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Enantioselective Synthesis and Absolute Configuration Assignment of Gabosine O. Synthesis of (+)- and (−)-Gabosine N and (+)- and (−)-Epigabosines N and O

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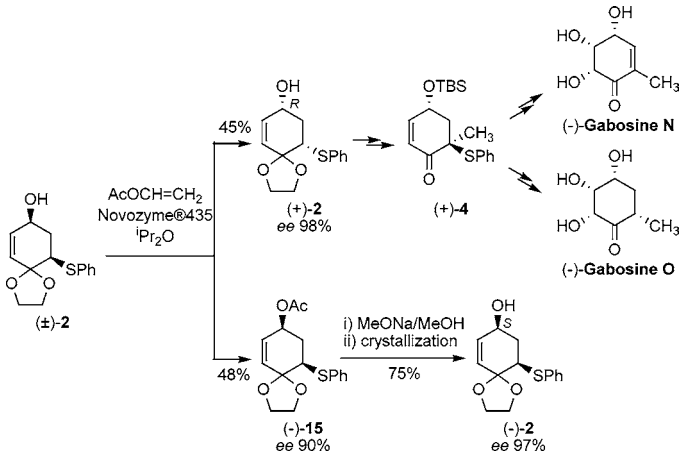
ABSTRACT



A rational approach to the synthesis of gabosines and other related carba-sugars starting from a masked *p*-benzoquinone has been designed. The enantioselective acetylation of the hydroxyketal 2 provides a practical entry to either enantiomer of the target products. The strategy has been applied to the synthesis of (+)- and (−)-gabosines N and O and (+)- and (−)-epigabosines N and O. The absolute configuration of natural gabosine O has been established.

The gabosine family comprises a group of secondary metabolites isolated from various *Streptomyces* strains with a closely related carba-sugar structure.[1] All the gabosines present a polyoxygenated methyl cyclohexane system as the common constitutional feature (Figure 1). Their structural diversity is originated by differences in the substituent positions, unsaturation degree, and/or relative and absolute configuration of their stereogenic centers. The absolute configurations of natural gabosines A,[1b] B,[2] C,[1a] D,[1b] E,[1b] F,[1b] I,[3] L,[1d] and N[1d] were already determined, whereas those of gabosines G, H, J, and O have not been established yet.

A variety of biological activities have been reported for some of the gabosines. For instance, gabosine C is the known

(1) First isolation of gabosine C, named KD16-U1: (a) Tatsuta, K.; Tsuchiya, T.; Mikami, N.; Umezawa, S.; Umezawa, H.; Naganawa, H. *J. Antibiot.* **1974**, *27*, 579. Isolation and structural assignment of gabosines A−K: (b) Bach, G.; Breiding-Mack, S.; Grabley, S.; Hammann, P.; Hütter, K.; Thiericke, R.; Uhr, H.; Wink, J.; Zeeck, A. *Liebigs Ann. Chem.* **1993**, 241. Synthetic studies indicate that the structure of gabosine K needs to be revised: (c) Metha, G.; Lakshminath, S. *Tetrahedron Lett.* **2000**, *41*, 3509. Isolation and structural assignment of gabosines L, N, and O: (d) Tang, Y.-Q.; Maul, C.; Hoefs, R.; Sattler, I.; Grabley, S.; Feng, X.-Z.; Zeeck, A.; Thiericke, R. *Eur. J. Org. Chem.* **2000**, 149.

(2) Müller, A.; Keller-Schierlein, W.; Bielecki, J.; Rak, G.; Stümpfel, J.; Zähner, H. *Helv. Chim. Acta* **1986**, *69*, 1829.

(3) Lubineau, A.; Billault, I. *J. Org. Chem.* **1998**, *63*, 5668.

