

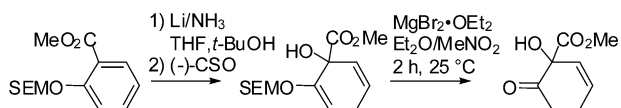
## Synthesis of Methyl 1-Hydroxy-6-oxo-2-cyclohexenecarboxylate, a Component of Salicortin and Tremulacin, and the Monomer of Idesolide

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We have developed a short and practical first synthesis of methyl 1-hydroxy-6-oxo-2-cyclohexenecarboxylate (**2**), which has been known as a component of salicortin and tremulacin since 1970. Birch reduction of the SEM ether of methyl salicylate followed by oxidation of the intermediate enolate with (–)-camphorsulfonyloxaziridine afforded the SEM enol ether of **2**. Hydrolysis of the SEM enol ether afforded **2**. We did not observe the dimerization of either racemic or optically enriched **2** to give idesolide (**1**).

Kim and co-workers recently isolated idesolide (**1**) from the fruits of *Idesia polycarpa* Maxim (see Figure 1).<sup>1</sup> The seeds of this tree have been used as an insecticide in Korea, and the leaves have hemostatic activity. The structure of idesolide was determined spectroscopically and by X-ray crystallography. Idesolide (**1**) is a hemiketal/ketal dimer of methyl 1-hydroxy-6-oxo-2-cyclohexenecarboxylate (**2**). The monomer **2** has also been isolated from several sources, including *Idesia polycarpa*.<sup>2–4</sup> Both **1** and **2** inhibit lipopolysaccharide-induced NO production in BV2 microglia at micromolar concentrations.<sup>1,4</sup>

The 1-hydroxy-6-oxo-2-cyclohexenecarboxylate moiety is also a significant component of several important willow and poplar glycosides that are related to the discovery and development of aspirin.<sup>5,6</sup> It is a component of salicortin (**3a**),<sup>7</sup>

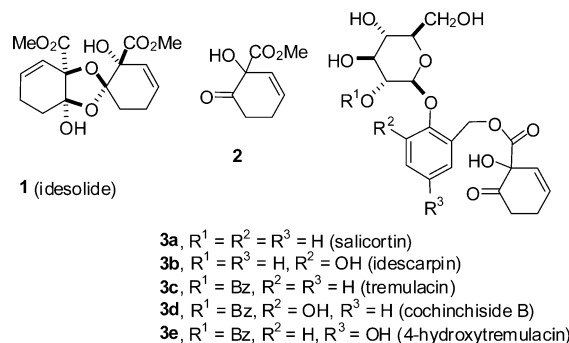
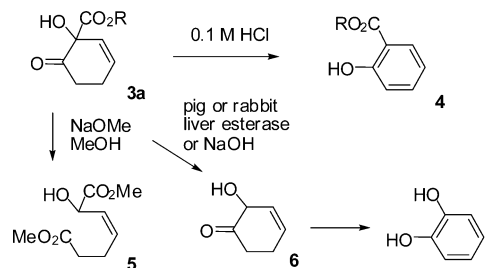


FIGURE 1. Selected naturally occurring 1-hydroxy-6-oxo-2-cyclohexenecarboxylate esters.

idescarpin (**3b**),<sup>8</sup> tremulacin (**3c**),<sup>7</sup> cochinichside B (**3d**),<sup>9</sup> and 4-hydroxytremulacin (**3e**).<sup>3</sup> Although the structures of salicortin and tremulacin were assigned in 1970,<sup>7</sup> the synthesis of the densely functionalized 1-hydroxy-6-oxo-2-cyclohexenecarboxylate moiety has not been reported. This ring system is somewhat unstable, undergoing dehydration in dilute hydrochloric acid to give salicylate esters (**4**) and ring cleavage with NaOMe in MeOH to provide diester **5** (see Scheme 1).<sup>7</sup> Hydrolysis of **3a** with aqueous base or pig/rabbit liver esterase yields a  $\beta$ -keto acid that decarboxylates to provide hydroxycyclohexenone **6**, which is readily oxidized to form catechol (**7**).<sup>7,10</sup>

