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Synthesis of the antiepileptic (*R*)-Stiripentol by a combination of lipase catalyzed resolution and alkene metathesis

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ABSTRACT

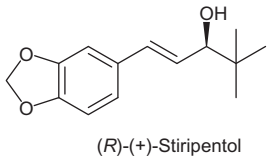
The enantiopure (ee >99%) antiepileptic (*R*)-(+)-Stiripentol has been stereoselectively synthesized via cross metathesis of 5-vinylbenzo[*d*][1,3]dioxole **1** and (*R*)-(+)-4,4-dimethylpent-1-en-3-ol (*R*)-(+)-**2**. A novel one-pot two-step pathway for the synthesis of 5-vinylbenzo[*d*][1,3]dioxole **1** starting from 3,4-dihydroxycinnamic acid has been introduced. A lipase catalyzed kinetic resolution access to enantiopure (*R*)-(+)-4,4-dimethylpent-1-en-3-ol (*R*)-(+)-**2** (ee >99%) has also been developed.

1. Introduction

Stiripentol (STP) (Diacomit®) is an antiepileptic drug pioneered by Biocodex (Gentilly, France). With respect to chemical structure, it is dissimilar to all market available antiepileptic drugs as it belongs to the group of aromatic allylic alcohols.[1] The European Union has approved Stiripentol orphan drug status for the treatment of severe myoclonic epilepsy in infants (Dravet syndrome). In addition, it has long been used as co-therapy for the treatment of epilepsy.[2] A recent report stated that STP acts at the neuronal level, increasing inhibitory GABAergic neurotransmission through positive allosteric modulation of $GABA_A$ receptors.[3] STP has long been considered to be an indirect antiepileptic, as it inhibits the enzymes responsible for metabolism of other antiepileptic drugs.[4] Stereochemically, Stiripentol is a secondary alcohol containing one asymmetric center (Fig. 1). Despite the marked differences in pharmacokinetics and antiepileptic potency between the enantiomers, it is still marketed as a racemic mixture.[4]

Over the last few years, biocatalysis has been recognized as a viable and popular technique in organic synthesis, especially in the production of enantiopure molecules and pharmaceutical compounds.[5] Most lipases have a wide range of non-natural substrates and are thus very versatile for applications in organic synthesis. They do not require cofactors and are commercially available in free and immobilized forms; in many cases, they exhibit good to excellent stereoselectivity[6].

Recently, olefin metathesis has become more generally utilized in synthetic organic chemistry. The process, by which alkylidene groups on alkenes are exchanged, has grown to be a powerful synthetic tool for C=C bond formation due to the development of a range of very stable ruthenium-based catalysts introduced by Grubbs et al.[7]



(*R*)-(+)-Stiripentol

Figure 1. Structure of (*R*)-(+)-Stiripentol.

In a previous study,[8] Stiripentol has been subjected to thorough investigations aimed at a resolution of the racemic mixture to its enantiomers using lipase catalyzed kinetic resolution technology. Careful selection of the lipases used and subsequent reaction optimization resulted in enantioenriched (*R*)-Stiripentol that was obtained in ee = 94%. Although the achieved result was acceptable, further enhancement was required to obtain enantiopure (*R*)-Stiripentol. The difficulties in these lipase-catalyzed resolution reactions have been attributed to the bulky substrate (Stiripentol) which pushed most of the lipases used to be completely inactive or in the best case very slow. Thus herein, it has been assumed that using a less bulky substrate could be helpful in the attainment of very high selectivity and enantiomeric purity. Hence, (*RS*)-(±)-4,4-dimethylpent-1-en-3-ol has been subjected to intensive kinetic resolution reactions catalyzed by lipases in order to afford (*R*)-(+)-4,4-dimethylpent-1-en-3-ol (*R*)-(+)-**2** which by further coupling with 5-vinylbenzo[*d*][1,3]dioxole **1** in a cross metathesis reaction could yield the desired enantiopure (*R*)-Stiripentol (Scheme 1).

