

## First total synthesis of ganglioside SJG-2 and evaluation of its neurite outgrowth activity

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SJG-2, a ganglioside found from the sea cucumber *Stichopus japonicus*, exhibits the most potent neurite outgrowth activity toward PC12 cells among gangliosides ever evaluated [1,2]. SJG-2 displays a unique sialic acid-congested glycan structure, which poses a highest-level challenge in the chemical synthesis (Fig. 1). In this study, we report the first total synthesis of ganglioside SJG-2. In the chemical synthesis of SJG-2, the most challenging subject is to install three sialic acids (Neus) at the vicinal 3,4-diol and the anomeric position of the outer Gal residue. First, to install Neu5 to the 3,4-diol, we have developed a Neu $\alpha$ (2,3)Gal with a free hydroxyl group at the C4 of Gal as a glycosyl acceptor. We found that the conformational fixation of the Neu residue by 1,5-lactamization and cyclic protection boosted the reactivity of the C4-OH of the Gal. By glycosylation using a macrobicyclic sialyl donor developed by our group [3], the disialyl Gal was produced in excellent yield with perfect  $\alpha$ -selectivity. Next, the disialyl Gal was successfully combined at the C8-OH of 1,5-lactamized Neu residue in a trisaccharide acceptor, producing a sialic acid-congested hexasaccharide. The hexasaccharide was converted into a glycosyl donor via 13 steps, which was then coupled with Glc-Cer cassette to afford the ganglioside framework. Finally, global deprotection delivered ganglioside SJG-2. The synthesized SJG-2 and its glycan part were subjected to biological evaluation, which revealed that both SJG-2 and the glycan part promoted neurite extension toward primary neurons.

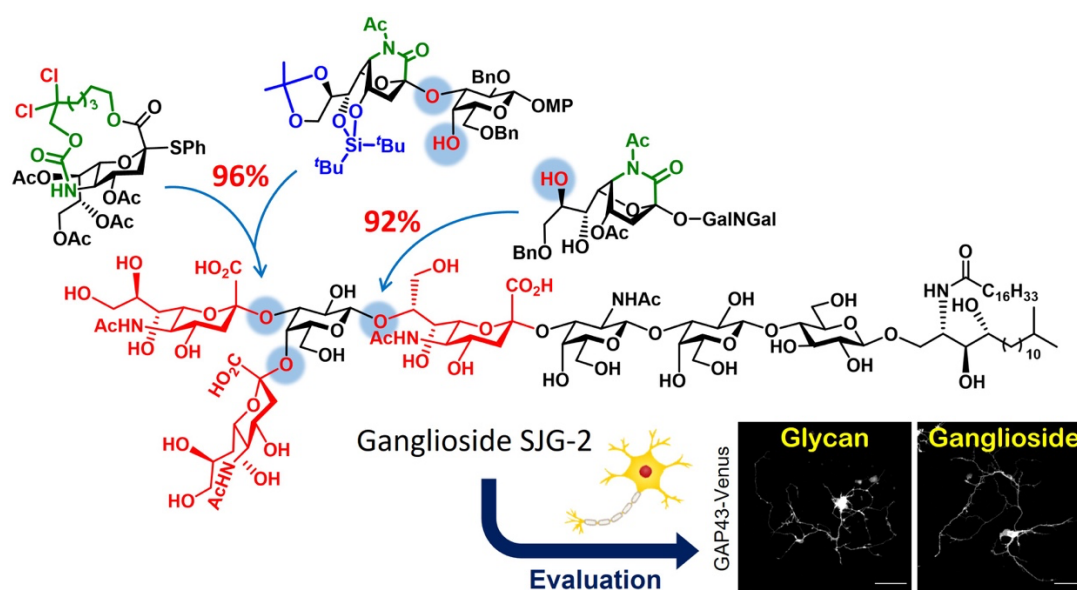


Figure 1. Chemical synthesis of ganglioside SJG-2 and evaluation of its neurite outgrowth activity

### Bibliographic references:

- [1] M. Kaneko et al. (2003), *Eur. J. Org. Chem.* 1004–1008.  
 [2] M. Kaneko et al. (2007), *Chem. Pharm. Bull.* (55) 462–463.  
 [3] N. Komura et al. (2019), *Science* (364) 677–680.