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Stereoselective Synthesis and Relative Configuration Assignment of Gabosine J

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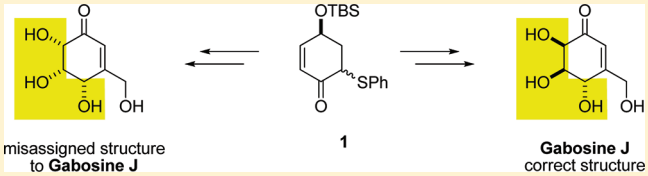
Supporting Information

ABSTRACT: The first total synthesis of (+)-gabosine J and that of the epimer at C4 of its enantiomer have been accomplished through an enantioselective approach from a common intermediate **1**. These syntheses have allowed us to establish the correct relative configuration of the natural metabolite, which was originally misassigned. This work, together with our former syntheses of other gabosines and related compounds, validates enone **1** as a general synthetic precursor for this kind of carbasugars.



INTRODUCTION

Gabosines are a class of secondary metabolites isolated from several *Streptomyces* strains with carbasugar structure (Figure 1).

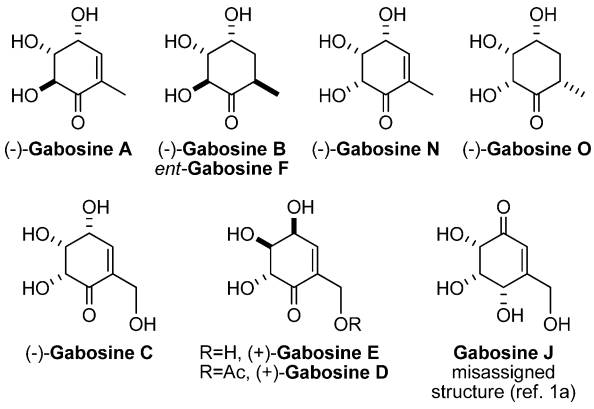


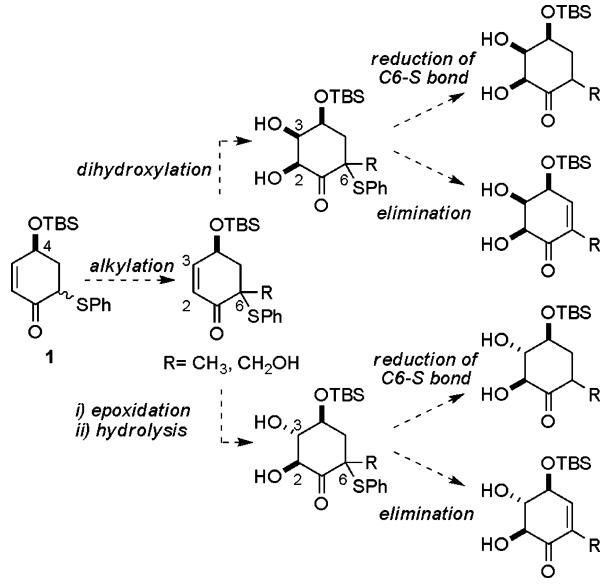
Figure 1. Some examples of gabosines.

This family of compounds shows high structural diversity due to differences in the unsaturation degree of the ring, the substituent positions, and the relative and absolute configuration of their stereogenic centers. To date, up to 14 different gabosines have been isolated.[1]

Some of these metabolites display interesting bioactivities such as antibiotic,[2] antitumor,[3] and DNA binding properties.[1b,4] Their promising biological activities and their challenging structural features have triggered a number of different approaches for their synthesis. Thus, in the past decades, the total syntheses of various gabosines were achieved by several teams developing different strategies. Some of them were based on Diels–Alder reactions,[5] while others started from benzene derivates,[6] carbohydrates,[7] (−)-quinic acid,[8] monoketals of cyclohexan-1,4-diones,[9] or, more recently, L-tartaric acid.[10] This extensive work has contributed to confirm the structure and absolute configuration of most gabosines, but the structure of gabosine J has not been confirmed yet.

Noteworthy, most of the synthetic strategies toward gabosines have been designed leading to one or few members of the family. However, in the past years, we have been investigating a general, stereodivergent, and enantioselective design (Scheme 1) in order

Scheme 1. Stereodivergent Synthetic Strategy to Gabosines and Related Compounds



to accomplish a large number of syntheses starting from a common intermediate.[9b,d] A crucial point of this project was the preparation of enones (4*R*,6*RS*)- and (4*S*,6*RS*)-**1** through an enzymatic resolution, in multigram scale, with absolute stereochemical control at C4.[11]

We have validated our strategy by synthesizing a number of gabosines and related compounds, among which are gabosines N

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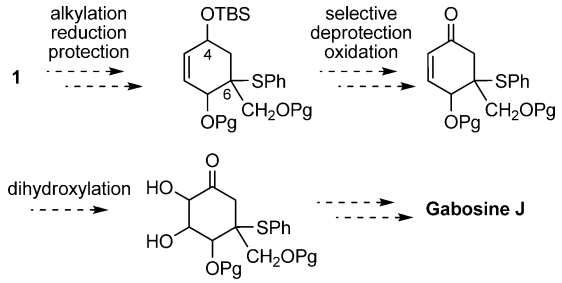
and O, with relative *cis*-configuration at the C2−C3 diol unit,[9b] and gabosines A, B, and F, with relative C2−C3 *trans*-configuration.[9d]

In order to increase the feasibility of enone **1** as the starting material for the stereodivergent synthesis of gabosines, we choose gabosine J as our next goal. Conversely to the other gabosines previously synthesized by us, gabosine J bears a hydroxymethyl substituent attached to the ring instead of a methyl group, and it also displays switched functionalization at C1 and C4 with respect to most gabosines. Moreover, to the best of our knowledge, gabosine J has not been previously synthesized, and no optical rotation value was described for the metabolite isolated from natural sources.

Adjustment of our general synthetic strategy to gabosine J (Scheme 2) required hydroxymethylation at C6, followed by

Scheme 2. Synthetic Plan for Gabosine J

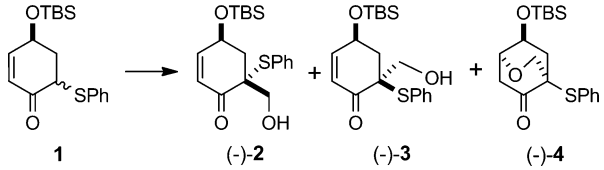


switching of the hydroxyl and carbonyl group positions of the γ-hydroxyenone moiety, and then a convenient sequence of known steps, including dihydroxylation and oxidation of the sulfide with concomitant elimination.