### SCHEME 1. Reactions of Salicortin (**3a**)



We were intrigued by the isolation of both the monomer **2** and the dimer idesolide (**1**) that apparently do not easily equilibrate with each other. 3-Hydroxybicyclo[2.2.1]heptan-2-one (**8**) dimerizes at room temperature overnight or at 4 °C for 1 week to provide the symmetrical dimer **9** whose structure was determined crystallographically (see Scheme 2).<sup>11</sup> The structures of other related dimers have been inferred from their symmetry.<sup>12</sup> Laurencione (**10**) formed the unsymmetrical dimer **11**, whose structure was shown by X-ray crystal structure determination to be analogous to that of idesolide (**1**).<sup>13</sup> Other dimers

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(2) Ekabo, O. A.; Farnsworth, N. R.; Santisuk, T.; Reutrakul, V. *J. Nat. Prod.* **1993**, *56*, 699–707.

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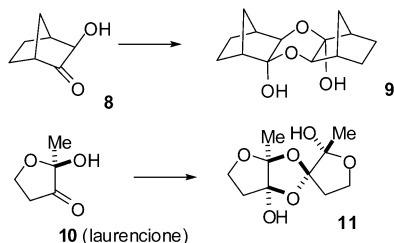
(11) Jauch, J.; Schurig, V.; Walz, L. Z. *Kristallogr.* **1991**, *196*, 255–260.

(12) Shurvell, H. F.; Petelenz, B. U.; Hester, R. E.; Girling, R. B. *J. Mol. Struct.* **1982**, *84*, 11–23.

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have been suggested to have structures analogous to **1** and **11** on the basis of the lack of symmetry in their  $^1\text{H}$  NMR spectra.<sup>14</sup>

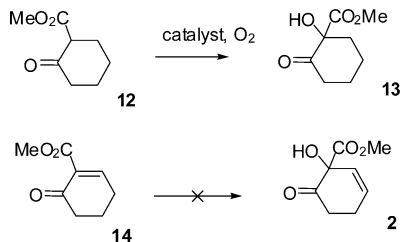
#### SCHEME 2. Dimerization of $\alpha$ -Hydroxyketones



We decided to synthesize methyl 1-hydroxy-6-oxo-2-cyclohexanecarboxylate (**2**) because (1) this functionally dense molecule has never been prepared, although it has been known as a component of salicortin and tremulacin since 1970;<sup>7</sup> (2) recent reports indicate that it inhibits NO production;<sup>1,4</sup> and (3) the isolation of both **2** and the dimer idesolid (**1**) with no apparent equilibration deserved further study.<sup>1,4</sup>

The hydroxylation of methyl 2-oxocyclohexanecarboxylate (**12**) to give methyl 1-hydroxy-2-oxocyclohexanecarboxylate (**13**) can be easily achieved with molecular oxygen and Ce(III), Co(II), or Mn(II) (see Scheme 3).<sup>15</sup> We hoped that we could carry out a similar transformation starting with methyl 6-oxo-1-cyclohexanecarboxylate (**14**).<sup>16</sup> Unfortunately, this and a variety of other approaches to **2** were unsuccessful.

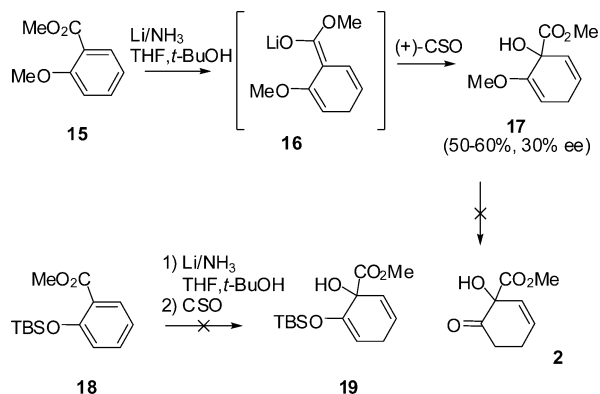
#### SCHEME 3. Unsuccessful Approach to **2**



