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Versicolactones A and B: total synthesis and structure revision

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ABSTRACT

To further determine absolute configurations of versicolactones A and B, total synthesis of versicolactones A and B and their six stereoisomers were reported in this Letter. The ^{1}H and ^{13}C NMR spectra of the synthetic *erythro*-stereoisomers matched perfectly with those of the natural products. Combined with the comparison of the specific rotations, the absolute configuration of versicolactones A and B were revised as (4*Z*,6*R*,7*S*)- and (4*E*,6*R*,7*S*)- from the corresponding (4*Z*,6*R*,7*R*)- and (4*E*,6*R*,7*R*)-6,7-dihydroxyocta-2,4-dien-4-lactone, respectively.

Lactones with 6,7-dihydroxyocta-2,4-dien skeleton, such as goniobutenolides A and B,[1] litchiol B,[2] and versicolactones A and B[3] have been identified from the natural resources. Among them, goniobutenolides A and B show cytotoxicity against human tumor cell lines; and versicolactones A and B were identified from the fermentation broth of the coral-associated fungus *Aspergillus versicolor* LCJ-5-4 by us.[3] The absolute configuration of the vicinal diols of versicolactones A and B was separately deduced as structures **1** and **2** by coupling constants and the comparison of the specific rotations with their analogues.[3] In order to further determine the absolute configurations of versicolactones A and B, eight stereoisomers including *threo*- **1**–**4** and *erythro*- **5**–**8** were enantioselectively synthesized. The comparisons of NMR and specific rotation data between synthetic isomers and the natural ones revealed that versicolactones A and B are identical to synthetic **5** and **6**, respectively. Thus, structures of versicolactones A and B should be revised as (4*Z*,6*R*,7*S*)- and (4*E*,6*R*,7*S*)-6,7-dihydroxyocta-2,4-dien-4-lactone, respectively (Fig. 1).

After survey of the considerable synthetic routes to prepare lactone derivatives available in the literature,[4–6] we decided to use the method developed by Pohmakotr[4] to synthesize the target molecules as shown in Scheme 1. The emphasis is to synthesize the four stereoisomers (**11a**–**11d**) of compound **11**.

The *threo*-intermediates (**11a** and **11b**) were easily prepared from dimethyl tartrate (**12** and **13**) with 40% overall yield by using a published procedure (Scheme 2).[7–9] However, two *erythro*-inter-

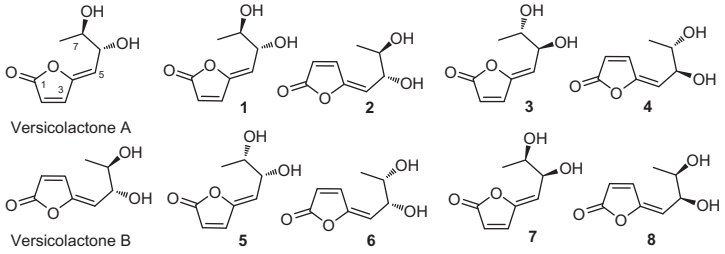

Figure 1. Structures of compounds **1**–**8** and versicolactones A and B in Ref. 3.

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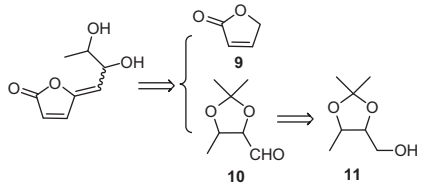
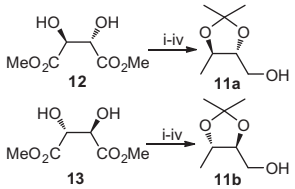


Scheme 1. Retro-synthetic analysis of versicolactones A and B.



