The Structure and Stereochemistry of Gabosine K: Syntheses of 7-*O*-Acetylstreptol and 7-*O*-Acetyl-1-*epi*-streptol

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Abstract: Gabosine K, whose structure was erroneously assigned previously as 7-*O*-acetyl-4-*epi*-streptol, has been synthesized for the first time from D-glucose via a key carbocyclization strategy, intramolecular direct aldol reaction of a 2,6-diketone, in 15 steps with 13.5% overall yield. In the same manner, (+)-7-*O*-acetyl-streptol has been constructed for NMR spectral comparison. The structure, relative and absolute configurations of (–)-gabosine K are now revised and established as (–)-7-*O*-acetyl-1-*epi*-streptol, that is, (1*R*,2*S*,3*S*,4*R*)-tetrahydroxy-5-acetoxymethylcyclohex-5-ene.
Since the specific rotation of the natural product is not available, the absolute configuration of natural gabosine K is either (–)-7-*O*-acetyl-1-*epi*-streptol or its enantiomer.

Key words: carbasugars, carbohydrates, stereoselective synthesis, aldol reactions, natural products

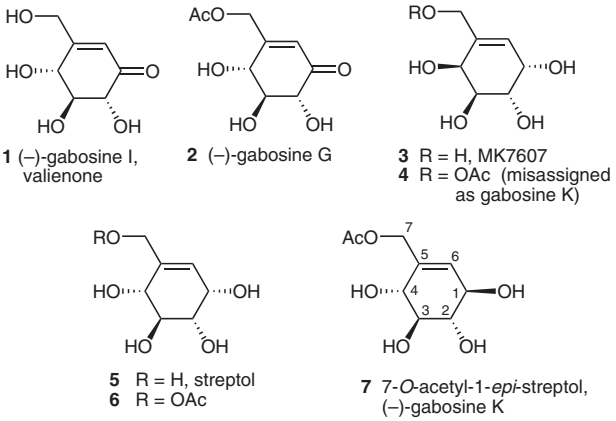

Figure 1 Structures of gabosines

Gabosines are a group of natural products, isolated from *Streptomyces* strains, that share a common multihydroxylated cyclohexanone or hexenone skeleton.[1,2] These secondary metabolites have been demonstrated to exhibit bioactivities such as antibiotic,[1] anticancer,[2] and weak DNA binding properties.[3] Gabosine C and its crotonyl ester COTC were isolated in 1974[4] whereas gabosines A to K were isolated in 1993.[1] In 2000, three more gabosines were also reported.[3] Our previous work has furnished gabosine I (**1**) and G (**2**) from δ-D-gluconolactone via a Horner–Wadsworth–Emmons olefination as the key step, and established the absolute configuration of (–)-gabosine G (**2**, Figure 1).[5] Gabosine I (**1**) is identical to valienone,[6] an intermediate for the biosynthesis of validamycin A.[7] To date, the structure and the stereochemistry of gabosine K was assigned as 7-*O*-acetyl-4-*epi*-streptol (**4**),[1] on the basis of its NMR spectral data which are closely related to those of (+)-streptol (**5**), a plant-growth inhibitor.[8,9]

In 2000, Mehta and coworkers disclosed a synthesis of racemic **4**.[10] However, the spectral data (^{1}H NMR, ^{13}C NMR) of synthetic **4** were similar but different from those of natural gabosine K, hence the structure of gabosine K needs to be revised. The deacetylated **4** is known as (+)-MK7607 (**3**), an effective herbicide.[11,12] We reason that (+)-streptol (**5**) is likely the biosynthetically carbonyl-reduction product of valienone (**1**), then it is feasible that gabosine K could be derived from the other reduction product, and could be 7-*O*-acetyl-1-*epi*-streptol (**7**). Our reasoning has proven to be correct.

The present work reports the first and stereoselective synthesis of (–)-7-*O*-acetyl-1-*epi*-streptol (**7**) from D-glucose with spectral data identical to those reported for the natural gabosine, thereby confirming the relative and absolute configurations of (–)-gabosine K as compound **7**. This work also reports a stereoselective synthesis of 7-*O*-acetylstreptol (**6**) for NMR spectral comparison. Our construction of hydroxylated carbacycles involves an intramolecular direct aldol reaction of sugar-derived 2,6-diketones.

