FULL PAPER

Filling some blanks on a diversity-oriented approach to gabosines: Enantioselective synthesis of (–)-epiepoxydon, (+)-phyllostine, (–)-gabosine D and (–)-gabosine E

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Abstract: The levorotatory antipodes of gabosines D and E were synthesized through a diversity-oriented approach that can be equally applied to the synthesis of the dextrorotatory enantiomers, isolated from natural sources. The approach relays on an initial desymmetrization of *p*-methoxyphenol followed by an enzymatic resolution that provides separately the two enantiomers of synthon **3**. This versatile synthon can be further elaborated to the diverse, targeted polyoxygenated cyclohexanes. Key steps of the synthesis of (–)-gabosines D and E from (4*R*,6*S*)-**3** are the stereoselective hydromethylation 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 allowed to synthesize also the anhydrogabosines (–)-epiepoxydon and (+)-phyllostine,

Introduction

Carbasugars present a wide variety of biological activities, such as glicosidase inhibition, antitumor, antiviral, antifungal, antibacterial and antimalarial. For this reason, their synthesis is of great importance in the discovery of new drugs, including cancer prevention agents.[1] Faced with the challenge of discovering new medicines, the absence of the shikimic acid biogenetic route in mammals increases the chances of succes if the effort is focussed on its analogues.[2] Within these analogues, gabosines form a family of secondary metabolites isolated from various *Streptomyces* strains, which can be considered a particular carbasugar subcategory.[3] Gabosines have been classified in four structural types, all of them presenting a polyoxygenated methylcyclohexane as common constitutional feature (Figure 1). Their structural diversity stems from the substituent position, unsaturation degree and/or relative and absolute configuration of their stereogenic centers.[4] In gabosines of types I and III, the methyl or hydroxymethyl appendage is located at the α-carbonyl position, while in those of type II it is attached to the β-carbonyl atom. 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 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 the colesterol biosynthesis[3b] and several gabosines present DNA binding properties.[3d]

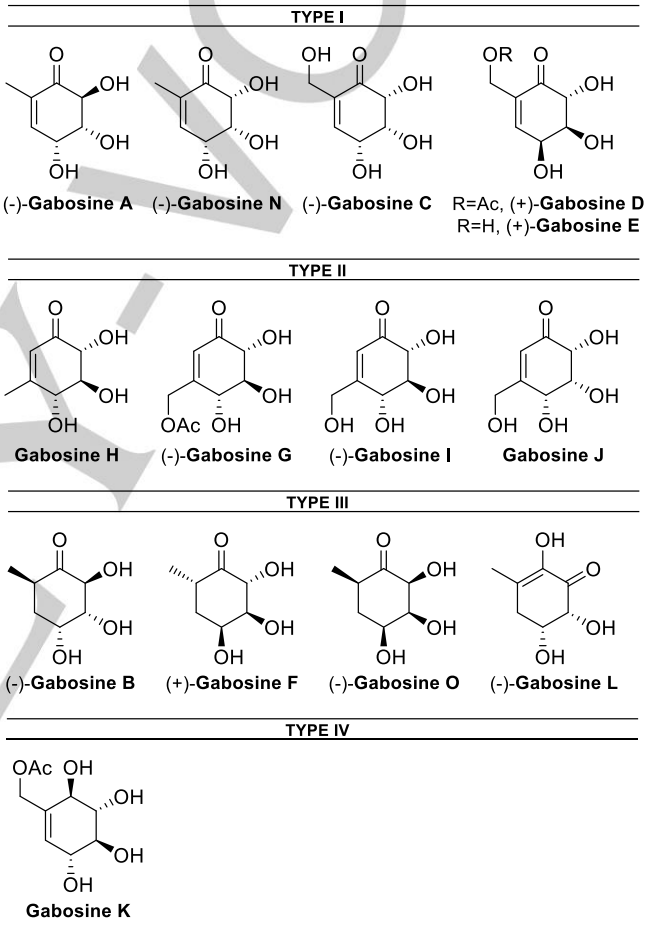

Figure 1. Structural classification of gabosines.

Recently, 4-*O*-decyl-gabosine D has been identified as a glutathione S-transferase inhibitor, displaying an optimum synergetic effect in combination with cisplatin against A549 human lung cancer cell line.[6]There are also some known epoxyquinone derivatives, most of them isolated from fungi, with anhydrogabosine structure.[4,7] Formally, the hydrolysis of the epoxide functionality on one of these compounds should furnish a gabosine, although this transformation is generally less straightforward than expected. In the last decades, extensive work has been published dealing with the synthesis of gabosines and anhydrogabosines, motivated not only by their promising biological activities, but also by the fact that the extremely

