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Syntheses of (−)-gabosine A, (+)-4-*epi*-gabosine A, (−)-gabosine E, and (+)-4-*epi*-gabosine E

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ABSTRACT

(+)-4-*epi*-Gabosine A **1** and (−)-gabosine A **2** have been synthesized starting from methyl α,D-glucopyranoside and methyl α,D-mannopyranoside, respectively, by utilizing Pd(0) catalyzed Stille coupling as the key step. On the other hand, syntheses of (+)-4-*epi*-gabosine E **3** and (−)-gabosine E **4** have been accomplished from methyl α,D-glucopyranoside and from methyl α,D-mannopyranoside, respectively, by utilizing DMAP catalyzed Morita–Baylis–Hillman reaction as the key step. Presence of acetyl group at C-6 position of sugar derived cyclic enone prevented the aromatization of MBH adduct. A plausible mechanism is also described.

1. Introduction

The gabosines, a class of carbasugars were isolated from *Streptomyces* strains in 1974 and since then they have stimulated manifold studies directed toward their total synthesis. Their interesting biological activities, such as antibiotic, anticancer, and DNA binding properties evoked intense interest in these natural products.[1,2] Several different gabosines have been identified (Fig. 1). The absolute configurations of gabosines A, D, E, and F[1b] and that of L and N[1a] were established by Thiericke and Zeeck. While the absolute configuration of gabosine C was determined by Tatsuta et al.[1d] the absolute configuration of gabosine B was established by Müller et al.[1c] On the other hand the absolute configurations of gabosines G,[3h] I,[3q] and O[3j] were established by their respective total synthesis. Recently, Shing et al. revised and established the relative and absolute configuration of gabosine K by its total synthesis.[3a] The biological activities associated with gabosines made them attractive targets for synthetic chemists. Several groups have reported the total synthesis of gabosines and also their epimers.[3,4] In the syntheses of gabosines, the carbocyclic framework has been synthesized by Diels–Alder reaction[3l,o] or from carbohydrates,[3a–h,k,p–r] while other syntheses utilized carbocylic starting materials like quinic acid[3m] and iodobenzene.[3n] Two syntheses of 4-*epi*-gabosine A have been reported in the literature. An enantioselective synthesis was described by Carreño et al.[3i] from [(*p*-tolylsulfinyl) methyl]-*p*-quinols, while Gree et al.[3g] synthesized 4-*epi*-gabosine A

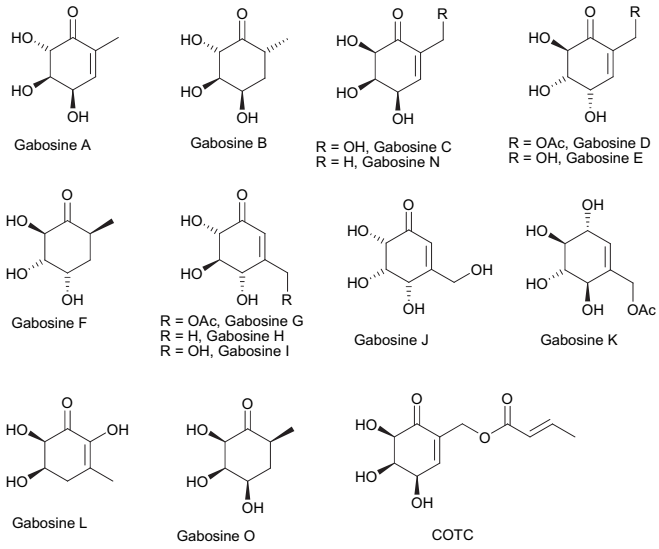

Fig. 1. The family of gabosine.

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from D-glucose by utilizing iron catalyzed tandem isomerization–intramolecular aldolization reaction as the key step to access cyclohexenone framework. (−)-Gabosine A has been synthesized by a chemoenzymatic approach from iodobenzene by Banwell et al.[3n] and by enantiospecific approach from (−)-quinic acid by Shinada et al.[3m] In year 2009, Shing et al. reported synthesis of (+)-gabosine A and E where the key cyclohexenone building block was constructed by an intramolecular aldol cyclization of a diketone derived from D-glucose.[3e] Moreover, while this manuscript was under preparation Toribio et al. reported a divergent approach toward the enantioselective synthesis of (+)-gabosine A along with several other gabosines and anhydrogabosines starting from easily available 4-(*tert*-butyl dimethylsilyloxy)-6-(phenylthio) cyclohex-2-enone.[4] Gabosine E has also been synthesized by utilizing intramolecular nitrile-oxide cycloaddition as the key step starting from D-ribose,[3r] methyl α,D-mannopyranoside,[3c] and (−)-quinic acid.[3m]

Our interest toward the synthesis of carbohydrate-based chiral building blocks (CBBs)[5] and their utilization for the synthesis of natural products or natural product like molecules[6] motivated us to take an attempt to synthesize biologically important gabosines by 'chiron approach'. Herein, we wish to report an efficient synthesis of (+)-4-*epi*-gabosine A, (−)-gabosine A, (+)-4-*epi*-gabosine E, and (−)-gabosine E from commercially available chiral pool materials like methyl α,D-glucopyranoside and methyl α,D-mannopyranoside.

