storage, forming colourless crystals.

For \((2a,3a,5a,6a,6a,8\beta,9a,10,10b,10b\beta)-3a,5a,6,6a,9a,10,10a,10b\)-octa-2,8-diphenyl-6,10-ethenonaphtho[1,2-d:6,7-d]bis[1,3]dioxole 35. mp 152–154 °C; \(\text{Vnmr/cm}^{-1}\) 3057, 1522, 1445 and 1055; \(\delta_h\) (CDCl3) 7.48–7.24 (10 H, m), 6.17 (2 H, m, 11-H and 12-H), 5.84 (1 H, s, 2-H), 5.68 (2 H, broadened AB, 4-H and 5-H), 5.61 (1 H, s, 8-H), 4.39–4.31 (3 H, m, 3a-H, 6a-H and 9a-H), 4.30 (1 H, br d, J 5.7, 10b-H), 3.14 (1 H, m, 10-H), 3.07 (1 H, m, 6-H) and 2.44 (2 H, broadened AB, 5a-H and 10a-H); saturation at \(\delta 6.17\) led to NOEs at \(\delta 3.14\) (4%) and 3.07 (4%), saturation at \(\delta 5.84\) led to NOEs at \(\delta 7.48–7.42\) (2%) and 4.30 (7%), saturation at \(\delta 5.61\) led to NOEs at \(\delta 7.48–7.42\) (3%) and a multiplet at \(\delta 4.38\) (3%), saturation at \(\delta 4.30\) led to NOEs at \(\delta 5.84\) (12%) and 3.14 (13%), saturation at \(\delta 3.14\) led to NOEs at \(\delta 6.17\) (4%), 4.30 (12%) and 2.44 (2%), saturation at \(\delta 3.07\) led to NOEs at \(\delta 6.17\) (4%), 5.68 (5%) and 2.44 (2%) and saturation at \(\delta 6.67\) led to NOEs at \(\delta 5.68\) (3%), double-doublets at 4.38 and 4.33 (9%), 3.14 (4%) and 3.07 (5%); \(\delta_c\) (CDCl3) 137.9, 136.1, 132.9 (C-11 or C-12), 129.7, 129.2 (C-11 or C-12), 129.1 (C-4 or C-5), 128.3 (4C), 127.4, 127.1, 126.4 (C-4 or C-5), 103.5 (C-2), 103.1 (C-8), 79.7 (C-10b), 79.0 (2C), 70.6, 40.8 (C-6 and C-10), 34.5 and 33.5; \(m/z\) 400 (1.6%, M⁺), 399 (4), 171 (14), 170 (28), 159 (37), 145 (27), 144 (25), 141 (20), 129 (22), 120 (31), 105 (100), 94 (40), 91 (72), 78 (31), 77 (55) and 66 (30); analysis: found C, 78.11; H, 5.99%; C₃₂H₂₅O₇ requires C, 77.98; H, 6.04%.

Dimerization of 6a

A sample of 6a (214 mg, 1.41 mmol) was kept at RT for 28 d. Flash chromatography (10% EtOAc in hexanes) gave 36 (41 mg, 19%) and 37 (129 mg, 60%) as colourless solids.

