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Synthesis of Gabosine A and N from Ribose by the Use of Ring-Closing Metathesis

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A concise synthetic route is described for the synthesis of gabosine A and N. The key step uses a zinc-mediated tandem reaction where methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranoside is fragmented to give an unsaturated aldehyde which is allylated in the same pot with 3-benzoyloxy-2-methylallyl bromide. The functionalized octa-1,7-diene, thus obtained, is converted into the six-membered gabosine skeleton by ring-closing olefin metathesis. Subsequent protective group manipulations and oxidation gives rise to gabosine N in a total of 8 steps from ribose while the synthesis of gabosine A employs an additional step for inverting a secondary hydroxy group.

Introduction

The gabosines are a family of secondary metabolites isolated from *Streptomyces* strains which share a common trihydroxy(methyl)cyclohexenone/-cyclohexanone skeleton.[1] A total of 14 different gabosines have been identified[2] and the absolute configuration has been established for gabosine A–F, I, L, N, and O (Figure 1). None of the 14 compounds display any significant biological activity, but weak DNA-binding properties have been shown for several gabosines.[1a] The biosynthesis of the gabosines occur through a pentose phosphate pathway in which sedoheptulose 7-phosphate cyclizes by an aldol condensation.[3] The chemical synthesis of the gabosines has been achieved by several strategies where the carbocyclic ring is either contained in the starting material [i.e. *p*-benzoquinone, (–)-quinine, or iodobenzene][4] or is created by a Diels–Alder reaction[5] or by cyclization of a carbohydrate.[6] In the latter case, the carbocyclization has been accomplished by an aldol condensation, a nitrile oxide cycloaddition, a Nozaki–Hiyama–Kishi reaction, a Horner–Wadsworth–Emmons olefination and by ring-closing olefin metathesis.

We have described a zinc-mediated tandem reaction for converting carbohydrates into acyclic dienes that can be cyclized by ring-closing metathesis.[7,8] In this reaction, methyl 5-iodopentofuranosides are treated with zinc metal and allylic bromides. First, a reductive fragmentation of the iodofuranoside takes place to produce an unsaturated aldehyde which is subsequently allylated in the same pot by the allylzinc reagent. In this way, the zinc metal serves a dual purpose by promoting both the reductive fragmentation and the subsequent allylation reaction.[7] By using this procedure, we have previously prepared several carbocyclic natural products from carbohydrates including 7-deoxypancratistatin,[9] cyclophellitol,[10] and calystegine B_2, B_3 and B_4.[11]

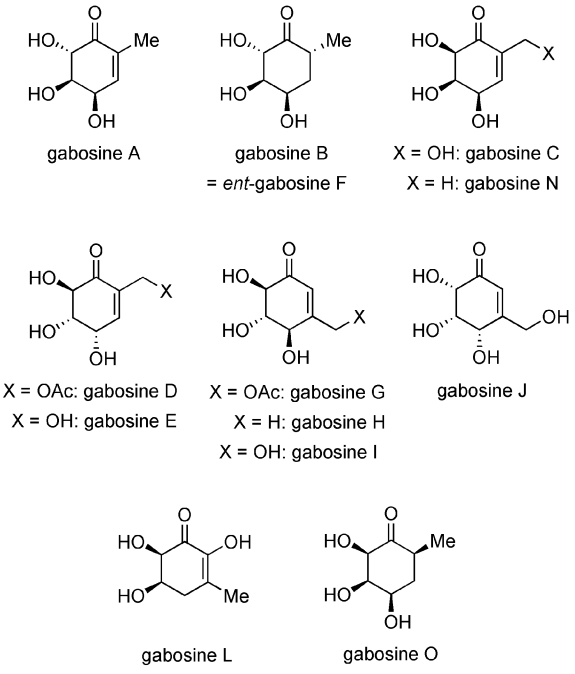

Figure 1. The gabosine family of secondary metabolites.

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We envisaged that the tandem reaction would also be an effective transformation for synthesis of the gabosines as illustrated with gabosine A and N in Figure 2. This would require allylic bromide **1** in order to install the methyl group in the product. Bromide **1** has not been described before, but the corresponding 3-benzoyloxyallyl bromide has been developed as an efficient α-hydroxyallylation agent of aldehydes in the presence of zinc or indium.[12] We have recently used 3-benzoyloxyallyl bromide in the tandem reaction with zinc for synthesis of the conduritols[13] and for chain elongation of aldoses in the presence of indium.[14] On the basis of these results we expected that the tandem reaction between **1** and the appropriate iodopentofuranoside could be achieved to give the desired octa-1,7-diene which upon ring-closure by metathesis would yield the gabosine skeleton.

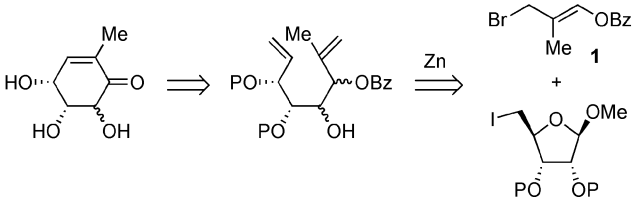
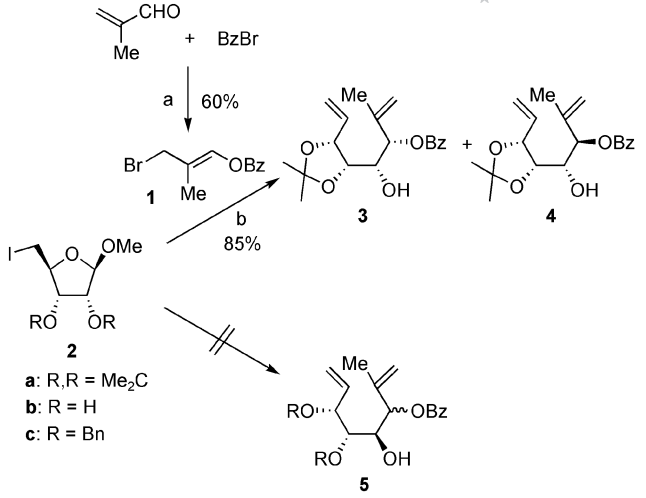


Figure 2. Retrosynthesis for gabosine A and N.

