Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 2587–2594

TETRAHEDRON: *ASYMMETRY*

Chemoenzymatic enantioselective synthesis of 3-hydroxy-2-pyrrolidinones and 3-hydroxy-2-piperidinones

Ahmed Kamal,* K. Venkata Ramana, A. Venkata Ramana and A. Hari Babu

Biotransformation Laboratory, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India

Received 19 May 2003; accepted 14 July 2003

Abstract—The enantioselective synthesis of 3-hydroxypyrrolidin-2-ones and 3-hydroxy piperidin-2-ones has been carried out in high enantiomeric excess employing immobilized lipase from *Pseudomonas cepacia*.

1. Introduction

Hydroxy substituted nitrogen heterocycles containing five- and six-membered rings are well known in nature and are components of many compounds with valuable pharmacological properties.[1] For instance, these *N*-substituted pyrrolidinones are of interest for the treatment of brain insufficiencies and as cognition activators.[2] In view of their low toxicities these have recently attracted much attention in the pharmaceutical arena.[3] In addition, several syntheses have been reported employing the racemic core of particularly, 3-hydroxy-2-pyrrolidinones as valuable building blocks for medicinally important compounds. However, the configuration at the 3-position in this heterocycle has exhibited extraordinary influence on the biological properties for some compounds by employing this as a precursor. Several examples in this context have been investigated which led to the development of enantioselective synthetic strategies for these 3-hydroxy substituted lactams.

In recent years, both chemical and enzymatic routes have been developed towards the enantioselective synthesis of 3-hydroxy substituted lactams particularly, 3-hydroxy-2-pyrrolidinone and 3-hydroxy-2-piperidinone.[3a,4–6] In the literature two conventional methods have been reported for the chiral 3-hydroxy-2-pyrrolidinones that involve laborious crystallization methodology and derivatization processes.[7,8] Recently, enzymatic processes have also been reported involving lactate dehydrogenase-catalyzed reductions.[9,10] Most of these methods are laborious and have limitations from the practical point of view, especially due to the use of expensive cofactors and very long reaction times. Some of the enzymatic methodologies mentioned in the literature employ alcohol dehydrogenase, hence these are expensive and lack practical applicability.

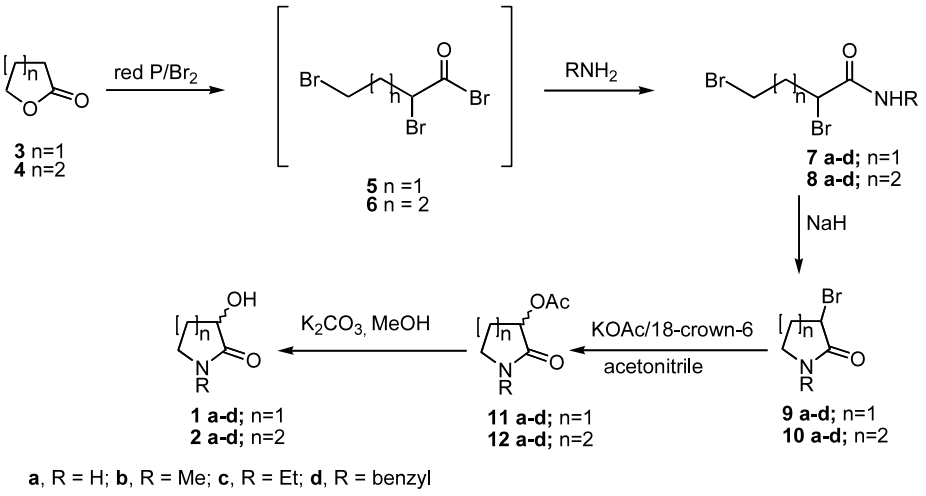
2. Results and discussion

There has been considerable interest in our laboratory for the total synthesis of natural products particularly employing chiral intermediates obtained through biotransformations or enzyme mediated processes.[11] In continuation of these efforts, a chemoenzymatic strategy has been investigated towards the synthesis of non-racemic chiral 3-hydroxylactams. In this chemoenzymatic process, the lactams have been synthesized starting from very economical starting materials, γ-butyrolactone or δ-valerolactone as shown in Scheme 1. The synthesis involves use of red phosphorus and bromine at 90°C to obtain the corresponding tribromo compounds **5**–**6**, which on treatment with appropriate amine followed by NaH afforded the *N*-substituted 3-bromolactams **9**–**10**. The racemic 3-acetoxylactams **11**–**12** have been obtained in quantitative yields from their 3-bromolactams in presence of KOAc/18-crown-6.

The subsequent resolution of the acetoxy precursors has been achieved by adopting a lipase-catalyzed alcoholysis. This strategy was chosen as it provides an easy product recovery and also it minimizes side reactions that may be expected in this class of substrates. The

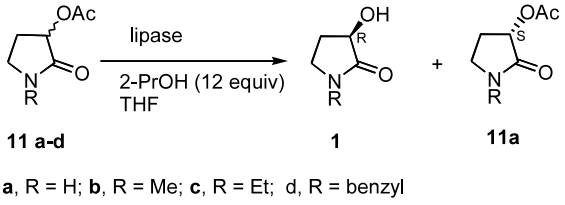
* Corresponding author. E-mail: ahmedkamal@iict.ap.nic.in

0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0957-4166(03)00548-2

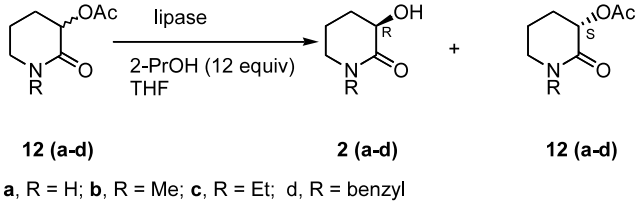


Scheme 1.

conversion of acetate **11a** to (*S*)-**1a** has been achieved by employing the immobilized lipases from *Pseudomonas cepacia* viz., 'Amano' PS-C lipase (~1100 U/mg), immobilized on chemically modified ceramic and 'Amano' PS-D lipase (~899 U/mg), immobilized on diatomaceous earth in 18 and 24 h, respectively, as shown in Scheme 2. Interestingly, lipase from the same source without immobilization has not given satisfactory results. Thus, this observation shows the importance of employing immobilized lipases. 'Amano' PS-C lipase has been found to be suitable for the resolution of such substrates. The corresponding alcohol (*R*)-**1a** and acetate (*S*)-**11a** have been obtained in >99% e.e. with 50% conversion while 'Amano' PS-D lipase afforded compound (*R*)-**1** in 50% e.e. with 40% conversion.



