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A Scalable Synthesis of 2*S*-Hydroxymutilin via a Modified Rubottom Oxidation

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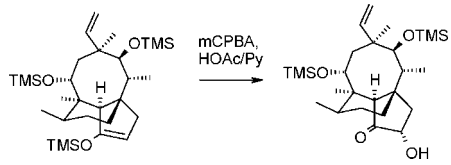
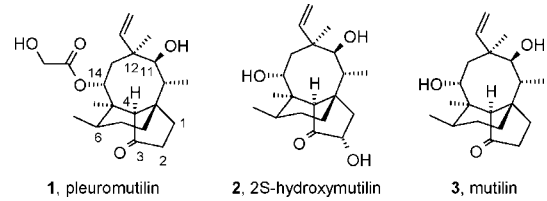


A scalable synthesis of 2*S*-hydroxymutilin from pleuromutilin was developed. The synthesis is highlighted by the Rubottom oxidation of a silyl enol ether, conducted in the presence of acetic acid and pyridine, which allows for an efficient and selective oxidation.

Pleuromutilin (**1**, Figure 1) is a naturally occurring antibiotic isolated from *Pleurotus mutilus* and other basidiomycetes.[1] The derivatives of pleuromutilin have received considerable attention in recent years because they fulfill the need for new antibiotics with a distinctly novel mode of action.[2] Derivatives of 2*S*-hydroxymutilin (**2**, Figure 1) have been identified as potent antimicrobial agents[3] and our interest in this class of compounds has necessitated a method to prepare 2*S*-hydroxymutilin that is amenable to large-scale synthesis.[4]

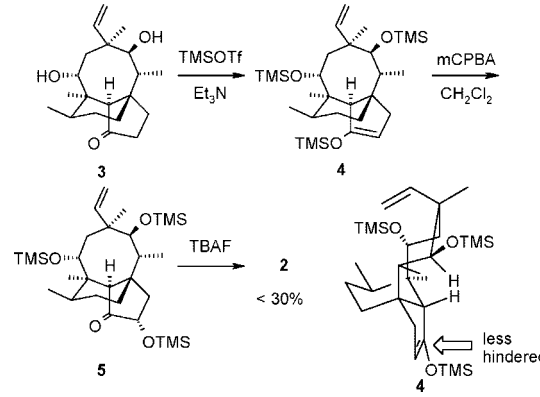
A straightforward approach to 2*S*-hydroxymutilin at the outset seemed to be α-hydroxylation of the cyclopentanone moiety of mutilin **3** via an oxidation of its silyl enol ether **4**,[5] with the oxidation expected to occur from the less hindered α face (Scheme 1).[6] However, during our early efforts, this transformation often resulted in complex mixtures. When the desired



1, pleuromutilin **2**, 2*S*-hydroxymutilin **3**, mutilin

FIGURE 1. Pleuromutilin, 2*S*-hydroxymutilin, and mutilin.

SCHEME 1. Proposed Route to 2*S*-Hydroxymutilin



product was obtained, the yield was unacceptably low (<30%); therefore, this three-step sequence was examined in greater detail.

A closer look at the silyl enol ether formation showed that under the initial reaction conditions (TMSOTf/Et_3N, Scheme 2), the desired 2,3-enol ether **4** was not formed exclusively. Regioisomeric 3,4-enol ether **7** was also formed (**4**/**7** ca. 15:1). The product mixture also appeared unstable: when stored as an oil in a refrigerator overnight, the ratio of the two enol ethers deteriorated to ~2.3:1 with a small amount of hydrolyzed ketone **8**. The ratio of the three was also very inconsistent and dependent on the workup solvent and procedure.

^1H revealed the presence of Et_3N^+H in crude **4**, leading to the hypothesis that this migration was catalyzed by a trace amount of acid in the product.[7] Thus, the enol ether migration was circumvented by using a nonacidic procedure: deprotonation of **3** with LiHMDS provided exclusively the kinetic enolate, and silylation with TMSCl provided the 2,3-silyl enol ether **4** in nearly quantitative yield after aqueous workup. The product was stable for months when stored cold, or even at room temperature as an oil.

