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New Diels–Alder Dimers of (1*S*,2*R*)-*cis*-1,2-Isopropylidene-dioxy-3-ethenylcyclohexa-3,5-diene

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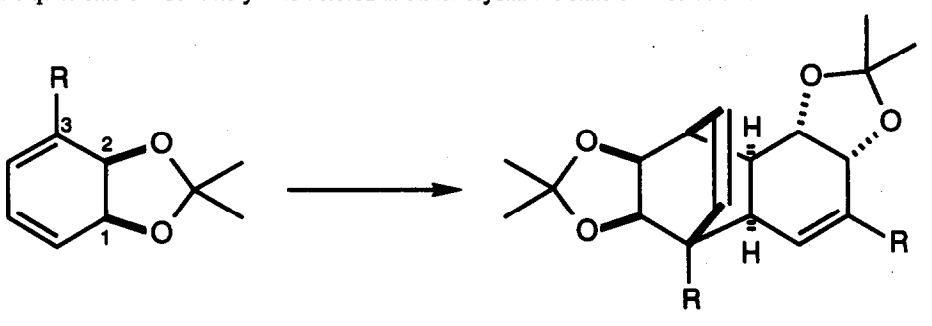
Abstract: The acetonide of the *cis*-diol metabolite, 1,2-dihydroxy-3-ethenylcyclohexa-3,5-diene, produced from the oxidation of styrene by *Pseudomonas putida* strain 39D, underwent intermolecular stereoselective Diels–Alder dimerizations to form three different types of compounds.

In order to expand the generality of the microbial dioxygenation of aromatics in synthesis we pursued the chemistry of new and substituted cyclohexadiene-*cis*-diols obtained by oxidation of aromatic substrates by a mutant strain (39D) of *Pseudomonas putida*.[1] During the course of this study we observed that the halogenated arene-*cis*-diol acetonides **1a** and **1b** underwent a stereoselective Diels–Alder dimerization to form stable, crystalline dimers (**2a** and **2b**) whose structure was confirmed by X-ray crystallography.[2] Identical observation was made by Ley's laboratories with the acetonide of bromodiene diol (**1a**)[3a] while Roberts published on a similar phenomenon in the case of the trifluoromethylcyclohexadiene-*cis*-diol acetonide (**1c**).[3b] It is noteworthy to add that while the acetonide -protected diene diols are prone to dimerizations via the Diels–Alder process, the free diols are inert to it and are quite stable indefinitely when stored in either crystalline state or in solution at 0° C.

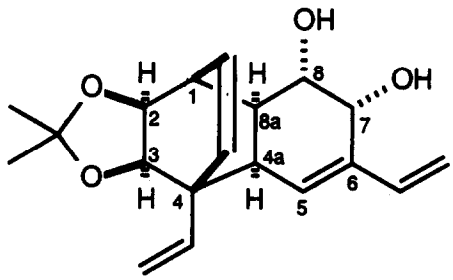


1a: R = Br
1b: R = Cl
1c: R = CF_3
1d: R = $CHCH_2$

2a: R = Br
2b: R = Cl
2c: R = CF_3
2d: R = $CHCH_2$

We now report that the acetonide of the diol obtained by microbial oxidation of styrene (**1d**) undergoes three regiochemically disparate Diels–Alder dimerizations leading in synthetically significant yields to compounds with fascinating potential as chiral synthons. Allowing **1d** to stand neat at RT for 2–3 weeks resulted in the formation of dimers **2d**, **4**, and **5** along with trace amounts of several other compounds. The major compound, comprising ~40% of the crude dimer mixture, was assigned structure

2d based on ^{1}H, ^{13}C, COSY, and HETCOR nmr spectroscopic data.[4] To prove the absolute stereochemistry, **2d** was converted to **3** by treatment with glacial acetic acid at RT for 36 hours. Nuclear Overhauser enhancement experiments performed with **3** proved that the stereochemistry of the major dimer **2d** is identical to that observed for the previously-known dimers **2a–c** whose absolute stereochemistry has been corroborated by X-ray crystallography.[2,3] Irradiation of H-2 (4.36 ppm) produced an enhancement of 8.3% of the resonance at 2.06 ppm corresponding to H-8a. Irradiation of H-3 (4.09 ppm) produced an enhancement of 11.5% of the signal of H-4a (2.39 ppm) while irradiation of this proton gave a 16% enhancement of H-3. These observations and the fact that the coupling constants in **2d** and **3** are almost identical to those in **2a** and **2b** confirm that the structures **2d** and **3** have the same absolute stereochemistry as the known dimers **2a-c**.