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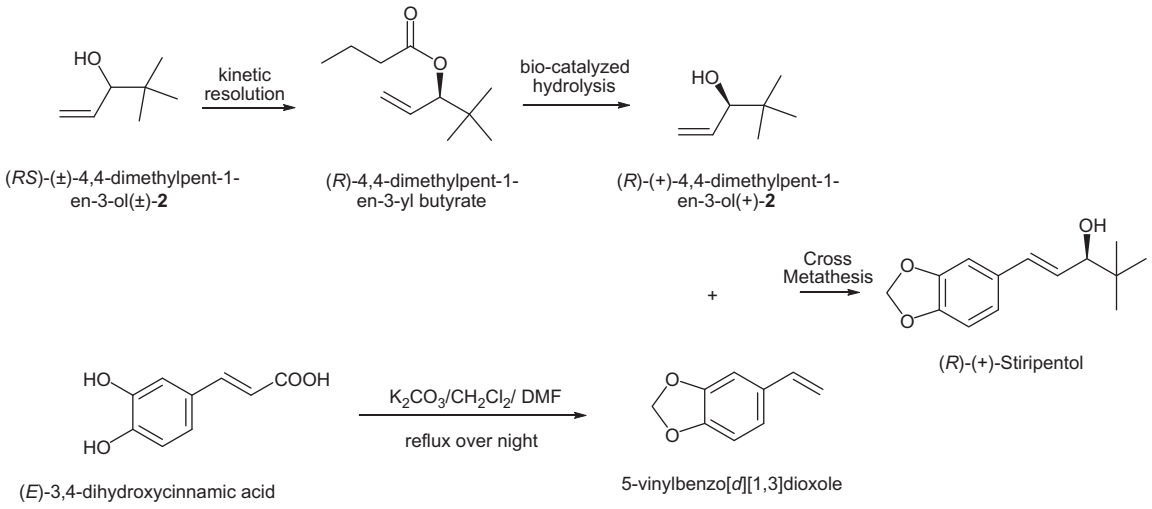


Scheme 1. Synthesis of (*R*)-(+)-Stiripentol.

2. Results and discussion

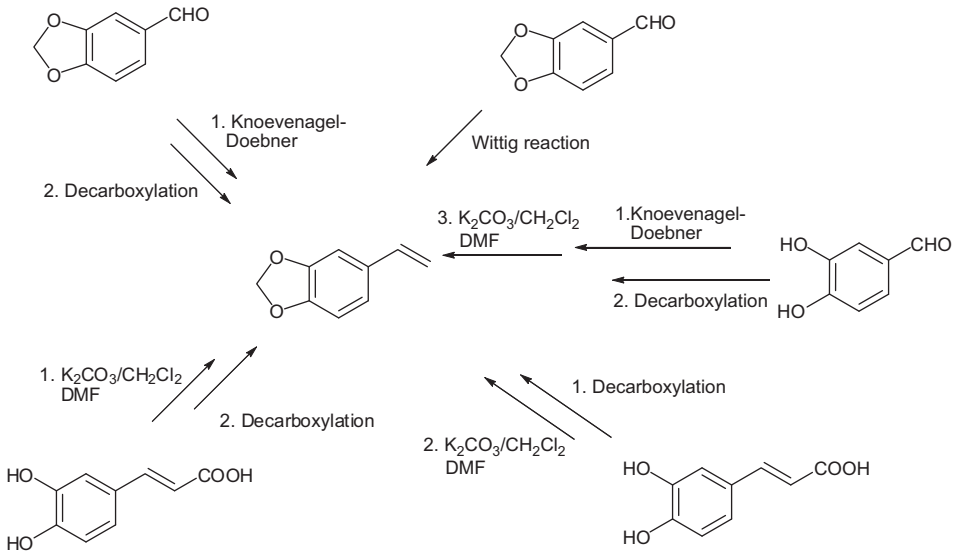
2.1. Synthesis of 5-vinylbenzo[*d*][1,3]dioxole 1

