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Synthesis of new series of iboga analogues

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ABSTRACT

Synthesis of new iboga-analogues, replacing the indole ring with a benzofuran moiety has been described. Starting materials are the suitably substituted benzofuran derivatives and have been synthesized by Pd-catalyzed reactions. The conversion of *endo*-6-methylcarboxylate substituted dehydroisoquinuclidine to *exo*-isomer, a key component of iboga-alkaloids has been achieved in the presence of NaOMe in methanol under reflux conditions.

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The iboga-alkaloids are naturally occurring indole alkaloids, which are found in a variety of African shrubs of the *Tabernanthe* genus. Members of this family of alkaloids combine the structural features of indole and isoquinuclidinyl ring fused by a seven-membered indoloazepine ring[1] (Fig. 1). Anti-addictive properties of ibogaine have been known for decades.[2,3] Apart from their anti-addictive properties, iboga-alkaloids and their congeners show a wide variety of pharamacological effects,[3] such as antifungal or antilipase, anti-HIV-1, anti-cholinesterasic and leishmanicide activities (against *Leishmania amazonensi*). However, the clinical application of ibogaine is limited because the natural ibogaine **2** is tremorigenic,[4] and neurotoxic, particularly due to the degeneration of brain cells (purkinje cells) if the dose is high.[5] Chemical modifications of iboga-alkaloids have been reported in order to have more potent analogues or congeners. So far a limited number of its analogues[6a–d] and congeners[6e–g] have been accessible. Mostly, the analogues have been reported either on the modification of indoloazepine ring[6a,b] of the natural scaffold (5,6-homologues or 6-nor of the iboga alkaloid skeleton) or in the mode of fusion of the indole ring to isoquinuclidine moiety (type **3**, indole-[3,2] fusion).[6c,d]

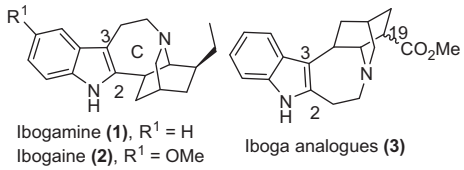
In the continuation of our research towards the synthesis of iboga-alkaloids,[6d] we describe herein the synthesis and characterization of iboga-analogues **4** and **5**, replacing the indole ring with a benzofuran moiety. The benzofuran moiety was chosen because it is a bioisostere of indole, the pharmacological properties might be unchanged and the synthesis of this compound could be easier than the natural ibogaine as benzofuran does not require any protection like indole. Moreover these compounds are expected to be more stable than the natural ibogaine which is heat and light sensitive and spontaneously oxidize in solution.[1a] CO_2Me at the C 19 carbon could be easily manipulated for further derivatization, as substitution at this carbon has biological importance.[7] In this direction, the conversion of *endo*-dehydroisoquinuclidine **6b** into *exo*-isomer **6a** is reported.

Retrosynthetically, the benzofuran analogues **4** and **5** could be broken into two components, 3- or 2-substituted benzofuran ethanol **8** or **9** and the common fragment, dehydroisoquinuclidine **7** (Scheme 1).

The requisite dehydroisoquinuclidine **6** was synthesized according to the literature procedure[8] (Scheme 2). Mixture of *exo*- and *endo*- isomers was separated by alumina column using dichloromethane as an eluent and obtained a ratio of 3.2:1 in favour of the less polar *endo*-product **6b**.[9]

The ^{1}H NMR of both isomers were a little complicated particularly, in case of *exo*-isomer, methylcarboxylate (CO_2Me) which gave two sharp singlets at δ 3.46 and δ 3.67 (Fig. 2).

Both isomers were further characterized by the iodolactonization method (Supplementary data). Appearance of two peaks of methylcarboxylate of *exo*-isomer **6a** could be explained due to



Ibogamine **(1)**, R^1 = H
Ibogaine **(2)**, R^1 = OMe

Iboga analogues **(3)**

Figure 1. Analogues and congeners of ibogaine.

