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First total synthesis of the highly potent antitumor lactones 8-chlorogoniodiol and parvistone A: Exploiting a bioinspired late-stage epoxide ring-opening

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ABSTRACT

The first protecting group-free total syntheses of the highly potent antitumor chlorinated styryllactone secondary metabolites 8-chlorogoniodiol, parvistone A, and one analogue 8-*epi*-parvistone A, have been accomplished from commercially available *trans*-cinnamaldehyde in five steps with high overall yields. The chlorine-bearing stereogenic center of these silent secondary metabolites was introduced via a bioinspired late-stage regioselective epoxide ring-opening strategy. Maruoka asymmetric allylation, acrylation, ring-closing metathesis and asymmetric epoxidation, greatly facilitate the synthesis of the key intermediates goniothalamin oxide and (6*S*,7*S*,8*S*)-isogoniothalamin oxide.

1. Introduction

More than 5000 halogen containing natural products have been discovered from Nature in the past few decades.[1] These halogenated natural products possess a broad range of biological activities of pharmacological interest, including antifungal, antitumor, antibiotic, anti-inflammatory and antiviral activities.[2] The presence of halogen atoms in many bioactive molecules has a profound influence on their biological activity.[3] A large number of drugs and drug candidates in clinical development are halogenated compounds. Some examples of halogenated natural products include the remarkably potent anticancer agents salinosporamide A, spongistatin, rebeccamycin, and calicheamicin, and a number of antibiotics, such as vancomycin, chlortetracycline, and chloramphenicol.

8-Chlorogoniodiol **1a** (Fig. 1) is the first styryllactone possessing a chlorine atom, which was isolated from the aerial parts of *Goniothalamus amuyon* by Yang-Chang Wu et al. in 2003.[4] It was also isolated from the same plant two years later by the same group, and evaluated for the cytotoxicity against several tumor cell lines.[5] 8-Chlorogoniodiol **1a** showed highly potent cytotoxicity against Human hepatocellular carcinoma (HepG2), Human hepatoma cell line (Hep3B), Human breast cancer cell lines (MDA-MB-231) and Human breast carcinoma (MCF-7) with IC_{50} values of 0.64, 3.64, 1.47 and 2.32 μg/mL respectively. It also showed significant selective cytotoxicity against human gastric cancer (HONE-1) cell line with an IC_{50} value of 4.87 ± .080 μg/mL.

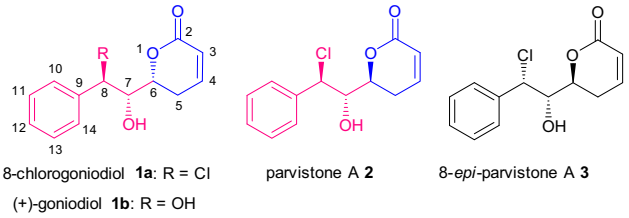

Figure 1. Structures of goniodiol and chlorinated analogues.

Parvistone A **2** is another new chlorinated styryllactone, very recently isolated from the leaves of *Polyalthia parviflora*,[6] a shrubby tree found in different Asian countries including Thailand, Malaysia, and Cambodia, which is found to possess cytotoxic activities against Hep G2, MDA-MB-231 and A549 cancer cell lines. In addition, parvistone A **2** exhibits selective anti-inflammatory activity against superoxide anion with IC_{50} value of 30.0 ± 2.5 μM.[6]

The styryllactone's activity was highly influenced by the substituents at C-8, and showed the potency order as follows: Cl > OCH_3 > epoxide > OH. The 8-chlorogoniodiol **1a** was 15-, 5- and 6-fold more potent than (+)-goniodiol **1b** against HepG2, Hep3B and MDA-MB-231 human cancer cell lines respectively.[4,5] In the case of human breast carcinoma (MCF-7) cell lines,

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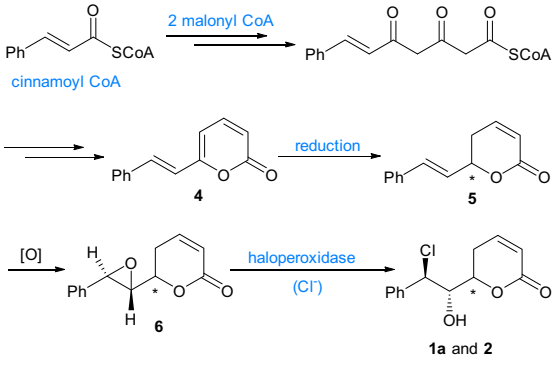
8-chlorogoniodiol **1a** (IC_{50} = 2.32 μg/mL) was more active than doxorubicin drug (DOX, IC_{50} = 2.51 μg/mL). The structures and the absolute configurations of 8-chlorogoniodiol and parvistone A were established by extensive 1D, 2D NMR spectroscopic analysis and X-ray crystallographic data.[4,6]

