Tetrahedron: *Asymmetry* 21 (2010) 578–581

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Synthesis of (*S*)-(+)-sotalol and (*R*)-(−)-isoproterenol via a catalytic enantioselective Henry reaction

Gonzalo Blay *, Víctor Hernández-Olmos, José R. Pedro *

Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner 50, E-46100-Burjassot, Spain

ARTICLE INFO

Article history:
Received 9 February 2010
Accepted 23 February 2010
Available online 13 April 2010

ABSTRACT

A unified approach for the synthesis of (*S*)-(+)-sotalol and (*R*)-(−)-isoproterenol has been developed. The enantioselective Henry reaction of the appropriate aldehyde in the presence of a camphor-derived amino pyridine–Cu(II) complex was the key step of the synthesis. The reduction of the nitro group to give the corresponding amino alcohols followed by reductive alkylation of the amine provided the target products with high enantiomeric excesses.

1. Introduction

Optically active arylethanolamines are important intermediates for the asymmetric synthesis of bioactive compounds such as adrenergic agents, antihelmintics, antidepressants, class II β-blockers, and class-III antiarrythmic agents.[1] Sotalol **1** is a class-III antiarrythmic drug[2] used for the effective control of reentrant ventricular arrhythmia, a major factor in most cases of sudden cardiac death in developed countries. The two enantiomeric forms of sotalol are equiactive on the cardiac action potential duration. The (*R*)-(−)-enantiomer has both β-blocking (class II) activity and potassium-channel-blocking (class-III) properties. The (*S*)-(+)-enantiomer has class-III properties similar to those of *l*-sotalol. However, the affinity of *d*-sotalol for β-adrenergic receptors is 30–60 times lower than the affinity of (*R*)-(−)-sotalol.[3] In recent years, (*S*)-(+)-sotalol has been obtained by chiral chromatographic separation[4] or resolution[5] of the racemic compound. Furthermore, it has been prepared via an asymmetric homogeneous hydrogenation of 4′-[(isopropylamino)acetyl]methanesulfonanilide,[6] enantioselective reduction of the carbonyl group in its precursor 4′-(chloroacetyl)methanesulfonanilide,[7] and resolution of bromohydrin precursors.[8]

On the other hand, isoproterenol (isoprenaline) is a potent β-adrenoreceptor of research and clinical interest. Its primary use is for bradicardia or heart block. It is also a highly effective bronchodilator and therefore used in the treatment of asthma and chronic obstructive pulmonary diseases.[9] The (*R*)-(−)-enantiomer of isoproterenol is approximately 90 times more potent than the (*S*)-(+)-enantiomer.[10] Enantiomerically pure isoproterenol is obtained by resolution with tartaric acid[11] and capillary zone electrophoresis using cyclodextrines as chiral selectors.[12] On the other hand, since the first enantioselective synthesis of isoproterenol reported by Corey using the asymmetric CBS (Corey, Bakshi, Shibata) reduction of 2-chloro-3′4′-dimethoxyacetophenone,[13] only one other enantioselective synthesis of isoproterenol via Sharpless asymmetric dihydroxylation of 3,4-dimethoxystyrene has to the best of our knowledge been reported.[14]

Due to the differences in activity shown by the two enantiomeric forms of these and other drugs, the development of new synthetic procedures that provide these compounds in enantiopure or highly enantioenriched form is desirable (Fig. 1).

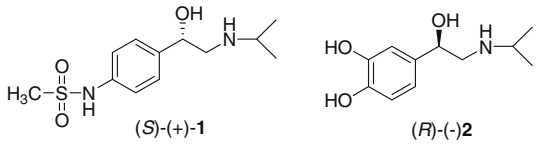


Figure 1. Structures of (*S*)-(+)-sotalol and (*R*)-(−)-isoproterenol.

Herein we report a synthetic approach to both (*S*)-(+)-sotalol and (*R*)-(−)-isoproterenol from appropriate and readily available aldehydes according to retro-synthetic Scheme 1. The synthetic sequence involves the addition of nitromethane to an aldehyde to give a nitroalkanol, which is subsequently reduced to an amino alcohol, followed by alkylation of the amine.