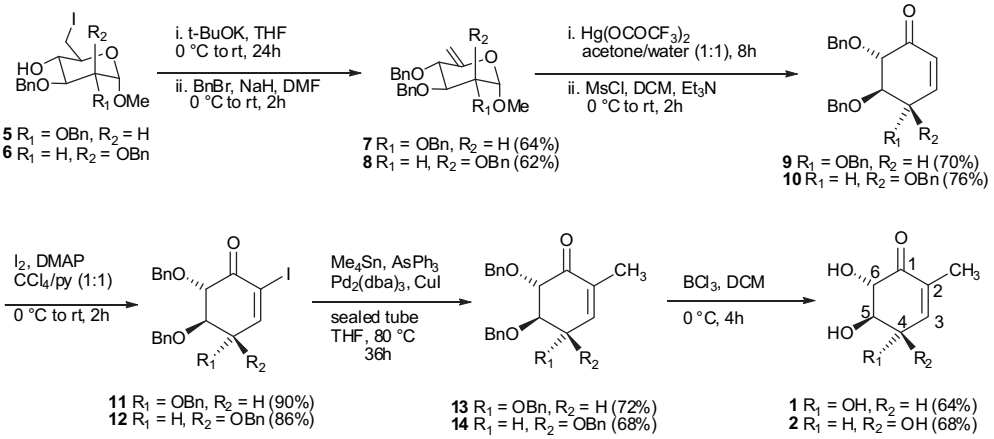
2. Results and discussion

Synthesis of (+)-4-*epi*-gabosine A (**1**) was commenced from methyl 6-deoxy-6-iodo-2,3-di-*O*-benzyl-α,D-glucopyranoside **5** that was easily available from methyl α,D-glucopyranoside in four steps in 62% yield.[7] Dehydrohalogenation of iodide **5** with ^{t}BuOK in THF[8] followed by benzylation of the resulting olefin provided tribenzylated product **7**. Its Ferrier's carbocyclization reaction[8,9] using mercury (II) trifluoroacetate $Hg(OCOCF_3)_2$ in acetone/H_2O (1/1) followed by mesylation produced enone **9**, the key precursor for the synthesis of (+) 4-*epi*-gabosine A. Treatment of **9** with iodine in pyridine/CCl_4 (1/1) in the presence of catalytic amount of DMAP furnished iodide **11**. Very few examples toward the synthesis of α-alkylenones involving Stille cross-coupling reactions are available in the literature.[10] Banwell et al. in their synthesis of (−)-gabosine A reported that conversion of α-iodoenones to α-methylenone was unsuccessful using palladium (0) catalyzed cross-coupling reactions with tetramethyltin, dimethylzinc or methylmagnesium chloride.[3n] Herein, we accomplished the synthesis of (+) 4-*epi*-gabosine A by successful utilization of palladium (0) catalyzed Stille cross-coupling reactions of α-iodide **11** with tetramethyltin reagent. Thus, conversion of iodide **11** to α-methylenone **13** was achieved by treating **11** with tetramethyltin, triphenylarsine, copper (I) iodide, and $Pd_2(dba)_3$ in a sealed tube at 80 °C.[11] The spectroscopic data of compound **13** were in good agreement to that reported in the literature.[3g] Debenzylation of Stille product **13** using BCl_3 in DCM at 0 °C provided (+)-4-*epi*-gabosine A **1** (Scheme 1). The spectroscopic data of compound **1** were also in full agreement to those reported in literature.[3g] Thus (+)-4-*epi*-gabosine A **1**was synthesized from methyl α,D-glucopyranoside in 11 steps and 12.9% overall yield that is comparable to previously reported synthesis of title compound from D-glucose (10 steps, 15.4% overall yield).[3g]

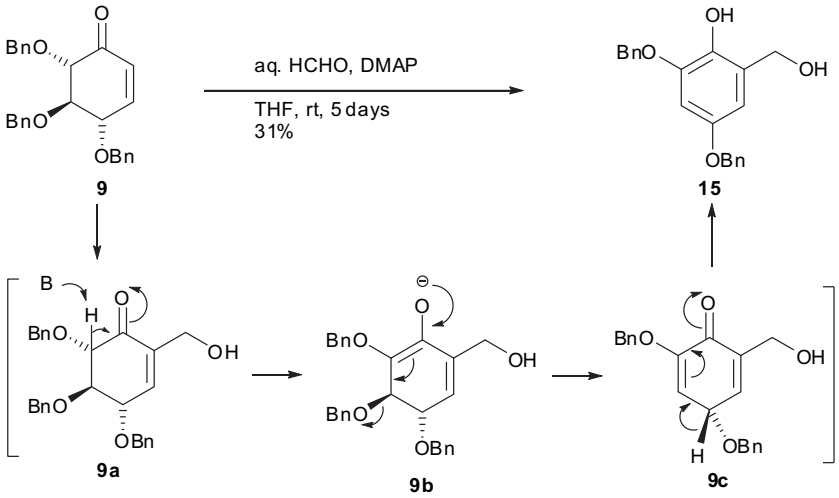
In order to synthesize (−)-gabosine A, we required a methyl glycopyranoside precursor whose stereochemistry at C2 should be opposite to that of methyl α,D-glucopyranoside. Therefore, we identified commercially available methyl α,D-mannopyranoside as a suitable starting material in this endeavor. Adopting the similar experimental protocols as described above to obtain 4-*epi*-gabosine A from its respective iodide, the Stille coupling of iodide **12** derived from **6** (easily available in 57% overall yield from methyl α,D-mannopyranoside)[7] furnished protected gabosine A **14**. Debenzylation of **14** using BCl_3 at 0 °C furnished the (−)-gabosine A **2**. The spectroscopic data of the synthesized natural product were in full agreement to those reported in the literature[3n] (Scheme 1). In this way (−)-gabosine A was harvested from methyl α,D-mannopyranoside in 11 steps (10.8% overall yield) and comparable to previous report by Shing et al. where (+)-gabosine A was synthesized from D-glucose in 15 steps with 14.4% yield.[3e]

For the synthesis of 4-*epi*-gabosine E we envisaged a Morita–Baylis–Hillman (MBH) reaction of enone **9** with formaldehyde under the conditions described by Cheng et al. (imidazole, 1 M $NaHCO_3$, THF)[12] that provided undesired complex mixture of products. However, treatment of enone **9** with aqueous formaldehyde in the presence of catalytic DMAP[13] in THF for 5 days furnished aromatized product **15** in 31% yield instead of the desired MBH adduct. The proposed plausible mechanism for the aromatization of MBH adduct of enone **9** is depicted in Scheme 2. The initially formed MBH adduct **9a** undergoes enolization under basic condition to give enolate **9b**. The β-elimination of the benzyloxy group from this enolate resulted in the formation of ketone **9c** that ultimately on keto–enol tautomerisation furnished highly stable aromatic compound **15** (Scheme 2).

However the aromatization of MBH adduct was prevented when the 6-*O*-acetyl protected enone **18** was used in place of **9**. Thus, dehydrohalogenation of iodide **5** followed by acetylation of the resulting product provided olefin **16**, which on Ferrier



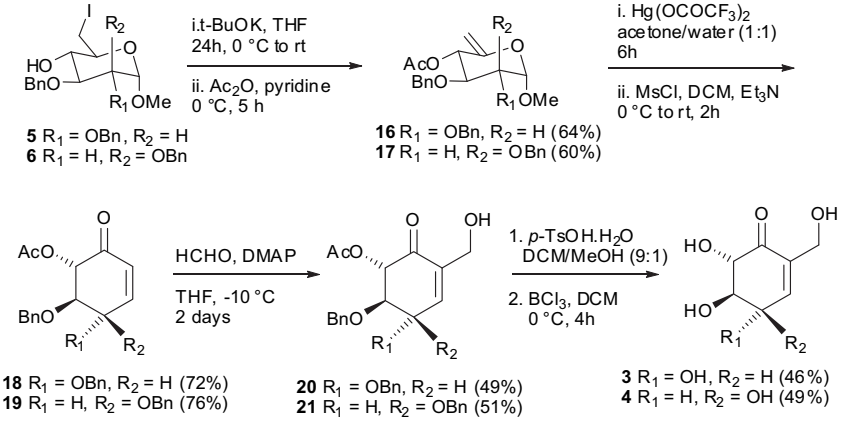
Scheme 1. Synthesis of (+)-4-*epi*-gabosine A and (−)-gabosine A.



