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Dimerization of Butenolide Structures. A Biomimetic Approach to the Dimeric Sesquiterpene Lactones (±)-Biatractylolide and (±)-Biepiasterolide

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The biomimetic synthesis of the bisesquiterpene lactones (±)-biatractylolide **1** and (±)-biepiasterolide **2** via dimerization of the captodative stabilized radical **8** is reported. Atractylon **7** has also been shown to be a possible intermediate during the biosynthesis of biatractylolide **1**, biepiasterolide **2**, atractylolide **3**, and hydroxyatractylolide **4**.

As part of our work on the biomimetic synthesis of bisesquiterpene lactones, we have recently described the total synthesis of biatractylolide and biepiasterolide through biomimetic radical dimerizations.[1] We now report further studies on these biomimetic transformations that shed new light on the proposed biosynthesis of these very interesting compounds.

Biatractylolide **1** and biepiasterolide **2** are novel bisesquiterpene lactones that have been isolated from the Chinese medicinal plant *Atractylodes macrocephala*.[2−4] Biologically, biatractylolide **1** is a potential blood pressure lowering agent,[5] with significant negative inotropic and chronotropic effects.

The structure of biatractylolide **1** has been elucidated by X-ray analysis, while that of biepiasterolide **2** has been determined by extensive NMR studies.[2−4] Both compounds have been shown to be dimeric bisesquiterpenoids joined at the C8−C8a bridgehead positions. The structural similarity of **1** and **2** with the naturally occurring sesquiterpene lactones atractylolide **3** and hydroxyatractylolide **4** has prompted speculation about the biosynthetic origin of biatractylolide **1** and biepiasterolide **2**. Atractylolide **3** and hydroxyatractylolide **4**, together with the closely related sesquiterpenes peroxyatractylolide **5**, atractylenolide **6**, and atractylon **7**, are naturally occurring constituents of *A. macrocephala* (Figure 1).[6]

Our proposal for the biomimetic synthesis of both biatractylolide **1** and biepiasterolide **2** involved the fusion of two units of atractylolide **3** or hydroxyatractylolide **4** through a key dimerization step that takes place via the captodative stabilized radical **8**[7] (or its equivalent).[8] Moreover, atractylolides **3** and **4** could emanate in vivo from atractylon **7**, given that Hikino has reported the aerial autoxidation of atractylon **7** into atractylolides **3** and **4** (Scheme 1).[9]

As a model system, we originally explored the dimerization aptitude of the model butenolide **12**, which incorporated critical features of atractylolide **3**. Butenolide **12** was efficiently synthesized through minor modification of the method of Minato and Nagasaki.[10] Pyrrolidine enamine **9** was initially alkylated to produce ester **10**, followed by hydrolysis to give crude acid **11** and cyclization to afford butenolide **12** in reasonable yield (Scheme 2).

After initial failed attempts to dimerize butenolide **12**,[1] di-*tert*-butyl peroxide (DTBP) was considered as a likely dimerization agent. DTBP has been shown to be an effective model for reactive radicals that promote hydrogen atom abstraction reactions in biological systems[11] and is known to effect dehydrodimerizations of alcohols, amides, polyhaloalkanes, esters, and ethers.[12] Finally,

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(1) (a) Bagal, S. K.; Adlington, R. M.; Marquez, R.; Baldwin, J. E.; Cowley, A. *Tetrahedron Lett*. **2003**, *44*, 4993. (b) Bagal, S. K.; Adlington, R. M.; Marquez, R.; Baldwin, J. E.; Cowley, A. *Org. Lett*. **2003**, *5*, 3049.

(2) Lin, Y.; Jin, T.; Wu, X.; Huang, Z.; Fan, J. *J. Nat. Prod*. **1997**, *60*, 27.

(3) Wang, B. D.; Yu, Y. H.; Teng, N. N.; Jiang, S. H.; Zhu, D. Y. *Huaxue Xuebao* **1999**, *57*, 1022.

(4) Huang, Z.; Lin, Y.; Liu, S.; Chan, W. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1999**, *38B*, 106. Note: In this article, the absolute stereochemistry at the C5 (C5a) center of the *trans*-C5 (C5a)−C10 (C10a) fused decalin ring system appears incorrectly assigned (according to the CIP system nomenclature) and should be 5*R* (5a*R*).

(5) Pu, H. L.; Wang, Z. L.; Huang, Q. J.; Xu, S. B.; Lin, Y. C.; Wu, X. Y. *Zhongguo Yaolixue Tongbao* **2000**, *16*, 60.

(6) (a) Wang, Y. S.; Chang, J. C.; Li, K. K.; Wu, C. H.; Tin, K.; Liu, Y. H. *Shaanxi Xinyiyao* **1980**, *9*, 47. (b) Zhang, Q. F.; Luo, S. D.; Wang, H. Y. *Chin. Chem. Lett.* **1998**, *9*, 1097. (c) Chen, Z. *Planta Med.* **1987**, *53*, 493.

(7) Janousek, Z.; Merenyi, R.; Viehe, H. G. *Acc. Chem. Res.* **1985**, *18*, 148.

(8) For example, a pinacol-type dimerization of a keto form of **4** followed by bislactonization.

(9) (a) Hikino, H.; Hikino, Y.; Yosioka, I. *Chem. Pharm. Bull*. **1964**, *12*, 755. (b) Hikino, H.; Hikino, Y.; Yosioka, I. *Chem. Pharm. Bull*. **1962**, *10*, 641.

(10) (a) Minato, H.; Nagasaki, T. *J. Chem. Soc. C* **1966**, 1866. (b) Minato, H.; Nagasaki, T. *J. Chem. Soc. C* **1966**, 377.

(11) Tanko, J. M.; Friedline, R.; Suleman, N. K.; Castagnoli, N. *J. Am. Chem. Soc*. **2001**, *123*, 5808.

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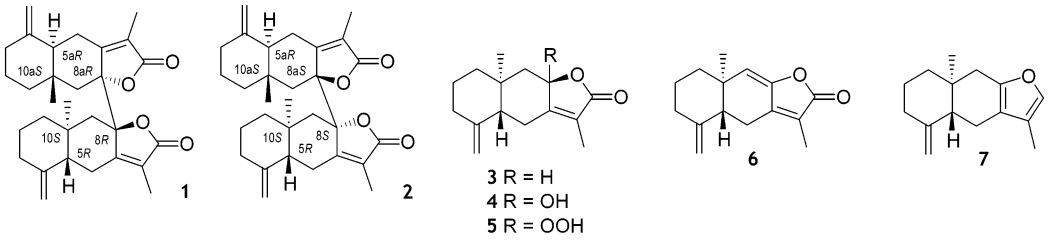
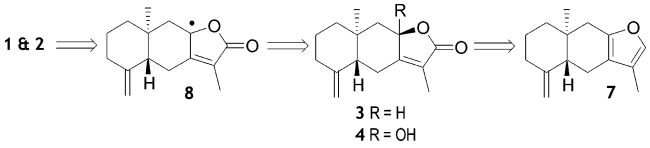
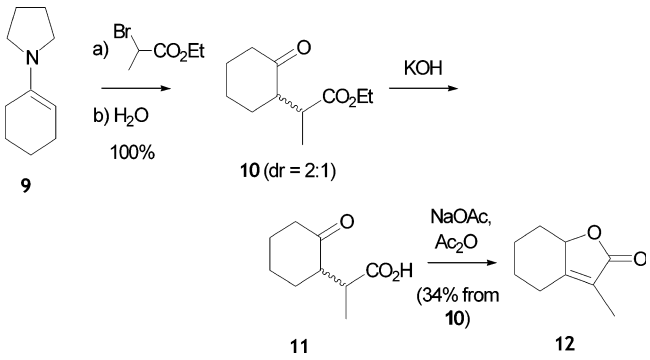


FIGURE 1. (+)-Biatractylolide **1**, biepiasterolide **2**, (+)-atractylolide **3**, (+)-hydroxyatractylolide **4**, (+)-peroxyatractylolide **5**, (+)-atractylenolide **6**, and (+)-atractylon **7**.

