An Alternative Approach to the Synthesis of Parvistone C

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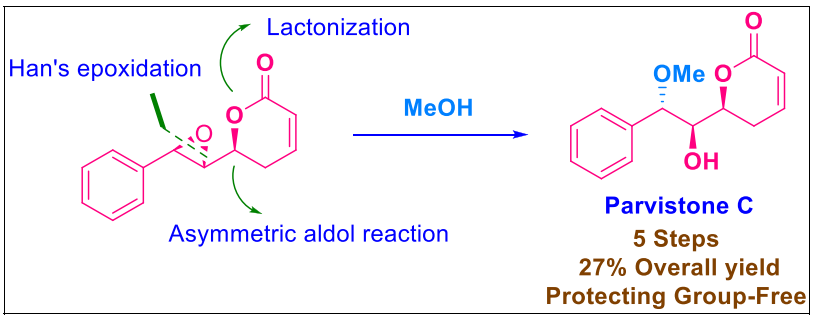

A stereoselective total synthesis of parvistone C, an oxygenated natural styryllactone, has been accomplished in excellent overall yield by employing asymmetric aldol reaction, asymmetric epoxidation and regioselective epoxide ring opening as the key steps. Our synthetic strategy is very simple, concise and no use of protecting groups.

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INTRODUCTION

Chiral lactone rings are widely distributed in many biologically active natural products [1]. Particularly, α,β-unsaturated δ-lactone gained the great attention of researchers due to a variety of pharmaceutical properties including antitumor, antifungal, antibacterial, and immunosuppressive properties [2]. A series of new 6*S*-styryllactones parvistone A-E were isolated from a methanolic extract of *Polyalthia parviflora* leaves by Liou *et al*. in 2014 [3]. Their structures were elucidated on the basis of NMR spectroscopy and single-crystal X-ray analysis. These compounds exhibit potent anti-inflammatory and cytotoxic properties. Parvistone C (**1b**) is structurally related to parvistone B (**1a**) and differs in the stereochemical configurations (Figure 1).

Recently, asymmetric total syntheses of parvistone A-E natural products have been reported in the literature [4]. Very recently, Radha Krishna *et al*. [4e] disclosed the first total synthesis of parvistone C (**1b**) starting from commercially available 1,3-propane diol in 13 steps with 13% overall yield. They employed a Sharpless asymmetric dihydroxylation, stereoselective aryl Grignard reactions, Still–Gennari olefination, and intramolecular cyclization as the key steps (Scheme 1). Herein, we report a five-step total synthesis of parvistone C (**1b**) from commercially available, inexpensive trans-cinnamaldehyde using a protecting group-free strategy.

RESULTS AND DISCUSSION

The retrosynthetic pathway of parvistone C (**1b**) is presented in Scheme 2. The key step is a *Mukaiyama* asymmetric aldol reaction to install lactone stereogenic center. The remaining two chiral centers could then be introduced by asymmetric epoxidation reaction followed by regioselective epoxide ring opening with methanol.

As shown in Scheme 3, our synthesis started with *Mukaiyama* asymmetric aldol reaction. Thus, trans-cinnamaldehyde **3** was allowed to react with Chan's diene **4** using catalytic amounts of Ti $(O^iPr)_4$/(*S*)-BINOL complex (10 mol%). This gave δ-hydroxy-β-ketoester **5** as a >95% enantiomeric excess (Chiral HPLC analysis)

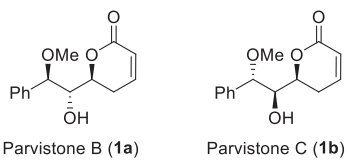
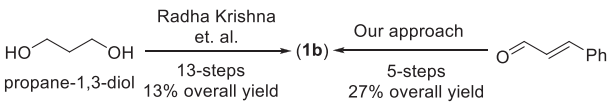
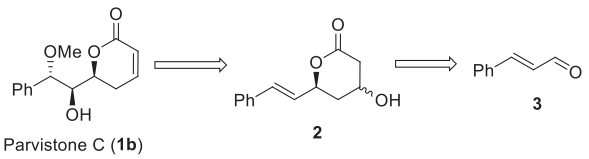


Figure 1. Structures of parvistone B (**1a**) and C (**1b**).

Scheme 1. Previous synthetic approach to parvistone C (**1b**).



Scheme 2. Retrosynthetic analysis of parvistone C (**1b**).



in 75% yield [5]. The aldol adduct **5** was then subjected to a carbonyl reduction with $NaBH_4$ to give the diol as the product. After, we have converted the diol to lactone **2** *via* hydrolysis of ester followed by intramolecular lactonization in 62% yield over two steps [6]. The elimination of hydroxyl group in β-hydroxy-δ-lactone **2** was performed smoothly to furnish the desired α,β-unsaturated δ-lactone (**6**) in 76% yield [7]. Next, the compound **6** was subjected to Han's reaction conditions [8] using (+)-(*R*,*R*)-salen-Mn (III) as the catalyst and Oxone as the oxidant at 0°C to furnish the desired goniothalamin oxide **7** with excellent regioselectivity and diastereoselectivity (dr, 98:2) in 81% yield. Finally, the

Scheme 3. Synthesis of parvistone C (**1b**).