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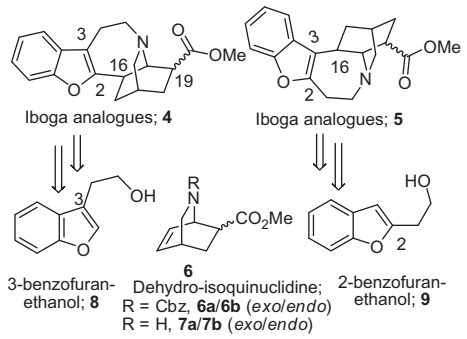
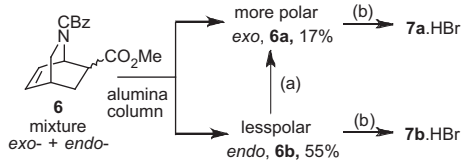


Scheme 1. Retrosynthetic strategy.



Scheme 2. Synthesis of dehydroisoquinuclidine. [a]Reagents and conditions: (a) NaOMe (1.5 equiv), MeOH, reflux; (b) 20% HBr–AcOH.

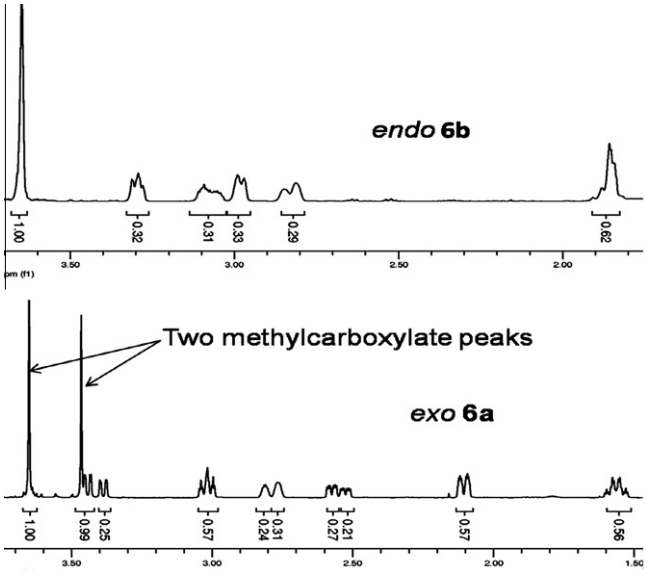


Figure 2. ^{1}H NMR (500 MHz) of compounds **6a** and **6b**.

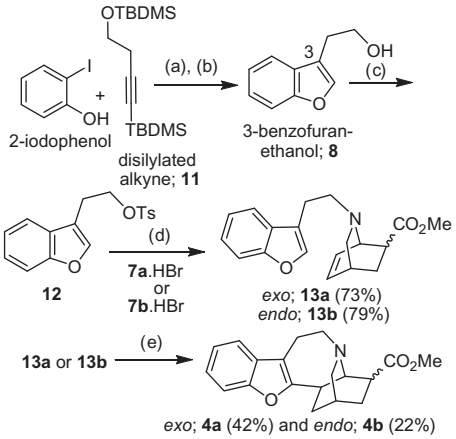
the presence of rotamers and it is prominent in the case of **6a**, as *exo*-CO_2Me lies in close proximity to Cbz group. Interestingly, two peaks became a broad singlet at δ 3.65 when the NMR spectrum was recorded at 60 °C in $CDCl_3$.

Natural ibogaine **2** carries an *exo*-substituted ethyl side chain at C 20. During cycloaddition reaction we obtained the *exo*-product as the minor isomer, consequently we tried to improve the yield of our *exo*-Diels–Alder product **6a**. In the connection of the synthesis of ibogaine analogues, Passarella, et al.[6g] were unsuccessful in isomerization of dehydroisoquinuclidines in the presence of LDA. Our initial effort for the conversion of kinetically controlled *endo*-product to *exo*-isomer using LDA at 50 °C furnished a complex mixture. Reducing the quenching temperature gave moderate