SCHEME 1. Biosynthetic Proposal for Biatractylolide 1 and Biepiasterolide 2



SCHEME 2



after extensive experimentation including the use of photochemical conditions,[13] an oxygen-free mixture of butenolide **12**, acetone, and DTBP (0.5 equiv) in a sealed tube at 140 °C afforded the desired dimers **14a** and **14b**, in an isolated yield of 34%. The dimerization presumably takes place through the captodative stabilized radical **13** (Scheme 3).

Model dimer **14** was obtained as a mixture of two diastereomers in a 6:1 ratio (as determined by NMR integration),[14] with the major diastereomer **14a** (*dl)* being separable by recrystallization from a 20% mixture of EtOAc in Et_2O. Although DTBP was a successful dimerization agent for butenolide **12**, the reaction yield could not be further optimized. At this point, we began exploring the possibility of dimerizing a halolactone, **15**, using metals and metal salts that have been shown to couple allylic and benzylic halides (Scheme 3).

Based on literature precedent,[15] the synthesis of halolactone **15** began with the reduction of lactone **12** followed by silylation of the resulting furan **16** to afford silylfuran **17** in reasonable yield (25%). The desired chloro lactone **19** was then generated in good overall yield by efficiently oxidizing silylfuran **17** with singlet oxygen to afford hydroxybutenolide **18**, which was then halogenated with excess thionyl chloride (Scheme 4).

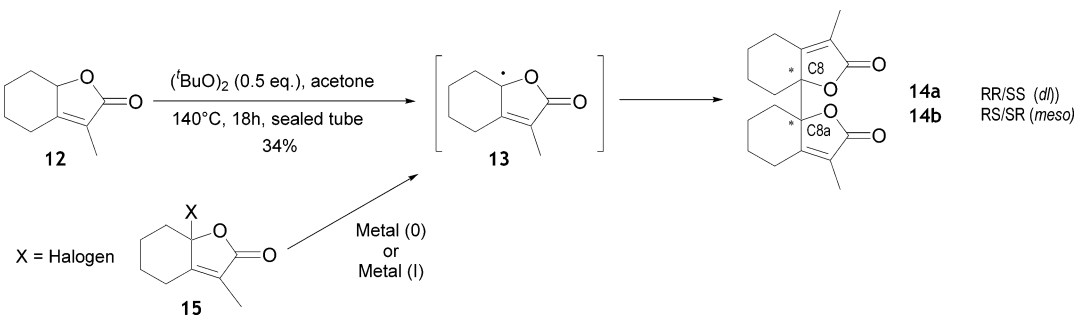
Unfortunately, zinc, copper bronze, or activated copper bronze (Vogel's method)[16] failed to dimerize chloro lactone **19** in higher than 2% yield. However, freshly prepared $Co(PPh_3)_3Cl$[17] afforded the dimerized adduct **14** at room temperature and in good yield (57%) through the general method of Yamada.[18] Diastereomers **14a** (*dl*) and **14b** (*meso*) were produced in a ratio greater than 98:2, respectively, and could be separated by crystallization (Scheme 5 and Table 1).[14]

The relative stereochemistry at both C8 and C8a in the major diastereomer *dl*-bis-butenolide **14a** was unequivocally shown to be the same as that which is characteristic of biatractylolide **1** and biepiasterolide **2** by X-ray analysis. Furthermore, the X-ray structure indicated that the C8−C8a bond is the longest in the molecule at 1.57 Å, which compares favorably with the corresponding bond length reported for biatractylolide **1** (1.59 Å; Figure 2).[4]

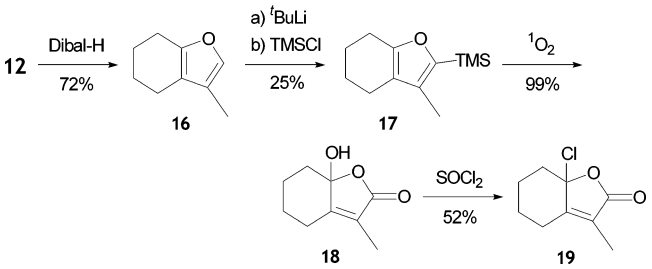
Upon completion of the dimerization studies of the model system, we began the synthesis of the complete monomer unit atractylolide **3** based on the work of Minato and Nagasaki.[10] Thus, reduction of the commercially available tetralone **20** to alcohol **21** proceeded cleanly over two steps. Enol ether **21** was then converted to ketone **22** by Oppenauer oxidation followed by cuprate addition and subsequent fluoride-mediated desilylation of the TMS enol ether intermediate. Finally, the ketone **23**[19] was generated by Wittig olefination and methyl ether hydrolysis (Scheme 6).

Alkylation of ketone **23** then afforded the keto ester **24** as a mixture of diastereomers through the corre-

SCHEME 3. Dimerization of Model Butenolide 12



SCHEME 4



SCHEME 5. Cobalt-Mediated Dimerization of Chloro Lactone 19

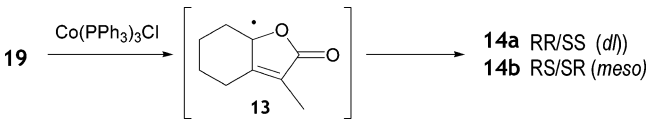


TABLE 1. Metal-Mediated Dimerization of Chloro Lactone 19 To Generate Dimer 14

coupling agent	temperature (°C)	reaction time (h)	solvent	yield of **14** (%)
copper	90−100	1	benzene	2
activated copper	90−100	1	benzene	2
zinc	20−25	24	EtOAc	no reaction
$Co(PPh_3)_3Cl$	20−25	2	benzene	57

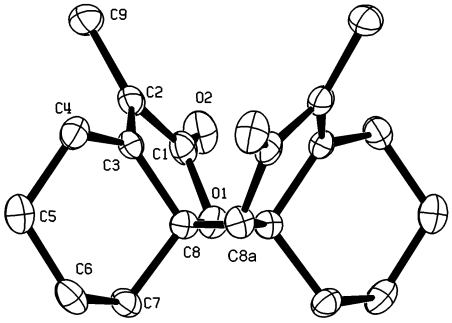


FIGURE 2. X-ray crystal structure of (±)-**14a**.

sponding pyrrolidine enamine. The target monomer atractylolide **3** was easily obtained in good yield by ester hydrolysis followed by lactonization of the corresponding keto acid **25**.

Regrettably, none of the desired dimers **1** and **2** were produced when atractylolide **3** was treated with our previously optimized thermal DTBP reaction conditions (0.5 equiv of DTBP, acetone, 140 °C, 18 h).[1] Use of stronger reaction conditions (0.5−2.0 equiv of DTBP, acetone, 120−170 °C, 18 h), however, afforded polymeric material, with the amount of polymeric material formed increasing as the severity of the conditions increased. We originally attributed the lack of dimerization to the increased functionality present in atractylolide **3** compared to that in the model system **12** (i.e., the axial methyl group and the exocyclic double bond). However, removal of the exocyclic double bond through hydrogenation generated butenolide **26**[9] as a mixture of diastereomers, which under the DTBP dimerization conditions failed to dimerize (Scheme 7).

Based upon these results, a possible explanation for the observed lack of DTBP-mediated dimerization is that the steric hindrance between the $^tBuO^\bullet$ radical (or possibly $Me^\bullet$ radical) conducting the hydrogen atom abstraction and the axial methyl group precludes the key abstraction (radical generation) process. These results corroborate the work of Tanko, in which he reports that $^tBuO^\bullet$ radicals require a relatively ordered transition state during hydrogen abstraction.[11] Thus, it is feasible that the hindrance caused by the axial methyl group disrupts the trajectory of approach of the $^tBuO^\bullet$ radical to atractylolide **3** so that the "ordered transition state" necessary for hydrogen atom abstraction is not possible (Figure 3).

