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Tetrahedron: *Asymmetry* 15 (2004) 909–912
Tetrahedron: *Asymmetry*

First asymmetric synthesis of the marine furanosesterterpene natural product, (18*S*)-variabilin, employing enzymatic desymmetrization of propanediol derivatives

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Received 22 December 2003; accepted 26 January 2004

Abstract—An efficient and stereodefined process is described for the first preparation of the marine furanosesterterpene tetronic acid, (18*S*)-variabilin, featuring lipase-catalyzed asymmetric desymmetrization of two types of propanediol precursors incorporating the terpene skeleton.

1. Introduction

Variabilin **1**, a unique furanosesterterpene tetronic acid of marine origin, was first isolated in 1973 by Faulkner[1] from the sponge, *Ircinia variabilis*, and subsequently from *Sarcotragus* sp.[2] in research for potential antiviral antitumor agents from marine invertebrates. Closely related linear sesterterpenes containing one or two furan units together with a conjugated tetronic acid moiety, ircinin-1 **2**, ircinin-2 **3** and fasciculatin **4** were also isolated by Minale and co-workers from *Ircinia oros*[3] and *Ircinia fasciculate*,[4] respectively (Fig. 1). A variety of geometric, stereo- and regioisomers of these natural products and other related types have since then been isolated and been shown to possess interesting antiviral and cytotoxic activity.[5] Their structural complexity coupled with diverse and potentially useful characteristics as antimicrobial agents described above make them inviting targets for synthesis. In spite of these attractive features, to the best of our knowledge, no report has appeared for three decades, although the synthesis of this type of compounds poses interesting and often unsolved problems of geometric- and/or stereocontrol. With these considerations in mind, we herein report the first and efficient asymmetric synthesis of (18*S*)-variabilin **1**[6] by means of elaboration of propanediol precursors containing a terpene unit through lipase-catalyzed asymmetric desymmetrization.

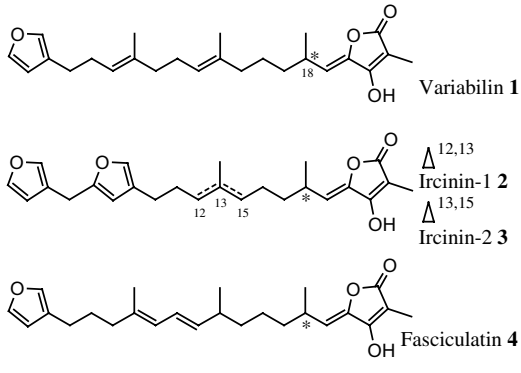

Figure 1.

2. Results and discussion

In formulating the synthetic plan for **1**, we envisioned a coupling reaction of the two intermediates **5** (furanyl side chain) and **6** (tetronic acid part), allowing the synthesis of target **1** (Fig. 2). Meanwhile, the crucial stereogenic center C(18) in **5** would have to be independently set in an asymmetric desymmetrization of the corresponding propanediol derivative **7** (path A). On the other hand, **5** could be disconnected into two parts, **8** and **9**, with the former originating from the same type asymmetric desymmetrization of the mono-terpene diol **10** (path B).

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doi:10.1016/j.tetasy.2004.01.031

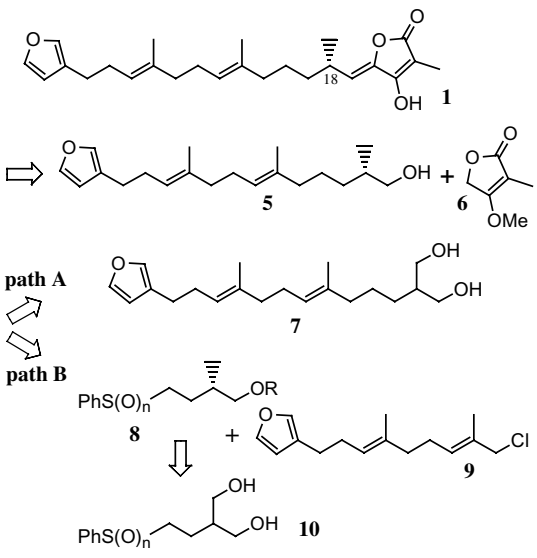
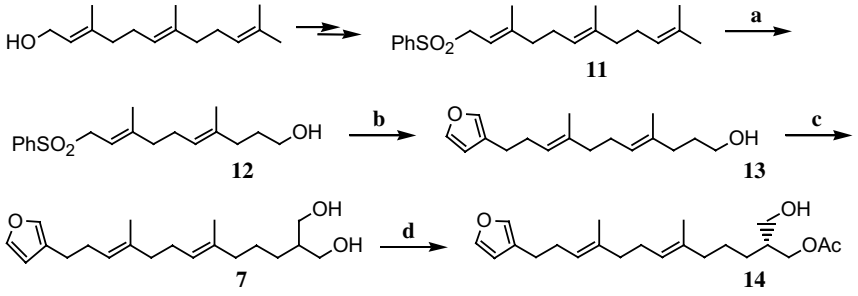


Figure 2.

