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Non-enzymatic kinetic resolution of 1,2-azidoalcohols using a planar-chiral DMAP derivative catalyst

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ABSTRACT

Optically pure 1,2-azidoalcohols are widely used as precursors for other high value organic products. A non-enzymatic kinetic resolution procedure for the stereoselective synthesis of chiral 1,2-azidoalcohols from the readily available racemic counterparts has been developed, employing a planar-chiral DMAP derivative catalyst. Following this procedure, a range of aromatic 1,2-azidoalcohols was obtained in good selectivities (up to S=45) and high enantiomeric excess (up to 99% ee).

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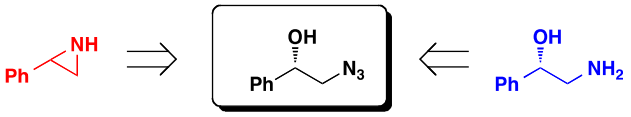
1. Introduction

The synthesis of enantiomerically pure compounds has emerged into one of the most important fields of organic synthesis.[1] In this context, synthetic approaches to optically pure aziridines and aminoalcohols have received special attention since they constitute important building blocks in the design of high-value products in both organic and pharmaceutical industry.[2] Particularly, 1,2-aminoalcohols are often used as chiral ligands for asymmetric catalysis[3] and are also present in biologically active compounds, e.g., β-adrenergic receptor blockers and immune stimulants.[4] A convenient approach to chiral aziridines and 1,2-aminoalcohols is to use 1,2-azidoalcohols as precursors (Scheme 1).[5]



Scheme 1. Retrosynthetic approaches to chiral aziridines and 1,2-aminoalcohols.

Several routes to enantiopure azidoalcohols are available, including the ring-opening of epoxides,[6] asymmetric reduction of the corresponding azidoketones[7] and also the enzymatic kinetic resolution of racemic azidoalcohols.[8] Using this approach, the enzymatic kinetic resolution of racemic 1,2-azidoalcohols was reported to yield products in high enantiomeric excess.[8]

Moreover, Bäckvall and Pàmies combined the enzymatic resolution of 1,2-azidoalcohols in combination with the ruthenium-catalysed alcohol racemization in a dynamic kinetic resolution, yielding acetylated 1,2-azidoalcohols in excellent yields and high enantiomeric excess.[9]

An alternative to enzymatic kinetic resolutions is to use a small molecule catalyst, such as chiral DMAP[10] and chiral amidines.[11] In 1996, Vedejs and Chen introduced a chiral DMAP derivative catalyst in the kinetic resolutions of 1-arylethanols.[12] The use of this catalyst in stoichiometric amounts in the presence of 2 equiv of a Lewis acid, led to enantiomerically enriched products with high enantiomeric excess.[12,13] Independently, Fu and co-workers developed the synthesis of planar-chiral ferrocenyl pyrrole/DMAP analogues.[14] The DMAP derivative (−)-**1** catalysed the kinetic resolution of secondary aryl and allylic alcohols (Scheme 2).[15] This catalytic system also proved to be very efficient in the kinetic resolution of a racemic *trans*-diol,[16] the desymmetrization of *meso*-diols,[16] propargylic alcohols,[17] and the secondary 1-arylamines[18] and indolines.[19] Since those early developments, kinetic resolution of secondary alcohols was achieved using different chiral DMAP-based catalysts.[20]

In this study, we wish to present the non-enzymatic kinetic resolution of a variety of 2-azido-1-arylethanols with good selectivities using the planar-chiral ferrocenyl DMAP catalyst (−)-**1**.

