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

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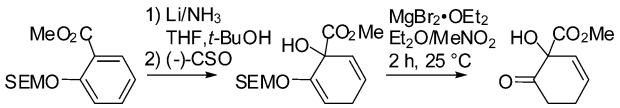


We have developed a short and practical first synthesis of methyl 1-hydroxy-6-oxo-2-cyclohexenecarboxylate (**2**), which has been known as a component of salicortin and tremulacin since 1970. Birch reduction of the SEM ether of methyl salicylate followed by oxidation of the intermediate enolate with (−)-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).[1] 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*.[2−4] Both **1** and **2** inhibit lipopolysaccharide-induced NO production in BV2 microglia at micromolar concentrations.[1,4]

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.[5,6] It is a component of salicortin (**3a**),[7]

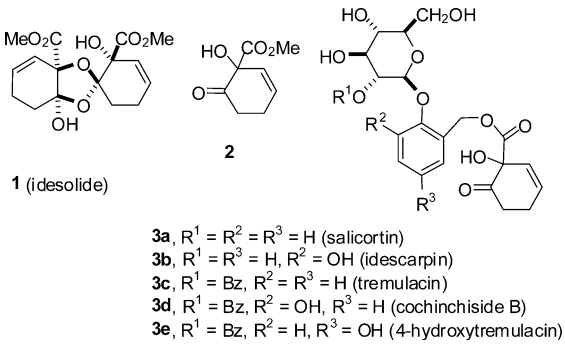
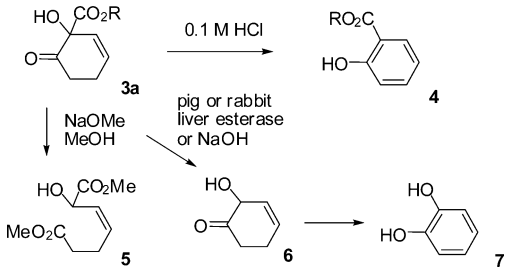


FIGURE 1. Selected naturally occurring 1-hydroxy-6-oxo-2-cyclohexenecarboxylate esters.

idescarpin (**3b**),[8] tremulacin (**3c**),[7] cochinchiside B (**3d**),[9] and 4-hydroxytremulacin (**3e**).[3] Although the structures of salicortin and tremulacin were assigned in 1970,[7] 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).[7] Hydrolysis of **3a** with aqueous base or pig/rabbit liver esterase yields a β-keto acid that decarboxylates to provide hydroxycyclohexenone **6**, which is readily oxidized to form catechol (**7**).[7,10]

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).[11] The structures of other related dimers have been inferred from their symmetry.[12] 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**).[13] Other dimers

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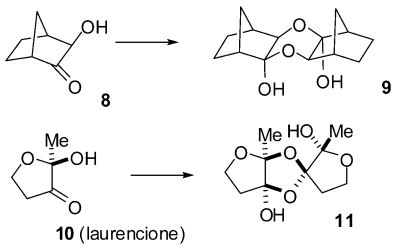
have been suggested to have structures analogous to **1** and **11** on the basis of the lack of symmetry in their ^{1}H NMR spectra.[14]

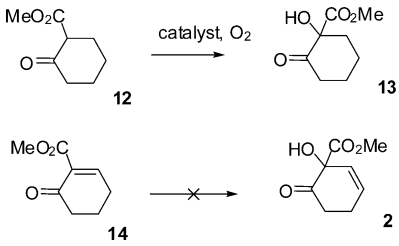
SCHEME 2. Dimerization of α-Hydroxyketones



We decided to synthesize methyl 1-hydroxy-6-oxo-2-cyclohexenecarboxylate (**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;[7] (2) recent reports indicate that it inhibits NO production;[1,4] and (3) the isolation of both **2** and the dimer idesolide (**1**) with no apparent equilibration deserved further study.[1,4]