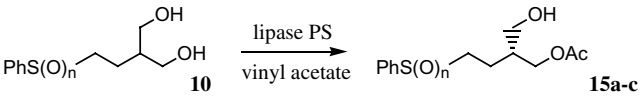
To begin with, an attempt to synthesize the linear precursor **5** based on path A is outlined in Scheme 1. Regioselective terminal olefin cleavage via epoxide formation of the allylic sulfone **11** prepared from farnesol (two steps), followed by reduction gave alcohol **12** in high yield.[7] This was subjected to the successive reactions of protection, furanylation in the presence of base, desulfonylation and deprotection, leading to the furanylated alcohol **13** in satisfactory yields, respectively. The remaining propanediol fragment in **7** was then introduced by the coupling reaction of **13** after bromination with the anion of diethyl malonate followed by reduction of the resulting diester with $LiAlH_4$ to produce the desired terpenediol **7**. After investigation of lipase-catalyzed asymmetric desymmetrization of **7** under a variety of conditions such as treatment with lipase PS (*Pseudomonas cepacia*), AK (*Pseudomonas fluorescence*), AY (*Candida rugosa*) or PL (*Alcaligenes* sp.), we found that the use of lipase PS {150 mg to the diol **7** (1.0 mmol)} with 2 equiv of vinyl acetate at rt for 4 h underwent a fast reaction to afford the monoacetate **14**, $[\alpha]_D^{23}$ +5.1 (*c* 1.59, $CHCl_3$), in 57% isolated yield with moderate stereoselectivity {72% ee, determined by chiral HPLC (chiralpak OD)}[8] as the optimal result.

With the above results in hand, we next turned our attention to the other synthetic route (path B) described in Figure 2. In order to obtain the chiral C-5 monoterpene fragment **8** with higher stereoselectivity, we examined the same type of lipase PS-catalyzed asymmetric desymmetrization of the 1,3-propanediol **10**. Representative results from our survey are summarized in Table 1. Whereas the asymmetric hydrolysis of the corresponding diacetates of **10** employing several enzymes in phosphate buffer solution gave the monoacetates **15** in moderate yields, but disappointingly with low ee, we were delighted to find that the reverse



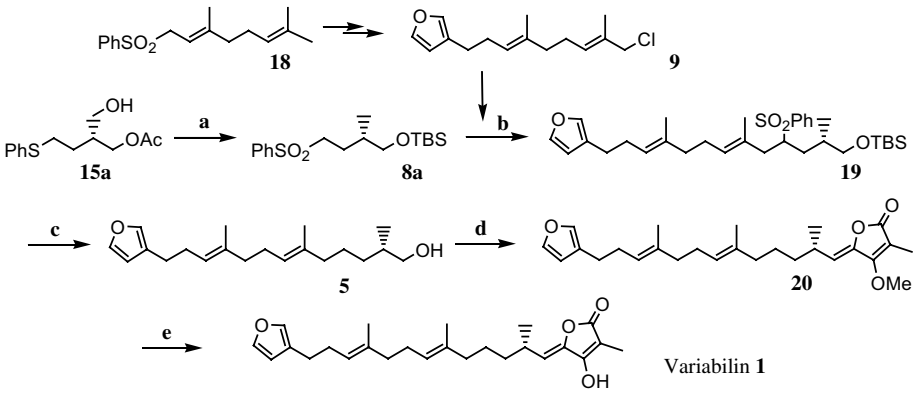
Scheme 1. Reagents and conditions: (a) **1**, NBS, *t*-BuOH–H_2O (7:2); **2**, KOH, MeOH; 70% (two steps); **3**, HIO_4, ether–THF (1:1); **4**, $NaBH_4$, EtOH; 81% (two steps); (b) **1**, TBSCl, imidazole, DMF, 97%; **2**, BuLi, 3-bromomethylfuran, THF, −78 to 0 °C, 79%; **3**, Na, THF–2-propanol (3:1); 0 °C, 76%; **4**, concd HCl, MeOH, 90%; (c) **1**, CBr_4, PPh_3, CH_2Cl_2, 78%; **2**, NaH, diethyl malonate, 1,4-dioxane, 87%; **3**, $LiAlH_4$, ether, 0 °C, 94%; (d) lipase PS, vinyl acetate, 57%.