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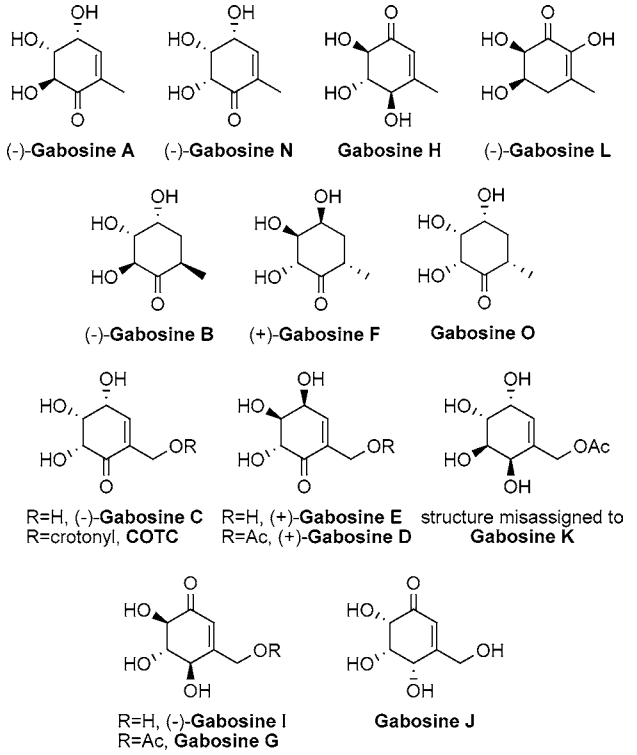
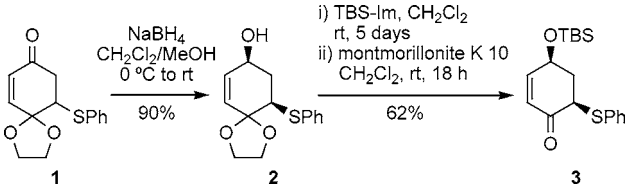


Figure 1. Gabosine family of secondary metabolites: structural classification.

antibiotic KD16-U1 and its crotonyl ester, named COTC, is a potent glyoxylase-I inhibitor that is potentially cytotoxic.[4,5] Gabosine E is a weak inhibitor of cholesterol biosynthesis,[1b] and the antibacterial activity[1a] and DNA-binding properties[1d] of several gabosines have also been described. Their peculiar structure and promising biological activity have motivated synthetic studies directed at these targets. As a result, syntheses of several gabosines have already been accomplished,[6] but a synthetic strategy suitable for a large number of these compounds from common synthetic intermediates has not been described hitherto. We have designed a rational, diversity-oriented approach to these compounds, completed the synthesis of each enantiomer of gabosines O and N and their C4 epimers, and established the previously unknown absolute configuration of natural gabosine O. These studies are described herein.

In previous investigations, we prepared a series of chiral *p*-benzoquinone derivatives and explored their synthetic

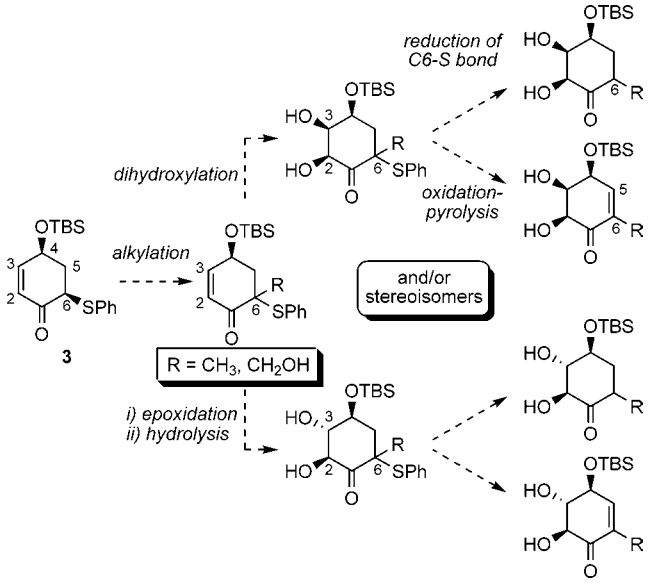
Scheme 1. Conversion of the Masked *p*-Benzoquinone **1** to Ketone **3**



utility. Compound **1** (Scheme 1) is a *p*-benzoquinone equivalent, with one of the carbonyl groups protected by ketalization and one of the carbon−carbon double bonds masked by addition of thiophenol. The racemate of **1** is easily available, and its chromatographic resolution can be efficiently performed.[7] The absolute configuration of (+)- and (−)-**1** was unequivocally established by chemical correlation.[8] Treatment of **1** with $NaBH_4$ exclusively furnishes the cis alcohol **2**, which can be converted to ketone **3** in good overall yield.[8,9]

We visualized ketone **3** as a very suitable starting material to undertake a systematic synthesis of gabosines and other related compounds through the strategy depicted in Scheme 2, which involves three main transformations: (i) alkylation

Scheme 2. Diversity-Oriented Synthetic Strategy to Gabosines and Related Compounds



of the doubly activated C6 position of **3** to introduce the methyl or hydroxymethyl substituent; (ii) dihydroxylation or epoxidation of the double bond to provide the cis or trans C2−C3 glycol unit, respectively; and (iii) reduction of the C6−S bond or oxidation to the sulfoxide followed by

