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Preparation of Chiral 4-Benzyloxymethyldihydrofuran-2-one Using Lipase-Catalyzed Kinetic Resolution: Synthesis of (−)-Virginiae Butanolide C (VB C)

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Abstract—Lipase-catalyzed kinetic resolution of the *N,N-dialkyl*-3-benzyloxymethyl-4-hydroxybutanamide **10a**,**b** afforded the acetate **11a**,**b** with (*R*) configuration, whereas the *N-monoalkyl*-3-benzyloxymethyl-4-hydroxybutanamide **10c**–**e** gave the acetate **11c**–**e** with (*S*) configuration. The butanamide **10** smoothly cyclized to give chiral 4-benzyloxymethyldihydrofuran-2-one **9** without racemization, which was effectively transformed into highly stereocontrolled virginiae butanolide C (VB C).

The chiral 3-alkoxymethyl butanolides **4** are the most useful precursors for the synthesis of A-factor **1** isolated from *Streptomyces griseus*,[1,2] virginiae butanolides (**VB**) **2** [**VB A**: R = $CH_2CH_2CH_2CH(CH_3)_2$,**VB B**: R = CH_2CH_2CH $(CH_3)CH_2CH_3$, **VB C**: R = CH_2CH_2 $CH_2CH_2CH_3$, **VB D**: R = $CH_2CH_2CH_2CH_2CH_2CH_3$,**VB E**: R = CH_2CH_2 $CH(CH_3)_2$] isolated from *Streptomyces virginiae*,[2c,3] and IM-2 **3** isolated from *Streptomyces FRI-5*[4] (Fig. 1). They have attractive bioactivities, for instance, A-factor is an autoregulator of differentiation and antibiotic biosynthesis in various streptomycetes.[2] Moreover, they are structurally homologous compounds, which have an alkyl group at the 2-position and a hydroxymethyl group at the 3-position based on the butanolide skeleton.

Recently, we reported that the lipase-catalyzed asymmetric desymmetrization of the 2-carbamoylmethyl-1,3-propanediol **5** afforded the (*S*)-acetate **6** with >99% ee.[5] For construction of the butanolide skeleton, the hydroxy group was protected with a benzyl group under the usual conditions to give the acetate **7**. Hydrolysis and cyclization of **7** smoothly proceeded to give the 3-benzyloxymethyl butanolide **9**; however, the racemate was obtained from a chiral HPLC analysis (Scheme 1). Thus, we concluded that even under the neutral conditions racemization occurred in the transformation of **6** to **7** due to an intramolecular transesterification. We now report herein a practical preparation of the chiral butanolide **9** using kinetic resolution of the butanamide **10**, and the synthesis of virginiae butanolide C.

Enantioselective acylation[6] of the butanamide **10** was investigated.[7] Results are shown in Table 1. Lipase PS (*Pseudomonas cepacia*, Amano) was marked best enantioselectivity among lipases tested.[8] Phenyl acetate was most effective acylating agent to give the acetate **11a** and the recovered alcohol **10a** in a good enantiomeric ratio of E[9] = 18.6 (entry 3) The absolute configuration of

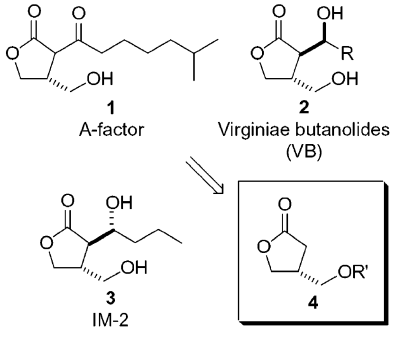

Figure 1. Chiral 3-alkoxymethyl butanolides.

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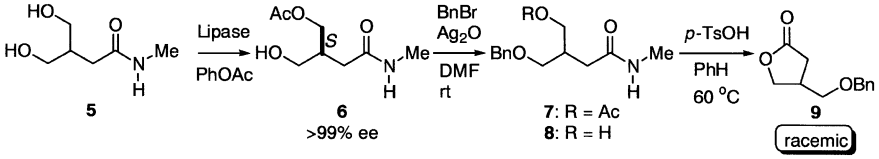
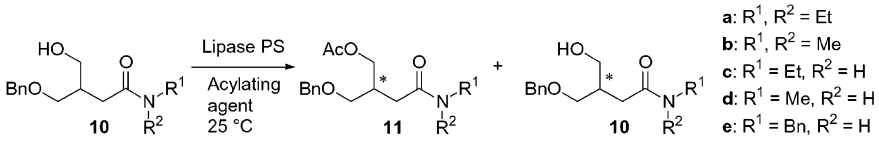
10a was determined to be (*R*) by comparison of the value of the optical rotation of 4-(phenylsulfanylmethyl)dihydrofuran-2-one after acid-catalyzed lactonization.[5] Simplified isolation from the reaction mixture was accomplished by using succinic anhydride as an acylating agent; only washing the reaction mixture with a saturated $NaHCO_3$ solution gave the alcohol (*R*)-**10** in 99% ee (entry 5).[10] Interestingly, kinetic resolution of the *N-monoalkyl*-butanamide **10c**–**e** showed the opposite enantioselectivity compared with *N,N-dialkyl*-butanamide **10a**,**b**. The absolute configuration of **11c**–**e** and **10c**–**e** was found to be (*S*). Thus, the (*R*)-enantiomer was more likely to be obtained from *N,N*-dialkylbutanamide (entries 1–7), while the (*S*)-enantiomer was