5-Vinylbenzo[*d*][1,3]dioxole **1** is a functionalized styrene, which is one of the most comprehensively investigated set of compounds due to its broad applications in the food and flavoring industries.[9] Also, it can act as an intermediate in the synthesis of various bioactive molecules[10] and many biological activities have been ascribed to these compounds.[11]

Synthetic strategies toward styrenes or vinyl phenols are ubiquitous and mainly depend on the starting material. For instance, starting with *trans*-cinnamic acids, decarboxylation at 240–260 °C in the presence of quinoline and metal salts is reported.[12] For ethylphenols catalytic dehydrogenation is the preferred strategy,[13] or alternatively achieved via Wittig synthesis[14] or from phenol in five steps as reported by Corson et al.[15] Starting with benzaldehyde derivatives, Knoevenagel condensation–decarboxylation[16,17] or Grignard addition–dehydration approaches[18] are also useful. Recently, the cross coupling of aryl halides and 2,4,6-trivinylcyclotriboroxane pyridine,[19] or arylboronic acids with vinyl bromide in the presence of palladium acetate[20] has also provided styrenes.

Herein, we focused on the synthesis of 5-vinylbenzo[*d*][1,3]dioxole **1** starting from dihydroxybenzaldehyde or dihydroxycinnamic acid. According to the starting material many pathways could be followed in order to attain the desired compound **1** (Scheme 2).

At the inception, the recently reported microwave assisted techniques for Knoevenagel condensation–decarboxylation of 3,4-dihydroxybenzaldehyde[17] or the decarboxylation of 3,4-dihydroxycinnamic acid[21] were attempted. Unfortunately, all microwave assisted experiments failed in our hands and resulted in charred reaction mixtures. We then shifted the investigations toward conventional decarboxylation methodology whereby high temperatures and basic catalysis are used. Accordingly, the reported procedure by Saga et al.[22] for the decarboxylation of cinnamic acid using cupric chloride, DBU and heating at 240 °C for 30 min was carried out, and resulted in 4-vinylbenzene-1,2-diol in a low 10% yield. The pure 4-vinylbenzene-1,2-diol was then subjected for further methylene bridge formation reaction according to the reported procedures by Aboul-Enein et al.[23] whereby 5-

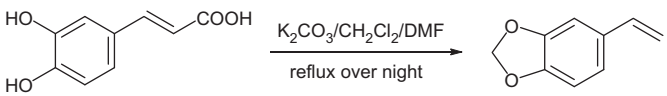


Scheme 2. Postulated pathways toward 5-vinylbenzo[*d*][1,3]dioxole **1**.

vinylbenzo[*d*][1,3]dioxole **1** has been obtained in 55% yield as a light yellow oil, giving **1** in a total yield of 5.5% over two steps. However, this method was still superior to the reported procedures for the synthesis of **1** by Sinha et al.[17] which afforded 4% yield.

In order to improve the yield of **1**, reversing the sequence of the reactions was investigated, by performing the methylene bridging reaction first, followed by the decarboxylation. Somewhat surprisingly, a one-pot two-step reaction was discovered whereby the methylene bridging and decarboxylation reactions occurred in the same pot when 3,4-dihydroxycinnamic acid was subjected to reaction conditions intended to introduce the methylene bridge. The product obtained was verified by spectroscopic analysis which showed data identical to those of 5-vinylbenzo[*d*][1,3]dioxole **1**.[10] It could be that anhydrous potassium carbonate, used in the methylene bridging reaction as a base, plays the role of DBU in the decarboxylation reaction. Also, it has been reported[22] that DMF could be used as a reaction medium where the high boiling point solvent will provide the heat needed for decarboxylation.

