Chemoenzymatic Synthesis of Idesolide from Benzoic Acid

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Abstract: Idesolide was synthesized in five steps from benzoic acid by base-catalyzed dimerization of hydroxy keto ester, obtained from diol, the product of the whole-cell fermentation of benzoic acid with *R. eutrophus B9*.

Key words: idesolide, hydroxy keto ester, diol, whole-cell fermentation, benzoic acid

In 2005 Kim and co-workers isolated idesolide (**1**) from the fruits of *Idesia polycarpa*, a tree native to Southeast Asia, known to contain bioactive compounds.[1] From 9 kg of fruit, Kim and his group isolated 32 g of mixed fractions that exhibited potent anti-inflammatory activity. Further purification yielded idesolide as a crystalline compound {mp 141–143 °C, $[\alpha]_D^{25}$ –230 (*c* 1, $CHCl_3$)} whose structure and relative stereochemistry was assigned by spectral methods and crystal structure analysis. The absolute stereochemistry of idesolide was determined in 2010 by Iwabuchi[2] by way of the first total synthesis of this unique unsymmetrical dimer via dimerization of hydroxy ketone **2** (Figure 1) prepared in ten steps from glutaraldehyde. Later that year, a nine-step enantioselective synthesis of idesolide via dimerization of **2** was reported by Kuwahara.[3]

Hydroxy ketone **2** is itself a natural product isolated from a number of species and identified by Fransworth in 1993 in *n*-BuOH extracts of *Homalium ceylanicum*.[4] In 2006 Sterk and co-workers[5] isolated hydroxy ketone **2** from *Dovyalis* species native to Central Africa and northern South America and confirmed the structure previously assigned by Farnsworth. This compound has also been identified as a structural component in several natural products such as the phenolic glycosides **3a–e** and **4a–c** (Figure 1) isolated from fruit, leaves, bark, and twigs of *Idesia polycarpa*, *Salix purpurea*, *Dovyalis abyssinica*, and other species.

The structural elucidation of the glycosides from willows and poplars, namely **3a–e**, was completed during the 1970s. For example, the structure of salicortin (**3a**), first isolated by Thieme in 1964 from the bark *Salix purpurea*,[6] was elucidated by Darling, along with the composition of

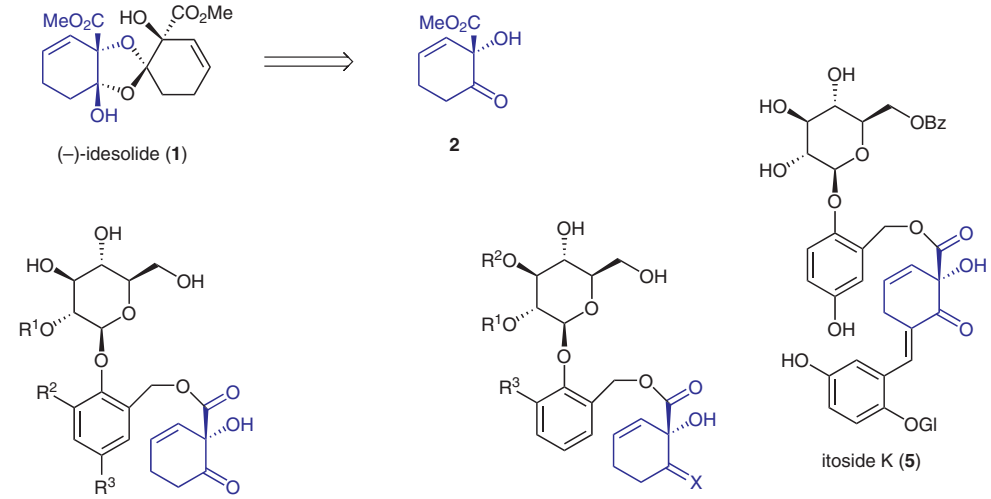

Figure 1 Structure of idesolide (**1**), its monomeric hydroxy ketone **2**, and related natural products