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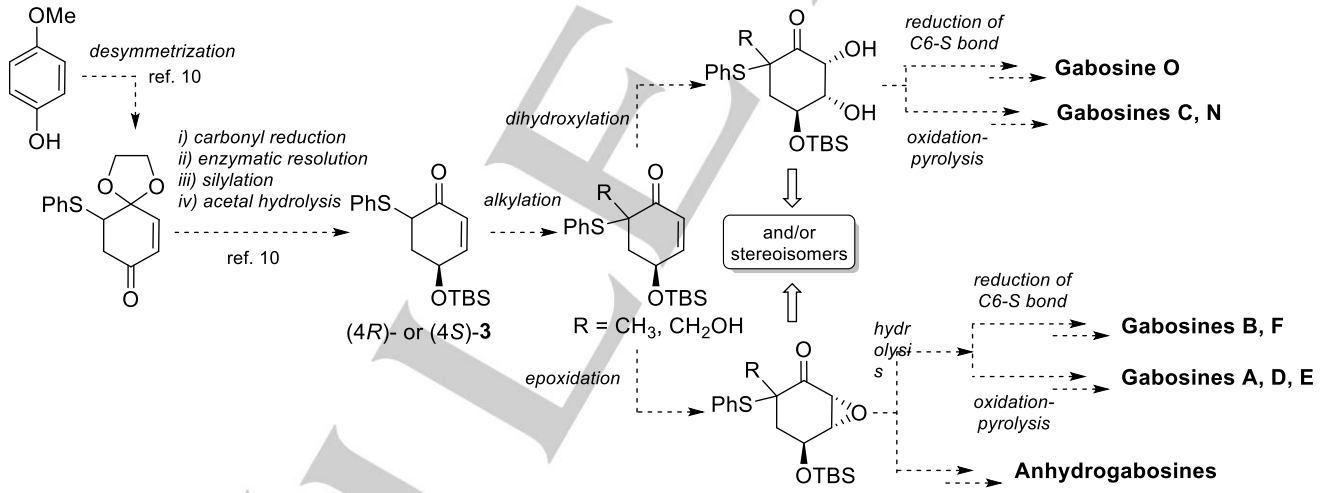
crowded functionalization of these small molecules makes them highly challenging synthetic targets.[4,8] The published synthetic strategies include biomimetic approaches, Diels-Alder methodology, desymmetrization of benzene or cyclohexanedione derivatives and chiral pool synthesis, mainly starting from carbohydrates or quinic acid. In our laboratories, we have been developing a project, which was devised to prepare a large number of these compounds in any antipodal form, from a common intermediate. In precedent 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 epimers of them, and the anhydrogabosines epiepoformin and epoformin.[9] Herein we present a new contribution to this field by disclosing new syntheses of (–)-gabosine D, (–)-gabosine E, (–)-epiepoxydon and (+)-phyllostine.

Results and Discussion

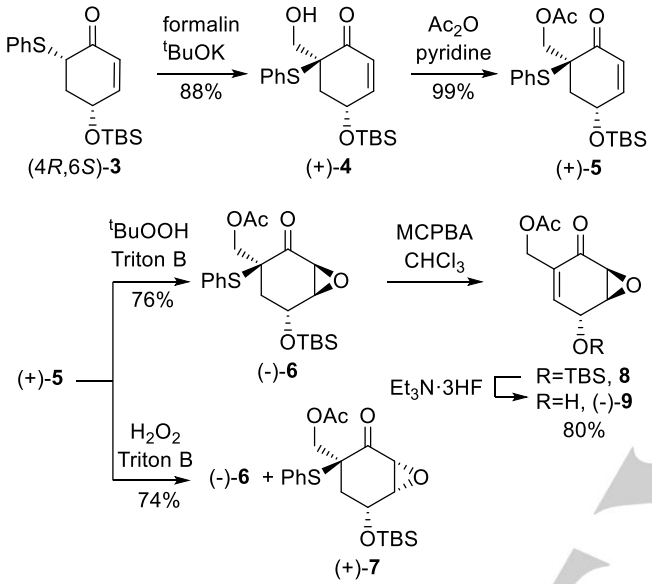
Our diversity-oriented proposal to gabosines and analogues is depicted in Scheme 1, where ketone **3** is the common starting material. This ketone is conveniently prepared from *p*-methoxyphenol in several gram scale and equally available for any configuration at C-4.[10] The double activated C-6 position of **3** can be conveniently alkylated (introduction of a methyl or hydroxymethyl group) and, then, the conjugated carbon-carbon double bond oxidized (dihydroxylation or epoxidation). Depending on the specific target, the sulfur residue may by 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 their dense functionalization and specific stereochemistry cause differences in the reactivity of similar intermediates. 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 in the type I subgroup. All the previously described syntheses of gabosines D and E started from chiral pool materials, more specifically, the natural, dextrorotatory antipodes 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 the starting ketone **3** is available in any configuration at C-4, this sequence of reactions is equally applicable to synthesize any enantiomer of the final gabosine.



Scheme 1. Diversity-oriented approach to gabosines and anhydrogabosines.

Conversion of enone (4*R*,6*S*)-**3** to the hydroxymethyl derivative (+)-**4** was accomplished in 88% yield by reaction with potassium *tert*-butoxide and formalin, as previously described 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 instead of a hydroxymethyl group at C-6, had been accomplished in excellent yield by using Triton B as the catalytic base and hydrogen peroxide or *tert*-butyl hydroperoxide as alternative oxidants, which delivered the epoxides with complementary facial stereoselectivities. However, enone (+)-**4** remained unchanged when submitted to any of these oxidation conditions. Considering that this lack of reactivity could be associated to the acidity of the hydroxyl proton, the alcohol was converted into the corresponding acetate. The acetate group is present in some of the target compounds and it provides a protection orthogonal to the silyl ether. Despite this modification,

to get a satisfactory conversion in the epoxidation of the acetate (+)-**5** it was necessary to use a stoichiometric amount of base. After this adjustment, the oxidation with *tert*-butyl hydroperoxide provided a unique stereoisomer of the epoxide, identified as (–)-**6**, in 76% yield, while the epoxidation with hydrogen peroxide furnished a 1:5 mixture of diastereomers (–)-**6** and (+)-**7**, respectively, in 74% isolated yield. The observed facial selectivities are consistent with those previously found in the analogous methyl substrates.[9b]



