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Gabosines

Filling Some Blanks in a Divergent Approach to Gabosines: Enantioselective Synthesis of (–)-Epiepoxydon, (+)-Phyllostine, (–)-Gabosine D, and (–)-Gabosine E

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Abstract: The levorotatory enantiomers of gabosines D and E were synthesized through a divergent approach that could equally well be applied to the synthesis of the dextrorotatory enantiomers, which have been isolated from natural sources. The approach relies on an initial desymmetrization of *p*-methoxyphenol, followed by an enzymatic resolution that separately provides the two enantiomers of synthon **3**. This versatile synthon can be further transformed into the diverse polyoxygenated cyclohexane target molecules. Key steps in the synthesis of (–)-gabosines D and E from (4*R*,6*S*)-**3** are the stereoselective hydroxymethylation at the α-carbonyl position leading to (+)-**4**, and the subsequent reagent-controlled epoxidation of the carbon–carbon double bond. A branching in the sequence also allowed the synthesis of the anhydrogabosines (–)-epiepoxydon and (+)-phyllostine.

Introduction

Carbasugars show a wide variety of biological activities, such as glycosidase inhibition, and antitumor, antiviral, antifungal, antibacterial, and antimalarial activities. For this reason, their synthesis is of great importance for the discovery of new drugs, including cancer-prevention agents.[1] The fact that the shikimic acid biosynthetic pathway is absent in mammals makes the synthesis of shikimic acid analogues an attractive prospect for the discovery of new medicines.[2] The gabosines are examples of such analogues; they form a family of secondary metabolites isolated from various *Streptomyces* strains and can be considered a particular subcategory of carbasugars.[3] Gabosines have been classified into four structural types, all of which have a polyoxygenated methylcyclohexane as a common structural feature (Figure 1). Their structural diversity stems from their positions of substituents, their degree of unsaturation, and/or the relative and absolute configurations of their stereogenic centres.[4] In gabosines of types I and III, the methyl or oxymethyl appendage is located at a position α to the carbonyl group, whereas in those of type II it is attached to an atom β to the carbonyl group. Gabosines of type IV do not have any carbonyl group, and those of type III lack the carbon–carbon double bond, which is present in the three other groups. Gabosines of types I and III have a *cis*-C-3/C-4 relative configuration. Some gabosines show interesting biological activities. For instance, gabosine C is the antibiotic known as KD16-U1, and its crotonate (COTC) is an antitumor agent.[5] Gabosine E inhibits cholesterol biosynthesis,[3b] and several gabosines show DNA-binding properties.[3d]

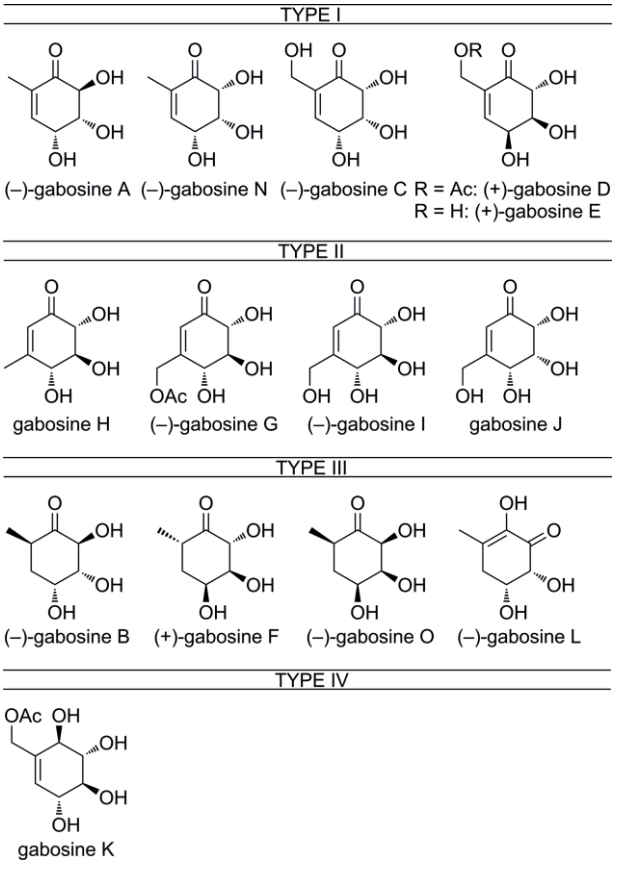

Figure 1. Structural classification of gabosines.