2. Results and discussion

A search for the optimal conditions for the resolution of the 2-azido-1-phenylethanols was performed (Table 1). Initial studies showed that triethylamine catalysed the acetylation of the 2-azido-

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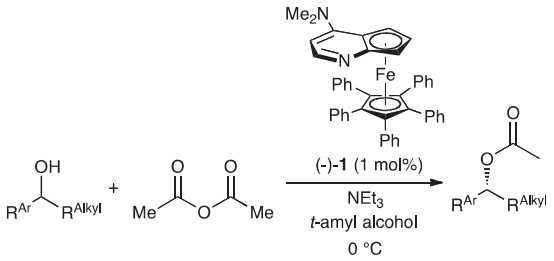
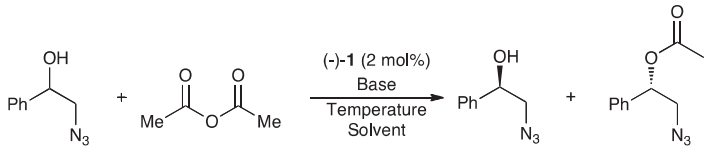


Scheme 2. Non-enzymatic kinetic resolution of secondary alcohols catalysed by planar-chiral DMAP derivative (−)-**1**.

triethylamine (0.75 equiv) was added. Fortunately, at this temperature, the rate of the reaction increased (6 h, 52% conv.) without any loss of the selectivity (S=17, Entry 5).[21]

In order to investigate the scope of the kinetic resolution, several 1,2-azidoalcohols with different substituents in the aromatic ring were reacted under the optimized conditions (Table 2). The kinetic resolutions of aromatic 1,2-azidoalcohols by catalyst (−)-**1** (2 mol %) at 0 °C in *tert*-amyl alcohol yielded the desired products with good selectivity (S=17–45) and excellent enantiomeric excess (up to 99%). The larger 2-naphthyl derivative led to better results in terms of selectivity and reactivity compared to the parent compound **2a** (3 h, 60% conv., S=45). The presence of an electron-withdrawing group in the 4-position, such as a nitro or cyano group also increases the selectivity factor (S=33 and 35, respectively). The electron-donating methyl, methoxy and benzoate group in the 4-position of the phenyl ring decreases the selectivity compared to the parent compound **2a** (Table 2, Entries 5–7), while compound **2h** having two methoxy substituents in the 2′- and 5′-position of the phenyl ring shows a slight improvement of the selectivity (Table 2, Entry 8). The aromatic 1,2-azidoalcohols **2i**–**j** having bromo substituents in the aromatic ring (Entries 9 and 10) also yielded the products with reasonable selectivity (S=13–20).

Table 1
Screening of reaction conditions for the kinetic resolution of 2-azido-1-phenylethanol by (−)-**1**[a]

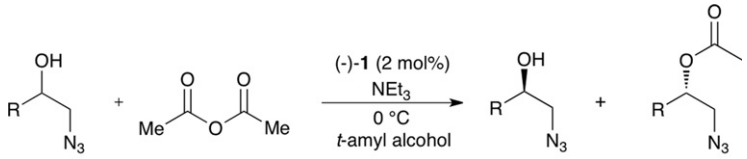


rac-**2a** (*R*)-**2a** (*S*)-**3a**

Entry	Base	Concn/M	Temp/°C	Time/h	Conv. (%)[b]	S[b]
1	None	0.5	rt	4	61	10
2	None	0.5	0	4	37	14
3	None	0.5	0	24	51	15
4	None	0.25	0	24	39	17
5	NEt_3[c]	0.25	0	6	52	17

[a] Reaction conditions: **2** (0.25 mmol), Ac_2O (0.75 equiv), (−)-**1** (0.005 mmol, 2 mol %) in *tert*-amyl alcohol (0.5 mL or 1 mL).
[b] Determined by chiral HPLC.
[c] NEt_3 (0.75 equiv).

Table 2
Kinetic resolution of aromatic 1,2-azidoalcohols by (−)-**1**[a]



rac-**2** (*R*)-**2** (*S*)-**3**

Entry	R	Time/h	Conv. (%)[b]	ee_{ROH} (%)[b]	S[b]
1	Ph (**2a**)	24	73	99.6	17
2	2-Napthyl (**2b**)	3	60	99.9	45
3	4′-NO_2–Ph (**2c**)	3	58	99.2	33
4	4′-CN–Ph (**2d**)	10	62	99.9	35
5	4′-Me–Ph (**2e**)	5	70	80.6	4
6	4′-OMe–Ph (**2f**)	13	65	98.6	14
7	4′-Benzoyl–Ph (**2g**)	20	58	92.7	16
8	2′,5′-DiOMe–Ph (**2h**)	13	60	99.0	24
9	3′-Br–Ph (**2i**)	9	61	98.6	20
10	4′-Br–Ph (**2j**)	4	63	96.6	13

[a] Reaction conditions: **2** (0.25 mmol), Ac_2O (0.75 equiv), triethylamine (0.75 equiv), (−)-**1** (0.005 mmol, 2 mol %) in *tert*-amyl alcohol (1.0 mL) at 0 °C.
[b] Determined by chiral HPLC.

