Asian Pub. Corp.

www.asianpubs.org

ARTICLE

Organocatalytic Chiral Synthesis of Centrally Acting Muscle Relaxant (*S*)-Mephenesin

Sharad P. Panchgalle[1,✉], Vijaykumar S. More[2], Abhay S. Bondge[3] and Kalimoddin I. Momin[4]

ABSTRACT

Chiral synthesis of centrally acting muscle relaxant (*S*)-mephenesin was achieved using L-proline catalyzed α-aminoxylation of 3-(2-methyl-phenxoy)propanal as chirality induction step. The chiral synthesis started with commercially available 2-cresol and was accomplished in four steps with overall yield 56%. The enantiomeric excess of final product (*S*)-mephenesin is >98%. The chiral purity was determined by chiral-HPLC using Chiralcel-OD column. The synthesis involves oxidation of primary alcohol to aldehyde with iodoxybenzoic acid (IBX) as one of the steps.

KEYWORDS

Mephenesin, Organocatalysis, L-Proline, α-Aminoxylation, Aldehyde, Iodoxybenzoic acid.

Asian Journal of Organic & Medicinal Chemistry

Volume: 7 Year: 2022
Issue: 2 Month: April–June
pp: 231–234
DOI: https://doi.org/10.14233/ajomc.2022.AJOMC-P394

Received: 2 June 2022
Accepted: 28 June 2022
Published: 29 June 2022

Author affiliations:

[1]Department of Chemistry, K.M.C. College, Khopoli-410203, India
[2]Department of Chemistry, Kai Rasika Mahavidyalay, Deoni-413519, India
[3]Department of Chemistry, Shivneri Mahavidyalaya, Shirur Anantpal-413544, India
[4]Department of Chemistry, Rajarshi Shahu Mahavidyalaya (Autonomous), Latur-413512, India

✉To whom correspondence to be addressed:

E-mail: panchgalle@gmail.com

Available online at: http://ajomc.asianpubs.org

INTRODUCTION

Among the common proteogenic α-amino acids, only glycine is achiral and others are chiral molecules. Proteins made up of these amino acids are chiral in nature. Proteins are important biomolecules found in cells of living organisms. Enantiomers show different reactions with other chiral molecules. This indicates that the living organism have different interaction with the enantiomers. In some cases, one enantiomer gives desired effect on living organism and other enantiomer gives severe side effects. Due to this scientific community turned towards chiral drug molecules instead of racemic drug molecules. The quest of chiral drug molecules can be fulfilled by resolution of racemic mixture [1-4] and asymmetric synthesis [5-8]. The resolution of racemic mixture is not the perfect solution for getting chiral molecules because half material will be waste in this method. To overcome drawbacks of resolution of racemic mixture, chemists designed asymmetric synthesis by using chiral catalysts. In last century, metal-ligand catalyst ruled over the scientific community [9-12]. Use of organometallic compounds as catalyst have limitations such as high toxicity of metal, disposal of metal catalyst after use, *etc*. In last few decades, use of chiral organic molecules as catalyst has emerged as front runner and the world came across the term "organo-catalysis" [13-18]. Organocatalysis gained the recognition in the form of 2021 Nobel Prize in Chemistry to Prof. Benjamin List and Prof. David W.C. McMillan. In recent years, many organocatalytic reactions are reported for getting variety of chiral molecules and chiral building blocks [19-23].

In year 2003, Hayashi *et al.* [24], MacMillan *et al.* [25] and Zhong [26] independently reported the organocatalytic α-aminoxylation reaction of aldehyde for synthesis of chiral 1,2-diols. This method of preparation of chiral 1,2-diol has several favourable things such as cheap antipodes of proline, low catalyst loading (10-20 mol%), high enantioselectivity and high yield of 1,2-diols.

