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Synthesis of Chinensines A−E

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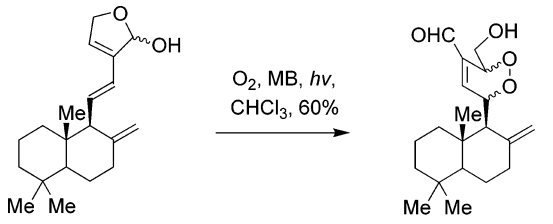

Short and efficient syntheses of coronarin E (**4**) and chinensines A−E (**5**−**9**) have been accomplished. The use of two different types of reaction of singlet oxygen ($^1O_2$) lies at the heart of the synthetic strategy. The syntheses have facilitated the clarification of certain previously unknown, or unconfirmed, stereochemical details (the relativity stereochemistries of chinensines D and E and the absolute stereochemistries for all the synthesized family members).

In 1997 a family of related compounds (**1**−**5** and **7**−**9**, Figure 1) were isolated from extracts of the aerial parts of a perennial shrub named *Alpinia chinensis*.[1] This plant, native to Hong Kong, has long been used in Chinese medicine to treat asthma and as an analgesic. Compound **6** (a 4-hydroxybutenolide that is regioisomeric with compound **5**) was isolated more recently, and independently of the other chinensine family members, in 2005 from extracts of the Southeast Asian plant species *Etlingera elatior*.[2] *E. Elatior* extracts have been shown to have interesting biological activities[2] among which cytotoxicity against the HeLa tumor cell line[3] and antitumor-promoting activity[4] stand out especially. These natural products (**1**−**9**)[5] all bear a variably oxidized northern portion attached to a decalin anchor of the labdane type. Certain characteristics of the former feature immediately attracted our attention because they bore all the hallmarks of singlet oxygen-mediated assemblage. It should be remembered that in Nature four essential prerequisites necessary for the production and reaction of singlet oxygen ($^1O_2$) are readily met. These criteria are the following: (a) natural sunlight providing visible spectrum radiation; (b) a proliferation of photosensitizers (e.g., tannins, porphyrins, and chlorophyll); (c) pervasive molecular dioxygen (≈20% of atmospheric air); and (d) an abundance of oxidizable substrates, such as terpenes. Our experience in using $^1O_2$ in the laboratory to achieve the biomimetic syntheses of a diverse range of natural products (particularly starting from naturally occurring furans[6])[7,8] led us to propose and investigate such a strategy for synthesizing key members of the chinensine family. Herein we report our success in converting our blueprint into reality by accomplishing the total syntheses of six members of the family, namely coronarin E (**4**) and chinensines A−E (**5**, **6**, **7**, **8**, and **9**, respectively).

It is our belief that Nature relies heavily on singlet oxygen when synthesizing the chinensine family members and this postulate informed our retrosynthetic analysis. It followed that the obvious starting point for these syntheses was the already well-known natural product,[1,9] bearing a furan moiety, named

(1) Sy, L.-K.; Brown, G. D. *J. Nat. Prod*. **1997**, *60*, 904−908.
(2) Mohamad, H.; Lajis, N. H.; Abas, F.; Ali, A. M.; Sukari, M. A.; Kikuzaki, H.; Nakatani, N. *J. Nat. Prod*. **2005**, *68*, 285−288.
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(4) Murakami, A.; Ali, A. M.; Mat-Salleh, K.; Koshimizu, K.; Ohigashi, H. *Biosci., Biotechnol., Biochem*. **2000**, *64*, 9−16.
(5) We have assigned the names chinensine A, B, C, D, and E to compounds **5**, **6**, **7**, **8**, and **9**, respectively, for ease of discussion. Please note that coronarin E (**4**) was known and named prior to the isolation of the chinensine family, see refs 1 and 9 and references therein.
(6) (a) Vassilikogiannakis, G.; Stratakis, M. *Angew. Chem, Int. Ed*. **2003**, *42*, 5465−5468. (b) Vassilikogiannakis, G.; Margaros, I.; Montagnon, T. *Org. Lett*. **2004**, *6*, 2039−2042. (c) Vassilikogiannakis, G.; Margaros, I.; Montagnon, T.; Stratakis, M. *Chem.-Eur. J.* **2005**, *11*, 5899−5907.
(7) Sofikiti, N.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G.; Stratakis, M. *Org. Lett*. **2005**, *7*, 2357−2359.
(8) Margaros, I.; Montagnon, T.; Tofi, M.; Pavlakos, E.; Vassilikogiannakis, G. *Tetrahedron* **2006**, *62*, 5308−5317.
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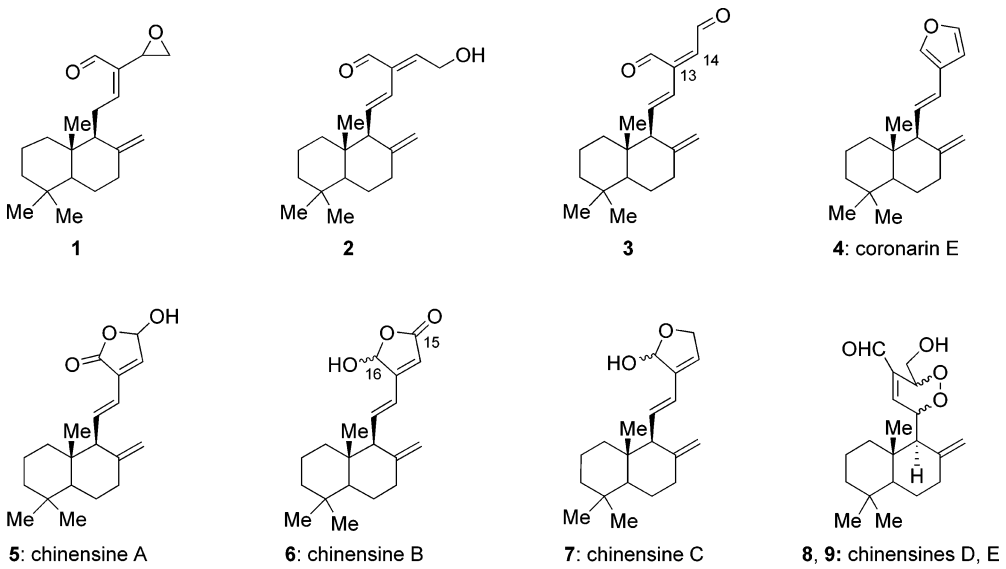
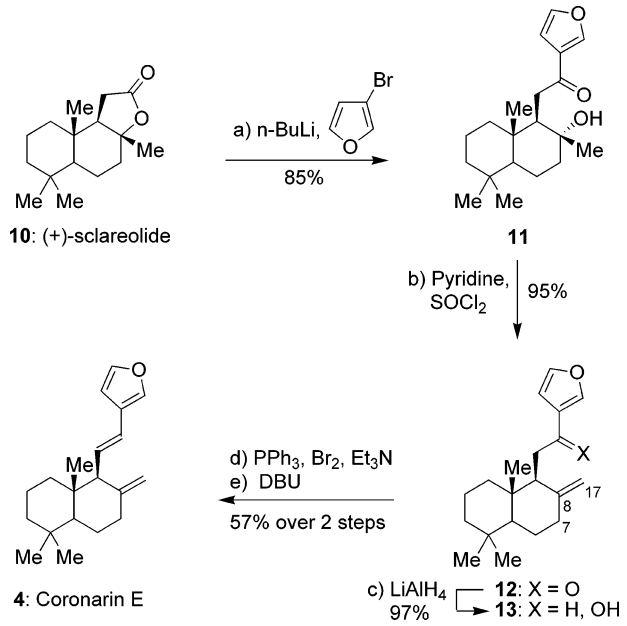


