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Chemoenzymatic synthesis of chiral enones from aromatic compounds

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Abstract—A series of chiral enones was successfully synthesized from chemoenzymatically produced chiral diols. These chiral enones are highly functionalized synthons, which can be used in the total synthesis of natural products such as forskolin and avermectins.

1. Introduction

α,β-Unsaturated ketones are among the most versatile building blocks in organic synthesis. Indeed, several natural products have been synthesized using enones as basic scaffolds.[1–5] Chiral enones are particularly interesting since they can be used in non-racemic total syntheses. Herein, we disclose the chemoenzymatic synthesis of chiral α,β-unsaturated ketones as highly functionalized intermediates for natural products synthesis starting from monosubstituted aromatic compounds.

These simple aromatics were converted to chiral cyclohexadienediols through whole-cell oxidation using *Pseudomonas putida* F39/D.[6–8] These compounds have been used extensively in organic synthesis due to their high functionality and enantiomeric purity.[9] Several aromatic compounds, possessing either electron-withdrawing or -donating groups have been used in the microbial oxidation. In particular, the efficient preparation of an enone from the cyclohexadienediol derived from anisol[10,11] constitutes one of the first synthetic applications of this diol.

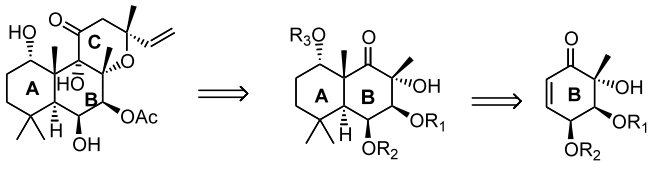
2. Results and discussion

2.1. Methylcyclohexadienediol-derived enones

Toluene-derived diene diol **1** is being studied in our laboratory as a potential starting material in the asymmetric synthesis of forskolin and its derivatives.[12] The proposed construction of the skeleton starts from an enone as a precursor of ring B. A tandem Michael–aldol addition sequence allows for the closure of ring A, and further olefination and cyclization give ring C of forskolin (Scheme 1).

Enone **5**, which contains all the required stereogenic centers of ring B in the correct arrangement, was obtained from toluene, via diol **1**, via a simple synthetic sequence (Scheme 2). Non-selective protection of **1** proceeded in high yields to give acetonide **2a** and acetate **2b**, which were then dihydroxylated via catalytic osmylation.

For both the acetate and the acetonide, the reaction occurred primarily on the more electron-rich double



Forskolin

Scheme 1.

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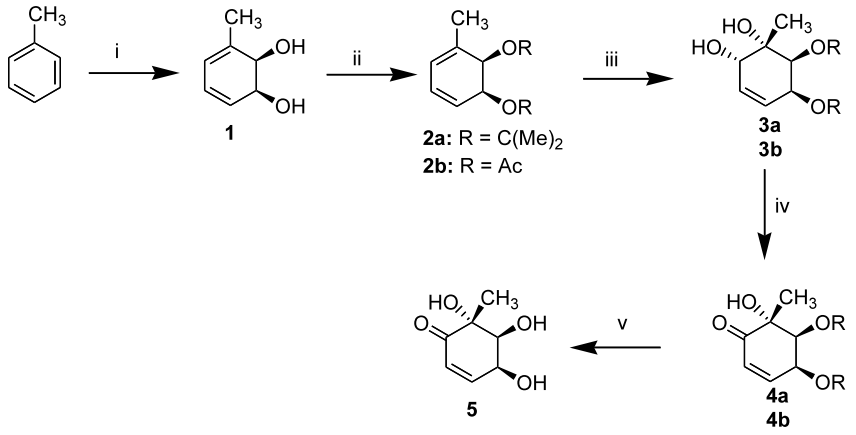


Scheme 2. *Reagents and conditions*: (i) *P. putida* F39/D; (ii) 2,2-dimethoxypropane (solvent), *p*-TsOH (catalytic), rt, 80% of **2a**, or acetic anhydride (solvent), NEt_3 (2.2 equiv.), DMAP (catalytic), 90% of **2b**; (iii) OsO_4 (catalytic), NMO (1.1 equiv.), acetone/water (1/1), 55% for R = C(Me)$_2$, 42% for R = Ac; (iv) Dess–Martin (1.5 equiv.), CH_2Cl_2, rt, overnight, 75% for R = C(Me)$_2$, 60% for R = Ac; (v) for **4a**: Dowex 50, MeOH/H_2O (1/5), 50°C, 86%.

