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Chiral (*R*)- and (*S*)-allylic alcohols via a one-pot chemoenzymatic synthesis

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Abstract—Chiral (*R*)- and (*S*)-allylic alcohols with an enantiomeric excess exceeding 99% have been prepared in good to high overall isolated yields through a two-step one-pot chemoenzymatic process based on the palladium-catalyzed Heck reaction of aryl iodides with butenone followed by an enzymatic reduction of the resultant vinylic substitution products. Alcohol dehydrogenases from *Lactobacillus brevis* and *Thermoanaerobacter species* were used to attain (*R*)- and (*S*)-stereoselectivity, respectively.

1. Introduction

Chiral allylic alcohols in enantiomerically pure form are useful building blocks in organic synthesis[1] and have found applications in the preparation of biologically active compounds.[2] Accordingly, the development of efficient approaches to the synthesis of this class of compounds is currently of great interest. Some of the most practical procedures available are based on kinetic resolution via asymmetric enzymatic acylation of racemic allylic alcohols [3] and on dynamic kinetic resolution methods. Chemoenzymatic dynamic kinetic resolution has been applied to racemic allylic alcohols,[4] which are enantioselectively acylated by a lipase in the presence of a ruthenium complex catalyzing the racemization of the unreacted substrate, and to racemic allylic acetates,[5] using a lipase as biocatalyst and a palladium complex as the racemization catalyst. The stereoselective reduction of α,β-unsaturated ketones has also been attempted by using whole cell bioconversion[6] and Ir(I)- and Ru(II)-catalyzed hydrogenation.[7,8]

All these procedures are based on the conversion of the preformed carbon framework into the desired chiral allylic alcohols. Due to the importance of enantiopure allylic alcohols, the development of alternative methods for their preparation is highly desirable. The development of a new chemoenzymatic process leading to the preparation of this class of compounds via the construction of the desired carbon framework followed by a direct stereoselective reduction step appeared particularly attractive. Based on the versatility of palladium catalysis for C–C bond forming reactions and on the ability of alcohol dehydrogenases to perform stereoselective reduction reactions of ketones,[8] we focused on a sequential procedure, which entails the formation of the required carbon skeleton via the Heck reaction of aryl iodides with butenone, in the first step, and the generation of enantiomerically pure allylic alcohols **4**, in the second step, through the enzyme-catalyzed enantioselective reduction of the resultant benzalacetones **2** (Scheme 1).

One of the main tasks of this project was to circumvent the intermediate purification and isolation steps by developing a one-pot protocol. One-pot syntheses are a subject of great current interest because of their economical and environmental advantages. However, a one-pot synthesis based on transition metal and enzyme catalysts can be extremely challenging, especially when the transition metal-catalyzed step involves a C–C bond forming reaction. Metal or reagent inhibition of the enzyme is not uncommon and suitable water/organic solvent mixtures need to be

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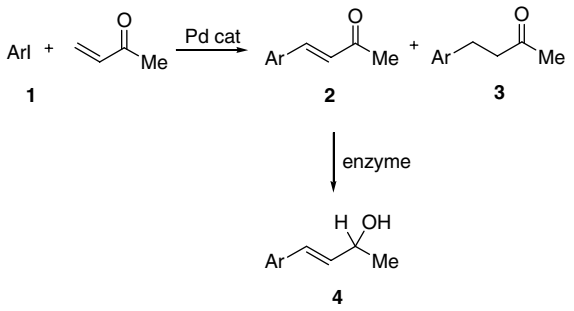


Scheme 1.

optimized. It is also essential that the C–C bond forming step does not yield by-products, which can be reduced stereoselectively by the enzyme such as, for example, hydroarylation (conjugate addition-type) derivatives **3**. Even modest amounts of these by-products would either require a wasteful and expensive purification of the reaction mixture derived from the Heck reaction (thus impairing the development of a one-pot process) or make the isolation of pure chiral allylic alcohols inconvenient.