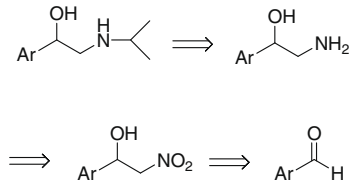
The key step in our synthetic strategy is the catalytic enantioselective Henry reaction between nitromethane and the aldehyde. As part of our research we have developed a highly enantioselective catalytic Henry reaction using copper complexes with aminopyridine ligands **3**, which provide the expected nitro alcohols with high enantiomeric excesses, up to 98% ee in some cases (Scheme 2).[15]

2. Results and discussion

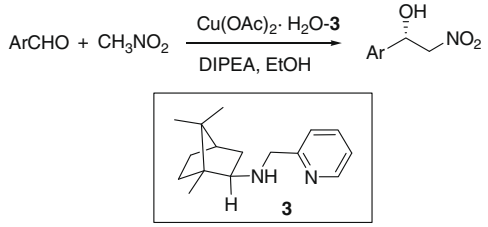
The synthesis of (*S*)-(+)-sotalol (Scheme 3) started from *N*-(4-formylphenyl)methanesulfonamide **4**, which can be prepared by

* Corresponding authors. Tel.: +34 963544329; fax: +34 963544328 (J.R.P.).
E-mail addresses: gonzalo.blay@uv.es (G. Blay), jose.r.pedro@uv.es (J.R. Pedro).

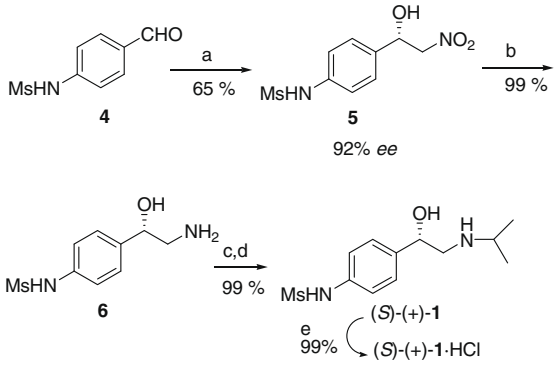
0957-4166/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2010.02.027



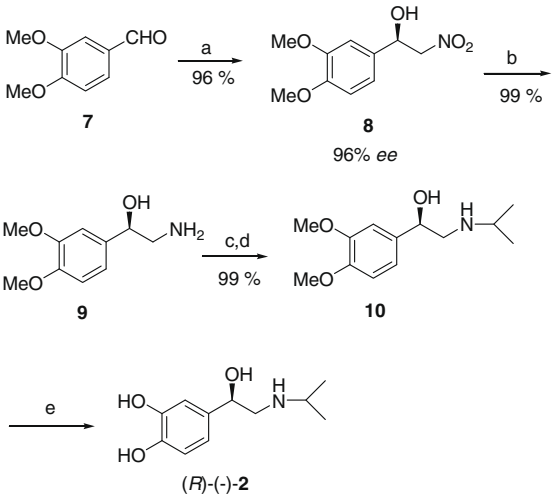
Scheme 1. Retro-synthetic approach to *N*-isopropyl-arylethanolamines.



Scheme 2. Enantioselective Henry reaction catalyzed by amino pyridine **3**–Cu(II) complexes.



Scheme 3. Enantioselective synthesis of (*S*)-(+)-sotalol. Reagents and conditions: (a) **3**, $Cu(OAc)_2{\cdot}H_2O$, DIPEA, EtOH, CH_3NO_2, −30 °C; (b) H_2, Pd/C, MeOH/EtOH; (c) EtOH, acetone; (d) $NaBH_4$; (e) HCl 5%.