Scheme 2.



Scheme 3.

This resolution process has been extended for the 3-acetoxy-2-piperidinones **12** as shown in Scheme 3. In this investigation the effect of *N*-substitution on these substrates for the lipase-mediated resolution has also been examined **11b–d**/**12a–d**. The corresponding 3-hydroxy-2-pyrrolidinones, 3-hydroxy-2-piperidinones and their acetates are obtained in 55 to >99% e.e. employing Amano PS-C lipase as illustrated in Table 1.

The effects of solvents have also been studied for this lipase-mediated resolution process and it was observed that this process is faster in polar solvents such as acetonitrile compared to the nonpolar solvents such as toluene. However, THF has been found to provide

Table 1. Amano PS-C lipase-mediated alcoholysis of 3-acetoxy-2-pyrrolidinones and 3-acetoxy-2-piperidinones

Substrate	°C	h	%e.e.[a] OH	% e.e.[a] OAc	% Conversion	E[b]
11a	28	20	>99	>99	50	1057
11b	28	24	98	95	47	282
11c	28	24	97	>99	49	227
11d	28	18	nd	45	45	nd
12a	45	24	>99	90	44	473
12b	45	28	nd	98	45	nd
12c	45	28	nd	96	49	nd
12d	28	18	>99	>99	50	1057

°C = temperature, h = time, nd = not determined.
[a] Chiral HPLC analysis.
[b] Enantiomeric ratio.[13]

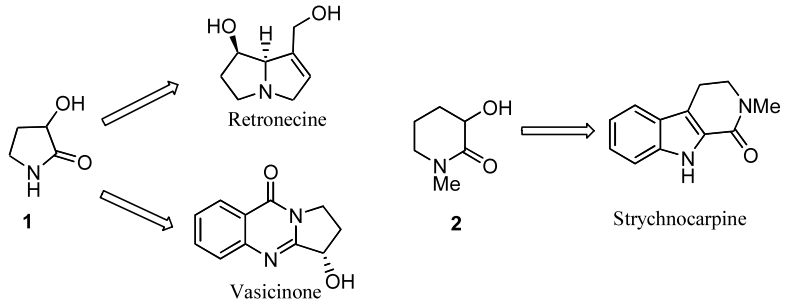


Figure 1.

good conversions with high enantiomeric excess. The differences in the temperature, reaction rates and effects of solvents in the resolution of acetates **11a–d** and **12a–d** may be attributed to a cumulative effect of interactions between lipase, substrate, carrier and solvent working in tandem.

In conclusion, an efficient and practical chemoenzymatic enantioselective synthesis of **1** and **2** has been achieved employing 'Amano' PS-C lipase-mediated alcoholysis. The present methodology has several advantages over the existing procedures and may find use towards the synthesis of biologically important compounds employing **1** and **2** as precursors in their homochiral form (Fig. 1).

3. Experimental

Unless specified all solvents were reagent grade and used without purification. Melting points have been recorded on an electrothermal apparatus and are uncorrected. ^{1}H NMR spectra were recorded as solutions in $CDCl_3$ and the chemical shifts are reported as parts per million (ppm, δ) on a 200 MHz instrument. Coupling constants are reported in hertz (Hz). Spectral patterns are designated as s, singlet; d, doublet; t, triplet; br, broad; m, multiplet. EI mass spectra were recorded on a VG 7070H micromass mass spectrometer at 200°C, 7 eV with a trap current of 200 μA and 4 kV acceleration voltage. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60F-254 on glass). Column chromatography was performed using Acme silica gel (60–120 mesh). HPLC analysis was performed on an instrument that consisted of a Shimadzu LC-6A system controller, SPD-6A fixed wave length UV monitor as detector, FCV-100B fraction collector and chromatopac C-R4A data processor as a recording integrator.

3.1. Preparation of 2,4-dibromobutyric acid bromide 5

In a three-necked round bottom flask equipped with a dropping funnel and an efficient condenser were placed freshly distilled γ-butyrolactone **3** (20 g, 0.23 mol) and red phosphorous (2.5 g, 0.43 g atom). To this bromine (40.43 g, 0.25 mol) was added over a half an hour interval, while the mixture was being stirred moderately and cooled in an ice bath. The mixture was heated to 70°C and an additional quantity of bromine (40.43 g, 0.25 mol) was added over a 30 min interval. After the completion of the addition of bromine, the temperature was raised to 80°C and maintained at that temperature for 3 h. Air was blown into the reaction mixture to remove excess of bromine and HBr completely. This reaction mixture was then distilled to obtain 45 g (63%) of the 2,4-dibromobutyric acid bromide **5** as a colorless liquid.

3.2. General procedure for the preparation of butyric acid amides 7a–c and 8a–c

To a mixture containing 10 ml of 28% aqueous amine, 15 ml water, 50 ml of $CHCl_3$, a solution 2,4-dibromobutyric acid bromide **5** (10g, 0.32 mmol) was added dropwise at 10–15°C. After the completion of the addition, the temperature was raised to 30°C and stirred for 30 min. The phases in reaction mixture were then separated and the aqueous layer was extracted with chloroform. The combined organic layers were washed with brine, dried over $MgSO_4$ to obtain crude solid. The solid thus obtained was washed with diethyl ether-hexane 1:1 solvent mixture to obtain dibromoamides **7** and **8** as white solids.