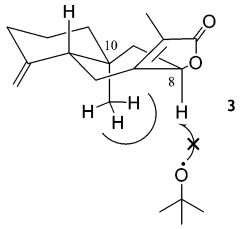
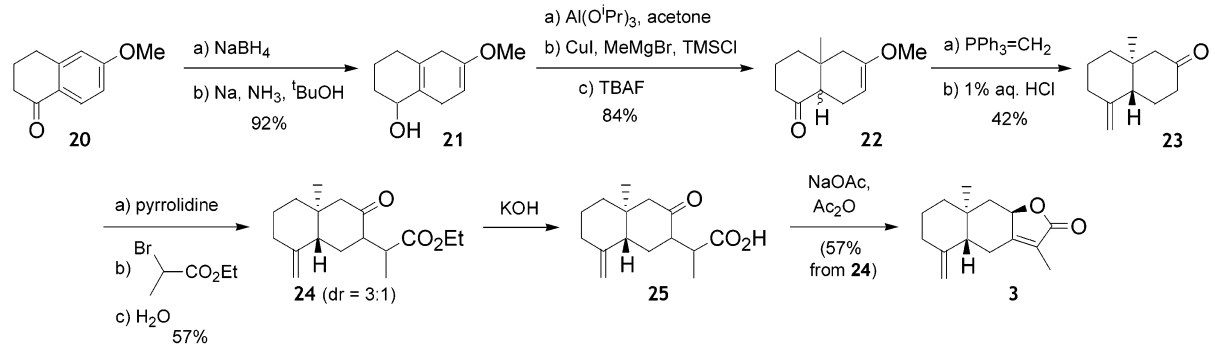


FIGURE 3. Proposed inhibition of hydrogen atom abstraction.

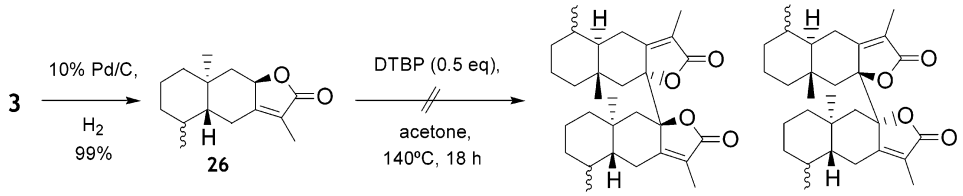
At this junction, our synthetic approach switched to our other promising model dimerization study,[1] in which radical **8** could be accessed from hydroxyatractylolide **4** via the corresponding chloroatractylolide **27** (Scheme 8).

Because the conversion of model butenolide **12** to hydroxybutenolide **18** by conventional methods required a four-step sequence together with a tedious chromatographic purification of silylfuran **17** from parent furan **16** (Scheme 4), a more efficient method to generate hydroxyatractylolide **4** was sought. To this end, atractylolide **3** was first transformed into silyloxy furan **28**,[20] which was then cautiously oxidized to afford the

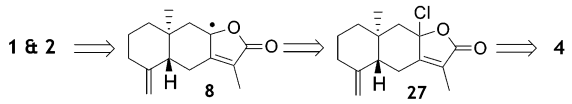
SCHEME 6



SCHEME 7



SCHEME 8. Proposed Synthesis of 1 and 2 from Hydroxyatractylolide 4



naturally occurring sesquiterpene hydroxyatractylolide **4** (Scheme 9).[6a]

The structure of hydroxyatractylolide **4** was corroborated by X-ray crystallography, which indicated that the hydroxyl group is located in an axial position (Figure 4).[21] This assignment is in agreement with the observations of Hikino et al.,[9] in which hydroxyatractylolide **4** was concluded to possess a 1,3-diaxial relationship between the angular methyl group and the hydroxyl group (Scheme 9), and presumably arises because of the equatorial attack of the carboxyl oxygen onto the ketone functionality.

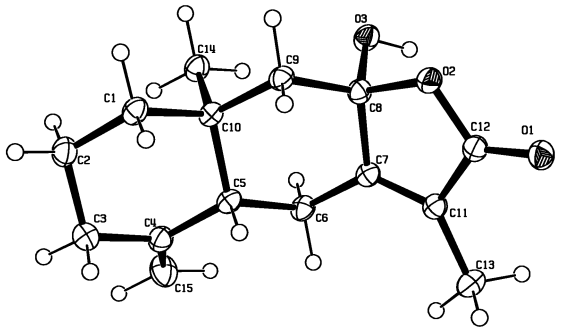


FIGURE 4. X-ray analysis of (±)-hydroxyatractylolide **4**.

Chloroatractylolide **27** could not be obtained from hydroxyatractylolide **4** under our previous halogenation conditions ($SOCl_2$, CH_2Cl_2, rt, 18 h),[1] although the natural product atractylenolide **6** was produced (most likely through an E1 mechanism). Interestingly, hydroxyatractylolide **4** was regenerated in good yields by stirring atractylenolide **6** with an aqueous base (Scheme 10). It is mechanistically plausible that this conversion involves nucleophilic attack by a hydroxide ion to open the lactone ring of butenolide **6**, thereby generating an enol, which can be transformed into the corresponding hydroxy lactone **4** via a keto acid intermediate.

Suitable halogenation conditions capable of generating the desired chloroatractylolide **27** in good yield (ca. 50%) were eventually developed by the addition of pyridine and operation at low temperature (−78 °C). However, unlike chloro lactone **19**, chloroatractylolide **27** could not be purified by flash chromatography because this led to the elimination of HCl. The most efficient chlorination of hydroxyatractylolide **4** generated a mixture of chloroatractylolide **27** and atractylenolide **6** in a 3:1 ratio, respectively (as determined by NMR integration). This inseparable mixture was then used in the subsequent coupling step without further purification. The stereochemistry of the newly introduced chlorine on the face opposite of the C-methyl group is based upon an S_N2-like attack from the less-hindered face of activated butenolide **4** (Scheme 11).

The critical dimerization step was then attempted by treating chloroatractylolide **27** with our previously developed dimerization conditions [$Co(PPh_3)_3Cl$, PhH, rt, 2 h].[1] This process proceeded cleanly to generate three dimeric adducts from which (±)-biatractylolide **1**, (±)-

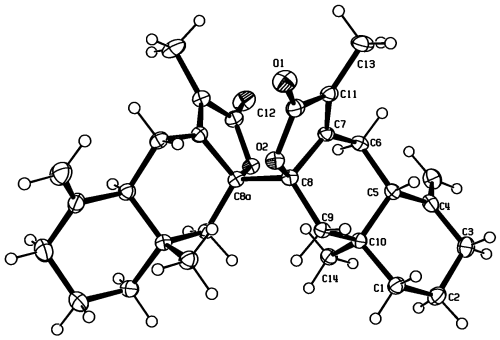
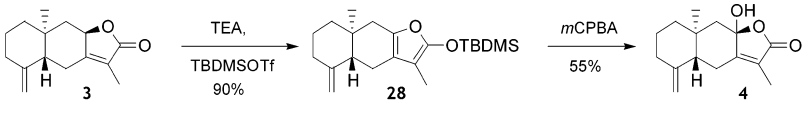


FIGURE 5. X-ray analysis of (±)-biatractylolide **1**.

biepiasterolide **2**, and another diastereoisomer (±)-**29** were isolated (Scheme 11).[22,23] The structures of synthetic (±)-biatractylolide **1** and (±)-biepiasterolide **2** were first

SCHEME 9



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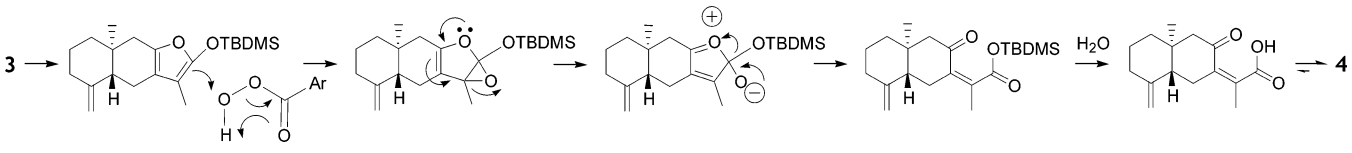
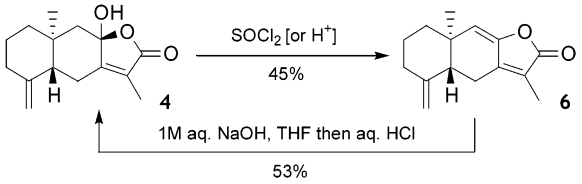


