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Synthesis of (+)-Zerumin B Using a Regioselective Singlet Oxygen Furan Oxidation

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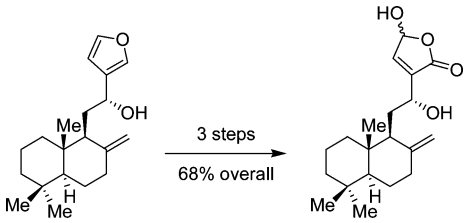
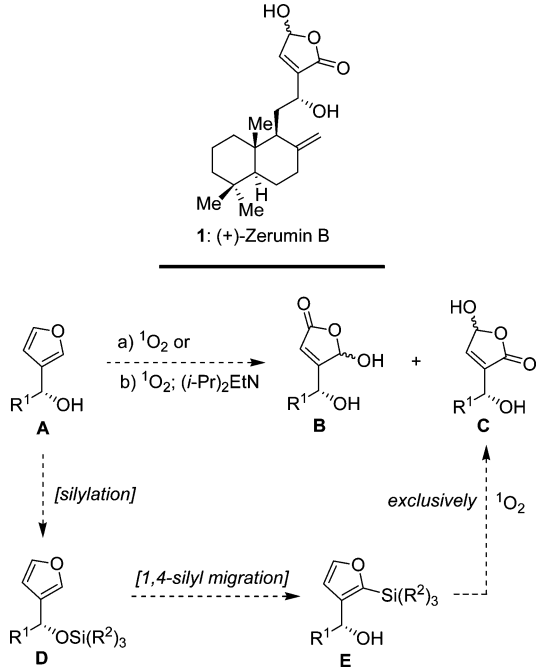


A short and efficient synthesis of the antitumor diterpenoid (+)-zerumin B has been accomplished starting from (+)-sclareolide. At the heart of the synthetic strategy lies the regioselective formation of the α-substituted γ-hydroxybutenolide moiety of zerumin B. This was achieved by means of a [1,4] O→C triisopropylsilyl migration followed by singlet oxygen ($^1O_2$) oxidation of the resulting 2-triisopropylsilyl-3-(α-hydroxy)alkylfuran.

(+)-Zerumin B was first isolated in 1996 from the Chinese medicinal plant *Alpinia zerumbet*.[1] In 2005, the same molecule was isolated, together with a number of other labdane diterpenes, from the popular vegetable *Curcuma mangga*.[2] This vegetable is a member of the Zingiberaceae family and is commonly grown in Thailand, Peninsular Malaysia, and Java.[3] The tips of young rhizomes and the shoots of *C. mangga* are consumed raw with rice and have a smell reminiscent of mango fruit. The rhizomes are used in Asian folk medicine to treat chest pains, fever, and general debility. It is also used in postpartum care, specifically to aid womb healing. Recently, however, perhaps a more important medicinal characteristic was discovered when (+)-zerumin B was also found to possess potent cytotoxicity (IC_{50} value of 0.59 μM) against the MCF-7 (breast cancer) cell line.

The first total synthesis of this interesting bioactive diterpenoid was recently reported by Boukouvalas and co-workers.[4] Addition of a silyloxyfuryltitanium reagent to an aldehyde and a silyloxyfuran oxyfunctionalization lie at the heart of their rapid synthesis. It is well-known that γ-hydroxybutenolides have often been prepared by photooxygenation of 3-substituted furans;[5] however, Boukouvalas avoided employing this strategy because it was deemed unsuitable, since it provides either mixtures of α- and β-substituted γ-hydroxybutenolides[5a−c] (**C** and **B**, Scheme 1) or solely the β-regiomers when Hunig' s base is included.[5c−j] Very recently, a regioselective photooxygenation of 3-bromofuran to 2-bromo-4-hydroxybutenolide (using DBU as base) was published, thus providing the first specific example of a way to counter this general lack of selectivity.[6] In the zerumin B system (Scheme 1), we predicted that regioselective formation of α-substituted γ-hydroxybutenolides might also be possible by utilization of the secondary hydroxyl group. Specifically, 3-(α-trialkylsilyloxy)alkylfurans of type **D** are known to undergo a [1,4] O→C silyl migration[7] to furnish 2-trialkylsilyl-3-(α-hydroxy)alkylfurans of type **E** (Scheme 1). The latter may then undergo a regioselective singlet oxygen ($^1O_2$) oxidation[8] yielding an α-substituted γ-hydroxybutenolide moiety (**C**, Scheme 1) such as is present in (+)-zerumin B. Based on this analysis, we hoped to employ just such a strategy to synthesize (+)-zerumin B.