3.3. 2,4-Dibromo butyric acid amide 7a

This compound was obtained following the above procedure using compound **5** (10g, 32 mmol) and 15 ml aqueous ammonia. Yield: 5.1 g, 65%; mp: 79–81°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.40–2.50 (m, 1H), 2.60–2.70 (m, 1H), 3.50–3.65 (m, 2H), 4.50–4.60 (m, 1H), 6.10–6.40 (br s, 2H).

3.4. *N*-Methyl-2,4-dibromo butyric acid amide 7b

This compound was obtained following the above procedure using compound **5** (10g, 32 mmol) and 10 mL of 40% aqueous methyl amine. Yield: 6.0 g, 72%; mp: 53–56°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.40–2.60 (m, 1H), 2.65–2.80 (m, 1H), 2.9 (d, 3H J = 3.0 Hz), 3.50–3.60 (m, 2H), 4.50–4.60 (m, 1H), 6.35–6.45 (br s, 1H).

3.5. *N*-Ethyl-2,4-dibromo butyric acid amide 7c

This compound was prepared according to the above procedure from 2,4-dibromo butyric acid bromide **5** (10g, 32 mmol) and 10 mL of aqueous ethylamine. Yield: 6.2 g, 70%; mp: 59–61°C; ^{1}H NMR (200 MHz,

$CDCl_3$): δ 1.20–1.30 (t, 3H, $J=5.0$ Hz), 2.40–2.50 (m, 1H), 2.7–2.8 (m, 1H), 3.50–3.70 (m, 4H), 4.60–4.70 (m, 1H), 6.20–6.35 (br s, 1H).

3.6. *N*-Benzyl-2,4-dibromo butyric acid amide 7d

To a solution of benzyl amine (1.8 g, 16 mmol) in dry CH_2Cl_2 was added triethyl amine and a solution of 2,4-dibromo butanoic acid bromide **5** (5 g, 16 mmol) in CH_2Cl_2 at zero degrees. The reaction was then brought to rt and stirred for 1 h. The reaction mixture was washed with water and the CH_2Cl_2 layer dried over Na_2SO_4 and concentrated to obtain a residue. The crude residue thus obtained was purified by silica gel (60–120 mesh) column chromatography using hexane: acetone gradient to obtain the product amide **7d**. Yield: 8.10 g in 83%; mp: 61–64°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.30–2.50 (m, 1H), 2.60–2.80 (m, 1H), 3.40–3.60 (m, 2H), 4.30–4.60 (m, 3H), 6.60–6.70 (br s, 1H), 7.20–7.40 (m, 5H).

3.7. 2,5-Dibromovaleric acid bromide 6

This compound was prepared according to the procedure described for the preparation of 2,4-dibromobutyric acid bromide **5** with the starting materials δ-valerolactone **4** (20g, 0.2 mol), red phosphorous (0.2 g atom) and two portions of bromine (34 g, 0.21 mol) each. Compound **6** (40 g) was obtained as a liquid after distilling once.

3.8. 2,5-Dibromovaleric acid amide 8a

This compound was obtained following the above procedure using compound **6** (10 g, 30 mmol) and 15 ml of 28% aqueous ammonia. Yield: 5.3 g, 66%; mp: 85–88°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00–2.40 (m, 4H), 3.35–3.45 (t, 2H, $J=5.4$ Hz), 4.30–4.40 (m, 1H), 6.05–6.25 (br s, 1H), 6.25–6.65 (br s, 1H).

3.9. *N*-Methyl-2,5-dibromovaleric acid amide 8b

This compound was obtained following the above procedure using compound **6** (10g, 30 mmol) and 10 ml of 40% aqueous methylamine. Yield: 5.7 g, 68%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00–2.40 (m, 4H), 2.80–2.90 (d, 3H, $J=3.5$ Hz), 3.40–3.50 (t, 2H, $J=5.4$ Hz), 4.30–4.40 (m, 1H), 6.40–6.70 (br s, 1H).

3.10. *N*-Ethyl-2,5-dibromovaleric acid amide 8c

This compound was prepared according to the above procedure from 2,5-dibromovaleric acid bromide **6** (10 g, 30 mmol) and 10 mL of aqueous ethyl amine. Yield: 6.3 g, 72%; mp: 63–65°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15–1.25 (t, 3H, $J=5.0$ Hz), 2.00–2.40 (m, 4H), 3.25–3.40 (q, 2H, $J=5.0$ Hz, 4.8 Hz), 3.40–3.50 (t, 2H, $J=5.0$ Hz), 4.30–4.40 (m, 1H), 6.45–6.65 (br s, 1H).

3.11. *N*-Benzyl-2,5-dibromovaleramide 8d

To a solution of benzyl amine (1.7 g, 15.8 mmol) in dry CH_2Cl_2 was added 9.0 g of triethylamine and a solution of 2,5-dibromopentanoic acid bromide **6** (5 g, 15 mmol) at zero degrees. The reaction was then brought to rt and stirred for 1 h. The reaction mixture was washed with water and the CH_2Cl_2 layer dried over Na_2SO_4, before concentration to obtain a residue which was purified by silica gel column chromatography using hexane: acetone gradient to obtain the product. Yield: 7.9 g, 85%; mp: 65–68°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00–2.40 (m, 4H), 3.55–3.70 (m, 2H), 4.45–4.80 (m, 3H), 7.20–7.40 (m, 5H).

3.12. 3-Bromo-2-pyrrolidinone 9a

To a solution of 2,4-dibromobutyramide **7a** (5 g, 20 mmol) in THF was added NaH (0.980 g, 40 mmol) slowly at 0–10°C and stirred at rt for 1 h. The reaction was monitored by TLC. The reaction mixture was concentrated and the residue obtained was taken into ice-cold water and extracted with $CHCl_3$. The chloroform layer was then washed with brine dried over Na_2SO_4 and concentrated to obtain crude compound. Purification of the crude compound with hexane: acetone mixture gave the title compound. Yield: 1.3 g, 30% yield; mp: 79–81°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.30–2.40 (m, 1H), 2.65–2.80 (m, 1H), 3.40–3.50 (m, 1H), 3.50–3.60 (m, 1H), 4.20–4.30 (m, 1H), 7.60 (br s, 1H); EIMS: m/z 163 [M^+], 165 [M^++2].

