Journal of Molecular Catalysis B: Enzymatic 66 (2010) 276–284

Contents lists available at ScienceDirect

Journal of Molecular Catalysis B: Enzymatic

journal homepage: www.elsevier.com/locate/molcatb

Biocatalytic enantioselective approach to 3-aryl-2-nitropropanols: Synthesis of enantioenriched (*R*)-5-methoxy-3-aminochroman, a key precursor to the antidepressant drug Robalzotan

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ARTICLE INFO

Article history:
Received 14 October 2009
Received in revised form 27 May 2010
Accepted 10 June 2010
Available online 16 June 2010

Keywords:
3-Aryl-2-nitropropanol
3-Aminochroman
Robalzotan
Baker's yeast
Lipase resolution

ABSTRACT

The results of our studies on the biocatalytic enantioselective synthesis of different 3-aryl-2-nitropropanols are presented. These compounds could be obtained in moderate to good ee both by baker's yeast mediated reduction of (*E*)-2-nitro-3-arylprop-2-en-1-ol precursors and by lipase kinetic resolution of racemic 3-aryl-2-nitropropanols. The synthesis of enantioenriched (*R*)-5-methoxy-3-aminochroman is also achieved. This important moiety is present in different molecules active toward the central nervous system and is also the precursor for the synthesis of Robalzotan (NAD299), a potent 5-HT_{1A} antagonist.

1. Introduction

The 3-aminochroman moiety **1** (Fig. 1) is a known pharmacophore which is present in different biologically active compounds [1]. The most representative is Robalzotan (NAD299) **2**, a potent 5-HT_{1A} antagonist [2] which was developed for the potential treatment of depression and anxiety [3]. Of particular interest is also the 5-methoxy-3-aminochroman derivative **3**, which constitutes the core of a family of molecules active toward the central nervous system through their ability to selectively interact with 5HT receptors. For example, compound **4** was discovered as a selective 5-HT_{1A} ligand vs other 5-HT sites and D_2 sites in rat brain membranes [4] while (+)-S 20499 **5** was developed for the treatment of anxiety and depression [5]. More recently, in the search for novel compounds possessing dual affinity at both the 5-HT_{1A} receptor and the 5-HT reuptake site, **6** was shown to possess neurochemical activity *in vivo* by producing acute and rapid increases in 5-HT in the rat frontal cortex [6]. 5-Methoxy-3-aminochroman **3** is also a precursor toward the synthesis of Robalzotan [7]. In order to achieve optically pure **2**, racemic **3** is resolved by means of L-tartaric acid at the beginning of the synthetic sequence. Up till now, the main way to obtain enantiomerically pure or enriched 3-aminochromans is the optical resolution through the formation of diastereoisomeric salts, usually with tartaric acid [7]. To the best of our knowledge, only two asymmetric syntheses of **3** have been described, both starting from a L-serine derivative [8], and no enantioselective synthesis of these interesting structures relying on a non-chiral pool approach has been reported.

In the search of a new biocatalytic enantioselective synthesis of chiral aminochroman derivatives, we thought that they could be derived from a chiral 3-(2-hydroxyaryl)-2-nitropropanol precursor **7** through a cyclization and nitro group reduction sequence (Fig. 2). This key intermediate **7** can be obtained by two different possible biocatalyzed transformations. In a first approach, **7** would be the result of a enantioselective baker's yeast mediated reduction of a 2-nitro-3-arylprop-2-en-1-ol precursor **8**, while in a second approach racemic nitroalcohols **7** would be resolved by means of a lipase catalyzed acetylation of the primary hydroxy group.

It should be noted that 3-aryl-2-nitropropanols **7** can represent useful intermediates also for the synthesis of phenylalaninols analogues bearing different substituents on the aromatic ring, which could be further converted to the corresponding aminoacids, thus opening the way to different non-natural phenylalanine derivatives. Although 3-aryl-2-nitropropanols are quite easily accessible in few synthetic steps, only few reports [9] are known on these molecules. More, no enantioselective synthesis of these potentially interesting structures has been reported, at the best of our knowledge.

In this paper, we describe a biocatalytic approach to the enantiosynthesis of different 3-aryl-2-nitropropanols. The utility of

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doi:10.1016/j.molcatb.2010.06.003

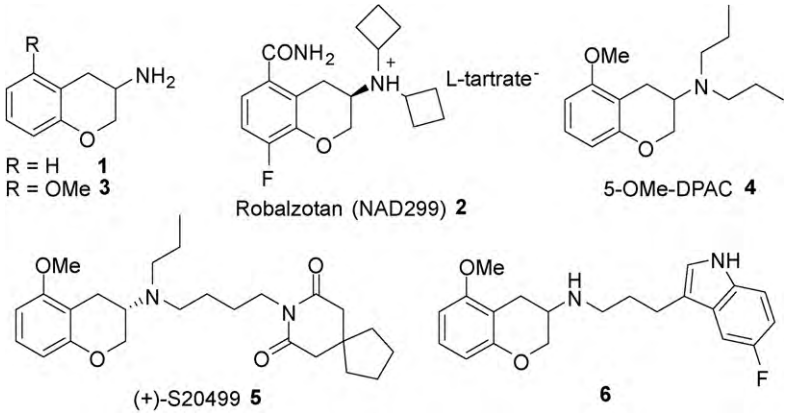


Fig. 1. Relevant molecules containing the 3-aminochroman moiety.

these compounds is then demonstrated by the synthesis of enantioenriched (*R*)-5-metoxy-3-aminochroman **3**.

2. Materials and methods

2.1. General

All solvents were distilled and properly dried, when necessary, prior to use. All chemicals were purchased from commercial sources and used directly, unless indicated otherwise. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (Merck); spots were visualized with UV light or by treatment with 1% aqueous $KMnO_4$ solution. Products were purified by flash chromatography on Merck silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded with Bruker 400 MHz Avance (^1H, 400 MHz; ^{13}C, 100 MHz) NMR spectrometer. Chemical shifts are reported in parts per million downfield from $SiMe_4$ ($\delta = 0.0$). HRMS spectra were measured on a Jeol SX 102 instrument equipped with its standard sources. Optical rotations were measured with a Jasco-DIP-181 digital polarimeter.

2.2. General procedure for the synthesis of 10a–g

The aldehyde (0.3 mol) was dissolved in 15 mL of acetic acid. Nitromethane (0.6 mol) was added followed by ammonium acetate (0.05 mol). The reaction was refluxed for 4 h, and then the mixture was poured in 50 mL of ice. Upon cooling a precipitate was formed which was filtered and washed with ethanol to afford pure **10a**–**g**.

2.2.1. (E)-(2-nitrovinyl)Benzene 10a

82% yield. Spectroscopic data are in agreement with literature [10].

