Short and Efficient Syntheses of Gabosine I, Streptol, 7-*O*-Acetylstreptol, 1-*epi*-Streptol, Gabosine K, and Carba-α-D-glucose from δ-D-Gluconolactone

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Abstract: δ-D-Gluconolactone was carbocyclized into an EOM-protected cyclohexenone in four steps involving perethoxymethylation, phosphonate anion addition, reduction, and oxidation with concomitant Horner–Wadsworth–Emmons alkenation. The stable key enone was efficiently transformed into gabosine I (five steps with 65% overall yield from δ-D-gluconolactone), streptol (six steps, 54% overall yield), 7-*O*-acetyl-streptol (seven steps, 42% overall yield), 1-*epi*-streptol (six steps, 49% overall yield), gabosine K (seven steps, 40% overall yield), and carba-α-D-glucopyranose (seven steps, 47% overall yield). The present chemical syntheses, from commercially available δ-D-gluconolactone, provide the highest overall yields of these molecules to date.

Key words: carbasugars, carbohydrates, stereoselective synthesis, Wittig reaction, natural products

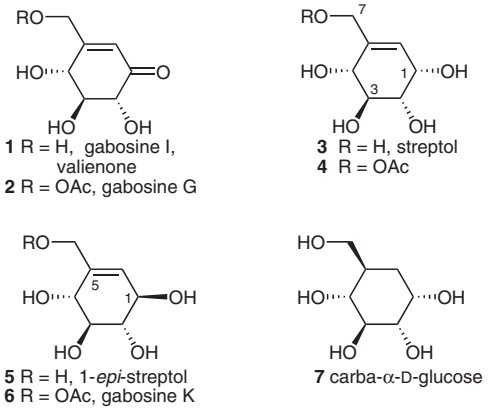

Figure 1 Structures of gabosines, streptols, and carba-α-D-glucose

Gabosines are a group of natural, multihydroxylated cyclohexanones or hexenones, isolated from *Streptomyces* strains.[1,2] Gabosines A–K were isolated in 1993 and have been demonstrated to exhibit bioactivities such as antibiotic,[1] anticancer,[2] and weak DNA-binding properties.[3] Gabosine I (**1**) is identical to valienone,[4] an intermediate for the biosynthesis of validamycin A (Figure 1).[5] The corresponding reduction product, the α-allylic alcohol **3**, is known as (+)-streptol and is a plant-growth inhibitor.[6,7] Its C-1 epimer **5** with a 7-OAc group was recently confirmed by us as gabosine K (**6**) via a synthesis involving a key aldolization of a 2,6-diketone derived from D-glucose.[8] Saturation of the double bond in streptol (**3**) furnishes carba-α-D-glucopyranose or pseudo-α-D-glucopyranose (**7**), an important sugar mimic acting as a tool for biochemical research.[9,10]

Our present research is focused on the short and facile construction of hydroxylated carbocycles from sugars which is coined 'carbocyclization of carbohydrates'. Our previous work already yielded gabosine I (**1**) and G (**2**) from δ-D-gluconolactone via a Horner–Wadsworth–Emmons (HWE) olefination as the key step, and established the absolute configuration of (–)-gabosine G (**2**).[11] In that synthesis, we employed a mixed acetal as the blocking group for the hydroxyl at C-1 and C-2. However, the mixed acetals are very acid sensitive and readily decomposed. We therefore searched for a robust alternative so that the carbocyclized enone could be stable enough to be elaborated into a variety of target molecules.

The present letter reports, from commercially available δ-D-gluconolactone, short, efficient, and enantiospecific syntheses of gabosine I (**1**), streptol (**3**), 7-*O*-acetyl-streptol (**4**), 1-*epi*-streptol (**5**), gabosine K (**6**), and carba-α-D-glucopyranose (**7**) using stable ethoxymethyl (EOM) ether for the hydroxyl protection and an intramolecular HWE olefination[12] as the key carbocyclization step. The construction of 1-*epi*-streptol (**5**) has not been addressed in the literature, and this paper documents its first synthesis.

