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A concise diastereoselective approach to (+)-dexoxadrol, (−)-*epi*-dexoxadrol, (−)-conhydrine and (+)-lentiginosine from (−)-pipecolinic acid

Chinmay Bhat, Santosh G. Tilve *

Department of Chemistry, Goa University, Taleigao-Plateau, Goa 403 206, India

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ABSTRACT

A new diastereoselective pathway for the total synthesis of (+)-dexoxadrol, first asymmetric synthesis of (−)-*epi*-dexoxadrol and formal synthesis of conhydrine and (+)-lentiginosine is presented using commercially available (−)-pipecolinic acid. The key reactions utilized are Sharpless asymmetric dihydroxylation and Wittig reaction. The paper further describes the study of effect of protecting groups on dihydroxylation of a terminal olefin in piperidine ring system.

1. Introduction

2-Substituted piperidine alkaloids are widely dispersed among the natural products and found to play vital role in various biological and medicinal applications.[1] The presence of active functional groups on the side chain and piperidine nucleus together plays a crucial role for their potent biological activities. Due to their unique and interesting structures, chemists are attracted towards the syntheses of these motifs as new drugs for the clinical trials.[2] As a result, over the last few decades many such synthetic drugs are produced and tested for the treatment of various diseases. Dexoxadrol **1** is one such alkaloid, first synthesized by Hardie et al. in 1960 as an anaesthetic drug along with etoxadrol **3**.[3] The subsequent clinical trials revealed that these compounds are efficient NMDA receptor antagonist by binding with the PCP cites and found to be more efficient than the available drugs memantine **4** and amantadine **5** (Fig. 1).[4] The detailed study on the biological behaviour of these molecules realized that, the presence of secondary amine, piperidine ring, five member oxygenated ring and the (*S*, *S*) stereochemistry altogether plays a crucial role for its enhanced activity.[5] The interesting structure and its potent biological activity prompted the synthetic chemists to design newer methods for different analogues of **1**. In recent years various substituted side-chain homologues of dexoxadrol **1** are synthesized and tested for different biological responses.[6]

There are three synthetic reports available for the synthesis of dexoxadrol so far (Scheme 1).[3,7] The Hardie's and Thukauf's methods involve substituted pyridines as starting materials, which eventually produce (+)-dexoxadrol **1** after racemic separation at the final stage.[3,7a] The first asymmetric synthesis developed by Etayo et al. manipulates mannitol successfully to convert to **1** diastereoselectively, using RCM as a key step.[7b]

2. Results and discussion

In continuation of our research directed towards the synthesis of 2-substituted piperidine and pyrrolidine alkaloids,[8] we undertook the synthesis of dexoxadrol **1** and its possible *epi* isomer **2** using commercially available (−)-pipecolinic acid. Our retrosynthetic approach is outlined in Scheme 2. Accordingly, our synthesis involves the formation of alkene **6** and diol **7** through Wittig and Sharpless asymmetric dihydroxylation (SAD), respectively.

The synthesis commenced with LAH reduction of commercially available (−)-pipecolinic acid to pipecolinol **9** in good yield (Scheme 3). The pipecolinol **9** obtained as a pale yellow solid was converted to benzyl carbamate **10a**. The aldehyde **11a** prepared by Swern oxidation of **10a** was immediately converted to alkene **6a** in 90% yield by carrying out Wittig reaction using $^{+}PPh_3CH_3Br^{-}$/NaHMDS. The dihydroxylation of alkene **6a** using OsO_4/NMO produced diols **7a** and **8a**. The stereochemistry of the diols **7a** and **8a**

* Corresponding author. Tel.: +91 832 6519317; e-mail addresses: santoshtilve@yahoo.com, stilve@unigoa.ac.in (S.G. Tilve).

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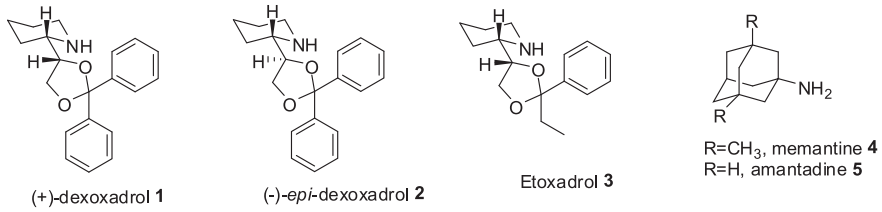
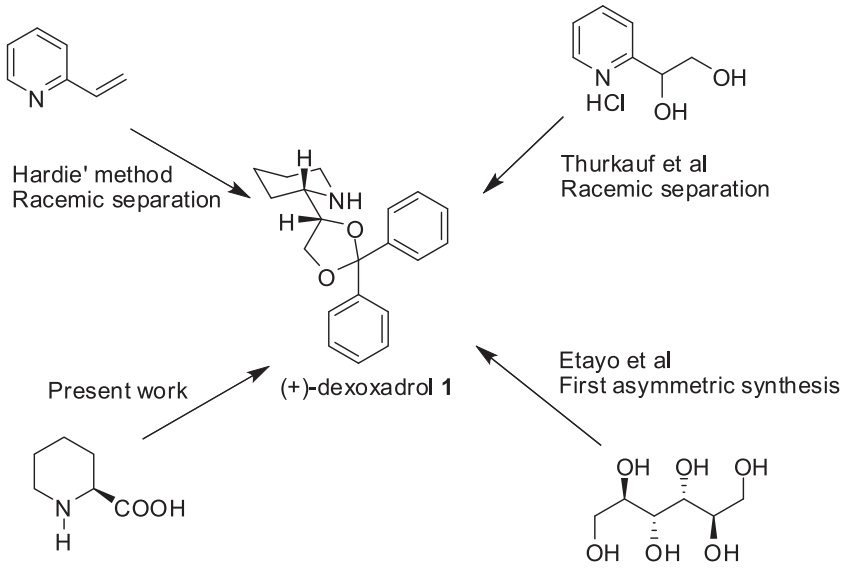
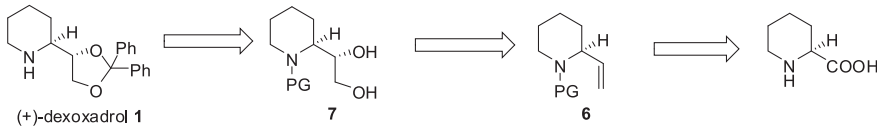


Fig. 1. Some of the NMDA receptor antagonists.