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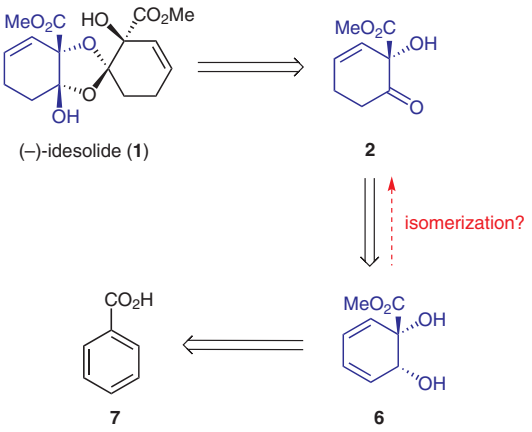
tremulacin (**3c**), in the early 1970s.[7] In 1997 Chou[8] isolated and identified idescarpin (**3b**) in the extracts of the fruit of *Idesia polycarpa*. Salicin derivatives **4a–c** were isolated and identified by Ishikawa in 2004[9] from the extracts of Taiwanese plant *Homalium cochinchinensis*, used in folk medicine to treat gonorrhea. Tremulacinols **4b** and **4c** were shown by Ishikawa to contain the reduced from of hydroxy keto ester **2** as a mixture of *trans* and *cis* isomers. In 2008 Tu and co-workers isolated itoside K (**5**)[10] from *Itoa orientalis* and identified the subunit **2** as its condensed form with the glucoside derived from 2,5-dihydroxy benzaldehyde (Figure 1).

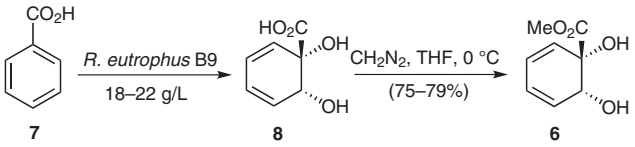
Despite the ubiquitous presence of the hydroxy keto ester component **2** in many natural products, its synthesis was not reported until 2007[11] when Snider and his group took active interest in the chemistry of this compound and its potential dimerization to idesolide (**1**). The Snider synthesis of **2** involved the Birch reduction of the 2-(trimethylsilyl)ethoxymethyl (SEM)-protected methyl salicylate followed by trapping the intermediate enolate with the Davis reagent and hydrolysis afforded **2** in ca. 38% overall yield (the Davis hydroxylation led, surprisingly, to only marginal asymmetric induction and additional enrichment, to the tune of 85% ee, was required by kinetic resolution of **2** with pig liver esterase). At five steps it was relatively efficient, despite the low levels of asymmetric induction. Two other syntheses have been reported since Iwabuchi's synthesis required nine steps from glutaraldehyde and employed an organocatalytic oxidative kinetic resolution. Kuwahara's ten-step preparation from cyclohexenone used the Sharpless epoxidation for the introduction of asymmetry.

We envisioned a relatively efficient access to **2**, and hence idesolide, via enzymatic dihydroxylation of benzoic acid with a mutant strain of *Ralstonia eutropha* B9 (formerly named *Alcaligenes eutrophus*) developed by Reiner and Hegeman.[12] Scheme 1 shows the retrosynthetic analysis for the synthesis of idesolide via **2**, which, in principle, should be accessible by a simple isomerization of the allylic alcohol in diol **6**. This compound is available from diol **8** (Scheme 2) obtained by fermentation of benzoic acid with the organism that overexpresses the enzyme benzoate dioxygenase.



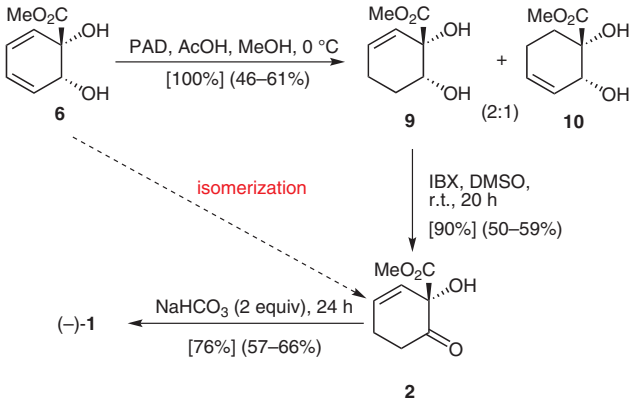
Scheme 1 Design for idesolide via enzymatic dihydroxylation of benzoic acid

The whole-cell fermentation of benzoic acid provided an excellent yield of diol **8** (Scheme 2) conveniently isolated from the fermentation broth as its mixed potassium/sodium salt[13] in 18–22 g/L amounts (quantified by HPLC) and >95% ee. Esterification with diazomethane provided the methyl ester **6**, a compound possessing the same oxidation state as the desired keto ester **2**.



