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Cascade enantioselective synthesis of γ-aryl-γ-butyrolactones with a delayed stereoselective step

Anil V. Karnik*, Suchitra S. Kamath

Department of Chemistry, University of Mumbai, Vidyanagari, Santacruz (E), Mumbai 400098, India

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Abstract

Enantioselective synthesis of γ-aryl-γ-butyrolactones is achieved using (*S*)-1-phenylethylamine as a chiral auxiliary. The synthesis involves cascade formation–destruction–formation of the chiral centre with a delayed stereoselective step. The actual stereoselective step has been found to be intramolecular nucleophilic attack on a diastereotopic carbocation formed, thereby resulting in the formation of non-racemic γ-aryl-γ-butyrolactones.

Keywords: Enantioselective synthesis; γ-Aryl-γ-butyrolactones; Chiral auxiliary; Diastereotopic carbocation

1. Introduction

γ-Butyrolactone frameworks are present in a large number of natural products and biologically active compounds, such as aroma[1,2] and flavour[2–4] components used in the perfume and food industry, sex attractant pheromones of different insects[5,6] and as plant-growth regulators.[7] The chiral γ-substituted-γ-butyrolactones are found as lichen, moss and fungus components,[8] polyketide metabolites, which are known to be hydrolysis products of (+)-antimycin A_3 (an antibiotic reagent effective against fungi and yeast),[9,10] phospholipase A_2 inhibitors,[11] muricatacins[12] with potent cytotoxicity against several human tumour cell lines and *Stemona* and *Croomia* alkaloids.[13–15] Since most of the naturally occurring chiral γ-substituted-γ-butyrolactones are found only as one enantiomer and biological activity is strongly dependent on their configuration, efficient and stereoselective synthetic routes to these active compounds in enantiomerically pure form are therefore highly desirable.

One of the approaches for the preparation of non-racemic γ-substituted-γ-butyrolactones involves enantioselective reduction of 3-aroylpropanoic acids and their derivatives achieved by chiral reagent, chiral catalyst or chiral auxiliary followed by lactonization. Noyori et al. reported BINAP–Ru(II) catalyzed enantioselective hydrogenation of prochiral 4-oxo carboxylic esters followed by acid catalyzed cyclization of the resulting hydroxy esters giving optically active γ-substituted-γ-butyrolactones.[16] Reduction of γ-keto acids with diisopinocampheylborane to the corresponding hydroxy acids with predictable stereochemistry in very high enantiomeric excess followed by cyclization to the corresponding γ-lactones was achieved by Ramachandran et al.[17] Moderate to good diastereoselectivity was achieved in the reduction of 1,4-keto esters controlled by anhydrosugar auxiliaries derived from D-glucose.[18] Chelation of the zinc cation appeared to be important for good selectivities and the reduction with sodium borohydride alone was unselective. Diastereoselective reduction of γ-keto esters was achieved using 2′-[2-(2-methoxyethoxy)ethoxy]-1,1′-binaphthalen-2-ol as a chiral auxiliary in the presence of Lewis acid.[19] Chelation of the oxygen atoms of the oxyethylene chain and the carbonyl groups to the Lewis acid ($MgBr_2$–Et_2O) plays an important role in the asymmetric induction. Enzymatic reduction of γ-keto acids followed by acid catalyzed lactonization also yields non-racemic γ-substituted-γ-butyrolactones.[20]

* Corresponding author. Tel.: +91 022 26526091; fax: +91 022 26528547.
E-mail address: avkarnik@chem.mu.ac.in (A.V. Karnik).

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Initial investigations into the enantioselective synthesis of γ-butyrolactones had been successfully carried out by our group.[21] Sodium borohydride reduction of chiral menthyl and bornyl esters of 3-aroylpropanoic acids followed by acid catalyzed cyclization at low temperature resulted in the formation of optically active γ-aryl γ-butyrolactones. A mechanism, close to the $A_{AL}1$ type mechanism, was proposed for the formation of optically active γ-aryl γ-lactones.[21]

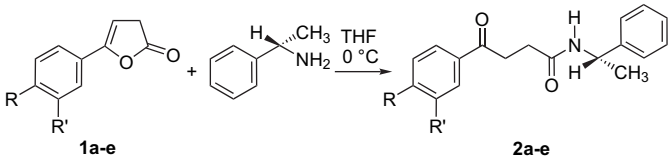
In any asymmetric synthesis, identification of stereoselective step is essential as this understanding of the mechanism can only result in better control over the stereochemical outcome. With this objective in mind the following work was carried out. In the present work, a chiral auxiliary route is invoked and a mechanism involving a delayed stereoselective step is proposed.