TABLE 2. Comparison of ^{1}H and ^{13}C NMR Data from Synthetic (±)-1 and (±)-2 with the Literature Data[2,3]

position	literature (+)-**1**[a] ^{1}H; ^{13}C (ppm)	synthetic (±)-**1**[b] ^{1}H; ^{13}C (ppm)	literature **2**[c] ^{1}H; ^{13}C (ppm)	synthetic (±)-**2**[b] ^{1}H; ^{13}C (ppm)
1	1.23 (1H, ddd), 1.61 (1H, m);[d] 42.5	1.22 (1H, td), 1.59−1.61 (1H, m); 42.1	1.40−1.65 (2H, m); 42.3	1.38−1.50 (1H, m), 1.53−1.59 (1H, m); 42.2
2	1.65 (2H, m);[d] 22.3	1.63−1.65 (2H, m); 22.3	1.40−1.65 (2H, m); 22.9	1.38−1.50 (1H, m), 1.60−1.66 (1H, m); 22.8
3	1.94 (1H, br q), 2.35 (1H, br d); 35.8	1.90−1.99 (1H, m), 2.35 (1H, br d); 35.8	2.08 (1H, ddm), 2.34 (1H, dm); 36.7	2.05−2.13 (1H, m), 2.37 (1H, dm); 36.8
4	147.8	147.9	148.2	148.1
5	1.72 (1H, dd); 52.7	1.71−1.75 (1H, m); 52.9	2.81 (1H, dd); 42.8	2.82 (1H, dd); 42.7
6	2.65 (1H, dd), 2.72 (1H, t); 27.8	2.65 (1H, dd), 2.78 (1H, t); 27.9	2.18 (1H, ddq), 2.63 (1H, dd); 24.9	2.19 (1H, ddd), 2.65 (1H, dd); 24.8
7	164.3	164.5	163.4	163.3
8	89.2	89.3	89.3	89.3
9	1.42 (1H, d), 2.82 (1H, d); 49.6	1.42 (1H, d), 2.82 (1H, d); 49.7	2.00 (1H, d), 2.31 (1H, d); 47.2	2.01 (1H, d), 2.32 (1H, d); 47.0
10	36.9	36.9	36.9	36.6
11	124.3	124.4	125.5	125.4
12	171.7	172.0	172.7	172.6
13	1.75 (3H, s); 8.3	1.75 (3H, s); 8.4	1.77 (3H, d); 8.7	1.79 (3H, d); 8.6
14	1.13 (3H, s); 17.1	1.13 (3H, s); 17.1	0.49 (3H, s); 19.1	0.50 (3H, s); 19.0
15	4.65 (1H, br s), 4.86 (1H, br s); 107.2	4.65 (1H, s), 4.86 (1H, s); 107.3	4.62 (1H, d), 4.86 (1H, d); 107.2	4.64 (1H, s), 4.87 (1H, s); 107.1

[a] NMR spectra were recorded in $CDCl_3$ at 400 MHz (^{1}H) and 22.5 MHz (^{13}C). [b] NMR spectra were recorded in $CDCl_3$ at 500 MHz (^{1}H) and 125.7 MHz (^{13}C). [c] NMR spectra were recorded in $CDCl_3$ at 400 MHz (^{1}H) and 100.6 MHz (^{13}C). [d] Overlapping.

SCHEME 10



corroborated by comparison of the NMR data to the reported literature data (Table 2)[2,3] and then unambiguously assigned using HRMS and X-ray spectroscopy (Figures 5 and 6).[21]

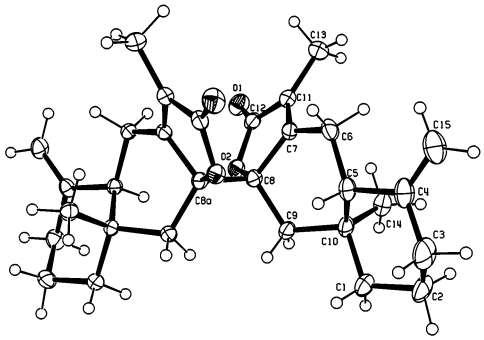


FIGURE 6. X-ray analysis of (±)-biepiasterolide **2**.

Furthermore, 1- and 2-D NMR analysis and HRMS suggest that the remaining diastereoisomer (±)-**29** was the 5R,10S,8R-8aR,10aR,5aS isomer (plus its enantiomer). This was confirmed by X-ray spectroscopy (Figure 7; see the Supporting Information). Attempts to optimize

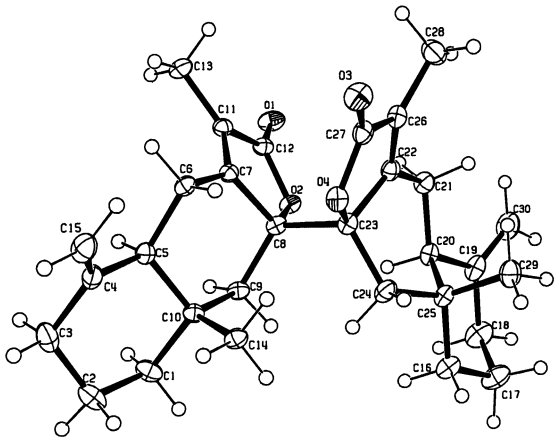
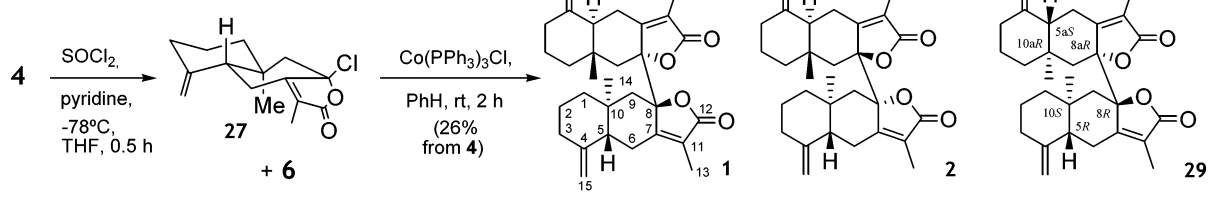


FIGURE 7. X-ray analysis of (±)-dimer **29** with crystallographic numbering system.

the dimerization yield by in situ conversion of chloroatractylolide **27** into the corresponding iodoatractylolide failed to improve the dimerization yield and product distribution.

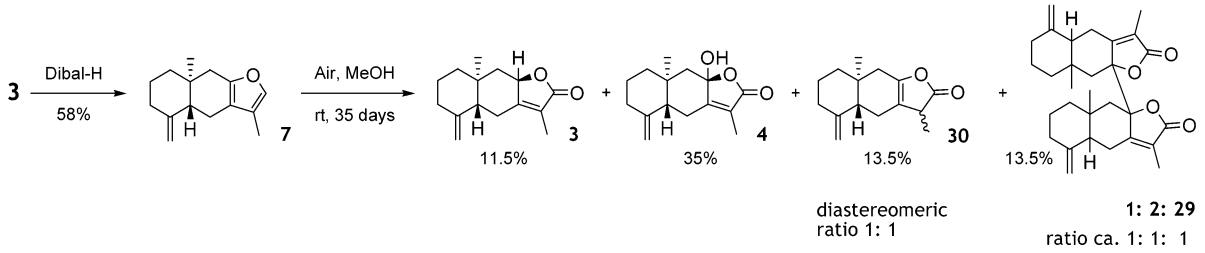
The high diastereoselectivity observed during the C8−C8a bond formation [*dl* ≫ *meso*] in the model dimeriza-

SCHEME 11[23]



Product Ratio: (±)-**1** : (±)-**2** : (±)-**29**
1 : 3 : 4

SCHEME 12[24]



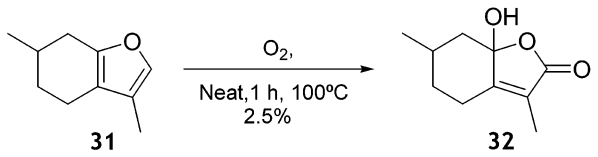
tion to bis-butenolide **14** through either the DTBP (Scheme 3) or $Co(PPh_3)_3Cl$ (Scheme 5) method does not have an obvious origin. However, it should be noted that an analogous high diastereoselectivity during C8−C8a bond formation in the real system was likewise observed, because (±)-**1**, (±)-**2**, and (±)-**29** all constitute "*dl*" forms (Scheme 11).

