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Lipase-catalyzed kinetic resolution of tetronic acid derivatives bearing a chiral quaternary carbon: total synthesis of (*S*)-(−)-vertinolide

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Abstract—We have developed a chemoenzymatic synthesis of (*S*)-vertinolide **1** with a chiral quaternary carbon atom at C5. In the kinetic resolution of tetronic acid precursor **6**, lipase PS-D furnished the recovered alcohol **6** with an (*R*)-stereochemistry in a ratio of 95% ee, whereas lipase AY gave (*S*)-alcohol **6** with 93% ee. Chemical transformations of (*S*)-alcohol **6** provided (*S*)-vertinolide **1** in 33% yield in five steps with no loss of enantiomeric excess.

1. Introduction

A number of fully substituted tetronic acid derivatives bearing a quaternary stereocenter at C5, for example, (*S*)-(−)-vertinolide **1**,[1,2] isogregatin B **2a**,[3] isoaspertetronin A **2b**,[3a,d,4] (*S*)-gregatin B **3a**,[5] gregatin A **3b**,[6,7] graminin A **3c**,[8] and (−)-ircinianin **4**[9] as shown in Figure 1, have been isolated. These naturally occurring tetronic acid derivatives display important biological properties, which have aroused great interest in their total synthesis. During our recent studies on chemoenzymatic total syntheses,[10] we were interested in the versatile synthesis of organic compounds containing quaternary carbon atoms. This is currently one of the most challenging topics in asymmetric organic chemistry. (*S*)-(−)-Vertinolide **1** is a mycotoxin isolated from *Verticillium intertextum*, and its structure was determined by X-ray crystallographic analysis by Dreiding et al. in 1981.[1] Takaiwa et al. established the (*S*)-absolute configuration at the quaternary stereogenic C5-center in 1983.[2] Previously, five successful syntheses of (*S*)-**1**, including the precursor synthesis were reported,[11] in which the chiral pool and chiral auxiliary approaches were employed. Herein, we report the chemoenzymatic total synthesis of (*S*)-(−)-vertinolide (**1**), that is, efficient lipase-catalyzed kinetic resolution of tetronic acid precursor **6** and chemical transformation of (*S*)-**6** into (*S*)-**1**, as shown in Scheme 1.

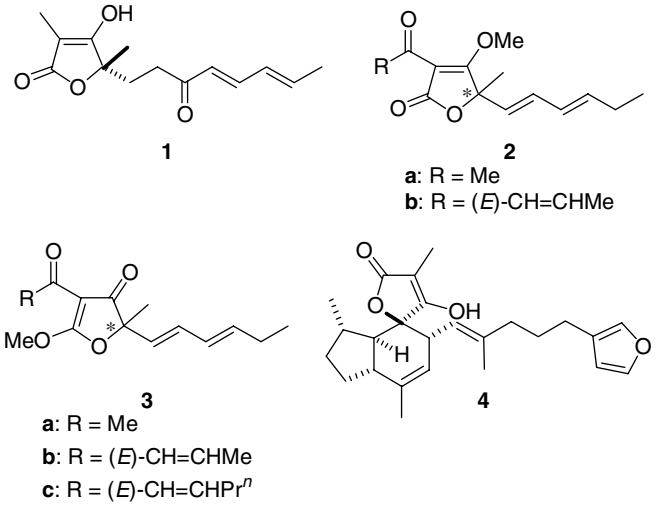

Figure 1. Fully substituted tetronic acid derivatives bearing a quaternary stereocenter at C5.

