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Tetrahedron Letters 44 (2003) 4993–4996

TETRAHEDRON LETTERS

Studies towards the biomimetic synthesis of bisesquiterpene lactones

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Received 26 March 2003; revised 1 May 2003; accepted 9 May 2003

Abstract—A possible biomimetic connection between atractylolide, hydroxyatractylolide and biatractylolide and biepiasterolide has been demonstrated by efficiently generating the biatractylolide and biepiasterolide core structures from atractylolide and hydroxyatractylolide model butenolides via a radicaloid intermediate in a single step in good yield.

Biatractylolide **1** and biepiasterolide **2** are novel bisesquiterpenoids recently isolated from the Chinese medicinal plant *Atractylodes macrocephala*.[1–3] Biologically, biatractylolide **1** has shown powerful 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** (Fig. 1).[5]

It is possible to propose a biomimetic synthesis for both biatractylolide **1** and biepiasterolide **2** in which the crucial dimerisation step takes place between two units of atractylolide **3** or hydroxyatractylolide **4** through the captodative stabilised 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 vivo (Scheme 1).

In order to test our biomimetic hypothesis, we decided to synthesise simplified atractylolide model systems and to explore their oxidative dimerisation chemistry. We now report the synthesis of the model butenolides **8** and **9** and their potential for a biomimetic synthesis of biatractylolide **1** and biepiasterolide **2** (Scheme 2).

In order to synthesise model butenolide **8**, pyrrolidine enamine **11** was alkylated to give ester **12**, which after saponification gave acid **13**. The crude acid **13** was converted into butenolide **8** with acetic anhydride and

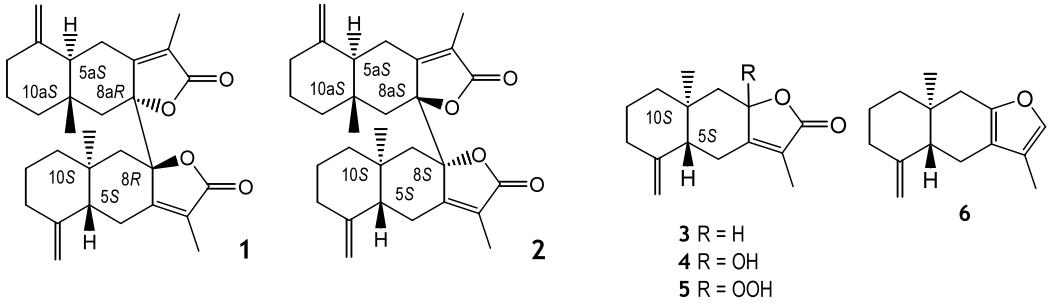

Figure 1. Naturally occurring sesquiterpenes isolated from *Atractylodes macrocephala*.

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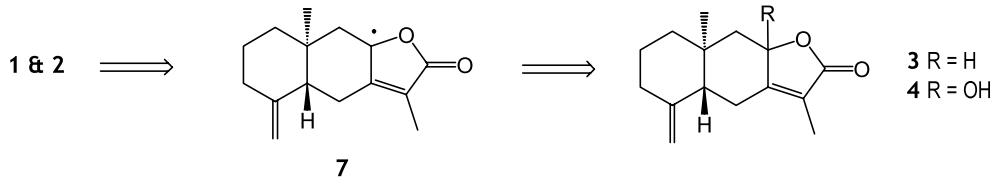
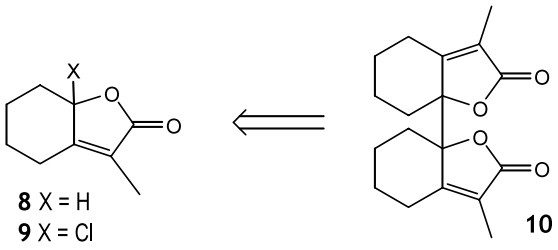
doi:10.1016/S0040-4039(03)01172-9



Scheme 1.

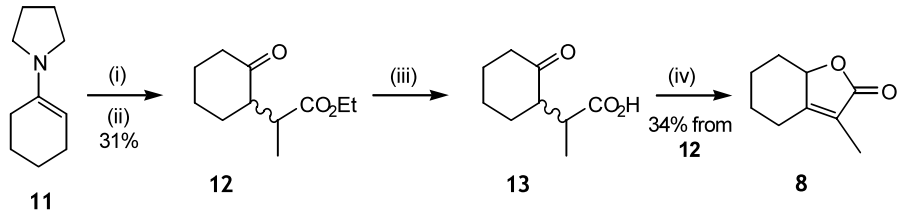


Scheme 2.

