Perkin 1 Abstracts: Solid Phase Organic Synthesis

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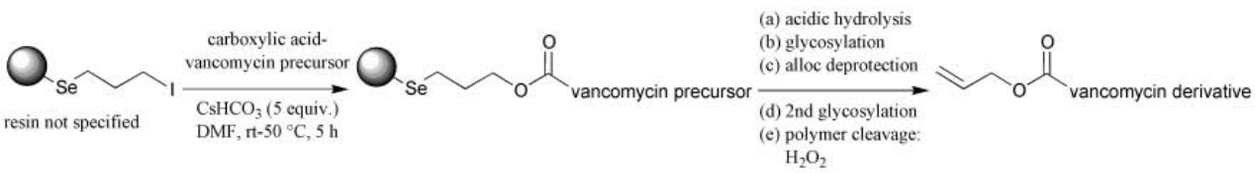
Perkin 1 Abstracts: Solid Phase Organic Synthesis are a selection of significant papers published in the recent literature covering the broad area of Solid Phase Organic Synthesis (SPOS). The abstracts cover preparation of single compounds on solid support as well as combinatorial libraries. Advances in new linker design are also covered.

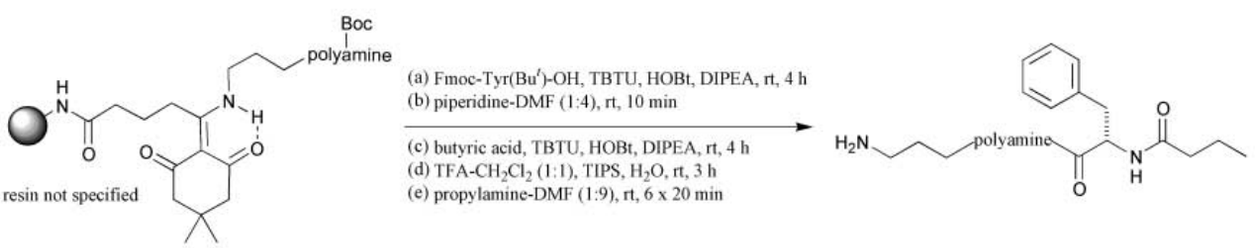
Selenium-based, pro-allyl safety-catch linker: semi-synthesis of vancomycin. ***Linker***



K. C. Nicolaou, N. Winssinger, R. Hughes, C. Smethurst and S. Young Cho, *Angew. Chem., Int. Ed.*, 2000, **39**, 1084.

(Yield 80%) 5 subsequent solution-phase steps complete the synthesis of vancomycin. Preparation of 2 similar polymer-bound selenium safety-catch linkers is also reported.

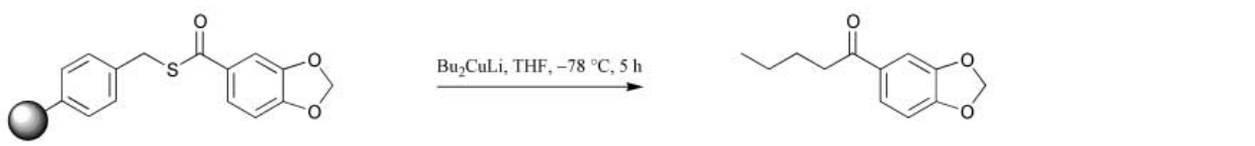
Polyamide analogues of philanthotoxins using a Dde-linker. ***Linker***



S. R. Chhabra, A. N. Khan and B. W. Bycroft, *Tetrahedron Lett.*, 2000, **41**, 1095.

2 examples (yields 75-65%, HPLC purity 100-90%). Polyamines were either constructed on the resin *via* sequential reductive alkylations or synthesised in solution prior to resin attachment.

Thioesters as traceless linkers in the synthesis of alcohols, ketones and lactones. ***Linker***

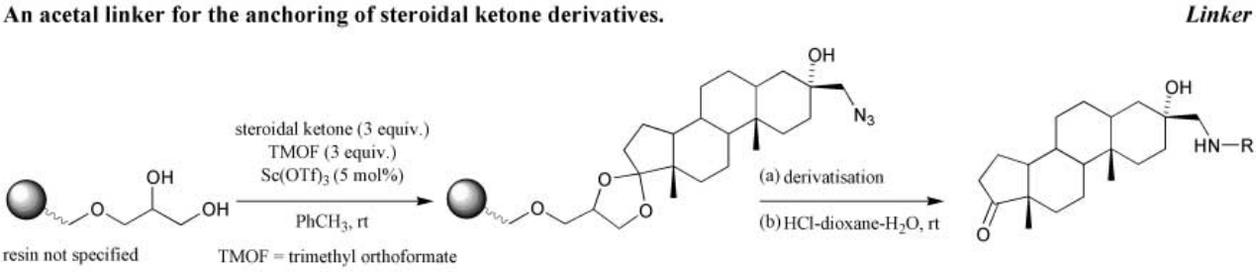


1 step from Merrifield resin

P. J. May, M. Bradley, D. C. Harrowven and D. Pallin, *Tetrahedron Lett.*, 2000, **41**, 1627.

1 example (53%). Cleavage of the illustrated polymer-bound thioester using $LiBH_4$ and PhMgBr gives 1° and 2° alcohols respectively (yields 83 and 45%). BCl_3 cleavage of a similar polymer-bound thioester gives the corresponding benzofuranone (yield 95%).