Scheme 2. DMAP catalyzed Morita–Baylis–Hillman reaction of enone **9**.

carbocyclization followed by mesylation furnished enone **18**. Its reaction with aqueous formaldehyde (37%) in the presence of DMAP in THF at room temperature was very slow and the adduct **20** was isolated in 28% yield only after 3 days. However, increment of the reaction temperature from room temperature to 40 °C led to decomposition of starting material. We then performed this reaction at a range of lower temperatures.[14a] Recently we observed that the similar MBH reaction with an enuloside at −10 °C increased the yield of the adduct.[14b] Here also the yield of the adduct **20** was increased from 28% to 49% when the reaction was performed by lowering the reaction temperature to −10 °C. Further lowering the temperature to −20 °C decreased the rate of the reaction significantly as monitored by TLC.

Attempts were then made to deacetylate the compound **20**. Deacetylation with $Sc(OTf)_3/MeOH/H_2O$ under the conditions described by Hiyama et al.[17] was futile and furnished complex mixture of products. Similarly, deacetylation of compound **20** with MeOH/

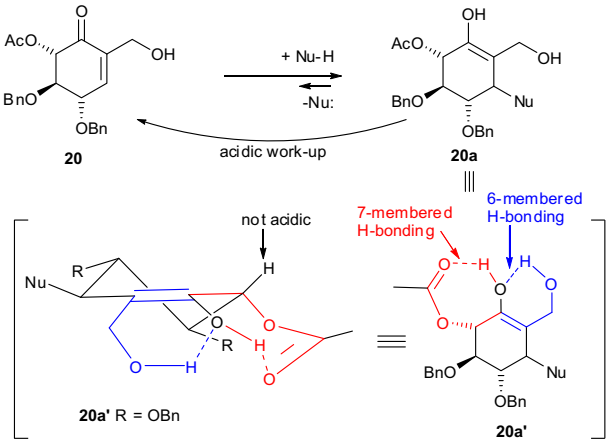


Scheme 3. Synthesis of (+)-4-*epi*-gabosine E and (−)-gabosine E.

Unlike the behavior of globally benzyl protected enone **9** on its MBH reaction to give the aromatic compound **15** as discussed above, the exact role of 6-OAc in **18** to deliver MBH adduct **20** was not clear, however, a plausible mechanism for the formation of **20** from enone **18** can be proposed as follows. Intramolecular hydrogen bonding can change chemical and structural properties of a molecule.[15] It has been reported in the literature that intramolecular hydrogen bonding favors keto–enol tautomeric equilibrium.[16] In our case, initially formed MBH adduct **20** may undergo Michael type addition with undefined nucleophile (may be solvent molecule or base) to give species **20a**. Here in this species, oxygen of the enol can form a six membered hydrogen bond with proton of the hydroxymethyl group and at the same time the carbonyl oxygen of the acetoxy group can also form seven membered hydrogen bond with enolic hydrogen of the same enol to give species **20a′** and thereby favoring the enol form over its keto form. Based on this fact it can be argued that hydrogen attached to the carbon bearing acetoxy group is not sufficiently acidic enough to be abstracted by a weak base like DMAP, essentially required for enolization to aromatize MBH adduct (Scheme 4).

Et_3N/H_2O (8/1/1)[18] at −15 °C to 0 °C was unsuccessful. Gratifyingly, the deacetylation of the adduct **20** with *p*-toluenesulfonic acid[19] followed by debenzylation with BCl_3 ultimately provided the target (+)-4-*epi*-gabosine E **3** in 6.4% overall yield and 11 steps from methyl α,D-glucopyranoside (Scheme 3).[20]

In order to synthesize gabosine E, we extended this strategy to the cyclic enone **19**, which was prepared from methyl α,D-mannopyranoside derived iodide **6** by adopting the similar reaction protocol used for the construction of enone **18** from **5** as shown in Scheme 3. The reaction of enone **19** with aqueous formaldehyde at −10 °C in the presence of DMAP as a base for 2 days produced the



Scheme 4. Proposed mechanism for the formation of MBH adduct **20**.

adduct **21** in 51% yield, which was finally converted to (−)-gabosine E **4** on deprotection (Scheme 3).[20] Thus (−)-gabosine E **4** was synthesized in 11 steps from methyl α,D-mannopyranoside in 6.5% overall yield. Although, here due to low yields in MBH reaction the overall yield was lower than the earlier reports (Gallos et al. reported 12% overall yield from methyl α,D-mannopyranoside in 11 steps and Lygo et al. reported in 12 steps and 10.5% overall yield from D-ribose), the acetyl group assisted MBH reaction uncovers interesting results.

3. Conclusions

In summary, herein an efficient and similar strategy for the synthesis of both (+)-4-*epi*-gabosine A and (−)-gabosine A starting from commercially available sugars has been disclosed. The key step in their synthesis was the conversion of α-iodoenone to α-methylenone by successful utilization of Pd(0) catalyzed Stille coupling. We have also completed the synthesis of (+)-4-*epi*-gabosine E and (−)-gabosine E by employing Morita–Baylis–Hillman (MBH) chemistry under identical conditions. The acetyl group at C-6 position in enones **18** and **19** prevented the aromatization of their MBH adducts. Application of this strategy to the construction of other cyclohexa(e)noid natural products is in progress and will be reported in due course.

4. Experimental

4.1. General

Organic solvents were dried by standard methods. All the products were characterized by ^{1}H, ^{13}C, IR, and ESI-MS spectroscopy. NMR spectra of all the synthesized compounds were recorded in $CDCl_3$ and CD_3OD at 25 °C on Bruker Avance DPX 200FT, Bruker Robotics, and Bruker DRX 300 Spectrometers at 200, 300 MHz (^{1}H) and 50, 75 MHz (^{13}C), respectively. Chemical shifts are given on the δ scale and are referenced to the TMS at 0.00 ppm for proton and 0.00 ppm for carbon. For ^{13}C NMR reference $CDCl_3$ appeared at 77.4 ppm. Mass spectra were recorded on a JEOLJMS-600H high resolution spectrometer using EI and DART mode at 70 eV and IR spectra on Perkin–Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Optical rotations were determined on an Autopol III polarimeter using a 1 dm cell at 28 °C in chloroform as the solvents; concentrations mentioned are in g/100 mL. Analytical TLC was performed using 2.5×5 cm plates coated with a 0.25 mm thickness of silica gel ($60F_{254}$), and visualization was accomplished with $CeSO_4$ (1% in 2 N H_2SO_4) followed by charring over hot plate. Silica gel (100–200 and 230–400 mesh) was used for column chromatography. Low-temperature reactions were performed by using immersion cooler with ethanol as the cooling agent.

4.1.1. Compound **7**. To a stirred solution of iodide **5** (1.5 g, 3.1 mmol) in THF (30 mL) was added ^{t}BuOK (1.04 g, 9.3 mmol) in portion wise at 0 °C over 2 h and allowed the reaction to stir for 24 h at room temperature. The reaction mixture was then diluted with ethyl acetate (30 mL) and washed with H_2O (2×15 mL) and brine (2×15 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure to give a residue (1.2 g).