2. Results and discussion

Recently we reported a short synthesis of racemic vertinolide *rac*-**1** via the Michael reaction of the anion derived from

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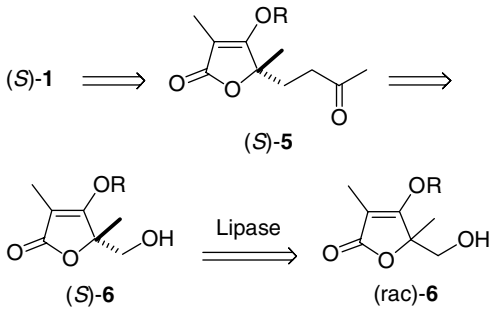
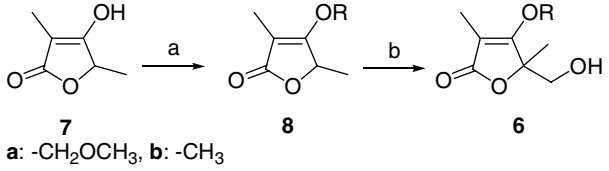


Scheme 1. Chemoenzymatic synthesis of (*S*)-(−)-vertinolide **1**.

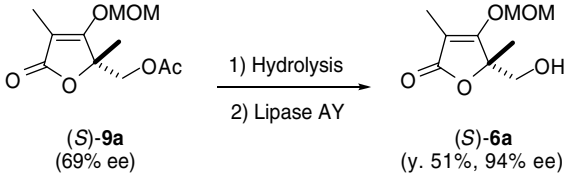
readily available tetronic acid with (*E*)-5-ethoxyocta-1,6-dien-3-one.[12] Unfortunately, our initial approaches to prepare a enantiopure vertinolide using lipase-catalyzed kinetic resolution of *rac*-**1** and/or the precursor **5** were unsuccessful. Although the construction of a tetronic acid skeleton bearing a quaternary stereocenter at C5 was expected to be difficult, we next examined lipase-catalyzed kinetic resolution of the tetronic acid precursor **6**. Starting alcohol **6** was prepared from the readily available tetronic acid derivative **7**[13] in two steps (Scheme 2). The hydroxy group was protected with either methoxymethyl[12] or methyl[14] groups to give the protected tetronic acid derivative **8** in high yields. The tetronic acid derivative **8** was treated with LDA at −78 °C. The resulting anion was reacted with paraformaldehyde in the presence of HMPA to give the desired alcohol **6**.



Scheme 2. Reagents and conditions: (a) CH_3OCH_2Cl, *i*-Pr_2NEt, 3 h, 99% for **8a**; Bu_4NOH, $(CH_3)_2SO_4$, 3 h, 96% for **8b**; (b) LDA, paraformaldehyde, THF, HMPA, −78 °C to rt, 12 h, 89% for **6a**, 84% for **6b**.

The kinetic resolution of alcohol **6** was next investigated,[15] with the results shown in Table 1. Enantioselectivity was dependent upon the nature of the lipase, for instance, Lipase OF (*Candida cyclindracea*, Meito Sangyo Co., Ltd), Chirazyme®L-2 (*Candida antarctica* (lipase B), Roche Molecular Biochemicals), and Lipozyme IM (*Mucor miehei*, Novo Nordisk) showed low to moderate enantiomeric ratio of E[16] = 1.9–3.9 (entries 1–3). The enantioselectivity was improved by using Lipase PS-D (*Burkholderia cepacia*, Amano Enzyme Co, Ltd) to give (*S*)-acetate **9** in 42% yield with 69% ee along with recovered (*R*)-alcohol **6** in 44% yield and 95% ee (entry 4). Interestingly, Lipase AY (*Candida rugosa*, Amano Enzyme Co, Ltd) reversed the enantioselectivity to give the recovered (*S*)-alcohol **6** with 93% ee (entry 5). Both enantiomers were obtained with high enantiomeric excess by use of lipase PS-D or AY. Alcohol **6b** also showed similar results (entries 6–8).

