Total syntheses of (+)-7-epi-goniofufurone, (+)-goniopypyrone and (+)-goniofufurone from a common precursor†

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Total syntheses of (+)-7-epi-goniofufurone, (+)-goniopypyrone and (+)-goniofufurone have been achieved from an advanced common precursor formed from D-(+)-mannitol by changing the carbinol protection profile.

The plant family Annonaceae has, for a long time, aroused considerable interest from the pharmacological point of view, due mainly to its polyketide constituents.[1] The genus *Goniothalamus* comprises several species of shrubs and trees growing in Asia and has long been recognized as a potential source of chemotherapeutic agents.[2] The extracts and leaves from these plants have traditionally been used for the treatment of edema and rheumatism,[3] as a pain killer and mosquito repellent,[4] and also as an abortifacient.[5] Bioactivity-directed studies by McLaughlin on the ethanolic extracts of the stem bark of *Goniothalamus giganteus* Hook f. Thomas have resulted in the isolation and characterization of a series of novel styryllactones that possess pesticidal, ratogenic and embryotoxic activity, and marginal to significant cytotoxic activity against several human tumor cell lines.[2a,6]

Related to the size of the lactone ring, these styryllactones can be classified into two main groups (Fig. 1). In the group comprising γ-lactones, (+)-goniofufurone **1** shows significant cytotoxic activity to several human tumor cell lines and moderate toxicity to brine shrimp (BS). In contrast, the isomeric (+)-7-epi-goniofufurone **2** is only weakly bioactive.[2a,6b–d,h,7] The absolute configurations were established independently by Shing and Jäger from the syntheses of *ent*-(−)-goniofufurone and (−)-epi-goniofufurone respectively.[8] (+)-Goniopypyrone **3**, a δ-lactone, is the most bioactive constituent and shows non-selective cytotoxicity to several human tumor cell lines such as lung carcinoma A-549, breast adenocarcinoma MCF-7, and colon adenocarcinoma HT-29. It also exhibits high toxicity to BS and causes significant inhibition of the formation of crown gall tumors on potato discs (PD).[6b,c] Shing *et al.* have confirmed its absolute configuration by total synthesis from D-*glycero*-D-*gulo*-heptono-γ-lactone.[9]

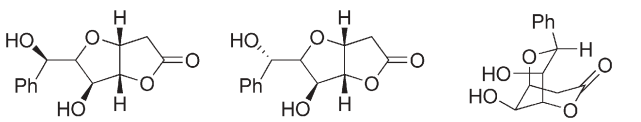

Fig. 1 Selected bioactive styryllactones from *Goniothalamus* species.

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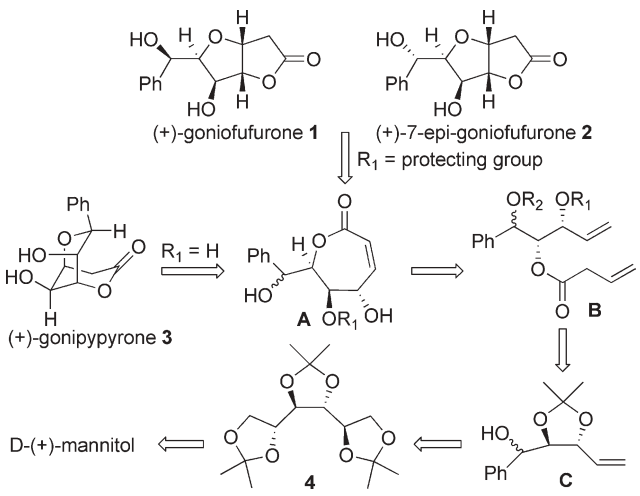
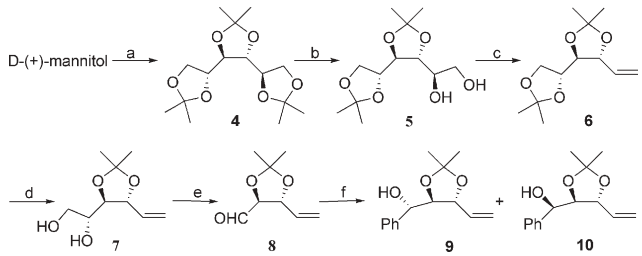
The combination of the fascinating structures and the broad spectrum biological activity has prompted comprehensive efforts for the syntheses of these styryllactones.[10] As a part of our continuing goal of the fabrication of the heavily oxygenated styryllactones, we have recently modified our previous poor yielding racemic strategy[11] and achieved formal total syntheses of Hagen's gland lactones and *trans*-kumausynes through an enantiospecific route that involves ring-closing metathesis and base-assisted single-step rearrangement of a 7-substituted-4,5-epoxy-2-oxepanone to the requisite 2,6-dioxabicyclo[3.3.0]octan-3-one skeleton as the two key steps.[12] In this communication, we disclose the syntheses of (+)-7-epi-goniofufurone **2**, (+)-goniopypyrone **3** and (+)-goniofufurone **1** from a single D-(+)-mannitol-derived precursor by employing the above rearrangement protocol, though in differential manners.

