Synthesis of *epi*-chloranthalactones A, B, D and E

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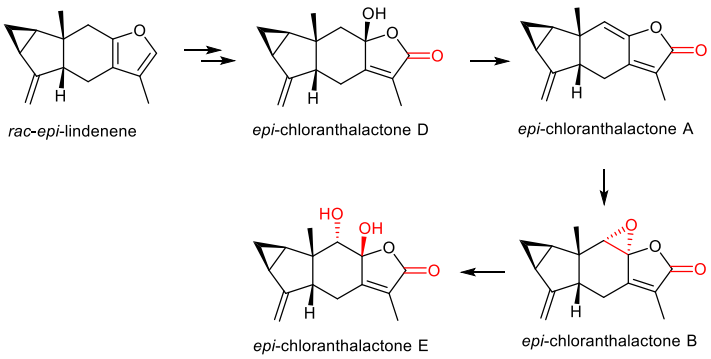

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Abstract The synthesis of various epimers of lindenane class of sesquiterpenes from *epi*-lindenene , based on a possible biosynthetic hypothesis, is described.

Key words Sesquiterpenes, Chloranthalactones, Aldol reaction, biosynthesis, oxidation.

Chloranthalactones A-E (**1**-**5**) are a group of sesquiterpene lactones with a common lindenane skeleton that were first isolated from the aerial and root parts of *Chloranthus japonicas* and the root of *Chloranthus glaber*.[1] These compounds were shown to be moderately cytotoxic against mouse lymphosarcoma L-5178Y cells. Compounds **1**-**5** are structurally similar to the natural product lindenene (**6**), which was isolated from the dried root of *Lindera strychnifolia* Vill.[2] This plant is a constituent of the Chinese drug T'ien T'ai wu yao. Despite the structural resemblance between lindenene (**6**) and chloranthalactones **A**-**E** (**1**-**5**), compound **6** is not found in any species of the Chloranthaceae. Although the chloranthalactones A-E (**1**-**5**) and lindenene (**6**) are not phytochemically related, one can postulate that **6** could be a possible biosynthetic precursor of compound **1**-**5**. It is interesting to note that **6** was also found in the coral *Acanthogorgia vagae*.[3] (Figure 1)

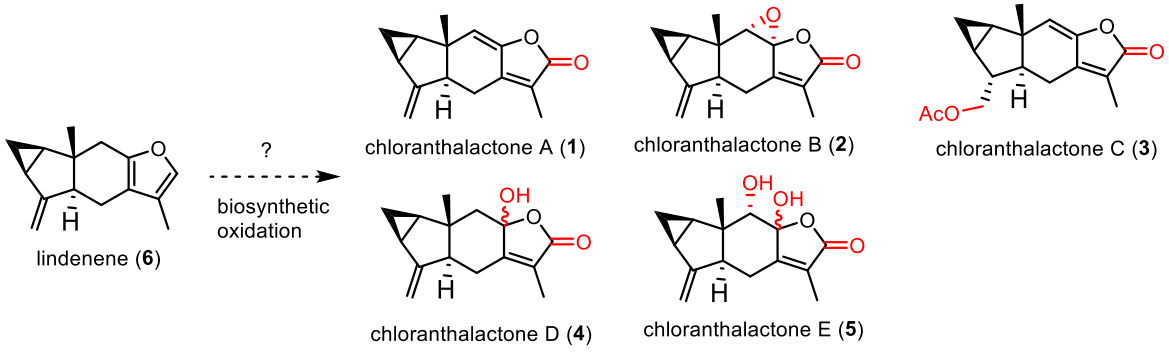


Figure 1 Possible biosynthetic relationship between lindenene (**6**) and the chloranthalactones A-E

The structural novelty of sesquiterpenes with the lindenane skeletons has posed a challenge to the synthetic organic chemistry community and a number of research groups have reported their synthetic efforts in this area.[4] We have previously completed the synthesis of *rac*-lindenene (**6**)[5] and would like to explore its possible conversion to various chloranthalactones. Since a supply of *rac*-*epi*-lindenene (**7**) was available in reasonable quantity in our laboratory, we therefore decided to test our biosynthetic hypothesis using it as the starting material. Our original plan was to investigate whether lindenene (**6**) could be transformed into lindenatriene (**8**), the putative biosynthetic precursor of the more complex terpene shizukaol A,[6] via various chloranthalactones as intermediates. However, we realised that *epi*-lindenene (**7**) could also be a

suitable precursor for such purpose as lindenatriene (**8**) is devoid of the C-5 stereocentre. Herein, we report our effort in the conversion of *rac-epi*-lindenene (**7**) to various *epi*-chloranthalactones (Figure 2).