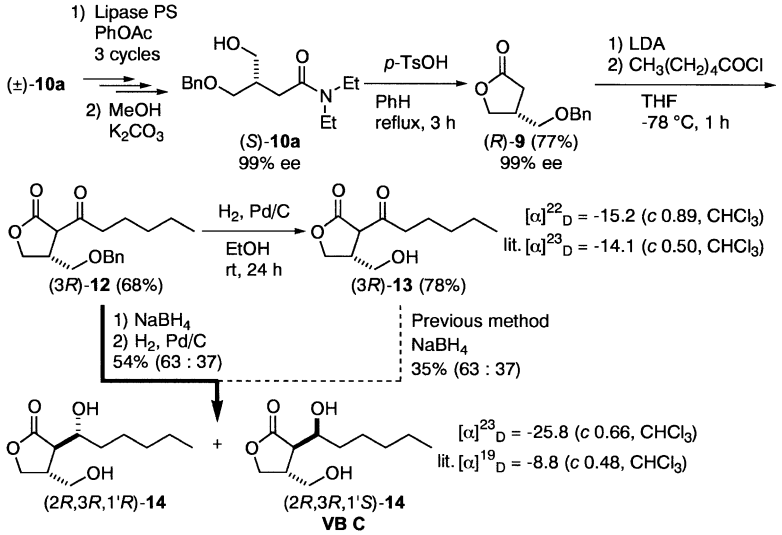
Scheme 1. Attempts to synthesis of 3-benzyloxymethyl butanolide **9** from the (*S*)-acetate **6**.

Table 1. Kinetic resolution of the butanamide **10** by lipase-catalyzed acylation



Entry	Substrate	Acylating agent[a]	Time (h)	**11** Yield[b] (ee)[c] (%)	Config.	**10** Yield[b] (ee)[d] (%)	Config.	*E*
1	**10a**	Isopropenyl acetate	9	20 (84)	*R*	75 (25)	*R*	14.1
2	**10a**	Vinyl acetate	2	37 (80)	*R*	51 (62)	*R*	14.3
3	**10a**	Phenyl acetate	3	33 (85)	*R*	60 (39)	*R*	18.6
4	**10a**	Phenyl acetate	2	53 (32)	*R*	20 (95)	*R*	2.7
5[e]	**10a**	Succinic anhydride[f]	4	43 (11)	*R*	31 (99)	*R*	—
6	**10b**	Phenyl acetate	2	38 (71)	*R*	54 (54)	*R*	9.0
7[e]	**10b**	Succinic anhydride[f]	8	48 (43)	*R*	35 (63)	*R*	—
8	**10c**	Phenyl acetate	1	38 (51)	*S*	32 (59)	*S*	4.1
9[e]	**10c**	Succinic anhydride[f]	5	54 (39)	*S*	41 (55)	*S*	—
10	**10d**	Phenyl acetate	12	26 (38)	*S*	49 (18)	*S*	2.5
11	**10e**	Phenyl acetate	10	40 (6)[g]	*S*	53 (9)[g]	*S*	1.2

[a]Acylating agent (2 equiv) was used unless otherwise noted.
[b]Isolated yields.
[c]Determined by HPLC analysis using Chiralpak AD after methanolysis of **11** to **10**.
[d]Determined by HPLC analysis using Chiralpak AD.
[e]*i*-Pr_2O was used as the solvent.
[f]Succinic anhydride (1 equiv) was used.
[g]Determined by optical rotation after transformation into **9**.