2.2.2. (E)-1-Methoxy-4-(2-nitrovinyl)benzene 10b

86% yield. Spectroscopic data are in agreement with literature [11].

2.2.3. (E)-1-Methoxy-3-(2-nitrovinyl)benzene 10c

80% yield. mp 91 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, $J = 13.7$ Hz, 1H), 7.56 (d, $J = 13.7$ Hz, 1H), 7.36 (t, $J = 8.3$ Hz, 1H), 7.14 (d, $J = 8.0$ Hz, 1H), 7.06–7.01 (m, 2H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 139.4, 137.7, 131.7, 130.8, 122.1, 118.3, 114.4, 55.8. FTIR ($CHCl_3$) 3108, 1636, 1577, 1511 cm^{-1}. HRMS *m/z* calcd for $C_9H_9NO_3$ 179.0582, found 179.0586.

2.2.4. (E)-1-Methoxy-4-(2-nitrovinyl)benzene 10d

80% yield. Spectroscopic data are in agreement with literature [12].

2.2.5. (E)-1-Fluoro-4-(2-nitrovinyl)benzene 10e

79% yield. mp 101 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, $J = 13.7$ Hz, 1H), 7.60–7.51 (m, 3H), 7.15 (t, $J = 8.5$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6 (d, $J = 254.6$ Hz, 1C), 132.4, 131.6, 125.9 (d, $J = 9.1$ Hz, 2C), 121.0 (d, $J = 3.6$ Hz, 1C), 111.4 (d, $J = 22.1$ Hz, 2C). FTIR ($CHCl_3$) 3013, 1636, 1600, 1507, 1341, 1245, 1269, 969 cm^{-1}. HRMS *m/z* calcd for $C_8H_6FNO_2$ 167.0383, found 167.0386.

2.2.6. (E)-2-(2-nitrovinyl)Phenol 10f

68% yield. mp 133 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, $J = 13.8$ Hz, 1H), 7.96 (d, $J = 13.8$ Hz, 1H), 7.43 (d, $J = 7.5$ Hz, 1H), 7.34 (t, $J = 7.5$ Hz, 1H), 7.00 (t, $J = 7.5$ Hz, 1H), 6.87 (d, $J = 7.5$ Hz, 1H), 6.52–5.58 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 138.8, 135.9, 133.6, 132.7, 121.8, 119.5, 117.0. FTIR ($CHCl_3$) 3236, 3018, 1627, 1605, 1512, 1452, 1336, 1236, 1197 cm^{-1}. HRMS *m/z* calcd for $C_8H_7NO_3$ 165.0426, found 165.0422.

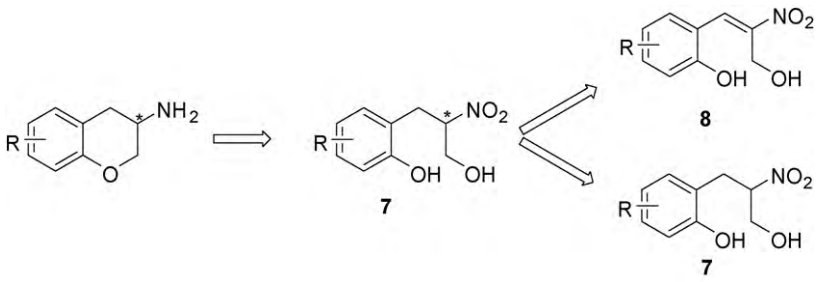


Fig. 2. Retrosynthetic approach to the chiral 3-aminochroman moiety.

2.2.7. (E)-3-Methoxy-2-(2-nitrovinyl)phenol 10g

65% yield. mp 79 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.36–10.65 (br s, 1H), 8.42 (d, *J* = 13.8 Hz, 1H), 8.08 (d, *J* = 13.8 Hz, 1H), 7.32 (t, *J* = 8.2 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.2, 159.5. 137.2, 134.2, 130.1, 108.4, 106.2, 102.0, 55.9. FTIR ($CHCl_3$) 3235, 3041, 1621, 1338, 1245, 1222, 1211, 1092 cm^{-1}. HRMS *m/z* calcd for $C_9H_9NO_4$ 195.0532, found 195.0528.

2.3. General procedure for the synthesis of 8a–g

Compound **10a–g** (0.1 mol) was dissolved in 70 mL of THF. Imidazole (0.1 mol) and anthranilic acid (0.1 mol) were added. Then 50 mL of 25% aq formaldehyde were added and the solution was stirred for 5 days. Then 50 mL of water was added followed by 50 mL of EtOAc. The organic layer was separated and washed with 1 M aq HCl. The organic phase was the dried over Na_2SO_4 and the solvent was evaporated under vacuum. The crude was purified by silica gel chromatography (hexane/EtOAc 7:3) to afford **8a–g**.

2.3.1. (E)-2-Nitro-3-phenylprop-2-en-1-ol 8a

71% yield. Spectroscopic data are in agreement with literature [13].

2.3.2. (E)-3-(2-methoxyphenyl)-2-Nitroprop-2-en-1-ol 8b

73% yield. mp 72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 6.98 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 4.60 (d, *J* = 6.5 Hz, 2H), 3.83 (s, 3H), 3.09 (t, *J* = 6.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 149.5, 133.9, 133.0, 131.0, 121.3, 120.9, 111.2, 57.0, 56.0. FTIR ($CHCl_3$) 3595, 3032, 1520, 1362, 1325, 1253, 1199 cm^{-1}. HRMS *m/z* calcd for $C_{10}H_{11}NO_4$ 209.0688, found 209.0693.

2.3.3. (E)-3-(3-methoxyphenyl)-2-Nitroprop-2-en-1-ol 8c

68% yield. mp 69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 2.0 Hz, 1H), 7.02 (dd, *J* = 7.7, 2.0 Hz, 1H), 4.70 (s, 2H), 3.84 (s, 3H), 2.66 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 150.0, 137.9, 132.8, 130.4, 122.7, 117.1, 115.4, 57.0, 55.6. FTIR ($CHCl_3$) 3491, 3028, 1552, 1377, 1356, 1211 cm^{-1}. HRMS *m/z* calcd for $C_{10}H_{11}NO_4$ 209.0688, found 209.0691.

2.3.4. (E)-3-(4-methoxyphenyl)-2-Nitroprop-2-en-1-ol 8d

73% yield. Spectroscopic data are in agreement with literature [13].

2.3.5. (E)-3-(4-fluorophenyl)-2-Nitroprop-2-en-1-ol 8e

65% yield. Spectroscopic data are in agreement with literature [13].