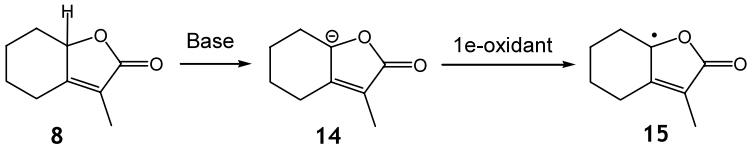
sodium acetate in reasonable yield after careful isolation and purification, by minor modification of the general method of Minato (Scheme 3).[9]

Initially, treatment of butenolide **8** with Tollens reagent was attempted under a variety of conditions based upon literature precedent.[10] However, butenolide **8** failed to oxidise to the desired dimer **10**, affording instead only recovered starting material. We then turned our attention to the resonance stabilised anion **14**. Oxidation of this anion with a 1-electron oxidant would then furnish the captodative stabilised butenolide radical **15** (Scheme 4).[11] Unfortunately, a wide variety of base and 1-electron oxidant combinations, failed to give any of the desired dimeric product **10**.

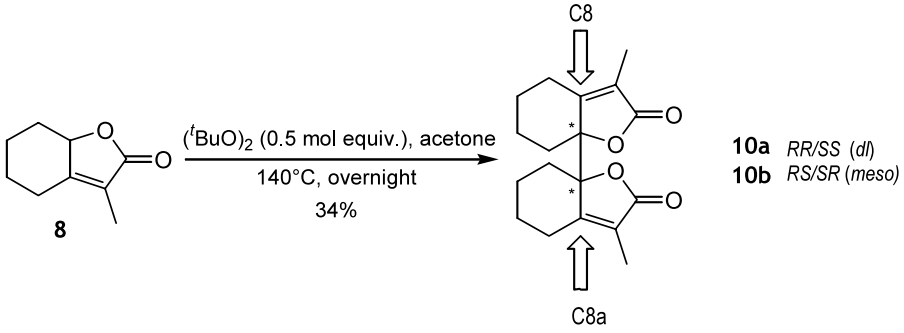
We next examined DTBP (di-*tert*-butyl peroxide) due to its use as a model for hydrogen atom abstraction reactions in biological systems,[12] as well as its known ability to effect dehydrodimerisations of polyhaloalkanes, alcohols, ethers, amides and esters.[13] Thus, a mixture of butenolide **8**, acetone and a stoichiometric amount of DTBP (0.5 mol equiv.) in the absence of oxygen, was placed in a sealed tube and heated to 140°C overnight. This procedure afforded the desired dimers **10a**/**10b** in an isolated yield of 34% after purification by column chromatography (Scheme 5).



Scheme 3. *Reagents and conditions*: (i) Ethyl α-bromo-propionate, dioxane, reflux, 16 h; (ii) water, reflux, 1 h; (iii) KOH–MeOH (5% w/v), rt, 2 h; (iv) NaOAc, Ac_2O, reflux, 3 h.



Scheme 4.



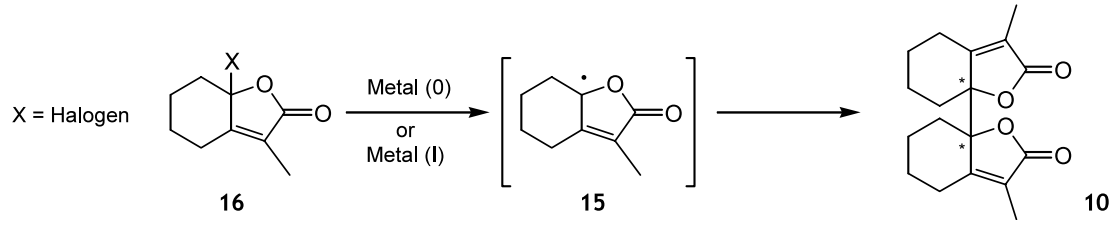
Scheme 5.

NMR indicated the presence of two diastereomeric dimers in a 6:1 ratio. Separation of the major diastereomer **10a** was successfully achieved by recrystallisation from a 20% mixture of EtOAc in Et_2O. However, despite our success using DTBP in obtaining model dimer **10**, we were unable to optimise the reaction yield further. This prompted us to consider alternative radical formation methods, which might afford the dimer. We were particularly intrigued by the reported ability of metals and metal salts to couple allylic and benzylic halides. We believed that such an approach might be successful in the dimerisation of a halobutenolide **16** (Scheme 6).

