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Total Synthesis of the Hydroxyketone Kurasoin A Using Asymmetric Phase-Transfer Alkylation

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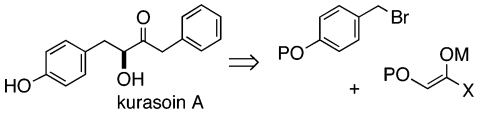

The total synthesis of the farnesyltransferase inhibitor kurasoin A has been achieved using a novel asymmetric phase-transfer-catalyzed glycolate alkylation reaction. 2,5-Dimethoxyacetophenone **7** with cinchonidinium catalyst **9** (10 mol %) and hydroxide base with pivaloyl benzyl bromide **8** provided S-alkylation product **10** in high yield (80−99%) and excellent enantioselectivity. Baeyer−Villiger oxidation, Weinreb amide formation, and benzyl Grignard addition to the TES-ether **17** gave the protected target. Lithium hydroxide and peroxide generated kurasoin A ($[\alpha]_D$ +8.4°) without isomerization.

Kurasoin A **1** and B **2** were isolated by Omura during a search for protein farnesyltransferase (PFTase) inhibitors from the soil fungus, *Paecilomyces* sp. (Figure 1).[1] These simple compounds hold potential for new lead development in that the aromatic substituents can be easily modified in a modular fashion around a central α-hydroxy ketone core.[2] A combination of NMR spectroscopy and synthesis was used to establish the absolute stereochemistry. A seven-step asymmetric route from 4-hydroxyphenyl-2-ethanol (5% overall yield) to kurasoin A **1** was used to establish the stereochemistry with a Sharpless asymmetric epoxidation that gave a key intermediate in low yield, 25%.[3] A racemic route to **1**, using benzyl Grignard addition to a Weinreb amide, was also reported.[4] We recently developed an efficient asymmetric, phase-transfer catalytic (PTC) glycolate alkylation process for the synthesis of α-hydroxy ester products, including a route to the diabetes drug (−)-ragaglitazar.[5] We now report the application of this new process for an efficient synthesis of kurasoin A together with important findings concerning the transformation of nonracemic ester products of this type into ketone products without isomerization and epimerization.

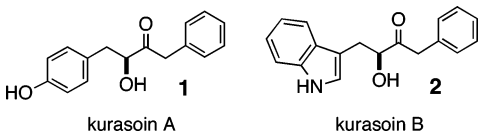

FIGURE 1. Hydroxyketone farnesyltransferase inhibitors kurasoin A and B.

The modular approach is accommodated through precursor **3** with suitable protecting groups for the phenolic and hydroxyl functionality (Scheme 1). The protecting groups P and P′ must be easily removed without epimerization of the α-hydroxyl, prevent tautomerization to the hydroxyketone isomer, and allow for benzyl addition to a suitable acyl derivative **4**. The 4-hydroxyphenyllactate intermediate **4** is assembled using a phase-transfer alkylation with the protected benzyl halide **5** and the glycolate enolate **6**. This flexible route can be easily modified, using alternative reagents for acyl addition and enolate alkylation, to directly access analogues of kurasoin A and B. Asymmetric, catalytic enolate alkylation with sp^3-electrophiles is a challenging transformation that has been met with only limited success with specific substrates. Koga pioneered the use of chiral polyamines for alkylation of cyclic silylenol ethers,[6] and List has recently demonstrated that iodoaldehydes undergo intramolecular proline-catalyzed alkylations.[7] More recently, Jacobsen has employed chromium−salen catalysts for the alkylation of cyclic tin enolates.[8]

We previously reported the development of asymmetric PTC glycolate alkylation of aryl ketone **7** with various electrophiles using the cinchonidine-derived catalyst **9** of Park and Jew, which was originally reported for glycine alkylation.[5] The benzhydryl group (DPM, diphenylmethyl) and the 2,5-dimethoxyphenyl ketone **7** were essential for both reactivity and the selectivity of the novel glycolate alkylation (Scheme 2). Alkylations of this type were previously limited to the benzophenone imine-protected glycine substrate of O'Donnell, where extended π-delocalization allows for enolate formation and catalyst interaction.[9] In this case for glycolate alkylation, it was found that liquid−solid PTC conditions with cesium hydroxide hydrate

(1) Uchida, R.; Shiomi, K.; Inokoshi, J.; Masuma, R.; Kawakubo, T.; Tanaka, H.; Iwai, Y.; Omura, S. *J. Antibiot.* **1996**, *49*, 932.

