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Stereoselective synthesis of (−)-gabosine C using a Nozaki–Hiyama–Kishi reaction and RCM☆

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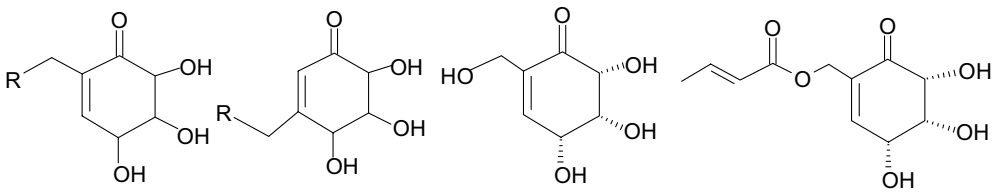
Abstract—An efficient synthesis of (−)-gabosine C **3** and a formal synthesis of (−)-COTC **4** are described using the Nozaki–Hiyama–Kishi (NHK) reaction and RCM as the key steps.

The gabosines, a class of carbasugars, have been isolated from *Streptomyces* strains. The majority contain trihydroxylated hydroxymethyl cyclohexenone structures as their common skeleton.[1] These unsaturated carbasugars present structural diversity due to variations at three asymmetric centers and differing substitutions at C-2 or C-3 as in structures **1** and **2**.[2] Gabosines and 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.[3] Gabosine related derivatives have been used as intermediates for the synthesis of biologically active compounds such as a L-fucosyltransferase inhibitor, valienamine and derivatives, and a pseudosugar C-disaccharide.[2]

(−)-Gabosine C **3**, identical to the antibiotic (−)-KD16-U1, was isolated in 1974 from the culture broth of *Streptomyces filipensis*.[4] It has been transformed into (−)-COTC **4** a glyoxalase-I inhibitor, by treatment with crotonic acid and $BF_3{\cdot}OEt_2$.[5] (−)-COTC, (2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-trihydroxycyclohex-2-enone) **4** was isolated from the culture broth of *Streptomyces griseosporeus* by Umezawa and co-workers[6] as cytotoxic and potentially cancerostatic with low toxicity and has been shown to act synergistically with aclarubicin, an anticancer drug.[6,7]

Considering their fascinating structures, biological activities, and versatility as synthons, we are interested in developing a new general access to the gabosine skeleton and have focused on the preparation of (−)-gabosine C **3** using the Nozaki–Hiyama–Kishi reaction[8] and RCM as the key steps. Although there are several reports of the synthesis of **3** and **4**,[9] our strategy is short and straightforward and is also useful for making other gabosine skeletons from carbohydrates.

Our approach to the synthesis of (−)-gabosine C **3** is shown in Scheme 1. 2,3-*O*-Isopropylidene-D-ribose was



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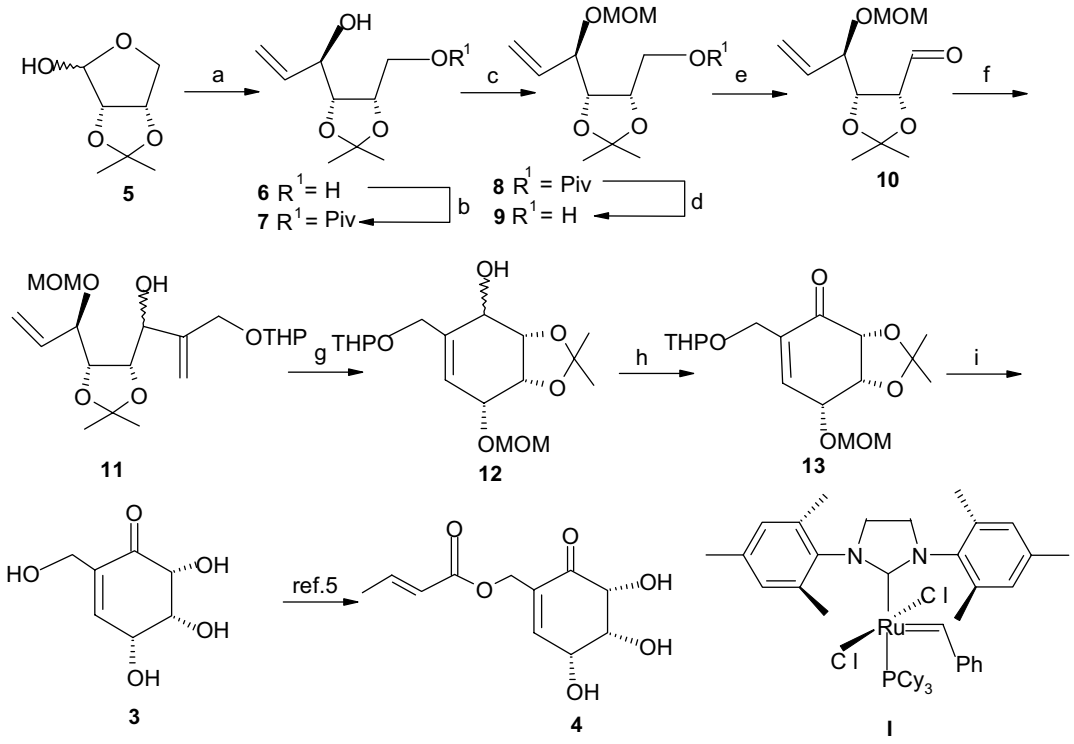
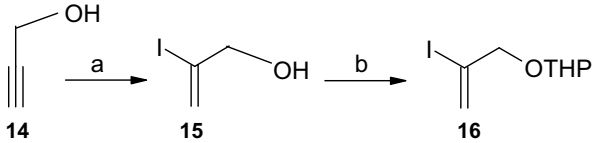