Retrosynthetic analysis of the styryllactones comprising γ- and δ-lactone motifs envisions the α,β-unsaturated lactone **A** (Scheme 1) as a key intermediate for its further transformation into the bicyclic species. Lactone **A** was traced to **B** that comprises three contiguous asymmetric centers and an alkene tether. Further disconnection of **B** shows it to be derivable from the known styryl alcohol **C**[13] *via* sequential protection of the hydroxyl group, acetonide cleavage, selective protection of the allyl alcohol, and esterification of the remaining alcohol. The alcohol **C** is readily accessible from tri-*O*-isopropylidene-D-(+)-mannitol **4**,[14] the terminal acetonides acting as surrogates to the generation of the styryl alcohol and the olefin.

The synthetic sequence commenced with the formation of the terminal diol **5** (Scheme 2) from the triacetonide **4** by a slight



Scheme 1 Retrosynthetic analysis of selected styryllactones.

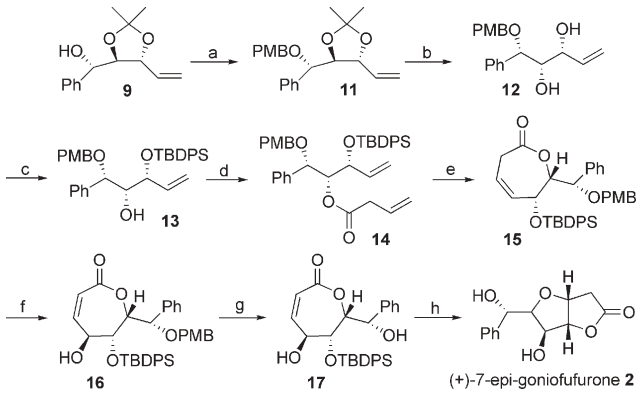


Scheme 2 *Reagents and conditions:* (a) (i) H_2SO_4, acetone, 25 °C, 6 h; (ii) aq. NaOH, 85%; (b) (i) EtOH, H_2O, HCl, 45 °C, 1 h; (ii) K_2CO_3, 99%; (c) (i) PPh_3–imidazole–iodine, toluene, 110 °C, 3 h; (ii) aq. $Na_2S_2O_3$, aq. $NaHCO_3$, 81%; (d) $CuCl_2{\cdot}2H_2O$, CH_3CN, 0 °C, 40 min, 99.9%; (e) $Pb(OAc)_4$, CH_2Cl_2, 0 °C, 3 h, 99%; (f) PhMgBr, THF, 0–25 °C, 8 h, 78%.

modification of a literature method.[14] $Pb(OAc)_4$-cleavage of **5** followed by Wittig reaction provided the terminal olefin **6** in poor yield along with an unidentifiable mixture of products. Ph_3P–imidazole–iodine in toluene, however, led to a smooth one-step conversion of **5** into **6** in 81% yield.[15] The diacetonide **6** underwent selective hydrolysis of the terminal acetonide using an equivalent amount of $CuCl_2{\cdot}2H_2O$ at 0 °C to generate the diol **7** in quantitative yield.[16] $Pb(OAc)_4$-cleavage of **7** furnished **8** which, without purification, was reacted with an excess of PhMgBr at 0 °C to provide the diastereomeric alcohols **9** and **10** in 1.5 : 1 ratio.[13] While the carbinol stereochemistry present in **9** is suitable for the syntheses of (+)-7-epi-goniofufurone **2** and (+)-goniopypyrone **3**, that in **10** is suitable for the synthesis of (+)-goniofufurone **1**. The key building blocks **9** and **10** were thus synthesized in a facile manner from D-(+)-mannitol in a combined 52% overall yield.