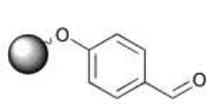
An acetal linker for the anchoring of steroidal ketone derivatives. ***Linker***



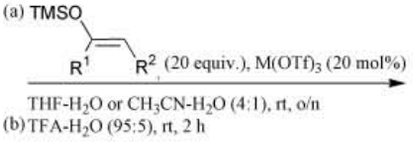
R. Maltais, M. Bérubé, O. Marion, R. Labrecque and D. Poirier, *Tetrahedron Lett.*, 2000, **41**, 1691.

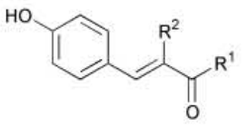
1 example (yield 70%, HPLC purity 94%). Anchoring and release of 4 steroidal ketones from the illustrated linker is also reported (yields 83-99%).

Polyoxyethylene-polyoxypropylene support (POEPOP): a hydrophilic resin for aqueous aldol reactions. ***Support***



3 steps from NovaSyn TG $POEPOP_{400}$, $POEPOP_{900}$ or $POEPOP_{15000}$ resin

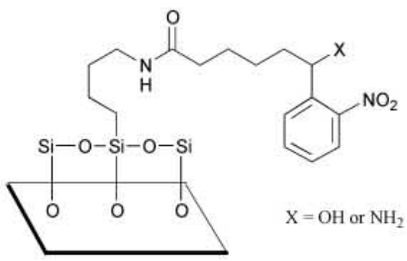




10 examples (yields 27-91%). 2 aldol reactions of a $POEPOP_{15000}$ support-bound *N*-terminal peptide aldehyde are also reported (yields >95%).

A. Graven, M. Grotli and M. Meldal, *J. Chem. Soc., Perkin Trans. 1*, 2000, 955.

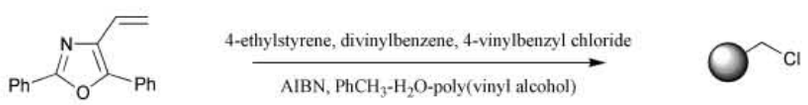
Nitrobenzyl-based photolabile surfaces: peptide preparation. ***Support***



The illustrated nitrobenzyl-based surface is prepared from 2-phenylcyclohexanone and aminopropylsiloxane-grafted controlled pore glass. After loading Fmoc-Gly-OH onto the nitrobenzyl surface, time and solvent dependent photorelease of Fmoc-Gly-NH_2 (if X = NH_2) or Fmoc-Gly-OH (if X = OH) is studied. Protected Leu-enkephalin-amide is also prepared on the illustrated surface (yield 40%, HPLC purity 88%).

T. D. Ryba and P. G. Harran, *Org. Lett.*, 2000, **2**, 851.

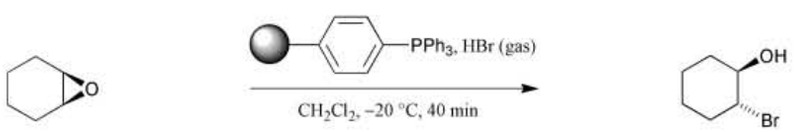
Scintillant-containing solid support. ***Support***



The illustrated macroporous resin, synthesised by suspension polymerisation techniques, is subjected to a scintillation counting assay.

B. Clapham and A. J. Sutherland, *Tetrahedron Lett.*, 2000, **41**, 2253.

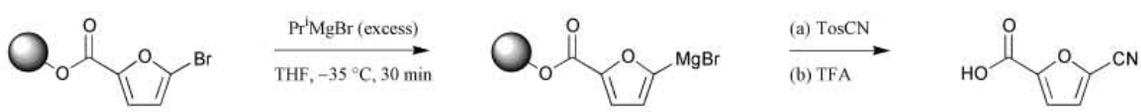
Polymer-supported triphenylphosphonium bromide as a source of hydrogen bromide for ring opening of epoxides. ***Reagent***



1 example (yield 83%). Solution-phase chemoselective ring opening of epoxides with triphenylphosphonium bromide to give the corresponding bromohydrins in the presence of ketal, benzyloxymethoxy and trimethylsilyl ether functionality is also reported.

C. A. M. Afonso, N. M. L. Vieira and W. B. Motherwell, *Synlett*, 2000, 382.

Polyfunctional polymer-supported magnesium reagents. ***Reagent***

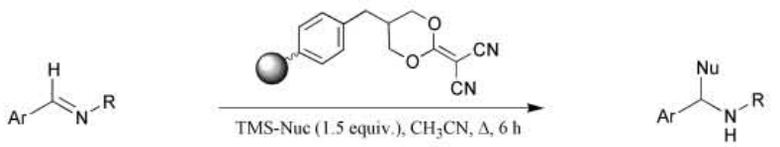


Wang resin

1 example (HPLC purity 82%) and 1 example of the allylation of polymer-supported magnesium bromothiophene (HPLC purity 95%). Solution-phase iodine-magnesium or bromine-magnesium exchange reactions for the preparation of functionalised aryl, alkenyl and alkyl magnesium reagents bearing ester, cyano or amide functional groups is also reported.

