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Carbocyclization of Carbohydrates: Diastereoselective Synthesis of (+)-Gabosine F, (−)-Gabosine O, and (+)-4-*epi*-Gabosine O

Tony K. M. Shing,* King H. So, and Wun S. Kwok

Department of Chemistry and Center of Novel Functional Molecules, The Chinese Univeristy of Hong Kong, Shatin, Hong Kong, China

tonyshing@cuhk.edu.hk

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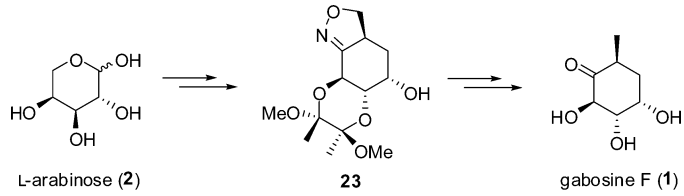
ABSTRACT



Exploitation of silica gel/chloramine T mediated intramolecular nitrile oxide−alkene cycloaddition (INOC) of sugar-derived oximes to carbocycles furnished the first synthesis of gabosine F from L-arabinose in 12 steps with 23% overall yield, thereby confirming its absolute configuration. Similarly, efficient syntheses of gabosine O and 4-*epi*-gabosine O were accomplished from D-mannose in 9 and 11 steps with 41% and 38% overall yields, respectively, involving INOC, regioselective dehydration, and diastereoselective hydrogenation as the key steps.

Gabosines (Figure 1) belong to a family of hydroxylated cyclohexenones and cyclohexanones that have been shown to display interesting bioactivities such as antibiotic, anticancer, and DNA binding properties.[1] Since the first isolation of gabosine C (**6**) from *Streptomyces* strains in 1974,[2] 15 other gabosines have been isolated. Within the family, gabosines B (**7**), F (**1**), and O (**3**) are saturated cyclohexanones, while the others are unsaturated cyclohexenones.

Previously, our group has successfully developed a short route to prepare unsaturated gabosines G (**8**) and I (**9**) from δ-D-gluconolactone via a key intramolecular Horner−Wadsworth−Emmons olefination.[3] In this paper, we focus on the syntheses of optically active gabosines with a saturated carbocycle.

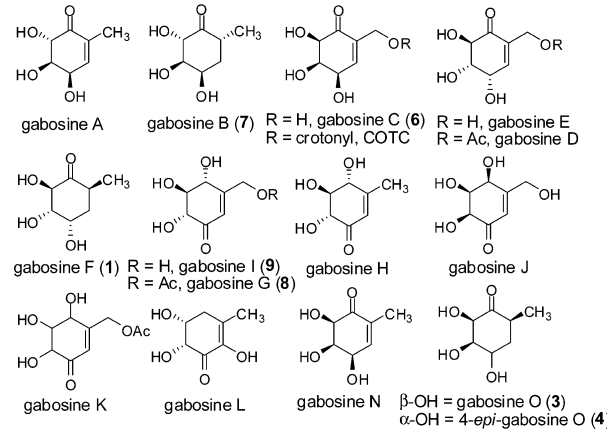


Figure 1. The gabosine family.

The first synthesis of racemic gabosine B (**7**) was achieved by Mehta and Lakshminath in 14 steps from 5,5-dimethox-

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ytetrachlorocyclopentadiene, giving a mixture of *rac*-gabosines B (**7**) and F (**1**), using the Grob-like "top-to-bottom" fragmentation as the key step.[4] Enantiopure gabosine B (**7**) was constructed by Shinada et al., starting from (−)-quinic acid and using a Mislow−Evans rearrangement as the key step, in 15 steps with 4.3% overall yield.[5] However, there is still no report on the synthesis of enantiopure gabosine F (**1**), which is the enantiomer of gabosine B (**7**).

The first synthesis of gabosine O (**3**) was accomplished by Figueredo et al. in 2006, using *p*-benzoquinone ethylene bisketal as the starting material and an enantioselective acetylation as the key step, in 11 stages with 0.9% overall yield.