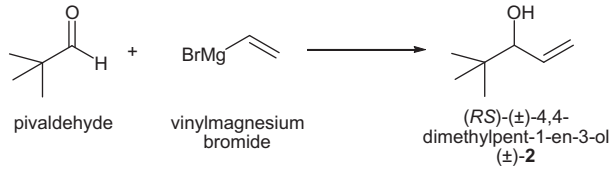
The one-pot two-step synthesis of 5-vinylbenzo[*d*][1,3]dioxole **1** provided the pure product in 61% yield and required no sophisticated purification procedures. This new procedure has been proved to be superior over the previously reported synthesis of 5-vinylbenzo[*d*][1,3]dioxole **1** by Sinha et al.[17] giving an improved yield. In addition, it is better than the reported procedures by Aslam et al.[10] being simpler and using more economic starting materials and catalysts (Scheme 3).



Scheme 3. One-pot two-step synthesis of 5-vinylbenzo[*d*][1,3]dioxole **1**.

2.2. Synthesis of (±)-4,4-dimethylpent-1-en-3-ol (±)-2

Typical Grignard reaction procedures were followed[24] for the synthesis of (±)-4,4-dimethylpent-1-en-3-ol (±)-**2**. Thus an equimolar amount of vinyl magnesium bromide and pivaldehyde was allowed to react in dry ethyl ether at reflux. The resulting magnesium complex was decomposed using saturated ammonium chloride solution and the reaction product was purified to afford racemic **2** as yellow oil in 75% yield (Scheme 4).



Scheme 4. Grignard synthesis of (*RS*)-(±)-4,4-dimethylpent-1-en-3-ol (*RS*)-(±)-**2**.

2.3. Lipase-catalyzed resolution of (*R*)-(+)-4,4-dimethylpent-1-en-3-ol (*R*)-(+)-2

After optimizing the chiral analyses for racemic 4,4-dimethylpent-1-en-3-ol **2** and the corresponding butanoate **3**, the screening of different lipases (11 lipases) for the enantioselective transesterification of (*RS*)-4,4-dimethylpent-1-en-3-ol (*RS*)-**2** was then performed (Scheme 5).

Screening all available lipases for activity in *n*-hexane and using vinyl butanoate as the acyl donor showed that three lipases gave mediocre to excellent enantiomeric ratios (*E*). Lipase immobilized on immobead 150 from *Candida rugosa* (*E* = 19.9), AMANO lipase AY30 (*E* = >300), and lipase A from *Candida antarctica* (CAL-A) (*E* = >300) gave in all cases (*R*)-**2** as the faster reacting enantiomer. This was then subsequently esterified selectively to afford (*R*)-**3** leaving the second enantiomer of the substrate (*S*)-**2** in an enantiomerically enriched form.

Further investigations have been performed in order to test the performance of these three enzymes in different organic solvents such as toluene, methyl *tert*butyl ether (MTBE), ethyl acetate (EtOAc), tetrahydrofuran (THF), and chloroform. Switching to other solvents or changing the acyl donor gave no major differences in the enantiomeric ratio in reactions using AMANO lipase AY30 or lipase A from *Candida antarctica*. Unfortunately, no improvement was observed when testing *Candida rugosa* lipase in these solvents or by attempting acyl donors other than vinyl butyrate.

The best process was based on a minimum reaction time and the best enantiomeric ratio was determined to be lipase A from *Candida antarctica* in toluene (Fig. 2). Using this procedure, the reaction was scaled up to 1 g of substrate which, after separation of the (*R*)-ester and (*S*)-alcohol by column chromatography using silica gel and $CHCl_3$ (100%) afforded (*S*)-alcohol (*S*)-(−)-**2** (0.4 g, ee = 75%), $[\alpha]_D^{20} = -6.2$ (*c* 10, $CHCl_3$), and (*R*)-butyrate (*R*)-(+)-**3** (0.33 g, ee >99%), $[\alpha]_D^{20} = +5.1$ (*c* 10, $CHCl_3$) which was subjected to further lipase A catalyzed hydrolysis in phosphate buffer pH 7.0 to afford (*R*)-alcohol (*R*)-(+)-**2** (0.1 g, ee >99%), $[\alpha]_D^{20} = +8.3$ (*c* 10, $CHCl_3$).