Although numerous extensive synthetic endeavours have been documented in the literature with regards to the total synthesis of diverse styryllactones,[7] the synthetic efforts toward highly potent bioactive chlorinated styryllactones have not yet been reported. Architecturally, 8-chlorogoniodiol and parvistone A are δ-lactones embedded with three contiguous stereogenic centers.

The presence of a chlorine-bearing stereogenic center at the active benzylic position, and an α,β-unsaturated δ-lactone skeleton made these molecules synthetically challenging. The highly potent biological activities of **1a** and **2**, their natural scarcity and their structural complexity of chlorine-bearing stereogenic center prompted us to explore the total synthesis of 8-chlorogoniodiol and parvistone A. In continuation of our syntheses of bioactive natural products,[8,9] we herein report the first total syntheses of the 8-chlorogoniodiol **1a**, parvistone A **2** and 8-*epi*-parvistone A **3** from inexpensive commercially available *trans*-cinnamaldehyde using the modern concept of step economy, atom economy and protecting group-free total synthesis.

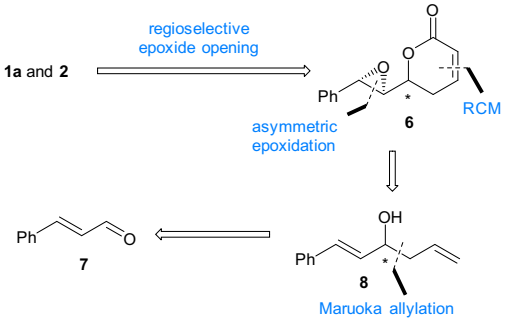
Through investigating the structures of styryllactones, a plausible biosynthetic pathway was proposed by Chang et al.[6] (Scheme 1). The condensation of cinnamoyl-CoA with two molecules of malonyl-CoA followed by reduction, lactonization and dehydration, provides lactone **4**. Hydrogenation of **4** could provide goniothalamin **5**, which could be further oxidized at the benzylic double bond to give the corresponding lactone epoxide **6**. Epoxide ring opening of **6** followed by chlorination in the presence of haloperoxidase generates the chlorinated styryllactones **1a** and **2**.



Scheme 1. Plausible biogenetic pathway of **1a** and **2**.

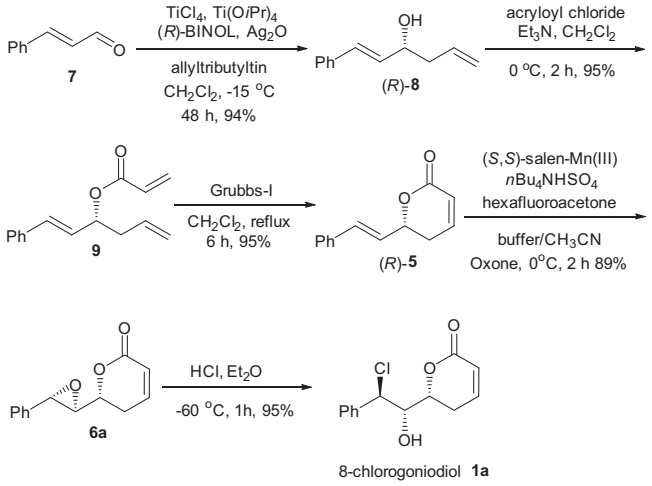
2. Results and discussion

Lactones **1a** and **2** contain three contiguous stereocenters and display a clear structural similarity. The structural difference between these two compounds lies in the configuration of the lactone centre. Biosynthetically, the chlorinated styryllactones have been proposed to originate from the lactone epoxide **6** precursor through a regio and stereoselective epoxide ring opening. Therefore, our retrosynthetic analysis of these natural products revealed that the commercially available *trans*-cinnamaldehyde would be an ideal starting material as outlined in Scheme 2. The asymmetric allylation, asymmetric epoxidation, acrylation and ring-closing metatheses are the key steps to secure the preparation of the key intermediate lactone epoxide **6**. Regioselective epoxide ring-opening of **6** with chloride should complete the total synthesis of the target chlorinated natural products.