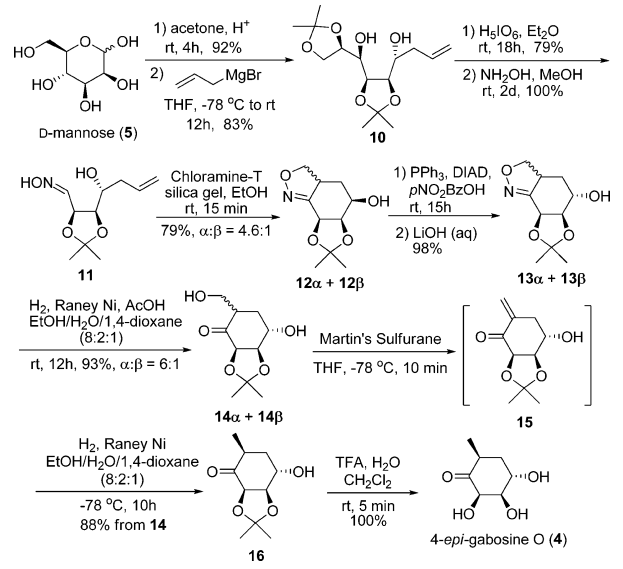
4-*epi*-Gabosine (**4**) was also obtained in 11 steps with an overall yield of 4.6%.[6] One year later, Carreño et al. reported a new synthesis of gabosine O (**3**) using enantiopure (*SR*)- and (*SS*)-[(p-tolylsulfinyl)methyl]-*p*-quinols as the chiral intermediates that allowed stereocontrolled conjugate additions of organoaluminium reagents to the cyclohexadienone. The asymmetric synthesis started from *p*-benzoquinone dimethyl monoketal and furnished gabosine O (**3**) in 10 steps with 13% overall yield.[7]

To synthesize gabosines with a saturated carbocycle, stereoselective construction of the carbocyclic framework is usually the key step. Previously, our group reported that silica gel/chloramine T mediated intramolecular nitrile oxide−alkene cycloaddition (INOC) of oximes with free hydroxy groups derived from carbohydrates afforded hydroxylated cycloadducts with excellent yields.[8]

Exploiting this facile construction of carbocycles from carbohydrates, we found that these INOC cycloadducts were converted readily into the saturated gabosines in a few steps and herein we report the first synthesis of enantiopure gabosines F (**1**) from L-arabinose (**2**), thereby confirming its absolute configuration. We also report efficient syntheses of gabosine O (**3**) and 4-*epi*-gabosine O (**4**) from D-mannose (5) with excellent overall yields.

The synthetic avenue toward 4-*epi*-gabosine O (**4**) is shown in Scheme 1 and starts from D-mannose (**5**). According to our previous endeavor,[8] D-mannose (**5**) was converted into oxime **11** via a sequence of reactions involving acetonation,[9] Grignard allylation, regioselective glycol cleavage oxidation,[10] and oximation in good overall yield. The oxime **11** cyclized through a silica gel/chloramine-T mediated INOC reaction to provide epimeric isoxazolines **12α** and **12*β*** in 65% and 14% yield, respectively.

Scheme 1. Synthesis of 4-*epi*-Gabosine O (**4**)



The configuration of the free alcohol in cycloadduct **12** was inverted by Mitsunobu reaction[11] followed by ester hydrolysis, resulting in almost quantitative transformation with either of the epimers **12α** or **12*β***, or the mixture. Alcohols **13α** and **13*β*** were therefore obtained in 49% overall yield from D-mannose in 7 steps.

Pure isoxazoline **13α** underwent hydrogenolysis with Raney-Ni/acetic acid[12] to give the corresponding hydroxy ketone. Interestingly, not only ketone **14α** but also **14*β*** were obtained. The longer the reaction time, the more **14*β*** emerged until an equilibrium was reached after 12 h where the ratio of **14α** to **14*β*** was 6:1. The ketones appeared to epimerize under the conditions. Pure isoxazoline **13*β*** also underwent hydrogenolysis and epimerization. The reaction reached equilibrium quickly in 2 h, resulting in the same ratio of ketones. Thus, both ketones **14α** and **14*β*** were obtained in a ratio of 6:1 regardless of the starting material (pure **13α** or **13*β*** or a mixture of both). It was more convenient to work on the mixture of epimers (**14α** + **14*β***) because the stereochemistry of C-6 would be lost in the subsequent elimination step.