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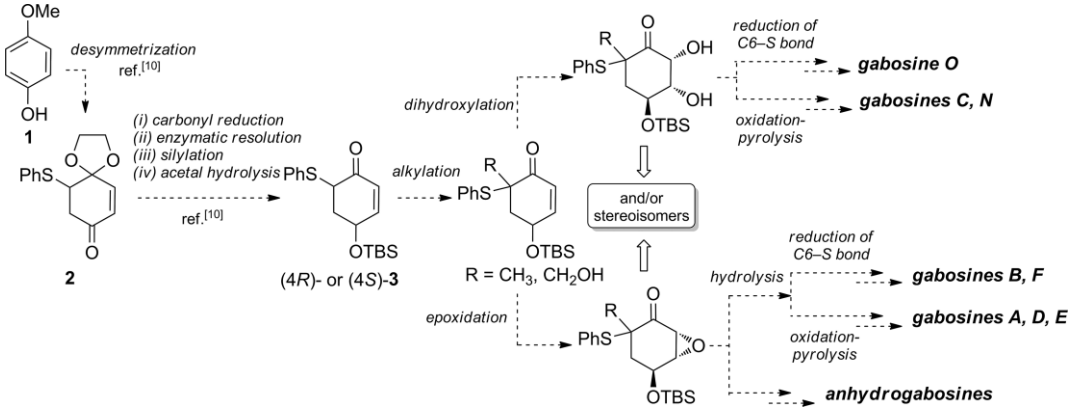
Recently, 4-*O*-decylgabosine D has been identified as a glutathione S-transferase inhibitor, showing an optimum synergetic effect in combination with cisplatin against the A549 human lung cancer cell line.[6] Some epoxyquinone derivatives with anhydrogabosine structures are also known, most of them isolated from fungi.[4,7] Formally, the hydrolysis of the epoxide functionality in one of these compounds should give a gabosine, although this transformation is generally less straightforward than expected. In recent decades, extensive work has been published on the synthesis of gabosines and anhydrogabosines, motivated not only by their promising biological activities, but also by the fact that the extremely crowded functionalization of these small molecules makes them highly challenging synthetic targets.[4,8] The published synthetic strategies include biomimetic approaches, Diels–Alder methods, desymmetrization of benzene or cyclohexanedione derivatives, and chiral-pool syntheses, mainly starting from carbohydrates or quinic acid. In our laboratories, we have been developing a project to prepare a large number of these compounds in either enantiomeric form, starting from a common intermediate. In previous reports, we described how our enantioselective approach succeeded in the preparation of gabosines N, O, A, B, F, C, and J, as well as some of their epimers, and also of the anhydrogabosines epiepoformin and epoformin.[9] In this paper, we present a new contribution to this field by disclosing new syntheses of (–)-gabosine D, (–)-gabosine E, (–)-epiepoxydon, and (+)-phyllostine.

Results and Discussion

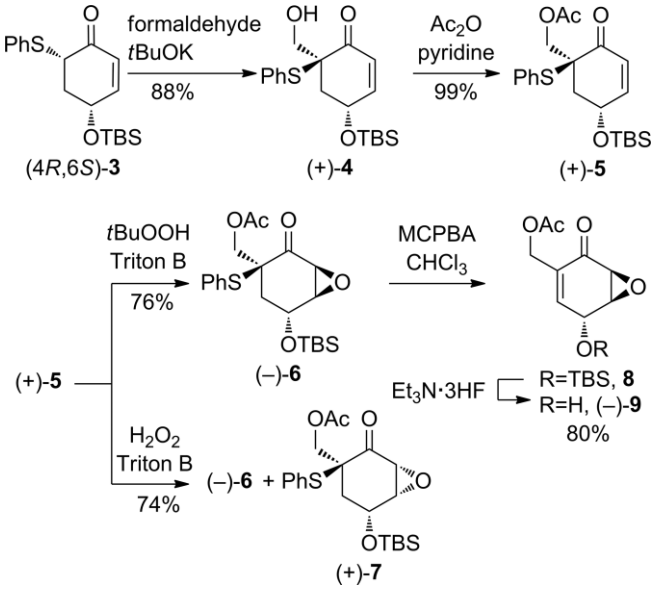
Our divergent proposal for the synthesis of gabosines and their analogues is shown in Scheme 1, where ketone **3** is the common starting material. This ketone is conveniently prepared from *p*-methoxyphenol (**1**) on a multigram scale and is equally available for either configuration at C-4.[10] The doubly activated C-6 position of **3** can be conveniently alkylated (introduction of a methyl or hydroxymethyl group), and then the conjugated carbon–carbon double bond can be oxidized (dihydroxylation or epoxidation). Depending on the specific target, the sulfur residue may be reductively removed, or eliminated to form a double bond. The formation of stereoisomers along the sequence leads to the production of stereochemically diverse analogues. Although the general strategy is broadly applicable, it must be tactically refined for each particular target, because the dense functionalization and specific stereochemistry cause similar intermediates to have different reactivities. This synthetic design is straightforward for gabosines of type I and III, while those of type II require a carbonyl group translocation after the alkylation step. Gabosines D and E, with an oxymethyl group at the α-carbonyl position and a relative *trans* configuration of the C-2/C-3 glycol were our blanks for the type I subgroup. All the previously described syntheses of gabosines D and E started from chiral-pool materials; more specifically, the natural, dextrorotatory enantiomers were prepared from D-ribose[11] and D-glucose,[12] and the levorotatory enantiomers from D-mannose[13] and quinic acid.[14] According to our general approach, the steps required to synthesize gabosines D and E were: hydroxymethylation of the activated position in **3**, epoxidation of the carbon–carbon double bond, elimination of thiophenol, and hydrolysis of the epoxide. Since starting ketone **3** is available with either configuration at C-4, this sequence of reactions is equally applicable to the synthesis of either enantiomer of the final gabosine.