3.13. 3-Bromo-1-methyl-2-pyrrolidinone 9b

This compound was prepared from 2,4-dibromo-*N*-methylbutyramide **7b** (5.5g, 21 mmol) and sodium hydride (0.960 g, 40 mmol). The product was obtained as a liquid. Yield: 2.8 g, 80% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00–2.20 (m, 1H), 2.40–2.55 (m, 1H), 3.00 (s, 3H), 3.30–3.40 (m, 1H), 3.55–3.65 (m, 1H), 4.40–4.45 (m, 1H); EIMS: m/z 177 [M^+], 179 [M^++2].

3.14. 3-Bromo-1-ethyl-2-pyrrolidinone 9c

This compound was prepared from 2,4-dibromo-*N*-ethylbutyramide **7c** (5 g, 19 mmol) and sodium hydride (0.920 g, 40 mmol). The product was obtained as a liquid. Yield: 2.7 g, 75%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20–1.30 (t, 3H, $J=7$ Hz), 2.25–2.45 (m, 1H), 2.60–2.80 (m, 1H), 3.30–3.45 (q, 2H, $J=6.5$ Hz), 3.60–3.80 (m, 2H), 4.40–4.50 (1H, t); EIMS: m/z 191 [M^+].

3.15. 3-Bromo-1-benzyl-2-pyrrolidinone 9d

This compound was prepared from 2,4-dibromo-*N*-benzylbutyramide **7d** (5 g, 14 mmol) and sodium hydride (0.740 g, 30 mmol). The product was obtained as a liquid. Yield: 3.2 g, 88%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35–2.55 (m, 1H), 2.55–2.75 (m, 1H), 3.60–3.80 (m, 2H), 4.30–4.55 (m, 2H), 4.40 (t, 1H), 7.20–7.60 (m, 5H). EIMS: m/z 253 [M^+].

3.16. 3-Bromo-2-piperidinone 10a

This compound was prepared according to the procedure described for the conversion of compounds **7a–c** to lactams **9a–c** from 2,5-dibromovaleramide **8a** (5.5 g,

21 mmol) and sodium hydride (1.0 g, 42 mmol). Yield: 1.5 g, 40%; mp: 114–117°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.80–1.90 (m, 1H), 2.20–2.40 (m, 3H), 3.20–3.50 (m, 2H), 4.50–4.60 (t, 1H, $J=6.8$ Hz), 6.00 (br s, 1H); EIMS: m/z 177 [M$^+$], 179 [M$^+$+2].

3.17. 3-Bromo-1-methyl-2-piperidinone 10b

This compound was prepared from *N*-methyl-2,5-dibromovaleramide **8b** (5 g, 18 mmol) and sodium hydride (0.770 g, 32 mmol). The product was obtained as a liquid. Yield: 2.4 g, 70%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.80–1.90 (m, 1H), 2.20–2.40 (m, 3H), 3.00 (s, 3H), 3.20–3.50 (m, 2H), 4.50–4.60 (t, 1H, $J=6.8$ Hz); EIMS: m/z 191 [M$^+$], 193 [M$^+$+2].

3.18. 3-Bromo-1-ethyl-2-piperidinone 10c

This compound was prepared from of 2,5-dibromo-*N*-ethylvaleramide **8c** (5 g, 17.5 mmol) and sodium hydride (0.84 g, 35 mmol). The product was obtained as a liquid. Yield: 2.5 g, 72%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10–1.20 (3H, t, $J=7$ Hz), 1.80–2.00 (m, 1H), 2.20–2.40 (m, 3H), 3.30–3.40 (m, 4H), 4.40–4.50 (m, 1H); EIMS: m/z 205 [M$^+$], 207 [M$^+$+2].

3.19. 3-Bromo-1-benzyl-2-piperidinone 10d

This compound was prepared from 5 g of 2,5-dibromo-*N*-benzylvaleramide **8d** (5 g, 14 mmol) and sodium hydride (0.69 g, 28 mmol). The product was obtained as a liquid. Yield: 3.2 g, 87%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.70–1.90 (m, 1H), 2.15–2.35 (m, 3H), 3.20–3.40 (m, 2H), 4.30–4.40 (d, 1H, $J=13$ Hz), 4.55–4.60 (m, 1H), 4.65–4.80 (d, 1H $J=13$ Hz), 7.20–7.60 (5H, m); EIMS: m/z 267 [M$^+$], 269 [M$^+$+2].

3.20. 3-Acetoxy-2-pyrrolidinone 11a

To a solution of 3-bromo-2-pyrrolidinone **9a** (1.0 g, 6.1 mmol) in dry acetonitrile was added KOAc (2.4 g, 24 mmol) and 18-crown-6 (.050 g, 0.2 mmol). This was refluxed for 5 h, while the reaction was monitored by TLC. The reaction mixture was filtered after the completion of the reaction and concentrated to afford crude solid product **11a**. The crude product was purified by column chromatography with hexane: acetone mixtures on silica gel (60–120 mesh) to obtain the acetoxy compound. Yield: 0.84 g, 96%; mp: 86–88°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.90–2.10 (m, 4H), 2.30–2.70 (m, 1H), 3.30–3.50 (m, 2H), 5.20 (t, 1H, $J=7.7$ Hz), 7.90–8.00 (br s, 1H); EIMS: m/z 100 [M$^+$–43].

3.21. 3-Acetoxy-1-methyl-2-pyrrolidinone 11b

This compound was prepared from 3-bromo-1-methyl-2-pyrrolidinone **9b** (2.5 g, 14 mmol), potassium acetate (5.5 g, 56 mmol) and 18-crown-6 (0.05 g, 0.20 mmol). The product was obtained as a liquid. Yield: 2.30 g, 95%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.90–2.10 (m, 4H), 2.30–2.70 (m, 1H), 3.0 (s, 3H), 3.30–3.50 (m, 2H), 5.20 (t, 1H, $J=7.0$ Hz); EIMS: m/z 157 [M$^+$].