RESULTS AND DISCUSSION

According to the plan, the hydroxymethylation of enone **1** was first investigated. The results are summarized in Table 1.

Table 1. Hydroxymethylation Studies of Enone (4*S*,6*RS*)-1[a]



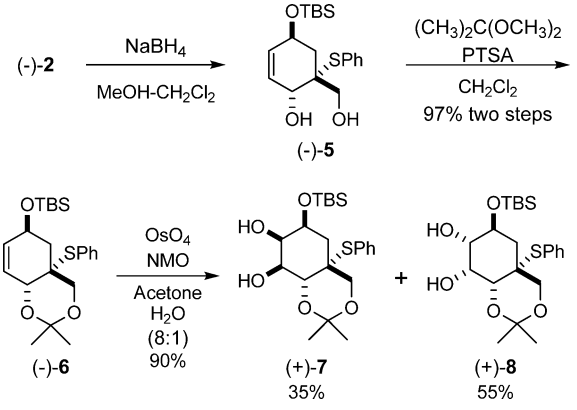
entry	reagent	yield (%)[b]	(−)-2:(−)-3:(−)-4
1[c]	CH_2O (g)	66	4.5:1:−
2[c]	Bt−CH_2OH	75	7.8:1:2.1
3[d,e]	Bt−CH_2OH	88	7.3:1:4.3
4[f]	Bt−CH_2OH	76	2.2:1:−
5[f,g]	Bt−CH_2OH	87	20.7:1:−
6[h,i]	formalin−MeOH	88	1:−:−

[a]All reactions were performed with 0.1 M solutions of (4*S*,6*RS*)-**1** and *t*BuOK in THF at −78 °C unless specified. [b]Isolated overall yield. [c]Workup: aq NH_4Cl. [d]Workup: aq NaOH. [e]LDA was used as the base. [f]Workup: silica gel. [g][(4*S*,6*RS*)-**1**] = 0.8 M and [*t*BuOK] = 0.5 M. [h]Workup: aq HCl. [i][(4*S*,6*RS*)-**1**] = 0.2 M and [*t*BuOK] = 0.2 M.

Bubbling of formaldehyde (prepared in situ by cracking of paraformaldehyde) into a solution of (4*S*,6*RS*)-**1** and *t*BuOK in THF at −78 °C gave a mixture of epimers (−)-**2** and (−)-**3** in moderate yield (Table 1, entry 1). In order to improve this result, several attempts were done by using 1*H*-benzotriazole-1-methanol, as the source of formaldehyde, under basic conditions (Table 1, entries 2−5). In those trials, we observed that the workup protocol had a crucial influence on the yield and/or product ratio. Thus, under the same reaction and workup conditions as in entry 1, where the reaction quenching was performed by addition of aqueous ammonium chloride, the total yield increased slightly, but, along with the expected products (−)-**2** and (−)-**3**, a bicyclic compound (−)-**4**, resulting of an intramolecular conjugated addition in (−)-**3**, was also isolated in considerable amount (Table 1, entry 2). Use of LDA as the base combined with basic workup (Table 1, entry 3) increased the total yield but also the ratio of (−)-**4** in the product mixture. Interestingly, we observed that a quick filtrate of the reaction mixture through a silica gel pad (Table 1, entry 4) furnished a mixture of (−)-**2** and (−)-**3** in overall 76% yield with no traces of byproduct (−)-**4**. An increase in the concentration of both starting **1** and *t*BuOK lead to good yield and stereoselectivity (Table 1, entry 5). The fact that this last result was not always reproducible led us to assay a different methodology. Hence, the hydroxymethylation was attempted with commercial 37% formalin stabilized with methanol and *t*BuOK as the base (Table 1, entry 6). Under these new reaction conditions, and after slightly acidic workup, alcohol (−)-**2** was obtained in 88% yield as a single product. This result was totally reproducible and made us to establish this last methodology as the one of choice to scale up the reaction to more than 5 g of starting enone **1**.

The regioselective reduction of enone (−)-**2** was carried out by reaction with $NaBH_4$ in CH_2Cl_2−methanol at −10 °C (Scheme 3) and furnished diol (−)-**5** as a single stereoisomer, as

Scheme 3. Synthesis of Diols (+)-7 and (+)-8



it was confirmed by ^1H NMR and ^{13}C NMR analysis. The efficient protection of the 1,3-diol as an acetal required extensive experimentation. Treatment of (−)-**5** with various reagents under standard reaction conditions (acetone/PTSA or $CuSO_4$, dimethoxymethyl benzene/PTSA, dimethoxymethane/P_2O_5 in CH_2Cl_2, dibromomethane/NaOH in DMF) gave either low conversion or decomposition products. But the use of 2,2-dimethoxypropane and a catalytic amount of PTSA in CH_2Cl_2 delivered acetonide (−)-**6** in 97% yield from ketone (−)-**2**.

In order to achieve the ketone functionalization for gabosine J, the acetonide (−)-**6** was desilylated and the free alcohol submitted to oxidation by reaction with the Dess-Martin periodinane. In contrast to our previous results in related compounds, and albeit exhaustive attempts were made, we were unable to dihydroxylate the resulting enone to the corresponding 2,3-diol.

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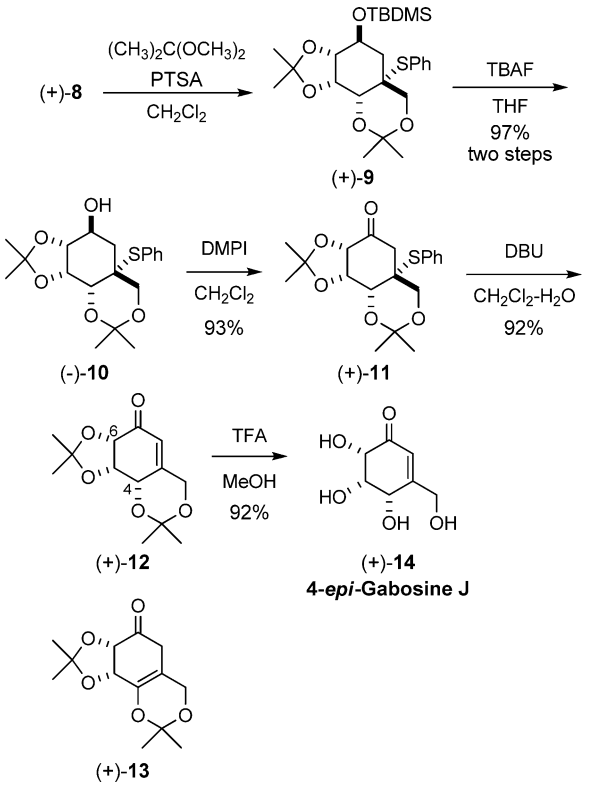
Consequently, we had to reconsider the sequential order of the individual steps. Dihydroxylation of (−)-**6** was easily accomplished under mild conditions with NMO and catalytic OsO_4 in acetone−H_2O, producing a separable mixture of diols (+)-**7** and (+)-**8** in 35 and 55% yield, respectively. The relative configuration of every diol was assigned on the basis of NOE experiments.