Scheme 4. Enantioselective synthesis of (*R*)-(−)-isoproterenol. Reagents and conditions: (a) *ent*-**3**, $Cu(OAc)_2{\cdot}H_2O$, DIPEA, EtOH, CH_3NO_2, −50 °C; (b) H_2, Pd/C, EtOH; (c) EtOH, acetone; (d) $NaBH_4$; (e) Ref. 14.

the treatment of *p*-aminobenzaldehyde with mesyl chloride in pyridine. Treatment of aldehyde **4** with nitromethane and diisopropylethylamine (DIPEA) in the presence of 10 mol % of the $Cu(OTf)_2$-**3** complex in EtOH at −30 °C provided nitro alcohol **5** in 65% yield and 92% ee. Unreacted aldehyde **4** (25%) was also recovered from the reaction mixture. Compound **5** was hydrogenated[16] on 10% Pd/C in MeOH/EtOH (1:2) to give amino alcohol **6** in almost quantitative yield. Finally, reductive alkylation[17] of the amine with acetone–$NaBH_4$ gave 92% ee (*S*)-(+)-sotalol quantitatively, which was further transformed into its hydrochloride upon treatment with HCl.

A similar strategy was used for the synthesis of (*R*)-(−)-isoproterenol (Scheme 4). In this case, commercially available 3,4-dimethoxybenzaldehyde **7** was used as starting material. The Henry reaction of this aldehyde with nitromethane was carried out with the opposite enantiomer of the amino pyridine ligand *ent*-**3** in order to obtain the nitro alcohol with the required (*R*)-configuration at the stereogenic center. By following our catalytic enantioselective procedure compound **8** was obtained in 96% yield and 96% ee. Hydrogenation of the nitro group under similar conditions to those described for the synthesis of sotalol gave compound **9** in a quantitative yield. Finally, reductive alkylation of the amine with acetone–$NaBH_4$ provided compound **10**, which showed a specific rotation $[\alpha]_D^{25} = -32.7$ (*c* 3.00, acetone). The synthesis of compound **10** has been previously reported by Taylor and Baird starting from (+)-(3,4-dimethoxyphenyl)oxirane.[18] However, these authors reported $[\alpha]_D^{25} = +9.3$ (*c* 2.9, acetone) for the compound prepared in that way. To remove any possible doubt about the stereochemical identity of our material and its specific rotation, we decided to prepare compound **10** by an alternative route. Thus, commercially available (*R*)-(−)-isoproterenol hydrochloride was subjected to selective alkylation[19] by treatment with potassium carbonate (3 equiv) and MeI (2.5 equiv) in DMF to give a product that showed the same spectroscopic data and identical specific rotation value and sign as compound **10** prepared according to Scheme 4. Deprotection of the phenolic ethers in compound **10** with ethanethiol/$AlCl_3$ to give (*R*)-(−)-isoproterenol has been reported by Kumar et al.[14]

3. Experimental part

3.1. General

Commercial reagents were used as purchased. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck Silica Gel 60, 0.040–0.063 mm. Specific optical rotations were recorded on a Perkin–Elmer 241 polarimeter using sodium light (D line 589 nm). NMR spectra were recorded on Bruker Avance spectrometers in deuterated solvents as stated, using residual non-deuterated solvent as an internal standard. The carbon type was determined by DEPT experiments. Mass spectra were recorded on a Fisons Instruments VG Autospec GC 8000 series. Mass spectra (EI) were run at 70 eV. Chiral HPLC analyses were performed in a Hitachi Elite Lachrom instrument equipped with a Hitachi UV diode-array L-4500 detector using chiral stationary columns from Daicel. Ligands **3** and *ent*-**3** were prepared according to our reported procedure.[15d]

3.2. (*S*)-(+)-*N*-[4-(1-Hydroxy-2-nitroethyl)phenyl] methanesulfonamide 5

Ligand **3** (13 mg, 0.05 mmol) dissolved in absolute EtOH (4 mL) was added to $Cu(OAc)_2{\cdot}H_2O$ (10 mg, 0.05 mmol) and the mixture was stirred for 1 h to give a deep blue solution. *N*-(4-Formylphenyl)methanesulfonamide[20] **4** (99 mg, 0.5 mmol) was added and the flask was placed into a bath at −30 °C. After 5 min, nitromethane (0.27 mL, 5 mmol) was added followed by DIPEA (87 μL,

