Noteworthy Chemistry

April 6, 2009

- An unusually concise synthesis of the potent antibiotic cribrostatin 6
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- Synthesize oseltamivir without chromatographic purification
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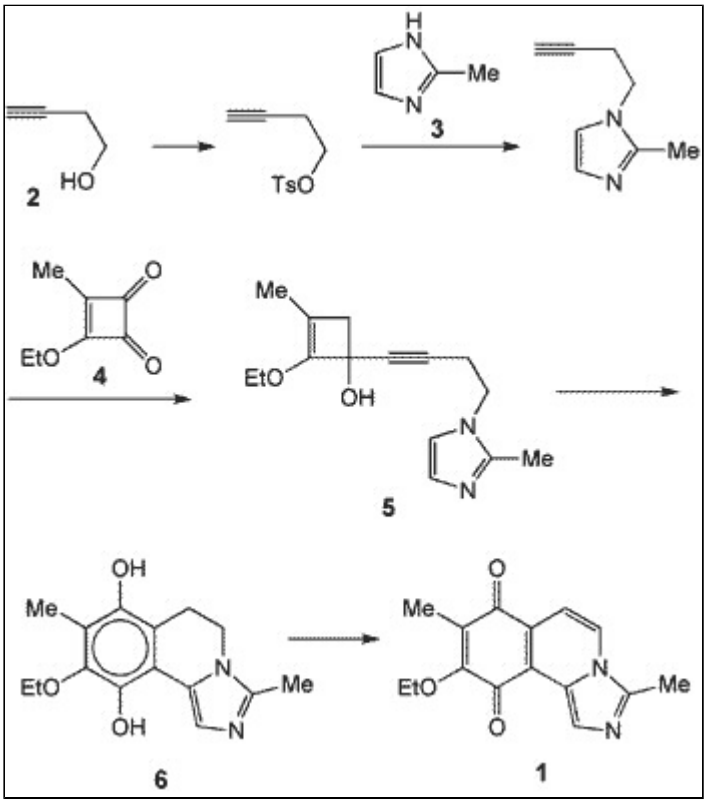
- Polymer-stabilized gold nanoparticles catalyze Suzuki–Miyaura reaction

Here’s an unusually concise synthesis of the potent antibiotic cribrostatin 6. The battle against multidrug-resistant Gram-positive bacteria now has another significant weapon: cribrostatin 6 (**1**), a structure that features a novel nitrogen-based tricyclic core. According to D. Knueppel and S. F. Martin* at the University of Texas at Austin, **1** inhibits the growth of several antibiotic-resistant Gram-positive bacteria and pathogenic fungi. Perhaps more importantly, its greatest activity is against *Staphylococcus pneumoniae*, the most common bacterial cause of acute respiratory infections that cause millions of deaths each year. In addition, **1** shows antineoplastic activity against human cancer cell lines at micromolar concentrations.



Compound **1** was originally isolated from *Cribrochalina* species of blue marine sponges (Pettit, G. R., et al. *J. Nat. Prod.* **2003,** *66*, 544–547). Although some syntheses have been developed for **1**, they are typically laborious procedures that require many steps. In contrast, the authors’ method produces **1** in ~14% overall yield and requires only four steps in the longest linear sequence, with a total of five steps from commercially available starting materials.

The overall synthesis strategy involves the reaction of butynol **2** and 2-methylimidazole **3** with squarate derivative **4** to assemble the key intermediate **5**. The authors visualize the conversion of **4** into **5** as a tandem 4π electrocyclic ring opening, radical cyclization, and homolytic aromatic substitution to give the desired tricyclic core (**6**) of the target molecule. Structure **6** is directly oxidized to the natural product **1** in one pot.