In general, the vinylic substitution of aryl iodides with butenone may form variable amounts of **3**, depending on reaction conditions.[9] However, we recently reported[9] that a variety of benzalacetones can be prepared in good to excellent yields from aryl iodides and butenone under solvent-free conditions in the presence of a high affinity proton acceptor (proton sponge). Thus, a reaction mixture composed of $Pd(OAc)_2$, tris-(2,4,6-trimethoxyphenyl)phosphine (ttmpp) and 1,8-bis(dimethylamino)naphthalene (proton sponge) allows compound **2** formation with no detectable amounts of **3**. Consequently, these experimental conditions appeared to be particularly suited for the chemoenzymatic approach to chiral allylic alcohols presented herein.

2. Results and discussion

The two-step, one-pot reaction was carried out as follows. In the first step (Heck reaction), compound **1a** was added to 3 equiv of butenone in the presence of 0.05 equiv of $Pd(OAc)_2$, 0.1 equiv of ttmpp and 1.1 equiv of proton sponge at 80 °C for 16 h. In the second step, after cooling the reaction mixture to room temperature, the raw product was resuspended in 4.5 mL methoxyethanol/isopropanol (1/2 v/v); then 100 mM phosphate buffer, pH 7.0 containing 4.45 μmol of NADP+ and 100 U enzyme [alcohol dehydrogenase enzyme from *Lactobacillus* brevis (LB-ADH) or alcohol dehydrogenase enzyme from *Thermoanaerobacter* species (T-ADH)] was added to a final volume of 9 mL. The reaction was carried out at room temperature for 6–8 h. The corresponding allylic alcohols were isolated in 78–80% overall yield.

Both enzymes are able to recycle NADPH from $NADP^+$ by oxidizing isopropanol to acetone while catalyzing the stereoselective reduction of the α,β-unsaturated ketone. The relatively high amount of the enzyme was needed because of the excess free butenone still present in the reaction mixture, which is reduced to the corresponding allylic alcohol. Importantly, no enzyme inhibition was observed due to the presence of palladium or other reagents in the reaction medium.

The experiment was repeated by adding the enzyme (LB-ADH) solution to the crude reaction mixture derived from the Heck reaction after concentration at a reduced pressure. Under these conditions, the desired allylic alcohol was isolated in 80% overall yield with the enantiomeric excess exceeding 99%. 50 U (instead of 100 U) of enzyme was necessary to obtain full substrate conversion, due to the removal of the competing butenone substrate during the concentration process. The absolute configuration of the allylic carbon, expected to be (*R*) on the grounds of the reported activity of the enzyme with dialkyl ketones,[8d] was confirmed by circular dichroism (CD) spectroscopy using enantiomers **4d** and **4d′** as reference samples of known stereochemistry.[10] A similar result was obtained with T-ADH, reported to give (*S*)-alkyl alcohols: (*S*)-**4a′** was isolated in 77% overall yield.

Having established the best conditions for our two-step one-pot route to chiral allylic alcohols, we extended the reaction to other aryl iodides. As shown by the results summarized in Table 1, a variety of aryl iodides afforded the corresponding (*R*)- (with LB-ADH) and (*S*)- (with T-ADH) allylic alcohols usually in good to high overall isolated yields with enantiomeric excess exceeding 99% with all the substrates investigated. Only with **1g** were the corresponding allylic alcohols **4g** and **4g′** isolated in low yields (Table 1, entry 7). In this case, **5g** and **5g′**, formed via stereoselective reduction of both the ketonic groups, were isolated as the main reaction products along with minor amounts of **6g** and **6g′** (Scheme 2). The absolute configurations of the stereogenic centers of **4a**–**f**,**i** and **4a′**–**f′**,**i′** were assigned using **4d** and **4d′** as reference samples[9] and those of **4h**, **4h′**, **5g** and **5g′** were assigned by derivatization of the alcohol groups with Mosher's acid.[10] The configuration of **4g**, **4g′**, **6g** and **6g′** was assigned based on the configurations of all the other chiral products prepared.

