Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2015, 7(1):201-205
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

A facile stereoselective total synthesis of (S)-N-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol

B. Narasimha Reddy[a] and R. P. Sing[a,b*]

[a]*Polymer Science and Engineering Division, National Chemical Laboratory, Pashan Road, Pune, India*
[b]*Present address: Advanced Research Centre in Pharmaceutical Sciences & Applied Chemistry, Bharthi Vidyapeeth University, Erandwane, Pune*

ABSTRACT

A novel and highly efficient synthesis of (S)-N-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol, a Notch-1-sparing-γ-secretase inhibitor employing sharpless asymmetric epoxidation of allyl alcohol has been accomplished. The synthesis also demonstrates the effective use of regioselective reductive opening of epoxy alcohols.

Key words: Notch-1-sparing-γ-secretase, Alzheimer's disease, Sharplessepoxidation, selective hydride reduction.

INTRODUCTION

Alzheimer's disease (AD) is a common neurodegenerative disease characterized by progressive deterioration of memory, dementia, severe behavioral abnormalities, ultimately leading to death.[1]The AD is believed to be caused by the accumulation of extracellular senile plaques made primarily by deposits of amyliod-beta (Aβ) peptides on the nerve cells that are produced by the proteolytic cleavage of amyloid precursor protein (APP). (S)-N-(5-chlorothiophene-2-sulfonyl)-b,b-diethylalaninol, a Notch-1-sparing-γ-secretase inhibitor has become an interesting synthetic target due to its promising activity in reducing the production of Aβ in vivo.[3] Despite its remarkable activity, a very few syntheses were reported in the literature.[3,4]

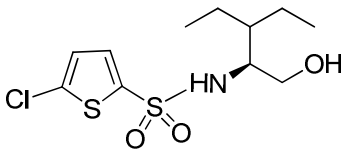


Fig. 1: (S)-N-(5-chlorothiophene-2-sulfonyl)-b,b-diethylalaninol (**1**)

In this communication we describe the synthesis of **1** starting from inexpensive, commercially available starting materials. Sharplessepoxidation of allyl alcohol followed by selective hydride reduction of epoxy alcohol affords 1,3-diol with high stereoselectivity.These chiral 1,3-diols are versatile synthetic intermediates for variety of biologically active molecules[5]. The retrosynthetic strategy of our synthesis is depicted in scheme 1, which involves Sharpless epoxidation and regioselective reductive opening of epoxide as the key reactions.

MATERIALS AND METHODS

General information: Solvents were purified and dried by standard procedures before use. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. IR spectra were recorded on Thermo Scientific-Nicolet 380 FT-IR Instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on Brucker AC-200 spectrometer. Elemental analysis was carried out on a Carlo Erba CHNS-O analyzer.

4.2. Ethyl 3-ethylpent-2-enoate, 3

To a stirred suspension of NaH (60 % dispersion in mineral oil,0.96g, 40mmol) in dry THF (50 mL) a solution of triethylphosphonoacetate (5.2 g, 24mmol) in dry THF (10 mL) was added dropwiseat 0 ^{o}C followed by the addition of a solution of 3-pentanone (1.4 g, 16mmol) in dry THF (10 mL). The reaction mixture was then stirred at 25 ^{o}C for 8 h. After completion of the reaction (monitored by TLC), it was quenched with saturated solution of ammonium chloride and the product with extracted with diethyl ether. The combined organic layer was then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure and column chromatographic purification (100-200 mesh, EtOAc/hexane, 1:9) gave α,β- unsaturated ester **3** as colorless liquid. Yield: 90%; IR ($CHCl_3$, cm^{-1}) 867, 1147, 1273, 1444, 1634, 1719, 2877, 2972; ^{1}H NMR (200 MHz, $CDCl_3$): 1.07 (t, *J* = 7.8 Hz, 6 H), 1.28 (t, *J* = 7.7 Hz, 3 H), 2.18 (q, *J* = 6.5, 8.1 Hz, 2 H), 2.60 (q, *J* = 8.1, 14.2 Hz, 2 H), 4.12 (q, *J* = 8.1, 16.1 Hz, 2 H), 5.59 (s, 1 H); ^{13}CNMR(50 MHz, $CDCl_3$): δ 11.9, 12.9, 14.2, 25.3, 30.7, 59.3, 113.6, 166.5, 167.2;Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32; found C, 69.29; H, 10.37%.