SCHEME 1. The Concept



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(2) Abas, F.; Lajis, N. H.; Shaari, K.; Israf, D. A.; Stanslas, J.; Yusuf, U. K.; Raof, S. M. *J. Nat. Prod.* **2005**, *68*, 1090−1093.

(3) Larsen, K.; Ibrahim, H.; Khaw, S. H.; Saw, L. G. *Gingers of Peninsular Malaysia*; Natural History Publication (Borneo): Kota Kinabalu, 1999.

(4) Boukouvalas, J.; Wang, J.-X.; Marion, O.; Ndzi, B. *J. Org. Chem.* **2006**, *71*, 6670−6673.

(5) For recent examples, see: (a) Held, C.; Fröhlich, R.; Metz, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1058−1060. (b) de la Torre, M. C.; García, I.; Sierra, M. A. *J. Nat. Prod.* **2002**, 65, 661−668. (c) Held, C.; Fröhlich, R.; Metz, P. *Adv. Synth. Catal.* **2002**, *344*, 720−727. (d) Demeke, D. Forsyth, C. J. *Tetrahedron* **2002**, *58*, 6531−6544. (e) Brohm, D.; Philippe, N.; Metzger, S.; Bhargava, A; Müller, O.; Lieb, F.; Waldmann, H. *J. Am. Chem. Soc.* **2002**, *124*, 13171−13178. (f) Demeke, D.; Forsyth, C. J. *Org. Lett.* **2003**, *5*, 991−994. (g) Miyaoka, H.; Yamanishi, M.; Kajiwara, Y.; Yamada, Y. *J. Org. Chem.* **2003**, *68*, 3476−3479. (h) Cheung, A. K.; Murelli, R.; Snapper, M. L. *J. Org. Chem.* **2004**, *69*, 5712−5719. (i) Izzo, I.; Avallone, E.; Della Monica, C.; Casapullo, A.; Amigo, M.; De Riccardis, F. *Tetrahedron* **2004**, *60*, 5587−5593. (j) Basabe, P.; Delgado, S.; Marcos, I. S.; Diez, D.; Diego, A.; De Román, M.; Urones, J. G. *J. Org. Chem.* **2005**, *70*, 9480−9485.

(6) Aquino, M.; Bruno, I.; Riccio, R.; Gomez-Paloma, L. *Org. Lett.* **2006**, *8*, 4831−4834.

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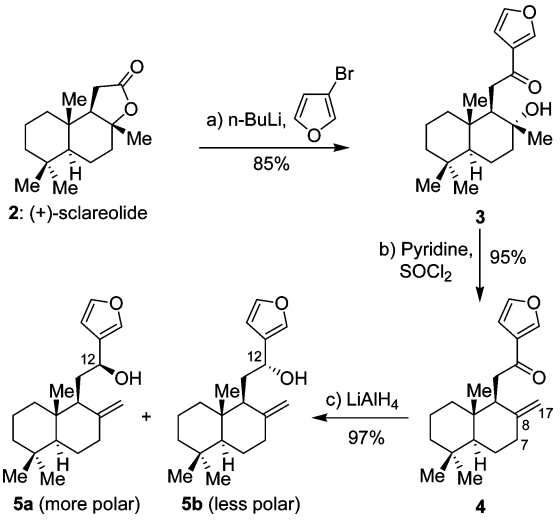
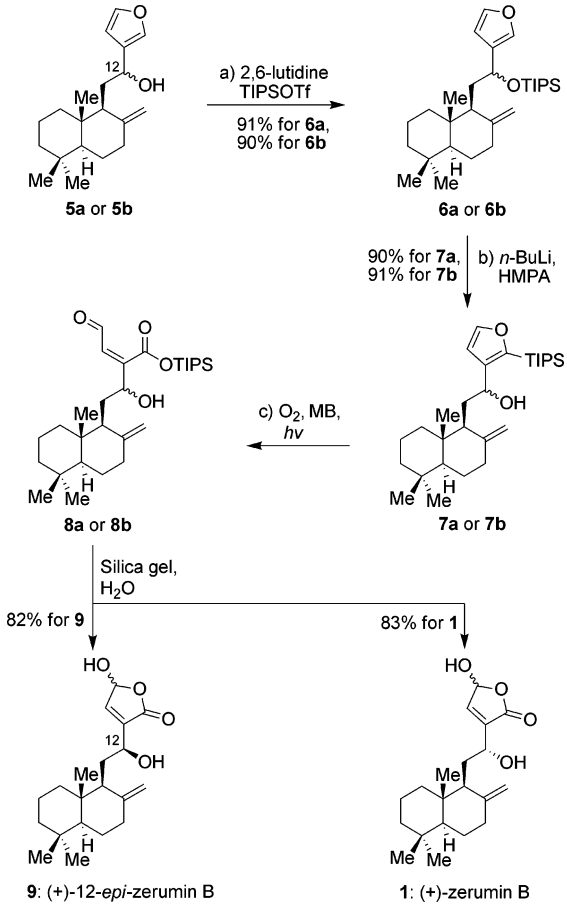
SCHEME 2. Synthesis of Furanols 5