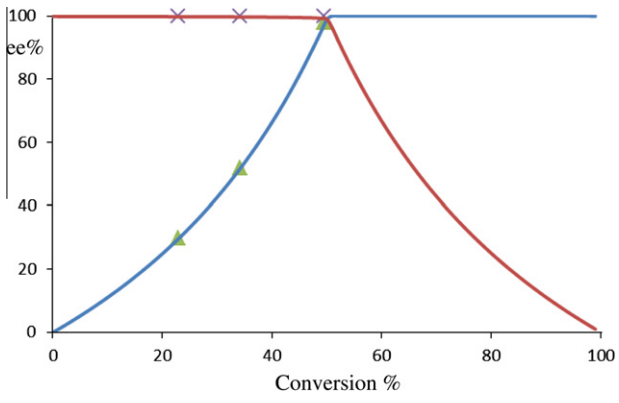
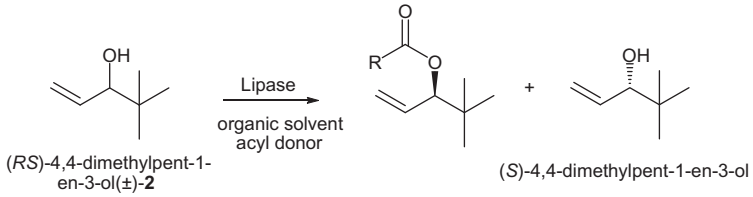


Figure 2. Progress of the kinetic resolution of rac-**2** by esterification with vinyl butanoate catalyzed by CALA, (X) product fraction (*R*)-**3**, (Δ) substrate fraction (*S*)-**2**.



Scheme 5. Lipase catalyzed transestrification of (±)-4,4-dimethylpent-1-en-3-ol (±)-**2**.

2.4. Synthesis of (*R*)-(+)-1-(benzo[*d*][1,3]dioxol-5-yl)-4,4-dimethylpent-1-en-3-ol (*R*)-(+)-4, (*R*)-(+)-Stiripentol using olefin metathesis

The high selectivity and reactivity of Grubbs' catalyst for carbon-carbon π-bond formation enable the use of cross metathesis (CM) as an excellent alternative to other alkene forming reactions.

The reported cross metathesis procedures by Nagarapu et al.[25] have been utilized in the synthesis of (*R*)-(+)-Stiripentol. Equimolar amounts of 5-vinylbenzo[*d*][1,3]dioxole **(1)** and (*R*)-(+)-4,4-dimethylpent-1-en-3-ol (*R*)-(+)-**2** were treated with 5 mol % of Grubbs' 2nd generation catalyst in dry dichloromethane. The product was purified using preparative thin layer chromatography (silica gel and $CHCl_3$) to give 5 mg of (*R*)-(+)-Stiripentol (15%, ee >99%). The low yield could be attributed to the occurrence of the homo-coupling reaction affording dimers of the starting materials instead of reacting further the cross-coupling product. Based on the observed coupling constant (^3J = 15.3 Hz, CH=CHPh) and coincident chromatographic behavior with a Stiripentol standard, it was concluded that no *Z*-isomers were formed. The ee was determined by chiral HPLC[8] and all spectroscopic data were in accordance with those reported earlier.[8]

3. Conclusion

By employing the cross-metathesis of 5-vinylbenzo[*d*][1,3]dioxole **1** and (*R*)-(+)-4,4-dimethylpent-1-en-3-ol (*R*)-(+)-**2** using Grubbs' second generation catalyst, access toward enantiopure (*R*)-(+)-Stiripentol has been achieved. 5-Vinylbenzo[*d*][1,3] dioxole **1** has been synthesized in 61% yield using a new concise, and straightforward pathway from 3,4-dihydroxycinnamic acid. The first lipase-catalyzed enantioselective resolution of (*RS*)-(±)-4,4-dimethylpent-1-en-3-ol (*RS*)-(±)-**2** has been reported to afford enantiopure (*R*)-(+)-4,4-dimethylpent-1-en-3-ol (*R*)-(+)-**2** in ee >99%.

