A short diastereoselective synthesis of *cis*-(2*S*,4*S*) and *cis*-(2*R*,4*R*)-4-hydroxyprolines

Vikas S. Gajare, Sandip R. Khobare, B. Malavika, R. Nagaraju, B. VenkateswaraRao, U.K. Syam Kumar

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Graphical Abstract

A short diastereoselective synthesis of *cis*-(2*S*,4*S*)-4- and *cis*-(*2R*,4*R*)-4-hydroxyproline

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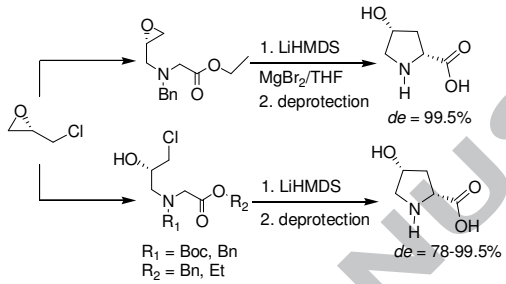

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A short diastereoselective synthesis of *cis*-(2*S*,4*S*) and *cis*-(2*R*,4*R*)-4-hydroxyprolines

Vikas S.Gajare,[ab] Sandip R. Khobare,[a] B. Malavika,[a] R. Nagaraju,[a] B. VenkateswaraRao,[b] U. K. Syam Kumar *[a]

[a]Technology Development Center, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd, Miyapur, Hyderabad 500049, India.

[b]AU College of engineering (A), Andhra University, Visakhapatanum 530003, India

Fax: 914023045439 / 5438

E-mail: *syam_kmr@yahoo.com*

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ABSTRACT

A concise synthesis of (2*R*,4*R*)-4-hydroxyproline **(1)** and (2*S*,4*S*)-4-hydroxyproline **(2)** have been developed in enantiomerically pure form from commercially available starting materials with excellent diastereoselectivity. The tightly bound chelation controlled transition state formed during the 5-exo-tet ring closure reaction is assumed to be the origin for high diastereoselectivity.

3- and 4-Hydroxyprolines has attracted widespread attention in the recent past as a useful chiral building block in organic synthesis. These chiral building blocks were extensively used for the synthesis of glycopeptides,[1] antimetabolite of glutamic acid, ACE inhibitors,[2] and 1-β-methylacarbapenem antibiotics. 3- and 4-Hydroxyprolines are also used in the agrochemical industry.[3] Recently the application of *cis*-4-hydroxyproline in topical medication is also disclosed.[4] One of the key structural fragment of naturally occurring phalloidine alkaloid is *cis*-(2*S*,4*S*)-4-hydroxyproline (**2**).[5] Chiraly pure 4-hydroxyproline was first isolated from gelatin hydrolyzates[6] and Luechs *et al.* reported the first synthesis of racemic 4-hydroxyproline in 1937.[7] Subsequently numerous methodologies were reported in literature for the synthesis of racemic 4-hydroxy-prolines.[8] The diastereo as well as enantioselective synthesis of (2*R*,4*R*)-hydroxyproline (**1**) and (2*S*,4*S*)-4-hydroxyproline (**2**) are rarely disclosed in the literature.

Papaioannou *et al.*[9] and Seki *et al.*[10] reported the synthesis of (2*R*,4*R*)-4-hydroxy-proline **1** by the inversion of stereocenter in (2*R*,4*S*)-4-hydroxyproline under Mitsunobu reaction conditions. The synthesis of **1** is also reported by Thirring *et al.*[11] from (-)-menthyl ester of hippuric acid.[12] However; both syntheses use the separation techniques for enriching the *de* of the required *cis* isomer. The enantioselective synthesis of **1** through stereocontrolled 1,4-*trans* alkylation of (6*S*)-methyl-4-(1*S*)-phenylethyl-1,4-morpholine-2,5-diones is a noteworthy approach.[13] Synthesis of **1** and **2** are also reported from the amino acid,[14a] carbohydrates,[14b] and 4-oxo-1,2-pyrrolidinedicarboxylic acid dimethyl ester.[15] Recently Kimura *et al.* demonstrated the synthesis of both enantiomers of *cis*-4-hydroxyproline using Wittig olefination protocol.[16]

