Tetrahedron 65 (2009) 2605–2609

Contents lists available at ScienceDirect

Tetrahedron

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

An efficient formal synthesis of (*S*)-dapoxetine from enantiopure 3-hydroxy azetidin-2-one

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ARTICLE INFO

Article history:
Received 27 July 2008
Received in revised form 11 November 2008
Accepted 14 November 2008
Available online 24 November 2008

Keywords:
Enantioselective synthesis
β-Lactams
Azetidin-2-ones
Reduction
Staudinger reaction

ABSTRACT

An efficient formal synthesis of *S*-(+) dapoxetine starting from 3-hydroxy azetidin-2-one is described. The intermediate (*S*)-3-(dimethyl amino)-3-phenylpropan-1-ol was synthesized in enantiopure form starting with 3-hydroxy azetidin-2-one in seven steps.

1. Introduction

Substituted azetidin-2-ones have been of sustained interest to the synthetic and medicinal chemists, as they are part structures of the penicillin antibiotics,[1–3] which have been proved to be a boon to the mankind. Apart from this, another field of β-lactam chemistry, which has shown an astonishing growth is their use as synthons for molecules of biological and medicinal interest.[4–6] The field has been reviewed[7c] extensively and continues to be an active area of research. We have been engaged in the use of enantiopure β-lactams as synthons for biologically important molecules and intermediates.[7,8] As a part of this research program, we herein present our work on an enantioselective formal synthesis of (*S*)-dapoxetine from an optically pure 3-hydroxy β-lactam.

Stress related ailments have seen a precipitous rise world over, with life becoming faster paced than ever. Depression is one such psychiatric disorder affecting people of all ages and genders around the globe. Treatment of depression, among other methods, involves use of selective serotonin re-uptake inhibitors (SSRI's). Prozac, Paxil, and Zoloft (Fig. 1) are few such SSRI's. (*S*)-Dapoxetine (**1**) (Fig. 2) is another such SSRI, which is structurally related to Prozac and is widely recommended against depression and bulimia.[9] In addition to its use as an SSRI, (*S*)-dapoxetine is now being tested as a cure for premature ejaculation,[10] a sexual disorder in men, which is another fall-out of high stress. Phase III clinical trials on patients with premature ejaculation have shown (*S*)-dapoxetine to be effective in delaying ejaculation without any major side effect except nausea. (*S*)-Dapoxetine thus, is a strong contender to join the class of Viagra®, Levittra®, Cialis®, and Dostinex® as a drug intended to better male sexual health. Very few reports are available in the literature for the synthesis of this potentially useful molecule. Recently, a report illustrated use of Sharpless asymmetric dihydroxylation for enantioselective synthesis of (*S*)-dapoxetine.[11] Another synthesis of (S)-dapoxetine by Gotor et al. uses enzymatic resolution of 3-amino-3-phenylpropan-1-ol with *Candida antarctica* lipase A (CAL-A) as the key step.[12] Use of radiochemical reaction has also been employed for the synthesis of (*S*)-dapoxetine from (*S*)-(+)-*N*-methyl-α-[2-(1-naphthalenyloxy)ethyl]benzene methanamine hydrochloride using methyl iodide.[13] Koizumi et al. have reported a formal synthesis of (*S*)-dapoxetine, wherein they achieved the synthesis of intermediate (*S*)-3-(dimethyl amino)-3-phenylpropan-1-ol (**15**) using 1,3-dipolar cycloaddition of (*R*)-(+)-*p*-tolyl vinyl sulfoxide with acyclic nitrones as the asymmetry inducing step with high yield and high enantiomeric excess.[14] We herein report for the first time, synthesis of **15**, a crucial intermediate for (*S*)-dapoxetine, from an enantiopure, substituted, 3-hydroxy β-lactam. The retro-synthetic strategy is shown in Scheme 1. We envisaged that intermediate **15** can be obtained from carbamate substituted β-lactam **12**, which in turn can be accessed from the 3-hydroxy β-lactam **8**. The starting 3-hydroxy β-lactam **8**