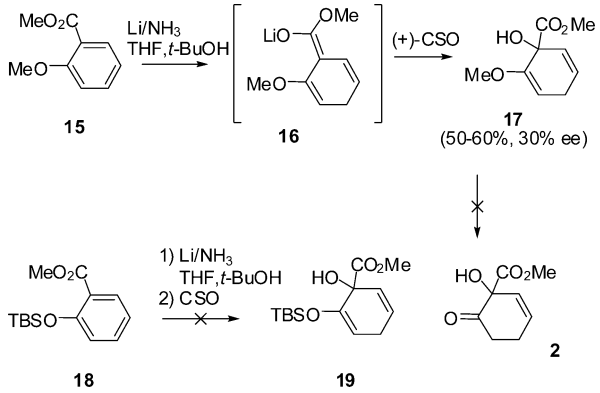
The hydroxylation of methyl 2-oxocyclohexanecarboxylate (**12**) to give methyl 1-hydroxy-2-oxocyclohexanecarboxylate (**13**) can be easily achieved with molecular oxygen and Ce(III), Co(II), or Mn(II) (see Scheme 3).[15] We hoped that we could carry out a similar transformation starting with methyl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

SCHEME 3. Unsuccessful Approach to 2



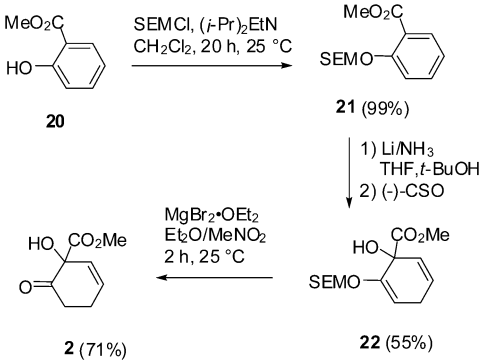
Eventually, we noted that Schultz had prepared enol ether **17** by the Birch reduction of methyl 2-methoxybenzoate (**15**) followed by trapping intermediate **16** with camphorsulfonyloxaziridine to give **17** in 50−60% yield and 30% ee (see Scheme 4).[17] Simple hydrolysis of the enol ether would 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**[18] 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 $(i\text{-Pr})_2$EtN in CH_2Cl_2 at 25 °C for 20 h afforded the desired SEM ether **21** in 99% yield (see Scheme 5).[19] 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 $MgBr_2$•OEt_2 in Et_2O/nitromethane[20] afforded the desired product **2** in 71% yield.

SCHEME 5. Synthesis of Methyl 1-Hydroxy-6-oxo-2-cyclohexenecarboxylate (2)



The spectral data of **2** are identical to those previously reported.[2,3] However, we were unable to observe the formation of the dimer idesolide (**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).

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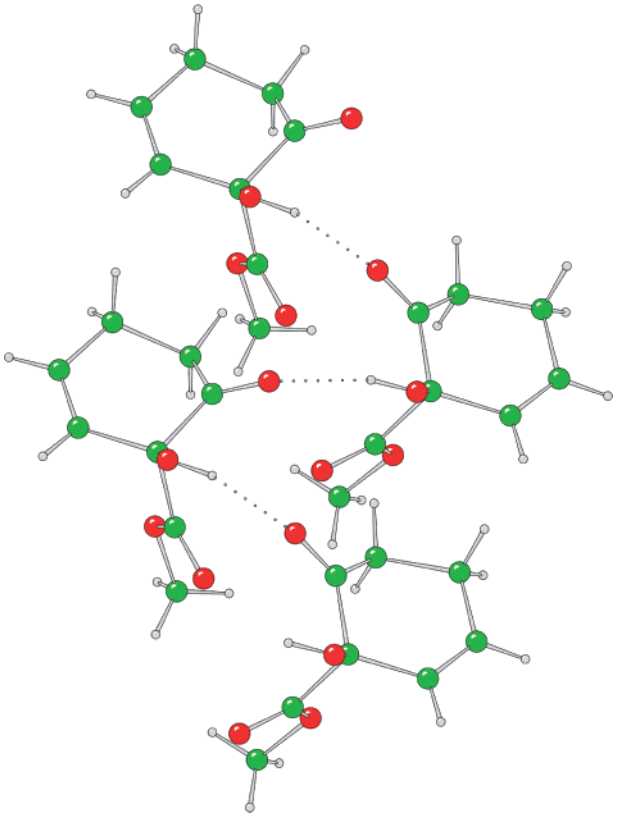


FIGURE 2. Three-dimensional representation and molecular structure of **2** established by X-ray structure determination.