3-Aryloxypropane-1,2-diols (Fig. 1) are chiral building blocks for bioactive compounds. Some important 3-aryloxy-proane-1,2-diols are listed in Fig. 2. Literature survey revealed that there are many routes for chiral 3-aryloxypropane-1,2-diols involving use of metal catalyst such as osmium tetroxide (OsO_4) for dihydroxylation [27], Jacobson catalyst for hydrolytic kinetic resolution [28,29] and enzymatic resolution [30,31].

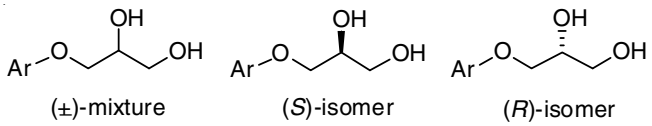


Fig. 1. 3-Aryloxy-1,2-propanediols

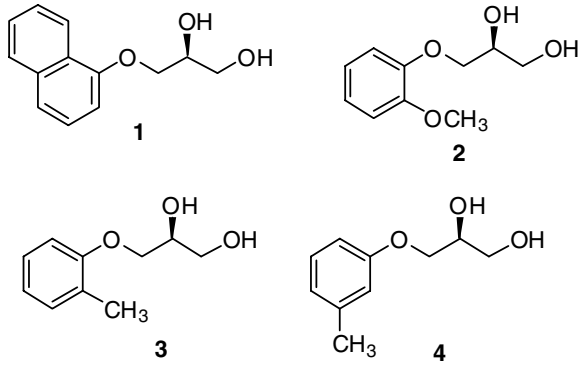


Fig. 2. Some important 3-aryloxy-1,2-propanediols

Our group was first to apply L-proline catalyzed asymmetric α-aminoxylation reaction for synthesis of chiral 3-aryloxypropane-1,2-diols. In 2009, the synthesis of (*S*)-3-(1′-naphthoxy)propane-1,2-diol (**1**) in > 98% ee and subsequently compound **1** converted into β-blockers *viz.* (*S*)-propranolol and (*S*)-naftopidil [32]. Using the same methodology, the organocatalytic asymmetric synthesis of (*S*)-guifenesin (**2**) and subsequently conversion of compound **2** into antihypertensive drug (*S*)-moprolol and skeletal muscle relaxant (*R*)-methocarbamol [33] is also reported.

(*S*)-Mephenesin (**3**) is a well-known centrally acting muscle relaxant. Literature has some reports for synthesis of compound **3**. Earlier reports involve dihydroxylation [27] of alkene with OsO_4, enzymatic resolution of racemic diol [30] and chiral pool approach [34]. Till date, nobody synthesized (*S*)-mephenesin (**3**) using organocatalysis. With our organocatalytic expertise towards the synthesis of chiral 3-aryloxypropane1,2-diol, we planned asymmetric synthesis of (*S*)-mephenesin (**3**) using L-proline catalyzed α-aminoxylation reaction of aldehyde.

EXPERIMENTAL

Reagents and solvents were of analytical grade or were purified by standard procedures prior to use. IR spectra were recorded on a Perkin-Elmer 1615 FT infrared spectrophotometer. ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded on a Bruker AC-200 spectrometer. The carbon resonances were assigned by use of DEPT experiments. Mass spectra were recorded at an ionization energy 70 eV on API Q STARPULSAR spectrometer using electrospray ionization. Microanalytical data were obtained on a Carlo-Erba CHNS–O EA 1108 elemental analyzer. Optical rotation was measured on Jasco P-1020 polarimeter. Progress of the reactions was monitored by TLC on Merck Silica Gel 60 F_{254} precoated plates and compounds were visualized by fluorescence quenching, by use of I_2 or by charring after treatment with a *p*-anisaldehyde–AcOH–H_2SO_4 mixture in ethanol. Column chromatography was performed on flash silica gel (230-400 mesh size).