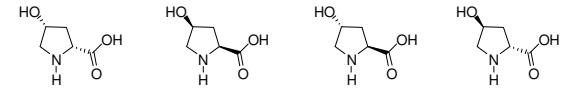
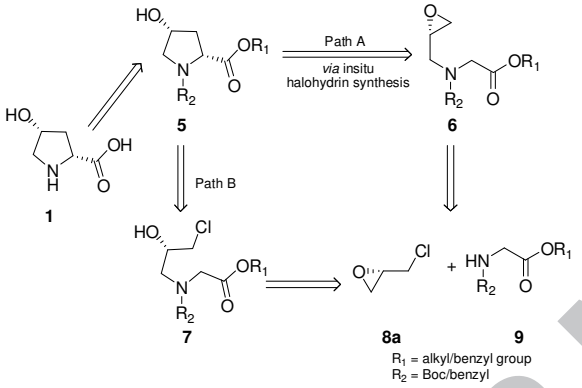


Figure 1. Stereoisomer's of 4-hydroxyproline

Though some of these syntheses commenced with chirally pure starting materials, the product 4-hydoxyproline is obtained with low diastereomeric excess. The lengthy synthetic sequence, use of complex and expensive reagents, and tedious purification procedures adapted for enriching the diastereomeric excess in these synthesis demands efficient protocols for the preparation of *cis*-(2*R*,4*R*)-4-hydroxyproline (**1**) and *cis*-(2*S*,4*S*)-4-hydroxyproline (**2**) in minimum number of stages. As a part of our efforts to develop new methodologies for the total synthesis of natural products,[17] herein we disclose our successful efforts towards

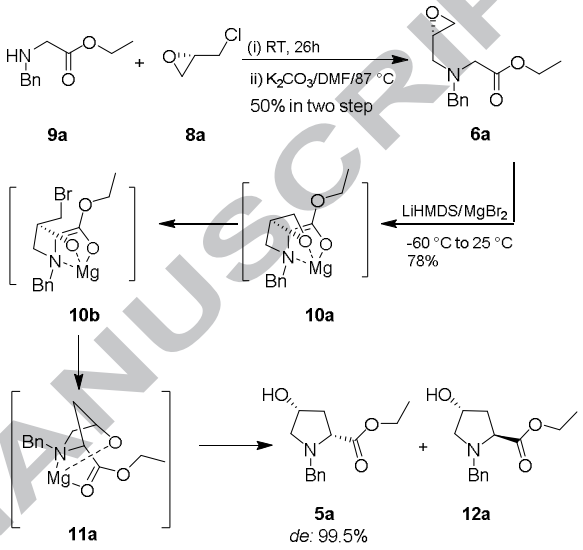
the development of a concise and highly diastereoselective synthesis of *cis*-(2*R*,4*R*)-4-hydroxyproline (**1**) and *cis*-(2*S*,4*S*)-4-hydroxyproline (**2**).

The retro synthetic approach for the diastereoselective synthesis of *cis*-(2*R*,4*R*)-4-hydroxyproline (**1**) is outlined in **Scheme 1**. The deprotection of *N*-Boc/*N*-benzyl proline ester **3** under standard deprotection conditions could easily generate (2*R*,4*R*)-4-hydroxyproline (**1**). The required proline ester **5** could be obtained from enantiomerically pure amino epoxide **6** under intramolecular 5-*exo-tet* ring closure conditions (*path A*) from a highly chelated Zn(II) or Mg(II) complexes. The reaction of optically pure (*S*)-epichlorohydrin (**8a)** and glycine ester **7** would generate chiral epoxide **6**. In Path-B, (2*R*,4*R*)-4-hydroxyproline (**1**) is envisaged to obtain from chirally pure chlorohydrins **7** by using the memory of chirality protocol.[18] The chlorohydrins **7** required for the synthesis of **1** could easily synthesized by the reaction of epichlorohydrin **8a** with glycine ester **9**.



