Total Synthesis of Gabosine H

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Abstract: Stereoselective total synthesis and assignment of the absolute configuration of the keto carba sugar gabosine H is presented. Pivotal reactions in the sequence include desymmetrization of the dimethylamide of tartaric acid and ring-closing metathesis.

Key words: gabosine H, natural products, stereoselective synthesis, ring-closing metathesis

Gabosines are secondary metabolites comprising hydroxylated branched cyclohexanone derivatives isolated from the culture broths of a number of *Streptomycetes* by Zeeck's group.[1] These compounds are also termed keto carba sugars owing to the replacement of the ring-oxygen atom of a cyclic monosaccharide with carbon. Hitherto, 14 gabosines have been isolated, and the absolute configuration of some of the gabosines has been established with the stereochemistry of others assigned by analogy. Although, gabosines do not possess any appreciable bioactivity, gabosine incorporated compounds exhibit a varied bioactive profile. This has led to the synthesis of gabosines by a number of research groups. Most of the syntheses involve chiral pool carbohydrates or quinic acid as the starting materials, while other asymmetric methodologies including a chemoenzymatic synthesis have also been reported.[2] Although, these reports are concerned with the synthesis of several of the gabosines, to the best of our knowledge no synthesis of gabosine H has been reported in the literature. Gabosine H (Figure 1) was isolated from the culture broth of *Streptomyces chromofuscus*, and the relative configuration was assigned by extensive NMR experiments. As a part of our program in the synthesis of natural products from tartaric acid, we report herein the total synthesis of gabosine H and assignment of its absolute stereochemistry.

Our approach to the synthesis of gabosine H is depicted in Scheme 1. Formation of the cyclohexenone was anticipated by ring-closing metathesis of the diene **2**, preparation of which was envisaged by addition of vinylmagnesium bromide to the γ-hydroxy amide **3**. Formation of the γ-hydroxy amide was proposed by desymmetrization of the bisdimethyl amide **4** of tartaric acid involving controlled addition of 2-propenylmagnesium bromide followed by stereoselective reduction.[3] Although, addition of vinylmagnesium bromide to the bis-Weinreb amide derived from tartaric acid leading to the 1,4-diketone is documented,[4] to the best of our knowledge, preferential formation of a monoketoamide by desymmetrization of the tartaric acid amide with controlled addition of such Grignard reagents has not been reported.

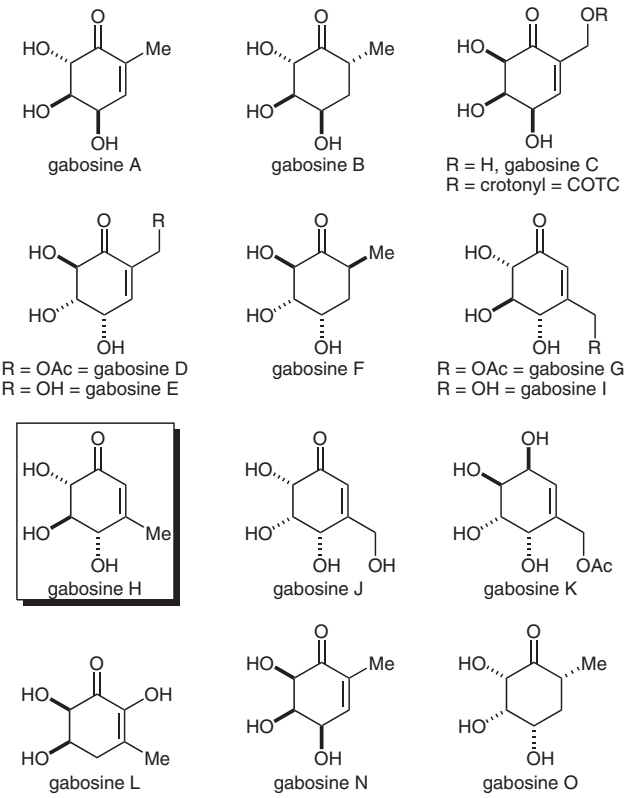

Figure 1 Gabosines isolated from a number of *Streptomycetes*

Owing to the reactivity of the resultant α,β-unsaturated ketone as a Michael acceptor, it is challenging to synthesize similar monoketoamides by addition of vinylmagnesium bromides. However, synthesis of such a ketone would pave the way to differently substituted cyclohexenols and hence the synthesis of a number of other natural products.