Herein, we describe a short synthesis of the two epimeric gabosines A and N by the use of a zinc-mediated tandem reaction and ring-closing olefin metathesis.

Results and Discussion

Gabosine A and N have the same stereochemistry at two hydroxy groups which will both originate from the pentose in the synthesis. The two natural products differ from each other at the third hydroxy group which will be installed in the tandem reaction (Figure 2). D-Ribose has the correct stereochemistry at C-2 and C-3 for both gabosines and the corresponding methyl furanoside **2a** is easy available in two steps from the parent pentose (Scheme 1).[15] Bromide **1** is prepared from methacrolein by haloacylation with benzoyl bromide. The synthesis is carried out in the same way as the preparation of 3-benzoyloxyallyl bromide from acrolein.[16] The kinetic product is initially formed by 1,2-addition to the aldehyde, but slowly equilibrates to the thermodynamic 1,4-addition product. The addition is rather slow, but the reaction can be accelerated by adding zinc(II) bromide as catalyst. Thus, treatment of methacrolein with benzoyl bromide and zinc(II) bromide gave the desired product in 76% yield after 2 h as a 4:3 mixture of the *E* and *Z* isomer which could not be separated by silica gel chromatography. When the reaction was performed in the absence of zinc(II) bromide the time for complete conversion increased significantly, but the yield was still acceptable and in this case only the *E* isomer was formed. Because this isomer is crystalline and completely stable at 5 °C we favored the latter synthesis of bromide **1**. Furthermore, the synthesis could be performed on a large scale and the reagent isolated without the use of flash chromatography.



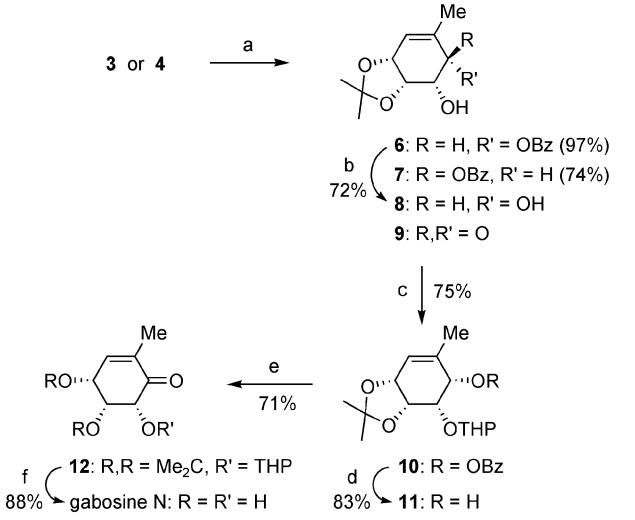
Scheme 1. Reagents and conditions: (a) CH_2Cl_2, room temp. (b) Zn, THF, H_2O, 40 °C, sonication.

The tandem reaction between **1** and **2a** was carried out in a THF/H_2O mixture under sonication at 40 °C. Treatment of furanoside **2a** with zinc for 2 h followed by addition of bromide **1** gave 85% yield of a 2:1 mixture of dienes **3** and **4** which could be separated by silica gel chromatography (Scheme 1). Notably, the stereochemistry at the hydroxy group is the same in **3** and **4** which make both compounds suitable for the synthesis of gabosine N. The structure of **3** and **4** was elucidated after ring-closing metathesis by ^{1}H NMR and by isopropylidene formation from the corresponding diol. The stereochemical outcome is in accordance with our earlier observations[13] and can be rationalized by the Felkin–Anh model.[17] The same mixture of **3** and **4** was obtained when the *E*:*Z* mixture of **1** was employed in the tandem reaction.

Because **3** and **4** both have the correct stereochemistry for gabosine N several experiments were carried out to invert the stereochemical outcome of the allylation in order to prepare gabosine A by the same reaction. We have shown earlier that the stereochemistry in the tandem reaction can be changed by using the unprotected ribofuranoside **2b**[18] or by using indium metal[10,18] where the latter is known to react by chelation control. However, treatment of **2b** with zinc in the presence of bromide **1** did not furnish the desired diene **5**. Instead, a complex mixture was obtained resulting from degradation of **2b** and self-coupling of **1**. When the same reaction was attempted with indium metal, self-coupling of **1** was the main product and very little fragmentation of **2b** occurred. It was therefore decided to carry out the fragmentation with zinc and isolate the intermediate aldehyde and then perform the subsequent allylation with indium. Only aldehydes that are prepared by fragmentation of protected ribofuranosides are sufficiently stable to be isolated. Hence, ribofuranosides **2a** and **2c** were fragmented with zinc followed by treatment of the corresponding aldehydes with **1** and indium. The allylations were carried out in the presence and in the absence of a Lewis acid[10] and in different solvent mixtures. Unfortunately, all attempts to

obtain a decent yield of diene **5** failed. In most cases, bromide **1** only underwent self-coupling and it appears that this reaction is faster than the allylation of the aldehydes. In other cases, small amounts of dienes were obtained as diastereomeric mixtures, but the major isomers had the same stereochemistry as in **3** and **4**. As a result, we decided to abandon the tandem reaction for synthesis of diene **5** and instead chose to invert the stereochemistry at the hydroxy group in **3** (vide infra).

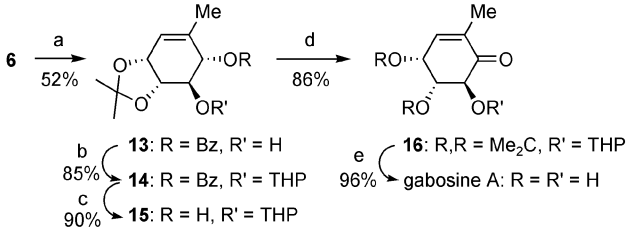
The next step involved ring-closing olefin metathesis and was carried out with Grubbs' 2nd generation catalyst[19] in refluxing dichloromethane. Under these conditions the major diastereomer **3** cyclized cleanly to give cyclohexene **6** in 97% yield (Scheme 2). However, the minor isomer **4** reacted more sluggishly and afforded the corresponding cyclohexene **7** in 74% yield. The yield of **7** did not improve by using Grubbs' 1st generation catalyst, Hoveyda–Grubbs' 2nd generation catalyst or by changing the solvent to refluxing toluene.