(2) (a) Kohl, N. E.; Wilson, F. R.; Mosser, S. D.; Giuliani, E.; DeSolms, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 9141. (b) Kohl, N. E.; Omer, C. A.; Conner, M. W.; Anthony, N. J.; Davide, J. P. *Nat. Med.* **1995**, *1*, 792.

(3) (a) Sunazuka, T.; Hirose, T.; Zhi-Ming, T.; Uchida, R.; Shiomi, K.; Harigaya, Y.; Omura, S. *J. Antibiot.* **1997**, *50*, 453. (b) Hirose, T.; Sunazuka, T.; Zhi-Ming, T.; Handa, M.; Uchida, R.; Shiomi, K.; Harigaya, Y.; Omura, S. *Heterocycles* **2000**, *53*, 777.

(4) Uchida, R.; Shiomi, K.; Sunazuka, T.; Inokoshi, J.; Nishizawa, A.; Hirose, T.; Tanaka, H.; Iwai, Y.; Omura, S. *J. Antibiot.* **1996**, *49*, 886.

(5) (a) Andrus, M. B.; Hicken, E. J.; Stephens, J. S. *Org. Lett.* **2004**, *6*, 2289. (b) Andrus, M. B.; Hicken, E. J.; Stephens, J. C.; Bedke, D. K. *J. Org. Chem.* **2005**, *70*, 9470. For auxiliary-based approaches to glycolate alkylation, see: (c) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165. (d) Schmidt, B.; Wildermann, H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1050. (e) Chappell, M. D.; Stachel, S. J.; Lee, C. B.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 1633. (f) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626.

(6) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829.

(7) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450.

(8) Doyle, A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62.

(9) (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (b) O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775. (c) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (d) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595. (e) Ooi, T.; Kameda, K.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519. (f) Jew, S.; Yoo, M.; Jeong, B.; Park, I. Y.; Park, H. *Org. Lett.* **2002**, *4*, 4245. (g) Park, H.; Jeong, B.; Yoo, M.; Lee, J.; Park, M.; Lee, Y.; Kim, M.; Jew, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036.

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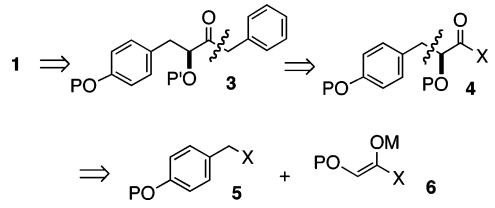
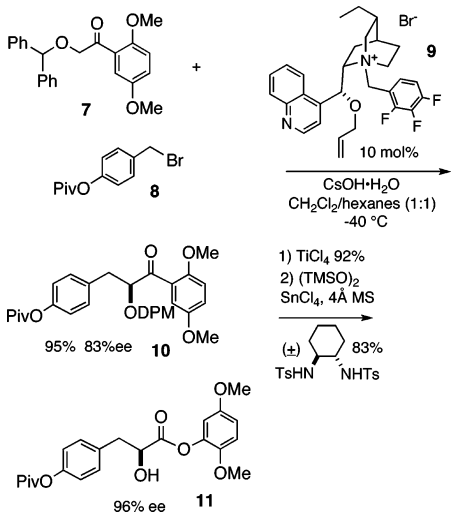
SCHEME 1. Retrosynthetic Analysis of 1 Includes Acyl Addition and Glycolate Alkylation



SCHEME 2. PTC Alkylation with Cinchonidinium Catalyst 9 and Baeyer−Villiger Oxidation Leading to Ester 11

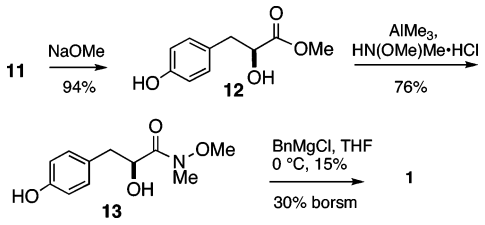


as base in a 1:1 mixture of methylene chloride and hexanes gave optimal results.[5b] Using **7**, pivaloyl benzyl bromide **8** (5 equiv), and cinchonidinium **9** (10 mol %, 24 h), *S*-ketone **10** was obtained in 95% isolated yield as previously reported. Chiral HPLC analysis indicated that the alkylation again occurred with 83% ee on gram scale. Use of other protected benzyl bromides, Bn (benzyl), TIPS (triisopropylsilyl), or Bz (benzoyl) in place of the pivaloyl group gave lower yield (60−70%) and selectivities (74−65% ee). In addition, the Piv-protected substrate **8** is crystalline (58−60 °C, mp) and is easily made from 4-hydroxybenzyl alcohol. The excess material following PTC alkylation can also be conveniently recovered during the isolation.