Scheme 2

Diol **6** was subjected to a diimide reduction with potassium azadicarboxylate (PAD), providing a 2:1 mixture of diols **9** and **10** (Scheme 3). This level of selectivity was the best obtained and no improvement in regioselectivity was noted in the similar reductions employing *tert*-butyl ester of **6** or the free acid **8**. The major isomer was oxidized with IBX in DMSO to furnish the desired keto ester **2**. Hydroxy ketone **2** proved to be a very sensitive compound that was prone to oxidative cleavage under several reaction and workup conditions. Neutral and aqueous workup conditions were required in order to isolate **2** without further degradation and allowed for precipitation of the reduced IBX byproducts from the reaction mixture.

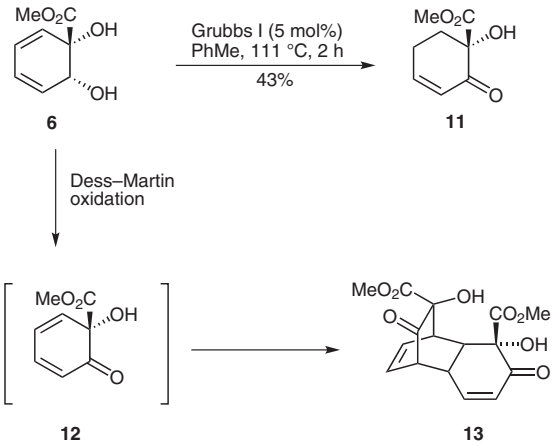


[values in brackets indicate conversion]

Scheme 3

The keto ester **2** was then subjected to several solid-supported reagents in attempts to effect the dimerization to (–)-**1**. Neutral alumina, basic alumina (Brockman Activity I), and ion-exchange resins (Amberlyst A-21 weakly basic and A-27 strongly basic) all resulted in low conversion to idesolide. The use of Amberlyst A-21 (weakly basic) provided the highest conversion at 33%. Treatment of **2** with $NaHCO_3$, conditions previously reported by Kuwahara and co-workers,[3] allowed for isolation of (–)-**1** in 66% yield without chromatography.

The direct isomerization of allylic alcohol **6** to ketone **2** was studied under various conditions with transition-metal catalysts. Iron carbonyl complexes [$Fe(CO)_5$, $Fe_2(CO)_9$, $Fe_3(CO)_{12}$] were investigated under both thermal and photolytic conditions and led to the degradation of **6**, mostly by rearomatization.[14] Ruthenium catalyst [TPAP, octanol, PhF, 90 °C;[15] $Ru_3(CO)_{12}$ (10 mol%), CH_2Cl_2, r.t. to 40 °C; $Ru_2Cl_2(CO)_4$ (10 mol%), CH_2Cl_2, r.t. to 40 °C; $RuCl_3 \cdot H_2O$, MeOH, 45–65 °C; $RuCl_2(PPh_3)_3$, MeOH, 45–65 °C] showed low reactivity toward **6** and slowly induced degradation. Crabtree's catalyst (5 mol%, CH_2Cl_2) and palladium hydride, generated from Pd/C and triethylamine,[16] provided results similar to those observed with the ruthenium and iridium catalysts – slow conversion and degradation. Treatment of **6** with Grubbs first-generation catalyst (5 mol%, toluene, reflux) did provide enone **11** in 43% yield, as the only identifiable compound from a complex mixture (Scheme 4).[17]



Scheme 4

In another attempt at selective formation of **2** we performed oxidation of **6**, which provided the corresponding dienone **12**, expected to be amenable to a selective 1,4-reduction. However, this compound proved unstable to further use because of rapid decomposition and dimerization to **13** via Diels–Alder cycloaddition. The Diels–Alder dimer was isolated in a low yield. The protected form of **12** was reported by Myers to be a reasonably stable compound undergoing slow dimerization at room temperature.[18]

It remains unclear why the allylic alcohol in **6** remained unreactive under the various, and usually reliable, conditions for isomerization to a ketone. Equally unclear is the mechanism of the isomerization of **6** with Grubbs first-generation catalyst. Nevertheless, we were able to synthesize idesolide in four steps and in 10–19% overall yield from the *cis*-dienediol (**8**, five steps from benzoic acid).

