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Divergent Approach to Gabosines and Anhydrogabosines: Enantioselective Syntheses of (+)-Epiepoformin, (+)-Epoformin, (+)-Gabosine A, and Gabosines B and F

Gladis Toribio,[a] Georgina Marjanet,[a] Ramon Alibés,[a] Pedro de March,[a] Josep Font,[a] Pau Bayón,*[a] and Marta Figueredo*[a]

Dedicated to Professor José Barluenga on the occasion of his 70th birthday

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A divergent approach to polyoxygenated methylcyclohexanes has been applied to synthesize several gabosines and anhydrogabosines. The starting hydroxycyclohexenone, which is readily available in any antipodal form, provides access to both enantiomers of the target compounds. The syntheses of anhydrogabosines involve three main transformations: α-methylation, epoxidation, and sulfur removal, whereas the syntheses of gabosines require an additional epoxide hydrolysis step. The strategy has been applied to the synthesis of (+)-epiepoformin, (+)-epoformin, (+)-gabosine A, and gabosines B and F, through straightforward sequences in good overall yields.

Introduction

The gabosine family comprises a group of secondary metabolites that have been isolated from various Streptomyces strains with a closely related carba-sugar structure. In 1993, Thiericke, Zeeck, and co-workers isolated eleven compounds that were named gabosines A–K (Figure 1), and classified into four structural types.[1] In 2000, the same authors disclosed the isolation of three additional members of the family: gabosines L, N, and O.[2] The structural diversity of the gabosines originates from differences in the substituent positions, degree of unsaturation, and/or the relative and absolute configuration of their stereogenic centers. Prior to being named gabosines, some of these compounds were already known. Thus, gabosine B had formerly been isolated from Actinomycetes strains,[3] gabosine C was identical to the previously known antibiotic KD16-U1,[4] and its crotonyl ester (COTC), also extracted from various Streptomyces strains,[5] was a recognized antitumor agent. Concerning their biological activity, it was also found that gabosines A, B, F, N, and O exhibit DNA-binding properties.[2,6]

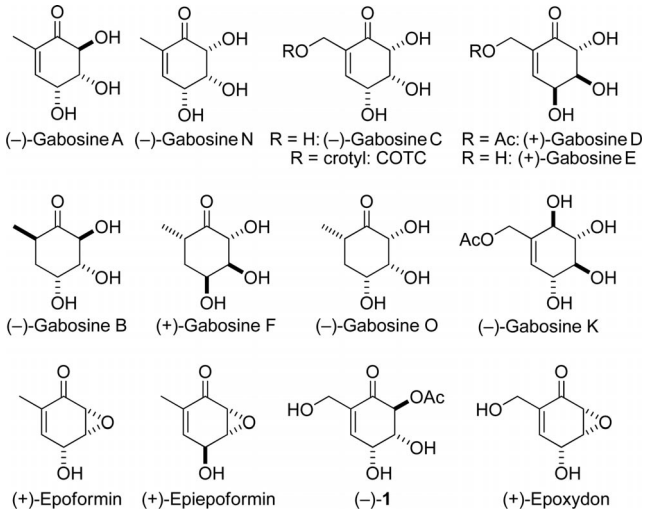

Figure 1. Representative examples of compounds with gabosine and anhydrogabosine structural pattern.

A number of other compounds, the isolation of which from natural sources is described in the literature, also present structural moieties that are consistent with the gabosine family. For instance, compound (–)-**1** was extracted from the fungus *Phyllostica* sp., the "Kurohagare" disease of red clover,[7] and an undefined stereoisomer of **1** was found in *Ophiosphaerella herpotricha*, a cause of spring dead spot of bermuda grass.[8] Moreover, several known epoxyquinol

[a] Department de Química, Universitat Autònoma de Barcelona, Edifici Cn, 08193 Bellaterra, Spain
Fax: +34-935811265
E-mail: marta.figueredo@uab.es

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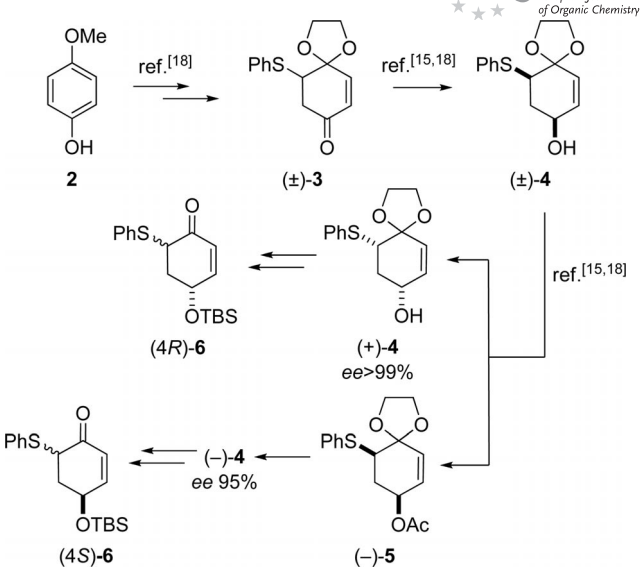
natural products possess anhydrogabosine structures.[9] Most of these compounds are phytotoxins. Among them, the first structural assignment corresponded to (+)-epoxydon, which presents an oxymethyl substituent at the α-carbonyl position (as in gabosines C, D, and E). Other natural anhydrogabosines display a methyl group at the α-carbonyl position (as in gabosines A and N), as is the case for (+)-epoformin and (+)-epiepoformin, among others. (+)-Epoformin was first isolated from *Penicillium claviforme*[10] and later found in a fungus of *Lagerstroemia indica* L.,[11] in *Phoma* sp.,[12] *Ophiosphaerella herpotricha*,[8] and *Penicillium vulpinum*;[13] (+)-epiepoformin was isolated from *Lagerstroemia indica* L.[11] It has been described that (+)-epiepoformin inhibited the germination of lettuce seeds.[11]

Some syntheses of gabosines and anhydrogabosines have been published, with a variety of strategies being employed, although several independently developed approaches present some common trends. Most synthetic strategies are either based on Diels–Alder reactions or they start from chiral pool materials, typically carbohydrates and quinic acid, although a few examples of alternative approaches were also described.[14] However, prior to our own work,[15] there was no suitable synthetic approach to the preparation of a large number of these compounds from common synthetic intermediates and in any antipodal form. Herein, we describe the application of our stereodivergent design for the enantioselective synthesis of gabosines and anhydrogabosines to the preparation of (+)-epoformin, (+)-epiepoformin, (+)-gabosine A, gabosine B, and gabosine F.