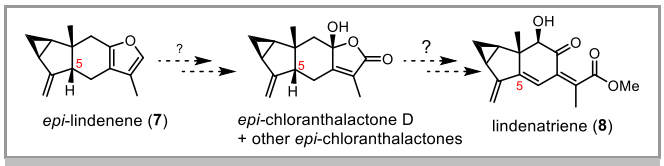
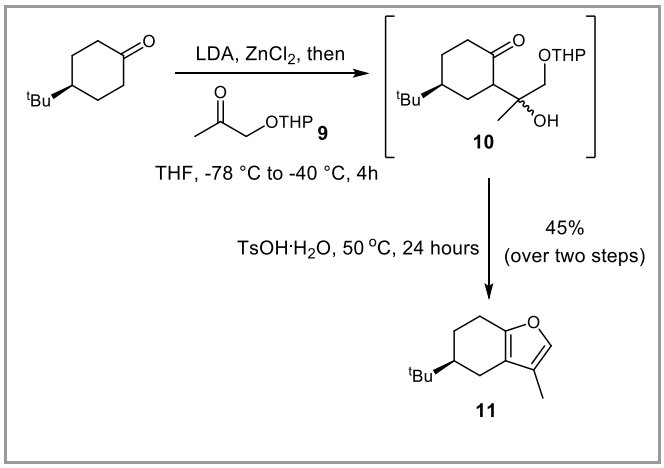


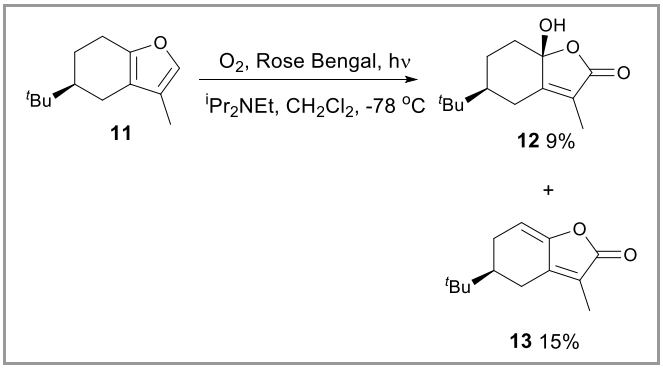
Figure 2 *Epi*-lindenene (**7**) as a possible precursor to various chloranthalactones

We envisaged that the butenolide motif in the chloranthalactones could be obtained by oxidation[7] of the furan ring in lindenene (**6**) and the same concept was applied to chemically modify *epi*-lindenene (**7**). Since the synthesis of **7** still required a considerable amount of effort, the initial investigations were conducted on model compound **11**. This compound could easily be prepared in two steps by aldol condensation of 4-*tert*-butylcyclohexanone with ketone **9** followed by acid catalysed dehydration[8] of the intermediate product **10** (Scheme 1).



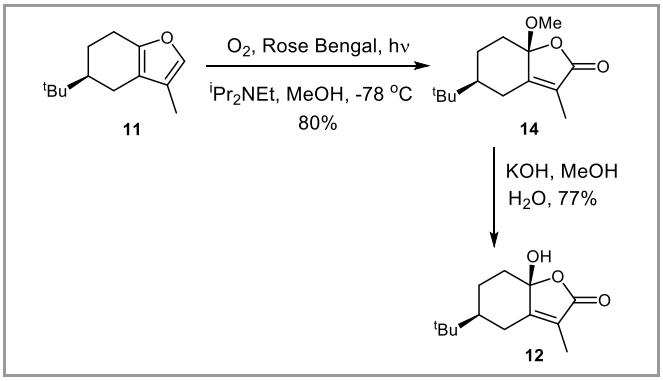
Scheme 1 Synthesis of model compound **11**

It is well documented that singlet oxygen oxidation of furan and base induced decomposition of the resultant *endo*-peroxide is a reliable method for generating the hydroxyfuranone moiety.[7] However, we found this transformation was not straightforward when it was performed on **11**. Initially exposure of **11** to singlet oxygen and Hünig's base in dichloromethane,[9] gave a mixture of products. Chromatographic purification of this mixture gave a low yield of the desired hydroxyfuranone **12** and its dehydrated product **13** (Scheme 2). The stereochemistry of hydroxyfuranone **12** can be rationalised by the reversible cyclisation of the ketoacid that was formed by the breakdown the endoperoxide intermediate. Therefore **12** is the thermodynamic product.