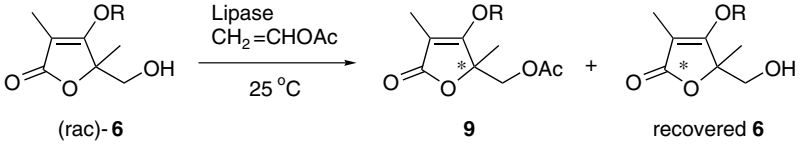
In spite of the (*S*)-configuration at C5 of naturally occurring vertinolide **1**, enantioselectivities of the (*S*)-acetate **9a** and yields of recovered (*S*)-alcohol **6a** were low (Table 1). Since we had found that lipase PS-D was favorable for the (*S*)-isomer, while lipase AY was unfavorable for it, the enantiopurity of the acetate **9a** (69% ee) was improved by hydrolysis, followed by lipase-AY catalyzed kinetic resolution, as shown in Scheme 3. These reactions provided the recovered alcohol **6a** with 94% ee in 51% yield.



Scheme 3. Reagents and conditions: (1) K_2CO_3, MeOH, rt, 2 h; (2) lipase AY, CH_2=CHOAc, 25 °C, 3 h.

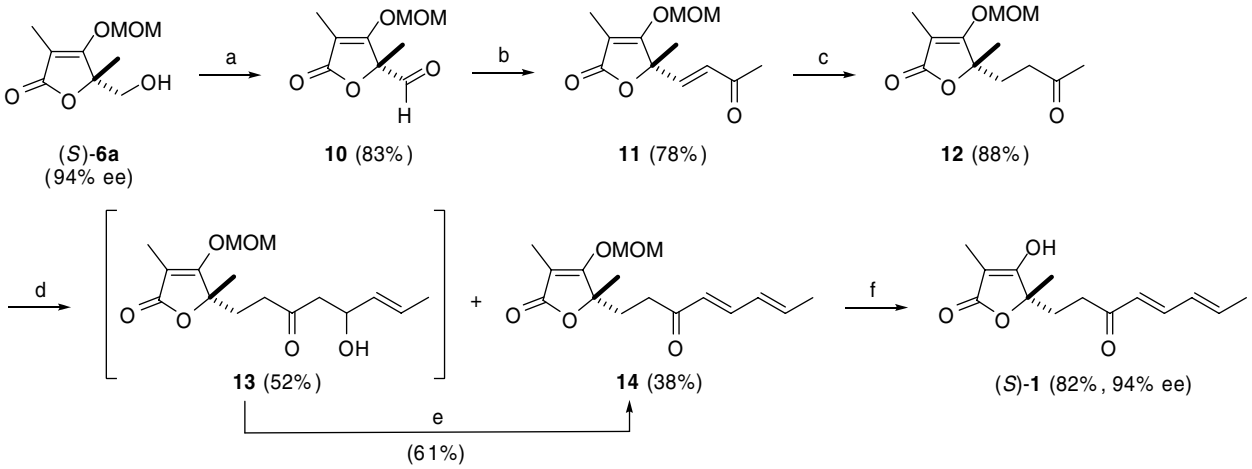
The preparation of (*S*)-vertinolide **1** required five steps and was achieved in a straightforward fashion, as shown in Scheme 4. Swern oxidation of alcohol **6a** (94% ee determined by HPLC) afforded aldehyde **10** in 83% yield. Wittig reaction of the formyl group followed by radical hydrogenation of the enone **11** furnished ketone **12**. An aldol reaction of ketone **12** with crotonaldehyde gave enone **14** in

Table 1. Lipase-catalyzed kinetic resolution of the alcohol **6**



Entry	Substrate	Lipase	Time (h)	Acetate **9**[a] yield (ee), config.	Recovered **6**[a] yield (ee), config.	*E* value
1	**6a**	OF	72	55 (21), *S*	32 (5), *R*	1.9
2	**6a**	Chirazyme®-L2	1	43 (46), *S*	44 (55), *R*	3.7
3	**6a**	Lipozyme IM	6	54 (42), *S*	29 (85), *R*	3.9
4	**6a**	PS-D	24	42 (69), *S*	45 (95), *R*	8.9
5	**6a**	AY	4	46 (78), *R*	32 (93), *S*	16.0
6	**6b**	Chirazyme®-L2	5	59 (31), *S*	26 (78), *R*	2.8
7	**6b**	PS-D	24	58 (50), *S*	32 (99), *R*	6.0
8	**6b**	AY	3	61 (19), *R*	15 (93), *S*	1.9

