JOC Article

Mild, Fast, and Stereoselective Epoxide Opening by Ketone Enolate Anions. Application to Synthesis of the Norlignan Curculigine

Gary H. Posner,* John P. Maxwell,† and Mehmet Kahraman

Department of Chemistry, School of Arts and Sciences, The Johns Hopkins University, Baltimore, Maryland 21218

ghp@jhu.edu

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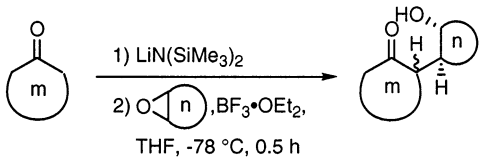
We report here that (1) enolate anions of five- to seven-membered cycloalkanones nucleophilically open cyclopentene and cyclohexene oxides in 57−76% yields and with 4−8:1 diastereoselectivity; (2) enolate anions formed regiospecifically via kinetic deprotonation of 2-cyclohexenone and 2-cycloheptenone open cyclohexene oxide in 60−62% yields and with 32−95:1 diastereoselectivity; and (3) an aryl methyl ketone enolate anion opens a monosubstituted epoxide as the key step in a short synthesis of the γ-hydroxyketone (GHK) aglycon of the natural product curculigine.

Introduction

Nucleophilic enolate anions and electrophilic epoxides are fundamental building blocks in diverse carbon−carbon bond-forming reactions, including synthesis of complex target molecules.[1,2] Although ester[3,4] (pK_a 25) and amide[5−7] (pK_a 28) enolate anions nucleophilically open epoxides, ketone (pK_a 20) enolate anions generally do not,[3,8] probably as a result of their greater thermodynamic stability. The electrophilicity of epoxides can be enhanced, however, by various Lewis acids. Crotti and colleagues have studied this topic intensively,[9] and they have applied especially Lewis acidic scandium triflate to facilitate ketone enolate anion opening of epoxides; typical reaction times are ≥18 h at room temperature. We reported recently in preliminary fashion a simple, mild (−78 °C) and rapid (<1 h) way to activate epoxides toward nucleophilic opening by ketone enolate anions: boron trifluoride−diethyl etherate (BF_3·OEt_2) added to a mixture of enolate and epoxide effectively promotes carbon−carbon bond formation to produce γ-hydroxy ketones (GHKs).[10] Now we report on the scope of this process, including (1) enolate anions of five- to seven-membered cycloalkanones nucleophilically opening cyclopentene and cyclohexene oxides in good yield and with good diastereoselectivity; (2) enolate anions formed regiospecifically via kinetic deprotonation of 2-cyclohexenone and 2-cycloheptenone opening cyclohexene oxide in good yield and with very good to excellent diastereoselectivity; and (3) an aryl methyl ketone enolate anion opening a monosubstituted epoxide as the key step in a short synthesis of the aglycon GHK of the natural product curculigine.

TABLE 1



m	n	product	% yield	dr (*syn*:*anti*) (H/H)
5	6	**1**	70	6:1
6	5	**2**	57	5:1
6	6	**3**	76	8:1
7	5	**4**	75	4:1
7	6	**5**	73	8:1

Coupling of Cycloalkanone Enolates with Cycloalkene Epoxides. Deprotonation of five- to seven-membered cycloalkanones with lithium hexamethyldisilazide in tetrahydrofuran at −78 °C followed sequentially by addition of either cyclopentene epoxide or cyclohexene epoxide and then dropwise addition of 1 equiv of neat, precooled BF_3·OEt_2 gave GHKs **1**−**5** in 57−76% yields and with 4−8:1 diastereoselectivity (Table 1). For all

* To whom correspondence should be addressed. Phone: 410-516-4670. Fax: 410-516-8420.

† Current address: Vertex Pharmaceuticals, Cambridge, MA.

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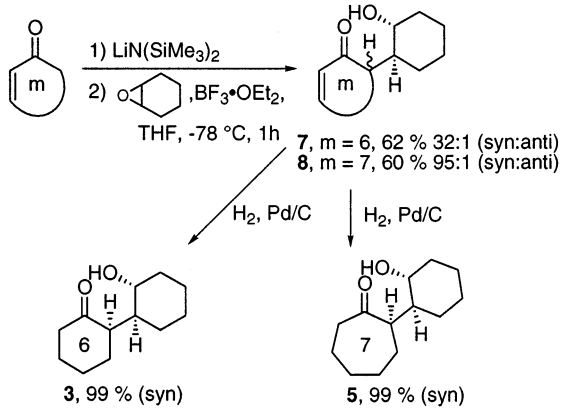
these GHKs **1**−**5**, the diastereomer with the two adjacent methine hydrogen atoms syn to each other predominated. Characteristic ^{1}H NMR absorptions of these GHKs are as follows. GHK **1**: C*H*OH proton of the major diastereomer δ 3.46−3.33 (m, 1H) and that of the minor diastereomer δ 3.36−3.24 (m, 1H). GHK **2**: C*H*OH of the major diastereomer δ 3.95−3.90 (m, 1H) and the minor diastereomer 3.78 (m, 1H). GHK **3**: syn diatereomer δ C*H*OH 3.30−3.22 (m, 1H), O*H* 2.58 (d, J = 8.0 Hz, 1H), 2.47−2.41 (m, 1H), 2.38−2.29 (m, 2H); anti diastereomer δ C*H*OH 3.92−3.24 (m, 1H), 2.80−2.75 (m, 1H). GHK **4**: C*H*OH of the major diastereomer δ 3.92 (dd, J = 12.4, 6.8 Hz, 1H) and the minor diastereomer δ 3.77−3.73 (m, 1H). GHK **5**: C*H*OH for the major diastereomer δ 3.33−3.23 (m, 1H); the minor diastereomer exists a mixture of the GHK and the corresponding hemiacetal δ 3.57−3.49 (m, 0.72H), 3.33−3.31 (m, 0.28H). Unequivocal assignment of relative stereochemistry to the GHKs **2**−**5** was achieved via X-ray crystallography of the corresponding *p*-nitrobenzoate esters. Oxidation of the major diastereomer of cyclopentanol GHK **2** gave the same diketone as oxidation of the major diastereomer of cyclohexanol GHK **1**, thereby confirming the syn stereochemistry of the major diastereomer of GHK **1**. Lower reaction temperature (−100 °C) did not raise the diastereoselelectivity of the coupling reactions. When initial ketone deprotonation was performed using sodium rather than lithium hexamethyldisilazide, the yield of GHK product was increased by 5−20% but the diastereoselectivity was severely diminished.