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doi:10.1016/j.tet.2008.11.042

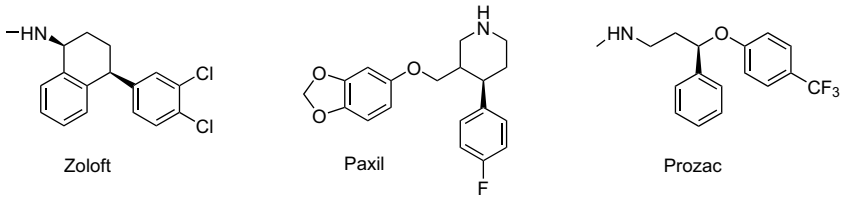


Figure 1. Zoloft, Paxil, and Prozac.

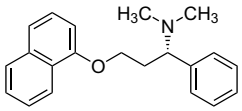
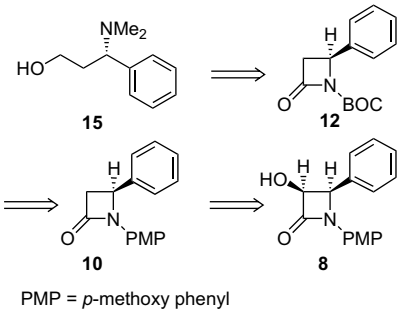


Figure 2. (*S*)-Dapoxetine (**1**).

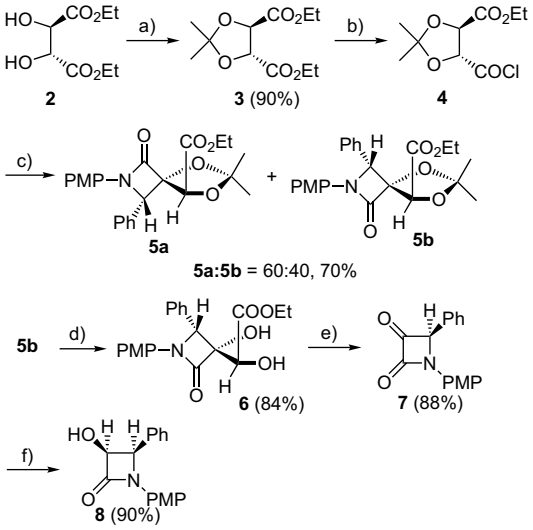


Scheme 1.

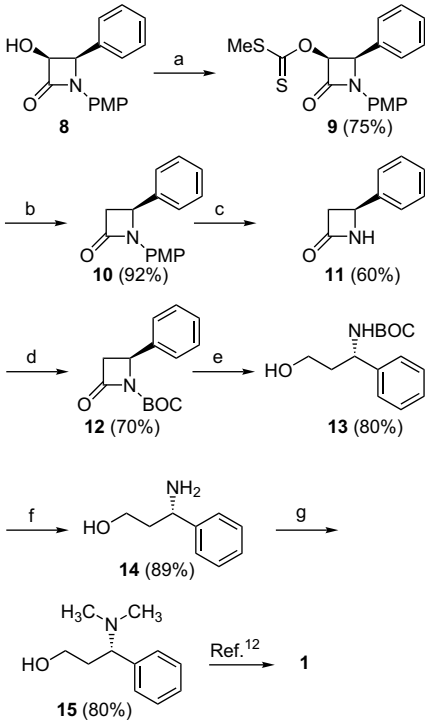
can be obtained from easily available chiral starting material (+)-diethyl L-tartrate in good yield.