Eventually, we noted that Schultz had prepared enol ether **17** by the Birch reduction of methyl 2-methoxybenzoate (**15**) followed by trapping intermediate **16** with camphorsulfonyloxaziridine to give **17** in 50–60% yield and 30% ee (see Scheme 4).<sup>17</sup> Simple hydrolysis of the enol ether would provide the desired product **2**. However, **2** is known to be unstable to the acidic conditions required to hydrolyze enol ethers, and all attempts to hydrolyze **17**, including those using soft Hg(II) or Pd(II) salts, gave either unreacted **17**, methyl 2-methoxybenzoate (**15**) resulting from dehydration of **17**, or complex mixtures. Therefore, we needed a protecting group that is sufficiently labile to be removed without the decomposition of the desired product **2** but robust enough to be compatible with the Birch reduction

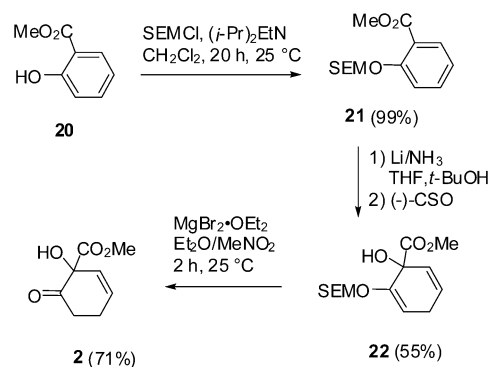
and oxygenation of the intermediate analogous to **16**. Although the TBS enol ether of **19** could probably be cleaved under mild conditions to give **2**, Birch reduction/oxidation of TBS ether **18**<sup>18</sup> failed to give **19**.

#### SCHEME 4. Birch Reduction/Oxidation Provides Enol Ether **17**



We then decided to investigate the Birch reduction/oxidation of SEM ether **21** with the expectation that the enol ether product could be cleaved with fluoride under mild conditions that would not destroy product **2**. Reaction of methyl salicylate (**20**) with SEM chloride and (*i*-Pr)<sub>2</sub>EtN in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C for 20 h afforded the desired SEM ether **21** in 99% yield (see Scheme 5).<sup>19</sup> Birch reduction of SEM ether **21** followed by trapping the intermediate with (–)-camphorsulfonyloxaziridine gave **22** in 55% yield with low enantiomeric excess. Unfortunately, all attempts to convert **22** to **2** using a variety of fluoride protocols gave either unreacted **22**, methyl salicylate (**20**) resulting from deprotection and dehydration of **22**, or complex mixtures. Finally, we were delighted to find that cleavage of the SEM enol ether of **22** with MgBr<sub>2</sub>•OEt<sub>2</sub> in Et<sub>2</sub>O/nitromethane<sup>20</sup> afforded the desired product **2** in 71% yield.

#### SCHEME 5. Synthesis of Methyl 1-Hydroxy-6-oxo-2-cyclohexanecarboxylate (**2**)



The spectral data of **2** are identical to those previously reported.<sup>2,3</sup> However, we were unable to observe the formation of the dimer idesolid (**1**) under a wide variety of conditions. It is important to note that synthetic **2** is almost racemic ( $[\alpha]_D -7$ ), while natural **2** is presumably optically pure ( $[\alpha]_D -185$ ).

(14) (a) Duggan, J. C.; Urry, W. H.; Schaefer, J. *Tetrahedron Lett.* **1971**, 4197–4200. (b) Heyns, K.; Köll, P. *Chem. Ber.* **1971**, *104*, 3835–3841. (c) Heyns, K.; Köll, P. *Chem. Ber.* **1973**, *106*, 611–622. (d) Yates, P.; Langford, G. E. *Can. J. Chem.* **1981**, *59*, 344–355. (e) Freimund, S.; Köpper, S. *Carbohydr. Res.* **1998**, *308*, 195–200. (f) Andersen, S. M.; Lundt, I.; Marcussen, J.; Yu, S. *Carbohydr. Res.* **1999**, *320*, 250–256.