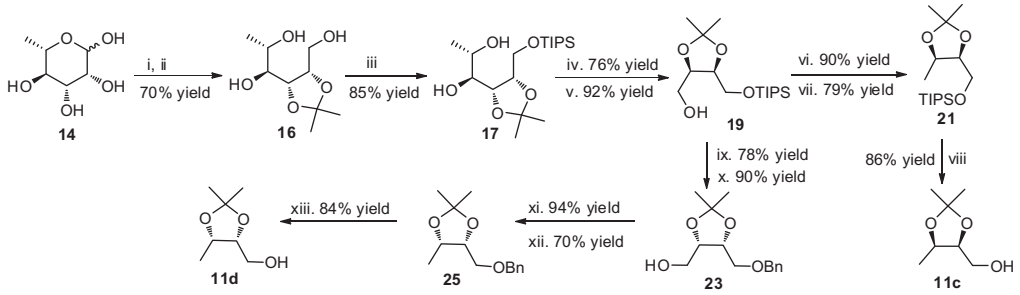
Scheme 2. Synthesis of *threo*-**11a** and **11b**. Reagents and conditions: (i) DMP, PTSA, CH_2Cl_2, reflux; (ii) $NaBH_4$, MeOH; (iii) TsCl, $(n\text{-}Bu)_4NHSO_4$; (iv) $LiAlH_4$/THF.

mediates (**11c** and **11d**) need to undergo chiral separation if they were prepared from the *meso*-dimethyl tartrate. Another selectable method to synthesize **11c** and **11d** is from D-lyxose and D-ribose but need to use the foul ethanethiol.[10] To avoid expensive chiral separation and the foul ethanethiol, we use a chiral pool of *erythro*-2,3-diol in L-rhamnose to synthesize *erythro*-**11c** and **11d** through protection, oxidation, and reduction steps (Scheme 3).

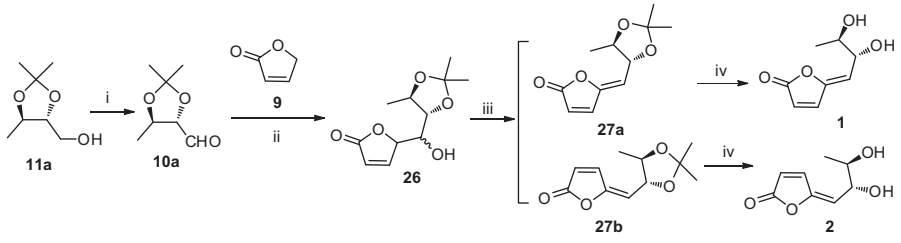
Compound **16** was synthesized in 70% yield from L-rhamnose through protection of *erythro*-vicinal diol[11] followed by $NaBH_4$ reduction.[12] The primary hydroxy group of **16** was protected by TIPSCl, and then oxidative cleavage of vicinal diol followed by reduction of aldehyde with $NaBH_4$ furnished alcohol **19** in 60% yield in three steps. The primary hydroxy group of **19** was activated using TsCl, and then replaced by $LiAlH_4$ to give compound **21** in 71% yield in two steps. Deprotection of TIPS of **21** with TBAF gave the *erythro*-**11c**. By interchanging protection between two primary hydroxy groups, another *erythro*-isomer (**11d**) could be prepared from compound **19**. Thus, compound **19** was transformed into *erythro*-**11d** in 39% yield after subjection to protection of primary hydroxy group with BnBr, deprotection of TIPS with TBAF, activation of a newly formed primary hydroxy group by TsCl followed by replacement with $LiAlH_4$, and debenzylation with H_2/Pd–C (Scheme 3).

2-Buten-4-lactone (**9**) was converted into lithiated butenolide by freshly prepared LDA at −78 °C in THF, and then was treated with freshly prepared **10a** by Swern oxidation of **11a**[9] at −78 °C to give **26** in 27% yield of two steps. Dehydration of butenolide **26** with Ac_2O–Et_3N–DMAP in dry CH_2Cl_2[13] gave **27a** and **27b** in 46% and 48% yields, respectively. The configuration of the double bond in the side chain of **27a** and **27b** was confirmed by NOESY correlations between H-3 with H-5 and H-6 (Figs. S47 and S50), respectively. Deprotection of isopropylidene of **27a** and **27b** with TFA in MeCN–H_2O afforded **1** and **2** in 62% and 68% yields, respectively (Scheme 4). By the same procedures, compounds **3** and **4**, **5** and **6**, and **7** and **8** were synthesized from **11b**, **11c**, and **11d**, respectively.

The ^1H and ^{13}C NMR data of compounds **1** and **2** (Table 1) were not consistent with the natural versicolactones A and B, especially the chemical shifts of C-5 and C-8. In contrast, NMR (Table 1, Figs. S85 and S86) and specific rotation data of the synthetic **5** ($[\alpha]_D$ −33.8) and **6** ($[\alpha]_D$ +20.5) were found to be identical with those published for versicolactones A ($[\alpha]_D^{25}$ −31.5) and B ($[\alpha]_D$ +19.8).[3] Therefore, the structure of natural products, versicolactones A and B should be revised as **5** and **6**, respectively.