4. Materials and methods

4.1. General

All solvents used were analytical grade (p.a.) and purchased from Sigma–Aldrich (Steinheim, Germany). Immobilized *Candida antarctica* lipase B (Novozym 435, activity 10,000 PLU/g, lot No. LC 200205) was from Novozymes (Bagsværd, Denmark). Lipase A from *Candida antarctica* immobilized on Immobead 150, (activity 500 U/g, lot No. 1388471) was bought from Sigma–Aldrich.

^{1}H NMR and ^{13}C NMR spectra were carried out on Bruker 400 MHz Spectrophotometer using TMS as an internal standard. Chemical shift values are recorded in the ppm δ scale. Optical rotations ($[\alpha]_D$) were determined at 20 °C using a Perkin–Elmer 341 instrument, concentrations are given in g/100 mL. AIKA KS 4000 shaker incubator was used for the enzyme reactions. Enantiomeric ratios, *E*, were calculated based on ping–pong bi–bi kinetics using the computer program *E & K Calculator* 2.1b0 PCC[26] based on the calculations of Chen and Rakes.[27,28] GC system was Varian 3400 gas chromatograph equipped with a chiral CP-Chirsil Dex CB column (25 m, 0.32 mm i.d., 0.25 lm film thickness).

4.2. Chiral chromatography analysis

4.2.1. Chiral GC analysis

Varian 3400 gas chromatograph equipped with a chiral CP-Chirsil Dex CB column (25 m, 0.32 mm i.d., 0.25 lm film thickness), temperature program 50–85 °C, 5 °C/min, 85–97 °C, 1 °C/min, 97–200 °C, 20 °C/min. Retention times, (*R*)-(+)-**2** = 12.9 min, (*S*)-(−)-**2** = 13.2 min, (*R*)-(+)-**3** = 22.0.

4.2.2. Chiral HPLC analysis[8]

Stiripentol was separated according to the reported procedures by Jacobsen et al.[8] using an Agilent 1100 HPLC system (Agilent, USA) with a quaternary pump and a variable wavelength UV detector and equipped with Chiracel OD-H® column ([cellulose tris (3,5 dimethylphenylcarbamate) coated on 5 μm silica-gel], i.d. 4.6 mm, 25 cm, film density 5 μm). *n*-Hexane, *tert*-butyl methyl ether (MTBE) and 2-propanol (2-PrOH) were used as eluents, flow rate 1 mL min^{-1}. Retention time Stiripentol (mobile phase 95:5:1) 27.9, 30.3 min.

4.3. Synthesis of 5-vinylbenzo[*d*][1,3]dioxole 1

4.3.1. One-pot two-step reaction

A solution of 3,4-dihydroxycinnamic acid (2 g, 0.011 mol) in DMF (20 mL) was added dropwise to a suspension of CH_2Cl_2 (1.4 mL, 0.02 mol) and K_2CO_3 (4 g, 0.028 mol) in DMF (30 mL). The mixture was stirred and heated at reflux for 18 h then cooled and filtered. The filtrate was concentrated, diluted with water, and extracted with ethyl acetate (3 × 100 mL). The filter cake was washed with ethyl acetate (25 mL). The organic layer was washed with 10% NaOH (25 mL), water (25 mL), dried (Na_2SO_4), and evaporated to afford 1.0 g (61%) of **1** as a yellow oil.[10] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.0 (d, *J* = 10.86 Hz, 1H, CHC*H*$_2$), 5.5 (d, *J* = 17.43 Hz, 1H, CHC*H*$_2$), 5.9 (s, 2H, OC*H*$_2$O), 6.5 (dd, *J* = 10.86, 17.43 Hz, 1H, C*H*CH$_2$), 6.5 (d, *J* = 8.08 Hz, 1H, Har), 6.75 (dd, *J* = 1.52, 7.83 Hz, 1H, Har), 6.9 (d, *J* = 1.52 Hz, 1H, Har).