3.22. 3-Acetoxy-1-ethyl-2-pyrrolidinone 11c

This compound was prepared from 3-bromo-1-ethyl-2-pyrrolidinone **9c** (2.5 g, 13 mmol), potassium acetate (5.5 g. 56 mmol) and 18-crown-6 (0.050 g, 0.20 mmol). The product was obtained as a liquid. Yield: 2.30 g, 97%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20–1.30 (t, 3H, $J=7.7$ Hz), 1.85–1.95 (m, 1H), 2.15 (s, 3H), 2.45–2.60 (m, 1H), 3.40–3.60 (m, 4H), 5.2 (t, 1H, $J=6.0$ Hz); EIMS: m/z 111 [M$^+$ –60].

3.23. 3-Acetoxy-1-benzyl-2-pyrrolidinone 11d

This compound was prepared from 3-bromo-1-benzyl-2-pyrrolidinone **9d** (2.5 g, 10 mmol), potassium acetate (3.9 g, 39.6 mmol) and 18-crown-6 (0.05 g, 0.20 mmol). The product was obtained as a liquid. Yield: 2.2 ml, 96%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.80–2.00 (m, 1H), 2.10 (s, 3H), 2.50–2.65 (m, 1H), 3.20–3.35 (m, 2H), 4.3 (d, 2H, $J=8.5$ Hz), 5.2 (t, 1H, $J=6.6$ Hz), 7.15–7.40 (m, 5H); EIMS: m/z 173 [M$^+$–60].

3.24. 3-Acetoxy-2-piperidinone 12a

This compound was prepared from 3-bromo-2-piperidinone **10a** (1.0 g, 5.6 mmol), potassium acetate (2.2 g, 22.5 mmol) and 18-crown-6 (0.05 g, 0.20 mmol). The product was obtained as a solid. Yield: 830 mg, 94%; mp: 69–71°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.70–1.90 (m, 3H), 2.15–2.25 (m, 4H), 3.30–3.45 (m, 2H), 5.2 (t, 1H, $J=5$ Hz), 7.40 (br s, 1H); EIMS: m/z 157 [M$^+$], 114 [M$^+$–43].

3.25. 3-Acetoxy-1-methyl-2-piperidinone 12b

This compound was prepared from 3-bromo-1-methyl-2-piperidinone **10b** (2.5 g, 13 mmol), potassium acetate (4.8 g, 49 mmol) and 18-crown-6 (0.05 g, 0.20 mmol). The product was obtained as a liquid. Yield: 2.2 g, 98%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60–1.80 (m, 3H), 2.00–2.20 (m, 4H), 2.90 (s, 3H), 3.20–3.50 (m, 2H), 5.20 (t, 1H, $J=5$ Hz); EIMS: m/z 171 [M$^+$].

3.26. 3-Acetoxy-1-ethyl-2-piperidinone 12c

This compound was prepared from 3-bromo-1-ethyl-2-piperidinone **10c** (2.5 g, 12 mmol), potassium acetate (4.8 g, 49 mmol) and 18-crown-6 (0.05 g, 0.20 mmol). The product was obtained as a liquid. Yield: 2.2 g, 98%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10–1.20 (t, 3H, $J=6.4$ Hz), 1.80–2.10 (m, 3H), 2.10–2.25 (m, 4H), 3.30–3.50 (m, 4H), 5.2 (1H, t, $J=5.6$ Hz); EIMS: m/z 185 [M$^+$].

3.27. 3-Acetoxy-1-benzyl-2-piperidinone 12d

This compound was prepared from 3-bromo-1-benzyl-2-piperidinone **10d** (2.3 g, 9.3 mmol), potassium acetate (3.6 g, 37 mmol) and 18-crown-6 (0.05 g, 0.20 mmol). The product was obtained as a liquid. Yield: 2.2 g, 95%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.90–2.10 (m, 3H), 2.10–2.30 (m, 4H), 3.20–3.30 (m, 2H), 4.5 (s, 2H), 5.2 (m, 1H), 7.2 (m, 5H); EIMS: m/z 187 [M$^+$–60] (loss of OAc group).

3.28. 3-Hydroxy-2-pyrrolidinone 1a

A solution of 3-acetoxy-2-pyrrolidinone **11a** (0.400 g, 2.8 mmol) in methanol was stirred with K_2CO_3 (0.036 g, 0.30 mmol) at rt. The reaction was monitored by TLC. After the completion of the reaction methanol was evaporated and the crude solids were repeatedly washed with acetone. The acetone extracts on concentration gave crude solid, which on filtering over a short silica gel pad with acetone yielded the 3-hydroxy-2-pyrrolidinone as solid. Yield: 0.170 g, 60%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.95–2.20 (m, 1H), 2.40–2.60 (m, 1H), 3.20–3.35 (m, 2H), 4.25–4.40 (m, 2H), 7.0 (br s, 1H); EIMS: m/z 101 [M$^+$].

3.29. 3-Hydroxy-1-methyl-2-pyrrolidinone 1b

This compound was obtained according to the procedure described for the preparation of compound **1a** from 3-acetoxy-1-methyl-2-pyrrolidinone **11b** (0.500 g, 3 mmol) and K_2CO_3 (0.072 g, 0.60 mmol). Yield: 0.207 g, 60%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85–2.00 (m, 1H), 2.10–2.20 (m, 1H), 2.90 (s, 3H), 3.20–3.45 (m, 2H), 4.20–4.30 (t, 1H, $J=6$ Hz); EIMS: m/z 115 [M$^+$].

3.30. 3-Hydroxy-1-ethyl-2-pyrrolidinone 1c

This compound was obtained according to the procedure described for the preparation of compound **1a** from 3-acetoxy-1-ethyl-2-pyrrolidinone **11c** (1.0 g, 6 mmol) and K_2CO_3 (0.140 g, 0.90 mmol). The product was obtained as a liquid. Yield: 0.540 g, 90%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10–1.20 (t, 3H, $J=5.5$ Hz), 1.90–2.05 (m, 1H), 2.35–2.50 (m, 1H), 3.20–3.50 (m, 4H), 4.15–4.40 (m, 2H); EIMS: m/z 129 [M$^+$], 111 [M$^+$−18].

