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Synthesis and Stereochemistry of the Antitumor Diterpenoid (+)-Zerumin B

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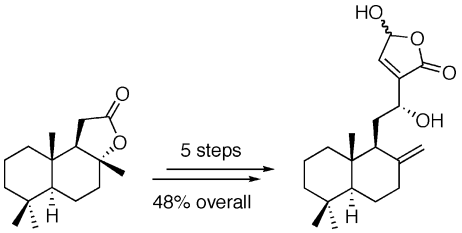

Starting from commercially available (+)-sclareolide, the first synthesis of zerumin B was achieved by a concise, highly efficient pathway featuring stereoselective addition of a new silyloxyfuryltitanium reagent to an aldehyde intermediate and silyloxyfuran oxyfunctionalization as key steps. The synthesis established the relative and absolute configuration of zerumin B along with its identity with a purportedly new diterpenoid isolated from the plant *Renealmia alpinia*.

(+)-Zerumin B (**1**) is a bioactive diterpenoid isolated in 1996 from the Chinese medicinal plant *Alpinia zerumbet*[1] and more recently from *Curcuma mangga*, a popular vegetable that is also used in Asian folk medicine for alleviating stomachache, chest pain, and fever, and in postpartum care to aid womb healing.[2] Significantly, the latter report revealed that **1** exhibits cytotoxic activity against a panel of human tumor cell lines with over 10-fold selectivity for MCF-7 breast cancer ($IC_{50} = 0.59\ \mu M$).[2]

The gross structure and relative stereochemistry around the decalin core of **1** were secured from NMR studies, whereas the C-12 stereochemistry and absolute configuration were not determined.[1] A distinct feature of **1** is the α-(1-hydroxyalkyl)-γ-hydroxybutenolide unit which is rarely encountered in natural products.[3,4] Interestingly, a reportedly new diterpenoid isolated from the plant *Renealmia alpinia* has been assigned the even more unusual isomeric structure **2** (Figure 1).[5] Intrigued by the potentially labile hydroxydihydrofuroic acid moiety, prone to acid-catalyzed dehydration,[6] we considered the possibility that structure **2** was incorrect. Not unexpectedly, examination of the

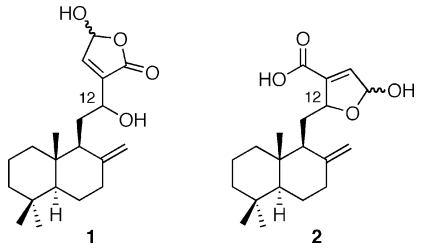

FIGURE 1. Structures originally assigned to zerumin B (**1**) and an unnamed diterpenoid from *R. alpinia* (**2**).

^1H and ^{13}C NMR data reported for **2** ($CDCl_3$)[5] and zerumin B (acetone-d_6)[1] revealed striking similarities, suggesting that the two compounds may indeed be identical.[7]

Herein, we disclose the first synthesis of zerumin B and its C-12 epimer by a concise, diastereochemically divergent pathway that allows unambiguous assignment of relative and absolute configuration to the natural product and establishes its identity with the purported diterpenoid **2**.

Central to our strategy, outlined in Scheme 1, was the appealing prospect of entirely regiocontrolled assemblage of the α-substituted γ-hydroxybutenolide unit by application of our silyloxyfuran oxyfunctionalization method (cf. **3** → **1**).[8,9] While γ-hydroxybutenolides have often been prepared by photooxygenation of 3-substituted furans,[10] this protocol would be unsuitable for the present task since it provides either mixtures of α- and β-substituted γ-hydroxybutenolides[10a−c] or solely the

(1) Xu, H.-X.; Dong, H.; Sim, K.-Y. *Phytochemistry* **1996**, *42*, 149−151.