For \((3a,5a,6a,6a,9a,10a,10b\beta)-3a,5a,6,6a,9a,10,10a,10b\)-octa-2,8,8,10,10-pentamethyl-6,10-ethenonaphtho[1,2-d:6,7-d]bis[1,3]dioxole 36. mp 92–93 °C; \(\text{Vnmr/cm}^{-1}\) 2985, 2935, 1375, 1238, 1207 and 1061; \(\delta_h\) (CDCl3) 6.07 (2 H, broad, narrow m, 11-H and 12-H), 5.56 (1 H, ddd, J 1.3, 3.4 and 10.3, 5-H), 5.49 (1 H, br d, J 10.3, 4-H), 4.19 (1 H, m, 3a-H), 4.06 (3 H, m, 6a-H and 9a-H), 3.01 (1 H, br d, J 9.0, 5a-H), 2.96 (2 H, m, 6-H and 10-H), 1.55 (3 H, s, 8-Me), 1.38 (3 H, s, 2-Me), 1.35 (3 H, s, 8-Me) and 1.33 (3 H, s, 2-Me); saturation at \(\delta 6.07\) led to NOEs at \(\delta 4.19\) (3%), 4.06 (0.6%) and 2.80 (5%), saturation at \(\delta 5.65\) led to NOEs at \(\delta 2.96\) (3%) and 2.80 (1%), saturation at \(\delta 5.49\) led to NOEs at \(\delta 4.19\) (2%) and 3.01 (4%), saturation at \(\delta 4.19\) led to NOEs at \(\delta 6.07\) (2%) and 5.49 (4%), saturation at \(\delta 4.06\) led to NOEs at \(\delta 6.07\) (2%), 2.96 (4%) and 2.80 (11%) and 1.35 (1%), saturation at \(\delta 2.80\) led to NOEs at \(\delta 6.07\) (7%), 5.56 (4%), 4.06 (8%), 3.01 (4%) and 2.96 (3%) and saturation at \(\delta 1.55\) led to NOEs at \(\delta 3.01\) (5%), 2.96 (5%) and 1.35 (1%); \(\delta_c\) (CDCl3) 134.6 (C-12), 131.1 (C-11), 130.3 (C-5), 126.8 (C-4), 111.9 (C-8), 107.4 (C-2), 77.9 (C-10b), 75.2 (C-6a or C-9a), 74.7 (C-6a or C-9a), 71.2 (C-3a), 40.8 (C-6 or C10), 40.3 (C-6 or C10), 30.5 (C-5a and C-10a), 28.4 (2-Me), 26.8 (2-Me), 26.3 (8-Me) and 24.4 (8-Me); \(m/z\) no M⁺, 289 (15%), 275 (2), 231 (3), 188 (40), 171 (85), 159 (30), 153 (19), 145 (20), 143 (26), 129 (26), 100 (50), 91 (34) and 43 (100); analysis: found C, 70.98; H, 7.91%; C₃₂H₂₅O₇ requires C, 71.03; H, 7.95%.
For (3α,5αβ,6α,6αβ,9αβ,10αβ,10βα)-3α,5α,6α,6αβ,9α,10α,10β-octahydro-2,2,8,8-tetramethyl-6,10-ethenonaphth[1,2-d]/7,8-d/1,3]dioxole 37: mp 149−151 °C (lit. 150−151 °C); νmax/cm−1 2987, 2930, 2911, 2884, 1456, 1365, 1236, 1046, and 886; δH (CDCl3) 5.99 (2 H, narrow m, 11-H and 12-H), 5.60 (1 H, dd, J 3.8 and 10.5, 5-H), 5.51 (1 H, d, J 10.3, 4-H), 4.30 (2 H, m, 6a-H and 9a-H), 4.20−4.14 (2 H, m, 3a-H and 10b-H), 2.87 (2 H, m, 6-H and 10-H), 2.36 (1 H, br d, J 9.1, 5a-H), 2.23 (1 H, d, J 9.1, 10a-H), 1.36 (3 H, s, 2-MeC), 1.34 (3 H, s, 2-MeC), 1.32 (3 H, s, 8-MeC) and 1.29 (3 H, s, 8-MeC); saturation at δ 5.99 led to NOEs at δ 4.17 (4%), 2.87 (5%) and 1.32 (0.3%), saturation at δ 5.60 led to NOEs at δ 2.87 (2%) and 2.36 (2%), saturation at δ 5.51 led to NOE at δ 1.47 (2%), saturation at δ 4.30 led to NOEs at δ 2.87 (3%), 2.36 (5%) 2.23 (10%) and 1.29 (1%), saturation at δ 4.17 led to NOEs at δ 5.99 (2%), 5.51 (4%), 2.87 (6%), 2.23 (3%) and 1.34 (0.7%), saturation at δ 2.87 led to NOEs at δ 5.99 (7%), 5.60 (6%), 4.30 (4%), 4.17 (10%), 2.36 (3%) and 2.23 (3%), saturation at δ 2.36 led to NOEs at δ 5.60 (4%), 4.30 (4%) and 2.87 (2%), saturation at δ 2.23 led to NOEs at δ 4.30 (4%), 4.17 (1.5%) and 2.87 (0.7%), saturation at δ 1.36 led to NOE at δ 5.51 (4%), saturation at δ 1.34 led to NOE at δ 4.17 (9%), saturation at δ 1.32 led to NOE at δ 5.99 (2%) and saturation at δ 1.29 led to NOE at δ 4.30 (6%); δC (CDCl3) 132.4 (C-12), 129.3 (C-5), 128.8 (C-11), 126.6 (C-4), 108.6 (C-8), 107.6 (C-2), 78.6 (C-6a or C-9a), 78.3 (C-6a or C-9a), 77.6 (C-10b), 70.9 (C-3a), 41.0 (C-6 or C-10), 40.7 (C-6 or C-10), 34.3 (C-10a), 33.1 (C-5a), 28.3 (2-MeC), 26.8 (2-MeC), 25.4 (8-MeC) and 25.0 (8-MeC); m/z no M*: 289 (12%), 246 (8), 246 (17), 188 (49), 197 (20), 158 (26), 145 (19), 143 (18), 131 (20), 129 (22), 119 (22), 100 (30), 95 (72), 91 (36) and 43 (100); analysis: found C, 71.00; H, 7.84%; C14H16O requires C, 71.03; H, 7.95%.