3. Conclusions

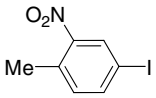
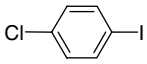
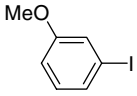
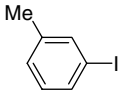
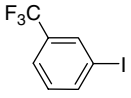
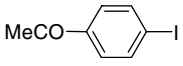
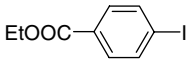
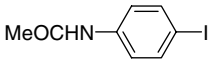
The present results set the basis for a novel chemoenzymatic synthesis of chiral allylic alcohols starting from simple aryl halides and vinyl ketones using a two-step one-pot method that entails the coupling of a palladium-catalyzed Heck reaction to a stereoselective enzyme-catalyzed reduction. The method proves to be superior in product yield and enantioselectivity to conventional dynamic kinetic resolution methods and paves the way for a number of applications by coupling the versatility of palladium catalyst to the appropriate use of alcohol dehydrogenases/ketoreductases with different substrate specificity.

4. Experimental

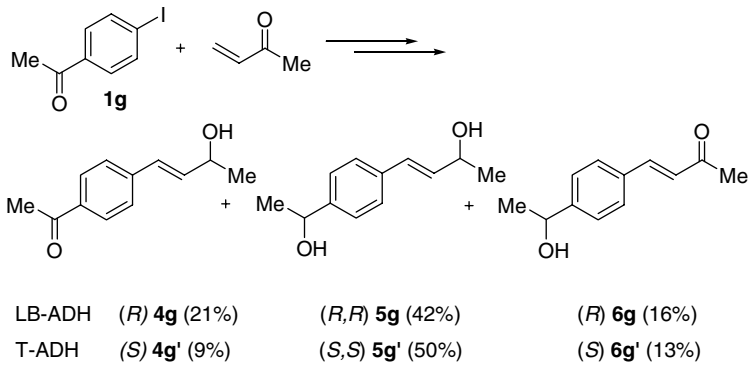
4.1. Materials and methods

Alcohol dehydrogenase enzymes from *Lactobacillus* brevis (LB-ADH) and from *Thermoanaerobacter* species (T-ADH) were obtained from Julich fine Chemicals (now

Table 1. Preparation of (*R*)- and (*S*)-allylic alcohols from aryl iodides and butenone through a one-pot palladium-catalyzed Heck reaction followed by alcohol dehydrogenase-catalyzed reduction step

Entry	Aryl iodide **1**		*t* (h) 1st-step	*t* (h) 2nd-step	Yield[a,b] (%)			
					(*R*)-**4**		(*S*)-**4**	
1		**1a**	16	2	80	**4a**	77	**4a′**
2		**1b**	16	2	84	**4b**	79	**4b′**
3		**1c**	24	4	77	**4c**	70	**4c′**
4	PhI	**1d**	16	2	85	**4d**	80	**4d′**
5		**1e**	92	4	67	**4e**	66	**4e′**
6		**1f**	16	4	74	**4f**	70	**4f′**
7		**1g**	18	4	21[c]	**4g**	9	**4g′**
8		**1h**	16	2	60	**4h**	80	**4h′**
9		**1i**	—[d]	2	74	**4i**	70	**4i′**

[a] Yields are given for isolated products.
[b] The ee was determined by enantioselective HPLC analysis and was found to always exceed 99%.
[c] Allylic alcohols **5g** (42%) and **5g′** (50%), formed via stereoselective reduction of both the ketonic groups, and **6g** (16%) and **6g′** (13%) were also isolated (Scheme 2).
[d] Enzyme-catalyzed reductions with LB-ADH and T-ADH were carried out on the isolated vinylic substitution product.



Scheme 2.