Observations in the Rubottom oxidation[8] of **4** further demonstrated the lability of the C4 proton in the presence of a neighboring carbocation. When silyl enol ether **4** was treated with mCPBA[9] in hexane, only a small amount of the desired

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(1) (a) Kavanagh, F.; Hervey, A.; Robbins, W. J. *Proc. Natl. Acad. Sci. U.S.A.* **1951**, *37*, 570. (b) Knauseder, F.; Brandl, E. *J. Antibiot.* **1976**, *29*, 125.

(2) Hunt, E. *Drugs Future* **2000**, *25*, 1163, and references cited therein.

(3) Brooks, G.; Hunt, E. PCT Int. Appl. WO 2001074788 A1, 2001.

(4) (a) 2*S*-Hydroxymutilin has been prepared via O−H insertion of 2-diazomutilin: see ref 3. However, large-scale application of this method is limited by the high cost of the diazotization reagent and the stability of the intermediates. (b) 2*S*-Hydroxymutilin has been obtained in the microbial hydroxylation of mutilin, see: Hanson, R. L.; Matson, J. A.; Brzozowski, D. B.; LaPorte, T. L.; Springer, D. M.; Patel, R. N. *Org. Process Res. Dev.* **2002**, *6*, 482.

(5) Direct oxidation of the enolate was also investigated. The oxidation with molecular oxygen often suffered from overoxidation to the diketone. Oxidation of the enolate with Davis oxaziridine was successful on a small scale, but was not deemed as a long-term option due to availability and safety concerns of the reagent.

(6) For the X-ray structure of mutilin see: (a) Dobler, M.; Dürr, B. G. *Cryst. Struct. Commun.* **1975**, *4*, 259. (b) Pilati, T. *Acta Crystallogr.* **1995**, *C51*, 2676. For a brief discussion of its conformation, see: (c) Boeckman, R. K.; Springer, D. M.; Alessi, T. R. *J. Am. Chem. Soc.* **1989**, *111*, 8284.

(7) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.

(8) For a general review on the Rubottom oxidation, see: Wolfe, J. P. Rubottom oxidation In *Name Reactions for Functional Group Transformations*; Li, J. J., Corey, E. J., Eds.; Wiley: New York, 2007, pp 282−290.

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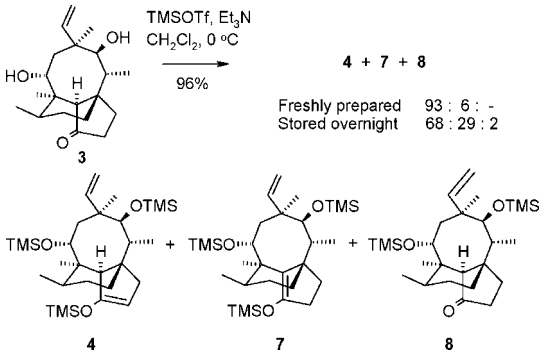
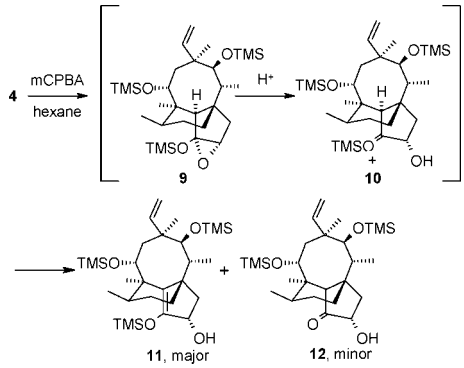
SCHEME 2. Migration of the 2,3-Enol Ether