1-phenylethanol **2a** at room temperature, and therefore, it was excluded in the first part of the screening. The reaction was run using **2a** (0.25 mmol), (−)-**1** (2 mol %), Ac_2O (0.75 equiv) at room temperature in *tert*-amyl alcohol (0.5 mL) leading to 61% conversion in 4 h with a selectivity factor (S) of 10 (Table 1, Entry 1). Performing the reaction at 0 °C led to an improvement of the selectivity (S=14–15), but the reaction slowed down reaching only 51% conversion in 24 h (Entries 2 and 3). The dilution of the reaction mixture (to 0.25 M) resulted in an increase of the selectivity (S=17) and a subsequent decrease of the rate of the reaction (24 h, 39% conv., Entry 4). In order to accelerate the reaction at 0 °C,

Finally, since 1,2-azidoalcohols are precursors to several pharmaceutically active β-blockers, such a (*R*)-pronethalol and (*R*)-nifenalol, the synthetic utility of the present method was further demonstrated in the preparation of the optically pure (*R*)-pronethalol (Fig. 1). The kinetic resolution of the azidoalcohol **2b** (using 1 mmol scale) was performed using the general procedure, obtaining compound (*R*)-**2b** in 43% yield with high enantiomeric purity (*S*=42, >99% ee). Compound (*R*)-**2b** was converted to (*R*)-pronethalol in 83% yield via the reduction of the azide and subsequent in situ reductive alkylation with acetone using hydrogen/platinum(IV) oxide in ethanol at room temperature.

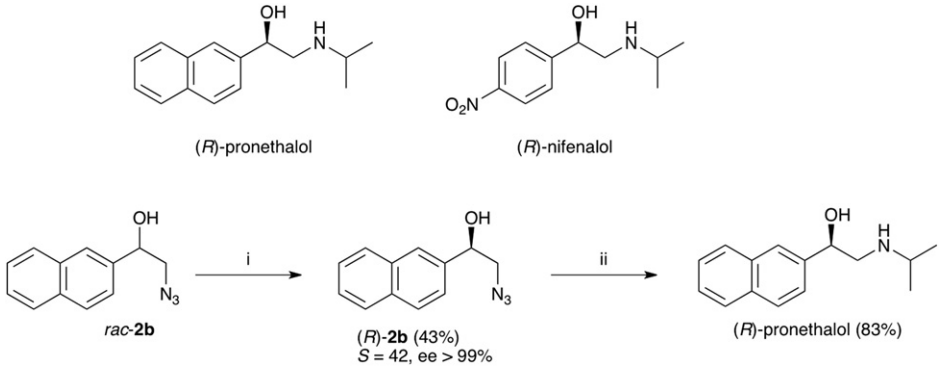


Fig. 1. Synthesis of (*R*)-pronethalol. (i) Compound *rac*-**2b** (1.0 mmol), Ac_2O (0.75 equiv), triethylamine (0.75 equiv), (−)-**1** (2 mol %) in *tert*-amyl alcohol (4.0 mL) at 0 °C. (ii) Compound (*R*)-**2b** (0.43 mmol), PtO_2 (0.5 equiv), acetone (1.5 equiv), H_2 (5 atm) in EtOH (5 mL), 4 h, room temperature.

3. Conclusion

In summary, we have demonstrated that the chiral DMAP derivative catalyst (−)-**1** catalysed the resolution for a range of aromatic 1,2-azidoalcohols with good selectivities (selectivity factor up to 45) and high enantiomeric excess (up to 99% ee) of the remaining alcohol. To the best of our knowledge, these results represent the first example of the kinetic resolution of aromatic 1,2-azidoalcohols using a chiral DMAP derivative catalyst.