Scheme 1. Retro synthetic analysis of *cis*-4-hydroxyproline

The synthesis of **1** initiated using commercially available enantiomerically pure (*S*)-epichlorohydrin (**8a)** and *N*-benzyl glycine ethyl ester **9a** (**Scheme 2**). The *N*-Benzyl glycine ethyl ester **9a** was reacted with (*S*)-epichlorohydrin **8a** at ambient temperature to yield the chlorohydrin **7a**, which was then *in situ* converted to the amino epoxide **6a** using potassium carbonate and DMF at elevated temperature in 50% yield.[19] The key step, the intramolecular oxirane ring opening of **6a** leading to the formation of ethyl (2*R*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (**5a**) was designed under 5-endo-tet ring opening reaction conditions. Thus, amino epoxide **6a** was reacted with bases like NaH, KO^{t}Bu, NaOEt and LDA over a wide range of temperatures; however these reactions were failed to yield the required product **5a**. The oxirane ring opening in **6a,** was also attempted with 1.5 equiv of LiHMDS in THF in the temperature range of -60 °C to 0 °C, however, this reaction also resulted in the formation of a complex mixture of products. The experiments conducted with higher equiv of LiHMDS at different temperatures in solvents like 2-MeTHF, CPME, toluene, as well as in MTBE were also failed to yield 4-hydroxypyrrolidine-2-carboxylate **5a**. The inability of the oxirane **6a** to undergo disfavored 5-*endo-tet* ring closure reaction prompted us to use oxophilic metal halide as additive in the reaction to stabilize the lithium enolate as well as for the *in situ* generation of halohydrin (**Scheme2**). Thus, when the oxirane ring opening was carried out in presence of Zn(II), Mg(II), Li(I), as well as Cu(II) halides, the required product **5a** was obtained in various percentages as summarized in **Table 1**. The best diastereoselectivity and yield was obtained when the oxirane ring opening in 6a**,** was attempted with 1.5 equiv of LIHMDS in the presence of 1 equiv of $MgBr_2$. The product hydroxypyrrolidine-2-carboxylate **5a** with SOR $[\alpha]_D^{20}$ = +37.9° (c 1.0, $CHCl_3$)[20] was isolated in 78% yield with 99.5% *de*.[20] In-order to check the chiral purity of the ethyl (2*R*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (**5a**) by HPLC method, other diastereomers were synthesized as per the reported literature protocols.



Scheme 2. Synthesis of *cis*-4-hydroxyproline from chiral epoxide **6a**

The diastereoselective intramolecular 5-exo-tet ring closure reaction of **6a** leading to the formation of ethyl (2*R*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (**5a**) is assumed to proceed *via* tightly bound chelation controlled transition states. The lithium enolate formed from chiral epoxide **6a** by deprotonation with LiHMDS forms a highly stabilized magnesium enolate with $MgBr_2$ along with the liberation of halide ion. The magnesium enolate then activates the epoxide *via* coordination and forms halohydrin **10b.** The hydroxyl oxygen of halohydrin, enolate oxygen, and tertiary amine together forms a tricoordinate complex with the magnesium ion. The metal coordinated transition states such as **10a, 10b,** and **11a** ensure that the enolate oxygen and the hydroxyl oxygen will have *syn* facial orientation. The formation of these tightly bound magnesium coordinate complexes **10a, 10b,** and **11a** drives the diastereoselectivity in the reaction. (**Scheme 2)**