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

The relative configuration of **6** and **7** was inferred from their ^{1}H NMR spectra, being particularly illustrative the pattern of the signal corresponding to H-4. For isomer **6**, H-4 (δ 4.54) presents identical coupling constant values of 3.1 Hz with proton H-3 (δ 3.58) and the two protons H-5 (δ 2.33 and 2.01). This data are in agreement with a pseudo-equatorial orientation of H-4 and, hence, 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 distance coupling between the coplanar H-3 and H-5. For isomer **7**, H-4 (δ 4.66) shows a coupling constant of 10.8 Hz with one of the protons H-5 (δ 2.40), 5.3 Hz with the other H-5 (δ 1.83) and 1.1 Hz with H-3 (δ 3.60), consistent with a pseudo-axial orientation. The *cis* relationship between the oxirane oxygen and the silyloxy group in **7** is in agreement with a 1.1 Hz long distance coupling between H-3 and the pseudo-equatorial H-5. According to the generally accepted mechanism, the first step in these epoxidation reactions is the attack of the peroxide anion to the β-carbonyl position of the double bond to form an enolate, followed by a 3-*exo-tet* cyclization that originates the oxirane. It seems reasonable that the bulky *tert*-butylperoxide approaches the double bond by the face contrary to 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 major product.

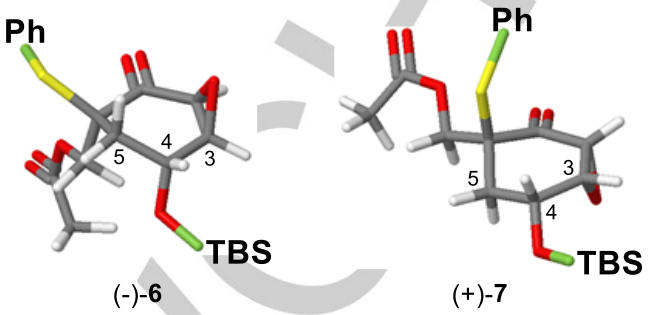
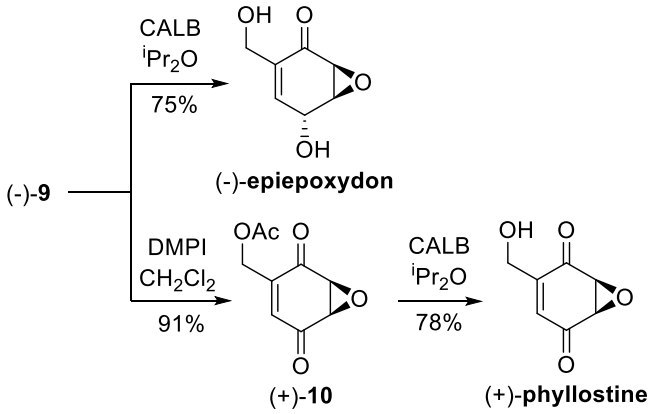


Figure 2. Preferred conformer of (–)-**6** and (+)-**7**.

When epoxide (–)-**6** was submitted to the oxidation-elimination protocol by treatment with MCPBA in refluxing chloroform, the isolation of the corresponding enone **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,c,d] led only to decomposition products, but treatment of the crude enone **8** with the complex $Et_3N{\cdot}3HF$[9b] proceeded conveniently to deliver the free alcohol (–)-**9** in 80% isolated yield for the two steps.

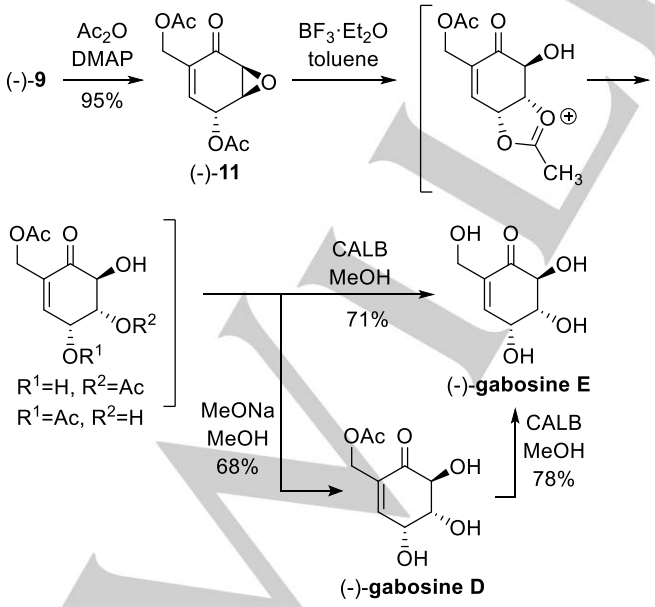
Alcohol **9** was recognized as an immediate synthetic precursor of the secondary metabolites epiepoxydon and phyllostine (Scheme 3). Actually, the synthesis of the racemic acetate (±)-**9** had been previously described by acetylation of (±)-epiepoxydon.[15] (+)-Epiepoxydon, isolated from various microorganisms,[16] has shown antibiotic and antifungal activity,[16b,c] β-1,3-glucan inhibition,[16e] and strong cytotoxicity against several human cancer cell lines.[16g] Several syntheses of racemic epiepoxydon[15,17] and the dextrorotatory antipode[18] have been reported, but, to the best of our knowledge, the levorotatory enantiomer had never been prepared. It was described that epiepoxydon is unstable even to weak bases[15] and, hence, the hydrolysis of the acetate (–)-**9** had to be performed under acidic or neutral conditions. Our best results were obtained by treatment of (–)-**9** with lipase acrylic resin from *C. Antarctica* (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,i,19,20] occasionally along with (+)-epiepoxydon. Several syntheses of the racemate[17a,b,21] and the levorotatory enantiomer[18a,b,c,22] and one synthesis of (+)-phyllostine[22a] had been reported. Oxidation of (–)-**9** with the Dess-martin periodinane, followed by hydrolysis of the acetate furnished (+)-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 $BF_3{\cdot}Et_2O$ mediated and acetate-assisted process.[9b,23]



