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Chemoenzymatic Approach to Enantiomerically Pure (*R*)-3-Hydroxy-3-methyl-4-pentenoic Acid Ester and Its Application to a Formal Total Synthesis of Taurospongin A

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This manuscript is dedicated to Professor Chi-Huey Wong on the occasion of his 60th birthday.

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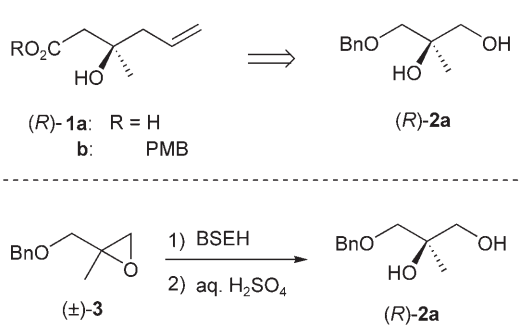
Abstract: (*R*)-3-Hydroxy-3-methyl-5-hexanoic acid *p*-methoxybenzyl ester **1b** was prepared by carbon-chain elongation on both termini of the starting material, (*R*)-3-benzyloxy-2-methylpropane-1,2-diol **2a**, which was prepared by an over-expressed *Bacillus subtilis* epoxide hydrolase-catalyzed enantioselective hydrolysis of the racemic 1-benzyloxymethyl-1-methyloxirane **3**. One of the key steps of the requisite transformation was the *Rhodococcus rhodochrous* NBRC 15564-mediated hydrolysis of a cyano group to a carboxyl group under neutral conditions, to exclude any racemization of the intermediate and/or product. The enantiomerically pure form of (*R*)-**1b** was applied to a new formal total synthesis of taurospongin A.

Keywords: amidase; bioconversion; epoxide hydrolase; hydrolysis; kinetic resolution; nitrile hydratase

Introduction

3-Hydroxy-3-methyl-5-hexanoic acid (**1a**), which has a tertiary alcohol on the β-position of the carboxylic acid together with an appropriately functionalized side chain, seems very attractive as the starting material for many biologically active compounds. Here we report an approach to a *p*-methoxybenzyl ester (*R*)-**1b**, by the carbon-chain elongation of (*R*)-3-benzyloxy-2-methylpropane-1,2-diol (**2a**) on both termini of the molecule. While so far (*R*)-**2a** in an enantiomerically pure state has been available[1] by means of microbial epoxide hydrolase-catalyzed enantioselective hydrolysis of readily available racemic epoxide **3**,[2] we also reported the use of an over-expressed *Bacillus subtilis* epoxide hydrolase (Scheme 1).[3] All the transformation steps should be carried out under the mildest conditions possible without any loss of the enantiomeric excess of the product. Otherwise, as the target molecule **1** has rather labile tertiary alcoholic hydroxy group at the β-position, it would be susceptible for elimination-addition of water or retro-aldol and aldol condensation of the molecule.

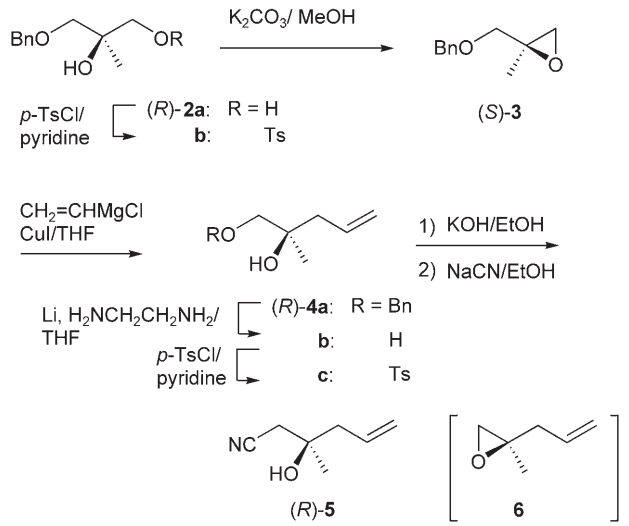


Scheme 1.