(2) (a) 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. (b) Abas, F. Phytochemical and Biological Activity Studies of *Comos caudatus* and *Curcuma mangga*, and the On-line Characterization of Bioactive Fractions from *Melicope ptelefolia*. Ph.D. Thesis, Universiti Putra Malaysia, 2005.

(3) (a) Geis, W.; Buschauer, B.; Becker, H. *Phytochemistry* **1999**, *51*, 643−649. (b) Grossmann, G.; Poncioni, M.; Bornand, M.; Jolivet, B.; Neuburger, M.; Séquin, U. *Tetrahedron* **2003**, *59*, 3237−3251.

(4) In contrast, many naturally occurring β-(1-hydroxyalkyl)-γ-hydroxybutenolides have been isolated over the years, mostly from marine sponges. See for example: (a) Gunasekera, G. P.; McCarthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1996**, *118*, 8759−8760. (b) Schmidt, E. W.; Faulkner, D. J. *Tetrahedron Lett.* **1996**, *37*, 3951−3954. (c) De Marino, S.; Iorizzi, M.; Zollo, F.; Debitus, C.; Menou, J.-N.; Ospina, L. F.; Alcaraz, M. J.; Payá, M. *J. Nat. Prod.* **2000**, *63*, 322−326. (d) Buchanan, M. S.; Edser, A.; King, G.; Whitmore, J.; Quinn, R. J. *J. Nat. Prod.* **2001**, *64*, 300−303. (e) Tsuda, M.; Endo, T.; Mikami, Y.; Fromont, J.; Kobayashi, J. *J. Nat. Prod.* **2002**, *65*, 1507−1508. (f) Scio, E.; Ribeiro, A.; Alves, T. M. A.; Romanha, A. J.; de Souza Filho, J. D.; Cordell, G. A.; Zani, C. L. *Phytochemistry* **2003**, *64*, 1125−1131. (g) Faulkner, D. J.; Newman, D. J.; Cragg, G. M. *Nat. Prod. Rep.* **2004**, *21*, 50−76.

(5) Yang, S.-W.; Zhou, B.-N.; Malone, S.; Werkhoven, M. C. M.; van Troon, F.; Wisse, J. H.; Kingston, D. G. I. *J. Nat. Prod.* **1999**, *62*, 1173−1174. As in the case of zerumin B, the C-12 stereochemistry and absolute configuration were not assigned.

(6) Dehydration of 2,5-dihydro-2-furanols to furans readily occurs under acidic conditions: (a) Tius, M. A.; Takaki, K. S. *J. Org. Chem.* **1982**, *47*, 3166−3168. (b) Allen, A. J.; Vaillancourt, V.; Albizati, K. F. *Org. Prep. Proc. Int.* **1994**, *26*, 1−84. (c) Hakimelahi, G. H.; Jain, M. L.; Ly, T. W.; Chen, I.-C.; Ethiraj, K. S.; Hwu, J. R.; Moshfegh, A. A. *J. Org. Chem.* **2001**, *66*, 7067−7071. (d) See also: Burke, B. A.; Chan, W. R.; Mangus, K. E.; Taylor, D. R. *Tetrahedron* **1969**, *25*, 5007−5011.

(7) For a timely review on misassigned natural products, see: Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012−1044.

(8) Boukouvalas, J.; Lachance, N. *Synlett* **1998**, 31−32.

(9) Previous use in total synthesis: (a) Boukouvalas, J.; Cheng, Y.-X.; Robichaud, J. *J. Org. Chem.* **1998**, *63*, 228−229. (b) Marcos, I. S.; Pedrero, A. B.; Sexmero, M. J.; Diez, D.; Basabe, P.; Hernández, F. A.; Urones, J. G. *Tetrahedron Lett.* **2003**, *44*, 369−372. (c) Bagal, S. K.; Adlington, R. M.; Baldwin, J. E.; Marquez, R. *J. Org. Chem.* **2004**, *69*, 9100−9108. (d) Marcos, I. S.; Pedrero, A. B.; Sexmero, M. J.; Diez, D.; García, N.; Escola, M. A.; Basabe, P.; Conde, A.; Moro, R. F.; Urones, J. G. *Synthesis* **2005**, 3301−3310.