Once having successfully completed the total synthesis of both biatractylolide **1** and biepiasterolide **2** through cobalt-mediated radical dimerizations, we decided to expand our butenolide dimerization investigation studies in order to be able to include a fresh look at the aerial autoxidation studies of Hikino and co-workers.[9] In his work, Hikino demonstrated that atractylon **7** undergoes aerial autoxidation when allowed to stand in the presence of air and methanol to generate atractylolide **3** and hydroxyatractylolide **4**. It is possible to speculate that the observed aerial autoxidation might itself proceed via a radical intermediate because triplet dioxygen is a diradical species. The radical intermediate formed could then be capable of dimerization. Hence, the aerial autoxidation of atractylon **7** might play a more crucial role in the biosynthesis of biatractylolide **1** and biepiasterolide **2** than originally proposed.

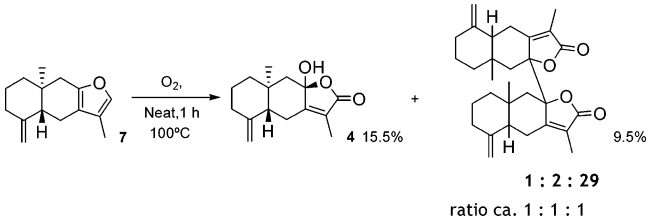
Atractylon **7** was efficiently generated by reduction of atractylolide **3** and then subjected to Hikino's aerial autoxidation conditions.[9] Oxidation of a methanolic solution of atractylon **7** in an open flask at room temperature for 35 days afforded a mixture of products from which atractylolide **3**, hydroxyatractylolide **4**, the novel butenolide **30**, and all three dimers (±)-**1**, (±)-**2**, and (±)-**29**, were isolated (Scheme 12).[22,24]

Woodward and co-workers had also previously reported oxygen-mediated furan oxidations, albeit under considerably more forceful conditions.[25] In their oxidation procedure, neat menthofuran **31** was converted to hydroxybutenolide **32** in low yield in an oxygen atmosphere at 100 °C (Scheme 13). Although these conditions were significantly different from those employed in Hikino's studies, we felt that they might provide us with further insight into the biosynthetic pathway of the observed dimerizations.

SCHEME 13



SCHEME 14[24]



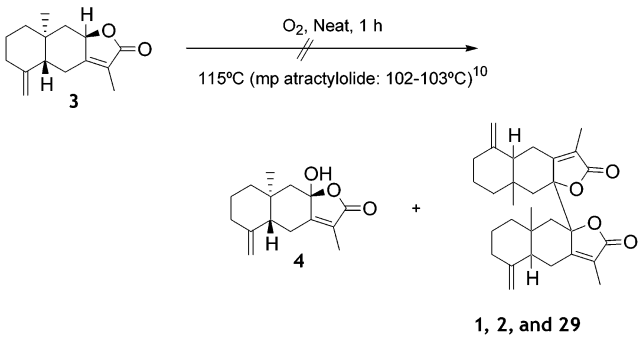
Interestingly, treatment of atractylon **7** under Woodward's conditions generated hydroxyatractylolide **4**, as well as dimerization adducts **1**, **2**, and **29** in reasonable yield.[22] However, atractylolide **3** and its isomer **30** were never detected in the reaction mixture (Scheme 14).

Modification of the reaction conditions (i.e., through the use of *tert*-butyl alcohol as a solvent combined with a slight decrease of the reaction temperature to 80 °C for 1 h) increased the yields of both hydroxyatractylolide **4** (27%) and the dimerization products **1**, **2**, and **29** (12%, diastereomeric ratio ca. 1:1:1),[22,24] while once again failing to produce any atractylolide **3** or isomer **30**.

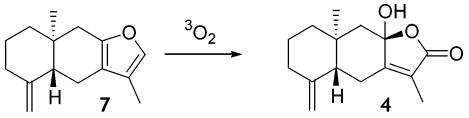
In a separate experiment, treatment of atractylolide **3** under the original Woodward[25] reaction conditions as a

(12) Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: Chichester, U.K., 1995; Vol. 3, p 1616.
(13) (a) Knowles, H. S.; Hunt, K.; Parsons, A. F. *Tetrahedron* **2001**, *57*, 8115. (b) Beaujean, M.; Mignani, S.; Merényi, R.; Jancusek, Z.; Viehe, H. G.; Kirch, M.; Lehn, J. M. *Tetrahedron* **1984**, *40*, 4395.
(14) The diastereomeric ratio was determined by NMR analysis conducted after a two-phase workup and careful purification by flash chromatography.
(15) (a) Wu, H. J.; Yen, C. H.; Chuang, C. T. *J. Org. Chem*. **1998**, *63*, 5064. (b) Shikari, R.; Tadano, K.; Ogawa, S. *J. Org. Chem*. **1996**, *61*, 2845. (c) Röhrig, S.; Hennig, L.; Findeisen, M.; Welzel, P. *Tetrahedron* **1998**, *54*, 3439.
(16) Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Wiley: New York, 1989; p 426.
(17) Aresta, M.; Rossi, M.; Sacco, A. *Inorg. Chim. Acta* **1969**, *3*, 227.
(18)) (a) Yamada, Y.; Momose, D.; Iguchi, K.; Sugiyama, T. *Tetrahedron Lett.* **1983**, *24*, 921. (b) Yamada, Y.; Momose, D. *Chem. Lett.* **1981**, 1277. (c) Yamada, Y.; Momose, D.; Iguchi, K.; Sugiyama, T. *Chem. Pharm. Bull.* 1984, *32*, 1840.
(19) Miller, R. B.; Nash, R. D. *J. Org. Chem.* **1973**, *38*, 4424.
(20) (a) Jefford, C. W.; Sledeski, A. W.; Rossier, J.; Boukouvalas, J. *Tetrahedron Lett*. **1990**, *31*, 5741. (b) Maltais, F.; Lachance, N.; Boukouvalas, J. *Tetrahedron Lett.* **1994**, *35*, 7897.
(21) The atomic coordinates for **4** (deposition number CCDC 235995), **1** (deposition number CCDC 207880), **2** (deposition number CCDC 207879), and **29** (deposition number CCDC 254587) are available upon request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K. The crystallographic numbering system differs from that used in the test; therefore, any request should be accompanied by the full literature citation of this paper.
(22) The dimer diastereomeric ratios were determined after careful purification by flash chromatography and preparative TLC by NMR analysis. Likewise, the diastereomeric ratio of butenolide **30** was determined by NMR analysis after purification.
(23) Yields quoted are based upon recovered hydroxyatractylolide **4**.
(24) Yields quoted are based upon recovered atractylon **7**.
(25) Woodward, R. B.; Eastman, R. H. *J. Am. Chem. Soc*. **1950**, *72*, 399.

SCHEME 15



SCHEME 16. Formal Dioxygen Addition to Atractylon 7 To Generate Hydroxyatractylolide 4



control failed to generate either the hydroxyatractylolide **4** or any of the dimeric structures **1**, **2**, and **29** and led only to the recovery of unreacted atractylolide **3** (Scheme 15).

Similarly, treatment of hydroxyatractylolide **4** under Hikino's conditions (open to air, methanol, rt, 35 days)[9] as a control failed to generate any of the dimeric structures **1**, **2**, and **29** and led only to the recovery of unreacted hydroxyatractylolide **4**.

By considering these results together, it is possible to form the following tentative conclusions regarding the synthesis of this family of terpenes:

1. Atractylolide **3** and hydroxyatractylolide **4** are unlikely to be direct biosynthetic precursors of biatractylolide **1** and biepiasterolide **2**.