The conversion of enone (4*R*,6*S*)-**3** into hydroxymethyl derivative (+)-**4** was accomplished in 88 % yield by reaction with potassium *tert*-butoxide and formaldehyde, as described previously for the synthesis of (–)-**4**[9c] (Scheme 2). In our previous syntheses of gabosines A and B,[9b] the epoxidation of an intermediate analogous to **4**, bearing a methyl group instead of a hydroxymethyl group at C-6, was accomplished in excellent yield by using Triton B as the catalytic base, and hydrogen peroxide or *tert*-butyl hydroperoxide as alternative oxidants that delivered the epoxides with complementary facial stereoselectivities. However, enone (+)-**4** remained unchanged when it was subjected to any of these oxidation conditions. Considering that this lack of reactivity could be associated with the acidity of the hydroxy proton, the alcohol was converted into the corresponding acetate. The acetate group is present in some of the target compounds, and it is a protecting group orthogonal to the silyl ether. Despite this modification, to obtain a satisfactory conversion in the epoxidation of acetate (+)-**5**, it was necessary to use a stoichiometric amount of base. After this adjustment, oxid-



Scheme 1. Diversity-oriented approach to gabosines and anhydrogabosines. TBS = *tert*-butyldimethylsilyl.

ation with *tert*-butyl hydroperoxide gave a unique stereoisomer of the epoxide, identified as (–)-**6**, in 76 % yield; epoxidation with hydrogen peroxide gave a 1:5 mixture of diastereomers (–)-**6**/(+)-**7** in 74 % isolated yield. The observed facial selectivities are consistent with those we previously found for the analogous methyl substrates.[9b]



Scheme 2. Preparation of key intermediate (–)-**9**.

The relative configurations of **6** and **7** were inferred from their ^{1}H NMR spectra, with the pattern of the signal due to H-4 being particularly characteristic. For isomer **6**, H-4 (δ = 4.54 ppm) shows identical coupling constant values of 3.1 Hz with the H-3 proton (δ = 3.58 ppm) and the two H-5 protons (δ = 2.33 and 2.01 ppm). These data are consistent with a pseudo-equatorial orientation of H-4 and, hence, a pseudo-axial location of the acetoxymethyl and silyloxy substituents (Figure 2). The *trans* relationship between this last group and the oxirane oxygen atom is confirmed by a 1.0 Hz long-range coupling between the coplanar H-3 and H-5 protons. For isomer **7**, H-4 (δ = 4.66 ppm) shows a coupling constant of 10.8 Hz with one of the H-5 protons (δ = 2.40 ppm), 5.3 Hz with the other H-5 proton (δ = 1.83 ppm), and 1.1 Hz with H-3 (δ = 3.60 ppm), consistent with a pseudo-axial orientation. The *cis* relationship between the oxirane oxygen atom and the silyloxy group in **7** is consistent with a 1.1 Hz long-range coupling between H-3 and the pseudo-equatorial H-5 proton. According to the generally accepted mechanism, the first step in these epoxidation reactions is the attack of the peroxide anion onto the β-carbonyl position of the double bond to form an enolate, and this is followed by a 3-*exo*-*tet* cyclization that forms the oxirane. It seems reasonable that the bulky *tert*-butyl peroxide approaches the double bond by the face opposite the bulky TBSO group at C-4. Conversely, the attack of the small hydroperoxide anion may be preferentially oriented by the formation of a hydrogen bond with the TBSO group, giving the opposite diastereoisomer as the major product.

When epoxide (–)-**6** was submitted to the oxidation–elimination protocol by treatment with MCPBA (*m*-chloroperbenzoic acid) in refluxing chloroform, isolation of the corresponding enone (i.e., **8**) was troublesome, because its polarity was very similar to that of *m*-chlorobenzoic acid. Consequently, the next desilylation step was attempted without purification of the intermediate. The reaction with TBAF in THF[9a,9c,9d] led only to decomposition products, but treatment of crude enone **8** with the complex $Et_3N{\cdot}3HF$[9b] proceeded to conveniently deliver free alcohol (–)-**9** in 80 % isolated yield over the two steps.

Alcohol **9** was recognized as an immediate synthetic precursor of the secondary metabolites epiepoxydon and phyllostine (Scheme 3). Actually, the synthesis of racemic acetate (±)-**9** has been described previously by acetylation of (±)-epiepoxydon.[15] (+)-Epiepoxydon, isolated from various microorganisms,[16] has shown antibiotic and antifungal activities,[16b,16c] β-1,3-glucanase inhibition,[16e] and strong cytotoxicity against several human cancer cell lines.[16g] Several syntheses of racemic epiepoxydon[15,17] and the dextrorotatory enantiomer[18] have been reported, but, to the best of our knowledge, the levorotatory enantiomer has never been prepared before. It has been reported that epiepoxydon is unstable even to weak bases,[15] and hence the hydrolysis of acetate (–)-**9** had to be carried out under acidic or neutral conditions. Our best results were obtained by treatment of (–)-**9** with acrylic-resin-supported *C. antarctica* lipase B (CALB) in diisopropyl ether saturated with water. Under these conditions, (–)-epiepoxydon was isolated in 75 % yield {$[\alpha]_D^{20}$ = –253 (*c* = 1.23, EtOH)}. (–)-Phyllostine, which is a tumor inhibitor,[19] has also been isolated from several microorganisms,[16h,16i,19,20] occasionally along with (+)-epiepoxydon. Several syntheses of the racemate[17a,17b,21] and the levorotatory enantiomer[18a,18b,18c,22] and one synthesis of