Scheme 2 Initial investigation on the oxidation of **11.**

In an attempt to improve this transformation, the same reaction was repeated in methanol. This gave methoxyfuranone **14** in good yield (80%) as the only product. This compound could be hydrolysed by potassium hydroxide to the desired hydroxyfuranone **12** in 77% yield (Scheme 3).



Scheme 3 Oxidation of **11** and hydrolysis of **14** to compound **12.**

Compound **14** was found to be crystalline and its structure was confirmed by X-ray diffraction (Figure 3).[10]

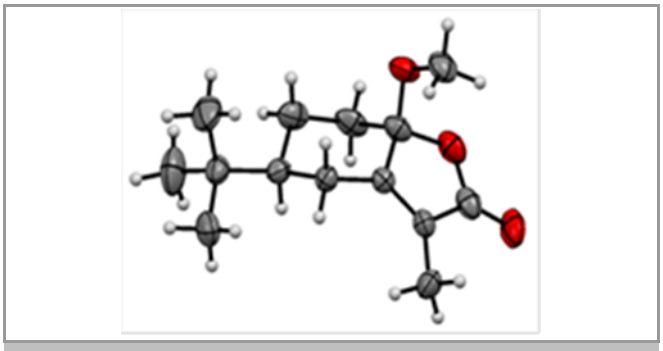
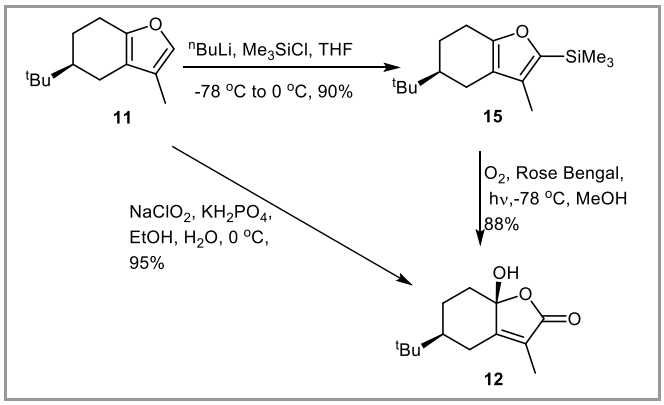


Figure 3 ORTEP representation of compound **14** with thermal ellipsoids at 50% probability

Interestingly when the oxidation of **11** was conducted in ethanol or *iso*-propanol, a mixture of **12** and the corresponding alkoxyfuranone was obtained.

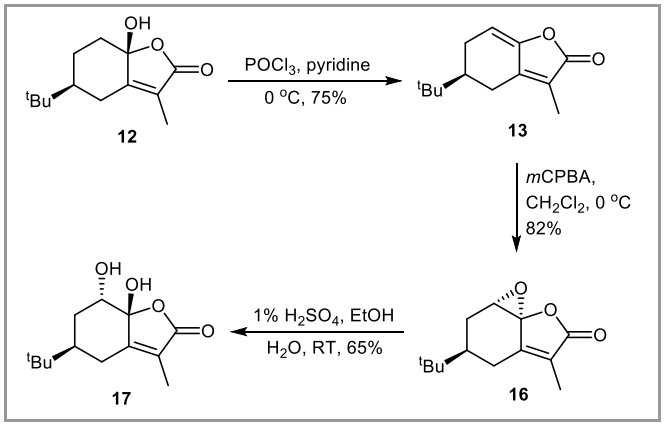
Despite the relative ease of the transformation from **11** into **12**, the overall yield was only about 62% over two steps. This

prompted us to explore other oxidation protocols in the hope of improving the overall yield of **12**. Garst and co-workers previously reported the oxidation of 2-trimethylsilylfuran to the corresponding hydroxyfuranone.[11] Based on Garst's precedence, **11** was converted to its 2-trimethylsilyl derivative **15**. Oxidation of **15** with singlet oxygen gave **12**. The overall yield of **12** was 79%, which was significantly higher than the earlier route.[12] Clive *et al.* reported a direct method for the oxidation of furan to hydroxyfuranone using sodium chlorite.[13] Application of Clive's method to **11** gave an excellent yield of **12** as product (Scheme 4).