Accordingly, careful addition of 1.5 equivalents of 2-propenylmagnesium bromide to the bisdimethylamide **4** furnished the monoketoamide **5** in 84% yield.[5] Reduction of the keto group in **5** with $NaBH_4$ in presence of $CeCl_3$ furnished the alcohol in 93% yield in 9:1 ratio.[6] Careful crystallization led to the isolation of the pure diastereomer **3** in 83% yield. Addition of vinylmagnesium bromide to **3** led to the α,β-unsaturated ketone **2** in 65% yield. Ring-closing metathesis (RCM) of **2** with Grubbs second-generation

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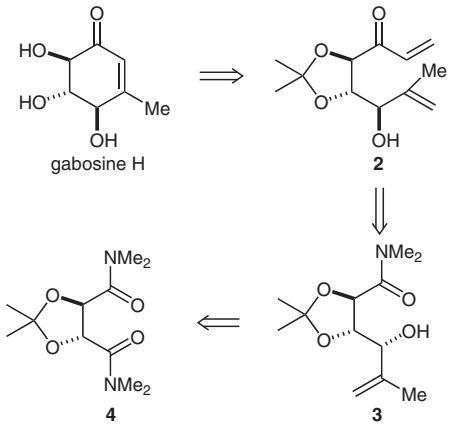
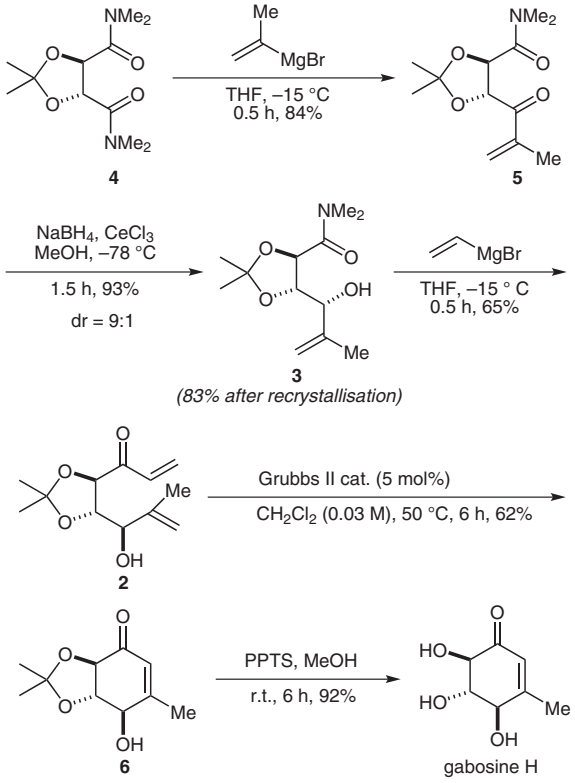


Scheme 1 Retrosynthesis for gabosine H

catalyst resulted in the cyclohexenone **6** in 62% yield. Deprotection of the acetonide in **6** by treating with PPTS in methanol afforded gabosine H in 92% yield (Scheme 2). Spectroscopic data of the synthesized gabosine H are the same as those of the natural product reported.[7] Furthermore, we confirm the absolute stereochemistry of gabosine H as 2*R*,3*S*,4*R* based on the specific rotation determined for our synthetic sample $[\alpha]_D$ –74 (*c* 0.6, MeOH) compared with the isolated natural product {lit[1] $[\alpha]_D$ –68.3 (*c* 0.58, MeOH)}.



Scheme 2 Total synthesis of gabosine H

In conclusion, a concise synthesis of gabosine H, a trihydroxycyclohexenone, was accomplished from tartaric acid amide in a five-step sequence. The key reaction in the synthesis is the formation of a γ-hydroxyamide derived from tartaric acid involving desymmetrization by controlled addition of 2-propenylmagnesium bromide and stereoselective reduction. Further application of this strategy for different gabosines is under way.

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(5) Formation of minor amounts of 1,4-diketone resulting from the addition of Grignard reagent to both amides is observed.

(6) The dr of the product alcohol was estimated to be 9:1 by ^{1}H NMR.