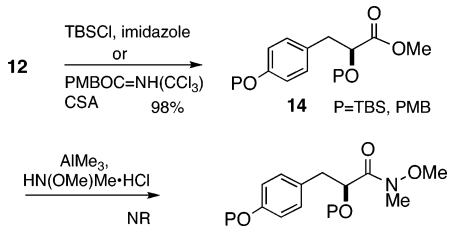
At this point, the labile DPM group was removed by treating **10** with titanium tetrachloride at −78 °C to give the free hydroxyl product in 92% yield (Scheme 2). The pivaloate ester remained in place under these conditions. The Baeyer−Villiger conditions of Shibasaki−Noyori using bis-trimethylsilylperoxide (2 equiv), tin tetrachloride, and racemic cyclohexane−bistoluenesulfonamide with added 4 Å molecular sieves[10] generated the desired aryl ester **11** in 83% isolated yield. Use of MCPBA (*m*-chloroperbenzoic acid) and other peracids failed to produce the desired ester. Recrystallization of the product **11** (94−96 °C, mp) from diethyl ether generated the ester in highly enantioenriched form (96% ee). Total isolated yield in this case, including both the Baeyer−Villiger oxidation and the recrystallization steps, was 75%. These peroxide conditions do not promote alkene epoxidation and expand the scope of the PTC alkylation reaction to allyl electrophiles, where the alkene functionality is maintained.[5b]

(10) (a) Sawanda, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 10521. (b) Göttlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, 971.

SCHEME 3. Weinreb Amide Formation and Benzyl Grignard Addition with Methyl 4-Hydroxyphenyllactate 12



SCHEME 4. Attempted Weinreb Amide Formation Using TBS and PMB Ethers 14

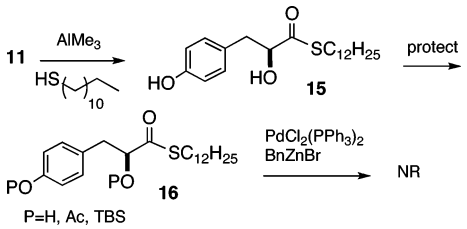


At this point, the *S*-ester **11** was prepared for benzyl addition to a suitable acyl derivative, and a quick end of the synthesis was anticipated. Treatment with sodium methoxide in methanol−THF cleanly provided the methyl ester diol **12** without racemization (Scheme 3). This key hydroxyphenyllactate is the intermediate employed previously by Omura, reported to give kurasoin A following Weinreb amide formation and benzyl Grignard addition.[4] While a 67% yield was reported with use of 6 equiv of *N*,*O*-dimethylhydroxyamine hydrochloride and trimethylaluminum, in our hands, **12** was found to give amide **13** in 30% yield. It was found that, by increasing the amounts of the reagents to 7 equiv (64 h), **13** was finally obtained in 76% yield. Again following the previous report,[4] the benzyl Grignard addition step was also addressed. With 5 equiv of benzyl Grignard (2 M, THF) at 0 °C, the final target kurasoin A was obtained with a disappointing 15% yield, not 65% as reported. Concentration and equivalents, solvents, and temperature variations did not lead to noticeable improvements for this step. Benzyllithium formed from toluene and *n*-butyllithium with added TMEDA (tetramethylethylenediamine) and other variations was also ineffective. If recovered starting material is taken into account, this final reaction can be seen to proceed using excess reagents at best with only a 30% yield, based on recovered starting material (borsm).

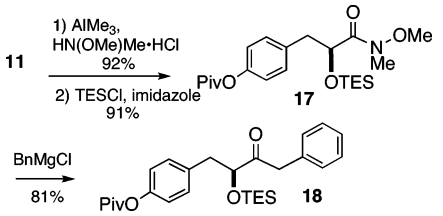
To improve the efficiency of amide formation, silyl and benzyl ether protected substrates were explored. Protection of the phenol hydroxyl at this point would also lower the number of equivalents of reagent needed for amide formation. Protection of **12** as either the TBS (*tert*-butyldimethylsilyl) or PMB (*p*-methoxybenzyl) ether under standard conditions gave bis-silyl and bis-PMB ethers **14** in high yields (Scheme 4). Surprisingly, there are only a few examples of α-hydroxy-protected esters that are known to successfully undergo Weinreb amide formation.[11] Much to our disappointment, **14** with P as TBS or PMB both failed to generate the corresponding amide, further illustrating a limitation to this important transformation.