SCHEME 3. Oxidation of 4 under Acidic Conditions

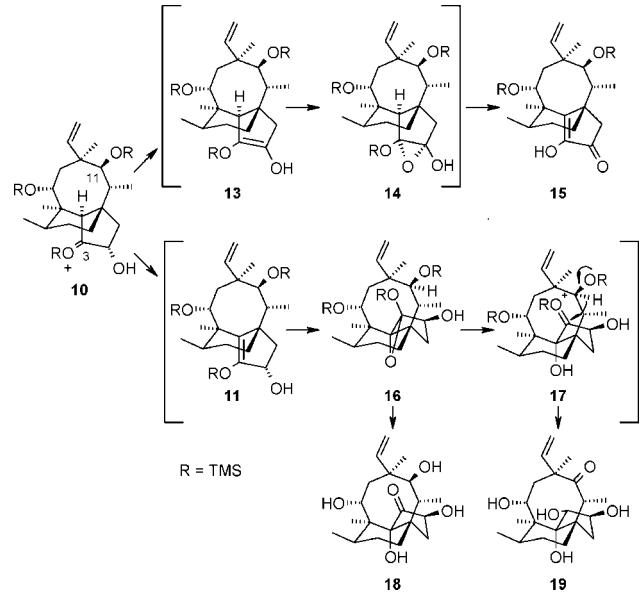


product **12** was observed. The major product obtained appeared to be oxidized enol ether **11**, presumably through an acid-catalyzed epoxide opening followed by loss of the C4 proton (Scheme 3).

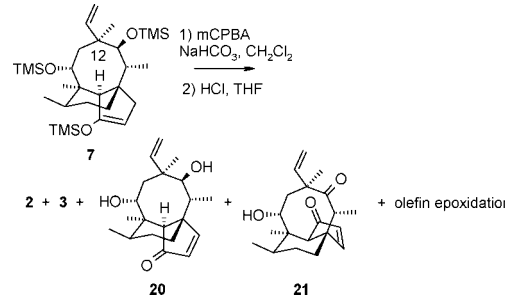
This problem was initially overcome by buffering the reaction system with $NaHCO_3$. The oxidation performed in the buffered systems provided the desired product, although the reaction was slow in several of the solvents screened (hexane, TBME, and toluene). The main side products appeared to be ketone **8** from hydrolysis of the silyl enol ether, as well as small amounts of overoxidation products. The latter was particularly problematic as attempts to drive the slow reaction to completion by additional mCPBA often led to more overoxidation products. These side products and the mechanism of their formation are shown in Scheme 4: the persistence of the intermediary siloxycarbocation **10** not only led to the normal double oxidation products (**15** and **18**),[10] the oxonium ion at C3 in intermediate **17** also underwent an intramolecular hydride transfer from C11 to give 2,3,4-triol **19**.[11]

Among all the solvents screened in the $NaHCO_3$-buffered oxidation, CH_2Cl_2 provided by far the fastest reaction. However, a complex reaction profile seriously detracted from the increased reaction rate. Several side products were observed, including (after desilylation) the hydrolysis product **3**, epoxides resulting from epoxidation of the terminal olefin moiety on C12, as well

SCHEME 4. Formation of Overoxidation Products



SCHEME 5. Oxidation in CH_2Cl_2 with $NaHCO_3$ Buffer



as enones **20** and **21** (Scheme 5). The exact mechanism for the formation of the two enones is unclear at the moment; however, the oxidation of C11 in **21** presumably proceeded by the intramolecular hydride transfer mechanism similar to that in the formation of **19**, which reinforced the notion that the persistence of the C3 oxonium ion intermediate **10** was detrimental to the efficiency of the reaction.

With a $NaHCO_3$ buffer, THF proved to be the best solvent, and provided complete reaction overnight. The epoxidation of the C12 olefin was also completely suppressed,[12] affording the desired product in good yield. However, difficulty was encountered when scale-up was attempted. The heterogeneous reaction suffered from poor reproducibility, giving significantly higher amounts of hydrolysis product **8** when performed at multigram scale. There was also growing concern about the compatibility of THF and mCPBA from a safety standpoint.[13] Therefore, another solvent system was needed for the oxidation reaction.

The reaction was vastly improved by using a mixture of acetic acid and CH_2Cl_2 as the reaction solvent. Consistent with previous observations, the oxidation in CH_2Cl_2 was rapid even at −20 °C. However, the addition of acetic acid led to a much cleaner reaction profile, affording a high-yielding α-hydroxylation of the cyclopentanone moiety (entry 3, Table 1). Addition of pyridine in this solvent mixture further improved the profile and led to a slightly higher yield (enrty 4).