Diels–Alder reactions with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)

A solution of PTAD in acetonitrile was added dropwise to an aqueous solution of the diene in acetone. The initial carminic colour of the PTAD faded as the solution was stirred at RT for 16–18 h. The solution was concentrated under vacuum, and the residue was analysed by 1H NMR spectroscopy in order to obtain the proportions of the adducts in Table 3. The adducts were isolated by chromatography (20−30% EtOAc in hexanes). Yields are for the isolated adducts.

Diels–Alder reaction of 1a with PTAD

PTAD (171 mg, 0.98 mmol) and 1a (109 mg, 0.89 mmol) provided 38 (193 mg, 68%), as colourless crystals, and some impure 39 (19 mg, 7% if pure).

For (5R,8S,10S,11R)-5,8-dihydro-10,11-dihydroxy-2-phenyl-5,8-ethano-1H-[1,2,4]triazolo[1,2-a]-pyridazine-1,3(2H)-dione 41: mp 224−225 °C; νmax/cm−1 1744 (m) and 1707; δH (CDCl3) 7.51−7.36 (5 H, m), 6.60 (2 H, apparent dd, J 3.1 and 4.2, 6-H and 7-H), 5.10 (2 H, m, 5-H and 8-H), 5.04 (2 H, narrow m, C-10 and C-11), 2.15 (6 H, s, 2 × OAc); saturation at δ 6.60 led to NOEs at δ 5.10 (10%) and 5.04 (1.5%), saturation at δ 5.10 led to NOEs at δ 6.60 (90%) and 5.04 (7%) and saturation at δ 5.04 led to NOEs at δ 6.60 (2%) and 5.10 (12%); δC (CDCl3) 169.8, 155.4, 131.1, 130.1, 129.2, 128.5, 125.6, 63.4, 53.1 and 20.6; m/z 371 (3%, M+), 329 (3), 269 (9), 228 (22), 227 (100), 119 (25), 80 (56) and 43 (71); analysis: found C, 58.27; H, 4.61; N, 11.34%; C19H17N2O3 requires C, 58.20; H, 4.62; N, 11.32%.

For (5R,8S,10S,11R)-5,8-dihydro-10,11-dihydroxy-2-phenyl-5,8-ethano-1H-[1,2,4]triazolo[1,2-a]-pyridazine-1,3(2H)-dione 42: mp 219−220 °C; νmax/cm−1 1749 and 1717; δH (CDCl3) 7.48−7.36 (5 H, m), 6.58 (2 H, dd, J 3.1 and 4.0, 6-H and 7-H), 5.46 (2 H, narrow m, 10-H and 11-H), 5.10 (2 H, m, 5-H and 8-H), 2.05 (6 H, s, 2 × OAC); saturation at δ 5.58 led to NOEs at δ 5.10 (11%), saturation at δ 5.46 led to NOEs at δ 5.10 (16%) and 2.05 (0.5%), saturation at δ 5.10 led to NOEs at δ 5.68 (8%) and 5.46 (8%) and saturation at δ 5.04 led to NOEs at δ 5.68 (1.5%), 5.46 (1.5%) and 5.10 (1%); δC (CDCl3) 169.2, 155.4, 130.9, 129.5 (C-6 and C-7), 129.1, 128.4, 125.3, 67.0 (C-10 and C-11), 51.4 (C-5 and C-8) and 20.2 (2 × OAC); m/z 371 (1%, M+), 329 (1), 311 (1), 269 (12), 228 (15), 227 (76), 119 (28), 80 (62) and 43 (100);
Diels–Alder reaction of 6a with PTAD