FIGURE 1. Selected members of the chinensine family of natural products.

coronarin E (**4**). It has been established for some time that furans can undergo a [4+2]-cycloaddition upon treatment with $^1O_2$ to yield an endoperoxide[10,11] that may then suffer either one of two fates: (a) nucleophilic opening by, for example, H_2O, followed by a reduction/elimination process to furnish the corresponding dialdehyde,[10] herein, we account for the formation of dialdehyde **3**, or (b) formation of a 4-hydroxybutenolide[12] in the presence of a mild base (e.g., naturally occurring amines), thus, we may also explain the formation hydroxybutenolides **5** and **6** from coronarin E (**4**). In turn, reduction of hydroxybutenolide **5** might be expected to furnish the hemiketal **7**, which we propose is the precursor to diastereomeric endoperoxides **8** and **9** (via a second [4+2]-cycloaddition). The latter stages of this sequence (**7** → **8** and **9**) represent a very minor adjustment to the biogenetic proposal delineated in the isolation paper,[1] which we hoped to justify through synthesis. In particular, the isolation chemists had proposed that the origin of endoperoxides **8** and **9** was diene **2** (itself the product of the extract's major component epoxide **1**). We preferred to propose diene **7** over diene **2** as precursor to the endoperoxides **8** and **9** for the following reasons: first, to participate in the [4+2]-cycloaddition, the *E*,*Z*-diene of **2** would be required to adopt an unfavorable *s-cis* configuration (in comparison to *E*,*E*-diene **7** where the *s-cis* configuration is easily adopted), and second, diene **2** is undoubtedly more electron deficient than diene **7**, a characteristic that might reasonably be expected to impact negatively its chances of undergoing a [4+2]-cycloaddition of this sort. It seemed highly probable to us then that the endoperoxides **8** and **9** in reality arose via a [4+2] reaction between the *E*,*E*-diene moiety of hemiketal **7** and $^1O_2$. It would be simple to differentiate between the two postulates by close examination of the stereochemistry of the endoperoxides, a structural feature not yet deconvoluted. The reaction between

SCHEME 1. Synthesis of Coronarin E (4)



dienes and $^1O_2$ is concerted[13] meaning that if *E*,*Z*-diene **2** is the cycloaddition substrate then the endoperoxide products would be expected to exhibit *trans* stereochemistry; on the other hand, our modified hypothesis with *E*,*E*-diene **7** as the cycloaddition substrate would translate to the corresponding *cis*-endoperoxides.

With its intact labdane skeleton, the commercially available lactone **10**, known as (+)-sclareolide, made an ideal starting point for the investigation. Furthermore, since sclareolide (**10**) is enantiomerically pure it provided the perfect tool with which to validate the absolute stereochemistry of certain chinensine family members whose stereochemistry had been tentatively assigned based on comparisons to other biogenetically close relatives.[1] (+)-Sclareolide (**10**) was converted into coronarin E (**4**) in five steps (Scheme 1). First, 3-lithiofuran, obtained from 3-bromofuran upon treatment with *n*-BuLi, was used to open