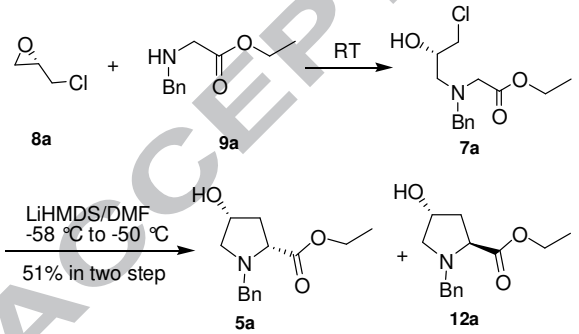
Table 1. Synthesis of *cis*-4-hydroxyproline from chiral epoxide **6a**

Entry	Substrate	Metal halide	Equiv of LiHMDS/ metal halide	Yield (%)	de(%)
1	6a	$ZnBr_2$	1.5/1.0	55[a]	98.5
2	6a	ZnI_2	1.5/1.0	63[a]	99.5
3	6a	$MgBr_2$	1.5/1.0	78[a]	99.5
4	6a	LiBr	1.5/1.0	30[b]	98.0

5	6a	LiCl	1.5/1.0	< 5%	Not analyzed
6	6a	$CuCl_2$	1.5/1.0	< 5%	Not analyzed

[a]The reaction terminated after 4h
[b]The reaction terminated after completion as per TLC

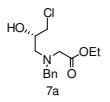
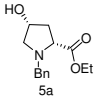
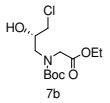
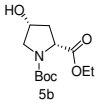
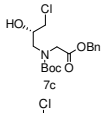
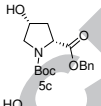
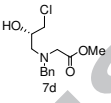
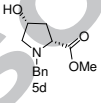
To get more mechanistic insight about the diastereoselective synthesis of (2*R*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (**5a**), we decided to use chiral chlorohydrin **7** instead of the epoxide **6** in the synthesis. For the synthesis of key intermediate ethyl-(S)-*N*-benzyl-*N*-(3-chloro-2-hydroxypropyl)glycinate(**7a),** ethyl benzyl glycinate **9a** was reacted with (*S*)-epichlorohydrin (**8a)** in neat conditions at 25-30 °C. When the 5-*exo tet* ring closure was attempted with LiHMDS in DMF at -60 °C, the required product (2*R*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (**5a**) was obtained approximately in 15% yield. Encouraged by this result, the reaction was attempted to optimize to improve the yield of required product **5a**. The use of excess equiv of LiHMDS didn't improve the yield of the reaction further. Surprisingly, when the reaction was conducted at slightly higher temperature (-50 °C), the required product (2*R*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (**5a**) was isolated in 51% yield with 99.5% *de*. The ring closure reaction went equally well when conducted in THF with LiHMDS at -50 °C and further maintenance at -5 °C over a period of 4h. The moderate yield as well as high diastereoselectivity achieved in this reaction is believed to be occurred by the *syn* complexation between the lithium enolate with –OH group, which is further stabilized by the coordinating solvents like DMF. (**Scheme 3**) Further variations in reaction conditions, and mol equiv of reagents didn't improve the yield of *cis*-4-hydroxy proline derivative **5a.** The synthesis of benzyl (*S*)-*N*-(tert-butoxycarbonyl)-*N*-(3-chloro-2-hydroxypropyl)glycinate (**7c)** was carried out by reacting glycine benzyl ester tosylate salt with (*S*)-epichlorohydrin (**8a)** in IPA followed by *in situ* Boc-protection in 51% overall yield. (**Table-2**)



Scheme 3. Synthesis of *cis*-4-hydroxyproline from chlorohydrin **7a**

To understand the impact of protecting groups in 4-hydroxypyrrolidine-2-carboxylate (**5**) synthesis, the reaction was carried out with different amine and acid protecting groups as described in **Table 2.** Amongst the protecting groups, the best yield (72%) of *cis*-proline derivative **5b** was obtained when the amine and acid functionality were protected with Boc and ethyl ester respectively; however a diminished *de* of 88% was obtained with these substrates.