bond, in 65% yield.[13] Then, the secondary alcohol in diols **3** was oxidized with Dess–Martin periodinane[14] to furnish the corresponding enones, **4a** and **4b**, in acceptable yields. Subsequently, the hydroxy groups could be conveniently deprotected to yield enone **5** with the correct regio- and stereochemistry of ring B of forskolin. Enone **4a** was deprotected easily using an acidic ion-exchange resin to give trihydroxyenone **5**, whose structure has been confirmed by X-ray analysis, as shown in Fig. 1. In this way, this compound was obtained in 36% overall yield from diol **1** through a short and efficient sequence.

Conversely, acetylated enone **4b** could not be successfully deprotected: It decomposed under basic deprotection conditions (K_2CO_3/MeOH and DBU/toluene), and was not hydrolyzed under enzymatic conditions, using *Candida cylindracea* lipase, in a pH 7.6 buffer, at 36°C, for 5 days.

The use of non-selective protecting groups described above to obtain enone **5** allow us ready access to simpler intermediates in order to evaluate the success of the synthetic approach, and may also produce useful chiral enones on its own turn. However, to obtain the correct stereoselectivity in the closure of ring A from enone **5** via the Michael–aldol addition sequence, selective protection of the diol system in **1** is required. The selective protection of the diol functionality was performed using the bulky silylating agent chlorothexyltrimethylsilane (Cl-THS)[15] that reacted with the less hindered hydroxy group. Following the previously described methodology, the corresponding enones **9** were obtained in acceptable yields (Scheme 3).

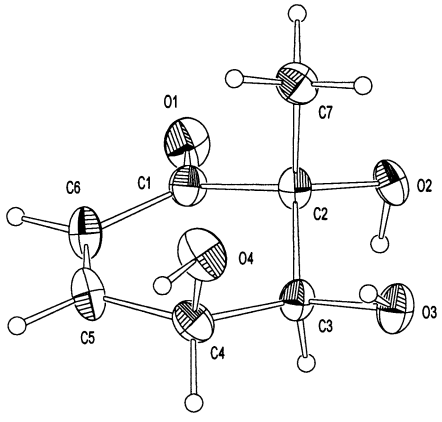


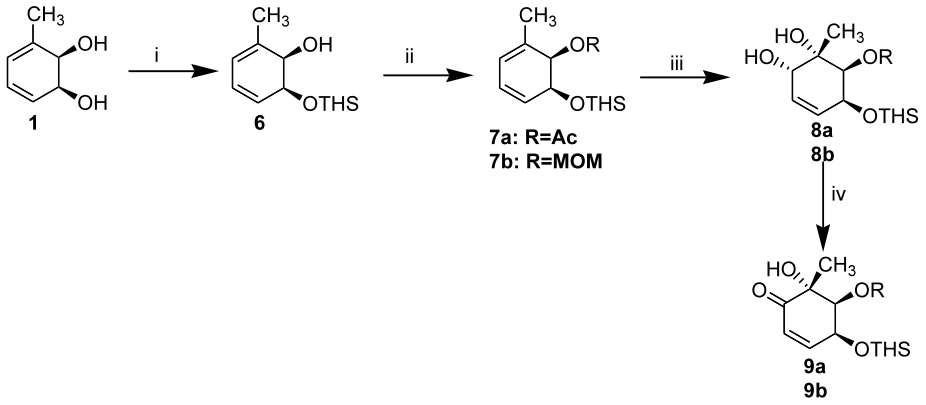
Figure 1.

Attempts to desilylate **9a** (using Bu_4NF/THF and HF/py) resulted in partial migration of the acetate group, producing a mixture of monoacetylated dihydroxyenones. However, **9a** could be deacetylated to afford **10** in moderate yields, while **9b** was conveniently desilylated yielding enone **11** (Scheme 4). The use of enone **11** in the construction of the A–B ring system of forskolin is currently under study and will be published in due course.

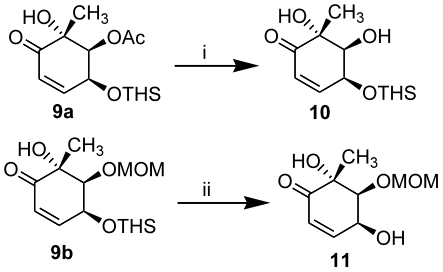
In summary, starting from diol **1** a set of differentially protected enones, resulting in mono-, di- and trihydroxyenones, was prepared.