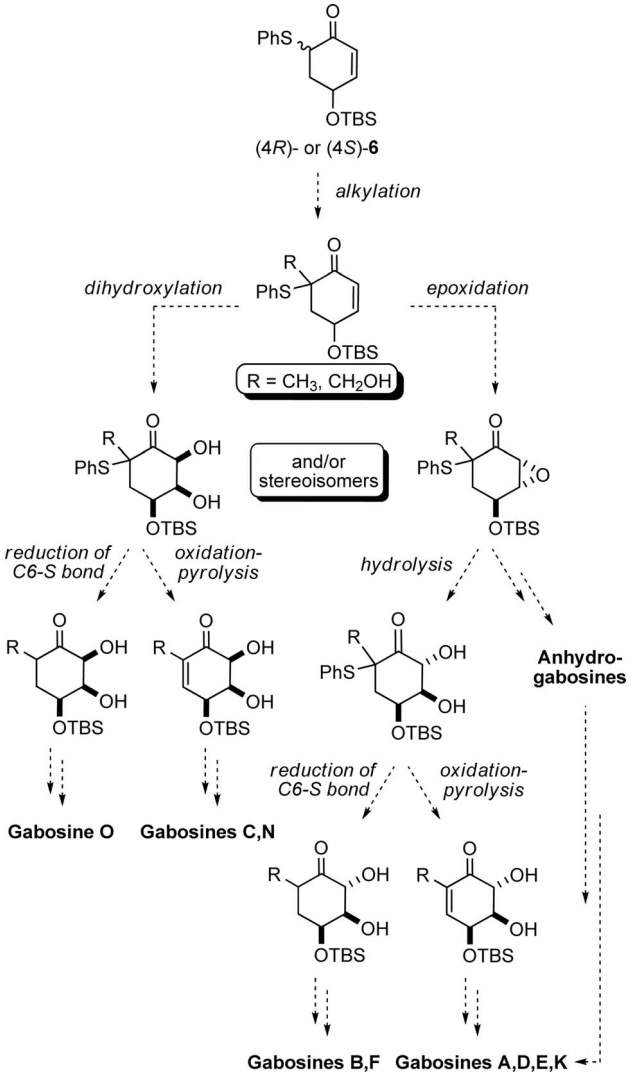
Results and Discussion

Synthetic Strategy: In former investigations, we prepared a series of chiral equivalents of *p*-benzoquinone[16] and explored their utility in synthetic organic chemistry.[17] One of our goals was to design an easily available and versatile precursor of polyfunctionalized cyclohexanes in both antipodal forms. This objective was accomplished by developing the protocol depicted in Scheme 1, where, starting from very accessible raw materials such as *p*-methoxyphenol, **2**, ethylene glycol, and thiophenol, multi-gram quantities of (±)-**3** can be readily prepared.[18] The reduction of (±)-**3** with $NaBH_4$ gives the *cis* alcohol (±)-**4** exclusively. Treatment of (±)-**4** with vinyl acetate and a catalytic amount of Novozyme 435 in diisopropyl ether furnishes the acetate (–)-**5** and the unreacted alcohol (+)-**4**. Methanolysis of the acetate (–)-**5** leads to recovery of the levorotatory alcohol (–)-**4**.[15,18] By silylation of alcohols (+)-**4** and (–)-**4** followed by hydrolysis of the acetal, the α-phenylthioketones (4*R*)-**6** and (4*S*)-**6** are easily synthesized, respectively.

Enone **6** was our material of choice to undertake a systematic synthesis of gabosines and anhydrogabosines through the strategy depicted in Scheme 2, which involves the following transformations: (i) alkylation of the doubly activated C-6 position of **6** to introduce the methyl or hydroxymethyl group; (ii) dihydroxylation of the double bond



Scheme 1. Preparation and kinetic resolution of the key cyclohexenol (±)-**4** and synthesis of ketones (4*R*)-**6** and (4*S*)-**6**.



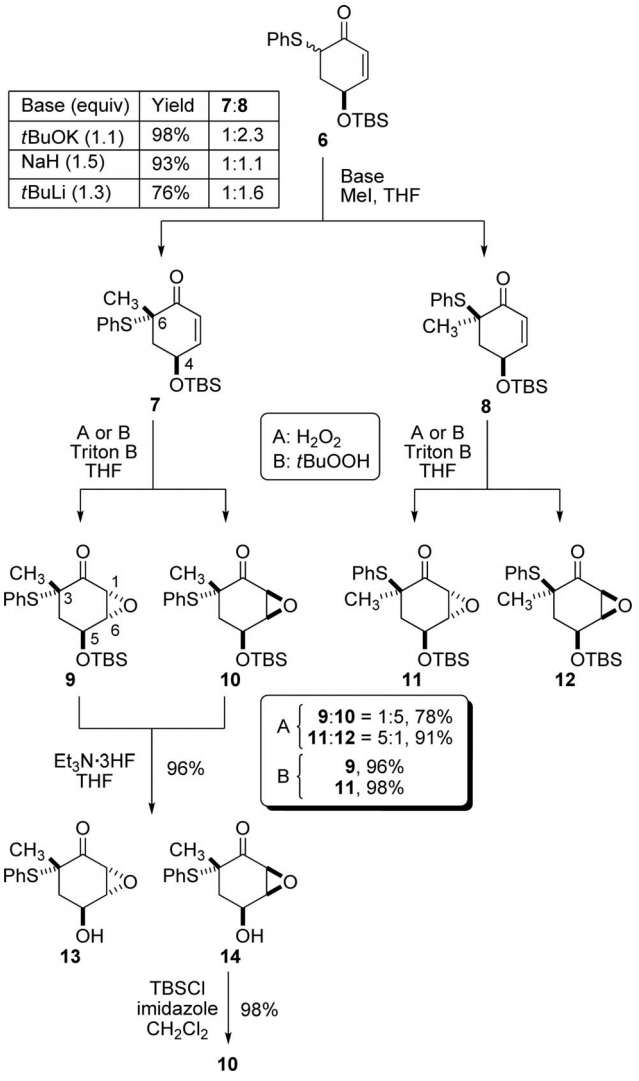
Scheme 2. Strategy for the synthesis of gabosines and anhydrogabosines.

to provide the *cis* α,β-glycol unit or epoxidation that can eventually give access to the *trans* α,β-glycol; and (iii) reduction of the C6–S bond or oxidation to the sulfoxide followed by pyrolysis to generate the conjugated C–C double bond, depending on the target compound.

In contrast to previous enantioselective syntheses that started from chiral pool materials, this divergent design should give access to a large number of gabosine and anhydrogabosine type compounds of both enantiomeric series. The results of the methylation and dihydroxylation steps were reported in a previous communication, along with the syntheses of gabonines O and N, and epigabosines O and N.[15] We have now explored the methylation–epoxidation pathway and developed new syntheses of the target compounds. Most reactions were initially performed with racemic substrates and, after establishing the best conditions, were repeated starting from enantiomerically pure precursors.

Methylation and Epoxidation Studies: The methylation of ketone **6** (Scheme 3) was accomplished by reaction of its enolate with methyl iodide in tetrahydrofuran (THF). This transformation was attempted using three different bases as a means of modulating the diastereofacial selectivity. A chromatographically separable mixture of the two epimers **7** and **8** was obtained in the three cases in high overall yields. Within the enantioselective pathway, methylation of (4*S*)-**6** using sodium hydride as the base furnished an approximate 1:1 mixture of the two epimers (4*S*,6*S*)-**7** and (4*S*,6*R*)-**8**, which were separated for subsequent studies.

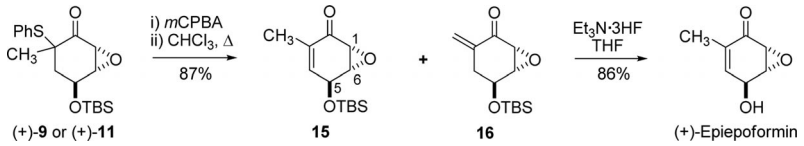
The epoxidation of enones **7** and **8** was assayed by reaction with hydrogen peroxide (Method A)[19] or potassium *tert*-butylhydroperoxide (Method B)[20] and Triton B in THF. Using Method A, the epoxidation of enone **7** delivered a mixture of oxiranes **9** and **10** in a 1:5 ratio and 78% overall yield, whereas epoxidation of enone **8** furnished a 5:1 mixture of the oxiranes **11** and **12** in 91% total yield. The observed stereoselectivity was in good agreement with that found in the dihydroxylation of the same enones with OsO_4 and *N*-methylmorpholine *N*-oxide (NMO), where we argued that the oxidant reagent approached the enone mainly on the face opposite to the bulky phenylsulfenyl group.[15] However, when the epoxidation of **7** and **8** was performed with the more sterically demanding oxidant (Method B), epoxides **9** and **11** were exclusively formed and isolated in 96 and 98% yield, respectively. The exclusive formation of epoxide **9**, with complete inversion of the facial selectivity when going from hydrogen peroxide to *tert*-butylhydroperoxide, provides evidence that the stereoselectivity of the former processes (epoxidation with H_2O_2/Triton B and dihydroxylation with OsO_4/NMO) were not merely governed by steric factors. For synthetic purposes, we judged it convenient to isolate epoxide **10**, which was the major product formed in the oxidation of **7** with hydrogen peroxide and, relative to C-5, presents a configuration of the oxirane stereocenters opposite to that of **9** and **11**. Because compounds **9** and **10** exhibited identical polarities, the mixture of epoxides was desilylated to the the corresponding alcohols **13** and **14**, which were separated by



Scheme 3. Preparation and epoxidation of methylcyclohexanones **7** and **8**.

chromatography; alcohol **14** was then converted back into the corresponding silylether in 98% yield. Within the optically active series, the epoxides (1*R*,3*S*,5*S*,6*S*)-**9** and (1*S*,3*S*,5*S*,6*R*)-**10** were readily prepared from the enone (4*S*,6*S*)-**7**, and the isomer (1*R*,3*R*,5*S*,6*S*)-**11** from the enone (4*S*,6*R*)-**8**.