2. Results and discussion

We started the synthesis of intermediate **15** with enantiopure 3-hydroxy β-lactam **8**, which was prepared easily by a reported method using stereoselective reduction of corresponding azetidin-2,3-dione.[15] We recently reported a method for an enantioselective synthesis of azetidin-2,3-diones bearing aromatic substituents on *N*-1 and *C*-4 of the β-lactam, from (+)-diethyl L-tartrate.[5d] Diethyl L-tartrate **2** was protected as its acetonide **3** using a reported protocol[16] (Scheme 2). Compound **3** was subjected to partial hydrolysis to afford mono acid, which was further converted to its acid chloride **4** by refluxing with oxalyl chloride in anhydrous dichloromethane in very good yield. This acid chloride **4** was used as such for Staudinger cycloaddition reaction with the imine derived from benzaldehyde and *p*-anisidine, to furnish diastereomeric mixture (60:40)[5d] of β-lactams **5a** and **5b**. The required diastereomer **5b** was obtained in enantiopure form by column chromatography. Spiro β-lactam **5b** was then subjected to the deprotection of acetonide using ferric chloride to obtain diol **6**, which on periodate cleavage yielded azetidin-2,3-dione **7** in excellent yield. Stereoselective reduction of the keto group of azetidin-2,3-dione **7** was achieved using sodium borohydride to get 3-hydroxy β-lactam (**8**)[15] in very good yield. The 3-hydroxy β-lactam (**8**) was converted to its xanthate derivative **9** using NaH, CS_2, and CH_3I, which was further subjected to reduction with *n*-Bu_3SnH and AIBN in toluene under reflux condition to furnish deoxygenated β-lactam **10** in excellent yield (Scheme 3). β-Lactam **10** was subjected to oxidative removal of the *p*-methoxy-phenyl group on the lactam nitrogen using ceric ammonium nitrate (CAN) to obtain compound **11** in 60% yield. This was then protected as its carbamate derivative with $(Boc)_2O$ in



Scheme 2. Reagents and conditions: (a) 2,2-dimethoxy propane benzene, PTSA, reflux, 5 h; (b) (i) NaOH, THF/H_2O, rt, 4–6 h, (ii) $(COCl)_2$, DCM, reflux, 5 h; (c) PMP–N=CH–Ph, Et_3N, DCM, −40 °C to rt, 15 h; (d) $FeCl_3$, DCM, rt, 2 h; (e) $NaIO_4$, acetone/water, rt, 6–8 h; (f) $NaBH_4$, MeOH, 0 °C, 2 h.



Scheme 3. Reagents and conditions: (a) NaH, CS_2, CH_3I, THF, 0 °C to rt, 6 h; (b) Bu_3SnH, AIBN, toluene, reflux, 3–4 h; (c) CAN, CH_3CN/H_2O, 0 °C, 1 h; (d) $(Boc)_2O$, DMAP, DCM, 0 °C to rt, 6 h; (e) LAH, THF, 0 °C to rt, 4 h; (f) TFA, DCM, 0 °C to rt, 2 h; (g) HCHO, $NaBH_3CN$, CH_3COOH, CH_3CN,rt, 2 h.

presence of DMAP in DCM to obtain β-lactam **12**. It was further reduced by LAH to get Boc protected amino alcohol **13** with desired stereochemistry in pure form after column chromatography. It has been shown that the reduction of substituted azetidinone with LAH yields corresponding amino alcohol in good yield.[17a] The reaction proceeds via an alkoxyalanate intermediate, which further breaks down to amino alcohol.[17b] In case of β-lactam **12**, we too got the reduced amino alcohol **13** in very good yield. Intermediate **13** was further subjected to Boc deprotection with TFA to get amino alcohol **14**. Although, bismethylation of **14** to furnish **15** using formic acid and formaldehyde under reflux conditions is known,[11] we adopted milder reaction conditions using formaldehyde and sodium cyanoborohydride at room temperature to deliver the desired *N*-bismethylated amino alcohol **15** in better yield. The spectral data and specific rotation of intermediate **15** were in good agreement with reported values $[\alpha]_D^{25}$ +39.0 (*c* 6, $CHCl_3$); lit.[11] $[\alpha]_D^{25}$ +39.2 (*c* 0.6, $CHCl_3$). Further elaboration of **15** to (*S*)-dapoxetine is a well established synthetic protocol.[12] Thus, enantioselective synthesis of intermediate **15**, in 17% overall yield, constitutes a formal synthesis of (*S*)-dapoxetine.