Scheme 2. Reagents and conditions: (a) 10% $(PCy_3)(C_3H_4N_2Mes_2)Cl_2Ru{=}CHPh$, CH_2Cl_2, 40 °C. (b) K_2CO_3, MeOH, room temp. (c) DHP, PPTS, CH_2Cl_2, room temp. (d) NaOMe, MeOH, room temp. (e) PDC, CH_2Cl_2, room temp. (f) AcOH, H_2O, room temp. → 40 °C.

To complete the synthesis of gabosine N the allylic position had to be oxidized to the ketone. These experiments were only performed with the major diastereomer **6**, but similar reactions can be envisioned from the minor isomer **7**. First, diol **8** was prepared by deprotection of **6** and it was attempted to carry out a selective allylic oxidation in the presence of PDC, MnO_2 or DDQ. However, these experiments only gave the desired ketone **9** in very low yield due to incomplete conversion or over-oxidation and it was therefore decided to protect the homoallylic hydroxy group in **6** prior to the oxidation. The THP group was chosen for this purpose since it can be removed under the same conditions as the isopropylidene acetal. Treatment of alcohol **6** with dihydropyran gave fully protected **10** in good yield which was followed by removal of the benzoate to give allylic alcohol **11**. The oxidation of **11** could now be accomplished in a satisfying yield with PDC to furnish protected gabosine **12**. Finally, deprotection under acidic conditions afforded gabosine N with spectral and physical data in excellent accordance with those reported for the natural product.[1a,4b]

The synthesis of gabosine A could be achieved by a similar sequence after inverting the hydroxy group in cyclohexene **6**. The inversion was carried out by initial conversion into the triflate followed by displacement with sodium nitrite in DMF to give alcohol **13** in 52% yield (Scheme 3). Attempts to improve the yield by using potassium nitrite in DMF or tetrabutylammonium nitrite in toluene[20] were not successful. Alcohol **13** was converted into gabosine A by using the same four steps as employed for gabosine N. THP protection gave acetal **14** and removal of the benzoate afforded alcohol **15** which was oxidized to the corresponding ketone **16** in 66% overall yield from **13**. Hydrolysis of the acetal protecting groups then furnished gabosine A with spectral and physical data in agreement with those reported for the natural product.[1b,4d]



Scheme 3. Reagents and conditions: (a) Tf_2O, pyridine, CH_2Cl_2, –20 °C → room temp., then $NaNO_2$, DMF, room temp. (b) DHP, PPTS, CH_2Cl_2, room temp. (c) NaOMe, MeOH, room temp. (d) PDC, CH_2Cl_2, room temp. (e) AcOH, H_2O, 40 °C.

Conclusions

In summary, we have developed an 8-step synthesis of gabosine N and a 9-step synthesis of gabosine A. In both cases, D-ribose serves as the starting material and the cyclohexene skeleton is created by a zinc-mediated tandem reaction followed by ring-closing olefin metathesis. The results emphasize the utility of these two reactions in the preparation of polyhydroxylated carbocyclic natural products from carbohydrates.

Experimental Section

General: CH_2Cl_2 was dried by distillation from CaH_2 while MeOH and DMF were dried with 4-Å molecular sieves. Zinc dust (< 10 micron) was activated immediately before use: zinc (5 g) in 1 M HCl (50 mL) was stirred at room temperature for 20 min and then filtered, rinsed with water and Et_2O and finally dried at high vacuum with a heat gun. Zinc(II) bromide was dried at high vacuum with a heat gun. All other reagents were obtained from commercial sources and used without further purification. Reactions were monitored by TLC using aluminium plates precoated with silica gel 60. Compounds were visualized by dipping in a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $Ce(SO_4)_2$ (10 g/L) in 10% aque-

ous H_2SO_4 followed by heating. Melting points are uncorrected. Flash column chromatography was performed with E. Merck silica gel 60 (particle size 0.040–0.063 mm). Optical rotations were measured with a Perkin–Elmer 241 polarimeter while IR spectra were recorded with a Bruker Alpha FT-IR spectrometer. NMR spectra were recorded with a Varian Mercury 300 instrument. Residual solvent peaks were used as internal reference in ^{1}H NMR (δ_{CHCl3} = 7.26 ppm and δ_{CD2HOD} = 3.31 ppm) while $CDCl_3$ (δ = 77.16 ppm) and CD_3OD (δ = 49.0 ppm) served as the internal standards in ^{13}C NMR spectroscopy. High-resolution mass spectra were recorded at the Department of Physics and Chemistry, University of Southern Denmark.

(*E*)-3-Bromo-2-methylprop-1-enyl Benzoate (1). Procedure with $ZnBr_2$: Benzoyl bromide (1.3 mL, 11.0 mmol) was added to a solution of freshly distilled methacrolein (770 mg, 11.0 mmol) in anhydrous CH_2Cl_2 and Et_2O (1:1, 18 mL) under nitrogen. The mixture was cooled to –20 °C followed by addition of anhydrous $ZnBr_2$ (25 mg, 0.11 mmol). The reaction was stirred at 0 °C for 2 h and then quenched by addition of saturated aqueous $NaHCO_3$ (15 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexane, 1:20) to give 2.12 g (76%) of the desired compound as a white crystalline mass (4:3 mixture of the *E* and *Z* isomer).