10.1021/jo0610154 CCC: $33.50
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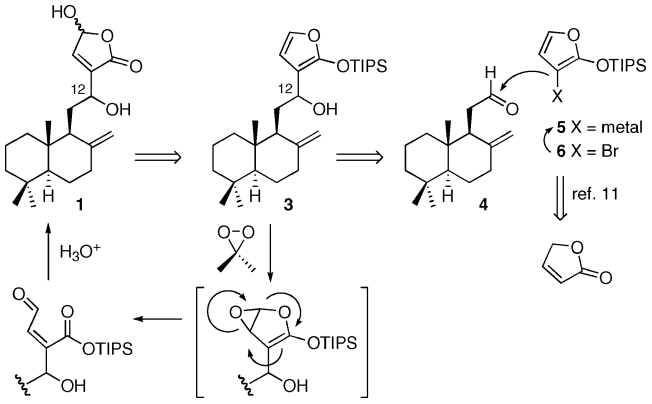
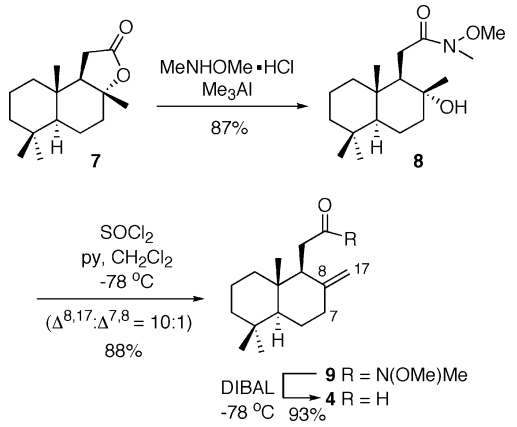
SCHEME 1. Retrosynthetic Analysis of 1



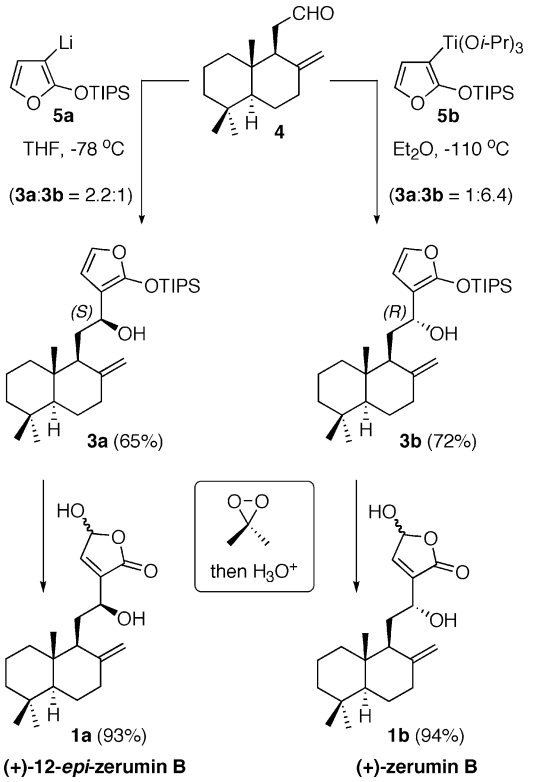
SCHEME 2. Preparation of Aldehyde 4



β-regiomers when Hünig's base is included.[10c−j] We were furthermore attracted to the possibility of controlling the challenging C-12 stereochemistry by 1,3-asymmetric induction in the addition of a 3-metalated 2-silyloxyfuran **5** to chiral aldehyde **4**. Reagent **5** would be derived from the newly described bromofuran **6**, obtainable in two steps from 2-(5*H*)-furanone.[11]

