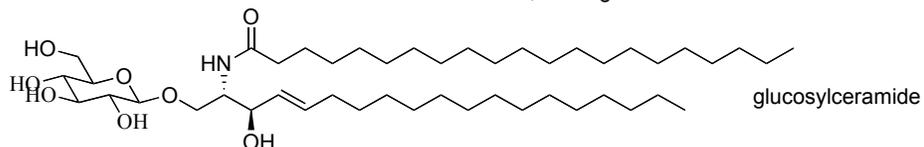


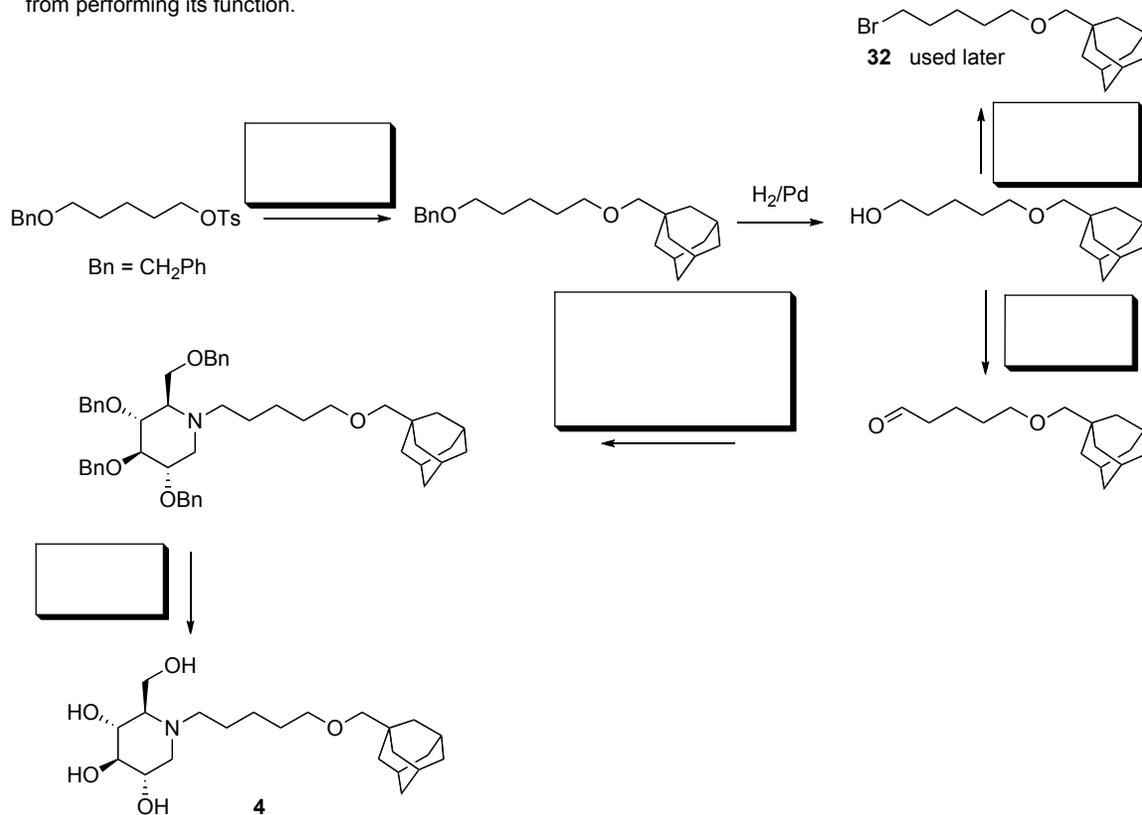
Synthesis of Glucosylceramide Synthase Inhibitors, H.S. Overkleeft, Leiden, 2007

Glucosylceramide is a precursor to a number of cell-signaling agents. Over-accumulation of this compound is seen in Gaucher's disease and other inherited illnesses, leading to liver ailments and bone deterioration.