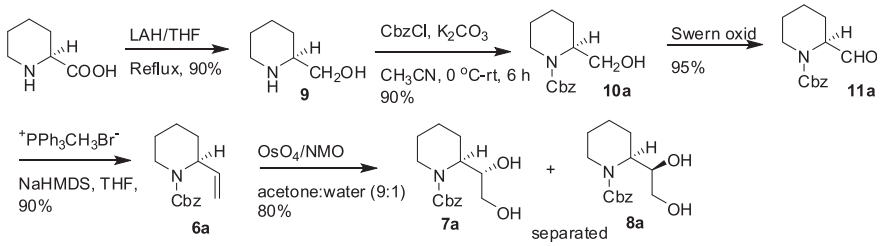
Scheme 1. Synthetic reports of dexoxadrol.



Scheme 2. Retrosynthetic approach.

was arbitrarily assigned as shown in Scheme 3. The exact ratio of **7a**/**8a** was determined based on HPLC method and it showed that they were formed in the proportions of 3:2.

not hold good for the system involving monosubstituted terminal double bond.[9] For achieving the required differential double diastereoselection, a different rule popularly called 'binding pocket'



Scheme 3. General synthetic approach.

In order to achieve better diastereoselectivity, it was necessary for us to employ Sharpless asymmetric dihydroxylation (SAD) using Sharpless ligands. The general elegant Sharpless rule for predicting the differential diastereoselectivity for the substituted olefin does

mnemonic is proposed by Sharpless where the reversal of facial selectivity for asymmetric dihydroxylation of terminal olefins is obtained.[9,10] Accordingly, the reversed facial selectivity could be achieved by selection of appropriate ligands for the

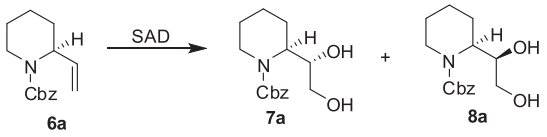
monosubstituted terminal olefins. Very few systems have been reported for manifesting this kind of unusual behaviour. Smith and co-workers observed this kind of same sense of diastereoselectivity while synthesizing calyculin.[11] During the synthesis of zaragozic acids similar unexpected diastereomeric outcomes were observed by Carreira's group.[12] It was also explained by Gardiner and Bruce by conducting the similar experiments for pyrrolidine system.[13] Recently, once again this abnormal behaviour was noticed by Díez and co-workers while synthesizing new proline analogues for organocatalysis.[14]

We thought of studying the Sharpless 'binding pocket' effect for our novel monosubstituted terminal olefin attached to piperidine system. The dihydroxylation was initially carried out in PHAL spacer using $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ (Scheme 4). Only one diastereomer was preferred by both the ligands. We then switched to AQN spacer and the similar results were noticed with further improvement in the formation of the same isomer. The same reaction was then studied shifting to ligands of PYR spacer. A remarkable diastereoselective differentiation was observed with enhancement of the other isomer with $(DHQD)_2PYR$. The HPLC chromatogram showed the formation of **8a** and **7a** with diastereoselective ratio of 7:3.

due to failure of **7a** to undergo acetalization. Thus **7a** on hydrogenolysis of −Cbz group afforded **12**. The amino diol **12** was then reacted with dimethoxybenzophenone in refluxing IPA to produce dexoxadrol **1**. The spectroscopic data were well matching with the reported values. The optical activity of **1**·HCl was recorded and further confirmed the formation of (+)-dexoxadrol and the assignment of stereochemistry of diols **7** and **8**. Similarly the first asymmetric synthesis of (−)-*epi*-dexoxadrol **2** was achieved from **8a**.

Moyano and co-workers have reported the synthesis of an important alkaloid conhydrine **13** by synthesizing epoxide **14** starting from an open chain molecule in several synthetic steps.[15] Conhydrine **13** is an alkaloid of hemlock family isolated basically from the leaves and seeds of the plant *Conium maculatum* L.[16] whose structure was first elucidated in 1933.[17] The (+)-conhydrine **13a** has attracted considerable synthetic interests due to its potent antitumour, antiviral and glycosidase inhibitory activities.[18] As a consequence, several synthetic routes have been manifested in the literature[15,19] for the synthesis of all different isomers and actively studied for numerous biological activities.

We envisioned that similar epoxides can be synthesized by simple synthetic transformation on either of alkene **6** or diol **7**. The



Ligands	7a (%)	8a (%)	Yield (7a+8a) (%)
No ligand	60	40	85
$(DHQ)_2PHAL$	79	21	81
$(DHQD)_2PHAL$	77	23	80
$(DHQ)_2AQN$	75	25	80
$(DHQD)_2AQN$	80	20	82
$(DHQ)_2PYR$	85	15	79
$(DHQD)_2PYR$	**31**	**69**	80

Scheme 4. Study of SAD on piperidine olefinic system.

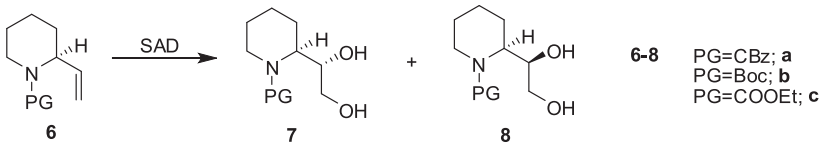
The stereochemistry of diols **7a** and **8a** was assigned at this stage based on Sharpless mnemonic.[14]

Next, we studied the effect of protecting groups on this reversal of double diastereoselection in piperidine system using PYR spacer. In this context, we prepared the Boc and COOEt protected alkenes **6b** and **6c** and subjected for dihydroxylation using PYR-based ligands (Scheme 5). Though there was not much difference in the diastereoselection by changing to −Boc group (**6b**) from −Cbz (**6a**), a considerable change was observed with −COOEt group (**6c**). The COOEt being sterically less hindered compared to −Cbz and −Boc offered a better reversal of facial selectivity to give predominantly **7c** and **8c** with $(DHQ)_2PYR$ and $(DHQD)_2PYR$, respectively.