To a solution of the above residue (1.2 g) in DMF (12 mL) was added sodium hydride (162 mg, 60% suspension in mineral oil) at 0 °C followed by dropwise addition of benzyl bromide (0.38 mL, 3.23 mmol) and then allowed the reaction to stir at room temperature. After completion of reaction (2 h), methanol (6 mL) was added to the reaction mixture and the resulting solution was concentrated at reduced pressure to a residue. Water was added to it and the mixture was extracted with diethylether (3×20 mL). The combined organic layer was dried over sodium sulfate and concentrated to a crude compound, which was purified using silica gel column chromatography to give **7** (884 mg, 64% yield from **5**).

Colorless oil, eluent for column chromatography: EtOAc/hexane (3/47, v/v); $[\alpha]_D^{28}$ +0.66 (*c* 0.80, $CHCl_3$); R_f 0.66 (1/4 EtOAc/hexane); IR (neat): ν=3022, 1638, 1460, 1217, 1162, 1113 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (15H, m), 4.92–4.77 (6H, m), 4.69–4.61 (3H, m), 3.99–3.89 (2H, m), 3.60 (1H, dd, *J*=3.3, 8.9 Hz), 3.42 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0 (=qC), 139.1 (ArqC), 138.5 (ArqC), 138.4 (ArqC), 128.8 (ArC), 128.77 (ArC), 128.72 (ArC), 128.44 (ArC), 128.38 (ArC), 128.3 (ArC), 128.2 (ArC), 128.1 (ArC), 127.9 (ArC), 99.4 (anomeric CH), 97.2 (=CH_2), 81.6 (CH), 79.9 (CH), 79.7 (CH), 76.1 (CH_2), 74.8 (CH_2), 73.9 (CH_2), 55.8 (CH_3); Mass (ESI-MS) *m*/*z* 446; found 469 $[M+Na]^{\bullet+}$; DART-HRMS: $[M+H]^{\bullet+}$, found 447.2178. $C_{28}H_{31}O_5$ requires 447.2172.

4.1.2. Compound ***8***. To a stirred solution of iodide **6** (1.0 g, 2.07 mmol) in THF (20 mL) was added ^{t}BuOK (696 mg, 6.21 mmol) in portion wise at 0 °C over 2 h and the stirring was continued for 24 h at room temperature. The reaction mixture was then diluted with ethyl acetate (20 mL) and washed with H_2O (2×10 mL) and brine (2×10 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure to give a residue (740 mg), which was used further without purification.

To the above residue dissolved in DMF at 0 °C were added sodium hydride (124 mg, 3.1 mmol) and benzyl bromide (0.25 mL, 2.1 mmol) and then the reaction was allowed to stir at room temperature. After completion of reaction (2 h), methanol (5 mL) was added to the reaction mixture and the resulting solution was concentrated at

reduced pressure to a residue. Water was added to the residue and this mixture was extracted with diethylether (3×15 mL). The combined organic layer was dried over sodium sulfate and concentrated to obtain a crude compound, which was purified using silica gel column chromatography to give **8** (570 mg, 62% yield).

Colorless oil, eluent for column chromatography: EtOAc/hexane (3/47, v/v); $[\alpha]_D^{28}$ −100.1 (*c* 0.47, $CHCl_3$); R_f 0.55 (3/17 EtOAc/hexane); IR (neat): ν=3016, 2920, 2366, 1655, 1216, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (15H, m), 4.81–4.61 (9H, m), 4.35–4.32 (1H, m), 3.89–3.83 (2H, m), 3.40 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2 (=qC), 138.9 (ArqC), 138.7 (2× ArqC), 128.73 (ArC), 128.70 (ArC), 128.2 (ArC), 128.1 (ArC), 128.0 (ArC), 127.96 (ArC), 127.91 (ArC), 101.2 (anomeric CH), 97.0 (=CH_2), 79.0 (CH), 76.9 (CH), 76.1 (CH), 73.9 (CH_2), 73.6 (CH_2), 73.3 (CH_2) 55.8 (CH_3); DART-HRMS: $[M+H]^{\bullet+}$, found 447.2166. $C_{28}H_{31}O_5$ requires 447.2172.

4.1.3. Compound ***9***. Mercury (II) trifluoroacetate (87 mg, 0.203 mmol) was added to a stirred suspension of compound **7** (900 mg, 2.02 mmol) in 20 mL acetone/water (2/1, v/v) at room temperature. After 8 h the reaction mixture was concentrated at reduced pressure to a residue that was dissolved in ethyl acetate (30 mL) and was washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to obtain clear oil (890 mg), which was used without further purification.

To this oil (890 mg) dissolved in DCM (15 mL) were added triethyl amine (2.5 mL) and methanesulfonyl chloride (0.64 mL, 4.6 mmol) at 0 °C. The reaction mixture was then warmed to room temperature and stirring was continued for 2 h. Saturated aqueous solution of NH_4Cl (15 mL) was added and the resulting solution was extracted with dichloromethane (4×20 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to a residue, which on purification by column chromatography furnished **9** (585 mg, 70% yield over two steps).

White semisolid, eluent for column chromatography: EtOAc/hexane (3/47, v/v); $[\alpha]_D^{28}$ +188.4 (*c* 0.38, $CHCl_3$); R_f 0.6 (1/4 EtOAc/hexane); IR (neat): ν=3020, 2361, 1693, 1648, 1216, 1072, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.18 (15H, m), 6.73 (1H, dd, *J*=1.9, 10.4 Hz), 5.96 (1H, dd, *J*=2.4, 10.4 Hz), 5.01(1H, d, *J*=11.4 Hz), 4.89 (1H, d, *J*=10.9 Hz), 4.77–4.64 (4H, m), 4.28 (1H, td, *J*=2.2, 7.7 Hz), 3.98–3.90 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8 (CO), 148.4 (=CH), 138.5 (ArqC), 138.1 (ArqC), 137.9 (ArqC), 128.9, 128.8, 128.6, 128.5, 128.42, 128.40, 128.3, 128.2, 128.1 (ArC and =CH), 85.0 (CH), 84.2 (CH), 79.3 (CH), 76.1 (CH_2), 74.9 (CH_2), 74.0 (CH_2); Mass (ESI-MS) *m*/*z* 414; found 432 $[M+NH_4]^{\bullet+}$; DART-HRMS: $[M]^{\bullet+}$, found 414.1825. $C_{27}H_{26}O_4$ requires 414.1831.

4.1.4. Compound ***10***. Mercury (II) trifluoroacetate (87 mg, 0.203 mmol) was added to a solution of compound **8** (900 mg, 2.02 mmol) in 20 mL acetone/water (2/1, v/v) at room temperature and left for stirring. After 8 h the reaction mixture was concentrated at reduced pressure to give a residue that was dissolved in ethyl acetate (30 mL) and was washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give a clear oil (885 mg), which was used without further purification.

To the oil (885 mg) dissolved in DCM (15 mL) were added triethyl amine (2.5 mL) and methanesulfonyl chloride (0.64 mL, 4.6 mmol) at 0 °C. The temperature of the reaction mixture was then raised to room temperature and stirring was continued for 2 h. Saturated aqueous solution of NH_4Cl (15 mL) was added to the reaction mixture and the resulting solution was extracted with dichloromethane (4×20 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give a residue, which was purified by column chromatography to furnish **10** (634 mg, 76% yield over two steps) as colorless oil.