Table 1
Conversion of *endo*-6-substituted dehydroisoquinuclidine to *exo*-isomer[a]

Entry	Base used	Quenching temp (°C)	Proton source	Ratio[b] exo:endo
1	LDA[c]	50	H_2O	Complex mixture
2	LDA	50	*t*-BuOH	Complex mixture
3	LDA	25	H_2O	56:44
4	LDA	25	*t*-BuOH	53:47
5	LDA	25	HCl (0.5 N)	Complex mixture
6	LDA	0	H_2O	30:70
7	LDA	0	*t*-BuOH	28:72
8	LDA	−78	H_2O	22:78
9	LDA	−78	*t*-BuOH	18:82
10	**NaOMe**	65	**MeOH**	90:10

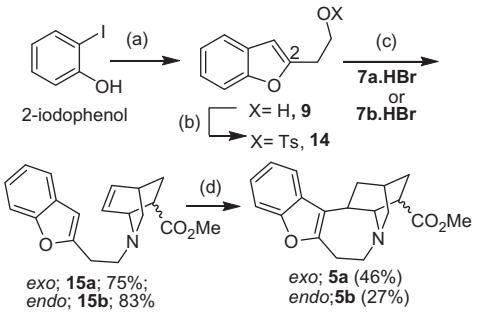
[a] Experiments were carried out with pure *endo* isomer **6b**.
[b] Ratios were calculated on the basis of chemical yield (after purification using alumina column).
[c] The solution of **6b** in THF was added dropwise to LDA and stirred for 2 h at −78 °C to generate the enolate.



Scheme 3. Synthesis of iboga analogues **4a** and **4b**. Reagents and conditions: (a) $Pd(OAc)_2$(10 mol %), LiCl (1.0 equiv), Na_2CO_3 (6.0 equiv),DMF, 100 °C; (b) TBAF (2.5 equiv), THF, 55% after two steps; (c) TsCl (1.2 equiv), Et_3N (2.0 equiv), DMAP (10 mol %) CH_2Cl_2, 71%; (d) K_2CO_3 (2.5 equiv), CH_3CN, 80 °C; (e) $PdCl_2(CH_3CN)_2$ (2.0 equiv.), $AgBF_4$ (4.0 equiv), Et_3N (1.0 equiv), CH_3CN followed by $NaBH_4$ (1.0 equiv), MeOH, 0 °C.

conversion at 25 °C. The epimerization of *N*-unprotected isoquinuclidine was reported earlier;[8b] however, experimental procedure or the isolation method of the product was not included in this Letter. We tried the isomerization of **7b** following their conditions[8b] but failed to isolate any product and the mass spectra of the crude product show a peak corresponding to the free amino acid. However, under similar conditions, the Cbz-protected *endo*-isomer **6b** underwent 90% conversion to the *exo*-isomer[10] (Table 1). Cbz-deprotection of **6a** and **6b** was performed separately using 20% HBr–AcOH and HBr salt of **7a** and **7b** was then used in the next step for the synthesis of iboga-analogues (Scheme 2).

The 3-benzofuranethanol **8** was synthesized using Larock's heteroannulation reaction[11a] between 2-iodophenol and internal alkyne **11** followed by the treatment with tetrabutyl ammonium fluoride and obtained 55% yield in two steps. The internal alkyne **11** was in turn synthesized from 3-butyn-1-ol in the presence of *n*-BuLi and *tert*-butyldimethylsilyl chloride[11b] in 70% yield. The TBDMS protection was chosen because it survived under the heteroannulation conditions, whereas other silyl-based protecting



Scheme 4. Synthesis of iboga analogues **5a** and **5b**. Reagents and conditions: (a) 3-butyn-1-ol (1 equiv), $Pd(OAc)_2$ (5 mol %), CuI (5 mol %), PPh_3 (5 mol %), Et_3N, rt, 16 h, 87%; (b) TsCl (1.2 equiv), Et_3N (2.0 equiv), DMAP (10 mol %), CH_2Cl_2, 71%; (c) K_2CO_3 (2.5 equiv), CH_3CN, 80 °C; (d) $PdCl_2(CH_3CN)_2$ (2.0 equiv), $AgBF_4$ (4.0 equiv.), Et_3N (1.0 equiv), CH_3CN followed by $NaBH_4$ (1.0 equiv), MeOH, 0 °C.