2.3.6. (E)-2-(3-hydroxy-2-nitroprop-1-enyl)Phenol 8f

52% yield. mp 122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45–9.81 (br s, 1H), 8.26 (s, 1H), 7.59 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.35 (td, *J* = 7.7, 1.4 Hz, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.92 (t, *J* = 7.7 Hz, 1H), 5.82–5.31 (br s, 1H), 4.52 (s, 2H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 157.0, 149.4, 132.4, 131.7, 130.1, 119.2, 118.4, 115.6, 54.8. FTIR ($CHCl_3$) 3593, 3254, 3030, 1519, 1455, 1362, 1324, 1236 cm^{-1}. HRMS *m/z* calcd for $C_9H_9NO_4$ 195.0532, found 195.0527.

2.3.7. (E)-2-(3-hydroxy-2-nitroprop-1-enyl)-3-Methoxyphenol 8g

52% yield. mp 103 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56–9.02 (br s, 1H), 8.51 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 6.71–6.63 (m, 2H), 4.77 (s, 2H), 3.79 (s, 3H), 2.85–2.73 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 158.6, 147.8, 133.7, 131.3, 109.9, 105.9, 103.3, 56.3, 55.8. FTIR ($CHCl_3$) 3596, 3242, 3032, 1528, 1351 cm^{-1}. HRMS *m/z* calcd for $C_{10}H_{11}NO_5$ 225.0637, found 225.0641.

2.4. General procedure for the synthesis of 15a–e

Compound **10b** and **10d–g** (0.15 mol) was dissolved in 300 mL of $CHCl_3$ and 100 mL of iPrOH and 70 g of SiO_2 were added. Then $NaBH_4$ (0.23 mol) was added in portions. After 1 h 15 mL of acetic acid were added dropwise. The reaction mixture was filtered on celite and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with brine. The organic layer was then dried and evaporated under reduced pressure to afford the product without further purification.

2.4.1. 1-Methoxy-2-(2-nitroethyl)benzene 15a

88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (td, *J* = 7.6, 1.7 Hz, 1H), 7.16 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.95–6.88 (m, 2H), 4.60 (t, *J* = 7.3 Hz, 2H), 3.85 (s, 3H), 3.32 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 131.0, 129.2, 124.4, 121.1, 110.9, 75.2, 55.7, 29.5. FTIR ($CHCl_3$) 3311, 3254, 1519, 1455, 1362, 1324, 1236 cm^{-1}. HRMS *m/z* calcd for $C_9H_{11}NO_3$ 181.0739, found 181.0736.

2.4.2. 1-Methoxy-4-(2-nitroethyl)benzene 15b

81% yield. Spectroscopic data are in agreement with literature [14].

2.4.3. 1-Fluoro-4-(2-nitroethyl)benzene 15c

93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 8.6, 5.3 Hz, 2H), 6.97 (t, *J* = 8.6 Hz, 2H), 4.56 (d, *J* = 7.5 Hz, 2H), 3.24 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7 (d, *J* = 246.3 Hz, 1C), 131.3 (d, *J* = 2.9 Hz, 1C), 129.8 (d, *J* = 8.3 Hz, 2C), 115.3 (d, *J* = 21.4 Hz, 2C), 75.8, 32.1. FTIR ($CHCl_3$) 3319, 3032, 1523, 1369, 1244, 1123 cm^{-1}. HRMS *m/z* calcd for $C_8H_8FNO_2$ 169.0539, found 169.0544.

2.4.4. 2-(2-nitroethyl)Phenol 15d

83% yield. Spectroscopical data are in agreement with literature [15].

2.4.5. 3-Methoxy-2-(2-nitroethyl)phenol 15e

89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.05 (br s, 1H), 6.98 (t, *J* = 7.8 Hz, 1H), 6.42 (d, *J* = 7.8 Hz, 1H), 6.37 (d, *J* = 7.8 Hz, 1H), 4.47 (t, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 3.32 (t, *J* = 7.2 Hz, 2H). FTIR ($CHCl_3$) 3574, 3211, 1517, 1448, 1319, 1274 cm^{-1}. ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 155.3, 127.9, 110.0, 108.1, 97.5, 73.5, 55.2, 21.3. HRMS *m/z* calcd for $C_9H_{11}NO_4$ 197.0688, found 197.0684.

2.5. General procedure for the baker's yeast reduction of 8a–g and of 13

To a mechanically stirred mixture of commercial baker's yeast (200 g) in tap water (0.8 L) at 35 °C was added a solution of glucose (50 g) in water (100 mL). After 1 h was added in one portion the substrate **8a–g** (10 mmol) adsorbed on the resin XAD 1180 (20 g). The vigorous stirring was continued for 24 h. Then, the mixture was filtered on a sintered glass funnel (porosity 0, >165 μm) and the resin was washed with acetone (50 mL) and EtOAc (4× 100 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give an oil that was submitted to column chromatography purification using *n*-hexane/EtOAc (8:2) as eluant to give **12a–e**.

2.6. General procedure for the synthesis of 12b and 12d–g

Compound **15a–e** (0.10 mmol) was dissolved in 80 mL of methanol. The pH was adjusted to 8 with 0.1 M aq NaOH and formaldehyde (0.15 mmol, 37% aq solution) was added. After 45′

the solution is acidified with 1 M aq HCl and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give an oil that was purified by column chromatography with *n*-hexane/EtOAc (8:2) as eluant to give **12b** and **12d–g**.

2.6.1. 2-Nitro-3-phenylpropan-1-ol 12a

(R_f = 0.21 *n*-hexane/EtOAc 8:2); mp 71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.08 (m, 5H), 4.75–4.68 (m, 1H), 3.96–3.85 (m, 2H), 3.23 (dd, *J* = 14.0, 7.2 Hz, 1H), 3.07 (dd, *J* = 14.0, 7.4 Hz, 1H), 2.15–2.02 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.5, 123.7 (2C), 123.6 (2C), 122.3, 84.5, 57.0, 30.5. FTIR ($CHCl_3$) 3398, 3031, 1561, 1297, 1193 cm^{-1}. HRMS *m/z* calcd for $C_9H_{11}NO_3$ 181.0739, found 181.0742. Chiral HPLC conditions: Chiralcel OD column; eluant 98:2 *n*-hexane/*i*-PrOH; flow rate, 0.7 mL/min; λ = 210 nm; t_R = (*R*) 80.25 min, (*S*) 94.31 min.

2.6.2. 3-(2-methoxyphenyl)-2-Nitropropan-1-ol 12b

(R_f = 0.25 *n*-hexane/EtOAc 8:2); mp 87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (td, *J* = 7.8, 1.8 Hz, 1H), 7.05 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.87–6.80 (m, 2H), 4.91–4.84 (m, 1H), 3.94 (dd, *J* = 12.4, 7.4 Hz, 1H), 3.86 (dd, *J* = 12.4, 3.4 Hz, 1H), 3.78 (s, 3H), 3.21–3.08 (m, 2H), 3.08–2.90 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 131.3, 129.3, 123.7, 121.1, 110.8, 88.9, 63.2, 55.6, 31.4. FTIR ($CHCl_3$) 3404, 3033, 1553, 1246, 1203 cm^{-1}. HRMS *m/z* calcd for $C_{10}H_{13}NO_4$ 211.0845, found 211.0844. Chiral HPLC conditions: Chiralcel OD column; eluant 98:2–95:5 *n*-hexane/*i*-PrOH; flow rate, 0.7 mL/min; λ = 210 nm; t_R = (*S*) 50.98 min, (*R*) 53.53 min.