To show that the GHK major syn diastereomers **1**−**5** are the kinetic products of these enolate−epoxide coupling reactions, the pure syn diastereomer of cyclohexanone **3** was equilibrated in ethanolic potassium hydroxide at room temperature for 2 days into a 2:3 ratio of syn:anti diastereomers. The same thermodynamic 2:3 syn:anti ratio was obtained also via basic equilibration starting with the pure anti diastereomer of GHK **3**. Similar equilibration results were obtained with GHKs **1** and **5**.

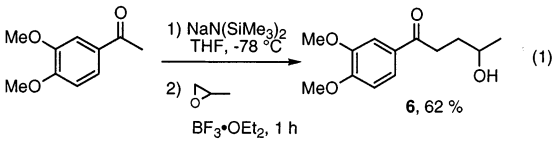
An additional example of an acyclic ketone enolate opening of a simple epoxide is shown in eq 1, illustrating further the usefulness of BF_3·OEt_2 in promoting these coupling reactions to form GHK **6**. Using an acyclic ketone enolate to open cyclohexene epoxide in the presence of BF_3·OEt_2 proceeded well chemically but with poor diastereocontrol (eq 2). When cyclooctene epoxide was used, cyclohexanone lithium enolate gave no significant amount of GHK.

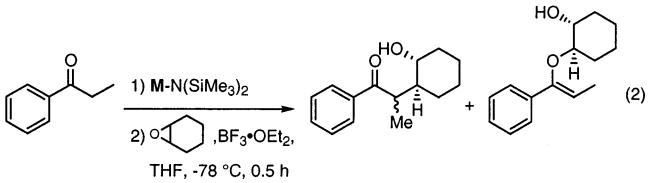
Highly Diastereoselective Coupling of 2-Cycloalkenone Kinetic Enolates with Cyclohexene Epoxide. The level of diastereoselectivity in enolate opening of epoxides was considerably higher (as determined by NMR spectroscopy of crude product mixtures) when the kinetic lithium enolate of 2-cyclohexenone and of 2-cycloheptenone was treated first with cyclohexene epoxide and then with 1 equiv of neat, precooled BF_3·OEt_2 at −78 °C in THF (Scheme 1). Catalytic hydrogenation of the initial olefinic GHKs **7** and **8** produced the same major GHK products **3** and **5** shown in Table 1. Thus, this two-step reaction sequence (Scheme 1) allows easy transformation of 2-cyclohexenone and 2-cycloheptenone into the corresponding syn GHKs **3** and **5**, each

SCHEME 1



with three contiguous stereogenic centers, in 32−95:1 diastereomeric ratio and in 60−62% overall yields.





M	% yield (syn:anti) (Me/H)	O-alkylation % yield
Li	25 (1:3)	42
Na	79 (2:1)	18
K	86 (3:1)	5
Crotti conditions (RT, 36 h):[9] Li	89 (1:1.1)	

As before, using sodium rather than lithium hexamethyldisilazide gave substantially poorer stereochemical control. 2-Cyclohexenone kinetic lithium enolate anion did not open cyclopentene epoxide or *cis*-2-butene epoxide well. Likewise, 2-cycloheptenone kinetic lithium enolate did not open cyclopentene epoxide well.

Synthesis of Natural Product Curculigine Aglycon. Some norlignan glucosides have been isolated from tuberous rhizomes and have been found in vivo to be potently anti-arrhythmic.[11] Structurally related curculigine was isolated also in very small amounts from the same plant and was characterized as its peracetylated glucoside penta-O-methylated ether.[12] We report here a short synthesis of the aglycon (−)-**15** of this norlignan glucoside, starting from allylic alcohol **9**,[13] in which the key convergent synthetic step involves BF_3·OEt_2-assisted opening of monosubstituted epoxide (−)-**12** by an aryl methyl ketone enolate anion (Scheme 2). In this key

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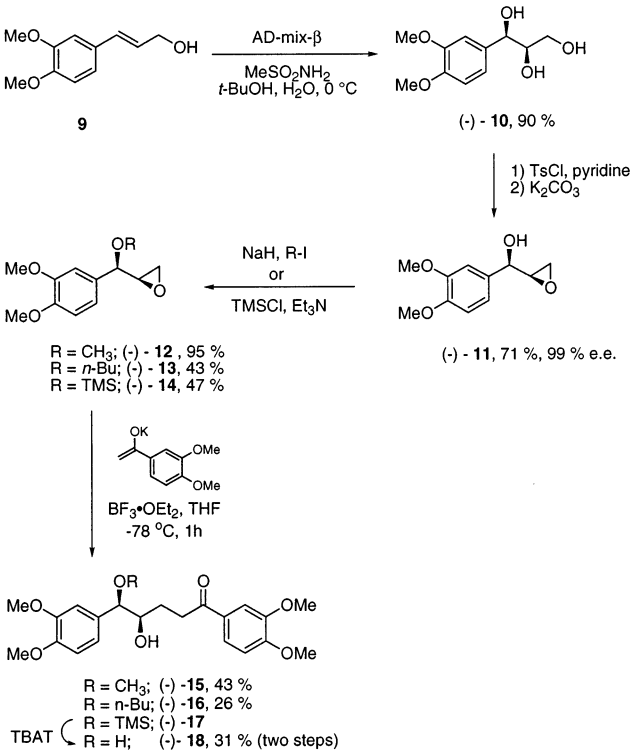
SCHEME 2



step to form GHK (−)-**15**, the potassium enolate was found to give better yields than either the sodium or lithium enolate. Because the aglycon (−)-**15** has not been characterized in the literature, the corresponding known compounds (−)-**16** and (−)-**18** were synthesized in the same manner as (−)-**15** (Scheme 2). This provides confirmation of relative and absolute stereochemistry of these natural product aglycons. GHK (−)-**18** was obtained from coupling of the TMS ether epoxide (−)-**14** with the aryl methyl ketone enolate ion, followed by desilylation with tetrabutylammonium triphenyldifluorosilicate (TBAT),[14] an anhydrous, crystalline fluoride source.