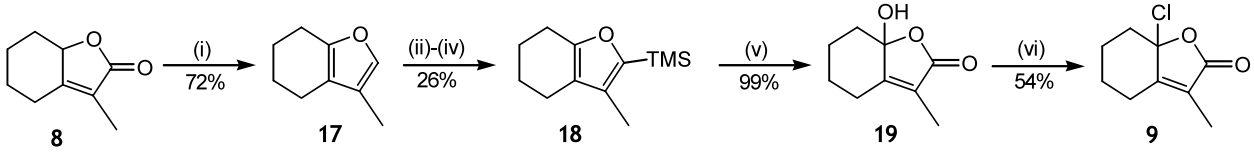
Thus, reduction of lactone **8** followed by silylation of the resulting furan **17**, afforded the desired silylfuran **18** in reasonable yield.[14] Singlet oxygen oxidation of furan **18** then yielded the expected hydroxybutenolide **19** in excellent yield.[15] Finally, treatment of hydroxybutenolide **19** with excess thionyl chloride afforded the desired chlorobutenolide **9** in good yield (Scheme 7).[16]

With the chlorobutenolide readily available, we focused our attention on improving the dimerisation yields. Thus, treatment of chlorobutenolide **9** with either zinc,[17] copper bronze,[10] or activated copper bronze (Vogel's method),[18] failed to afford the dimerised adduct **10** in higher than 2% yield. However, treatment of chlorobutenolide **9** with freshly prepared $Co(PPh_3)_3Cl$ under Yamada's conditions afforded the desired dimer **10** in excellent yield (56%) as a (>98:2) mixture of *dl:meso* **10a**:**10b** diastereomers at room temperature (Scheme 8, Table 1).[19,20]

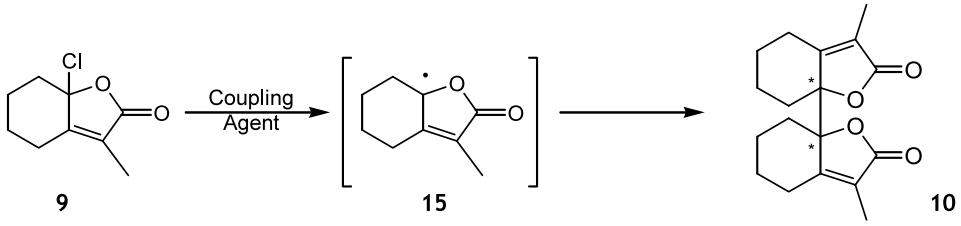
X-Ray analysis of this newly formed *dl*-bis-butenolide **10a** unambiguously demonstrated that the major diastereomer has the same relative stereochemistry at both C_8 and C_{8a} as that of biatractylolide **1** and biepiasterolide **2**.[21] Furthermore, the X-ray structure corroborates the natural product assignment by showing that the C_8 and C_{8a} bond is the longest in the molecule at 1.57 Å, compared to 1.59 Å in biatractylolide **1** and 1.58 Å in biepiasterolide **2** (Fig. 2).



Scheme 6.



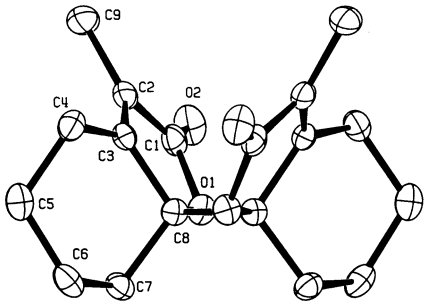
Scheme 7. *Reagents and conditions*: (i) Dibal-H, THF, −25°C; (ii) ^{t}BuLi, pentane, THF, −50°C; (iii) TMSCl, THF, 0°C to rt; (iv) satd aq. NH_4Cl, −78°C; (v) O_2, cat. Rose Bengal, 150 W tungsten lamp, MeOH, −78°C; (vi) $SOCl_2$, DCM, rt.



Scheme 8.

Table 1. Metal-mediated coupling of chlorolactone **9** to afford dimer **10**

Coupling agent	Temperature (°C)	Reaction time (h)	Solvent	Yield of **10** (%)
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	56



10a

Figure 2. X-Ray crystal structure of **10a**. Hydrogen atoms and the minor disorder component are omitted.

In conclusion, we have demonstrated a possible biomimetic connection between atractylolide **3** or hydroxyatractylolide **4** and biatractylolide **1** and biepiasterolide **2** by efficiently generating the core structure **10a** from the model butenolides **8** and **9** in a single step and high diastereoselectivity via a radicaloid intermediate **15**. We are currently working on ways to optimise our radical dimerisation strategy and to apply it to a biomimetic synthesis of biatractylolide **1** and biepiasterolide **2**.

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