2. Results and discussion

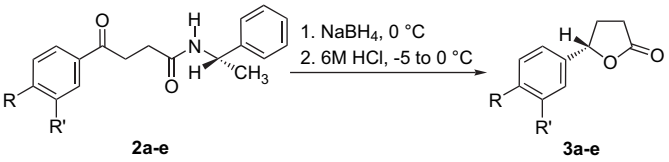
In this work we have employed a chiral amine as chiral auxiliary resulting in the formation of 3-aroyl propanamides. Effectively we decreased the electrophilic nature of the carbonyl group of the propanoic acid derivative compared to the 3-aroyl propanoates employed in our earlier work. This would minimize the chances of lactonization by nucleophilic attack of the hydroxyl group on the carbonyl carbon of the propanoic acid derivative.

We aimed at studying the route, which involves creation of only one chiral centre but undergoes a series of reactions for the formation of the same. Our approach for enantioselective formation of γ-aryl-γ-butyrolactones involved the use of (*S*)-1-phenylethylamine as a chiral auxiliary. The synthesis of novel chiral ketoamides of 3-aroylpropanoic acids and (*S*)-1-phenylethylamine and their utility in the preparation of optically active γ-aryl-γ-butyrolactones are discussed.

The chiral ketoamides of 3-aroylpropanoic acids were synthesized by first converting the γ-keto acids into reactive butenolides followed by their reactions with optically active amine. The reaction of butenolides (**1a**–**e**) with (*S*)-1-phenylethylamine resulted in the formation of novel chiral ketoamides, (*S*)-3-aroyl-*N*-(α-phenylethyl)propanamides (**2a**–**e**) (Scheme 1).



Scheme 1. Synthesis of novel chiral ketoamides.



Scheme 2. Enantioselective synthesis of (*S*)-γ-aryl-γ-butyrolactones.

The next step in our investigation was the enantioselective synthesis of γ-aryl-γ-butyrolactones. This was achieved in a one-pot reaction by sodium borohydride reduction of (*S*)-3-aroyl-*N*-(α-phenylethyl)propanamides (**2a**–**e**) followed by acid catalyzed lactonization (Scheme 2).

The enantiomeric excesses of (*S*)-γ-aryl-γ-butyrolactones (**3a**–**e**) were determined by HPLC using a chiral stationary phase (Chiralcel OD-H, *n*-hexane/2-propanol 95:5) (Table 1).

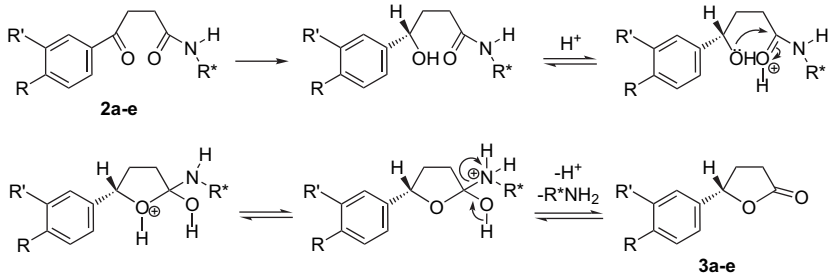
There are two major possibilities for the formation of non-racemic γ-aryl-γ-butyrolactones (**3a**–**e**). The first possibility is that optical induction occurs in the reduction step. Nucleophilic attack of the chiral hydroxyl group on the carbonyl of amide followed by subsequent removal of the amine could result in the formation of optically active γ-aryl-γ-butyrolactones ($A_{AC}2$ type mechanism) (Scheme 3).

The second possibility is that optical induction does not occur in the reduction step. The γ-hydroxyamide obtained by reduction loses water molecule on protonation resulting in the formation of a diastereotopic carbocation. Nucleophilic attack of the carbonyl oxygen of the chiral amide in an enantioselective manner on the carbocation could result in the formation of non-racemic γ-aryl-γ-butyrolactones ($A_{AL}1$ type mechanism). Asymmetric induction could be expected to occur in this step under the dissymmetric influence of the chiral auxiliary (Scheme 4).