M. Rottländer, L. Boymond, L. Bérillon, A. Leprêtre, G. Varchi, S. Avolio, H. Laaziri, G. Quéguiner, A. Ricci, G. Cahiez and P. Knochel, *Chem. Eur. J.*, 2000, **6**, 767.

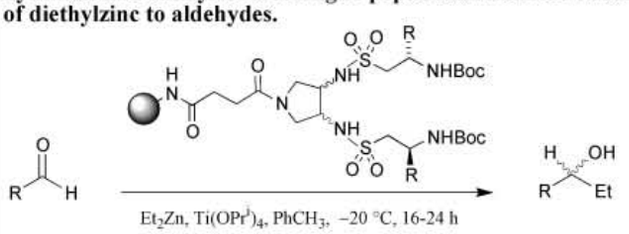
Mannich-type reaction catalysed by a reusable, polymer-supported dicyanoketene ethylene acetal: aldimine-selective reactions in the presence of aldehydes. ***Catalyst***



35 examples (yields 0, 9-100%). The illustrated catalyst, prepared by copolymerisation of monomeric dicyanoketene acetal bearing a styrene moiety with ethylene glycol dimethylacrylate, is also used for the chemoselective preparation of 2 β-amino ketones in the presence of aldehydes (yields 63-64%).

N. Tanaka and Y. Masaki, *Synlett*, 2000, 406.

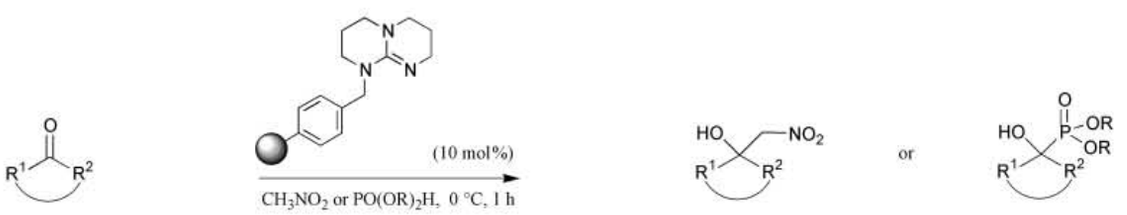
Synthesis and catalysis screening of peptidosulfonamide tweezers: enantioselective addition of diethylzinc to aldehydes. ***Catalyst***



A 10-member library of peptidosulfonamide tweezer catalysts is prepared and screened in a simultaneous substrate screening procedure for the ability to enantioselectively catalyse the illustrated $Ti(OPr^i)_4$-mediated addition of $ZnEt_2$ to aldehydes (yields 0-78%, ee 0-32%). Preparation of the catalyst from poly(ethylene glycol) polystyrene resin and the solution-phase synthesis of the corresponding homogeneous catalyst is also reported.

A. J. Brouwer, H. J. van der Linden and R. M. J. Liskamp, *J. Org. Chem.*, 2000, **65**, 1750.

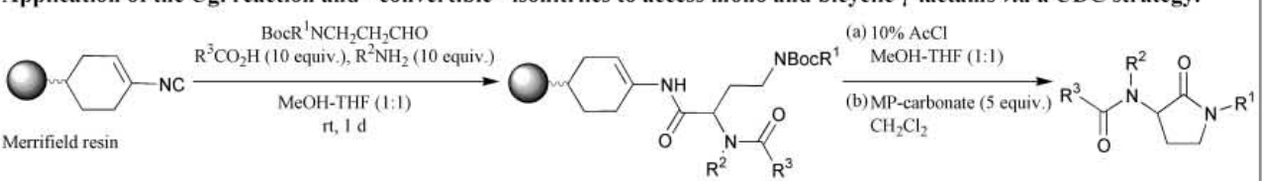
Catalysis of the Henry reaction and addition of dialkyl phosphites to carbonyl compounds. ***Catalyst***



Several examples (yields 75-95%). Similar chemistry using α,β-unsaturated ketones as substrates for the Henry reaction is also reported (yields 70-98%).

D. Simoni, R. Rondanin, M. Morini, R. Baruchello and F. P. Invidiata, *Tetrahedron Lett.*, 2000, **41**, 1607.

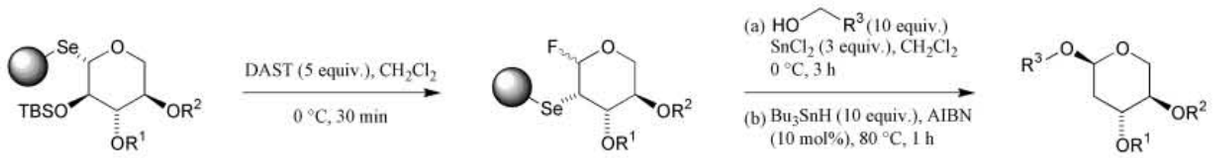
Application of the Ugi reaction and "convertible" isonitriles to access mono and bicyclic γ-lactams *via* a UDC strategy.