CODEXIS inc., Redwood City, CA, USA). NADP sodium salt was purchased from Sigma Aldrich Co. Units were determined for each enzyme on acetophenone according to published procedures.[8a] Melting points were determined with a Büchi B-545 apparatus and are uncorrected. Reaction products were purified on axially compressed columns, packed with SiO_2 25–40 μm (Macherey Nagel), connected to a Gilson solvent delivery system and to a Gilson refractive index detector, and eluting with *n*-hexane/ethyl acetate mixtures. IR spectra were recorded with a Jasco FT/IR-430

spectrometer. ^{1}H NMR spectra (400 MHz), ^{13}C NMR spectra (100.6 MHz), and ^{19}F NMR spectra (376.3 MHz) were recorded with a Bruker Avance 400 spectrometer. Low resolution mass spectra were recorded with a Shimadzu GC–MS QP-2010S spectrometer. Enantioselective HPLC analyses were performed by using stainless-steel Chiralcel OB-H (250 × 4.6 mm I.D.), Chiralpak AS-H (250 × 4.6 mm I.D.), and Chiralcel OD (250 × 4.6 mm I.D. and 250 × 10 mm I.D.) (Daicel, Chemical Industries, Tokyo, Japan) columns. HPLC-grade solvents were supplied by Carlo Erba (Milan, Italy). HPLC apparatus consisted of a Perkin Elmer (Norwalk, CT, USA) 200 lc pump equipped with a Rheodyne (Cotati, CA, USA) injector, a 200-μL sample loop, a HPLC Perkin Elmer oven, and a Perkin Elmer 290 detector. The signal was acquired and processed by Clarity software (DataApex, Prague, The Czech Republic).

Specific rotations were measured at a wavelength of 589 nm by a Perkin Elmer polarimeter model 241 equipped with a Na lamp. The volume of the cell was 1 mL and the optical path was 10 cm. The system was maintained at the temperature of 20 °C by a Neslab RTE 740 cryostat.

The CD spectra of enantiomers of chiral analytes, dissolved in a *n*-hexane/2-propanol 90/10 mixture (concentration about 0.2 mg/mL) in a quartz cell (0.1 cm-path length) at 25 °C, were measured by using a Jasco (Jasco, Ishikawacho, Hachioji City, Tokyo, Japan) Model J-700 spectropolarimeter in the 350–220 nm spectral range. The spectra are average computed over three instrumental scans and the intensities are presented in terms of $[\Phi]$ values (mdeg).

4.2. Absolute configuration assignment

The absolute configuration of enantiomers **4a**, **4a′**, **4b**, **4b′**, **4c**, **4c′**, **4e**, **4e′**, **4f**, **4f′**, and **4i**, **4i′** was empirically assigned by comparison of their CD spectra with those of enantiomers **4d** and **4d′**. The enantioseparation of the reference compound was obtained on semipreparative scale by HPLC using a Chiralcel OD CSP column and *n*-hexane/2-propanol 90/10 (v/v) as eluent. As reported in the literature,[9] under these conditions, the (*R*)-(+)-enantiomer was eluted before the (*S*)-(−)-enantiomer. The CD spectrum of (*R*)-(+)-**4d** showed a single diagnostic positive band at 251 nm. The CD pattern of (+)-enantiomers of unknown stereochemistry was very similar with a positive CD band located around 250 nm. In all cases, the (−)-enantiomers exhibited the corresponding CD mirror-images. The absolute configurations of **4h**, **4h′**, **5g** and **5g′** were assigned by derivatization of the alcohol groups with Mosher's acid.[11]

