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A new chemoenzymatic Baylis–Hillman approach for the synthesis of enantiomerically enriched umbelactones

Ahmed Kamal,* Tadiparthi Krishnaji and P. Venkat Reddy

Biotransformation Laboratory, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—An efficient and convenient strategy for the enantioselective synthesis of enantiomerically enriched umbelactones is described utilizing a lipase-mediated resolution protocol, Baylis–Hillman reaction and ring closing metathesis as key steps. The lipase-resolution is carried out using several lipases from various sources in different solvents to afford the required intermediate **8** in good yield and high enantioselectivity.

The butenolide ring system is found in natural products and is also featured in intermediates used for the synthesis of biologically important compounds.[1] Butenolides have shown to exhibit a wide range of biological activities themselves such as insecticidal, bactericidal, fungicidal, antibiotic, anticancer, anti-inflammatory, antiallergic and antipsoriasis, together with cyclo-oxygenase and phospholipase A_2 inhibition.[2] Different routes to these compounds have been reported.[3] (*R*)-Umbelactone-**1** is one example of a naturally occurring γ-(hydroxymethyl)-α,β-butenolide which has been isolated from *Memycelon umbelatum* Brum.[4] The crude extracts of this plant have shown various biological activities including antiviral (activity against Ranikhet disease virus), antiamphetory and spasmolytic. Thus various synthetic approaches for umbelactones have been reported (Fig. 1).[5]

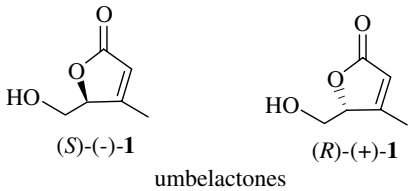

Figure 1.

In continuation of our activity[6] in the development of chemoenzymatic syntheses for molecules of biological interest, we describe herein a new and efficient synthesis of both optically pure forms of umbelactones utilizing a lipase-catalyzed resolution, a Baylis–Hillman protocol and ring-closing metathesis (RCM) as key steps. To the best of our knowledge, this is the first chemoenzymatic report describing the synthesis of both forms of the umbelactones. A retrosynthetic analysis is outlined in Scheme 1. Enantiomerically pure (*R*)-(+)-**1** and (*S*)-(−)-**1** could be synthesized from (*R*)-**8** and (*S*)-**8** which in turn could be obtained by lipase-catalyzed resolution of allylic alcohol **8**, which itself, could be obtained from **3**.

Accordingly, the syntheses of **1** commenced from ester **3** as a precursor, which was prepared in quantitative yield from aldehyde **2** upon treatment with methyl acrylate and quinuclidine using the Baylis–Hillman strategy.[7] The hydroxyl group of **3** was protected as the TBS ether using TBSCl and imidazole to give **4** in high yield. α,β-Unsaturated ester **4** was reduced[8] to the allylic alcohol **5** with DIBAL-H in CH_2Cl_2 at −78 °C in 95% yield, which on subsequent tosylation with tosyl chloride and triethylamine in CH_2Cl_2 (in the presence of a catalytic amount of DMAP) gave tosyl ether **6** in 75% yield. Next, **6** was reduced using $LiAlH_4$ in THF to produce **7**, and upon TBS deprotection using TBAF in THF, the required intermediate 1-benzyloxy-3-methylbut-3-en-2-ol **8** was obtained.

Having successfully completed the synthesis of **8**, our focus was to develop a lipase-catalyzed transesterification

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* Corresponding author. Tel.: +91 40 27193157; fax: +91 40 27193189; e-mail addresses: ahmedkamal@iict.res.in; ahmedkamal@iictnet.org