groups (TMS or TES) gave a mixture of products.[11b] Compound **8** was then converted into the tosyl derivative **12**, which was then conjugated separately to isoquinuclidine **7a**.HBr and **7b**.HBr in the presence of K_2CO_3/CH_3CN at 80 °C to obtain **13a** and **13b**, respectively. Pd(II)–Ag(I) mixed metal mediated cyclization was originally developed by Trost for the synthesis of ibogamine[12] and we applied this methodology to its analogues **13a** and **13b** to obtain **4a**[13] and **4b** in 42% and 22% yields, respectively (Scheme 3). It is worth to mention here that while synthesizing iboga-scaffolds,[8a] we had a difficulty in both heteroannulation and cyclization steps particularly using *endo*-isomers where a mixture of regioisomers was obtained and 2-iodoaniline was required to protect with tosyl group. We also realized that handling the benzofuran-substituted products and work-up procedures were much easier than the corresponding iboga-alkaloids.

For the synthesis of iboga analogues **5**, the requisite benzofuran alcohol **9** was synthesized in one pot from 2-iodophenol via Sonogashira coupling with 3-butyn-1-ol at room temperature. Subsequent tosylation and conjugation to **7a**. HBr and **7b**.HBr afforded **15a** and **15b** in 75% and 83% yields, respectively.

When compound **15a** was subjected to the mixed-metal-mediated cyclization method, gratifyingly the reaction proceeded smoothly to give the desired product **5a**[14] in 46% yield. A similar cyclization of compound **15b** also delivered the product **5b**, though in lower yield (27%) (Scheme 4). Surprisingly, the *endo*-isomers **13b** and **15b** were more polar than their *exo*-isomers which were not in the case of **6b**.

All new compounds have been characterized by IR, NMR, and mass spectroscopy. The protons of isoquinuclidine rings of **4b** and **5a** have been assigned by the decoupled ^1H NMR and their coupling constants were confirmed as well (Fig. 3).

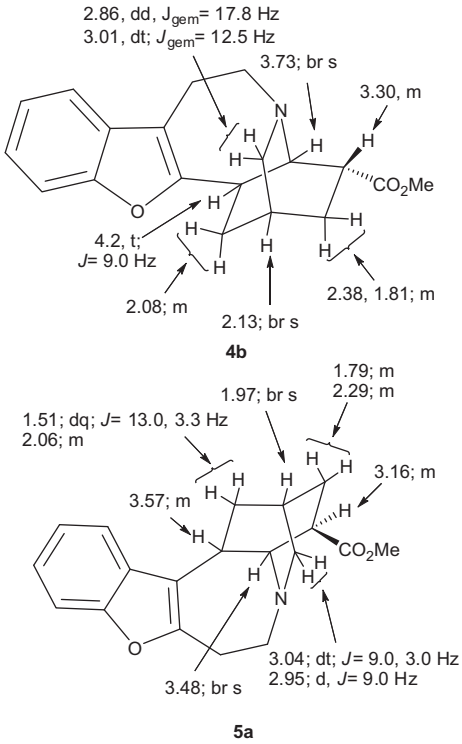


Figure 3. Proton assignments of compounds **4b** and **5a**.

The structure of the compounds **4b** and **5b** was confirmed by the X-ray crystallographic analysis (Fig. 4).

In summary, we have reported the synthesis of benzofuran-analogues of iboga alkaloids. Our synthetic approach is non-biochemical, extremely short, flexible and also anticipated that minor modifications of the starting materials (phenol and alkyne) should provide access to several other analogues of this alkaloid family for biological screening. Also functional group transformation of C 19 ester can provide us the true SAR to optimize the potency and efficacy of the analogues. Conversion of *endo*-6-substituted dehydroisoquinuclidine into its *exo*-isomer, a key component of iboga-alkaloids has been achieved.