The present results are in agreement with the Gardiner's view that the extent of differential diastereoselectivity also depends on the steric bulkiness of the substituent present on the double bond.[13]

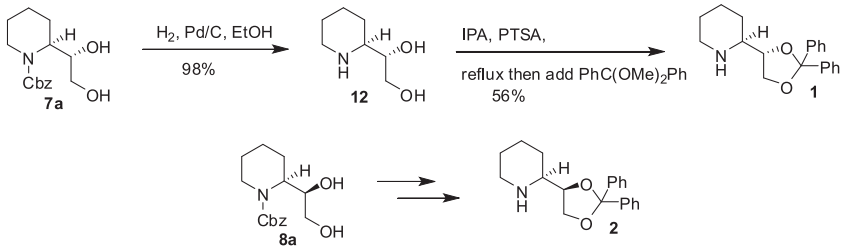
The planned synthetic approach was then proceeded to accomplish the total synthesis of dexoxadrol **1** (Scheme 6). It was necessary for us to deprotect Cbz prior to required acetal formation

epoxidation of alkenes **6** using *m*-CPBA was found to be unsatisfactory due to the formation of isomers and decomposition. Then the diol **8a** was subjected for monotosylation. Even though the synthesis of monotosylated compound **15b** appeared to be simple, the initial experimentations using different stoichiometric ratio of pyridine or Et_3N resulted either in getting ditosylated product or in poor yield. The other alternate methods tried for this were also not encouraging. Most of the times it ended in substantial amount of ditosylated compound with a very less formation of the anticipated **14b**. Recently Zhu et al. described the selective monotosylation of vicinal diols and cyclisation to corresponding epoxide for the synthesis of several antimalarial drugs by using catalytic amount of K_2CO_3.[20] Inspired by this, we adopted the same procedure in our case to furnish the synthesis of epoxide **14b** from **8a** by reacting with TsCl followed by treatment with 0.2 equiv of K_2CO_3. However for the synthesis of epoxide **14a** from diol **7a**, 1.0 equiv of K_2CO_3 had to be used. The synthesis of epoxides **14a** and **14b** accomplished the formal synthesis of (+)-α-conhydrine **13a** and (−)-β-conhydrine **13b** (Scheme 7).

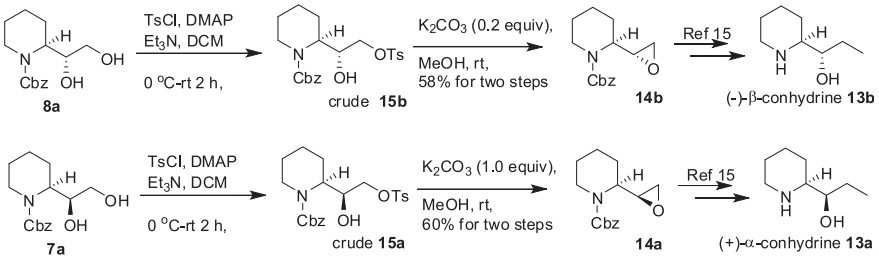


Ligands	$(DHQ)_2PYR$ (% of 7:8)	Yield (7+8) (%)	$(DHQD)_2PYR$ (% of 7:8)	Yield (7+8) (%)
PG=Cbz	85:15	79	31:69	80
PG=Boc	82:18	82	41:59	80
PG=COOEt	90:10	85	15:85	79

Scheme 5. The effect of protecting groups on diastereoselectivity.



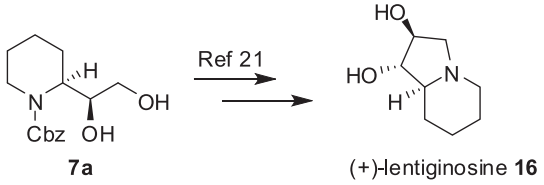
Scheme 6. Synthesis of dexoxadrol and *epi*-dexoxadrol.



Scheme 7. Formal synthesis of conhydrine.

The recent synthetic report by Vankar and co-workers describes a total synthesis of (+)-lentiginosine **16** from diol **7a** prepared by synthetic manoeuvring of D-mannitol.[21] (+)-Lentiginosine **16**, a naturally occurring isomer was isolated from *Astragalus lentiginosus* in 1990.[22] Being a hydroxylated alkaloid, serves as sugar mimics by acting as a potent selective inhibitor of α-glucosidase and amyloglucosidase.[23] Due to its unique structure and interesting biological activities, various synthetic routes have been established involving mainly chiral pool, organocatalytic and chiral auxiliary methods.[19e,21,23b,24]

Incidentally during our synthetic manoeuvring of dexoxadrol, the same diol **7a** is obtained from another chiral source (−)-pipecolic acid. Thus the synthesis of diol **7a** provides a straightforward formal synthetic approach to (+)-lentiginosine **16** (Scheme 8).



Scheme 8. Formal synthesis of (+)-lentiginosine.

3. Conclusion

In summary we have successfully synthesized (+)-dexoxadrol and (−)-*epi*-dexoxadrol starting from chiral source (−)-pipecolinic acid. Incidentally, this is the first asymmetric synthesis of (−)-*epi*-dexoxadrol. The results also uncovered the study of Sharpless dihydroxylation on terminal olefins for the hitherto unreported olefinic piperidine system and the effect of protecting groups on mismatching double diastereoselection. The paper also presents short and facile synthetic routes for the formal synthesis of conhydrine and (+)-lentiginosine.

4. Experimental

4.1. General remarks

Chemicals and solvents were purchased from commercial suppliers and purified by standard techniques whenever necessary. Column chromatography was performed on silica gel (60–120 mesh). ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE 400 instrument. Chemical shifts are expressed in δ relative to tetramethylsilane (TMS). The spectra were recorded in $CDCl_3$ as solvent (δ=7.28 ppm for ^1H, δ=77.0 ppm for ^{13}C). The

multiplicities of carbon signals were obtained from DEPT 135 experiment. Optical rotations (concentration in grams/100 mL solvent) were measured using sodium D line on a ADP 220 polarimeter. Infrared spectra (IR) were recorded on a Shimadzu FTIR instrument. High-resolution mass spectra (HRMS) were recorded on a Micro Mass ES-QTOF Mass spectrometer.