4.3. HPLC conditions for the determination of enantiomeric excess

Enantiomeric excesses were determined by enantioselective HPLC using polysaccharide-based chiral stationary phases (CSPs). The CSP/eluent system and the corresponding chromatographic data for each compound analyzed are summarized as follows (k_1 and k_2 are the retention factors of the less retained and the more retained enantiomer, respectively): Chiralpak AS-H/*n*-hexane-2-propanol 90/10, $k_1 = 3.16$ (*R*)-(+)-**4a**, $k_2 = 4.11$ (*S*)-(−)-**4a′**; Chiralcel OB-H/*n*-hexane-2-propanol 90/10, $k_1 = 0.86$ (*S*)-(−)-**4b′**, $k_2 = 1.13$ (*R*)-(+)-**4b**; Chiralcel OB-H/*n*-hexane-2-propanol 90/10, $k_1 = 2.44$ (*S*)-(−)-**4c′**, $k_2 = 2.97$ (*R*)-(+)-**4c**; Chiralcel OD/*n*-hexane-2-propanol 90/10, $k_1 = 1.94$ (*R*)-(+)-**4d**, $k_2 = 3.34$ (*S*)-(−)-**4d′**; Chiralpak AS-H/*n*-hexane-2-propanol 90/10, $k_1 = 0.82$ (*R*)-(+)-**4e**, $k_2 = 1.07$ (*S*)-(−)-**4e′**; Chiralpak AS-H/*n*-hexane-2-propanol 90/10, $k_1 = 0.61$ (*R*)-(+)-**4f**, $k_2 = 0.81$ (*S*)-(−)-**4f′**; Chiralpak AS-H/*n*-hexane-2-propanol 50/50, $k_1 = 1.72$ (*S*)-(−)-**4g**, $k_2 = 2.50$ (*R*)-(+)-**4g′**; Chiralcel OB-H/*n*-hexane-2-propanol 50/50, $k_1 = 0.37$ (*S*)-(−)-**4h′**, $k_2 = 0.98$ (*R*)-(+)-**4h**; Chiralcel OB-H/*n*-hexane-2-propanol 50/50, $k_1 = 0.24$ (*S*)-(−)-**4i′**, $k_2 = 0.46$ (*R*)-(+)-**4i;** Chiralpak AS-H/*n*-hexane-2-propanol 50/50, $k_1 = 0.37$ (*R*)-(+)-**5g**, $k_2 = 0.56$ (*S*)-(−)-**5g′**; Chiralpak AS-H/*n*-hexane-2-propanol 50/50, $k_1 = 1.43$ (*R*)-(+)-**6g**, $k_2 = 1.69$ (*S*)-(−)-**6g′**.

4.4. GC/MS

GC/MS analyses were performed on an Agilent 6850A gas chromatograph coupled to a 5973N quadrupole mass selective detector (Agilent Technologies, Palo Alto, CA, USA). Gas-chromatographic separations were carried out on an Agilent HP-5MS fused-silica capillary column (30 m × 0.25 mm I.D., film thickness, 0.25 μm). Injection mode: splitless at a temperature of 260 °C. Column temperature program: 70 °C (1 min) then to 280 °C at a rate of 10 °C/min and held for 15 min. The carrier gas was helium at a constant flow of 1.0 mL/min. The spectra were obtained in electron impact mode at 70 eV ionization energy and a mass range scan from m/z 30 to 500; ion source temperature, 280 °C; ion source vacuum 10–5 Torr.

4.5. Typical procedure for the one-pot synthesis of enantiopure allylic alcohols 4a–h and 4a′–4h′

A mixture of **1a** (0.263 g, 1 mmol), 3-buten-2-one (0.250 mL, 3 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol), 1,8-bis(dimethylamino)naphthalene (0.236 g, 1.1 mmol) and ttmpp (0.053 g, 0.1 mmol) was warmed at 80 °C with stirring for 16 h. After this time, the reaction mixture was cooled at room temperature and concentrated under a reduced pressure. The residue was resuspended in 4.5 mL methoxyethanol/isopropanol (1/2 v/v). Then 100 mM phosphate buffer, pH 7.0 containing 4.45 μmol NADP+ and 100 U enzyme (LB-ADH) was added to a final volume of 9 mL. The reaction was carried out at room temperature (25 °C) for 2 h. A 50 μL aliquot of the reaction mixture was extracted with 200 μL AcOEt and analyzed by GC/MS. The reaction mixture was then diluted with AcOEt, washed twice with a saturated NH_4Cl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (SiO_2, 35 g; *n*-hexane/AcOEt 65/35 v/v) to give 0.166 g (80% yield) of (2*R*,3*E*)-4-(3-nitro,4-methylphenyl)-3-buten-2-ol **4a**: oil; $[\alpha]_D^{20} = +17.0$ (*c* 0.16, MeOH). IR (neat): 3375, 2971, 1665, 1526, 1348 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.95 (s, 1H), 7.48 (d, $J = 7.9$ Hz, 1H), 7.27 (d, $J_1 = 4.3$ Hz, 1H), 6.57 (d, $J = 15.9$ Hz, 1H), 6.33 (dd, $J_1 = 15.9$ Hz, $J_2 = 5.9$ Hz, 1H), 4.53–4.50 (m, 1H), 2.57 (s, 3H), 1.89 (sb, 1H) 1.38 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 149.4, 136.2,