(9) The Rubottom oxidation was also attempted with in situ generated peroxyimidic acid and dioxirane. Unfortunately, hydrolysis of the silyl enol ether became a serious side reaction in both cases. A significant amount of olefin epoxidation was also observed when methyl(trifluoromethyl)dioxirane was used as the oxidant.

(10) For an example of double oxidation under Rubottom conditions, see: Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 3323.

(11) The acid-catalyzed rearrangement from mutilin to the 4-epimutilin skeleton is well known: Berner, H.; Schulz, G.; Schneider, H. *Tetrahedron* **1980**, *36*, 1807.

(12) This was confirmed by the observation that the C12 olefin in **8** did not undergo epoxidation when exposed to $NaHCO_3$-buffered mCPBA in THF.

(13) *Bretherick's Handbook of Reactive Chemical Hazards*; Urben, P. G., Ed.; Butterworth-Heinemann: Burlington, MA, 1999.

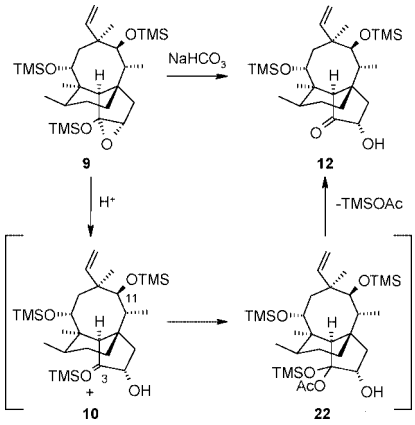
TABLE 1. Buffer Effect on the Rubottom Oxidation

4 2

	buffer/solvent	conditions	hydrolysis	yields,[a] %
1	$NaHCO_3$/THF	−10 °C to rt, overnight	trace to 34%	42−75
2	$NaHCO_3/CH_2Cl_2$	−10 to 0 °C, 2 h	—[b]	—[b]
3	$HOAc/CH_2Cl_2$	−10 °C, 1.5 h	trace	69
4	$Py/HOAc/CH_2Cl_2$	−10 °C, 1.5 h	trace	78

[a] Isolated yields. [b] Complex mixture, see text.

SCHEME 6. Plausible Mechanism for Additive Effect



While $NaHCO_3$ and other inorganic bases are routinely used to buffer the Rubottom reaction involving acid-sensitive substrates, acetic acid has not been widely used as an additive in this reaction. However, both seem to facilitate the Rubottom reaction of silyl enol ether **4**. A plausible explanation of their different roles in this reaction is shown in Scheme 6. A basic buffer would inhibit the formation of **10** from the presumed silyloxyoxirane intermediate **9**,[14] while favoring the epoxide opening initiated by a direct nucleophilic attack on the TMS group (**9** to **12**). Addition of HOAc, on the other hand, would accelerate the formation of **10**, but it would also trap the latter to form **22**,[15] which then collapses to yield the desired product **12**. In this case, both a basic and an acidic additive help in suppressing the buildup of oxonium intermediate **10**,[16] which is responsible for several of the side reaction pathways described above.[17] The large amount of acetic acid in the reaction system can also minimize the concentration of **10** by cleaving the O−Si bond, although the TMS cleavage of silyl enol ether **4** is clearly not as fast as its oxidation as only trace amounts of hydrolysis were observed. This is particularly remarkable considering the high acid-sensitivity and migratory tendency of silyl enol ether **4**.

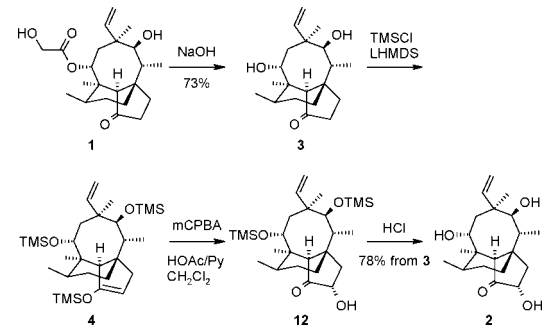
(14) (a) Dodd, J. H.; Starrett, J. E.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 1811. (b) Paquette, L. A.; Lin, H.-S.; Gallucci, J. C. *Tetrahedron Lett.* **1987**, *28*, 1363. (c) Gleiter, R.; Staib, M.; Ackermann, U. *Liebigs Ann.* **1995**, 1655.