3. Conclusion

In conclusion, an enantioselective formal synthesis of (*S*)-dapoxetine, an SSRI type of drug against depression and a potential cure of premature ejaculation in men, was achieved from a substituted 3-hydroxy β-lactam in 17% overall yield. The synthesis illustrates the use of β-lactam synthon method for molecules of medicinal interest.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on Brüker AV 200, AV 400 spectrometers, and chemical shifts are reported in parts per million, downfield from tetramethylsilane for ^1H NMR. Infrared spectra were recorded on Perkin Elmer Infrared Spectrophotometer, Model 599-B or Shimadzu FTIR-8400 using sodium chloride optics. Melting points were determined on a Buchi melting point apparatus and are uncorrected. The microanalyses were performed on a Carlo-Erba, CHNS-O EA 1108 elemental analyzer available in Division of Organic Chemistry, National Chemical Laboratory, Pune. Optical rotations were recorded on ADP 220 polarimeter Bellingham+Stanley Ltd. under standard conditions. Mass spectra were recorded on API QSTAR PULSAR using electron spray ionization (ESI) method.

4.2. (3*S*,4*R*)-3-Hydroxy-1-(4-methoxy-phenyl)-4-phenyl-azetidin-2-one (8)

To a solution of dione **7** (0.037 g, 0.14 mmol) in methanol (3 mL) was added sodium borohydride (0.008 g, 0.21 mmol) in portion wise manner at 0 °C. After addition was complete, the reaction mixture was stirred at 0 °C for 2 h (TLC). Ice was then added carefully to the reaction mixture at 0 °C and stirred for half an hour at same temperature. Methanol was then evaporated on the rotary evaporator and to the residue was added CH_2Cl_2 (15 mL). Organic layer was then washed with H_2O (3×5 mL) and brine (5 mL). Organic extracts were then dried over anhydrous Na_2SO_4 and concentrated in vacuo to obtain crude compound **8**, which was purified by column chromatography (50% EtOAc/pet. ether) to get pure 3-hydroxy β-lactam **8** (0.033 g, 90%) as a white solid. Mp 201–201 °C. [Found C, 71.50; H, 5.69; N, 5.03%. $C_{16}H_{15}NO_3$ requires C, 71.36; H, 5.61; N 5.20%.] R_f (50% EtOAc/pet. ether) 0.3; $[\alpha]_D^{30}$ −179.0 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3315, 1715 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.55–7.23 (7H, m, Ar), 6.80 (d, 2H, *J*=8.8 Hz, Ar), 5.27 (1H, d, *J*=5.4 Hz, C*H*–N), 5.20 (1H, d, *J*=5.4 Hz, C*H*–OH), 3.76 (3H, s, OCH_3), 2.67 (1H, br s, –O*H*); δ_C (50 MHz, $CDCl_3$) 165.4, 156.5, 133.2, 130.6, 129.1, 129.0, 127.5, 118.8, 114.5, 77.2, 62.1, 55.5; MS (*m*/*z*): 270 (M+1).

4.3. (3*S*,4*R*) Dithiocarbonic acid *O*-[1-(4-methoxy-phenyl)-2-oxo-4-phenyl-azetidin-3-yl] ester *S*-methyl ester (9)