2. Biatractylolide **1**, biepiasterolide **2**, atractylolide **3**, hydroxyatractylolide **4**, dimer **29**, and the novel butenolide **30** are all likely to be autoxidation products of atractylon **7** generated by the oxidation of atractylon **7** to higher oxidation levels. The degree of oxidation can vary, and the product formed depends on the oxidation level that atractylon **7** is promoted to. Each oxidation level leads to different oxidation products.

3. Hydroxyatractylolide **4** is likely to be an autoxidation product of atractylon **7** derived from formal dioxygen addition (Scheme 16).

4. Atractylolide **3** and the novel butenolide **30** are likely to be autoxidation products of atractylon **7** derived formally from oxygen atom addition (Scheme 17).

5. If the autoxidation of atractylon **7** can be linked to our own cobalt-mediated dimerization study of chloroatractylolide **27** [in which a captodative stabilized radical **8** can be proposed as a precursor of biatractylolide **1**, biepiasterolide **2**, and the dimer **29** (Scheme 11)], then the autoxidation of atractylon **7** would *also* need to proceed by formal oxygen atom addition and hydrogen atom abstraction in order to generate the same radical precursor **8** which leads to the observed dimeric adducts **1**, **2**, and **29** (Scheme 18).

Conclusions

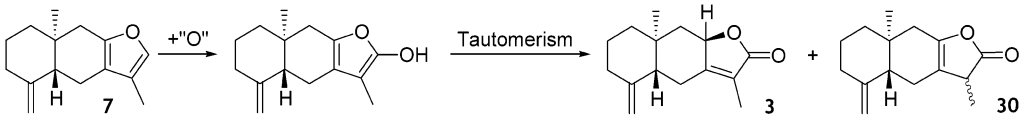
In conclusion, we have completed the synthesis of the bisesquiterpene lactones biatractylolide **1** and biepiasterolide **2** through a biomimetic approach. During this process, we have correlated the work of Hikino with our own results and demonstrated that, under chemical conditions, atractylon **7** is a possible intermediate during the synthesis of (+)-biatractylolide **1**, biepiasterolide **2**, (+)-atractylolide **3**, and (+)-hydroxyatractylolide **4**. We have also shown that, under such conditions, atractylolide **3** and hydroxyatractylolide **4** are competing products to the dimerization reaction and not intermediate species en route to (±)-biatractylolide **1** and (±)-biepiasterolide **2**.

Experimental Section

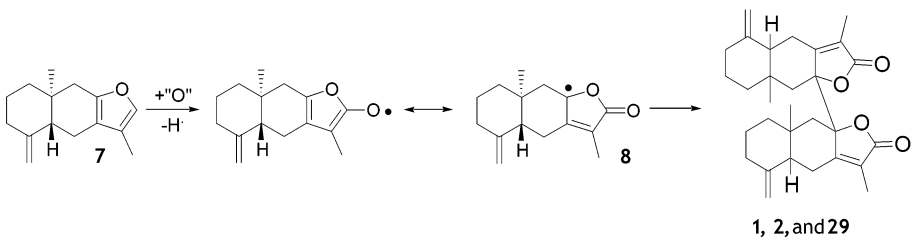
3,3′-Dimethyl-4,5,6,7,4′,5′,6′,7′-octahydro[7a,7′a]bibenzofuranyl-2,2′-dione (14). ***Caution!*** Reactions in sealed tubes and ampules must be performed behind a safety shield, and all organic peroxides should be handled with due care.

1. DTBP-Mediated Dimerization. A solution of butenolide **12** (200 mg, 1.31 mmol, 1 equiv), di-*tert*-butyl peroxide (121 μL, 0.66 mmol, 0.5 equiv), and acetone (0.5 mL) was placed in an ampule, which was degassed with three freeze−pump−thaw cycles and then sealed. After heating to 140 °C for 18 h overnight, the ampule was opened at room temperature under an atmosphere of argon. The residue was diluted with Et_2O, washed with water, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was placed under high vacuum at 50 °C overnight and then purified by flash chromatography (CH_2Cl_2) to yield the title compound **14** (66.6 mg, 34%) as a white solid in a 6:1 *dl/meso* mixture of diastereomers.

SCHEME 17. Formal Oxygen Atom Addition to Atractylon 7 To Generate Atractylolide 3 and Isomer 31



SCHEME 18. Formal Oxygen Atom Addition and Hydrogen Atom Abstraction from Atractylon 7



Recrystallization from Et_2O/EtOAc (4:1) allowed the pure, major *dl* diastereomer to be isolated.

2. $Co(PPh_3)_3Cl$-Mediated Dimerization. Chloro lactone **19** (100 mg, 0.54 mmol, 1 equiv) dissolved in benzene (1 mL) was added to a suspension of $CoCl(PPh_3)_3$ (570 mg, 0.65 mmol, 1.2 equiv) in benzene (4 mL) under argon, and the resulting mixture was stirred at room temperature for 2 h under argon. The reaction mixture was diluted with Et_2O and filtered, and the filtrate was washed with water and concentrated to dryness in vacuo. Purification by flash chromatography [petroleum ether 30−40/Et_2O (7:3)] gave the title compound **14** as a white solid (46 mg, 57%), and mainly as the *dl* diastereomer. Only trace *meso* diastereomer was detected.

3. Data for (±)-*dl* Diastereomer 14a: mp 188−189 °C (from 4:1 Et_2O/EtOAc); R_f 0.3 (CH_2Cl_2); IR (film) ν_{max}(cm^{-1}) 2947s, 2864m, 1747s, 1672m, 1447m, 1266s, 1018s, 737s; MS (CI) *m/z* 303 [MH^+, 25%], 152 [100]; HRMS calcd for $C_{18}H_{26}NO_4$ (MNH_4^+) 320.1862, found 320.1855

4. NMR Data for (±)-*dl* Diastereomer 14a: $\delta_{H/2}$ (400 MHz, $CDCl_3$) 1.10−1.30 (1H, m), 1.36 (1H, td, J = 14.0 and 5.0 Hz), 1.64−1.73 (1H, m), 1.75 (3H, s), 2.03−2.23 (3H, m), 2.63 (1H, dm, J = 13.5 Hz), 2.87 (1H, dm, J = 14.0 Hz); $\delta_{C/2}$ (100.6 MHz, $CDCl_3$) 8.4, 21.4, 26.8, 27.6, 37.2, 88.2, 122.5, 166.1, 172.9.

5. NMR Data for (±)-*meso* Diastereomer 14b. The *meso* diastereomer was not isolated in pure form: $\delta_{H/2}$ (400 MHz, $CDCl_3$) 1.10−1.30 (1H, m), 1.40−1.50 (1H, m), 1.50−1.62 (1H, m), 1.80−2.00 (1H, m), 1.90 (3H, s), 1.96−2.04 (1H, m), 2.03−2.23 (1H, m), 2.44−2.52 (1H, m), 2.66−2.84 (1H, m); $\delta_{C/2}$ (100.6 MHz, $CDCl_3$) 8.4, 22.5, 26.2, 27.7, 36.7, 87.8, 122.5, 166.3, 172.9.

7a-Chloro-3-methyl-5,6,7,7a-tetrahydro-4*H*-benzofuran-2-one (19). To a solution of hydroxybutenolide **18** (50.0 mg, 0.3 mmol, 1 equiv) in CH_2Cl_2 (2.2 mL) under argon at room temperature was added freshly distilled thionyl chloride (110 μL, 1.5 mmol, 5 equiv), and the mixture was stirred for 18 h. The solvent and excess thionyl chloride were evaporated under reduced pressure, and the residue was purified by flash chromatography [petroleum ether 30−40/CH_2Cl_2 (9:1)] to give the title compound **19** as a clear oil (29 mg, 52%): R_f 0.25 [petroleum ether 30−40/Et_2O/CH_2Cl_2 (8:1:1)]; IR (film) ν_{max}(cm^{-1}) 2915s, 2866m, 1778s, 1689m, 1440m, 1286m; NMR δ_H (500 MHz, $CDCl_3$) 1.24−1.35 (1H, m), 1.69−1.76 (1H, m), 1.79−1.89 (2H, m), 1.84 (3H, s), 2.02−2.08 (1H, m), 2.46 (1H, tm, J = 14.0 Hz), 2.66 (1H, dm, J = 13.5 Hz), 2.76 (1H, dm, J = 14.0 Hz); NMR δ_C (125.7 MHz, $CDCl_3$) 8.2, 21.9, 24.2, 25.8, 41.2, 99.9, 120.6, 161.7, 170.7; MS (CI) *m/z* 187 [MH^+, 2%], 151 [100]. HRMS calcd for $C_9H_{15}{}^{35}ClNO_2$ (MNH_4^+) 204.0791, found 204.0787.