4.2. General procedures and characterization

*4.2.1. LAH reduction of (−)-pipecolinic acid to (−)-pipecolinol **9**.* To a well stirred suspension of LAH (2.0 g, 50 mmol) in anhyd THF under N_2 atm was added pipecolinic acid (5.0 g, 40 mmol) at 0 °C in three portions over a period of 40 min. The reaction mixture was slowly brought to rt, stirred for 6 h and then refluxed for 8 h. It was then cooled in an ice bath and a solution of 10% KOH (5 mL) was added drop wise over a period of 1 h. H_2O (5 mL) was then added and brought to rt in 30 min. The residue was then filtered to get rid of white precipitate of $Al(OH)_3$ and the filtrate was concentrated under vacuum. The pale yellow colour residual liquid was diluted with DCM (100 mL) and dried over anhyd Na_2SO_4 (if a thin layer of water persists over DCM, should be separated before drying over anhyd Na_2SO_4). It was then concentrated under reduced pressure to give essentially pure pale yellow thick liquid of pipecolinol **9** (4.2 g, 95%), which should immediately be preserved at 0 °C or consumed for the next reaction. IR (neat): ν_{max}=3500 cm^{-1} (broad peak).

(Note: The pipecolinol thus formed is essentially pure and should be utilized as soon as possible in order to achieve better yield in the next reaction. The storage of it at rt should be avoided since it turns dark yellow and the yield of the subsequent reaction would substantially go down).

*4.2.2. Synthesis of **10a**, **10b** and **10c**.* Compound **10a**: To a mixture of pipecolinol (2.0 g, 17 mmol) and K_2CO_3 (4.7 g, 34 mmol) in CH_3CN (20 mL) cooled to 0 °C, was added benzylchloroformate (50% in toluene) (6.5 mL, 19 mmol) over a period of 15 min. The reaction mixture was further stirred at the same temperature for 6 h. It was then concentrated under reduced pressure and diluted with DCM (50 mL). The water was added (30 mL) and the organic compound was separated. The organic layer was further washed with dil HCl (20 mL×2) followed by brine solution (20 mL), dried over anhyd Na_2SO_4 and concentrated in vacuo. The crude mixture was column chromatographed (SiO_2, hexane/EtOAc, 7:3) to give Cbz-pipecolinol **10a** as a pale yellow thick liquid (3.9 g, 90%).

R_f=0.25 (hexane/EtOAc, 7:3); $[\alpha]_D^{26}$ −36.5 (*c* 1.0, $CHCl_3$) {lit.[25a] $[\alpha]_D$ −30.2 (*c* 1.1, $CHCl_3$) for 85% ee}; IR (neat): ν_{max}=3500, 2995, 1690, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 1.34–1.64 (m, 6H, H-4, H-5, H-3), 2.02 (br s, 1H, OH), 2.85–2.90 (m, 1H, H-6A), 3.52–3.56 (m, 1H, H-6B), 3.71–3.76 (m, 1H, H-2), 3.94–3.96 (m, 1H, H-1′A), 4.25–4.30 (m, 1H, H-1′B), 5.05 (s, 2H, CH_2Ph), 7.20–7.28 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.5 (C-4), 25.1 (C-5), 25.2 (C-3), 40.1 (C-6), 52.8 (C-2), 61.2 (C-1′), 67.2 (*C*H_2Ph), 127.8 (PhCH), 127.9 (PhCH), 128.5 (PhCH), 136.7 (PhC), 156.6 (NCO).[25a]

Compound **10b**: To a mixture of pipecolinol (2.0 g, 17 mmol) and Et_3N (4.7 mL, 34 mmol) cooled to 0 °C in DCM (30 mL), was added $(Boc)_2O$ (4.4 mL, 20 mmol) drop wise over a period of 10 min. The reaction mixture was further stirred at the same temperature for 6 h. It was then treated with dil HCl (20 mL) and the organic layer was separated, washed with brine (20 mL×2), dried over anhyd Na_2SO_4 and then concentrated under reduced pressure. The crude mixture was purified by column chromatography (SiO_2, hexane/EtOAc, 8:2) to afford **10b** as a colourless thick liquid (3.2 g, 85%), which slowly turned to a crispy solid on prolonged cooling.

R_f=0.30 (hexane/EtOAc, 8:2); $[\alpha]_D^{26}$ −40.0 (*c* 1.0, $CHCl_3$) {lit.[25b] $[\alpha]_D^{25}$ −40.1 (*c* 1.0, $CHCl_3$) for 98% ee}; IR (neat): ν_{max}=3450, 2995, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 1.33–1.64 (m, 6H, H-4, H-5, H-3), 1.39 (s, 9H, ^{t}Bu*H*), 1.95 (br s, 1H, OH), 2.76–2.82 (m, 1H, H-6A), 3.52–3.55 (m, 1H, H-6B), 3.71–3.76 (m, 1H, H-2), 3.85–3.88 (m, 1H, H-1′A), 4.20–4.23 (m, 1H, H-1′B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.6 (C-4), 25.2 (C-5, C-3), 28.4 (^{t}BuC), 39.9 (C-6), 52.4 (C-2), 61.6 (C-1′), 79.8 (O*C*-^{t}Bu), 156.3 (NCO).[25b]

Compound **10c**: To a mixture of pipecolinol (2.0 g, 17 mmol) and K_2CO_3 (2.8 g, 20 mmol) in CH_3CN cooled to 0 °C, was added ethylchloroformate (2.0 mL, 21 mmol) over a period of 10 min. The reaction mixture was further stirred at the same temperature for 6 h. It was then concentrated under reduced pressure and diluted with DCM (30 mL). The organic layer was further treated with dil HCl (20 mL×2) followed by brine solution (20 mL) and dried over anhyd Na_2SO_4 and concentrated in vacuo. The crude mixture was column chromatographed (SiO_2, hexane/EtOAc, 9:1) to give **10c** as a pale yellow thick liquid (2.7 g, 82%).