Eluent for column chromatography: EtOAc/hexane (2/23, v/v); $[\alpha]_D^{28}$ −323.2 (*c* 0.92, $CHCl_3$); R_f 0.55 (1/4 EtOAc/hexane); IR (neat): ν=3020, 2922, 2365, 1692, 1216, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (15H, m), 6.81 (1H dd, *J*=3.2, 10.2 Hz), 6.01 (1H, d, *J*=10.2 Hz), 4.86–4.60 (6H, m), 4.44 (1H, t, *J*=3.0 Hz), 4.24 (1H, d, *J*=7.3 Hz), 4.02–3.99 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8 (CO), 146.2 (=CH), 138.4 (ArqC), 138.3 (ArqC), 138.1 (ArqC), 129.2, 128.9, 128.8, 128.7, 128.4, 128.3, 128.2, 128.1 (ArC, =CH), 80.0 (CH), 78.8 (CH), 73.9 (CH_2), 73.6 (CH_2), 73.2 (CH), 72.9 (CH_2); DART-HRMS: $[M]^{\bullet+}$, found 414.1839. $C_{27}H_{26}O_4$ requires 414.1831.

4.1.5. Compound ***11***. To a precooled solution of enone **9** (200 mg, 0.48 mmol) in pyridine/CCl_4 (1 mL:1 mL) was added a solution of iodine (301 mg, 1.19 mmol) in pyridine and CCl_4 (1 mL:1 mL) at 0 °C. The entire reaction mixture was stirred for 2 h at room temperature and then saturated aqueous $Na_2S_2O_3$ (4 mL) was added to it. The mixture was extracted with diethylether (3×10 mL). The combined organic layer was dried and concentrated under reduced pressure to give a residue, which on column chromatography purification provided iodide **11** (233 mg, 90% yield).

White solid, eluent for column chromatography: EtOAc/hexane (1/19, v/v); $[\alpha]_D^{28}$ +65.7 (*c* 0.98, $CHCl_3$); R_f 0.62 (1/4 EtOAc/hexane); IR (KBr): ν=3028, 2924, 2865, 1698, 1593, 1083, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (1H, d, *J*=2.1 Hz), 7.44–7.25 (15H, m), 5.08 (1H, d, *J*=11.2 Hz), 4.94 (1H, d, *J*=10.9 Hz), 4.80–4.69 (4H, m), 4.30 (1H, dd, *J*=2.1, 8.0 Hz), 4.09 (1H, d, *J*=10.5 Hz), 3.96 (1H, dd, *J*=8.0, 10.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2 (CO), 156.4 (=CH), 138.3 (ArqC), 137.8 (ArqC), 137.5 (ArqC), 129.0, 128.80, 128.78, 128.72, 128.6, 128.5, 128.3, 128.2 (ArC), 102.6 (qC), 84.4 (CH), 82.5 (CH), 80.6 (CH), 76.2 (CH_2), 74.9 (CH_2), 74.1 (CH_2); DART-HRMS: $[M]^{\bullet+}$, found 540.0810. $C_{27}H_{25}IO_4$ 540.0798.

4.1.6. Compound ***12***. A solution of iodine (376 mg, 1.48 mmol) in pyridine and CCl_4 (1.2 mL:1.2 mL) was added to a precooled solution of enone **10** (250 mg, 0.60 mmol) in a mixture of pyridine and CCl_4 (1.2 mL:1.2 mL) at 0 °C. The resulting mixture was stirred for 2 h at room temperature and then saturated aqueous $Na_2S_2O_3$ (5 mL) was added to it. The mixture was extracted with diethylether (3×10 mL). The combined organic layer was dried and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography to provide iodide **12** (281 mg, 86% yield).

Colorless oil, eluent for column chromatography: EtOAc/hexane (3/47, v/v); $[\alpha]_D^{28}$ −286.1 (*c* 0.77, $CHCl_3$); R_f 0.61 (1/4 EtOAc/hexane); IR (neat): ν=3427, 3022, 2927, 2363, 1698, 1218 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (1H, d, *J*=3.5 Hz), 7.39–7.26 (15H, m), 4.82–4.56 (6H, m), 4.40–4.34 (2H, m), 4.01 (1H, dd, 1H, *J*=3.0, 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.6 (CO), 154.9 (=CH), 138.1 (ArqC), 137.8 (ArqC), 137.6 (ArqC), 128.9, 128.8, 128.5, 128.4, 128.3 (ArC), 103.9 (qC), 78.7 (CH), 78.4 (CH), 75.4 (CH), 73.9 (CH_2), 73.7 (CH_2), 73.0 (CH_2); DART-HRMS: $[M]^{\bullet+}$, found 540.0798. $C_{27}H_{25}IO_4$ requires 540.0798.

4.1.7. Compound ***13***. A steel seal tube was charged with $Pd_2(dba)_3$ (11 mg, 0.012 mmol), triphenylarsine (7 mg, 0.023 mmol), copper (I) iodide (4.3 mg, 0.023 mmol), tetramethyltin (121 mg, 0.67 mmol), iodide **11** (125 mg, 0.23 mmol), and THF (3 mL). The reaction mixture in the seal tube was flushed with nitrogen before the tube was sealed. The seal tube containing the reaction mixture was heated at 80 °C for 36 h. After being cooled to room temperature the reaction mixture was diluted with ether (20 mL) and washed with 10% aqueous $Na_2S_2O_3$ (10 mL) and 10% aqueous potassium fluoride (10 mL). The organic phase was separated, dried (Na_2SO_4), and concentrated under reduced pressure to give residue,

which on column purification afforded the pure coupling product **13** as a white semisolid (72 mg, 72%).

Eluent for column chromatography: EtOAc/hexane (3/47, v/v); $[\alpha]_{D^{28}}$ +41.7 (*c* 0.34, $CHCl_3$); R_f 0.55 (1/4 EtOAc/hexane); IR (KBr): ν=3022, 2924, 1686, 1523, 1216, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.25 (15H, m), 6.58 (1H, br s); 5.09 (1H, d, *J*=11.3 Hz), 4.96 (1H, d, *J*=11.0 Hz), 4.83–4.67 (4H, m), 4.32–4.29 (1H, m), 4.03–3.89 (2H, m), 1.82 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6 (CO), 143.0 (=CH), 138.4 (qC), 138.1 (ArqC), 138.0 (ArqC), 135.1 (ArqC), 128.6, 128.5, 128.3, 128.2, 128.0, 127.98, 127.87, 127.82 (ArC), 84.8 (CH), 84.0 (CH), 78.7 (CH), 75.6 (CH_2), 74.7 (CH_2), 73.6 (CH_2), 15.3 (CH_3); Mass (ESI-MS) *m*/*z* 428; found 446 $[M+NH_4]^{\bullet+}$, 429 $[M+H]^{\bullet+}$; DART-HRMS: $[M+H]^{\bullet+}$, found 429.2069. $C_{28}H_{29}O_4$ requires 429.2066.