In a manner analogous to that reported by de la Torre,[12] aldehyde **4** was prepared from commercially available (+)-sclareolide (**7**) by conversion to Weinreb amide **8**,[13] dehydration, and amide reduction (Scheme 2). The limiting factor of this approach has been the modest 2:1 regioselectivity of the dehydration of **8** with thionyl chloride (pyridine, 0 °C).[12] After a brief investigation of this process, we were pleased to find

SCHEME 3. Diastereochemically Divergent Synthesis of (+)-Zerumin B and Its 12-Epimer



that, by simply running the reaction at −78 °C in pyridine/CH_2Cl_2, the $\Delta^{8,17}/\Delta^{7,8}$ ratio improved to 10:1, thereby providing the exocyclic olefin **9** in a yield of 88% after chromatography. Subsequent DIBAL reduction afforded **4** in excellent yield, making the three-step sequence especially attractive for preparing this widely used intermediate.[14,15]

In accord with previous observations on the addition of 3-lithiofuran to aldehyde **4**,[15] reaction of silyloxyfuryllithium **5a** with **4** (THF, −78 °C) provided the easily separable C-12-(*S*) and (*R*) epimers **3a** and **3b** in a modest 2.2:1 ratio (Scheme 3).[16] Performing the reaction at −110 °C had little effect on selectivity (2.7:1) or yield of the major isomer (65%). Impor-

(10) Recent examples: (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.

(11) Boukouvalas, J.; Marion, O. *Synlett* **2006**, 1511−1514.

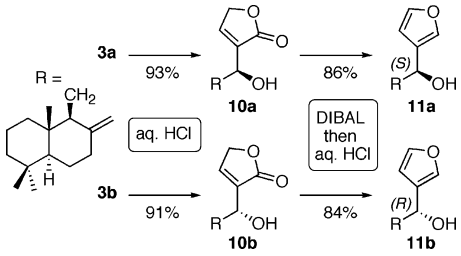
(12) de la Torre, M. C.; García, I.; Sierra, M. A. *Tetrahedron Lett.* **2002**, *43*, 6351−6353.

(13) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685−2688.

(14) Alternative syntheses of **4**: (a) Barrero, A. F.; Manzaneda, E. A.; Altarejos, J.; Salido, S.; Ramos, J. M.; Simmonds, M. S. J.; Blaney, W. M. *Tetrahedron* **1995**, *51*, 7435−7450. (b) Müller, M.; Schröder, J.; Magg, C.; Seifert, K. *Tetrahedron Lett.* **1998**, *39*, 4655−4656. (c) Villamizar, J.; Fuentes, J.; Salazar, F.; Tropper, E.; Alonso, R. *J. Nat. Prod.* **2003**, *66*, 1623−1627.

(15) Kolympadi, M.; Liapis, M.; Ragoussis, V. *Tetrahedron* **2005**, *61*, 2003−2010.

(16) The stereochemistry of **3a** and **3b** was established by conversion to the known furans **11a** and **11b** (ref 15), whose stereostructures have been determined by the modified Mosher ester method as well as by NMR comparison with closely related compounds: (a) Giang, P. M.; Son, P. T.; Otsuka, H. *Nat. Med.* **2004**, *58*, 230−233. (b) Turner, J. A.; Herz, W. *J. Org. Chem.* **1977**, *42*, 1900−1904.



tantly, substantially improved diastereoselectivity *in the opposite direction* (1:6.4), as required for the synthesis of zerumin B (vide infra), was achieved with the new silyloxyfuryltitanium reagent **5b**, delivering the C-12-(*R*)-isomer **3b** in 72% yield after chromatography. While the actual cause of such reversal is not fully understood, the value of furyltitanium reagents for attaining 1,3-asymmetric induction is undisputable, as earlier indicated by our work on the synthesis of dysidiolide[9a] and recently by Sibi and He in their synthesis of ricciocarpins.[17]