In conclusion, we have demonstrated that diverse epoxides are easily, rapidly, and diastereoselectively opened by various cycloalkanone lithium enolates in the presence of BF_3•OEt_2 in THF solvent at −78 °C. Outstanding diastereoselectivity is evident when the kinetic lithium enolates of 2-cyclohexenone and 2-cycloheptenone open cyclohexene oxide. This type of BF_3•OEt_2-promoted opening of a monosubstituted epoxide by a methyl ketone enolate anion is featured as the key carbon−carbon bond-forming step in the synthesis of the norlignan natural product aglycon (−)-**15**. The fundamental carbon−carbon bond-forming reactions described here between ketone enolates and oxiranes using BF_3•OEt_2 are expected to be useful to the international synthetic organic chemistry community.

Experimental Section

All reactions were run in flame-dried glassware under an argon atmosphere. NMR spectra were recorded on a Varian XL 400 spectrometer (^{1}H NMR at 400 MHz, ^{13}C at 100 MHz) with chloroform, tetramethylsilane, or d_4-CH_3OH as an internal reference. Chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Electospray ionization (ESI) mass spectrometry analysis was performed with a 3-tesla Fourier Transform mass spectrometer. Electron impact (EI) ionization was performed using 70 eV ionization conditions. Solvents were distilled prior to use; methylene chloride (CH_2Cl_2) was distilled from CaH_2, tetrahydrofuran (THF) and diethyl ether (ether) were distilled from benzophenone sodium ketyl, chloroform ($CHCl_3$) was distilled from 4 Å molecular sieves, and dimethyl sulfoxide (DMSO) was dried over CaH_2 and distilled. All other starting materials and reagents were purchased from commercial sources. All ketones used in the study were dried over $MgSO_4$ and all except for 3,4-dimethoxyacetophenone were distilled under reduced pressure before use. Cycloheptenone was further purified by flash silica gel column chromatography. Flash silica gel refers to particle size 400−230 mesh. Medium-pressure liquid chromatography (MPLC) was performed with FMI pump and prepacked silica gel column (Si 60, 40−63μ).

GHK 1. To a solution of LHMDS (1.0 M in THF, 1.10 mL, 1.10 mmol, 1.1 equiv) in THF (2 mL) at −78 °C was added cyclopentanone (89 μL, 1.0 mmol, 1.0 equiv) over 1 min. Cyclohexene oxide (0.200 mL, 1.98 mmol, 2.0 equiv) was added after 20 min, followed by neat BF_3•OEt_2 (0.140 mL, 1.10 mmol, 1.1 equiv) over 5 min. After 1 h the reaction was quenched at −78 °C by the addition of saturated aqueous NH_4Cl solution (2 mL), and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography with petroleum ether/EtOAc (6:1) to obtain 128 mg (0.702 mmol, 70%) of a mixture of the two diastereomers in a 6:1 ratio as determined by ^{1}H NMR analysis. The diastereomers were subjected to further flash silica gel chromatographic analysis in order to obtain separate amounts of each for individual characterization. Data for **GHK 1** (major isomer): R_f = 0.20 petroleum ether/EtOAc (6:1, 3×). ^{1}H NMR ($CDCl_3$): δ 3.46−3.33 (m, 1H), 2.27−2.22 (m, 2H), 2.08−1.79 (m, 6H), 1.77−1.60 (m, 4H), 1.30−1.12 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 222.67, 72.16, 52.60, 45.85, 38.64, 36.57, 30.91, 26.04, 25.35, 24.28, 21.40. FTIR (neat, cm^{-1}): 3434.7, 2927.9, 2855.0, 1731.0, 1449.8, 1159.5, 1063.5, 923.8. HRMS (M + Na): calcd 205.1204, found 205.1201. Data for **GHK 1** (minor isomer): R_f = 0.14 pet ether/EtOAc (6:1, 3×). ^{1}H NMR ($CDCl_3$): δ 3.36−3.24 (m, 1H), 2.62−2.56 (m, 1H), 2.44−2.24 (m, 2H), 2.17−2.00 (m, 4H), 1.83−1.61 (m, 4H), 1.54−1.48 (m, 1H), 1.31−1.14 (m, 4H), 1.08−0.98 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 223.22, 73.40, 51.50, 44.63, 39.35, 36.60, 27.80, 25.69, 25.41, 25.20, 21.05. FTIR (neat, cm^{-1}): 3417.4, 2928.8, 2856.2, 1731.3, 1449.3, 1405.3, 1162.1, 1061.8. HRMS (M + Na): calcd 205.1199, found 205.1211.

GHK 2. To a solution of LHMDS (1.0 M in THF, 1.10 mL, 1.10 mmol, 1.1 equiv) in THF (2 mL) at −78 °C was added cyclohexanone (0.100 mL, 0.96 mmol, 1.0 equiv) over 1 min. Cyclopentene oxide (0.170 mL, 1.95 mmol, 2.0 equiv) was added after 15 min, followed by neat BF_3•OEt_2 (0.140 mL, 1.10 mmol, 1.1 equiv) over 5 min. After 1 h the reaction was quenched at −78 °C by the addition of saturated aqueous NH_4Cl solution (2 mL), and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography with petroleum ether/EtOAc (6:1) to obtain 100 mg (0.549 mmol, 57%) of a mixture of the two diastereomers in 5:1 ratio as determined by ^{1}H NMR analysis. The diastereomers were subjected to further flash silica gel chromatographic analysis in order to obtain sufficient amounts of each for individual characterization. Data for **GHK 2** (major