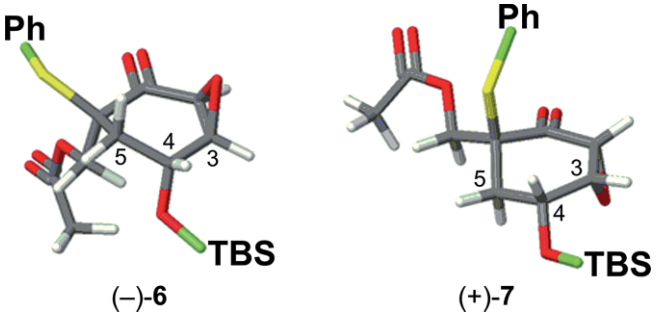
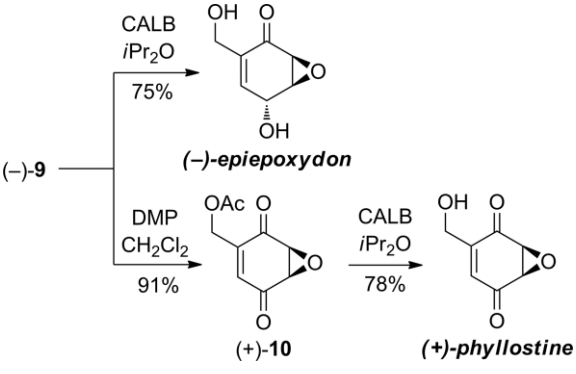


Figure 2. Preferred conformers of (–)-**6** and (+)-**7**.

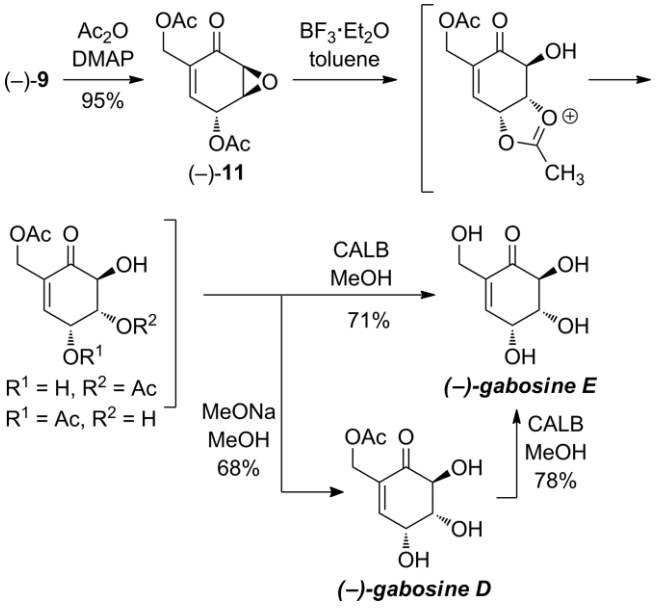


Scheme 3. Synthesis of (–)-epiepoxydon and (+)-phyllostine.

(+)-phyllostine[22a] have been reported previously. Oxidation of (–)-**9** with the Dess–Martin periodinane (DMP), followed by hydrolysis of the acetate gave (+)-phyllostine in 71 % overall yield {$[\alpha]_D^{20}$ = +117 (*c* = 0.86, EtOH)}.

To complete the synthesis of gabosines D and E from **9**, it was necessary to convert the epoxide into the corresponding *trans*-diol. In related systems, this transformation was accomplished through a BF_3·Et_2O-mediated and acetate-assisted process.[9b,23]

Accordingly, diacetate (–)-**11** was prepared by reaction of monoacetate (–)-**9** with acetic anhydride and DMAP [4-(dimethylamino)pyridine]. It was then treated with BF_3·Et_2O in toluene (Scheme 4). This reaction gave a mixture of diacetates that, without separation, was submitted to methanolysis. Unexpectedly, treatment of this mixture with sodium methoxide in methanol resulted in the selective deacetylation of the secondary acetates, delivering (–)-gabosine D in 68 % yield over the two steps {$[\alpha]_D^{20}$ = –85 (*c* = 0.95, MeOH)}. This observed chemoselectivity is remarkable, since the selective deprotection of polyacetylated carbohydrate derivatives usually requires more sophisticated reagents.[24] In a complementary approach, methanolysis in the presence of CALB led to full deacetylation, giving (–)-gabosine E in 71 % overall yield {$[\alpha]_D^{20}$ = –147 (*c* = 1.02, MeOH)}. Under identical conditions, (–)-gabosine D was transformed into (–)-gabosine E in 78 % yield.



Scheme 4. Synthesis of (–)-gabosine D and (–)-gabosine E.

Conclusions

We have presented new syntheses of (–)-gabosine D, (–)-gabosine E, and (+)-phyllostine, and the first synthesis of (–)-epiepoxydon, all starting from a common intermediate (–)-**9**. These syntheses form part of a general divergent approach that also allows the preparation of the respective antipodes. Acetate (–)-**9** was prepared in five steps and 53 % yield from chiral substrate (4*R*,6*S*)-**3**, which is available on a multigram scale and in either enantiomeric form through a short sequence starting from *p*-methoxyphenol and involving a crucial enzymatic resolution step. All the previously reported enantioselective syntheses of gabosines D and E started from natural chiral-pool materials and were thus directed to a particular enantiomer of the target compound. In this work, the total syntheses of (–)-gabosines D and E were both completed in eight steps and 36 % overall yield from (4*R*,6*S*)-**3**. The first synthesis of (–)-epiepoxydon and a new synthesis of (+)-phyllostine were accomplished starting from (4*R*,6*S*)-**3**, in six and seven steps and 40 and 38 % overall yields, respectively.