Exposure of the individual isomers **3a** and **3b** to dimethyldioxirane in acetone and subsequent quenching with Amberlyst-15/aq acetone[8] led uniquely to the corresponding γ-hydroxybutenolides **1a** and **1b**, which exhibited distinctly different physical and spectral properties. Direct ^{1}H and ^{13}C NMR comparison with authentic zerumin B and the purported *R. alpinia* constituent **2** revealed that **1b** was identical to both. The specific rotation of **1b** ($[\alpha]^{23}_D$ +42.8, *c* 0.25, acetone) was in close accord with that of natural zerumin B ($[\alpha]_D$ +40, *c* 0.01, acetone).[2b] Although optical data for **2** are unavailable, it can be assumed to have the same absolute configuration as zerumin B since another diterpenoid from *R. alpinia* has been shown to belong to the labdane series.[18]

In conclusion, the first synthesis of zerumin B has been accomplished in concise, regio- and stereocontrolled fashion from commercially available (+)-sclareolide (five steps, 48% overall yield). The synthesis establishes the relative and absolute stereochemistry of zerumin B as **1b** and further allows revision of the proposed structure for an unnamed constituent of *R. alpinia*, from **2** to **1b**.

Experimental Section

(*R*)-1-(2-(Triisopropylsilyloxy)furan-3-yl)-2-((1*S*,8a*S*)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)ethanol (3b) and (*S*)-1-(2-(Triisopropylsilyloxy)furan-3-yl)-2-((1*S*,8a*S*)-5,5,-8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)ethanol (3a). To a stirred solution of 3-bromo-2-(triisopropylsilyloxy)furan (**6**)[11] (81.7 mg, 0.26 mmol) in dry Et_2O (0.5 mL) under Ar at −78 °C was dropwise added *n*-BuLi (2.5 M in hexanes, 104 μL, 0.26 mmol). The colorless solution was stirred for 30 min at −78 °C and 20 min at −23 °C. After cooling to −78 °C, to the resulting solution of lithiofuran **5a** was added $ClTi(OPr\text{-}i)_3$ (1.0 M in hexanes, 256 μL, 0.26 mmol) dropwise. The solution turned bright yellow instantly. The resulting solution of furyltitanium **5b** was stirred at −78 °C for 5 min and then at −20 °C for ca. 10 min when there was some precipitate appearing. The mixture was cooled to −110 °C before dropwise addition of aldehyde **4** (25.0 mg, 0.107 mmol) in dry Et_2O (200 μL). The solution was stirred for 3 h at −110 °C and then for 1 h at −78 °C. The mixture was slowly warmed to −20 °C over 1 h before quenching with saturated aqueous $NaHCO_3$ (3 mL). After separation of the organic layer, the aqueous phase was extracted with diethyl ether (1 mL × 4). