

# SYNTHESIS OF NATURAL PRODUCTS

## Improved path found to staurosporine and related biologically active compounds

**C**hemists at Yale University have come up with a general route to synthesize staurosporine and three related compounds. The technique takes roughly half as many steps and produces 10 times as much staurosporine, compared with the first—and, until now, only—method for total synthesis of this natural product.

Staurosporine and the related compounds—(+)-K252a, (+)-RK286c, and (+)-MLR-52—are bacterial metabolites with a wide range of biological activities. Staurosporine itself has drawn a lot of attention because at nanomolar concentrations it inhibits the protein kinase C family of enzymes. These enzymes affect many cellular events, and inhibiting them may be of use in treating diseases such as cancer.

The method for constructing the four compounds via a common route was developed by Yale assistant professor of chemistry John L. Wood, graduate student Brian M. Stoltz, and undergraduate student Steven N. Goodman [*J. Am. Chem. Soc.*, **118**, 10656 (1996)].

Wood's team has achieved an "absolutely spectacular and very short synthesis" of a target that has caught the eye of both the synthetic and pharmaceutical communities, comments Amos B. Smith III, chemistry professor at the University of Pennsylvania.

"The paper describes a brilliant series of maneuvers," adds Samuel J. Danishefsky, chemistry professor at Columbia University and director of the Laboratory for Bioorganic Chemistry at Memorial Sloan-Kettering Cancer Center, New York City. Danishefsky and coworkers were the first to carry out total synthesis of staurosporine [*J. Am. Chem. Soc.*, **118**, 2825 (1996)]. The Yale group's synthesis "is far more concise than our effort," Danishefsky says. "I salute John Wood on this substantial advance in organic synthesis."

The structures of staurosporine and the related compounds can be viewed as having two parts. The top part is an aromatic heterocyclic unit, from which the compounds get their collective name—indolo-

carbazoles. The bottom part is a carbohydrate attached to the top part through glycosidic bonds to nitrogens. Joining the carbohydrate to the upper unit is the critical construction step.

In the synthesis of staurosporine by Danishefsky's group, the pyranose glycosidic bonds were built stepwise from glycal-type precursors. The group accomplished the final ring closure "efficiently from the specific substrate with the staurosporine substitution pattern," notes Stuart W. McCombie, a distinguished research fellow at Schering-Plough Research Institute, Kenilworth, N.J. But the final cyclization step may not be generally applicable, he adds.

The success of Wood's team stems

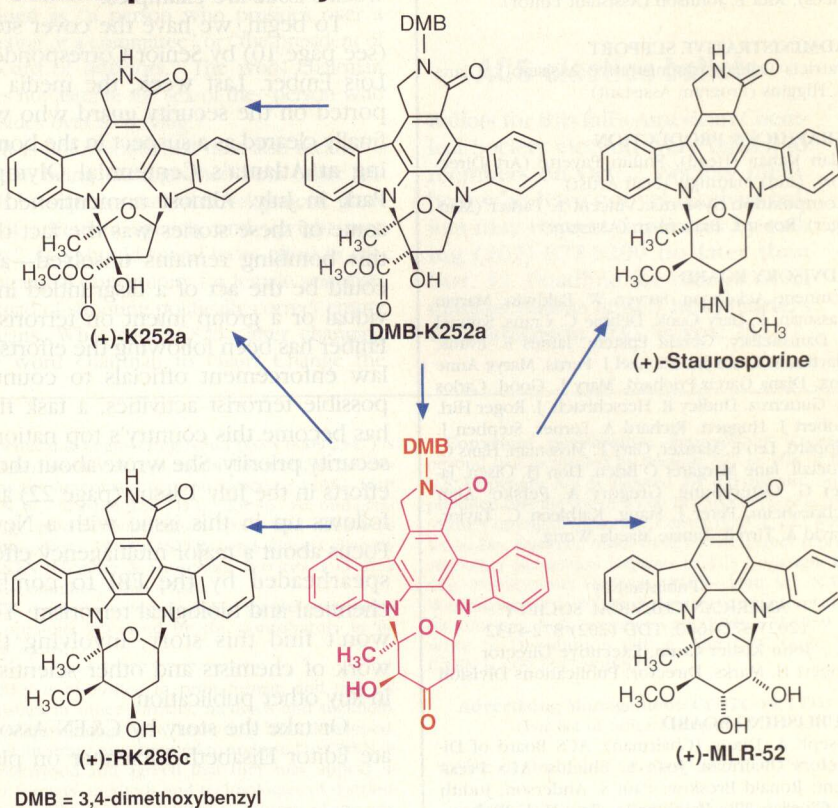
from recognizing that a common precursor to the pyranosylated compounds can be formed by expanding a furanose ring. This strategy is based on previous studies by Wood's and McCombie's groups that showed that forming glycosidic bonds to an indolocarbazole in a single operation is easier with a furanose than a pyranose.

Wood developed the chemistry for building the furanose ring and joining it to the indolocarbazole in a prior synthesis of (+)-K252a [*J. Am. Chem. Soc.*, **117**, 10413 (1995)]. Expanding the furanose of an intermediate in that synthesis leads to the common precursor to pyranosylated indolocarbazoles.