Experimental Section

General Remarks: All commercially available reagents and solvents were used as purchased from suppliers without further purification. Thin-layer chromatography (TLC) was carried out on 0.20 mm plates Alugram® Sil G/UV_{254}. TLC spots were visualized with UV light or with an anisaldehyde stain. Chromatographic purification of products was carried out by flash chromatography using 230–400 mesh silica gel. ^{1}H NMR spectra were recorded with Bruker ARX400 (400 MHz) and DPX250 (250 MHz) spectrometers. Proton chemical shifts are reported in ppm ($CDCl_3$, δ = 7.26 ppm; CD_3OD, δ = 3.31 ppm; CD_3COCD_3, δ = 2.09 ppm). ^{13}C NMR spectra were recorded with Bruker ARX400 (100 MHz) and DPX250 (63 MHz) spectrometers. Carbon chemical shifts are reported in ppm ($CDCl_3$, δ = 77.16 ppm; CD_3OD, δ = 49.00 ppm; CD_3COCD_3, δ = 205.87 ppm). All spectra were recorded at 298 K. The abbreviations used to describe signal multiplicities are: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), ddt (doublet of doublet of triplets), and m (multiplet); *J* indicates the coupling constants. Infrared spectra were recorded with a Sapphire-ATR spectrophotometer. Peaks are reported in cm^{-1}. High-resolution mass spectra (HRMS) were recorded with a Bruker micrOTOF-Q spectrometer using electrospray ionization (Q-TOF). Specific optical rotations were measured with a Propol Automatisches Dr. Kermchen polarimeter at 20 ± 2 °C with an optical path length of 0.05 dm; or with a J-715 (Jasco) polarimeter with a temperature regulator, using a 0.1 dm long cuvette. Melting points were determined with a Reichert Kofler hot-stage melting point apparatus.

(4*R*,6*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-hydroxymethyl-6-phenylthiocyclohexen-2-one [(+)-4]: A solution of *t*BuOK (1.6 g, 14.1 mmol) in THF (3.6 mL) was slowly added to a solution of enone (4*R*,6*S*)-**3** (4.3 g, 12.8 mmol) in THF (33 mL) at 0 °C. The mixture was stirred for 5 min, then formaldehyde (commercial 37 % aqueous solution with 10–15 % MeOH; 1.1 mL, 14.6 mmol) was slowly added. The resulting mixture was stirred at 0 °C for 45 min. Water (15 mL) was then added to the mixture, and it was slightly acidified with HCl (4 % aq.). The mixture was extracted with CH_2Cl_2 (4 × 15 mL), then the combined organic extracts were dried with $MgSO_4$, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (hexanes/EtOAc, 9:1) to give (+)-**4** (4.1 g, 88 %) as a yellow solid. M.p. 93–95 °C (hexanes/EtOAc). $[\alpha]_D^{20}$ = +123 (*c* = 1.09, $CHCl_3$). The spectroscopic data are identical to those described for (–)-**4**.[9c]

[(1*S*,5*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-oxo-1-(phenylthio)-cyclohex-3-en-1-yl]methyl Acetate [(+)-5]: Ac_2O (750 µL, 7.93 mmol) was added to a stirred solution of alcohol (+)-**4** (1.93 g, 5.28 mmol) in pyridine (50 mL), and the mixture was stirred overnight. Then, the volatiles were removed under vacuum to give ester

(+)-**5** (2.13 g, 99 %) as a liquid. R_f = 0.42 (hexane/EtOAc, 5:1). $[\alpha]_D^{20}$ = +46 (*c* = 1.05, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2953, 2930, 2856, 1743, 1680, 1377, 1225, 1068 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.43–7.30 (m, 5 H), 6.81 (dt, *J* = 10.3, *J* = 2.0 Hz, 1 H), 5.96 (dd, *J* = 10.3, *J* = 2.1 Hz, 1 H), 4.98 (ddt, *J* = 10.0, *J* = 5.4, *J* = 2.1 Hz, 1 H), 4.35 (d, *J* = 11.0 Hz, 1 H), 4.18 (d, *J* = 11.0 Hz, 1 H), 2.42 (dd, *J* = 13.8, *J* = 10.0 Hz, 1 H), 2.24 (ddd, *J* = 13.8, *J* = 5.4, *J* = 2.0 Hz, 1 H), 2.01 (s, 3 H), 0.93 (s, 9 H), 0.17 (s, 3 H), 0.14 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 191.4, 170.6, 152.7, 137.6, 130.3, 129.2, 127.7, 126.9, 66.2, 65.5, 55.4, 40.3, 25.9, 20.9, 18.3, –4.5, –4.6 ppm. HRMS (ESI^+): calcd. for $C_{21}H_{30}O_4SSiNa$ $[M + Na]^+$ 429.1526; found 429.1529.