9 examples (HPLC purity 40-85%) and the preparation of 3 bicyclic-keto -piperazines *via* a similar route are reported (HPLC purity 65-90%). 2 other similar routes for the preparation of 18 γ-lactams—one route employing a solution phase equivalent of the illustrated polymer-bound cyclohexenyl isonitrile and the other, an isonitrile safety-catch linker—are also reported.

C. Hulme, L. Ma, M.-P. Cherrier, J. J. Romano, G. Morton, C. Duquenne, J. Salvino and R. Labaudiniere, *Tetrahedron Lett.*, 2000, **41**, 1883.

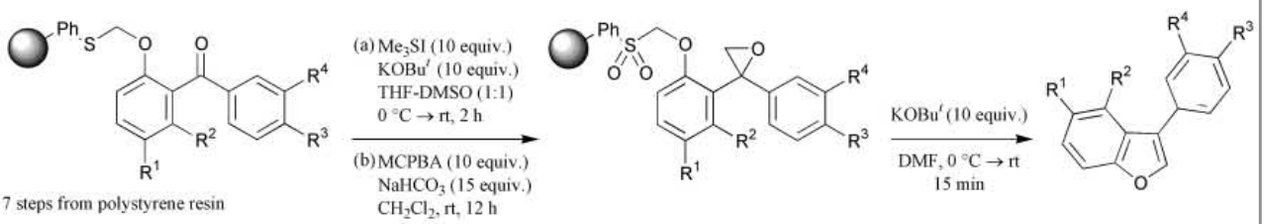
1,2-Seleno migrations in carbohydrate chemistry: synthesis of 2-deoxy glycosides, 2-deoxy orthoesters and allyl orthoesters.



9 examples (yields 11-32%). Preparation of 9 orthoesters and 3 allyl orthoesters *via* similar routes is also reported (yields 2-20%).

K. C. Nicolaou, H. J. Mitchell, K. C. Fylaktakidou, H. Suzuki and R. M. Rodríguez, *Angew. Chem., Int. Ed.*, 2000, **39**, 1089.

Functionalised 3-arylbenzofurans by a cyclofragmentation-release pathway.

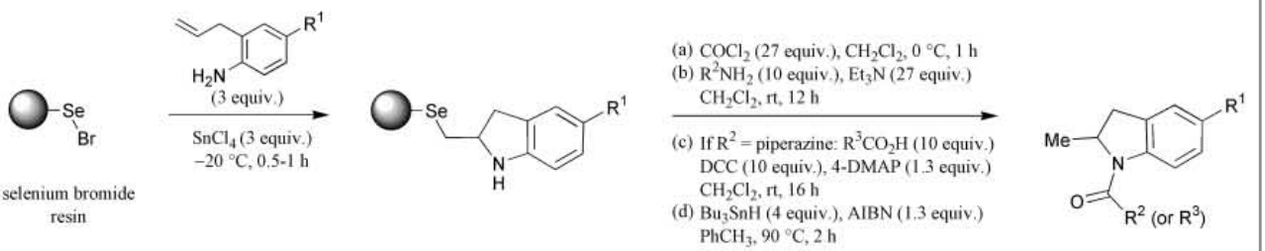


7 steps from polystyrene resin

K. C. Nicolaou, S. A. Snyder, A. Bigot and J. A. Pfefferkorn, *Angew. Chem., Int. Ed.*, 2000, **39**, 1093.

16 examples (yields 6-37%).

Substituted indolines

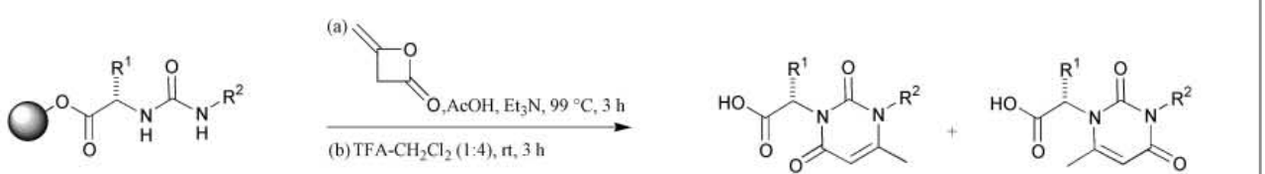


selenium bromide resin

K. C. Nicolaou, A. J. Roecker, J. A. Pfefferkorn and G.-Q. Cao, *J. Am. Chem. Soc.*, 2000, **122**, 2966.

9 examples (yields 14-34%). Preparation of 5 polycyclic indolines *via* a similar route is also reported (yields 13-36%).