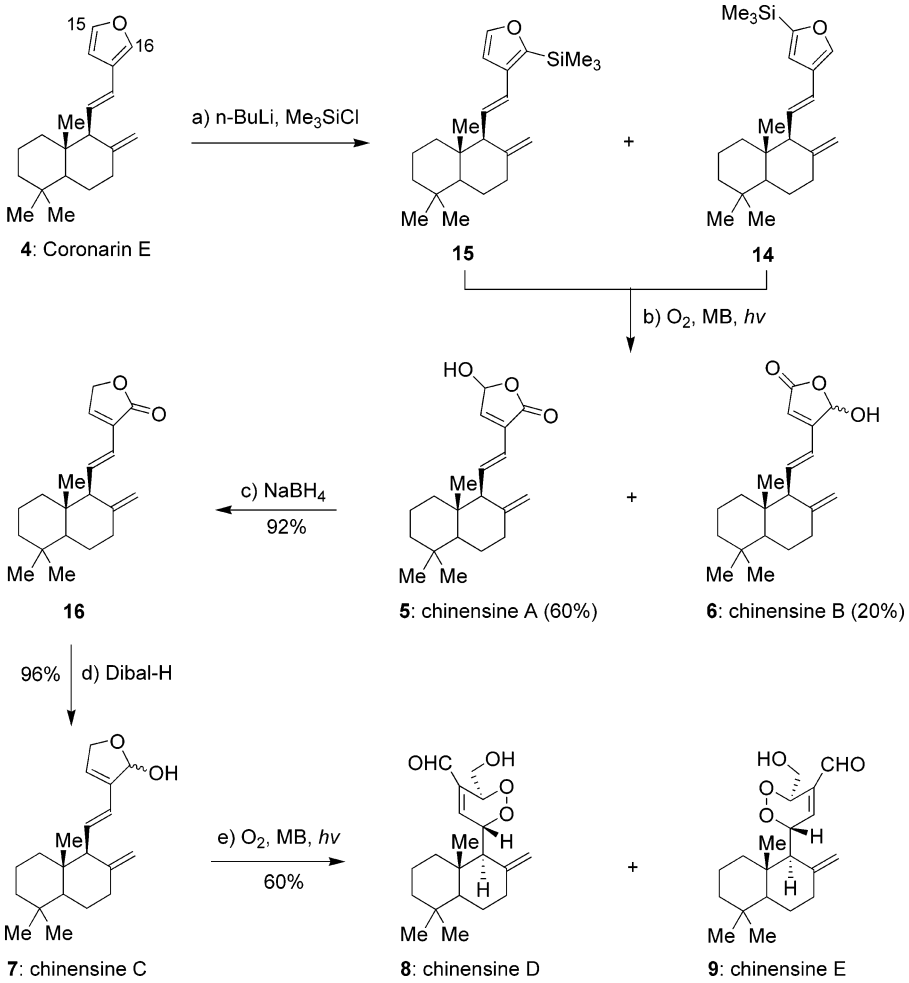
(10) (a) Feringa, B. L. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 469−488 and references therein. (b) For mechanistic work see: Clennan, E. L.; Mehrsheikh-Mohammadi, M. E. *J. Am. Chem. Soc.* **1984**, *106*, 7112−7118.

(11) For the first isolation of reasonable quantities of highly sensitive furan endoperoxides see: (a) Gollnick, K.; Griesbeck, A. *Tetrahedron* **1985**, *41*, 2057−2068. (b) Gollnick, K.; Griesbeck, A. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 726−727.

(12) Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773−2776.

(13) (a) Clennan, E. L. *Tetrahedron* **1991**, *47*, 1343−1382. (b) Adam, W.; Prein, M. *Acc. Chem. Res.* **1996**, *29*, 275−283.

SCHEME 2. Use of $^1O_2$ to Synthesize Chinensine Family Members



sclareolide **10**'s lactone moiety giving hydroxyketone **11** (yield 85%, **11** is itself a natural product[14]). After much experimentation, the best conditions to affect the dehydration of **11** and maximize the exocyclic:endocyclic double bond ratio were found to be the combination of $SOCl_2$ and pyridine (yield 95%). These reagents gave an exocyclic:endocyclic ratio of 14:1 ($\Delta^{8,17}$:$\Delta^{7,8}$, Scheme 1), a ratio that represented a vast improvement on those obtained from the initial methods[15] investigated. The furylic ketone **12** was then reduced to the corresponding diastereomeric mixture (that was equimolar and separable by column chromatography) of alcohols **13** (also natural products[16]) with $LiAlH_4$ in 97% yield. Once again, finding suitable dehydration conditions demanded our attention because the standard acidic conditions generally employed for such transformations, when applied to alcohols **13**, prompted an undesired double bond ($\Delta^{8,17}$) migration from exocyclic to endocyclic. For example, use of PTSA furnished dehydrated material in a yield of 73%, but the exocyclic:endocyclic ratio dropped from 14:1 to 4.5:1. Finally, we settled upon conversion of alcohols **13** to the corresponding bromides followed by elimination under basic conditions (DBU), thus affording coronarin E (**4**) in a lower yield (57% over two steps), but without contamination from double bond migration.

The stage was now almost set for the testing of the first key $^1O_2$-mediated cascade reaction sequence that lay at the heart of our synthetic strategy. First, however, a synthetic trick had to be employed both to improve the yield and to bias the regiochemical outcome of this reaction sequence. Although the [4+2] reaction between $^1O_2$ and furans is well-known,[10] transformation of the resultant endoperoxide into the corresponding 4-hydroxybutenolide by the action of base[12] has been shown to proceed only in very low yields. Careful placement of a silicon group at the C-16 (for synthesis of chinensines A and C−E), or C-15 (for chinensine B, Scheme 2) should affect a stabilizing influence and would thus alleviate such problems.[7,17] Fortunately, we had earlier developed a protocol for achieving the regioselective ortholithiation of furans bearing an unsaturated 3-position substituent at the more hindered 2-position of the furan (in preference to the alternative 5-position).[18] This procedure was now applied to accomplish the silylation

(14) Zdero, C.; Bohlmann, F.; Niemeyer, H. M. *Phytochemistry* **1991**, *30*, 1597−1601.