Scheme 2. Retrosynthetic analysis of **1a** and **2**.

The preparation of the key building blocks **6a** and **6b** was achieved in a concise and scalable way from inexpensive commercially available *trans*-cinnamaldehyde.[9] The synthesis of goniothalamin oxide **6a** was envisaged by the Maruoka asymmetric allylation[10] of commercially available *trans*-cinnamaldehyde **7** with allyltributyltin, in the presence of (*R*)-BINOL, $Ti(O^iPr)_4$, and Ag_2O at −15 °C to give homoallylic alcohol (*R*)-**8** in 94% yield and with 94% ee. Alcohol (*R*)-**8** was treated with acryloyl chloride in the presence of triethylamine in CH_2Cl_2 to furnish the corresponding acryloyl ester **9**. Ring closing metathesis[11] of the two terminal double bonds in **9** was performed using a first generation Grubb's catalyst in CH_2Cl_2 at reflux to provide desired unsaturated lactone (*R*)-**5**. Epoxidation of α,β-unsaturated δ-lactone (*R*)-**5** with *m*-chloroperoxybenzoic acid in CH_2Cl_2 at 0 °C yielded a 3:2 mixture of diastereoisomers, with the desired epoxide lactone **6a** as the major isomer. The catalytic asymmetric epoxidation of (*R*)-**5** under Han's reaction conditions[12] with Oxone® in the presence of (*S*,*S*)-salen–Mn(III) catalyst yielded the key intermediate goniothalamin oxide **6a** in 89% yield with a 98:2 diastereomeric ratio (Scheme 3).



Scheme 3. Synthesis of 8-chlorogoniodiol **1a**.

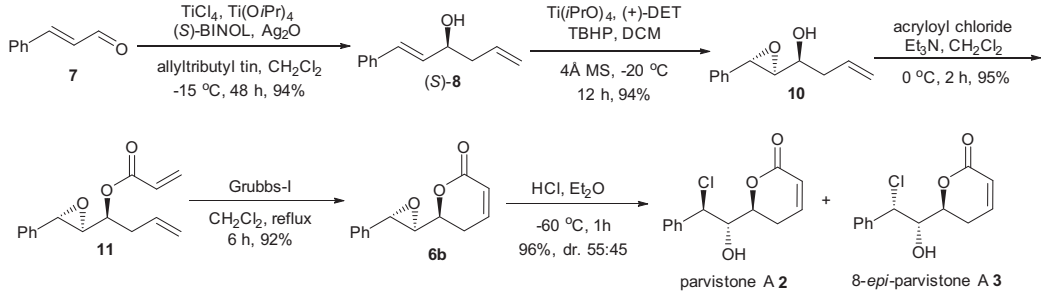
At this stage, the introduction of the halogen-bearing stereogenic center in a highly regio- and stereoselective manner via S_N2 opening of epoxide **6a** with a chloride nucleophile was evaluated. Initially, the substrate goniothalamin oxide **6a** in Et_2O was treated with $SOCl_2$ at 0 °C.[13] After 1 h, an inseparable mixture of 8-chlorogoniodiol **1a** and its C-8 epimer (dr. 8:2) was obtained in 95% yield. Further attempts to improve the diastereoselectivity by switching the catalyst to chlorotrimethylsilane (TMSCl)[14] in $CHCl_3$ at 0 °C gave a similar result. When the hydrochloric acid in ether was used at −60 °C, the reaction proceeded well to give an improved diastereomeric ratio (>10:1) with 95% yield.[14] At this

stage, the pure enantiomer of 8-chlorogoniodiol **1a**[15] was obtained by recrystallization. The spectroscopic data of synthetic **1a** matched well with that reported for the natural product (Table 1). Moreover, the specific rotation value of synthetic **1a** was $[\alpha]_D^{25}$ = +13.1 (*c* 0.3, $CHCl_3$), which corresponded to the reported value $[\alpha]_D^{25}$ = +13.7 (*c* 0.3, $CHCl_3$)[4] for the natural product.