The dimerization of keto ester **2**, found in many naturally occurring phenolic glycosides, proved surprisingly problematic under a number of diverse conditions confirming the experience of others who investigated its chemistry. Similarly, the chemistry of diene **6**, especially its reluctance to isomerization, seems to warrant further research. Our synthesis of idesolide compares well with those reported in the literature, in spite of the experimental difficulties encountered. Future work will need to address the selectivity of the reduction of the allylic olefin in either ester **6** or acid **8** in order to optimize the production of **2** and increase the yield of idesolide.

General Experimental Section

All nonaqueous reactions were conducted in an argon atmosphere using standard Schlenk techniques for the exclusion of moisture and air. All solvents were distilled unless otherwise noted. Analytical TLC was performed on EMD Silica gel 60 Å 250 μm TLC plates with F-254 indicator. Flash column chromatography was performed using Silicycle SiliaFlash P60 (230–400 mesh). Melting points were recorded on a Hoover Unimelt apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer One FT-IR spectrometer. Optical rotation was measured on a Perkin-Elmer 341 polarimeter at a wavelength of 589 nm. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz and 600 MHz Bruker spectrometer. All chemical shifts are referenced to TMS or residual undeuterated solvent. Data for ^{1}H NMR spectra are reported as follows: chemical shift {multiplicity [singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m)], coupling constants [Hz], integration}. ^{13}C NMR spectra were recorded with complete proton decoupling, and the chemical shifts are reported in ppm (C) relative to TMS. Mass spectra and high resolution mass spectra were performed by the analytical division at Brock University. Combustion analyses were performed by Atlantic Microlabs, Atlanta, GA.

Methyl (1*S*,6*R*)-1,6-Dihydroxycylohexa-2,4,-diene Carboxylate (6)

To a pre-chilled solution of *ipso*-diene diol carboxylic acid (**8**, 4.0 g, 25.6 mmol) in THF (32 mL, 0.8 M) at ca. 5 °C (ice bath) was added a preformed solution of diazomethane (excess) in Et_2O dropwise over 30 min. The addition of the ethereal solution of diazomethane was continued until consumption of starting material was observed by TLC analysis (hexanes–EtOAc = 1:1, CAM). The reaction mixture turned from a slight yellow to a full yellow color over the course of diazomethane addition. The reaction mixture was removed from the ice bath and allowed to warm to r.t. with stirring. After warming to ambient temperature the reaction mixture was concentrated in vacuo to provide orange oil (quantitative by mass). The crude material was chromatographed on silica gel (hexanes–EtOAc = 1:1) to yield 3.39 g (78% yield) *ipso*-diene diol methylester (**6**) as white needle-like crystals after crystallization from Et_2O. R_f = 0.23 (hexane–EtOAc = 1:1); mp 59–60 °C (Et_2O); $[\alpha]_D^{20}$ –96.696 (*c* 1.0, $CHCl_3$). FT-IR (film): 3412, 1736, 1641, 1564, 1439, 1407, 1265, 1085, 1044, 945, 854, 816 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.17 (q, *J* = 5.07 Hz, 1 H), 5.98 (md, *J* = 1.34, 9.50 Hz, 1 H), 5.85 (td, *J* = 1.00, 9.71 Hz, 1 H), 4.87 (s, 1 H), 3.90 (s, 1 H), 2.89 (s, 2 H). ^{13}C (75 MHz, $CDCl_3$): δ = 175.59, 131.97, 126.83, 124.65, 122.74, 73.85, 70.90, 53.70; MS (EI$^+$): *m/z* = 170. HRMS: *m/z* calcd for $C_8H_{10}O_4$: 170.05852; found: 170.05791. Anal Calcd: C, 56.47; H, 5.92. Found: C, 56.44; H, 5.87.

Methyl (1*S*,6*R*)-1,6-Dihydroxycyclohex-2-ene Carboxylate (9)

To a stirred, chilled (ice bath) solution of ester diol **6** (399 mg, 2.34 mmol) in anhyd MeOH (5.8 mL) was added potassium azodicarboxylate (1.35 g, 7.03 mmol) in portions over 5 min. This yellow slurry was allowed to stir at slightly lower temperature (ca. 5 °C) for 15 min prior to a portionwise addition of a solution of AcOH (glacial, 11.7 mmol) in MeOH (2 mL) over ca. 1.5 h. The rate of addition of AcOH–MeOH was dictated by the rate of N_2 (g) evolution (bubbler) observed from the reaction mixture. The reaction was