2.2. Methoxycyclohexadienediol-derived enone

Microbial dihydroxylation of anisol produces methoxycyclohexadienediol **12**, which is an unstable metabolite that decomposes to aromatic products even under mild conditions.[10] In order to make this diol synthetically useful we intended to control its reactivity by performing a Diels–Alder reaction in which **12** was treated with the Cookson dienophile.[16] The expected cycloaddition adduct was not observed. Instead, enone **13** was isolated in 90% yield, as shown in Scheme 5. We propose a Diels–Alder reaction followed by collapse of the adduct to the enone to account for the formation of **13**. The absolute stereochemistry at C4 in enone **13** was not unambiguously confirmed, but, as free diols generate *endo-syn* adducts,[10,17,18] the most probable configuration is *S*, which is in agreement with observed spectroscopic data.



Scheme 3. *Reagents and conditions*: (i) THSCl (1.1 equiv.), imidazole (2.2 equiv.), DMF, 0°C, 85%; (ii) acetic anhydride (solvent), NEt_3 (1.2 equiv.), DMAP (catalytic), 0°C, 80% or chloromethylmethyl ether (1 equiv.), DIPEA (1.1 equiv.), CH_2Cl_2, 0°C→rt, 80%; (iii) OsO_4 (catalytic), NMO (1.1 equiv.), acetone/water (1/1), 70% for R = Ac, 52% for R = MOM; (iv) Dess–Martin (1.5 equiv.), CH_2Cl_2, rt, overnight, 75% for R = Ac, 80% for R = MOM.



Scheme 4. *Reagents and conditions*: (i) K_2CO_3 (2.5 equiv.), MeOH, rt, 35%; (ii) Bu_4NF (1.2 equiv.), THF, 0°C→rt, 52%.

2.3. Chlorocyclohexadienediol-derived enones

The dienic system in chlorocyclohexadienediol reacts with electrophiles preferentially at the distal alkene moiety to produce compounds such as **15** and **17**, as opposed to the previous cases (Scheme 6).[9] These compounds can be used as precursors to α,β-unsaturated ketones, **16**, **18**, and **19**. In these enones, the chlorinated system offers new possibilities of functionalization through conjugate substitution of the chlorine atom by nucleophiles.

To produce the desired enones, chlorocyclohexadienediol was prepared through microbial oxidation of chlorobenzene and then quantitatively protected as the corresponding acetonide **14**.[13] Functionalization of **14** through the distal alkene was attempted via hydroboration–oxidation using catecholborane[19,20] (no reaction observed) and oxymercuration–demercuration[21] (decomposition to aromatic products occurred). Harsher methods (such as HBr addition with or without phase transfer agents) resulted in deprotection of the diol system followed by aromatization. Attempts to synthesize **17** via Wacker oxidation[22] resulted in decomposition through Diels–Alder dimerization[23] of the starting acetonide with no oxidation observed.

Finally, **14** was reacted via catalytic osmium tetraoxide dihydroxylation producing **15**[13] and via bromohydrin synthesis producing **17**.[24] Two different enones, **16** and **18**, were then synthesized by oxidation of the allylic alcohols with Dess–Martin periodinane[14] (MnO_2 gave no reaction after 15 days) in moderate to good yields as shown in Scheme 6. In the case of the diol **15**, equimolar addition of oxidizing agent resulted in extremely poor yields of **16**, while increasing the amounts of Dess–Martin reagent caused overoxidation to the corresponding diketone. The best results were obtained using 2 equivalents of oxidizing agent, resulting in 45% isolated yield, the remainder being diketone (30%) and unreacted starting material, which could be recycled. On the other hand, the bromoketone **18** was obtained in good yield and debrominated[25] with Zn/NH_4Cl in moderate yield to give the corresponding enone **19**.