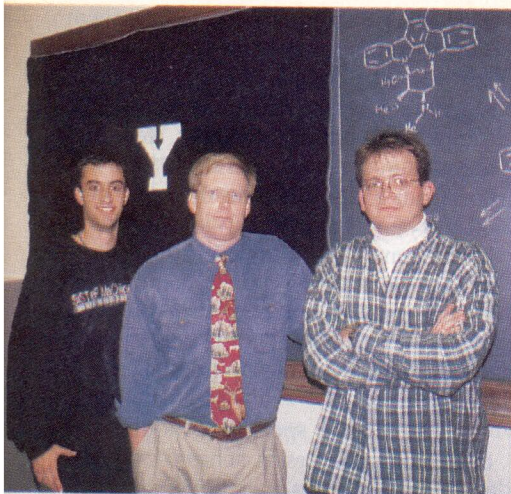
McCombie says Wood's chemistry is notable because a highly stereocontrolled  $\alpha$ -ketol rearrangement promoted by a Lewis acid is used—first to construct the chiral furanose precursor, then to expand the ring. Although expansion could lead to a mixture of products, only one pyranosylated product is formed in high yield. From that, members of the staurosporine family can be obtained easily.

Three paths converge to the furanosylated indolocarbazole that precedes ring expansion. One path, starting with glycine ethyl ester, combines with a second

### Common precursor easily yields members of staurosporine family







**Goodman (from left), Wood, and Stoltz achieved spectacular synthesis.**

path, starting with *o*-toluidine, to construct the top part of the molecule. A third path, starting with methyl-2-diazo-3-oxobutyrate, assembles the furanose, which is then attached to the top part.

The expanded ring can easily contract. Thus, the synthesis unites the furanose and pyranose members of this group of natural products through a common intermediate, which, says Wood, "may be similar to that used by nature."

*Maureen Roubi*

## NIH genome lab head reports data fabrication

Francis S. Collins, director of the Human Genome Project at the National Institutes of Health, is retracting five published research papers because, he says, some of the data in them were fabricated by one of his former students.

Collins, who also heads a research laboratory at NIH, sent a letter to research colleagues last month to inform them of what he called "a stunning series of data misrepresentations and outright fabrications, extending over a period of at least two years." He did not name the student involved, whom he said had confessed to the falsifications.

A full inquiry is under way, Collins added, involving NIH, the Department of Health & Human Services' Office of Research Integrity (ORI), and a research university he did not name. The University of Michigan—where Collins has remained a professor of internal medicine and human genetics since his move to NIH in 1993—has issued a statement saying it is investigating admissions of data

fabrication by one of its graduate students who worked in Collins' laboratory both at Michigan and at NIH.

The deception was first detected when a reviewer for another manuscript from Collins' lab became suspicious of data presented in one of the figures. "Careful analysis of laboratory notebooks, photographs, X-ray films, and [the student's] Ph.D. dissertation thesis uncovered additional examples where the authenticity of data could not be verified," Collins' letter says.

"Many will wonder whether I as the research mentor was paying sufficient attention to this individual if such deliberate and systematic assaults on scientific truth were occurring," Collins continued. Collins said he had frequent interactions with the student for three years and had no reason to question his honesty.

"Even in retrospect, I am not sure how these deceptions could have been uncovered sooner," he added. "Science cannot operate in an atmosphere where every participant is considered suspect until proven otherwise. We are all vulnerable to breaches of this sort."

The work involves study of a gene called *CBFβ* that has been associated with human leukemia. Certain cell lines that were reported to overexpress this gene apparently never existed. And other experiments in which portions of the gene were deleted or the gene's product was fused with other proteins also appear to have been fabricated.

Institutions ordinarily have four months to conduct investigations into serious misconduct, says Chris B. Pascal, acting director of ORI, although that period can be extended if necessary. As is its policy, ORI will not comment on whether an inquiry is taking place until the inquiry is completed. If found guilty, a researcher could face penalties ranging from increased supervision—such as having to get all research data certified by someone outside the laboratory before they can go into a paper or grant application—to debarment from federal research support for up to 10 years.

*Rebecca Rawls*

## Industry, unions agree on OSHA butadiene rule

The Occupational Safety & Health Administration has reduced allowable workplace exposure to 1,3-butadiene to 1 ppm, well below the previous 1,000-ppm threshold. The standard is the result of a negotiated rulemaking involving OSHA, industry, and

labor unions. The lower standard goes into effect as soon as it is published in the *Federal Register*, expected this week.

OSHA says the rule affects about 9,700 workers at 225 industrial sites in the U.S. and estimates that compliance will cost employers about \$2.9 million per year. There is evidence that exposure to 1,3-butadiene can increase workers' risk of such cancers as leukemia. OSHA claims that reducing the permissible exposure level to 1 ppm will prevent at least 79 cancer deaths per year that would have occurred among workers, given a 45-year working lifetime of exposure to 1,3-butadiene.

The final standard also includes a 15-minute short-term exposure limit of 5 ppm and an action level set at 0.5 ppm. The action level triggers exposure monitoring, medical surveillance, and training requirements.

The new standard is based largely on a recommendation made jointly to OSHA by the Chemical Manufacturers Association, the International Institute of Synthetic Rubber Producers (IISRP), the United Steelworkers' Rubber Workers Conference, and the International Chemical Workers Union.

"The United Steelworkers of America is pleased with the release of this standard," says the union's Health, Safety & Environmental Department representative, Jim Frederick. The union is the primary representative of employees exposed to butadiene.

CMA Vice President Langley Spurlock also welcomes the new standard and praises the process by which it was reached. "During the past year, industry and labor worked together to develop draft regulatory language that has resulted in a better rule," Spurlock says. "We believe the new standard—as well as other provisions that pertain to exposure monitoring, the use of respirators, hazard communication, worker training, and medical surveillance—are protective of workers' health."

Synthetic rubber manufacturers, which are the major users of 1,3-butadiene, say they can accept this rule. IISRP members already control employee exposure to butadiene through a variety of engineering controls, work practices, and respiratory programs. Exposure levels for many years have run below 10 ppm—well below the previous OSHA limit.

Industry does have some reservations about the data OSHA used to generate the new standard. "We do not agree with OSHA's interpretations of the science" surrounding butadiene toxicity, Spurlock says. Neither CMA nor the rub-