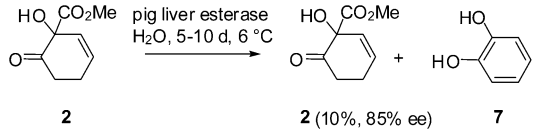
The relative stereochemistry of the two halves of idesolide is identical, indicating it is formed from a single enantiomer of **2**. Dimerization of **2** should be favored at high concentration by Le Chatelier's principle and at low temperatures based on entropic considerations. Therefore, we kept a 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···O2 [x, 3/2 − y, z − 1/2; O···O, 2.857 Å, O−H···O, 155.4°]. Inspection of Figure 2 reveals that the complete hydrogen bond set is an infinite zigzag chain, graph set **C(5)**,[21] 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.[17] 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.[22] 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.[23] 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 × 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: ^{1}H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 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 $NaC_{14}H_{22}O_4Si$ (MNa^+) 305.1185, found 305.1200.

Methyl 1-Hydroxy-2-((2-(trimethylsilyl)ethoxy)methoxy)-cyclohexa-2,5-dienecarboxylate (22). Anhydrous NH_3 (5 mL) was added to a dried three-neck flask equipped with a condenser at −78 °C under 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*,8a*R*)-(camphorylsulfonyl)-oxaziridine (413 mg, 1.8 mmol) in DME (4 mL) was immediately added to the solution. After 30 min, excess solid NH_4Cl was added, and the mixture was allowed to warm to 25 °C. CH_2Cl_2 was added, and the mixture was filtered. After concentration at reduced pressure, Et_2O was added to the resulting residue. The mixture was filtered through a $MgSO_4$ plug, and the filtrate was concentrated under reduced pressure. Flash chromatography on MeOH-deactivated silica gel (10:1 hexanes/EtOAc to 3:1 hexanes/EtOAc) afforded 165 mg (55%) of **22** as a colorless oil: $[\alpha]^{23}_D$ −4 (*c* 1.275, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 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}C NMR ($CDCl_3$) δ 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 $NaC_{14}H_{24}O_5Si$ (MNa^+) 323.1291, found 323.1302.

Methyl 1-Hydroxy-6-oxo-2-cyclohexenecarboxylate (2). Et_2O (2 mL) was added to $MgBr_2$•OEt_2 (1.033 g, 4 mmol), and the mixture was stirred at 25 °C until no solid $MgBr_2$•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 Et_2O, and the resulting solution was stirred at 25 °C for 2 h. The solution was diluted with EtOAc (10 mL) and water (10 mL). The layers were separated, and the aqueous layer was saturated with solid NaCl followed by extraction with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography on MeOH-deactivated silica gel (0.5% MeOH in CH_2Cl_2) afforded 60 mg (71%) of **2** as a light yellow oil. The oil was kept neat at 0 °C for 1−2 days, yielding off-white crystals that were washed with Et_2O: mp 70−72 °C; $[\alpha]^{23}_D$ −7.11 (*c* 0.61, $CHCl_3$); {lit.[3] $[\alpha]^{25}_D$ −185.9 (*c* 0.59, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$) δ 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}C NMR ($CDCl_3$) δ 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 $C_8H_{10}O_4$ (M^+) 170.0579, found 170.0580. The spectral data are identical to those previously reported.[3] Chiral GC analysis (80 °C, 4 min, 1 °C/min to 200 °C, t_R(major) = 59.74 min, t_R (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 °C in aqueous phosphate buffer (pH ∼ 7, 0.5 mL). Pig liver esterase (3 mg, 20 units/mg) was added, and the mixture was stirred at 6 °C for 8 days. The mixture was diluted with water (5 mL) and CH_2Cl_2 (5 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined extracts were washed with 10% aqueous $NaHCO_3$ (to remove catechol) and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography on MeOH-deactivated silica gel (10:1 hexanes/EtOAc) yielded 3 mg (10%) of **2** as a colorless oil in 85% ee as determined by chiral GC analysis (80 °C, 4 min, 1 °C/min to 200 °C, t_R(major) = 59.74 min, t_R (minor) = 59.25). The oil was stored neat at 25 °C for 4 weeks. NMR analysis did not reveal any idesolide (**1**) formation.

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Supporting Information Available: Copies of ^{1}H and ^{13}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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