Greg Tabor

Classics in Solid-Phase Synthesis

What is solid phase-synthesis?

A method in which molecules are bound on a bead and synthesized step-by-step in a reactant solution

Benefits

-Easier to remove excess reactant or byproduct from the product
-Possibility to use excess reagents
-No reliance on standard protocols of water-quenching, solvent extraction, drying, evaporation, and chromatography at each step
-Single pot transformations
-Supports linear and convergent synthesis
-Immobilization facilitates use of toxic, obnoxious or volatile compounds

Drawbacks

-Adaptation and optimization from conventional solution phase
-Following progress on solid-supports
-Availability of starting materials
-Development of solid-phase reagents
-Stability of solid-phase covalent bond

Uses

Starting material is a bead which binds to the building block. At first, this bead is added into the solution of the protected building block and stirred. Solution is removed and the bead is washed. After all steps are finished, the synthesized compound is cut off from the bead.

Used for the synthesis of peptides, deoxyribonucleic acid (DNA), and other molecules that need to be synthesized in a certain alignment.

Beginnings of Solid-Phase Synthesis: Peptides

Merrifield, R.B.; *J. Am. Chem. Soc.*, **1963**, *85* (14), pp 2149-2154

Finding a suitable polymer
-Insoluble in all of the solvents which were used and have a stable physical form which permitted ready filtration
-Had to contain a functional group to which amino acid could be linked by a covalent bond

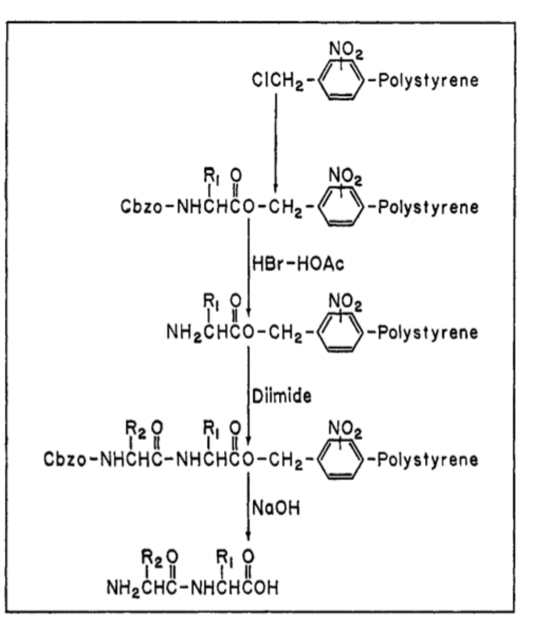
Cellulose, polyvinyl alcohol, polymethacrylate and sulfonated polystyrene. The one which worked best was a chloromethylated copolymer of styrene and divinylbenzene.

Resin consisted of 200-400 mesh beads which possessed a porous gel structure allowed ready penetration of reagents

Although diffusion and steric hindrance were no doubt important factors, they were not serious enough to prevent the desired reactions from proceeding to completion.

The reaction rates were slower than corresponding ones in solution

First example of solid-phase synthesis



Classics in Solid-Phase Synthesis

Techniques in Solid-Phase Synthesis

-Filtration -Scavenging -Catch and release

a) The simplest case - No by-products

b) The more complex case - Excess coupling component or by-product formed

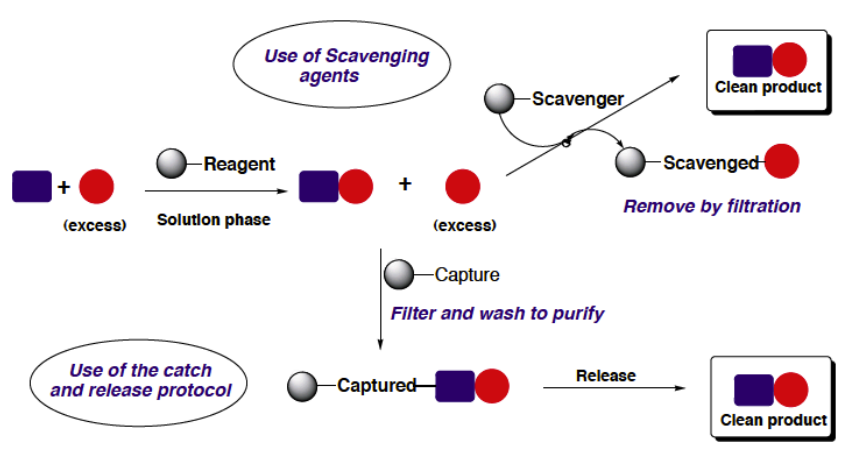
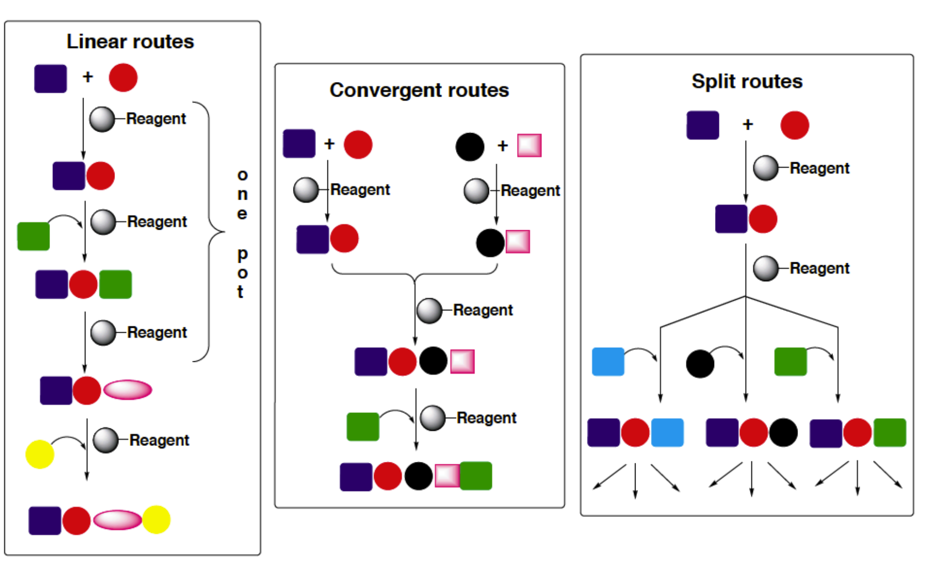