0.5 mmol). The reaction mixture was stirred at −30 °C for 4 days. Then the solvent was removed under reduced pressure and the product was isolated by column chromatography eluting with hexane/EtOAc mixtures (7:3–5:5) to give 25 mg of recovered starting material and 85 mg (65% yield, 87% yield respect to consumed starting material) of compound **5**: $[\alpha]_D^{25} = +19.5$ (*c* 0.54, MeOH, 92% ee); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.78 (br s, 1H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.05 (d, *J* = 4.8 Hz, 1H), 5.25–5.19 (m, 1H), 4.81 (dd, *J* = 12.3, 3.0 Hz, 1H), 4.54 (dd, *J* = 12.3, 9.9 Hz, 1H), 2.98 (s, 3H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 138.0 (C), 135.7 (C), 127.2 (2 × CH), 119.5 (2 × CH), 81.8 (CH_2), 69.5 (CH), 39.2 (CH_3); MS(EI) *m*/*z* (%) 242 (M^+-H_2O, 0.6), 199 (100), 120 (33), 92 (41); HRMS: 242.0370 (M^+-H_2O), $C_9H_{10}N_2O_4S$ requires 242.0361; ee (92%) was determined by HPLC (Chiralcel AD–H), hexane–*i*-PrOH 80:20, 1 mL/min, major enantiomer (*S*) t_r = 14.7 min, minor enantiomer (*R*) t_r = 16.7 min.

3.3. (*S*)-(+)-*N*-[4-(2-Amino-1-hydroxyethyl)phenyl] methanesulfonamide 6

To a solution of compound **5** (99 mg, 0.38 mmol) in MeOH (1.5 mL) and EtOH (3 mL) was added 10% Pd/C (35 mg). The mixture was stirred under a hydrogen atmosphere (balloon) for 16 h. After this time, the catalyst was removed upon filtration through a short pad of Celite. The pad was washed with MeOH. Concentration of the filtrates under reduced pressure gave 88 mg (>99% yield) of compound **6**: $[\alpha]_D^{25} = +23.6$ (*c* 1.03, MeOH, 92% ee); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.26 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 4.39 (dd, *J* = 7.8, 4.5 Hz, 1H), 2.93 (s, 3H), 2.64 (dd, *J* = 12.9, 4.5 Hz, 1H), 2.55 (dd, *J* = 12.9, 7.8 Hz, 1H); ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.26 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 2.71 (unresolved m, 2H); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 140.2 (C), 139.5 (C), 128.2 (2 × CH), 121.8 (2 × CH), 75.1 (CH), 49.9 (CH_2), 39.2 (CH_3); MS(EI) *m*/*z* (%): 230 (M^+, 0.1), 212 (27), 200 (17), 133 (100), 122 (16); HRMS: 230.0724 (M^+), $C_9H_{12}N_2O_3S$ requires 230.0725.

3.4. (*S*)-(+)-Sotalol 1

A solution of **6** (80 mg, 0.35 mmol) and acetone (64 μL, 0.58 mmol) in EtOH (0.8 mL) was stirred at rt for 1 h. Then, the reaction mixture was cooled to 0 °C (ice bath) and $NaBH_4$ (20 mg, 0.52 mmol) was added. After stirring for 1 h, the reaction mixture was filtered through silica gel eluting with MeOH to give 94 mg (>99% yield) of (*S*)-(+)-sotalol: $[\alpha]_D^{25} = +19.3$ (*c* 0.27, MeOH, 92% ee); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.21 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 5.16 (br s, 1H), 4.49 (dd, *J* = 8.1, 4.2 Hz, 1H), 3.36 (br s, 1H), 2.85 (s, 3H), 2.71 (m, *J* = 6.3 Hz, 1H), 2.61 (dd, *J* = 11.7, 4.2 Hz, 1H), 2.54 (dd, *J* = 11.7, 8.1 Hz, 1H), 0.95 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75.5 MHz, MeOD) δ 141.3 (C), 139.5 (C), 128.0 (2 × CH), 121.9 (2 × CH), 73.0 (CH), 55.6 (CH_2), 49.7 (CH), 39.1 (CH_3), 22.6 (CH_3), 22.4 (CH_3); MS(EI) *m*/*z* (%) 272 (M^+, 2.2), 254 (42), 185 (42), 175 (87), 106 (100), 72 (81); HRMS: 272.1198 (M^+), $C_{12}H_{20}N_2O_3S$ requires 272.1195; ee (92%) was determined by HPLC (Chiralpak AD–H), hexane–*i*-PrOH 85:15, 1 mL/min, major enantiomer (*S*) t_r = 16.2 min, minor enantiomer (*R*) t_r = 20.4 min.

