Solid-Phase Biomimetic Synthesis of Carpanone-like Molecules

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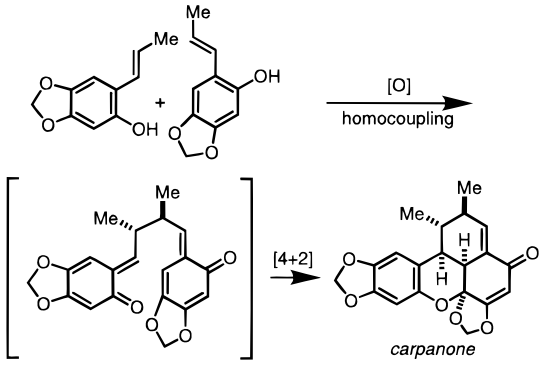
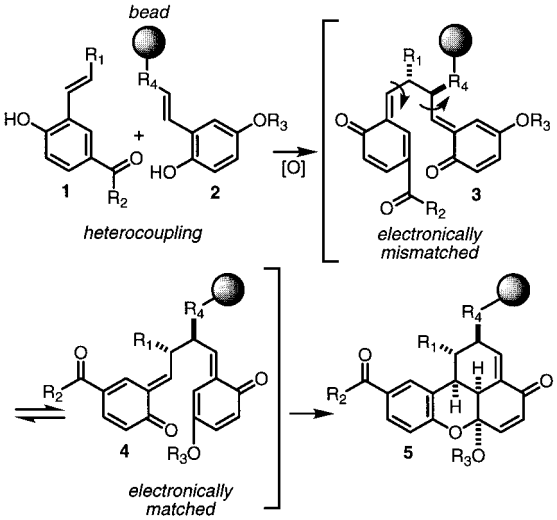
The advances of split-pool organic synthesis[1] and high-throughput biological screens[2] have provided new opportunities for the discovery of man-made molecules with novel biological properties. Realization of these new opportunities will be accelerated by the development of solid-phase reactions that dramatically increase molecular complexity while simultaneously accessing diverse structures. Biomimetic reactions that mimic natural product biosyntheses[3] are well suited to this approach because they often convert simple starting materials to complex structures under mild conditions. While this is an attractive concept, two significant challenges are (1) developing biomimetic transformations that access a diverse range of structures and (2) performing these reactions in the solid-phase. This communication reports the development of biomimetic reactions in the solid-phase that result in one-step construction of tetracyclic molecules from readily accessible starting materials. The reactions are based on ones implicated in the biosynthesis of carpanone and other members of the benzoxanthenone class of natural products.[4]

The biomimetic synthesis of carpanone (Scheme 1, [O] = $PdCl_2$), first accomplished by Chapman, occurs by diastereoselective oxidative homocoupling of an electron-rich *o*-hydroxystyrene followed by rapid endo-selective inverse electron demand Diels−Alder cycloaddition.[5] To broaden the scope of this biomimetic synthesis, with the goal of constructing a split-pool synthesis library of carpanone-like molecules more diverse than those isolated from nature, it was necessary to develop a reaction that would result in intermolecular oxidative heterodimerization of dissimilar *o*-hydroxystyrenes. To our knowledge, this level of selectivity has not been observed for β,β-phenolic couplings in natural or laboratory systems.

Scheme 1



Scheme 2



Our plan involved the use of electronically differentiated *o*-hydroxystyrenes (Scheme 2). Under the influence of a suitable oxidant, the oxidatively more reactive electron-rich phenol **2**, immobilized in the solid-phase to reduce its propensity for homodimerization, will react preferentially with the oxidatively less reactive electron-deficient phenol **1** in solution.[6] Following oxidative heterocoupling, inverse electron demand Diels−Alder transition states **3** and **4** are possible. The electronically preferred transition state **4** should be favored affording tetracycle **5** directly.[7] In a single biomimetic reaction in the solid-phase, tetracyclic molecules will be constructed with control over five stereocenters and four initial positions of diversity (R_1−R_4).