To a cooled suspension of NaH (60%; 0.47 g, 11.8 mmol) in anhydrous THF (5 mL) was added 3-hydroxy-β-lactam **8** (0.80 g, 2.97 mmol) as a solution in THF (5 mL) slowly. After the addition was complete, the reaction mixture was stirred at room temperature for 30 min. The solution was cooled to 0 °C and a solution of CS_2 (0.53 mL, 8.91 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 1.5 h at 0 °C, MeI (1.10 mL, 17.8 mmol) was then added at the same temperature, and the reaction mixture was stirred at room temperature for 3 h. After the reaction was complete (TLC), a saturated aq solution of NH_4Cl (10 mL) was added, and THF was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and the organic layer was washed with H_2O (20 mL), brine (20 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product, which was then purified by flash column chromatography (10% EtOAc/pet. ether) to furnish compound **9** (0.79 g, 75%) as a white solid. Mp 135 °C. [Found: C, 60.12; H, 4.72; N, 3.96; S, 17.86%. $C_{18}H_{17}NO_3S_2$ requires C, 60.14; H, 4.77; N, 3.90; S, 17.84%.] R_f (20% EtOAc/pet. ether) 0.4; $[\alpha]_D^{30}$ +33.3 (*c* 0.9, $CHCl_3$); ν_{max} ($CHCl_3$) 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.37–7.27 (7H, m, Ar), 6.81 (2H, d, *J*=8.9 Hz, Ar), 6.68 (1H, d, *J*=4.8 Hz, C*H*–OC=S), 5.42 (1H, d, *J*=4.8 Hz, C*H*–N), 3.76 (3H, s, OCH_3), 2.29 (3H, s, SCH_3); δ_C (50 MHz, $CDCl_3$) 213.6, 160.5, 156.5, 131.8, 130.0, 128.7, 128.3, 128.1, 118.8, 114.3, 81.6, 61.6, 55.3, 18.8; MS: (*m*/*z*)=360 (M+1).

4.4. (*S*)-1-(4-Methoxy-phenyl)-4-phenyl-azetidin-2-one (10)

A solution of Bu_3SnH (0.58 mL, 2.15 mmol) and AIBN (15 mg) in anhydrous toluene (5 mL) was added drop wise to a refluxing solution of xanthate (0.26 g, 0.72 mmol) in anhydrous toluene (10 mL) under argon atmosphere. The reaction mixture was then refluxed for 3 h (TLC). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (10% EtOAc/pet. ether) to afford **10** (0.168 g, 92%) as a white fluffy solid. Mp 98 °C. [Found: C, 75.95; H, 6.09; N, 5.60%. $C_{16}H_{15}NO_2$ requires C, 75.87; H, 5.97; N, 5.53%.] R_f (20% EtOAc/pet. ether) 0.3; $[\alpha]_D^{30}$ −40 (*c* 0.2, $CHCl_3$); ν_{max} ($CHCl_3$) 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.28–7.13 (7H, m, Ar), 6.69 (2H, d, *J*=8.9 Hz, Ar), 4.90–4.86 (1H, m, C*H*–N), 3.64 (3H, s, OCH_3), 3.45 (1H, dd, *J*=5.5, 15 Hz, OCCH_2'), 2.83 (1H, dd, *J*=2.5, 15 Hz, OCC*H*); δ_C (50 MHz, $CDCl_3$) 163.9, 155.8, 138.2, 131.3, 129.0, 128.4, 125.8, 118.0, 114.1, 55.3, 53.9, 46.8; MS: (*m*/*z*)=254 (M+1).

4.5. (*S*)-4-Phenyl-azetidin-2-one (11)

A solution of $(NH_4)_2Ce(NO_3)_6$ (0.97 g, 1.77 mmol) in water (7 mL) was added drop wise to a solution of (*S*)-1-(4-Methoxy-phenyl)-4-phenyl-azetidin-2-one (**10**) (0.15 g, 0.59 mmol) in acetonitrile (7 mL) at 0 °C. The mixture was stirred at this temperature for 1 h. Water (10 mL) was added, it was extracted with ethyl acetate (3×15 mL), and washed with saturated solution of $NaHCO_3$ (2×10 mL). The aqueous layer of $NaHCO_3$ was extracted again with ethyl acetate (1×10 mL), and the combined organic extracts were washed with 40% $NaHSO_3$ (3×10 mL) and brine (10 mL). It was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to get crude product, which was purified by flash column chromatography (70% EtOAc/pet. ether) to furnish **11** (0.052 g, 60%) as a very viscous liquid. [Found: C, 73.39; H, 6.09; N,