(15) For reports of similar failures with these methods see: Kolympadi, M.; Liapis, M.; Ragoussis, V. *Tetrahedron* **2005**, *61*, 2003−2010.

(16) (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.

(17) For the silyl stabilization concept, see: Adam, W.; Rodriguez, A. *Tetrahedron Lett.* **1981**, *22*, 3505−3508. For direct comparisons between the photoxygenations of silyl-substituted 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.

(18) Tofi, M.; Georgiou, T.; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2005**, *7*, 3347−3350.

of coronarin E (**4**) affording a 1:3 mixture of regioisomers **14**:**15** (**15** being required for synthesis of chinensines A and C−E and **14** only for chinensine B, Scheme 2). Following this silylation, the newly secured substrates **14** and **15** were subjected to the $^1O_2$-reaction conditions, namely, bubbling oxygen through the reaction solution containing 10^{-4} M Methylene Blue as sensitizer while irradiating with visible spectrum light (2 min). The desired 4-hydroxybutenolides **5** and **6**, chinensines A and B, respectively, were separated from the reaction mixture (**15** → **5** and **14** → **6**, **5**:**6** = 3:1 after purification, 80% overall for two steps). Hydroxybutenolide **5** was produced as a single diastereomer (by ^{1}H and ^{13}C NMR) in accordance with the isolation where only one diastereomer was found.[1] In contrast, hydroxybutenolide **6** was produced as an equimolar mixture of diastereoisomers. Hydroxybutenolide **6** was isolated as a mixture of diastereoisomers.[2] After the failure of our attempts to reduce hydroxybutenolide **5** (chinensine A) directly to the lactol **7** (chinensine C), we opted to take a stepwise approach. Thus, sodium borohydride was used to obtain lactone **16**[19] from hydroxybutenolide **5** in 92% yield. Lactone **16** was then further reduced with Dibal-H to furnish the desired diastereomeric lactols **7** (chinensines C, Scheme 2) in 96% yield. In the investigation's denouement, chinensine C (**7**) was transformed to the desired diastereomeric mix (1.3:1) of *cis*-endoperoxides **8** and **9** (chinensines D and E, respectively) upon relatively prolonged treatment (20 min) with $^1O_2$ in 60% isolated yield. The spectral data for synthetic samples of compounds **4**−**9** (coronarin E and chinensines A−E, respectively) matched exactly with the data reported for the natural products.[1,2] That the data for the natural and synthetic diastereomeric endoperoxides matched exactly was important because it established the relative stereochemistry of the endoperoxides as being *cis* for the first time. Furthermore, it would appear to validate our proposal that Nature synthesizes these compounds from chinensine C (**7**), and not from diene **2**. In addition, the absolute stereochemistry has been confirmed since the optical rotations of the synthetic compounds, with known absolute stereochemistry, are in agreement with the values reported for the natural products.

In summary, short and efficient syntheses of chinensines A−E have been achieved that allowed the determination of the relative stereochemistry of the endoperoxide rings of chinensines D an E and the absolute stereochemistries for all the synthesized family members. Singlet oxygen has been shown to be a powerful synthetic tool whose mode of reaction (i.e., a concerted [4+2]-cycloaddition with a diene) has, in this case, helped to clarify some biogenetic details for the chinensine family of secondary metabolites.

Experimental Section

8α-Hydroxy-15,16-epoxylabda-13(16),14-diene-12-one (11). To a solution of 3-bromofuran (118 μL, 1.24 mmol, 2.3 equiv) in dry THF (2 mL) at −78 °C was added slowly *n*-BuLi (743 μL, 1.18 mmol, 2.2 equiv). After 5 min of stirring at −78 °C, the solution was added dropwise (using a precooled cannula) to a solution of (+)-sclareolide (**10**, 135 mg, 0.54 mmol, 1.0 equiv) in dry THF (2 mL) at −78 °C. The mixture was allowed to warm from −78 to −40 °C over a ca. 20 min period before the reaction was quenched with brine (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 6 mL). The combined organic layers were dried over $MgSO_4$ and filtered. After evaporation of the solvent under reduced pressure, the solid residue was pulverized and washed 3 to 5 times with small quantities of hexanes/EtOAc (20:1 v/v) thus providing **11** (146 mg, 85%), which was directly used in the next step.

11: $[\alpha]^{24}_D$ +21.3 (*c* 2.50, $CHCl_3$) [lit.[14] $[\alpha]^{24}_D$ +20.0 (*c* 0.49, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.43 (d, J = 1.3 Hz, 1H), 6.78 (d, J = 1.3 Hz, 1H), 2.85 (dd, J_1 = 17.2 Hz, J_2 = 4.9 Hz, 1H), 2.80 (dd, J_1 = 17.2 Hz, J_2 = 4.9 Hz, 1H), 2.13 (t, J = 4.9 Hz, 1H), 1.95 (td, J_1 = 12.5 Hz, J_2 = 3.1 Hz, 1H), 1.70 (br d, J = 14.0 Hz, 2H), 1.60−1.25 (m, 6H), 1.15 (s, 3H), 1.13 (m, 1H), 1.04 (dd, J_1 = 12.3 Hz, J_2 = 2.1 Hz, 1H), 0.92 (dt, J_1 = 13.4 Hz, J_2 = 3.9 Hz, 1H), 0.87 (s, 3H), 0.85 (s, 3H), 0.79 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 147.0, 144.1, 127.7, 108.9, 73.0, 55.9, 55.8, 44.6, 41.7, 39.4, 38.6, 36.3, 33.3, 33.2, 23.3, 21.4, 20.6, 18.3, 15.7 ppm; HRMS (ESI+) calcd for $C_{20}H_{30}O_3Na$ 341.2087 [M + Na^+], found 341.2090.