According to the relative configuration assigned to gabosine J,[1a] the major isomer (+)-**8** was the appropriate intermediate to continue the synthesis (Scheme 4). Thus, diol (+)-**8** was converted to the corresponding acetonide (+)-**9**, using the procedure described above for the successful conversion of diol (−)-**5** into (−)-**6**. Subsequent removal of the silylic protection delivered the alcohol (−)-**10** in 97% yield from (+)-**8**.

Scheme 4. Synthesis of 4-*epi*-Gabosine J, (+)-14, Final Steps



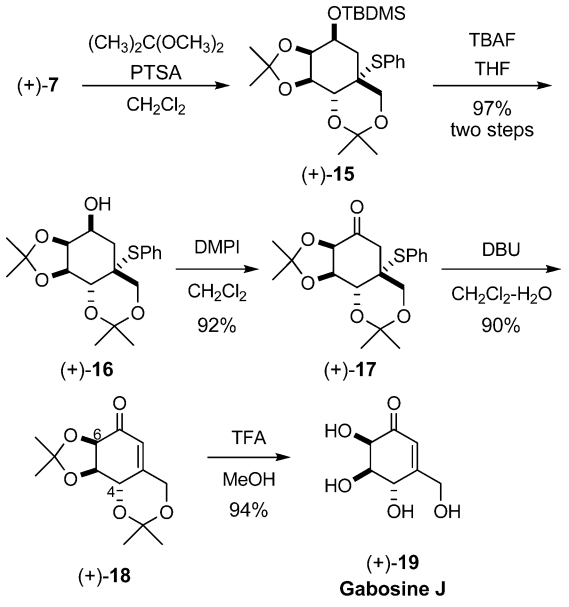
Ketone (+)-**11** was achieved in 93% yield by Dess-Martin oxidation of (−)-**10**. Interestingly, we observed that long reaction times and/or basic workup favored the production of traces of the elimination product (+)-**12**. This fact prompted us to assay the *β*-elimination of thiophenol, instead of the alternative oxidation−pyrolysis protocol, in order to obtain enone (+)-**12**. However, treatment of (+)-**11** with DBU in CH_2Cl_2 furnished a 5.3:1 mixture of (+)-**12** and (+)-**13**, respectively. After exhaustive study of the reaction conditions, we discovered that by performing the reaction in a biphasic medium (CH_2Cl_2−H_2O), enone (+)-**12** can be obtained exclusively and in excellent yield (92%). Finally, the bisacetonide (+)-**12** was submitted to methanolysis yielding the tetrahydroxyenone (+)-**14** with the putative structure of gabosine J.[1a] However, the ^{1}H NMR and ^{13}C NMR spectra of (+)-**14** do not match those reported for natural gabosine J (Table 2), and therefore, the structure assigned to the metabolite isolated from natural sources must be corrected.

Table 2. Comparison of ^{13}C NMR Data (δ) in MeOD of (+)-14, (+)-19, and Natural Gabosine J

	C1	C2	C3	C4	C5	C6	CH_2
ref 1a	199.9	122.2	162.3	69.9	73.9	76.6	63.3
(+)-**14**	200.0	121.0	166.0	70.8	76.8	77.4	62.4
(+)-**19**	199.9	122.1	162.3	69.9	73.8	76.5	63.3

With this purpose, we performed a parallel sequence starting from diol (+)-**7** that ended up with the diastereoisomeric tetrahydroxyenone (+)-**19** and was accomplished in 75% overall yield (Scheme 5). Satisfactorily, we found a complete matching between the set of signals of both the ^{1}H and ^{13}C NMR spectra of (+)-**19** in comparison with those of natural gabosine J.[1a]

Scheme 5. Synthesis of Natural Gabosine J, (+)-19, Final Steps



The final tetrahydroxyenones **14** and **19** are only soluble in very polar solvents such as MeOH and water. In these solvents, the ^{1}H NMR signals of all the protons are too close to obtain reliable NOE data. Although epimerization of the stereogenic centers of the intermediates **9**−**12** and **15**−**18** was never detected, to further confirm the relative configuration of **14** and **19**, we performed NOE experiments on the bisacetonides **12** and **18** (the ultimate precursors of the final gabosines). In the ^{1}H NMR spectrum of the all cis isomer **12** in $CDCl_3$, the signals corresponding to the significant protons appear clearly differentiated, but for the trans−cis isomer **18**, it was necessary to register the spectrum in C_6D_6, where the signals were better distinguished, allowing to acquire reliable NOE data. Thus, selective irradiation in the appropriate solvent of the signal corresponding to H-4 shows positive NOE in the signal of H-6 for the all cis isomer **12** and no effect for the cis−trans isomer **18**. It can be hence concluded that the correct structure of the product extracted from natural sources and named gabosine J is that of **19**. Since the specific rotation of the metabolite isolated from *Streptomyces kurssanovii* (strain FH-S 1175)[1a] was not described and we were unable to obtain a sample extracted from this source, the value measured for (4*R*,5*R*,6*R*)-**19**, $[\alpha]^{24}_D$ = +61.7 (*c* 1.50, MeOH), still does not permit us to establish the absolute configuration of natural gabosine J.

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CONCLUSION

In summary, herein we have described the first and enantioselective total synthesis of a compound with the putative structure of gabosine J. We have also completed the synthesis of the natural metabolite and, hence, definitively established the relative configuration of natural gabosine J, which is the epimer at C4 of the originally proposed structure. It has been demonstrated that cyclohexenone **1**, which is readily prepared in multigram scale with any desired configuration at C4, is a versatile starting material for the synthesis of gabosines.