^{13}C NMR ($CDCl_3$, 100 MHz): 101, 105, 109, 112, 121, 132, 136, 147,148.

4.3.2. Two step reaction

4.3.2.1. Synthesis of 4-vinylbenzene-1,2-diol. A mixture of dihydroxycinnamic acid (1 g, 5.5 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.7 g, 11 mmol), and $CuCl_2$ (0.08 g, 0.59 mmol) was heated at 240 °C for 30 min. The mixture was cooled, dissolved in water, acidified with HCl (10%, aqueous) until pH 1, filtered, extracted with ethyl acetate (3 × 50 mL), then evaporated under vacuum, and purified using column chromatography (silica gel, $CHCl_3/CH_3OH$ 4/1 v/v) to afford 80 mg (10%) of 4-vinylbenzene-1,2-diol as yellow oil.[29] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.9 (d, *J* = 10.86 Hz, 1H, CHC*H*$_2$), 5.4 (d, *J* = 17.43 Hz, 1H, CHC*H*$_2$), 6.5 (dd, *J* = 10.86, 17.43 Hz, 1H, C*H*CH$_2$), 6.7 (m, 3H, Har). ^{13}C NMR ($CDCl_3$, 100 MHz): 110, 112, 115, 119, 120, 130, 137, 145.

4.3.2.2. Synthesis of 5-vinylbenzo[*d*][1,3]dioxole 1. A solution of 4-vinylbenzene-1,2-diol (50 mg, 0.36 mmol) in DMF (1 mL) was added dropwise to a suspension of CH_2Cl_2 (0.35 mL, 0.005 mol) and K_2CO_3 (150 mg, 0.028 mol) in DMF (10 mL). The mixture was stirred and heated at reflux for 4 h then cooled and filtered. The filtrate was concentrated, diluted with water, and extracted with ethyl acetate (3 × 10 mL). The filter cake was washed with ethylacetate (10 mL). The organic layer was washed with 10% NaOH (10 mL), water (10 mL), dried (Na_2SO_4), and evaporated to afford 30 mg (55%) of **1** as a yellow oil.[10] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.2 (d, *J* = 10.8 Hz, 1H, CHC*H*$_2$), 5.6 (d, *J* = 17.4 Hz, 1H, CHC*H*$_2$), 6.0(s, 2H, OC*H*$_2$O), 6.7 (dd, *J* = 10.8, 17.4 Hz, 1H, C*H*CH$_2$), 6.8 (d, *J* = 8.0 Hz, 1H, Har), 6.9 (dd, *J* = 1.52, 7.83 Hz, 1H, Har), 7.0 (d, *J* = 1.52 Hz, 1H, Har). ^{13}C NMR ($CDCl_3$, 100 MHz): 101, 105, 108, 112, 121, 132, 136, 147,148.

4.4. Synthesis of (±)-4,4-dimethylpent-1-en-3-ol (±)-2

To an ice cooled stirred solution of vinyl magnesium bromide (25 ml of 1.0 mol solution in THF, 2.3 g, 17 mmol) in tetrahydrofuran was added dropwise a solution of pivaldehyde (2.0 ml, 1.5 g, 17 mmol) in dry ether. The mixture was allowed to heat at reflux

overnight. The reaction was cooled and saturated ammonium chloride solution was added until no more solid in the aqueous phase was observed, the organic layer was separated, dried over anhydrous sodium sulfate anhydrous, and evaporated under vacuum to afford 1.5 g (75%) of racemic-**2** as a pale yellow oil.[24] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.9 (s, 9H, *t*-butyl), 5.0 (d, J = 6.82 Hz, 1H, C*H*OH), 5.2 (m, 2H, CH=CH_2), 5.8 (m, 1H, C*H*=CH$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): 26, 36, 81, 116, 138.IR: 3500 (OH).