4.3. Ethyl-3-ethylpent-2-en-1-ol, 4

To a suspension of Lithium Aluminium hydride (0.486 g,12.8 mmol) in dry THF at 0^{o}C under N_2 atmosphere was added a drop wise solution of $AlCl_3$ (0.577 g, 4.3 mmol) in THF. The reaction mixture was stirred at the same temperature for 30 min. To this stirred suspension, was added a drop wise solution of unsaturated ester **3** (1 g, 8.54 mmol) in THF over a period of 10 min and stirred at 0^{o}C for 1h. The reaction mixture was then quenched with water and filtered through Celite. The residue was washed with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed over silica gel (100-200 mesh, EtOAc/hexane, 2:8) yielding pure allylalcohol**4** as colorless liquid; Yield 78%;IR (neat, cm^{-1}): 906, 995, 1020,1115, 1236, 1409, 1619, 2861, 2983, 3356; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85-1.06 (m, 6H), 1.45 (br s, 1H), 2.1-2.15 (m, 4H), 4.17(d, J = 6.95 Hz, 2H), 5.32-5.39 (t, J = 7.07 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.31, 13.51, 23.42, 28.94, 58.79, 121.52, 148.59;Anal. Calcd for$C_7H_{14}O$: C, 73.63; H, 12.36; found C, 73.96; H, 12.46%.

4.4. (S)-(3,3-diethyloxiran-2-yl)methanol, 5

(-)- Diethyl tartarate (0.2g, 1mmol), Ti(O-iPr)$_4$ (0.23g,0.8mmol) were added sequentially to a suspension of 4A^o molecular sieves (3 g) in CH_2Cl_2 (20 mL) at -20 ^{o}C and the suspension was stirred for 30 min. A solution of Compound **4**(0.3 g, 2.6 mmol) in dry CH_2Cl_2 (15 mL) was then added drop wise at the same temperature followed by the addition of tBuOOH (0.45 g, 2 mmol)) and the reaction mixture was stirred for 12 h at -10 ^{o}C.After completion of the reaction (as monitored by TLC), the reaction was quenched with 20% NaOH solution saturated with NaCl(1 mL) and the reaction mixture was stirred vigorously for another 30 min at RT. The resulting reaction mixture was filtered through celite, the solvent was evaporated, and the crude product was purified by column chromatography over silica gel (100-200 mesh, EtOAc/hexane 3:7) to afford pure epoxy alcohol **5**as colorless viscous liquid: Yield 87%; $[\alpha]_D^{25}$ + 17.9 (*c* 0.6, $CHCl_3$);IR (neat, cm^{-1}): 798, 889, 1097, 1257, 1367, 2857, 3365; ^{1}H NMR (200 MHz, $CDCl_3$): δ0.89-1.02 (m, 6H), 1.47-1.69 (m, 4H), 2.09 (br s, 1H), 2.98-3.03 (m, 1H), 3.64-3.73 (m, 1H), 3.82-3.91 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.74, 9.95, 23.1, 27.17, 61.87, 63.06, 64.86;Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84; found C, 64.92; H, 10.37%.

4.5. (R)-3-ethylpentane-1,2-diol, 6

To a stirred solution of compound **5** (1.225g, 5mmol) in dry benzene, was added diisobutylaluminium hydride (1M solution in toulene, 5 mL) dropwise at room temperature. The reaction mixture was stirred for 1h at the same temperature and upon completion of the reaction; reaction mixture was diluted with a saturated solution of sodium potassium tartarate and stirred for another 4h. The organic phase was separated and the aqueous phase was treated with EtOAc thrice. The combined organic layer was then washed with water, brine and finally dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure to give crude product, which was further purified by column chromatography over silica gel (100-200 mesh, EtOAc/hexane 1:9) to afford pure product**7**as colorless liquid in 87% yield; $[\alpha]_D^{25}$ -4.9 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}): 1073, 1124, 1379, 1461, 2875, 2961, 3387; ^{1}H NMR

(200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.4 Hz, 6 H), 1.29-1.52 (m, 5 H), 2.04-2.16 (m, 2 H), 3.44-3.70 (m, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.3, 11.4, 21.2, 21.6, 43.7, 64.9, 73.6. Anal. Calcd for$C_7H_{16}O_2$: C, 63.60; H, 12.20; found C, 63.63; H, 12.25%.