3.31. 3-Hydroxy-1-benzyl-2-pyrrolidinone 1d

This compound was obtained according to the procedure described for the preparation of compound **1a** from 3-acetoxy-1-benzyl-2-pyrrolidinone **11d** (1.0 g, 4.3 mmol) and K_2CO_3 (0.120 g, 0.85 mmol). The product was obtained as a liquid. Yield: 0.700 g, 85%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85–2.00 (m, 1H), 2.30–2.45 (m, 1H), 3.10–3.30 (m, 2H), 4.35–4.45 (m, 3H), 5.05–5.25 (br s, 1H), 7.15–7.40 (m, 5H); EIMS: m/z 191 [M$^+$].

3.32. 3-Hydroxy-2-piperidinone 2a

This compound was obtained according to the procedure described for the preparation of compound **1a** from 3-acetoxy-2-piperidinone **12a** (0.400 g, 2.5 mmol) and K_2CO_3 (0.036 g, 0.30 mmol). The product was obtained as a liquid. Yield: 0.170 g, 60%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.80–2.10 (m, 3H), 2.20–2.40 (m, 1H), 3.30–3.50 (m, 2H), 3.60–3.80 (br s, 1H), 3.95–4.10 (m, 1H), 6.40–6.50 (br s, 1H); EIMS: m/z 115 [M$^+$], 97 [M$^+$−18].

3.33. 3-Hydroxy-1-methyl-2-piperidinone 2b

This compound was obtained according to the procedure described for the preparation of compound **1a** from 3-acetoxy-1-methyl-2-piperidinone **12b** (0.500 g, 3.1 mmol) and K_2CO_3 (0.072 g, 0.60 mmol). The product was obtained as a liquid. Yield: 0.250 g, 70%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.80–2.10 (m, 3H), 2.20–2.40 (m, 1H), 3.0 (s, 3H), 3.60–3.80 (br s, 1H), 3.95–4.10 (m, 1H).

3.34. 3-Hydroxy-1-ethyl-2-piperidinone 2c

This compound was obtained according to the procedure described for the preparation of compound **1a** from 3-acetoxy-1-ethyl-2- piperidinone **12c** (1.0 g, 5.8 mmol) and K_2CO_3 (0.150 g, 1.08 mmol). The product was obtained as a liquid. Yield: 0.530 g, 93%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05–1.25 (t, 3H, $J=5.8$ Hz), 1.45–1.70 (m, 1H) 1.70–1.90 (m, 2H), 2.15–2.25 (m, 1H), 3.30–3.50 (m, 4H), 3.70–3.85 (br s, 1H), 3.90–4.00 (m, 1H).

3.35. 3-Hydroxy-1-benzyl-2-piperidinone 2d

This compound was obtained according to the procedure described for the preparation of compound **1a** from 3-acetoxy-benzyl-2- piperidinone **12d** (1.0 g, 4 mmol) and K_2CO_3 (0.110 g, 0.80 mmol). The product was obtained as a liquid. Yield: 0.350 g, 85%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65–1.95 (m, 3H), 2.10–2.30 (m, 1H), 3.10–3.25 (m, 2H), 3.60–3.90 (br s, 1H), 4.00–4.10 (dd, 1H, $J=4.5$ Hz, 7.1 Hz), 4.40–4.70 (dd, 2H, $J=13$ Hz, 16 Hz), 7.15–7.40 (m, 5H); EIMS: m/z 205 [M$^+$].

3.36. Enzymatic deacylation of 3-acetoxylactams

To a solution of the acetoxy lactams **11a**–**d** and **12a**–**d** (100 mg) in THF (50 mL) was added 4 Å molecular sieves powder, lipase (110 mg) and 2-propanol (10 equiv.). This reaction mixture was stirred on a rotary shaker. The reaction was monitored by TLC. After the reaction proceeded for 50% conversion the molecular sieves and the lipase were filtered off. The filtrate was concentrated under reduced pressure and the crude was purified by silica gel chromatography (60–120 mesh, *n*-hexane:acetone). The structure analysis data obtained for the alcohol and the acetate products matched well with the chemically obtained racemic samples. HPLC analysis[12] was done either for the mixture of both acetate and alcohol or the pure compounds for determination of chiral purities.

3.37. 3-Acetoxy-2-pyrrolidinone 11a

This compound was enzymatically deacylated following the procedure described above. The lipase-mediated alcoholysis attained near 51% conversion in 20 h. The products obtained displayed the following characteristics.

3.38. (*R*)-3-Hydroxy-2-pyrrolidinone 1a

$[\alpha]_D^{25} = +120.0$ (*c* 1, $CHCl_3$): ^1H NMR (200 MHz, $CDCl_3$): δ 1.95–2.20 (m, 1H), 2.40–2.60 (m, 1H), 3.20–3.35 (m, 2H), 4.25–4.40 (m, 2H), 7.0 (br s, 1H); EIMS: *m*/*z* 101 [M^+].

3.39. (*S*)-3-Acetoxy-2-pyrrolidinone 11a

$[\alpha]_D^{25} = -30.4$ (*c* 1, $CHCl_3$): ^1H NMR (200 MHz, $CDCl_3$): δ 1.90–2.20 (m, 4H), 2.30–2.70 (m, 1H), 3.30–3.50 (m, 2H), 5.20 (t, 1H, $J = 7.7$ Hz), 7.90–8.00 (br s, 1H); EIMS: *m*/*z* 100 [$M^+ - 43$].

3.40. 3-Acetoxy-1-methyl-2-pyrrolidinone 11b

This compound was enzymatically deacylated following the procedure described above. The lipase-mediated alcoholysis attained near 47% conversion in 24 h. The products obtained displayed the following characteristics.