Procedure without $ZnBr_2$: Freshly distilled methacrolein (15.0 mL, 181.7 mmol) was dissolved in anhydrous CH_2Cl_2 (200 mL) under nitrogen. Benzoyl bromide (22.0 mL, 183.5 mmol) was added at 0 °C and the solution was stirred at room temperature for 10 d. The mixture was concentrated in vacuo and the residue dissolved in pentane. Cooling to –20 °C gave white crystals which were isolated and recrystallized from pentane to afford **1** (27.8 g, 60%). R_f = 0.19 (EtOAc/heptane, 1:10). M.p. 61–62 °C. IR (KBr): $\tilde{\nu}$ = 3096, 2844, 2913, 1727, 1451, 1382, 1287, 1162, 1122, 704 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14–8.08 (m, 2 H), 7.66–7.57 (m, 2 H), 7.52–7.45 (m, 2 H), 4.07 (s, 2 H), 1.98 (d, *J* = 1.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2, 134.0, 133.9, 130.1, 128.9, 128.8, 119.2, 36.5, 13.2 ppm. HRMS: calcd. for $C_{11}H_{11}BrO_2Na$ [M + Na]$^+$ 276.9835; found 276.9848.

3-Benzoyl-1,2,7,8-tetradeoxy-5,6-*O*-isopropylidene-2-*C*-methyl-D-*allo*- and -D-*altro*-octa-1,7-dienitol (3 and 4): Activated Zn (1.21 g, 18.5 mmol) was added to a degassed solution of ribofuranoside **2a**[15] (1.07 g, 3.4 mmol) in THF/H_2O (4:1, 30 mL). The mixture was sonicated at 40 °C under nitrogen until TLC revealed full conversion to the aldehyde (2 h). A deoxygenated solution of bromide **1** (1.28 g, 5.1 mmol) in THF (8.0 mL) was then added in two portions; one after 2 h and one after 3.5 h of sonication. After sonicating for an additional 2 h 45 min at 40 °C, the reaction mixture was filtered through a plug of Celite and the filter cake was rinsed thoroughly with CH_2Cl_2. The filtrate was washed with saturated aqueous $NaHCO_3$ (30 mL) and H_2O (2 × 30 mL). The combined aqueous phases were extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (EtOAc/heptane, 1:5) gave dienes **3** and **4** (0.95 g, 85%) as a separable 2:1 mixture.

3: R_f = 0.33 (EtOAc/heptane, 1:2). $[\alpha]_D^{30}$ = –5.0 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3499, 3074, 2986 2925, 2855, 1720, 1650, 1611, 1452, 1373, 1318, 1270, 1218, 1110, 1070, 1027, 874, 712 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10–8.05 (m, 2 H), 7.58 (tt, *J* = 1.4, 7.4 Hz, 1 H), 7.49–7.41 (m, 2 H), 6.05 (ddd, *J* = 7.2, 10.4, 17.4 Hz, 1 H), 5.68 (d, *J* = 3.1 Hz, 1 H), 5.43 (ddd, *J* = 1.2, 1.7, 17.2 Hz, 1 H), 5.30 (ddd, *J* = 1.1, 1.7, 10.4 Hz, 1 H), 5.20–5.18 (m, 1 H), 5.15 (p, *J* = 1.5 Hz, 1 H), 4.71–4.65 (m, 1 H), 4.09–4.05 (m, 2 H), 2.01 (d, *J* = 4.2 Hz, OH), 1.94 (s, 3 H), 1.49 (s, 3 H), 1.34 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 140.6, 134.3, 133.3, 130.3 129.8, 128.6, 118.5, 116.1, 109.3, 79.1, 77.8, 77.5, 70.9, 28.0, 25.5, 20.3 ppm. HRMS: calcd. for $C_{19}H_{24}O_5Na$ [M + Na]$^+$ 355.1516; found 355.1530.

4: R_f = 0.27 (EtOAc/heptane, 1:2). $[\alpha]_D^{29}$ = –2.8 (*c* = 1.5, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3490, 3091, 3071, 2987, 2937, 1725, 1654, 1602, 1452, 1379, 1316, 1270, 1218, 1116, 1070, 1027, 918, 875, 712 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14–8.08 (m, 2 H), 7.58 (tt, *J* = 1.4, 7.4 Hz, 1 H), 7.50–7.42 (m, 2 H), 6.07 (ddd, *J* = 6.7, 10.4, 17.1 Hz, 1 H), 5.61 (s, 1 H), 5.46 (d, *J* = 17.1 Hz, 1 H), 5.32 (d, *J* = 10.8 Hz, 1 H), 5.07–5.02 (m, 2 H), 4.73 (t, *J* = 6.4 Hz, 1 H), 4.20 (dd, *J* = 6.1, 9.2 Hz, 1 H), 3.85 (ddd, *J* = 1.9, 4.7, 9.2 Hz, 1 H), 1.99 (d, *J* = 4.8 Hz, OH), 1.88 (s, 3 H), 1.48 (s, 3 H), 1.28 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 141.1, 133.7, 133.3, 130.1, 129.8, 128.6, 118.2, 112.9, 109.0, 78.7, 77.1, 76.2, 69.0, 28.1, 25.5, 20.1 ppm. HRMS: calcd. for $C_{19}H_{24}O_5Na$ [M + Na]$^+$ 355.1516; found 355.1521.

