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Biomimetic Synthesis of Biatractylolide and Biepiasterolide

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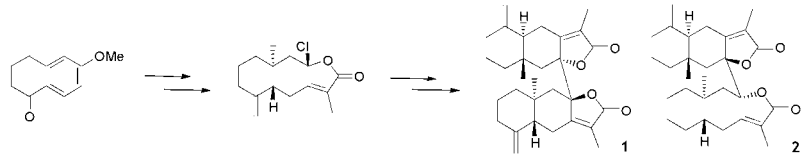
ABSTRACT



The biomimetic synthesis of the bisesquiterpenoids biatractylolide 1 and biepiasterolide 2 is reported.

Biatractylolide **1** and biepiasterolide **2** are structurally novel bisesquiterpenoids recently isolated from the chinese medicinal plant *Atractylodes macrocephala*.[1−3] Biologically, biatractylolide **1** has shown significant negative inotropic and chronotropic effects, making it a potential blood pressure lowering agent.[4]

Structurally, both biatractylolide **1** and biepiasterolide **2** are dimeric sesquiterpenic lactones joined at the C_8-C_{8a} bridgehead positions as proven by X-ray analysis.[1−3] Biosynthetically, it is believed that both biatractylolide **1** and biepiasterolide **2** originate from the naturally occurring sesquiterpene lactones atractylolide **3** or hydroxyatractylolide **4** which are closely related to the sesquiterpenes peroxyatractylolide **5** and atractylon **6** (Figure 1).[5]

It is feasible to propose a biomimetic approach for the synthesis for both biatractylolide **1** and biepiasterolide **2** in

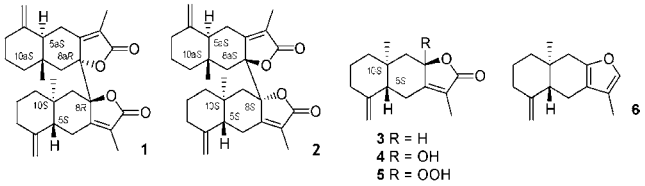


Figure 1. Biatractylolide **1**, biepiasterolide **2**, atractylolide **3**, hydroxyatractylolide **4**, peroxyatractylolide **5**, and atractylon **6**.

which the key dimerization step takes place between two units of atractylolide **3** or hydroxyatractylolide **4** through the captodative stabilized radical **7** [6] (or its equivalent).[7] Furthermore, Hikino has reported the aerial autoxidation of atractylon **6** into atractylolides **3** and **4**.[8] Thus, atractylolides **3** and **4** could emanate from atractylon **6** *in vitro* (Scheme 1).

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(1) Lin, Y.; Jin, T.; Wu, X.; Huang, Z.; Fan, J. *J. Nat. Prod.* **1997**, *60*, 27.
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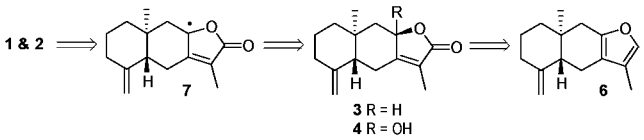
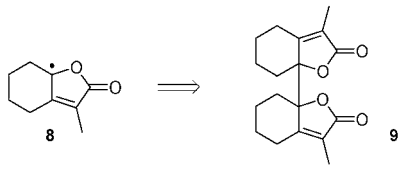
Scheme 1. Proposed Biosynthesis of Biatractylolide **1** and Biepiasterolide **2**



We have recently reported our work on the model monomer radical **8**, which was efficiently generated and its dimerization chemistry explored to successfully generate the model dimer **9** with high *RR*/*SS*−*RS*/*SR* diastereoselectivity (Scheme 2).[9]

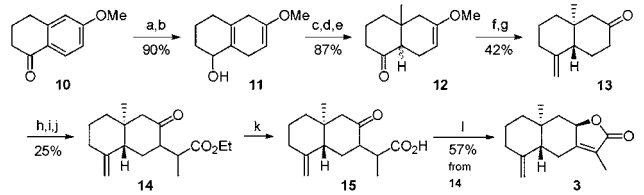
Scheme 2. Synthesis of the Dimer Core **9** from Monomer Unit **8**



We now report the synthesis of the complete monomer units atractylolide **3** and hydroxyatractylolide **4** and their potential as synthons for the captodative stabilized radical **7** to enable a biomimetic dimerization to generate both biatractylolide **1** and biepiasterolide **2**.