Initially, we screened a series of oxidants for their ability to cross-couple electronically differentiated substrates **6** and **7**[8] (Scheme 3). Only $PhI(OAc)_2$ afforded heterocoupled product **8**.[9] All other oxidants tested resulted in exclusive formation of **9**, resulting from intrabead homocoupling.[10] It is interesting to note that $PhI(OAc)_2$ was the only oxidant in the screen that did not proceed through a phenoxy radical intermediate.[11]

Following HF−pyridine promoted removal from the solid-phase (0.15 mmol/g) a 55% yield of tetracycle **8** was isolated as a single isomer, resulting from complete electronic control of the inverse electron demand cycloaddition. The solid-phase reaction afforded a 1.7:1 ratio of heterocoupled adduct **8** and homocoupled adduct **9** starting from silicon-linked resin **7** (Entry B). Compound

(1) (a) Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. *Int. J. Pept. Protein Res.* **1991**, *37*, 487−493. (b) Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. *Nature* **1991**, *354*, 82−84. (c) Nicolaou, K. C.; Pastor, J.; Winssinger, N.; Murphy, F. *J. Am. Chem. Soc.* **1998**, *120*, 5132−5133. (d) Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 8565−8566.

(2) For a recent review of high-throughput biological screening, see: Fernandes, P. B. *Curr. Opin. Chem. Biol.* **1998**, *2*, 597−603.

(3) Braun, M. *Org. Synth. Highlights* **1991**, 232−9.

(4) (a) Brophy, G. C.; Mohandas, J.; Slaytor, M.; Sternhell, S.; Watson, T. R.; Wilson, L. A. *Tetrahedron Lett.* **1969**, *10*, 5159−5162. (b) Jakupovic, J.; Eid, F. *Phytochemistry* **1987**, *26*, 2427−2429.

(5) Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 6696.

(6) For intermolecular oxidative biaryl heterocoupling, see: (a) Young, D. A.; Young, E.; Roux, D. G.; Brandt, E. U.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2345. (b) Hovorka, M.; Gunterova, J.; Zavada, J. *Tetrahedron Lett.* **1990**, *31*, 413.

(7) The preference for transition state **4** is based upon the strong preference of acrolein for ethyl vinyl ether over itself in an inverse electron demand heterocycloaddition reaction. For examples, see: Longley, R. I.; Emerson, W. S. *J. Am. Chem. Soc.* **1950**, *72*, 3079.

(8) Hu, Y.; Porco, J. A., Jr.; Labadie, J. W.; Gooding, O. W. *J. Org. Chem.* **1998**, *63*, 4518−4521.

(9) All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS. See the Supporting Information for details.

(10) $PdCl_2$-NaOAc, Co(Salen)-O_2, Mn(Salen)-O_2, $CuCl_2$-$tBuNH_2$, Fe(Salen)-O_2, O_2-*hν*-rose bengal, $PhI(OCOCF_3)_2$, and VOF_3 led exclusively to homodimerization. Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1981**, *22*, 4437.

(11) Varvoglis, A. *Best Synthetic Methods: Hypervalent Iodine in Organic Synthesis*; Academic Press: New York, 1997.

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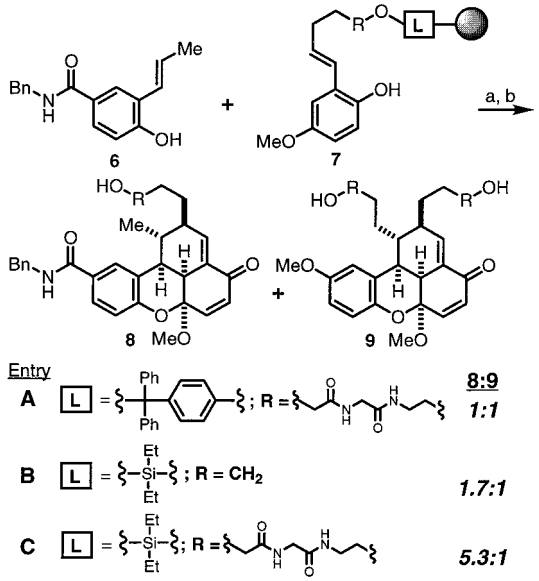
Scheme 3[a]

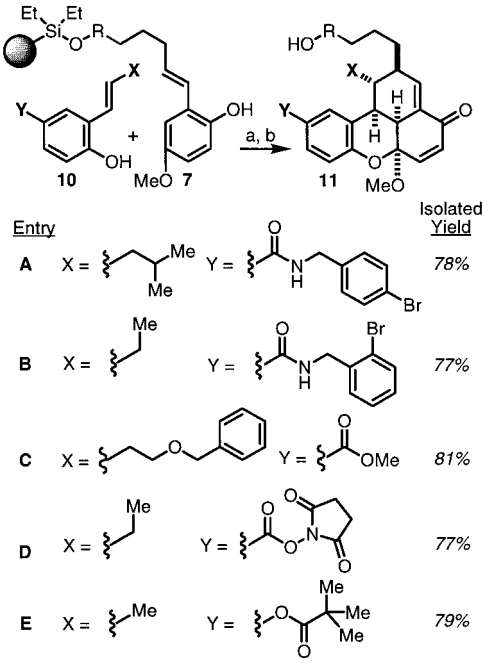


[a] Conditions: (a)10 equiv of **6**, $PhI(OAc)_2$, CH_2Cl_2−THF, agitation, 25 °C, 2 h. (b) For Si-linker: HF−pyridine, THF, 25 °C, then TMSOMe. For Trityl linker: 2% TFA, 20% Et_3SiH, CH_2Cl_2.