*4.1.8. Compound **14**.* A steel seal tube was charged with $Pd_2(dba)_3$ (9 mg, 0.0096 mmol), triphenylarsine (5.6 mg, 0.0184 mmol), copper (I) iodide (3.4 mg, 0.018 mmol), tetramethyltin (97 mg, 0.54 mmol), iodide **12** (100 mg, 0.184 mmol), and THF (2.5 mL). The seal tube containing the above reaction mixture was flushed with nitrogen before the tube was sealed. The reaction mixture in the seal tube was then heated at 80 °C for 36 h. It was cooled to room temperature and the resulting reaction mixture was diluted with ether (50 mL), washed with 10% aqueous $Na_2S_2O_3$ and 10% aqueous potassium fluoride. The organic phase was separated, dried (Na_2SO_4), and concentrated under reduced pressure to give colorless oil, which was purified by silica gel column chromatography to afford **14** as a white solid (54 mg, 68% yield).

Colorless oil, eluent for column chromatography: EtOAc/hexane (3/47, v/v); $[\alpha]_{D^{28}}$ −260.2 (*c* 0.23, $CHCl_3$); R_f 0.56 (1/4 EtOAc/hexane); IR (neat): ν=3023, 2920, 2853, 2371, 1687, 1217, 1064 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.25 (15H, m), 6.59 (1H, d, *J*=3.1 Hz), 4.90 (1H, d, *J*=11.5 Hz), 4.79 (2H, dd, *J*=7.7, 12.2 Hz), 4.69–4.63 (3H, m), 4.35–4.33 (2H, m), 3.95 (1H, dd, 1H, *J*=3.3, 7.9 Hz), 1.80 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4 (CO), 140.8 (=CH), 138.5 (qC and ArqC), 138.3 (ArqC), 136.5 (ArqC), 128.83, 128.75, 128.72, 128.4, 128.2, 128.1 (ArC), 80.5 (CH), 79.0 (CH), 74.2 (CH_2), 73.6 (CH_2), 72.95 (CH), 72.89 (CH_2), 16.0 (CH_3); DART-HRMS: $[M+H]^{\bullet+}$, found 429.2077. $C_{28}H_{29}O_4$ requires 429.2066.

*4.1.9. (+)-4-epi-Gabosine A (**1**).* A solution of BCl_3 (0.70 mL, 1 M in DCM) was added to a stirred solution of tribenzylated compound **13** (50 mg, 0.117 mmol) in dry DCM (5 mL) at 0 °C under argon atmosphere and allowed the reaction to stir at same temperature for 4 h. After completion of reaction, methanol was added to the reaction mixture. Evaporation of the solvent containing the reaction mixture at reduced pressure provided a residue, which was purified using silica gel column chromatography to a white semisolid **1** (12 mg, 64% yield).

Eluent for column chromatography: EtOAc/hexane (4/1, v/v); $[\alpha]_{D^{28}}$ +291.2 (*c* 0.323, MeOH); R_f 0.21 (4/1 EtOAc/MeOH); IR (KBr): ν=3447, 2923, 1690, 1218, 1073 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 6.64 (1H, br s), 4.28 (1H, br d, *J*=8.0 Hz), 3.96 (1H, d, *J*=10.9 Hz), 3.52 (1H, dd, *J*=8.4, 10.7 Hz), 1.80 (3H, s, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 200.1 (CO), 147.9 (=CH), 134.7 (qC), 80.0 (CH), 78.0 (CH), 72.5 (CH), 15.2 (CH_3); DART-HRMS: $[M+H]^{\bullet+}$, found 159.0637. $C_7H_{11}O_4$ requires 159.0657.

*4.1.10. (−)-Gabosine A (**2**).* A solution of BCl_3 (0.76 mL, 1 M in DCM) was added to a solution of tribenzylated compound **14** (54 mg, 0.126 mmol) in DCM at 0 °C under argon atmosphere. The reaction mixture was stirred at same temperature for 4 h. Afterward methanol was added to the reaction mixture. The solution containing the reaction mixture was evaporated at reduced pressure to give a residue, which was purified by using silica gel column chromatography to give **2** (13.6 mg, 68% yield).

Colorless oil, eluent for column chromatography: EtOAc/hexane (4/1, v/v); $[\alpha]_{D^{28}}$ −402.0 (*c* 0.08, MeOH); R_f 0.22 (4/1 EtOAc/MeOH); IR (neat): ν=3443, 2924, 1692, 1216, 1032 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 6.75 (1H, dd, *J*=1.4, 5.6 Hz), 4.39 (1H, t, *J*=4.3 Hz), 4.33 (1H, d, *J*=9.9 Hz), 3.73 (1H, dd, *J*=3.8, 9.9 Hz), 1.82 (3H, s); ^{13}C NMR (75 MHz, CD_3OD) δ 200.5 (CO), 143.1 (=CH), 136.9 (qC), 75.1 (CH), 73.9 (CH), 67.5 (CH), 15.7 (CH_3); DART-HRMS: $[M+H]^{\bullet+}$, found 159.0640. $C_7H_{11}O_4$ requires 159.0657.

*4.1.11. Compound **15**.* A mixture of compound **9** (207 mg, 0.5 mmol), 40% aqueous formaldehyde (0.1 mL, 1 mol), 0.1 mL of THF, and DMAP (7 mg, 0.05 mmol), was stirred for 5 days at room temperature. 1 N HCl was then added to this reaction mixture to acidify it. It was then extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with water (2×5 mL) and brine (2×5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to a residue, which on purification using column chromatography provided compound **15** (52 mg, 31%).

Colorless semisolid, eluent for column chromatography: EtOAc/hexane (6/19, v/v); R_f 0.40 (2/3 EtOAc/hexane); IR (KBr): ν=3424, 2925, 2858, 2367, 1678, 1613, 1490, 1222, 1145, 1079, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.28 (10H, m), 6.62 (1H, d, *J*=2.6 Hz), 6.56 (1H, d, *J*=2.5 Hz), 5.63 (1H, s, OH), 5.08 (2H, s), 5.01 (2H, s), 4.73 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5 (ArqC), 146.5 (ArqC), 138.4 (ArqC), 137.4 (ArqC), 136.4 (ArqC), 129.1 (ArC), 128.9 (ArC), 128.8 (ArC), 128.33 (ArC), 128.27 (ArC), 128.19 (ArC), 127.9 (ArC), 126.9 (ArqC), 105.9 (ArC), 101.4 (ArC), 71.5 (CH_2), 71.0 (CH_2), 62.1 (CH_2); DART-HRMS: $[M]^{\bullet+}$, found 336.1359. $C_{21}H_{20}O_4$ requires 336.1362.