In order to validate the proposal, deconvoluting a rapid synthesis of the requisite 3-substituted furan **5**[9] (Scheme 2) was essential. A good source of the intact labdane skeleton is the commercially available lactone **2**, known as (+)-sclareolide, so we chose to start our investigation from this compound. A protocol was developed that converted (+)-sclareolide (**2**) into furan **5** in just three high-yielding steps (Scheme 2). The lactone moiety of (+)-sclareolide was used to quench the 3-lithiofuran anion, obtained from 3-bromofuran, on treatment with *n*-BuLi, to afford hydroxy ketone **3** in 85% yield. Effective conditions by which to affect the dehydration of **3**, while maximizing the exo-/endocyclic double bond ratio, took some experimentation to find. It was discovered, finally, that a combination of $SOCl_2$ and pyridine[4,9,10] (yield 95%) gave excellent results. This combination of reagents gave an exo-/endocyclic ratio of 14:1 ($\Delta^{8,17}/\Delta^{7,8}$ Scheme 2). This ratio is in stark contrast to those obtained earlier when using other common dehydration methods where unacceptably poor ratios had been obtained. The furylic ketone **4** was then reduced to the corresponding diastereomeric mixture (equimolar and separable using column chromatography) of natural alcohols **5**[11] using $LiAlH_4$ in 97% yield. The very fact that the alcohols **5a** or **5b** (Scheme 2) are naturally occurring compounds suggests that our strategy of direct photooxygenation ($^1O_2$) might represent a biomimetic proposal for the synthesis of (+)-zerumin B.

With diastereomeric alcohols **5a** and **5b** in hand, the hurdle of regioselective silylation of the more sterically hindered 2-position of the furan ring now needed to be tackled. All attempts at direct silylation (*n*-BuLi followed by a TMSCl quench) of this position utilizing the directing effect of hydroxyl at C-12 resulted in the formation of a mixture of different mono- and bis-silylated products. In order to overcome this problem, a two-step procedure was therefore adopted. Thus, silylation

SCHEME 3. Regioselective Preparation of 7a and 7b Using [1,4] O→C Silyl Migration and Subsequent Photooxygenation to (+)-*epi*-Zerumin B and (+)-Zerumin B



of the hydroxyl group of **5a** and **5b** under standard conditions (2,6-lutidine, TIPSOTf, Scheme 3) gave triisopropylsilyl ethers **6a** or **6b** in 91% and 90% yield, respectively. Treatment of **6a** or **6b** with 1.2 equiv of *n*-BuLi in the presence of 1.2 equiv of HMPA[7] cleanly transformed them to the corresponding 2-triisopropylsilyl-3-(α-hydroxy)alkylfurans **7a** or **7b** in 90% and 91% yield, respectively (Scheme 3).