[(1*S*,3*S*,5*R*,6*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-oxo-3-(phenylthio)-7-oxabicyclo[4.1.0]hept-3-yl]methyl Acetate [(–)-6]: Triton B (40 % in MeOH; 840 µL, 1.85 mmol) was added dropwise to an ice-cooled solution of enone (+)-**5** (605 mg, 1.69 mmol) and *t*BuOOH (70 % in water; 360 µL, 2.52 mmol) in THF (20 mL). The mixture was stirred for 30 min, then the reaction was quenched with water (10 mL), and the mixture was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 10:1 to 5:1) to give epoxide (–)-**6** (475 mg, 76 %) as a white solid. R_f = 0.74 (hexane/CH_2Cl_2, 1:9). M.p. 99–101 °C (hexanes/EtOAc). $[\alpha]_D^{20}$ = –86 (*c* = 1.13, $CDCl_3$). IR (ATR): $\tilde{\nu}$ = 2953, 2930, 2856, 1743, 1699, 1227, 1097, 1053, 1007 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.37 (m, 3 H), 7.35–7.29 (m, 2 H), 4.54 (q, *J* = 3.1 Hz, 1 H), 4.07 (d, *J* = 12.1 Hz, 1 H), 4.00 (dd, *J* = 12.1, *J* = 1.0 Hz, 1 H), 3.58 (ddd, *J* = 4.2, *J* = 3.1, *J* = 1.0 Hz, 1 H), 3.55 (d, *J* = 4.2 Hz, 1 H), 2.33 (ddd, *J* = 15.0, *J* = 3.1, *J* = 1.0 Hz, 1 H), 2.15 (s, 3 H), 2.01 (ddd, *J* = 15.0, *J* = 3.1, *J* = 1.0 Hz, 1 H), 0.84 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.5, 170.5, 137.8, 130.3, 129.1, 129.0, 66.8, 65.3, 59.4, 55.2, 53.0, 34.3, 25.7, 21.0, 18.1, –4.75, –4.78 ppm. HRMS (ESI^+): calcd. for $C_{21}H_{30}O_5SSiNa$ $[M + Na]^+$ 445.1535; found 445.1534.

[(1*R*,3*S*,5*R*,6*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-oxo-3-(phenylthio)-7-oxabicyclo[4.1.0]hept-3-yl]methyl Acetate [(+)-7]: Triton B (40 % in MeOH; 190 µL, 0.42 mmol) was added dropwise to an ice-cooled solution of enone (+)-**5** (154 mg, 0.38 mmol) and H_2O_2 (30 % in water; 59 µL, 0.57 mmol) in THF (5 mL). The mixture was stirred for 30 min, then the reaction was quenched with water (3 mL), and the mixture was extracted with CH_2Cl_2 (4 × 2 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 10:1 to 5:1) to give (–)-**6** (21 mg, 13 %) and (+)-**7** (97 mg, 61 %). Data for (+)-**7**: R_f = 0.44 (hexane/$CHCl_3$, 1:9). M.p. 75–78 °C (hexane/$CHCl_3$). $[\alpha]_D^{20}$ = +11 (*c* = 1.42, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2953, 2928, 2856, 1744, 1713, 1472, 1439, 1377, 1225, 1101, 1070, 1032 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.47–7.31 (m, 5 H), 4.66 (ddd, *J* = 10.8, *J* = 5.3, *J* = 1.1 Hz, 1 H), 4.17 (d, *J* = 11.1 Hz, 1 H), 4.12 (d, *J* = 11.1 Hz, 1 H), 3.60 (dt, *J* = 3.7, *J* = 1.1 Hz, 1 H), 3.43 (d, *J* = 3.7 Hz, 1 H), 2.40 (dd, *J* = 13.9, *J* = 10.8 Hz, 1 H), 2.02 (s, 3 H), 1.83 (ddd, *J* = 13.9, *J* = 5.3, *J* = 1.1 Hz, 1 H), 0.95 (s, 9 H), 0.18 (s, 3 H), 0.15 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 193.5, 170.6, 137.9, 130.7, 129.4, 127.3, 65.6, 64.9, 57.6, 55.8, 53.9, 31.7, 25.9, 20.9, 18.3, –4.45, –4.51 ppm. HRMS (ESI^+): calcd. for $C_{21}H_{30}O_5SSiNa$ $[M + Na]^+$ 445.1535; found 445.1537.

[(1*S*,5*R*,6*R*)-5-Hydroxy-2-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]methyl Acetate [(–)-9]: A solution of MCPBA (132 mg, 0.65 mmol) in $CHCl_3$ (4 mL) was added dropwise to a stirred solution of (–)-**6** (230 mg, 0.54 mmol) in $CHCl_3$ (6 mL) at reflux temperature. The mixture was stirred for 1 h; then the solvent was removed under reduced pressure. The residual white solid was dissolved in THF (10 mL), and $Et_3N{\cdot}3HF$ (100 µL, 0.61 mmol) was added. The mixture was stirred overnight. Then, water was added (4 mL), and the mixture was neutralized with Na_2CO_3 (saturated aq. solution). The mixture was extracted with CH_2Cl_2 (4 × 5 mL), and the combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 1:1) to give alcohol (–)-**9** (103.0 mg, 80 %) as an oil. R_f = 0.18 (hexane/EtOAc, 1:1). $[\alpha]_D^{20}$ = –177 (*c* = 0.86, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3435, 2955, 2924, 2852, 1740, 1684, 1439, 1373, 1231, 1032 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.62 (ddt, *J* = 4.8, *J* = 2.6, *J* = 1.4 Hz, 1 H), 4.79 (dd, *J* = 13.6, *J* = 1.4 Hz, 1 H), 4.73–4.66 (m, 2 H), 3.80 (ddd, *J* = 3.7, *J* = 2.6, *J* = 1.2 Hz, 1 H), 3.50 (dd, *J* = 3.7, *J* = 1.2 Hz, 1 H), 3.16 (br. s, 1 H), 2.08 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.7, 171.0, 140.3, 132.5, 63.0, 60.6, 57.8, 53.4, 20.9 ppm. HRMS (ESI^+): calcd. for $C_9H_{10}O_5Na$ $[M + Na]^+$ 221.0420; found 221.0417.