PTAD (121 mg, 0.689 mmol) and 6a (105 mg, 0.689 mmol) provided 43 (256 mg, 97%) as colourless crystals. For (3a,4β,10β,10aα)-3a,4,10,10a-tetrahydro-2,2-dimethyl-7-phenyl-4,10-ethenoo-h-1,3-dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-6,8(7H)-dione 43: mp 248–250 °C; νmax/cm−1 1713; δH (CDCl3) 7.46–7.36 (5 H, m), 6.42 (2 H, dd, J 3.4 and 3.8, 11-H and 12-H), 5.15 (2 H, m, 4-H and 10-H), 4.66 (2 H, narrow m, 3α-H and 10α-H), 1.35 (6 H, s, 2 × CH3); saturation at δ 6.42 led to NOEs at δ 5.15 (10%), saturation at δ 5.15 led to NOEs at δ 6.42 (90%) and 4.66 (6%), saturation at δ 4.66 led to NOEs at δ 5.15 (14%) and 1.35 (1%) and saturation at δ 1.35 led to NOEs at δ 6.42 (3%) and 4.66 (11%); δC (CDCl3) 155.6, 130.7, 129.1, 128.8 (C-11 and C-12), 128.4, 125.5, 112.1, 73.8 (C-3a and C-10α), 52.3 (C-4 and C-10), 25.4 (CH3) and 25.3 (CH2); νmax/cm−1 1732, 1725; δH (CDCl3) 6.51 (1 H, br t, J ≈ 6.3), 6.36 (1 H, br t, J ≈ 7.0), 5.15 (1 H, br m), 5.04 (1 H, br m), 4.47 (2 H, br m), 4.40–4.10 (4 H, br m), 1.36–1.23 (6 H, m), 1.32 (3 H, s), and 1.29 (3 H, s); saturation at δ 6.40 led to NOEs at δ 5.15 (10%) and 5.04 (11%), saturation at δ 5.10 led to NOEs at δ 6.51 (11%), 6.36 (11%) and 4.47 (8%), saturation at δ 4.47 led to NOEs at δ 5.15 (14%), 5.04 (14%) and 1.29 (0.5%), saturation at δ 1.32 led to NOEs at δ 6.51 (4%) and 6.36 (3%) and saturation at δ 1.29 led to NOE at δ 4.47 (9%); δC (CDCl3) (Many signals were broadened, which did not allow detection of the carboxyils.) 133.5, 128.7, 111.0, 73.7, 73.1, 62.9, 62.6, 53.5, 51.3, 25.5, 25.4, 14.4 and 14.3; νmax/cm−1 326 (1.5%, Mγ), 311.1253 (7, M− − CH3, C6H5NO2 requires 311.1243), 268 (2), 226 (6), 196 (6), 195 (5), 167 (14), 153 (20), 123 (16), 95 (29), 81 (100), 80 (13) and 43 (22).

Diels–Alder reaction of 6a with DEAD

DEAD (123 mg, 0.71 mmol) and 6a (108 mg, 0.71 mmol) provided 46 (223 mg, 96%) as a colourless oil. For diethyl (3a,4β,7β,7αα)-3a,4,7,7α-tetrahydro-2,2-dimethyl-4,7-etheno-1,3-dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-6,8(7H)-dione 46: νmax/cm−1 1737 and 1725; δH (CDCl3) 6.51 (1 H, br t, J ≈ 6.3), 6.36 (1 H, br t, J ≈ 7.0), 5.15 (1 H, br m), 5.04 (1 H, br m), 4.47 (2 H, br m), 4.40–4.10 (4 H, br m), 1.36–1.23 (6 H, m), 1.32 (3 H, s), and 1.29 (3 H, s); saturation at δ 6.40 led to NOEs at δ 5.15 (10%) and 5.04 (11%), saturation at δ 5.10 led to NOEs at δ 6.51 (11%), 6.36 (11%) and 4.47 (8%), saturation at δ 4.47 led to NOEs at δ 5.15 (14%), 5.04 (14%) and 1.29 (0.5%), saturation at δ 1.32 led to NOEs at δ 6.51 (4%) and 6.36 (3%) and saturation at δ 1.29 led to NOE at δ 4.47 (9%); δC (CDCl3) (Many signals were broadened, which did not allow detection of the carboxyils.) 133.5, 128.7, 111.0, 73.7, 73.1, 62.9, 62.6, 53.5, 51.3, 25.5, 25.4, 14.4 and 14.3; νmax/cm−1 326 (1.5%, Mγ), 311.1253 (7, M− − CH3, C6H5NO2 requires 311.1243), 268 (2), 226 (6), 196 (6), 195 (5), 167 (14), 153 (20), 123 (16), 95 (29), 81 (100), 80 (13) and 43 (22).