2.6.3. 3-(3-methoxyphenyl)-2-Nitropropan-1-ol 12c

(R_f = 0.25 *n*-hexane/EtOAc 8:2); mp 81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 8.0 Hz, 1H), 6.81 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.73 (s, 1H), 4.83–4.75 (m, 1H), 4.04–3.91 (m, 2H), 3.79 (s, 3H), 3.28 (dd, *J* = 13.9, 7.2 Hz, 1H), 3.11 (dd, *J* = 13.9, 7.5 Hz, 1H), 2.35–2.27 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 136.7, 130.3, 121.5, 115.1, 113.1, 90.0, 62.8, 55.5, 36.2. FTIR ($CHCl_3$) 3411, 3033, 1547, 1257, 1212 cm^{-1}. HRMS *m/z* calcd for $C_{10}H_{13}NO_4$ 211.0845, found 211.0841. Chiral HPLC conditions: chiralcel OD column; eluant 9:1 *n*-hexane/*i*-PrOH; flow rate, 1 mL/min; λ = 210 nm; t_R = (major) 16.50 min, (minor) 18.25 min.

2.6.4. 3-(4-methoxyphenyl)-2-Nitropropan-1-ol 12d

(R_f = 0.20 *n*-hexane/EtOAc 8:2); mp 80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 4.79–4.70 (m, 1H), 3.96 (dd, *J* = 12.4, 8.2 Hz, 1H), 3.87 (dd, *J* = 12.4, 3.0 Hz, 1H), 3.75 (s, 3H), 3.35–2.19 (br s, 1H), 3.15 (dd, *J* = 14.1, 8.2 Hz, 1H), 3.01 (dd, *J* = 14.1, 6.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.3 (2C), 127.2, 114.6 (2C), 91.0, 62.9, 55.6, 35.4. HRMS *m/z* calcd for $C_{10}H_{13}NO_4$ 211.0845, found 211.0849. FTIR ($CHCl_3$) 3436, 3034, 1550, 1255 cm^{-1}. Chiral HPLC conditions: chiralcel OD column; eluant 9:1 *n*-hexane/*i*-PrOH; flow rate, 1 mL/min; λ = 210 nm; t_R = (*R*) 14.65 min, (*S*) 29.61 min.

2.6.5. 3-(4-fluorophenyl)-2-Nitropropan-1-ol 12e

(R_f = 0.28 *n*-hexane/EtOAc 8:2); mp 69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 8.5, 5.1 Hz, 2H), 6.99 (t, *J* = 8.6 Hz, 2H), 4.79–4.71 (m, 1H), 4.01–3.89 (m, 2H), 3.22 (dd, *J* = 14.4, 7.8 Hz, 1H), 3.09 (dd, *J* = 14.4, 6.7 Hz, 1H), 2.80–2.71 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1 (d, *J* = 250.3 Hz, 1C), 130.8–129.9 (3C), 115.6 (d, *J* = 21.8 Hz, 2C), 89.9, 62.3, 34.9. FTIR ($CHCl_3$) 3553, 3043, 1517, 1325, 1266, 1106 cm^{-1}. HRMS *m/z* calcd for $C_9H_{10}FNO_3$ 199.0645, found 199.0641. Chiral HPLC conditions: Chiralcel OD column; eluant 95:5 *n*-hexane/*i*-PrOH; flow rate, 0.7 mL/min; λ = 210 nm; t_R = (major) 31.07 min, (minor) 34.30 min.

2.6.6. 2-(3-hydroxy-2-nitropropyl)Phenol 12f

(R_f = 0.11 *n*-hexane/EtOAc 8:2); mp 97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (br s, 1H), 7.16 (td, *J* = 7.6, 1.8 Hz, 1H), 7.11 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.88 (td, *J* = 7.6, 1.6 Hz, 1H), 6.81 (dd, *J* = 7.6, 1.8 Hz, 1H), 4.89–4.81 (m, 1H), 4.07 (dd, *J* = 12.9, 3.0 Hz, 1H), 3.90 (dd, *J* = 12.9, 6.0 Hz, 1H), 3.36–3.22 (m, 2H), 2.51–2.23 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 131.1, 129.3, 121.6, 120.7, 115.8, 88.9, 63.0, 31.1. FTIR ($CHCl_3$) 3308, 3022, 1550, 1237, 1198 cm^{-1}. HRMS *m/z* calcd for $C_9H_{11}NO_4$ 197.0688, found 197.0693. Chiral HPLC conditions: Chiralcel OD column; eluant 9:1 *n*-hexane/*i*-PrOH; flow rate, 1 mL/min; λ = 210 nm; t_R = (*S*) 21.10 min (*R*) 27.30 min.

2.6.7. 2-(3-hydroxy-2-nitropropyl)-3-Methoxyphenol 12g

(R_f = 0.10 *n*-hexane/EtOAc 8:2); mp 93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–7.41 (br s, 1H), 6.95 (t, *J* = 8.0 Hz, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 6.35 (d, *J* = 8.0 Hz, 1H), 4.74–4.66 (m, 1H), 3.87 (dd, *J* = 12.7, 2.9 Hz, 1H), 3.80 (dd, *J* = 12.7, 6.4 Hz, 1H), 3.68 (s, 3H), 3.27–3.15 (m, 2H), 2.92–2.76 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 155.9, 128.8, 110.2, 108.8, 102.9, 87.2, 62.5, 55.7, 23.6. FTIR ($CHCl_3$) 3454, 3036, 1549, 1366, 1292, 1093 cm^{-1}. HRMS *m/z* calcd for $C_{10}H_{13}NO_5$ 227.0794, found 227.0789. Chiral HPLC conditions: Chiralcel OD column; eluant 95:5 *n*-hexane/*i*-PrOH; flow rate, 0.7 mL/min; λ = 210 nm; t_R = (*S*) 54.71 min (*R*) 59.98 min.

2.6.8. 3-Nitrochroman 14

Spectroscopical data are in agreement with literature [4]. Chiral HPLC conditions: Chiralcel OD column; eluant 98:2 *n*-hexane/*i*-PrOH; flow rate, 0.7 mL/min; λ = 210 nm; t_R = (major) 36.91 min, (minor) 39.06 min.