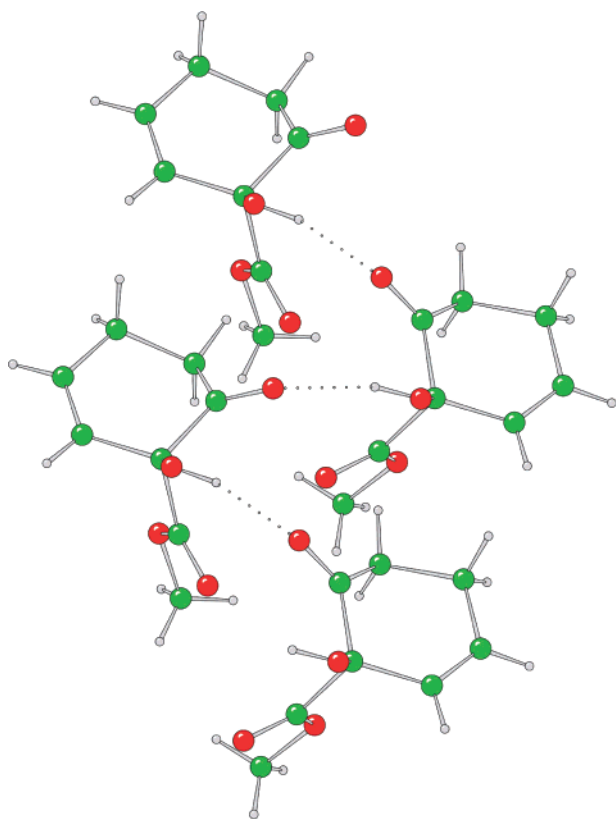
(15) (a) Christoffers, J.; Werner, T.; Frey, W.; Baro, A. *Eur. J. Org. Chem.* **2003**, 4879–4886. (b) Baucherel, X.; Levoirier, E.; Uziel, J.; Juge, S. *Tetrahedron Lett.* **2000**, *41*, 1385–1387. (c) Christoffers, J. *J. Org. Chem.* **1999**, *64*, 7668–7669.

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**FIGURE 2.** Three-dimensional representation and molecular structure of **2** established by X-ray structure determination.

The relative stereochemistry of the two halves of idesolide is identical, indicating it is formed from a single enantiomer of **2**. Dimerization of **2** should be favored at high concentration by Le Chatelier's principle and at low temperatures based on entropic considerations. Therefore, we kept a neat sample of **2** at 0–25 °C for several days. However, under these conditions, the racemic monomer, mp 70–72 °C, crystallized.

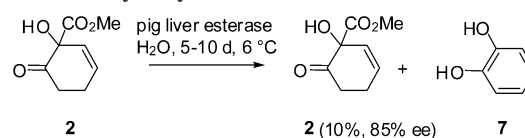
The structure of **2** was confirmed by X-ray crystallography. Compound **2** crystallizes in the racemic space group  $P2_1/c$ , with  $Z = 4$ , indicating that there are two molecules of each enantiomer in the unit cell. Figure 2 shows four symmetry-related molecules of **2**. There is a hydrogen bond from the alcohol of one enantiomer to the ketone of the other  $O1-H11 \cdots O2$  [ $x, 3/2 - y, z - 1/2$ ;  $O \cdots O$ , 2.857 Å,  $O-H \cdots O$ , 155.4°]. Inspection of Figure 2 reveals that the complete hydrogen bond set is an infinite zigzag chain, graph set  $C(5)$ ,<sup>21</sup> that propagates along the  $c$ -axis of the unit cell.