EXPERIMENTAL SECTION

(4*S*,6*R*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-hydroxymethyl-6-phenylthiocyclohex-2-enone, (−)-2. A solution of ^{t}BuOK (2.18 g, 19.4 mmol) in THF (5 mL) was slowly added to a solution of enone (4*S*,6*RS*)-**1** (5.87 g, 17.6 mmol) in THF (45 mL) at 0 °C. After stirring for 5 min, formaldehyde (commercial 37% aqueous solution with 10−15% MeOH, 1.5 mL, 20.1 mmol) was slowly added. The resulting mixture was stirred for 45 min at 0 °C. Water (20 mL) was added to the mixture, and it was slightly acidified with 4% HCl. Organics were extracted from the mixture with CH_2Cl_2 (4 × 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (hexanes/AcOEt, 9:1) affording (−)-**2** (5.62 g, 88%) as a yellow solid: mp 95−97 °C; $[\alpha]_D^{20} = -122$ (*c* 1.07, $CHCl_3$); R_f (hexanes/AcOEt, 5:1) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.36 (m, 3H), 7.34−7.28 (m, 2H), 6.82 (dt, *J* = 10.3, 2.0 Hz, 1H), 5.95 (dd, *J* = 10.3, 2.3 Hz, 1H), 4.96 (dddd, *J* = 10.0, 5.4, 2.3, 2.0 Hz, 1H), 3.91 (d, *J* = 11.7 Hz, 1H), 3.53 (d, *J* = 11.7 Hz, 1H), 2.51 (dd, *J* = 13.9, 10.0 Hz, 1H), 2.24 (ddd, *J* = 13.9, 5.4, 2.0 Hz, 1H), 1.92 (br s, 1H), 0.93 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 153.3, 137.5, 130.1, 129.1, 128.2, 127.1, 65.9, 65.7, 58.0, 40.5, 25.9, 18.2, −4.5, −4.6; IR (ATR) 3462, 2951, 2928, 2856, 1672, 1254, 1066, 1007 cm^{-1}; HRMS (ESI+) Calcd. for $[C_{19}H_{28}O_3SSi + Na^+]$ 387.1426, found 387.1418.

During the study of this reaction, samples of ketones (−)-**3** and (−)-**4** were occasionally isolated.

Experimental Procedure for Entry 3 in Table 1. Triisopropylamine (87 μL, 0.624 mmol) was added dropwise to a stirred solution of *n*-BuLi (390 μL, 0.62 mmol) in THF (6 mL) at −10 °C. The solution was stirred at 0 °C for 30 min and then cooled to −78 °C. Next, a solution of enone (4*S*,6*RS*)-**1** (69 mg, 0.21 mmol) in THF (2 mL) was added dropwise, and the mixture was stirred for additional 30 min. Then, 1*H*-benzotriazole-1-methanol (62 mg, 0.42 mmol) in THF (4 mL) was slowly added over a 10 min period and kept 2 h at the same temperature. Quenching with water (10 mL) was followed by extractions with diethyl ether (3 × 10 mL). The combined organic extracts were washed with 4 M NaOH, then dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by flash chromatography (hexanes/AcOEt, 9:1) affording (−)-**2** (39 mg, 51%), (−)-**3** (5.3 mg, 7%), and (−)-**4** (23 mg, 30%).

(4*S*,6*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-hydroxymethyl-6-phenylthiocyclohex-2-enone, (−)-3. White solid: mp 45−47 °C; $[\alpha]_D^{20} = -20$ (*c* 1.01, $CHCl_3$); R_f (hexanes/AcOEt, 5:1) 0.1; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.46−7.41 (m, 2H), 7.39−7.30 (m, 3H), 6.73 (dd, *J* = 10.2, 3.4 Hz, 1H), 6.01 (dd, *J* = 10.2, 1.4 Hz, 1H), 4.56 (dddd, *J* = 5.8, 5.3, 3.4, 1.4 Hz, 1H), 3.74 (d, *J* = 11.6 Hz, 1H), 3.59 (d, *J* = 11.6 Hz, 1H), 2.53 (ddd, *J* = 14.2, 5.3, 0.6 Hz, 1H), 2.17 (ddd, *J* = 14.2, 5.8, 0.6 Hz, 1H), 2.01 (br s, 1H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 196.0, 149.5, 137.5, 129.77, 129.73, 129.0, 127.6, 65.2, 64.2, 58.4, 39.9, 25.9, 18.2, −4.51, −4.52; IR (ATR) 3421, 2953, 2928, 2856, 1672, 1471, 1254, 1101 cm^{-1}; HRMS (ESI+) Calcd. for $[C_{19}H_{28}O_3SSi + Na^+]$ 387.1426, found 387.1422.

(1*S*,4*S*,7*S*)-7-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-phenylthio-2-oxabicyclo[2.2.2]octan-5-one, (−)-4. White solid: mp 53−56 °C; $[\alpha]_D^{20} = -10$ (*c* 1.31, $CHCl_3$); R_f (hexanes/AcOEt, 5:1) 0.6; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.34 (m, 3H), 4.18 (m, 1H), 4.00 (m, 1H), 3.91 (dd, *J* = 9.4, 2.6 Hz, 1H), 3.74 (d, *J* = 9.4 Hz, 1H), 2.93 (dd, *J* = 19.5, 1.11 Hz, 1H), 2.68 (dd, *J* = 19.5, 3.1 Hz, 1H), 2.38 (dd, *J* = 13.9, 8.9 Hz, 1H), 1.84 (dt, *J* = 13.9, 2.6 Hz, 1H), 0.84 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 206.4, 137.5, 129.4, 128.9, 128.4, 71.8, 69.1, 66.0, 56.4, 40.8, 40.0, 25.6, 17.8, −4.8, −4.9; IR (ATR) 2953, 2928, 2856, 1472, 1252, 1119, 1101, 1065, 1003 cm^{-1}; HRMS (ESI+) Calcd. for $[C_{19}H_{28}O_3SSi + Na^+]$ 387.1426, found 387.1418.