The synthesis of gabosine I (**1**) is shown Scheme 1. Global alkylation of δ-D-gluconolactone with EOM chloride in 2,6-lutidine gave tetraether **8** in 93% yield. Nucleophilic addition of lithiated dimethyl methylphosphonate to the lactone carbonyl afforded lactol **9** in 95% yield. Direct oxidation of lactol **9** to the corresponding diketone followed by HWE cyclization proved difficult, hence the hemiacetal was reduced by borohydride to give diol **10** in an excellent yield. Several oxidation protocols were attempted, and Swern oxidation[13] was found to be the most efficient and the subsequent intramolecular HWE olefination was effected in the same pot. The olefination was better induced by triethylamine than by diisopropylethylamine (DIPEA). Addition of lithium salt[14] did not improve the reaction yield, beyond salting out the organic materials. Thus enone **11** was harvested from diol **10** in 80% yield. Complete deprotection of **11** by acid hydrolysis smoothly provided (–)-gabosine I (**1**) in an excellent

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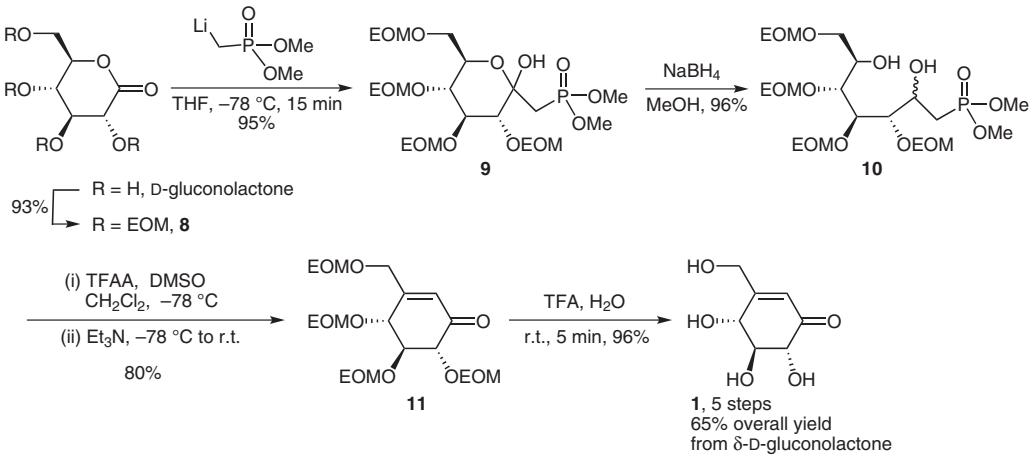


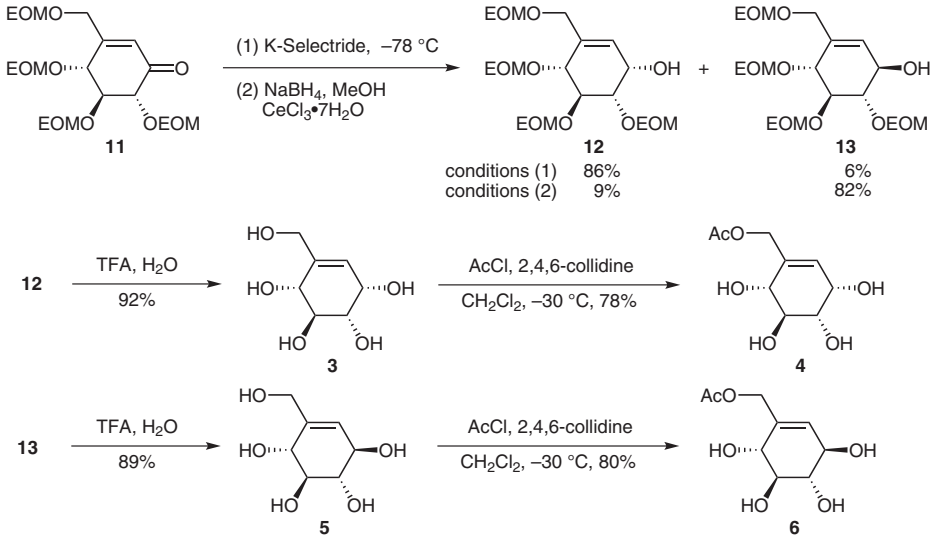
Scheme 1 Synthesis of gabosine I (**1**)