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure below 40 °C. The ratio of **3b**/**3a** was 6.4:1 (^{1}H NMR). The residue was purified by chromatography on basic silica gel[19] (eluted with hexanes−diethyl ether, 100:1, v/v) to provide alcohol **3b** as a colorless oil (36.3 mg, 72%), followed by elution with hexanes−diethyl ether (30:1, v/v) to give alcohol **3a** (colorless oil, 6.4 mg, 13%). Alcohol **3b**: R_f = 0.63 (hexanes−diethyl ether/3:1; CAM); $[\alpha]^{24}_D$= +40.2° (*c* 0.59, basic Al_2O_3 neutralized $CHCl_3$); IR (ν_{max}, NaCl, neat) 3462, 2945, 2868, 1643, 1524, 1462, 1418, 1277, 1250, 1228, 1141, 1041, 1011, 907, 884, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.75 (1H, d, *J* = 2.3 Hz), 6.30 (1H, d, *J* = 2.3 Hz), 4.82 (1H, dd, *J* = 2.9, 1.4 Hz), 4.66 (1H, br d, *J* = 10.0 Hz), 4.49 (1H, m), 2.40 (1H, ddd, *J* = 12.9, 4.1, 2.4 Hz), 2.05 (2H, m), 1.87 (1H, ddd, *J* = 14.3, 10.0, 1.9 Hz), 1.77 (1H, dm, *J* = 13.0 Hz), 1.74 (1H, ddt, *J* = 12.8, 5.1, 2.5 Hz), 1.66 (1H, ddd, *J* = 14.3, 11.0, 2.5 Hz), 1.60−1.45 (2H, m), 1.39 (1H, dm, *J* = 13.0 Hz), 1.34 (1H, m), 1.28 (3H, m), 1.20 (1H, m), 1.19 (1H, dd, *J* = 12.6, 2.5 Hz), 1.14 (1H, m), 1.10 (18H, d, *J* = 7.3 Hz), 0.87 (3H, s), 0.81 (3H, s), 0.67 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.5, 148.8, 131.2, 109.9, 106.5, 100.4, 64.1, 55.4, 52.3, 42.1, 39.2, 39.0, 38.2, 33.61, 33.56, 32.2, 24.4, 21.7, 19.3, 17.6, 14.6, 12.4; HRMS (EI) *m*/*z* (M^+) calcd for $C_{29}H_{50}O_3Si$ 474.3529, found 474.3520. Alcohol **3a**: colorless oil, R_f = 0.40 (hexanes−diethyl ether/3:1; CAM); $[\alpha]^{24}_D$ = +5.5° (*c* 1.2, basic Al_2O_3 neutralized $CHCl_3$); IR (ν_{max}, NaCl, neat) 3396, 2945, 2868, 1643, 1525, 1462, 1419, 1388, 1248, 1141, 1057, 996, 898, 853, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.78 (1H, d, *J* = 2.3 Hz), 6.29 (1H, d, *J* = 2.3 Hz), 4.84 (1H, dd, *J* = 2.9, 1.5 Hz), 4.74 (1H, m), 4.69 (1H, dd, *J* = 9.2, 5.4 Hz), 2.33 (1H, ddd, *J* = 12.7, 4.1, 2.4 Hz), 1.89 (2H, m), 1.86 (1H, m), 1.74 (1H, ddt, *J* = 12.6, 4.8, 2.4 Hz), 1.73 (1H, dm, *J* = 13.0 Hz), 1.52 (1H, m), 1.45 (1H, m), 1.38 (1H, dm, *J* = 12.0 Hz), 1.35 (1H, dm, *J* = 13.0 Hz), 1.28 (1H, m), 1.25 (3H, m), 1.10 (1H, m), 1.07 (18H, d, *J* = 7.3 Hz), 0.95 (1H, dd, *J* = 12.7, 2.8 Hz), 0.83 (1H, m), 0.82 (3H, s), 0.77 (3H, s), 0.69 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.0, 148.7, 131.5, 109.4, 106.5, 99.4, 64.8, 55.4, 52.6, 42.0, 39.4, 38.8, 38.1, 33.6, 33.5, 31.4, 24.2, 21.7, 19.3, 17.6, 14.5, 12.3; HRMS (EI) *m*/*z* (M^+) calcd for $C_{29}H_{50}O_3Si$ 474.3529, found 474.3520.