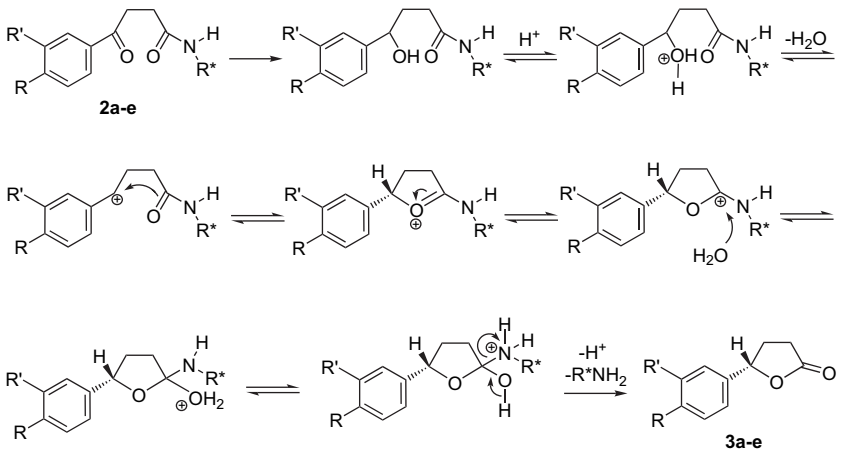
The first possibility of asymmetric reduction of prochiral ketones followed by lactonization appeared to be quite a strong possibility. However, there were two aspects, which worked against this proposed mechanism. The dissymmetric influence

Table 1
Percentage enantiomeric excess data of enantioselective synthesis of (*S*)-γ-aryl-γ-butyrolactones

Entry	Compound	R	R′	Yield	ee (%)
1	**3a**	H	H	56	67
2	**3b**	CH_3	H	65	69
3	**3c**	OCH_3	H	57	73
4	**3d**	CH_3	CH_3	66	71
5	**3e**	Cl	H	59	68



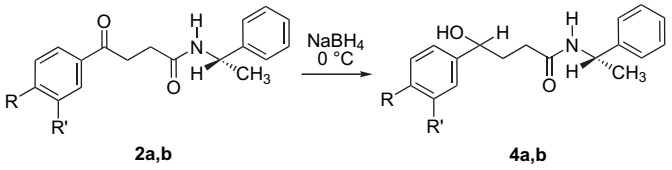
Scheme 3. First possibility—$A_{AC}2$ type mechanism.



Scheme 4. Proposed mechanism ($A_{AL}1$ type mechanism) for the enantioselective formation of (*S*)-γ-aryl-γ-butyrolactones.

of the chiral auxiliary situated five atomic centres away was less likely to influence the chiral induction significantly (67% ee, experimental result). Secondly, the carbonyl of amide group is not sufficiently electrophilic and hence the $A_{AC}2$ type lactonization becomes a remote possibility under acidic conditions.

To confirm the second possibility, it was decided to isolate the intermediate hydroxyamide **4** (Scheme 5).



Scheme 5. Preparation of γ-hydroxyamide.

The hydroxyamide was found to be formed as a mixture of two diastereoisomers. The formation of **4** as a mixture of two diastereoisomers in almost equal proportion (Fig. 1a) supports the second possibility, i.e., $A_{AL}1$ type mechanism for the formation of non-racemic γ-aryl-γ-butyrolactones. The % diastereomeric excess of **4** does not match the % enantiomeric excess found for **3** (Fig. 1), which indicates that the chiral centre formed initially during reduction step goes to the carbocation stage in the subsequent step (acid catalyzed removal of protonated hydroxyl group). The benzylic cations are resonance stabilized and hence the formation of diastereotopic carbocation is favoured. This is in accordance with our previously reported enantioselective synthesis of γ-substituted γ-butyrolactones.[21]

Lactone formation via the intermediate diastereotopic carbocation is the route, which needed a closer look. The % ee found are satisfactory to good (67–73% ee). The diastereoselectivity in the reduction step was almost non-existent as established by HPLC analysis of the isolated hydroxyamide indicating that the chiral auxiliary was unable to exert any dissymmetric influence on the first reduction step. The direct nucleophilic displacement of the hydroxyl group by intramolecular attack of the amide carbonyl would have resulted in the same proportion of enantioselectivity as that observed for the intermediate hydroxyamide. The enhancement of enantioselectivity clearly indicates that the reduced carbinol carbon goes to the carbocation stage in order to facilitate enantioselective formation of γ-substituted-γ-lactones. Thus the results indicate that a reaction where only one chiral centre is created, can actually involve a series of steps where the chiral centre can be created and destroyed before actual formation of products. In view of these results all similar reactions, which involved such series of reactions need to be verified to find out the actual step responsible for the final data as regards stereoselectivity observed.