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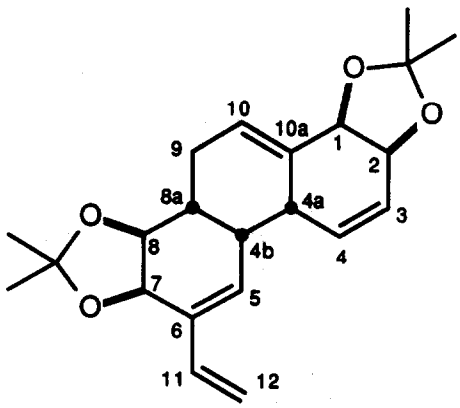
The regiochemistry of **4** and **5** (each ~30 % of the crude dimer mixture) was easily determined by COSY nmr experiments, which unequivocally demonstrated the ^{1}H–^{1}H connectivities (see ref. 4 for assignments). In the nOe experiment of **4** enhancements of 12% and 7.7% were observed at H-4a (3.15 ppm) and H-8a (2.46 ppm), respectively, upon irradiation of H-8a and H-4a, respectively, confirming the syn disposition of all three ring junction protons. The evidence for their β-orientation was a 4.2%



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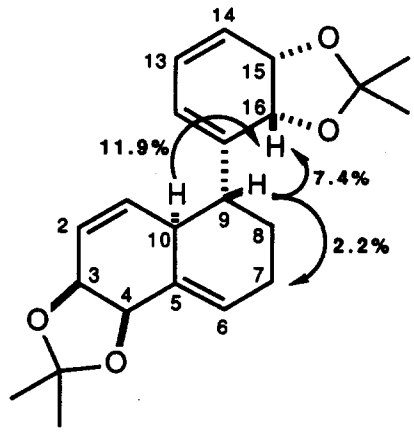

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enhancement of H-9 (2.04 ppm) upon irradiation of H-8 (4.32 ppm)–not possible if all ring junction

protons are α-oriented–and the small value of the coupling constant between H-8 and H-8a (3Hz, suggesting anti-orientation). The absolute stereochemistry assignment follows from the known configuration at C-1, C-2, C-7, and C-8.

The assignment of **5** is more difficult and cannot be made without ambiguity regarding the relative stereochemistry at C-9 and C-10.[5] The evidence for the anti-arrangement of the two protons comes from the value of the coupling constant (7.4 Hz for the dihedral angle of 145°). Of the four possible isomers only two can have this value . Of these two the proposed arrangement is consistent with the observed nOe enhancements involving the signals at H-9, H-10, and H-16, taking into account rotation around the C-9/C-11 bond. An unambiguous structure proof for dimers **4** and **5** will have to await the preparation of a suitable crystalline derivative for x-ray analysis.

While the Diels–Alder dimerization of **1d** does not appear to be, based on these initial observations, as regioselective as that of **1a-c**, compounds **2d**, **4**, and **5** are all formed diastereoselectively;[4] contain many chiral centers (eight, seven, and six, respectively); and have the potential to be converted to highly-functionalized compounds by a variety of different chemical methods. It is fascinating to visualize, for example, a steroid or a diterpene framework in **4**, while **5** may portend to useful synthons in the compactin family of compounds.

The formation of three different carbon skeletons from a single, readily-available starting material under very mild conditions deserves further investigation, and we are continuing to examine both this dimerization and those of more highly functionalized arene-*cis*-diols of type **1d** (for example, the 4-, 5-, or 6-chloro-substituted derivatives of **1d**).[6] Among the objectives of such endeavor is the assessment whether the use of different conditions and/or catalysts in the Diels-Alder cycloaddition will allow for predominant formation of any one of these compounds (**2d**, **4**, or **5**) and thus make possible a choice for the controlled preparation of a desired structure by this method. The determination of the generality of the dimerization and possible identification of new chiral synthons will also be addressed.

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(4) Data for **2d**: $[\alpha]_D$ = +73.8° (*c* 0.81, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.19 (1H, dd, 17.7, 11.0), 6.04-5.97 (2H, m), 5.92 (1H, dd, 17.7, 11.0), 5.69 (1H, d, 3.8), 5.43 (1H, dd, 11.0, 0.8), 5.37

(1H, d, 17.7), 5.30 (1H, dd, 17.7, 0.8), 5.02 (1H, d, 11.0), 4.44 (1H, d, 5.2), 4.36 (1H, dd, 7.4, 3.7), 4.11 (1H, d, 7.4), 4.09 (1H, dd, 5.2, 3.2), 2.96 (1H, m), 2.40 (1H, dd, 9.3, 3.2), 2.25 (1H, dt, 9.3, 2.1), 1.35 (3H, s), 1.30 (3H, s), 1.27 (3H, s), 1.26 (3H, s); ^{13}C NMR δ 138.6 (CH), 136.9 (CH), 134.6 (C), 132.3 (CH), 129.4 (CH), 128.7 (CH), 116.8 (CH_2), 114.0 (CH_2), 108.9 (C), 108.2 (C), 82.1 (CH), 79.0 (CH), 77.6 (CH), 70.4 (CH), 49.7 (C), 40.4 (CH), 39.6 (CH), 36.3 (CH), 28.0 (CH_3), 26.7 (CH_3), 25.4 (CH_3), 25.0 (CH_3); CI MS: [M+1] 357 (5), 307 (5), 299 (30), 241 (45), 223 (10), 121 (100), 120 (50), 107 (10), 91 (15); CI HRMS: Calcd. for $C_{22}H_{29}O_4$ [M+1] 357.2066, found 357.2075.