Table 2. Synthesis of **3** from halohydrin **7** in DMF/THF at -50 °C

Entry	Substrate	Product	de (%)	Yield (%)
1	 7a	 5a	99.5	51
2	 7b	 5b	88.0	72
3	 7c	 5c	77.3	54
4	 7d	 5d	99.0	49

The formation of hydroxyl proline ester **5b** and **5c** with lesser *de* are probably due to the increased steric repulsion between the bulky amine and acid protecting groups which partially block the *syn* facial metal complexation between the lithium enolate and hydroxyl groups in the transition states of **14** and **15** respectively. **(Figure 2)**

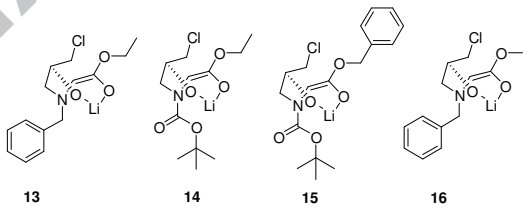
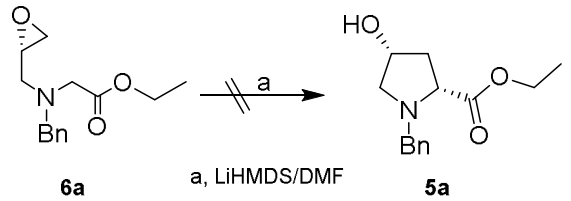


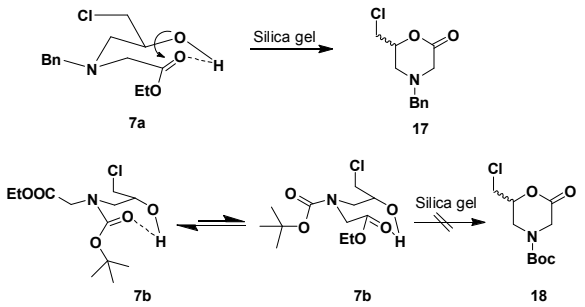
Figure 2. Transition state for the formation of **5a**, **5b**, **5c**, and **5d**

The chiral epoxide **6a** when subjected to hetero annulation reaction using DMF/LiHMDS/THF, it failed to yield *cis*-4-hydroxy proline derivative **5a,** which clearly proves that reaction didn't proceed as per less preferred 5-*endo tet* Baldwin cyclization pathway**.** React IR studies were also conducted to check the intermediacy of epoxide **6a** during the conversion of halohydrin **7a** to *cis*-4-hydroxy proline derivative **5**. These studies clearly rule out the intermediacy of epoxide **6a** during the conversion of chlorohydrin **7a** to *cis*-proline derivative **5a** and the reaction proceed through the preferred Baldwin's 5-*exo tet* pathway.[22] (**Scheme 4**)



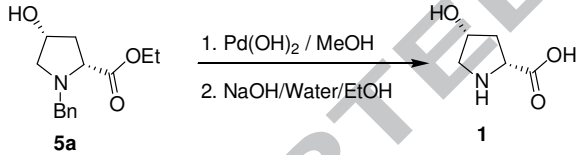
Scheme 4. Attempted Synthesis of 4-hydroxyproline from epoxide **6a**

Interestingly, during the course of the purification of halohydrin **7a** by silica gel column chromatography, lactone **17** was isolated in 20% yield. This silica gel assisted lactonization of **7a** is probably due to the favored conformational orientation of **7a** *via* hydrogen bonding between the carbonyl carbon of ethyl ester and the hydroxyl group**,** which favors the intramolecular lactonization. The halohydrin **7b** has failed to yield the lactone **18** even after stirring **7b** with silica gel in various percentage of hexane and ethyl acetate mixture (**Scheme 5**) on prolonged time, as well as at elevated temperature.