(11) (a) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879. (b) Hulme, A. N.; Montgomery, C. H. *Tetrahedron Lett.* **2003**, *44*, 7649. (c) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809. (d) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1355.

SCHEME 5. Thioester Formation and Attempted Palladium-Catalyzed Benzylzinc Coupling



SCHEME 6. Amide Formation and Benzyl Grignard Addition with TES (triethylsilyl) Ether 17

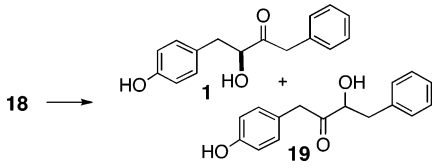


An alternative approach to benzyl ketone installation under palladium catalysis following the conditions of Fukuyama was also explored (Scheme 5).[12] Thioesters have recently been shown to undergo coupling reactions with alkyl zinc reagents, including benzyl zinc bromide under palladium catalyst conditions. The needed dodecylthio ester **15** was produced from **11**, and various protecting groups were then explored for the α-hydroxyl **16,** including acetate and TBS. Using standard conditions with 10 mol % of $PdCl_2(PPh_3)_2$ in toluene with benzyl zinc bromide, attempted couplings with **16** (P = Ac and H) gave only complex mixtures, and TBS-**16** showed only unreacted starting material under these mild coupling conditions.

Undaunted, we returned to the aryl ester **11** in an effort to establish a direct, efficient route through acyl activation and benzyl addition. Gratifyingly, direct addition to the aryl ester using *N*,*O*-dimethylhydroxyamine hydrochloride and trimethylaluminum was found to give the corresponding hydroxy amide in 92% isolated yield (Scheme 6). Aryl esters had not been known previously to undergo this type of transformation. Due to the lack of reactivity found previously with the TBS group, the smaller, more labile TES (triethylsilyl) group was installed to give **17** in high yield. It was unclear how these conditions would affect the pivaloate ester and if removal of this group could occur without racemization. Danishefsky reported an α-TES ether Weinreb amide that was shown to react with a Grignard reagent to give a ketone product.[13] Following this lead, it was found that benzyl Grignard addition proved efficient at 0 °C, giving the desired benzyl ketone **18** in high isolated yield, 81%.

Even with the success of the benzyl Grignard addition, it remained unclear how the TES and Piv groups would be removed without racemizing the hydroxyl stereocenter. Indeed, intermediate **18** was found to be highly sensitive to the known deprotection conditions for these groups (Table 1).[14] Treatment of **18** with HCl (3 M) in dioxane at 80 °C (entry 1) gave only decomposition. NaOH (3 N), followed by acidification with dilute HCl (1 M), proved to be superior, generating product **1**

TABLE 1. Deprotection Conditions to Kurasoin A 1



entry	conditions	combined yield, %	ratio **1**:**19**
1	3 M HCl, dioxane, 80 °C	decomp.	
2	3 N NaOH, then 1 M HCl	63	75:25
3	TBAF, THF then 1 N NaOH	51	92:8
4	TBAF, THF then $LiOH/H_2O_2$	65	100:0

with removal of both the Piv ester and TES ether in 63% yield (entry 2). In this case, 25% of the material was found to be the racemic, isomerized hydroxy ketone **19**, presumed to arise by enolization and tautomerization of **1**.[15] To minimize the amount of this unwanted isomerization product, TBAF (tetrabutylammonium fluoride) was used followed by treatment with NaOH and acidification (entry 3). Under these conditions, kurasoin A **1** was obtained in 51% with only 8% formation of **19**. Finally, it was found that use of TBAF followed by addition of lithium hydroxide and hydrogen peroxide generated kurasoin A **1** in 65% yield ($[\alpha]_D$ +8.4°, mp 120−122 °C, nat. material $[\alpha]_D$ +7 °, mp 121−123°)[1] identical in all respects to natural material.

