A short and efficient synthesis of the antitumor diterpenoid (+)-zerumin B has been accomplished starting from (+)-scclareolide. 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 (‘O₂) oxidation of the resulting 2-trisopropylsilyl-3-(α-hydroxy)alkylfurans.

(+)-Zerumin B was first isolated in 1996 from the Chinese medicinal plant Alpinia zerumbet. In 2005, the same molecule was isolated, together with a number of other labdane diterpenes, from the popular vegetable Curcuma mangga. This vegetable is a member of the Zingiberaceae family and is commonly grown in Thailand, Peninsular Malaysia, and Java. The 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 wound healing. Recently, however, perhaps a more important medicinal characteristic was discovered when (+)-zerumin B was also found to possess potent cytotoxicity (IC₅₀ 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. Addition of a silyloxyfuryltitanium reagent to an aldehyde and the latter may then undergo a regioselective singlet oxygen oxidation 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.

In order to validate the proposal, deconvoluting a rapid synthesis of the requisite 3-substituted furan 5\(^\dagger\) (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 (\(\Delta^6,17/\Delta^7,8\) Scheme 2). This ratio is in stark contrast to those obtained earlier when using other common dehydration methods where unacceptable 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 \(8^\dagger\) 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-1 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 of the hydroxyl group of 5a and 5b under standard conditions (2,6-lutidine, TIPSOTf, Scheme 3) gave trisopropysilyl 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\(^\dagger\) cleanly transformed them to the corresponding 2-triisopropylsilyl-3-(\(\alpha\)-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\(^\dagger\) 8a or 8b (Scheme 3). In situ hydrosilation of silyl esters 8a or 8b yielded the corresponding \(\gamma\)-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 \(^13C\) NMR data for 9 and 1 matched exactly that reported in the literature.\(^\dagger\) As expected, both compounds are equimolar mixtures of diastereomeric \(\gamma\)-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 hydrosilation of the intermediate silyl ester 8a. An equimolar mixture of diastereoisomers were observed in \(^1H\) NMR after chromatographic purification using silica gel.\(^\dagger\)

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


The regioselective transformation of a 3-substituted furan into B has been accomplished. The key step of the synthesis involved the reaction was quenched with NaHCO₃ (2 mL). 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 NaHCO₃ (2 mL). The reaction mixture was diluted with Et₂O (10 mL) and washed with H₂O (5 mL). The organic layer was dried (MgSO₄), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc 1:2 v/v) afforded the 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: 1H NMR (300 MHz, CDCl₃) 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, J₁ = 10.0 Hz, J₂ = 1.5 Hz, 1H), 4.47 (s, 1H), 3.41 (dd, J₁ = 12.7 Hz, J₂ = 4.0 Hz, J₃ = 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); 13C NMR (125 MHz, CDCl₃) 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 (13C), 18.0 (13C), 14.7, 12.6 (3C) ppm; HRMS (ESI⁺) calcd for C₁₁₂H₂₂₀O₂SiNa₄₈₁.₃₄₇₈ [M + Na⁺], found 481.₃₄₇₈.

6a: 1H NMR (300 MHz, CDCl₃) 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, J₁ = 10.5 Hz, J₂ = 4.3 Hz, 1H), 4.69 (s, 1H), 2.36 (dd, J₁ = 12.7 Hz, J₂ = 4.1 Hz, J₃ = 2.4 Hz, 1H), 1.99−1.05 (m, 12H), 1.05−0.96 (m, 21H), 0.92 (s, 3H), 0.82 (s, 3H), 0.78 (s, 3H), 0.70 (s, 3H); 13C NMR (125 MHz, CDCl₃) δ = 149.0, 140.9, 138.2, 131.9, 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 (13C), 14.8, 12.3 (3C); HRMS (ESI⁺) calcd for C₂₉H₄₀O₂SiNa₄₈₁.₃₄₇₈ [M + Na⁺], found 481.₃₄₇₈.  

A solution of the furan 7b (82 mg, 0.18 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 NH₄Cl (1 mL), diluted with Et₂O (10 mL), and washed with H₂O (5 mL). The organic layer was dried (MgSO₄), 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%).

7b: 1H NMR (300 MHz, CDCl₃) 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 (dd, J₁ = 12.8 Hz, J₂ = 3.8 Hz, J₃ = 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); 13C NMR (75 MHz, CDCl₃) 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, 35.1, 33.8, 32.7, 21.7, 19.4, 18.8 (3C), 18.7 (3C), 14.6, 11.7 (3C); HRMS (ESI⁺) calcd for C₉₂H₁₄₂O₃SiNa₄₈₁.₃₄₇₈ [M + Na⁺], found 481.₃₄₇₈.

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Supporting Information Available: Copies of 1H NMR and 13C 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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