9 resulted from an oxidative homocoupling between two molecules of **7** attached to the same resin bead. Although lowering the loading level of the resin resulted in a modest reduction in intrabead reactions for entry B (Scheme 3) (0.3 mmol/g → 1:1 **8**/**9**; 0.15 mmol/g → 1.7:1 **8**/**9;** 0.075 mmol/g → 4:1), it was crucial that the loading level remain as high as possible to facilitate future biological screens. As a result of these issues combined with the lack of detailed information regarding the orientation of molecules attached to the solid-phase, the factors contributing to intrabead coupling, excluding resin loading levels, had to be determined on an empirical basis.[12] A diminution in homocoupling was observed when R contained amide bonds. For instance, the silicon-based linker combined with an amide-based spacer (entry C) provided the highest degree of heterocoupled product (5.3:1) at a loading level of 0.15 mmol/g, whereas the silicon linker and a hydrocarbon spacer (entry B) afforded only a slight preference for heterocoupling (1.7:1). A trityl-based linker and an amide spacer (entry A) afforded a 1:1 ratio of **8** and **9** (Scheme 3).

To explore the generality of the solid-phase biomimetic reaction for diversity-oriented synthesis, a series of electron-deficient phenols were constructed and tested in the solid-phase synthesis (Scheme 4). Electron-withdrawing groups in the Y position of **10** that led to productive solid-phase heterocoupling included amides (entries **A** and **B**), ester (entry **C**), activated ester (**D**), and acylated phenol (entry **E**). The X position tolerated alkyl and heteroatom containing groups with isolated yields between 77 and 81%. In each case, the tetracyclic adducts were obtained as single isomers resulting from complete electronic control during

Scheme 4[a]



[a] Conditions: (a) 10 equiv of **10**, $PhI(OAc)_2$, CH_2Cl_2−THF, agitation, 25 °C, 2 h. (b) HF−pyridine, THF, 25 °C, then TMSOMe. Isolated yields are based upon resin **7**. For R, see entry **C**, Scheme 3.

the inverse electron demand Diels−Alder cycloadditions. A small (∼10%) amount of compound **9**, resulting from dimerization of **7**, was also isolated from these experiments.

In conclusion, biomimetic solid-phase synthesis of carpanone-like molecules has been accomplished. Combining an amide-based linker and silyl attachment to the solid-phase diminished competing intrabead coupling. These results highlight the intriguing possibility of controlling reactions in the solid-phase by altering the structure of the linker.[13] In the six experiments reported in this study, the biomimetic solid-phase reaction tolerated a range of functionality, making it amenable to diversity-oriented synthesis and construction of libraries of carpanone-like molecules. Experiments are underway to functionalize the carpanone-like compounds in the solid-phase en route to split-pool synthesis of a 100,000-member library and high-throughput biological screens.[14] We are also investigating the correlation between solid-phase linker structure and the control of site−site interactions in the solid-phase.

Currently, biomimetic reactions and syntheses are used to access a single natural product. If biomimetic reactions are generalized, for the purpose of diversity-oriented synthesis, and combined with split-pool synthesis techniques, they may become a powerful method of constructing a wide range of natural product-like structures for discovery of molecules with new biological properties.

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Supporting Information Available: Details of experimental procedures and analytical data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Intrabead reactions have been observed and a reduction of intrabead interactions can be achieved on an adhoc basis by lowering the loading level of the resin. For a discussion, see: (a) Rapoport, H.; Crowley, J. I. *Acc. Chem. Res.* **1976**, *9*, 135−144. (b) Yan, B. *Combinatorial Chem. High Throughput Screening* **1998**, *1*, 215−229.

(13) Tollner, K.; Biro-Popovitz, R.; Lahav, M.; Milstein, D. *Science* **1997**, *278*, 2100.

(14) For the synthesis of nonnatural carpanone-like molecules with biological activity, see: Maeda, S.; Masuda, H.; Tokoroyama, T. *Chem. Pharm. Bull.* **1995**, *43*, 935−940.