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

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



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

Conclusions

In summary, herein we have presented new syntheses of (–)-gabosine D, (–)-gabosine E and (+)-phyllostine and the first synthesis of (–)-epiepoxydon from a common intermediate (–)-**9**, as part of a general diversity-oriented approach that enables the preparation of the respective antipodes as well. The acetate (–)-**9** was prepared in 5 steps and 53% yield from the chiral substrate (4*R*,6*S*)-**3**, which is available in several gram scale and any antipodal form through a short sequence starting from *p*-methoxyphenol and involving a crucial enzymatic resolution step. All the enantioselective syntheses of gabosines D and E previously described started from natural chiral pool materials, involved at least 11 steps, and their total yields oscillated between 5% and 18%. In the present work, the total syntheses of (–)-gabosine D and E were both completed in 8 steps and 36% overall yield from (4*R*,6*S*)-**3**. The first synthesis of (–)-epiepoxydon and a new synthesis of (+)-phyllostine have been accomplished from (4*R*,6*S*)-**3** in 6 and 7 steps and 40% and 38% total yield, respectively.

Experimental Section

General: All commercially available reagents and solvents were used as purchased from suppliers without further purification. Thin-layer chromatography (TLC) was performed on 0.20 mm thin plates Alugram® Sil G/UV_{254}. Visualization TLC spots was performed by UV light or by anisaldehyde stain. Chromatographic purification of products was accomplished by flash chromatography using 230-400 mesh silica gel. ^{1}HNMR spectra were recorded on Bruker ARX400 (400 MHz) or DPX250 (250 MHz) spectrometers. Proton chemical shifts are reported in ppm ($CDCl_3$, δ 7.26 ppm; CD_3OD, 3.31 ppm; CD_3COCD_3, 2.09 ppm). ^{13}CNMR spectra were recorded on Bruker ARX400 (100 MHz) or DPX250 (63 MHz) spectrometers. Carbon chemical shifts are reported in ppm ($CDCl_3$, δ 77.16 ppm; CD_3OD, 49.00 ppm; 205.87 CD_3COCD_3, ppm). All spectra have been registered at 298K. The abbreviation used to describe signals multiplicities are: s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), ddd (double double doublet), dt (double triplet), ddt (double double triplet), m (multiplet) and J to indicate the coupling constants. Infrared spectra were recorded on a Sapphire-ATR spectrophotometer. Peaks are reported in cm^{-1}. High resolution mass spectra (HRMS) were recorded in a Bruker micrOTOF-Q spectrometer using ESI-MS (Q-TOF). Specific optical rotation was measured on a Propol Automatisches Dr. Kermchen polarimeter at 20 ± 2 °C through a 0.05 dm optical path length or on a J-715 (Jasco) polarimeter with temperature regulator, using a 0.1 dm long cuvette. $[\alpha]_D^{20}$ are given in 10^{-1} deg cm^2 g^{-1}. Melting points were determined on a REICHERT Koffler hot stage melting point apparatus, and are uncorrected.

(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. After stirring for 5 min, formaldehyde (commercial 37% aqueous solution with 10-15% MeOH, 1.1 mL, 14.6 mmol) was slowly added. The resulting mixture was stirred for 45 min at 0 °C. Water (15 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 x 15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (hexanes/EtOAc, 9:1) affording (+)-**4** as a yellow solid (4.1 g, 88%); m.p.