9.61%. C_9H_9NO requires C, 73.45; H, 6.16; N, 9.52%.] R_f (70% EtOAc/pet. ether) 0.3; $[\alpha]_D^{30}$ −40 (*c* 0.1, $CHCl_3$); ν_{max} ($CHCl_3$) 3411, 1765 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.30–7.19 (5H, m, Ar), 6.23 (1H, br s, N*H*), 4.66 (1H, m, C*H*-N), 3.44–3.32 (1H, m, OCCH_2'), 2.81 (1H, dd, *J*=2.09, 14.09 Hz, OCCH_2); δ_C (50 MHz, $CDCl_3$) 167.9, 140.2, 128.4, 127.6, 125.3, 49.7, 47.4; MS: (*m*/*z*)=148 (M+1).

4.6. (*S*)-2-Oxo-4-phenyl-azetidine-1-carboxylic acid *tert*-butyl ester (12)

$(Boc)_2O$ (0.94 mL, 4.08 mmol) and DMAP (0.398 g, 3.26 mmol) were added to a solution of azetidin-2-one **11** (0.400 g, 2.72 mmol) in CH_2Cl_2 (10 mL) at 0 °C, and the reaction mixture was stirred for 6 h. Then, CH_2Cl_2 (10 mL) was added, and it was washed with a saturated solution of $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to get crude product, which was purified by column chromatography (20% EtOAc/pet. ether) to furnish title β-lactam **12** (0.470 g, 70%) as a viscous liquid. [Found: C, 68.05; H, 6.91; N, 5.60%. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66%.] R_f (20% EtOAc/pet. ether) 0.2; $[\alpha]_D^{30}$ −33.3 (*c* 0.3, $CHCl_3$); ν_{max} ($CHCl_3$) 1805 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.36–7.25 (5H, m, Ar), 4.85 (1H, m, C*H*–N), 3.36 (1H, dd, *J*=6.1, 16 Hz, OCCH_2'), 2.85 (1H, dd, *J*=3.15, 16 Hz, OCCH_2), 1.31 (9H, s, OC(CH_3)$_3$); δ_C (50 MHz, $CDCl_3$) 164.9, 147.3, 138.1, 128.7, 128.4, 125.8, 83.1, 53.6, 45.9, 27.7; MS: (*m*/*z*)=248 (M+1).

4.7. *S*-(3-Hydroxy-1-phenyl-propyl)-carbamic acid *tert*-butyl ester (13)

To a suspension of LAH (0.204 g, 5.37 mmol) in THF (5 mL) was added β-lactam **12** (0.332 g, 1.33 mmol) in THF (5 mL) drop wise at 0 °C under inert atmosphere. The reaction mixture was allowed to attain room temperature and stirred for total 4 h. After completion of reaction (TLC), a saturated solution of Na_2SO_4 was added to the reaction mixture at 0 °C and it was stirred for an hour. THF was then evaporated on rotary evaporator and to the residue was added ethyl acetate (15 mL). It was washed with water (10 mL). The aqueous layer was washed with ethyl acetate (2×5 mL). Combined organic extracts were washed with brine (5 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo to get the crude product, which was purified by column chromatography using (40% EtOAc/pet. ether) to furnish **13** (0.269 g, 80%) as a white solid. Mp 104 °C. [Found: C, 66.81; H, 8.57; N, 5.65%. $C_{14}H_{21}NO_3$ requires C, 66.91; H, 8.42; N, 5.57%.] R_f (30% EtOAc/pet. ether) 0.2; $[\alpha]_D^{30}$ −53.1 (*c* 7.0, acetone); ν_{max} ($CHCl_3$) 3337 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.38–7.27 (5H, m, Ar), 4.99 (1H, m, C*H*–N), 3.72–3.65 (2H, m, OCH_2), 2.7 (2H, br s, O*H*, N*H*), 2.17–1.79 (2H, m, CCH_2C), 1.44 (9H, s, OC(CH_3)$_3$); δ_C (50 MHz, $CDCl_3$) 156.3, 141.9, 128.7, 127.4, 126.3, 79.9, 58.9, 51.5, 39.3, 28.2; MS: (*m*/*z*)=252 (M+1).