6-Methyl-1,3-disubstituted uracils

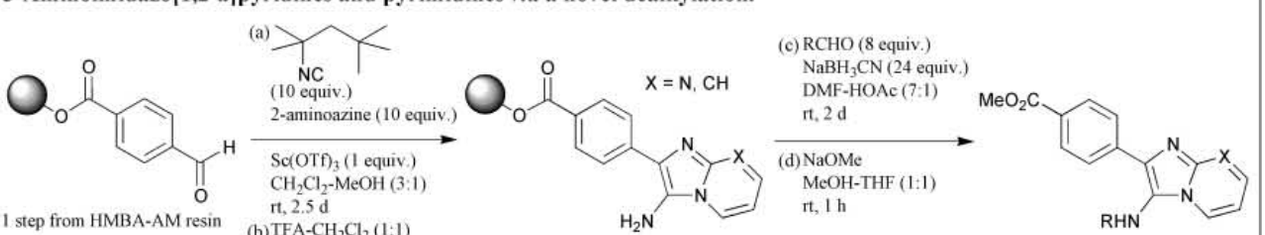


2 steps from Wang resin

A. Wahhab and J. Leban, *Tetrahedron Lett.*, 2000, **41**, 1487.

12 examples (yields 45-91%, purity 70->95%). The ratio of the illustrated regioisomeric uracils is controlled by selection of appropriately substituted ureas.

3-Aminoimidazo[1,2-*a*]pyridines and pyrimidines *via* a novel dealkylation.

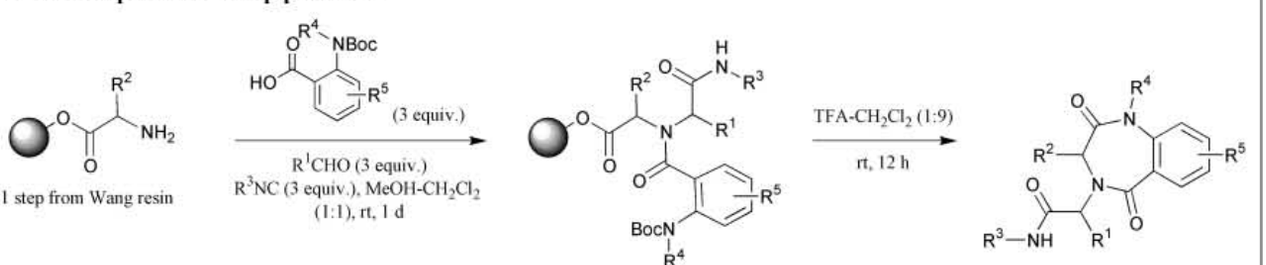


1 step from HMBA-AM resin

C. Blackburn and B. Guan, *Tetrahedron Lett.*, 2000, **41**, 1495.

14 examples (yields 0, 5-95%, HPLC purity <5, 5-95%). Preparation of a further 10 aminoimidazo[1,2-*a*]pyridines and pyrimidines, *via* similar routes, is also reported.

Benzodiazepines and ketopiperazines.

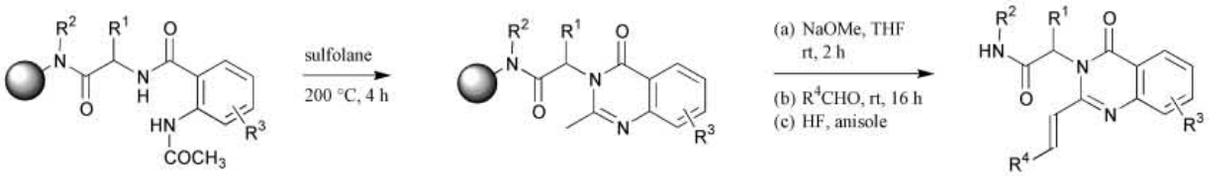


1 step from Wang resin

C. Hulme, L. Ma, N. Vasant Kumar, P. H. Krolikowski, A. C. Allen and R. Labaudiniere, *Tetrahedron Lett.*, 2000, **41**, 1509.

9750-member library (LCMS purity 10-54%). Preparation of 3 ketopiperazines *via* a similar route is also reported (LCMS purity 37-59%).

Styrylquinazolinones

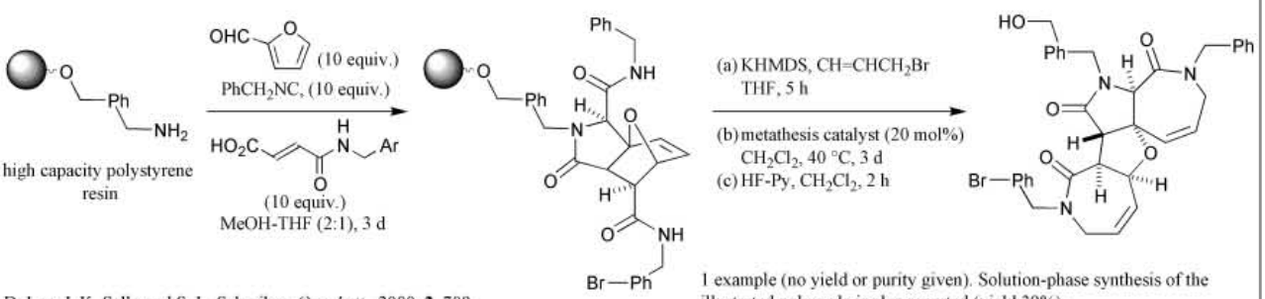


7 steps from MBHA resin

M. Theoclitou, J. M. Ostresh, V. Hamashin and R. A. Houghten, *Tetrahedron Lett.*, 2000, **41**, 2051.

13 examples (yields 75-90%, HPLC purity 62-93%).