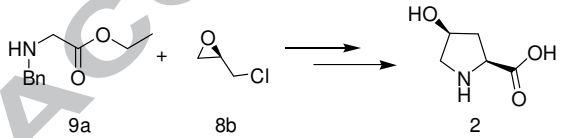
Scheme 5. The lactonization of chlorohydrin **7a**

The ethyl (2*R*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate **5a** was then converted to (2*R*, 4*R*)-4-hydroxy-proline (**1**) by debenzylation with $Pd(OH)_2$ followed by hydrolysis of ester with aqueous sodium hydroxide in 80% yield (**Scheme 6**) over two steps. The SOR, spectral and analytical data of (2*R,4R*)-4-hydroxypyrrolidine-2-carboxylic acid **1** thus obtained is identical to the values reported in the literature.



Scheme 6. Synthesis of (2*R*, 4*R*)-4-hydroxy-proline (**1**)

In a similar way, (2*S*,4*S*)-4-hydroxypyrrolidine-2-carboxylic acid **2** was also synthesized in high *de* (99.5%) in moderate yields starting from (*R*)-epichlorohydrin **8b** and glycine ester **9a** as described in **Scheme 7**.



Scheme 7. Synthesis of (2*S*, 4*S*)-4-hydroxy-proline (**2**)

In conclusion, a concise and highly diastereoselective synthesis of (2*R*,4*R*)-4-hydroxyprolineand (2*S*,4*S*)-4-hydroxyprolinein high *de* have been developed from readily accessible starting materials in moderate yields. The high *de* observed in the synthesis of *cis* 4-hydroxyproline is probably due to the highly chelated complex formed during the *exo tet* ring closure process, as well as *via* the stabilization of the enolate by coordinating solvent. The application of this methodology for the diastereoselective synthesis of densely functionalized diverse products is under progress and will report in due course of time.