R_f=0.30 (hexane/EtOAc, 8.5:1.5); $[\alpha]_D^{26}$ −39.5 (*c* 1.0, $CHCl_3$); {lit.[25c] $[\alpha]_D^{20}$ −36.6 (*c* 0.40, $CHCl_3$)}; IR (neat): ν_{max}=3410, 2955, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 1.19 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 1.32–1.68 (m, 6H, H-4, H-5, H-3), 2.80–2.86 (m, 2H, H-6A and OH), 3.53–3.57 (m, 1H, H-6B), 3.70–3.75 (m, 1H, H-2), 3.90–3.94 (m, 1H, H-1′A), 4.05 (q, *J*=7.2 Hz, 2H, OCH_2CH_3), 4.22–4.27 (m, 1H, H-1′B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.6 (OCH_2CH_3), 19.4 (C-4), 25.0 (C-5), 25.2 (C-3), 39.9 (C-6), 52.5 (C-2), 61.0 (C-1′), 61.4 (OCH_2CH_3), 156.8 (NCO).[25c]

*4.2.3. General procedure for the synthesis of **11** (**a**, **b**, **c**) by Swern oxidation.* To a solution of $(COCl)_2$ (1.2 mmol) in DCM (10 mL) cooled to −78 °C was added DMSO (1.5 mmol). The carbamate protected pipecolinol **10** (**a**, **b**, **c**) (1 mmol) was then added drop wise over a period of 5 min. The reaction mixture was brought to −50 °C in 15 min and Et_3N (3 mmol) was added over a period of 5 min. It was then stirred for 10 min at the same temperature and further stirred at rt for 15 min. The reaction mixture was further diluted with DCM (10 mL) and the organic layer was washed with very dil HCl (0.1 N, 10 mL×2) and brine solution (10 mL×2). It was then dried over anhyd Na_2SO_4 and concentrated under reduced pressure to afford aldehyde **11** (**a**, **b**, **c**) as a thick liquid, which without any further purification was immediately consumed for the next reaction.

*4.2.4. General procedure for Wittig reaction for the synthesis of alkenes **6a**, **6b** and **6c**.* The commercially available salt $^+PPh_3CH_3Br^-$ (1.07 g, 3.0 mmol) was stirred at 0 °C with dry THF (10 mL) in a three-necked 50 mL round bottom flask under N_2 atm sealed with a septum at one end. NaHMDS (1 M in THF) (1.5 mL, 1.5 mmol) was purged with the help of a syringe into the reaction mixture and appearance of the pale yellow colour was noticed. The stirring was continued for further 10 min and the corresponding aldehyde **11** (1 mmol) was added. The disappearance of the yellow colour was observed. The reaction mixture was then brought to rt and stirred for 2 h. It was concentrated in vacuo and quenched with saturated aq NH_4Cl (5 mL). The solution was diluted with DCM (25 mL) and the organic layer was separated. It was then washed with saturated aq NH_4Cl solution (10 mL×3) and dried over anhyd Na_2SO_4, concentrated under vacuum and purified by column chromatography (SiO_2, hexane/EtOAc, 9.5:0.5) to afford **6**.

*4.2.4.1. (S)-Benzyl-2-vinylpiperidine-1-carboxylate **6a**.* Obtained as a pale yellow thicky liquid (90%); R_f=0.80 (hexane/EtOAc, 9.5:0.5); $[\alpha]_D^{28}$ −17.5 (*c* 0.2, $CHCl_3$); IR (neat): ν_{max}=1690, 1675, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.45–1.80 (m, 6H, H-4, H-5, H-3), 2.91–2.98 (m, 1H, H-6A), 4.06–4.09 (m, 1H, H-6B), 4.91–4.92 (m, 1H, H-2), 4.92–5.24 (m, 2H, H-2′), 5.17 (s, 2H, CH_2Ph), 5.76–5.84 (m, 1H, H-1′), 7.32–7.38 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.4 (C-4), 25.2 (C-5), 28.9 (C-3), 40.1 (C-6), 52.7 (C-2), 67.0 (*C*H_2Ph), 115.9 (C-2′), 127.7 (PhCH), 127.9 (PhCH), 128.5 (PhCH), 136.5 (C-1′), 136.9 (PhCH), 155.8 (*NC*O); HRMS: *m*/*z* calcd for $C_{15}H_{19}NO_2Na$ $[M+Na]^+$:268.1313; found: 268.1313.

4.2.4.2. tert-Butyl-(2S)-2-vinylpiperidine-1-carboxylate ***6b***. Obtained as a pale yellow thicky liquid (70%); R_f=0.85 (hexane/EtOAc, 9.5:0.5); $[\alpha]_D^{27}$ −32.8 (*c* 0.2, $CHCl_3$) {lit.[25d] $[\alpha]_D^{20}$ −30.9 (*c* 0.24, $CHCl_3$)}; IR (neat): ν_{max}=1700, 1670, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.18–1.69 (m, 6H, H-4, H-5, H-3), 1.38 (s, 9H, ^tBuH), 2.72–2.79 (m, 1H, H-6A), 3.85–3.89 (m, 1H, H-6B), 4.70–4.71 (m, 1H, H-2), 5.04 (dd *J*=58.8 and 10.4 Hz, 2H, H-2′), 5.64–5.72 (m, 1H, H-1′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.4 (C-4), 24.5 (C-5), 27.4 ($OC(CH_3)_3$), 27.9 (C-3), 38.7 (C-6), 51.4 (C-2), 76.2 (CH_2Ph), 114.4 (C-2′), 135.8 (C-1′), 154.4 (NCO); HRMS: *m*/*z* calcd for $C_{12}H_{21}NO_2Na$ $[M+Na]^+$: 234.1470; found: 234.1470.[25d]

4.2.4.3. Ethyl-(2S)-2-vinylpiperidine-1-carboxylate ***6c***. Obtained as a pale yellow thicky liquid (68%); R_f=0.83 (hexane/EtOAc, 9.5:0.5); $[\alpha]_D^{26}$ −33.9 (*c* 0.2, $CHCl_3$); IR (neat): ν_{max}=1695, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.18 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 1.32–1.71 (m, 6H, H-4, H-5, H-3), 2.77–2.84 (m, 1H, H-6A), 3.91–3.95 (m, 1H, H-6B), 4.04–4.09 (m, 2H, OCH_2CH_3), 4.70–4.80 (m, 1H, H-2), 4.97–5.14 (m, 2H, H-2′), 5.65–5.74 (m, 1H, H-1′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.7 (OCH_2CH_3), 19.4 (C-4), 25.5 (C-5), 28.8 (C-3), 39.8 (C-6), 52.5 (C-2), 61.2 (OCH_2CH_3), 115.8 (C-2′), 136.6 (C-1′), 155.1 (NCO); HRMS: *m*/*z* calcd for $C_{10}H_{17}NO_2Na$ $[M+Na]^+$: 206.1157; found: 206.1157.