Diversity-orientated organic synthesis: 7-5-5-7 polycyclic ring synthesis.

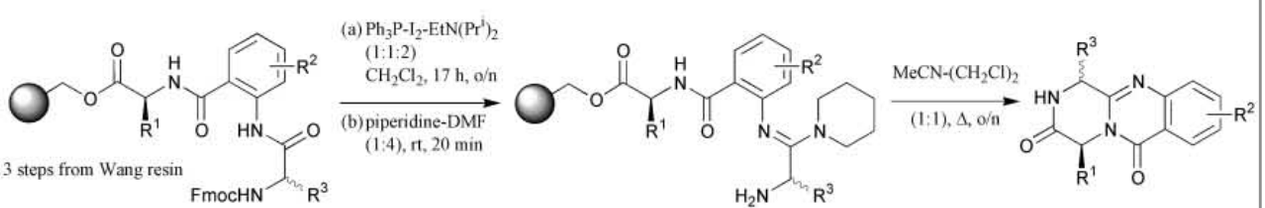


high capacity polystyrene resin

D. Lee, J. K. Sello and S. L. Schreiber, *Org. Lett.*, 2000, **2**, 709.

1 example (no yield or purity given). Solution-phase synthesis of the illustrated polycycle is also reported (yield 39%).

Pyrazino[2,1-*b*]quinazoline-3,6-diones

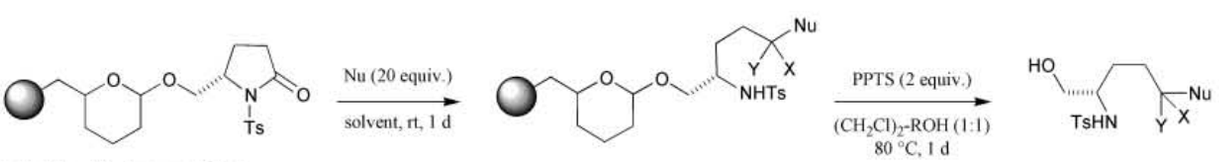


3 steps from Wang resin

H. Wang and A. Ganesan, *J. Comb. Chem.*, 2000, **2**, 186.

Preparation of a 12-member library is reported (yields 23-78%, HPLC purity 74-98%). Preparation of 2 diazepinoquinazolones *via* a similar route is also reported (yields 9-10%).

Amino alcohol derivatives from (L)-pyroglutamic acid.

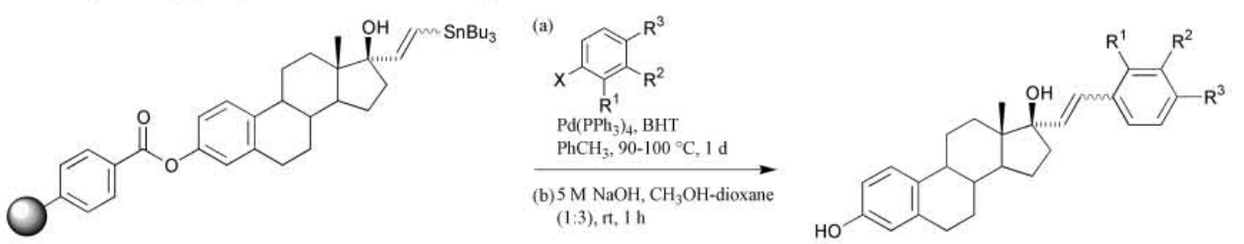


1 step from dihydropyran-linked polystyrene resin

J. Cossy, L. Tresnard and D. G. Pardo, *Synlett*, 2000, 409.

8 examples (yields 59-94%).

17α-*E*/*Z*-(X-Phenyl)-vinyl estradiols: ER-LBD ligands.



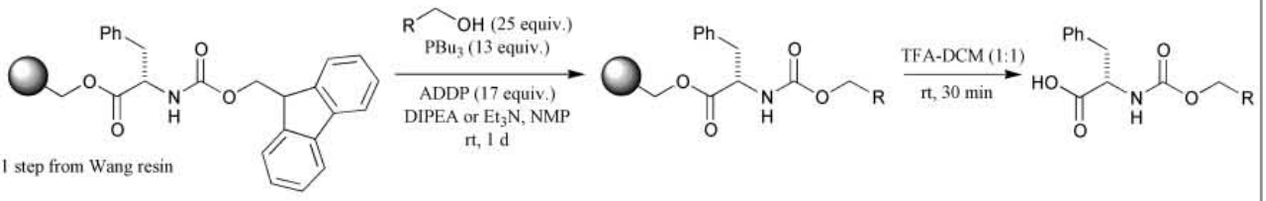
2 steps from carboxy polystyrene resin

BHT = 3,5-di-*tert*-butyl-4-hydroxytoluene

C. Y. Lee and R. N. Hanson, *Tetrahedron*, 2000, **56**, 1623.

8 examples (yields 17-75%).

_O_-Alkyl carbamates _via_ the Mitsunobu reaction.