*4.1.12. Compound **16**.* To a stirred solution of iodide **5** (0.75 g, 1.55 mmol) in THF (15 mL) was added ^{t}BuOK (0.52 g, 4.66 mmol) in portion wise at 0 °C over 2 h and allowed the reaction to stir at room temperature for 24 h. The reaction mixture was then diluted with ethyl acetate (15 mL) and washed with H_2O (2×10 mL) and brine (2×10 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure to give a residue (0.6 g).

To a solution of above residue (0.6 g) in pyridine (4 mL) was added acetic anhydride (0.3 mL, 3.3 mmol) at 0 °C and allowed this reaction mixture to warm to room temperature. After 5 h, the reaction mixture was concentrated under reduced pressure to a residue, which on column chromatography purification yielded compound **16** (394 mg, 64%).

Colorless oil, eluent for column chromatography: EtOAc/hexane (3/47, v/v); $[\alpha]_{D^{28}}$ +26.1 (*c* 0.63, $CHCl_3$); R_f 0.6 (1/4 EtOAc/hexane); IR (KBr): ν=3020, 2361, 1743, 1663, 1216, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.26 (10H, m), 5.38 (1H, td, *J*=2.1, 9.3 Hz), 4.89 (1H, d, *J*=11.6 Hz), 4.83 (1H, d, *J*=12.1 Hz), 4.71–4.64 (4H, m), 4.45 (1H, t, *J*=1.7 Hz), 3.96 (1H, t, *J*=9.5 Hz), 3.68 (1H, dd, *J*=3.3, 9.5 Hz), 3.43 (3H, s, OMe), 2.02 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 (CO), 151.6 (qC), 138.8 (ArqC), 138.1 (ArqC), 128.9, 128.7, 128.5, 128.4, 128.1, 128.0 (ArC), 99.3 (CH), 96.5 (=CH_2), 79.5 (CH), 79.3 (CH), 75.7 (CH_2), 74.0 (CH_2), 71.5 (CH), 56.0 (CH_3), 21.1 (CH_3); Mass (ESI-MS) *m*/*z* 398; found 416 $[M+NH_4]^{+\bullet}$; DART-HRMS: $[M+H]^+$, found 399.1796. $C_{23}H_{27}O_6$ requires 399.1808.

*4.1.13. Compound **17**.* Similar synthetic procedure as adopted for compound **16** was followed to obtain **17** from iodide **5**. Yield: 60%, colorless oil, eluent for column chromatography: EtOAc/hexane (1/9, v/v); $[\alpha]_{D^{28}}$ −30.6 (*c* 0.98, $CHCl_3$); R_f 0.6 (1/4 EtOAc/hexane); IR (neat): ν=3021, 2363, 1746, 1663, 1218, 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 (10H, m), 5.79 (1H, d, *J*=8.6 Hz), 4.80–4.77 (2H, m), 4.72–4.68 (2H, m), 4.65–4.52 (2H, m), 4.45 (1H, brs), 3.87–3.81 (2H, m), 3.41 (3H, s, OMe), 2.08 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.0 (CO), 153.1 (qC), 138.5 (ArqC), 138.4 (ArqC), 128.8, 128.2, 128.1, 128.0, 127.9 (ArC), 101.1 (CH), 96.4 (CH_2), 77.1 (CH), 75.1 (CH), 73.6 (CH_2), 72.8 (CH_2), 69.9 (CH), 55.9 (CH_3), 21.3

(CH_3); DART-HRMS: $[M+H]^+$, found 399.1781. $C_{23}H_{27}O_6$ requires 399.1808.

*4.1.14. Compound **18**.* To a suspension of compound **16** (398 mg, 1 mmol) in 10 mL acetone/water (2/1, v/v) mercury (II) trifluoroacetate (43 mg, 0.1 mmol) and allowed the reaction mixture to stir for 6 h. The reaction mixture was then concentrated under reduced pressure to give a residue that was dissolved in ethyl acetate (15 mL) and was washed with water (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to obtain clear oil (390 mg), which was used without further purification.

To this oil (390 mg), dissolved in DCM (15 mL), were added triethyl amine (1.2 mL) and methanesulfonyl chloride (0.31 mL, 2.2 mmol) at 0 °C. The temperature of the reaction mixture was then brought to room temperature and stirring was continued for additional 2 h. Saturated aqueous solution of NH_4Cl (15 mL) was added and the resulting solution was extracted with dichloromethane (4×20 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to a residue, which on purification by column chromatography furnished **18** as colorless oil (264 mg, 72% over two steps).

Colorless oil, eluent for column chromatography: EtOAc/hexane (7/43, v/v); $[\alpha]_D^{28}$ +277.4 (*c* 0.67, $CHCl_3$); R_f 0.52 (1/4 EtOAc/hexane); IR (KBr): ν=3030, 2923, 2361, 1743, 1696, 1237, 1060, 1019 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.26 (10H, m), 6.87 (1H, dd, *J*=1.9, 10.4 Hz), 6.08 (1H, dd, *J*=2.4, 10.4 Hz), 5.42 (1H, d, *J*=11.2 Hz), 4.88–4.73 (4H, m), 4.46 (1H, td, *J*=2.2, 8.2 Hz), 4.03 (1H, dd, *J*=8.2, 11.2 Hz), 2.13 (3H, s, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 192.4 (CO), 170.2 (CO), 148.9 (=CH), 138.2 (ArqC), 137.7 (ArqC), 128.9, 128.8, 128.5, 128.3, 128.2, 128.1, 127.9 (ArC and =CH), 83.1 (CH), 79.4 (CH), 77.3 (CH), 75.7 (CH_2), 74.0 (CH_2), 20.9 (CH_3); Mass (ESI-MS) *m*/*z* 366; found 384 $[M+NH_4]^+$; DART-HRMS: $[M+H]^+$, found 367.1552. $C_{22}H_{23}O_5$ requires 367.1545.

*4.1.15. Compound **19**.* Mercury (II) trifluoroacetate (43 mg, 0.1 mmol) was added to a suspension of compound **17** (398 mg, 1 mmol) in 10 mL acetone/water (2/1, v/v). The reaction mixture was allowed to stir for 6 h. Afterward it was then concentrated under reduced pressure to obtain a residue that was dissolved in ethyl acetate (15 mL). The residue was washed with water (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to obtain clear oil (396 mg), which was used without further purification.

Triethylamine (1.2 mL) and methanesulfonyl chloride (0.31 mL, 2.2 mmol) were added to the oil (396 mg) dissolved in DCM (15 mL) at 0 °C. The reaction mixture was then warmed to room temperature and stirring was continued for another 2 h. Saturated aqueous solution of NH_4Cl (15 mL) was added and the resulting solution was extracted with dichloromethane (4×20 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to a residue, which on purification by column chromatography furnished **19** as colorless oil (279 mg, 76% over two steps).