Fig. 1. Solid-supported reagents in synthesis. (a) The simple case—no by-products generated. (b) A more complex case—the use of excess coupling components or by-product removal.

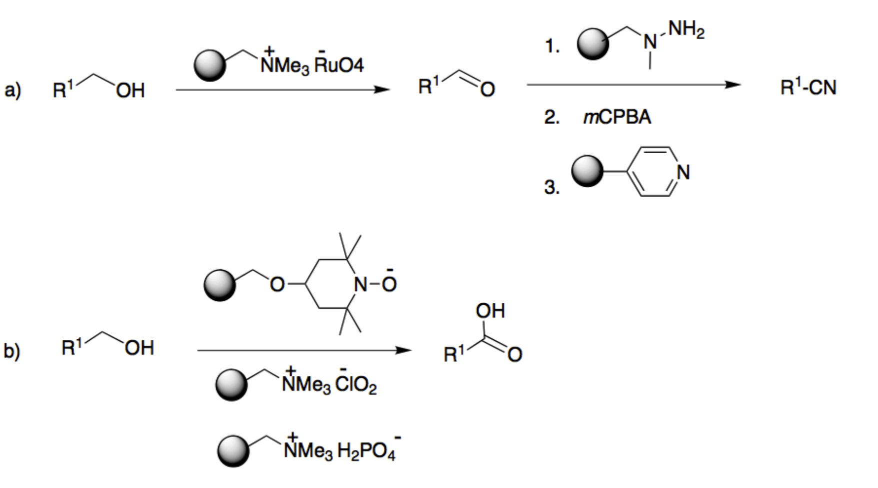
Ley, S.V.; Baxendale, I. R. *Chem. Rec.* 2002, **2**, 377–388

Opportunities for solid-supported reagents

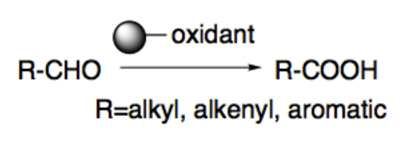


Potential Industrial Uses

Use of solid phase to convert readily available species to common fuctional groups



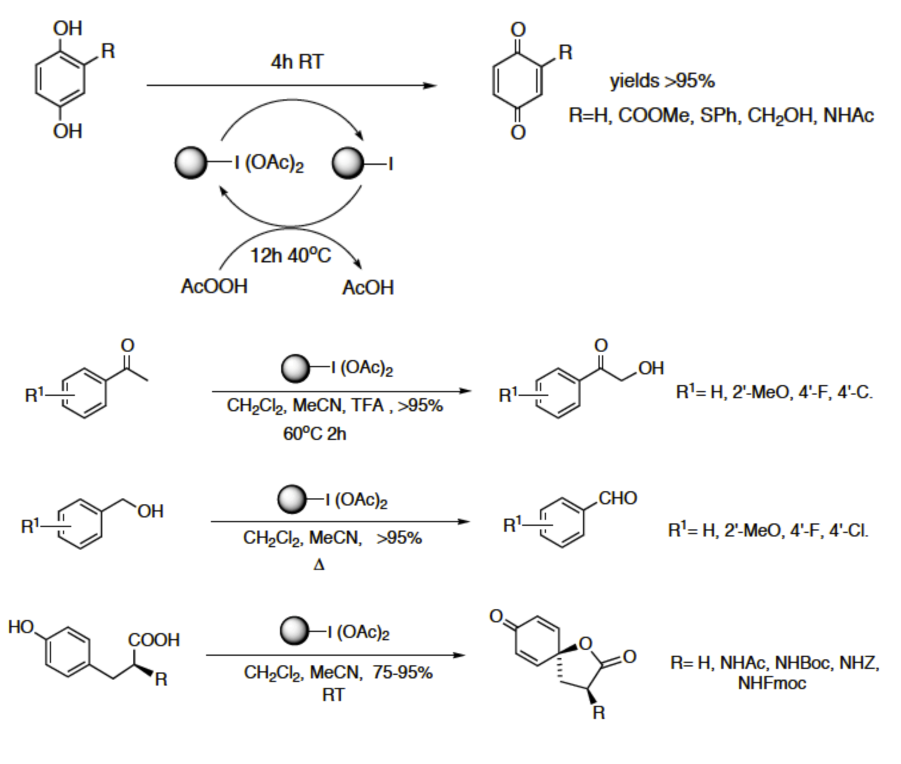
Classics in Solid-Phase Synthesis



R=alkyl, alkenyl, aromatic

Although conversion from alcohol to acid using conventional methods is straightforward, the solid-phase method only requires filtration through a silica column.