3. Conclusion

The process does not involve dry conditions and does not use expensive chiral metal catalysts/reagents such as BINAP–Ru(II), diisopinocampheylborane, etc. In this methodology, the stereoselective step does not involve diastereoselective carbonyl group reduction. Rather the stereoselective step has been shown to be involving the diastereotopic carbocation in the cyclization

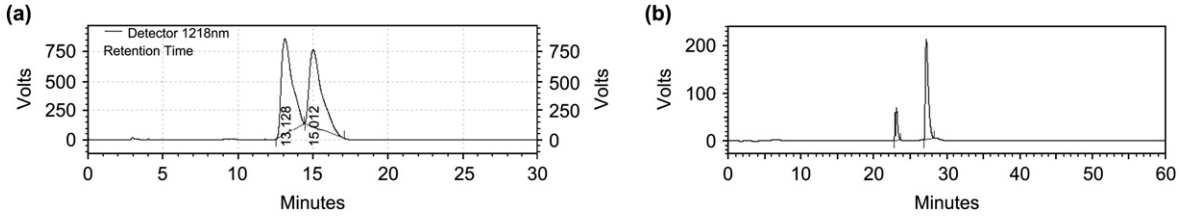


Figure 1. HPLC chromatogram of (a) (*R*,*S*)-4-hydroxy-4-phenyl-*N*-(α*S*-phenylethyl)butanamide **4a** and (b) (*S*)-γ-phenyl-γ-butyrolactone **3a**.

process. Establishment of actual stereoselective step can facilitate the use of more efficient and inexpensive chiral auxiliaries.

4. Experimental

4.1. General

Optical rotations were measured on Jasco DIP-1000 digital polarimeter. Enantiomeric excesses were determined on HPLC Thermo Finnigan spectra system using Daicel Chiralcel OD column with UV detector. IR spectra were recorded on Shimadzu FTIR-4200. ^{1}H NMR and ^{13}C NMR spectra were scanned in $CDCl_3$ on Bruker (300 MHz) and Varian Mercury Plus (400 MHz) spectrometers with TMS as an internal standard. Elemental analyses were carried on Carlo Enra instrument EA-1108 Elemental analyzer. Mass spectra were obtained by using MS in ESI mode. All melting points are uncorrected. Temperatures are recorded in degree Celsius. Boiling point of petroleum ether used was in the range of 60–80 °C. 5-Arylfuran-2(3*H*)-ones or butenolides (**1a–e**) were prepared by lactonization of 3-aroylpropanoic acids using acetic anhydride following literature procedure.[22]

4.1.1. Preparation of (*S*)-3-aroyl-*N*-(α-phenylethyl)-propanamides *2a–e*

A solution of 5 mmol of butenolide (**1a–e**) and 0.73 g (0.77 mL, 6 mmol) of (*S*)-1-phenylethylamine in 25 mL of THF was stirred at 0 °C for 4 h. The reaction was quenched with dilute hydrochloric acid and extracted with chloroform. The organic extract was washed with sodium carbonate solution, dried over anhydrous sodium sulfate and evaporated. The crude compound obtained was washed well with ice-cold ether to give (**2a–e**) as white solid.