3.41. (*R*)-3-Hydroxy-1-methyl-2-pyrrolidinone 1b

$[\alpha]_D^{25} = +126.5$ (*c* 1, $CHCl_3$): ^1H NMR (200 MHz, $CDCl_3$): δ 1.85–2.00 (m, 1H), 2.10–2.20 (m, 1H), 2.90 (s, 3H), 3.20–3.45 (m, 2H), 4.20–4.30 (t, 1H, $J = 6$ Hz); EIMS: *m*/*z* 115 [M^+].

3.42. (*S*)-3-Acetoxy-1-methyl-2-pyrrolidinone 11b

$[\alpha]_D^{25} = -31.0$ (*c* 1, $CHCl_3$): ^1H NMR (200 MHz, $CDCl_3$): δ 1.90–2.10 (m, 4H), 2.30–2.70 (m, 1H), 3.0 (s, 3H), 3.30–3.50 (m, 2H), 5.20 (t, 1H, $J = 7.0$ Hz); EIMS: *m*/*z* 157 [M^+].

3.43. 3-Acetoxy-1-ethyl-2-pyrrolidinone 11c

This compound was enzymatically deacylated following the procedure described above. The lipase-mediated alcoholysis proceeded to 49% conversion in 24 h. The products obtained displayed the following characteristics.

3.44. (*R*)-3-Hydroxy-1-ethyl-2-pyrrolidinone 1c

$[\alpha]_D^{25} = +131.0$ (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.10–1.20 (t, 3H, $J = 5.5$ Hz), 1.90–2.05 (m, 1H), 2.35–2.50 (m, 1H), 3.20–3.50 (m, 4H), 4.15–4.40 (m, 2H); EIMS: *m*/*z* 129 [M^+].

3.45. (*S*)-3-Acetoxy-1-ethyl-2-pyrrolidinone 11c

$[\alpha]_D^{25} = -25.2$ (*c* 1, $CHCl_3$): ^1H NMR (200 MHz, $CDCl_3$) δ 1.20–1.30 (t, 3H, $J = 7.7$ Hz), 1.85–1.95 (m, 1H), 2.15 (s, 3H), 2.45–2.60 (m, 1H), 3.40–3.60 (m, 4H), 5.2 (t, 1H, $J = 6.0$ Hz); EIMS: *m*/*z* 111 [$M^+ - 60$] (Loss of OAc group).

3.46. 3-Acetoxy-1-benzyl-2-pyrrolidinone 11d

This compound was enzymatically deacylated following the procedure described above. The lipase-mediated alcoholysis proceeded to 45% conversion in 18 h. The products obtained displayed the following characteristics.

3.47. (*R*)-3-Hydroxy-1-benzyl-2-pyrrolidinone 1d

$[\alpha]_D^{25} = +32.5$ (*c* 1, $CHCl_3$): ^1H NMR (200 MHz, $CDCl_3$): δ 1.85–2.00 (m, 1H), 2.30–2.45 (m, 1H), 3.10–3.30 (m, 2H), 4.35–4.45 (m, 3H), 5.05–5.25 (br s, 1H), 7.15–7.40 (m, 5H); EIMS: *m*/*z* 191 [M^+].

3.48. (*S*)-3-Acetoxy-1-benzyl-2-pyrrolidinone 11d

$[\alpha]_D^{25} = -51.2$ (*c* 1, $CHCl_3$): ^1H NMR (200 MHz, $CDCl_3$): δ 1.80–2.00 (m, 1H), 2.10 (s, 3H), 2.50–2.65 (m, 1H), 3.20–3.35 (m, 2H), 4.30 (d, 2H, $J = 8.5$ Hz), 5.20 (t, 1H, $J = 6.6$ Hz), 7.15–7.40 (5H, m); EIMS: *m*/*z* 173 [$M^+ - 60$] (loss of acetoxy group).

3.49. 3-Acetoxy-2-piperidinone 12a

This compound was enzymatically deacylated following the procedure described above. The lipase-mediated alcoholysis proceeded to 50% conversion in 24 h. The products obtained displayed the following characteristics.

3.50. (*R*)-3-Hydroxy-2-piperidinone 2a

$[\alpha]_D^{25} = +6.0$ (*c* 1, $CHCl_3$): ^1H NMR (200 MHz, $CDCl_3$): δ 1.80–2.10 (m, 3H), 2.20–2.40 (m, 1H), 3.30–3.50 (m, 2H), 3.60–3.80 (br s, 1H), 3.95–4.10 (m, 1H), 6.40–6.50 (br s, 1H); EIMS: *m*/*z* 115 [M^+].

3.51. (*S*)-3-Acetoxy-2-piperidinone 12a

$[\alpha]_D^{25} = -1.5$ (*c* 1, $CHCl_3$): ^1H NMR (200 MHz, $CDCl_3$): δ 1.70–1.90 (m, 3H), 2.15–2.25 (m, 4H), 3.30–3.45 (m, 2H), 5.2 (t, 1H, $J = 5$ Hz), 7.40 (br s, 1H); EIMS: *m*/*z* 157 [M^+], 114 [$M^+ - 43$].

3.52. 3-Acetoxy-1-methyl-2-piperidinone 12b

This compound was enzymatically deacylated following the procedure described above. The lipase-mediated alcoholysis proceeded to 45% conversion in 28 h. The products obtained displayed the following characteristics.

3.53. (*R*)-3-Hydroxy-1-methyl-2-piperidinone 2b

^1H NMR (200 MHz, $CDCl_3$): δ 1.80–2.10 (m, 4H), 2.20–2.40 (m, 1H), 3.0 (s, 1H), 3.60–3.80 (s br, 1H), 3.95–4.10 (m, 1H).

3.54. (*S*)-3-Acetoxy-1-methyl-2-piperidinone 12b

^1H NMR (200 MHz, $CDCl_3$): δ 1.60–1.80 (m, 3H), 2.00–2.20 (m, 4H), 2.90 (s, 3H), 3.20–3.50 (m, 2H), 5.2 (t, 1H, $J = 5$ Hz); EIMS: *m*/*z* 171 [M^+].