135.9, 133.0, 132.5, 130.6, 126.8, 122.3, 68.5, 23.5, 20.3. Anal. Calcd for $C_{11}H_{13}NO_3$, C, 63.76; H, 6.32; N, 6.76. Found C, 63.70; H, 6.26; N, 6.70. MS *m/z* (relative intensity) 207 (M^+, 3%), 43 (100%), 115 (28%).

4.5.1. (2*R*,3*E*)-4-(4-Chlorophenyl)-3-buten-2-ol 4b. Mp: 60–62 °C {lit.[12] mp: 61–61 °C}. $[\alpha]_D^{20} = +17.5$ (*c* 0.18, MeOH) {lit. [12] $[\alpha]_D^{22} = +27.3$ (*c* 0.6, $CHCl_3$), $[\alpha]_D^{20} = +17.7$ (*c* 1.5, CH_2Cl_2)}.

4.5.2. (2*R*,3*E*)-4-(3-Methoxyphenyl)-3-buten-2-ol 4c. Oil. $[\alpha]_D^{20} = +18.6$ (*c* 0.19, MeOH). IR (neat): 3389, 2968, 1597, 1579, 1487 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.25 (q, 1H), 6.99 (d, $J = 7.8$ Hz, 1H), 6.93 (s, 1H), 6.82 (d, $J = 5.8$ Hz, 1H), 6.54 (d, $J = 15.9$ Hz, 1H), 6.27 (dd, $J_1 = 15.9$ Hz, $J_2 = 6.3$ Hz, 1H); 4.52–4.48 (m, 1H), 2.07 (sb, 1H), 1.39 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 159.8, 138.2, 133.9, 129.6, 129.2, 119.2, 113.3, 111.8, 68.8, 55.2, 23.4. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found C, 73.99; H, 7.85. MS *m/z* (relative intensity): 178 (M^+, 36%), 115 (46%), 135 (100%).

4.5.3. (2*R*,3*E*)-4-Phenyl-3-buten-2-ol 4d. Mp 57–59 °C. $[\alpha]_D^{20} = +18.3$ (*c* 0.36, MeOH). IR (KBr): 3390, 2976, 2965, 1492 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.40–7.23 (m, 5H), 6.58 (d, $J = 16.0$ Hz, 1H), 6.27 (dd, $J_1 = 15.9$ Hz, $J_2 = 6.4$ Hz, 1H), 4.53–4.47 (m, 1H), 1.87 (sb, 1H), 1.39 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 136.7, 133.6, 129.4, 128.6, 127.7, 126.5, 68.9, 23.5. Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found C, 81.09; H, 8.20. MS *m/z* (relative intensity): 148 (M^+, 47%), 43 (100%), 131 (20%).

4.5.4. (2*R*,3*E*)-4-(3-Methylphenyl)-3-buten-2-ol 4e. Oil. $[\alpha]_D^{20} = +20.5$ (*c* 0.31, MeOH). IR (neat): 3363, 2967, 2923, 1383 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.30–7.21 (m, 3H), 7.08 (d, $J = 6.2$ Hz, 1H), 6.55 (d, $J = 15.9$ Hz, 1H), 6.26 (dd, $J_1 = 15.9$ Hz, $J_2 = 6.4$ Hz, 1H), 4.53–4.46 (m, 1H), 2.36 (s, 3H), 1.46 (sb, 1H), 1.33 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 138.2, 136.7, 133.4, 129.5, 128.5, 128.4, 127.2, 123.7, 69.0, 23.4, 21.4. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found C, 81.37; H, 8.79. MS *m/z* (relative intensity): 162 (M^+, 36%), 129 (100%), 91 (35%).