Enones **16**, **18**, and **19** are highly functionalized intermediates with interesting synthetic potential for the preparation of natural products. In particular, enone **19** can be used as a building block for the synthesis of avermectines. The chlorinated α,β-unsaturated ketone system can also be further functionalized by conjugate substitution reactions.[26]

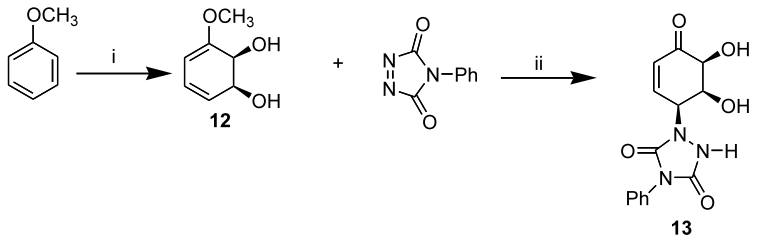
3. Conclusions

A series of highly functionalized, polyoxygenated chiral enones, **4**, **5**, **9**–**11**, **13**, **16**, **18**, and **19**, with potential applications as synthetic intermediates have been successfully synthesized via simple reactions. The reported synthetic sequences are short and allow the rapid preparation of these synthons in multigram quantities.

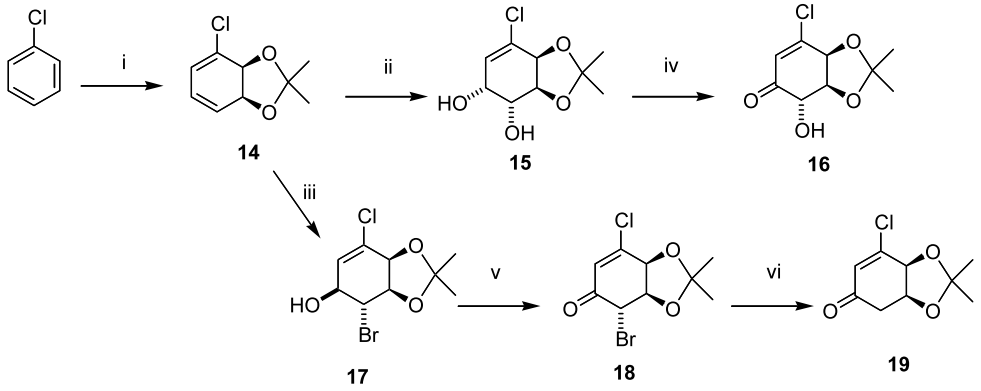
4. Experimental

4.1. General

All non-hydrolytic reactions were carried out in a nitrogen atmosphere with standard techniques for the



Scheme 5. *Reagents and conditions*: (i) *P. putida* F39/D; (ii) CH_2Cl_2, 0°C, 1 h, 90%.



Scheme 6. *Reagents and conditions*: (i) *P. putida* F39/D then 2,2-dimethoxypropane, *p*-TsOH (cat.), rt, 90%; (ii) OsO_4 (catalytic), NMO (1.1 equiv.), acetone/water (1/1), reflux, overnight, 80%; (iii) NBS (1.1 equiv.), water, DME, 0°C, darkness, 1 h, 70%; (iv) Dess–Martin periodinane (1.1 equiv.), CH_2Cl_2, rt, overnight, 45%; (v) Dess–Martin periodinane (1.1 equiv.), CH_2Cl_2, rt, overnight, 75%; (vi) Zn (1.1 equiv.), NH_4Cl (30% in water), rt, 10 min, 50%.

exclusion of air. All solvents were distilled prior to use. Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. Mass spectra were recorded on a Shimadzu GC–MS QP 1100 EX instrument using the electron-impact mode (70 eV) or chemical ionization (if indicated) or on a Finnigan MATQSQ spectrometer. Infrared spectra were recorded either on neat samples (KBr disks) or in solution (with solvent substraction) on Perkin–Elmer 1310 or Bomem, Hartmann & Braun FTIR spectrometers. Proton NMR spectra were obtained on Bruker Avance DPX-400, Bruker AC-200, or Varian XL-100 instruments. Carbon NMR were obtained on Bruker Avance DPX-400 at 100 MHz. Proton chemical shifts (δ) are reported in ppm downfield from tetramethylsilane as an internal reference (0.0 ppm), and carbon chemical shifts are reported in ppm relative to the center line of the $CDCl_3$ triplet (77.0 ppm). Combustion analyses were performed in a Fisons EA 1108 CHNS-O analyser. X-Ray studies were done on a AFC75-Rigaku single-crystal diffractometer, over recrystallized samples. Optical rotations were measured on a Perkin–Elmer 241 polarimeter using a 2 mL cell. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

Diols **1**, **12** and **14** were obtained by fermentation of the corresponding arenes.[27] Analytical TLC was performed on silica gel 60F-254 plates and visualized with UV light (254 nm) and/or *p*-anisaldehyde in acidic ethanolic solution. Flash column chromatography was performed using silica gel (Kieselgel 60, EM Reagents, 200–400 mesh).