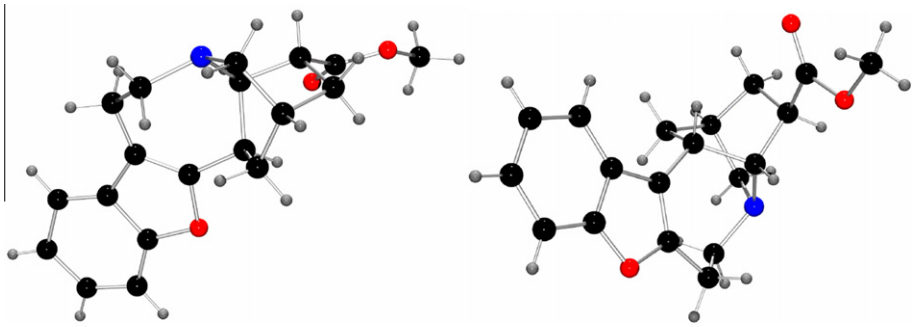


Figure 4. Crystal structure of compounds **4b** and **5b**.

Acknowledgements

S. S. thanks DST, India, for financial support by a grant [SR/S1/OC-38/2007]. S. P. and S. P. are thankful to CSIR for their fellowship. Crystal structure determination was performed at the DST-funded National Single Crystal Diffractometer[15,16] Facility at the Department of Inorganic Chemistry, IACS.

Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.040.