4.6. (R)-1-((tert-butyldimethylsilyl)oxy)-3-ethylpentan-2-ol, 7

To a solution of diol**5** (1.97 g, 15.14 mmol) in dry CH_2Cl_2 (50 mL) at 0 ^oC was added imidazole (1.54 g, 22.70 mmol) and *tert*-butyldimethylsilyl chloride (2.51 g, 16.65 mmol). The reaction mixture was then stirred at 25 ^oC for 4 h. After completion of reaction (monitored by TLC), it was diluted with CH_2Cl_2, washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave the crude product which was then purified by column chromatography over silica gel (100-200 mesh, EtOAc/hexane 2:8)to furnish **6** as colorless liquid.Yield: 82%; $[\alpha]_D^{25}$ -5.0 (*c* 1.6, $CHCl_3$); IR (neat, cm^{-1}): 836, 1097, 1256, 1462, 2858, 2929, 2958, 3437; ^1H NMR (200 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.86-0.98 (m, 15H), 1.33–1.53 (m, 6H), 2.37 (br.s, 1H), 3.46-3.69 (m, 3 H);^{13}C NMR (50 MHz, $CDCl_3$): δ -5.3, -5.2, 11.2, 11.4, 18.3, 21.1, 21.6, 25.9, 43.2, 65.5, 72.9; Anal. Calcd for$C_{13}H_{30}SiO_2$: C, 63.35; H, 12.27; found C, 63.68; H, 12.21%.

4.7. ((*S*)-2-azido-3-ethylpentyloxy)(tert-butyl)dimethylsilane, 8

Compound **7** (312 mg, 1mmol) and triethylamine (0.3 g, 3 mmol) were dissolved in dry CH_2Cl_2 (15 mL), and the solution cooled to 0 ^oC.Methanesulfonyl chloride (229.2 mg, 2 mmol) was added, and then the resulting solution was stirred at 0 ^oC for 30 min. After TLC showed that the reaction was complete, more CH_2Cl_2 (20 mL) was added. The organic phase was washed with brine and then dried over anhydrous Na_2SO_4. After the solvent was removed under vaccum, the crude product was dissolved in DMF and NaN_3 (390 mg, 6 mmol) was added. The reaction mixture was then stirred at 60 ^oC for 30 h. After the completion of reaction (monitored by TLC), the reaction mixture is then partitioned between EtOAc and brine. The organic layer is further washed with brine, dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude product which on column chromatography over silica gel (100-200 mesh, EtOAc/hexane 1:9) gave the corresponding azide **8**.Yield: 74%; $[\alpha]_D^{25}$:-21.8 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 837, 964, 1214, 1251, 1459, 1490, 1603, 2113, 2894, 3069; ^1H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.85-0.92 (m, 15H), 1.34-1.38 (m, 5H), 3.39-3.45 (m, 1H), 3.64-3.79 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -5.7, 11.2, 11.3, 18.2, 21.7, 22.6, 25.8, 41.9, 65.1, 66.2; Anal. Calcd for $C_{13}H_{29}N_3OSi$: C, 57.52; H, 10.77; N, 15.48; found C, 57.51; H, 10.85; N, 15.55%.