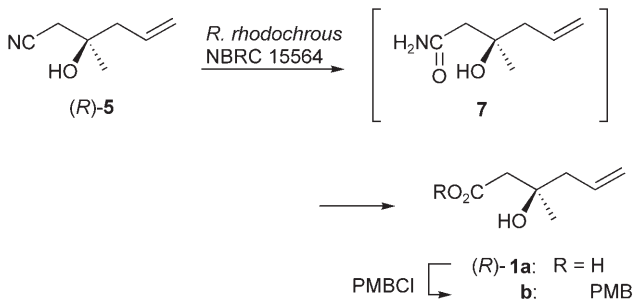
Results and Discussion

Carbon-Chain Elongation and the Functional Group Transformations under Mild Conditions

Towards the synthesis of (*R*)-**1b**, the primary hydroxy group of diol (*R*)-**2a** was selectively tosylated, and the tosylate **2b** was converted to the epoxide (*S*)-**3**.[3] This was treated with vinylmagnesium chloride in THF in the presence of CuI to give (*R*)-**4a** in almost a quantitative yield. Next, the benzyl protective group in **4a** was selectively removed, by treatment with lithium-ethylenediamine-THF,[4] a modified Benkeser reduction. These reaction conditions and work-up are ad-



Scheme 2.



Scheme 3.

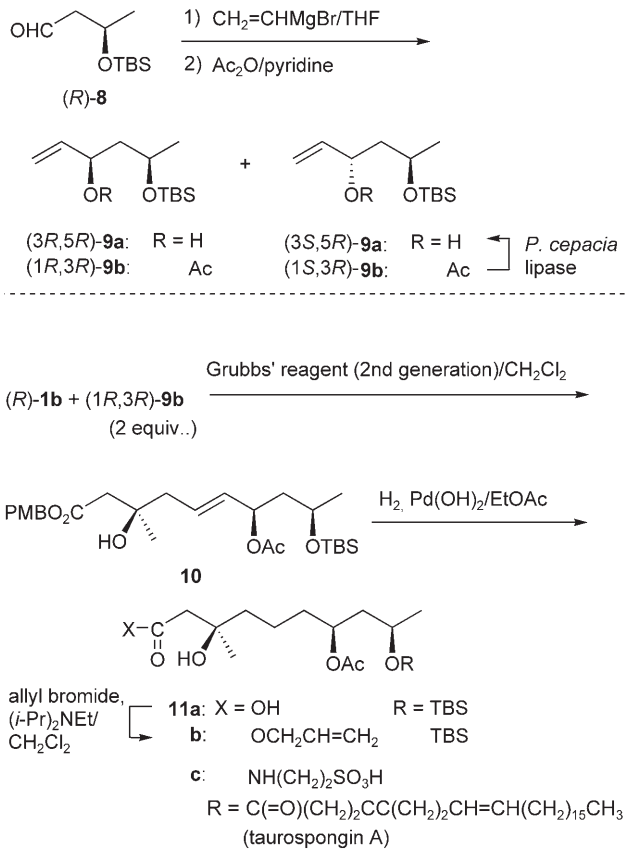
vantageous for water-soluble or highly volatile compounds, as the work-up and purification procedure is very simple. The desired diol (*R*)-**4b** was obtained in 61% yield, under these conditions at −10 °C for 3 h. Prolonged reaction at higher temperature caused the unexpected over-reduction on the terminal olefin. The liberated primary hydroxy group in **4b** was tosylated, and the resulting tosylate **4c** (83%) was successively treated with KOH in EtOH and NaCN to give nitrile (*R*)-**5** in one pot without the isolation of the intermediate, an epoxide **6** (Scheme 2).