*4.1.1.1. (S)-3-Benzoyl-N-(α-phenylethyl)propanamide **2a**.* White solid (1.19 g, 85%); mp 133 °C; $[\alpha]_D^{19}$ −84.5 (*c* 1, $CHCl_3$); IR (KBr): 3337, 3057, 3033, 2972, 2925, 1685, 1654, 1596, 1579, 1526, 1494, 1445 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, *J*=6.9 Hz, 2H; ArH), 7.59–7.55 (m, 1H; ArH), 7.49–7.44 (m, 2H; ArH), 7.32–7.26 (m, 5H; ArH), 6.04 (br s, 1H; NH), 5.15–5.07 (m, 1H; CH), 3.41–3.33 (m, 2H; CH_2), 2.66–2.61 (m, 2H; CH_2), 1.49 (d, *J*=6.9 Hz, 3H; CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ 199.2 (Ar–CO), 171.1 (NH–CO), 143.3, 136.7, 133.3, 128.6, 128.1, 127.2, 126.1 (aromatic carbons), 48.9 (Ar–C–NH), 34.1 (CH_2), 30.4 (CH_2), 21.9 (Me of Ph–$CHCH_3$). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 76.81; H, 6.84; N, 4.89.

*4.1.1.2. (S)-3-(4′-Methylbenzoyl)-N-(α-phenylethyl)propanamide **2b**.* White solid (1.27 g, 86%); mp 133 °C; $[\alpha]_D^{19}$ −86.2 (*c* 1, $CHCl_3$); IR (KBr): 3309, 3063, 3028, 2973, 2925, 1682, 1651, 1607, 1540, 1493, 1446 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J*=7.8 Hz, 2H; ArH), 7.31–7.24 (m, 7H; ArH), 6.03 (br s, 1H; NH), 5.15–5.06 (m, 1H; CH), 3.38–3.31 (m, 2H; CH_2), 2.64–2.60 (m, 2H; CH_2), 2.41 (s, 3H; CH_3), 1.49 (d, *J*=6.6 Hz, 3H; CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ 198.8 (Ar–CO), 171.3 (NH–CO), 144.1, 143.4, 134.1, 129.3, 128.6, 128.2, 127.2, 126.1 (aromatic carbons), 48.8 (Ar–C–NH), 34.0 (CH_2), 30.4 (CH_2), 21.9 (Me of Ph–$CHCH_3$), 21.7 (Ar–Me). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.29; H, 7.12; N, 4.75. Found: C, 77.35; H, 7.17; N, 4.68; *m/z*: 296.85 $[M+H]^+$.

*4.1.1.3. (S)-3-(4′-Methoxybenzoyl)-N-(α-phenylethyl)propanamide **2c**.* White solid (1.21 g, 78%); mp 119–121 °C; $[\alpha]_D^{19}$ −91.7 (*c* 1, $CHCl_3$); IR (KBr): 3262, 3065, 2976, 2929, 2843, 1671, 1640, 1598, 1563, 1509, 1494, 1449 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J*=8.7 Hz, 2H; ArH), 7.30–7.24 (m, 5H; ArH), 6.91 (d, *J*=8.7 Hz, 2H; ArH), 6.10 (br s, 1H; NH), 5.13–5.04 (m, 1H; CH), 3.86 (s, 3H; CH_3), 3.34–3.26 (m, 2H; CH_2), 2.63–2.58 (m, 2H; CH_2), 1.48 (d, *J*=6.6 Hz, 3H; CH_3). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.31; H, 6.75; N, 4.50. Found: C, 73.24; H, 6.84; N, 4.44.

*4.1.1.4. (S)-3-(3′,4′-Dimethylbenzoyl)-N-(α-phenylethyl)propanamide **2d**.* White solid (1.38 g, 89%); mp 138 °C; $[\alpha]_D^{19}$ −75.6 (*c* 1, $CHCl_3$); IR (KBr): 3323, 3060, 3031, 2974, 2922, 1679, 1646, 1607, 1572, 1537, 1493, 1447 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75–7.70 (m, 2H; ArH), 7.31–7.20 (m, 6H; ArH), 6.15 (br s, 1H; NH), 5.13–5.09 (m, 1H; CH), 3.40–3.27 (m, 2H; CH_2), 2.63–2.57 (m, 2H; CH_2), 2.31 (s, 6H; 2×CH_3), 1.48 (d, *J*=6.9 Hz, 3H; CH_3). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.67; H, 7.44; N, 4.53. Found: C, 77.75; H, 7.47; N, 4.45.