(±)-Hydroxyatractylolide (4).[9,26] To a stirred solution of furan **28** (69.0 mg, 0.2 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at room temperature was added *m*CPBA (70% purity, 49.0 mg, 0.2 mmol, 1 equiv), and the reaction mixture was stirred for 30 min under argon. Five percent aqueous $Na_2S_2O_3$ (1 mL) was added, and stirring continued for a further 10 min. The aqueous layer was extracted with $CHCl_3$, and the organic layers were combined, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography [petroleum ether 30−40/Et_2O (4:1)] gave the title compound **4** (27.0 mg, 55%) as a white solid: mp 196−198 °C [lit.[9] (+)-**4** 197−197.5 °C]; R_f 0.35 (7:3 petroleum ether 30−40/EtOAc); IR (KBr, disk) ν_{max} (cm^{-1}) 3344br m, 1739s, 1697m, 1426m, 940m, 897m; NMR δ_H (500 MHz, $CDCl_3$) 1.04 (3H, s), 1.20−1.30 (1H, m), 1.54−1.62 (1H, m), 1.55 (1H, d, J = 14.0 Hz), 1.60−1.75 (2H, m), 1.82 (3H, s), 1.83−1.87 (1H, m), 1.93−2.00 (1H, m), 2.27 (1H, d, J = 14.0 Hz), 2.36 (1H, br d, J = 13.0 Hz), 2.45 (1H, t, J = 13.0 Hz), 2.63 (1H, d, J = 13.0 Hz), 3.54 (1H, br s), 4.61 (1H, s), 4.87 (1H, s); NMR δ_C (125.7 MHz, $CDCl_3$) 8.1, 16.5, 22.2, 24.5, 36.0, 36.6, 41.2, 51.1, 51.6, 103.5, 106.7, 122.0, 148.4, 160.9, 172.3; MS (CI) *m/z* 249 [MH^+, 20%], 231 [100]; HRMS calcd for $C_{15}H_{21}O_3$ (MH^+) 249.1491, found 249.1497.

(±)-3,8a,3′,8′a-Tetramethyl-5,5′-dimethylene-4,4a,5,6,7,8,-8a,9,4′,4′a,5′,6′,7′,8′,8′a,9′-hexadecahydro[9a,9′a]bi[naphtho-[2,3-*b*]furanyl]-2,2′-dione (1, 2, 29, and 30).[2−4] To a solution of hydroxyatractylolide **4** (500 mg, 2.0 mmol, 1 equiv) and pyridine (1.63 mL, 20 mmol, 10 equiv) in THF (25 mL) at −78 °C and under argon was added freshly distilled thionyl chloride (0.73 mL, 10 mmol, 5 equiv), and the resulting solution was stirred for 30 min. Et_2O (30 mL) and 0.1 M aqueous HCl (10 mL) were then added, and the solution was allowed to warm to room temperature. The organic layer was separated and washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo at room temperature to give a mixture of chloroatractylolide **27** and atractylenolide **6** in a 3:1 ratio, respectively, as a colorless oil: IR (film) ν_{max} (cm^{-1}) 2933s, 1778s, 1691m, 1651m, 1265s, 1098m, 738s; NMR δ_{Hmax} (400 MHz, $CDCl_3$) 1.86 (3H, s), 4.62 (1H, s), 4.88 (1H, s); NMR δ_C (100.6 MHz, $CDCl_3$) 98.3 (C−Cl). The crude chloroatractylolide **27** was dissolved in benzene (8 mL) and added to a suspension of $CoCl(PPh_3)_3$ (2.1 g, 2.4 mmol, 1.2 equiv) in benzene (12 mL) under argon, and the resulting mixture was stirred at room temperature for 2 h under argon. The reaction mixture was filtered, and the filtrate was washed with water and concentrated to dryness in vacuo. Purification by flash chromatography [petroleum ether 30−40/CH_2Cl_2/Et_2O (8:1:1)] gave recovered hydroxyatractylolide **4** (43.0 mg) and the dimer compounds as a white solid (164 mg) and a mixture of three diastereomers in a 1:3:4 ratio. Further purification by preparative chromatography [petroleum ether 30−40/CH_2Cl_2/Et_2O (8:1:1)] gave (±)-biatractylolide **1** (14.0 mg, 3%), (±)-biepiasterolide **2** (43.0 mg, 10%), and diastereomer (±)-**29** (57.0 mg, 13%).

(±)-Biatractylolide (1):[2,4] white solid (14.0 mg, 3%); mp 210−211 °C (from EtOH, lit.[2,4] (+)-**1** 210−212 °C); R_f 0.3 [petroleum ether 30−40/CH_2Cl_2/Et_2O (8:1:1)]; IR (KBr, disk) ν_{max} (cm^{-1}) 3436br m, 2930s, 1757s, 1670m, 1648m, 1439m, 1105m, 1012m, 986m, 888m, 732m; NMR $\delta_{H/2}$ (500 MHz, $CDCl_3$) 1.13 (3H, s), 1.22 (1H, td, J = 12.0 and 6.0 Hz), 1.42 (1H, d, J = 14.5 Hz), 1.59−1.61 (1H, m), 1.63−1.65 (2H, m), 1.71−1.75 (1H, m), 1.75 (3H, s), 1.90−1.99 (1H, m), 2.35 (1H, br d, J = 13.0 Hz), 2.65 (1H, dd, J = 13.0, 3.5 Hz), 2.78 (1H, t, J = 13.0 Hz), 2.82 (1H, d, J = 14.5 Hz), 4.65 (1H, s), 4.86 (1H, s); NMR $\delta_{C/2}$ (125.7 MHz, $CDCl_3$) 8.4, 17.1, 22.3, 27.9, 35.8, 36.9, 42.1, 49.7, 52.9, 89.3, 107.3, 124.4, 147.9, 164.5, 172.0; MS (EI) *m/z* 485 [MNa^+, 100%], 463 [MH^+, 36%]; HRMS calcd for $C_{30}H_{42}NO_4$ (MNH_4^+) 480.3114, found 480.3109.

(±)-Biepiasterolide (2):[3] white solid (43.0 mg, 10%); mp 205−208 °C (from EtOH, lit.[3] 203−205 °C); R_f 0.3 [petroleum ether 30−40/CH_2Cl_2/Et_2O (8:1:1)]; IR (KBr, disk) ν_{max} (cm^{-1}) 2925s, 1763s, 1670m, 1641m, 1432m, 1018m, 882m; NMR $\delta_{H/2}$ (500 MHz, $CDCl_3$) 0.50 (3H, s), 1.38−1.50 (2H, m), 1.53−1.59 (1H, m), 1.60−1.66 (1H, m), 1.79 (3H, d, J = 2.0 Hz), 2.01 (1H, d, J = 15.0 Hz), 2.05−2.13 (1H, m), 2.19 (1H, ddd, J = 17.5, 8.0, and 2.0 Hz), 2.32 (1H, d, J = 15.0 Hz), 2.37 (1H, dm, J = 13.5 Hz), 2.65 (1H, dd, J = 17.5 and 10.0 Hz), 2.82 (1H, dd, J = 10.0 and 8.0 Hz), 4.64 (1H, s), 4.87 (1H, s); NMR $\delta_{C/2}$ (125.7 MHz, $CDCl_3$) 8.6, 19.0, 22.8, 24.8, 36.6, 36.8, 42.2, 42.7, 47.0, 89.3, 107.1, 125.4, 148.1, 163.3, 172.6; MS (EI) *m/z* 485 [MNa^+, 100%], 463 [MH^+, 20%]; MS (CI) *m/z* 463 [MH^+, 40%], 232 [100], 231 [55]; HRMS calcd for $C_{30}H_{42}NO_4$ (MNH_4^+) 480.3114, found 480.3117.