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isomer): R_f = 0.30 hexanes/EtOAc (2:1). ^{1}H NMR ($CDCl_3$): δ 3.95−3.90 (m, 1H), 3.13 (d, J = 2.4 Hz, 1H), 2.54−2.49 (m, 1H), 2.40−2028 (m, 2H), 2.24−2.17 (m, 1H), 2.14−2.04 (m, 2H), 1.94−1.88 (m, 1H), 1.84−1.76 (m, 2H), 1.75−1.61 (m, 4H), 1.56−1.46 (m, 2H), 1.31−1.22 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 215.53, 74.91, 53.68, 47.22, 42.34, 35.56, 30.05, 28.98, 28.25, 25.07, 23.24. FTIR (neat, cm^{-1}): 3411.0, 2938.3, 2863.4, 1704.1, 1448.2, 1310.5, 1130.5, 981.5. HRMS (M + Na): 205.1204, found 205.1208. Data for **GHK 2** (minor isomer): R_f = 0.39 hexanes/EtOAc (2:1). ^{1}H NMR ($CDCl_3$): δ 3.95 (s, 1H), 3.78 (m, 1H), 2.48−2.43 (m, 1H), 2.40−2.24 (m, 2H), 2.20−2.07 (m, 2H), 1.98−1.55 (m, 9H), 1.44−1.34 (m, 1H), 1.17−1.06 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 112.3, 77.50, 71.99, 70.37, 68.58, 66.59, 66.26, 65.55, 64.94, 64.18, 63.76. FTIR (neat, cm^{-1}): 3427.9, 2939.2, 2863.3, 1698.5, 1448.3, 1311.2, 1029.7, 984.4. HRMS (M + Na): calcd 205.1204, found 205.1206.

GHK 3. To a solution of LHMDS (1.0 M in THF, 1.10 mL, 1.10 mmol, 1.1 equiv) in THF (2 mL) at −78 °C was added cyclohexanone (0.100 mL, 0.96 mmol, 1.0 equiv) over 1 min. This was stirred for 60 min, and then cyclohexene oxide (0.200 mL, 1.98 mmol, 2.0 equiv) was added, followed after 10 min by neat BF_3·OEt_2 (0.135 mL, 1.05 mmol, 1.1 equiv) over 5 min. After 1 h the reaction was quenched at −78 °C by the addition of aqueous pH 7.0 phosphate buffer solution (2 mL), and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography with petroleum ether/EtOAc (6:1) to obtain 129 mg [0.657 mmol, 68%, R_f = 0.41 hexanes/EtOAc (2:1)] of the major diastereomer and 17 mg (0.086 mmol, 9%) of the minor diastereomer as viscous liquids. Data for **GHK 3** (major isomer): ^{1}H NMR ($CDCl_3$): δ 3.30−3.22 (m, 1H), 2.58 (d, J = 8.0 Hz, 1H), 2.47−2.41 (m, 1H), 2.38−2.29 (m, 2H), 2.12−1.95 (m, 5H), 1.82−1.61 (m, 5H), 1.49−1.43 (m, 1H), 1.34−1.17(m, 4H). ^{13}C NMR ($CDCl_3$): δ 216.02, 71.60, 55.14, 42.69, 42.38, 36.86, 30.23, 28.06, 27.54, 26.05, 25.71, 24.96. FTIR (neat, cm^{-1}): 3431.1, 2931.5, 2856.6, 1703.5, 1448.9, 1132.0, 1062.4, 1051.1. HRMS: (M + Na): calcd 219.1361, found 219.1366. Data for **GHK 3** (minor isomer): ^{1}H NMR ($CDCl_3$): δ 3.30−3.24 (m, 1H), 2.80−2.75 (m, 1H), 2.47−2.41 (m, 1H), 2.36−2.27 (m, 1H), 2.11−1.96 (m, 5H), 1.76−1.60 (m, 2H), 1.53−1.39 (m, 3H), 1.38−1.18 (m, 4H), 0.97−0.88 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 214.15, 72.10, 50.65, 43.26, 42.44, 36.98, 29.89, 27.99, 27.59, 26.91, 25.82, 25.36, 25.12. FTIR (neat, cm^{-1}): 3393.4, 2930.0, 2857.3, 1704.7, 1448.8, 1131.9, 1069.7, 1056.4. HRMS: (M + Na): calcd 219.1361, found 219.1364.

GHK 4. To a solution of LHMDS (1.0 M in THF, 4.4 mL, 4.4 mmol, 1.1 equiv) in THF (8 mL) at −78 °C was added cycloheptanone (0.47 mL, 4.1 mmol, 1.0 equiv) dropwise. Cyclopentene oxide (0.98 mL, 8.0 mmol, 2.0 equiv) was added after 25 min, followed by neat BF_3·OEt_2 (0.54 mL, 4.3 mmol, 1.1 equiv) over 5 min. After 1 h the reaction was quenched at −78 °C by the addition of saturated aqueous NH_4Cl solution (10 mL), and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo to give a 4:1 ratio of a mixture of isomers as determined by ^{1}H NMR analysis. The crude product was purified by MPLC eluted with 25% ethyl acetate in toluene to obtain 0.46 mg of the major isomer and 0.11 mg of the minor isomer. Data for **GHK 4** (major isomer): ^{1}H NMR ($CDCl_3$): δ 3.92 (dd, J = 12.4, 6.8 Hz, 1H), 3.35 (br, 1H), 2.68−2.63 (m, 1H), 2.46−2.43 (m, 2H), 2.03−1.73 (m, 7H), 1.68−1.47 (m, 4H), 1.40−1.14 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 218.16, 74.30, 54.25, 49.20, 43.20, 35.12, 29.40, 29.36, 29.29, 27.96, 24.13, 22.44. FTIR (neat, cm^{-1}): 3425.1, 2931.5, 2859.8, 163.7, 1453.6, 1342.9, 1168.0, 1092.0, 1072.7, 935.5. HRMS (M + Na): calcd 219.1355, found 219.1369. Data for **GHK 4** (minor isomer): ^{1}H NMR ($CDCl_3$): δ 3.77−3.73 (m 1H), 2.67 (br, 1H), 2.52−2.42 (m, 3H), 1.99−1.77 (m, 7H), 1.73−1.51 (m, 4H), 1.41−1.26 (m, 3H), 1.21−1.12 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 218.74, 77.65, 57.03, 50.61, 43.16, 34.61, 30.06, 3014, 29.38, 28.40, 24.27, 22.55. FTIR (neat, cm^{-1}): 3425.1, 2931.5, 2859.8, 163.7, 1453.6, 1342.9, 1168.0, 1092.0, 1072.7, 935.5. HRMS (M + Na): calcd 219.1355, found 219.1358.

