Syntheses of Gabosine A, B, D, and E from Allyl Sulfide Derived from (–)-Quinic Acid

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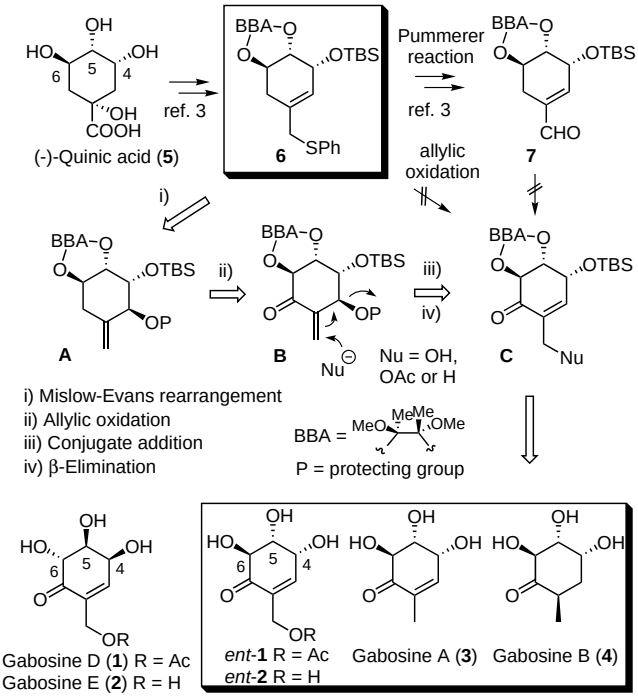
Abstract: An efficient conversion of allyl sulfide **6** prepared from (–)-quinic acid (**5**) to gabosines was achieved by a series of sequential reactions: i) Mislow–Evans rearrangement, ii) SeO_2 oxidation, iii) conjugate addition of sodium hydroxide or sodium acetate, and iv) elimination of the methoxymethyloxy group.

Key words: gabosine, cyclitol, allyl sulfide, quinic acid, conjugate addition

Gabosines isolated from *Streptomyces* strains are a class of carba-sugars bearing 2-methylcyclohexane as their common carbon skeleton (Scheme 1).[1] Gabosines and their related natural products are known to exhibit a variety of biological activities such as antiprotozoal activity, DNA binding properties, and inhibition of glyoxalase-I and glycosidases.[1] Their diverse activities and highly oxygenated structures have prompted extensive synthetic studies focusing on preparative efficiency and regio- and stereoselective construction of the concomitant hydroxy groups onto the 2-methylcyclohexane framework.[2] We wish to report herein a new and efficient entry to the syntheses of gabosine A and B, and enantiomers of gabosine D and E starting with allyl sulfide **6** derived from (–)-quinic acid in a highly stereoselective manner.

Novel features of the present work are the use of allyl sulfide **6**[3] as a common synthetic precursor in which consecutive trihydroxy groups at C4, C5, and C6 corresponding to gabosines are already installed. Consequently, the key step to the present syntheses focused on the conversion of the allyl sulfide moiety into conjugated α,β-unsaturated cyclohexenone **C**, a plausible precursor common to gabosines. Preliminary experiment was conversion of **6** or **7** to the key intermediate **C**. However, the allylic oxidation of **6** with SeO_2 was unsuccessful, giving an undesired aldehyde **7** in poor yield. Similarly, allylic oxidation of **7** prepared by Pummerer reaction from **6**[3] resulted in recovery of the starting material. These facts prompted us to examine a stepwise approach to the desired **C** which involves: i) conversion to *exo*-methylene alcohol **A** by Mislow–Evans rearrangement,[4] ii) allylic oxidation leading to **B**,[5] and iii) conjugate addition of a nucleophile such as hydride, hydroxide, or acetate to **B**, iv) β-elimination of the OP group to produce **C**.



Scheme 1

Initially, we examined the conversion of **6** to *exo*-methylene compound **12** which corresponds to **B** in Scheme 2. Oxidation of allyl sulfide **6** with *m*CPBA afforded a 1:1 mixture of sulfoxide **8** which, upon thermolysis in the presence of $(EtO)_3P$, provided allyl alcohol **9** as a single diastereomer in 98% yield.[6,7] Allyl alcohol **9** was protected with a methoxymethyl (MOM) group to give MOM ether **10**. Allylic oxidation of **10** using SeO_2 in the presence of pyridine *N*-oxide as a co-oxidant gave a mixture of α,β-unsaturated ketone **12**,[8] and alcohols **11a** and **11b**.[7] Yields and ratios of the above allylic oxidation varied according to the amount of SeO_2 and pyridine *N*-oxide. As a result, the best total yields (81%) of α,β-unsaturated ketone **12** and the mixture of **11a** and **11b** were obtained under the optimized conditions (1 equiv of SeO_2 and 0.5 equiv of pyridine *N*-oxide in dioxane). A mixture of alcohols **11a** and **11b** was smoothly oxidized to the ketone **12** by the Albright–Goldman oxidation.[9]

Our next attempts were the conversion of the unsaturated ketone **12** into the enantiomers of gabosine D (**1**) and E (**2**), respectively, via a conjugate addition of water or acetate followed by β-elimination of the methoxymethyloxy (MOMoxy) group at C3 (Scheme 2). Conjugate addition