3.55. 3-Acetoxy-1-ethyl-2-piperidinone 12c

This compound was enzymatically deacylated following the procedure described above. The lipase-mediated alcoholysis proceeded to 49% conversion in 28 h. The products obtained displayed the following characteristics.

3.56. (*R*)-3-Hydroxy-1-ethyl-2-piperidinone 2c

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05–1.25 (t, 3H, $J=5.8$ Hz), 1.45–1.70 (m, 1H) 1.70–1.90 (m, 2H), 2.15–2.25 (m, 1H), 3.30–3.50 (m, 4H), 3.70–3.85 (s br, 1H), 3.90–4.00 (m, 2H).

3.57. (*S*)-3-Acetoxy-1-ethyl-2-piperidinone 12c

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10–1.20 (t, 3H, $J=6.4$ Hz), 1.80–2.10 (m, 3H), 2.10–2.25 (m, 4H), 3.30–3.50 (m, 4H), 5.2 (1H, t, $J=5.6$ Hz); EIMS: m/z 185 [M^+].

3.58. 3-Acetoxy-1-benzyl-2-piperidinone 12d

This compound was enzymatically deacylated following the procedure described above. The lipase-mediated alcoholysis proceeded to 50% conversion in 18 h. The products obtained displayed the following characteristics.

3.59. (*S*)-3-Acetoxy-1-benzyl-2-piperidinone 12d

$[\alpha]_D^{25}=-10.0$ (c 1, $CHCl_3$): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.9–2.10 (m, 3H), 2.1–2.30 (m, 4H), 3.20–3.4 (m, 2H), 4.5 (s, 2H), 5.2 (m, 1H), 7.2 (m, 5H); EIMS: m/z 206 [M^+–43].

3.60. (*R*)-3-Hydroxy-1-benzyl-2-piperidinone 2d

$[\alpha]_D^{25}=+12.0$ (c 1, $CHCl_3$): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65–1.95 (m, 3H), 2.10–2.30 (m, 1H), 3.10–3.25 (m, 2H), 3.60–3.90 (br s, 1H), 4.00–4.10 (dd, 1H, $J=4.5$ Hz, 7.1 Hz), 4.40–4.70 (dd, 2H, $J=13$ Hz, 16 Hz), 7.15–7.40 (m, 5H); EIMS: m/z 205[M^+].

Acknowledgements

We are thankful to the Department of Science and Technology, New Delhi for the financial support for Grants-in-Aid project under SERC (No. SP/S1/G-47/99). Two of the authors K.V.R. and A.H.B. are thankful to CSIR, New Delhi for the award of Research Fellowship.

References

1. (a) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 491; (b) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 619.
2. Aschwanden, W.; Kyburz, E. Europ. Patent 0071216, *Chem. Abstr.* **1983**, *98*, 1605825t.
3. (a) Vedjs, E.; Larsen, S.; West, F. G. *J. Org. Chem.* **1985**, *50*, 2170; (b) Eguchi, S.; Suzuki, T.; Okawa, T.; Matsushita, Y. *J. Org. Chem.* **1996**, *61*, 7316; (c) Peter, A.; Chung-Chen, W. Eur. Pat. Appl. EP620225, US Appl. 48, 688 *Chem. Abstr.* **1995**, *122*, 187252m; (d) Tameo, I.; Kazuhiko, K.; Koji, H.; Matsushita, T.; Yamaguchi, T. Jp-04,103,584 *Chem. Abstr.* **1992**, *117*, 21225m; (e) Peter, A.; Chung-Chen, W. US. Pat. 5, 523, 400 *Chem. Abstr.* **1996**, *125*, 114389; (f) Tetsuya, A.; Osamu, U JP06, 199, 870 *Chem. Abstr.* **1994**, *121*, 300881k; (g) Tatuya, H.; Nobuo, N. pct Int. Appl. WO 0069, 8117; *Chem. Abstr.* **2000**, *133*, 362699.
4. (a) Hua, D. H.; Miao, S. W.; Bharati, S. N.; Katsulisa, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682; (b) Goel, O. P.; Krolls, U.; Lewis, E. P. *Org. Prepn. Proc. Int.* **1985**, *17*, 91.
5. (a) Burger, K.; Pires, R. *Tetrahedron* **1997**, *53*, 9213; (b) Tanabe et al., Jpn. Pat. 17962, **1962**. *Chem. Abstr.* **1963**, *59*, 11262.
6. (a) Lyle, R. E.; Spicer, C. K. *Tetrahedron Lett.* **1970**, *29*, 1133; (b) Hamilton, P.; Ortiz, P. *Biochemical Preparations* **1955**, *4*, 76; (c) Herdier, C.; Dimmerling, A. *Heterocycles* **1984**, *22*, 2277.
7. Ringdahl, B.; Craig, J. C. *Acta Chem. Scand. B* **1980**, *34*, 731.
8. Glynn, M.; Khatoon, V. S. PCT Int. Appl. **1997**, WO 97 19, 920; *Chem. Abstr.* **1997**, *127*, 95193t.
9. Benley, J. M.; Wadsworth, H. J.; Wills, C. L. *J. Chem. Soc., Chem. Commun.* **1995**, 231.
10. Gibbs, G.; Hateley, M. J.; Mclaren, L.; Welham, M.; Wills, C. L. *Tetrahedron Lett.* **1999**, *40*, 1069.
11. (a) Kamal, A.; Ramana, K. V.; Rao, M. V. *J. Org. Chem.* **2001**, *66*, 997; (b) Kamal, A.; Sandbhor, M.; Ramana, K. V. *Tetrahedron: Asymmetry* **2002**, *13*, 815; (c) Kamal, A.; Khanna, G. B. R.; Ramu, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2039.
12. HPLC analysis was performed by using a chiralcel (Diacel) OD or OJ columns with hexane: 2-propanol solvent system at 215 nm wavelength and 1 ml min^{-1} flow rate.
13. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.