Scheme 4 Synthesis of **12** from **11.**

Compound **12** was then dehydrated by phosphoryl chloride to enol-ester **13**, based on the literature precedent established by Uchida.[1] **13** was then epoxidised using *m*CPBA to afford compound **16**. The acid catalysed hydrolysis of epoxide **16** gave diol **17** as product (Scheme 5).



Scheme 5 Chemical modifications of hydroxyfuranone **12** to diol **17.**

Both **16** and **17** were crystalline solids and found to be suitable for X-ray diffraction studies. For compound **16**, its crystal structure clearly showed the *trans* relationship between the *tert*-butyl and epoxide entity (Figure 4).[10]

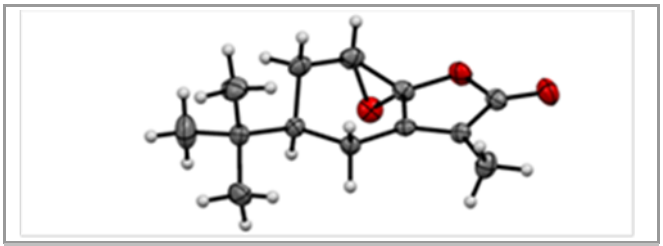


Figure 4 ORTEP representation of compound **16** with thermal ellipsoids at 50% probability.

The X-ray crystal structure of **17** (Figure 5) showed the hydroxyl groups of the diol were in *trans*-diaxial arrangement[9] which suggested that the ring opening of epoxide **16** occurred according to the Fürst-Plattner rule.[14]

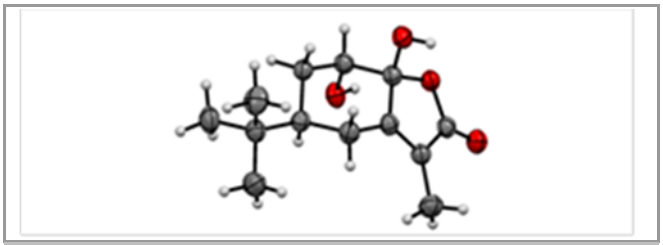
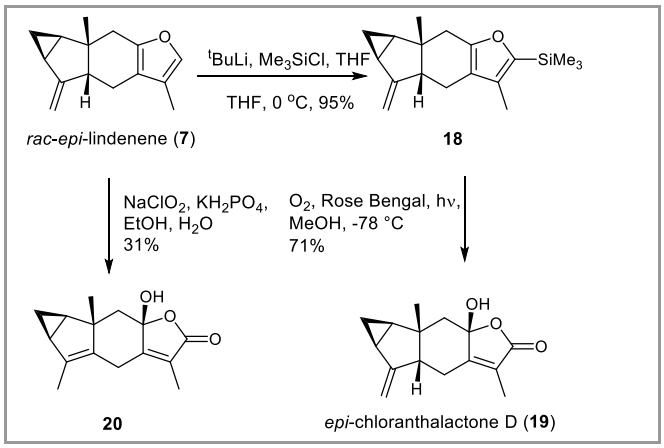


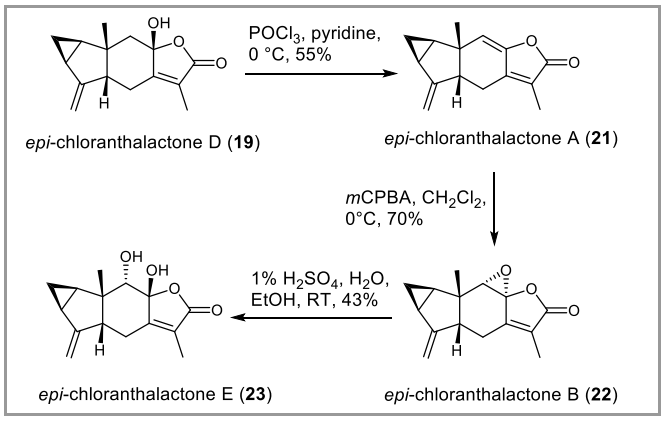
Figure 5 ORTEP representation of compound **17** with thermal ellipsoids at 50% probability.