(1*S*,2*S*,3*S*,6*R*)-3-Benzoyloxy-2-hydroxy-4,8,8-trimethyl-7,9-dioxabicyclo[4.3.0]non-4-ene (6): Grubbs' 2nd generation catalyst (151 mg, 0.18 mmol) was added to a degassed solution of diene **3** (578 mg, 1.7 mmol) in anhydrous CH_2Cl_2 (54 mL) under nitrogen. The solution was protected from sunlight and stirred at reflux under nitrogen for 4 d. The reaction was stopped by addition of charcoal (5.52 g) and the mixture was filtered through a plug of Celite. The filtrate was concentrated in vacuo and purified by flash column chromatography (heptane/Et_2O, 3:1) to afford the target compound (511.5 mg, 97%) as a white solid. R_f = 0.52 (EtOAc/heptane, 1:1). $[\alpha]_D^{29}$ = +65.0 (*c* = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3408, 3072, 2987, 2933, 2866, 1711, 1454, 1371, 1348, 1277, 1223, 1108, 1036, 1014, 712 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14–8.09 (m, 2 H), 7.59 (tt, *J* = 2.1, 7.4 Hz, 1 H), 7.49–7.42 (m, 2 H), 5.79–5.74 (m, 1 H), 5.70 (bd, *J* = 3.8 Hz, 1 H), 4.67–4.61 (m, 1 H), 4.45 (dd, *J* = 3.2, 6.5 Hz, 1 H), 4.12 (dt, *J* = 3.5, 6.9 Hz, 1 H), 2.47 (d, *J* = 6.9 Hz, OH), 1.83 (d, *J* = 0.8 Hz, 3 H), 1.56 (s, 3 H), 1.43 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 134.4, 133.5, 130.0, 129.8, 128.6 123.1, 110.6, 74.0, 72.0, 71.4, 67.3, 27.3, 25.9, 20.2 ppm. HRMS: calcd. for $C_{17}H_{20}O_5Na$ [M + Na]$^+$ 327.1203; found 327.1212.

(1*S*,2*S*,3*R*,6*R*)-3-Benzyloxy-2-hydroxy-4,8,8-trimethyl-7,9-dioxabicyclo[4.3.0]non-4-ene (7): A degassed solution of diene **4** (34 mg, 0.10 mmol) and Grubbs' 2nd generation catalyst (7.4 mg, 0.0087 mmol) in freshly distilled CH_2Cl_2 (24 mL) was protected from sunlight and stirred at reflux under argon for 3 d. The reaction mixture was evaporated on Celite and purified by flash column chromatography (heptane → heptane/EtOAc, 4:1) to give the desired compound (23 mg, 74%) as a white solid. R_f = 0.29 (EtOAc/heptane, 2:1). $[\alpha]_D^{25}$ = –40.4 (*c* = 1.0, $CDCl_3$). IR (film): $\tilde{\nu}$ = 3459, 3066, 3036, 2985, 2924, 2855, 1720, 1452, 1380, 1268, 1235, 1110, 1047, 1031, 712 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11–8.06 (m, 2 H), 7.59 (tt, *J* = 2.1, 7.4 Hz, 1 H), 7.50–7.42 (m, 2 H), 5.84 (dd, *J* = 1.0, 8.1 Hz, 1 H), 5.57 (dq, *J* = 1.9, 3.3 Hz, 1 H), 4.69–4.64 (m, 1 H), 4.56 (ddd, *J* = 0.7, 2.9, 5.6 Hz, 1 H), 3.97 (dt, *J* = 2.9, 8.1 Hz, 1 H), 2.66 (d, *J* = 8.1 Hz, OH), 1.78 (dd, *J* = 1.3, 2.6 Hz, 3 H), 1.43 (s, 3 H), 1.40 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 134.6, 133.5, 130.0, 129.8, 128.6, 124.1, 109.9, 75.9, 74.1, 73.1, 71.8, 27.8, 26.5, 19.2 ppm. HRMS: calcd. for $C_{17}H_{20}O_5Na$ [M + Na]$^+$ 327.1203; found 327.1212. Deprotection with NaOMe in MeOH gave the corresponding diol as described below for **8**. No reaction occurred when the diol was treated with

2,2-dimethoxypropane and camphorsulfonic acid at room temperature for 1 h.

(1*S*,2*S*,3*S*,6*R*)-2,3-Dihydroxy-4,8,8-trimethyl-7,9-dioxabicyclo[4.3.0]-non-4-ene (8): K_2CO_3 (49 mg, 0.36 mmol) was added to a solution of benzoate **6** (0.107 g, 0.38 mmol) in anhydrous MeOH (10 mL) and the mixture was stirred at room temperature under nitrogen for 3 h. The reaction was quenched with 1 M HCl until neutral pH, followed by extraction with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (EtOAc/heptane, 1:1) gave diol **8** (50 mg, 72%) as white crystals. R_f = 0.13 (EtOAc/heptane, 1:1). $[\alpha]_D^{25}$ = +69.9 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3447, 3002, 2931, 2858, 1370, 1231, 1177, 1083, 1038, 975 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.40 (dq, *J* = 1.4, 2.8 Hz, 1 H), 4.55–4.50 (m, 1 H), 4.48–4.44 (m, 1 H), 3.84 (dd, *J* = 4.1, 11.4 Hz, 1 H), 3.77–3.69 (m, 1 H), 3.34 (d, *J* = 9.3 Hz, OH), 2.74 (d, *J* = 11.5 Hz, OH), 1.84 (t, *J* = 1.5 Hz, 3 H), 1.38 (s, 3 H), 1.31 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.0, 122.2, 110.3, 76.7, 73.6, 70.5, 67.5, 28.2, 26.4, 21.0 ppm. HRMS: calcd. for $C_{10}H_{16}O_4Na$ $[M + Na]^+$ 223.0941; found 223.0931. Reaction with 2,2-dimethoxypropane and camphorsulfonic acid at room temperature for 40 min gave 73% yield of the corresponding bis(isopropylidene) compound.