3-(2-Methylphenoxy)propanol (7): To a 100 mL two-necked round bottom flask equipped with reflux condenser and rubber septum was charged 2-cresol (**6**) (2.160 g, 20 mmol) and 10% aqueous NaOH solution (20 mL) and stirred. After formation of homogeneous solution, 3-bromopropanol (3.056 g, 22 mmol) was added and refluxed for 6 h. The progress of reaction was checked by TLC analysis. After completion of reaction, the reaction mixture extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with water (1 × 50 mL), brine, dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. Residue was purified by flash column chromatography (silica gel) using EtOAc-petroleum ether (15:85) as an eluent, affording the alcohol **7**. Yield: 2.357 g (71%); yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 2.01-2.13 (m, 2H), 2.22 (s, 3H), 3.88 (t, *J* = 6 Hz, 2H), 4.12 (t, *J* = 6 Hz, 2H), 6.82-6.91 (m, 2H), 7.12-7.20 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 15.85, 31.81, 59.29, 64.59, 110.52, 120.02, 126.11, 126.48, 130.25, 156.58.

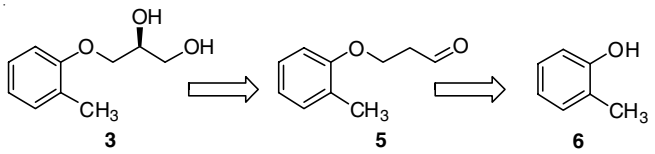
3-(2-Methylphenoxy)propanal (5): To a 50 mL two neck round bottom flask equipped rubber septum and two-way stop cork with argon balloon was added alcohol **7** (2.098 g, 12.63 mmol) and anhydrous DMSO (15 mL) and stirred. To this stirring solution was added iodoxybenzoic acid (IBX, 5.304 g, 18.94 mmol, 1.5 equiv.) and content of flask was stirred at room temperature for 2 h. The reaction mixture was diluted with water (10 mL) and then with diethyl ether (100 mL). The two layers were separated and diethyl ether layer was filtered through a bed of celite. The filtrate was washed with water (2 × 50 mL), brine, dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure to afford aldehyde **5**. Yield: 1.866 g (90%); yellow oil; IR ($CHCl_3$, cm^{-1}): 3064, 3004, 2958, 2837, 2358, 2046, 1725, 1593, 1504, 1253, 744; ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 2.17 (s, 3H), 2.87-2.94 (m, 2H), 4.32 (t, *J* = 6 Hz, 2H), 6.82-6.91 (m, 2H), 7.11-7.20 (m, 2H), 9.88 (t, *J* = 1.77 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 15.85, 43.00, 61.44, 110.76, 110.95, 120.59, 126.59, 130.50, 156.30, 200.36 ppm.

(*S*)-3-(2-Methylphenoxy)propane-1,2-diol or (*S*)-mephenesin (3): To a 100 mL two-necked round bottom flask equipped rubber septum and two-way stop corked with argon balloon was added aldehyde **5** (0.901 g, 5.494 mmol) and nitrosobenzene (0.587 g, 5.494 mmol) and acetonitrile (50 mL) and stirred at -20 ºC. To this stirring solution was added L-proline (0.126 g, 1.095 mmol, 20 mol %). The reaction