2.7. General procedure for the lipase mediated resolution of 12b and 12d–g

1 g of the substrate was dissolved in 10 mL of MTBE and 10 mL of vinyl acetate, then 1 g of the enzyme was added. The mixture was stirred for 1–12 h and then filtered. The solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (hexane/EtOAc 7:3).

2.7.1. 3-(2-methoxyphenyl)-2-Nitropropyl acetate 16b.

(R_f = 0.23, hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (td, *J* = 7.8, 1.8 Hz, 1H), 7.03 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.87–6.81 (m, 2H), 5.08–5.00 (m, 1H), 4.45–4.34 (m, 2H), 3.79 (s, 3H), 3.18 (dd, *J* = 13.8, 7.8 Hz, 1H), 3.10 (dd, *J* = 13.8, 6.8 Hz, 1H), 1.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 157.8, 131.2, 129.6, 123.0, 121.1, 110.9, 85.7, 63.9, 55.6, 32.0, 20.7. FTIR ($CHCl_3$) 3024, 1746, 1557, 1238 cm^{-1}. HRMS *m/z* calcd for $C_{12}H_{15}NO_5$ 253.0950, found 253.0947. Chiral HPLC conditions: Chiralcel OD column; eluant 98:2 *n*-hexane/*i*-PrOH; flow rate, 0.7 mL/min; λ = 210 nm; t_R = (*S*) 20.84 min, (*R*) 16.86 min.

2.7.2. 3-(4-methoxyphenyl)-2-Nitropropyl acetate 16d

(R_f = 0.20, hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.92–4.83 (m, 1H), 4.42–4.35 (m, 2H), 3.73 (s, 3H), 3.18 (dd, *J* = 14.3, 8.1 Hz, 1H), 3.01 (dd, *J* = 14.3, 6.3 Hz, 1H), 2.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 158.9, 129.7 (2C), 125.8, 114.2 (2C), 86.9, 63.0, 55.0, 35.2, 20.1. FTIR ($CHCl_3$) 3038, 1749, 1554, 1266, 1324 cm^{-1}. HRMS *m/z* calcd for $C_{12}H_{15}NO_5$ 253.0950, found 253.0944. Chiral HPLC conditions: Chiralcel OD column; eluant 95:5 *n*-hexane/*i*-PrOH; flow rate, 0.7 mL/min; λ = 210 nm; t_R = (*R*) 22.82 min, (*S*) 26.33 min.

2.7.3. 3-(4-fluorophenyl)-2-Nitropropyl acetate 16e

(R_f = 0.20, hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 8.7, 5.3 Hz, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 4.95–4.86 (m, 1H), 4.48–4.37 (m, 2H), 3.23 (dd, *J* = 14.5, 8.5 Hz, 1H), 3.07 (dd, *J* = 14.4,

6.4 Hz, 1H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 162.1 (d, J = 250.1 Hz, 1C), 130.3 (d, J = 7.6 Hz, 2C), 129.8, 115.7 (d, J = 20.3 Hz, 2C), 86.8, 63.0, 35.2, 20.2. FTIR ($CHCl_3$) 3042, 1748, 1560, 1511, 1249, 1366, 1047 cm^{-1}. HRMS m/z calcd for $C_{11}H_{12}FNO_4$ 241.0750, found 241.0755. Chiral HPLC conditions: Chiralcel OD column; eluant 95:5 n-hexane/i-PrOH; flow rate, 0.7 mL/min; λ = 210 nm; t_R = (minor) 20.57 min, (major) 22.51 min.

2.7.4. 3-(2-hydroxyphenyl)-2-Nitropropyl acetate 16f

(R_f = 0.18, hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11–7.64 (br s, 1H), 7.11 (td, J = 8.1, 1.9 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.82–6.77 (m, 2H), 5.19–5.11 (m, 1H), 4.51–4.40 (m, 2H), 3.23 (dd, J = 13.9, 7.6 Hz, 1H), 3.17 (dd, J = 13.9, 7.1 Hz, 1H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 154.3, 130.7, 128.7, 120.6, 120.2, 115.1, 84.9, 63.4, 31.3, 20.1. FTIR ($CHCl_3$) 3291, 3037, 1746, 1557, 1240, 1197 cm^{-1}. HRMS m/z calcd for $C_{11}H_{13}NO_5$ 239.0794, found 239.0791. Chiral HPLC conditions: Chiralcel OD column; eluant 98:2 n-hexane/i-PrOH; flow rate, 1 mL/min; λ = 210 nm; t_R = (R) 66.03 min, (S) 71.84 min.

2.7.5. 3-(2-hydroxy-6-methoxyphenyl)-2-Nitropropyl acetate 16g

(R_f = 0.25, hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (t, J = 8.3 Hz, 1H), 6.73–6.63 (br s, 1H), 6.46–6.40 (m, 2H), 5.06–4.98 (m, 1H), 4.54 (dd, J = 12.2, 8.9 Hz, 1H), 4.33 (dd, J = 12.2, 3.1 Hz, 1H), 3.79 (s, 3H), 3.33 (dd, J = 13.3, 6.6 Hz, 1H), 3.25 (dd, J = 13.3, 8.1 Hz, 1H), 2.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 158.7, 155.3, 128.7, 109.3, 108.2, 102.7, 84.7, 63.7, 55.3, 24.2, 20.4. FTIR ($CHCl_3$) 3434, 2962, 1755, 1464, 1380, 1159 cm^{-1}. HRMS m/z calcd for $C_{12}H_{15}NO_6$ 269.0899 found 269.0897. Chiral HPLC conditions: Chiralcel OD column; eluant 98:2 n-hexane/i-PrOH; flow rate, 0.7 mL/min; λ = 210 nm; t_R = (R) 89.84 min, (S) 100.02 min.

2.8. 2-(2-amino-3-hydroxypropyl)-3-Methoxyphenol 19

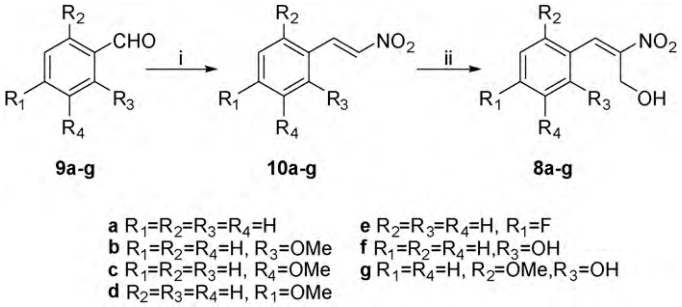
(R_f = 0.10, hexane/EtOAc 7:3); Compound **12g** (2.5 g, 11.0 mmol), was dissolved in 50 mL of ethanol and 500 mg of wet Ni-Raney were added. The mixture was stirred under hydrogen atmosphere for 48 h and then filtered over celite to remove the catalyst. The solvent was evaporated under reduced pressure to afford **19** (1.93 g, 89% yield) without further purification. mp 122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (t, J = 8.1 Hz, 1H), 6.48 (d, J = 8.2 Hz, 1H), 6.34 (d, J = 8.2 Hz, 1H), 5.05–4.31 (br s, 4H), 3.75 (s, 3H), 3.56–3.45 (br m, 2H), 3.38–3.28 (br m, 1H), 3.11 (dd, J = 13.4, 11.2 Hz, 1H), 2.88 (dd, J = 13.4, 3.0 Hz, 1H). FTIR ($CHCl_3$) 3410, 3381, 3318, 1576, 1480, 1323, 1059 cm^{-1}. HRMS m/z calcd for $C_{10}H_{15}NO_3$ 197.1052, found 197.1059.