In our previous investigation, β-allylic alcohol **12** and α-allylic alcohol **13** were prepared from D-glucose in 11 steps with 20% overall yield and 9 steps with 25% overall yield, respectively, using an intramolecular direct aldol cyclization of diketone **8** to cyclohexanone **9** as the key step (Scheme 1).[13,14] Conversion of **13** into 7-*O*-acetylstreptol (**6**) is straightforward and hence protection of **13** with TBSCl afforded silyl ether **14** from which the isopropylidene group was selectively removed to give diol **15** in a good yield. Regioselective acetylation of the primary alcohol in **15** furnished acetate **16**. Acid hydrolysis then provided (+)-7-*O*-acetylstreptol (**6**) that was thus synthesized from D-glucose in 13 steps with 15.9% overall yield.[15]

The transformation of the allylic alcohol **12** is shown in Scheme 2. Silylation of the free alcohol in **12** provided silyl ether **17**. Selective hydrolysis of the terminal isopropylidene group in **17** gave diol **18** that was subjected to

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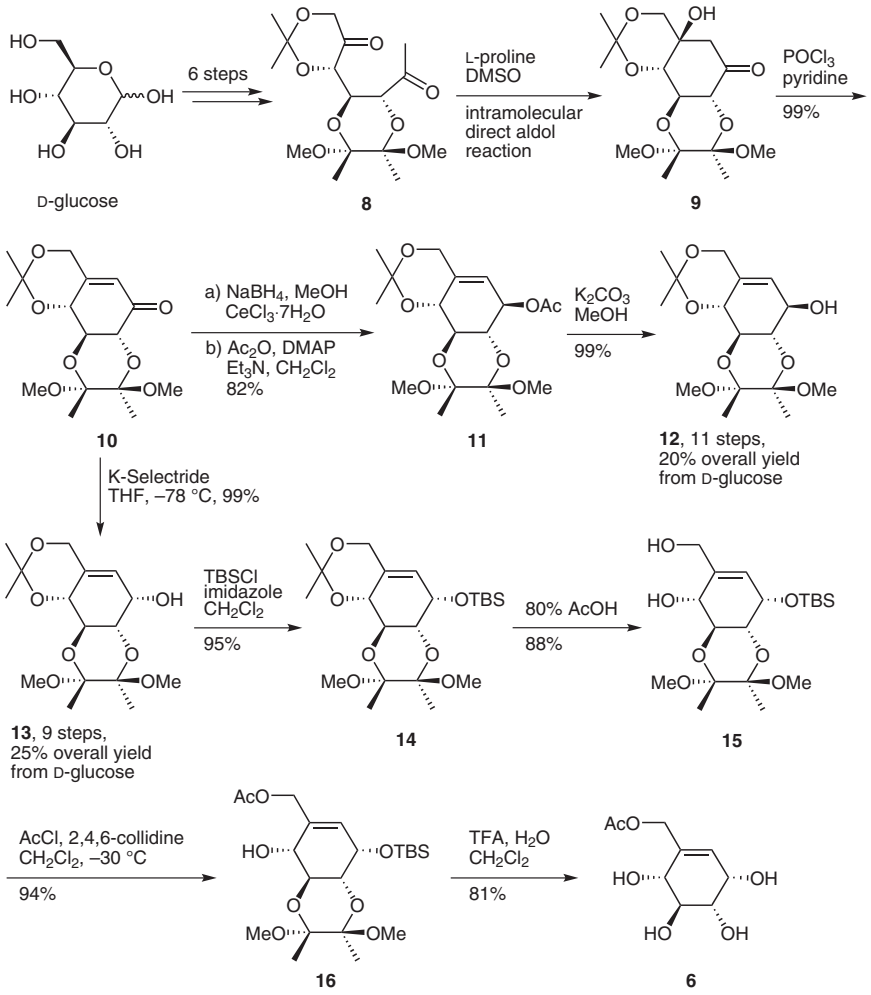
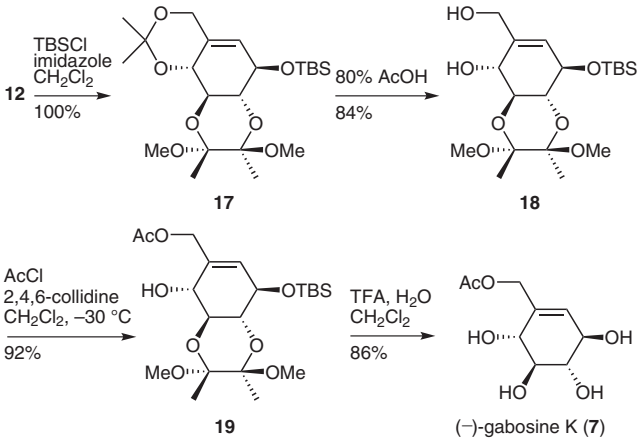


Scheme 1 Synthesis of 7-*O*-acetylstreptol (**6**)