The synthesis of the complete monomer unit **3** followed minor modification of the work by Minato and Nagasaki and began with ketone **10**, which was reduced to the corresponding alcohol and then subjected to Birch reduction conditions to generate enol ether **11**. Careful Oppenauer oxidation of alcohol **11** followed by a 1,4-cuprate addition with simultaneous trapping of the resulting enolate, followed by careful silyl ether hydrolysis, generated the desired ketone **12**. Wittig olefination followed by methyl ether hydrolysis generated the known key ketone intermediate **13** (Scheme 3).[10]

Scheme 3. Synthesis of Atractylolide **3**[a]



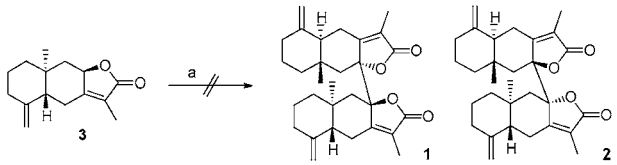
[a] Key: (a) $NaBH_4$, CH_3OH, rt, 3 h; (b) Na, NH_3, ^tBuOH, −33 °C, 2 h; (c) $Al(O^iPr)_3$, toluene, acetone, 87 °C (oil bath), 4.5 h; (d) CuI, MeMgBr, TMEDA, TMSCl, THF, rt, 16 h; (e) TBAF, THF, rt, 20 min; (f) PPh_3CH_2, DMSO, 55 °C, 18 h; (f) 35% aq HCl; (h) pyrrolidine, PhH, reflux, 6 h; (i) ethyl α-bromopropionate, dioxane, reflux, 16 h; (j) dioxane, H_2O, reflux, 1 h; (k) KOH−CH_3OH (5% w/v), rt, 2 h then HCl, H_2O; (l) NaOAc, Ac_2O, reflux, 2 h.

Ketone **13** was then converted into the corresponding pyrrolidine enamine and subsequently alkylated to generate ethyl ester **14** as a mixture of diastereomers. Ester hydrolysis proceeded cleanly to afford the corresponding acid **15**, which was then successfully cyclized to produce the desired butenolide atractylolide **3** in good yield.

Once the butenolide atractylolide **3** was available, we focused our attention on the dimerization step. As in the case with the model system,[9] we initially explored the possibility of using DTBP (di-*tert*-butyl peroxide) as a radical generator. DTBP has been reported as a model for hydrogen atom abstraction reactions in biological systems[11] as well being known to effect the dehydrodimerizations of polyhaloalkanes, alcohols, ethers, amides, and esters.[12]

Unfortunately, treatment of atractylolide **3** under previously optimized reaction conditions (0.5 equiv of DTBP, acetone, 140 °C, 24 h)[9] failed to produce any of the desired dimers **1** or **2**. However, treatment of atractylolide **3** under more forceful conditions only afforded polymeric material as well as crude traces of what appeared to be the product of the $^tBuO^•$ radical having been incorporated. The presence of these undesired side products increased as the severity of the reaction conditions increased (Scheme 4).

Scheme 4. Attempted DTBP Dimerization of Atractylolide **3**[a]



[a] Key: (a) DTBP (0.5 equiv−2.0 equiv), acetone, 120−170 °C, 24 h.

Although disappointing, this lack of dimerization is not surprising considering the increase in functionality in atractylolide **3** compared with our model system **8** (i.e., the exocylic double bond and the C_8 methyl group), which may have detrimental effects on the dimerization.

To shed some light on this process, the exocyclic double bond was removed before dimerization, by hydrogenation to afford butenolide **16** as a mixture of diastereomers. However, treatment of butenolide **16** under the DTBP dimerization conditions still failed to afford any dimerization adducts (Scheme 5).