This compound was treated with 5% aqueous HCl (1 equiv) to give (*S*)-(+)-sotalol hydrochloride quantitatively: $[\alpha]_D^{25} = +28.7$ (*c* 1.05, H_2O, 92% ee), lit.[8] $[\alpha]_D^{25} = +34.4$ (*c* 1.00, H_2O).

3.5. (*R*)-(−)-1-(3,4-Dimethoxyphenyl)-2-nitroethanol 8

Ligand *ent*-**3** (27 mg, 0.11 mmol) dissolved in absolute EtOH (8 mL) was added to $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.10 mmol) and the mixture was stirred for 1 h to give a deep blue solution. 3,4-Dimethoxybenzaldehyde **7** (336 mg, 2.0 mmol) was added and the flask was introduced in a bath at −50 °C. After 5 min, nitromethane (1.1 mL, 20 mmol) was added followed by DIPEA (348 μL, 2.0 mmol). After 27 h, the solvent was removed under reduced pressure and the reaction product was isolated by column chromatography eluting with hexane/EtOAc (9:1–6:4) to give 453 mg (99%) of compound **8**: $[\alpha]_D^{25} = -27.1$ (*c* 2.01, CH_2Cl_2, 96% ee), lit.[21] $[\alpha]_D^{25} = +26.8$ (*c* 2.02, CH_2Cl_2, 78% ee, (*S*)-enantiomer); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91–6.89 (m, 2H), 6.85–6.83 (m, 1H), 5.38 (dt, *J* = 9.3, 2.7 Hz, 1H), 4.59 (dd, *J* = 12.9, 9.3 Hz, 1H), 4.47 (dd, *J* = 12.9, 3.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H) 2.99 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.3 (C), 130.7 (C), 118.3 (CH), 111.3 (CH), 108.8 (CH), 81.3 (CH_2), 78.8 (CH), 55.9 (2 × CH_3); ee (96%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 80:20, 1 mL/min, major enantiomer (*R*) t_r = 15.9 min, minor enantiomer (*S*) t_r = 20.8 min.

3.6. (*R*)-(−)-2-Amino-1-(3,4-dimethoxyphenyl)ethanol 9

To a solution of compound **8** (399 mg, 1.76 mmol) in EtOH (20 mL) was added 10% Pd/C (135 mg). The mixture was stirred under a hydrogen atmosphere (balloon) for 22 h. The mixture was filtered through a short pad of Celite to remove the catalyst. Removal of the solvent under reduced pressure afforded 345 mg (99%) of compound **9**. $[\alpha]_D^{25} = -24.0$ (*c* 1.08, EtOH, 96% ee), lit.[22] $[\alpha]_D^{25} = -29.7$ (*c* 0.72, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.91–6.89 (m, 2H), 6.81 (dd, *J* = 8.1, 1.8 Hz, 1H), 5.13 (br s, 1H), 4.36 (dd, *J* = 7.2, 4.5 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 2.63 (dd, *J* = 12.9, 4.5 Hz, 1H), 2.55 (dd, *J* = 12.9, 7.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.0 (C), 148.4 (C), 135.1 (C), 118.0 (CH), 111.0 (CH), 109.0 (CH), 74.0 (CH), 55.9 (CH_3), 55.8 (CH_3), 49.2 (CH_2).