(15) (a) The trapping of silyloxy carbocation with MCBA has been reported: Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427. (b) For a related example see: Rubottom, G. M.; Gruber, J. M.; Boeckman, R. K.; Ramaiah, M.; Medwid, J. B. *Tetrahedron Lett.* **1978**, *19*, 4603.

(16) For evidence in the intermediacy of the siloxycarbocation, see ref 14b.

(17) An intramolecular pathway is also possible: as the bulky silyl group presumably resides on the less crowded α face, the acetate could attack the oxonium ion **10** from the β-face and the resultant stereoisomer would undergo a 1,4-silicon shift to generate the α-hydroxyketone moiety. However, the corresponding 2-silyloxy product was never isolated.

SCHEME 7. Scalable Synthesis of 2*S*-Hydroxymutilin



After the oxidation, the desilylation of the O11 and O14 TMS groups with use of TBAF provided the desired product, though it was slow and often led to an unidentified complex mixture. Desilylation under acidic conditions provided a faster and much cleaner transformation: when treated with HCl, the O11 TMS was desilylated within 5−10 min, while the more hindered O14 TMS was removed in 1−2 h.

This synthetic sequence was performed successfully at a kilogram scale. Mutilin **3** was obtained from hydrolysis of pleuromutilin[18] and was converted into silyl enol ether **4** smoothly by using LHMDS/TMSCl. The Rubottom oxidation was carried out by controlled addition of **4** into a cold mixture of acetic acid, pyridine, and mCPBA. It proved very important to have efficient cooling to maintain the low reaction temperature necessary for the high selectivity, as well as to minimize consumption of mCPBA by pyridine during the time of addition. After desilylation and crystallization, 2*S*-hydroxymutilin **2** was obtained in 78% yield (Scheme 7).[19]

In summary, the Rubottom oxidation of silyl enol ether **4** was studied in detail. The lability of H4 in the presence of a neighboring carbocation proved detrimental to the efficiency of the reaction. This reaction was improved by buffering the reaction with an inorganic base, or, more interestingly, acetic acid. The role of acetic acid is presumably to minimize the concentration of oxonium intermediate **10**. This modified procedure with acetic acid allowed for an efficient and selective oxidation of **4** and a synthesis of 2*S*-hydroxymutilin from pleuromutilin on a kilogram scale.

Experimental Section

General. Unless otherwise indicated, all reactions were conducted in glass-lined reactors under a nitrogen atmosphere. Solvents and reagents were obtained from commercial sources and used without further purification. Pleuromutilin **1** was obtained via fermentation.

Mutilin 3. A mixture of pleuromutilin **1** (1.2 kg, 3.17 mol) and NaOH (50% w/w, 963 g, 12 mol, 3.8 equiv) in ethanol (7.2 L) and water (4.5 L) was stirred at 50 °C for 3 h. The mixture was concentrated. The crystalline product was isolated by filtration, washed with water (1.7 L × 2) and heptane (0.7 L), and then dried under vacuum to provide 740 g (2.31 mol, 73%) of product. ES-MS: *m/z* 285 ($M - 2H_2O + H^+$), 303 ($M - H_2O + H^+$), 343 ($M + Na^+$), 384 ($M + Na^+ + CH_3CN$). ^1H NMR ($CDCl_3$, 300.13 MHz) δ (ppm) 6.11 (dd, $J = 17.8$, 11.1 Hz, 1H), 5.28−5.41 (m, 2H), 4.36 (dd, $J = 7.3$, 5.8 Hz, 1H), 3.42 (t, $J = 6.6$ Hz, 1H), 2.13−2.32

(18) Pleuromutilin **1** was obtained from fermentation.