4.2. (1*S*,2*R*)-1-(Dimethylthexylsilyl)oxy-2-*O*-methoxymethyl-3-methyl-3,5-cyclohexadien-2-ol, 7b

To a solution of monosilylated diol **6**[15] (2 g, 7.5 mmol) in CH_2Cl_2 (30 mL) at 0°C was added diisopropylethylamine (1.1 g, 8.3 mmol) and chloromethylmethyl ether (0.6 g, 7.5 mmol). After 20 h of stirring the solvent was evaporated and the residue was dissolved in Et_2O. The ethereal solution was neutralized with saturated aqueous $NaHCO_3$, washed with 10% aqueous $CuSO_4$ (3×), and with brine (2×), and dried over $MgSO_4$, and filtered, and then the solvent was evaporated to yield **7b** (1.8 g, 80%). Due to the instability of this compound no further attempts were made towards its purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 3H), 0.18 (s, 3H), 0.90 (m, 12H), 1.62 (m, 1H), 1.96 (s, 3H), 3.37 (s, 3H), 3.74 (d, J=5.4 Hz, 1H), 4.54 (m, 1H), 4.66 (d, J=6.8 Hz, 1H), 4.94 (d, J=6.8 Hz, 1H), 5.72 (d, J=9.4 Hz, 1H), 5.82 (s, 1H), 5.87 (m, 1H).

4.3. (1*S*,2*S*,3*S*,4*S*)-4-(Dimethylthexylsilyl)oxy-3-*O*-methoxymethyl-2-methyl-5-cyclohexen-1,2,3-triol, 8b

To a stirred solution of **7b** (1.7 g, 5.4 mmol) in a 1/1 mixture of acetone/water (20 mL) was added *N*-methylmorpholine-*N*-oxide (0.77 g, 6.5 mmol) and a catalytic amount of OsO_4 at rt. The mixture was protected from light and stirred for 6 h. The acetone was then evaporated and the residue dissolved in EtOAc. The organic solution was successively washed with saturated aqueous $NaHSO_3$ (1×) and 10% aqueous $CuSO_4$. The

combined aqueous layers were then extracted with EtOAc (2×) and the combined organic layers were washed with brine (1×), and dried over $MgSO_4$. Evaporation of the solvent gave a yellow oil, which was chromatographed (silica gel, EtOAc/hexanes: 20/80) yielding **8b** (0.98 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.13 (d, $J=2.3$ Hz, 3H), 0.16 (d, $J=4.8$ Hz, 3H), 0.84–0.90 (m, 12H), 1.38 (d, $J=10.6$ Hz, 3H), 1.64 (m, 1H), 3.01 (s, 1H), 3.32 (s, 1H), 3.34 (s, 3H), 3.77 (d, $J=3.6$ Hz, 1H), 4.12 (m, 1H), 4.55 (m, 1H), 4.71 (d, $J=6.8$ Hz, 1H), 4.86 (d, $J=6.8$ Hz, 1H), 5.53–5.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −2.5, −2.3, 18.9, 19.0, 20.5, 20.6, 23.7, 25.4, 34.3, 56.5, 69.0, 71.2, 128.5, 129.3, 131.3. Due to the instability of this compound it was not possible to obtain other characterization data.

4.4. General procedure for Dess–Martin oxidation

To a solution of the corresponding alcohol (diols **3a**,[13] **3b**,[13] **8a**,[13] **8b**, **15**[13] or bromohydrin **17**[24]) in CH_2Cl_2 was added a solution of Dess–Martin reagent (1.5 equiv.). After stirring overnight at rt, the CH_2Cl_2 was evaporated and the residue partitioned between Et_2O and saturated aqueous $NaHCO_3$. Then $Na_2S_2O_3$ (7 equiv.) was added and the mixture was stirred to dissolve the solid. After phase separation, the aqueous layer was extracted with Et_2O (3×) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ until no more CO_2 evolved, and then with brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated to give a residue, which was purified by chromatography (silica gel, EtOAc/hexanes).

