

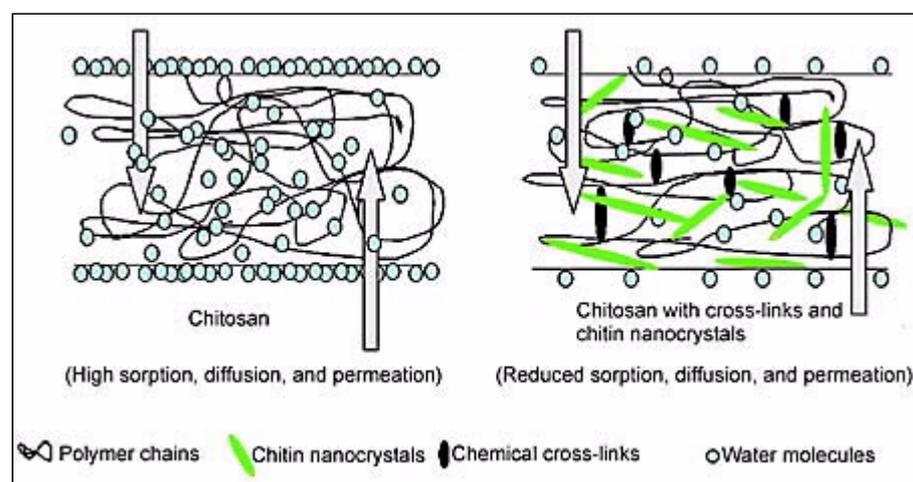
Noteworthy Chemistry

June 15, 2009

- Tailor barrier properties in chitosan–chitin cross-linked films
- Cleave ethers in the presence of diazonium salts
- This achiral terpolymer has a double helical structure
- Here's a short, efficient synthesis of oseltamivir phosphate
- Allow entropic effects to dominate a classical resolution
- Generate new topology by “clicking” long chains into large rings

Tailor barrier properties in these chitosan–chitin nanocomposite cross-linked films. A. P. Mathew*, M.-P. G. Laborie, and K. Oksman at Luleå University of Technology (Skellefteå, Sweden) and Washington State University (Pullman) describe the morphological and barrier properties of chitosan–chitin nanocomposites cross-linked with glutaraldehyde. The authors obtained thin, optically transparent films with the yellowish tint of 5 or 10 wt% chitosan in chitin nanocomposites upon cross-linking. They determined spectroscopically that glutaraldehyde cross-linking (~95% gel content) occurs primarily with chitosan and that the chitin nanocrystals were retained after cross-linking and extraction with dilute AcOH. The chitosan and chitin retain their amorphous and crystalline characters, respectively, after cross-linking.

The authors report that the 13–20 nm diam chitin nanocrystal fillers are well dispersed within the cross-linked chitosan matrix. Significant amounts of water are taken up by un-cross-linked and cross-linked chitosan–chitin nanocomposites within 2 min. The uptake plateau decreases from 150 to 115% with an increase in chitin content from 5 to 10% in the un-cross-linked particles. The decrease is more significant with cross-linking from 105% in the chitosan matrix to 70% in the nanocomposites. The degree of water uptake is highly pH-dependent.



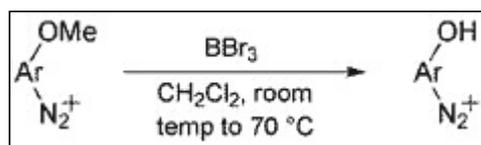
By analyzing the equilibrium water uptake, the authors determined that coefficients of sorption, diffusion, and permeability are reduced with increasing chitin content; but the permeation coefficient decreases and the diffusion coefficient increases upon cross-linking. They suggest that surface sorption is the dominant parameter in water uptake in the chitosan–chitin nanocomposites. (*Biomacromolecules* **2009**, *10*, Article ASAP DOI: [10.1021/bm9002199](https://doi.org/10.1021/bm9002199); **LaShanda Korley**)

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Cleave ethers in the presence of diazonium salts. Diazonium salts are important intermediates in azo coupling reactions, and more recently in Pd-mediated C–C coupling. This class of compounds can be prepared easily and isolated as tetrafluoroborates, but until now the only reaction that tolerated diazonium groups has

been nucleophilic substitution.

N. H. Nguyen, C. Cougnon* and F. Gohier* at the University of Maine (Le Mans, France) developed an aryl ether-group deprotection process that tolerates diazonium groups. They used an excess of BBr₃ in CHCl₂ to achieve the transformation. The aromatic ring can contain additional substituents such as methyl, methoxy, or nitro groups; it can also be pyridine, naphthalene, or biphenyl. Multiple methoxy groups are all cleaved.