Regioselective activation of the primary alcohol followed by elimination was then studied to access enone **15**. Attempts with activating reagents such as methanesulfonyl chloride, triflic anhydride, TFAA, or Martin's sulfurane were fruitless. Re-examination of the reaction showed that the enone started to decompose above −20 °C, indicating that the enone **15** generated had to be transformed into the next stage in one pot at low temperature.

Martin's sulfurane was chosen because it causes activation and elimination in one pot without the addition of an external

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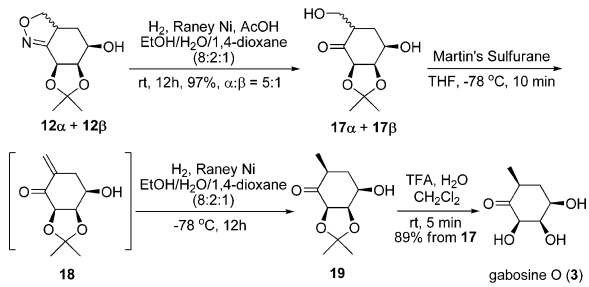
base.[13] However, it is usually employed for secondary and tertiary alcohols efficiently, while primary alcohols typically form ether-dimers instead of the elimination product.[14] In this instance, however, when a mixture of **14α** and **14*β*** was reacted with Martin's sulfurane at −78 °C, the enone **15** was generated. It could be reduced smoothly and stereoselectively at the alkene moiety to give the corresponding *β*-methyl ketone **16** via catalytic hydrogenation with Raney-Ni at −78 °C in excellent overall yield. The desired (*S*)-methyl group emerged because the *β*-face of **15** was hindered by the bulky isopropylidene ring and the hydrogen could be delivered from the less hindered α-face selectively. The stereochemistry of ketone **16** was confirmed by ^{1}H NMR spectral analysis.[15]

Mild acid hydrolysis of ketone **16** afforded target **4** in a quantitative yield and with spectral data in good agreement with the literature values. 4-*epi*-Gabosine O (**4**) was thus synthesized from D-mannose (**5**) in 11 steps with 38% overall yield. This is the first enantiospecific synthesis of 4-*epi*-gabosine O (**4**) with specific rotation [α] +15.6 (*c* 0.30, MeOH), which is in accord with that of the previous enantioselective synthesis {[α] +12.2 (*c* 0.49, MeOH)}.[6] The overall yield of our route (11 steps, 38%) was much higher than that of the previous synthesis[6] (11 steps, 4.6% overall yield).

Using the aforesaid strategy, synthesis of natural gabosine O (**3**) started from the mixture of isoxazolines **12α** and **12*β***, which was converted into the mixture of ketones **17α** and **17*β*** via hydrogenolysis with Raney-Ni in acetic acid (Scheme 2). The two ketones were in equilibrium and the ratio of

Scheme 2. Synthesis of Gabosine O (**3**) from **12**

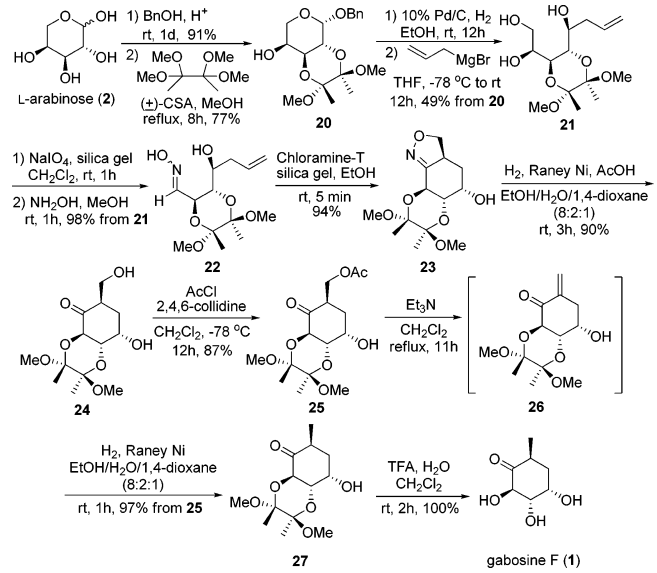


17α to **17*β*** eventually attained 5:1, respectively. These underwent regioselective dehydration of the primary alcohol with Martin's sulfurane at −78 °C to enone **18** followed by catalytic hydrogenation with Raney-Ni to give 2,3-*O*-isopropylidene gabosine O (**19**). The stereoselectivity of the hydrogenation of enone **18** was rationalized in a way similar to that of enone **15** described above.