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References and notes

1. (a) Kaeothip, S.; Ishiwata, A.; Ito Y. *Org. Biomol. Chem.* **2013**, *11*, 5892-5907; (b) Shinohara, H.; Matsubayashi, Y. *Plant Cell Physiol.* **2013**, *54*, 369-374; (c) Wakamiya, T.; Yamanoi, K.; Kanou, K.; Shiba, T. *Tetrahedron Lett.* **1987**, *28*, 5887-5888.
2. (a) Pippel, D. J.; Young L. K.; Letavic, M. A.; Ly, K. S.; Naderi, B.; Soyode-Johnson, A.; Stocking, E. M.; Carruthers, N. I.; Mani, N. S. *J. Org. Chem.* **2010**, *75*, 4463-4471; (b) Thottathil, J. K.; Moniot, J. L. *Tetrahedron Lett.* **1986**, *27*, 151-154; (c) Kronenthal, D. R.; Mueller, R. H.; Kuester, P. L.; Kissick, T. P.; Johnson, E. J. *Tetrahedron Lett***.** **1990**, *31*, 1241-1244.
3. (a) Ducho, C.; Hamed, R. B.; Batchelar, E. T.; Sorensen, J. L.; Odell, B.; Schofield, C. J. *Org. Biomol. Chem.* **2009**, *7*, 2770-2779; (b) Remuzon, P. *Tetrahedron,* **1996**, *52*, 13803-13835.
4. Suzuki, R.; Tojo, Y.; Mizumoto, C.; Hasegawa, K.; Ashida, Y.; Hosoi, Jun-ichi.; Sato, K, US20120122951 A1**.**
5. (a) Wieland, H.; Witkop, B. *Liebigs. Ann. Chem.* **1940**, *543*, 171-183; (b) Yu M.; Deming, T. J. *Macromolecules*, **1998**, *31*, 4739-4745; (c) Ohtani, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y.; Hirsh S. *J. Am. Chem. Soc.* **1992**, *114***,** 8472-8479.
6. Irreverre, F.; Morita, K.; Robertson, A. V.; Witkop, B. *J. Am. Chem. Soc.* **1963**, *85*, 2824-2831.
7. Leuchs H., *Berlin*. **1905**, *38*, 1937-1943.
8. Roberson, A.V.; Katz, E.; Witkop, B. *J. Org. Chem.* **1962**, *27*, 2676-2677.
9. Papaioannou, D.; Stavropoulos, G.; Kargiannis, K.; Francis, G. W.; Brekke, T.; Aksnes, D. W. *Acta Chem. Scand.* **1990**, *44*, 243-251.
10. (a) Seki, M.; Matsumoto, K. *Biosci. Biotech. Biochem.* **1995**, *59*, 1161-1162; (b) Madau, A.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry,* **1996**, *7*, 825-830.
11. Mehlfuhrer, M.; Berner, H.; Thirring, K. *J. Chem. Soc., Chem. Commun*. **1994**, 1291.
12. Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglish, W.; Reuter, H.; Puff, H. *Tetrahedron,* **1985**, *41*, 1693-1701.
13. Graziani, L.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **1996**, 1341-1346.
14. (a) Burger, K.; Rudolph, M.; Fehn, S. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 285-287; (b) Mereyala, H. B.; Pathuri, G.; Nagarapu, L. *Synthetic Comm.* **2012**, *42*, 1278-1287.
15. (a) Sigmund, A. E.; Hong, W.; Shapiro, R.; Dicosimo, R. *Adv. Synth. Catal*. **2001**, *343*, 587-590; (b) Christian, K.; Wolfgang, H. *Beilstein J. Org. Chem.* **2011**, *7,* 1643-1647.
16. Kimura, R.; Nagano, T.; Kinoshita, H. *Bull. Chem. Soc. Jpn*, **2002**, *75*, 2517-2525.
17. (a) Srinivasan, A. K.; Shyamapada, B.; Syam Kumar, U. K, *Org. Biomol. Chem.* **2014**, *12,* 6105-6113 (b) Suresh Babu, M.; Ramamohan, M.; Raghunadh, A.; Raghavendra Rao, K.; Vilas H. Dahanukar, Pratap, T. V.; Syam Kumar, U. K.; Dubey P. K. *Tet Lett, **2014**,* 55, 4739-4741 (c) Raghunadh, A.; Suresh Babu, M.; Ramamohan, M.; Raghavendra Rao, K.; Krishna, T.; Gangadhara Chary, R.; Rao, V. L.; Syam Kumar U. K. *Tet Lett*, **2014**, *55*, 2986-2990 (d) Sandip. R. K.; Vikas, S. G.; Subbarao, J.; Syam Kumar U. K.; Y. L. N. Murthy, *Tet Lett*, **2013**, *54*, 2909-2912 (e) Shankar, R.; More, Satish S.; Madhubabu, M. V.; Vembu, N.; Syam Kumar, U. K. *Synlett*, **2012**, *23*, 1013–1020 (f) Raghunadh, A.; Suresh Babu, M.; Anil Kumar, N.; Santosh, G.; Rao, V.L.; Syam Kumar, U. K. *Synthesis*, **2012**, *44*, 283–289 (g) Shankar, R.; Manoj, B. W.; Madhubabu, M. V.; Vembu, N.; Syam Kumar, U. K. *Synlett***,** **2011**, *6*, 844–0848 (h) Manoj B. W.; Shankar, R.; Syam Kumar U. K.; Gill, C. H. *Synlett*, **2011**, *1*, 84–88 (i) Shanmugapriya, D.; Shankar, R.; Satyanarayana, G.; Vilas, H. D.; Syam Kumar, U. K.; Vembu, N. *Synlett*, **2008**, *19*, 2945–2950
18. Kolaczkowski, L.; Barnes, D. M. *Org. Lett*. **2007**, *9*, 3029-3032.