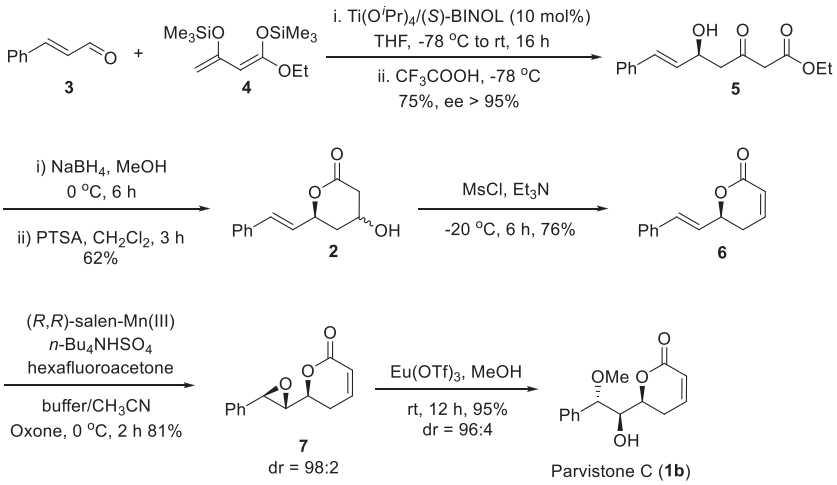
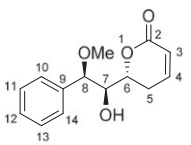


Table 1

Comparison of ^{1}H-NMR and ^{13}C-NMR data of natural parvistone C and synthetic **1b**.



^{1}H-NMR				^{13}C-NMR			
H	Natural	Synthetic	$(\Delta\delta)_{N,S}$	C	Natural	Synthetic	$(\Delta\delta)_{N,S}$
				2	164.0	164.0	0.0
3	6.05 (dd, 9.5, 2.4)	6.04 (ddd, 9.6, 2.7, 0.8)	−0.01	**3**	120.8	120.8	0.0
4	6.97 (dt, 9.5, 6.4, 2.4)	6.97 (ddd, 9.6, 6.1, 2.1)	0.00	**4**	146.0	145.9	−0.1
5	2.26 (ddd, 18.2, 6.4, 4.0)	2.25 (dddd, 18.1, 6.1, 3.7, 0.7)	−0.01	**5**	26.2	26.1	−0.1
	2.84 (ddt, 18.2, 13.2, 2.4)	2.83 (ddt, 18.1, 12.7, 2.1)	−0.01				
6	4.95 (ddd, 12.6, 4.0, 1.2)	4.95 (ddd, 12.7, 3.8, 1.5)	0.00	**6**	76.1	76.1	0.0
7	3.61 (dt, 8.4, 1.2)	3.61 (dd, 9.0, 1.5)	0.00	**7**	74.8	74.8	0.0
8	4.38 (d, 8.4)	4.38 (d, 8.8)	0.00	**8**	81.9	81.9	0.0
Ph	7.41–7.36 (m, 5H)	7.44–7.31 (m, 5H)		**9**	138.5	138.5	0.0
OMe	3.22 (s)	3.22 (s)	0.00	**10**	127.8	127.8	0.0
				11	128.7	128.6	−0.1
				12	128.5	128.5	0.0
				13	128.7	128.6	−0.1
				14	127.8	127.8	0.0
				OMe	56.7	56.7	0.0

stereoselective and regioselective epoxide ring-opening of goniothalamin oxide **7** with methanol in the presence of Lewis acid Eu $(OTf)_3$ provided the target natural product parvistone C (**1b**) in 95% yield with 96:4 dr. The ^{1}H-NMR and ^{13}C-NMR data of natural parvistone C were well agreed with our synthetic compound **1b** (Table 1).

CONCLUSIONS

The protecting group-free stereoselective total synthesis of lactone natural product parvistone C (**1b**) was achieved in simple five steps without using any protecting group from readily available starting material trans-cinnamaldehyde with 27% overall yield. Key transformations of our synthetic scheme include an asymmetric aldol reaction and asymmetric epoxidation and regioselective epoxide ring opening.

EXPERIMENTAL

General. Solvents were dried over standard drying agents and freshly distilled prior to use. All moisture-sensitive reactions were carried out under nitrogen. Organic solutions were dried over anhydrous $MgSO_4$ and concentrated below 40°C *in vacuo*. All column chromatographic separations were performed on silica gel of 60–120 mesh. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ solvent at 300, 400, 500 MHz, and 75, 100, 125 MHz, respectively, using tetramethylsilane as internal standard. Optical rotations were measured with a digital polarimeter at 25°C. Mass spectra were recorded on a mass spectrometer by electrospray ionization (ESI-MS). High-resolution mass spectra (ESI-HRMS) were recorded on an ESI-QTOF mass spectrometer.

General procedure for the synthesis of (*R*)-6-((1*R*,2*R*)-1-hydroxy-2-methoxy-2-phenylethyl)-5,6-dihydro-2H-pyran-2-one (Parvistone C) (1b). To a stirred solution of compound **8** (40 mg, 0.18 mmol) in methanol (1 mL) was added Eu $(OTf)_3$ (12.2 mg, 0.02 mmol) at room temperature and stirred for 12 h. The methanol was removed under vacuum, and the residue was purified by flash column chromatography (hexane: EtOAc, 6:4) to provide parvistone C (**1b**) (43 mg, 95%) as a white solid. $[\alpha]_D^{25} = -219$ (*c* 0.5, $CHCl_3$), HRESIMS *m/z* 271.0936 $[M + Na]^+$ (Calcd for $C_{14}H_{16}O_4Na$, 271.0940).

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