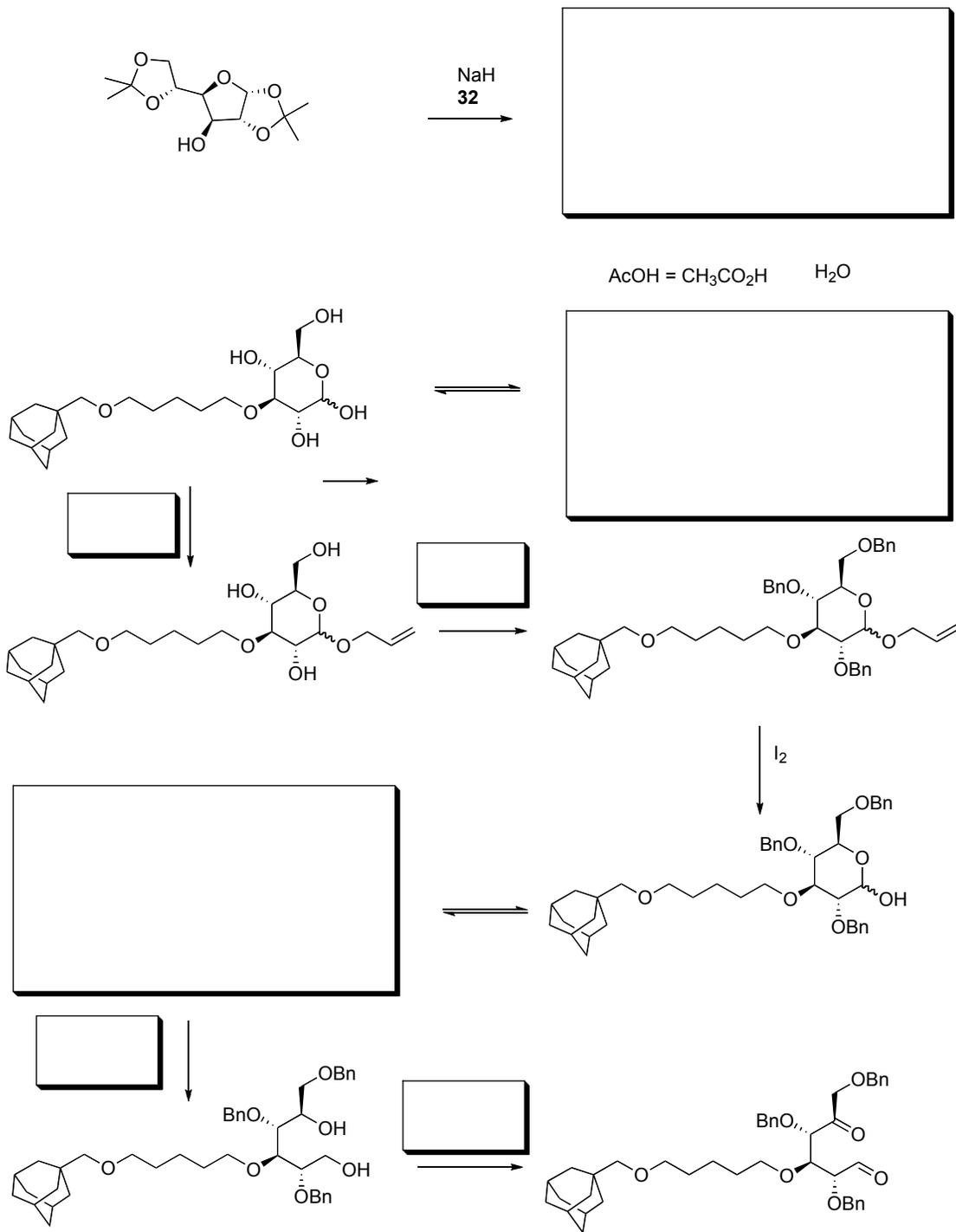


Goal: develop a drug that will inhibit glucosylceramide synthase at low doses, reducing the amount of glucosylceramide produced in the body, without affecting other important enzymes