(19) The process could be further streamlined by using propyl acetate as a single solvent through oxidation, desilylation, and isolation, allowing the entire sequence to be conducted in one reaction vessel without formal isolation of the intermediates, while providing 2*S*-hydroxymutilin in 58% overall yield.

(m, 3H), 2.05 (m, 1H), 1.88−1.96 (dd, J = 15.9, 7.8 Hz, 1H), 1.42−1.78 (m, 7H), 1.37 (s, 3H), 1.16 (s, 3H), 1.08−1.18 (m, 1H), 0.98 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ (ppm) 217.7, 139.4, 115.8, 75.0, 66.7, 59.0, 45.3, 45.2, 45.0, 42.3, 36.8, 36.4, 34.4, 30.3, 28.6, 27.1, 25.0, 18.1, 13.4, 11.2.

Silyl Enol Ether 4. A solution of mutilin **3** (300 g, 0.936 mol, 1 equiv) and trimethylsilyl chloride (426 mL, 3.37 mol, 3.6 equiv) in THF (3 L) was cooled to −18 °C. LiHMDS in hexanes (1.0 M, 3.1 L, 3.3 equiv) was slowly added while maintaining the internal temperature below −8 °C. After 2 h of stirring the reaction was deemed complete by TLC. The crude mixture was diluted with cyclohexane (1.5 L) and then quenched with saturated aq $NaHCO_3$ (1.5 L). The organic layer was washed with saturated aq $NaHCO_3$ (1.0 L), concentrated, and used in the next step without further purification (quantitative yield assumed). An analytically pure sample can be obtained after flash column chromatography: ^{1}H (d_8-toluene, 400.13 MHz) δ (ppm) 6.35 (dd, J = 17.37, 11.16 Hz, 1 H), 5.35 (dd, J = 17.57, 1.86 Hz, 1 H), 5.25 (dd, J = 11.17, 1.65 Hz, 1 H), 4.69 (d, J = 7.86 Hz, 1 H), 4.50 (s, 1 H), 3.86 (d, J = 6.62 Hz, 1 H), 2.83 (s, 1 H), 2.28−2.46 (m, 1 H), 2.10−2.20 (m, 1 H), 1.81−1.92 (m, 1 H), 1.72−1.80 (m, 1 H), 1.63−1.72 (m, 1 H), 1.53−1.62 (m, 2 H), 1.51 (s, 2 H), 1.40 (s, 2 H), 1.31−1.39 (m, 1 H), 1.09 (d, J = 7.03 Hz, 2 H), 0.94 (d, J = 7.03 Hz, 2 H), 0.21 (s, 9 H), 0.19 (s, 9 H), 0.12 (s, 9 H). ^{13}C NMR (d_8-toluene, 100.62 MHz) δ (ppm) 159.0, 142.6, 116.2, 100.3, 78.5, 69.0, 53.1, 48.6, 48.5, 45.6, 43.5, 39.4, 38.0, 36.7, 33.0, 29.8, 28.6, 19.4, 17.2, 14.1, 2.0, 1.4, 0.4.