The stage was now set for the singlet oxygen-mediated oxidation of furans **7a** and **7b**. Visible light irradiation of a solution of **7a** or **7b** (maximum amount used = 150 mg) in CH_2Cl_2, containing catalytic amounts of methylene blue (10^{-4} M), with O_2 bubbling through it, for just 1 min, resulted in the complete consumption of the starting materials accompanied by the formation of the stable silyl esters[8] **8a** or **8b** (Scheme 3). In situ hydrolysis of silyl esters **8a** or **8b** yielded the corresponding γ-hydroxybutenolides (+)-12-*epi*-zerumin B (**9**) and (+)-zerumin B (**1**) and was easily achieved on addition of a small amount of silica gel (SiO_2) and a few drops of water. ^1H and ^{13}C NMR data for **9** and **1** matched exactly that reported in the literature.[4] As expected, both compounds are equimolar mixtures of diasteromeric γ-hydroxybutenolides. It is worth mentioning that only one of the two diastereomers of (+)-12-*epi*-zerumin B was detected by ^1H NMR right after the hydrolysis of the intermediate silyl ester **8a**. An equimolar mixture of diastereoisomers were observed in ^1H NMR after chromatographic purification using silica gel.[12]

(8) For the silyl stabilization concept, see: Adam, W.; Rodriguez, A. *Tetrahedron Lett*. **1981**, *22*, 3505−3508. For direct comparisons between the photoxygenations of silyl- and unsubstituted furans, see: (a) Bury, P.; Hareau, G.; Kocieński, P.; Dhanak, D. *Tetrahedron* **1994**, *50*, 8793−8808. (b) Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1996**, *61*, 2845−2852.

(9) For a recent synthesis from us, see: Margaros, I. Vassilikogiannakis, G. *J. Org. Chem.* **2007**, *72*, 4826−4831.

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(11) (a) Jung, M.; Ko, I.; Lee, S. J. *J. Nat. Prod.* **1998**, *61*, 1394−1396. (b) Villamizar, J.; Fuentes, J.; Salazar, F.; Tropper, E.; Alonso, R. *J. Nat. Prod.* **2003**, *66*, 1623−1627.

In conclusion, a fast (six steps in total) and efficient (overall yield 53%) synthesis of (+)-zerumin B and (+)-12-*epi*-zerumin B has been accomplished. The key step of the synthesis involved the regioselective transformation of a 3-substituted furan into the α-substituted γ-hydroxybutenolide moiety[13] of the natural compound by the utilization of a [1,4] O→C silyl migration followed by an oxidation with $^1O_2$.

Experimental Section

Diastereomeric (1-(Furan-3-yl)-2-((1*S*,8a*S*)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)ethoxy)triisopropylsilane (6a,b). To a solution of furanol **5b** (66 mg, 0.22 mmol, 1.0 equiv, less polar diastereoisomer) in dry DCM (3 mL) was added 2,6-lutidine (53 μL, 0.46 mmol, 2.1 equiv). The reaction mixture was cooled to −5 °C, and TIPSOTf (92 μL, 0.34 mmol, 1.56 equiv) was added dropwise. Stirring was continued for 15 min before the reaction was quenched with $NaHCO_3$ (2 mL). The reaction mixture was diluted with Et_2O (10 mL) and washed with H_2O (5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc = 50:1 v/v) afforded TIPS-protected alcohol **6b** (90 mg, 90%). Exactly the same experimental procedure was applied in the case of furanol **5a** (60 mg, 0.20 mmol, of the more polar diastereoisomer) to give the TIPS-protected alcohol **6a** (83 mg, 91%).

6b: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.34 (t, J = 1.5 Hz, 1H), 7.30 (s, 1H), 6.43 (d, J = 1.0 Hz, 1H), 4.86 (d, J = 1.4 Hz, 1H), 4.80 (dd, J_1 = 10.0 Hz, J_2 = 1.5 Hz, 1H), 4.47 (s, 1H), 2.41 (ddd, J_1 = 12.7 Hz, J_2 = 4.0 Hz, J_3 = 2.3 Hz, 1H), 2.14 (br d, J = 11.0 Hz, 1H), 2.07−1.05 (m, 12H), 1.05−0.93 (m, 21H), 0.90 (s, 3H), 0.81 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 149.2, 142.7, 138.0, 131.1, 108.9, 106.6, 65.7, 55.8, 52.3, 42.3, 39.3, 38.9, 38.2, 35.2, 33.7, 33.6, 24.4, 21.7, 19.4, 18.2 (3C), 18.0 (3C), 14.7, 12.6 (3C) ppm; HRMS (ESI+) calcd for $C_{29}H_{50}O_2SiNa$ 481.3478 [M + Na^+], found 481.3473.