*4.1.1.5. (S)-3-(4′-Chlorobenzoyl)-N-(α-phenylethyl)propanamide **2e**.* White solid (1.25 g, 79%); mp 134–136 °C; $[\alpha]_D^{19}$ −85.7 (*c* 1, $CHCl_3$); IR (KBr): 3304, 3065, 3029, 2974, 2925, 1684, 1648, 1590, 1570, 1546, 1494, 1447 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, *J*=8.4 Hz, 2H; ArH), 7.43 (d, *J*=8.4 Hz, 2H; ArH), 7.38–7.30 (m, 5H; ArH), 6.00 (br d, *J*=6.3 Hz, 1H; NH), 5.15–5.06 (m, 1H; CH), 3.42–3.22 (m, 2H; CH_2), 2.70–2.55 (m, 2H; CH_2), 1.49 (d, *J*=6.9 Hz, 3H; CH_3). Anal. Calcd for $C_{18}H_{18}ClNO_2$: C, 68.46; H, 5.71; Cl, 11.25; N, 4.44. Found: C, 68.37; H, 5.75; Cl, 11.31; N, 4.51.

4.1.2. Enantioselective synthesis of (*S*)-γ-aryl-γ-butyrolactones *3a–e*

To a stirred solution of 2 mmol of chiral ketoamide (**2a–e**) in 20 mL of methanol at 0 °C, 38 mg (1 mmol) of sodium borohydride was added in portions and the mixture was stirred for 2 h at the same temperature. Once complete conversion of **2** was observed on TLC, the reaction mixture was treated with 100 mL of cold 6 M HCl. The mixture was stirred for further 12 h at −5 to 0 °C. The reaction mixture was extracted with chloroform, dried over anhydrous sodium sulfate and evaporated. The crude compound was crystallized using petroleum ether to give (**3a–e**) as white crystals (majority of γ-aryl-γ-butyrolactones are solids).

*4.1.2.1. (S)-γ-Phenyl-γ-butyrolactone **3a**.* Colourless oil (0.18 g, 56%); $[\alpha]_D^{19}$ −22.6 (*c* 0.5, CH_2Cl_2) (lit.[23] $[\alpha]_D$ +31.0 (*c* 0.675, CH_2Cl_2) for 92% ee in the *R*-isomer); IR (KBr): 3064, 3034, 2985, 2950, 1770, 1606, 1496, 1455 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$): δ 7.40–7.31 (m, 5H; ArH), 5.49 (t, 1H; CH), 2.69–2.60 (m, 3H; CH_2, CH), 2.24–2.12 (m, 1H; CH). Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.07; H, 6.17. Found: C, 74.15; H, 6.11.

4.1.2.2. (S)-γ-(4-Methylphenyl)-γ-butyrolactone ***3b***. White crystals (0.23 g, 65%); mp 71–72 °C; IR (KBr): 2926, 1765, 1615, 1520, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J*=8.3 Hz, 2H; ArH), 7.20 (d, *J*=8.3 Hz, 2H; ArH), 5.48 (t, 1H; CH), 2.69–2.59 (m, 3H; CH_2, CH), 2.36 (s, 3H; CH_3), 2.23–2.15 (m, 1H; CH). Anal. Calcd for $C_{11}H_{12}O_2$: C, 75.00; H, 6.82. Found: C, 75.07; H, 6.85.

4.1.2.3. (S)-γ-(4-Methoxyphenyl)-γ-butyrolactone ***3c***. White crystals (0.22 g, 57%); mp 48–50 °C; IR (KBr): 2969, 2843, 1762, 1611, 1517, 1457 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, *J*=8.7 Hz, 2H; ArH), 6.89 (d, *J*=8.7 Hz, 2H; ArH), 5.44 (t, 1H; CH), 3.80 (s, 3H; CH_3), 2.67–2.57 (m, 3H; CH_2, CH), 2.22–2.16 (m, 1H; CH). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.75; H, 6.25. Found: C, 68.68; H, 6.16.

4.1.2.4. (S)-γ-(3,4-Dimethylphenyl)-γ-butyrolactone ***3d***. White crystals (0.25 g, 66%); mp 76–77 °C; IR (KBr): 2963, 2920, 2855, 1769, 1615, 1505, 1456, 1444 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J*=7.6 Hz, 1H; ArH), 7.10 (s, 1H; ArH), 7.05 (d, *J*=7.6 Hz, 1H; ArH), 5.45 (t, 1H; CH), 2.67–2.58 (m, 3H; CH_2, CH), 2.27 (s, 3H; CH_3), 2.26 (s, 3H; CH_3), 2.24–2.14 (m, 1H; CH). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.79; H, 7.37. Found: C, 75.83; H, 7.29.