(1*R*,2*S*,3*S*,6*R*)-3-Benzoyloxy-4,8,8-trimethyl-2-tetrahydropyranyloxy-7,9-dioxabicyclo[4.3.0]non-4-ene (10): DHP (0.4 mL, 4.4 mmol) and PPTS (14 mg, 0.056 mmol) were added to a solution of alcohol **6** (657.7 mg, 2.16 mmol) in anhydrous CH_2Cl_2 (20 mL). The solution was stirred at room temperature under argon overnight. The reaction was stopped by addition of saturated aqueous $NaHCO_3$ until neutral pH. The phases were separated and the organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (heptane/EtOAc, 5:1) to give **10** (627.0 mg, 75%) as a colorless oil and a mixture of two diastereomers. R_f = 0.44 (EtOAc/heptane, 1:1). IR (film): $\tilde{\nu}$ = 3070, 2981, 2939, 2873, 1715, 1452, 1369, 1270, 1232, 1109, 1069, 1054, 1016, 963, 919, 709 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.13–8.06 (m, 4 H), 7.52 (tt, *J* = 1.4, 7.4 Hz, 2 H), 7.44–7.36 (m, 4 H), 5.82–5.78 (m, 2 H), 5.62–5.58 (m, 2 H), 4.95–4.89 (m, 2 H), 4.66–4.58 (m, 2 H), 4.56–4.50 (m, 2 H), 4.15 (dt, *J* = 2.6, 4.7 Hz, 2 H), 4.00–3.84 (m, 2 H), 3.55–3.44 (m, 2 H), 1.78 (t, *J* = 1.3 Hz, 3 H), 1.76 (t, *J* = 1.4 Hz, 3 H), 1.70–1.59 (m, 8 H), 1.57 (s, 3 H), 1.55 (s, 3 H), 1.53–1.43 (m, 4 H), 1.41 (s, 3 H), 1.40 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 166.9, 133.0, 132.8, 132.8, 131.5, 130.6, 130.3, 130.0, 128.4, 128.3, 126.4, 125.2, 111.0, 110.8, 97.2, 96.3, 74.5, 73.9, 73.6, 72.0, 69.8, 69.4, 69.3, 66.4, 63.0, 61.8, 30.1, 30.1, 28.3, 28.0, 26.8, 26.6, 25.5, 25.4, 20.8, 20.5, 19.5, 18.3 ppm. HRMS: calcd. for $C_{22}H_{28}O_6Na$ $[M + Na]^+$ 411.1778; found 411.1774.

(1*R*,2*S*,3*S*,6*R*)-3-Hydroxy-4,8,8-trimethyl-2-tetrahydropyranyloxy-7,9-dioxabicyclo[4.3.0]non-4-ene (11): Fully protected **10** (150 mg, 0.386 mmol) was dissolved in 10% NaOMe in anhydrous MeOH (10 mL) and stirred at room temperature for 3 h. The mixture was evaporated in vacuo and purified by flash column chromatography (heptane/EtOAc, 3:1) to give **11** (91 mg, 83%) as a colorless oil and a mixture of two diastereomers. R_f = 0.28 and 0.33 (EtOAc/heptane, 1:1). IR (film): $\tilde{\nu}$ = 3529, 2983, 2937, 2874, 1440, 1371, 1227, 1133, 1120, 1075, 1051, 1029, 1012, 985, 970, 814 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.41–5.37 (m, 1 H), 5.34 (dq, *J* = 1.4, 2.8 Hz, 1 H), 4.92 (dd, *J* = 3.1, 4.3 Hz, 1 H), 4.77 (dd, *J* = 3.2, 4.5 Hz, 1 H), 4.58–4.50 (m, 2 H), 4.48–4.43 (m, 2 H), 4.02–3.92 (m, 4 H), 3.88 (dd, *J* = 1.9, 4.2 Hz, 1 H), 3.82 (dd, *J* = 2.4, 3.9 Hz, 1 H), 3.55–3.44 (m, 2 H), 1.96–185 (m, 2 H), 1.83 (s, 3 H), 1.82 (s, 3 H), 1.80–1.66 (m, 4 H), 1.57–1.46 (m, 6 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.33 (s, 3 H), 1.32 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 136.9, 121.9, 120.5, 110.8, 110.5, 99.2, 95.9, 76.4, 74.3, 74.3, 73.6, 73.6, 70.2, 69.9, 67.1, 63.1, 62.9, 30.7, 30.5, 28.2, 27.8, 26.8, 26.4, 25.4, 25.3, 21.2, 20.7, 19.7, 19.6 ppm. HRMS: calcd. for $C_{15}H_{24}O_5Na$ $[M + Na]^+$ 307.1516; found 307.1529.

(1*R*,2*R*,6*R*)-4,8,8-Trimethyl-3-oxo-2-tetrahydropyranyloxy-7,9-dioxabicyclo[4.3.0]non-4-ene (12): PDC (0.235 g, 0.63 mmol) was added to a solution of alcohol **11** (51 mg, 0.18 mmol) in anhydrous CH_2Cl_2 (15 mL) and the mixture was stirred at room temperature under nitrogen for 20 h. The solution was concentrated in vacuo and purified by flash column chromatography (heptane/EtOAc, 2:1) to give **12** (36 mg, 71%) as a colorless oil and a mixture of two diastereomers. R_f = 0.33 (EtOAc/heptane, 1:1). IR (film): $\tilde{\nu}$ = 2984, 2937, 2871, 1699, 1453, 1379, 1351, 1229, 1145, 1120, 1074, 1024, 971, 889 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.32–6.28 (m, 1 H), 4.93–4.89 (m, 1 H), 4.82–4.76 (m, 2 H), 4.56 (d, *J* = 2.6 Hz, 1 H), 3.92–3.84 (m, 1 H), 3.55–3.46 (m, 1 H), 1.96–1.84 (m, 3 H), 1.81 (t, *J* = 1.4 Hz, 3 H), 1.62–1.50 (m, 3 H), 1.37 (s, 3 H), 1.32 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.0, 139.2, 134.5, 111.7, 99.5, 78.5, 74.9, 73.2, 63.1, 30.3, 28.0, 27.2, 25.6, 19.5, 15.6 ppm. Only NMR spectroscopic data for the major diastereomer are reported. HRMS: calcd. for $C_{15}H_{22}O_5Na$ $[M + Na]^+$ 305.1359; found 305.1346.