(1*R*,4*S*,6*R*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-hydroxymethyl-6-phenylthiocyclohex-2-enol, (−)-5. $NaBH_4$ (51 mg, 1.35 mmol) was added in portions to a stirred solution of enone (−)-**2** (500 mg, 1.37 mmol) in MeOH (7 mL) and CH_2Cl_2 (7 mL) at −10 °C. After 3 h, water (5 mL) was added to the reaction mixture, and then it was slightly acidified by addition of 4% HCl. The organic layer was separated, and the aqueous one was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to furnish diol (−)-**5** as a white solid (501 mg), which was used without further purification: mp 133−136 °C; $[\alpha]_D^{20} = -28$ (*c* 1.09, $CHCl_3$); R_f (hexanes/AcOEt, 2:1) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.56 (m, 2H), 7.41−7.33 (m, 3H), 5.81 (m, 2H), 4.54 (m, 1H), 4.23 (s, 1H), 3.59 (d, *J* = 12.0 Hz, 1H), 3.44 (d, *J* = 12.0 Hz, 1H), 3.37−2.90 (br, 2H), 1.84 (dd, *J* = 14.0, 5.6 Hz, 1H), 1.61 (dd, *J* = 14.0, 6.2 Hz, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 131.4, 129.5, 129.27, 129.25, 128.2, 70.0, 67.1, 65.5, 60.4, 35.4, 25.9, 18.1, −4.5, −4.6; IR (ATR) 3228, 2955, 2929, 2889, 2856, 1252, 1074, 1045 cm^{-1}; HRMS (ESI+) Calcd. for $[C_{19}H_{30}O_3SSi + Na^+]$ 389.1583, found 389.1585.

***tert*-Butyl{[(4a*R*,6*S*,8a*R*)-2,2-dimethyl-4a-phenylthio-4a,5,6,8a-tetrahydro-4*H*-1,3-benzodioxin-6-yl]oxy}dimethylsilane, (−)-6.** A 50 mL round-bottomed flask equipped with a stir bar was charged with (−)-**5** (501 mg, 1.37 mmol), 2,2-dimethoxypropane (3.4 mL, 27.6 mmol), and CH_2Cl_2 (14 mL). The mixture was stirred, and *p*-TsOH (3.1 mg, 0.016 mmol) was immediately added. The reaction evolution was monitored by TLC (hexane/AcOEt, 2:1), and water (6 mL) was added after all the starting material was consumed. The organic layer was separated, and the aqueous one was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum. The product was purified by flash chromatography (hexanes/AcOEt, 5:1), affording (−)-**6** (540 mg, 97% from (−)-**2**) as a white solid: mp 113−116 °C; $[\alpha]_D^{20} = -101$ (*c* 1.03, $CHCl_3$); R_f (hexanes/AcOEt, 5:1) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.59 (m, 2H), 7.37−7.31 (m, 3H), 5.73 (d, *J* = 10.3 Hz, 1H), 5.65 (d, *J* = 10.3 Hz, 1H), 4.85 (m, 1H), 4.74 (m, 1H), 3.57 (d, *J* = 12.0 Hz, 1H), 3.50 (d, *J* = 12.0 Hz, 1H), 1.90 (ddd, *J* = 13.5, 6.6, 1.2 Hz, 1H), 1.59 (s, 3H), 1.49 (s, 3H), 1.44 (dd, *J* = 13.5, 8.8 Hz, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 132.2, 131.6, 129.0, 128.9, 128.2, 100.5, 73.1, 67.0 (2C), 55.3, 37.1, 29.7, 26.0, 19.6, 18.3, −4.47, −4.51; IR (ATR) 2951, 2929, 2854, 1471, 1379, 1252, 1196, 1130, 1095, 1061, 1032 cm^{-1}; HRMS (ESI+) Calcd. for $[C_{22}H_{34}O_3SSi + Na^+]$ 429.1896, found 429.1894.

Diols (+)-7 and (+)-8. NMO (340 mg, 2.90 mmol) was added to a solution of compound (−)-**6** (464 mg, 1.14 mmol) in acetone (9.8 mL) and water (1.2 mL) at room temperature. After total dissolving, OsO_4 (2.5% in ^{t}BuOH, 720 μL, 0.057 mmol) was added to the reaction flask, and the resulting mixture was stirred for 60 h. Then, aq $Na_2S_2O_3$ (10%, 5 mL) was added to the reaction mixture. After 30 min stirring, the mixture was slightly acidified by addition of 4% HCl and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification of the crude material by flash chromatography (hexanes/AcOEt, 9:1) furnished (+)-7 (174 mg, 35%) and (+)-**8** (279 mg, 55%).

(4a*R*,6*S*,7*R*,8*S*,8a*R*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,2-dimethyl-4a-phenylthiohexahydro-4*H*-1,3-benzodioxine-7,8-diol, (+)-7. Data: $[\alpha]_D^{20} = +10$ (*c* 1.15, $CHCl_3$); R_f (hexanes/AcOEt, 2:1) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.55 (m, 2H), 7.39−7.30 (m, 3H), 4.51 (ddd, *J* = 9.9, 5.8, 3.1 Hz, 1H), 4.21−4.15 (m, 2H), 4.10 (d, *J* = 9.8 Hz, 1H), 3.56 (s, 2H), 2.61 (br s, 1H), 2.45 (br s, 1H), 1.58 (s, 3H), 1.52−1.44 (m, 2H), 1.50 (s, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 130.7, 129.3, 129.1, 100.9, 73.8, 73.5, 69.3, 68.0, 67.9, 51.4, 32.6, 29.7, 25.9, 19.8, 18.1, −4.4, −4.5; IR (ATR) 3475, 2897, 2928, 2856, 1381, 1252, 1196, 1118,

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1062 cm^{-1}; HRMS (ESI+) Calcd. for $[C_{22}H_{36}O_5SSi + Na^+]$ 463.1950, found 463.1956.

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,2-dimethyl-4a-phenylthiohexahydro-4*H*-1,3-benzodioxine-7,8-diol, (+)-8. Data: $[\alpha]_D^{20}$ = +9.4 (*c* 1.07, $CHCl_3$); R_f (hexanes/AcOEt, 2:1) 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63−7.60 (m, 2H), 7.40−7.31 (m, 3H), 4.38 (ddd, *J* = 10.8, 9.2, 4.8 Hz, 1H), 4.19 (ddd, *J* = 5.3, 3.4, 2.8 Hz, 1H), 3.79 (d, *J* = 2.8 Hz, 1H), 3.48 (s, 2H), 3.42 (ddd, *J* = 9.2, 6.8, 3.4 Hz, 1H), 3.20 (d, *J* = 5.3 Hz, 1H), 2.63 (d, *J* = 6.8 Hz, 1H), 1.80 (dd, *J* = 13.9, 4.8 Hz, 1H), 1.60 (s, 3H), 1.46 (s, 3H), 1.12 (dd, *J* = 13.9, 10.8 Hz, 1H), 0.86 (s, 9H), 0.15 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 130.9, 129.5, 129.1, 100.6, 76.0, 74.7, 72.5, 69.5, 68.9, 52.2, 36.9, 29.6, 25.9, 19.5, 18.2, −4.17, −4.24; IR (ATR) 3446, 2928, 2854, 1381, 1248, 1119, 1065 cm^{-1}; HRMS (ESI+) Calcd. for $[C_{22}H_{36}O_5SSi + Na^+]$ 463.1950, found (M + Na^+) 463.1957.