(+)-Zerumin B (1b). To a solution of alcohol **3b** (36.0 mg, 75.8 μmol) in acetone (2 mL) at −78 °C was added dimethyldioxirane in acetone[20] (1 mL, ca. 0.07−0.09 M) dropwise. After 10 min, the reaction was shown to be incomplete by TLC. Another portion of dimethyldioxirane in acetone (0.7 mL, ca. 0.07−0.09 M) was then added. After 20 min, the solvent was removed under vacuum (−78 °C to room temperature), and the residue was dissolved in acetone−water (10:1, 2 mL) and Amberlyst-15 (5 mg) was added at room temperature. After stirring for 15 min, the volatiles were evaporated under reduced pressure, and the residue was subjected to chromatography on silica gel (with a pad of $MgSO_4$, 4 mm on top) eluted with CH_2Cl_2−MeOH (150:1 to 50:1, v/v) to give (+)-zerumin B (**1b**, 23.9 mg, 94%): R_f = 0.16 (CH_2Cl_2−MeOH /20:1, CAM); mp 174−175 °C (colorless needles from hexanes−CH_2Cl_2); lit.[2b] 156−158 °C (crystals), $[\alpha]^{22}_D$ = +42.8° (*c* 0.25, acetone); lit.[2b] $[\alpha]_D$ = +40 (*c* 0.01, acetone); IR (ν_{max}, NaCl, neat) 3377, 2944, 2867, 1751, 1689, 1643, 1459, 1388, 1339, 1256, 1094, 1056, 1007, 888 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.04 (1H, br s), 6.12 (1H, br s), 4.89 (1H, m), 4.69 (1H, br s), 4.55 (1H, br d, *J* = 9.9 Hz), 4.09 (1H, br s), 2.49 (1H, br s), 2.42 (1H, ddd, *J* = 12.8, 4.1, 2.5 Hz), 2.05 (1H, d, *J* = 11.9 Hz), 2.03 (1H, td, *J* = 12.8, 5.1 Hz), 1.87 (1H, dd, *J* = 13.6, 11.9 Hz), 1.75 (1H, dm, *J* = 12.8 Hz), 1.69 (1H, dm, *J* = 12.7 Hz), 1.68 (1H, m), 1.53 (2H, m), 1.40 (1H, dm, *J* = 13.0 Hz), 1.34 (1H, qd, *J* = 12.8, 4.1 Hz), 1.19 (1H, td, *J* = 13.0, 4.3 Hz), 1.16 (1H, dd, *J* = 12.8, 2.6 Hz), 1.05 (1H, td, *J* = 12.7, 4.1 Hz), 0.88 (3H, s), 0.81 (3H, s), 0.68 (3H, s); ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.13 (1H, br s), 6.64 (1H, br s), 6.16 (1H, br s), 4.96 (1H, m), 4.87 (1H, br s), 4.43 (1H, br d, *J* = 10.4 Hz), 4.32 (1H, br d, *J* = 5.5 Hz), 2.40 (1H, ddd, *J* = 12.8, 3.7, 2.7 Hz), 2.21 (1H, d, *J* = 11.7 Hz), 2.02 (1H, td, *J* = 12.8, 5.1 Hz), 1.91 (1H, br t, *J* = 12.7 Hz), 1.76 (1H, dm, *J* = 12.8 Hz), 1.69 (1H, dm, *J* = 12.8 Hz), 1.60 (1H, m), 1.50 (1H, m), 1.47 (1H, m), 1.40 (1H, dm, *J* = 12.8 Hz), 1.35 (1H, qd, *J* = 12.8, 4.2 Hz), 1.22 (1H, td, *J* = 12.8, 4.1 Hz), 1.19 (1H, dd, *J* = 12.7, 2.1 Hz), 1.09 (1H, td, *J* = 12.8, 3.6 Hz), 0.89 (3H, s), 0.82 (3H, s), 0.69 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3 (br), 148.2 (br), 143.1 (br),

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141.4 (br), 107.2, 97.0 (br), 65.6, 55.5, 51.9, 42.1, 39.3, 39.1, 38.3, 33.61, 33.58, 30.5, 30.2, 24.4, 21.7, 19.3, 14.6; ^{13}C NMR (acetone-d_6, 100 MHz) δ 170.9, 148.9, 144.8, 142.9, 107.8, 98.0, 65.3, 56.2, 52.5, 42.7, 39.7, 39.6, 38.9, 34.1, 33.8, 31.8, 25.0, 21.9, 19.9, 15.0.