3.7. (*R*)-(−)-1-(3,4-Dimethoxyphenyl)-2-(isopropylamino)ethanol 10

A solution of **9** (316 mg, 1.60 mmol) and acetone (293 μL, 2.7 mmol) in EtOH (2 mL) was stirred at rt for 1 h. Then, the reaction mixture was cooled to 0 °C (ice bath) and $NaBH_4$ (91 mg, 2.4 mmol) was added. After stirring for 1 h, the reaction mixture was chromatographed on silica gel (AcOEt/MeOH) to give 361 mg (94%) of compound **10**. $[\alpha]_D^{25} = -32.7$ (*c* 3.00, acetone, 96% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, *J* = 1.5 Hz, 1H), 6.87 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 4.59 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.44 (br s, 1H), 2.87 (dd, *J* = 12.0, 3.9 Hz, 1H), 2.80 (m, *J* = 6.3 Hz, 1H), 2.63 (dd, *J* = 12.0, 9.0 Hz, 1H), 1.06 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.0 (C), 148.3 (C), 135.5 (C), 117.9 (CH), 111.0 (CH), 108.9 (CH), 71.8 (CH), 55.9 (CH_3), 55.8 (CH_3), 54.6 (CH_2), 48.5 (CH), 23.1 (CH_3), 23.0 (CH_3); ee (96%) was determined by HPLC (Chiralpak AY-H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*R*) t_r = 13.6 min, minor enantiomer (*S*) t_r = 18.9 min.

Acknowledgments

Financial support from the Ministerio de Educación y Ciencia and FEDER (CTQ 2006-14199) and from Generalitat Valenciana (ACOMP/2009/338) is gratefully acknowledged. V.H.-O. thanks the Universitat de València for a pre-doctoral grant (V segles program).

References and notes

1. *Pharmaceutical Chemistry of Antihypertension Agents*; Szasz, G., Budvari-Barany, Z., Eds.; CRC Press: Boston, 1991.
2. (a) Taggart, P.; Sutton, P.; Donaldson, R. *Clin. Sci.* **1985**, *69*, 631–636; (b) Foster, R. T.; Carr, R. A. *Anal. Profiles Drug Subst. Excip.* **1992**, *21*, 501–533; (c) Midha, K.