Scheme 2. Synthesis of virginiae butanolide C (VB C).

obtained from *N*-monoalkylbutanamide (entries 8–11). These tendencies were in good accord with the results of stereoselectivity in the lipase-catalyzed asymmetric desymmetrization of the 2-carbamoylmethyl-1,3-diols **5**.[5]

The enantiomerically pure alcohol (*S*)-**10a** was obtained by kinetic resolution repeatedly (**11a**: 1st 60% ee; 2nd 94% ee, 3rd >99%ee, total yield 21%) followed by hydrolysis, which was employed in the synthesis of virginiae butanolide C (VB C) as shown in Scheme 2. Cyclization of the (*S*)-alcohol **10a** gave (*R*)-3-benzyloxymethyl-4-butanolide (*R*)-**9** in 77% yield without racemization as revealed by a chiral HPLC analysis. The butanolide (*R*)-**9** was treated with LDA at −78 °C, and the resulting anion was reacted with hexanoyl chloride to give the butanolide (3*R*)-**12** in 68% yield. An analogue of A-factor (3*R*)-**13** was obtained by deprotection of the benzyl group in 78% yield. Reduction/deprotection of (3*R*)-**12** gave a diastereomeric mixture of **14**, which was readily separated by column chromatography to afford VB C (2*R*,3*R*,1′*S*)-**14** and its epimer (2*R*, 3*R*,1′*R*).[11] A higher value of the optical rotation of synthetic VB C was observed compared with that reported in the literature,[2c] therefore, it is suggested that partial racemization via $NaBH_4$ reduction of **13** might have occurred in a previous preparation of VB C.[2c]

In conclusion, we have shown high enantioselectivity in the kinetic resolution of the butanamide **10**. This present reaction would provide a practical strategy for asymmetric synthesis of natural products including 3-alkoxymethyl butanolide skeleton.

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References and Notes

1. Isolation: Kleiner, E. M.; Pilner, S. A.; Soifer, V. S.; Onoprienko, V. V.; Balasheva, T. A.; Rozynov, B. V.; Khoklov, S. A. *Bioorg. Khim.* **1976**, *2*, 1142.
2. (a) Asymmetric synthesis: Crawforth, J. M.; Fawcett, J.; Rawlings, B. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1721. (b) Parsons, P. J.; Lacrouts, P.; Buss, A. D. *J. Chem. Soc., Chem. Commun.* **1995**, 437. (c) Mori, K.; Chiba, N. *Liebigs Ann. Chem.* **1990**, 31. (d) Posner, G. H.; Weitzberg, M.; Jew, S.-s. *Synth. Commun.* **1987**, *17*, 611. (e) Mori, K.; Yamane, K. *Tetrahedron* **1982**, *38*, 2919.
3. (a) Kondo, K.; Higuchi, Y.; Sakuda, S.; Nihira, T.; Yamada, Y. J. *Antibiotics* **1989**, *42*, 1873. (b) Nihira, T.; Shimizu, Y.; Kim, H. S.; Yamada, Y. J. *Antibiotics* **1988**, *41*, 1828. (c) Yamada, Y.; Sugamura, K.; Kondo, K.; Yanagimoto, M.; Okada, H. J. *Antibiotics* **1987**, *40*, 496.
4. Sato, K.; Nihira, T.; Sakuda, S.; Yanagimoto, M.; Yamada, Y. J. *Ferment. Bioeng.* **1989**, *68*, 170.
5. Takabe, K.; Iida, Y.; Hiyoshi, H.; Ono, M.; Hirose, Y.; Fukui, Y.; Yoda, H.; Mase, N. *Tetrahedron: Asymmetry* **2000**, *11*, 4825.
6. Typical procedure: a solution of the butanamide **10a** (100 mg, 0.358 mmol) and Lipase PS (10.7 mg, 30 mg/mmol of **10a**) in vinyl acetate (2 equiv) was stirred at 25 °C for an appropriate time; then, Lipase PS was removed through filtration, and concentrated to give a crude oil, which was purified by column chromatography (silica gel, eluent: hexane–AcOEt) to give the monoacetate **11a** and the recovered alcohol **10a**.
7. We also examined the enantioselective hydrolysis and transesterification of the acetate **11a**,**b** in the presence of Lipase PS in a buffer and ethanol solution, respectively; however, low enantioselectivities (11–57% ee) was observed.
8. The enantioselectivities were dependent upon the nature of the lipase used, for instance, Lipase A (*Aspergillus niger*, Amano) showed reverse enantioselectivity to give (*S*)-acetate **11a** (57% ee).
9. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
10. High enantiomeric excess of the acetate 11 was not obtained, because acetylation of the alcohol 10 slowly proceeded in the absence of Lipase PS. See Hyatt, J. A.; Skelton, C. *Tetrahedron: Asymmetry* **1997**, *8*, 523.
11. Revised structure of the virginiae butanolides is reported by Yamada et al.; see: Sakuda, S.; Yamada, Y. *Tetrahedron Lett.* **1991**, *32*, 1817.