***tert*-Butyl(dimethyl){[(3a*S*,4*S*,5a*R*,9a*R*,9b*R*)-2,2,8,8-tetramethyl-5a-phenylthio-hexahydro-3a*H*-[1,3]dioxolo[4,5-*h*][1,3]-benzodioxin-4-yl]oxy}silane, (+)-9.** A 25 mL round-bottomed flask equipped with a stir bar was charged with diol (+)-**8** (259 mg, 0.59 mmol), 2,2-dimethoxypropane (1.4 mL, 11.39 mmol), and CH_2Cl_2 (6 mL). The mixture was stirred, and *p*-TsOH (2.0 mg, 0.011 mmol) was immediately added. The reaction evolution was monitored by TLC (hexane/AcOEt, 2:1), and water (3 mL) was added after all the starting material was consumed. The organic layer was separated, and the aqueous one was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum affording (+)-**9** (285 mg) as a white solid, which was used without further purification: mp 147−150 °C; $[\alpha]_D^{20}$ = +9.0 (*c* 1.72, $CHCl_3$); R_f (hexanes/AcOEt, 2:1) 0.6; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65−7.61 (m, 2H), 7.38−7.29 (m, 3H), 4.68 (ddd, *J* = 11.2, 6.7, 5.3 Hz, 1H), 4.36 (dd, *J* = 5.3, 3.4 Hz, 1H), 4.06 (d, *J* = 3.4 Hz, 1H), 4.00 (dd, *J* = 6.7, 5.3 Hz, 1H), 3.37 (d, *J* = 12.2 Hz, 1H), 3.30 (d, *J* = 12.2 Hz, 1H), 1.84 (dd, *J* = 13.9, 5.3 Hz, 1H), 1.71 (s, 3H), 1.67 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H), 1.15 (dd, *J* = 13.9, 11.2 Hz, 1H), 0.91 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 132.0, 129.1, 128.9, 111.8, 100.9, 82.8, 75.7, 73.7, 71.0, 67.7, 50.4, 37.7, 29.9, 28.4, 26.8, 26.0, 19.3, 18.1, −4.0, −4.4; IR (ATR) 2987, 2929, 2854, 1381, 1367, 1252, 1219, 1196, 1165, 1107, 1068, 1055, 1024 cm^{-1}; HRMS (ESI+) Calcd. for $[C_{25}H_{40}O_5SSi + Na^+]$ 503.2263, found 503.2257.

The same procedure starting from diol (+)-7 (163 mg, 0.37 mmol) yielded (+)-**15** (181 mg) as a white solid, which was also used without further purification.

***tert*-Butyl(dimethyl){[(3a*R*,4*S*,5a*R*,9a*R*,9b*S*)-2,2,8,8-tetramethyl-5a-phenylthio-hexahydro-3a*H*-[1,3]dioxolo[4,5-*h*][1,3]-benzodioxin-4-yl]oxy}silane, (+)-15.** Data: mp 104−107 °C; $[\alpha]_D^{20}$ = +16° (*c* 1.75, $CHCl_3$); R_f (hexanes/AcOEt, 2:1) 0.7; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58−7.53 (m, 2H), 7.39−7.30 (m, 3H), 4.70 (ddd, *J* = 9.8, 5.4, 4.6 Hz, 1H), 4.41 (t, *J* = 4.6 Hz, 1H), 4.30 (dd, *J* = 8.5, 4.6 Hz, 1H), 4.11 (d, *J* = 8.5 Hz, 1H), 3.62 (d, *J* = 12.2 Hz, 1H), 3.56 (d, *J* = 12.2 Hz, 1H), 1.60−1.49 (m, 2H), 1.54 (s, 3H), 1.51 (s, 3H), 1.47 (s, 3H), 1.38 (s, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 130.3, 129.0, 128.8, 109.0, 100.2, 77.0, 75.9, 75.2, 67.7, 66.4, 50.9, 33.7, 29.3, 28.4, 25.8, 25.7, 18.9, 18.0, −4.6, −4.7; IR (ATR) 2987, 2929, 2856, 1381, 1250, 1219, 1124, 1047 cm^{-1}; HRMS (ESI+) Calcd. for $[C_{25}H_{40}O_5SSi + Na^+]$ 503.2263, found 503.2251.

(3a*R*,4*S*,5a*R*,9a*R*,9b*R*)-2,2,8,8-Tetramethyl-5a-phenylthio-hexahydro-3a*H*-[1,3]dioxolo[4,5-*h*][1,3]benzodioxin-4-ol, (−)-10. To a solution of compound (−)-**9** (285 mg, 0.59 mmol) in THF (6 mL), TBAF (1 M in THF, 650 μL, 0.65 mmol) was added. The reaction mixture was stirred at 60 °C until total conversion of the starting material (monitored by TLC, hexanes/AcOEt, 1:1). The solvent was removed under vacuum, and the product was purified by flash chromatography (hexanes/AcOEt, 2:1) to provide alcohol (−)-**10** (211 mg, 97% from (+)-**8**): mp 178−180 °C; $[\alpha]_D^{20}$ = −19 (*c* 1.12, $CHCl_3$); R_f (hexanes/AcOEt, 1:1) 0.1; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.60 (m, 2H), 7.40−7.27 (m, 3H), 4.81 (ddd, *J* = 11.9, 7.3, 5.0 Hz, 1H), 4.39 (dd, *J* = 5.2, 3.5 Hz, 1H), 4.05 (d, *J* = 3.5 Hz, 1H), 4.02 (dd, *J* = 7.3, 5.2 Hz, 1H), 3.39 (d, *J* = 12.2 Hz, 1H), 3.31 (d, *J* = 12.2 Hz, 1H), 2.76 (br s, 1H), 1.91 (dd, *J* = 13.7, 5.0 Hz, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 1.47 (s, 3H), 1.41 (s, 3H), 1.12 (dd, *J* = 13.7, 11.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 131.5, 129.2, 128.9, 112.3, 100.9, 82.5, 75.6, 73.8, 70.3, 67.6, 50.8, 35.7, 29.8, 28.4, 26.7, 19.3; IR (ATR) 3435, 2987, 2937, 2854, 1383, 1367, 1219, 1196, 1163, 1113, 1097, 1049, 1014, 1001 cm^{-1}; HRMS (ESI+) Calcd. for $[C_{19}H_{26}O_5S + Na^+]$ 389.1399, found 389.1403.