(7) All compounds exhibited satisfactory analytical data. Compound **5**: $[\alpha]_D$ –25.5 (*c* 2.6, $CHCl_3$). IR (neat): 2989,

2938, 1654, 1374, 1157, 1054 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.29 (s, 1 H), 6.00 (d, *J* = 1.0 Hz, 1 H), 5.68 (d, *J* = 5.8 Hz, 1 H), 4.99 (d, *J* = 5.8 Hz, 1 H), 3.16 (s, 3 H), 2.98 (s, 3 H), 1.90 (s, 3 H), 1.44 (s, 3 H), 1.43 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.4, 168.0, 142.3, 128.8, 112.2, 78.1, 75.1, 37.0, 35.8, 26.3, 26.2, 17.5. HRMS: *m/z* calcd for $C_{12}H_{19}NO_4$ + Na: 264.1212; found: 264.1205.

Compound **3**: mp 74–75 °C; $[\alpha]_D$ –26.5 (*c* 1.8, $CHCl_3$). IR (KBr): 3386, 2970, 2984, 2948, 1641, 1057, 1040, 890 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.06 (s, 1 H), 4.95 (s, 1 H), 4.82–4.79 (m, 1 H), 4.52 (d, *J* = 7.0 Hz, 1 H), 4.08 (dd, *J* = 7.9, 3.0 Hz, 1 H), 3.13 (s, 3 H), 2.96 (s, 3 H), 2.59 (d, *J* = 8.2 Hz, 1 H), 1.82 (s, 3 H), 1.46 (s, 3 H), 1.38 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 144.7, 112.1, 110.6, 78.6, 74.6, 73.7, 37.0, 35.7, 26.8, 26.1, 18.8. HRMS: *m/z* calcd for $C_{12}H_{21}NO_4$ + Na: 266.1368; found: 266.1357.

Compound **2**: $[\alpha]_D$ +23.3 (*c* 1.8, $CHCl_3$). IR (neat): 3459, 2989, 2924, 1699, 1609, 1403, 1374, 1213, 1088, 1061 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.82 (ddd, *J* = 17.4, 10.6, 2.4 Hz, 1 H), 6.45 (ddd, *J* = 17.4, 2.4, 1.5 Hz, 1 H), 5.86 (ddd, *J* = 17.4, 2.4, 1.5 Hz, 1 H), 5.04–4.96 (m, 2 H), 4.51–4.49 (m, 1 H), 4.38–4.34 (m, 1 H), 4.13–4.12 (m, 1 H), 2.50–2.48 (br s, 1 H), 1.79 (s, 3 H) 1.49 (s, 3 H) 1.34 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7, 144.1, 131.5, 130.8, 113.0, 111.3, 80.8, 78.7, 74.7, 26.8, 26.0, 18.6. HRMS: *m/z* calcd for $C_{12}H_{18}O_4$ + Na: 249.1103; found: 249.1101.

Compound **6**: mp 122–126 °C; $[\alpha]_D$ +88.2 (*c* 1.0, $CHCl_3$). IR (KBr): 3453, 2989, 2929, 2873, 1708, 1378, 1232, 1072, 1059 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.86 (s, 1 H), 4.55 (br d, *J* = 7.4 Hz, 1 H), 4.09 (d, *J* = 10.7 Hz, 1 H), 3.85 (dd, *J* = 10.4, 8.4 Hz, 1 H), 3.45–3.25 (br s, 1 H), 2.07 (s, 3 H), 1.46 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4, 161.3, 125.8, 113.0, 81.4, 79.7, 73.5, 26.8, 26.5, 19.5. HRMS: *m/z* calcd for $C_{10}H_{14}O_4$ + Na: 221.0790; found: 221.0802.

Gabosine H: mp 118–119 °C; $[\alpha]_D$ –74.0 (*c* 0.6, MeOH). IR (KBr): 3431, 2894, 2876, 1657, 1625 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 5.92 (s, 1 H), 4.23 (d, *J* = 8.4 Hz, 1 H), 4.01 (d, *J* = 10.8 Hz, 1 H), 3.56 (dd, *J* = 10.8, 2.4 Hz, 1 H), 2.07 (s, 3 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 199.4, 165.7, 125.0, 79.1, 78.0, 75.1, 20.0. HRMS: *m/z* calcd for $C_7H_{10}O_4$ + Na: 181.0477; found: 181.0477.