The authors suggest a mechanism that explains their observation that para-substituted diazonium ethers react less readily than their meta-substituted isomers. In the para-ethers, the diazonium group is resonance stabilized, making the oxygen electrons less available to participate in the reaction. (*J. Org. Chem.* **2009**, *74*, [3955–3957](#), [José C. Barros](#))

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This achiral terpolymer has a double helical structure. The DNA double-helix structure has spurred researchers to investigate similar molecular structures, but producing double-helical structures from achiral synthetic molecules is challenging. H. Jinnai, V. Abetz, and coauthors at Kyoto Institute of Technology and GKSS Research Center Geesthacht (Germany) observed double helical morphology in achiral triblock copolymers when using transmission electron microtomography (TEM), a new, powerful tool for visualizing 3-D structures in materials.

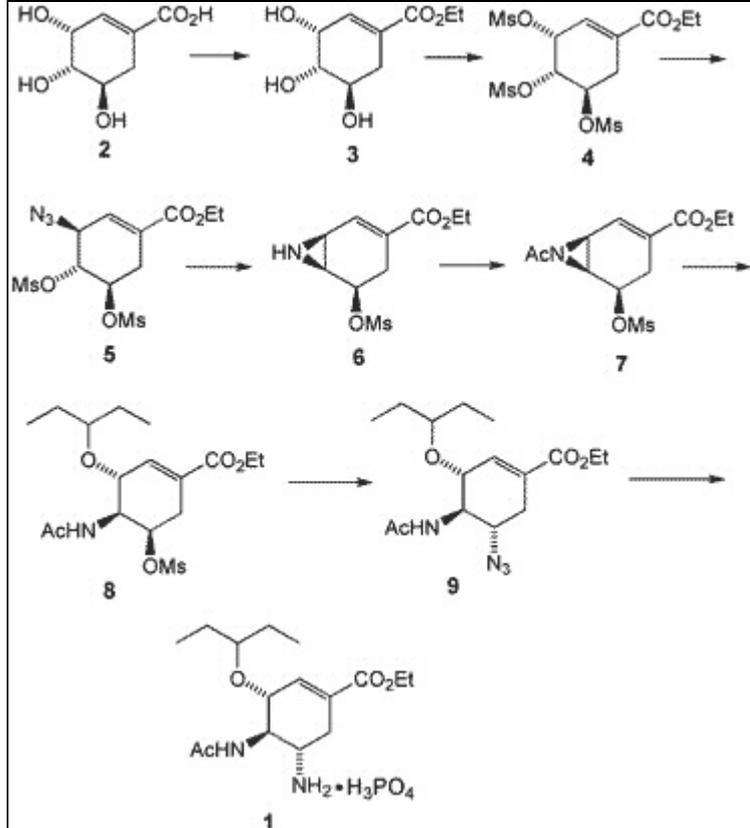
The terpolymer consists of polystyrene, polybutadiene, and poly(methyl methacrylate) (PMMA). The PMMA block occupies 70% of the volume and forms the matrix. The other two components (21 and 9%, respectively) contribute the cylindrical microdomains. The TEM images show left- and right-handed helical structures.

The pitch, the diameter of the polystyrene core microdomains, and the diameter of the polybutadiene microdomains were ~48, ~40, and ~10 nm, respectively. The double helical morphology is retained when the volume of the polystyrene component is raised as high as 37%. (*Soft Matter* **2009**, *5*, [2042–2046](#); [Sally Peng Li](#))

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Here's a short, efficient synthesis of oseltamivir phosphate. The development of oseltamivir phosphate (**1**; trade name Tamiflu) has generated much excitement because it is the only available oral drug useful for prophylaxis and treatment of human influenza and the H5N1 avian virus. It is one of only two antivirals that is effective against the H1N1 strain that has infected a small number of humans around the world. The concern over a possible swine flu pandemic has prompted renewed research toward large-scale preparation of **1**.

Hoffman-La Roche's industrial synthesis of **1** seems to be the best method, but it is a long synthetic route with a relatively low yield. X.-X. Shi and co-workers at East China University of Science and Technology (Shanghai) developed a significantly shorter route to **1** that starts from (–)-shikimic acid (**2**), a natural product that is commercially available in large quantities in China.