4. Experimental section

4.1. General

Commercially available reagents were purchased from Sigma–Aldrich Co. and used without further purification. Thin Layer Chromatography (TLC) was performed on ALUGRAM® SIL G/UV_{254} plates (0.2 mm), using UV-light (254 nm) for visualization. Flash column chromatography was performed using Merck silica gel (0.04–0.06 mm). ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Varian Mercury 300 MHz, Varian Unity 400 MHz or Varian Unity 500 MHz spectrometer. The chemical shift values (δ) are given in parts per million (ppm) and are referred to the residual peak of the deuterated solvent used ($CDCl_3$). IR spectra were recorded on a Perkin–Elmer Spectrum One (ATR Technique). High-resolution mass spectra were provided by Stenhagen Analys AB.

The enantiomeric separations of **2a**,**b**,**d**,**e**,**h**–**j** and **3a**–**j** were performed by high performance liquid chromatography (HPLC) with a Young Lin 9100 instrument using the appropriate chiral column (250×4.6 mm) at 25 °C with *n*-hexane and isopropanol as eluents. The enantiomeric separation of **2c**,**f**,**g** was achieved converting the alcohol to the corresponding acetate using DMAP and triethylamine in DCM. The selectivity (*S*) values were calculated with the equation: $S=\ln[(1-c)(1-ee_{ROH})]/\ln[(1-c)(1+ee_{ROH})]$.

Racemic 1,2-azidoalcohols *rac*-**2a**–**j** were prepared 'one pot' from the corresponding α-bromoacetophenone by the addition of sodium azide followed by reduction of the ketone using sodium borohydride.[22,23] The corresponding racemic acetates *rac*-**3a**–**j** were prepared by acetylation under basic conditions.[24,25]

4.2. General procedure for the kinetic resolution

Catalyst (−)-**1** (3.3 mg, 0.005 mmol), azidoalcohol *rac*-**2a**–**j** (0.25 mmol) and *tert*-amyl alcohol (1.0 mL) were sequentially added to a vial. The vial was capped and stirred at room temperature to help dissolve the catalyst. The reaction mixture was cooled to 0 °C, and then triethylamine (26 μL, 0.19 mmol) and acetic anhydride (18 μL, 0.19 mmol) were added. After an appropriate amount of time, the reaction mixture was quenched by the addition of a large excess of methanol. The resulting solution was concentrated, and the unreactive alcohol, the acetate, and the catalyst were separated by flash chromatography using increasing polarity mixtures of pentane/ethyl acetate as eluent. Characterization data for these compounds are as follows (copies of the HPLC chromatograms, ^1H and $^{13}C\{^1H\}$ spectra are included in Supplementary data).

*4.2.1. (R)-2-Azido-1-phenylethanol ((R)-**2a**).*[26] Yellow oil (11.0 mg, 27% yield); ee 99.9%, Kromasil 5-CellCoat, *n*-hexane/*i*-PrOH=90:10, 0.5 mL/min, 220 nm, $t_R[(R)/(S)]$=17.0/18.8 min; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.32 (m, 5H, Ar–H), 4.88 (dd, *J*=8.1, 3.9 Hz, 1H, CH), 3.51–3.42 (m, 2H, CH_2), 2.47 (br, 1H, OH). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 140.6, 128.8, 128.5, 126.0, 73.6, 58.2.

*4.2.2. (R)-2-Azido-1-(naphthalen-2-yl)ethanol ((R)-**2b**).*[27] White solid (21.3 mg, 40% yield); mp 82–83 °C (Lit.[27] 80–81 °C); ee 99.9%, Kromasil 5-CellCoat, *n*-hexane/*i*-PrOH=90:10, 0.75 mL/min, 220 nm, $t_R[(R)/(S)]$=21.8/26.3 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87–7.46 (m, 7H, Ar–H), 5.05 (dd, *J*=7.8, 4.2 Hz, 1H, CH), 3.61–3.51 (m, 2H, CH_2), 2.46 (s, 1H, OH). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.0, 133.4, 133.3, 128.6, 128.1, 127.8, 126.5, 126.4, 125.1, 123.7, 73.7, 58.1.