In summary, a novel, seven-step phase-transfer catalysis-based approach to the simple farnesyltransferase inhibitor kurasoin A has been developed using efficient glycolate alkylation and Grignard addition in 24% overall yield. The modular approach also allows for the ready incorporation of diverse substituents on both sides of the core hydroxy ketone functionality. New insights into Weinreb amide formation and reactivity were also obtained together with new deprotection conditions for this sensitive substrate.

Experimental Section

(*S*)-4-(3-(Methoxy(methyl)amino)-3-oxo-2-(triethylsilyloxy)-propyl)phenyl pivalate (17). To a flame dried 10 mL round-bottom flask were added *N*,*O*-dimethylhydroxylamine hydrochloride (0.073 g, 0.750 mmol) and CH_2Cl_2 (1.3 mL). Then $AlMe_3$ (0.370 mL, 2.0 M in hexane) was added dropwise, and the solution was stirred at ambient temperature for 30 min. Then (*S*)-2,5-dimethoxyphenyl 2-hydroxy-3-(4-phenylpivalate)propanoate **11** (0.050 g, 0.124 mmol) was added to a CH_2Cl_2 solution (1.0 mL + 0.3 mL rinse), and the mixture was stirred for 5 h at ambient temperature. The reaction was then quenched by the addition of a 0.5 M HCl solution (2 mL) and diluted with CH_2Cl_2 and H_2O. The layers were mixed and separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with a saturated aqueous NaCl solution, dried over Na_2SO_4, filtered, and concentrated. The residual oil was purified via radial chromatography (1 mm plate, 60% EtOAc/hexane) to afford 0.036 g (92%) of alcohol, (*S*)-4-(2-hydroxy-3-(methoxy(methyl)amino)-3-oxopropyl)phenyl pivalate, as a yellow oil: TLC R_f = 0.34 (80% EtOAc/hexane); $[\alpha]^{23}_D$ −38.0° (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24−7.22 (m, 2H), 6.99−6.98 (m, 2H), 4.61 (bm, 1H), 3.71 (s, 3H), 3.32 (bm, 1H), 3.24 (s, 3H), 3.05, (dd, *J* = 3.5, 13.5 Hz, 1H), 2.86 (dd, *J* = 7.5, 14.0 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.3, 174.2, 150.1, 134.8, 130.5, 121.5, 69.8, 61.6,

(12) Fukuyama, T.; Tokuyama, H. *Aldrichimica Acta* **2004**, *37*, 87.
(13) Rivkin, A.; Biswas, K.; Chou, T.-C.; Danishefsky, S. J. *Org. Lett.* **2002**, *4*, 4081.
(14) Bengtsson, S.; Hogberg, T. *J. Org. Chem.* **1993**, *58*, 3538.
(15) (a) Creary, X.; Geiger, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 4151. (b) Hartman, M.; Christian, R.; Zbiral, E. *Liebigs Ann. Chem.* **1990**, 83. (c) Ivonin, S. P.; Lapandin, A. V. *Synth. Commun.* **2004**, *34*, 3727.

40.6, 39.2, 32.6, 27.3. To a 25 mL round-bottom flask containing (*S*)-4-(2-hydroxy-3-(methoxy(methyl)amino)-3-oxopropyl)phenyl pivalate (0.032 g, 0.104 mmol) was added DMF (1.0 mL) followed by imidazole (0.028 g, 0.416 mmol). Then chlorotriethylsilane (0.035 mL, 0.208 mmol) was added, and the reaction was stirred at ambient temperature for 5 h at which time H_2O (10 mL) was added and the mixture extracted with EtOAc (3 × 10 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated. The product was isolated via radial chromatography (1 mm plate, 20% EtOAc/hexane) to provide 0.040 g (91%) of the title compound **17** as a colorless oil: TLC $R_f = 0.52$ (40% EtOAc/hex); $[\alpha]^{23}_D$ +3.1° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24−7.21 (m, 2H), 6.97−6.94 (m, 2H), 4.69 (bm, 1H), 3.52 (s, 3H), 3.17 (s, 3H), 3.05 (dd, J = 5.4, 13.2 Hz, 1H), 2.87 (dd, J = 7.8, 13.2 Hz, 1H), 1.35 (s, 9H), 0.89−0.84 (m, 9H), 0.55−0.46 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.4, 150.1, 135.4, 130.8, 121.5, 70.9, 41.0, 39.3, 32.7, 27.4, 6.8, 4.8; HRMS (FAB$^+$) found 446.2344 [M + Na]$^+$, calcd 446.2333 for $C_{22}H_{37}O_5NSiNa$.