(–)-Epiepoxydon: Acrylic-resin-supported *C. antarctica* lipase B (2 mg) was added to a stirred solution of acetate (–)-**9** (15 mg, 0.08 mmol) in *i*Pr_2O saturated with water (2 mL) at room temperature. The mixture was stirred for 3 d; then the enzyme was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc) to give the epoxide (–)-epiepoxydon (9 mg, 75 %) as an oil. R_f = 0.25 (hexane/EtOAc, 1:2). $[\alpha]_D^{20}$ = –253 (*c* = 1.23, EtOH) {ref.[16a] $[\alpha]_D^{20}$ = +194 (*c* = 1.57, EtOH), ref.[16d] $[\alpha]_D^{20}$ = +261 (*c* = 1, MeOH) for the antipode}. IR (ATR): $\tilde{\nu}$ = 3343, 1676, 1240, 1020 cm^{-1}. ^1H NMR (400 MHz, CD_3COCD_3): δ = 6.71 (m, 1 H), 4.91 (d, *J* = 7.4 Hz, 1 H), 4.65 (m, 1 H), 4.29–4.10 (m, 3 H), 3.77 (m, 1 H), 3.41 (d, *J* = 3.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 194.1, 139.1, 137.0, 63.3, 59.1, 58.8, 54.2 ppm. HRMS (ESI^+): calcd. for $C_7H_6O_4Na$ $[M + Na]^+$ 179.0318; found 179.0322.

[(1*S*,6*R*)-2,5-Dioxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl]methyl Acetate [(+)-10]: Dess–Martin periodinane (15 % in CH_2Cl_2; 0.3 mL, 0.14 mmol) was added dropwise to a solution of alcohol (–)-**9** (21 mg, 0.11 mmol) in CH_2Cl_2 (2 mL), and the reaction mixture was stirred at room temperature for 2 h. A 1:1 mixture of saturated aqueous $NaHCO_3/Na_2S_2O_3$ (0.1 M) (1 mL) was added. The mixture was stirred for 1 h; then the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 2:1) gave (+)-**10** (20 mg, 91 %). R_f = 0.58 (hexane/EtOAc, 1:1). $[\alpha]_D^{20}$ = +110.5 (*c* = 1.17, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3051, 2928, 1743, 1686, 1628, 1371, 1219, 1045, 1005 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.54 (q, *J* = 1.9 Hz, 1 H), 4.98 (dd, *J* = 17.0, *J* = 1.9 Hz, 1 H), 4.83 (dd, *J* = 17.0, *J* = 1.9 Hz, 1 H), 3.87 (d, *J* = 3.7 Hz, 1 H), 3.84 (dd, *J* = 3.7, *J* = 1.9 Hz, 1 H), 2.14 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.9, 190.8, 170.0, 143.9, 131.7, 59.6, 54.2, 54.1, 20.8 ppm. HRMS (ESI^+): calcd. for $C_9H_8O_5Na$ $[M + Na]^+$ 219.0264; found 219.0263.

(+)-Phyllostine: Acrylic-resin-supported *C. antarctica* lipase B (2 mg) was added to a stirred solution of acetate (+)-**10** (17 mg, 0.09 mmol) in *i*Pr_2O saturated with water (2 mL) at room temperature. The mixture was stirred for 3 d; then the enzyme was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc) to give the epoxide (+)-phyllostine (11 mg, 78 %) as an oil. R_f = 0.46 (hexane/EtOAc, 1:2). $[\alpha]_D^{20}$ = +117 (*c* = 0.86, EtOH) {ref.[19] $[\alpha]_D^{20}$ = –106 (*c* = 1, EtOH) for the antipode}. IR (ATR): $\tilde{\nu}$ = 3350, 1802, 1736, 1685 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.67 (q, *J* = 1.9 Hz, 1 H), 4.57 (dd, *J* = 17.3, *J* = 1.9 Hz, 1 H), 4.39 (dd, *J* = 17.3, *J* = 1.9 Hz, 1 H), 3.85–3.82 (m, 2 H), 2.15 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.7, 190.8, 147.6, 130.8, 59.2, 54.0 (2 C) ppm. HRMS (ESI^+): calcd. for $C_7H_6O_4Na$ $[M + Na]^+$ 177.0158; found 177.0162.