mixture was stirred at -20 ºC for 24 h. To this cooled reaction mixture, methanol (25 mL) and $NaBH_4$ (0.313 g, 8.236 mmol) was added and reaction mixture was stirred for 10 min at -20 ºC. Phosphate buffer was added to reaction mixture for quenching of reaction. The reaction mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated on a rotary evaporator under reduced pressure to afford crude aminoxy alcohol. The crude aminoxy alcohol was used as it was for next step. To a single necked round bottom flask containing crude aminoxy alcohol was added methanol (30 mL) and then added 10% Pd/C (70 mg) carefully. The reaction mixture was then stirred under a hydrogen atmosphere (1 atm. of H_2) for 6 h. The reaction was monitored by TLC analysis. After completion of the reaction, the reaction mixture was filtered through a celite pad and then concentrated to near dryness. Purification by flash column chromatography (silica gel) using EtOAc-petroleum ether (40:60) as an eluent afforded (*S*)-mephenesin **3**. Yield: 0.880 g (88%); white crystals; m.p.: 90-91 ºC {Lit. [34] m.p.: 90-91 °C}; $[\alpha]_{25}^{D}$= -19.16 (*c* 0.910, hexane:2-propanol 4:1) {Lit. [30] $[\alpha]_{25}^{D}$ = -19.16 (*c* 0.910, hexane:2-propanol 4:1)} ee >98% [Chiral HPLC analysis: Chiralcel OD (250 × 4.6 mm) column; eluent: 2-propanol: petroleum ether 7.5:92.5; flow rate: 1 mL/min, detector: 220 nm t_R = 15.85 min, t_S = 15.18 min]; IR ($CHCl_3$, cm^{-1}): 3448, 3064, 3004, 2881, 2580, 1652, 1647, 1593, 742 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 1.63 (brs, 2H), 2.22 (s, 3H), 3.73-3.91 (m, 2H), 3.93-4.20 (m, 3H), 6.80-6.92 (m, 2H), 7.12-7.19 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 16.17, 63.79, 68.97, 70.54, 111.06, 120.93, 126.58, 126.87, 130.74, 156.37 ppm; LC-MS: *m/z* = 205.16 (M^+ + Na); Anal. calcd. (found) % for $C_{10}H_{14}O_3$: C, 65.92 (65.87); H, 7.74 (7.76).

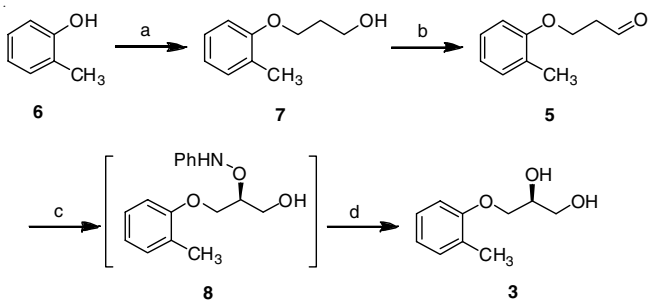
RESULTS AND DISCUSSION

The retrosynthetic analysis of (*S*)-mephenesin (**3**) shows that compound **3** can be easily obtained from aldehyde **5** through L-proline catalyzed α-aminoxylation reaction and aldehyde **5** can be easily obtained from 2-cresol (**6**) (**Scheme-I**).



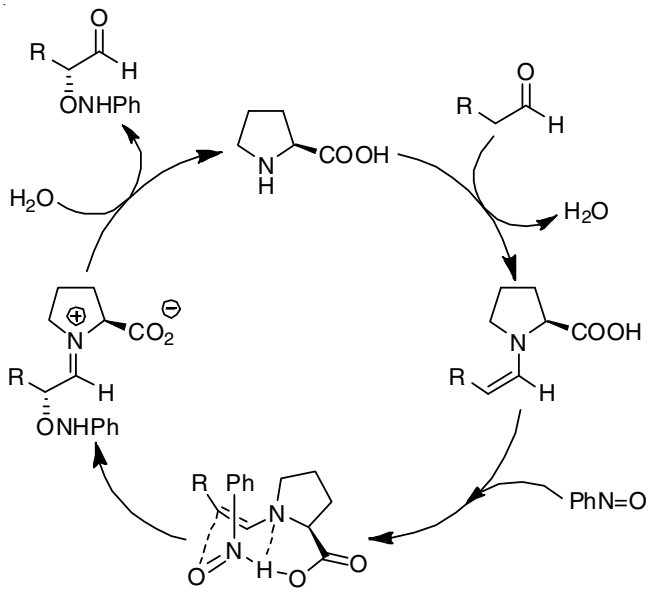
Scheme-I: Retrosynthetic analysis of (*S*)-mephenesin