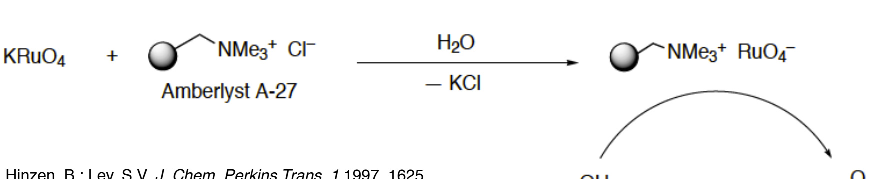
Hypervalent iodine reagents



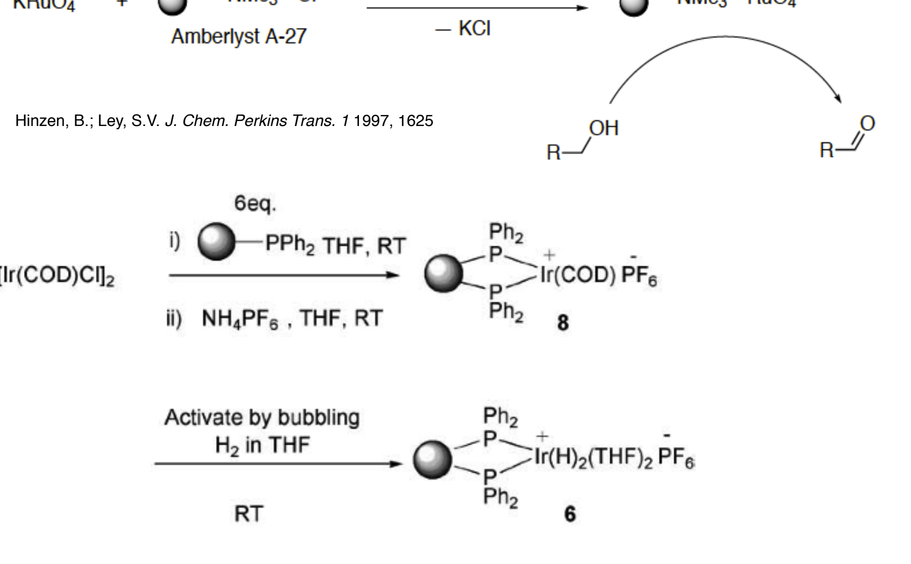
Ley, S.V.; Krutzik, P.O.; Hart, M.E.; Chamberlin, A.R. *J. Comb. Chem.* 2002, **4**, 95

Conversion from conventional to solid-phase

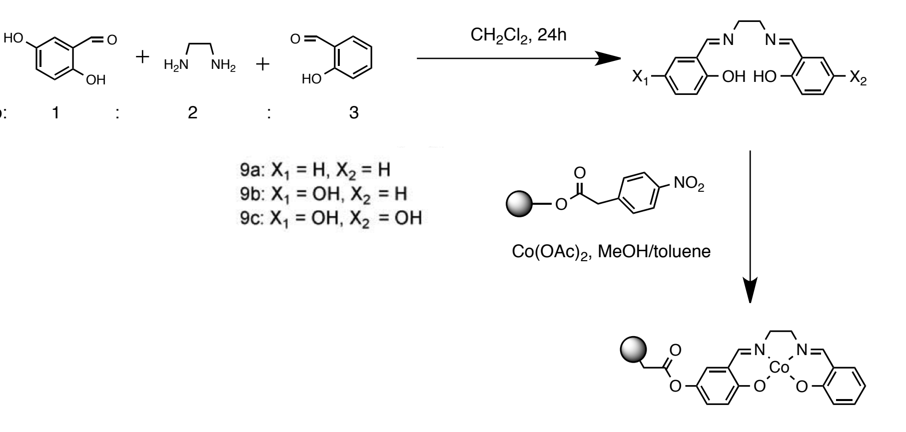
Polymer supported perruthenate (PSP) solid-phase version of tetrapropyl ammonium perruthenate (TPAP)