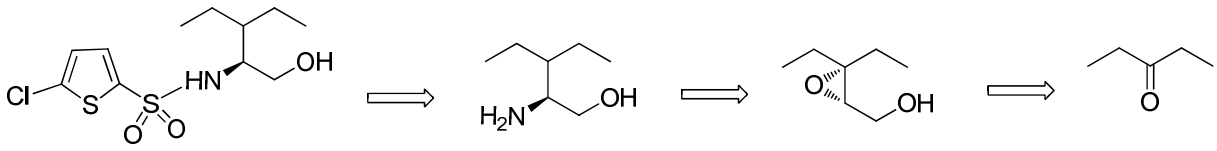
4.8. (S)-2-amino-3-ethylpentan-1-ol, 9

To a suspension of $LiAlH_4$ (1.01 g, 26.66 mmol) in dry THF (30 mL), a solution of azido compound **8** (5.0 g, 24.24 mmol) in THF (50 mL) was added dropwise at 0 °C. The reaction mixture was then stirred at 50 ^oC for 12 h. After completion of reaction (monitored by TLC), it was quenched with aq. 20% solution of sodium hydroxide (2 mL) at 0 °C. The reaction mixture was filtered through sintered funnel, dried over anhydrous Na_2SO_4 and concentrated. Purification by column chromatography over silica gel (100-200 mesh, EtOAc/hexane 7:3) gave the amino alcohol **10** as a colorless liquid.Yield: 98%; $[\alpha]_D^{25}$ -12.3 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}): 3020, 2930, 2857, 1722, 1572, 1472, 1215; ^1H NMR (200 MHz, $CDCl_3$): 0.83-0.92 (m, 6H), 1.23-1.42 (m, 5H), 2.34 (br.s, 3H), 2.83 (m, 1H), 3.26-3.35 (m, 1H), 3.57-3.69 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.4, 11.5, 21.4, 21.8, 44.8, 54.9, 64.3; Anal. Calcd for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.67; found C, 64.34; H, 12.86; N, 10.42%.

4.9. (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol, 1

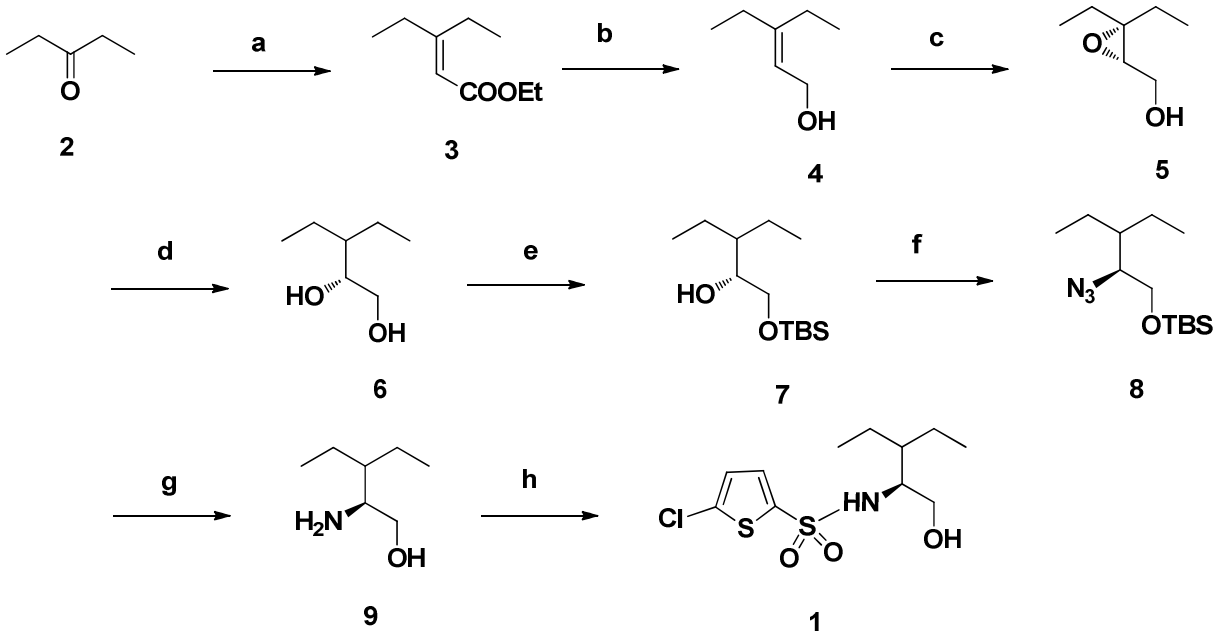
To a solution of amino alcohol **9** (1.0 g, 11.2 mmol) in dry CH_2Cl_2 (50 mL) at 0 ºC was added imidazole (0.916 g, 13.4 mmol,) after stirring for 10 min.,5-chlorothiophene-2-sulfonyl chloride(1.8 g, 12.3 mmol,) was added and the reaction mixture was stirred at 25 ºC for 3 h. After completion of the reaction, solvent was removed under reduced pressure and the crude product was then purified by column chromatography over neutral Al_2O_3 (pet ether: EtOAc, 70:30).Yield: 90%; Colorless crystalline solid; m.p.114-116^oC (crystallized from heptane:ethylacetate, 4:1) {lit.[3a]m.p. 115-117.6 ^oC}; $[\alpha]_D^{25}$ +10.3 (*c* 0.6, MeOH) {lit.[3a] $[\alpha]_D^{25}$ +10.81 (1% solution, MeOH)}; IR ($CHCl_3$, cm^{-1}):1093,1133,1339,1456,1617,2882,2956,3034,3065,3301,3515;^1H NMR (200 MHz, $CDCl_3$) δ 0.78-0.87 (m, 6H), 1.17-1.34 (m, 5H), 1.94 (br. s, 1H), 3.30-3.42 (m, 1H), 3.57-3.60 (m, 2H), 4.93 (br. s, 1H), 6.93 (d, *J* = 4.1 Hz, 1H), 7.42 (d, *J* = 4.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.4, 11.7, 22.7, 21.9, 42.7, 57.8, 62.6, 126.6, 131.5, 137.3, 140.1; Anal. Calcd for $C_{11}H_{18}ClNO_3S_2$: C, 42.37; H, 5.82; N, 4.49; found C, 42.26; H, 5.71; N, 4.55%.