19. ***(S)-ethyl 2-(benzyl (oxiran-2-ylmethyl)amino)acetate) (6a)***: pale yellow viscous liquid. (Yield = 50%)^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.26 (t, *J* = 7.3 Hz, 3H), 2.47 (dd, *J* = 2.9 Hz, 1H), 2.63 – 2.73 (m, 2H), 2.98 (dd, *J* = 3.4, 1H), 3.01 – 3.11 (m, 1H), 3.45 (s, 2H), 3.81 (d, *J* = 13.7 Hz, 1H), 3.92 (d, *J* = 13.7 Hz, 1H), 4.14 (q, *J* = 7.4 & 6.8 Hz, 2H), 7.25 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.2, 44.69, 51.08, 54.66, 56.03, 58.76, 60.24, 127.17, 128.27, 128.89, 138.55, 171.27. IR: 3685, 3019, 2400, 1732, 1520, 1495, 1477, 1214, 775, 669. HRMS (ESI): Calcd for $C_{14}H_{20}NO_3$ $(M+H)^+$ 250.1443, found 250.1433. $[\alpha]_D^{25}$ = 1.22 ° (c 0.5, $CHCl_3$).
20. Heindl, C.; Hubner, H.; Gmeiner, P. *Tetrahedron: Asymmetry*, **2003**, *14*, 3141-3152.
21. ***Procedure for the synthesis of 5a***: A solution of (S)-ethyl 2-(benzyl (oxiran-2-ylmethyl)amino)acetate) **6a** (500 mg, 2.01 mmol) in THF (7.5 mL, 15 vol) was cooled to – 60 °C and was added 1.5 equiv of 1 M LiHMDS in THF (3 mL, 3.01 mmol). The reaction mixture was then allowed to warm to – 15 °C for 10 minutes and cooled to -60 °C. $MgBr_2$. etherate (622 mg, 2.41 mmol, 1 equiv) or $Zn(II)I_2$ (1 equiv) in THF (2.5 v) was added into the reaction mixture over a period of 30 minutes. The reaction mixture was then maintained at room temperature and was stirred for 3 h. It was then cooled to -10 °C, quenched with aqueous saturated NH_4Cl solution (50 mL) and diluted with ethyl acetate (25 mL). The layers were separated, the aqueous layer extracted with ethyl acetate (2X 10 mL). The combined organic layers were washed with water, 10% brine solution, dried over sodium sulfate and evaporated. Crude product was then purified by column chromatography on silica gel (230-400 mesh) using ethyl acetate and hexane (1:4) to afford 390 mg of title compound as a pale yellow liquid. Yield: 78% ($MgBr_2$), 63 % (ZnI_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.21 (t, *J* = 7.4 Hz, 3H), 1.9 - 2.0 (m, 1H), 2.33 – 2.4 (m, 1H), 2.64 (dd, *J* = 3.9 and 4.4 Hz, 1H), 3.01 (d, *J* = 9.8 Hz, 1H), 3.2 (brs, 1H), 3.33 (dd, 3.5 and 3.4 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.87 (d, *J* = 13.2 Hz, 1H), 4.07 (m, 2H), 4.24 (m, 1H), 7.2-7.31 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.06, 39.11, 58.07, 60.96, 61.78, 63.39, 70.91, 127.18, 128.2, 128.92, 138.01, 175.10. IR: 3451, 1729, 1454, 1376, 1216, 756, 700. HRMS (ESI): Calcd for $C_{14}H_{20}NO_3$ $(M+H)^+$ 250.1443, found 250.1436. $[\alpha]_D^{20}$ = +39.04° (c 1.0, $CHCl_3$), $[\alpha]_D^{20}$ = +37.9° (c 1.0, $CHCl_3$). % *de* (HPLC) = 99.5.
22. Nicolaou, K. C, Prasad, C. V. C.; Somer, P. K.; Hwang, C.-K. *J. Am. Chem, Soc.* **1989**, *111*, 5331-5334.

Supplementary Material

Supplementary data (detailed experimental analysis and spectral analysis including ^{1}H, ^{13}C, and HRMS associated with this article can be found, in the online version, at http://