4.2.5. Procedure for Upjohn method of dihydroxylation of ***6a*** *for the synthesis of* ***7a*** *and* ***8a***. To stirred solution of **6a** (0.24 g, 1 mmol) in 10 mL of acetone and water (1:1), was added NMO (0.12 g, 1.0 mmol) followed by OsO_4 (1.3 mL, 5 mol %, 1% aq solution). The reaction mixture was stirred at rt for 6 h and quenched by saturated aq Na_2SO_3 (10 mL). The organic compound was extracted in ethyl acetate (25 mL×3), dried over anhyd Na_2SO_4 and concentrated in vacuo to furnish the mixture of diols **7a** and **8a** (0.24 g, 85%). The ratio of **7a**/**8a** was found using HPLC (Kromasil, IPA/hexane 1:4, flow rate 1.5 mL/min). The separation of **7a** and **8a** was achieved by slow elution on column chromatography (SiO_2, hexane/EtOAc, 7:3).

4.2.6. Procedure for SAD of ***6*** *for the synthesis of* ***7*** *and* ***8***

4.2.6.1. Preparation of AD-mix α. Prepared by premixing K_2CO_3 (0.41 g, 3 mmol), $K_3Fe(CN)_6$ (0.98 g, 3 mmol), $CH_3SO_2NH_2$ (0.09 g, 1 mmol), $K_2OsO_4{\cdot}2H_2O$ (4 mol %), Ligand [$(DHQ)_2PYR$/$(DHQ)_2AQN$/$(DHQ)_2PYR$] (10 mol %).

4.2.6.2. Preparation of AD-mix β. Prepared by premixing K_2CO_3 (0.41 g, 3 mmol), $K_3Fe(CN)_6$ (0.98 g, 3 mmol), $CH_3SO_2NH_2$ (0.09 g, 1 mmol), $K_2OsO_4{\cdot}2H_2O$ (4 mol %), Ligand [$(DHQD)_2PYR$/$(DHQD)_2AQN$/$(DHQD)_2PYR$] (10 mol %).

A solution of AD-mix α/AD-mix β in 10 mL $^tBuOH/H_2O$ (1:1) was stirred for 30 min at rt. The reaction mixture was cooled to 0 °C, added requisite alkene **6** (1 mmol) in 1 mL ^tBuOH and the stirring was continued for 30 min at the same temperature. It was then brought to rt and further stirred till the completion of reaction indicated by TLC. The reaction mixture was then quenched by saturated aq Na_2SO_3 (5 mL) and extracted with EtOAc (15 mL×2). The combined organic layer was dried over anhyd Na_2SO_4, concentrated and subjected to column chromatography to remove the impurities without separating the isomers **7** and **8** (Silica gel, 100% EA). The diastereomeric mixture was then subjected to HPLC to find the diastereomeric ratio of **7** and **8** (Kromasil, eluent IPA/*n*-hexane 1:4, flow rate 1.5 mL/min). The separation of diastereomers **7** and **8** was then achieved by very slow elution through column chromatography (SiO_2, hexane/EtOAc, 7:3).

4.2.6.3. Benzyl-(2S)-2-[(1S)-1,2-dihydroxyethyl] piperidine-1-carboxylate ***7a***. After following the standard procedure of SAD using the ligand $[DHQ]_2PYR$ (0.17 g, 10 mol %), compound **6a** (0.5 g, 2 mmol) afforded **7a** as a colourless thick liquid (0.34 g, 75%) (SiO_2, hexane/EtOAc, 7:3); R_f=0.4 (hexane/EtOAc, 1:1); $[\alpha]_D^{28}$ −26.2 (*c* 0.07, $CHCl_3$), $[\alpha]_D^{28}$ −24.2 (*c* 0.05, CH_2Cl_2) {lit.[21] $[\alpha]_D^{28}$ −36.15 (*c* 1.3, CH_2Cl_2)}; IR (neat): ν_{max}=3500, 1699, 1650, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43–1.66 (m, 6H, H-5, H-4, H-3), 2.19 (br s, 1H, −OH), 2.70–2.76 (m, 1H, H-6A), 3.10 (br s, OH), 3.48–3.51 (m, 1H, H-6B), 3.59–3.62 (m, 1H, H-2), 3.72–3.83 (m, 1H, H-1′), 4.06–4.12 (m, 2H, H-2′), 5.11–5.20 (m, 2H, CH_2Ph), 7.33–7.40 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.9 (C-4), 24.2 (C-5), 25.1 (C-3), 40.9 (C-6), 50.1 (C-2), 62.5 (C-2′), 67.7 (CH_2Ph), 67.8 (C-1′), 127.1 (PhCH), 128.1 (PhCH), 129.0 (PhCH), 136.1 (PhC), 155.1 (NCO).[21]

4.2.6.4. Benzyl (2S)-2-[(1R)-1,2-dihydroxyethyl] piperidine-1-carboxylate ***8a***. After following the standard procedure of SAD using the ligand $[DHQD]_2PYR$ (0.17 g, 10 mol %), compound **6a** (0.5 g, 2 mmol) afforded **8a** as a colourless thick liquid (0.25 g, 55%) (SiO_2, hexane/EtOAc, 7:3); R_f=0.4 (hexane/EtOAc, 1:1); $[\alpha]_D^{21}$ −17.4 (*c* 0.05, $CHCl_3$), $[\alpha]_D^{21}$ −11.4 (*c* 0.6, CH_2Cl_2) {lit.[25g] $[\alpha]_D$ +41.8 (*c* 0.5, CH_2Cl_2)}; IR (neat): ν_{max}=3400, 1699, 1650, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.46–1.68 (m, 6H, H-5, H-4, H-3), 2.90–3.11 (br s, 2H, −OH), 3.50–3.61 (m, 1H, H-6A), 3.73–3.76 (m, 1H, H-6B), 3.99–4.01 (m, 1H, H-2), 4.01–4.20 (m, 2H, H-2′), 4.30–4.32 (m, 1H, H-1′), 5.16 (s, 2H, CH_2Ph), 7.33–7.37 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.6 (C-4), 25.0 (C-5), 25.9 (C-3), 40.7 (C-6), 51.2 (C-2), 64.3 (C-2′), 67.4 (CH_2Ph), 71.1 (C-1′), 127.8 (PhCH), 128.0 (PhCH), 128.5 (PhCH), 136.6 (PhC), 155.5 (NCO).[25g]