RESULTS AND DISCUSSION



Scheme 1. Retrosynthesis of compound **1**.

As outlined in scheme 2, the synthesis of **1** commences with commercially available 2-pentanone, which on Horner-Wardsworth-Emmons olefination with triethyl phosphonoacetate in presence of NaH in dry THF yielded α,β–unsaturated ester **3** in 90% yield. The compound **3** was subsequently reduced to allyl alcohol**4** by employing alane reduction conditions[6] *(*$LiAlH_4$, $AlCl_3$, THF, 0^oC, 1h, 90%). The allyl alcohol **3** was then subjected to Sharpless asymmetric epoxidation[7] with titanium tetraisopropoxide and t-butyl hydroperoxide in presence of (-)- DET to produce epoxy alcohol **5** in 87% yields.



Scheme 2*: Reagents and conditions:(a) triethylphosphonoacetate, NaH, dry THF, 0 ºC-RT, 8 h, 90%;(b)* $LiAlH_4$*,* $AlCl_3$*, THF,0°C, 1h, 78%; (c) (-)- DET, Ti(O-iPr)*$_4$*, TBHP, dry* CH_2Cl_2*, molecular sieves 4 A°, -15 °C, 87%; (d) DIBAL-H, benzene, RT, 1h, 89% ;(e)TBSCl, imid,* CH_2Cl_2*, 0-25 ºC, 4 h, 82%;(f)(i) MsCl,* Et_3N*, 30 min; (ii)* NaN_3*, dry DMF, 60 ºC, 30 h, 74%; (g)* $LiAlH_4$*, dry THF, 50 ºC, 12 h, 98%; (h) 5-chlorothiophene-2-sulfonyl chloride,* Et_3N*, dry* CH_2Cl_2*, 0 °C, 30 min., 90%.*

Regioselective hydride reduction[8] of epoxyalcohol **5** with DIBAL-H in benzene at room temperature afforded diol **6** in good yield. The primary hydroxyl group in **6** was then selectively protected as its TBS ether using TBSCl and Imidazole in dry DCM to yield **7** in 82 % yield. Further, the remaining secondary hydroxyl group was converted to its mesylate (a good leaving group) with methanesulfonyl chloride and triethyl amine as base. As the mesylates are generally unstable, the crude mesylate was immediately treated with NaN_3 in DMF at 60 ^oC to afford azide compound **7** in 74% yields. The azide group in **7** was reduced with $LiAlH_4$ in dry THF at 50 ^oC to yield amino alcoholic compound **8** with the simultaneous removal TBS group[9].

Then the final task was to condense amino alcohol **8** with commercially available 5-chlorothiophene-2-sulfonyl chloride, which was accomplished in presence of Et_3N in dry DCM to get target molecule **1** in 90% yield.