(±)-Dimer 29. White solid (57.0 mg, 13%); np 240−242 °C (from EtOAc); R_f 0.3 [petroleum ether 30−40/CH_2Cl_2/Et_2O (8:1:1)]; IR (KBr, disc) ν_{max} (cm^{-1}) 3433 br m, 2927s, 1754s, 1667m, 1645m, 1440m, 1261m, 1099m, 1018m, 894m; δ_H (500 MHz, $CDCl_3$) 0.51 (3H, s), 1.16 (3H, s), 1.20 (1H, dd, J 13.0, 4.5 Hz), 1.36−1.66 (7H, m), 1.45 (1H, d, J 14.5 Hz), 1.68−1.72 (1H, m), 1.76 (3H, s), 1.78 (3H, d, J 2.0 Hz), 1.94 (1H, br q, J 13.0 Hz), 1.98 (1H, d, J 15.0 Hz), 2.06 (1H, br t, J 13.0 Hz), 2.34 (1H, br d, J 13.0 Hz), 2.34−2.38 (1H, m), 2.38−2.43 (1H, m), 2.42 (1H, d, J 15.0 Hz), 2.48 (1H, t, J 12.5 Hz), 2.57−2.64

(26) Huang, B. S.; Sun, J. S.; Chen, Z. L. *Zhiwu Xuebao* **1992**, *34*, 614.

(1H, m), 2.61 (1H, dd, *J* 12.5, 3.5 Hz), 2.69 (1H, dd, *J* 10.0, 8.0 Hz), 2.77 (1H, d, *J* 14.5 Hz), 4.60 (1H, s), 4.66 (1H, s), 4.84 (1H, s), 4.87 (1H, s); δ_C (125.7 MHz, $CDCl_3$) 8.5 (2C's), 18.2, 18.4, 22.4, 22.7, 25.6, 27.5, 35.6, 36.4, 36.5, 36.9, 42.3 (2C's), 43.2, 46.8, 50.8, 54.0, 88.0, 90.2, 106.8, 107.2, 124.0, 126.1, 147.9, 148.0, 163.9, 165.7, 172.3, 172.5; MS (CI) *m/z* 463 [MH^+, 13%], 233[100]; HRMS calcd for $C_{30}H_{39}O_4$ (MH^+) 463.2848, found 463.2841.

Autoxidation of (±)-Atractylon (7). All yields quoted are based upon recovered atractylon **7**, and all diastereomeric ratios were measured after purification.

Procedure 1: Aerial Oxidation under Hikino's Conditions.[9] A mixture of (±)-atractylon **7** (50.0 mg, 0.23 mmol) in methanol (1 mL) was left standing open to air for 35 days. The solvent was removed under reduced pressure. The reaction mixture was diluted with Et_2O and 1 M aqueous NaOH. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography [petroleum ether 30−40/CH_2Cl_2 (9:1)] gave recovered atractylon **7** (13 mg), atractylolide **3** (4.6 mg, 11.5%), and atractylolide isomer **30** (5.4 mg, 13.5%) as a mixture of diastereomers in a 1:1 ratio. The diastereomers of isomer **30** were not separated further, although NMR data for the individual compounds could be obtained by using COSY, HMQC, and HMBC NMR analysis.

(±)-3,8a-Dimethyl-5-methylene-4a,5,6,7,8,8a,9,9a-octahydro-3*H*-naphtho[2,3-*b*]furan-2-one (30):[27] colorless oil obtained as a mixture of diastereomers in a 1:1 ratio; R_f 0.4 [petroleum ether 30−40/CH_2Cl_2/Et_2O (8:1:1)]; IR (film) ν_{max} (cm^{-1}) 3400w, 2964s, 2930s, 1798s, 1718m, 1643m, 1262s, 1076s, 1015s, 799m; MS (CI) *m/z* 233 [MH^+, 100%], 250 [MNH_4^+, 38%]; HRMS calcd for $C_{15}H_{21}O_2$ (MH^+) 233.1542, found 233.1537.

1. NMR Data for Diastereomer 30a: δ_H (500 MHz, $CDCl_3$) 0.81 (3H, s), 1.34 (3H, d, $J = 6.0$ Hz), 1.43−1.71 (4H, m), 2.00−2.15 (5H, m), 2.18−2.25 (1H, m), 2.40 (1H, dm, $J = 13.0$ Hz), 3.10−3.18 (1H, m), 4.61 (1H, s), 4.85 (1H, s); δ_C (125.7 MHz, $CDCl_3$) 14.2, 17.4, 21.6, 23.2, 36.4, 36.9, 37.9, 41.1, 41.5, 45.3, 107.4, 114.0, 147.3, 148.8, 180.3.

2. NMR Data for Diastereomer 30b: δ_H (500 MHz, $CDCl_3$) 0.81 (3H, s), 1.33 (3H, d, $J = 6.0$ Hz), 1.43−1.71 (4H, m), 2.00−2.15 (5H, m), 2.18−2.25 (1H, m), 2.40 (1H, dm, $J = 13.0$ Hz), 3.10−3.18 (1H, m), 4.61 (1H, s), 4.85 (1H, s); δ_C (125.7 MHz, $CDCl_3$) 14.1, 17.3, 21.4, 23.2, 36.3, 36.9, 37.9, 40.5, 41.5, 45.0, 107.3, 113.9, 147.2, 148.7, 180.2.

Further purification by preparative chromatography [petroleum ether 30−40/CH_2Cl_2/Et_2O (8:1:1)] gave (±)-biatractylolide **1** (2.1 mg, 5.5%), (±)-biepiasterolide **2** (1.4 mg, 3.5%), and diastereomer (±)-**29** (1.8 mg, 4.5%).

The alkaline layer was adjusted to pH 7 with 1 M aqueous HCl, and the aqueous layer was extracted with Et_2O. The organic extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography [petroleum ether 30−40/EtOAc (7:3)] gave hydroxyatractylolide **4** as a white solid (14.9 mg, 35%).

Procedure 2: Woodward Conditions.[25] Neat (±)-atractylon **7** (100 mg, 0.46 mmol) was heated to 100 °C for 1 h with magnetic stirring while oxygen was bubbled through the flask. The reaction mixture was cooled to room temperature and diluted with Et_2O and 1 M aqueous NaOH. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography [petroleum ether 30−40/CH_2Cl_2 (9:1)] gave recovered atractylon **7** (13.8 mg). Further purification by preparative chromatography [petroleum ether 30−40/CH_2Cl_2/Et_2O (8:1:1)] gave (±)-biatractylolide **1** (2.5 mg, 2.5%), (±)-biepiasterolide **2** (3.4 mg, 3.5%), and diastereomer (±)-**29** (3.4 mg, 3.5%).

The alkaline layer was adjusted to pH 7 with 1 M aqueous HCl, and the aqueous layer was extracted with Et_2O. The organic extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography [petroleum ether 30−40/EtOAc (7:3)] gave hydroxyatractylolide **4** as a white solid (15.4 mg, 15.5%).

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Supporting Information Available: General experimental methods; experimental procedures and spectroscopic data for compounds **3**, **6**, **7**, **12**, **16**−**18**, **21**−**24**, **26**, **28**, and CoCl(PPh_3)$_3$; copies of NMR spectra for compounds **1**, **2**, **3**, **4**, **7**, **14a/14b**, **19**, **29**, and **30**; and X-ray crystallographic data for compounds **1**, **2**, **4**, and **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Bohlmann, F.; Dutta, L. N.; Knauf, W.; Robinson, H.; King, R. M. *Phytochemistry* **1980**, *19*, 433.