Compound **7b**: After following the standard procedure of SAD using the ligand $[DHQ]_2PYR$ (0.17 g, 10 mol %), compound **6b** (0.42 g, 2 mmol) afforded **7b** as a colourless thick liquid (0.28 g, 72%) (SiO_2, hexane/EtOAc, 7:3); R_f=0.4 (hexane/EtOAc, 2:3); $[\alpha]_D^{26}$ −55.7 (*c* 0.2, $CHCl_3$) {lit.[25f] $[\alpha]_D$ −59.5 (*c* 0.9, $CHCl_3$)}; IR (neat): ν_{max}=3400, 1688, 1423 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.18–1.57 (m, 6H, H-5, H-4, H-3), 1.39 (s, 9H, ^tBuH), 2.01–2.09 (m, 1H, H-6A), 2.53–2.60 (m, 1H, H-6B), 3.40–3.56 (m, 3H, H-2, H-2′), 3.60–3.73 (m, 1H, H-1′), 3.88–3.97 (m, 2H, −OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.9 (C-4), 23.0 (C-5), 24.1 (C-3), 27.3 ($C(CH_3)_3$), 40.0 (C-6), 49.6 (C-2), 63.2 (C-2′), 66.8 (C-1′), 79.6 (^tBuCO), 155.5 (NCO) (extra signals appeared due to the presence of rotamers); HRMS: *m*/*z* calcd for $C_{12}H_{23}NO_4Na$ $[M+Na]^+$: 268.1585; found: 268.1525.[25f]

Compound **8b**: After following the standard procedure of SAD using the ligand $[DHQD]_2PYR$ (0.17 g, 10 mol %), compound **6b** (0.42 g, 2 mmol) afforded **8b** as a colourless thick liquid (0.2 g, 50%) (SiO_2, hexane/EtOAc, 7:3); R_f=0.4 (hexane/EtOAc, 2:3); $[\alpha]_D^{21}$ −40.6 (*c* 0.05, $CHCl_3$) {lit.[19e] $[\alpha]_D^{27}$ +27.1 (*c* 1.0, $CHCl_3$) for *RS* isomer}; IR (neat): ν_{max}=3400, 1670, 1423 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.30–1.57 (m, 6H, H-5, H-4, H-3), 1.39 (s, 9H, ^tBuH), 2.89 (br s, 2H, OH), 3.01–3.02 (m, 1H, H-6A), 3.44–3.46 (m, 1H, H-6B), 3.47–3.49 (m, 1H, H-2), 3.80–3.88 (m, 2H, H-2′), 4.10–4.15 (m, 1H, H-1′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.6 (C-4), 24.0 (C-5), 24.8 (C-3), 27.4 (^tBuC), 39.8 (C-6), 42.3 (C-2), 51.0 (C-1′), 63.2 (C-2′), 70.2 (^tBuCO), 155.8 (NCO); HRMS: *m*/*z* calcd for $C_{12}H_{23}NO_4Na$ $[M+Na]^+$: 268.1585; found: 268.1525.[25e]

Compound **7c**: After following the standard procedure of SAD using the ligand $[DHQ]_2PYR$ (0.17 g, 10 mol %), compound **6c** (0.36 g, 2 mmol) afforded **7c** as a colourless thick liquid (0.30 g, 85%) (SiO_2, hexane/EtOAc, 7:3); R_f=0.35 (hexane/EtOAc, 2:3); $[\alpha]_D^{21}$ −49.2 (*c* 0.04, $CHCl_3$); IR (neat): ν_{max}=3500, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.19 (t, *J*=6.8 Hz, 3H, OCH_2CH_3), 1.35–1.58 (m, 6H, H-5, H-4, H-3), 2.09–2.11 (m, 1H, H-6A), 2.59–2.66 (m, 1H, H-6B), 3.01–3.02 (m, 1H, H-2), 3.44–3.57 (m, 2H, H-2′), 3.75–3.76 (m, 1H, H-1′), 3.95–4.01 (m, 2H, OH), 4.07–4.09 (m, 2H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.6 (OCH_2CH_3), 18.9 (C-5), 24.1 (C-4), 25.1 (C-3), 40.7 (C-6), 43.3 (C-2), 51.3 (C-2′), 61.9 (C-1′), 67.8 (OCH_2CH_3), 156.1 (NCO) (extra signals are appeared due to the presence of rotamers); HRMS: *m*/*z* calcd for $C_{10}H_{19}NO_4Na$ $[M+Na]^+$: 240.1212; found: 240.1212.

Compound **8c**: After following the standard procedure of SAD using the ligand $[DHQD]_2PYR$ (0.17 g, 10 mol %), compound **6c** (0.36 g, 2 mmol) afforded **8c** as a colourless thick liquid (0.23 g, 80%) (SiO_2, hexane/EtOAc, 7:3); R_f=0.35 (hexane/EtOAc, 2:3); $[\alpha]_D^{21}$ −36.3 (*c* 0.03, $CHCl_3$); IR (neat): ν_{max}=3500, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.18–1.22 (m, 3H, OCH_2CH_3), 1.35–1.59 (m, 6H, H-5, H-4, H-3), 2.10–2.11 (m, 1H, H-6A), 2.58–2.65 (m, 1H, H-6B), 3.01–3.03 (m, 1H, H-2), 3.43–3.56 (m, 2H, H-2′), 3.70–3.75 (m, 1H, H-1′), 3.94–3.98 (m, 2H, OH), 4.00–4.09 (m, 2H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.6 (OCH_2CH_3), 17.9 (C-5), 23.1 (C-4), 24.1 (C-3), 39.7 (C-6), 42.3 (C-2), 50.3 (C-2′), 60.9 (C-1′), 66.8 (OCH_2CH_3), 156.1 (NCO); HRMS: *m*/*z* calcd for $C_{10}H_{19}NO_4Na$ $[M+Na]^+$: 240.1212; found: 240.1212.

*4.2.6.5. (+)-Dexoxadrol **1**.* To a solution of **7a** (0.28 g, 1 mmol) in EtOH (10 mL) was added 10% Pd/C (0.028 g, 10% w/w) and hydrogenated using Parr hydrogenator (2.5 atm) at rt for 6 h. The solution was filtered and concentrated under reduced pressure to afford essentially pure **12** (0.13 g, 95%). The disappearance of carbonyl stretching in IR indicated the formation of product;[26] IR (neat): ν_{max}=3300, 3000, 1440 cm^{-1}.