4.5. Synthesis of (±)-4,4-dimethylpent-1-en-3-yl butyrate (±)-3

To a stirred solution of (±)-**2** (0.5 g, 0.004 mol) in pyridine (30 mL), was added butanoic anhydride (1.95 mL, 1.89 g, 0.012 mol). The mixture was heated at reflux overnight, cooled, poured over HCl (200 mL, 10% aq), and extracted with diethyl ether (2 × 50 mL). The ethereal layer was separated, dried (Na_2SO_4), and evaporated to afford 0.5 g (62%) of (±)-4,4-dimethylpent-1-en-3-yl butyrate (±)-**3** as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.9 (s, 9H, *t*-butyl), 0.95 (t, J = 7.33, 7.58 Hz, 3H, OCOCH$_2$CH$_2$*CH*$_3$), 1.7 (m, 2H, OCOCH$_2$*CH*$_2$CH$_3$), 2.3 (t, J = 7.33, 7.07 Hz, 2H,OCO*CH*$_2$CH$_2$CH$_3$), 5.0 (d, J = 6.82 Hz, 1H, *CH*OCO), 5.2 (m, 2H, CH=CH_2), 5.8 (m, 1H, C*H*=CH$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): 14, 19, 26, 34, 36, 81, 118, 133, 172.

4.6. Lipase-catalyzed synthesis of (*R*)-(+)-4,4-dimethylpent-1-en-3-ol (*R*)-(+)-2

(±)-4,4-Dimethylpent-1-en-3-ol (±)-**2** (1 g, 8.7 mmol) was dissolved in *n*-hexane (25 mL) in a 50 mL round bottom flask followed by the addition of vinyl butanoate (2.3 mL, 17 mmol, 2.0 g, 2 equiv) and Lipase A from *Candida antarctica* (2 g) immobilized on Immobead 150. The mixture was heated to 35 °C, stirred at 300 rpm, and monitored by GC. After 9 h, the reaction was stopped by enzyme filtration and the solvent together with the excess of vinyl butyrate was evaporated under reduced pressure. The residual (*R*)-ester and (*S*)-alcohol mixture was separated by column chromatography using silica gel and $CHCl_3$ (100%) to afford (*S*)-alcohol (*S*)-(−)-**2** (0.4 g, ee = 75%), $[\alpha]_D^{20} = -6.2$ (*c* 10, $CHCl_3$), and (*R*)-butanoate (*R*)-(+)-**3** (0.33 g, ee >99%), $[\alpha]_D^{20} = +5.1$ (*c* 10, $CHCl_3$) which was subjected to further lipase catalyzed hydrolysis in phosphate buffer pH 7.0 to afford (*R*)-alcohol (*R*)-(+)-**2** (0.1 g, ee >99%), $[\alpha]_D^{20} = +8.3$ (*c* 10, $CHCl_3$).

4.7. Synthesis of (*R*)-(+)-1-(benzo[*d*][1,3]dioxol-5-yl)-4,4-dimethylpent-1-en-3-ol (*R*)-(+)-4, (*R*)-(+)-Stiripentol

To a stirred solution of 5-vinylbenzo[*d*][1,3]dioxole **1** (22 mg, 0.15 mmol) and (*R*)-(+)-4,4-dimethylpent-1-en-3-ol (*R*)-(+)-**2** (17 mg, 0.15 mmol) in dry DCM (5 mL), Grubbs' second generation catalyst (7 mg, 5 mol %) was added and the mixture was heated at overnight under argon, the reaction mixture was cooled, and the product purified using preparative thin layer chromatography (silica gel and $CHCl_3$) to afford 5 mg of (*R*)-(+)-Stiripentol (15%, ee >99%). The enantiomeric excess was calculated according to the reported procedures by Jacobsen et al.[8]

Acknowledgements

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