CONCLUSION

In conclusion, the stereoselective total synthesis of(S)-N-(5-chlorothiophene-2-sulfonyl)-b,b-diethylalaninol, a potent Notch-1-sparing-γ-secretase inhibitor has been accomplished starting from inexpensive 2-pentanone by the successful application of Sharplessepoxidation and selective hydride reduction of epoxy alcohols. The synthetic route can conveniently be utilized for the synthesis of analogs of **1**.

Acknowledgements
One of the authors, B.N.R. thanks CSIR, New Delhi for the award of research fellowship. The authors are also thankful to the Director, NCL for constant support and encouragement.

REFERENCES

[1] (a) Suzhen, D.;Yale, D.;Yinghe, H.; Zheng, Z. *Translational Neurodegeneration* **2012**, 1:18; (b) Hardy, J. A.; Higgins, G. A. *Science* **1992**, *256*, 184; (c) Schenk, D. B.; Rydel, R. E.; May, P.; Little, S.; Panetta, J.; Lieberburg, I.; Sinha, S.*J. Med.Chem.***1995**,*38*, 4141; (d) Katzman, R. N. *Engl. J. Med*. **1986**, *314*, 964.
[2] (a) Hardy J,; Higgins G. A.*Science* **1992,***256*, 184;(b) Hardy, J.; Selkoe, D. J,;*Science***2002**, *297*, 353.
[3] (a) Mayer, S. C.; Kreft, A. F.; Harrison, B.; Gharbia, M. A.; Antane, M.;Aschmies, S.; Atchison, K.; Chlenov, M.; Cole, D. C.; Comery, T.; Diamantidis, G.;Ellingboe, J.; Fan, K.; Galante, R.; Gonzales, C.; Ho, D. M.; Hoke, M. E.; Hu, Y.;Huryn, D.; Jain, U.; Jin, M.; Kremer, K.; Kubrak, D.; Lin, M.; Lu, P.; Magolda, R.Martone, R.; Moore, W.; Oganesian, A.; Pangalos, M. N.; Porte, A.; Reinhart, P.;Resnick, L.; Riddell, D. R.; Reines, J. S.; Stock, J. R.; Sun, S. C.; Wagner, E.; Wang,T.; Woller, K.; Xu, Z.; Zaleska, M. M.; Zeldis, J.; Zhang, M.; Zhou, H.; Jacobsen, J.S. *J. Med. Chem*. **2008**, *51*, 7348; (b) Cole, D. C.; Stock, J. R.; Kreft, A. F.; Antane, M.;Aschmies, S. H.; Atchison, K. P.; Casebier, D. S.; Comery, T. A.; Diamantidis, G.;Ellingboe, J. W.; Harrison, B.L.; Hu, Y.; Jin, M.; Kubrak, D. M.; Lu, P.; Mann, C. W.;Martone, R. L.; Moore, W.J.; Oganesian, A.; Riddell, D. R.; Reines, J. S.; Sun, S. C.;Wagner, E.; Wang, Z.;Woller, K. R.; Xu, Z.; Zhou, H.; Jacobsen, J. S. *Bioorg. Med. Chem.Lett.***2009**, *19*,926.
[4] Varun, R.; Pandurang V. C.; Vilas B. C.;Gurunath S.; Sudalai, A. *Tetrahedron Lett*. **2010**, *51*, 6565.
[5] (a) Sabitha, G.; Bhaskar, V.; Yadav, J.S.*Tetrahedron Letters*. **2006**, *47*,8179; (b) Godwia, C.G Pais,;Fernandes, R.; kumar, P.*Tetrahedron* **1999**, *55*, 13445; (c) Bode, E. S.; Wolberg, M.; Muller, M. *Synthesis* **2006**, *47*, 8179-8181.
[6] Yadav, J.S.; Suresh Reddy, Ch. *Org. Lett.* **2009**, *11*, 1705.
[7] (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1980**, *102*, 5974 (b) Gao, Y.; Hanson, R.M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
[8] James M. F.; YishitoK. *Tetrahedron Lett.* **1982**, *23*, 2713.
[9] Erik F. J.; Johannes, B.; Arnevander, G. *J. Org. Chem.* **1994,** *59***,** 7133.