Hinzen, B.; Ley, S.V. *J. Chem. Perkins Trans. 1* 1997, 1625



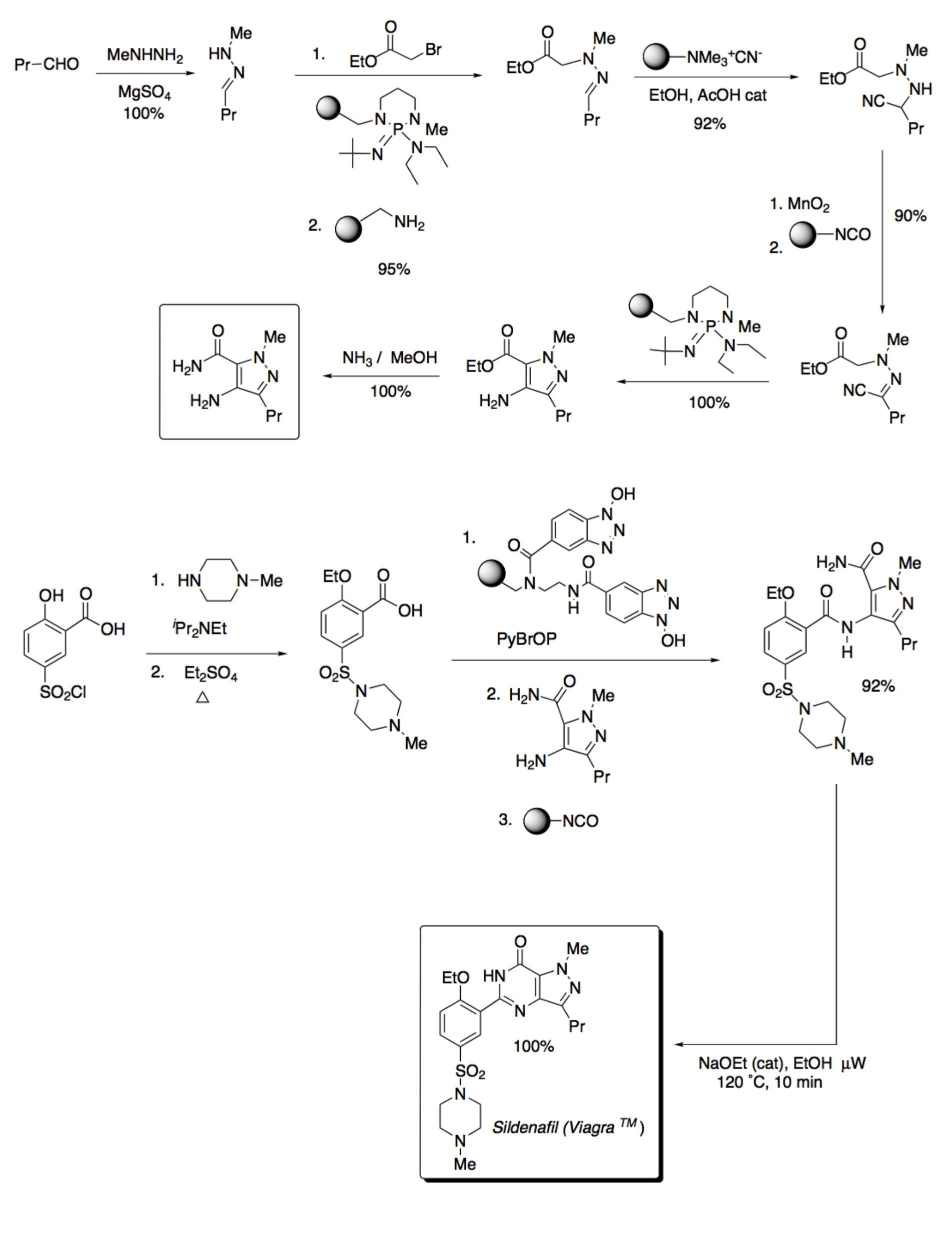
Baxendale, I.R.; Lee, A.-L.; Ley, S.V. *Synlett* 2001, 1482

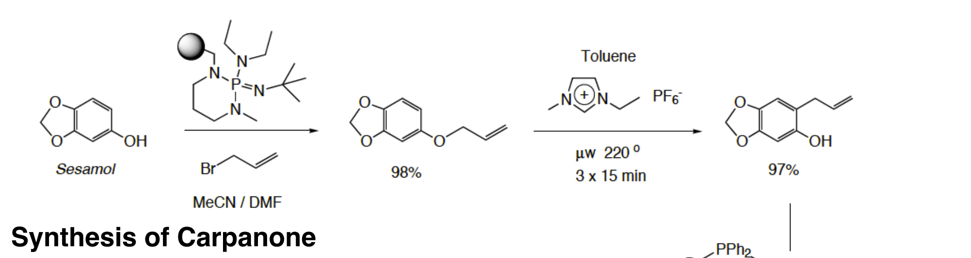


Classics in Solid-Phase Synthesis

Synthesis of Sildenafil

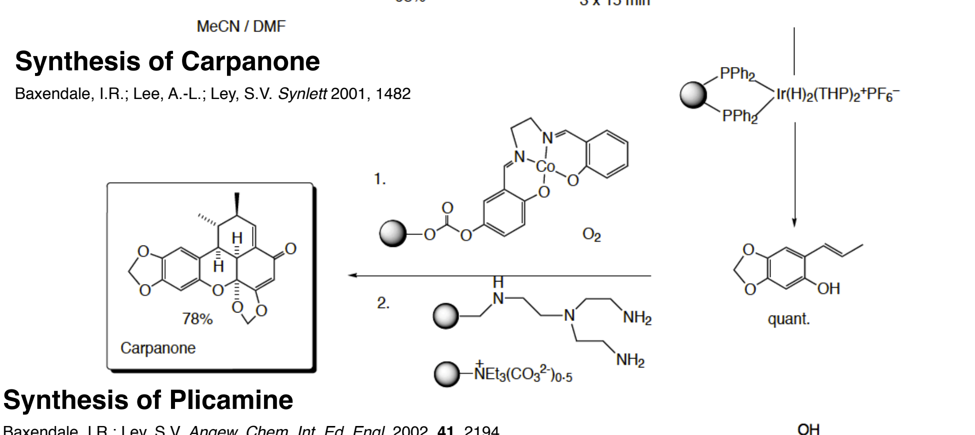
Baxendale, I.R.; Ley, S.V. *Bioorg. Med. Chem. Lett.* 2000, **10**, 1983