This result points to the possibility that we could be observing a high degree of steric hindrance between the axial

(7) E.g., a pinacol-type dimerization of the keto form of **4**, followed by bis-lactonization.

(8) Hikino, H.; Hikino, Y.; Yosioka, I. *Chem. Pharm. Bull.* **1962**, *10*, 641.

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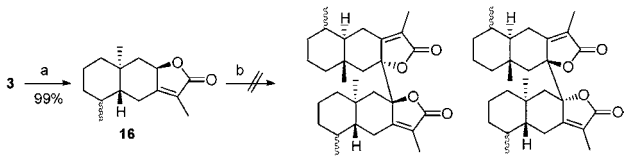
(10) Minato, H.; Nagasaki, T. *J. Chem. Soc. C* **1966**, 1866.

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

(12) Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: Chichester, 1995; Vol. 3, p 1616.

Scheme 5. Attempted Dimerization of Reduced Atractylolide **16**[a]



[a] Key: (a) 10% Pd/C, H_2, 48 h; (b) DTBP (0.5 equiv), acetone, 140 °C, 24 h.

methyl group and the $^tBuO^\bullet$ radical conducting hydrogen atom abstraction. Furthermore, Tanko has recently reported on the relatively ordered transition state required by $^tBuO^\bullet$ radicals during the hydrogen abstraction step.[11] Thus, it is possible that the hindrance provided by the methyl group disrupts this orderly transition state, increasing its activation energy. Consequently, Michael addition to initiate polymerization may become a more feasible reaction pathway (Figure 2).

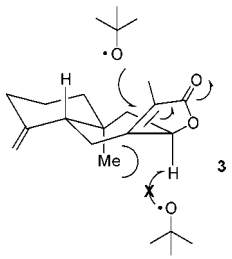
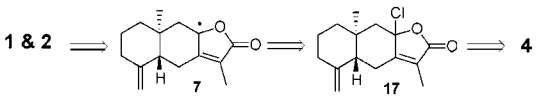


Figure 2. Proposed inhibition of hydrogen atom abstraction.

At this point, it was decided to generate radical **7** from hydroxyatractylolide **4** by converting it into the corresponding chloroatractylolide **17**, based on the second successful strategy used in model dimerizations (Scheme 6).[9]

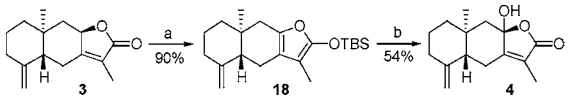
Scheme 6. Proposed Synthesis of **1** and **2** from Hydroxyatractylolide **4**



Our synthesis of hydroxyatractylolide **4** began with atractylolide **3**, which was efficiently converted into silyloxy furan **18**. Careful oxidation followed by desilylation of furan **18** afforded the naturally occurring sesquiterpene hydroxyatractylolide **4** (Scheme 7).[13]

(13) (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.

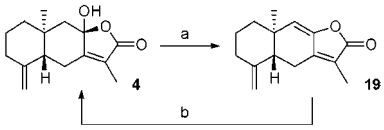
Scheme 7. Total Synthesis of Hydroxyatractylolide **4**[a]



[a] Key: (a) TEA, TBDMSCl, THF, 30 °C, 24 h; (b) *m*-CPBA, DCM, rt, 30 min.

Next, we focused on the conversion of the hydroxyl moiety into a halide unit. However, treatment of hydroxyatractylolide **4** under our own previously developed reaction conditions ($SOCl_2$, rt, 24 h)[9] failed to generate any of the desired chloroatractylolide **17**, affording instead the natural product atractylenolide **19** through what we believe to be an E1 mechanism. Interestingly, treatment of atractylenolide **19** under basic conditions regenerated hydroxyatractylolide **4** in good yields (Scheme 8).

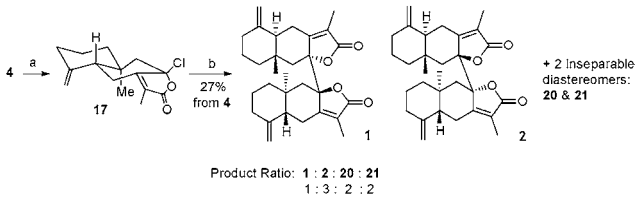
Scheme 8. Interconversion of Hydroxyatractylolide **4** and Atractylenolide **19**[a]



[a] Key: (a) $SOCl_2$, rt (or H^+, 95 °C); (b) ^-OH, rt.