As per retrosynthetic analysis, we started the synthesis of (*S*)-mephenesin (**3**) with commercially available 2-cresol **6** (**Scheme-II**). 2-Cresol (**6**) on refluxing with 3-bromopropanol in presence of aqueous NaOH solution undergoes Williamson reaction and afforded alcohol **7** in 71% yield. The oxidation of primary alcohol **7**, carried out by treating it with 2-iodoxybenzoic acid (IBX) in anhydrous DMSO at room temperature, gave aldehyde **5** in 90% yield.The triplet at 9.88 δ ppm in ^{1}H NMR spectra and peak at 200. 36 δ ppm in ^{13}C NMR spectra confirmed the presence of aldehyde group in compound **5**. For α-aminoxylation reaction, a solution of aldehyde **5** in acetonitrile treated with nitrosobenzene in presence of L-proline



Scheme-II: Reagents and conditions: (a) 3-bromopropanol, 10% aq NaOH, reflux, 6 h, 71%; (b) 2-iodoxybenzoic acid, $(CH_3)_2SO$, rt, 2 h, 90%; (c) Nitrosobenzene, L-proline, CH_3CN, -20 °C, 24 h then $NaBH_4$, MeOH, -20 °C, 0.5 h; (d) 10% Pd/C, MeOH, H_2, rt, 6 h, for two steps 88%

(20 mol%) at -20 ºC for 24 h and resultant solution then treated with $NaBH_4$ in methanol in same pot to afford crude aminoxy compound **8**. The crude aminoxy compound **8** without purification treated with H_2 gas (1 atm) in presence of 10% Pd/C in methanol resulted in breaking of O-N bond and afforded (*S*)-mephenesin (**3**). The ^{1}H NMR spectra of (*S*)-mephenesin (**3**) shows the methine proton at C-2 overlapped with two methylene protons of C-1 at 3.93-4.20 δ ppm. The ^{1}H NMR spectra and ^{13}C NMR spectra of (*S*)-mephenesin (**3**) were in good agreement with the structure. The optical purity of (*S*)-mephenesin (**3**) was determined by chiral HPLC using Chiralcel OD (250 × 4.6 mm) column and was found to be >98%. The catalytic cycle for α-aminoxylation reaction of aldehyde is shown in **Scheme-III**.



Scheme-III: Catalytic cycle of L-proline catalyzed α-aminoxylation of aldehyde

Conclusion

An efficient and enantioselective synthesis of centrally acting muscle relaxant (*S*)-mephenesin was achieved in 56% overall yield starting with commercially available 2-cresol. The L-proline catalyzed α-aminoxylation reaction of aldehyde was the chirality induction step and afforded >98% optical purity. High yields, high ee, availability of starting material and organo-

catalytic green asymmetric reaction are highlights of this approach.

ACKNOWLEDGEMENTS

One of the authors, SPP, thanks Department of Science and Technology for financial support to K.M.C. College, Khopoli, India under DST-FIST scheme.