15,16-Epoxylabda-8(17),13(16),14-triene-12-one ($\Delta^{8,17}$-12). To a solution of **11** (144 mg, 0.45 mmol) in dry dichloromethane (3 mL) at room temperature was added dry pyridine (73 μL, 0.91 mmol, 2.0 equiv).[20] After the mixture was cooled to −78 °C, a solution of thionyl chloride (164 μL, 2.26 mmol, 5.0 equiv) in dry dichloromethane (1.5 mL) and dry pyridine (302 μL, 3.74 mmol, 8.25 equiv) was added over a period of ca. 15 min. The reaction mixture was stirred for 30 min at the same temperature before being quenched with saturated aqueous $NaHCO_3$ (10 mL). The reaction mixture was then allowed to warm to room temperature and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 8 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The crude **12** obtained after evaporation of the solvent under reduced pressure was directly used for the next reaction (129 mg, 95%, $\Delta^{8,17}$-**12**:$\Delta^{7,8}$-**12** = 14:1).

$\Delta^{8,17}$-12: $[\alpha]^{24}_D$ −65.1 (*c* 1.25, $CHCl_3$) [lit.[21] $[\alpha]^{24}_D$ −63.1 (*c* 0.13, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.42 (d, J = 1.4 Hz, 1H), 6.77 (d, J = 1.4 Hz, 1H), 4.71 (s, 1H), 4.37 (s, 1H), 2.94 (dd, J_1 = 16.7 Hz, J_2 = 9.7 Hz, 1H), 2.75 (dd, J_1 = 16.7 Hz, J_2 = 3.6 Hz, 1H), 2.65 (br d, J = 9.9 Hz, 1H), 2.38 (ddd, J_1 = 13.0 Hz, J_2 = 4.1 Hz, J_3 = 2.3 Hz, 1H), 2.14 (dt, J_1 = 13.0 Hz, J_2 = 5.2 Hz, 1H), 1.74 (qd, J_1 = 12.7 Hz, J_2 = 2.7 Hz, 1H), 1.60−1.10 (m, 8H), 0.89 (s, 3H), 0.82 (s, 3H), 0.76 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.2, 148.9, 146.5, 143.8, 127.9, 108.5, 106.2, 54.8, 50.9, 41.7, 39.0, 38.7, 37.2, 36.1, 33.3, 33.2, 23.7, 21.5, 19.0, 14.5 ppm; HRMS (ESI+) calcd for $C_{20}H_{28}O_2Na$ 323.1982 [M + Na^+], found 323.1982.

Diastereomeric 15,16-epoxy-12-hydroxylabda-8(17),13(16),-14-triene (13a/13b). To a solution of $LiAlH_4$ (16 mg, 0.43 mmol, 4.0 equiv) in dry THF (1.5 mL) was added dropwise a solution of ketone **12** (129 mg, 0.43 mmol, 1.0 equiv) in dry THF (3.0 mL). The reaction mixture was stirred for 30 min before being quenched with brine (2 mL). The reaction mixture was diluted with EtOAc (10 mL) and stirred for 30 min with a solution of Rochelle's salt (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude diastereomeric alcohols were used without further purification (126 mg, 97%). For the purposes of full spectroscopic characterization the two diastereomers were separated by flash column chromatography (silica gel, hexanes:EtOAc = 10:1 → 4:1, v/v).

13a (less polar diastereomer): $[\alpha]^{24}_D$ +43.3 (*c* 2.15, $CHCl_3$) [lit.[15] $[\alpha]^{24}_D$ +45.9 (*c* 0.49, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.38 (s, 1H), 6.41 (s, 1H), 4.87 (d, J = 1.3 Hz, 1H),

(19) Compound **16** is also a natural product: (a) Nakatani, N.; Kikuzaki, H.; Yamaji, H.; Yoshio, K.; Kitora, C.; Okada, K.; Padolina, W. G. *Phytochemistry* **1994**, *37*, 1383−1388. (b) Xiao, P.; Sum, C.; Zahid, M.; Ishrud, O.; Pan, Y. *Fitoterapia* **2001**, *72*, 837−838.

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

(21) De la Torre, M. C.; Garcia, I.; Sierra, M. A. *J. Org. Chem.* **2003**, *68*, 6611−6618.

4.68 (dd, $J_1 = 9.6$ Hz, $J_2 = 2.1$ Hz, 1H), 4.48 (s, 1H), 2.42 (ddd, $J_1 = 12.7$ Hz, $J_2 = 3.9$ Hz, $J_3 = 2.4$ Hz, 1H), 2.12−2.01 (m, 2H), 1.85−1.71 (m, 3H), 1.62−1.46 (m, 2H), 1.43−1.29 (m, 2H), 1.24−1.07 (m, 2H), 0.93−0.75 (m, 2H), 0.89 (s, 3H), 0.81 (s, 3H), 0.69 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 143.1, 138.4, 130.2, 108.5, 106.4, 65.2, 55.3, 52.3, 42.0, 39.2, 38.9, 38.2, 33.53, 33.50, 32.6, 24.3, 21.6, 19.3, 14.5 ppm; HRMS (ESI+) calcd for $C_{20}H_{30}O_2Na$ 325.2138 [M + Na^+], found 325.2136.