Synthetic, racemic monomer **2** did not dimerize to give any idesolide (**1**) under a wide variety of conditions, including storage neat at 0–100 °C and stirring in  $D_2O$  with or without  $MgCl_2$ . We suspected that this might be a result of the fact that racemic **2** crystallizes under the conditions (high concentration, low temperature) that should favor dimerization, whereas natural, optically pure **2** has been reported only as an oil. We therefore investigated routes to optically enriched **2**.

Schultz reported that **17** was formed in about 30% ee.<sup>17</sup> However, chiral GC analysis revealed that our sample of **2** was virtually racemic, indicating that different enantiomeric excesses

may be obtained from the Birch reduction/oxidation of **15** and **21**. In an attempt to improve the enantioselectivity, we examined the oxidation of **15** using the more bulky oxidant dichlorocamphorsulfonyloxaziridine.<sup>22</sup> No **17** was obtained, indicating that this reaction is sensitive to the steric bulk of the oxidant. We then considered procedures for the kinetic resolution of **2**. Tanyeli and co-workers reported hydrolytic kinetic resolution of methyl 1-methyl-2-methoxy-2,5-cyclohexadienecarboxylate with pig liver esterase afforded the recovered ester in 36% yield and 93% ee.<sup>23</sup> We therefore treated racemic **2** with pig liver esterase in pH 7 phosphate buffer at 6 °C for 5–10 days. This afforded catechol and optically enriched **2** in 10% yield and 85% ee as determined by chiral GC analysis (see Scheme 6). The hydrolysis product decarboxylates to give hydroxyketone **6**, which is completely oxidized to catechol under these conditions. The oxidation may be catalyzed by impurities in the liver alcohol dehydrogenase. This optically enriched sample of **2** also failed to dimerize to idesolide on standing at 0–25 °C for several days.

#### SCHEME 6. Hydrolytic Kinetic Resolution of **2**



Kim and co-workers did not note any interconversion of idesolide (**1**) and monomer (**2**) during their solution spectroscopic studies. This suggests that there is a significant kinetic barrier to the formation/decomposition of idesolide (**1**), which is both a ketal and a hemiketal. Our failure to observe the formation of idesolide (**1**) from either racemic or optically enriched **2** suggests that we have not achieved the same conditions that result in dimerization of **2** to give **1** in the fruits of *Idesia polycarpa*.

In conclusion, we have developed a short and practical first synthesis of methyl 1-hydroxy-6-oxo-2-cyclohexenecarboxylate (**2**), which has been known as a component of salicortin and tremulacin since 1970. We did not observe the dimerization of either racemic or optically enriched **2** to give idesolide (**1**).

#### Experimental Section

**Methyl 2-(((2-Trimethylsilyl)ethoxy)methoxy)benzoate (21).** 2-(Trimethylsilyl)ethoxymethyl chloride (1.42 mL, 8 mmol) was added to a solution of methyl salicylate (609 mg, 4 mmol) in dry  $CH_2Cl_2$  (2 mL) under  $N_2$  and cooled to 0 °C. Diisopropylamine (2.79 mL, 16 mmol) was added over 5 min. The solution was warmed to 25 °C and stirred for 20 h. The solution was poured into ice-cold water (20 mL), and the mixture was extracted with  $Et_2O$  ( $3 \times 20$  mL). The combined  $Et_2O$  extracts were washed with water and brine, dried over  $MgSO_4$ , and concentrated under reduced pressure. Flash chromatography on MeOH-deactivated silica gel (6:1 hexanes/ $EtOAc$ ) afforded 1.127 g (99%) of **21** as a colorless oil:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.75 (br d, 1,  $J = 8$  Hz), 7.41 (ddd, 1,  $J = 8, 8, 2$  Hz), 7.21 (br d, 1,  $J = 8$  Hz), 7.00 (ddd, 1,  $J = 8, 8, 2$  Hz), 5.29 (s, 2), 3.87 (s, 3), 3.79 (t, 2,  $J = 8.2$  Hz), 0.94 (t, 2,  $J = 8.2$  Hz),  $-0.02$  (s, 9);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  166.5, 156.7, 133.1, 131.2, 121.14, 121.10, 116.2, 93.3, 66.4, 51.8, 17.9,  $-1.6$  (3 C); IR (neat) 2953, 2897, 1733, 1601, 1490, 1454, 1434, 1299, 1250,