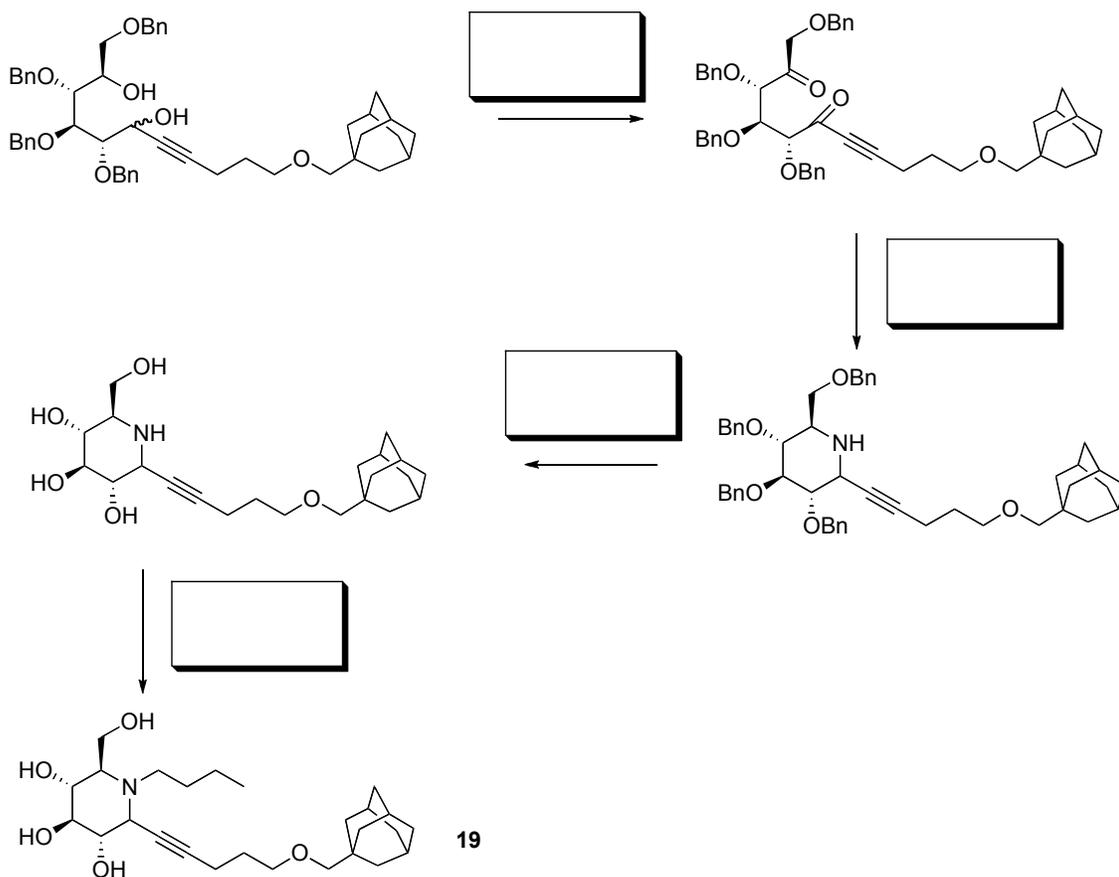
Target compounds may resemble glucosylceramide. Based on the "lock-and-key" model of enzyme function, these compounds could be accepted into the enzyme, but once inside, they must differ in a way that prevents the enzyme from performing its function.



Synthesis of Glucosylceramide Synthase Inhibitors, H.S. Overkleeft, Leiden, 2007, part 2



Synthesis of Glucosylceramide Synthase Inhibitors, H.S. Overkleef, Leiden, 2007, part 4



IC₅₀ for inhibitors against selected enzymes

(IC₅₀ = concentration in μM needed to reduce enzyme activity by half)

	Glucosylceramide Synthase	α-Glucosidase	Maltase	Sucrase
4	0.2	0.4	19	4.5
16	>100	150	>100	35
19	25	255	>100	>100

Which inhibitor is the most powerful inhibitor of glucosylceramide synthase? Explain.

Which inhibitor seems like the most promising drug candidate? Explain.