Finally, modification of the reaction conditions by the addition of pyridine gave the desired chloroatractylolide **17** in good yield. The newly introduced chlorine atom is believed to be on the least hindered α-face of the atractylolide, consistent with an S_N2-like chloride ion attack from the α-face of the atractylolide (Scheme 9).

Scheme 9. Total Synthesis of Biatractylolide **1** and Biepiasterolide **2**[a]



[a] Key: (a) $SOCl_2$, pyridine, THF, -60 °C, 30 min; (b) $Co(PPh_3)_3Cl$, PhH, rt, 2 h.

Once chloroatractylolide **17** was available, the crucial dimerization step was attempted. Thus, treatment of chloroatractylolide **17** under our previously developed dimerization conditions ($Co(PPh_3)_3Cl$, PhH, rt, 2 h)[9] generated a set of four compounds from which biatractylolide **1**, biepiasterolide **2**, and a mixture of two inseparable diastereoisomers **20** and **21** could be isolated.

The structures of biatractylolide **1** and biepiasterolide **2** were corroborated by NMR to the reported structures[1−3] and unambiguously assigned using high-resolution mass spectroscopy (HRMS) and X-ray spectroscopy (Figures 3 and

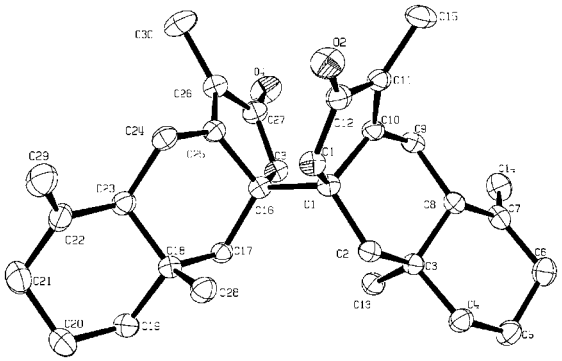


Figure 3. X-ray analysis of biatractylolide **1**.

4).[14,15] The remaining inseparable mixture is believed to contain the other two possible diastereoisomers arising from the dimerization process, as determined by 1- and 2-D NMR analysis and HRMS.

In conclusion, we have demonstrated a possible biomimetic correlation between atractylolide **3**, hydroxyatractylolide **4** and biatractylolide **1**, biepiasterolide **2** in which the key dimerization step takes place through a captodative stabilized radical **7**. The chemical synthesis of atractylolide

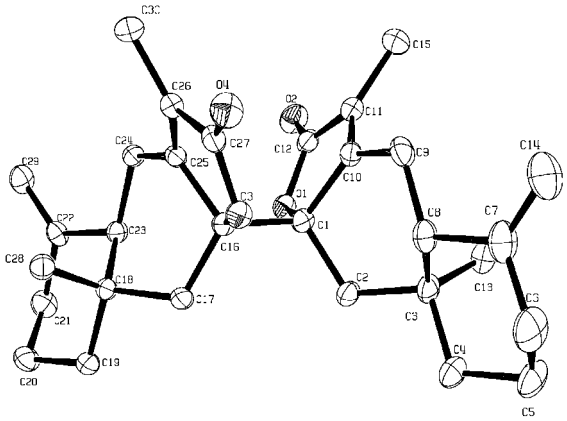


Figure 4. X-ray analysis of biepiasterolide **2**.

3, hydroxyatractylolide **4**, and atractylenolide **19** is also reported along with methods for their interconversion. We are currently working on the development of a more efficient and enantioselective synthesis, as well as on improving the scope and selectivity of the dimerization step.

Acknowledgment. We thank Oxford University for funding for S.K.B.

Supporting Information Available: Experimental procedures and NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The atomic coordinates for **1** are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (Deposition no. CCDC 207880). 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.

(15) The atomic coordinates for **2** are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (Deposition no. CCDC 207879). 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.