The acetonide **19** was then hydrolyzed to afford natural gabosine O (**3**) that was synthesized from D-mannose (**5**) in 9 steps with 41% overall yield. The specific rotation, [α] +21.0 (*c* 0.07, MeOH), and the NMR spectral data are in good agreement with the literature values.[6,7] This is also the first enantiospecific synthesis of Gabosine O (**3**), and the overall yield was much higher than that of the previous construction performed by Figueredo et al. (11 steps, 0.9% overall yield) in 2006[6] and Carreño et al. (10 steps, 13% overall yield) in 2007.[7]

The synthetic route toward gabosine F (**1**) is shown in Scheme 3 and starts from L-arabinose (**2**). Our previous

Scheme 3. Synthesis of Gabosine F (**1**)



work[8] has shown that L-arabinose (**2**) was transformed into oxime **22** via a reaction sequence involving benzyl glycosidation,[16] diacetalization,[17] hydrogenolytic debenzylation, Grignard allylation, glycol cleavage oxidation,[18] and oximation in good overall yield. The silica gel/chloramine T mediated INOC of oxime **22** occurred to give cycloadduct **23** in 94% yield.

The heterocyclic ring in isoxazoline **23** was hydrogenolyzed over Raney-Ni smoothly to give hydroxy ketone **24**. Regioselective acetylation[19] of the primary alcohol in **24** with collidine as base furnished acetate **25** in 87% yield. Elimination of acetic acid from α-acetoxy ketone **25** with triethylamine gave the corresponding exocyclic enone **26**. The stability of this enone **26**, in contrast to **15** and **18**, might be ascribed to the *trans*-diacetal protecting group, which resembles a stable *trans*-decalin system. Catalytic hydrogenation over Raney nickel afforded the *β*-methyl ketone **27**. The stereoselectivity of the hydrogenation might be attribut-

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able to the "anchor effect" of the axial free α-alcohol,[20] which directed the approach of the hydrogen from the α-face, thus leading to the desired β-methyl ketone **27**.

Removal of the *trans*-diacetal blocking group then furnished the target molecule gabosine F (**1**). The specific rotation, [α] +88.4 (*c* 0.69, MeOH) {lit. [α] +94 (*c* 1.0, MeOH)}, and the NMR spectral data are in good agreement with the literature values.[1a] Thus enantiopure gabosine F (**1**) was synthesized for the first time from L-arabinose (**2**) in 12 steps with 23% overall yield, thereby confirming the absolute configuration of the natural product.

In conclusion, facile and efficient carbocyclization of carbohydrate derivatives to provide hydroxylated cyclohexanones has been demonstrated by using the high-yielding silica gel/chloramine T mediated intramolecular nitrile oxide−alkene cycloaddition (INOC) of sugar-derived oximes to furnish enantiospecific and efficient syntheses of gabosine O (**3**) and 4-*epi*-gabosine O (**4**) from D-mannose (**5**) in 9 and 11 steps with 41% and 38% overall yields, respectively. These chemical yields are superior to those reported previously. By using the same strategy, the first enantiospecific synthesis of optically pure gabosine F (**1**) was achieved from L-arabinose (**2**) in 12 steps with an overall yield of 23%, thereby confirming the absolute configuration of the natural product. All three syntheses involved an INOC reaction, a regioselective dehydration, and diastereoselective hydrogenation as the key steps. The present carbocyclization of sugar derivatives should provide a facile and valuable entry to the construction of enantiopure hydroxylated cyclohexanoid natural products and pharmaceuticals.

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Supporting Information Available: Additional information, experimental procedures, and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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