4.5. (2*R*,3*S*,4*S*)-3,4-Isopropylidenedioxy-2-hydroxy-2-methyl-5-cyclohexen-1-one, 4a

Yield: 75%; mp 72.0–73.0°C; $[\alpha]_D^{25}=+110.8$ (c 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 3H), 1.44 (s, 3H), 1.45 (s, 3H), 3.11 (s, 1H), 4.42 (dd, $J=6.0$, 1.0 Hz, 1H), 4.86 (m, 1H), 6.11 (dd, $J=10.2$, 1.2 Hz, 1H), 6.76 (ddd, $J=10.2$, 3.2, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 26.4, 27.4, 72.0, 74.5, 80.8, 111.6, 127.3, 144.3, 199.2; MS (CI, CH_4) m/z (%): 199 ($(M+1)^+$, 17), 198 (M^+, 4), 183 (16), 169 (5), 141 (70), 123 (100), 115 (51), 114 (11), 113 (13), 97 (58), 95 (59), 81 (10), 59 (16), 43 (61); IR (KBr): 3410, 2980, 2920, 2880, 1675, 1380 (d), 1225, 1040, 1060 cm^{-1}. Anal. calcd for $C_{10}H_{14}O_4$: C, 60.60; H, 7.11. Found: C, 60.26; H, 7.34%.

4.6. (2*R*,3*S*,4*S*)-3,4-Diacetoxy-2-hydroxy-2-methyl-5-cyclohexen-1-one, 4b

Yield: 60%; $[\alpha]_D^{25}=+123.7$ (c 0.19, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.46 (s, 3H), 2.10 (s, 3H), 2.12 (s, 3H), 4.78 (s, 1H), 5.42 (d, $J=4.0$ Hz, 1H), 6.00 (ddd, $J=4.0$, 4.0, 1.0 Hz, 1H), 6.26 (dd, $J=10.0$, 1.0 Hz, 1H), 6.82 (dd, $J=10.0$, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 21.1, 21.9, 66.4, 73.5, 75.1, 129.4, 143.4, 170.2, 198.6; MS (CI, CH_4) m/z (%): 139 (11), 97 (36), 84 (21), 74 (17), 43 (100); IR (KBr): 3447, 2924, 1750, 1696, 1372, 1283 cm^{-1}. Anal. calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.24; H, 5.85%.

4.7. (2*R*,3*S*,4*S*)-3-Acetoxy-4-(dimethylthexylsilyl)oxy-2-hydroxy-2-methyl-5-cyclohexen-1-one, 9a

Yield: 75%; $[\alpha]_D^{25}=+80.7$ (c 0.15, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$): δ 0.13 (s, 6H), 0.86 (m, 12H), 1.42 (s, 3H), 1.48–1.80 (m, 1H), 2.14 (s, 3H), 3.48 (broad s, 1H), 4.78 (t, $J=6.0$ Hz, 1H), 5.18 (d, $J=5.0$ Hz, 1H), 6.10 (d, $J=5.0$ Hz, 1H), 6.75 (dd, $J=11.0$, 5.0 Hz, 1H); MS (EI, 20 eV) m/z, (%): 257 (1), 197 (100), 169 (29), 153 (71), 139 (5) 117 (30), 95 (13), 75 (41), 73 (28), 43 (37).

4.8. (2*R*,3*S*,4*S*)-4-(Dimethylthexylsilyl)oxy-3-*O*-methoxymethyl-2,3-dihydroxy-2-methyl-5-cyclohexen-1-one, 9b

Yield: 80%; $[\alpha]_D^{25}=+108.8$ (c 6.1, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 3H), 0.19 (s, 3H), 0.85 (s, 6H), 0.86 (d, $J=1.9$ Hz, 3H), 0.88 (d, $J=1.9$ Hz, 3H), 1.45 (s, 3H), 1.63 (m, 1H), 3.43 (s, 3H), 3.85 (d, $J=4.3$, 1H), 4.59 (t, $J=4.6$ Hz, 1H), 4.79 (d, $J=6.5$ Hz, 1H), 4.89 (d, $J=6.5$ Hz, 1H), 6.06 (d, $J=10.1$ Hz, 1H), 6.78 (dd, $J=10.1$, 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −2.2, −2.3, 18.9, 19.0, 20.5, 20.6, 23.2, 25.5, 34.4, 56.5, 67.1, 97.4, 127.0, 147.8, 199.1 Due to the instability of this compound it was not possible to obtain other characterization data.