To a refluxing solution of **12** (0.14 g, 1 mmol) in IPA with PTSA (cat), was added dimethoxybenzophenone (1.61 g, 7 mmol) and refluxed further for 1 h. The reaction mixture was cooled, concentrated and as such subjected to column purification to give pure **1** (SiO_2, hexane/EtOAc, 7:3) (0.18 g, 60%). To compound **1** (0.31 g, 1 mmol) in EtOAc (5 mL), passed dry HCl gas liberated from the reaction of concd H_2SO_4 over NaCl. The reaction mixture was concentrated to dryness to give pure **1**·HCl (0.27 g, 80%).

R_f=0.3 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D^{26}$ +34.5 (*c* 0.05, MeOH) (of HCl salt); {lit.[3] $[\alpha]_D^{25}$ +33.9 (*c* 2.0, MeOH)}; IR (neat): ν_{max}=3330 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.10–1.13 (m, 1H), 1.27–1.49 (m, 3H), 1.60–1.63 (m, 1H), 1.72–1.75 (m, 2H), 1.82–1.85 (m, 1H), 2.59–2.65 (m, 1H), 2.85–2.88 (m, 1H), 3.09–3.12 (br d, *J*=11.6 Hz, 1H), 3.94–3.97 (m, 1H), 4.09–4.10 (m, 1H), 4.14–4.15 (m, 1H), 7.28–7.37 (m, 6H), 7.48–7.50 (m, 2H), 7.54–7.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 26.1, 28.1, 46.5, 57.9, 65.9, 79.3, 109.5, 126.1, 126.2, 128.0, 128.2, 141.9, 142.1.[7b]

*4.2.6.6. (−)-epi-Dexoxadrol **2**.* Similar procedure was followed for the synthesis of (−)-*epi*-dexoxadrol **2** (0.15 g, 50%); R_f=0.3 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D^{26}$ −42.5 (*c* 0.04, $CHCl_3$) (of HCl salt); IR (neat): ν_{max}=3330 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.14–1.17 (m, 1H), 1.25–1.35 (m, 1H), 1.36–1.51 (m, 2H), 1.60–1.63 (m, 1H), 1.78–1.81 (m, 1H), 2.39 (br s, 2H), 2.59–2.65 (m, 2H), 3.11–3.14 (m, 1H), 3.85 (br s, 1H), 4.04 (s, 2H), 7.28–7.33 (m, 6H), 7.49–7.54 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.9, 25.6, 27.9, 46.2, 59.9, 67.3, 80.1, 109.8, 126.1, 126.3, 128.0, 128.1, 128.2, 142.0, 142.3.

*4.2.6.7. Synthesis of **14b**.* To a mixture of **8a** (0.26 g, 1 mmol), Et_3N (0.2 mL, 1.4 mmol) and DMAP (0.007 g, 0.06 mmol) in DCM (10 mL) was added TsCl (0.19 g, 1 mmol) at 0 °C. The reaction mixture was brought to rt in 30 min and further stirred for 2 h at rt. It was then diluted with DCM (20 mL), washed with saturated aq $NaHCO_3$ (10 mL×3) and 1 N HCl (10 mL×3). The combined organic layer was dried over anhyd Na_2SO_4 and concentrated under reduced pressure to give essentially pure monotosylate **15b**. The crude compound **15b** was stirred in MeOH (10 mL) at rt, added K_2CO_3 (0.03 g, 0.2 mmol). The reaction mixture was further stirred for 30 min and then concentrated to dryness. It was diluted with DCM (25 mL), washed with H_2O and saturated aq $NaHCO_3$ (15 mL×3). The organic layer was dried over anhyd Na_2SO_4 and purified by column chromatography (SiO_2, hexane/EtOAc, 9:1) to afford **14b** (0.15 g, 58%).

The spectroscopic data were comparable with the literature.[15] R_f=0.8 (hexane/EtOAc, 9:1); $[\alpha]_D^{28}$ −30.3 (*c* 0.04, $CHCl_3$); IR (neat): ν_{max}=1700, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.58–1.75 (m, 6H, H-4, H-5, H-3), 2.65–2.67 (m, 1H, H-6A), 2.95–3.01 (m, 1H, H-6B), 3.08–3.11 (m, 1H, H-2), 3.80–4.03 (m, 1H, H-2′A), 4.23–4.30 (m, 1H, H-2′B), 4.62–4.63 (m, 1H, H-1′), 5.01–5.08 (m, 2H, $PhCH_2$), 7.19–7.30 (m, 5H, PhH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7 (C-4), 24.2 (C-5), 30.4 (C-3), 41.3 (C-6), 54.2 (C-2), 69.0 (C-2′), 71.9 (CH_2Ph), 76.5 (C-1′), 127.9 (PhCH), 128.0 (PhCH), 128.6 (PhCH), 128.7 (PhCH), 129.0 (PhCH), 136.8 (PhC), 144.5, 155.8 (NCO) (some extra signals are observed due to the presence of rotamers).

Similar procedure was repeated for the synthesis of **14a** (0.18 g, 60%); R_f=0.85 (hexane/EtOAc, 9:1); $[\alpha]_D^{28}$ −25.0 (*c* 0.05, $CHCl_3$); IR (neat): ν_{max}=1700, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.17–1.84 (m, 6H, H-4, H-5, H-3), 2.43 (br s, 1H), 2.65–2.66 (m, 1H), 2.94–2.98 (m, 1H), 3.05–3.08 (m, 1H), 3.99–4.02 (m, 1H), 4.20–4.23 (m, 1H), 4.62 (s, 1H), 5.04 (s, 1H), 7.23–7.28 (5H, PhH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2 (C-4), 25.1 (C-5), 27.5 (C-3), 41.5 (C-6), 44.5 (C-2′), 53.4 (C-1′), 65.3 (C-2′), 67.1 (CH_2Ph, C-1′), 126.9 (PhCH), 127.6 (PhCH), 127.8 (PhCH), 127.9 (PhCH), 128.5 (PhCH), 136.8 (PhC), 155.8 (NCO) (some extra signals are observed due to the presence of rotamers).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.10.082.

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