The same procedure starting from acetonide (+)-**15** (181 mg, 0.38 mmol) furnished (+)-**16** (133 mg, 97% from (+)-7).

(3a*S*,4*S*,5a*R*,9a*R*,9b*S*)-2,2,8,8-Tetramethyl-5a-phenylthio-hexahydro-3a*H*-[1,3]dioxolo[4,5-*h*][1,3]benzodioxin-4-ol, (+)-16. Data: mp 98−100 °C; $[\alpha]_D^{20}$ = +3.2 (*c* 1.23, $CHCl_3$); R_f (hexanes/AcOEt, 1:1) 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59−7.55 (m, 2H), 7.40−7.31 (m, 3H), 4.66−4.58 (m, 2H), 4.37 (dd, *J* = 8.3, 5.5 Hz, 1H), 4.14 (d, *J* = 8.3 Hz, 1H), 3.58 (d, *J* = 12.3 Hz, 1H), 3.54 (d, *J* = 12.3 Hz, 1H), 2.23 (br s, 1H), 1.76 (dd, *J* = 14.3, 6.0 Hz, 1H), 1.56 (s, 6H), 1.49 (s, 3H), 1.42 (s, 3H), 1.38 (dd, *J* = 14.3, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 130.1, 129.4, 129.2, 109.5, 100.4, 76.3, 76.2, 75.5, 67.5, 65.9, 50.7, 33.8, 29.6, 28.3, 25.9, 19.3; IR (ATR) 3460, 2987, 2937, 2852, 1381, 1219, 1196, 1111, 1063, 1038 cm^{-1}; HRMS (ESI+) Calcd. for $[C_{19}H_{26}O_5S + Na^+]$ 389.1399, found 389.1402.

(3a*S*,5a*R*,9a*R*,9b*R*)-2,2,8,8-Tetramethyl-5a-phenylthiotetra-hydro-3a*H*-[1,3]dioxolo[4,5-*h*][1,3]benzodioxin-4(5*H*)-one, (+)-11. Dess-Martin periodinane (15% in CH_2Cl_2, 1.5 mL, 0.72 mmol) was added dropwise to a solution of alcohol (−)-**10** (180 mg, 0.49 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred overnight at room temperature. $Na_2S_2O_3$ (0.1 M solution saturated with $NaHCO_3$, 2 mL) was added, and after stirring for 1 h, the organic layer was separated, and the aqueous one was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexanes/AcOEt, 1:1) provided (+)-**11** (167 mg, 93%) as a white solid: mp 161−163 °C; $[\alpha]_D^{20}$ = +43 (*c* 1.22, $CHCl_3$); R_f (hexanes/AcOEt, 1:1) 0.2; ^1H NMR (250 MHz, $CDCl_3$) δ 7.67−7.61 (m, 2H), 7.38−7.29 (m, 3H), 4.73 (dd, *J* = 5.7, 3.5 Hz, 1H), 4.52 (d, *J* = 3.5 Hz, 1H), 4.38 (d, *J* = 5.7 Hz, 1H), 3.51 (d, *J* = 12.3 Hz, 1H), 3.35 (d, *J* = 12.3 Hz, 1H), 2.57 (d, *J* = 14.6 Hz, 1H), 2.19 (d, *J* = 14.6 Hz, 1H), 1.71 (s, 3H), 1.69 (s, 3H), 1.55 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 203.0, 138.7, 130.0, 129.6, 129.1, 113.6, 101.2, 79.7, 77.7, 72.9, 66.2, 50.7, 44.5, 29.8, 27.3, 26.4, 19.2; IR (ATR) 2987, 2935, 2883, 1728, 1383, 1254, 1223, 1196, 1157, 1111, 1066, 1024 cm^{-1}; HRMS (ESI+) Calcd. for $[C_{19}H_{24}O_5S + Na^+]$ 387.1242, found 387.1235.

The same procedure starting from alcohol (+)-**16** (117 mg, 0.32 mmol) yielded ketone (+)-**17** (108 mg, 92%).

(3a*R*,5a*R*,9a*R*,9b*S*)-2,2,8,8-Tetramethyl-5a-phenylthiotetra-hydro-3a*H*-[1,3]dioxolo[4,5-*h*][1,3]benzodioxin-4(5*H*)-one, (+)-17. Data: mp 123−125 °C; $[\alpha]_D^{20}$ = +95 (*c* 1.22, $CHCl_3$) R_f (hexanes/AcOEt, 1:1) 0.6; ^1H NMR (250 MHz, $CDCl_3$) δ 7.55−7.50 (m, 2H), 7.42−7.32 (m, 3H), 4.88 (d, *J* = 7.5 Hz, 1H), 4.73 (t, *J* = 7.5 Hz, 1H), 4.14 (d, *J* = 7.5 Hz, 1H), 3.61 (d, *J* = 12.6 Hz, 1H), 3.54 (d, *J* = 12.6 Hz, 1H), 2.44 (d, *J* = 17.7 Hz, 1H), 2.22 (d, *J* = 17.7 Hz, 1H), 1.61 (s, 3H), 1.54 (s, 6H), 1.42 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 202.3, 138.3, 130.1, 129.5, 128.3, 111.6, 100.5, 78.2, 78.0, 76.8, 65.7, 49.4, 43.3, 29.5, 27.5, 25.3, 19.2; IR (ATR) 2987, 2937, 1728, 1682, 1373, 1217, 1196, 1159, 1105, 1061, 1010 cm^{-1}; HRMS (ESI+) Calcd. for $[C_{19}H_{24}O_5S + Na^+]$ 387.1242, found 387.1232.