4.5.5. (2*R*,3*E*)-4-(3-Trifluoromethylphenyl)-3-buten-2-ol 4f. Oil. $[\alpha]_D^{20} = +11.3$ (*c* 0.23, MeOH). IR (neat): 3349, 2974, 2874, 1591 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.61 (s, 1H),7.53–7.39 (m, 3H), 6.60 (d, $J = 15.9$ Hz, 1H), 6.34 (dd, $J_1 = 15.9$ Hz, $J_2 = 6.1$ Hz, 1H), 4.53–4.50 (m, 1H), 2.11 (sb, 1H), 1.39 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 137.6, 135.6, 131.1 (q, $J = 32$ Hz), 129.6, 129.1, 127.9, 124.1 (q, $J = 3.8$ Hz), 124.0 (q, $J = 272$ Hz), 123.1 (q, $J = 3.8$ Hz), 68.6, 23.5. ^{19}F NMR ($CDCl_3$) δ: −62.8. Anal. Calcd for $C_{11}H_{11}F_3O$: C, 61.11; H, 5.13. Found C, 61.00; H, 5.05. MS *m/z* (relative intensity): 216 (M^+, 10%), 43 (100%), 129 (17%).

4.5.6. (2*R*,3*E*)-4-(4-Acetylphenyl)-3-buten-2-ol 4g. Mp 59–61 °C. $[\alpha]_D^{20} = +22.2$ (*c* 0.06, MeOH). IR (KBr): 3263, 2981, 1678, 1601 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.93 (d, $J = 8.3$ Hz, 2H), 7.47 (d, $J = 8.3$ Hz, 2H), 6.64 (d, $J = 15.9$ Hz, 1H), 6.39 (dd, $J_1 = 15.9$ Hz, $J_2 = 6.0$ Hz, 1H), 4.55 (t, $J = 6.2$ Hz, 1H), 2.6 (s, 3H), 1.8 (sb, 1H), 1.41 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 197.6, 141.4, 136.5, 136.0, 128.7, 128.1, 126.5, 68.6, 26.5, 23.3. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found C, 75.70; H, 7.39. MS *m/z* (relative intensity): 190 (M^+, 10%), 43 (100%), 147 (12%).

4.5.7. (2*R*,3*E*)-4-(4-Ethoxycarbonylphenyl)-3-buten-2-ol 4h. Mp 66–68 °C. $[\alpha]_D^{20} = +16.0$ (*c* 0.12, MeOH). IR (KBr): 3484, 2972, 1715, 1698 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.98 (d, $J = 8.3$ Hz 2H), 7.40 (d, $J = 8.3$ Hz, 2H), 6.59 (d, $J = 15.9$ Hz, 1H), 6.37 (dd, $J_1 = 15.9$ Hz, $J_2 = 6.0$ Hz, 1H) 4.52–4.50 (m, 1H), 4.40–4.34 (m, 2H), 2.24 (sb, 1H), 1.40–1.37 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 166.5, 141.2, 136.3, 129.9, 129.3, 128.2, 126.3, 68.6, 61.0, 23.4, 14.3. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found C, 70.85; H, 7.29. MS *m/z* (relative intensity): 220 (M^+, 15%), 43 (100%), 105 (27%).