Scheme 2 Synthesis of (–)-gabosine K [7-*O*-acetyl-1-*epi*-streptol (**7**)]

regioselective acetylation to provide acetate **19**. Removal of the acid-labile blocking groups furnished 7-*O*-acetyl-1-*epi*-streptol (**7**) in a good yield.[15]

The spectral data (^{1}H NMR, ^{13}C NMR) of racemic **4**,[10] (+)-7-*O*-acetylstreptol (**6**) and 7-*O*-acetyl-1-*epi*-streptol (**7**) are compared with those[1] of natural gabosine K.[15] The ^{1}H NMR spectral data of **7** in MeOH-d_4 (Table 1) are in accord with the literature values,[1] and the ^{13}C NMR data of **7** have perfect match with those of natural gabosine K (Table 2). The ^{1}H NMR spectrum of **7** in acetone-d_6 reveals all the coupling constants and the large J values ($J_{1,2}$ = 7.4 Hz, $J_{2,3}$ = 10.1 Hz, and $J_{3,4}$ = 7.4 Hz) indicate that H_1, H_2, H_3, and H_4 are in pseudo-axial orientation (Figure 2). Therefore, the absolute configuration of (–)-gabosine K (**7**) {$[\alpha]_D^{20}$ –47.9 (*c* 0.52, MeOH)} is now established as 1*R*,2*S*,3*S*,4*R*.

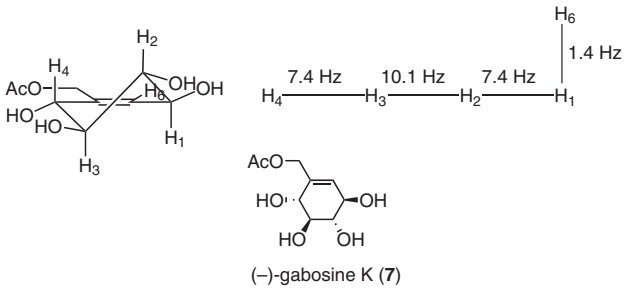


Figure 2 Conformation of **7** in acetone-d_6

To conclude, (–)-gabosine K [7-*O*-acetyl-1-*epi*-streptol (**7**)] was synthesized from D-glucose in 15 steps with 13.5% overall yield using an intramolecular direct aldol

Table 1 Comparison of ^{1}H NMR Spectral Data of Natural Gabosine K with Those of Synthetic **4**, **6**, and **7**[a]

Compd **4**[10]	Compd **6**	Compd **7**	Natural gabosine K[1]
2.07 (s)	2.06 (s)	2.06 (s)	2.06 (s)
3.87–3.90 (m)	3.44 (dd, *J* = 10.1, 4.2 Hz)	3.35–3.42 (m)	3.39 (m, *J* = 8, 6.5 Hz)
4.23–4.27 (m)	3.71 (dd, *J* = 10.1, 7.3 Hz)	4.04–4.08 (m)	4.04–4.18 (m)
4.60 (d, *J* = 13.5 Hz)	3.94 (dd, *J* = 7.3, 0.7 Hz)	4.52 (d, *J* = 13.5 Hz)	4.53 (d, *J* = 13.5 Hz)
4.70 (d, *J* = 13.5 Hz)	4.18 (d, *J* = 4.6 Hz)	4.72 (d, *J* = 13.2 Hz)	4.73 (d, *J* = 13.5 Hz)
5.75–5.85 (m)	4.57 (d, *J* = 13.3 Hz)	5.59 (d, *J* = 1.2 Hz)	5.59 (m)
	4.76 (d, *J* = 13.3, 0.8 Hz)		
	5.80–5.82 (m)		

[a] Chemical shift in ppm in MeOH-d_4.

Table 2 Comparison of ^{13}C NMR Spectral Data of Natural Gabosine K with Those of Synthetic **4**, **6**, and **7**[a]

Compd **4**[10]	Compd **6**	Compd **7**	Natural gabosine K[1]
20.8	19.2	20.7	20.8
65.8	63.5	64.8	64.8
67.4	66.0	73.0	73.0
68.0	70.9	73.5	73.5
70.7	71.9	77.1	77.1
70.9	72.4	77.5	77.5
128.2	124.4	128.8	128.8
137.2	137.9	136.2	136.2
172.5	171.0	172.5	172.5

[a] Chemical shift in ppm in MeOH-d_4.

reaction of 2,6-diketone **8** as the key step. However, the specific rotation of natural gabosine K has not been reported and a recent communication with Prof. Zeeck[1] confirms that the rotation value is not available. As a consequence, the absolute configuration of the natural product is either (–)-gabosine K (**7**) or its enantiomer.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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