4.9. (4*S*,5*S*,6*S*)-3-Chloro-4,5-isopropylidenedioxy-6-hydroycyclohex-2-en-1-one, 16

Yield: 45%; $[\alpha]_D^{25}=-33.1$ (c 0.16, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 3H), 1.59 (s, 3H), 3.60 (broad s, 1H), 4.33 (d, $J=7.4$ Hz, 1H), 4.43 (dd, $J=7.4$, 6.3 Hz, 1H), 4.85 (d, $J=6.2$ Hz, 1H), 6.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.4, 28.2, 74.7 76.1, 78.9, 112.6, 127.8, 152.3, 194.9; MS (EI, 70 eV) m/z (%): 205 (3), 203 (10), 163 (2.5), 161 (7); IR (KBr): 3420, 3050, 2980, 2870, 1700, 1620, 1365 (d), 1240, 1220, 1160, 1120, 1070 cm^{-1}.

4.10. (4*S*,5*S*,6*S*)-6-Bromo-3-chloro-4,5-isopropylidene-dioxycyclohex-2-en-1-one, 18

Yield: 75%; $[\alpha]_D^{20}=-69.3$ (c 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.39 (s, 3H), 4.40 (s, 1H), 4.76 (s, 2H), 6.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.2, 27.8, 41.9, 74.3, 78.3, 113.3, 125.5, 154.6, 187.4; EM (EI, 70 eV) m/z (%): 269 (9), 267 (19), 265 (11), 227 (2), 225 (7), 223 (6); IR (KBr): 2990, 2940, 1685, 1610, 1375 (d), 1340, 1290, 1230, 1150, 1070 cm^{-1}.

4.11. (2*R*,3*S*,4*S*)-2-Methyl-2,3,4-trihydroxy-5-cyclohexen-1-one, 5

Enone **4a** (200 mg, 1 mmol) was dissolved in MeOH (2 mL). Water (10 mL) and catalytic amounts of acidic resin DOWEX 50 WX8-200 were added, and the reaction mixture was heated at 50°C for 12 h. The resin was filtered off and EtOAc was added in order to evaporate water by vacuum azeotropic distillation. The residue was chromatographed (silica gel, EtOAc) yielding enone **5** (137 mg, 86%); mp 139.0–141.5°C; $[\alpha]_D^{25}=$

+175.4 (*c* 0.7, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 1.36 (s, 3H), 3.93 (dd, $J=3.7$, 2.0 Hz, 1H), 4.77 (m, 1H), 5.93 (dd, $J=10.4$, 2.2 Hz, 1H), 6.75 (dt, $J=10.4$, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 20.1, 66.7, 75.2, 77.3, 126.6, 149.3, 199.4; MS (CI, CH_4) m/z (%): 159 ($(M+1)^+$, 26), 141 (40), 123 (100), 113 (20), 95 (99); IR (KBr): 3350, 2920, 2880, 1680, 1445, 1370, 1290, 1150, 1090, 1045 cm^{-1}. Anal. calcd for $C_7H_{10}O_4$: C, 53.20; H, 6.33. Found: C, 53.15; H, 6.54%.

Crystallographic data (excluding structure factors) for enone **5** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 182304. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.12. (2*R*,3*S*,4*S*)-2,3-Dihydroxy-4-(dimethylthexylsilyl)-oxy-2-methyl-5-cyclohexen-1-one, 10

To a solution of enone **9a** (50 mg, 0.15 mmol) in MeOH (5 mL) was added K_2CO_3 (52 mg, 0.375 mmol) at rt. After stirring for 3 h, the MeOH was evaporated and the residue was dissolved in EtOAc. The organic layer was washed with brine (2×), dried over $MgSO_4$, and the solvent was evaporated. The residue was chromatographed (silica gel, EtOAc/hexanes: 30/70) yielding enone **10** (15 mg, 35%). $[\alpha]_D^{25}=+106.6$ (*c* 0.43, acetone); ^{1}H NMR (100 MHz, $CDCl_3$): δ 0.20 (s, 3H), 0.90 (m, 12H), 1.42 (s, 3H), 1.50–1.90 (m, 1H), 3.42 (s, 2H), 4.65 (dd, $J=8.0$, 4.0 Hz, 1H), 4.90 (m, 1H), 6.12 (d, $J=2.0$ Hz, 1H), 6.75 (ddd, $J=11.0$, 4.0, 2.0 Hz, 1H).