Table 1. Lipase PS-catalyzed asymmetric desymmetrization of the propanediols **10**[a]



Entry	*n* (Compound)	Temperature (°C)	Time (h)	Yield (%)[b]	Ee (%)[c]	Confign (%)[d]
1	0 (**15a**)	27	1	95	98	*R*
2	1 (**15b**)	25	2	70	95	*R*
3	2 (**15c**)	25	6	75	91	*R*

[a] The diols **10** (1.0 mmol), lipase PS (40 mg) and vinyl acetate (2.0 mmol) in ether (3 mL) were stirred.
[b] Isolated yield.
[c] Determined by HPLC analysis (Daicel chiralcel OJ).[9]
[d] The absolute configuration of **15** was determined after derivatization to the known vinyl alcohol.[10]



Scheme 2. Reagents and conditions: (a) **1**, MsCl, pyridine; **2**, $LiAlH_4$, ether, 0 °C; 94% (two steps); **3**, TBSCl, imidazole, DMF; 97%; **4**, *m*-CPBA. CH_2Cl_2, 84%; (b) BuLi, HMPA, **5**, 0 °C, 84%; (c) **1**, Na, THF–2-propanol, (2:3), 76%; **2**, concd HCl, MeOH, 94%; (d) **1**, TPAP (tetrapropylammonium perruthenate), NMO, CH_2Cl_2, 68%; **2**, LDA, methyl tetronate, THF, −78 °C; **3**, MsCl, pyridine, 0 °C, 73% (two steps); (e) PrSLi, HMPA, 0 °C, 83%.

asymmetric esterification of **10** smoothly brought about the desired compounds **15** in both high chemical and high enantiomeric excesses (up to 98% ee), respectively.

We further focused our research on the synthesis of (18*S*)-variabilin **1** in light of the above outcome as shown in Scheme 2. Initially, the mono-acetate **15a** was converted into the silyl ether **8a** through a three-step sequence, which was in turn coupled with the furanyl side chain **9** prepared from the sulfone **18** under the similar conditions indicated in Scheme 1, leading to the silyl sulfone **19** in satisfactory yield. This was then submitted to desulfonylation and deprotection to provide **5**, $[\alpha]_D^{21}$ −5.5 (*c* 0.91, $CHCl_3$),[8,10] the chiral segment of **1** in 72% (two steps) yield. Finally, a coupling reaction of **5** after TPAP-induced oxidation[12] to the aldehyde intermediate was effected with methyl tetronate in the presence of LDA at low temperature followed by the subsequent dehydroxylation under basic conditions and demethylation to complete the first asymmetric synthesis of desired (18*S*)-**1** accompanied with its (20*E*)-isomer ($Z/E = 2.8{:}1$, determined by ^1H NMR) as a colorless oil, $[\alpha]_D^{21}$ −37.4 (*c* 0.77, $CHCl_3$).[13]

3. Conclusion

In summary, this work constitutes the first synthesis of the naturally occurring furanosesterterpene, (18*S*)-variabilin, through lipase-catalyzed asymmetric desymmetrization of the 1,3-propanediol derivatives and will be widely applicable to the synthesis of other terpeniod natural products.

Acknowledgements

We are grateful to Amano Pharmaceutical Co., Ltd. and Meito Sangyo Co., Ltd. for a geneous gift of some enzymes.

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30, 6291–6294; (f) Ramos Tombo, G. M.; Schär, H.-P.; Fernandez, X.; Busquets, I.; Ghisalba, O. *Tetrahedron Lett.* **1986**, *27*, 5707–5710. The absolute configuration of the generated stereogenic center in **14** was determined to be *R* by the two-step transformation (mesylation and reduction) into the known alcohol **5**, whose specific rotation indicated $[\alpha]_D^{23}$ −4.3 (*c* 1.12, $CHCl_3$).

9. Unfortunately studies on the lipase-catalyzed diastereo- and/or enantioselective kinetic resolution of the sulfinyl compound **15b** were not performed in detail, since the enantioselectivity of both **15a** and **15b** was easily determined by HPLC after oxidative derivatization to the known compound **15c**.
10. The absolute configuration of **15** was easily characterized to be *R* based on the specific rotation of synthesized **17**, $[\alpha]_D^{24}$ +24.9 (*c* 1.13, $CHCl_3$) {lit. 90% ee, $[\alpha]_D$ +24.1 (*c* 1.00, $CHCl_3$)[11]}, through the four-step sequence as shown below.

The correlation between enantioselectivity and the structure of these sulfur compounds (**15a**–**c**) is less clear, however, the obtained stereoselectivity would be attributed to the size of the cavity (so-called pocket size) constituted by peptide linkages in the enzyme employed.

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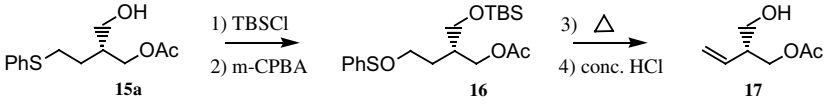

15a **16** **17**