93-95 °C (hexanes/EtOAc); $[\alpha]_D^{20}$ = +123 (*c* 1.09, $CHCl_3$). The spectroscopic data were 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 affording 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): 2953, 2930, 2856, 1743, 1680, 1377, 1225, 1068 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.43-7.30 (m, 5H), 6.81 (dt, *J* = 10.3 Hz, *J* = 2.0 Hz, 1H), 5.96 (dd, *J* = 10.3 Hz, *J* = 2.1 Hz, 1H), 4.98 (ddt, *J* = 10.0 Hz, *J* = 5.4 Hz, *J* = 2.1 Hz, 1H), 4.35 (d, *J* = 11.0 Hz, 1H), 4.18 (d, *J* = 11.0 Hz, 1H), 2.42 (dd, *J* = 13.8 Hz, *J* = 10.0 Hz, 1H), 2.24 (ddd, *J* = 13.8 Hz, *J* = 5.4 Hz, *J* = 2.0 Hz, 1H), 2.01 (s, 3H), 0.93 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H) 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 $C_{21}H_{30}O_4SSiNa$ 429.1526 $[M + Na]^+$; 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 ^tBuOOH (70% in water, 360 µL, 2.52 mmol) in THF (20 mL). After 30 min stirring, the reaction was quenched with water (10 mL) and the organics were extracted with CH_2Cl_2 (4 x 5 mL). The combined organics extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 10:1 to 5:1) to furnish a white solid identified as epoxide (–)-**6** (475 mg, 76%); 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): 2953, 2930, 2856, 1743, 1699, 1227, 1097, 1053, 1007 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.37 (m, 3H), 7.35-7.29 (m, 2H), 4.54 (q, *J* = 3.1 Hz, 1H), 4.07 (d, *J* = 12.1 Hz, 1H), 4.00 (dd, *J* = 12.1 Hz, *J* = 1.0 Hz, 1H), 3.58 (ddd, *J* = 4.2 Hz, *J* = 3.1 Hz, *J* = 1.0 Hz, 1H), 3.55 (d, *J* = 4.2 Hz, 1H), 2.33 (ddd, *J* = 15.0 Hz, *J* = 3.1 Hz, *J* = 1.0 Hz, 1H), 2.15 (s, 3H), 2.01 (ddd, *J* = 15.0 Hz, *J* = 3.1 Hz, *J* = 1.0 Hz, 1H), 0.84 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H) 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 $C_{21}H_{30}O_5SSiNa$ 445.1535 $[M + Na]^+$; 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). After 30 min stirring, the reaction was quenched with water (3 mL) and the organics were extracted with CH_2Cl_2 (4 x 2 mL). The combined organics extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 10:1 to 5:1) to furnish (–)-**6** (21 mg, 13%) and (+)-**7** (97 mg, 61%); 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): 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, 5H), 4.66 (ddd, *J* = 10.8 Hz, *J* = 5.3 Hz, *J* = 1.1 Hz, 1H), 4.17 (d, *J* = 11.1 Hz, 1H), 4.12 (d, *J* = 11.1 Hz, 1H), 3.60 (dt, *J* = 3.7 Hz, *J* = 1.1 Hz, 1H), 3.43 (d, *J* = 3.7 Hz, 1H), 2.40 (dd, *J* = 13.9 Hz, *J* = 10.8 Hz, 1H), 2.02 (s, 3H), 1.83 (ddd, *J* = 13.9 Hz, *J* = 5.3 Hz, *J* = 1.1 Hz, 1H), 0.95 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H) 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 $C_{21}H_{30}O_5SSiNa$ 445.1535 $[M + Na]^+$; 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 the reflux temperature. After stirring for 1 h, the solvent was removed under reduced pressure. The remaining white solid was dissolved in THF (10 mL), $Et_3N{\cdot}3HF$ (100 µL, 0.61 mmol) was added and the mixture was stirred overnight. Then, water was added (4 mL) and the mixture was neutralized with Na_2CO_3 saturated solution. The organics were extracted with CH_2Cl_2 (4 x 5 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 1:1) furnishing alcohol (–)-**9** as an oil (103.0 mg, 80%); R_f 0.18 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ = -177 (*c* 0.86, $CHCl_3$). IR (ATR): 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 Hz, *J* = 2.6 Hz, *J* = 1.4 Hz, 1H), 4.79 (dd, *J* = 13.6 Hz, *J* = 1.4 Hz, 1H), 4.73-4.66 (m, 2H), 3.80 (ddd, *J* = 3.7 Hz, *J* = 2.6 Hz, *J* = 1.2 Hz, 1H), 3.50 (dd, *J* = 3.7 Hz, *J* = 1.2 Hz, 1H), 3.16 (bs, 1H), 2.08 (s, 3H) 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 $C_9H_{10}O_5Na$ 221.0420 $[M + Na]^+$; found 221.0417.