The authors note that their method is highly modular in that it allows ready modification of the starting materials to lead to related compounds with desirable bioactive properties. (*Angew. Chem., Int. Ed*. **2009,** *48,* **2569–2571**; **W. Jerry Patterson**)

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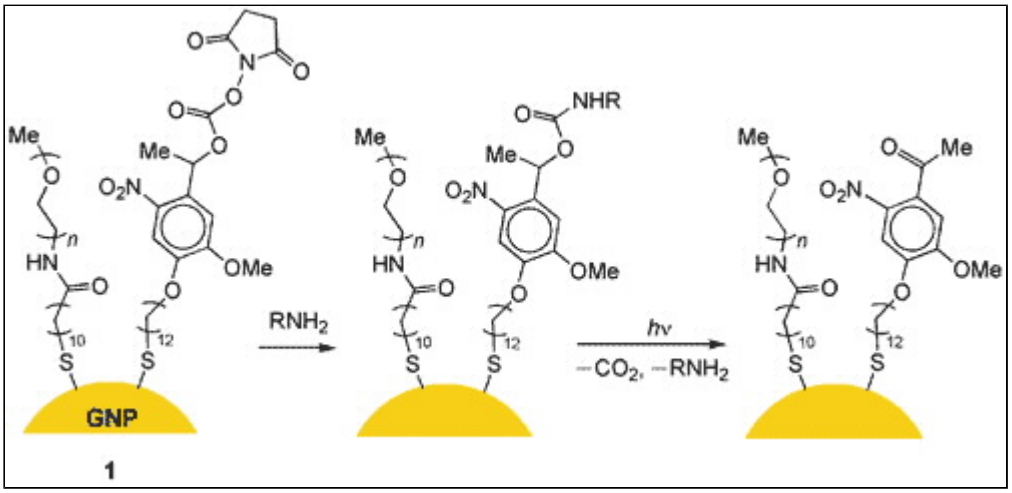
Release me: Photoresponsive coated gold nanoparticles as nanocarriers. J. Nakanishi* and colleagues at the National Institute for Materials Science (Ibaraki, Japan), the Japanese Science and Technology Agency (Saitama), and Kanagawa University (Japan) have developed colloidal gold nanoparticle (GNP) amine carrier systems that are capable of activated cellular signaling. The key to the signaling process is to incorporate a labile succinimidyl ester linkage that undergoes near-UV photocleavage on the GNP surface.



The authors coated GNPs with self-assembled monolayer mixtures of two disulfides: one with a caging ligand (on the right in structure **1**) and one with poly(ethylene glycol) (PEG) groups (on the left). Using thermogravimetric analysis and near-UV absorption studies, they determined that the ratio of caging ligand to PEG in **1** is 200:95. After the GNP carriers are mixed with 11-azido-3,6,9-trioxaundecan-1-amine (RNH_2), they exhibit IR absorption peaks characteristic of carbamate (1722 cm^{-1}) and azide (2100 cm^{-1}) formation. After irradiation at 365 nm and filtration, IR studies show that the azidoamine is released from the surface of the GNP.

The researchers also developed histamine–GNP cages and observed preservation of photophysical properties upon attachment to the GNP surface. The bioactivity of the histamine is disabled by its conjugation to the surface of the GNP; the active state is regenerated by near-UV–initiated release. The authors believe these studies will lead to advances in intracellular signaling using a photoresponsive caging mechanism. (*J. Am. Chem. Soc.* **2009,** *131,* **3822–3823**; **LaShanda Korley**)

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Match surface energies to obtain high field-effect mobility. Organic field-effect transistors (OFETs) play an essential role in making low-cost, large-area electronic products. Much effort has been devoted to modifying dielectric–semiconductor interfaces to adjust the surface energy of the gate dielectric and enhance field-effect mobility.

Polymeric dielectrics are promising gate materials for making flexible OFETs. Controlling the surface energy of the gate dielectric and the morphology of the semiconductor deposited onto it, however, is challenging. J. Gao, J. B. Xu, and coauthors at the Chinese University of Hong Kong and the University of Groningen (The Netherlands) attacked this problem with a simple approach.