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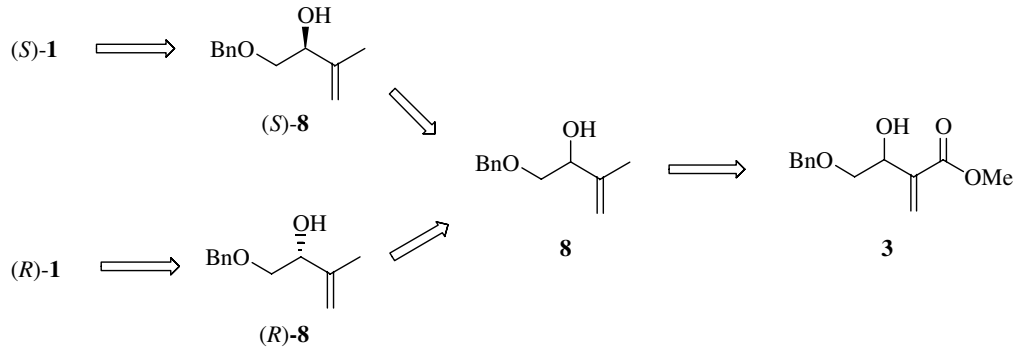
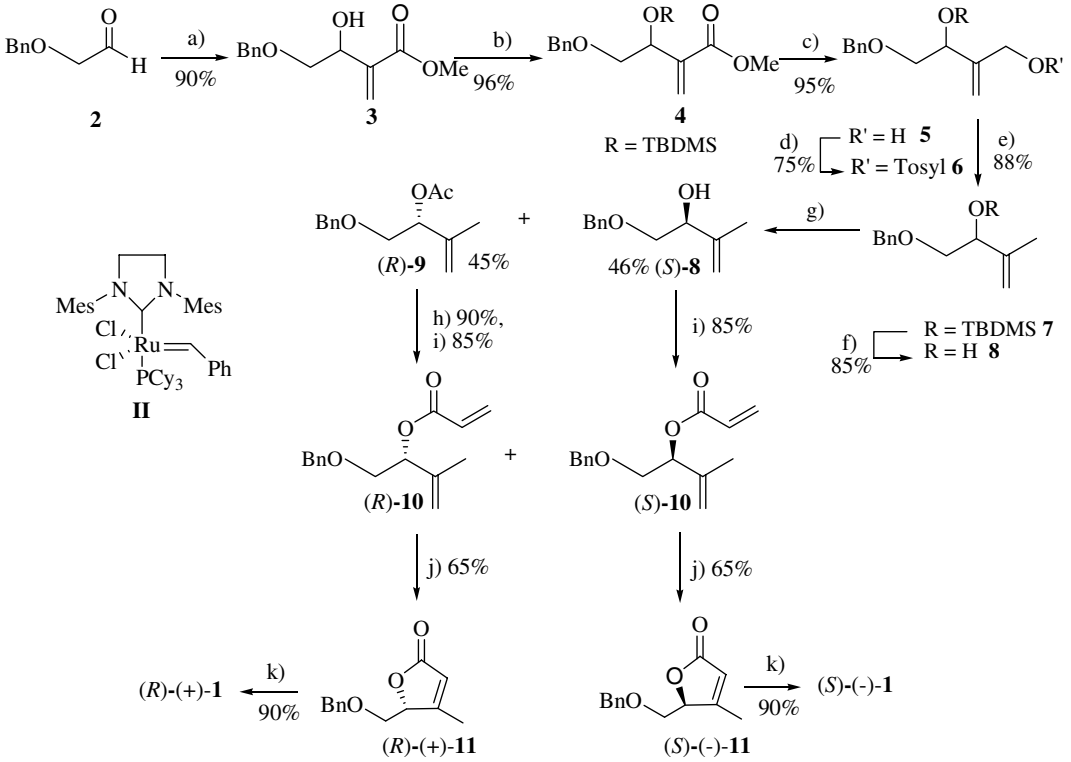


Scheme 1. Retrosynthesis of umbelactones.

of the allylic alcohol system to obtain enantiomerically pure acetate (*R*)-**9** and alcohol (*S*)-**8**, which are required for the synthesis of enantiomerically enriched umbelactones (*R*)-**1** and (*S*)-**1** (Scheme 2). In the first series of experiments, the efficiency of various commercially available lipases obtained from different sources was investigated for the transesterification of **8**. Amongst all the lipases screened, *Burkholderia cepacia* (PS-C) and CAL-B gave the best conversions and high enantiomeric excesses as shown in Table 1. It is well known that different solvents affect the enantiotopic selectivity as well as the reaction rate for the lipase-catalyzed kinetic resolutions. Therefore, the affect of different solvents was examined on the resolution of substrate **8** employing lipase PS-C. A quantitative measurement of the solvent can be determined by the parameter *P*, the partition coefficient of the solvent between octanol and water, and the corresponding log *P* values for the solvents examined are given in Table 2. The catalytic activity was low in polar solvents having log $P < 2$, moderate in solvents having log *P* between 2 and 4, and was high in apolar solvents having log $P > 4$. Hydrophobic solvents such as hexane, toluene and diisopropyl ether gave better results compared to hydrophilic solvents including acetone and THF. From these results, hexane appeared to be the solvent of choice for this transesterification with respect to yields and enantiomeric excess (Table 2). The enantiomeric excess was calculated from the enantiomeric ratios obtained by HPLC employing a chiral OB-H column (Daicel).



Scheme 2. Reagents and conditions: (a) Methyl acrylate, quinuclidine, MeOH, 8 h; (b) TBDMSCl, imidazole, CH_2Cl_2, DMAP, 0 °C to rt, 6 h; (c) DIBAL-H, CH_2Cl_2, −78 °C, 1 h; (d) TsCl, Et_3N, CH_2Cl_2, DMAP, rt, 4 h; (e) $LiAlH_4$, THF, 1 h; (f) TBAF, THF, 0 °C to rt, 2 h; (g) Lipase PS-C, vinyl acetate, hexane, 6 h; (h) K_2CO_3, MeOH, 0 °C to rt, 1 h; (i) Acryloyl chloride, Et_3N, CH_2Cl_2, DMAP, 0 °C to rt, 30 min; (j) **II**, CH_2Cl_2, 35 °C, 48 h; (k) $TiCl_4$, CH_2Cl_2,0 °C to rt, 10 min.