GHK 5. To a solution of LHMDS (1.0 M in THF, 1.10 mL, 1.10 mmol, 1.1 equiv) in THF (2 mL) at −78 °C was added cycloheptanone (0.118 mL, 1.0 mmol, 1.0 equiv) dropwise over 2 min. Cyclohexene oxide (0.200 mL, 1.98 mmol, 2.0 equiv) was added after 60 min, followed by neat BF_3·OEt_2 (0.140 mL, 1.10 mmol, 1.1 equiv) over 5 min. After 1 h the reaction was quenched at −78 °C by the addition of saturated aqueous NH_4-Cl solution (2 mL), and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography with petroleum ether/EtOAc (6:1) to obtain 133 mg [0.632 mmol, 63%, R_f = 0.49 hexanes/EtOAc (2:1)] of the major diastereomer as a white solid (mp = 66.0−67.5 °C) and 22 mg (0.105 mmol, 10%) of the minor diastereomer. Data for **GHK 5** (major isomer): ^{1}H NMR ($CDCl_3$): δ 3.33−3.23 (m, 1H), 2.87 (d, J = 6.0 Hz, 1H), 2.61 (ddd, J = 13.6, 12.0, 2.8 Hz, 1H), 2.50−2.38 (m, 2H), 2.04−1.83 (m, 4H), 1.80−1.56 (m, 6H), 1.46−1.07 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 219.47, 71.22, 55.55, 48.74, 44.05, 36.09, 30.34, 29.65, 29.52, 26.44, 26.03, 25.22, 24.97. FTIR (neat, cm^{-1}): 3410.5, 2927.0, 2854.2, 1691.6, 1679.4, 1459.9, 1450.8, 1344.0, 1186.1, 1170.0, 1145.8, 1129.7, 1063.2, 1023.0, 942.0. Elemental analysis: calcd % C: 74.24, H: 10.54; found % C: 74.18, H: 10.54. HRMS (M + Na): calcd 233.1517, found 233.1518. Data for **GHK 5** (minor isomer): ^{1}H NMR 28:72 keto-alcohol/hemiketal ($CDCl_3$/D_2O): δ 3.57−3.49 (m, 0.72H), 3.33−3.31 (m, 0.28H), 2.68−2.62 (m, 0.3H), 2.58−2.46 (m, 0.7H), 2.03−1.58 (m, 11H), 1.42−0.05 (m, 8H). ^{13}C NMR ($CDCl_3$): (keto alcohol assignments) δ 218.82, 80.19, 55.74, 53.25, 38.96, 31.82, 31.12, 30.32, 27.62, 26.34, 25.90, 24.43, 23.94; (hemiketal assignments) δ 109.43, 72.68, 54.32, 48.40, 43.90, 36.59, 30.45, 28.69, 27.99, 27.14, 25.72, 25.35, 25.14. FTIR (neat, cm^{-1}): 3396.7, 2927.6, 2854.9, 1691.8, 1451.4, 1355.6, 1342.6, 1313.9, 1277.4, 1217.4, 1207.0, 1170.5, 1141.8, 1115.7, 1089.6, 1068.8, 1047.9, 982.7, 941.0. HRMS (M + Na): calcd 233.1517, found 233.1517.

1-(3,4-Dimethoxyphenyl)-4-hydroxypentan-1-one (6). To a solution of NaHMDS (1.0 M in THF, 1.10 mL, 1.1 mmol, 1.2 equiv) in THF (2 mL) at −78 °C was added a solution of 3,4-dimethoxypropiophenone (181 mg, 1.0 mmol, 1.0 equiv) in THF (1.5 mL) over MS 4 Å. The reaction was stirred for 60 min, and then propylene oxide (0.140 mL, 2.0 mmol, 2.0 equiv) was added to the reaction, followed after an additional 5 min by neat BF_3·OEt_2 (0.140 mL, 1.1 mmol, 1.1 equiv). After 60 min the reaction was quenched at − 78 °C by the addition of aqueous pH 7.0 phosphate buffer solution (4 mL) and diluted with brine (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography with petroleum ether/EtOAc (1:1) to obtain 148 mg (0.62 mmol, 62%) of product as a colorless oil. Data for **6**: ^{1}H NMR ($CDCl_3$): δ 7.56 (dd, J = 8.4, 2.0 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.86−3.79 (m, 1H), 3.11−2.97 (m, 2H), 2.62−2.39 (s, 1H), 1.92−1.84 (m, 1H), 1.82−1.73 (m, 1H), 1.19 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 199.58, 153.33, 149.01, 130.11, 122.94, 110.21, 110.07, 67.50, 56.11, 56.01, 34.54, 33.50, 23.83. FTIR: (neat, cm^{-1}): 3430.7, 2965.1, 2934.4, 2840.5, 1670.9, 1595.1, 1515.8, 1463.6, 1417.7, 1344.1, 1269.6, 1160.9, 1131.0, 1022.5. HRMS (M + Na): calcd 261.1097, found 261.1102.

GHK 7. To a solution of LHMDS (1.0 M in THF, 1.10 mL, 1.10 mmol, 1.1 equiv) in THF (3 mL) at −78 °C was added 2-cyclohexen-1-one (0.100 mL, 1.03 mmol, 1.0 equiv). The enolate solution was stirred for 60 min, and then cyclohexene oxide (0.200 mL, 1.98 mmol, 1.9 equiv) was added to the reaction. After 10 min, neat BF_3·OEt_2 (0.130 mL, 1.03 mmol,

1.0 equiv) was added over 6 min. The reaction was continued for an additional 60 min at −78 °C and then quenched at reaction temperature by the addition of pH 7.0 phosphate buffer solution (4 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography with petroleum ether/EtOAc (3:1) to obtain 124 mg (0.638 mmol, 62%) of a single diastereomer as a clear oil that solidified upon refrigeration (mp 36−37.5 °C). Data for GHK **7**: ^{1}H NMR ($CDCl_3$): δ 6.96−6.91 (m, 1H), 6.02 (ddd, J = 6.0, 2.8, 0.8 Hz, 1H), 3.38−3.29 (m, 1H), 2.51−2.43 (m, 1H), 2.42−2.32 (m, 1H), 2.30−2.21 (m, 2H), 2.04−1.98 (m, 3H), 1.75−1.67 (m, 2H), 1.55−1.48 (m, 2H), 1.32−1.20 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 202.78, 149.86, 130.15, 72.32, 50.74, 43.38, 36.96, 29.97, 26.79, 26.13, 25.31, 23.50. FTIR (neat, cm^{-1}): 3441.4, 2929.0, 2854.5, 1667.7, 1449.5, 1426.9, 1387.1, 1218.4, 1131.7, 1062.9, 1046.8. HRMS (M + Na): calcd 217.1199, found 217.1187.