The researchers built OFETs by depositing copper phthalocyanine (CuPc) semiconductors onto dielectric layers of poly(methyl methacrylate) (PMMA)–polystyrene (PS) blends. The highest field-effect mobility [0.01 $cm^2/(V{\cdot}s)$] is obtained when the surface energy of the polymer dielectrics is modulated to match that of the semiconductor by adjusting the PMMA/PS blend ratio to 1:3. The high mobility results from the desired morphology and favors growth of CuPc on the dielectric layer. This finding demonstrates the advantage of using insulating polymer blends to control the surface energy of the gate dielectric to achieve better OFET performance. (*Appl. Phys. Lett*. **2009,** *94,* **093302**; **Ben Zhong Tang**)

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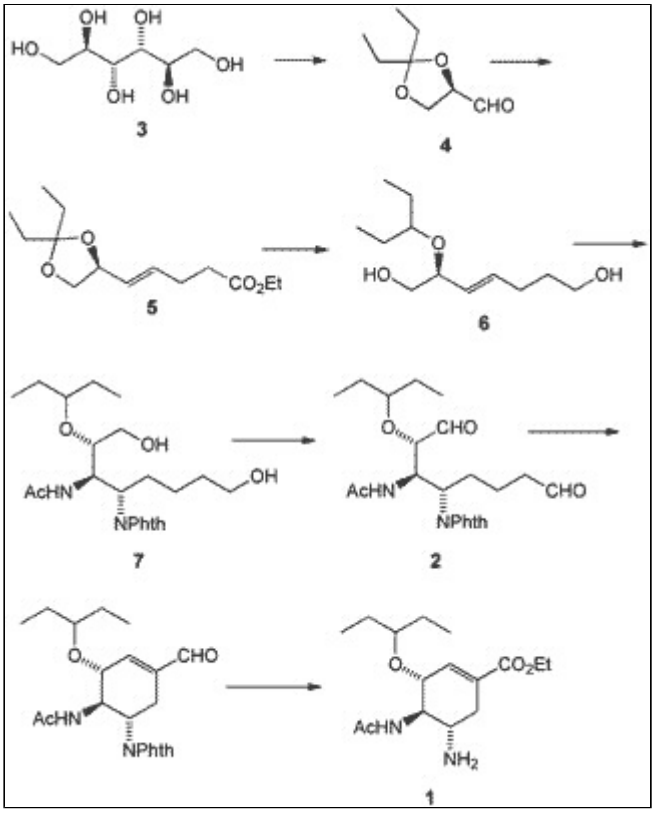

Synthesize oseltamivir without chromatographic purification. Oseltamivir phosphate (**1**·H_3PO_4, trade name Tamiflu) is a neuraminidase inhibitor that is active against the avian flu virus (H5N1). Its current preparation is based on a semisynthesis from shikimic acid.

T. Mandai* and T. Oshitari at Kurashiki University of Science & the Arts (Japan) report a new synthesis route to **1** that uses an intramolecular aldol condensation of dialdehyde **2** as a key step. The synthesis begins with the conversion of readily available D-mannitol (**3**) to known aldehyde **4**, and then to ester **5**. Cleavage of **5** gives 3-pentyl ether **6**, which is diastereoselectively dihydroxylated to diol **7**, the precursor to **2**. Phth is a phthalimido protecting group.

The key aldol condensation of **2** proceeds in presence of $Bn_2NH{\cdot}CF_3CO_2H$ and toluene to form the cyclohexene ring in good yields without byproducts formed from aromatization or elimination reactions. This 18-step sequence does not require any chromatographic purification steps, which is a great advantage for scaling up the process. Unfortunately, the synthesis uses potentially explosive azides. (*Synlett* **2009,** 783–786; **José C. Barros**)

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Gold "mining": Is it a rod or a sphere? Y. Liu, E. N. Mills, and R. J. Composto* at the University of Pennsylvania (Philadelphia) probed the optical properties of nanocomposite films of gold nanorods (~42 nm long, ~13 nm diam) modified on their surfaces with poly(ethylene glycol) (PEG) dispersed in a matrix of poly (methyl methacrylate) (PMMA). The UV–vis absorption peaks of the matrix-dispersed nanorods are red-shifted compared with the nanorods in water. Upon thermal annealing of nanorod–PMMA nanocomposites at 60 °C, the nanorod aspect ratio is decreased as indicated by a blue shift in the longitudinal (high-wavelength) plasmon resonance peak. The blue shift increases and occurs more rapidly by increasing annealing temperature from 60 to 200 °C; this causes a decrease in the average aspect ratio of the nanorods. The low- and high-wavelength plasmon resonance peaks merge when annealing is continued at 200 °C for 8 days; primarily spherical gold nanoparticles are produced.