Table 1. Transesterification of 1-benzyloxy-3-methyl-but-3-en-2-ol **8** with various lipases[a] in hexane

Entry	Lipase	Time (h)	Yield[b] (%)	Alcohol ee[c] (%)	Yield[b] (%)	Acetate ee[c] (%)	Conversion (%)	Enantiomeric ratio *E*
1	PS-C	4	46	98	45	>99	0.49	782
2	CAL-B	10	45	96	44	>99	0.49	782
3	PS-D	24	64	80	31	98	0.45	221
4	PS	48	80	21	15	97	0.18	79.6
5	CCL	120	82	20	7	97	0.17	81.8
6	CRL	120	82	—	5	—	—	—
7	P	120	85	—	6	—	—	—
8	MML	120	88	—	4	—	—	—

[a] *Pseudomonas cepacia* lipase immobilized on modified ceramic particles (PS-C), *Pseudomonas cepacia* lipase immobilized on diatomite (PS-D), *Pseudomonas cepacia* (PS) obtained form Amano pharmaceutical company Japan, lipase immobilized from *Mucor meihei* (MML), *Pseudomonas fluorescens* lipase immobilized in Sol–Gel-AK on sintered glass (P), *Candida antartica* lipase immobilized in Sol–Gel-AK on sintered glass (CAL B) from Fluka, *Candida cyclindracea* lipase (CCL) and *Candida rugosa* lipase (CRL) (Sigma).
[b] Isolated yields.
[c] Determined by HPLC (chiral column OB-H; Daicel) employing hexane:*n*-propanol (95:5) as the mobile phase at 0.5 mL/min and monitored by UV (254 nm).

Table 2. Effect of different solvents on the transesterification of 1-benzyloxy-3-methyl-but-3-en-2-ol **8** by lipase PS-C[a]

Entry	Solvent	Log *P*	Time (h)	Alcohol yield[b] (%)	ee[c] (%)	Acetate yield[b] (%)	ee[c] (%)	Conversion (%)	Enantiomeric ratio *E*
1	Hexane	3.5	4	45	98	45	>99	0.49	782
2	Toluene	2.5	10	48	90	32	>99	0.48	599.2
3	Diisopropyl ether	−1.9	24	55	88	30	98	0.47	312.5
4	*t*-Butyl methyl ether	—	36	60	75	25	95	0.44	8.8
5	Acetonitrile	−0.33	240	80	59.5	10	94.5	0.38	693
6	Acetone	−0.23	240	85	55	6	90	0.38	33
7	Tetrahydrofuran	0.49	240	85	—	6	—	—	—
8	Chloroform	2.0	240	88	—	5	—	—	—
9	Dioxane	−1.1	240	—	—	—	—	—	—

[a] *Pseudomonas cepacia* lipase immobilized on modified ceramic particles (PS-C) purchased from Amano Pharmaceutical Co., Japan.
[b] Isolated yields.
[c] Determined by HPLC (chiral column OB-H; Daicel) employing hexane:*n*-propanol (95:5) as the mobile phase at 0.5 mL/min and monitored by UV (254 nm).

After about 50% conversion of **8**, as monitored by HPLC, the two products (*S*)-**8** and (*R*)-**9** were separated by column chromatography. Alcohol (*S*)-**8** upon esterification[9] using acryloyl chloride and triethylamine in CH_2Cl_2 furnished acryl ester (*S*)-**10** in a high yield, which upon ring-closing metathesis (RCM)[10] with Grubbs' 2nd generation catalyst **II** gave α,β-unsaturated lactone (*S*)-**11**. Finally, (*S*)-**11**, upon debenzylation[11] using $TiCl_4$ in CH_2Cl_2, gave the required enantiomerically pure umbelactone (*S*)-(−)-**1** {$[\alpha]_D^{25}$ −10.5 (*c* 1.0, $CHCl_3$), lit.[5e] $[\alpha]_D^{25}$ −9.5 (*c* 1.0, $CHCl_3$)} in 90% yield. In a similar manner (*R*)-(+)-**1** was obtained by hydrolysis of (*R*)-**9** using K_2CO_3 in MeOH followed by esterification (85%), RCM (65%) and debenzylation (90%) {$[\alpha]_D^{25}$ +9.81 (*c* 1.75, $CHCl_3$), lit.[5e] $[\alpha]_D^{25}$ +9.5 (*c* 1.0, $CHCl_3$)}.

In conclusion, we have developed a simple and efficient method for the preparation of both forms of enantiomerically pure umbelactones employing a lipase-mediated resolution protocol, Baylis–Hillman reaction and ring-closing metathesis as the key steps. This lipase-catalyzed transesterification of **8** has been optimized with respect to different lipases and solvents.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.139.

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