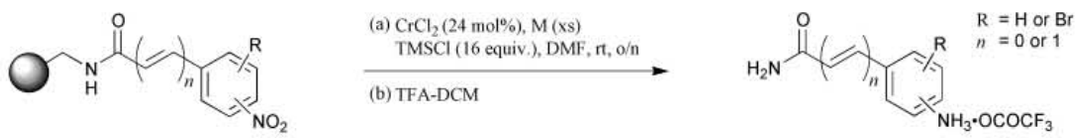


1 step from Wang resin

F. Zaragoza and H. Stephensen, *Tetrahedron Lett.*, 2000, **41**, 2015.

8 examples (yields 40-96%, ELS purity 88-100%).

Chromium-manganese or chromium-zinc catalysed reductions.



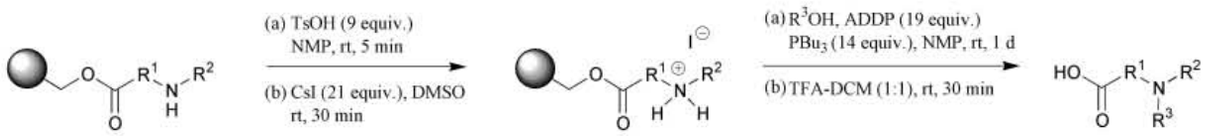
2 steps from Rink amide resin

M = Mn, Zn

A. Hari and B. L. Miller, *Org. Lett.*, 2000, **2**, 691.

An apparatus is designed for chromium-manganese or chromium-zinc catalysed reductions of nitroarenes which allows recycling of the stoichiometric reductant (Mn or Zn) (4 examples, yields 15, 81-90%). The use of chromium-manganese in a catalytic Nozaki-Hiyama-Kishi coupling is also reported (yield 72%).

Tertiary benzylamines

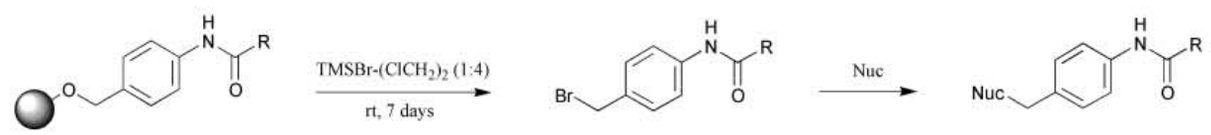


1 step from Wang resin

F. Zaragoza and H. Stephensen, *Tetrahedron Lett.*, 2000, **41**, 1841.

5 examples (yields 66-97%, HPLC purity 60-100%).

Library synthesis _via_ solution phase capping of solid phase linkages.

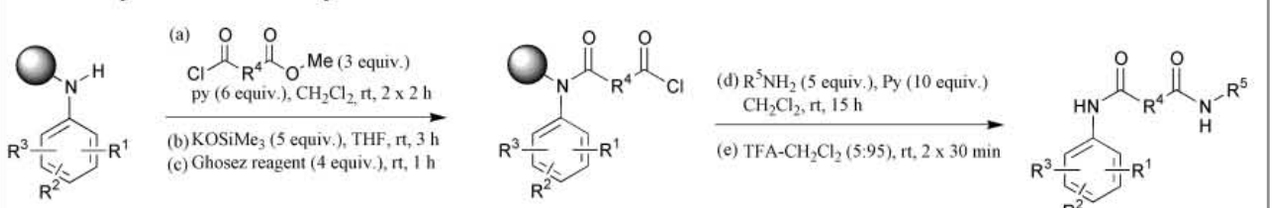


1 step from methoxytrityl resin

S. J. Teague and I. A. S. Walters, *Tetrahedron Lett.*, 2000, **41**, 2023.

Library synthesis is reported (LCMS purity >50%). Preparation of polymer-bound 3° amines and thiols and their subsequent capping with electrophiles is also reported (yields and purities not given).

Diamides: potential bone resorption inhibitors.



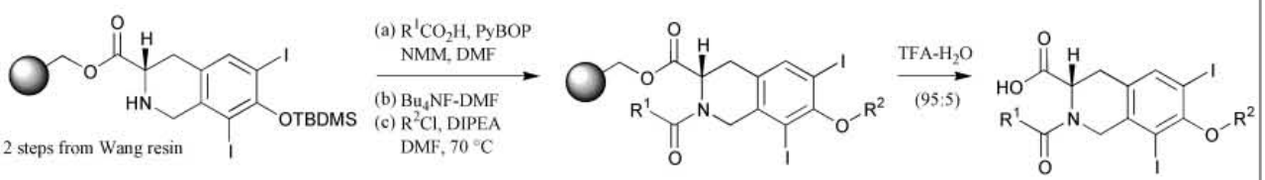
1 step from Rink acid resin

Ghosez reagent = 1-chloro-*N*,*N*,2-trimethylpropenylamine

K. M. Edvinsson, M. Herslöf, P. Holm, N. Kann, D. J. Keeling, J. P. Mattsson, B. Nordén and V. Shcherbukhin, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 503.

Preparation and biological evaluation of an 800-member library is reported (representative yields 32-100%, representative HPLC purities 58-92%).