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1130, 1080, 991, 860, 836, 757; HRMS (TOF MS ES+) calcd for  $\text{NaC}_{14}\text{H}_{22}\text{O}_4\text{Si}$  ( $\text{MNa}^+$ ) 305.1185, found 305.1200.

**Methyl 1-Hydroxy-2-((2-(trimethylsilyl)ethoxy)methoxy)-cyclohexa-2,5-dienecarboxylate (22).** Anhydrous  $\text{NH}_3$  (5 mL) was added to a dried three-neck flask equipped with a condenser at  $-78^\circ\text{C}$  under  $\text{N}_2$ . *tert*-Butyl alcohol (0.1 mL, 1 mmol) and a solution of **21** (282 mg, 1 mmol) in anhydrous THF (2.5 mL) were added. Lithium metal (42 mg, 6 mmol) was added until a dark blue solution was achieved, and the solution was stirred for 15 min. Piperylene was added to the reaction dropwise until the blue coloration disappeared, and (–)-(2*S*,8*aR*)-(camphorylsulfonyl)-oxaziridine (413 mg, 1.8 mmol) in DME (4 mL) was immediately added to the solution. After 30 min, excess solid  $\text{NH}_4\text{Cl}$  was added, and the mixture was allowed to warm to  $25^\circ\text{C}$ .  $\text{CH}_2\text{Cl}_2$  was added, and the mixture was filtered. After concentration at reduced pressure,  $\text{Et}_2\text{O}$  was added to the resulting residue. The mixture was filtered through a  $\text{MgSO}_4$  plug, and the filtrate was concentrated under reduced pressure. Flash chromatography on MeOH-deactivated silica gel (10:1 hexanes/ $\text{EtOAc}$  to 3:1 hexanes/ $\text{EtOAc}$ ) afforded 165 mg (55%) of **22** as a colorless oil:  $[\alpha]_D^{23} -4$  (*c* 1.275,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  6.11 (ddd, 1,  $J = 9.8, 3.2, 3.2$  Hz), 5.66 (br d, 1,  $J = 9.8$  Hz), 5.37 (dd, 1,  $J = 3.4, 3.4$  Hz), 5.02 (d, 1,  $J = 6.6$  Hz), 5.07 (d, 1,  $J = 6.6$  Hz), 3.90 (s, 1, OH), 3.78 (s, 3), 3.65 (t, 2,  $J = 8.2$  Hz), 2.90 (br, 2,  $w_{1/2} = 0.90$ ), 0.94 (t, 2,  $J = 8.2$  Hz), 0.01 (s, 9);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  174.1, 149.5, 129.0, 125.1, 100.0, 92.4, 71.4, 66.1, 53.3, 26.6, 17.9,  $-1.5$  (3 C); IR (neat) 3513, 2953, 2894, 1740, 1690, 1249, 1168, 1079, 860, 836; HRMS (TOF MS ES+) calcd for  $\text{NaC}_{14}\text{H}_{24}\text{O}_5\text{Si}$  ( $\text{MNa}^+$ ) 323.1291, found 323.1302.