(–)-**Epiepoxydon:** Lipase acrylic resin from *C. Antarctica* (2 mg) was added to a stirred solution of acetate (–)-**9** (15 mg, 0.08 mmol) in $^iPr_2O$ saturated with water (2 mL) at room temperature. After 3 days stirring, the enzyme was filtered off and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc) to furnish an oily residue identified as the epoxide (–)-epiepoxydon (9 mg, 75%); R_f 0.25 (hexane/EtOAc, 1:2); $[\alpha]_D^{20}$ = -253 (*c* 1.23, EtOH) [lit.[16a] +194 (*c* 1.57, EtOH) for the antipode]. IR (ATR): 3343, 1676, 1240, 1020 cm^{-1}. ^1H NMR (400 MHz, CD_3COCD_3): δ = 6.71 (m, 1H), 4.91 (d, *J* = 7.4 Hz, 1H), 4.65 (m, 1H), 4.29-4.10 (m, 3H), 3.77 (m, 1H), 3.41 (d, *J* = 3.7 Hz, 1H) 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 $NaHCO_3$ and 0.1M $Na_2S_2O_3$ (1 mL) was added and, after stirring for 1 h, the organic layer was separated and the aqueous one extracted with CH_2Cl_2 (3 x 1 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 2:1) provided (+)-**10** (20 mg, 91%); R_f 0.58 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ = +110.5 (*c* 1.17, $CHCl_3$). IR (ATR): 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, 1H), 4.98 (dd, *J* = 17.0 Hz, *J* = 1.9 Hz, 1H), 4.83 (dd, *J* = 17.0 Hz, *J* = 1.9 Hz, 1H), 3.87 (d, *J* = 3.7 Hz, 1H), 3.84 (dd, *J* = 3.7 Hz, *J* = 1.9 Hz, 1H), 2.14 (s, 3H) 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:** Lipase acrylic resin from *C. Antarctica* (2 mg) was added to a stirred solution of acetate (+)-**10** (17 mg, 0.09 mmol) in $^iPr_2O$ saturated with water (2 mL) at room temperature. After 3 days stirring, the enzyme was filtered off and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc) to furnish an oily residue identified as the epoxide (+)-phyllostine (11 mg, 78%); R_f 0.46 (hexane/EtOAc, 1:2); $[\alpha]_D^{20}$ = +117 (*c* 0.86, EtOH)) [lit.[19] –106 (*c* 1, EtOH) for the antipode]. IR (ATR): 3350, 1802, 1736, 1685 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.67 (q, *J* = 1.9 Hz, 1H), 4.57 (dd, *J* = 17.3 Hz, *J* = 1.9 Hz, 1H), 4.39 (dd, *J* = 17.3 Hz, *J* = 1.9 Hz, 1H), 3.85-3.82 (m, 2H), 2.15 (bs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.7, 190.8, 147.6, 130.8,

59.2, 54.0 (2C) 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) and extracted with $CHCl_3$ (5 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 2:1) furnished (–)-**11** (96 mg, 95%); R_f 0.48 (hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ = -258 (*c* 1.50, $CHCl_3$). IR (ATR): 2928, 2854, 1738, 1689, 1371, 1217, 1026 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.56 (ddt, *J* = 5.0 Hz, *J* = 2.5 Hz, *J* = 1.6 Hz, 1H), 5.82 (dq, *J* = 5.0 Hz, *J* = 1.1 Hz,1H), 4.80-4.77 (m, 2H), 3.75 (ddd, *J* = 3.7 Hz, *J* = 2.5 Hz, *J* = 1.1 Hz, 1H), 3.55 (dd, *J* = 3.7 Hz, *J* = 1.1 Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H) 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 $C_{11}H_{12}O_6Na$ 263.0526 [M + Na]$^+$; found 263.0529.

(–)-**Gabosine D:** $BF_3{\cdot}Et_2O$ (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 fir 1 h. Then, the reaction mixture was allowed to warm to room temperature and stirring was continued for two additional hours. Water (10 mL) was added, the organic layer was separated and the aqueous one was extracted with $CHCl_3$ (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (hexanes/EtOAc, 1:2) affording an inseparable mixture of diacetates (77 mg), which was processed to the next step. MeONa (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 and the residue was diluted with water (2 mL) and slightly acidified with 2% HCl. The aqueous solution was extracted with CH_2Cl_2 (4 x 2 mL), the combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated under vacuum. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH, 9:1) furnished (–)-**gabosine D** (38 mg, 68% for the two steps) as a white crystalline solid; R_f 0.32 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D^{20}$ = -85 (*c* 0.95, MeOH)) [lit.[3b] +86 (*c* 1, MeOH) for the antipode]. IR (ATR): 3345, 2890, 1761, 1692 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ = 6.92 (dd, *J* = 1.2 Hz, *J* = 5.3 Hz, 1H), 4.73 (m, 2H), 4.48 (ddd, *J* = 5.3 Hz, *J* = 4.1 Hz, *J* = 1.2 Hz, 1H), 4.33 (d, *J* = 9.6 Hz, 1H), 3.78 (dd, *J* = 9.6 Hz, *J* = 4.1 Hz, 1H), 2.05 (s, 3H) 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: CALB (1 mg) was added to a stirred solution of a mixture of the previously prepared acetates (15 mg) in MeOH (1 mL). After 5 days stirring at room temperature, the enzyme was filtered off and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 9:1) to furnish a white crystalline solid identified as (–)-gabosine E, (9 mg, 71% for the two steps); R_f 0.15 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D^{20}$ = -147 (*c* 1.02, MeOH) [lit.[3b] +148 (*c* 0.95, MeOH) for the antipode].. IR (ATR): 3330, 2932, 1690 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ = 6.91 (dt, *J* = 5.4 Hz, *J* = 1.2 Hz, 1H), 4.48 (m, 1H), 4.34 (d, *J* = 9.8 Hz, 1H), 4.25 (dd, *J* = 15.4 Hz, *J* = 1.2 Hz, 1H), 4.21 (dd, *J* = 15.4 Hz, *J* = 1.2 Hz, 1H), 3.76 (dd, *J* = 9.8 Hz, *J* = 3.9 Hz, 1H) 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 $C_7H_6O_4Na$: 197.0419 [M + Na]$^+$; found 197.0423.

*From (–)-**gabosine D***: CALB (1 mg) was added to a stirred solution of (–)-**gabosine D** (20 mg, 0.09 mmol) in MeOH (1 mL). After 4 days stirring at room temperature, the enzyme was filtered off and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 9:1) to furnish a white crystalline solid identified as (–)-**gabosine E** (12 mg, 78%).