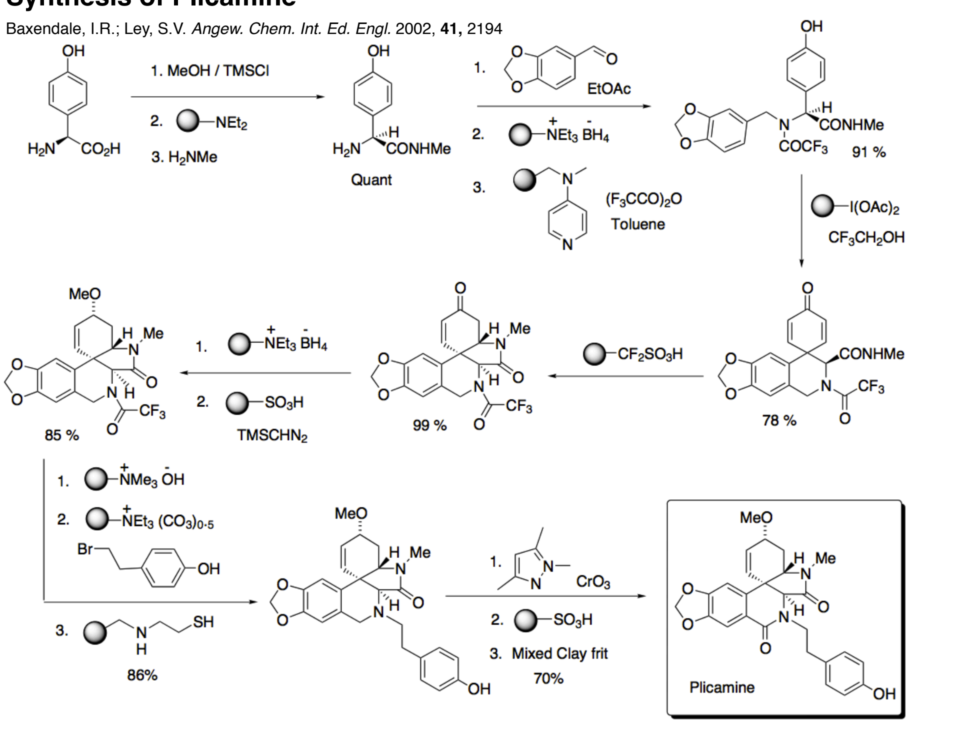
Synthesis of Carpanone

Baxendale, I.R.; Lee, A.-L.; Ley, S.V. *Synlett* 2001, 1482



Synthesis of Plicamine

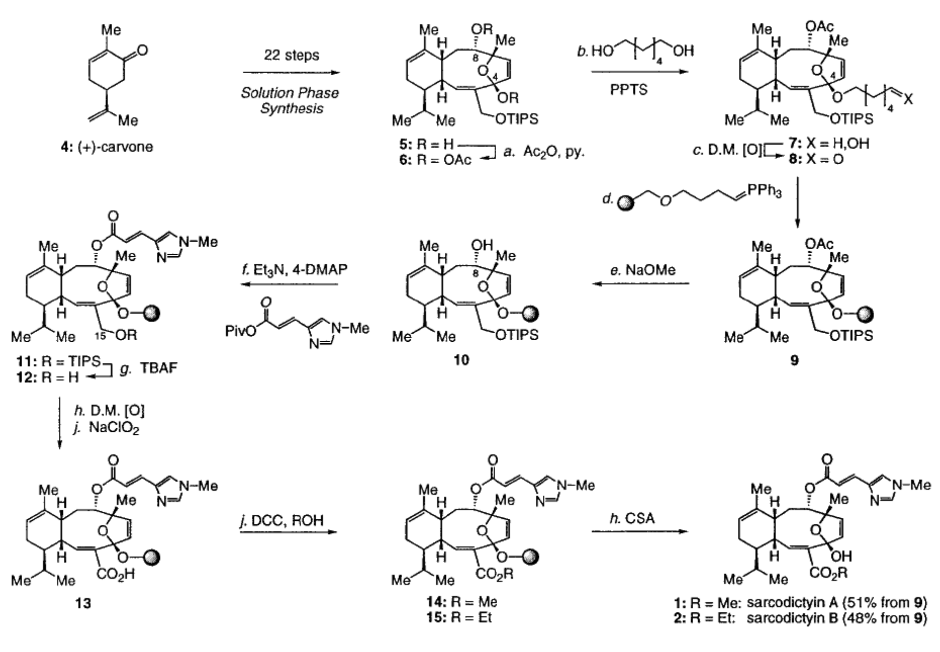
Baxendale, I.R.; Ley, S.V. *Angew. Chem. Int. Ed. Engl.* 2002, **41**, 2194