13b (more polar diastereomer): $[\alpha]^{24}_D$ +10.8 (*c* 1.35, $CHCl_3$) [lit.[15] $[\alpha]^{24}_D$ +8.50 (*c* 0.50, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.33 (s, 1H), 6.41 (d, $J = 1.0$ Hz, 1H), 4.88 (d, $J = 1.3$ Hz, 1H), 4.72 (d, $J = 1.3$ Hz, 1H), 4.70 (dd, $J_1 = 9.6$ Hz, $J_2 = 4.8$ Hz, 1H), 2.37 (ddd, $J_1 = 12.7$ Hz, $J_2 = 3.9$ Hz, $J_3 = 2.4$ Hz, 1H), 1.98−1.13 (m, 9H), 1.10 (dt, $J_1 = 13.5$ Hz, $J_2 = 3.9$ Hz, 1H), 0.97 (dd, $J_1 = 12.6$ Hz, $J_2 = 2.6$ Hz, 1H), 0.94−0.75 (m, 2H), 0.82 (s, 3H), 0.78 (s, 3H), 0.69 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 143.4, 139.6, 128.7, 108.2, 106.6, 65.9, 55.2, 52.8, 41.9, 39.4, 38.7, 38.1, 33.5, 33.4, 31.8, 24.3, 21.6, 19.3, 14.5 ppm; HRMS (ESI+) calcd for $C_{20}H_{30}O_2Na$ 325.2138 [M + Na^+], found 325.2140.

Coronarin E (4): Method A. To a preheated solution (100 °C) of the diastereomeric alcohols (126 mg, 0.42 mmol, 1.0 equiv) in toluene (8 mL) in a sealed tube was added PTSA (2 mg, 0.01 mmol, 0.024 equiv) portionwise. After $1^1/_2$ h at the same temperature the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (4 mL). The layers were separated. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford a mixture of coronarin E:$\Delta^{7,8}$-isomer = 4.5:1 (starting material, $\Delta^{8,17}$-**13**:$\Delta^{7,8}$-**13** = 14:1). Purification by column chromatography (silica gel, hexanes) afforded pure coronarin E (71 mg of $\Delta^{7,8}$-isomer, 60%).

Coronarin E (4): Method B. To a solution of PPh_3 (245 mg, 0.93 mmol, 1.5 equiv) in DCM (3.5 mL) at 0 °C was added dropwise Br_2 (48 μL, 0.93 mmol, 1.5 equiv). After a further 5 min, Et_3N (234 μL, 1.68 mmol, 2.7 equiv) was added and then the mixture was stirred for 5 min.[22] A solution of the diastereomeric alcohols **13** (188 mg, 0.62 mmol, 1.0 equiv) in CH_2Cl_2 (1.8 mL) was then added dropwise and the mixture was allowed to warm to room temperature. After 2 h the mixture was concentrated in vacuo and purified by flash column chromatography on silica gel, with hexanes−EtOAc (30:1, v/v) to afford the corresponding bromides as orange oil. A solution of these diastereomeric bromides (192 mg, 0.53 mmol) in DBU and toluene (2.5 mL, 1:4) was heated to reflux overnight. The mixture was then allowed to cool, diluted with Et_2O, and washed with brine. The layers were separated and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a mixture: coronarin E:$\Delta^{7,8}$-isomer = 12:1 (starting material, $\Delta^{8,17}$-alcohols:$\Delta^{7,8}$-alcohols = 14:1). Purification by flash column chromatography (silica gel, hexanes:EtOAc = 60:1 v/v) afforded coronarin E (101 mg, 57%, over 2 steps) as a colorless oil.

Coronarin E (4): $[\alpha]^{24}_D$ +21.6 (*c* 1.3, $CHCl_3$) [lit.[16a,23] $[\alpha]^{24}_D$ +21.3 (*c* 0.44, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.35 (s, 1H), 6.55 (s, 1H), 6.21 (d, $J = 15.7$ Hz, 1H), 5.98 (dd, $J_1 = 15.7$ Hz, $J_2 = 9.8$ Hz, 1H), 4.74 (d, $J = 1.8$ Hz, 1H), 4.54 (d, $J = 1.8$ Hz, 1H), 2.45 (qd, $J_1 = 13.5$ Hz, $J_2 = 2.1$ Hz, 1H), 2.40 (ddd, $J_1 = 9.7$ Hz, $J_2 = 4.2$ Hz, $J_3 = 2.1$ Hz, 1H), 2.13 (dt, $J_1 = 13.1$ Hz, $J_2 = 4.9$ Hz, 1H), 1.73 (qd, $J_1 = 10.3$ Hz, $J_2 = 2.7$ Hz, 1H), 1.60−1.37 (m, 5H), 1.22 (dt, $J_1 = 13.9$ Hz, $J_1 = 4.0$ Hz, 1H), 1.14 (dd, $J_1 = 12.6$ Hz, $J_2 = 2.5$ Hz, 1H), 1.06 (dt, $J_1 = 13.3$ Hz, $J_2 = 3.1$ Hz, 1H), 0.93 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 143.2, 139.6, 128.2, 124.5, 121.7, 108.0, 107.6, 61.4, 54.8, 42.3, 40.7, 39.1, 36.7, 33.55, 33.53, 23.4, 21.9, 19.1, 15.0 ppm; HRMS (ESI+) calcd for $C_{20}H_{28}ONa$ 307.2032 [M + Na^+], found 307.2032.

Chinensine A (5) and Chinensine B (6). To a stirred solution of coronarin E (**4**, 71 mg, 0.25 mmol, 1.0 equiv) in dry THF (5 mL) at −15 °C was added *n*-BuLi (1.6 M in hexane, 390 μL, 0.63 mmol, 2.5 equiv) dropwise. After 10 min of stirring at −15 °C, TMS-Cl (670 μL, 0.58 mmol, 2.3 equiv) was added and the reaction mixture allowed to warm to ambient temperature and then quenched with brine (2.0 mL). The layers were separated and the aqueous phase was extracted with Et_2O (5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The resulting crude mixture of **14** and its regioisomer **15** (**14**:**15**, 1:3) was used without further purification.

