Synthesis of LY2886721

**Significance:** LY2886721 is a BACE inhibitor that is of interest for the treatment of Alzheimer’s disease. In the key intramolecular dipolar cycloaddition, nitrone (Z)-E underwent kinetic selection to afford a mixture of cycloadducts (dr = 6:1) from which the desired isoxazolidine F was isolated in 55% yield by crystallization.

**Comment:** Minimizing formation of a desfluoro impurity during hydrogenolysis of the isoxazolidine ring and removal of the benzyl chiral auxiliary (H → I) was a key challenge. The final acylation occurred without competing acylation of the aminothiazine nitrogen to afford LY2886721 in 17% overall yield on a multi-kilogram scale.

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**DOI:** 10.1055/s-0035-1560844; Reg-No.: K06315SF