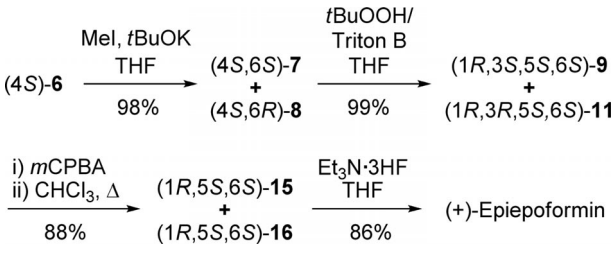
Generation of the conjugated double bond. Total syntheses of (+)-epiepoformin and (+)-epoformin, and the formal syntheses of (–)-theobroxide and (+)-4-epigabosine A: In previous work by other authors, racemic epoformin and epiepoformin were synthesized from *p*-benzoquinone through a strategy based on Diels–Alder/retro-Diels–Alder reactions.[21] Some years later, an asymmetric version of the same strategy led to the synthesis of (+)-epiepoformin.[22] Two additional enantioselective syntheses of (+)-epiepoformin were accomplished by using chiral auxiliaries,[23] and another approach made use of the enzymatic reduction of a cyclohexanone.[24] (–)-Epiepoformin has recently been synthesized from the enzymatic dihydroxylation product of iodobenzene.[25] Both (+)-epoformin and (+)-epiepoformin



Scheme 4. Oxidation/pyrolysis of **9** and **11** and synthesis of epiepoformin.

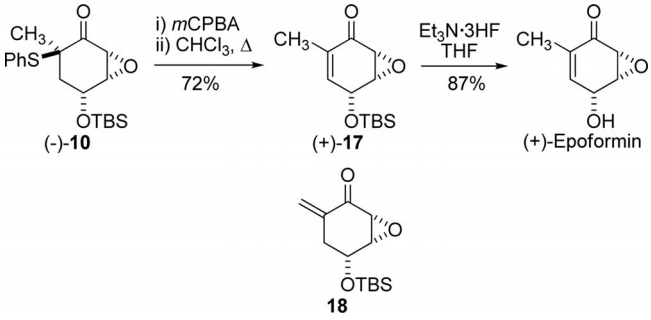
were also synthesized from (–)-quinic acid.[26] The overall yields of these syntheses range from 4 to 50%. In our approach, epoxides **9** and **11** were suitable intermediates for epiepoformin, whereas epoxide **10** was an appropriate precursor for the synthesis of epoformin. Considering that **9** and **11** are epimers at C3, the oxidation/pyrolysis protocol providing the conjugated double bond should, in principle, give rise to the same olefin. In practice, when **9** and **11** were separately treated with *m*-chloroperoxybenzoic acid (*m*-CPBA) in chloroform at 0 °C and then heated, a mixture of the endo- and exocyclic olefins **15** and **16** was obtained in the same ratio (5.5:1) and good overall yield (Scheme 4). It was described that isomerization of **16** to **15** can be accomplished by treatment with Pd/C preactivated under a hydrogen atmosphere, with variable yields of between 31 and 71% because of the sensitivity to small changes in the reaction conditions.[27] However, this transformation proved to be unnecessary because treatment of the mixture of epoxides **15** and **16** with the complex $Et_3N{\cdot}3HF$ furnished epiepoformin as the sole product in 86% isolated yield.

In view of these results, a straightforward and highly efficient synthesis of epiepoformin was completed in four steps starting from **6**: (i) methylation to **7** and **8**, (ii) epoxidation to **9** and **11**, (iii) oxidation/pyrolysis to **15** and **16**, and (iv) deprotection, without performing any chromatographic separation in 74% total yield (Scheme 5). When this sequence of reactions was applied to (4*S*)-**6**, the dextrorotatory enantiomer of epiepoformin was furnished, $[\alpha]_D$ = +315 (*c* = 1.1, EtOH).[28] The conversion of (+)-epiepoformin into (–)-theobroxide and (+)-4-epigabosine A was described previously.[23b]



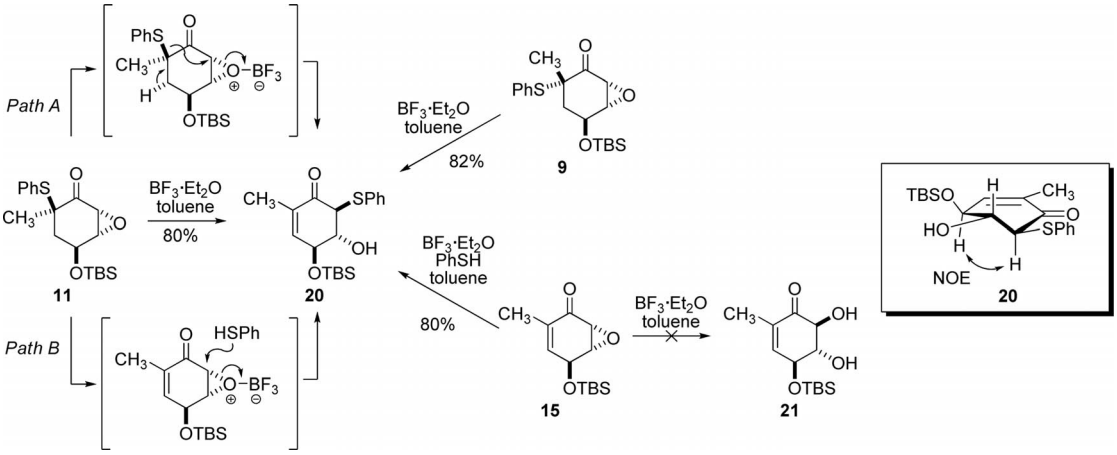
Scheme 5. Synthesis of (+)-epiepoformin.

A parallel sequence of reactions was then applied to epoxyketone **10** (Scheme 6). Oxidation to the sulfoxide and subsequent pyrolysis delivered the expected mixture of endo- and exocyclic olefins **17** and **18**, but the less stable isomer **18** readily isomerized to **17** during the chromatographic purification on silica gel. Deprotection of the hydroxyl group in **17** furnished the target compound. The parallel enantioselective pathway starting from (–)-**10** furnished natural epoformin in 63% overall yield. The specific rotation value of the synthetic material, $[\alpha]_D$ = +109 (*c* = 0.20, EtOH), was in agreement with the previously reported data.[10,26a]



Scheme 6. Oxidation/pyrolysis of **10** and synthesis of epoformin.

Cleavage of the epoxide. Total synthesis of gabosine A: Starting from chiral pool materials, two syntheses of (–)-gabosine A,[29] the natural enantiomer, and one of its levorotatory antipode[30] have been described, with overall yields below 15%. A third synthesis of (–)-gabosine A was completed starting from the enzymatic dihydroxyation product of iodobenzene in 58% total yield.[31] Formally, regioselective hydrolysis of the epoxide in (+)-epiepoformin or (–)-epoformin could deliver (+)-gabosine A, whereas the corresponding antipode, which is equally available through our approach, would deliver the naturally occurring enantiomer. However, it was described that hydrolysis of the epoxide in epiepoformin was a troublesome transformation that could only be achieved by treatment with aqueous sodium acetate in 45% yield;[23b] furthermore, this reaction delivered 4-epigabosine A, an epimer of the natural product. In view of this precedent, for the synthesis of gabosine A, we decided to assay the hydrolysis of the epoxide with a former intermediate lacking the conjugated C–C double bond; it was thought that the higher flexibility could benefit the desired transformation. Accordingly, ketone **11** was treated with various hydrolytic reagents, including NaOAc/H_2O,[23b] trifluoroacetic acid (TFA)/THF/H_2O,[32] and $Sc(OTf)_3$/AcOH,[33] however, in all cases, this led to full recovery of the starting material. In contrast, the reaction of **11** with $BF_3{\cdot}Et_2O$ in toluene delivered a unique product, which was identified as **20**, in 80% yield (Scheme 7). The regio- and stereochemistry of **20** was determined with the help of NMR analyses, including selective NOE experiments. Considering the relative configuration of the stereocenters in **20**, we speculated that its formation may have occurred through an intramolecular process with migration of the sulfide group to open the oxirane, which was electronically activated by the Lewis acid (path A). To test this