A solution of the mixture of **14** and **15** (116 mg, 0.32 mmol) in CH_2Cl_2 (8 mL) containing Methylene Blue (10^{-4} M) was placed in a test tube with oxygen bubbling gently through it. The solution was cooled to 0 °C and irradiated with a xenon 300 W lamp for 2 min after which complete transformation of the starting material was observed (based on TLC). The solvent was removed in vacuo and the liquid residue was purified by flash column chromatography (silica gel, hexanes:EtOAc = 8:1 to 2:1 v/v) to afford chinensine A (**5**, 47 mg, 60% over two steps) and chinensine B (**6**, 16 mg, 20% over two steps).

Chinensine A (5): $[\alpha]^{24}_D$ +7.88 (*c* 3.40, $CHCl_3$) [lit.[1] $[\alpha]^{24}_D$ +33.7 (*c* 0.35, $CHCl_3$)]. The optical rotation of a very pure sample of compound **5** (see ^{1}H and ^{13}C-spectrum) was measured many times; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (dd, $J_1 = 15.8$ Hz, $J_2 = 10.3$ Hz, 1H), 6.86 (br s, 1H), 6.12 (br s, 1H), 6.08 (d, $J = 15.8$ Hz, 1H), 4.75 (br s, 1H), 4.46 (br s, 1H), 4.34 (br s, −OH), 2.43 (qd, $J_1 = 13.5$ Hz, $J_2 = 1.8$ Hz, 1H), 2.38 (br d, $J = 10.1$ Hz, 1H), 2.07 (dt, $J_1 = 13.0$ Hz, $J_2 = 4.8$ Hz, 1H), 1.70 (br d, $J_1 = 13.0$ Hz, 1H), 1.56−1.13 (m, 6H), 1.08 (dd, $J_1 = 12.5$ Hz, $J_2 = 2.2$ Hz, 1H), 0.99 (br t, $J = 12.9$ Hz, 1H), 0.89 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 149.2, 140.9, 139.5, 132.4, 120.2, 108.4, 96.3, 62.2, 54.6, 42.2, 40.8, 39.3, 36.7, 33.5 (2C), 23.3, 21.9, 19.0, 15.0 ppm; HRMS (ESI+) calcd for $C_{20}H_{28}O_3Na$ 339.1931 [M + Na^+], found 339.1932.

Chinensine B (6): ^{1}H NMR (500 MHz, $CDCl_3$) δ =6.58 (br dd, $J_1 = 16.0$ Hz, $J_2 = 10.4$ Hz, 1H + 1H), 6.30 (d, $J = 16.0$ Hz, 1H + 1H), 6.26 (br s, 1H + 1H), 5.85 (s, 1H + 1H), 4.78 (s + s, 1H + 1H), 4.46 (s, 1H), 4.38 (s, 1H), 4.10 (br s, 2 × OH), 2.46 (d + d, $J = 10.4$ Hz, 1H + 1H), 2.44 (m, 1H + 1H), 2.09 (dt, $J_1 = 13.8$ Hz, $J_2 = 5.3$ Hz, 1H + 1H), 1.75−1.00 (m, 9H + 9H), 0.90 (s, 3H + 3H), 0.87 (s, 3H + 3H), 0.84 (s, 3H + 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6 (2C), 161.3 (2C), 148.9, 148.6, 144.0 (2C), 122.7 (2C), 115.4 (2C), 108.9, 108.5, 97.8 (2C), 62.1 (2C), 54.7, 54.6, 42.2 (2C), 41.0, 40.9, 39.6, 39.5, 36.6 (2C), 33.5 (4C), 23.2 (2C), 21.9 (2C), 19.0 (2C), 15.1 (2C) ppm; HRMS (ESI+) calcd for $C_{20}H_{28}O_3Na$ 339.1931 [M + Na^+], found 339.1932.

Labda-8(17),11,13-trien-15(16)-olide [*E*] (16). To a solution of chinensine A (**5**, 47 mg, 0.15 mmol, 1.0 equiv) in MeOH (1.5 mL) was added $NaBH_4$ (7.7 mg, 0.20 mmol, 1.5 equiv) at ambient temperature. After 15 min of stirring, a few drops of a solution containing concentrated H_2SO_4/MeOH (1/10, v/v) was added until the reaction mixture became clear. After being stirred for 1 min more the mixture was diluted with EtOAc (6 mL) and washed with brine. The layers were separated and the aqueous phase was extracted with EtOAc (3 × 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude lactone **16** was used without further purification (41 mg, 92%).

16: $[\alpha]^{24}_D$ +15.5 (*c* 2.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (br s, 1H), 6.89 (dd, $J_1 = 15.8$ Hz, $J_2 = 10.2$ Hz, 1H), 6.11 (d, $J = 15.8$ Hz, 1H), 4.80 (br s, 2H), 4.76 (d, $J = 1.5$ Hz, 1H), 4.50 (d, $J = 1.5$ Hz, 1H), 2.44 (ddd, $J_1 = 13.5$ Hz, $J_2 = 4.2$ Hz, $J_3 = 2.2$ Hz, 1H), 2.37 (br d, $J = 10.0$ Hz, 1H), 2.08 (m, 1H), 1.74−1.35 (m, 6H), 1.18 (dt, $J_1 = 13.6$ Hz, $J_2 = 3.5$ Hz, 1H), 1.09 (dd, $J_1 = 12.5$ Hz, $J_2 = 2.7$ Hz, 1H), 1.00 (br t, $J_1 = 13.6$ Hz, 1H), 0.89 (s, 3H), 0.87 (s, 3H), 0.83 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 149.3, 142.4, 136.8, 129.4, 120.6, 108.4, 69.6,

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62.1, 54.7, 42.2, 40.8, 39.2, 36.7, 33.5 (2C), 23.3, 21.9, 19.0, 15.0 ppm; HRMS (ESI+) calcd for $C_{20}H_{28}O_2Na$ 323.1982 [M + Na^+], found 323.1983.