Diels–Alder reaction of 7 with DEAD

DEAD (266 mg, 1.52 mmol) and 7 (153 mg, 0.76 mmol) provided 47 (142 mg, 50%) as a pale yellow oil. For diethyl (2a,3αβ,4α,7αβ)-3a,4,7α-tetrahydro-2-phenyl-4,7-etheno-1,3-dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-6,8(7H)-dione 47: νmax/cm−1 1737 and 1703; δH (CDCl3) 7.37 (5 H, br m), 6.62 (1 H, br t, J ≈ 6.1), 6.48 (1 H, br t, J ≈ 7.2), 5.69 (1 H, s), 5.30 (1 H, br m), 5.20 (1 H, br m), 4.56 (1 H, br m), 4.52 (1 H, br m), 4.34–4.10 (4 H, m) and 1.35–1.23 (6 H, m); saturation at δ 6.62 and 6.48 led to NOEs at δ 6.37 (0.6%), 5.30 (4%) and 5.20 (4%), saturation at δ 5.69 led to NOEs at δ 7.37 (2%) and 4.56 and 4.52 (3%), saturation at δ 5.30 and 5.20 led to NOEs at δ 6.62 (6%), 6.48 (6%) and 4.56 and 4.52 (5%), saturation at δ 4.54 led to NOEs at δ 5.69 (6%), 5.30 (4%) and 5.20 (5%) and saturation at δ 4.22 led to NOE at δ 1.35–1.23 (1%); δC (CDCl3) (Many signals were broadened, which did not allow detection of the carboxyils.) 133.1, 133.8, 129.8, 129.0, 128.3, 127.2, 104.7, 73.9, 73.4 (br), 63.0, 62.7, 53.3 (br), 51.0 (br), 14.4 and 14.3; νmax/cm−1 374.1472 (0.5%, M−−, C6H5NO2 requires 374.1478), 302 (3), 268 (3), 239 (5), 196 (10), 195 (8), 167

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Diels–Alder reaction of 8 with DEAD

DEAD (483 mg, 2.77 mmol) and 8 (222 mg, 1.10 mmol) provided 48 (224 mg, 54%) as a pale pink oil.

For diethyl (2a,3a,4b,7b,7a-tetrahydro-2-phenyl-4,7-etheno-1,3-dioxolo[4,5-d]pyridazine-5,6-dicarboxylate 48: $v_{\text{max}}$/cm$^{-1}$ 1720; $\delta_{\text{H}}$ (CDCl$_3$) 7.35 (5 H, narrow m), 6.69 (1 H, br t, $J \approx 6.1$), 6.56 (1 H, br t, $J \approx 6.6$), 6.02 (1 H, s, 2-H), 5.27 (1 H, br m), 5.17 (1 H, br m), 4.69 (1 H, br m), 4.56 (1 H, br m), 4.31–4.10 (4 H, m, OCH$_2$CH$_2$) and 1.27 (6 H, br t, $J$ 7.0, OCH$_2$CH$_3$); saturation at $\delta$ 6.69 and 6.56 led to NOEs at $\delta$ 6.02 (8%), 5.27 (10%) and 5.17 (10%), saturation at $\delta$ 6.02 led to NOEs at $\delta$ 7.35 (1%), 6.69 (1%) and 6.56 (1%), saturation at $\delta$ 5.27 and 5.17 led to NOEs at $\delta$ 6.69 (11%), 6.56 (11%), 4.69 (9%) and 4.56 (9%) and saturation at $\delta$ 4.69 and 4.56 led to NOEs at $\delta$ 5.27 (12%) and 5.17 (12%); $\delta_{\text{C}}$ (CDCl$_3$) (Many signals were broadened, which did not allow detection of the carbonyls.) 138.1, 134.3, 130.1, 129.1, 128.3, 125.8, 106.0, 74.7, 73.7 (br), 62.9, 62.6, 53.3, 51.3 (br), 14.3 and 14.2; $m/z$ 374.1466 (0.7, M+, C$_{19}$H$_{22}$N$_2$O$_6$ requires 374.1476), 174.9, 154.5, 135.3, 128.3, 125.8, 106.0, 74.7, 73.7 (br), 62.9, 62.6, 53.3, 51.3 (br), 14.3 and 14.2; $m/z$ 374.1466 (0.7, M+, C$_{19}$H$_{22}$N$_2$O$_6$ requires 374.1476), 302 (3), 268 (2), 239 (4), 196 (9), 195 (7), 167 (16), 153 (21), 123 (16), 105 (18), 95 (11), 91 (9), 81 (100), 80 (11), 78 (11) and 77 (15).

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