Hydrogenation of 7. A solution of **7** (34 mg, 0.175 mmol) in EtOAc (2 mL) was stirred with 10% Pd on carbon under an atmosphere of H_2 at room temperature for 20 min. The reaction was then filtered through a pad of Celite, and the solvent was removed by evaporation to yield 34 mg of *syn*-**3** (0.173 mmol, 99%) as a clear colorless oil.

GHK 8. To a solution of LHMDS (1.0 M in THF, 4.40 mL, 4.40 mmol, 1.1 equiv) in THF (8 mL) at −78 °C was added 2-cyclohepten-1-one (80% technical grade purified as noted above, 0.445 mL, 4.0 mmol, 1.0 equiv). The enolate solution was stirred for 60 min, and then cyclohexene oxide (0.800 mL, 7.91 mmol, 2.0 equiv) was added to the reaction. After 10 min, neat $BF_3{\cdot}OEt_2$ (0.560 mL, 4.42 mmol, 1.1 equiv) was added over 5 min. The reaction was continued for an additional 60 min at −78 °C and then quenched at reaction temperature by the addition of pH 7.0 phosphate buffer solution (3 mL), and additional water (10 mL) was added to the solution. The aqueous layer was extracted with CH_2Cl_2/ether (2:1, 3 × 30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography with petroleum ether/EtOAc (3:1) to obtain 508 mg (2.44 mmol, 60%) as a colorless oil. Data for **GHK 8**: ^{1}H NMR ($CDCl_3$): δ 6.48 (dt, J = 12, 5.2 Hz, 1H), 5.96 (dt, J = 12, 1.6 Hz, 1H), 3.33−3.26 (m, 1H), 3.14 (d, J = 6.0 Hz, 1H), 2.67−2.63 (m, 1H), 2.39−2.34 (m, 2H), 1.98−1.94 (m, 1H), 1.86−1.74 (m, 5H), 1.67−1.56 (m, 3H), 1.21−1.13 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 208.89, 145.60, 132.48, 71.23, 55.91, 47.08, 36.37, 30.74, 30.11, 26.09, 25.37, 24.97, 23.97. FTIR (neat, cm^{-1}): 3423.8, 3019.1, 2926.0, 2859.1, 2665.8, 1651.2, 1448.2, 1418.2, 1397.7, 1235.7, 1171.0, 1073.8, 908.2. HRMS (M + Na): calcd 231.1355, found 231.1368.

Hydrogenation of 8. A solution of **8** (10 mg, 0.048 mmol) in EtOAc (2 mL) was stirred with 10% Pd on carbon under an atmosphere of H_2 at room temperature for 60 min. The reaction was then filtered through a pad of Celite, and the solvent was removed by evaporation to yield 10 mg of *syn*-**5** (0.048 mmol, 100%) as a clear colorless oil.

1-(3,4-Dimethoxyphenyl)-1(*R*),2(*R*),3-trihydroxypentane (−)-10. Water (75 mL) and *tert*-butyl alcohol (75 mL) were stirred with AD-mix-β (18.75 g) and methanesulfonamide (1.277 g, 13.43 mmol, 1.0 equiv) at room temperature for 30 min and then cooled to 0 °C. 3,4-Dimethoxy-*trans*-cinnamyl alcohol **9** (2.6 g, 13.4 mmol, 1.0 equiv) was then added in one portion. The reaction was stirred in the dark for 48 h, then Na_2SO_3 (20 g) was added, and the mixture stirred for 30 min. The contents of the flask were transferred to a separatory funnel, and the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and purified by flash silica gel column chromatography (EtOAc) to yield 2.81 g of (−)-**10** (12.3 mmol, 92%) as a white solid. $[\alpha]^{24}_D$ = −29.0 (MeOH, c = 0.12), lit.[15] $[\alpha]^{21}_D$ = −32.1 (MeOH, c = 0.28). ^{1}H NMR (CD_3OD): δ 7.03 (s, 1H), 6.96 (s, 2H), 4.55 (d, J = 6.0 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.68−3.64 (m, H), 3.48 (dd, J = 11.2, 4.0 Hz, 1H), 3.34 (dd, J = 11.2, 6.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 149.15, 149.03, 131.23, 129.89, 126.72, 119.83, 111.24, 108.96, 63.95, 56.06, 55.96. FTIR (neat, cm^{-1}): 3410.5, 3020.9, 2940.3, 2836.6, 1658.4, 1641.9, 1517.3, 1467.8, 1422.7, 1318.5, 1263.6, 1235.7, 1155.1, 1102.2, 1023.6, 991.2.

Epoxy Alcohol (−)-11. A solution of triol (−)-**10** (1.084 g, 4.75 mmol, 1.0 equiv) in pyridine (60 mL) at 0 °C was treated with tosyl chloride (948 mg, 4.97 mmol, 1.05 equiv). The reaction was stirred overnight and then filtered through a plug of flash silica gel to yield 1.61 g crude material. The crude product was dissolved in MeOH/CH_2Cl_2 (33 mL, 10:1) at 0 °C and treated with K_2CO_3 (585 mg, 4.23 mmol). The reaction was stirred for 1 h and then filtered through a plug of flash silica gel with EtOAc/hexanes (1:1) to yield 708 mg of product (3.37 mmol, 71% for two steps) as an oil that solidified upon refrigeration (mp 75.5−77.0 °C). $[\alpha]^{25}_D$ = −5.8 (c = 0.090, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 6.99 (d, J = 2.0 Hz, 1H), 6.96−6.93 (m, 1H), 6.87 (d, J = 8.4 Hz, 1H), 4.44 (t, J = 5.2 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.25−3.22 (m, 1H), 2.86 (dd, J = 4.8, 4.0 Hz, 1H), 2.83 (dd, J = 4.8, 2.8 Hz, 1H), 2.29 (d, J = 5.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 174.14, 149.40, 149.17, 133.04, 118.87, 111.29, 109.61, 74.35, 56.14, 56.12, 45.57. FTIR (neat, cm^{-1}): 3457.3, 2983.0, 2958.5, 2936.0. 2836.2, 1735.9, 1604.1, 1593.4, 1518.0, 1465.9, 1415.3, 1262.6, 1238.0, 1140.3, 1027.1, 916.8, 849.4, 800.8. HRMS (M + Na): calcd 233.0784, found 233.0790. 98% ee determined by HPLC (t_R 21.59 min, Chiracel AD 10% 2-propanol/hexane, 1.0 mL/min).