The results of the initial studies for the regioselective protection of the two terminal hydroxyl groups leaving the middle one free for esterification were frustrating. The reaction of the triol obtained from acetonide cleavage of **9** as a 3,5-benzylidene derivative using *p*-methoxybenzaldehyde dimethyl acetal and PPTS gave a complex mixture. The three-step conversion involving sequential PMB protection of the free carbinol in **9**, acetonide cleavage, and DDQ-promoted transformation to the 3,5-benzylidene derivative[17] was also unsuccessful as it generated only the 4,5-benzylidene compound. We therefore investigated several combinations of protecting groups for the sequential protection of the styryl alcohol and the allylic alcohol formed from acetonide cleavage. PMB and TBDPS used for the protection of the styryl alcohol and the allyl alcohol, respectively, offered excellent yields and selectivity. Thus, PMB protection of the styryl alcohol in **9** and acetonide cleavage by aqueous AcOH produced the diol **12** (Scheme 3). Reaction of **12** with 1.0 equiv. of TBDPSCl and 3.0 equiv. of imidazole furnished a 1 : 8 mixture of the bis-protected and the requisite mono-protected products that were separated easily by radial chromatography.

Esterification of **13** with vinylacetic acid led to the formation of **14** in 77% yield along with the isolation of the starting material which was separated easily by radial chromatography. To avoid isomerization of the double bond by prolonged exposure to the reaction conditions, the reaction was arrested before complete disappearance of the starting material. Grubbs' ring-closing metathesis of **14** proceeded well under dilute conditions and the seven-membered ring lactone **15** was isolated in 82% yield. The

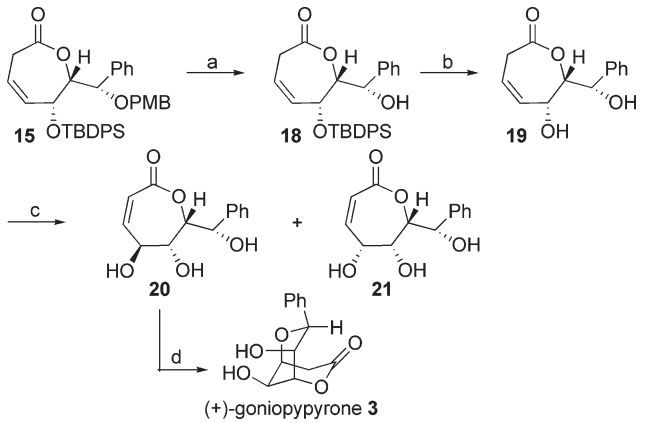


Scheme 3 *Reagents and conditions:* (a) *p*-methoxybenzyl bromide, NaH, THF, 0–25 °C, 6 h, 93%; (b) 5 : 2 AcOH–H_2O, 50 °C, 4 h, 99%; (c) TBDPSCl, imidazole, CH_2Cl_2, 0–25 °C, 12 h, 95%; (d) vinylacetic acid, DCC, DMAP, CH_3CN, 0–25 °C, 10 h, 77%; (e) 5 mol% Grubbs' 2nd generation catalyst, C_6H_6, 80 °C, 10 h, 82%; (f) *m*-CPBA, $NaHCO_3$, 45 °C, 48 h, 78%; (g) 5% HF in CH_3CN, 25 °C, 24 h, 78%; (h) (i) DBU, $CHCl_3$, 25 °C, 24 h, 70%; (ii) TBAF, AcOH, THF, 0 °C, 5 min, 98%.

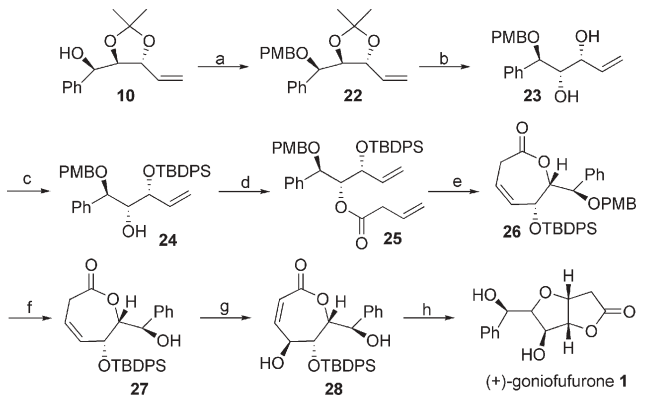
Ru-catalyst was noted to cause isomerization of the isolated olefin in **14** in conjugation with the carbonyl function under the reaction conditions, necessitating arrest of the reaction before completion.