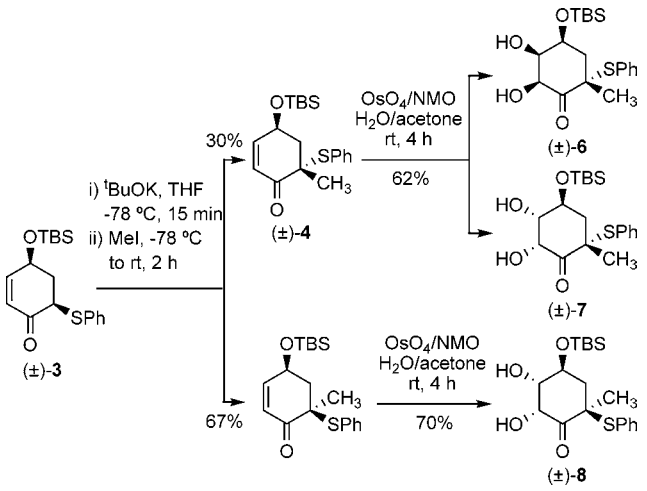
(4) Chimura, H.; Nakamura, H.; Takita, T.; Takeuchi, T.; Umezawa, H.; Kato, K.; Saito, S.; Tomisawa, T.; Iitaka, Y. *J. Antibiot.* **1975**, *28*, 743.
(5)) Sugimoto, Y.; Suzuki, H.; Yamaki, H.; Nishimura, T.; Tanaka, N. *J. Antibiot.* **1982**, *35*, 1222.
(6) Gabosines *ent*-C and E: (a) Lygo, B.; Swiatyj, M.; Trabsa, H.; Voyle, M. *Tetrahedron Lett.* **1994**, *35*, 4197; gabosine C and COTC: (b) Tatsuta, K.; Yasuda, S.; Araki, N.; Takahashi, M.; Kamiya, Y. *Tetrahedron Lett.* **1998**, *39*, 401. (c) Huntley, C. F. M.; Wood, H. B.; Ganem, B. *Tetrahedron Lett.* **2000**, *41*, 2031. (d) Takahashi, T.; Yamakoshi, Y.; Okayama, K.; Yamada, J.; Ge, W.-Y.; Koizumi, T. *Heterocycles* **2002**, *56*, 209. (e) Ramana, G. V.; Rao, B. V. *Tetrahedron Lett.* **2005**, *46*, 3049. Gabosine I: ref 3. (±)-Gabosine B and putative structure of (±)-gabosine K: ref 1c. Gabosine A: (f) Banwell, M. G.; Bray, A. M.; Wong, D. J. *New J. Chem.* **2001**, *25*, 1351. Gabosines A, B, *ent*-D, and *ent*-E: (g) Shinada, T.; Fuji, T.; Ohtani, Y.; Yoshida, Y.; Ohfune, Y. *Synlett* **2002**, 1341.

(7) (a) de March, P.; Escoda, M.; Figueredo, M.; Font, J. *Tetrahedron Lett.* **1995**, *36*, 8665. (b) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Medrano, J. *An. Quim. Int. Ed.* **1997**, *93*, 81.
(8) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; García-García, E.; Rodríguez, S. *Tetrahedron: Asymmetry* **2000**, *15*, 4473.

pyrolysis to generate the C5−C6 double bond, depending on the target gabosine.

The synthetic studies were first undertaken starting from racemic **3**. Treatment of **3** with potassium *tert*-butoxide and an excess of methyl iodide furnished a 1:2.2 mixture of ketones **4** and **5** in 97% total yield (Scheme 3). The epimeric

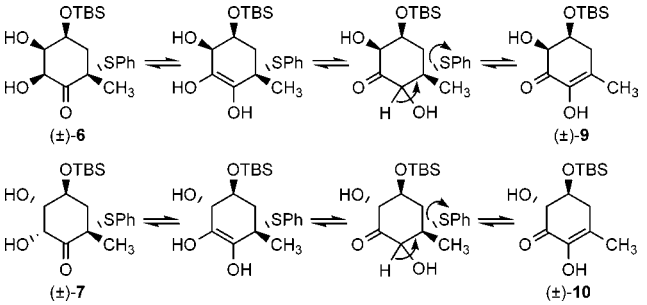
Scheme 3. Partial Synthetic Sequence to Gabosines O and N: The Alkylation and Dihydroxylation Steps



ketones were chromatographically separated, and their relative stereochemistry was assigned by ^{1}H NMR, with the help of nOe experiments. By changing the base to sodium hydride, ketones **4** and **5** could be obtained in ca. 1:1 ratio, although in slightly lower yield. The reaction of ketone **4** with *N*-methylmorpholine *N*-oxide in the presence of osmium tetroxide delivered diols **6** and **7** in a 2.8:1 ratio and 62% total yield. Dihydroxylation of ketone **5** under the same reaction conditions furnished exclusively diol **8**. These results suggest that the stereoselectivity of the reaction is directed by steric factors, with the oxidant reagent approaching the enone mainly on the face opposite to the bulky phenylsulfenyl group.[10]