Methyl Ether Epoxide (−)-12. To a slurry of NaH (60% in mineral oil, 47 mg, 1.18 mmol, 2.9 equiv) in THF/DMSO (11 mL, 10:1) at room temperature was added a solution of (−)-**11** (86 mg, 0.41 mmol, 1.0 equiv) in THF (2 mL). The reaction was stirred at room temperature for 40 min, and then iodomethane (50 μL, 0.82 mmol, 2.0 equiv) was added. After 4 h the reaction was quenched at 0 °C by the addition of ice and transferred to a separatory funnel containing brine (7 mL). The product was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography with hexanes/EtOAc (3:1) to yield 89 mg (0.40 mmol, 97%) of (−)-**12** as a colorless oil. $[\alpha]^{25}_D$ = −20.6 (c = 0.18, MeOH). ^{1}H NMR ($CDCl_3$): δ 6.90−6.86 (m, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.84 (d, J = 6.4 Hz, 1H), 3.36 (s, 3H), 3.18 (m, 1H), 2.74 (t, J = 4.6, 1H), 2.61 (dd, J = 4.8, 2.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 149.48, 149.25, 130.69, 119.78, 111.20, 109.82, 85.02, 57.16, 56.15, 56.12, 55.49, 44.52. FTIR (neat, cm^{-1}): 2963.2, 2920.1, 2846.5, 1593.1, 1513.0, 1502.8, 1462.1, 1454.1, 1411.6, 1255.9, 1231.1, 1135.5, 1085.8, 1023.2, 805.0. HRMS (M + Na): calcd 247.0941, found 247.0938.

Butyl Ether Epoxide (−)-13. To a slurry of NaH (60% in mineral oil, 71 mg, 1.78 mmol, 2.6 equiv) in THF/DMSO (11 mL, 10:1) at room temperature was added a solution of (−)-**11** (146 mg, 0.695 mmol, 1.0 equiv) in THF (2 mL). The reaction was stirred at room temperature for 30 min and then cooled to 0 °C, and 1-iodobutane (0.240 mL, 2.11 mmol, 3.0 equiv) was added. After 3 h the reaction was quenched by the addition of ice and transferred to a separatory funnel containing brine (10 mL). The product was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by preparative plate TLC (2 mm, silica gel, 2:1 hexanes/EtOAc) to yield 78 mg (0.293 mmol, 42%) of (−)-**13** as a colorless oil. $[\alpha]^{23}_D$ = −31.8 (c = 0.24, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 6.89 (br s, 1H), 6.83 (br s, 1H), 6.82 (br s, 1H), 3.91 (d, J = 6.4 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.47−3.36 (m, 2H), 3.15 (ddd, J = 6.4, 4.0, 2.4 Hz, 1H), 2.70 (dd, J = 4.8, 4.4 Hz, 1H), 2.56 (dd, J = 4.8, 2.8 Hz, 1H), 1.63−1.51 (m, 2H), 1.43−1.30 (m, 2H), 0.87 (t, J = 7.6 Hz, 3H). ^{13}C NMR

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($CDCl_3$): δ 149.28, 148.99, 131.28, 119.53, 111.06, 109.79, 83.16, 69.08, 56.00, 55.50, 44.50, 32.00, 19.47, 14.03. FTIR (neat, cm^{-1}): 2942.7, 2932.6, 2870.0, 1601.7, 1592.7, 1514.4, 1463.1, 1417.5, 1262.7, 1231.3, 1137.7, 1091.9, 1027.5, 918.0, 858.6, 804.4, 743.3. HRMS (M + Na): 289.1410, found 289.1402.

TMS Ether Epoxide (−)-14. A solution of (−)-**11** (193 mg, 0.918 mmol, 1.0 equiv), triethylamine (0.330 mL, 2.37 mmol, 2.6 equiv), and trimethylsilyl chloride (0.150 mL, 1.18 mmol, 1.3 equiv) in CH_2Cl_2 (8 mL) was stirred at 0 °C for 2 h. The solvent was evaporated, and the crude product was dissolved in ether and filtered through basic Al_2O_3. After evaporation of the ether, 122 mg (0.432 mmol, 47%) of (−)-**14** was obtained as a white solid (mp 68−70 °C). $[\alpha]^{24}_D = -17.1$ (c = 0.12, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 6.94 (d, J = 1.6 Hz, 1H), 6.86−6.81 (m, 2H), 4.32 (d, J = 6.0 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.10 (m, 1H), 2.76 (dd, J = 4.8, 4.0 Hz, 1H), 2.63 (dd, J = 4.8, 2.8 Hz, 1H), 0.11 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 149.12, 148.78, 133.57, 118.66, 110.96, 109.63, 76.26, 56.82, 56.06, 45.36, 0.30. FTIR (CH_2Cl_2, cm^{-1}): 3024.2, 3002.6, 2960.2, 2931.6, 2861.1, 1594.0, 1515.3, 1465.3, 1263.6, 1254.1, 1223.9, 1139.7, 1086.9, 1027.8, 937.8, 876.1, 845.5. HRMS (M + Na): calcd 305.1180, found 305.1179.