REFERENCES

1. W.H. Brooks, W.C. Guida and K.G. Daniel, The Significance of Chirality in Drug Design and Development, *Curr. Top. Med. Chem.*, **11**, 760 (2011); https://doi.org/10.2174/156802611795165098
2. L.D. Barron, Chirality and Life, *Space Sci. Rev.*, **135**, 187 (2008); https://doi.org/10.1007/s11214-007-9254-7
3. F. Faigl, E. Fogassy, M. Nogradi, E. Palovics and J. Schindler, Strategies in Optical Resolution: A Practical Guide, *Tetrahedron Asymm.*, **19**, 519 (2008); https://doi.org/10.1016/j.tetasy.2008.02.004
4. A. Ghanem and H.Y. Aboul-Enein, Lipase-Mediated Chiral Resolution of Racemates in Organic Solvents, *Tetrahedron Asymm.*, **15**, 3331 (2004); https://doi.org/10.1016/j.tetasy.2004.09.019
5. D.J. Ager and M.L. East, Asymmetric Synthetic Methodology, CRC Press, Boca Raton, Ed.: 1st, pp. 1-512 (1995).
6. M. Christmann and S. Brase, Asymmetric Synthesis: The Essentials, Wiley: New York, Ed.: 2nd, pp. 1-395 (2007).
7. J.D. Morrison, Asymmetric Synthesis, Academic Press: New York, vol. 1-5, pp. 1-392 (2012).
8. V. Andrushk and N. Andrushko, Stereoselective Synthesis of Drugs and Natural Products, Wiley: New York, Ed.: 1st, pp. 1-1836 (2013).
9. W.S. Knowles, Asymmetric Hydrogenations (Nobel Lecture), *Angew. Chem. Int. Ed.*, **41**, 1998 (2002); https://doi.org/10.1002/1521-3773(20020617)41:12<1998::AID-ANIE1998>3.0.CO;2-8
10. R. Noyori, Asymmetric Catalysis: Science and Opportunities (Nobel Lecture), *Angew. Chem. Int. Ed.*, **41**, 2008 (2002); https://doi.org/10.1002/1521-3773(20020617)41:12<2008::AID-ANIE2008>3.0.CO;2-4
11. K.B. Sharpless, Searching for New Reactivity (Nobel Lecture), *Angew. Chem. Int. Ed.*, **41**, 2024 (2002); https://doi.org/10.1002/1521-3773(20020617)41:12<2024::AID-ANIE2024>3.0.CO;2-O
12. F.D. Toste and S.-L. You, Asymmetric Synthesis Enabled by Organometallic Complexes, *Organometallics*, **38**, 3899 (2019); https://doi.org/10.1021/acs.organomet.9b00627
13. P.I. Dalko and L. Moisan, Enantioselective Organocatalysis, *Angew. Chem. Int. Ed.*, **40**, 3726 (2001); https://doi.org/10.1002/1521-3773(20011015)40:20<3726::AID-ANIE3726>3.0.CO;2-D
14. P.I. Dalko and L. Moisan, In the Golden Age of Organocatalysis, *Angew. Chem. Int. Ed.*, **43**, 5138 (2004); https://doi.org/10.1002/anie.200400650
15. K.N. Houk and B. List, Asymmetric Organocatalysis, *Acc. Chem. Res.*, **37**, 487 (2004); https://doi.org/10.1021/ar040216w
16. B. List, Organocatalysis: A Complementary Catalysis Strategy Advances Organic Synthesis, *Adv. Synth. Catal.*, **346**, 1021 (2004); https://doi.org/10.1002/adsc.200404163
17. C. Bolm, Catalysis with Organic Molecules: A Success Story in Modern Catalytic Chemistry, *Adv. Synth. Catal.*, **346**, 1022 (2004); https://doi.org/10.1002/adsc.200404222
18. J. Seayad and B. List, Asymmetric Organocatalysis, *Org. Biomol. Chem.*, **3**, 719 (2005); https://doi.org/10.1039/b415217b
19. Y. Zhang and W. Wang, Recent Advances in Organocatalytic Asymmetric Michael Reactions, *Catal. Sci. Technol.*, **2**, 42 (2012); https://doi.org/10.1039/C1CY00334H
20. B. List, R.A. Lerner and C.F. Barbas, Proline-Catalysed Direct Asymmetric Aldol Reactions, *J. Am. Chem. Soc.*, **122**, 2395 (2000); https://doi.org/10.1021/ja994280y
21. Y. Alvarez-Casao, E. Marques-Lopez and R.P. Herrera, Organocatalytic Enantioselective Henry Reactions, *Symmetry*, **3**, 220 (2011); https://doi.org/10.3390/sym3020220