*4.2.3. (R)-2-Azido-1-(4′-nitrophenyl)ethanol ((R)-**2c**).*[26] Orange solid (21.3 mg, 41% yield); mp 51–53 °C; ee 99.2%, Kromasil 5-CellCoat, *n*-hexane/*i*-PrOH=90:10, 0.5 mL/min, 254 nm, $t_R[(R)/(S)]$=23.8/25.6 min; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J*=8.6 Hz, 2H, Ar–H), 7.57 (d, *J*=8.6 Hz, 2H, Ar–H), 5.04–5.01 (m, 1H, CH), 3.52–3.49 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 148.4, 147.7, 127.1, 124.0, 72.6, 57.8.

*4.2.4. (R)-2-Azido-1-(4′-cyanophenyl)ethanol ((R)-**2d**).*[26] Yellow solid (17.9 mg, 38% yield); mp 52–53 °C; ee 99.9%, Kromasil 5-CellCoat, *n*-hexane/*i*-PrOH=95:5, 0.75 mL/min, 220 nm, $t_R[(R)/(S)]$=37.0/42.5 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J*=8.3 Hz, 2H, Ar–H), 7.50 (d, *J*=8.3 Hz, 2H, Ar–H), 4.95–4.92 (m, 1H, CH),

3.51–3.42 (m, 2H, CH_2), 2.69 (br, 1H, OH). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 146.0, 132.7, 126.9, 118.7, 112.3, 72.8, 58.0.

*4.2.5. (R)-2-Azido-1-(4′-methylphenyl)ethanol ((R)-**2e**).*[28] Yellow oil (13.3 mg, 30% yield); ee 80.6%, Kromasil 5-CellCoat, *n*-hexane/*i*-PrOH=95:5, 0.75 mL/min, 220 nm, t_R[(*R*)/(*S*)]=15.4/19.6 min; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J*=8.2 Hz, 2H, Ar–H), 7.15 (d, *J*=8.2 Hz, 2H, Ar–H), 4.74 (dd, *J*=8.2, 3.9 Hz, 1H, CH), 3.39 (dd, *J*=12.7, 8.2 Hz, 1H, CH_2), 3.32 (dd, *J*=12.7, 3.9 Hz, 1H, CH_2), 2.80 (br, 1H, OH), 2.33 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 138.1, 137.7, 129.3, 125.9, 73.2, 57.9, 21.1.

*4.2.6. (R)-2-Azido-1-(4′-methoxyphenyl)ethanol ((R)-**2f**).*[28] Slightly yellow oil (16.9 mg, 35% yield); ee 98.6%, Kromasil 5-CellCoat, *n*-hexane/*i*-PrOH=90:10, 0.5 mL/min, 254 nm, t_R[(*R*)/(*S*)]=13.4/15.5 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J*=8.7 Hz, 2H, Ar–H), 6.92 (d, *J*=8.7 Hz, 2H, Ar–H), 4.82 (dd, *J*=8.1, 4.0 Hz, 1H, CH), 3.82 (s, 3H, CH_3), 3.50–3.38 (m, 2H, CH_2), 2.49 (br, 1H, OH). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.7, 132.9, 127.3, 114.2, 73.1, 58.14, 55.4.

*4.2.7. (R)-4-(2-Azido-1-hydroxyethyl)phenyl benzoate ((R)-**2g**).* White solid (28.3 mg, 40% yield); mp 92–93 °C; ee 92.7%, Kromasil 5-CellCoat, *n*-hexane/*i*-PrOH=99:1, 0.5 mL/min, 220 nm, t_R[(*R*)/(*S*)]=22.0/27.3 min; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21–7.22 (m, 9H, Ar–H), 5.42 (m, 1H, CH), 3.53–3.44 (m, 2H, CH_2), 2.42 (br, 1H, OH). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.3, 150.9, 138.4, 133.8, 130.3, 129.5, 128.7, 127.2, 122.1 73.1, 58.2. IR(neat): ν (cm^{-1})=3432 (br, OH), 2093 (s, N_3), 1721 (s, C=O). HRMS (ESI) calcd for $C_{15}H_{13}N_3NaO_3^+$ [$M+Na^+$]: 306.0849, found: 306.0836.