2.9. tert-Butyl 1-hydroxy-3-(2-hydroxy-6-methoxyphenyl)propan-2-ylcarbamate 20.

Compound **19** (1.8 g, 9.1 mmol), was dissolved in 40 mL of dry acetonitrile and Boc anhydride (2.38 g, 10.9 mmol), was added. The mixture was stirred for 24 h then the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc 8:2, R_f = 0.18) to afford **20** (2.1 g, 78% yield) whose spectroscopic data were in agreement with literature [8a].

2.9.1. 5-Methoxy-3-aminochroman 3

Compound **20** was converted in to compound **3** by a two-step sequence according to a previously reported procedure [8a] (46% yield after two steps). Spectroscopic data were in agreement with literature.



Scheme 1. Reagents and conditions: (i) $MeNO_2$, AcOH, $AcONH_4$ (65–86%); (ii) CH_2O, Imidazole, Anthranilic acid (52–73%).

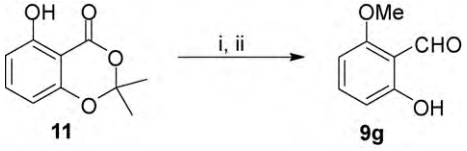
3. Results and discussion

3.1. Studies on baker's yeast mediated reduction of (E)-β-aryl-α-nitroalkene precursors 8

We first studied the baker's yeast mediated reduction of a series of β-aryl-α-nitroalkene derivatives **8**. The biocatalytic reduction of activated double bonds, in particular of α,β unsaturated aldehydes and ketones, is a well known topic in organic chemistry [16] and the utility of baker's yeast for this transformation has been demonstrated [17]. The reduction of substituted α-nitroalkenes by baker's yeast has also been studied [18]. The enantioselectivity was found to be a function of the position of the substituent on the double bond: while β,β-disubstituted α-nitroalkenes gave the corresponding saturated product with excellent ee, the presence of substituents at the α-position of the double bond gave scarce enantioselectivity. Investigation [19] of the mechanism of this reaction showed that a reversible non-stereoselective protonation occurs at the α-carbon, followed by a stereoselective addition of hydride at the β-position. Recently, isolated enzymes have been exploited for the reduction of activated double bonds [20] and it was reported that α-substituted-α-nitroalkenes can be reduced with good ee by means of cloned reductases [21] or by microbial extracts from *Clostridium sporogenes* [22]. The biocatalytic reduction of 2-nitro-3-phenylprop-2-en-1-ols **8** has never been reported until now. Thus, we decided to investigate the baker's yeast reduction of compounds **8a**–**g**, which were prepared according to Scheme 1.

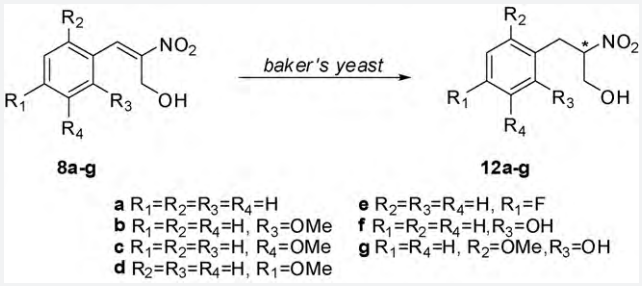
Reaction of commercially available aromatic aldehydes **9a**–**f** with nitromethane in the presence of acetic acid and ammonium acetate [23], gave the (E)-β-aryl-α-nitroalkenes **10** in good yields. The non-commercially available aldehyde **9g** was prepared starting from **11** [24] as reported in Scheme 2. A Morita–Baylis–Hillman reaction of **10a**–**g** with formaldehyde using imidazole as base and anthranilic acid as additive [25] allowed to obtain the desired **8a**–**g** in good yields.

Compounds **8a**–**g** were then submitted to reduction by baker's yeast. For practical work-up, the starting materials were adsorbed on non-polar resins (XAD 1180) [26] and then added to a water suspension of baker's yeast in the presence of glucose. After 24 h the mixture was filtered and the resin was washed with EtOAc to recover the reaction product. The conversion was estimated by GC/MS and ^{1}H NMR analysis on the crude and the ee of the reduced



Scheme 2. Reagents and conditions: (i) Me_2SO_4, K_2CO_3 (86%); (ii) DIBAL-H, THF, −78 °C (68%).

Table 1
Baker's yeast mediated reduction of **8a–g**.



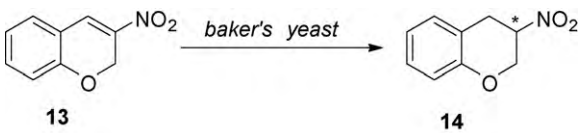
Compound	Conversion[a]	ee[b] (config.)
12a	98%	20% (*R*)
12b	76%	4% (*R*)
12c	93%	24% (nd)
12d	96%	42% (*R*)
12e	96%	26% (nd)
12f	7%	0%
12g	5%	0%

[a] Conversions are calculated from GC/MS and ^{1}H NMR analysis on the crude.
[b] ee are determined by chiral HPLC on a chiralcell OD column using hexane/isopropanol as eluant. See Section 2 for details.

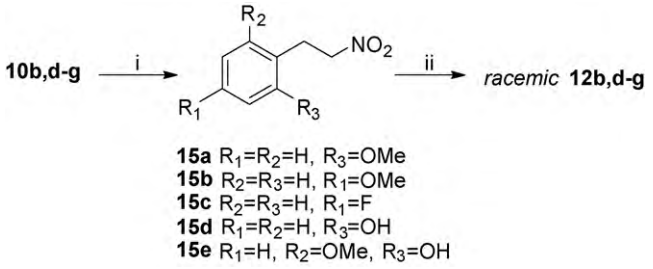
products were measured by chiral HPLC. Results are reported in Table 1.