(+)-12-*epi*-Zerumin B (1a). Using the same procedure described for **1b** but starting from **3a** (29.0 mg) afforded (+)-12-*epi*-zerumin B (**1a**, 19.0 mg, 93%) as colorless gum: $R_f = 0.16$ (CH_2Cl_2−MeOH 20:1, CAM); $[\alpha]^{22}_D$ +5.5° (*c* 0.85, acetone); IR (ν_{max}, NaCl, neat) 3377, 2944, 2867, 1751, 1689, 1643, 1459, 1388, 1339, 1256, 1094, 1056, 1007, 888 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03 (0.5 H, t, $J = 1.1$ Hz), 6.99 (0.5 H, t, $J = 1.0$ Hz), 6.19 (0.5 H, br s), 6.10 (0.5 H, br s), 5.02 (1H, br s), 4.89 (0.5 H, m), 4.88 (0.5 H, m), 4.69 (0.5 H, br s), 4.67 (0.5 H, br s), 4.51 (1H, br t, $J = 7.1$ Hz), 2.39 (1H, dm, $J = 12.7$ Hz), 2.02 (1H, m), 1.95 (1H, m), 1.85 (1H, m), 1.74 (1H, m), 1.73 (1H, m), 1.66 (0.5 H, d, $J = 10.0$ Hz), 1.55 (0.5 H, d, $J = 10.0$ Hz), 1.53 (1H, m), 1.50 (1H, m), 1.38 (1H, dm, $J = 13.3$ Hz), 1.31 (1H, m), 1.16 (1H, m), 1.09 (0.5H, dd, $J = 12.7$, 2.7 Hz), 1.07 (0.5H, dd, $J = 12.5$, 2.7 Hz), 0.95 (1H, m), 0.86 (3H, s), 0.79 (3H, s), 0.67 (3H, s); ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.13 (1H, br s), 6.66 (1H, br s), 6.15 (1H, br s), 4.82 (1H, br s), 4.68 and 4.65 (1H, 2br s), 4.48 (1H, br s), 4.14 (1H, br s), 2.24 (1H, br d, $J = 12.7$ Hz), 2.00 (1H, br m), 1.98 (1H, br m), 1.81 (1H, m), 1.78 (1H, m), 1.77 (1H, m), 1.73 (1H, m), 1.59 (1H, td, $J = 13.5$, 3.4 Hz), 1.46 (1H, dm, $J = 13.5$ Hz), 1.38 (1H, dm, $J = 13.5$ Hz), 1.31 (1H, qd, $J = 12.8$, 4.1 Hz), 1.20 (1H, m), 1.13 (1H, dd, $J = 12.7$, 2.7 Hz), 1.05 (1H, br m), 0.86 (3H, s), 0.81 (3H, s), 0.70 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 170.6, 149.4, 149.2, 145.0, 144.5, 139.7, 138.7, 107.1, 107.0, 97.4, 97.3, 67.3, 66.8, 55.5, 55.4, 53.4, 53.2, 42.0, 41.9, 39.9, 39.8, 39.0, 38.9, 38.20, 38.16, 33.6 (2C), 33.5 (2C), 29.8, 29.4, 24.3, 21.7, 19.3, 19.2, 14.5, 14.4; ^{13}C NMR (acetone-d_6, 100 MHz) δ 171.0, 170.8, 150.1, 150.0, 146.1, 146.0, 141.2, 141.0, 106.8, 106.7, 97.9, 97.8, 66.2, 66.1, 53.1, 52.8, 32.1, 31.9, 56.1, 42.7, 40.3, 39.5, 38.7, 34.1, 33.9, 25.0, 21.9, 19.8, 14.7; HRMS (EI) *m*/*z* (M^+) calcd for $C_{20}H_{30}O_4$ 334.2144, found 334.2149.

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Supporting Information Available: Experimental procedures and characterization data, including NMR spectra, and comparison of NMR data of **1b**, natural zerumin B, and the purported diterpenoid **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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