(1*S*,2*R*,6*S*)-5-Oxo-7-oxabicyclo[4.1.0]hept-3-ene-2,4-diyl Diacetate [(–)-11]: DMAP (56 mg, 0.46 mmol) and acetic anhydride (45 μL, 0.48 mmol) were added to a solution of alcohol (–)-**9** (84 mg, 0.42 mmol) in $CHCl_3$ (10 mL) at 0 °C. The reaction mixture was stirred for 15 min; and then it was poured into ice-cooled water (10 mL). The mixture was extracted with $CHCl_3$ (5 × 5 mL). The combined organic extracts were dried with $MgSO_4$, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 2:1) gave (–)-**11** (96 mg, 95 %). R_f = 0.48 (hexane/EtOAc, 1:1). $[\alpha]_D^{20}$ = –258 (*c* = 1.50, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2928, 2854, 1738, 1689, 1371, 1217, 1026 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 6.56 (ddt, *J* = 5.0, *J* = 2.5, *J* = 1.6 Hz, 1 H), 5.82 (dq, *J* = 5.0, *J* = 1.1 Hz, 1 H), 4.80–4.77 (m, 2 H), 3.75 (ddd, *J* = 3.7, *J* = 2.5, *J* = 1.1 Hz, 1 H), 3.55 (dd, *J* = 3.7, *J* = 1.1 Hz, 1 H), 2.14 (s, 3 H), 2.09 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 191.9, 170.3, 169.8, 135.4, 134.9, 64.1, 60.4, 55.3, 53.0, 20.9, 20.8 ppm. HRMS (ESI^+): calcd. for $C_{11}H_{12}O_6Na$ $[M + Na]^+$ 263.0526; found 263.0529.

(–)-Gabosine D: BF_3•Et_2O (48 μL, 0.36 mmol) was added to an ice-cooled solution of diacetate (–)-**11** (87 mg, 0.36 mmol) in toluene (10 mL), and the mixture was stirred for 1 h. Then, the reaction mixture was warmed to room temperature, and stirring was continued for a further 2 h. Water (10 mL) was added, the organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 5 mL). The combined organic extracts were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (hexanes/EtOAc, 1:2) to give an inseparable mixture of diacetates (77 mg), which was used in the next step. NaOMe (12 mg, 0.22 mmol) was added to a solution of this mixture (55 mg) in MeOH (4 mL), and the mixture was stirred at room temperature for 3 h. Then, the solvent was removed under reduced pressure. The residue was diluted with water (2 mL) and slightly acidified with HCl (2 % aq.). The aqueous solution was extracted with CH_2Cl_2 (4 × 2 mL), the combined organic extracts were dried with $MgSO_4$, and the solvent was evaporated under vacuum. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH, 9:1) gave (–)-gabosine D (38 mg, 68 % over two steps) as a white crystalline solid. R_f = 0.32 ($CHCl_3$/MeOH, 9:1). $[\alpha]_D^{20}$ = –85 (*c* = 0.95, MeOH) {ref.[3b] $[\alpha]_D^{20}$ = +86 (*c* = 1, MeOH) for the antipode}. IR (ATR): $\tilde{\nu}$ = 3345, 2890, 1761, 1692 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 6.92 (dd, *J* = 1.2, *J* = 5.3 Hz, 1 H), 4.73 (m, 2 H), 4.48 (ddd, *J* = 5.3, *J* = 4.1, *J* = 1.2 Hz, 1 H), 4.33 (d, *J* = 9.6 Hz, 1 H), 3.78 (dd, *J* = 9.6, *J* = 4.1 Hz, 1 H), 2.05 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 198.7, 172.2, 144.7, 135.1, 75.1, 73.8, 67.0, 61.5, 20.6 ppm. HRMS (ESI^+): calcd. for $C_7H_6O_4Na$ $[M + Na]^+$ 239.0524; found 239.0523.

(–)-Gabosine E. From the Mixture of Acetates: Acrylic-resin-supported *C. antarctica* lipase B (1 mg) was added to a stirred solution of a mixture of the diacetates prepared as described in the preceding section (15 mg) in MeOH (1 mL). The mixture was stirred at room temperature for 5 d; then the enzyme was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 9:1) to give (–)-gabosine E (9 mg, 71 % over two steps) as a white crystalline solid. R_f = 0.15 ($CHCl_3$/MeOH, 9:1). $[\alpha]_D^{20}$ = –147 (*c* = 1.02, MeOH) {ref.[3b] $[\alpha]_D^{20}$ = +148 (*c* = 0.95, MeOH) for the antipode}. IR (ATR): $\tilde{\nu}$ = 3330, 2932, 1690 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 6.91 (dt, *J* = 5.4, *J* = 1.2 Hz, 1 H), 4.48 (m, 1 H), 4.34 (d, *J* = 9.8 Hz, 1 H), 4.25 (dd, *J* = 15.4, *J* = 1.2 Hz, 1 H), 4.21 (dd, *J* = 15.4, *J* = 1.2 Hz, 1 H), 3.76 (dd, *J* = 9.8, *J* = 3.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 199.6, 141.8, 139.9, 75.0, 73.8, 67.0, 59.5 ppm. HRMS (ESI^+): calcd. for $C_7H_6O_4Na$ $[M + Na]^+$ 197.0419; found 197.0423. **From (–)-Gabosine D:** Acrylic-resin-supported *C. antarctica* lipase B (1 mg) was added to a stirred solution of (–)-gabosine D (20 mg, 0.09 mmol) in MeOH (1 mL). The mixture was stirred at room temperature for 4 d; then the enzyme was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 9:1) to give (–)-gabosine E (12 mg, 78 %) as a white crystalline solid.

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