Data for 3: ^{1}H NMR ($CDCl_3$) δ 6.26 (1H, dd, 17.6, 10.8), 6.15 (1H, s), 6.14 (1H, d, 2.6), 5.90 (1H, dd, 17.7, 10.9), 5.75 (1H-5, d, 2.7), 5.48 (1H, d, 10.9), 5.37 (1H, d, 17.6), 5.29 (1H, d, 17.7), 5.03 (1H, dd, 10.8, 0.5), 4.43 (1H-7, d, 2.8), 4.36 (1H-2, dd, 7.1, 3.2), 4.09 (1H-3, d, 7.1), 3.28 (1H-8, bm), 3.25 (1H-1, m), 2.39 (1H-4a, bd, 9.9), 2.28 (-OH, bs), 2.21 (-OH, bs), 2.06 (1H-8a, dt, 9.9, 2.0), 1.32 (3H, s), 1.28 (3H, s); ^{13}C NMR δ 138.6 (CH), 137.3 (C), 136.7 (CH), 131.3 (CH), 130.9 (CH), 130.6 (CH), 117.0 (CH_2), 111.9 (CH_2), 108.8 (C), 82.6 (CH), 78.8 (CH), 71.4 (CH), 65.5 (CH), 48.4 (C), 41.0 (CH), 38.2 (CH), 37.6 (CH), 25.4 (CH_3), 24.9 (CH_3).

Data for 4: $[\alpha]_D$ = +18.8° (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.23 (1H-11, dd, 17.6, 11.0), 5.78 (1H-10, m), 5.75 (1H-3, ddt, 10.9, 2.5, 1.2), 5.64 (1H-4, bd, 10.2), 5.55 (1H-5, bs), 5.33 (1H-12t, d, 17.6), 5.03 (1H-12c, d, 11.0), 4.82 (1H-7, dd, 6.4, 1.1), 4.55 (1H-2, m), 4.50 (1H-1, bd, 4.9), 4.32 (1H-8, dd, 6.4, 2.7), 3.15 (1H-4a, m), 2.89 (1H-4b, bm), 2.46 (1H-8a, m), 2.04 (1H-9, dddd, 18.4, 6.5, 4.3, 2.5), 1.56 (1H-9, ddt, 18.4, 10.9, 3.2), 1.402 (3H, s), 1.398 (3H, s), 1.38 (3H, s), 1.36 (3H, s); ^{13}C NMR δ 137.4 (CH), 136.4 (C), 132.6 (C), 130.9 (CH), 129.5 (CH), 128.6 (CH), 128.0 (CH), 113.0 (CH_2), 109.3 (C), 108.4 (C), 78.3 (CH), 76.6 (CH), 73.9 (CH), 69.8 (CH), 35.8 (CH), 34.4 (CH), 32.5 (CH), 28.2 (CH_3), 27.1 (CH_3), 27.0 (CH_3), 25.2 (CH_3), 24.7 (CH_2); CI MS: 307 (100), 291 (20), 221 (75), 195 (15), 180 (25), 165 (20).

Data for 5: $[\alpha]_D$ = +211.4° (*c* 0.325, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.97 (1H-13, dd, 9.7, 5.9), 5.85 (1H-6, m), 5.78 (1H-14, dd, 9.7, 3.9), 5.67 (1H-12, bd, 5.9), 5.61 (1H-2, ddd, 10.1, 2.5, 0.8), 5.58 (1H-1, d, 10.1), 4.65 (1H-15, ddd, 8.6, 3.9, 0.3), 4.60 (1H-4, bd, 5.5), 4.57 (1H-3, dd, 5.5, 2.5), 4.47 (1H-16, d, 8.6), 3.36 (1H-10, m), 2.84 (1H-9, bt, 7.4), 2.16-2.00 (2H-7, m), 1.72 (1H-8, ddt, 12.8, 5.1, 2.8), 1.56 (1H-8, m), 1.41 (3H, s), 1.38 (3H, s), 1.37 (3H, s), 1.35 (3H, s); ^{13}C NMR δ 138.5 (C), 135.5 (C), 132.0 (CH), 127.6 (CH), 126.2 (CH), 124.3 (CH), 123.0 (CH), 119.3 (CH), 108.9 (C), 105.3 (C), 79.0 (CH), 75.5 (CH), 73.3 (CH), 71.3 (CH), 38.8 (CH), 33.3 (CH), 27.6 (CH_3), 26.9 (CH_3), 26.4 (CH_3), 25.1 (CH_3), 24.3 (CH_2), 23.9 (CH_2); CI MS: 355 (10), 299 (40), 283 (25), 241 (100), 223 (95), 147 (100), 129 (70), 120 (55), 107 (45).

(5) As pointed out by a referee, the structure as drawn would correspond to an exo transition state in the cycloaddition. The preparation of a suitable derivative for an X-ray analysis is in progress.

(6) A dimer formation was observed with the acetonide derived from 1,2-dihydroxy-6-chloro-3-ethenylcyclohexa-3,5-diene. The determination of its structure is in progress.

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