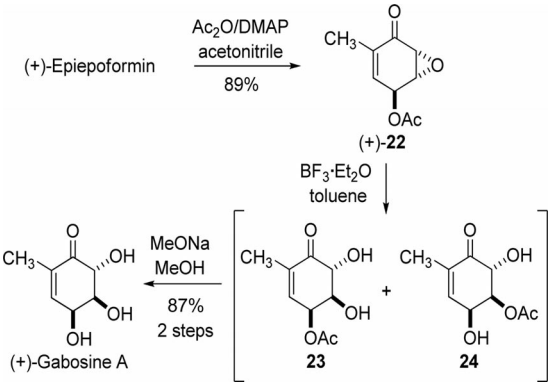


Scheme 7. Attempted hydrolysis of the oxirane in **11** and formation of **20**.

hypothesis, the diasteromeric ketone **9** was submitted to identical reaction conditions and it was found that compound **20** was also formed in similar yield. This result suggested that elimination of thiophenol probably occurred prior to epoxide opening (path B). In agreement with this assumption, enone **15** readily delivered alcohol **20** as the sole product when treated with $BF_3{\cdot}Et_2O$ in toluene in the presence of 1 equiv. thiophenol. The addition of thiophenol to related epoxyquinones under neutral conditions was shown to occur with identical regioselectivity, although at a much lower rate.[34] Enone **15** was then submitted to identical reaction conditions, except for the absence of thiophenol, in an attempt to form the corresponding *trans* diol **21**; unfortunately, the starting material was recovered unchanged.

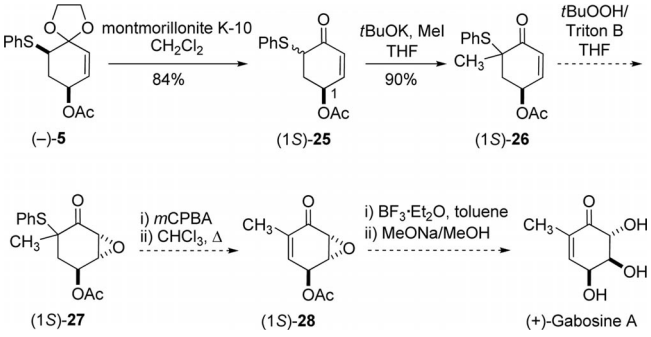
In a related system, cleavage of 2,3-epoxycyclohexanone to the *trans* diol was described to take place in 67% yield through a $BF_3{\cdot}Et_2O$ mediated and acetate-assisted process.[35] Considering this precedent, the acetyl derivative of (+)-epiepoformin, (+)-**22**, was prepared and treated with $BF_3{\cdot}Et_2O$ in toluene at 0 °C for 2 h (Scheme 8). This reaction furnished a mixture of acetates **23** and **24** that, without separation, was submitted to methanolysis in basic medium affording (+)-gabosine A in 87% yield for the two steps. The specific rotation of the synthetic material was $[a]_D$ = +128 (c = 0.30, MeOH) {ref.[1a] –132 (c = 1, MeOH) for the natural antipode}.

Because the presence of the vicinal acetate proved to be crucial for cleavage of the epoxide, we decided to develop a more straightforward synthesis of gabosine A starting from the acetate (–)-**5**, produced through enzymatic resolution of (±)-**4**. The synthetic plan, shown in Scheme 9, would involve seven chemical transformations in only five experimental operations: (i) hydrolysis of the ketal, (ii) methylation, (iii) stereoselective epoxidation, (iv) oxidation/pyrolysis, and (v) epoxide cleavage/methanolysis. Along this sequence, the separation of isomers in each individual step would be unnecessary. In practice, the two initial transformations took place as expected, however, unfortunately, the epoxidation of the acetate (1*S*)-**26** was less stereoselective



Scheme 8. Synthesis of (+)-gabosine A from (+)-epiepoformin.

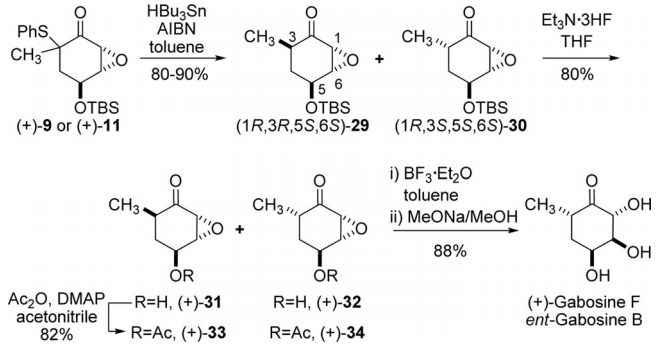
than the corresponding reaction of the silylether analogues **7** and **8**. Moreover, partial hydrolysis of the epoxyacetates took place spontaneously, furnishing a complex mixture of products that could not be converted into the target compound in a reproducible manner. Consequently, in this case, the straightforward approach from (–)-**5** to (+)-gabosine A proved ineffective.



Scheme 9. Attempted synthesis of (+)-gabosine A from acetate (–)-**5**.

Reduction of the C–S bond; Total syntheses of gabosines B and F: Shinada and Ohfune described an enantioselective synthesis of (–)-gabosine B starting from (–)-quinic acid,[29a]

and a synthesis of the racemate had been previously reported.[1b] Recently, an enantioselective synthesis of the dextrorotatory antipode, which is also the natural gabosine F, has been accomplished from L-arabinose.[36] Formally, gabosines B and F could be obtained from dihydroepiepoformin and/or dihydroepoformin by stereoselective hydrolysis of the epoxide function. According to our approach, the synthesis of these natural products and their analogues required the reduction of the C(sp^3)–S bond in compounds **9** and/or **11** (Scheme 10). This transformation was performed by treating each epimeric sulfide with HBu_3Sn in the presence of AIBN in toluene as the solvent, at reflux temperature. Both reactions led to the formation of a mixture of the expected reduction products **29** and **30** in similar yield (80–90%) and identical ratio (6.6:1), which can presumably be linked to the relative stability of the isomers, which can equilibrate under the reaction conditions. Desilylation of the mixture furnished the corresponding alcohols **31** and **32** in 80% overall yield, which were acetylated to give the starting material for the epoxide cleavage. This transformation was accomplished through the same two-step protocol used for gabosine A, without isolation of the intermediate diols, in 88% total yield and with concomitant epimerization at C-6 to furnish exclusively one diastereomer; the physical data of this diastereoisomer were identical to those of natural gabosines B/F. Starting from (+)-**9**, (+)-**11**, or any mixture of both epimers, the synthetic sequence resulted in the formation of the dextrorotatory product, gabosine F. Analogously, the levorotatory antipode, gabosine B, was prepared from (–)-**9** and/or (–)-**11**.



Scheme 10. Reduction of the C–S bond in **9** and **11** and synthesis of gabosine B/F.

Conclusions

Our design for the synthesis of polyoxygenated cyclohexanes has been successfully applied to the enantioselective syntheses of several gabosine and anhydrogabosine type compounds. The common starting material for these syntheses are the easily available enones (4*R*)-**6** or (4*S*)-**6**, depending on the required configuration of the target compound. The syntheses of anhydrogabosines involve three main transformations: α-methylation, epoxidation, and sulfur removal, whereas the syntheses of gabosines with *trans* configuration of the α,β-glycol unit requires an additional epoxide hydrolysis step that works well only on vicinal acetoxy derivatives. Although the stereoselectivities of the α-methylation and epoxidation steps can be modulated by an appropriate choice of base or oxidant, respectively, for some synthetic purposes the separation of diastereomers is unnecessary. Thus, the total synthesis of (+)-epiepoformin was completed in only four steps from (4*S*)-**6** with 74% overall yield. The synthesis of (+)-epoformin was accomplished in two steps and 63% yield starting from the epoxide (1*R*,3*R*,5*R*,6*S*)-**10**, which can, in turn, be prepared from (4*R*)-**6**. (+)-Gabosine A was synthesized from (+)-epiepoformin in three steps and 76% yield. Gabosines B and F were respectively prepared from (–)-**9** or (–)-**11** and (+)-**9** or (+)-**11**. It is remarkable that the syntheses of these gabosines could also be accomplished starting from (4*R*)-**6** or (4*S*)-**6**, respectively, in seven steps without any chromatographic separation of the isomers, in 50% overall yield.