Next step was the transformation of the cyano group to a carboxylic acid. In our first attempts for the hydrolysis under strongly basic conditions, the reaction was very slow. The conversion required harsh conditions such as 120 °C for 2 days, however, the yield of the desired product **1b**, after isolation as the corresponding *p*-methoxybenzyl ester (PMB) was as low as 7%, due to the labile properties of the β-hydroxynitrile structure of the substrate. Moreover, this key functional group transformation was not satisfactorily possible by any attempted conditions which had been known for effective transformations of cyano to carboxyl group under mild conditions,[5–11] such as transition metal complex-catalyzed reactions.

To solve this obstacle, an enzyme-catalyzed hydration of nitrile followed by hydrolysis of the amide[12–15] was effective. In our hands, with the cultured whole cells of *Rhodococcus rhodochrous* NBRC 15564, the sequential action of two enzymes, nitrile hydratase and amidase in one pot provided the desired product, (*R*)-**1b** in a total yield of 60% from tosylate **4c** in four steps, after direct treatment with PMB chloride of the crude hydrolysate (Scheme 3). HPLC analysis with a chiral stationary phase supported the 100% *ee* of **1b**. In a separate experiment, incubation of racemic nitrile **5** provided racemic **1b**. These results indicate that neither the nitrile hydratase nor the amidase in this microorganism worked in an enantioselective manner on the nitrile **5** or the intermediacy amide **7**. While amidases had in many cases worked enantioselectively on β-alkoxy- and acyloxy-substituted nitriles,[16–19] the loss of stereoselection had also been observed when the substituent was altered from alkoxy and/or acyloxy to a hydroxy group.[16,20–21] In this case, as the antipodal substrate, (*S*)-**5** can be prepared from the enantiomerically pure form of (*R*)-epoxide **3**,[3] this total procedure in Scheme 2 and Scheme 3 would also work well to provide (*S*)-**1b**.

Application to the Formal Total Synthesis of Taurospongin A

After the above-mentioned tertiary hydroxy ester (*R*)-**1b**, bearing a terminal olefin, in an enantiomerically pure state became available, it was further transformed to a known synthetic intermediate [(*R*)-**11b**] of taurospongin A (**11c**),[22,23] by means of Grubbs' cross-metathesis coupling reaction. To this end, the counterpart, allylic acetate (1*R*,3*R*)-**9b** (*syn*-**9b**) was prepared starting from ethyl (*R*)-3-hydroxybutanoate, *via* an ethanolysis of the biodegrable polymer, poly β-hydroxybutyrate (PHB).[24] The known aldehyde **8**[25] was treated with vinylmagnesium bromide and the resulting allylic alcohol **9a** was subsequently acetylated to give a stereoisomeric mixture of acetates **9b**, in a range of *syn*:*anti* = 1.3–1.5:1 (Scheme 4). Disappointingly, all attempts towards the more selective formation of the *syn*-alcohol were in vain, even by changing the Lewis acidity of the vinylmetal species (MgCl, MgBr, Ce) and the protective group of the remote hydroxy group from silyl to, e.g., *p*-methoxybenzyl. As either the diastereomeric pair of alcohols **9a** or acetates **9b** were hardly separable on silica gel column chromatography, we decided to use a lipase-catalyzed kinetic resolution of the diastereomers of **9b**. The two candidates for enzymes which so far had been reported to satisfy such requrements, the stereoselective hydrolysis of allylic acetates, *Pseudomonas cepacia* lipase[26,27] and *Candida antarctica* lipase[28] were com-



Scheme 4.

pared. Preliminary experiments revealed that the former had a higher catalytic activity and enantioselectivity (E value: 48) than the latter (26). Incubation of the mixture of **9b** with *P. cepacia* lipase (Amano PS-C) in buffer solution at 40 °C provided (1*R*,3*R*)-**9b** in 59% yield and 99.9% *de* as the unreacted recovery.