Intended chromatographic separation of **6** and **7** led to the isolation of significant quantities of enones **9** and **10** (Scheme 4), in detriment of the initially produced sulfenyl ketones.

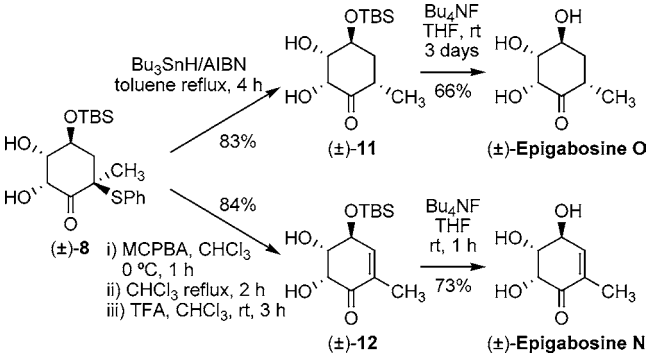
Scheme 4. Proposed Mechanism for the Formation of **9** and **10** during the Chromatographic Purification (Silica Gel) of **6** and **7**



These new enones are likely to be formed via various keto−enolic equilibria, which favor the elimination of thiophenol. During the chromatographic purification of dihydroxyketone **8**, enones **9** and **10** were also detected; however the degradation process was less important in this case, and ketone **8** could be isolated in 70% yield. Therefore, the synthetic pathway was first continued with this intermediate.

Standard desulfurization of **8**, followed by O-desilylation gave a new compound, the C4 epimer of gabosine O, which we have named epigabosine O, whereas sulfide oxidation followed by pyrolysis of the sulfoxide and desilylation furnished the hitherto unknown epigabosine N (Scheme 5).

Scheme 5. Final Steps of the Synthesis of Epigabosines O and N



We next assessed the same transformations starting from a 2.8:1 mixture of diastereomeric ketones **6** and **7** (Scheme 6). Desulfurization provided the expected ketone **13** derived from **6** as the major product, along with a minor quantity of ketone **11**, presumably formed by reduction of **7** and C6 epimerization. The major isomer **13** was isolated in 53% yield and converted to gabosine O by desilylation. The oxidation−pyrolysis protocol applied to a 3.3:1 mixture of **6** and **7** furnished a mixture of enones **14** and **12**, from where the major isomer **14** was separated in 60% yield and converted to gabosine N.

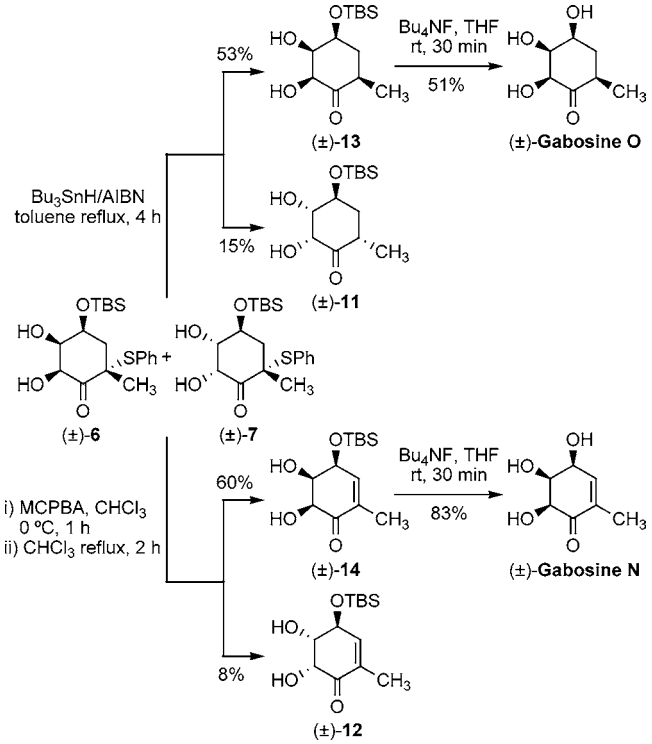
Having completed the aforementioned syntheses, our preparation of enantiopure gabosines required us to repeat the former sequences, starting from enantiopure (+)- and/or (−)-**2**. This endeavor was particularly interesting in the case of gabosine O, for which the absolute configuration of the levorotatory natural antipode was still unknown.