Chinensine C (7). To a solution of **16** (41 mg, 0.14 mmol, 1.0 equiv) in dry CH_2Cl_2 (1 mL) at −78 °C was added dropwise Dibal-H (1.0 M in hexane, 246 μL, 0.25 mmol, 1.8 equiv) over a period of 15 min.[24] The reaction was stirred for a further 30 min at −78 °C and quenched at the same temperature by adding MeOH (1.5 mL). The homogeneous mixture was allowed to warm to room temperature over a period of 1 h until a white precipitate appeared. The cloudy solution was filtered through a pad of celite that was washed copiously with Et_2O. The filtrate was concentrated under reduced pressure to give the crude diastereomeric lactols **7** in 1:1 ratio (40 mg, 96%), which were used directly in the next step.

Chinensine C (7): $[\alpha]^{24}_D$ +24.2 (*c* 2.0, CHCl3) [lit.[1] $[\alpha]^{24}_D$ +17.6 (*c* 0.23, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18−6.04 (m, 6H, 3H for each diastereomer), 5.91 (br s, 2H, 1H for each diastereomer), 4.80 (d, J = 15.0 Hz, 2H, 1H for each diastereomer), 4.75 (br s, 2H, 1H for each diastereomer), 4.57 (d, J = 15.0 Hz, 2H, 1H for each diastereomer), 4.51 (d, J = 1.6 Hz, 1H), 4.45 (d, J = 1.6 Hz, 1H), 2.68 (m, 2H, 1H for each diastereomer), 2.44 (br d, J = 11.7 Hz, 2H, 1H for each diastereomer), 2.34 (br d, J = 9.2 Hz, 2H, 1H for each diastereomer), 2.07 (m, 4H, 2H for each diastereomer), 1.75−1.33 (m, 10H, 5H for each diastereomer), 1.18 (br t, J = 13.3 Hz, 2H, 1H for each diastereomer), 1.09 (br d, J = 12.5 Hz, 2H, 1H for each diastereomer), 1.00 (br t, J = 11.8 Hz, 2H, 1H for each diastereomer), 0.89 (br s, 6H, 3H for each diastereomer), 0.833 (br s, 6H, 3H for each diastereomer), 0.827 (s, 3H), 0.82 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 149.7, 138.90, 138.86, 133.6, 133.4, 125.4, 125.3, 123.7, 123.6, 108.3, 108.0, 102.7, 102.6, 73.56, 73.55, 61.81, 61.78, 54.7 (2C), 42.3 (2C), 40.83, 40.80, 39.2, 39.1, 36.7 (2C), 33.55 (2C), 33.54 (2C), 23.3 (2C), 21.9 (2C), 19.11, 19.09, 15.0 (2C) ppm; HRMS (ESI+) calcd for $C_{20}H_{28}O_2Na$ 323.1982 [M − 2 + Na^+], found 323.1984.

Chinensines D and E (8 and 9). A solution of lactols **7** (40 mg, 0.13 mmol) in CH_2Cl_2 (4 mL) containing Methylene Blue (10^{-4} M) was placed in a test tube with O_2 gently bubbling through it. The solution was cooled to 0 °C and irradiated with a xenon 300 W lamp for ca. 20 min after which time complete consumption of the starting material was observed by ^{1}H NMR. The solvent was removed in vacuo and the residue was purified by flash column chromatography (silica gel, hexanes:EtOAc = 6:1 to 2:1 v/v) to afford the inseparable diastereomeric endoperoxides (27 mg, 60%, major diastereomer:minor diastereomer = 1.3:1).

Chinensines D and E (8 and 9): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (s, 1H major), 9.50 (s, 1H minor), 7.23 (t, J = 1.4 Hz, 1H major), 6.94 (t, J = 1.4 Hz, 1H minor), 5.39 (t, J = 1.7 Hz, 1H minor), 5.33 (d, J = 5.5 Hz 1H major), 4.99 (br s, 1H major), 4.81 (s + s, 1H major + 1H minor), 4.74 (m, 1H major + 1H minor), 4.65 (s, 1H minor), 3.93 (m, 2H major + 2H minor), 2.41 (m, 1H major), 2.33 (m, 1H minor), 2.25−1.07 (m, 12H major + 12H minor), 0.97 (s, 3H minor), 0.95 (s, 3H major), 0.88 (s, 3H minor), 0.87 (s, 3H major), 0.84 (s, 3H minor), 0.82 (s, 3H major) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 190.2, 152.78, 152.73, 147.0, 144.4, 137.2, 136.8, 110.7, 109.4, 80.0, 79.3, 79.0, 78.6, 62.8, 62.3, 62.2, 59.5, 55.8, 55.6, 42.0, 41.9, 41.5, 41.0, 40.0, 39.0, 38.1 (2C), 33.8, 33.7 (2C), 33.6, 24.1, 24.0, 21.7, 21.6, 19.2, 19.2, 16.9, 16.4 ppm; HRMS (ESI+) calcd for $C_{20}H_{30}O_4Na$ 357.2036 [M + Na^+], found 357.2037.

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

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