yield, identical in all respects to the one synthesized[11] by us previously. The overall yield (65%) of the present work is far superior to our last synthesis (20.3%)[11] and is the best overall yield for the preparation of gabosine I in the literature.[15,16]

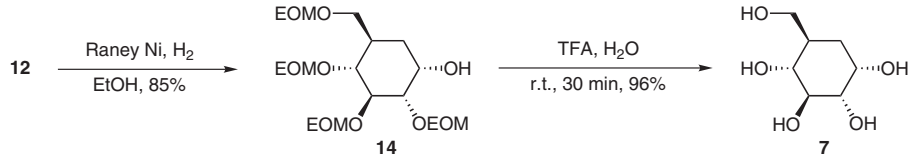
The syntheses of streptol (**3**), 7-*O*-acetylstreptol (**4**), 1-*epi*-streptol (**5**), and gabosine K (**6**) are shown in Scheme 2.[16] Regio- and stereoselective hydride 1,2-reduction of enone **11** with K-Selectride afforded α-alcohol **12** preponderantly whereas with $NaBH_4$ furnished β-alcohol **13** as the major product. Acid hydrolysis of all the EOM ethers in **12** gave streptol (**3**) which was regioselectively acetylated to form 7-*O*-acetyl-streptol (**4**) in good yields. The spectral data (^1H and ^{13}C NMR) of streptol (**3**) are in accord with those in the literature.[4] Compound **4** was identical to 7-*O*-acetyl-streptol synthesized by us recently.[8] Thus streptol (**3**) and 7-*O*-acetyl-streptol (**4**) were synthesized from δ-D-gluconolactone in six and seven steps with 54% and 42% overall yield, respectively. On the other hand, acid hydrolysis of **13** provided 1-*epi*-streptol (**5**) for the first time which was regioselectively acetylated to give gabosine K (**6**), identical to the one synthesized by us recently.[8] Thus 1-*epi*-streptol (**5**) and gabosine K (**6**) were synthesized from δ-D-gluconolactone in six and seven steps with 49% and 40% overall yield, respectively.[16]

The transformation of the allylic alcohol **12** into carba α-D-glucose is shown in Scheme 3. Stereoselective hydrogenation with Raney nickel was believed to proceed with an anchor effect[17] of the C-1 α-hydroxy group, and the hydrogen was delivered from the α-face, leading to the D-gluco configuration as shown in **14** in a good yield.[16] Complete deprotection under acidic conditions furnished carba-α-D-glucopyranose (**7**), identical in all respects to the one synthesized by us previously.[10b] Thus, carba-α-D-glucopyranose (**7**) was made from δ-D-gluconolactone in seven steps with 47% overall yield.

To conclude, (–)-gabosine I (**1**), streptol (**3**), 1-*epi*-streptol (**5**), 7-*O*-acetylstreptol (**4**), gabosine K (**6**), and carba-α-D-glucopyranose (**7**) were synthesized from δ-D-gluconolactone in five to seven steps with 40–65% overall yields using an intramolecular HWE alkenation as the key step.



Scheme 2 Syntheses of streptol (**3**), 7-*O*-acetylstreptol (**4**), 1-*epi*-streptol (**5**), and (–)-gabosine K (**6**)



Scheme 3 Synthesis of carba-α-D-glucopyranose (**7**)

The present syntheses offer the shortest route to these molecules with highest overall yields to date. It is noteworthy that the facile and high-yielding construction of enone **11** makes it an attractive intermediate for elaboration into a wide variety of hydroxylated cyclohexenoid natural products or molecules of pharmaceutical interest.

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

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