Experimental Section

General Procedure for the Epoxidation Reaction. Method A: To an ice-cooled solution of (±)-**7** (500 mg, 1.43 mmol) in THF (8.3 mL), H_2O_2 (30% in water, 950 μL, 9.29 mmol) and Triton B (40% in water, 65 μL, 0.14 mmol) were added. After stirring at 0 °C for 15 min, the reaction mixture was warmed to room temperature and the progress of the reaction was monitored by GC analysis. After disappearance of the starting olefin, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated NH_4Cl solution. The organic layer was separated, the aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc, 20:1 to 5:1) to furnish a white solid that was identified as a 1:5 mixture of epoxides (±)-**9** and (±)-**10** (397 mg, 1.09 mmol, 76%). The same reaction starting from (4*S*,6*S*)-**7** (1.0 g, 2.87 mmol) furnished a 1:5 mixture of (1*R*,3*S*,5*S*,6*S*)-**9** and (1*S*,3*S*,5*S*,6*R*)-**10** (820 mg, 2.25 mmol, 78%). The same reaction starting from (4*R*,6*R*)-**7** (122 mg, 0.35 mmol) furnished a 1:5 mixture of (1*S*,3*R*,5*R*,6*R*)-**9** and (1*R*,3*R*,5*R*,6*S*)-**10** (102 mg, 0.28 mmol, 80%).

Method B: The same protocol starting from a solution of (±)-**7** (780 mg, 2.24 mmol) in THF (13 mL), *t*BuOOH (70% in water, 1.08 mL, 7.86 mmol) and Triton B (40% in water, 102 μL, 0.22 mmol) afforded a solid residue, which was purified by flash chromatography (hexanes/EtOAc, 5:1) to provide exclusively epoxide (±)-**9** (765 mg, 2.10 mmol, 94%) as a white solid. The same reaction starting from (4*S*,6*S*)-**7** (200 mg, 0.57 mmol) furnished (1*R*,3*S*,5*S*,6*S*)-**9** (200 mg, 0.55 mmol, 96%).

(±)-(1*RS*,3*SR*,5*SR*,6*SR*)-5-(*tert*-Butyldimethylsilyloxy)-3-methyl-3-(phenylthio)-7-oxabicyclo[4.1.0]heptan-2-one [(±)-9]: R_f = 0.48 (hexanes/EtOAc, 5:1); m.p. 71–74 °C (hexanes/EtOAc); R_t (GC) = 11.545 min. ^{1}H NMR (360 MHz, $CDCl_3$, 25 °C): δ = 7.41 (m, 3 H, ArH), 7.33 (m, 2 H, ArH), 4.53 [q, $^3J_{H,H} \approx 2.8$ Hz, 1 H, 5-H], 3.55 (m, 2 H, 1-H, 6-H), 2.30 (dd, $^2J_{H,H}$ = 14.6, $^3J_{H,H}$ = 2.8 Hz, 1 H, 4-H), 2.01 (ddd, $^2J_{H,H}$ = 14.6, $^3J_{H,H}$ = 4.0, $^4J_{H,H}$ = 1.0 Hz, 1 H, 4-H), 1.35 (s, 3 H, Me), 0.86 (s, 9 H, *t*Bu), 0.11 (s, 3 H, SiMe), 0.10 (s, 3 H, SiMe) ppm. ^{13}C NMR (90 MHz, $CDCl_3$): δ = 201.3, 137.7, 130.4, 129.8, 128.8, 67.1, 59.3, 55.2, 50.5, 40.1, 27.3, 25.8, 18.1, –4.7 ppm. IR (ATR): $\tilde{\nu}$ = 2927, 2855, 1704, 1132, 1105 cm^{-1}. HRMS (CI^+): calcd. for $C_{19}H_{28}O_3SSiNa$: 387.1421; found: 387.1431 [M + Na^+].

(+)-(1*R*,3*S*,5*S*,6*S*)-9: M.p. 126–128 °C (hexanes/EtOAc). $[\alpha]_D^{20}$ = +6.7 (*c* = 0.79, $CHCl_3$).

(±)-(1*RS*,3*RS*,5*RS*,6*SR*)-5-(*tert*-Butyldimethylsilyloxy)-3-methyl-3-(phenylthio)-7-oxabicyclo[4.1.0]heptan-2-one [(±)-10]: R_t (GC) = 10.755 min. Epoxide **10** was isolated and characterized after flash chromatographic separation of the unprotected analogues **13** and **14** and subsequent TBS protection of **14** (see the Supporting Information for details).

Mixture of (1*RS*,3*RS*,5*SR*,6*SR*)- and (1*RS*,3*SR*,5*RS*,6*SR*)-5-(*tert*-butyldimethylsilyloxy)-3-methyl-3-(phenylthio)-7-oxabicyclo[4.1.0]-heptan-2-one [(±)-11 and (±)-12]: Following Method A, starting from (±)-**8** (250 mg, 0.72 mmol), an inseparable 5:1 mixture of epoxides (±)-**11** and (±)-**12** (239 mg, 0.65 mmol, 91%) was isolated as a white solid. MS (ESI^+): *m*/*z* (%) = 387 (100) $[M + Na]^+$. $C_{19}H_{28}O_3SSi$ (364): calcd. C 62.59, H 7.74, S 8.80; found C 62.36, H 7.90, S 8.62.

(1*RS*,3*RS*,5*SR*,6*SR*)-5-(*tert*-Butyldimethylsilyloxy)-3-methyl-3-(phenylthio)-7-oxabicyclo[4.1.0]heptan-2-one [(±)-11]: Following Method B, starting from (±)-**8** (512 mg, 1.47 mmol), epoxide (±)-**11** (525 mg, 1.44 mmol, 98%) was isolated as a white solid. R_f = 0.44 (hexanes/EtOAc, 5:1); m.p. 100–102 °C (hexanes/EtOAc); R_t (GC) = 10.878 min. ^1H NMR (360 MHz, $CDCl_3$, 25 °C): δ = 7.35 (m, 5 H, ArH), 4.45 (m, 1 H, 5-H), 3.52 (dd, $^3J_{H,H}$ = 3.4, $^4J_{H,H}$ = 0.9 Hz, 1 H, 1-H), 3.49 (ddd, $^3J_{H,H}$ = 3.4, $^3J_{H,H}$ = 2.2, $^4J_{H,H}$ = 1.2 Hz, 1 H, 6-H), 2.25 (dd, $^2J_{H,H}$ = 15.3, $^3J_{H,H}$ = 4.1 Hz, 1 H, 4-H), 2.09 (ddd, $^2J_{H,H}$ = 15.3, $^3J_{H,H}$ = 2.0, $^4J_{H,H}$ = 1.2 Hz, 1 H, 4-H), 1.27 (s, 3 H, Me), 0.98 (s, 9 H, *t*Bu), 0.18 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR (90 MHz, $CDCl_3$, 25 °C): δ = 194.0, 137.9, 130.9, 129.7, 128.7, 64.3, 56.7, 52.9, 52.1, 38.7, 26.0, 22.9, 18.3, –4.6 ppm. IR (ATR): $\tilde{\nu}$ = 2957, 2926, 2855, 1703, 1248, 1107 cm^{-1}.

(+)-(1*R*,3*R*,5*S*,6*S*)-11: The same reaction starting from (4*S*,6*R*)-**8** (1.00 g, 2.87 mmol) furnished (1*R*,3*R*,5*S*,6*S*)-**11** (1.02 g, 2.8 mmol, 98%). M.p. 126–128 °C (hexanes/EtOAc); $[\alpha]_D^{20}$ = +5.5 (*c* = 0.84, $CHCl_3$).

Mixture of (±)-9 and (±)-11: Following Method B, starting from a mixture of (±)-**7** and (±)-**8** (230 mg, 0.66 mmol), a mixture of epoxides (±)-**9** and (±)-**11** (233 mg, 0.64 mmol, 97%) was isolated as a white solid.