monitored by evolution of nitrogen gas and by TLC (EtOAc–hexanes = 2:1). Note: Compound **9** co-elutes with starting material **6** and can be differentiated by the fact that only **6** is UV active. After the addition was complete the reaction mixture was allowed to stir at ca. 5 °C for an additional 20 min prior to slowly warming to r.t. The reaction mixture at ambient temperature was concentrated to dryness and reconstituted in EtOAc (15 mL) to produce a white slurry. The slurry was filtered twice and the filtrate concentrated to provide a colorless oil (576 mg). The crude oil was chromatographed on silica gel (3:1 to 1:1 hexanes–EtOAc) to yield 155 mg of diol **9** as a white crystalline solid (40% yield single isomer; 81% overall yield, combined isomers **9** and **10**).

Compound **9**: R_f = 0.50 (EtOAc–hexanes = 2:1); mp 68–71 °C (EtOAc); $[\alpha]_D^{20}$ –36.083 (*c* 1.0, $CHCl_3$). FT-IR (film): 3441, 2953, 1735, 1436, 1262, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.68–1.85 (m, 1 H), 1.86–1.97 (m, 1 H), 2.21–2.32 (m, 2 H), 3.86 (s, 3 H), 4.04 (dd, *J* = 11.68, 3.77 Hz, 1 H), 5.62 (dt, *J* = 9.80, 2.07 Hz, 1 H), 6.05 (ddd, *J* = 9.70, 4.24, 3.01 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.77, 132.90, 125.35, 73.82, 70.85, 53.42, 26.47, 24.91. MS (EI^+): *m/z* = 172. HRMS: *m/z* calcd for $C_8H_{12}O_4$: 172.07; found: 172.07388. Anal Calcd: C, 55.81; H, 7.02. Found: C, 55.68; H, 7.15.

Compound **10**: light brown oil. R_f = 0.39 (EtOAc–hexanes = 2:1); $[\alpha]_D^{20}$ –21.924 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.85 (md, *J* = 1.51, 8.61 Hz, 1 H), 5.58 (qd, *J* = 2.04, 10.19 Hz, 1 H), 4.50 (m, *J* = 1.81 Hz, 1 H), 2.32 (m, *J* = 3.42 Hz, 1 H), 2.08 (m, *J* = 2.21 Hz, 1 H), 2.05–1.65 (m, 4 H), 1.50–1.35 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.25, 128.99, 127.93, 74.50, 72.25, 69.03, 53.23, 34.35, 30.32, 24.05, 21.17, 19.86. MS (EI^+): *m/z* = 172. HRMS: *m/z* calcd for $C_8H_{12}O_4$: 172.07; found: 172.07356. Anal Calcd: C, 55.81; H, 7.02. Found: C, 53.89; H, 7.49.

Methyl (1*S*)-1-Hydroxy-6-oxocyclohex-2-enecarboxylate (2)

To a solution of diol **9** (409 mg, 2.37 mmol) in DMSO (7.9 mL) was added 2-iodoxybenzoic acid (1.99 g, 7.12 mmol) in portions over 1 min. The white slurry turned to a light yellow and clear mixture over several minutes. The reaction was monitored by TLC analysis (hexanes–EtOAc = 1:1) and stirred at r.t. for 15.5 h prior to workup. The reaction mixture appeared as a slightly yellow-white slurry and was filtered. The filtrate was dropped into a stirring volume of H_2O (18 mL) and produced a white precipitate that was stirred at r.t. for 0.5 h prior to filtration. The mother liquor was extracted with Et_2O (10 × 8 mL, 7 × 7 mL, 6 × 4 mL) and EtOAc (2 × 6 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated to provide an orange oil (585 mg crude). The crude material was subjected to silica gel chromatography (hexanes–EtOAc = 2:1) and provided 240 mg (59% yield) of α-hydroxy ketone **2** as a colorless oil that was stored for short periods of time in the freezer. R_f = 0.58 (hexanes–EtOAc = 1:1); $[\alpha]_D^{20}$ –239.702 (*c* 1.0, $CHCl_3$). FT-IR (film): 3468, 2957, 1744, 1725, 1438, 1259, 1138, 1040, 996, 875, 813 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.46–2.71 (m, 3 H), 2.88–2.95 (m, 1 H), 3.72 (s, 3 H), 4.33 (s, 1 H, OH), 5.72 (dt, *J* = 1.67, 9.74 Hz, 1 H), 6.06 (dt, *J* = 3.83, 9.72, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.78, 170.36, 131.88, 127.62, 77.99, 53.46, 35.11, 26.89. MS (EI^+): *m/z* = 170. HRMS: *m/z* calcd for $C_8H_{10}O_4$: 170.06; found: 170.05791.