Tetramethyl 1-*O*-Methyl Curculigine aglycon (−)-15. To KHMDS (163 mg, 0.82 mmol, 2.1 equiv) in THF (4 mL) at −78 °C was added a solution of 3,4-dimethoxyacetophenone (138 mg, 0.766 mmol, 2.0 equiv) in THF (2 mL). This was stirred for 1 h, and then a solution of (−)-**12** (86 mg, 0.38 mmol, 1.0 equiv) in THF (1.6 mL) was added to the reaction. After 10 min, neat $BF_3{\cdot}OEt_2$ (0.100 mL, 0.789 mmol, 2.0 equiv) was added dropwise over 5 min. The reaction was quenched after 1 h by the addition of aqueous pH 7.0 phosphate buffer solution and then transferred to a separatory funnel containing brine (10 mL). The aqueous layer was extracted with CH_2Cl_2/Et_2O (30 mL, 2:1) and CH_2Cl_2 (2 × 25 mL). The organic layers were combined and washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash silica gel column chromatography to yield 66 mg of (−)-**15** (0.163 mmol, 43%) as a colorless oil. $[\alpha]^{25}_D = -22.8$ (c = 0.10, MeOH). ^{1}H NMR (CD_3OD): δ 7.58 (dd, J = 8.4, 2.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.94−6.91 (m, 2H), 6.87 (dd, J = 8.0, 2.0 Hz, 1H), 3.94 (d, J = 7.2 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.73 (ddd, J = 8.4, 7.2, 4.0 Hz, 1H), 3.22 (s, 3H), 3.07 (ddd, J = 16.8, 8.6, 5.8 Hz, 1H), 2.94 (ddd, J = 16.8, 8.6, 7.0 Hz, 1H), 1.70−1.55 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 198.92, 153.21, 149.33, 149.15, 149.00, 130.66, 130.27, 122.83, 120.66, 111.04, 110.20, 110.06, 110.02, 88.05, 74.64, 56.70, 56.14, 56.05, 55.98, 34.50, 27.21. FTIR (neat, cm^{-1}): 3504.6, 2997.3, 2934.6, 2836.8, 1671.1, 1593.3, 1515.2, 1463.8, 1417.5, 1264.4, 1152.2, 1110.6, 1024.2, 876.1, 810.8, 765.3. HRMS (M + Na): calcd 427.1727, found 427.1695.

Tetramethyl 1-*O*-Butyl Curculigine Aglycon (−)-16. To KHMDS (80 mg, 0.40 mmol, 2.1 equiv) in THF (2 mL) at −78 °C was added a solution of 3,4-dimethoxyacetophenone (68 mg, 0.375 mmol, 2.0 equiv) in THF (1 mL). This was stirred for 1 h at −78 °C, and then a solution of (−)-**13** (50 mg, 0.188 mmol, 1.0 equiv) in THF (1.0 mL) was added to the reaction. After stirring for 10 min, neat $BF_3{\cdot}OEt_2$ (48 μL, 0.37 mmol, 2 equiv) was added. The reaction was quenched after 1 h by the addition of aqueous pH 7.0 phosphate buffer solution and then transferred to a separatory funnel containing brine (10 mL). The aqueous layer was extracted with CH_2Cl_2/Et_2O (30 mL, 2:1) and CH_2Cl_2 (2 × 25 mL). The organic layers were combined, washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by preparative layer silica gel chromatography (500 μm, 70% EtOAc/hexanes) to yield 22 mg of (−)-**16** (0.049 mmol, 26%) as a colorless oil. $[\alpha]^{24}_D = -23.8$ (c = 0.26, MeOH). ^{1}H NMR ($CDCl_3/CD_3OD$ 7:3): δ 7.68−7.45 (m, 2H), 7.01−6.82 (m, 4H), 4.05 (d, J = 7.6 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 3.80−3.72 (m, 1H), 3.47−3.36 (m, 2H), 3.24−3.17 (m, 1H), 3.05−2.92 (m, 1H), 1.76−1.71 (m, 2H), 1.63−1.56 (m, 2H), 1.44−1.36 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C NMR (CD_3OD): δ 201.78, 155.46, 151.00, 150.84, 150.74, 134.14, 131.70, 124.67, 122.18, 113.10, 112.58, 112.11, 112.07, 87.72, 75.81, 70.17, 56.95, 56.88, 56.85, 35.94, 33.51, 29.52, 20.92, 14.73. HRMS (M + Na): calcd 469.2197, found 469.2186. NMR data are consistent with the literature values.[12b]

Tetramethyl 1-Hydroxy Curculigine Aglycon (−)-18. To KHMDS (140 mg, 0.70 mmol, 2.0 equiv) in THF (4 mL) at −78 °C was added a solution of 3,4-dimethoxyacetophenone (123 mg, 0.68 mmol, 2.0 equiv) in THF (1 mL). This was stirred for 1 h at −78 °C, and then a solution of (−)-**14** (96 mg, 0.34 mmol, 1.0 equiv) in THF (2 mL) was added to the reaction. After stirring for 10 min, neat $BF_3{\cdot}EtO_2$ (86 μL, 0.68 mmol, 2 equiv) was added. The reaction was quenched after 45 min by the addition of aqueous pH 7.0 phosphate buffer solution and then transferred to a separatory funnel containing brine (10 mL). The aqueous layer was extracted with CH_2Cl_2/Et_2O (45 mL, 2:1) and CH_2Cl_2 (2 × 30 mL). The organic layers were combined, washed with brine (10 mL), dried ($MgSO_4$), and concentrated to give 214 mg crude material. A portion of the crude material (18 mg, 8.4%) was dissolved in CH_2Cl_2 (1.5 mL) at room temperature and treated with tetrabutylammonium triphenyldifluorosilicate (TBAT)[14] (8 mg, 15 μmol). This was stirred for 5 min, and then the solvent was evaporated. The crude material was purified by preparative layer silica gel chromatography (500 μm, EtOAc eluent) to yield 3.5 mg of (−)-**18** (31%) as a white solid (mp = 129−130 °C, lit. 125−126 °C). $[\alpha]^{24}_D = -15.7$ (c = 0.135, $CHCl_3$), lit.[12a] $[\alpha]^{20}_D = -15.5$ (c = 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.58 (dd, J = 8.4, 2.0 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 6.93−6.83 (m, 4H), 4.42 (d, J = 6.4 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.78−3.67 (m, 1H), 3.16 (br d, J = 3.2 Hz, 1H), 3.10 (dt, J = 7.0, 1.6 Hz, 2H), 2.82 (br s, 1H), 1.86−1.77 (m, 2H). HRMS (M + Na): calcd 413.1571, found 413.1584. NMR data are consistent with the literature values.[12a]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **1**−**8**, **9**−**16**, and **18** and X-ray data for *p*-nitrobenzoate derivatives of GHKs **2**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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