Perkin 1 Abstracts: Natural Product Synthesis

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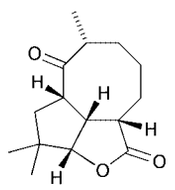
Perkin 1 Abstracts: Natural Product Synthesis aims to highlight syntheses that have been recently published. It includes brief descriptions of *biological activity* and *key steps*. A more comprehensive list of Natural Product syntheses and isolations can be found in *Natural Product Updates*.

(+)-Asteriscanolide

Biological activity: not reported.

Key steps: (a) asymmetric Michael addition of a propargylic alcohol to (*S*)-(+)-2-(toluene-*p*-sulfinyl)cyclopent-2-enone followed by an intramolecular Michael additon of the resultant enolate to an alkynyl ester generates the two 5-membered rings in a single operation; (b) ring closing metathesis to generate the 8-membered ring.

L. A. Paquette, J. Tae, M. P. Arrington and A. H. Sadoun, *J. Am. Chem. Soc.*, 2000, **122**, 2742.

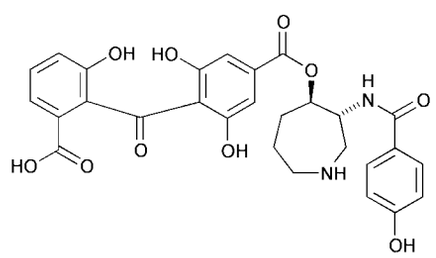


(–)-Balanol

Biological activity: (a) metabolite produced by *Verticillium balanoides* and *Fusarium merismoides*; (b) lead structure in the search for selective inhibitors of protein kinase C (PKC).

Key steps: (a) Sharpless epoxidation of a divinylmethanol; (b) ring closing alkene metathesis.

A. Fürstner and O. R. Thiel, *J. Org. Chem.*, 2000, **65**, 1738.

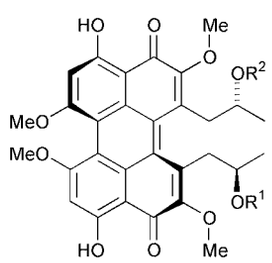


Calphostins A-D

Biological activity: potent and specific inhibitor of protein kinase C.

Key steps:(a) construction of an *o*-naphthoquinone *via* benzannulation of a chromium carbene complex; (b) oxidative dimerisation of an *o*-naphthoquinone to the perylenequinone.

C. A. Merlic, C. C. Aldrich, J. Albaneze-Walker and A. Saghatelian, *J. Am. Chem. Soc.*, 2000, **122**, 3224.



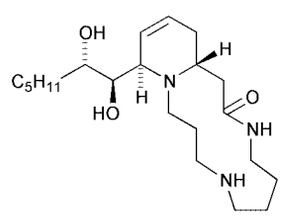
	R^1	R^2
A	Bz	Bz
B	Bz	H
C	Bz	$CO_2C_6H_4$-*p*-OH
D	H	H

(+)-Cannabisativine

Biological activity: isolated from *Cannabis sativa* L.

Key steps: addition of a metalloenolate to chiral 1-acylpyridinium salts.

J. T. Kuethe and D. L. Comins, *Org. Lett.*, 2000, **2**, 855.

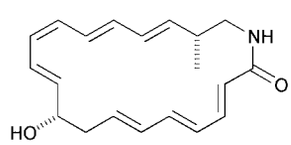


Cyclamenol A

Biological activity: (a) isolated from *Streptomyces* sp. MH846; (b) inhibits adhesion of leukocytes to endothelial cells.

Key steps: (a) pinacol coupling using $[V_2Cl_3{\bullet}(THF)_6][Zn_2Cl_6]$; (b) formation of polyene system by fragmentation of a thiocarbonate using trimethyldiazaphospholidine.

M. Nazaré and H. Waldmann, *Angew. Chem., Int. Ed.*, 2000, **39**, 1125.

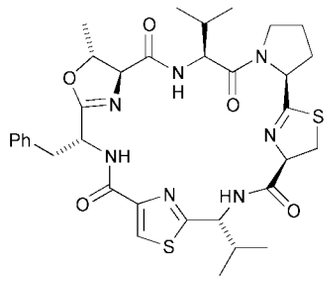


Cyclodidemnamide

Biological activity: moderate toxicity toward human colon cells.