22. R.I. Storer, D.E. Carrera, Y. Ni and D.W.C. MacMillan, Enantioselective Organocatalytic Reductive Amination, *J. Am. Chem. Soc.*, **128**, 84 (2006); https://doi.org/10.1021/ja057222n
23. T. Vilaivan and W. Bhanthumnavin, Organocatalyzed Asymmetric α-Oxidation, α-Aminoxylation and α-Amination of Carbonyl Compounds, *Molecules*, **15**, 917 (2010); https://doi.org/10.3390/molecules15020917
24. Y. Hayashi, J. Yamaguchi, K. Hibino and M. Shoji, Direct Proline Catalyzed Asymmetric α-Aminoxylation of Aldehydes, *Tetrahedron Lett.*, **44**, 8293 (2003); https://doi.org/10.1016/j.tetlet.2003.09.057
25. S.P. Brown, M.P. Brochu, C.J. Sinz and D.W.C. MacMillan, The Direct and Enantioselective Organocatalytic α-Oxidation of Aldehydes, *J. Am. Chem. Soc.*, **125**, 10808 (2003); https://doi.org/10.1021/ja037096s
26. G. Zhong, A Facile and Rapid Route to Highly Enantiopure 1,2-Diols by Novel Catalytic Asymmetric α-Aminoxylation of Aldehydes, *Angew. Chem. Int. Ed.*, **42**, 4247 (2003); https://doi.org/10.1002/anie.200352097
27. I.A. Sayyed, V.V. Thakur, M.D. Nikalje, G.K. Dewkar, S.P. Kotkar and A. Sudalai, Asymmetric Synthesis of Aryloxypropanolamines *via* OsO_4-Catalyzed Asymmetric Dihydroxylation, *Tetrahedron*, **61**, 2831 (2005); https://doi.org/10.1016/j.tet.2005.01.074
28. M. Muthukrishnan, D.R. Garud, R.R. Joshi and R.A. Joshi, Concise Synthesis of β-Blockers (*S*)-Metoprolol and (*S*)-Betaxolol using Hydrolytic Kinetic Resolution, *Tetrahedron*, **63**, 1872 (2007); https://doi.org/10.1016/j.tet.2006.12.016
29. R.B. Kawthekar and G.-J. Kim, Enantioselective Synthesis of β-Blockers *via* Hydrolytic Kinetic Resolution of Terminal Oxiranes by using Bimetallic Chiral {{2,2′-[cyclohexane-1,2-diyl*bis*(nitrilomethylidyne)]*bis*[phenolato]}(2-)}cobalt ([Co(salen)])-Type Complexes, *Helv. Chim. Acta*, **91**, 317 (2008); https://doi.org/10.1002/hlca.200890037
30. F. Theil, S. Ballschuh, A. Kunath and H. Schick, Kinetic Resolution of *rac*-3-(2-Methylphenoxy)propane-1,2-diol (Mephenesin) by Sequential Lipase-Catalyzed Transesterification, *Tetrahedron Asymm.*, **2**, 1031 (1991); https://doi.org/10.1016/S0957-4166(00)86153-4
31. F. Theil, K. Lemke, S. Ballschuh, A. Kunath and H. Schick, Lipase-Catalysed Resolution of 3-Aryloxy-1,2-propanediol Derivatives-towards an Improved Active Site Model of *Pseudomonas cepacia* Lipase (Amano PS), *Tetrahedron Asymm.*, **6**, 1323 (1995); https://doi.org/10.1016/0957-4166(95)00166-M
32. S.P. Panchgalle, R.G. Gore, S.P. Chavan and U.R. Kalkote, Organocatalytic Enantioselective Synthesis of β-Blockers: (*S*)-Propranolol and (*S*)-Naftopidil, *Tetrahedron Asymm.*, **20**, 1767 (2009); https://doi.org/10.1016/j.tetasy.2009.07.002
33. S.P. Panchgalle, S.S. Kunte, S.P. Chavan and U.R. Kalkote, Exploration of L-Proline-Catalyzed α-Aminoxylation of Aldehyde to (*S*)-Guaifenesin-Related Drug Molecules, *Synth. Commun.*, **41**, 1938 (2011); https://doi.org/10.1080/00397911.2010.493631
34. A.A. Bredikhin, Z.A. Bredikhina, V.G. Novikova, A.V. Pashagin, D.V. Zakharychev and A.T. Gubaidullin, Three Different Types of Chirality-Driven Crystallization within the Series of Uniformly Substituted Phenyl Glycerol Ethers, *Chirality*, **20**, 1092 (2008); https://doi.org/10.1002/chir.20648