Dimethyl (1′*R*,2′*S*,3a*S*,7a*R*)-3a,6,7,7a-Tetrahydro-2′,7a-dihydroxyspiro{1,3-benzodioxole-2,1′-[3]cyclohexene}-2′,3a-dicarboxylate [(–)-Idesolide (1)]

To a solution of α-hydroxy ketone **2** (45 mg, 0.261 mmol) in $CHCl_3$ was added anhyd $NaHCO_3$ (44 mg, 0.522 mmol), and the heterogenous mixture, including stir bar, was concentrated on a rotoevaporator with slow rotation in attempts to concentrate the oil at the bottom of the round-bottom flask and evenly distribute the $NaHCO_3$. The resulting colorless oil, spiked with $NaHCO_3$, was subjected to slow stirring under argon atmosphere. After several hours the stirring was inhibited by the viscosity of the crude reaction mixture. The reaction mixture was allowed to stand at r.t. under argon atmosphere. NMR analysis after 43 h indicated a 1:0.6 ratio of idesolide to monomer **2**. The reaction was allowed to proceed for an additional 5.5 h before the mixture was diluted with $CHCl_3$ and filtered. The filtrate was concentrated in vacuo to provide 54 mg of a colorless oil that was stored at –78 °C overnight. Oily white crystals were observed, and the crude material was triturated with pentanes (4 × 0.2 mL) and hexanes (6 × 0.2 mL) to provide 25 mg of (–)-idesolide (**1**, 57% yield) as white crystalline solid. R_f = 0.48 (hexanes–EtOAc = 1:1); mp 136–139 °C; $[\alpha]_D^{20}$ –242.523 (*c* 1.0, $CHCl_3$). FT-IR (film): 3365, 3030, 2955, 2848, 1755, 1738, 1439, 1350, 1259, 1124, 975, 802, 751 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 6.01 (m, 2 H), 5.61 (dd, *J* = 1.83, 9.99 Hz, 1 H), 5.49 (dd, *J* = 2.52, 10.08 Hz, 1 H), 3.93 (s, 3 H), 3.79 (s, 3 H), 2.41 (m, 2 H), 2.27 (m, 4 H), 2.15 (m, 1 H), 1.85 (m, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.21, 169.09, 132.47, 130.68, 126.54, 126.17, 110.96, 102.17, 86.44, 76.70, 54.26, 52.78, 31.05, 29.74, 24.40, 22.44. MS (EI^+): *m/z* = 340. HRMS: *m/z* calcd for $C_{16}H_{20}O_8$: 340.12; found: 340.11499. Anal Calcd: C, 56.47; H, 5.92. Found: C, 55.27; H, 5.84.

Methyl (1*S*)-1-Hydroxy-2-oxocyclohex-3-ene carboxylate (11)

To a solution of diene **6** (65 mg, 0.381 mmol) in toluene (1.5 mL) was added Grubbs first-generation catalyst (15 mg, 0.019 mmol) under argon and with stirring. The lightly colored brown/yellow solution quickly turned purple upon addition of catalyst. The reaction was heated to 111 °C and turned to a clear brown color over several minutes. The reaction was monitored by TLC analysis and deemed complete after approximately 17 h. The reaction mixture was concentrated to dryness, and the crude black oil (70 mg) was chromatographed on silica gel (hexanes–EtOAc = 2:1 to hexanes–EtOAc = 1:1) to yield 28 mg (43% yield) of enone **11** as a light brown/red oil. R_f = 0.52 (hexanes–EtOAc = 1:1). FT-IR (film): 3460, 2955, 2938, 1741, 1681, 1436, 1389, 1259, 1220, 1198, 1139, 1114, 1070 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.09 (m, 1 H), 6.17 (d, *J* = 10.20 Hz, 1 H), 4.24 (OH, s, 1 H), 3.79 (s, 3 H), 2.62 (m, 3 H), 2.10 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.76, 170.68, 152.74, 126.63, 52.98, 32.06, 24.21. MS (EI^+): *m/z* = 170. HRMS: *m/z* calcd for $C_8H_{10}O_4$: 170.06; found: 170.05791.

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