*4.2.8. (R)-2-Azido-1-(2′,5′-dimethoxyphenyl)ethanol ((R)-**2h**).*[28] White solid (22.3 mg, 40% yield); mp 54–55 °C; ee 99.0%, Kromasil 5-CellCoat, *n*-hexane/*i*-PrOH=95:5, 0.5 mL/min, 220 nm, t_R[(*R*)/(*S*)]=27.2/31.0 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04–6.73 (m, 3H, Ar–H), 5.07 (dd, *J*=7.8, 3.8 Hz, 1H, CH), 3.79 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.47 (dd, *J*=12.5, 3.8 Hz, 1H, CH_2), 3.41 (dd, *J*=12.5, 7.8 Hz, 1H, CH_2), 2.98 (br, 1H, OH). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.9, 150.4, 129.7, 113.6, 113.1, 111.5, 69.8, 56.5, 55.8.

*4.2.9. (R)-2-Azido-1-(3′-bromophenyl)ethanol ((R)-**2i**).*[29] Brown oil (21.2 mg, 35% yield); ee 98.6%, Kromasil 5-CellCoat, *n*-hexane/*i*-PrOH=90:10, 0.5 mL/min, 220 nm, t_R[(*R*)/(*S*)]=16.5/21.2 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53–7.21 (m, 4H, Ar–H), 4.89–4.68 (m, 1H, CH), 3.50–3.27 (m, 2H, CH_2), 2.63 (m, 1H, OH). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 143.0, 131.6, 130.5, 129.3, 124.8, 123.1, 72.9, 58.2.

*4.2.10. (R)-2-Azido-1-(4′-bromophenyl)ethanol ((R)-**2j**).*[27] Yellow solid (21.2 mg, 35% yield); mp 60–61 °C (Lit.[27] 66–67 °C); ee 96.6%, Kromasil 5-CellCoat, *n*-hexane/*i*-PrOH=90:10, 0.5 mL/min, 220 nm, t_R[(*R*)/(*S*)]=16.1/18.4 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J*=7.7 Hz, 2H, Ar–H), 7.23 (d, *J*=7.7 Hz, 2H, Ar–H), 4.81 (m, 1H, CH), 3.50–3.31 (m, 2H, CH_2), 2.72 (br, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7, 132.0, 127.9, 122.5, 73.0, 58.1.

4.3. Synthesis of (*R*)-pronethalol[6a]

2-Azido-1-(naphthalen-2-yl)ethanol (213 mg, 1 mmol) was resolved following the general procedure described above (Section 4.2). The obtained optically pure alcohol (91.7 mg, 0.43 mmol, >99% ee, *S*=42) was dissolved in EtOH (5.0 mL). Then, platinum dioxide (49 mg, 0.22 mmol), acetone (50 μL, 0.65 mmol) and molecular sieves (4 Å) were added. The reaction mixture was stirred at room temperature under H_2 atmosphere (5 atm) during 4 h. The desired (*R*)-pronethalol was obtained as a white solid (82 mg, 83% yield) after filtration over Celite. $[\alpha]_D^{20}$ −19.4 (*c* 3.5, EtOH). [Lit.[30] $[\alpha]_D$ −22 (*c* 1, EtOH)]; mp 58–59 °C (Lit.[31] 53 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 8.13–7.69 (m, 4H, Ar–H), 7.71–7.32 (m, 3H, Ar–H), 4.87 (dd, *J*=8.7, 3.7 Hz, 1H, C*H*OH), 3.05 (dd, *J*=12.1, 3.7 Hz, 1H, CH_2), 2.96–2.84 (m, 1H, $CH(CH_3)_2$), 2.78 (dd, *J*=12.1, 8.7 Hz, 1H, CH_2), 2.68 (br, 1H, OH), 1.13 (d, *J*=2.5 Hz, 3H, CH_3), 1.11 (d, *J*=2.5 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.6, 133.4, 133.1, 128.2, 127.8, 126.1, 125.8, 124.6, 124.2, 124.1, 72.1, 54.7, 48.84, 23.1, 23.0.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.10.077.

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