**Methyl 1-Hydroxy-6-oxo-2-cyclohexenecarboxylate (2).**  $\text{Et}_2\text{O}$  (2 mL) was added to  $\text{MgBr}_2 \cdot \text{OEt}_2$  (1.033 g, 4 mmol), and the mixture was stirred at  $25^\circ\text{C}$  until no solid  $\text{MgBr}_2 \cdot \text{OEt}_2$  remained (approximately 15 min) and two liquid phases were present. Nitromethane (763 mg, 12.5 mmol) was added to the two-phase system, resulting in a one-phase solution. The solution was added to **22** (150 mg, 0.5 mmol) in 2 mL of  $\text{Et}_2\text{O}$ , and the resulting solution was stirred at  $25^\circ\text{C}$  for 2 h. The solution was diluted with  $\text{EtOAc}$  (10 mL) and water (10 mL). The layers were separated, and the aqueous layer was saturated with solid  $\text{NaCl}$  followed by extraction with  $\text{EtOAc}$  ( $3 \times 15$  mL). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. Flash chromatography on MeOH-deactivated

silica gel (0.5% MeOH in  $\text{CH}_2\text{Cl}_2$ ) afforded 60 mg (71%) of **2** as a light yellow oil. The oil was kept neat at  $0^\circ\text{C}$  for 1–2 days, yielding off-white crystals that were washed with  $\text{Et}_2\text{O}$ : mp  $70-72^\circ\text{C}$ ;  $[\alpha]_D^{23} -7.11$  (*c* 0.61,  $\text{CHCl}_3$ ); {lit.<sup>3</sup>  $[\alpha]_D^{25} -185.9$  (*c* 0.59,  $\text{CHCl}_3$ )};  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  6.13 (ddd, 1,  $J = 10.0, 3.6, 3.6$  Hz), 5.79 (d, 1,  $J = 10.0$  Hz), 4.23 (s, 1, OH), 3.80 (s, 3), 3.00 (ddd, 1,  $J = 14.0, 6.8, 6.8$  Hz), 2.77–2.64 (m, 2), 2.62–2.55 (m, 1);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  205.4, 170.3, 131.9, 127.5, 77.9, 53.4, 35.1, 26.9; IR (neat) 3462, 2956, 1727, 1439, 1253, 1224, 1140, 1103, 914, 733; HRMS (TOF MS ES+) calcd for  $\text{C}_8\text{H}_{10}\text{O}_4$  ( $\text{M}^+$ ) 170.0579, found 170.0580. The spectral data are identical to those previously reported.<sup>3</sup> Chiral GC analysis ( $80^\circ\text{C}$ , 4 min,  $1^\circ\text{C}/\text{min}$  to  $200^\circ\text{C}$ ,  $t_{\text{R}}(\text{major}) = 59.74$  min,  $t_{\text{R}}(\text{minor}) = 59.25$ ) indicated 1–2% ee.

**Enzymatic Hydrolysis of Methyl 1-Hydroxy-6-oxocyclohex-2-enecarboxylate (2).** Racemic methyl 1-hydroxy-6-oxocyclohex-2-enecarboxylate (**2**) (25 mg, 0.15 mmol) was chilled to  $6^\circ\text{C}$  in aqueous phosphate buffer (pH  $\sim 7$ , 0.5 mL). Pig liver esterase (3 mg, 20 units/mg) was added, and the mixture was stirred at  $6^\circ\text{C}$  for 8 days. The mixture was diluted with water (5 mL) and  $\text{CH}_2\text{Cl}_2$  (5 mL), and the layers were separated. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 5$  mL). The combined extracts were washed with 10% aqueous  $\text{NaHCO}_3$  (to remove catechol) and brine, dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. Flash chromatography on MeOH-deactivated silica gel (10:1 hexanes/ $\text{EtOAc}$ ) yielded 3 mg (10%) of **2** as a colorless oil in 85% ee as determined by chiral GC analysis ( $80^\circ\text{C}$ , 4 min,  $1^\circ\text{C}/\text{min}$  to  $200^\circ\text{C}$ ,  $t_{\text{R}}(\text{major}) = 59.74$  min,  $t_{\text{R}}(\text{minor}) = 59.25$ ). The oil was stored neat at  $25^\circ\text{C}$  for 4 weeks. NMR analysis did not reveal any idesolide (**1**) formation.

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**Supporting Information Available:** Copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral data, and X-ray crystallographic data (CIF file) for **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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