6a: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36 (t, J = 1.5 Hz, 1H), 7.22 (s, 1H), 6.40 (d, J = 1.1 Hz, 1H), 4.87 (s, 1H), 4.82 (dd, J_1 = 10.5 Hz, J_2 = 4.3 Hz, 1H), 4.69 (s, 1H), 2.36 (ddd, J_1 = 12.7 Hz, J_2 = 4.1 Hz, J_3 = 2.4 Hz, 1H), 1.99−1.05 (m, 12H), 1.05−0.96 (m, 21H), 0.92 (m, 1H), 0.82 (s, 3H), 0.78 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 149.0, 142.8, 139.1, 129.5, 108.8, 106.2, 66.2, 55.4, 52.6, 42.0, 39.3, 38.6, 38.3, 33.8, 33.5, 33.46, 24.4, 21.7, 19.3, 18.1 (3C), 18.0 (3C), 14.8, 12.3 (3C); HRMS (ESI+) calcd for $C_{29}H_{50}O_2SiNa$ 481.3478 [M + Na^+], found 481.3473.

Diastereomeric 1-(2-(Triisopropylsilyl)furan-3-yl)-2-((1*S*,8a*S*)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)ethanol (7a,b). To a stirred solution of TIPS-protected furanol **6b** (90 mg, 0.20 mmol, 1.0 equiv) in dry THF (3 mL) at ambient temperature was added dry HMPA (41 μL, 0.24 mmol, 1.2 equiv) followed by dropwise addition of *n*-BuLi (1.6 M in Hex, 147 μL, 0.24 mmol, 1.2 equiv). After 15 min of stirring, the reaction mixture was quenched with satd NH_4Cl (1 mL), diluted with Et_2O (10 mL), and washed with H_2O (5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification with flash column chromatography (silica gel, hexanes/EtOAc = 50:1 v/v) afforded TIPS furanol **7b** (82 mg, 91%). Exactly the same experimental procedure was applied in the case of **6a** (83 mg, 0.18 mmol) to afford 75 mg of **7a** (90%).

7b: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.61 (d, J = 1.6 Hz, 1H), 6.51 (d, J = 1.6 Hz, 1H), 4.82 (s, 1H), 4.72 (d, J = 10.4 Hz, 1H), 4.47 (s, 1H), 2.41 (ddd, J_1 = 12.8 Hz, J_2 = 3.8 Hz, J_3 = 2.6 Hz, 1H), 2.16 (br d, J = 11.3 Hz, 1H), 2.13−1.92 (m, 2H), 1.86−1.48 (m, 5H), 1.45−1.15 (m, 8H), 1.10 (d, J = 7.4 Hz, 9H), 1.07 (d, J = 7.4 Hz, 9H), 0.88 (s, 3H), 0.81 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.8, 148.8, 146.8, 140.6, 107.9, 106.2, 64.2, 55.4, 52.2, 42.1, 39.4, 39.0, 38.3, 33.61, 33.58, 32.3, 24.5, 21.7, 19.4, 18.8 (3C), 18.7 (3C), 14.6, 11.7 (3C); HRMS (ESI+) calcd for $C_{29}H_{50}O_2SiNa$ 481.3478 [M + Na^+], found 481.3473.

7a: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.63 (d, J = 1.6 Hz, 1H), 6.49 (d, J = 1.6 Hz, 1H), 4.88 (d, J = 1.1 Hz, 1H), 4.79 (s, 1H), 4.74 (t, J = 7.1 Hz, 1H), 2.34 (ddd, J_1 = 12.8 Hz, J_2 = 3.9 Hz, J_3 = 2.4 Hz, 1H), 2.05−1.13 (m, 14H), 1.11 (d, J = 7.4 Hz, 9H), 1.04 (d, J = 7.4 Hz, 9H), 1.00−0.84 (m, 2H), 0.82 (s, 3H), 0.78 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 154.5, 149.3, 147.0, 139.4, 107.6, 107.0, 65.7, 55.2, 52.6, 41.9, 39.6, 38.9, 38.0, 33.5(2C), 31.8, 24.2, 21.7, 19.3, 18.9 (3C), 18.7 (3C), 14.4, 11.8 (3C); HRMS (ESI+) calcd for $C_{29}H_{50}O_2SiNa$ 481.3478 [M + Na^+], found 481.3473.