Grubbs' second-generation catalyst (10 mol%)-mediated cross-metathesis coupling reaction[29] between the two components (*R*)-**1b** and (1*R*,3*R*)-**9b** (two molar excess) worked well to give the desired ester **10** in 77% yield. Finally, saturation of the olefin as well as the deprotection of PMB ester *via* hydrogenolysis with $Pd(OH)_2$ in EtOAc, and subsequent allylation of the free carboxyl group in **11a** provided (*R*)-**11b** in 76% through two steps (Scheme 4). In the former step, the major side reaction was the hydrogenolysis of the allylic oxygen functionality, and the use of conventional Pd-C, other polar solvents, or even homogeneous Wilkinson's catalyst promoted this undesired path and, moreover, the loss of TBS protective group. The spectral and optical rotation data of the present (*R*)-**11b** were in good agreement with the previously reported value, $[\alpha]_D^{23}$: −1.45° (*c* 0.97, $CHCl_3$) {lit.[23] $[\alpha]_D$: −1.17° (*c* 1.37, $CHCl_3$)}.

Conclusions

We were successful in developing a route to the suitably functionalized β-hydroxy ester, (*R*)-**1b** by carbon-chain elongation and functional group transformation of (*R*)-**2a**. As an application of the enantiomerically pure form of (*R*)-**1b**, the formal total synthesis of taurospongin A was demonstrated. In contrast to all the attempted chemical transformations, the biocatalytic hydrolysis of a cyano to a carboxyl group with *Rhodococcus rhodochrous* NBRC 15564 under neutral conditions worked well, to exclude any racemization of the intermediate.

Experimental Section

Characterization data of all of the compounds including spectroscopic and analytical data and the general remarks about the equipment used are available as Supporting Information.

(*R*)-1-Benzyloxy-2-methyl-4-pentene-2-ol (4a)

A solution of vinylmagnesium chloride (1.0 M, 13.5 mL, 13.5 mmol in THF) was degassed to remove traces of oxygen by the repeat of evacuation and then introduction of N_2 under atomospheric pressure several times. The mixture was then cooled to −78 °C. CuI (0.171 g, 0.898 mmol) was added under the flow of N_2. The reaction temperature was raised to −50 °C, **3**[3] (0.811 g, 4.55 mmol) in dry THF (0.4 mL) was added to the reaction mixture and stirred for 3 h. After the mixture had been warmed to room temperature, a saturated aqueous solution of NH_4Cl (10 mL) was added to the dark-colored mixture reaction. The mixture was diluted with EtOAc, and then the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue (0.97 g) was charged on a silica gel column (28 g). Elution with hexane-EtOAc (4:1) gave (*R*)-**4a** as a colorless oil; yield: 0.845 g, 4.10 mmol (90%). $[\alpha]_D^{21}$: −10.3° (*c* 1.02, $CHCl_3$) [lit.[30] (*R*)-**4a**: $[\alpha]_D^{20}$: −2° (*c* 0.5, $CHCl_3$)]. Its NMR spectrum was identical with that reported previously.[30]

(*R*)-2-Methyl-4-pentene-1,2-diol (4b)

A solution of **4a** (2.00 g, 11.2 mmol) in THF (51 mL) and ethylenediamine (5.2 mL, 78.6 mmol) was degassed to remove any traces of oxygen by the repetitive application of ultrasonic (70–80 W) under evacuation and then introduction of N_2 under atomospheric pressure several times. The mixture was then cooled to −10 °C. Lithium shot (0.39 g, 56.2 mmol) was added in several portions under a flow of N_2. After 2 h, the reaction was quenched by addition of 2 M HCl and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue (1.02 g) was charged on a silica gel column (40 g). Elution with hexane-EtOAc (2:1) afforded **4b** as a colorless oil; yield: 0.794 g, 6.84 mmol (61%). $[\alpha]_D^{19}$: +21.8° (*c* 1.02, EtOH). Its NMR spectrum was identical with that reported previously.[31]

(*R*)-2-Hydroxy-2-methyl-4-pentenyl *p*-Toluenesulfonate (4c)