Scheme 3. Synthesis of *erythro*-**11c** and **11d**. Reagents and conditions: (i) *p*-TsOH/DMP, acetone, rt, 2 h; (ii) $NaBH_4$, H_2O, 0 °C to rt, 2 h; (iii) TIPSCl, imidazole, DMAP, CH_2Cl_2, 0 °C to rt, 6 h; (iv) $NaIO_4$, AcOH, H_2O/EtOH, pH 5, 5 °C to rt, 1 h; (v) $NaBH_4$, H_2O/THF, 0 °C to rt, 2 h; (vi) TsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 6 h; (vii) $LiAlH_4$, THF, 65 °C, 5 h; (viii) TBAF, THF, 0–10 °C, 20 min; (ix) BnBr, NaH, DMF, 0 °C to rt, overnight; (x) TBAF, THF, 0–10 °C, 20 min; (xi) TsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 6 h; (xii) $LiAlH_4$, THF, 65 °C, 5 h; (xiii) H_2/Pd/C, EtOAc/MeOH, rt, overnight.



Scheme 4. Synthesis of **1** and **2**. Reagents and conditions: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (ii) LDA, THF, −78 °C, 1.5 h; (iii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 2 h; (iv) TFA, MeCN/H_2O 2:1, 0 °C to rt, 2 h.

Table 1
^{1}H (600 MHz) and ^{13}C (150 MHz) NMR data for versicolactones A and B, and compounds **1**, **2**, **5**, and **6** (in DMSO-d_6, TMS, δ ppm)

Position	Versicolactone A		Versicolactone B		1		2		5		6	
	δ_H (J = Hz)	δ_C	δ_H (J = Hz)	δ_C	δ_H (J = Hz)	δ_C	δ_H (J = Hz)	δ_C	δ_H (J = Hz)	δ_C	δ_H (J = Hz)	δ_C
1		169.6		169.6		169.8		169.5		169.7		169.5
2	6.43, dd (0.6, 5.4)	119.3	6.46, dd (1.7, 6.1)	120.1	6.44, dd (0.6, 5.4)	119.6	6.47, dd (1.8, 5.6)	120.2	6.44, dd (5.4)	119.3	6.47, dd (1.8, 5.6)	120.1
3	7.87, d (5.4)	145.5	8.16, d (6.1)	142.8	7.86, d (5.4)	145.7	8.16, d (5.6)	142.8	7.87, d (5.4)	145.6	8.16, dd (0.7, 5.6)	142.7
4		149.1		150.3		149.2		150.3		149.1		150.3
5	5.47, d (9.2)	117.2	5.78, dd (1.2, 8.6)	117.0	5.49, d (9.3)	117.0	5.77, dd (1.6, 8.4)	116.2	5.48, d (9.2)	117.3	5.78, dd (1.8, 8.7)	117.0
6	4.26, ddd (5.1, 5.1, 9.2) [a]	70.0	4.16, ddd (5.3, 5.4, 8.6)	71.2	4.27, ddd (5.3, 5.3, 9.4)	70.0	4.30, ddd (5.1, 5.1, 8.5)	70.8	4.26, ddd (5.2, 5.2, 9.3)	70.0	4.16, ddd (5.4, 5.4, 8.7)	71.2
7	3.60, 'dq' like (5.1, 6.2) [a]	69.4	3.57, 'dq' like (5.4, 6.3)	69.6	3.58, 'dq' like (5.3, 6.3)	69.4	3.62, 'dq' like (5.1, 6.4)	69.5	3.60, 'dq' like (5.2, 6.3)	69.4	3.56, 'dq' like (5.4, 6.3)	69.6
8	1.02, d (6.4)	19.0	1.06, d (6.3)	19.6	1.01, d (6.4)	18.7	0.99, d (6.4)	18.1	1.03, d (6.3)	19.1	1.05, d (6.3)	19.6

[a] The $J_{5,6}$ and $J_{7,8}$ values in Ref. 3 were wrong assigned as 5.1 and 9.2 Hz, respectively (Figs. S85 and S86).

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures, and ^{1}H and ^{13}C NMR spectra of the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.120.

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