Next, we turned our attention to the total synthesis of parvistone A **2** (Scheme 4). The enantiomerically pure alcohol (*S*)-**8** (94% ee) was prepared from the commercially available *trans*-cinnamaldehyde using Maruoka asymmetric allylation reaction. Sharpless asymmetric epoxidation[16] of alcohol (*S*)-**8** in the presence of (+)-diethyl tartrate, *tert*-butyl hydroperoxide, and $Ti(O^iPr)_4$ in CH_2Cl_2 provided the desired epoxyalcohol **10** as sole product. However, the treatment of alcohol (*S*)-**8** with m-chloroperbenzoic acid (m-CPBA) performed at room temperature in DCM allowed the corresponding epoxides to be obtained in a 1.5:1 mixture, with the desired epoxide **10** as a minor isomer. The treatment of epoxyalcohol **10** with acryloyl chloride gave the corresponding acryloyl ester **11**, which was then subjected to RCM using Grubbs' first-generation catalyst in CH_2Cl_2 to furnish the desired (6*S*,7*S*,8*S*)-isogoniothalamin oxide **6b** in 92% yield. Similarly, intermediate **6b** was also obtained from δ-lactone (*S*)-**5** by (*S*,*S*)-salen–Mn(III) catalyzed epoxidation with Oxone® as a 98:2 diastereomeric ratio in 90% yield. Finally, the ring-opening of oxirane **6b** was achieved with HCl in Et_2O at −60 °C to obtain a mixture of diastereomers **2** and **3**. These chlorinated lactones were efficiently separated by flash column chromatography to give natural parvistone A **2** and unnatural 8-*epi*-parvistone A **3** in 53 and 43% yields, respectively.[17–19] The spectroscopic data of synthetic **2** matched well with that reported for the natural product (Table 2). Moreover,

Table 1
Comparison of ^1H and ^{13}C NMR data of synthetic **1a** and natural 8-chlorogoniodiol

^1H NMR				^{13}C NMR			
H	Natural	Synthetic	$(\Delta\delta)_{N,S}$	C	Natural	Synthetic	$(\Delta\delta)_{N,S}$
				2	163.5	163.5	0.0
3	6.05 (dd, 9.8, 2.6)	6.06 (ddd, 9.7, 3.6, 0.7)	0.01	3	120.8	120.8	0.0
4	6.98 (ddd, 9.8, 6.2, 2.0)	6.99 (ddd, 9.7, 6.3, 2.0)	0.01	4	145.7	145.7	0.0
5	2.87 (ddt, 18.4, 12.8, 2.6)	2.87 (m)	0.00	5	26.2	26.2	0.0
	2.32 (ddd, 18.4, 6.4, 4.0)	2.33 (m)	0.01				
6	5.16 (dd, 12.8, 4.0)	5.16 (ddd, 12.7, 3.7, 1.2)	0.00	6	75.8	75.8	0.0
7	3.96 (d, 9.0)	3.97 (br t, 8.0)	0.01	7	75.4	75.4	0.0
8	5.12 (d, 9.0)	5.12 (d, 9.7)	0.00	8	60.0	60.0	0.0
Ph	7.39 (m, 5H)	7.41 (m, 5H)	0.02	9	138.1	138.0	−0.1
				10	128.1	128.1	0.0
				11	128.9	128.9	0.0
				12	129.0	129.0	0.0
				13	128.9	128.9	0.0
				14	128.1	128.1	0.0



Scheme 4. Synthesis of parvistone A **2** and 8-*epi*-parvistone A **3**.

Table 2
Comparison of ^1H and ^{13}C NMR data of synthetic **2** and natural parvistone A

^1H NMR				^{13}C NMR			
H	Natural	Synthetic	$(\Delta\delta)_{N,S}$	C	Natural	Synthetic	$(\Delta\delta)_{N,S}$
				2	163.4	163.1	−0.3
3	6.02 (ddd, 10.4, 2.8, 1.2)	6.01 (ddd, 9.7, 2.7, 1.0)	−0.01	3	121.0	121.0	0.0
4	6.91 (ddd, 10.4, 5.8, 2.8)	6.91 (ddd, 9.7, 6.1, 2.5)	0.00	4	145.2	145.2	0.0
5	2.54 (ddt, 19.7, 5.8, 1.2)	2.52 (ddt, 18.4, 6.1, 1.0)	−0.02	5	24.6	24.6	0.0
	2.62 (ddt, 19.7, 10.8, 2.8)	2.61 (ddt, 18.4, 10.9, 2.5)	−0.01				
6	4.36 (ddd, 10.8, 5.8, 4.0)	4.35 (ddd, 10.8, 6.4, 4.2)	−0.01	6	77.2	77.2	0.0
7	4.32 (ddd, 9.6, 5.6, 4.0)	4.32 (dt 5.4, 2.5)	0.00	7	75.5	75.5	0.0
8	5.13 (d, 5.6)	5.13 (d, 5.4)	0.00	8	62.1	62.1	0.0
Ph	7.42 (m, 5H)	7.43 (m, 5H)	0.01	9	136.4	136.4	0.0
				10	128.5	128.5	0.0
				11	128.6	128.6	0.0
				12	129.0	129.0	0.0
				13	128.6	128.6	0.0
				14	128.5	128.5	0.0