Classics in Solid-Phase Synthesis

Development of Diversity Oriented Libraries

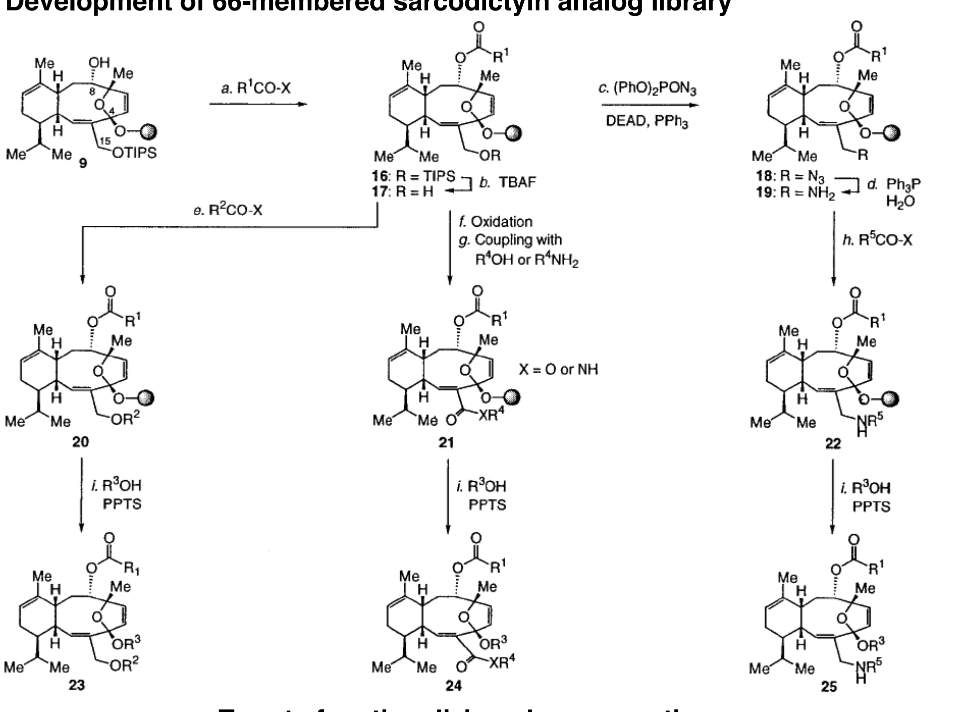
Semisynthesis of sarcodictyins A and B



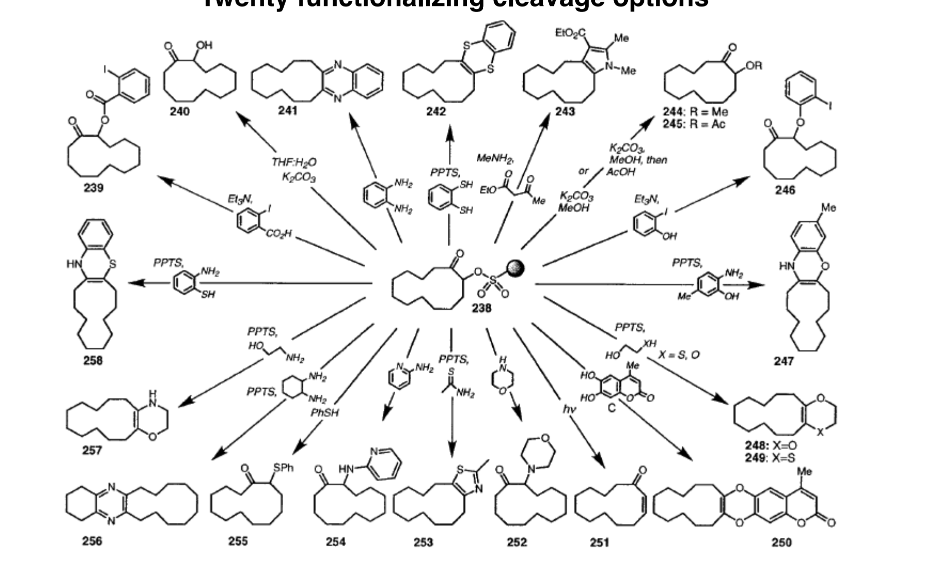
Development of an advanced intermediate that could be tethered to allow for maximum installation of diversity elements

Nicolaou KC, Pfefferkorn JA. Solid phase synthesis of complex natural products and libraries thereof. *Biopolymers (Pept. Sci.)* 2001; **60**: 171–193