The authors converted shikimic acid to ethyl shikimate (**3**) by a known procedure and treated **3** with MeSO_2Cl , Et_3N , and a catalytic amount of 4-(dimethylamino)pyridine to give mesylate **4**. Next, **4** was treated with NaN_3 to give azide **5** with highly stereoselective substitution at the allylic C–3 position. The configuration at C–3 was reversed from (*R*) to (*S*). The regioselectivity of this step allowed the mesylate groups at C–4 and C–5 to remain undisturbed.

Compound **5** was treated successively with Ph_3P , Et_3N , and H_2O to produce aziridine **6**, which was quickly acylated with Ac_2O and Et_3N to form *N*-acetylaziridine **7**. The reaction of **7** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in 3-pentanol supplied the key ring-opening of the aziridine ring with excellent stereoselectivity to provide compound **8** with the desired stereocenters at C–3 and C–4. The remaining mesylate group at C–5 was removed by azide in a nucleophilic displacement to give **9**, with another (*R*)-to-(*S*) configuration reversal. In the final step, the authors replaced the azide group with a primary amine phosphate salt (based on their earlier work) to produce target compound **1**.

The yields for the individual steps throughout this synthesis were high and resulted in an overall yield of 47%. The synthetic route was reduced from 13 to 8 steps. The authors note that easy crystallization of **4** and simple purification of **6** without chromatography enhances the potential of the procedure as an industrial process. (*J. Org. Chem.* **2009**, *74*, **3970–3973**; **W. Jerry Patterson**)

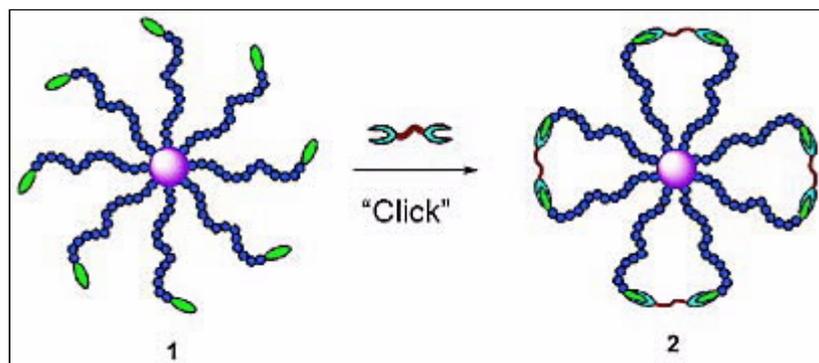
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Use a large volume of solvent to allow entropic effects to dominate a classical resolution. The classical resolution of 2-[3-fluoro-4-(methoxycarbonyl)phenyl]pyrrolidine with *D*-tartaric acid gives a salt containing an 87:13 ratio of the (*S*)- to the (*R*)-enantiomer. A 9:1 ratio appears to be the thermodynamic “well” for this system and means that a single-crystallization strategy is not feasible.

D. M. Barnes and co-workers at Abbott Laboratories (North Chicago, IL) adopted a double-crystallization strategy; the crystallization medium was critical to their success. They reasoned that the loss of desired product is determined by enthalpy-driven solubility, whereas rejection of the minor enantiomer is entropy-driven. This means that obtaining a high-quality diastereomeric salt requires large volumes of solvent, and this was borne out in practice. A 74% yield of the desired salt with a final enantiomeric ratio of 99.5:0.5 was obtained by crystallizing a starting 92.5:7.5 salt mixture in 60 volumes of MeOH. (*Org. Process Res. Dev.* **2009**, *13*, **225–229**; **Will Watson**)

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Generate a new topological structure by “clicking” long chains into large rings. Creating polymers with new topological structures is not only esthetically appealing, but it may generate materials with unique properties. A research team led by S. Liu at the University of Science and Technology of China (Hefei) has added a new topology to the long list of polymer structures.



The researchers designed and synthesized a quatrefoil-shaped polystyrene that contains a polyhedral oligo (silsesquioxane) core by radical polymerization and a “click” reaction. Azidation of a chlorinated oligo (silsesquioxane), followed by a click reaction with propargyl 2-bromobutyrate gives an octafunctional initiator, which initiates the atom-transfer radical polymerization of styrene to yield a bromine-capped star polystyrene. The azidation produces a star-linear polystyrene with eight arms (**1**). Intramolecular ring closure of **1** using propargyl ether as a difunctional linker gives star-cyclic polystyrene (**2**). The cyclic polymer undergoes glass transition at a temperature higher than its linear counterpart because of the ring topology. (*Macromolecules* **2009**, *42*, 2903–2910; **Ben Zhong Tang**)

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