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Organic Synthesis

New Routes To Tamiflu Emerge

Research groups in the U.S. and Japan develop routes that avoid shikimic acid

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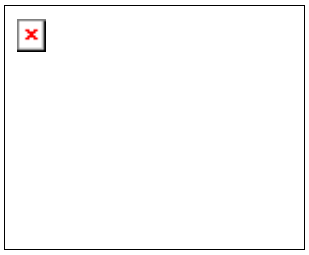


As concerns about the H5N1 avian flu virus spread and governments around the world stockpile the Roche antiviral drug Tamiflu, researchers have been seeking new routes to the active ingredient oseltamivir phosphate. Two new syntheses have just been published, one from Elias J. Corey's lab at Harvard University and the other from Masakatsu Shibasaki's group at the University of Tokyo.

Unlike Roche's current commercial process, both routes avoid the use of (–)-shikimic or (–)-quinic acids, complex starting materials that are expensive and in limited supply. They also both depend on an asymmetric catalytic step early in the synthesis to create a key building block. They differ, however, in that the Corey route does not involve hazardous azide intermediates.

"Our synthetic pathway has several advantages over the current Roche production method," Corey says. "It is shorter, doesn't involve any hazardous substances, begins with very cheap starting materials that are pennies per pound, and has excellent overall yield." Corey's overall yield is about 30%—about twice that of the commercial route and significantly higher than the approximately 1% that can be calculated for Shibasaki's.

The reaction sequence developed by Corey and coworkers Ying-Yeung Yeung and Sungwoo Hong begins with the reaction of 1,3-butadiene and 2,2,2-trifluoroethyl acrylate in the presence of an oxazaborolidinium catalyst (*J. Am. Chem. Soc.*, published online April 25, dx.doi.org/10.1021/ja0616433). This Diels-Alder step can be carried out on a multigram scale at room temperature with greater than 100:1 enantioselectivity and 97% yield of the (1*S*)-cyclohex-3-enecarboxylic acid 2,2,2-trifluoroethyl ester building block, they say.

A key step in the synthesis by Shibasaki and coworkers Yuhei Fukuta, Tsuyoshi Mita, Nobuhisa Fukuda, and Motomu Kanai is the asymmetric desymmetrization of a *meso*-aziridine with trimethylsilyl azide using a chiral yttrium catalyst (*J. Am. Chem. Soc.*, published online April 25, dx.doi.org/10.1021/ja061696k). The *meso*-aziridine is based on what Shibasaki calls a relatively inexpensive starting material, 1,4-cyclohexadiene.

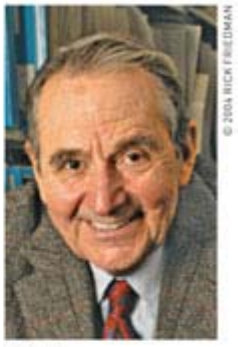
Although Roche researchers declined to comment on the new synthetic routes, a spokeswoman says the company is in contact with the authors of both papers. Both the technical potential and regulatory impact of any new route still have to be explored, she comments. In his group's paper, Corey, who serves as an adviser to Palo Alto-based Roche Biosciences, thanks Roche researchers in Switzerland for their encouragement.

Roche has been obtaining the shikimic acid starting material via extraction from Chinese star anise fruit and fermentation processes. It has recently signed up more than 15 external contractors to help it expand production of both intermediates and finished materials (C&EN, March 20, page 10). With this help, Roche says it will be able to produce 400 million flu treatments annually by the end of

2006.

Whereas the Japanese researchers have applied for a patent, Corey and coworkers have put their process in the public domain. "I hope the work will stimulate others to work on different ways of synthesizing Tamiflu," Corey says. "Although our route is already very efficient, it's conceivable that when you put new developments together, you'll have an even better and cheaper process. I think the Tamiflu supply problem is solved."

RING OPENING Shibasaki and coworkers make an initial key structure for synthesizing oseltamivir through a catalytic enantioselective desymmetrization reaction.



Corey

Shibasaki

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