Development of 66-membered sarcodictyin analog library

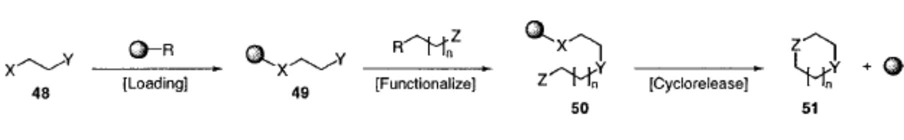


Twenty functionalizing cleavage options

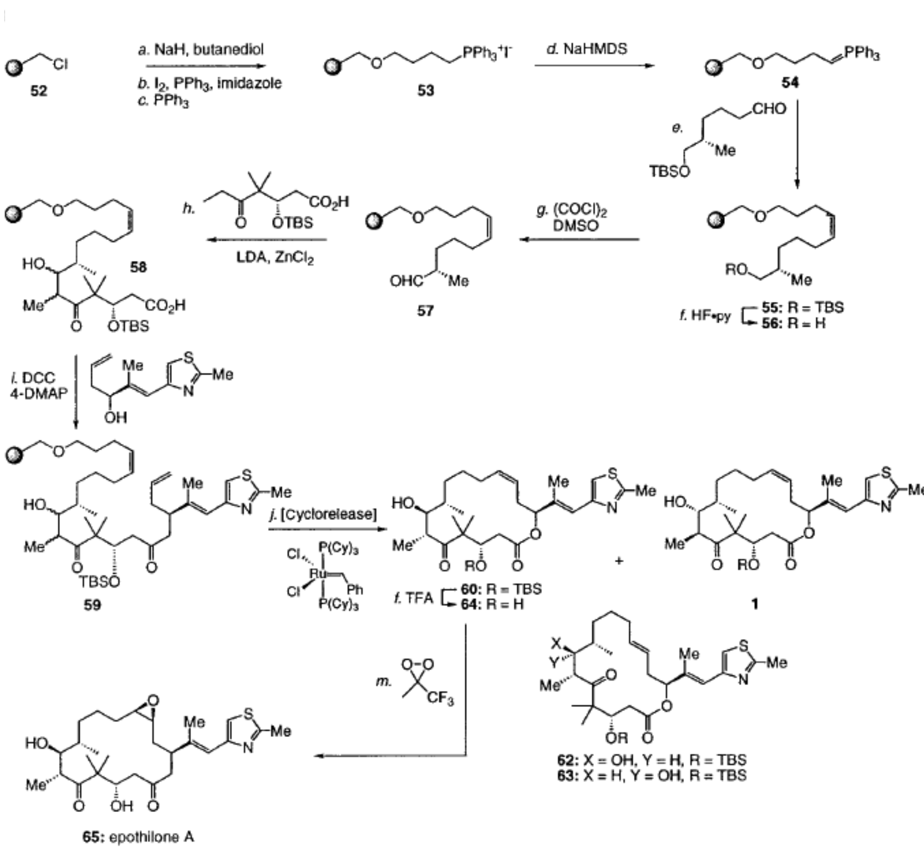


Classics in Solid-Phase Synthesis

Cyclorelease Strategies

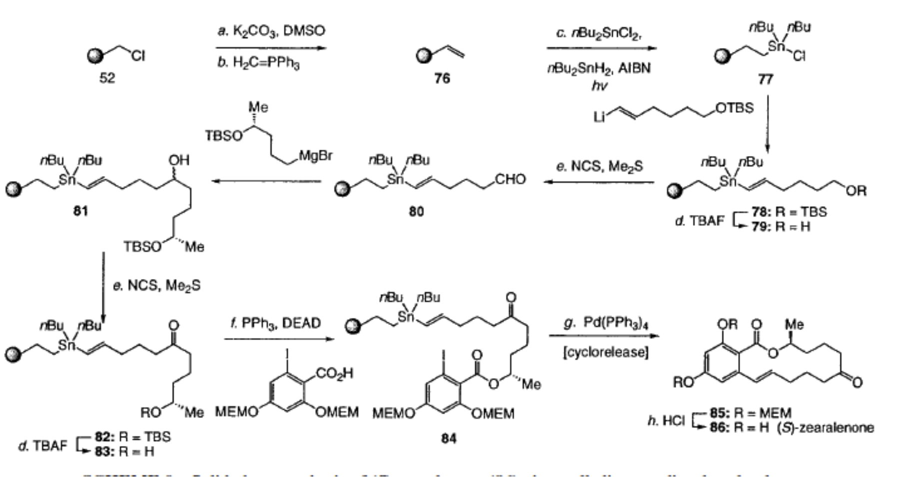


Synthesis of epithilone A: Olefin metathesis cyclorelease

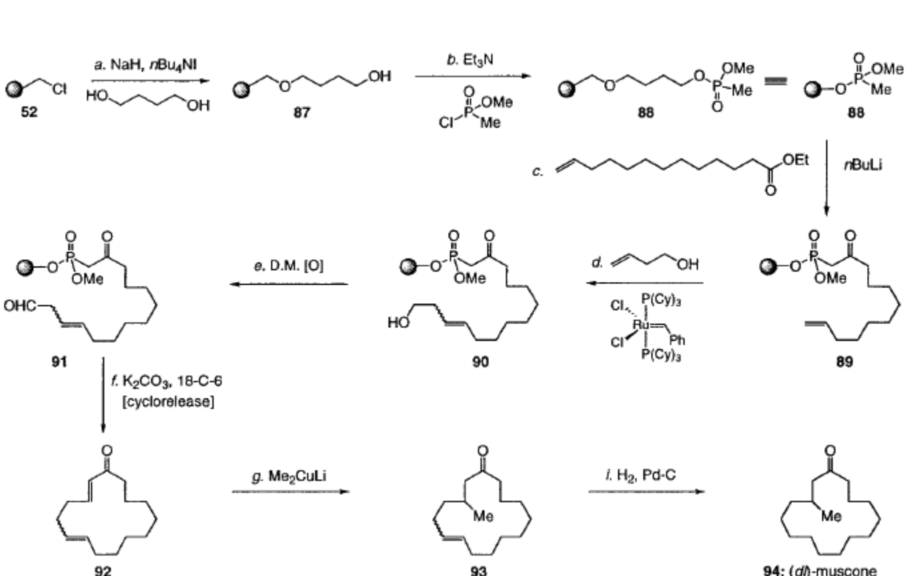


Nicolaou KC, Pfefferkorn JA. Solid phase synthesis of complex natural products and libraries thereof. *Biopolymers (Pept. Sci.)* 2001; **60**: 171–193