Colorless oil, eluent for column chromatography: EtOAc/hexane (4/21, v/v); $[\alpha]_D^{28}$ −210.9 (*c* 0.766, $CHCl_3$); R_f 0.48 (3/7 EtOAc/hexane); IR (neat): ν=3023, 2931, 2365, 1748, 1700, 1652, 1220, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (10H, m), 6.84 (1H, dd, *J*=5.6, 10.0 Hz), 6.09 (1H, d, *J*=10.0 Hz), 5.87 (1H, d, *J*=10.4 Hz), 4.87 (1H, d, *J*=12.0 Hz), 4.76–4.66 (3H, m), 4.28 (1H, dd, *J*=3.5, 5.5 Hz), 3.96 (1H, dd, *J*=3.4, 10.4 Hz), 2.17 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3 (CO), 170.3 (CO), 144.7 (=CH), 138.2 (ArqC), 138.0 (ArqC), 130.4 (=CH), 128.9, 128.4, 128.3, 128.1 (ArC), 77.7 (CH), 75.2 (CH), 73.6 (CH_2), 73.4 (CH_2), 71.4 (CH), 21.1 (CH_3); DART-HRMS: $[M+H]^+$, found 367.1528. $C_{22}H_{23}O_5$ requires 367.1545.

*4.1.16. Compound **20**.* To a suspension of compound **18** (183 mg, 0.5 mmol), 40% aqueous formaldehyde (0.1 mL, 1 mmol) in 0.1 mL of THF was added DMAP (7 mg, 0.05 mmol) at −10 °C and the resulting mixture was stirred for 2 days at the same temperature. It was then acidified with dropwise addition of 1 N HCl. The solution was extracted with ethyl acetate (3×10 mL) and the combined organic layer was washed with water (2×5 mL) and brine (2×5 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure to a residue, which on purification using column chromatography provided compound **20** (97 mg, 49%).

Colorless oil, eluent for column chromatography: EtOAc/hexane (1/3, v/v); $[\alpha]_D^{28}$ +199.8 (*c* 0.073, $CHCl_3$); R_f 0.40 (2/3 EtOAc/hexane); IR (neat): ν=3421, 3022, 1742, 1694, 1648, 1520, 1216, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.28 (10H, m), 6.89 (1H, d, *J*=1.4 Hz), 5.44 (1H, d, *J*=11.3 Hz), 4.91–4.78 (4H, m), 4.49 (1H, dd, *J*=1.9, 8.2 Hz), 4.32 (2H, d, *J*=4.9 Hz), 4.05 (1H, dd, *J*=8.2, 11.2 Hz), 2.16 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.8 (CO), 170.3 (CO), 144.0 (=CH), 138.2 (qC), 137.7 (ArqC), 137.5 (ArqC), 129.0, 128.8, 128.5, 128.4, 128.3, 128.2 (ArC), 83.0 (CH), 78.9 (CH), 77.3 (CH), 75.7(CH_2), 73.9 (CH_2), 60.4 (CH_2), 20.9 (CH_3); Mass (ESI-MS) *m*/*z* 396; found 395 $[M-H]^{\bullet+}$; DART-HRMS: $[M+H]^{\bullet+}$, found 397.1651. $C_{23}H_{25}O_6$ requires 397.1651.

*4.1.17. Compound **21**.* The experimental procedure to obtain compound **20** from **18** as described above was similarly followed to obtain **21** from **19**. Yield: 51%, colorless oil, eluent for column chromatography: EtOAc/hexane (1/3, v/v); $[\alpha]_D^{28}$ −70.6 (*c* 0.28, $CHCl_3$); R_f 0.40 (2/3 EtOAc/hexane); IR (neat): ν=3430, 3021, 1749, 1696, 1373, 1219, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.25 (10H, m), 6.83 (1H, br s), 5.33 (1H, d, *J*=2.1 Hz), 4.83–4.74 (2H, m), 4.68–4.60 (2H, m), 4.48 (1H, br s), 4.42–4.39 (1H, m), 4.34–4.32 (2H, m), 2.17 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 191.6 (CO), 169.9 (CO), 141.9 (=CH), 137.8 (qC), 137.3 (ArqC), 137.1 (ArqC), 128.7, 128.28, 128.23, 128.17, 127.8, 127.7 (ArC), 78.8 (CH), 76.4 (CH), 75.6 (CH), 73.9 (CH_2), 71.5 (CH_2), 60.2 (CH_2), 20.7 (CH_3); EI-HRMS: $[M+H]^{\bullet+}$, found 397.1671. $C_{23}H_{25}O_6$ requires 397.1651.

*4.1.18. (+)-4-epi-Gabosine E (**3**).* To a stirred solution of compound **20** (40 mg, 0.101 mmol) in CH_2Cl_2/MeOH (9/1) was added *p*-toluenesulfonic acid monohydrate (20 mg, 0.101 mmol). The stirring was continued for 24 h. After disappearance of starting material, reaction mixture was diluted with DCM and passed through a short column of silica. Concentration of organic layer under reduced pressure provided a residue (32 mg), which was used further without purification.

To the above residue (32 mg) dissolved in dry DCM (2 mL) at 0 °C was added BCl_3 (0.4 mL, 1 M solution in DCM) under argon atmosphere and the reaction mixture was continued at same temperature for 4 h. After completion of reaction, methanol (2 mL) was added to the reaction mixture. Evaporation of reaction mixture at reduced pressure furnished a residue, which was purified using silica gel column chromatography (8 mg, 46%).

Brownish semisolid, eluent for column chromatography: MeOH/$CHCl_3$ (1/3, v/v); $[\alpha]_D^{28}$ +43.6 (*c* 0.11, MeOH); R_f 0.49 (1/9 MeOH/$CHCl_3$); IR (KBr): ν=3424, 2927, 1690, 1649, 1544, 1218, 1066 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 6.91 (1H, br s), 4.29–4.24 (1H, m), 4.20–4.09 (1H, m), 3.94–3.90 (1H, m), 3.47 (1H, dd, *J*=8.6, 10.6 Hz), 3.27–3.25 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9 (CO), 148.5 (=CH), 135.3 (=qC), 79.9 (CH), 78.2 (CH), 72.6 (CH), 69.3 (CH_2); DART-HRMS: $[M]^+$, found 174.0588. $C_7H_{10}O_5$ requires 174.0528.

*4.1.19. (−)-Gabosine E (**4**).* Similar synthetic procedure as adopted for compound **3** was followed to obtain **4** from **21**.Yield: 49%, brownish semisolid, eluent for column chromatography: MeOH/$CHCl_3$ (1/3, v/v); $[\alpha]_D^{28}$ −103.0 (*c* 0.125, MeOH); R_f 0.49 (1/9 MeOH/

$CHCl_3$); IR (KBr): ν=3424, 2927, 1690, 1648, 1520, 1219, 1051 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 6.91 (1H, br s), 4.73 (1H, br s), 4.45–4.41 (2H, m), 4.34 (1H, d, J=2.3 Hz), 4.24 (1H, d, J=12.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2 (CO), 149.3 (=CH), 135.3 (=qC), 77.9 (CH), 77.2 (CH), 69.5 (CH), 40.9 (CH_2); DART-HRMS: $[M]^+$, found 174.9943. $C_7H_{10}O_5$ requires 174.0528.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.04.082. These data include MOL files and InChiKeys of the most important compounds described in this article.

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