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the specific rotation value of synthetic **2** was $[\alpha]_D^{25} = -114$ (*c* 0.21, CH_2Cl_2), which corresponded to the reported value $[\alpha]_D^{22} = -124$ (*c* 0.22, CH_2Cl_2)[6] for the natural product.

3. Conclusion

In conclusion, we have disclosed a highly efficient stereoselective total synthesis of 8-chlorogoniodiol **1a**, parvistone A **2** and 8-*epi*-parvistone A **3** for the first time. The key step in their total syntheses is the bioinspired late-stage epoxide ring-opening reaction. 8-Chlorogoniodiol **1a**, parvistone A **2** and 8-*epi*-parvistone A **3** were synthesised in five linear steps from inexpensive commercially available *trans*-cinnamaldehyde in excellent overall yields. This concise and protecting group-free synthetic strategy provides new insights in the potential synthesis of these halogenated secondary metabolites and offers opportunities to create analogues for anticancer drug discovery.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.01.005.

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15. *Experimental procedure and analytical data for 8-chlorogoniodiol **1a**:* To a stirred solution of goniothalamin oxide **9a** (0.5 g, 2.31 mmol) in CH_2Cl_2 (50 mL) at −60 °C was added 4 M HCl in Et_2O (2.89 mL, 11.5 mmol), and the reaction mixture was stirred for a further 1 h. The solvent was evaporated under reduced pressure, and purified by flash column chromatography (hexane: EtOAc, 6:4) to give 8-chlorogoniodiol **1a** (554 mg, 95%, dr: >10:1). Pure 8-chlorogoniodiol **1a** (320 mg, 55%) was obtained by recrystallization. $[\alpha]_D^{25}$ = +13.1 (*c* 0.3, $CHCl_3$), lit.[4] $[\alpha]_D^{25}$ = +13.7 (*c* 0.3, $CHCl_3$). ESI MS: *m/z* 253 $[M+H]^+$, 275 $[M+Na]^+$. HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{13}H_{14}O_3Cl$: 253.06260; found: 253.06227.
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17. *Experimental procedure for parvistone A **2** and 8-epi-parvistone A **3**:* To a stirred solution of (6*S*,7*S*,8*S*)-isogoniothalamin oxide **6b** (0.5 g, 2.31 mmol) in CH_2Cl_2 (50 mL) at -60 °C was added 4 M HCl in Et_2O (2.89 mL, 11.5 mmol), and the reaction mixture was stirred for a further 1 h. The solvent was evaporated under reduced pressure, and purified by flash column chromatography (hexane:EtOAc, 6:4) to give parvistone A **2** (308 mg, 52.8%) and 8-*epi*-parvistone A **3** (252 g, 43.2%).
18. *Analytical data for parvistone A **2***: $[\alpha]_D^{25} = -114$ (*c* 0.21, CH_2Cl_2), lit.[6] $[\alpha]_D^{22} = -124$ (*c* 0.22, CH_2Cl_2). ESI MS: *m/z* 253 $[M+H]^+$, 275 $[M+Na]^+$. HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{13}H_{14}O_3Cl$: 253.06260; found: 253.06260.
19. *Analytical data for 8-epi-parvistone A **3***: $[\alpha]_D^{25} = -33.2$ (*c* 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.33 (m, 5H), 6.92 (ddd, *J* = 9.7, 5.6, 2.8 Hz, 1H), 6.01 (dt, *J* = 9.7, 2.4 Hz, 1H), 5.39 (d, *J* = 3.3 Hz, 1H), 4.48 (ddd, *J* = 10.7, 7.2, 5.0 Hz, 1H), 4.10–4.05 (m, 1H), 2.59–2.47 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.1, 145.1, 137.8, 128.9, 128.8 (2C), 127.5 (2C), 121.1, 76.9, 75.8, 63.4, 25.3 ppm. ESI MS: *m/z* 253 $[M+H]^+$, 275 $[M+Na]^+$. HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{13}H_{14}O_3Cl$: 253.06260; found: 253.06261.