References and notes

1. (a) Alper, K. R. *The Alkaloids* **2001**, *56*, 1–38; (b) Sundberg, R. J.; Smith, S. Q. *The Alkaloids* **2002**, *59*, 281–376.
2. (a) Mash, D. C.; Staley, J. K.; Baumann, M. H.; Rothmann, R. B.; Hearn, W. L. *Life Sci.* **1995**, *57*, 45–50; (b) Lotsof, H. S. *Maps* **1995**, *5*, 16–27; (c) Touchette, N. *Nat. Med.* **1995**, *1*, 288–289; (d) Popik, P.; Layer, R. T.; Skolnick, P. *Pharmacol. Rev.* **1995**, *47*, 235–253.
3. (a) Maciulaitis, R.; Kontrimaviciute, V.; Bressolle, F. M. M.; Briedis, V. *Hum. Exp. Toxicol.* **2008**, *27*, 181–194; (b) Gallo, C. C.; Renzil, P.; Loizzo, S.; Loizzo, A.; Capasso, A. *Pharmacologyonline* **2009**, *3*, 906–920.
4. Glick, S. D.; Rossman, K.; Rao, N. C.; Maisonneuve, I. M.; Carlson, J. N. *Neuropharmacology* **1992**, *31*, 497–500.
5. O'Hearn, E.; Molliver, M. E. *J. Neurosci.* **1997**, *17*, 8828–8841.
6. Analogues: (a) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836–4842; (b) Sundberg, R. J.; Cherney, R. J. *J. Org. Chem.* **1990**, *55*, 6028–6037; (c) Sundberg, R. J.; Hong, J.; Smith, S. Q.; Sabat, M. *Tetrahedron* **1998**, *54*, 6259–6292; (d) Jana, G. K.; Sinha, S. *Tetrahedron Lett.* **2010**, *51*, 1994–1996; Congeners: (e) Repke, D. B.; Artis, D. R.; Nelson, J. T.; Wong, E. H. F. *J. Org. Chem.* **1994**, *59*, 2164–2171; (f) Efange, S. M. N.; Mash, D. C.; Khare, A. B.; Ouyang, Q. *J. Med. Chem.* **1998**, *41*, 4486–4491; (g) Passarella, D.; Favia, R.; Giardini, A.; Lesma, G.; Martinelli, M.; Silvani, A.; Danieli, B.; Efange, S. M. N.; Mash, D. C. *Bioorg. Med. Chem.* **2003**, *11*, 1007–1014.
7. Bandarage, U. K.; Kuehne, M. E.; Glick, S. D. *Tetrahedron* **1999**, *55*, 9405–9424.
8. (a) Jana, G. K.; Sinha, S. *Tetrahedron Lett.* **2010**, *51*, 1441–1443; (b) Street, L. J.; Baker, R.; Book, T.; Kneen, C. O.; MacLeod, A. M.; Merchant, K. J.; Showell, G. A.; Saunders, J.; Herbert, R. H.; Freedman, S. B.; Harley, E. A. *J. Med. Chem.* **1990**, *33*, 2690–2697.
9. *Selected characterization data for* **6a**: IR (neat): ν 2953, 2874, 1732, 1694, 1415 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)*: δ 1.52–1.59 (1H, m), 2.08–2.09 and 2.118–2.123 (1H, m), 2.50–2.54 and 2.56–2.59 (1H, m), 2.76–2.76 (1H, m), 2.99–3.04 (1H, m), 3.37–3.40 and 3.43–3.45 (1H, dd, J = 10.2, 1.5), 3.46 and 3.65 (3H, s), 4.98–5.10 (3H, m), 6.41–6.49 (2H, m), 7.25–7.33 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$)*: δ 25.06 and 25.25, 30.16 and 30.36, 44.27 and 44.56, 47.41 and 47.81, 48.10 and 48.50, 51.95 and 52.25, 66.78 and 66.92, 127.68, 127.86, 127.98, 128.04, 128.48, 128.56, 128.67, 131.78, 132.25, 135.20 and 135.47, 137.00 and 137.17, 155.02 and 155.61, 173.63 and 174.06; HRMS (ESI) $(M+Na)^+$ calcd for $C_{17}H_{19}NO_4Na^+$ = 324.1212. Found 324.1213.
Selected characterization data for **6b**: IR (neat): ν 2915, 2879, 1432, 1693, 1415, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.86–1.92 (2H, m), 2.83–2.87 (1H, m), 2.99–2.99 (1H, m), 3.01–3.13 (1H, m), 3.30–3.33 (1H, m), 3.67 (3H, s), 5.09–5.21 (3H, m), 6.32–6.39 (1H, m), 6.43–6.48 (1H, m), 7.31–7.38 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$)*: δ 26.10 and 26.25, 30.49 and 30.72, 43.82 and 44.12, 46.85 and 47.18, 47.22 and 47.52, 51.97, 66.96 and 67.01, 127.89, 127.95, 128.01, 128.53, 130.32 and 130.72, 135.19 and 135.50, 136.92, 154.85 and 155.27, 173.20; HRMS (ESI) $(M + Na)^+$ calcld for $C_{17}H_{19}NO_4Na^+$ = 324.1212, Found 324.1213. *(NMR spectra of both isomers are complicated due to CBz-rotamers.)