K.; Hirsh, M.; Lo, W.-Y. Int. Patent WO 2002013794 A1 20020221, 2002.; (d) Sankaranarayanan, A. U.S. Patent US2001004643 A1 20010621, 2001.
3. (a) Funck-Brentano, C. *Eur. Heart J.* **1993**, *14*, 30–35; (b) Touboul, P. *Eur. Heart J.* **1993**, *14*, 24–29; (c) Connors, S. P.; Dennis, P. D.; Gill, E. W.; Terrar, D. A. *J. Med. Chem.* **1991**, *34*, 1570–1577; (d) Doggrell, S. A. *Chirality* **1993**, *5*, 8–14; (e) Beyer, T.; Brachmnn, J.; Kuebler, W. *J. Cardiovasc. Pharm.* **1993**, *22*, 240–246.
4. (a) Delee, E.; Le Garrec, L.; Jullien, I.; Beranger, S.; Pascal, J. C.; Pinhas, H. *Chromatographia* **1987**, *24*, 357–359; (b) Le Garrec, L.; Delee, E.; Pascal, J. C.; Jullien, I. *J. Liq. Chromatogr.* **1987**, *10*, 3015–3023; (c) Okamoto, Y.; Aburatani, R.; Hatano, K.; Hatada, K. *J. Liq. Chromatogr.* **1988**, *11*, 2147–2163; (d) Mehvar, R. *J. Chromatogr.* **1989**, *493*, 402–408; (e) Gasparrini, F.; Misiti, D.; Villani, C. *J. Chromatogr.* **1991**, *539*, 25–36; (f) Gubitz, G.; Pierer, B.; Wendelin, W. *Chirality* **1992**, *4*, 333–337; (g) Lobell, M.; Schneider, M. P. *J. Chromatogr.* **1993**, *633*, 287–294.
5. Simon, A.; Thomis, J. A. U.S. 5089526 A 19920218, 1992.
6. Smith, P.; Brodfuehrer, P. R.; Dillon, J. L.; Vemishetti, P. *Synth. Commun.* **1995**, *25*, 1093–1098.
7. (a) Brodfuehrer, P. R.; Smith, P.; Dillon, J. L.; Vemishetti, P. *Org. Process Res. Dev.* **1997**, *1*, 176–178; (b) Kamal, A.; Sandbhor; Shaik, A. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4581–4583.
8. Kapoor, M.; Anand, N.; Ahmad, K.; Koul, S.; Chimni, S. S.; Taneja, S. C.; Qazi, G. N. *Tetrahedron: Asymmetry* **2005**, *16*, 717–725.
9. (a) Brittain, R. T.; Jack, D.; Ritchie, A. C.. In *Advances in Drug Research*; Harper, N. J., Simmonds, A. B., Eds.; Academic Press: New York, 1970; Vol. 5, pp 197–253; (b) Brooks, Wesley W.; Conrad, C. H. *Comp. Med.* **2009**, *59*, 339–343; (c) Vilskersts, R.; Liepinsh, E.; Kuka, J.; Cirule, H.; Veveris, M.; Kalvinsh, I.; Dambrova, M. *Cardiovasc. Drug Ther.* **2009**, *23*, 281–288; (d) Hu, Y.; Guo, D.-H.; Liu, P.; Rahman, K.; Wang, D.-X.; Wang, B. *Pharmazie* **2009**, *64*, 53–57; (e) Elesber, A.; Nishimura, R. A.; Rihal, C. S.; Ommen, S. R.; Schaff, H. V.; Holmes, D. R. *Am. J. Cardiol.* **2008**, *101*, 516–520; (f) Konishi, Y.; Magoon, J.; Mullick, A. Int. Patent WO 2007109882 A1 20071004, 2007.; (g) Cosnier, A. Fr. Patent FR 2625677 A1 19880107, 1988.; (h) Kraft, E. R.; Hoskins, S. L.; Enkhbaatar, P.; Traber, D. L. Int. Patent WO 2009088553 A1 20090716, 2009.; (i) Konishi, Y.; Magoon, J.; Jarussophon, S. Int. Patent WO 2008092257 A1 20080807, 2008.
10. (a) Kerschbaum, E.; Benedikt, K. *Monatsch* **1952**, 1090; (b) Beccari, E.; Beretta, A.; Lawendel, J. S. *Science* **1953**, *118*, 249–250.
11. (a) Delmar, G. S.; Macallum, E. N. U.S. Patent US 2715141, 1955.; (b) Ikeda, T.; Kuninaka, A.; Hiroshi, Y. JP Patent JP 50093933 19750726, 1975.
12. Lin, X.; Zhu, C. *Huaxue Yanjiu Yu Yingyong* **2000**, *12*, 645–647.
13. Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1990**, *31*, 601–604.
14. Kumar, P.; Upadhyay, R. K.; Pandey, R. K. *Tetrahedron: Asymmetry* **2004**, *15*, 3955–3959.
15. (a) Blay, G.; Climent, E.; Fernández, I.; Hernández-Olmos, V.; Pedro, J. R. *Tetrahedron: Asymmetry* **2006**, *17*, 2046; (b) Blay, G.; Climent, E.; Fernández, I.; Hernández-Olmos, V.; Pedro, J. R. *Tetrahedron: Asymmetry* **2007**, *18*, 1603; (c) Blay, G.; Domingo, L. R.; Hernández-Olmos, V.; Pedro, J. R. *Org. Biomol. Chem.* **2008**, *6*, 468; (d) Blay, G.; Climent, E.; Fernández, I.; Hernández-Olmos, V.; Pedro, J. R. *Chem. Eur. J.* **2008**, *14*, 4725; (e) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. *Chem. Commun.* **2008**, 4840–4842.
16. Takaoka, E.; Yoshikawa, N.; Yamada, Y. M. A.; Sasai, H.; Shibasaki, M. *Heterocycles* **1997**, *46*, 157–163.
17. Hirose, K.; Fujiwara, A.; Matsunaga, K.; Aoki, N.; Tobe, Y. *Tetrahedron: Asymmetry* **2003**, *14*, 555–566.
18. Baird, C. P.; Taylor, P. C. *J. Chem. Soc., Perkin. 1* **1998**, 3399–3403.
19. Johnson, S. M.; Connelly, S.; Wilson, I. A.; Kelly, J. W. *J. Med. Chem.* **2008**, *51*, 260–270.
20. Prepared according to literature procedures: (a) Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839–842; (b) Weber, V.; Rubat, C.; Duroux, E.; Lartigue, C.; Madeslcaire, M.; Coudert, P. *Bioorg. Med. Chem.* **2005**, *13*, 4552–4564.
21. Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861–863.
22. Pratesi, P. *J. Chem. Soc.* **1959**, 4062–4065.