4.8. (*S*)-3-Amino-3-phenyl-propan-1-ol (14)

To a solution of **13** (0.030 g, 0.12 mmol) in DCM (2 mL) was added TFA (0.3 mL) drop wise at 0 °C. It was kept at 0 °C for half an hour and then allowed to come to room temperature and stirred for further 1.5 h. After completion (TLC), the reaction mixture was concentrated in vacuo to remove DCM and TFA. The residue was then dissolved in methanol (3 mL) and Et_3N (0.016 mL, 0.12 mmol) was added and the resultant solution was passed through a short column of silica gel with methanol as an eluent. The methanol fractions were concentrated in vacuo to furnish **14** as a white hygroscopic solid (0.016 g, 89%). [Found: C, 71.32; H, 8.80; N, 9.35%. $C_9H_{13}NO$ requires C, 71.49; H, 8.67; N, 9.26%.] R_f (MeOH) 0.3; $[\alpha]_D^{30}$ −11.4 (*c* 2.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3200–3380 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.38–7.15 (5H, m, Ar), 3.86 (3H, br s, NH_2, O*H*), 3.69–3.63 (3H, m, OCH_2, C*H*–N), 2.32–1.77 (2H, m, CCH_2C); δ_C (50 MHz, $CDCl_3$) 128.9, 128.6, 126.9, 126.2, 58.9, 55.1, 35.9; MS: (*m*/*z*)=152 (M+1).

4.9. (*S*)-3-Dimethylamino-3-phenyl-propan-1-ol (15)

To a solution of **14** (0.12 g, 0.807 mmol) in acetonitrile was added, 30% aq formaldehyde solution (0.325 mL) followed by sodium cyanoborohydride (0.081 g, 1.29 mmol) and it was allowed to stir at room temperature. A few drops of glacial acetic acid were added to maintain the pH near neutrality. The solution was stirred at room temperature for 2 h. After completion of the reaction (TLC), the reaction mixture was concentrated in vacuo. To the residue was added 2 N aq KOH (10 mL). It was then extracted with ethyl acetate (3×10 mL). The ethyl acetate layer was then washed with 1 N HCl (3×5 mL). The combined HCl extracts were basified with solid KOH and then extracted with ethyl acetate (3×10 mL). Combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford crude product, which was purified by column chromatography (40% EtOAc/MeOH) to furnish **15** (0.115 g, 80%) as a hygroscopic solid. [Found: C, 73.78; H, 9.48; N, 7.88%. $C_{11}H_{17}NO$ requires C, 73.70; H, 9.56; N, 7.81%.] R_f (40% EtOAc/MeOH) 0.3; $[\alpha]_D^{30}$ +39.0 (*c* 6.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3335 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.32–7.15 (5H, m, Ar), 5.16 (1H, br s, O*H*), 3.90–3.80 (2H, m, OCH_2), 3.80–3.69 (1H, m, C*H*–N), 2.48–2.32 (1H, m, CCH_2'C), 2.18 (6H, s, N(CH_3)$_2$), 1.76–1.66 (1H, m, CCH_2C); δ_C (50 MHz, $CDCl_3$) 136.1, 129.0, 128.8, 128.3, 127.9, 127.1, 70.0, 63.1, 41.0, 32.1; MS: (*m*/*z*)=180 (M+1).

Acknowledgements

Authors, P.M.C. and A.S.K., thank University Grants Commission and Council of Scientific and Industrial Research, New Delhi respectively for research fellowships.

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