4.5.8. (2*R*,3*E*)-4-(4-Acetamidophenyl)-3-buten-2-ol 4i. Mp 103–105 °C. $[\alpha]_D^{20} = +31.0$ (*c* 0.11, MeOH). IR (KBr): 3295, 2923, 1665, 1536 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.4 (d, $J = 8.3$ Hz, 2H), 7.3 (d, $J = 8.2$ Hz, 2H), 6.5 (d, $J = 15.9$ Hz, 1H),6.19 (dd, $J_1 = 15.9$ Hz, $J_2 = 6.4$ Hz, 1H), 4.48 (t, $J = 6.2$ Hz, 1H), 2.1 (s, 3H), 1.25 (d, $J = 6.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 168.3, 137.3, 132.9, 132.8, 128.7, 127.0, 119.9, 68.9, 24.5, 23.4. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N 6.82. Found C, 70.25; H, 7.34; N 6.79. MS *m/z* (relative intensity): 205 (M^+, 14%), 43 (100%), 145 (21%).

4.5.9. (2*S*,3*E*)-4-(3-Nitro,4-methylphenyl)-3-buten-2-ol 4a′. $[\alpha]_D^{20} = -16.0$ (*c* 0.15, MeOH).

4.5.10. (2*S*,3*E*)-4-(4-Chlorophenyl)-3-buten-2-ol 4b′. $[\alpha]_D^{20} = -18.0$ (*c* 0.17, MeOH).

4.5.11. (2*S*,3*E*)-4-(3-Methoxyphenyl)-3-buten-2-ol 4c′. $[\alpha]_D^{20} = -18.8$ (*c* 0.19, MeOH).

4.5.12. (2*S*,3*E*)-4-Phenyl-3-buten-2-ol 4d′. $[\alpha]_D^{20} = -19.5$ (*c* 0.49, MeOH).

4.5.13. (2*S*,3*E*)-4-(3-Methylphenyl)-3-buten-2-ol 4e′. $[\alpha]_D^{20} = -21.0$ (*c* 0.28, MeOH).

4.5.14. (2*S*,3*E*)-4-(3-Trifluoromethylphenyl)-3-buten-2-ol 4f′. $[\alpha]_D^{20} = -10.4$ (*c* 0.28, MeOH).

4.5.15. (2*S*,3*E*)-4-(4-Acetylphenyl)-3-buten-2-ol 4g′. $[\alpha]_D^{20} = -18.9$ (*c* 0.05, MeOH).

4.5.16. (2*S*,3*E*)-4-(4-Ethoxycarbonylphenyl)-3-buten-2-ol 4h′. $[\alpha]_D^{20} = -16.5$ (*c* 0.11, MeOH).

4.5.17. (2*S*,3*E*)-4-(4-Acetamidophenyl)-3-buten-2-ol 4i′. $[\alpha]_D^{20} = -22.0$ (*c* 0.15, MeOH).

4.5.18. (2*R*,3*E*)-4-[4-((*R*)-1-Hydroxyethyl)phenyl]-3-buten-2-ol 5g. Mp 94–98 °C. $[\alpha]_D^{20} = +64.8$ (*c* 0.05, MeOH); IR (KBr): 3339, 2965, 2868, 1574 cm^{-1}. ^1H NMR ($CDCl_3$) δ:

7.36–7.28 (m, 4H), 6.54 (d, $J = 15.8$ Hz, 1H), 6.24 (dd, $J_1 = 15.9$ Hz, $J_2 = 6.4$ Hz, 1H), 4.90–4.86 (m, 1H), 4.48 (t, $J = 6.0$ Hz, 1H), 2.32 (sb, 1H), 2.08 (sb, 1H), 1.48 (d, $J = 6.4$ Hz, 3H), 1.37 (d, $J = 6.3$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 145.3, 136.0, 133.5, 129.0, 126.6, 125.7, 70.1, 68.9, 25.1, 23.4. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found C, 74.95; H, 8.35. MS *m*/*z* (relative intensity): 192 (M^+, 7%), 91 (100%), 177 (25%).

4.5.19. (2*S*,3*E*)-4-[4-((*S*)-1-Hydroxyethyl)phenyl]-3-buten-2-ol 5g′. $[\alpha]_D^{20} = -51.1$ (*c* 0.06, MeOH).

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