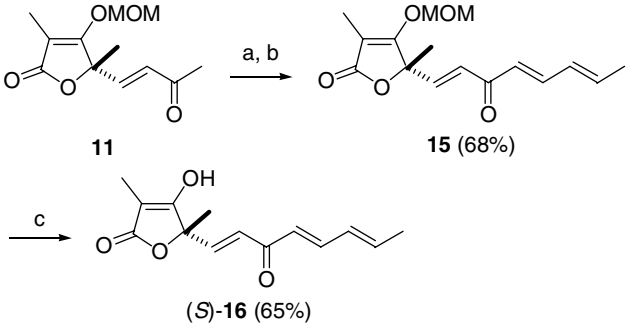
[a] Determined by chiral-phase HPLC analysis (CHIRALPAK AD, hexane–EtOH = 95:5, 0.4 mL/min, λ = 254 nm).



Scheme 4. Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C, 2 h; (b) NaH, $[CH_3COCH_2PPh_3]^+Br^-$, THF, rt, 14 h; (c) Bu_3SnH, AIBN, benzene, reflux, 1 h; (d) LDA, (*E*)-$CH_3CH{=}CHCHO$, THF, −78 °C, 2 h; (e) basic alumina, CH_2Cl_2, rt, 1 h; (f) concd HCl, AcOH, rt, 2 h.

38% yield and alcohol **13** in 52% yield, which was readily dehydrated to enone **14** in the presence of basic alumina. Finally, removal of the MOM group yielded (*S*)-vertinolide **1** (94% ee determined by HPLC), which showed a specific rotation of −25.8 (lit.[1] $[\alpha]_D^{20} = -25.0$). No loss of enantiopurity was observed in the chemical transformation of (*S*)-**6a** into (*S*)-**1**. In addition, physical and spectral properties of synthetic vertinolide **1** matched those of natural vertinolide **1**.[1,2,11]

Our strategy is easily adaptable to the synthesis of (*S*)-dehydrovertinolide **16** as shown in Scheme 5. The highly conjugated enone **16** was synthesized by a similar procedure to that described above.



Scheme 5. Reagents and conditions: (a) LDA, (*E*)-$CH_3CH{=}CHCHO$, THF, −78 °C, 8 h; (b) basic alumina, CH_2Cl_2, rt, 1 h; (c) AcOH, H_2O, 60 °C, 3 h.

3. Conclusion

In conclusion, we have developed a chemoenzymatic synthesis of (*S*)-vertinolide **1** with a chiral quaternary carbon atom at C5. The lipase-catalyzed kinetic resolution of the tetronic acid derivatives **6** demonstrated good enantioselectivity, in which both enantiomers were obtained with high enantiomeric excess by the use of lipase PS-D or AY. Chemical transformation of (*S*)-alcohol **6** provided chiral (*S*)-vertinolide **1** in 33% yield in five steps with no loss of enantiomeric excess. We hope that our simple synthesis will be helpful for solving unidentified properties of (*S*)-**1** in the future.

Acknowledgments

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15. Typical procedure: To a solution of the alcohol **6** (0.5 mmol) in vinyl acetate (3 mL), lipase (50 mg) was added, and stirred at 25 °C for an appropriate time. Lipase was removed through filtration and washed with ethyl acetate, and the combined organic filtrates were concentrated to give a crude oil, which was purified by column chromatography (silica gel, eluent: hexane–AcOEt) to give the acetate **9** and the recovered alcohol **6**.
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