Synthesis of (S)-zearalenone: Palladium-mediated cyclorelease



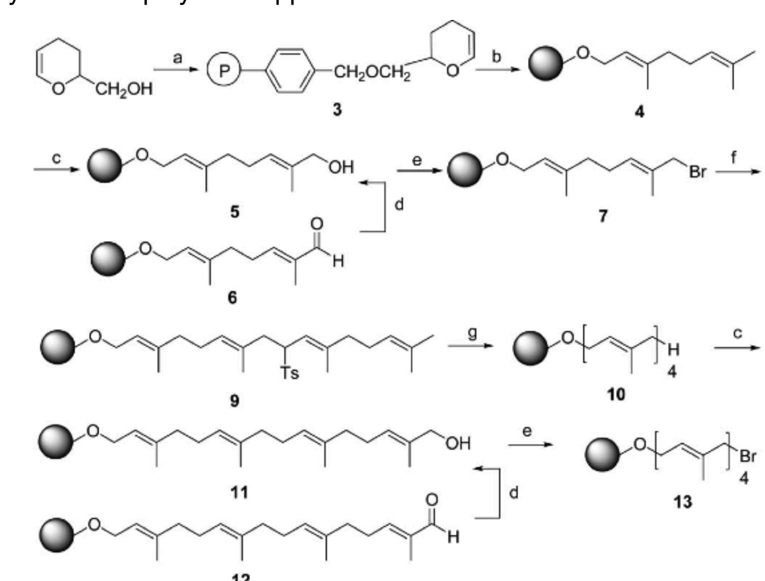
Synthesis of (dl)-muscone: Horner-Wadsworth-Emmons mediated cyclorelease



Classics in Solid-Phase Synthesis

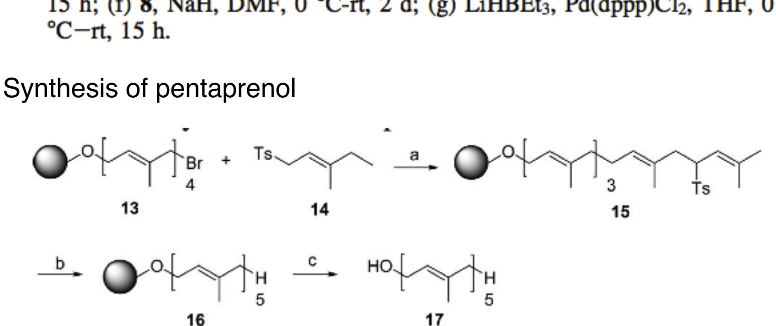
Total synthesis of solanesol

Synthesis of polymer-supported bromide



[a] Conditions: (a) 1. NaH, THF, rt, 2 h; 2. Merrifield's resin, rt, 16 h; (b) **2**, PPTS, 1,2-dichloroethane, 80 °C, 2 d; (c) SeO_2, *t*BuOOH, salicylic acid, CH_2Cl_2, rt, 2 d; (d) $LiAlH_4$, THF, 0 °C–rt, 4 h; (e) PBr_3, CH_2Cl_2, 0 °C–rt, 15 h; (f) **8**, NaH, DMF, 0 °C-rt, 2 d; (g) $LiHBEt_3$, $Pd(dppp)Cl_2$, THF, 0 °C–rt, 15 h.

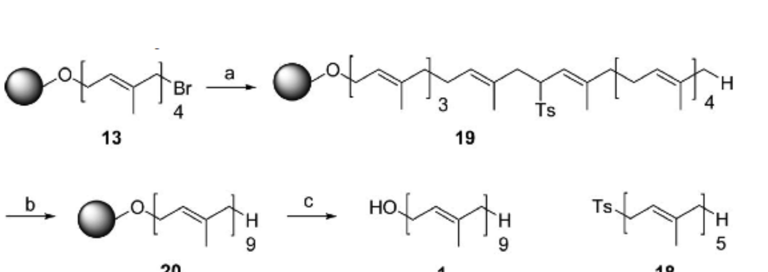
Synthesis of pentaprenol



[a] Conditions: (a) NaH, DMF, 0 °C, 2 d; (b) $LiHBEt_3$, $Pd(dppp)Cl_2$, THF, 0 °C–rt, 15 h; (c) PPTS, 1:1 *n*-butanol/1,2-dichloroethane, 80 °C, 16 h.

J. Comb. Chem., **2008**, *10* (4), pp 605–610
J. Braz. Chem. Soc., Vol. 21, No. 8, 1401-1423, 2010

Final Steps



[a] Conditions: (a) **18**, potassium *t*-butyl-hydroxide, DMF, 0 °C, 10 h; (b) $LiHBEt_3$, $Pd(dppp)Cl_2$, THF, 0 °C–rt, 20 h; (c) PPTS, 1:1 *n*-butanol/1,2-dichloroethane, 80 °C, 16 h.