As already mentioned, the enantiomers of **2** were available by reduction of the precursor ketone (+)- or (−)-**1**, which can be resolved by liquid chromatography on cellulose triacetate on a scale of several hundred milligrams.[8] Nevertheless, to avoid tedious chromatographic separations, we decided to investigate an alternative route to (+)- and (−)-**2**. We found that treatment of (±)-**2** with vinyl acetate

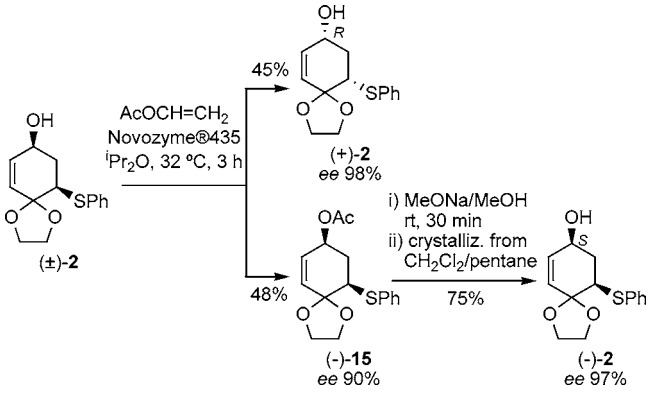
(9) Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Marjanet, G. *Tetrahedron: Asymmetry* **2004**, *15*, 1151.

(10) For sterically controlled facial selectivity in dihydroxylation reactions of related systems, see: Kwon, Y.-U.; Lee, C.; Ghung, S.-K. *J. Org. Chem.* **2002**, *67*, 3327.

Scheme 6. Final Steps of the Synthesis of Gabosines O and N



Scheme 7. Enzymatic Resolution of (±)-**2**



and a catalytic amount of Novozyme 435 in diisopropyl ether[11] furnished the acetate (−)-**15** in 43% yield and 90% ee and the unreacted alcohol (+)-**2** in 45% yield and 98% ee[12] (Scheme 7). Methanolysis of the acetate (−)-**15** led to the recovery of (−)-**2** whose ee was raised to 97% by repeated crystallization from dichloromethane/pentane with 75% chemical yield.

Starting from (+)-**2**, we completed the synthesis of (−)-gabosine N ($[\alpha]_D = -142°$ (*c* 0.16, MeOH)),[13] (−)-gabosine O ($[\alpha]_D = -10.5°$ (*c* 0.38, MeOH)), (−)-epigabosine N ($[\alpha]_D = -92°$ (*c* 0.26, MeOH)), and (−)-epigabosine O ($[\alpha]_D = -8.2°$ (*c* 0.49, MeOH)). Starting from (−)-**2**, we synthesized (+)-gabosine N ($[\alpha]_D = +180°$ (*c* 0.15, MeOH)),[13] (+)-gabosine O ($[\alpha]_D = +20°$ (*c* 0.30, MeOH)),[13] (+)-epigabosine N ($[\alpha]_D = +120°$ (*c* 0.40, MeOH)), and (+)-epigabosine O ($[\alpha]_D = +12.2°$ (*c* 0.49, MeOH)). The absolute configuration of natural gabosine O was thus established as 2*R*,3*R*,4*R*,6*S*.

In summary, a general strategy has been designed for the synthesis of gabosines and other related compounds which has been successfully applied to several carba-sugars with cis C2/C3 relative configuration. Work is in progress to complete the synthesis of other related targets, including those with trans C2/C3 relative configuration.

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Supporting Information Available: Experimental procedures, a listing of spectral data of new compounds, significant ^{1}H- and ^{13}C NMR spectra, and CHPLC chromatograms of **2** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) See related resolutions in: (a) Morgan, B. S.; Hoenner, D.; Evans, P.; Roberts, S. M. *Tetrahedron: Asymmetry* **2004**, *15*, 2807. (b) Raminelli, C.; Comasseto, J. V.; Andrade, L. H.; Porto, A. L. M. *Tetrahedron: Asymmetry* **2004**, *15*, 3117.

(12) Enantiomeric excesses were determined by CHPLC analyses.

(13) Gabosine N: lit.[1d] −152° (*c* 0.89, H_2O). Gabosine O: lit.[1d] −21.0° (*c* 0.1, MeOH).