Gabosine N: Ketone **12** (36 mg, 0.13 mmol) was dissolved in 80% acetic acid in H_2O (2.0 mL) and stirred under nitrogen for 23 h at room temperature followed by 16 h at 40 °C. The reaction mixture was cooled to room temperature and concentrated in vacuo to give a residue that was purified by flash column chromatography (EtOAc/MeOH, 99:1) to afford gabosine N (17.7 mg, 88%) as white crystals. R_f = 0.12 (EtOAc). $[\alpha]_D^{25}$ = –150.5 (*c* = 0.3, CD_3OD) [lit.[1a] $[\alpha]_D^{20}$ = –152.0 (*c* = 0.89, H_2O), lit.[4b] $[\alpha]_D$ = –142 (*c* = 0.16, MeOH)]. M.p. 174–176 °C (MeOH) [lit.[4b] 174–175 °C (MeOH), lit.[1a] 182.5–183.3 °C]. IR (film): $\tilde{\nu}$ = 3427, 3308, 3244, 2943, 2925, 2851, 1680, 1408, 1343, 1197, 1132, 1044, 1022, 937, 854 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ = 6.48 (dq, *J* = 1.5, 2.2 Hz, 1 H), 4.58–4.54 (m, 1 H), 4.34 (dt, *J* = 2.5, 3.4 Hz, 1 H), 4.23 (d, *J* = 2.5 Hz, 1 H), 1.81 (dd, *J* = 1.5, 2.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 200.2, 145.9, 134.5, 77.7, 76.6, 69.2, 15.3 ppm. NMR spectroscopic data are in accordance with literature values.[1a,4b] HRMS: calcd. for $C_7H_{10}O_4Na$ $[M + Na]^+$ 181.0471; found 181.0475.

(1*S*,2*R*,3*S*,6*R*)-3-Benzoyloxy-2-hydroxy-4,8,8-trimethyl-7,9-dioxabicyclo[4.3.0]non-4-ene (13): A solution of alcohol **6** (1.79 g, 5.9 mmol) in freshly distilled CH_2Cl_2 (40 mL) under nitrogen was cooled to –20 °C followed by addition of pyridine (2.14 mL, 26.5 mmol) and Tf_2O (1.48 mL, 8.8 mmol). The reaction mixture was slowly warmed to room temperature and after 1.5 h the reaction was quenched with 2 M HCl (85 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (45 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude trifluoromethanesulfonate (2.57 g, 5.9 mmol) as a black residue, which was used directly in the next step. The crude trifluoromethanesulfonate was redissolved in anhydrous DMF under nitrogen, $NaNO_2$ (1.62 g, 23.5 mmol) was added and the mixture stirred at room temperature for 5.5 h. The reaction mixture was diluted with H_2O (120 mL) followed by extraction with Et_2O (5 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane, 1:5 → 1:1) to give alcohol **13** (933 mg, 52%) as a slightly yellow oil.

R_f = 0.49 (EtOAc/heptane, 1:1). $[\alpha]_D^{25}$ = –12.0 (*c* = 2.0, CD_3OD). IR (film): $\tilde{\nu}$ = 3459, 3064, 3043, 2985, 2925, 2859, 1719, 1452, 1379, 1316, 1268, 1249, 1216, 1115, 1060, 1026, 979, 907, 710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.11–8.05 (m, 2 H), 7.59 (tt, *J* = 1.4, 7.4 Hz, 1 H), 7.50–7.42 (m, 2 H), 5.76–5.67 (m, 2 H), 4.69–4.63 (m, 1 H), 4.21 (dd, *J* = 6.3, 9.0 Hz, 1 H), 3.98 (t, *J* = 8.9 Hz, 1 H), 1.77 (dd, *J* = 1.3, 2.7 Hz, 3 H), 1.55 (s, 3 H), 1.41 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 139.1, 133.5, 130.0, 129.6, 128.6, 120.1, 110.6, 77.9, 74.7, 72.7, 72.3, 28.4, 26.1, 18.9 ppm. HRMS: calcd. for $C_{17}H_{20}O_5Na$ $[M + Na]^+$ 327.1203; found 327.1216.

(1*R*,2*R*,3*S*,6*R*)-3-Benzoyloxy-4,8,8-trimethyl-2-tetrahydropyranyloxy-7,9-dioxabicyclo[4.3.0]non-4-ene (14): DHP (0.5 mL, 5.5 mmol) and PPTS (140 mg, 0.56 mmol) were added to a solution of alcohol **13** (850 mg, 2.79 mmol) in freshly distilled CH_2Cl_2 (60 mL). The mixture was stirred at room temperature under nitrogen overnight. The reaction was stopped by addition of saturated aqueous $NaHCO_3$ (100 mL) followed by extraction with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated in vacuo and purified by flash column chromatography (heptane/EtOAc, 9:1→4:1) to give **14** (925 mg, 85%) as a colorless oil and a mixture of two diastereomers. R_f = 0.72 (EtOAc/heptane, 1:1). IR (film): $\tilde{\nu}$ = 3063, 2983, 2938, 2868, 1722, 1452, 1380, 1317, 1265, 1247, 1217, 1162, 1119, 1062, 1029, 986, 966, 869, 710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.12–8.03 (m, 4 H), 7.59–7.53 (m, 2 H), 7.48–7.40 (m, 4 H), 5.81–5.67 (m, 4 H), 5.21 (t, *J* = 2.6 Hz, 1 H), 4.83 (t, *J* = 3.3 Hz, 1 H), 4.68–4.58 (m, 2 H), 4.29 (dt, *J* = 6.1, 8.3 Hz, 2 H), 4.19–4.08 (m, 3 H), 3.64–3.54 (m, 1 H), 3.46–3.37 (m, 1 H), 3.23–3.14 (m, 1 H), 1.78–1.70 (m, 8 H), 1.62–1.58 (m, 4 H), 1.55 (s, 9 H), 1.40 (s, 3 H), 1.39 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 166.2, 139.3, 138.1, 133.4, 133.1, 130.2, 129.9, 129.8, 129.7, 128.7, 128.4, 120.9, 120.1, 110.2, 110.2, 99.0, 97.3, 78.5, 76.1, 75.6, 74.6, 73.0, 72.6, 72.6, 62.1, 61.3, 30.6, 30.5, 28.3, 28.1, 26.6, 26.5, 25.4, 25.3, 19.1, 19.0, 18.5 ppm. HRMS: calcd. for $C_{22}H_{28}O_6Na$ $[M + Na]^+$ 411.1778; found 411.1796.