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[1] a) O. Arjona, A. M. Gómez, J. C. López, J. Plumet, *Chem. Rev.* **2007**, *107*, 1919-2036; b) R. G. Soengas, J. M. Otero, A. M. Estévez, A. P. Rauter, V. Cachatra, J. C. Estévez, R. J. Estévez, *Carbohydr. Chem.* **2012**, *38*, 263-302.

[2] Y. Usami, H. Ichikawa, M. Arimoto, *Int. J. Mol. Sci.* **2008**, *9*, 401-421.

[3] a) T. Tsushiya, N. Mikami, S. Umezawa, H. Umezawa, H. Naganawa, *J. Antibiot.* **1974**, *27*, 579-586; b) G. Bach, S. Breiding-Mack, S. Grabley, P. Hammann, K. Hütter, R. Thiericke, H. Uhr, J. Wink, A. Zeeck, *Liebigs Ann. Chem.* **1993**, 241-250; c) A. Maier, C. Maul, M. Zerlin, S. Grabley, R. Thiericke, *J. Antibiot.* **1999**, *52*, 952-959; d) Y.-Q. Tang, C. Maul, R. Hoefs, I. Sattler, S. Grabley, X.-Z Feng, A. Zeeck, R. Thiericke, *Eur. J. Org. Chem.* **2000**, 149-153.

[4] P. Bayón, M. Figueredo, *Chem. Rev.* **2013**, *113*, 4680-4707.

[5] a) H. Chimura, H. Nakamura, T. Takita, T. Takeuchi, H. Umezawa, K. Kato, S. Saito, T. Tomisawa, Y. Iitaka, *J. Antibiot.* **1975**, *28*, 743-748; b) Y. Sugimoto, H. Suzuki, H. Yamaki, T. Nishimura, N. Tanaka, *J. Antibiot.* **1982**, *35*, 1222-1230; c) C. F. M. Huntley, D. S. Hamilton, D. J. Creighton, B. Ganem, *Org. Lett.* **2000**, *2*, 3143-3144; d) D. S. Hamilton, Z. Ding, B. Ganem, D. Creighton, *Org. Lett.* **2002**, *4*, 1209-1212; e) D. Kamiya, Y. Uchihata, E. Ichikawa, K. Kato, K. Umezawa, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1111-1114.

[6] C.-H. Wang, H. T. Wu, H. M. Cheng, T.-J. Yen, I.-H. Lu, H. C. Chang, S.-C. Jao, T. K. M. Shing, W.-S. Li, *J. Med. Chem.* **2011**, *54*, 8574-8581.

[7] J. Marco-Contelles, M. T. Molina, S. Anjum, *Chem. Rev.* **2004**, *104*, 2857-2899.

[8] D. H. Mac, S. Chandrasekhar, R. Grée, *Eur. J. Org. Chem.* **2012**, 5881-5895.

[9] a) R. Alibés, P. Bayón, P. de March, M. Figueredo, J. Font, G. Marjanet, *Org. Lett.* **2006**, *8*, 1617-1620; b) G. Toribio, G. Marjanet, R. Alibés, P. de March, J. Font, P. Bayón, M. Figueredo, *Eur. J. Org. Chem.* **2011**, 1534-1543; c) M. A. Fresneda, R. Alibés, J. Font, P. Bayón, M. Figueredo, *J. Org. Chem.* **2012**, *77*, 5030-5035; d) M. A. Fresneda, R. Alibés, J. Font, P. Bayón, M. Figueredo, *Org. Biomol. Chem.* **2013**, *11*, 6562-6568.

[10] P. Bayón, G. Marjanet, G. Toribio, R. Alibés, P. de March, M. Figueredo, J. Font, *J. Org. Chem.* **2008**, *73*, 3486-3491.

[11] B. Lygo, M. Swiatyj, H. Trabsa, M. Voyle, *Tetrahedron Lett.* **1994**, *35*, 4197-4200.

[12] T. K. M. Shing, H. M. Cheng, *Org. Biomol. Chem.* **2009** *7*, 5098-5102.

[13] a) C. I. Stathakis, M. N. Athanatou, J. K. Gallos, *Tetrahedron Lett.* **2009**, *50*, 6916-6918; b) V. Kumar, P. Das, P. Ghosal, A. K. Shaw, *Tetrahedron* **2011**, *66*, 4539-4546.

[14] T. Shinada, T. Fuji, Y. Ohtani, Y. Yoshida, Y. Ohfune, *Synlett* **2002**, *8*, 1341-1343.

[15] D. T.-W. Chou, B. Ganem, *J. Am. Chem. Soc.* 1980, **102**, 7987-7988.