(*S*)-4-(3-Oxo-4-phenyl-2-(triethylsilyloxy)butyl)phenyl pivalate (18). To a 25 mL round-bottom flask containing (*S*)-4-(3-(methoxy(methyl)amino)-3-oxo-2-(triethylsilyloxy)propyl)phenyl pivalate (0.114 g, 0.269 mmol) was added THF (4.5 mL), and the solution was cooled to 0 °C. Then benzylmagnesium chloride (0.540 mL, 2.0 M in THF) was added slowly over 5 min. The reaction mixture was stirred at 0 °C for 2.5 h at which time H_2O was added (15 mL), and the mixture was then extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified via radial chromatography (1 mm plate, 5% EtOAc/hexane) to afford 0.100 g (82%) of the desired product **18** as a colorless oil: TLC R_f = 0.75 (40% EtOAc/hex); $[\alpha]^{23}_D$ −46.0° (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31−7.22 (m, 3H), 7.19−7.16 (m, 2H), 7.07 (d, J = 7.0 Hz, 2H), 6.98−6.96 (m, 2H), 4.36 (dd, J = 4.5, 7.5 Hz, 1H), 3.77 (d, J = 16.5 Hz, 1H), 3.67 (d, J = 17.0 Hz, 1H), 2.92 (dd, J = 4.5, 13.5 Hz, 1H), 2.84 (dd, J = 7.5, 13.5 Hz, 1H), 1.36 (s, 9H), 0.90−0.87 (m, 9H), 0.54−0.45 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.7, 177.2, 150.2, 134.3, 134.0, 131.0, 130.0, 128.6, 127.0, 121.5, 79.6, 45.1, 41.2, 39.2, 27.3, 6.9, 4.8; HRMS (FAB$^+$) found 455.2608 [M + H]$^+$, calcd 455.2612 for $C_{27}H_{39}O_4Si$.

(+)-Kurasoin A (1). To a 25 mL round-bottom flask containing (*S*)-4-(3-oxo-4-phenyl-2-(triethylsilyloxy)butyl)phenyl pivalate **18** (0.038 g, 0.084 mmol) was added THF (2.0 mL), and the solution was cooled to 0 °C. Then tetrabutylammonium fluoride (0.090 mL, 1.0 M in THF) was added, and the reaction mixture was stirred at 0 °C for 15 min. Then H_2O (1.0 mL) was added followed by H_2O_2 (0.038 mL, 30% aqueous). Then LiOH(H_2O) (0.007 g, 0.167 mmol) was added, and the reaction mixture was stirred for an additional 25 min at 0 °C. Then a saturated aqueous $Na_2S_2O_3$ solution (2 mL) was added followed by a saturated aqueous NH_4Cl solution (20 mL). The mixture was then extracted with EtOAc (1 × 15 mL) and CH_2Cl_2 (3 × 15 mL). Then combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was then dissolved in a minimal amount of CH_2Cl_2 and purified via column chromatography (40% EtOAc/hexane) to provide 0.014 g (65%) of the title compound **1** as a white solid: TLC R_f = 0.39 (50% EtOAc/hex); $[\alpha]^{23}_D$ +8.4° (*c* 0.5, CH_3OH), lit.[2] synthetic = $[\alpha]^{22}_D$ +9° (*c* 1.0, CH_3OH), natural = $[\alpha]^{22}_D$ +7° (*c* 0.1, CH_3OH); mp = 120−122 °C, lit.[2] mp = 121−123 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.28−7.01 (m, 7H), 6.70−6.68 (m, 2H), 4.33 (dd, J = 5.0, 7.5 Hz, 1H), 3.78 (d, J = 17.0 Hz, 1H), 3.72 (d, J = 16.5 Hz, 1H), 2.95 (dd, J = 5.0, 14.5 Hz, 1H), 2.75 (dd, J = 7.5, 14.0 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 212.4, 157.3, 135.6, 131.7, 131.0, 129.6, 129.5, 127.9, 116.3, 78.9, 46.7, 40.4. HRMS (FAB$^+$) found 279.0989 [M + Na]$^+$, calcd 279.0992 for $C_{16}H_{16}O_3$-Na.

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Supporting Information Available: Experimental procedures and characterization for all compounds, and NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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