4.1.2.5. (S)-γ-(4-Chlorophenyl)-γ-butyrolactone ***3e***. Colourless oil (0.23 g, 59%); IR (KBr): 3068, 2987, 2951, 1789, 1599, 1495, 1457 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, *J*=7.8 Hz, 2H; ArH), 7.25 (d, *J*=7.8 Hz, 2H; ArH), 5.47 (t, 1H; CH), 2.66–2.63 (m, 3H; CH_2, CH), 2.23–2.12 (m, 1H; CH). Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.07; H, 4.58; Cl, 18.07. Found: C, 61.01; H, 4.49; Cl, 18.15.

4.1.3. Preparation of γ-hydroxyamides ***4a,b***

Sodium borohydride (38 mg, 1 mmol) was added in portions to **2** (2 mmol) in 20 mL of methanol at 0 °C, and the mixture stirred for 2 h. The reaction mixture was poured into cold water and extracted with chloroform. The organic extract was dried over anhydrous sodium sulfate, which on evaporation afforded the pure γ-hydroxyamides **4**.

4.1.3.1. 4-Hydroxy-4-phenyl-N-(αS-phenylethyl)butanamide ***4a***. White solid (0.56 g, 99%); mp 80–81 °C; $[\alpha]_D^{19}$ −74.1 (*c* 1, $CHCl_3$); IR (KBr): 3553, 3295, 3063, 3030, 2970, 2922, 2864, 1645, 1546, 1494, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.26 (m, 10H; ArH), 5.93 (br s, 1H; NH), 5.16–5.07 (m, 1H; CH), 4.76–4.72 (m, 1H; CH), 3.70 (br s, 1H; OH), 2.34–2.29 (m, 2H; CH_2), 2.07–2.00 (m, 2H; CH_2), 1.47 (d, *J*=7.2 Hz, 3H; CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ 172.6 (NH–CO), 144.5, 143.1, 128.7, 128.4, 127.4, 127.3, 126.2, 125.7 (aromatic carbons), 48.9 (Ar–C–NH), 34.3 (CH_2), 33.0 (CH_2), 21.7 (Me of Ph–$CHCH_3$). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.33; H, 7.42; N, 4.95. Found: C, 76.27; H, 7.49; N, 4.86; *m/z*: 283 $[M]^+$. For *R*-isomer, mp 79–80 °C; $[\alpha]_D^{19}$ +73.1 (*c* 1, $CHCl_3$).

4.1.3.2. 4-Hydroxy-4-(4′-methylphenyl)-N-(αS-phenylethyl)-butanamide ***4b***. White solid (0.58 g, 98%); mp 100–102 °C; $[\alpha]_D^{19}$ −66.3 (*c* 1, $CHCl_3$); IR (KBr): 3558, 3306, 3063, 3029, 2973, 2923, 2868, 1646, 1542, 1493, 1444 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.26 (m, 5H; ArH), 7.22 (d, *J*=7.8 Hz, 2H; ArH), 7.13 (d, *J*=7.8 Hz, 2H; ArH), 5.94 (br s, 1H; NH), 5.15–5.07 (m, 1H; CH), 4.73–4.69 (m, 1H; CH), 3.52 (br s, 1H; OH), 2.33–2.29 (m, 5H; CH_3, CH_2), 2.06–2.02 (m, 2H; CH_2), 1.47 (d, *J*=7.2 Hz, 3H; CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ 172.6 (NH–CO), 143.1, 141.5, 136.9, 129.0, 128.6, 127.3, 126.1, 125.7 (aromatic carbons), 48.9 (Ar–C–NH), 34.4 (CH_2), 33.0 (CH_2), 21.7 (Me of Ph–$CHCH_3$), 21.1 (Ar–Me). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.77; H, 7.74; N, 4.71. Found: C, 76.71; H, 7.79; N, 4.75; *m/z*: 298.37 $[M+H]^+$. For *R*-isomer, mp 100–102 °C; $[\alpha]_D^{19}$ +70.1 (*c* 1, $CHCl_3$).

Supplementary data

Chiral HPLC analysis of (*S*)-γ-aryl-γ-butyrolactones and γ-hydroxyamides are available in supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.01.077.

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