(1*R*,2*R*,3*S*,6*R*)-3-Hydroxy-4,8,8-trimethyl-2-tetrahydropyranyloxy-7,9-dioxabicyclo[4.3.0]non-4-ene (15): Fully protected **14** (595 mg, 1.53 mmol) was dissolved in 10% NaOMe in anhydrous MeOH (60 mL) and stirred at room temperature for 3 h. The mixture was concentrated in vacuo and purified by flash column chromatography (heptane/EtOAc, 4:1) to give alcohol **15** (393 mg, 90%) as a colorless oil and a mixture of two diastereomers. R_f = 0.51 and 0.63 (EtOAc/heptane, 1:1). IR (film): $\tilde{\nu}$ = 3442, 3037, 2982, 2936, 2860, 1453, 1441, 1372, 1243, 1215, 1135, 1072, 1047, 1022, 1007, 975, 890 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.54–5.45 (m, 2 H), 4.79 (dd, *J* = 2.6, 5.5 Hz, 1 H), 4.62–4.50 (m, 2 H), 4.40 (d, *J* = 1.7 Hz, 1 H), 4.31 (t, *J* = 5.8 Hz, 1 H), 4.14–4.07 (m, 2 H), 4.04–3.91 (m, 3 H), 3.87–3.80 (dd, *J* = 5.0, 8.5 Hz, 1 H), 3.59 (t, *J* = 8.5 Hz, 1 H), 3.56–3.47 (m, 2 H), 2.99 (d, *J* = 8.5 Hz, OH), 1.96–1.77 (m, 3 H), 1.87–1.85 (m, 3 H), 1.84–1.83 (m, 3 H), 1.61–1.47 (m, 9 H), 1.47 (s, 3 H), 1.43 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.1, 138.2, 120.4, 117.3, 110.0, 109.7, 102.7, 99.4, 84.3, 76.7, 75.9, 75.2, 72.7, 71.1, 70.5, 65.6, 64.0, 31.5, 30.9, 28.5, 28.2, 26.6, 26.1, 25.3, 25.1, 21.4, 20.4, 20.3, 19.0 ppm. HRMS: calcd. for $C_{15}H_{24}O_5Na$ $[M + Na]^+$ 307.1516; found 307.1521.

(1*R*,2*S*,6*R*)-4,8,8-Trimethyl-3-oxo-2-tetrahydropyranyloxy-7,9-dioxabicyclo[4.3.0]non-4-ene (16): Celite (1.8 g) and PDC (1.8 g, 4.78 mmol) were added to a solution of alcohol **15** (389 mg, 1.37 mmol) in freshly distilled CH_2Cl_2 (65 mL) and the reaction mixture was stirred at room temperature under argon for 26 h. The mixture was filtered through a plug of Celite, and concentrated in vacuo to give a slightly yellow oil, which was purified by flash column chromatography (heptane/EtOAc, 3:1) to afford **16** (334 mg, 86%) as a colorless oil and a mixture of two diastereomers. R_f = 0.62 (EtOAc/heptane, 1:1). IR (film): $\tilde{\nu}$ = 2985, 2938, 2886, 1698, 1453, 1380, 1371, 1240, 1219, 1167, 1125, 1063, 1031, 977, 966, 856 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.54 (dq, *J* = 1.5, 4.2 Hz, 1 H), 6.50–6.46 (m, 1 H), 4.98 (t, *J* = 3.3 Hz, 1 H), 4.87 (t, *J* = 3.2 Hz, 1 H), 4.80–4.74 (m, 2 H), 4.54–4.41 (m, 4 H), 4.13–4.03 (m, 1 H), 3.98–3.89 (m, 1 H), 3.52–3.41 (m, 2 H), 1.86 (t, *J* = 1.4 Hz, 3 H), 1.85 (t, *J* = 1.4 Hz, 3 H), 1.80–1.67 (m, 5 H), 1.61–1.52 (m, 7 H), 1.52 (s, 3 H), 1.47 (s, 3 H), 1.43 (s, 3 H), 1.40 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.2, 196.1, 137.5, 136.0, 135.8, 111.2, 111.1, 98.6, 97.8, 78.5, 77.7, 76.6, 71.7, 71.6, 62.2, 61.9, 30.4, 30.2, 28.1, 28.0, 26.7, 25.5, 25.4, 19.0, 18.7, 16.2, 15.9 ppm. HRMS: calcd. for $C_{15}H_{22}O_5Na$ $[M + Na]^+$ 305.1359; found 305.1368.

Gabosine A: Ketone **16** (52 mg, 0.184 mmol) was dissolved in 80% acetic acid in H_2O (3.0 mL) and stirred under nitrogen for 9 h at 40 °C. The reaction mixture was cooled to room temperature, concentrated and co-concentrated with H_2O to give a residue that was purified by flash column chromatography (EtOAc) to afford gabosine A (28 mg, 96%) as a white crystalline material. R_f = 0.16 (EtOAc). $[\alpha]_D^{25}$ = –125.4 (*c* = 0.8, CD_3OD) lit.[1b] $[\alpha]_D^{20}$ = –132 (*c* = 1, MeOH), lit.[4d] $[\alpha]_D$ = –131 (*c* = 0.27, MeOH). M.p. 56–60 °C (MeOH). IR (film): $\tilde{\nu}$ = 3354, 2955, 2924, 2862, 1684, 1448, 1236, 1139, 1092, 1028 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ = 6.75 (dq, *J* = 1.5, 5.6 Hz, 1 H), 4.41–4.36 (m, 1 H), 4.32 (d, *J* = 10.0 Hz, 1 H), 3.73 (dd, *J* = 4.0, 10.0 Hz, 1 H), 1.82 (dd, *J* = 0.9, 1.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 200.4, 143.0, 136.9, 75.0, 73.9, 67.4, 15.6 ppm. NMR spectroscopic data are in accordance with literature values.[1b,4d] HRMS: calcd. for $C_7H_{10}O_4Na$ $[M + Na]^+$ 181.0471; found 181.0472.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra for compounds **1**, **3**, **4**, **6**–**8**, **10**–**16**, gabosine A and N.

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