Most of the products were obtained with high conversions. The enantioselectivity was modest and it was influenced by the substitution pattern of the aromatic ring. The best result was obtained with compound **12d**, bearing a *p*-methoxy substituent on the aromatic ring (42% ee). Moving the methoxy group to the *meta* and *ortho* position of the phenyl ring produced a lowering of the ee (24% ee for **12c** and 4% ee for **12b** respectively). This finding is in contrast with the observation that for the bioreduction of arylenones, the best result was obtained with the methoxy substituent in the *meta* position [27]. The presence of the phenol function in compounds **12f** and **12g** inhibited the activity of baker's yeast and the desired reduced product **12g**, precursor to the synthesis of **3**, was obtained with no enantioselection, in 5% conversion together with unreacted starting material.

The absolute configuration of the newly formed stereocenter was established for both **12a** and **12d** by reduction of the nitro group with Zn and 30% aq H_2SO_4 to give the corresponding known aminoalcohols. The optical rotatory power of the obtained products ($[\alpha]_D^{25}$ = +5.1, *c* 1.0, EtOH for aminoalcohol from **12a** [28] and $[\alpha]_D^{25}$ = +5.5, *c* 1.8, MeOH for aminoalcohol from **12d** [29]) compared with the literature value for their enantiomerically pure forms allowed to assign the *R* configuration for both **12a** and **12d**. The absolute configuration of **12b** was determined according to Scheme 5 (*vide infra*). We also performed the baker's yeast mediated reduction of **13** [30] (Scheme 3), and the 3-nitrochroman derivative **14** was obtained in 86% of conversion and 21% ee ($[\alpha]_D^{25}$ = +19.2, *c* 1.3, $CHCl_3$, absolute configuration not determined). In earlier reports [18a], the low stereoselectivity of the baker's yeast mediated reduction of disubstituted nitroolefines was attributed to racemization of the products because of acidity of the proton in α position of the nitro moiety. In a recent work [18b],



Scheme 3. Baker's yeast mediated reduction of **13**.



Scheme 4. Reagents and conditions: (i) $NaBH_4$, SiO_2, $CHCl_3$/i-PrOH (81–93%); (ii) CH_2O, NaOH, MeOH (48–71%).

the rate of racemization of the nitroalkane product under the same conditions as the baker's yeast reduction was evaluated. Results confirmed that racemization is a very slow process, thus supporting the observation that the low stereoselectivity were not a result of non-enzymatic racemization of the product, because the reduction with yeast was completed within some hours (24 h in our case).

3.2. Studies on lipase mediated kinetic resolution of racemic primary 2-nitroalcohols

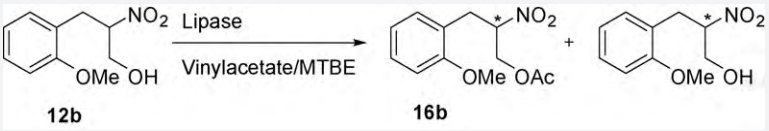
Since compounds **8f** and **8g** could not be reduced with baker's yeast, we decided to achieve the desired optically active **12g** by means of a lipase catalyzed kinetic resolution of the corresponding primary 2-nitro alcohol. To the best of our knowledge this strategy has never been reported before in the literature. Substrates were prepared according to the synthetic sequence reported in Scheme 4. The reduction of **10b** and **10d–g** with $NaBH_4$ at 0 °C in THF/MeOH gave the products with poor yields. Running the reaction in $CHCl_3$/i-PrOH at room temperature in the presence of SiO_2, [31] afforded the wanted 2-aryl nitroethane compounds **15a–e** in good yields. The nitroaldol reaction of **15a–e** with formaldehyde in MeOH with catalytic amount of NaOH, gave the racemic 3-aryl-2-nitropropanols **12b** and **12d–g** with satisfactory yields.

A preliminary screening for the best performing lipase was performed on racemic **12b** (see Table 2). The substrate was reacted in a vinylacetate/MTBE 1:1 solution with *Pig Pancreatic Lipase*, lipase from *Candida rugosa*, and *Amano PS* lipase. Reactions with both the *PPL* and *C. rugosa* proceed very quickly with good conversion (25′ and 45% conv. for *PPL*; 20′ and 55% conv. for *C. Rugosa*). This rapid acetylation led to low ee. Better results were obtained with lipase from *Amano PS*. In this case a slower reaction occurred and after 1 h the acetylated product **16b** was obtained with 19% of conversion and 73% of ee. The unchanged **12b** was obtained in 81% yield and 17% ee. Notably an inversion of configuration of the acetylated product was observed for *C. rugosa*.

The absolute configuration of **16b** (as obtained from *Amano PS* catalyzed resolution) was estabilished by converting the residual enantioenriched **12b** (ee 17% by chiral HPLC) into the known sulfonamide **17** by a reduction of the nitro group with Zn and conc. HCl followed by reaction with benzensulfonyl chloride, according to Scheme 5. The optical rotatory power of **17** ($[\alpha]_D^{25}$ = +11.1, *c* 1.0, acetone) compared with the literature [32] value for enantiomerically pure **17** ($[\alpha]_D^{25}$ = +66.5, *c* 1.0, acetone) allowed to confirm a *R* configuration for the major enantiomer of unreacted **12b** and a *S* configuration for the major enantiomer of the acetylated product **16b**. The ee calculated from the measured optical rotator power (19.5% ee) is in agreement with that derived by chiral HPLC analysis (17% ee).

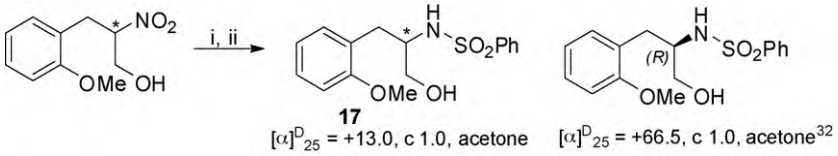
The *R* configuration of the untransformed product **12b** is the correct one for the obtainment of the (*R*)-5-metoxy-3-aminochroman precursor of Robalzotan. For this reason in order to improve the ee of (*R*)-**12b**, we repeated the *Amano PS* lipase mediated resolu-

Table 2
Lipase mediated resolution of racemic **12b**.



Lipase	Time	Conversion[a]	ee **16b**[b]	*E*	Configuration
PPL	25′	45%	16%	1.6	*S*
C. rugosa	20′	55%	17%	1.5	*R*
Amano PS	1 h	19%	73%	7.6	*S*
Amano PS	4 h	33%	67%	6.9	*S*

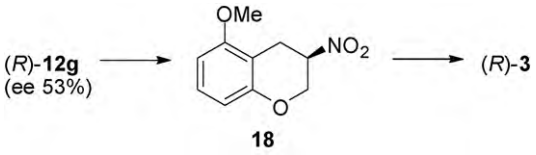
[a] Conversions are estimated from ^{1}H NMR analysis on the crude.
[b] ee are determined by chiral HPLC on a chiralcell OD column using hexane/isopropanol as eluant. See Section 2 for details.