The authors note that the stabilization of the rod shape is controlled by the PEG ligands on the nanorod surface, and that, above the glass-transition temperature of the PMMA, the PEG chains have sufficient mobility to diffuse to the matrix upon detachment from the nanorod surface, resulting in the thermally induced reshaping. They show by the constant nanorod number density that fragmentation of the nanorod does not occur, but that there is an increase in the concentration of gold relative to PMMA at higher annealing

temperatures and longer annealing times (e.g., 200 °C for 8 days). The researchers exploited the tunability of the nanorod shape by thermal annealing to construct a film with gradient optical properties. (*J. Mater. Chem.* **2009,** *19,* Advance Article DOI: **10.1039/b901782h**; **LaShanda Korley**)

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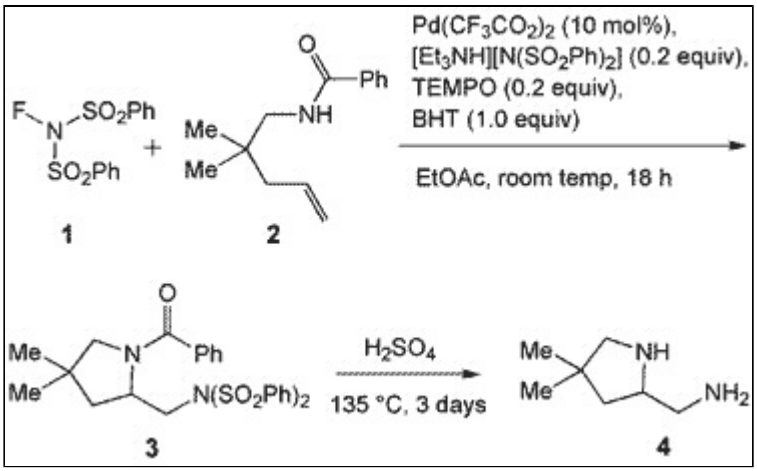
Diaminate unactivated alkenes with *N*-fluorobenzenesulfonimide. Because of the value of vicinal diamines for their biological activity and use as chiral auxiliaries and ligands for asymmetric synthesis, several diamination methods have been developed. They are generally limited, however, in substrate scope, or they are useful only for activated alkenes.

P. A. Sibbald and F. E. Michael* at the University of Washington (Seattle) report an innovative method for the palladium-catalyzed diamination of unreactive alkenes in which the reagent *N*-fluorobenzenesulfonimide (**1**)—normally a source of electrophilic fluorine—serves as an electrophilic aminating agent. This mode of reactivity of **1** is unprecedented.



Aminoalkene substrates, illustrated by **2**, are treated with **1** using a palladium catalyst complex in the presence of $[Et_3NH][N(SO_2Ph)_2]$, 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO), and 2,6-di-*tert*-butyl-4-methylphenol (BHT) to form the protected diamination product (**3**). All three additives are necessary to optimize yields of **3** and to minimize byproduct formation.

Deprotection of both amine groups in **3** is accomplished by using aqueous H_2SO_4 to give the free diamine (**4**) in good yield. Alternatively, one N-protecting group at a time can be selectively removed under mild conditions to obtain the resulting diamines in different protected forms. (*Org. Lett.* **2009,** *11,* **1147–1149**; **W. Jerry Patterson**)

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Polymer-stabilized gold nanoparticles catalyze Suzuki–Miyaura cross-coupling reactions in water. J. Han, Y. Liu, and R. Guo* at Yangzhou University (China) synthesized the nanoparticles by using a simple one-step chemical redox reaction between $HAuCl_4$ and 2-aminothiophenol. The aminothiophenol reducing agent also acts as a stabilizer because its polymeric form is an effective capping agent.

The size of the gold nanoparticles depends on the $HAuCl_4$/2-aminothiophenol mol ratio. Precise control over the size of the nanoparticles and the thickness of the stabilizer is crucial to the catalytic activity of this gold catalyst. (*J. Am. Chem. Soc.* **2009,** *131,* **2060–2061**; **George Xiu Song Zhao**)

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