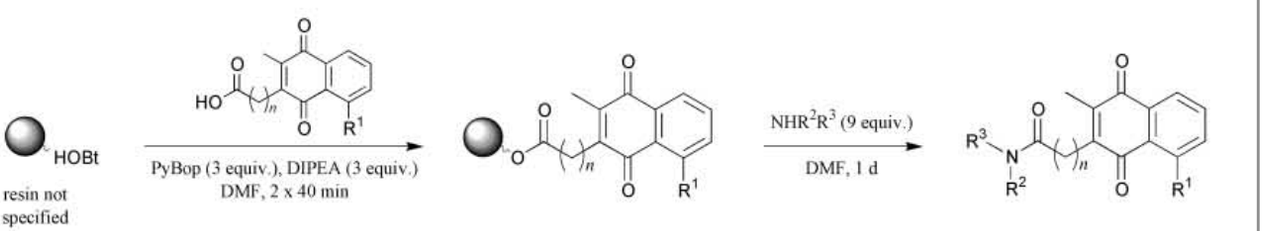
Tetrahydroisoquinolines: inhibitors of protein phosphatase CDC25B.



E. L. Fritzen, A. S. Brightwell, L. A. Erickson and D. L. Romero, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 649.

Preparation and biological evaluation of a 75-member library is reported (no yields given).

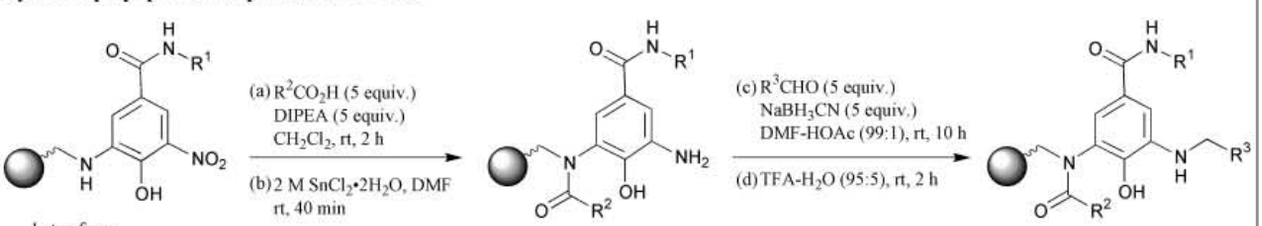
1,4-Naphthoquinones: potential inhibitors of trypanothione.



L. Salman-Chemin, A. Lemaire, S. De Freitas, B. Deprez, C. Sergheraert and E. Davioud-Charvet, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 631.

Preparation and biological evaluation of a 1360-member library is reported. Solution-phase synthesis of mono- and bis-1,4-naphthoquinones is also reported.

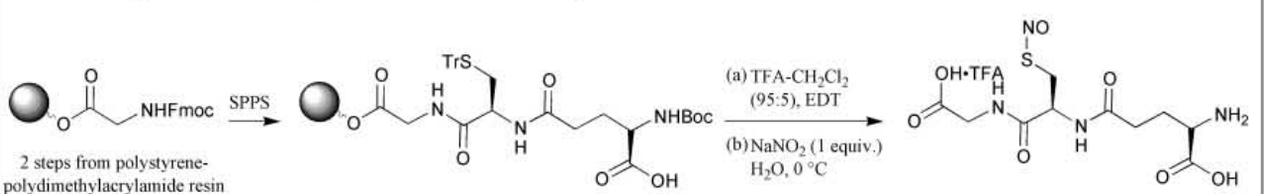
Cyclic depsipeptides: hapalosin mimetics.



J. A. Olsen, K. J. Jensen and J. Nielsen, *J. Comb. Chem.*, 2000, **2**, 143.

Preparation of a 12-member hapalosin mimetic library *via* the illustrated route and a similar route is reported.

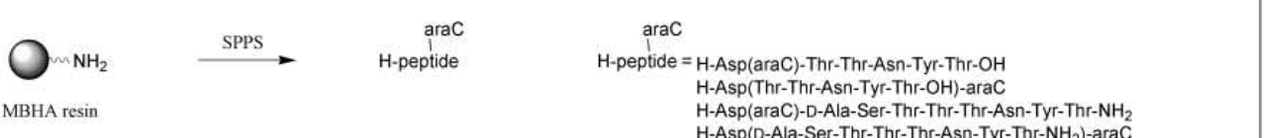
***S*-Nitroso-D-glutathione: biological evaluation of enantiopure thionitrites.**



M. Cavero, A. Hobbs, D. Madge, W. B. Motherwell, D. Selwood and P. Potier, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 641.

An Fmoc SPPS strategy was employed for the first solid phase synthesis of D-glutathione (yield 20%). Biological evaluation of 3 pairs of enantiomeric thionitrites, including the illustrated D-glutathione, is also reported.

Peptide T-araC conjugates: selective targeting of $CD4^+$ receptors to achieve antiproliferative activity.



S. Manfredini, M. Marastoni, R. Tomatis, E. Durini, S. Spisani, A. Pani, T. Marceddu, C. Musiu, M. E. Marongiu and P. La colla, *Bioorg. Med. Chem.*, 2000, **8**, 539.

The first solid phase synthesis of 4 peptide T-araC conjugates, which avoids protection of the glycoside portion of araC and employs mild procedures, is reported (yields 79-93%, HPLC purity >90%).