(1*RS*,3*SR*,5*RS*,6*SR*)-5-(*tert*-Butyldimethylsilyloxy)-3-methyl-3-(phenylthio)-7-oxabicyclo[4.1.0]heptan-2-one [(±)-12]: Repeated flash chromatography of a mixture of (±)-**11** and (±)-**12** allowed the isolation of an analytical sample of (±)-**12**: R_t (GC) = 11.185 min. ^1H NMR (360 MHz, $CDCl_3$, 25 °C): δ = 7.38 (m, 5 H, ArH), 4.22 (dd, $^3J_{H,H}$ = 11.3, 4.8 Hz, 1 H, 5-H), 3.53 (dd, $^3J_{H,H}$ = 4.3, $^4J_{H,H}$ = 1.4 Hz, 1 H, 6-H), 3.46 (d, $^3J_{H,H}$ = 4.3 Hz, 1 H, 1-H), 2.36 (dd, $^2J_{H,H}$ = 13.1, $^3J_{H,H}$ = 11.3 Hz, 1 H, 4-H), 1.83 (ddd, $^2J_{H,H}$ = 13.1, $^3J_{H,H}$ = 4.8, $^4J_{H,H}$ = 1.4 Hz, 1 H, 4-H), 1.27 (s, 3 H, Me), 0.91 (s, 9 H, *t*Bu), 0.11 (s, 3 H, SiMe), 0.10 (s, 3 H, SiMe) ppm. ^{13}C NMR (90 MHz, $CDCl_3$, 25 °C): δ = 202.2, 137.8, 137.7, 130.3, 129.8, 66.1, 60.2, 56.0, 50.7, 38.7, 25.8, 25.1, 18.2, –4.5, –4.6 ppm.

Mixture of (1*R*,3*S*,5*S*,6*S*)-9 and (1*R*,3*R*,5*S*,6*S*)-11: The same reaction starting from a mixture of (4*S*,6*S*)-**7** and (4*S*,6*R*)-**8** (600 mg, 1.72 mmol) furnished a mixture of (1*R*,3*S*,5*S*,6*S*)-**9** and (1*R*,3*R*,5*S*,6*S*)-**11** (627 mg, 1.72 mmol, 100%).

Mixture of (1*S*,3*R*,5*R*,6*R*)-9 and (1*S*,3*S*,5*R*,6*R*)-11: The same reaction starting from a mixture of (4*R*,6*R*)-**7** and (4*R*,6*S*)-**8** (1.24 g, 3.56 mmol) furnished a mixture of (1*S*,3*R*,5*R*,6*R*)-**9** and (1*S*,3*S*,5*R*,6*R*)-**11** (1.28 g, 3.51 mmol, 99%).

General Procedure for the Oxidation/Pyrolysis Step: To a solution of (±)-**11** (400 mg, 1.09 mmol) in $CHCl_3$ (13 mL) at 0 °C, a solution of anhydrous *m*-CPBA (224 mg, 1.09 mmol) in $CHCl_3$ (3 mL) was continuously added during 1 h at the same temperature. The reaction mixture was monitored by GC analysis until completion. The solution was washed with saturated $NaHCO_3$ solution and the organic layer was separated, dried with anhydrous $MgSO_4$ and filtered. The filtrate was concentrated to around 15 mL and heated to reflux temperature for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc, 15:1 to 5:1) to afford a 5.5:1 mixture of epoxides (±)-**15** and (±)-**16** (215 mg, 0.84 mmol, 69%). The same reaction starting from a 1:7.6 mixture of (±)-**9** and (±)-**11** (396 mg, 1.09 mmol) furnished a 5.5:1 mixture of (±)-**15** and (±)-**16** (207 mg, 0.81 mmol, 75%). The same reaction starting from (1*R*,3*R*,5*S*,6*S*)-**11** (614 mg, 1.68 mmol) furnished a 5.5:1 mixture of (1*R*,5*S*,6*S*)-**15** and (1*R*,5*S*,6*S*)-**16** (373 mg, 1.47 mmol, 87%). The same reaction starting from a 7.1:1 mixture of (1*R*,3*S*,5*S*,6*S*)-**9** and (1*R*,3*R*,5*S*,6*S*)-**11** (610 mg, 1.68 mmol) furnished a 5.5:1 mixture of (1*R*,5*S*,6*S*)-**15** and (1*R*,5*S*,6*S*)-**16** (376 mg, 1.48 mmol, 88%). The spectroscopic data of **15** and **16** were in accordance with those described in the literature.[27]

(1*RS*,5*RS*,6*SR*)-5-(*tert*-butyldimethylsilyloxy)-3-methyl-7-oxabicyclo[4.1.0]hept-3-en-2-one and (1*RS*,5*RS*,6*SR*)-5-(*tert*-butyldimethylsilyloxy)-3-methylene-7-oxabicyclo[4.1.0]heptan-2-one [(±)-17]: Following the general procedure and starting from (±)-**10** (119 mg, 0.33 mmol), olefin (±)-**17** (57 mg, 0.22 mmol, 69%) was isolated. R_t (GC) = 5.145 min. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 6.13 (m, 1 H, 4-H), 4.74 (m, 1 H, 5-H), 3.67 (dt, $^3J_{H,H}$ = 4.0, $^3J_{H,H} \approx {}^4J_{H,H} \approx$ 2.7 Hz, 1 H, 6-H), 3.43 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H, 1-H), 1.80 (m, 3 H, Me), 0.96 (s, 9 H, *t*Bu), 0.18 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 194.4, 141.5, 131.8, 66.3, 54.6, 53.2, 25.9, 15.9, 14.2, –4.4, –4.5 ppm. HRMS (CI^+): calcd. for $C_{13}H_{22}O_3SiNa$ 277.1230; found 277.1232 $[M + Na^+]$.

(+)-(1*R*,5*R*,6*S*)-17: The same reaction starting from (1*R*,3*R*,5*R*,6*S*)-**10** (116 mg, 0.32 mmol) furnished (1*R*,5*R*,6*S*)-**17** (58 mg, 0.23 mmol, 72%). $[\alpha]_D^{20}$ = +86 (*c* = 0.85, $CHCl_3$).

(±)-Epiepoformin: A solution of epoxides (±)-**15** and (±)-**16** (280 mg, 1.10 mmol) in THF (14.5 mL) at room temperature was treated with $Et_3N{\cdot}3HF$ (1.0 mL, 6.13 mmol). The reaction mixture was stirred for 12 h at the same temperature, then CH_2Cl_2 (16 mL) and a saturated aqueous solution of $NaHCO_3$ (16 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under vacuum. The oily residue was purified by flash chromatography (hexanes/EtOAc, 5:1) to give (±)-epiepoformin (132 mg, 0.94 mmol, 86%) as a white solid. R_f = 0.56 (EtOAc); m.p. 59–61 °C (hexanes/EtOAc). ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 6.45 (ddq, $^3J_{H,H}$ = 5.5, $^4J_{H,H}$ = 2.6, $^4J_{H,Me}$ = 1.3 Hz, 1 H, 4-H), 4.65 (br. s, 1 H, 5-H), 3.77 (ddd, $^3J_{H,H}$ = 3.7, 1.3, $^4J_{H,H}$ = 2.6 Hz, 1 H, 6-H), 3.48 (dd, $^3J_{H,H}$ = 3.7, $^4J_{H,H}$ = 1.1 Hz, 1 H, 1-H), 2.38 (br. s, 1 H, OH), 1.83 (dd, $^4J_{H,H}$ = 1.3, $^5J_{H,H}$ = 1.2 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 194.3, 138.9, 134.8, 63.5, 57.8, 53.5, 16.1 ppm.

(+)-Epiepoformin: The same reaction starting from (1*R*,5*S*,6*S*)-**15** and (1*R*,5*S*,6*S*)-**16** (376 mg, 1.48 mmol) furnished (1*R*,5*S*,6*R*)-epiepoformin (178 mg, 1.27 mmol, 86%). M.p. 88–90 °C (hexanes/EtOAc). $[\alpha]_D^{20}$ = +315 (*c* = 1.1, EtOH).

(±)-Epoformin: A solution of epoxide (±)-**17** (45 mg, 0.18 mmol) in THF (2.5 mL) at room temperature, was treated with $Et_3N{\cdot}3HF$ (167 μL, 1.03 mmol). The reaction mixture was stirred at the same temperature for 48 h then CH_2Cl_2 (2.5 mL) and a saturated aqueous solution of $NaHCO_3$ (2.5 mL) were added. The organic layer

was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under vacuum. The oily residue was purified by flash chromatography (hexanes/EtOAc, 5:1) to give epoformin (21 mg, 0.15 mmol, 85%). R_f = 0.40 (hexanes/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.27 (s, 1 H, 4-H), 4.63 (br. s, 1 H, 5-H), 3.83 (m, 1 H, 6-H), 3.51 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H, 1-H), 2.19 (d, $^3J_{H,H}$ = 9.9 Hz, 1 H, OH), 1.82 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz $CDCl_3$, 25 °C): δ = 193.9, 140.3, 132.6, 65.2, 54.6, 53.9, 15.9 ppm.