Oxidation of **15** by *m*-CPBA and $NaHCO_3$ in CH_2Cl_2 by the Immediate Solvent Evaporation Method (ISEM)[18] furnished the γ-hydroxy-α,β-unsaturated-7-membered ring lactone **16** in 78% yield based on 60% of the starting material having been recovered. Cleavage of the PMB group with 5% HF in CH_3CN furnished the diol **17** in 78% yield which rearranged, on exposure to DBU, to the required bicyclo[3.3.0] skeleton through a two-step protocol involving (a) transformation of the seven-membered ring lactone into a five-membered ring lactone, and (b) a second ring closure through an intramolecular Michael addition. Finally, desilylation using TBAF afforded (+)-7-epi-goniofufurone **2**. The spectral and physical properties of the synthetic (+)-7-epi-goniofufurone **2** were identical to those reported in the literature.[6d]

The long reaction time required for the epoxidation and moderate yields of PMB-cleavage using HF and DBU-promoted rearrangement prompted us to remove all the protecting groups before the oxidation of the double bond in the RCM product. We wished to generate triol **20** (Scheme 4) and study its rearrangement, hoping to generate both (+)-7-epi-goniofufurone through γ-lactone formation from the engagement of the C5-alcohol and (+)-goniopypyrone through δ-lactone formation from the engagement of the C6-alcohol in the first step of the rearrangement. Cleavage of PMB in **15** using Ph_3CBF_4, according to a literature procedure,[19] proceeded smoothly to generate the alcohol **18** in 95% yield. Reflux of **18** with CBr_4 in MeOH generated **19** in 85% yield.[20] Oxidation of the double bond using *t*-BuOOH–$VO(acac)_2$ afforded a 5 : 1 mixture of the γ-hydroxy-α,β-unsaturated lactones **20** and **21**. DBU treatment of **20** led to the formation of only (+)-goniopypyrone **3** in excellent yield. The spectral and physical properties of the synthetic (+)-goniopypyrone **3** were identical to those reported in the literature.[6c] The failure to form (+)-7-epi-goniofufurone is in accord with Vatèle's observation[21a] that dismisses Shing's hypothesis[21b] of (+)-7-epi-goniotriol being a biogenetic precursor of (+)-7-epi-goniofufurone.



Scheme 4 *Reagents and conditions:* (a) Ph_3CBF_4, CH_2Cl_2, 25 °C, 30 s, 95%; (b) CBr_4, MeOH, 65 °C, 12 h, 85%; (c) *t*-BuOOH–$VO(acac)_2$, C_6H_6, 0–25 °C, 10 h, 80%; (d) DBU, $CHCl_3$, 25 °C, 0.5 h, 84%.



Scheme 5 *Reagents and conditions:* (a) *p*-methoxybenzyl bromide, NaH, THF, 0–25 °C, 6 h, 91%; (b) 5 : 2 AcOH–H_2O, 50 °C, 4 h, 99%; (c) TBDPSCl, imidazole, CH_2Cl_2, 0–25 °C, 12 h, 73%; (d) vinylacetic acid, DCC, DMAP, CH_3CN, 0–25 °C, 8 h, 78%; (e) 5 mol% Grubbs' 2nd generation catalyst, C_6H_6, 80 °C, 10 h, 85%; (f) Ph_3CBF_4, CH_2Cl_2, 25 °C, 5 min, 94.5%; (g) *m*-CPBA, CH_2Cl_2, 45 °C, 24 h, 96%; (h) (i) DBU, $CHCl_3$, 25 °C, 24 h, 82%; (ii) TBAF, AcOH, THF, 0 °C, 5 min, 99%.

The synthesis of (+)-goniofufurone **1** from **10** by following the steps outlined in Scheme 3 was problematic for achieving epoxidation of the species equivalent to **15**. However, PMB-cleavage before epoxidation worked well as shown in Scheme 5. The key intermediate **28** rearranged to (+)-goniofufurone **1** after DBU-treatment and desilylation, in that order. The spectral and physical properties of synthetic (+)-goniofufurone **1** were identical to those reported in the literature.[6c]

In summary, we have achieved the total syntheses of (+)-7-epi-goniofufurone, (+)-goniopypyrone and (+)-goniofufurone from a common precursor simply by changing the sequence of carbinol protection and thus allowing the formation of either a γ-lactone or a δ-lactone in the first step of the rearrangement that leads to further ring closure to generate, respectively, the bicyclo[3.3.0] skeleton of goniofufurones or the [3.3.1] skeleton of goniopypyrone.

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