To a solution of **4b** (0.297 g, 2.56 mmol) in pyridine (5.6 mL) was added *p*-toluenesulfonyl chloride (0.740 g, 3.87 mmol) at 0 °C. After stirring for 24 h at room temperature, the reaction was quenched by the addition of water (10 mL), and the mixture was extracted with EtOAc. The organic layer was washed with 1 M HCl, saturated aqueous $NaHCO_3$ solution, and brine. The solution was dried over Na_2SO_4, and concentrated under vacuum. The residue (0.601 g) was charged on a silica gel column (12 g). Elution with hexane-EtOAc (3:1) afforded **4c** as a colorless oil; yield: 0.574 g, 2.12 mmol (83%). $[\alpha]_D^{19}$: −0.52° (*c* 0.96, EtOH). This was employed for the next step without further purification.

p-Methoxybenzyl (*R*)-3-Hydroxy-3-methyl-5-hexenoate (1b)

A solution of **4c** (0.197 g, 0.729 mmol) in EtOH (0.67 mL) was added KOH (50.0 mg, 0.891 mmol) in EtOH (0.67 mL) at 0 °C. After stirring for 10 min, water (2 mL) and NaCN (0.11 g, 2.24 mmol) was added. The mixture was warmed to 120 °C and stirred for an additional 1 h. The mixture was diluted with Et_2O, the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum to give crude **5**; yield: 96.3 mg.

A mixture of **5** in phosphate buffer (0.1 M, 0.6 mL, pH 7.0) and cultured wet cells of *R. rhodochrous* NBRC15564 prepared according to the previous paper[32] was stirred for 4 days at 35 °C. The supernatant was saturated with NaCl and mixed with EtOAc. The mixture was stirred for 1 h and filtered through a pad of Celite. The organic layer of the filtrate was separated and the aqueous layer was acidified with HCl (2 M) to pH 2 and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum to give crude **1a** (0.112 g). This was dissolved in DMF (3 mL) and to this was added KOH (0.10 g, 1.78 mmol) and *p*-methoxybenzyl chloride (0.3 mL, 2.21 mmol). After stirring for 14 h, the reaction was quenched by the addition of water (10 mL), and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue (0.517 g) was charged on a silica gel column (15 g). Elution with hexane-EtOAc (4:1) afforded (*R*)-**1b** as a colorless oil; yield: 0.116 g (0.438 mmol, 60%). $[\alpha]_D^{22}$: −1.68° (*c* 0.85, EtOH); HPLC: > 99.9% *ee* [Chiralcel OJ-H, 0.46 cm × 25 cm; hexane-*i*-PrOH (15:1), 0.5 mL min^{-1}], t_R = 49.9 min [(*R*), single peak]. No peak ascribable to (*S*)-isomer [t_R = 52.2 min] was detected.

(3*RS*,5*R*)-5-*tert*-Butyldimethylsilyloxy-1-hexen-3-ol (9a)

To a solution of vinylmagnesium bromide (0.94 M, 3.3 mL, 3.10 mmol in THF) was added (*R*)-**8** (0.195 g, 0.964 mmol) in dry THF (0.5 mL) at −78 °C under an argon atmosphere. After 1 h, the reaction mixture was warmed to room temperature, stirred for an additional 6 h and quenched by dropwise addition of saturated aqueous NH_4Cl solution (5 mL) at 0 °C. The mixture was diluted with EtOAc, the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue (0.212 g) was charged on a silica gel column (6.5 g). Elution with hexane-EtOAc (4:1) gave **9a** as a diastereomeric mixture; yield: 0.181 g (0.786 mmol, 82%). The ratio between (3*R*,5*R*)-**9a** [*syn*-**9a**], (3*S*,5*R*)-**9a** [*anti*-**9a**] was estimated as 1.44:1 by comparing the ^{1}H NMR signal of the each component.