(+)-Epoformin: The same reaction starting from (1*R*,5*R*,6*S*)-**17** (34 mg, 0.13 mmol) furnished (1*R*,5*R*,6*R*)-epoformin (16 mg, 0.12 mmol, 87%) as a colorless oil. $[\alpha]_D^{20}$ = +109 (*c* = 0.20, EtOH).

(1*R*,2*S*,6*R*)-4-Methyl-5-oxo-7-oxabicyclo[4.1.0]hept-3-en-2-yl Acetate [(+)-22]: To a solution of (+)-epiepoformin (131 mg, 0.93 mmol) in anhydrous acetonitrile (4.5 mL) at 0 °C under a nitrogen atmosphere, DMAP (126 mg, 1.03 mmol) and acetic anhydride (350 μL, 3.74 mmol) were added. The solution was warmed to room temperature and stirred for 5 min, then the reaction mixture was poured into ice water and extracted with CH_2Cl_2. The combined organic extracts were washed with cold water and a saturated aqueous solution of $NaHCO_3$. The solution was dried with $MgSO_4$ and the solvent was removed under reduced pressure to furnish an oily residue. Purification of this material by flash chromatography (EtOAc) yielded (+)-**22** as an oil (151 mg, 0.83 mmol, 89%). R_f = 0.68 (EtOAc). $[\alpha]_D^{20}$ = +94 (*c* = 0.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.36 (dqn, $^3J_{H,H}$ = 6.3, $^4J_{H,H} \approx$, $^4J_{H,Me} \approx$ 1.4 Hz, 1 H, 3-H), 5.72 (ddd, $^3J_{H,H}$ = 6.3, 2.5, $^4J_{H,H}$ = 1.1 Hz, 1 H, 2-H), 3.72 (ddd, $^3J_{H,H}$ = 3.5, 2.5, $^4J_{H,H}$ = 1.4 Hz, 1 H, 1-H), 3.52 (dd, $^3J_{H,H}$ = 3.5, $^4J_{H,H}$ = 1.1 Hz, 1 H, 6-H), 2.12 (s, 3 H, OAc), 1.86 (d, $^4J_{H,H}$ = 1.1 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 193.7, 170.0, 136.7, 134.4, 64.7, 55.2, 53.1, 20.9, 16.1 ppm. IR (ATR): $\tilde{\nu}$ = 2928, 1737, 1684, 1369, 1219 cm^{-1}. HRMS (ESI+): calcd. for $C_9H_{10}O_4Na$ 205.0471; found 205.0472 [M + Na$^+$].

(+)-Gabosine A: To an ice-cooled solution of acetate (+)-**22** (17 mg, 0.09 mmol) in toluene (1 mL), $BF_3{\cdot}Et_2O$ (12 μL, 0.09 mmol) was added. The reaction mixture was stirred at 0 °C for 2 h, then neutralized with $NaHCO_3$ and extracted with EtOAc (3 × 0.5 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (EtOAc), affording a 3.1:1 mixture of acetates **23** and **24** (18 mg, 0.09 mmol, 97%) as an oil (see the Supporting Information for analytical data). The mixture of acetates was dissolved in MeOH (0.2 mL), NaOMe (4.8 mg, 0.09 mmol) was added, and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was diluted in water and made slightly acidic with 2% HCl. The aqueous solution was extracted with CH_2Cl_2 (3 × 0.1 mL), the combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. Purification of the residue by flash chromatography (EtOAc) furnished (+)-gabosine A (12.6 mg, 0.08 mmol, 90%) as a white crystalline solid. R_f = 0.20 (EtOAc). $[\alpha]_D^{20}$ = +128 (*c* = 0.3, MeOH). ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 6.78 (dq, $^3J_{H,H}$ = 5.6, $^4J_{H,Me}$ = 1.4 Hz, 1 H, 3-H), 4.42 (m, 1 H, 4-H), 4.36 (d, $^3J_{H,H}$ = 10.0 Hz, 1 H, 6-H), 3.76 (dd, $^3J_{H,H}$ = 10.0, 3.9 Hz, 1 H, 5-H), 1.85 (dd, $^4J_{H,H}$ = 1.4, $^5J_{H,Me}$ = 1.2 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 201.3, 143.9, 137.7, 75.9, 74.8, 68.3, 16.4 ppm.

Mixture of (1*RS*,3*RS*,5*SR*,6*SR*)- and (1*RS*,3*SR*,5*SR*,6*SR*)-5-(*tert*-Butyldimethylsilyloxy)-3-methyl-7-oxabicyclo[4.1.0]heptan-2-one [(±)-29 and (±)-30]: To a boiling solution of (±)-**9** (363 mg, 0.99 mmol) in anhydrous toluene (9.0 mL), a solution of AIBN (17.3 mg, 0.10 mmol) and Bu_3SnH (315 μL, 1.19 mmol) in anhydrous toluene (5.1 mL) was continuously added over 73 min. After 1 min, the reaction mixture was cooled and the solvent was evaporated under vacuum to give an oily residue, which was purified by flash chromatography (hexanes to hexanes/EtOAc, 5:1) to provide a 6.6:1 mixture of epoxides (±)-**29** and (±)-**30** (204 mg, 0.79 mmol, 80%) as an oil. The same protocol starting from (±)-**11** (52 mg, 0.14 mmol) furnished a mixture of (±)-**29** and (±)-**30** (33 mg, 0.13 mmol, 90%) in an identical ratio (see the Supporting Information for analytical data).

Mixture of (1*R*,3*R*,5*S*,6*S*)-29 and (1*R*,3*S*,5*S*,6*S*)-30: The same reaction starting from a mixture of (1*R*,3*S*,5*S*,6*S*)-**9** and (1*R*,3*R*,5*S*,6*S*)-**11** (500 mg, 1.37 mmol) furnished a mixture of (1*R*,3*R*,5*S*,6*S*)-**29** and (1*R*,3*S*,5*S*,6*S*)-**30** (278 mg, 1.1 mmol, 79%).

Mixture of (1*S*,3*S*,5*R*,6*R*)-29 and (1*S*,3*R*,5*R*,6*R*)-30: The same reaction starting from a mixture of (1*S*,3*R*,5*R*,6*R*)-**9** and (1*S*,3*S*,5*R*,6*R*)-**11** (800 mg, 2.19 mmol) furnished a mixture of (1*S*,3*S*,5*R*,6*R*)-**29** and (1*S*,3*R*,5*R*,6*R*)-**30** (456 mg, 1.78 mmol, 81%).

Mixture of (1*RS*,3*RS*,5*SR*,6*RS*)- and (1*RS*,3*SR*,5*SR*,6*RS*)-5-Hydroxy-3-methyl-7-oxabicyclo[4.1.0]heptan-2-one [(±)-31 and (±)-32]: A solution of a 6.6:1 mixture of epoxides (±)-**29** and (±)-**30** (336 mg, 1.31 mmol) in THF (17.4 mL) at room temperature, was treated with $Et_3N{\cdot}3HF$ (1.24 mL, 7.61 mmol). The reaction mixture was stirred for 20 h at the same temperature, then CH_2Cl_2 (23 mL) and a saturated aqueous solution of $NaHCO_3$ (23 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under vacuum to give a 1:1 mixture of alcohols (±)-**31** and (±)-**32** (149 mg, 1.05 mmol, 80%) as an oily residue. After repeated flash chromatography (hexanes/EtOAc, 10:1 to 1:1) analytical samples of (±)-**31** and (±)-**32** were isolated.

(±)-31: R_f = 0.20 (EtOAc). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 4.58 (br. s, 1 H, 5-H), 3.56 (t, $^3J_{H,H}$ = 3.5 Hz, 1 H, 6-H), 3.29 (d, $^3J_{H,H}$ = 3.5 Hz, 1 H, 1-H), 2.48 (tq, $^3J_{H,H}$ = 9.3, 7.2 Hz, 1 H, 3-H), 1.86 (m, 3 H, 2 × 4-H, OH), 1.14 (d, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me) ppm. ^{13}C NMR (90 MHz, $CDCl_3$, 25 °C): δ = 205.8, 64.9, 56.2, 54.4, 36.3, 32.3, 15.5 ppm. IR (ATR): $\tilde{\nu}$ = 3401, 2932, 1704, 1058 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_7H_{10}O_3Na$ 165.0528; found 165.0527 [M + Na$^+$].