2*S*-Hydroxymutilin 2. A mixture of mCPBA (∼77%, 562 g, 2.51 mol, 1.5 equiv) and DCM (9.0 L) was cooled to −25 °C with stirring. To the mixture was added acetic acid (2.25 L, 39.3 mol, 23 equiv) followed by pyridine (0.743 L, 9.19 mol, 5.5 equiv) while maintaining the internal temperature at less than −20 °C. To the cold mixture was slowly added a solution of silyl enol ether **4** (900 g, 1.68 mol) in DCM (2.7 L) over 100 min while maintaining the internal temperature at less than −20 °C. After ∼0.5 h of stirring, the reaction temperature was raised to −10 °C over 75 min and the reaction was quenched with 10% aq Na_2SO_3 (1.8 L). After 0.5 h of stirring at rt, the organic layer was separated and then washed twice with water (2 × 3.6 L). The organic layer was concentrated to ∼4 L. To the residue was added ethyl acetate (4.5 L) and the mixture was concentrated to ∼4 L. The crude mixture was diluted with cyclohexane (4.5 L) and then washed with saturated aq $NaHCO_3$ (2 × 3.6 L). The crude hydroxyketone **12** was used directly in the next step, but an analytically pure sample can be obtained after flash column chromatography: ES-MS: m/z 503 (M + Na^+), 544 (M + Na^+ + CH_3CN). ^{1}H ($CDCl_3$, 400.13 MHz) δ (ppm) 6.16 (dd, J = 17.6, 11.2 Hz, 1H), 5.12−5.40 (m, 2H), 4.43 (d, J = 8.1 Hz, 1H), 4.00 (td, J = 8.6, 2.3 Hz, 1H), 3.44 (d, J = 6.0 Hz, 1H), 3.02 (br, 1H), 2.25−2.34 (m, 1H), 2.21 (m, 1H), 2.07 (dd, J = 13.0, 8.7 Hz, 1H), 1.87−1.99 (m, 2H), 1.23−1.56 (m, 5H), 1.35 (s, 3H), 1.08 (s, 3H), 0.94−1.12 (m, 1H), 0.88 (m, 6H), 0.13 (s, 9H), 0.12 (s, 9H). ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ (ppm) 219.5, 140.8, 116.2, 77.1, 72.5, 67.4, 57.4, 47.4, 45.0, 43.8, 42.1, 38.8, 36.3, 35.1, 33.0, 29.0, 26.9, 18.2, 14.8, 12.4, 1.3, 1.0.

The resulting solution of hydroxyketone **12** was cooled to 5−10 °C and treated with 1.4 N HCl/MeOH (2.4 L, prepared from conc HCl and MeOH). The reaction mixture was stirred until complete hydrolysis was achieved (∼1 h). The reaction mixture was quenched with saturated aq $NaHCO_3$ (1.8 L) and concentrated to remove ∼7 L of solvents, during which the product started to precipitate. To the vigorously stirred mixture was added water (1.8 L). The resulting slurry was stirred for 0.5 h and filtered. The residue was washed with water (1.35 L) and heptane (0.9 L). The wet cake was dried in a vacuum oven at 45 °C overnight. The dry white solid product weighed 578 g and contained ∼8% of mutilin **3**.

Further purification and crystallization of 2-hydroxymutilin **2** was demonstrated on a 50 g scale: to a stirred mixture of crude product (50 g) in 50 mL of THF at 55−60 °C was slowly added 750 mL of cyclohexane. After being stirred for ∼1 h at 60 °C, the mixture was allowed to cool slowly to rt. The mixture was stirred for 1 h and filtered, then the residue was washed with cyclohexane (250 mL). The product was dried under vacuum: 38 g, 78% (from mutilin **3**) and free of **3**. ES-MS: m/z 301 (M − $2H_2O$ + H^+), 359 (M + Na^+), 400 (M + Na^+ + CH_3CN). ^{1}H ($CDCl_3$, 400.13 MHz) δ (ppm) 6.12 (dd, J = 17.9, 11.2 Hz, 1H), 5.27−5.38 (m, 2H), 4.34 (d, J = 7.7 Hz, 1H), 3.99 (t, J = 8.6 Hz, 1H), 3.39 (d, J = 6.3 Hz, 1H), 2.20 (m, 1H), 2.05−2.15 (m, 2H), 1.89−1.97 (m, 2H), 1.66 (d, J = 15.9 Hz, 1H), 1.34−1.54 (m, 4H), 1.39 (s, 3H), 1.15 (s, 3H), 0.95−0.99 (m, 7H). ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ (ppm) 218.8, 139.5, 115.7, 74.6, 72.2, 66.8, 57.4, 45.34, 45.30, 42.8, 42.0, 38.1, 36.6, 34.8, 32.5, 28.7, 26.9, 18.1, 13.8, 11.6.[20]

Supporting Information Available: Experimental details, characterizations, and ^{1}H, ^{13}C, and 2D NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801969E

(20) For a detailed spectroscopic and computational study of 2*S*-hydroxymutilin, see: Vogt, F. G.; Spoors, G. P.; Su, Q.; Andemichael, Y. W.; Wang, H.; Potter, T. C.; Minick, D. J. *J. Mol. Struct.* **2006**, *797*, 5.