10. *Endo-exo conversion using NaOMe/MeOH:* To a reflux solution of sodium methoxide (47 mg, 0.872 mmol) in anhydrous methanol (2.0 mL) was slowly added the methanolic (3.0 mL) solution of compound **6b** (175 mg, 0.581 mmol) under argon atmosphere. The reaction mixture was refluxed for a period of 7 h. Methanol was removed in vacuo, crude reaction mixture was diluted with dichloromethane (20 mL). The organic extract was washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo to give crude yield 90% (157 mg). After purification by alumina column using dichloromethane as eluent, the yield of *exo*-isomer was 141 mg (80.6%) and *endo*-isomer was recovered 16 mg (9%).
11. (a) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270–3271; (b) Bishop, B. C.; Cottrell, I. F.; Hands, D. *Synthesis* **1997**, 1315–1320.
12. Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930–3931.
13. *Preparation and characterization data for* **4a**: To a slurry of bis(acetonitrile)palladium dichloride (194 mg, 0.75 mmol) in CH_3CN (1.5 mL) was added Et_3N (52 μL, 0.37 mmol) under an argon atmosphere. Silver tetrafluoroborate (290 mg, 1.48 mmol) was added and the orange heterogeneous mixture immediately became yellow. After 15 min, a solution of **13a** (116 mg, 0.37 mmol) in CH_3CN (2.0 mL) was added. The deep red solution was then stirred for 1 h at room temperature then heated at 70 °C for 12 h under argon atmosphere. The reaction mixture was cooled to 0 °C, MeOH (1.0 mL) was added, followed by addition of $NaBH_4$ (16 mg, 0.43 mmol) portionwise. The solution was stirred for 1 h at 0 °C. The reaction mixture was filtered through a pad of Celite, washed with methanol (5 mL). The organic extract was concentrated in vacuo and purified by column chromatography (100–200 mesh Silica gel) using EtOAc in petroleum ether (PE:EtOAc, 9:1 to 1.5:1) as eluent to get the compound **4a** (48 mg, 42%) as a colorless oil (R_f = 0.39, PE:EtOAc, 2.3:1).
IR (neat, $CHCl_3$): ν 2933, 2864, 1735, 1456, 1203, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.71 (1H, dq, J = 15.0, 3.5 Hz), 1.77–1.83 (1H, m), 1.98 (1H, br s), 2.04–2.09 (1H, m), 2.27–2.31 (1H, m), 2.52–2.54 (1H, m), 2.69 (1H, ddd, J = 11.0, 6.5, 1.6 Hz), 2.98 (1H, d, J = 9.0 Hz), 3.04 (1H, dt, J = 9.0, 3.0 Hz), 3.18–3.24 (2H, m), 3.29–3.36 (2H, m), 3.56 (1H, br s), 3.73 (3H, s), 7.19-7.23 (2H, m), 7.36 (1H, dd, J = 6.8, 1.75 Hz), 7.40 (1H, dd, J = 6.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.2, 25.9, 26.4, 33.2, 39.6, 45.4, 49.1, 52.1, 52.9, 56.1, 110.7, 116.3, 118.8, 122.3, 123.5, 130.7, 153.7, 159.2, 175.2; HRMS (ESI) $(M+H)^+$ calcld for $C_{19}H_{21}NO_3H^+$ = 312.1600. Found 312.1594.
14. *Selected characterization data for* **5a**: The procedure was same as reported for the synthesis of **4a** (above). The crude product obtained from compound **15a** (115 mg, 0.37 mmol) was purified by column chromatography on silica gel using EtOAc in PE as eluent to yield the compound **5a** (53 mg, 46%) as a colorless oil (R_f = 0.38, PE:EtOAc, 4:1). IR (neat, $CHCl_3$): ν 2953, 1732, 1607, 1450, 1251, 745 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$): δ 1.51 (1H, dq, J = 13.0, 3.3 Hz), 1.77–1.83 (1H, m), 1.97 (1H, br s), 2.05–2.11 (1H, m), 2.27–2.32 (1H, m), 2.71–2.75 (2H, m), 2.95 (1H, d, J = 9.0 Hz), 3.04 (1H, dt, J = 9.0, 3.0 Hz), 3.13–3.26 (3H, m), 3.48 (1H, br s), 3.53–3.60 (1H, m), 3.73 (3H, s), 7.17–7.22 (2H, m), 7.35–7.38 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.7, 26.11, 26.36, 33.2, 34.1, 45.9, 49.1, 50.8, 51.9, 58.1, 110.6, 118.3, 121.6, 122.2, 123.5, 129.7, 151.9, 153.8, 175.3; HRMS (ESI) $(M+H)^+$ calcld for $C_{19}H_{21}NO_3H^+$ = 312.1600. Found 312.1594.
15. Bruker, version 2.1-0; Bruker AXS, Inc.: Madison, WI, 2006.
16. X-ray crystallographic data for compounds **4b** and **5b** have been deposited to the Cambridge Crystallographic Data Centre and assigned the deposition numbers CCDC 809688 for **4b** and CCDC 809689 for **5b**.