4.13. (2*R*,3*S*,4*S*)-2-Methyl-3-*O*-methoxymethyl-2,3,4-trihydroxy-5-cyclohexen-1-one 11

To a stirred solution of enone **9b** (200 mg, 0.58 mmol) in anhydrous THF (15 mL) was added Bu_4NF (0.8 mL of a 1 M solution in THF) at 0°C and the reaction was allowed to warm to rt. After 5 h the solvent was evaporated and the residue was dissolved in EtOAc. This solution was washed with brine (2×), dried over $MgSO_4$, and the solvent was evaporated to give a residue which was chromatographed (silica gel, EtOAc/hexanes: 60/40) yielding enone **11** (61 mg, 52%); $[\alpha]_D^{25}=+63.7$ (*c* 6.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 3H), 3.17 (broad s, 2H), 3.46 (s, 3H), 3.90 (d, $J=4.6$ Hz, 1H), 4.65 (t, $J=4.6$ Hz, 1H), 4.82 (d, $J=6.5$ Hz, 1H), 4.94 (d, $J=6.5$ Hz, 1H), 6.16 (dd, $J=10.2$, 0.7 Hz, 1H), 6.92 (dd, $J=10.2$, 4.6 Hz, 1H). Due to the instability of this compound it was not possible to obtain other characterization data.

4.14. 1-((1*S*,5*S*,6*S*)-5,6-Dihydroxy-4-oxocyclohex-2-en-1-yl)-4-phenyl-1,2,4-triazolidine-3,5-dione, 13

To a solution of cyclohexadienediol **12**[10,11] (300 mg, 2.1 mmol) in CH_2Cl_2 (10 mL) was slowly added a solution of 4-phenyl-1,2-triazoline-3,5-dione (368 mg, 2.1 mmol) in 20 mL of CH_2Cl_2. After 1 h of stirring the solvent was evaporated and the residue was chromatographed (silica gel, EtOAc/hexanes: 80/20) yielding enone **13** (580 mg, 90%); mp 159–162°C; $[\alpha]_D^{20}=-37.0$ (*c* 0.54, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.43 (d, $J=2.6$ Hz, 1H), 4.59 (dd, $J=5.5$, 2.6 Hz, 1H), 4.88 (s, 1H), 5.37 (dd, $J=5.5$, 2.9 Hz, 1H), 6.18 (dd, $J=10.2$, 2.9 Hz, 1H), 6.89 (dt, $J=10.2$, 1.8 Hz, 1H), 7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.8, 75.4, 75.5, 126.1, 128.2, 128.8, 128.8, 131.6, 144.0, 153.2, 153.5, 198.0; MS (CI, CH_4) m/z (%): 302 ($(M-1)^+$, 0.9), 286 (100), 245 (39), 213 (79), 152 (28), 126 (32), 125 (21), 120 (29), 94 (63); HRMS calcd for $C_{14}H_{11}N_3O_4$ (M^+-H_2O): 285.0746. Found: 285.0676; IR (KBr): 3400, 1740, 1650, 1480, 1420, 1280, 1260, 1120 cm^{-1}.

4.15. (4*S*,5*S*)-3-Chloro-4,5-isopropylidenedioxycyclohex-2-en-1-one, 19

To a solution of enone **18** (0.18 g, 0.64 mmol) in THF (0.5 mL) was added aqueous 30% NH_4Cl (10 mL) and Zn dust (45 mg, 0.69 mmol). The mixture was stirred at rt and after 10 min was extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (3×10 ml), dried over $MgSO_4$, and the solvent was evaporated. The residue was chromatographed (silica gel, EtOAc/hexanes: 20/80) yielding enone **19** as a clear oil (65 mg, 50%); $[\alpha]_D^{20}=-33.1$ (*c* 0.16, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 3H), 1.42 (s, 3H), 2.72 (dd, $J=17.6$, 3 Hz, 1H), 2.97 (dd, $J=17.4$, 2.5 Hz, 1H), 4.70 (m, 2H), 6.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8, 27.9, 39.0, 73.4, 74.9, 111.2, 128.8, 155.7, 193.2; MS (EI, 70 eV) m/z (%): 189 (14), 187 (43), 147 (18), 145 (55); IR (KBr): 2990, 2920, 1685, 1610, 1500, 1375 (d), 1300, 1220, 1110 cm^{-1}.

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