Having gathered sufficient information on the chemical modifications of model compound **11**, we then attempted similar transformations using *rac*-*epi*-lindenene (**7**) as starting material. Deprotonation of **7** with *n*-butyllithium and quenching the resultant anion with chlorotrimethysilane delivered **18** which was oxidised by singlet oxygen to *epi*-chloranthalactone D (**19**). It should be noted that this reaction was selective and no allylic oxidation of the exocyclic olefin was observed. Surprisingly, attempts to streamline the synthesis by subjecting *epi*-lindenene (**7**) to Clive's one step oxidation reaction that successfully oxidised the model compound **11** instead yielded compound **20** in moderate yield in which the migration of the double bond to the endocyclic position was observed despite the presence of monopotassium phosphate as buffer (Scheme 6).



Scheme 6 Chemical modification of *rac-epi*-lindenene (**7**).

Compound **19** was then dehydrated with phosphoryl chloride[1] and pyridine to *epi*-chloranthalactone A (**21**) which was converted to *epi*-chloranthalactone B (**22**), using *m*CPBA without affecting the exocyclic double bond. Ring opening of **22** with a catalytic amount of sulphuric acid delivered *epi*-chloranthalactone E (**23**) as product (Scheme 7).



Scheme 7 Chemical modifications of *epi*-chloranthalactone D (**19**) to the other *epi*-chloranthalactone derivatives.

In summary we have investigated various methods for the oxidative conversion of the furan ring to hydroxyfuranone, a moiety that is found in the natural product chloranthalactone D (**4**). By using *epi*-lindenene (**7**) as starting material, *epi*-chloranthalactone D (**19**) was successfully synthesised via singlet oxygen oxidation. This compound was found to be a versatile precursor for the synthesis of *epi*-chloranthalactones A, B, D and E. We believe that this route will provide an expeditious approach towards the synthesis of the natural chloranthalactones.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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(10) The X-ray crystallographic data has been deposited with the Cambridge Crystallographic Data Centre (CCDC 1587570 (**14**), 1587571 (**16**) and 1587572 (**17**)). These files can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/dat_request/cif.

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(12) To a stirred solution of silylfuran **15** (362mg, 1.53mmol) in MeOH (50mL) and THF (10mL) was added Rose Bengal (10mg), and the mixture was cooled to -78°C. A steady stream of $O_{2(g)}$ was bubbled through the solution, and the reaction was irradiated with two 150W tungsten lamps for 2h, after which the lamps were removed and the flow of O_2 ceased. The reaction mixture was warmed to RT and the solvents removed *in vacuo* to yield a crude pink coloured residue, which was purified by flash chromatography (P.E. 30-40:Et_2O, 1:1) to furnish hydroxybutenolide **12** (326mg, 95%). m.p. 142-143°C; R_f 0.15 (P.E. 30-40:Et_2O, 1:1); ν_{max}(KBr disc)/cm^{-1} 3341s br, 3080m, 2931s, 2861s, 1740s, 1699s, 1430m, 1121s, 890m; δ_H(400MHz, $CDCl_3$) 0.96 (9H, s, ^{t}Bu), 1.22 (1H, app t, J = 7.0Hz, 5-CH), 1.49-1.59 (2H, m, 6-CH, 7-CH), 1.81 (3H, s, 3-C-CH_3), 1.86 (1H, m, 6-CH),

2.09 (1H, dt, J = 12.5Hz, 1.5Hz, 4-CH), 2.42 (1H, dd, J = 3.0Hz, 10.0Hz, 7-CH), 2.74 (1H, dm, J = 13.0Hz, 4-CH), 3.20 (1H, br s, OH); δ_C(100.6MHz, $CDCl_3$) 8.1 (3-C-$\underline{C}H_3$), 23.3 (6-C), 26.2 (4-C), 27.5 (RC($\underline{C}H_3$)$_3$), 32.8 (R$\underline{C}$(CH_3)$_3$), 37.7 (7-C), 49.7 (5-C), 103.2 (7a-C), 121.4 (3-C), 161.4 (3a-C), 173.2 (2-C); *m/z* (ES)$^-$ 223.26 [(M−H)$^-$, 100%].

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