(+)-Zerumin B (1) and (+)-*epi*-Zerumin B (9). A solution of the furan **7b** (82 mg, 0.18 mmol, 1.0 equiv) in DCM (8 mL) containing methylene blue (10^{-4} M) was placed in a test tube, and oxygen was bubbled gently through it. The solution was cooled to 0 °C and irradiated with a xenon 300 W lamp for 1 min after which complete consumption of the starting material was observed (based on TLC). SiO_2 and a few drops of H_2O were added, and the mixture was stirred vigorously for 1 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography (silica gel, hexanes/EtOAc = 2:1 → 1:2 v/v) to afford (+)-zerumin B (**1**, 50 mg, 83%, 1/1 ratio of diastereoisomers). Exactly the same experimental procedure was applied to the case of furan **7a** (75 mg, 0.16 mmol) to afford (+)-*epi*-zerumin B (45 mg, 82%, 1/1 ratio of diastereoisomers).

(+)-Zerumin B (1): $[\alpha]_D^{24}$ +41.7 (c = 4.0, acetone) [lit.[4] $[\alpha]_D^{24}$ +42.8 (c = 0.25, acetone)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.04 (s, 1H + 1H), 6.11 (s, 1H + 1H), 4.91 (br s, 1-OH + 1-OH), 4.88 (s, 1H + 1H), 4.67 (s, 1H + 1H), 4.53 (br d, J = 9.9 Hz, 1H + 1H), 2.76 (br s, 1-OH + 1-OH), 2.41 (md, J = 12.9 Hz, 1H + 1H), 2.09−0.95 (m, 13H + 13H), 0.88 (s, 3H + 3H), 0.80 (s, 3H + 3H), 0.67 (s, 3H + 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.4 (2C), 148.2 (2C), 143.1 (2C), 141.4 (2C), 107.2 (2C), 97.1, 96.9, 65.5 (2C), 55.5 (2C), 51.8 (2C), 42.0 (2C), 39.3 (2C), 39.0 (2C), 38.2 (2C), 33.6 (4C), 29.7 (2C), 24.3 (2C), 21.7 (2C), 19.3 (2C), 14.6 (2C); HRMS (ESI+) calcd for $C_{20}H_{30}O_4Na$ 357.2042 [M + Na^+], found 357.2036.

(+)-*epi*-Zerumin B (9): $[\alpha]_D^{24}$ +5.9 (c = 0.84, acetone) [lit.[4] $[\alpha]_D^{24}$ +5.5 (c = 0.85, acetone)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.04 (s, 1H), 6.99 (s, 1H), 6.11 (br s, 1H + 1H), 5.44 (br s, 1-OH + 1-OH), 4.88 (br s, 1H + 1H), 4.68 (br s, 1H + 1H), 4.51 (br t, J = 6.5 Hz, 1H + 1H), 3.30 (br s, 1-OH + 1-OH), 2.39 (br d, J = 12.5 Hz, 1H + 1H), 2.10−0.88 (m, 13H + 13H), 0.86 (s, 3H + 3H), 0.78 (s, 3H + 3H), 0.67 (s, 3H + 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.1, 170.7, 149.3, 149.1, 145.4, 144.8, 139.6, 138.5, 107.1, 106.9, 97.52, 97.37, 67.2, 66.5, 55.44 55.40, 53.3, 53.0, 42.0 (2C), 39.9, 39.8, 38.93, 38.89, 38.18, 38.13, 33.54 (2C), 33.47 (2C), 29.8, 29.4, 24.3 (2C), 21.7 (2C), 19.24, 19.22, 14.44, 14.39; HRMS (ESI+) calcd for $C_{20}H_{30}O_4Na$ 357.2042 [M + Na^+], found 357.2036.

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

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(12) For a very recent example of base-assisted regio- and diastereoselective conversion of 3-substituted furans to 3-substituted 4-hydroxybutenolides, see: Patil, S. N.; Liu, F. *Org. Lett.* **2007**, *9*, 195−198.

(13) After completion of this work, a very interesting fluoride-assisted regioselective conversion of 3-substituted furans to α-substituted γ-hydroxybutenolides using singlet oxygen was reported: Patil, S. N.; Liu, F. *J. Org. Chem.* **2007**, *72*, 6305−6308.