[16] a) H. Nagasawa, A. Suzuki, S. Tamura *Agr. Biol. Chem.* **1978**, *42*, 1303-1304; b) J. Sekiguchi, G. M. Gaucher, *Biochem. J.* **1979**, *182*, 445-453;

c) J. B. Gloer, S. M. Truckenbrod, *Appl. Environ. Microb.* **1988**, *54*, 861-864; d) T. Nagata, A. Tadahiro, Y. Ando, A. Hirota, *Biosci. Biotech. Bioch.* **1992**, *56*, 810-811; e) Y. Fukushima, Y. Sakagami, S. Marumo, *Bioorg. Med. Chem.* **1993**, *3*, 1219-1222; f) C. Iwamoto, K. Minoura, T. Oka, T. Ohta, S. Hagishita, A. Numata, *Tetrahedron* **1999**, *55*, 14353-14368; g) C. Klemke, S. Kehraus, A. D. Wright, G. M. Koenig, *J. Nat. Prod.* **2004**, *67*, 1058-1063; h) H. Hussain, M. K. Tchimene, I. Ahmed, K. Meier, M. Steinert, S. Draeger, B. Schulz, K. Krohn, *Nat. Prod. Commun.* **2011**, *6*, 1905-1906; i) H. Hussain, N. Root, F. Jabeen, A. Al-Harrasi, A. Al-Rawahi, M. Ahmad, Z. Hassan, G. Abbas, F. Mabood, A. Shah, A. Badshah, A. Khan, R. Ahmad, I. R. Green, S. Draeger, B. Schulz, K. Krohn, *Chin. Chem. Lett.* **2014**, *25*, 1577-1579.

[17] a) A. Ichihara, K. Oda, S. Sakamura, *Tetrahedron Lett.* **1972**, *13*, 5105-5108; b) A. Ichihara, R. Kimura, K. Oda, S. Sakamura, *Tetrahedron Lett.* **1976**, *17*, 4741-4744; c) T. Genski, R. J. K. Taylor, *Tetrahedron Lett.* **2002**, *43*, 3573-3576.

[18] a) T. Kamikubo, K. Ogasawara, *Tetrahedron Lett.* **1995**, *36*, 1685-1688; b) T. Kamikubo, K. Hiroya, K. Ogasawara, *Tetrahedron Lett.* **1996**, *37*, 499-502; c) G. Mehta, K. Islam, *Tetrahedron Lett.* **2004**, *45*, 7683-7687; d) T. Tachihara, T. Kitahara, *Tetrahedron* **2003**, *59*, 1773-1780.

[19] S. Sakamura, J. Ito, R. Sakai, *Agr. Biol. Chem.* **1971**, *35*, 105-110.

[20] a) J. Sekiguchi, G. M. Gaucher, *Can. J. Microbiol.* **1979**, *25*, 881-887; b) P. Venkatasubbaiah, C. G. Van Dyke, W. S. Chilton, *Mycologia* **1992**, *84*, 715-723; c) P. Venkatasubbaiah, N. A. Tisserat, W. S. Chilton, *Mycopathologia* **1994**, *128*, 155-159; d) F. M. Talontsi, P. Facey, M. D. K. Tatong, M. T. Islam, H. Frauendorf, S. Draeger, A. von Tiedemann, H. Laatsch, *Phytochemistry* **2012**, *83*, 87-94; e) A. J. Flewelling, J. A. Johnson, C. A. Gray, *Nat. Prod. Commun.* **2013**, *8*, 373-374.

[21] a) A. Ichihara, K. Oda, K., S. Sakamura, *Agr. Biol. Chem.* **1971**, *35*, 445-464; b) A. Ichihara, K. Oda, S. Sakamura, *Agr. Biol. Chem.* **1974**, *38*, 163-´169; c) A. Ichihara, R. Kimura, K. Oda, K. Moriyasu, S. Sakamura, *Agr. Biol. Chem.* **1982**, *46*, 1879-1883; d) T. Saitoh, E. Suzuki, A. Takasugi, R. Obata, Y. Ishikawa, K. Umewaza, S. Nishiyama, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5383-5386.

[22] (a) H. I. Chae, G.-S. Hwang, M. Y. Jin, D. H. Ryu, *Bull. Korean Chem. Soc.* **2010**, *31*, 1047-1050; b) H. Okamura, H. Shimizu, N. Yamashita, T. Iwagawa, M. Nakatani, *Tetrahedron* **2003**, *59*, 10159-10164.

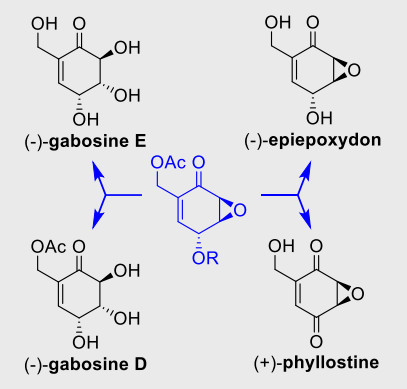
[23] G. Mehta, S. R. Pujar, S. S. Ramesh, K. Islam, *Tetrahedron Lett.* **2005**, *46*, 3373-3376.

[24] I. Nowak, C. T. Jones, M. J. Robins, *J. Org. Chem.* **2006**, *71*, 3077-3081 and references therein.

Entry for the Table of Contents

FULL PAPER

The levorotatory antipodes of gabosines D and E were synthesized through a diversity-oriented approach that can be equally applied to the synthesis of the dextrorotatory enantiomers. A branching in the sequence allowed to synthesize also the anhydrogabosines (–)-epiepoxydon and (+)-phyllostine,



Gabosines, Anhydrogabosines

Miguel Ángel Fresneda, Ramon Alibés, Pau Bayón, and Marta Figueredo**

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Filling some blanks on a diversity-oriented approach to gabosines: Enantioselective synthesis of (−)-epiepoxydon, (+)-phyllostine, (−)-gabosine D and (−)-gabosine E