Scheme 1. Reagents and conditions: (a) vinylmagnesium bromide, THF, −78 °C to 0 °C, 2 h, 70%; (b) Piv-Cl, 2,6-lutidine, DMAP, CH_2Cl_2, 0 °C to rt, 12 h, 74%; (c) MOM-Cl, DIPEA, TBAI, CH_2Cl_2, 0 °C to rt, 24 h, 83%; (d) NaOMe, MeOH, 0 °C to rt, 5 h, 75%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 3 h, (f) **16**, $CrCl_2$, $NiCl_2$, DMF, rt, 24 h, 84% (for the two steps); (g) Grubbs' second-generation olefin metathesis catalyst (**I**, 0.1 equiv), CH_2Cl_2, 80 °C, 48 h, 56% (86% yield based on recovered starting material **11** as a 1:1 diastereomeric mixture); (h) PDC, CH_2Cl_2, 0 °C to rt, 24 h, 78%; (i) Amberlyst® **15**, THF:H_2O (2:1), 70 °C, 5 h, 50%.

converted to 2,3-*O*-isopropylidene-L-erythronolactol **5** using a known procedure.[10] A Grignard reaction on **5** using a reported protocol afforded diol **6**[11] as the major isomer with high stereoselectivity ($[\alpha]_D^{25}$ +41.6 (*c* 1.4, $CHCl_3$) lit.[11] $[\alpha]_D$ −42.2 (*c* 1.8, $CHCl_3$) for its enantiomer). Selective protection of the primary hydroxyl group in **6** with Piv-Cl, in the presence of 2,6-lutidine gave **7** and then the secondary hydroxyl group was protected as the MOM ether to give **8**. Deprotection of the Piv group in **8** with NaOMe gave the alcohol **9** ($[\alpha]_D^{25}$ −48.5 (*c* 1.18, $CHCl_3$)). Oxidation of the alcohol **9** under Swern conditions yielded the aldehyde **10**. Using a Nozaki–Hiyama–Kishi reaction,[8] aldehyde **10** was treated with the iodo compound **16** (prepared from propargyl alcohol in two steps[12] Scheme 2), $CrCl_2$ and $NiCl_2$ in DMF to afford a diastereomeric mixture of dienes **11** (as a 1:1 diastereomeric mixture at the newly created stereogenic center). Treatment of these dienes **11** with Grubbs' second-generation olefin metathesis catalyst **I**[13] in CH_2Cl_2 at 80 °C furnished the cyclohexene **12** in 56% yield. Oxidation of alcohol **12** with PDC yielded the required compound **13**. Finally, removal of the MOM, THP, and acetonide protecting groups occurred in one step with Amberlyst® 15 in THF:H_2O (2:1) at 80 °C to afford (−)-gabosine C **3** which was purified by column chromatography and then crystallized from EtOAc to give a white solid whose physical (mp: 113–114 °C lit.[1b,4] 113–114 °C; $[\alpha]_D^{25}$ −166 (*c* 0.13, H_2O) lit.[9a] $[\alpha]_D^{28}$ −166 (*c* 0.17, H_2O)) and spectral data were in agreement with the reported values. Conversion of (−)-gabosine C **3** to its crotyl ester derivative (−)-COTC **4** has been reported previously by the Umezawa et al.[5]



Scheme 2. Reagents and conditions: (a) TMS-Cl, NaI, CH_3CN, H_2O, 0 °C to rt, 90 min, 61%; (b) DHP, PTSA (0.1 equiv), CH_2Cl_2, 0 °C to rt, 2 h, 86%.

In summary we have synthesized (−)-gabosine C, **3** using a Nozaki–Hiyama–Kishi reaction and RCM as the key steps. This strategy is suitable for synthesizing polyhydroxylated cyclohexene systems in general.

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