(3a*S*,9a*S*,9b*S*)-2,2,8,8-Tetramethyl-9a,9b-dihydro-3a*H*-[1,3]-dioxolo[4,5-*h*][1,3]benzodioxin-4(6*H*)-one (+)-12. Ketone (+)-**11** (122 mg, 0.33 mmol) was treated with DBU (10% in CH_2Cl_2, 0.5 mL, 0.33 mmol) in a biphasic system CH_2Cl_2 (7 mL)/water (7 mL) at room temperature. Then, DBU was added (1 equiv every 2 h) until total consumption of the starting material (monitored by TLC). After 9 h of reaction, the mixture was slightly acidified with 4% HCl, the organic layer was separated, and the aqueous one was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/Et_2O, 1:1) affording enone (+)-**12** (78 mg, 92%) as a white solid: mp 102−105 °C; $[\alpha]_D^{20}$ = +129 (*c* 1.73, $CHCl_3$); R_f (hexanes/Et_2O, 1:9) 0.4; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (td, *J* = 1.9, 1.9, 1.3 Hz, 1H), 4.84 (dddd, *J* = 4.3, 2.4, 1.9, 1.3 Hz, 1H), 4.71 (t, *J* = 4.3 Hz, 1H), 4.53 (ddd, *J* = 16.6, 2.4, 1.9 Hz, 1H), 4.40

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(dt, J = 16.6, 1.3 Hz,1H), 4.30 (d, J = 4.3 Hz, 1H), 1.50 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 159.9, 119.8, 111.6, 101.6, 76.3, 75.0, 65.6, 61.7, 27.6, 26.3, 24.9, 23.2; IR (ATR) 2987, 2937, 2897, 1680, 1381, 1219, 1173, 1157, 1090, 1063, 1030 cm^{-1}; HRMS (ESI+) Calcd. for [$C_{13}H_{18}O_5$ + Na^+] 277.1052, found 277.1046.

Analytical samples for the characterization of enone (+)-**13** were isolated through the study of this reaction.

(3a*S*,9b*R*)-2,2,8,8-Tetramethyl-6,9b-dihydro-3a*H*-[1,3]-dioxolo[4,5-*h*][1,3]benzodioxin-4(5*H*)-one, (+)-13. Oil: $[\alpha]_D^{20}$ = +34 (c 1.48, $CHCl_3$); R_f (hexanes/AcOEt, 2:1) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (d, J = 6.5 Hz, 1H), 4.56 (d, J = 6.5 Hz, 1H), 4.11 (d, J = 15.8 Hz, 1H), 4.04 (d, J = 15.8 Hz, 1H), 2.91 (s, 2H), 1.50 (s, 9H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 140.5, 112.1, 104.0, 100.1, 78.5, 76.9, 61.0, 36.3, 27.6, 26.2, 25.8, 23.0; IR (ATR) 2991, 2939, 1738, 1703, 1373, 1238, 1159, 1119, 1082, 1016 cm^{-1}; HRMS (ESI+) Calcd. for [$C_{13}H_{18}O_5$ + MeOH + Na^+] 309.1314, found 309.1312.

The same procedure starting from ketone (+)-**17** (91 mg, 0.25 mmol) yielded ketone (+)-**18** (59 mg, 92%) as a single compound.

(3a*R*,9a*S*,9b*R*)-2,2,8,8-Tetramethyl-9a,9b-dihydro-3a*H*-[1,3]-dioxolo[4,5-*h*][1,3]benzodioxin-4(6*H*)-one (+)-18. Oil: $[\alpha]_D^{20}$ = +131 (c 1.48, $CHCl_3$); R_f (hexanes/AcOEt, 2:1) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (q, J = 1.5 Hz, 1H), 4.58 (m, 1H), 4.51 (dt, J = 16.1, 1.5 Hz, 1H), 4.50–4.47 (m, 2H), 4.44 (ddd, J = 16.1, 1.9, 1.5 Hz, 1H), 1.52 (s, 3H), 1.51 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 157.7, 120.9, 110.9, 101.0, 77.8, 75.0, 69.5, 62.0, 27.4, 26.0, 25.5, 22.1; IR (ATR) 2989, 2939, 1684, 1383, 1219, 1163, 1086, 1072, 852, 781, 631 cm^{-1}; HRMS (ESI+) Calcd. for [$C_{13}H_{18}O_5$ + Na^+] 277.1052, found 277.1045.

(+)-4-*epi*-Gabosine J, (+)-14. To a stirred solution of compound (+)-**12** (50 mg, 0.20 mmol) in MeOH (2 mL), a drop of water and TFA (53 μL, 0.69 mmol) were successively added. After stirring for 3 h, the solvent was removed under reduced pressure. The oily residue was purified by flash chromatography ($CHCl_3$/MeOH, 9:1) to furnish (+)-4-*epi*-gabosine J, (+)-**14**, (31.5 mg, 92%) as a white crystalline solid: mp 166–169 °C; $[\alpha]_D^{20}$ = +82 (c 0.76, MeOH); R_f ($CHCl_3$/MeOH, 9:1) 0.1; ^{1}H NMR (400 MHz, CD_3OD) δ 6.14 (q, J = 2.0 Hz, 1H), 4.67 (dtd, J = 3.1, 2.0, 1.2 Hz, 1H), 4.48 (ddd, J = 18.2, 2.0, 1.2 Hz, 1H), 4.34 (dd, J = 3.1, 2.6 Hz, 1H) 4.28 (dt, J = 18.2, 2.0 Hz, 1H), 4.26 (d, J = 2.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 200.0, 166.0, 121.0, 77.4, 76.8, 70.8, 62.4; IR (ATR) 3273, 2916, 2850, 1680, 1479, 1439, 1410, 1342, 1223, 1209, 1157, 1117, 1047 cm^{-1}; HRMS (ESI+) Calcd. for [$C_7H_{10}O_5$ + Na^+] 197.0426, found 197.0420.

The same procedure starting from enone (+)-**18** (30 mg, 0.12 mmol) yielded gabosine J, (+)-**19**, (19 mg, 94%).

(+)-Gabosine J, (+)-19. Data: mp 113–115 °C; $[\alpha]_D^{20}$ = +62 (c 1.50, MeOH); R_f ($CHCl_3$/MeOH, 9:1) 0.1; ^{1}H NMR (250 MHz, CD_3OD) δ 6.10 (t, J = 1.9 Hz, 1H), 4.56 (d, J = 2.5 Hz, 1H), 4.41 (dd, J = 17.8, 1.9 Hz, 1H), 4.22 (dd, J = 17.8, 1.9 Hz, 1H), 4.21–4.16 (m, 2H); ^{13}C NMR (63 MHz, CD_3OD) δ 199.9, 162.3, 122.1, 76.5, 73.8, 69.9, 63.3; IR (ATR) 3294, 2914, 1676, 1437, 1205, 1117, 1088, 1041 cm^{-1}; HRMS (ESI+) Calcd. for [$C_7H_{10}O_5$ + Na^+] 197.0426, found 197.0421.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral data and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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