(±)-32: R_f = 0.18 (EtOAc). ^{1}H NMR (360 MHz, $CDCl_3$, 25 °C): δ = 4.44 (dd, $^3J_{H,H}$ = 8.6, 5.9 Hz, 1 H, 5-H), 3.57 (m, 1 H, 6-H), 3.34 (d, $^3J_{H,H}$ = 3.8 Hz, 1 H, 1-H), 2.75 (dqd, $^3J_{H,H}$ = 12.1, 6.7, 5.4 Hz, 1 H, 3-H), 2.32 (m, 1 H, 4-H), 1.70 (br. s, 1 H, OH), 1.59 (ddd, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 12.1, 8.6 Hz, 1 H, 4-H), 1.03 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, Me) ppm. ^{13}C NMR (90 MHz, $CDCl_3$, 25 °C): δ = 208.3, 65.3, 63.3, 55.5, 34.4, 31.2, 14.8 ppm. IR (ATR): $\tilde{\nu}$ = 3430, 2926, 1714, 1082 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_7H_{10}O_3Na$ 165.0528; found 165.0525 [M + Na$^+$].

Mixture of (1*R*,3*R*,5*S*,6*R*)-31 and (1*R*,3*S*,5*S*,6*R*)-32: The same reaction starting from a 6.6:1 mixture of epoxides (1*R*,3*R*,5*S*,6*S*)-**29** and (1*R*,3*S*,5*S*,6*S*)-**30** (114 mg, 0.44 mmol) furnished a 1:1 mixture of alcohols (1*R*,3*R*,5*S*,6*R*)-**31** and (1*R*,3*S*,5*S*,6*R*)-**32** (50 mg, 0.35 mmol, 79%).

Mixture of (1*S*,3*S*,5*R*,6*S*)-31 and (1*S*,3*R*,5*R*,6*R*)-32: The same reaction starting from a 6.6:1 mixture of epoxides (1*S*,3*S*,5*R*,6*R*)-**29** and (1*S*,3*R*,5*R*,6*R*)-**30** (180 mg, 0.70 mmol) furnished a 1:1 mixture of alcohols (1*S*,3*S*,5*R*,6*S*)-**31** and (1*S*,3*R*,5*R*,6*S*)-**32** (80 mg, 0.56 mmol, 80%). After repeated flash chromatography (hexanes/

EtOAc, 10:1 to 1:1), analytical samples of (1*S*,3*S*,5*R*,6*S*)-**31** and (1*S*,3*R*,5*R*,6*S*)-**32** were isolated.

(1*S*,3*S*,5*R*,6*S*)-31: oil; $[\alpha]_D^{20}$ = –28 (*c* = 0.14, $CHCl_3$).

(1*S*,3*R*,5*R*,6*S*)-32: oil; $[\alpha]_D^{20}$ = –36 (*c* = 0.11, $CHCl_3$).

Mixture of (1*RS*,2*SR*,4*RS*,6*RS*)- and (1*RS*,2*SR*,4*SR*,6*RS*)-4-Methyl-5-oxo-7-oxabicyclo[4.1.0]heptan-2-yl Acetate [(±)-33 and (±)-34]: To a solution of a 1:1 mixture of epoxides (±)-**31** and (±)-**32** (64 mg, 0.45 mmol) in anhydrous acetonitrile (4.2 mL) at 0 °C under N_2, DMAP (61 mg, 0.50 mmol) and acetic anhydride (171 μL, 1.81 mmol) were added. The reaction mixture was warmed to room temperature, stirred for 5 min and then poured into ice-water (2 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with cold water and a saturated aqueous solution of $NaHCO_3$, then dried with $MgSO_4$. Removal of the solvent under reduced pressure furnished an oily residue, which was purified by flash chromatography (EtOAc) to yield a 1:1 mixture of (±)-**33** and (**±**)-**34** (68 mg, 0.37 mmol, 82%) as an oil (see the Supporting Information for analytical data).

Mixture of (1*R*,2*S*,4*R*,6*R*)-33 and (1*R*,2*S*,4*S*,6*R*)-34: The same reaction starting from a 1:1 mixture of alcohols (1*R*,3*R*,5*S*,6*R*)-**31** and (1*R*,3*S*,5*S*,6*R*)-**32** (46 mg, 0.32 mmol) furnished a 1:1 mixture of acetates (1*R*,2*S*,4*R*,6*R*)-**33** and (1*R*,2*S*,4*S*,6*R*)-**34** (48 mg, 0.25 mmol, 80%).

Mixture of (1*S*,2*R*,4*S*,6*S*)-33 and (1*S*,2*R*,4*R*,6*S*)-34: The same reaction starting from a 1:1 mixture of alcohols (1*S*,3*S*,5*R*,6*S*)-**31** and (1*S*,3*R*,5*R*,6*S*)-**32** (36 mg, 0.26 mmol) furnished a 1:1 mixture of acetates (1*S*,2*R*,4*S*,6*S*)-**33** and (1*S*,2*R*,4*R*,6*S*)-**34** (40 mg, 0.22 mmol, 84%).

(±)-Gabosine B/F: To an ice-cooled solution of acetates (±)-**33** and (±)-**34** (76 mg, 0.41 mmol) in toluene (4.5 mL), $BF_3{\cdot}Et_2O$ (52 μL, 0.41 mmol) was added and the mixture was stirred at 0 °C for 2 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (EtOAc) to afford a mixture of the expected diols (79 mg, 0.39 mmol, 96%) as a yellow oil. To a solution of the mixture (48 mg, 0.24 mmol) in MeOH (0.5 mL), was added NaOMe (12.8 mg, 0.24 mmol) and the mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum and the residue was diluted in water and neutralized with TFA (to ca. pH 7). Purification of the residue by flash chromatography ($CHCl_3$/MeOH, 20:1) furnished gabosine B/F (35 mg, 0.22 mmol, 92%) as a white crystalline material. R_f = 0.24 ($CHCl_3$/MeOH, 9:1). ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 4.43 (d, $^3J_{H,H}$ = 10.0 Hz, 1 H, 2-H), 4.13 (br. q, $^3J_{H,H} \approx$ 3.0 Hz, 1 H, 4-H), 3.49 (dd, $^3J_{H,H}$ = 10.0, 3.0 Hz, 1 H, 3-H), 2.96 (dqd, $^3J_{H,H}$ = 13.0, 6.6, 5.9 Hz, 1 H, 6-H), 2.15 (ddd, $^2J_{H,H} \approx {}^3J_{H,H} \approx$ 14.0, $^3J_{H,H}$ = 5.9, 3.2 Hz, 1 H, 5-H), 1.45 (td, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 2.6 Hz, 1 H, 5-H), 1.06 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 212.3, 80.0, 79.0, 70.6, 39.0, 38.7, 14.6 ppm.

(+)-Gabosine F: The same protocol starting from acetates (1*R*,2*S*,4*R*,6*R*)-**33** and (1*R*,2*S*,4*S*,6*R*)-**34** (30 mg, 0.16 mmol) furnished a mixture of diols (29 mg, 0.14 mmol, 86%), part of which (20 mg, 0.10 mmol) was converted into gabosine F (15 mg, 0.10 mmol, 92%). $[\alpha]_D^{20}$ = +89 (*c* = 0.32, MeOH).

(–)-Gabosine B: The same protocol starting from acetates (1*S*,2*R*,4*S*,6*S*)-**33** and (1*S*,2*R*,4*R*,6*S*)-**34** (22 mg, 0.12 mmol) furnished a mixture of diols (22 mg, 0.11 mmol, 89%), part of which (14 mg, 0.07 mmol) was converted into gabosine B (10 mg, 0.06 mmol, 90%). $[\alpha]_D^{20}$ = –88 (*c* = 0.51, MeOH).

Supporting Information (see footnote on the first page of this article): General methods and materials; procedures for the preparation and characterization data of compounds **7**, **8**, **10**, **13**–**15**, **20**, **23**–**26**, **29**, **30**, **33**, and **34**; NMR spectra of compounds **7**–**17**, **20**, **22**–**26**, **29**–**34**, epiepoformin, epoformin, gabosine A, and gabosine B/F.

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