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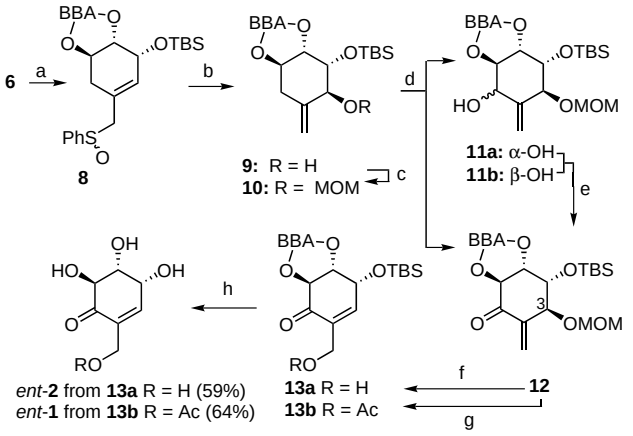
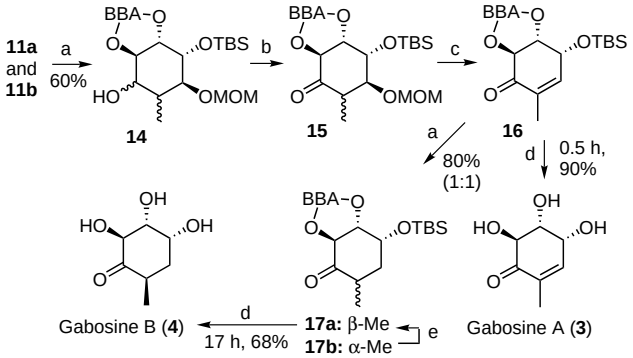


Scheme 2 Conditions: a) 1.4 equiv *m*CPBA, CH_2Cl_2, 20 min (90%). b) $(EtO)_3P$, EtOH, reflux, 16 h (98%). c) MOMCl, 2 equiv *i*-Pr_2NEt, CH_2Cl_2, 16 h (90%). d) 1 equiv SeO_2, 0.5 equiv pyridine *N*-oxide, 1,4-dioxane, reflux, 16 h (**11a**, **11b** (1:1 → 3:2), 54%; **12**, 27%). e) Ac_2O, DMSO (3:2), 18 h (65%). f) 0.1 N NaOH, THF (1:9), 40 min (68%). g) 5 equiv AcONa, AcOH, 110 °C, 2.5 h (71%). h) TFA–H_2O (1:20), CH_2Cl_2, 2–4 h.

of H_2O in the presence of a weak base such as DABCO was unsuccessful, resulting in recovery of **12** even at elevated temperature (~100 °C). On the other hand, the use of 0.1 N sodium hydroxide afforded the desired allyl alcohol **13a** in 68% yield. Similarly, an acetoxy group was introduced to **12** using sodium acetate in acetic acid to afford acetate **13b** in 71% yield. The protecting groups of **13a** and **13b** were removed with TFA to give *ent*-**2** and *ent*-**1**, respectively. The spectroscopic data of the synthetic *ent*-**2** and *ent*-**1** were identical in all respects with those of the natural products, respectively, except for the sign of optical rotation.[1c]



Scheme 3 Conditions: a) 10% Pd–C (50% w/w), H_2, MeOH, 6 h. b) 1.2 equiv Dess–Martin periodinane, CH_2Cl_2 (67%), 4.5 h. c) 0.1 N NaOH, THF, 3 h (81%). d) TFA, H_2O (1:20), CH_2Cl_2. e) 0.5 equiv DBU, C_6H_6, reflux, 16 h (89%).

It was envisioned that the addition of hydride to **12** would provide a common intermediate **16** for the syntheses of gabosines A (**3**) and B (**4**). However, several attempts for the 1,4-conjugate reduction, using the Wilkinson catalyst/H_2, CuCl/$PhMe_2SiH$, or $Pd(OAc)_2/Et_3SiH$ were unsuccessful, giving the starting **12** as the major product. Therefore, we examined an alternative approach to **16** involving: i) catalytic hydrogenation of the *exo*-olefin group of **11a** and **11b**, ii) oxidation to ketone **15**, and iii) β-elimination of the MOMoxy group (Scheme 3). Hydrogenation of the mixture of **11a** and **11b** followed by oxidation using Dess–Martin periodinane afforded ketone **15**, whose exposure to aqueous sodium hydroxide effected elimination of the MOMoxy group to give the desired unsaturated ketone **16**. Removal of the protecting groups with TFA gave gabosine A (**3**). It has been reported that hydrogenation of **3** gave **4** in only 22% yield.[1c] We repeated the same procedure and found that the reaction gave a mixture of **4** and its α-Me isomer (1:1) in poor yield. From these results, we considered that protected **16** would be an appropriate precursor for this conversion in view of the stereoselectivity and the product yield. Protected **16** was subjected to the hydrogenation, leading to a mixture of **17a** and **17b** in 80% yield. However, the ratio was 1:1. Since the α-methyl group of **17b** is placed in an axial orientation on the conformationally rigid bicyclic ring, we assumed that **17a** would be epimerized to β-isomer **17a**. As expected, **17b** underwent epimerization by treatment with DBU to give the desired **17a**, which, upon deprotection with TFA, gave gabosine B (**4**). The spectroscopic data and optical rotation of the synthetic **3** and **4** were identical in all respects with those of the natural products.[1c,2d,10]

In conclusion, we have demonstrated an efficient conversion of allyl sulfide **6** to gabosines A, B, *ent*-D, and *ent*-E in a highly regio- and steroselective manner. The present synthesis involves several stereoselective transformations on the cyclohexane ring as exemplified by Mislow–Evans rearrangement and epimerization of **17b** to **17a**. These results would provide new insight into the syntheses of carba-sugars and other cyclitols via allyl sulfide **6** as the useful synthetic precursor.

Acknowledgement

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