Scheme 5. Reagents and conditions: (i) Zn, HCl conc., EtOH (92%); (ii) $PhSO_2Cl$, TEA, DCM (87%).

tion of racemic **12b** and, under the same conditions, after 4 h the acetylated product was isolated after chromatographic separation in 33% yield and 67% ee, while residual nitroalcohol was achieved in 67% yield and 33% ee. This latter enantioenriched product was then resolved again to afford (*R*)-**12b** with 97% ee and with an overall 21% yield, after two resolution steps. Following these promising results we studied the substrate scope for this novel lipase mediate resolution of 3-aryl-2-nitropropanols. Results are reported in Table 3.

Again a relation between the substitution pattern of the aromatic ring and the ee is evident. For **12d** and **12e**, both bearing a substituent in the *para* position, the resolution is less efficient if compared with **12b** and **12f**. The presence of two substituents in the *ortho* position is also detrimental, and the desired compound **12g** was obtained in 24% yield and 53% ee. It is worth to notice that for **12f** and **12g** the acetylation occurred with high chemoselectivity; in fact only the primary alcoholic function was acetylated, while the phenol moiety remained unchanged. The absolute configuration of compound **12f** was established by transformation into **12b** (Me_2SO_4, K_2CO_3) while for **12g** was determined to be *R* by converting it in o the target (*R*)-**3** (*vide infra*).



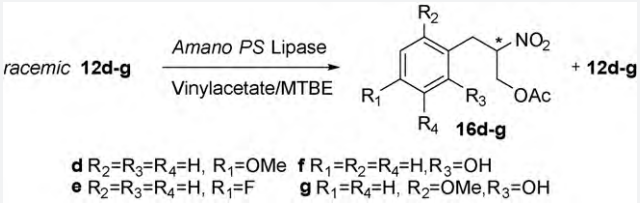
Scheme 6. Synthetic strategy to obtain (*R*)-**3**.

3.3. Synthesis of enantioenriched (R)-5-methoxy-3-aminochroman

In order to obtain enantioenriched (*R*)-**3**, we investigated the intramolecular cyclization reaction of enantioenriched (*R*)-**12g**, obtained from *Amano PS* mediated resolution, to give intermediate **18** which, after reduction of the nitro group, would afford (*R*)-**3**. We tested different reaction conditions to make the cyclic arylether **18** by activating the alcoxy function toward an intramolecular nucleophilic displacement by the phenol function (Scheme 6).

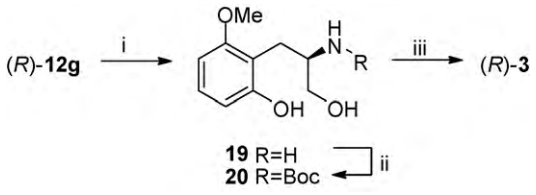
This transformation proved to be a non-trivial issue. We first tried to tosylate the primary alcohol function, but treatment of

Table 3
Lipase mediated resolution of racemic **12d–g**.



Substrate	Time	Conversion[a]	ee **16d–g** (config.)[b]	ee **12d–g** (config.)[b]	*E*
12d	6 h	43%	36% (*S*)	28% (*R*)	2.7
12e	6 h	37%	23% (nd)	14% (nd)	1.8
12f	6 h	46%	51% (*S*)	43% (*R*)	4.6
12g	6 h	37.5%	31% (*S*)	19% (*R*)	2.2
12g	12 h	76%	17% (*S*)	53% (*R*)	2.2

[a] Conversions are estimated from ^{1}H NMR analysis on the crude.
[b] ee are determined by chiral HPLC on a chiralcell OD column using hexane/isopropanol as eluant. See Section 2 for details.



Scheme 7. Reagents and conditions: (i) H_2, Ni-Raney, EtOH (86%); (ii) Boc_2O, acetonitrile (78%); (iii) see Ref. [8a].

(*R*)-**12g** with tosylchloride in DCM with catalytic amount of TEA, quantitatively afforded the tosylation of the phenol oxygen, leaving unchanged the function. When we tried to convert the primary alcohol function into a bromide (PBr_3 or NBS/PPh_3) or into an iodide derivative (I_2/PPh_3/Imidazole) we could only obtain an inseparable mixture of products deriving from the degradation of the starting material. Also cyclization under Mitsunobu conditions (DIAD, PPh_3) failed to achieve the desired nitrochroman **18**. We ascribed these events to the presence of the nitro group; for example, it is well known that γ-nitroalcohols, under Mitsunobu conditions react at the nitro function, giving cyclic alkylnitronates [33]. For these reasons, we decided to first reduce the nitro function to the amino group by hydrogenation in the presence of Ni-Raney in ethanol to afford **19** (Scheme 7).

The crude product **19** was then protected at the amino group with Boc. Treating **19** with Boc anhydride in DCM in the presence of TEA gave poor yields due to the competing formation of the oxazolidinone derivative involving the β-aminoalcohol moiety [34]. Better results were obtained by reacting **19** with Boc anhydride in acetonitrile without catalyst to afford **20** whose spectroscopical data are in agreement with literature [8a]. The measure of the optical rotatory power of **20** ($[\alpha]_D^{25}$ = +5.7, *c* 1.0, $CHCl_3$, $[\alpha]_D^{25}$ = +11.2, *c* 1.0, $CHCl_3$ from lit.) allowed to confirm the *R* configuration and a calculated 51% ee is in agreement with ee measured by chiral HPLC. **20** could be finally converted to the (*R*)-5-metoxy-3-aminochroman **3** following a previously reported procedure [8a] through a Mitsunobu–Boc deprotection sequence.

4. Conclusions

In conclusion we have reported a biocatalytic approach to the synthesis of 3-aryl-2-nitropropanols. We investigated the baker's yeast mediated reduction of (*E*)-2-nitro-3-arylprop-2-en-1-ols and a novel lipase mediated kinetic resolution of racemic 3-aryl-2-nitropropanols. Starting from (*R*)-**12g**, obtained from *Amano PS* mediated resolution with a 53% ee, we could achieve the synthesis of enantioenriched (*R*)-5-metoxy-3-aminochroman, a key precursor to the antidepressant drug Robalzotan. This work can also be inspiration for others to look more closely in the bioreductions of 2-nitro-3-arylprop-2-en-1-ols, using more specific bioreagents, such as isolated and/or overexpressed enzymes as well as engineered strains with higher reductase activity. Nonetheless, cheap and easy to handle baker's yeast can still be the reagent of choice when it happens that the complex multi-enzyme system working during its fermentation can perform biotransformations with stereoselectivity. Further studies on the enantioselective synthesis of the pharmacologically interesting 3-aminochroman moiety are in due of course in our laboratory.

Acknowledgement

We are grateful for the generous financial support from the E.U. INTENANT project.

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