(1*RS*,3*R*)-3-*tert*-Butyldimethylsilyloxy-1-vinylbutyl Acetate (9b)

A solution of **9a** (0.178 g, 0.773 mmol) and Ac_2O (1.0 mL) in pyridine (1.0 mL) was stirred at room temperature for 24 h. The mixture was quenched by the addition of ice and stirred for 1 h. Then, the mixture was concentrated under vacuum, and extracted with EtOAc. The organic layer was washed with 1 M HCl, saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated under vacuum. The residue (0.224 g) was charged on a silica gel column (6 g). Elution with hexane-EtOAc (10:1) afforded (1*RS*,3*R*)-**9b** as a colorless oil; yield: 0.215 g (quantitative). This was employed for the next step without further purification.

Pseudomonas cepacia Lipase-Catalyzed Hydrolysis of (1*RS*,3*R*)-9b

A mixture of lipase PS-C (0.2 g) and (1*RS*,3*R*)-**9b** (30.7 mg, 0.113 mmol) in phosphate buffer (0.1 M, 0.6 mL, pH 7.0) was stirred for 18 h at 40 °C. The reaction mixture was diluted with brine and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue (29.6 mg) was charged on a silica gel column (1 g). Elution with hexane-EtOAc (10:1) gave (1*R*,3*R*)-**9b** (*syn*-**9b**: yield: 18.2 mg, 0.0668 mmol, 59%, 99.9% *de*) and (3*S*,5*R*)-**9a** (*anti*-**9a**: yield: 7.7 mg, 0.0334 mmol, 30%, 87.3% *de*) as a colorless oil. (1*R*,3*R*)-**9b**: $[\alpha]_D^{21}$: −7.96° (*c* 0.97, EtOH).

p-Methoxybenzyl (3*R*,7*S*,9*R*)-7-Acetoxy-9-(*tert*-butyldimethylsilyloxy)-3-hydroxy-3-methyl-5-decenoate (10)

To a mixture of (*R*)-**1b** (63.5 mg, 0.240 mmol) and (1*R*,3*R*)-**9b** (0.133 g, 0.488 mmol) in CH_2Cl_2 (1.2 mL) was added second-generation Grubbs' catalyst (20 mg, 0.0236 mmol). The reaction was heated to 45 °C for 15 h and then cooled to room temperature. The reaction mixture was concentrated under vacuum. The residue (0.25 g) was charged on a silica gel column (6 g). Elution with hexane-EtOAc (5:1) gave **10** as a pale yellow oil; yield: 91.9 mg (0.181 mmol, 77%). $[\alpha]_D^{24}$: +7.66° (*c* 1.61, EtOH).

Allyl (3*R*,7*S*,9*R*)-7-Acetoxy-9-(*tert*-butyldimethylsilyloxy)-3-hydroxy-3-methyldecanoate (11b)

A solution of **10** (60.9 mg, 0.120 mmol) in EtOAc (1.6 mL) was stirred with $Pd(OH)_2$ (30 mg, Aldrich, Wet, Degussa type) at room temperature for 1 h under H_2. The mixture was filtered through No. 5C paper and the filtrate was concentrated under vacuum to give crude **11a**; yield: 50.4 mg.

To a solution of **11a** in CH_2Cl_2 (1.2 mL) was added *N*,*N*-diisopropylethylamine (0.2 mL, 1.18 mmol), followed by allyl bromide (0.154 mL, 1.78 mmol). The resulting mixture was stirred for 14 h, then concentrated. The residue (59.4 mg) was purified by silica gel column (4.0 g). Elution with hexane-EtOAc (10:1) afforded **11b** as a colorless oil;

yield: 39.2 mg (0.091 mmol, 76% isolated yield; 50% based on the recovery). $[\alpha]_D^{23}$: −1.45° (*c* 0.97, $CHCl_3$), [lit.[23]: $[\alpha]_D$: −1.17° (*c* 1.37, $CHCl_3$)]. Its IR and NMR spectra were identical with those reported previously.[23]

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