Key steps: novel double cyclodehydration using Burgess' reagent to sequentially form a chiral thiazoline ring and a chiral oxazoline ring from a preformed cyclopeptide intermediate.

C. D. J. Boden, M. Norley and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 2000, 883.

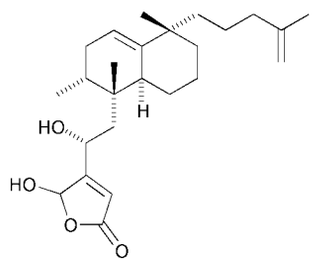


Dysidiolide

Biological activity: (a) inhibits the protein phosphatase cdc25A (IC_{50} – 9.4 μM) that promotes the G1/S transition of the cell cycle by dephosphorylation of the cyclin-cyclin dependent kinase complex; (b) inhibits the growth of human carcinoma cells and murine leukemia cells.

Key steps: (a) intermolecular Diels–Alder reaction; (b) construction of a quarternary carbon centre by methylation of an exocyclic enolate.

M. Takahashi, K. Dodo, Y. Hashimoto and R. Shirai, *Tetrahedron Lett.*, 2000, **41**, 2111.

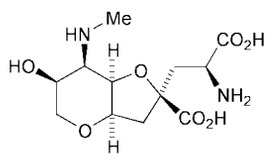


(–)-Dysiherbaine

Biological activity: potent neurotoxin reminiscent of domic acid that appears to function as an agonist for non-NMDA type glutamate receptors in the central nervous system.

Key steps: (a) intramolecular S_N2 substitutions of a carbamate anion on an epoxide and an alkoxide on a secondary mesylate to construct the bicyclic skeleton stereospecifically from L-xylose; (b) Claisen variant for allylation of carbohydrate aldehydes to construct the alanine side chain.

B. B. Snider and N. A. Hawryluk, *Org. Lett.*, 2000, **2**, 635.

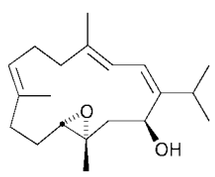


(+)-11,12-Epoxysarcophytol A

Biological activity: isolated from marine soft coral *Lobophytum*.

Key steps: (a) chemoselective and enantioselective CBS reduction of a ketone; (b) macrocyclisation of a cyanohydrin silyl ether-derived carbanion by an intramolecular alkylation process; (c) asymmetric Sharpless epoxidation.

J. Lan, Z. Liu, H. Yuan, L. Peng, W.-D. Z. Li, Y. Li, Y. Li and A. S. C. Chan, *Tetrahedron Lett*, 2000, **41**, 2181.

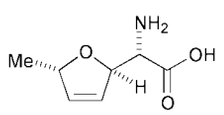


(+)-Furanomycin

Biological activity: (a) substrate of the isoleucyl aminoacyl tRNA synthetase ($AARS^{Ile}$) and substitutes for isoleucine in protein translation *in vitro*; (b) inhibitor of the growth of *Escherichia coli* and a number of other bacteria.

Key steps: (a) $ZnBr_2$-mediated stereoselective lithiated acetylide addition on Garner's aldehyde ; (b) Ag^+-mediated cyclisation of an α-allenic alcohol to construct the *trans*-2,5-dihydrofuran.

M. P. VanBrunt and R. F. Standaert, *Org. Lett.*, 2000, **2**, 705.

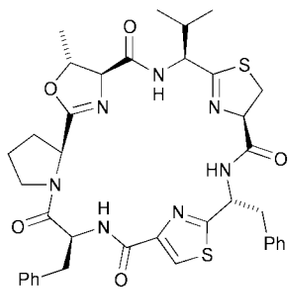


Lissoclinamide 5

Biological activity: (a) isolated from the ascidian *Lissoclinum patella*; (b) immunoregulatory; (c) antibiotic; (d) antitumoral.

Key steps: a "one-pot" double cyclodehydration sequence.

C. D. J. Boden and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 2000, 875.

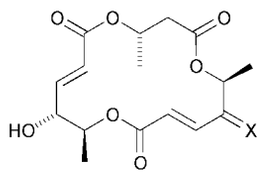


Macrosphelides A and B

Biological activity: strongly inhibit the adhesion of human leukemia HL-60 cells to human umbilical-vein endothelial cells without inhibiting the growth of mammalian cell lines and microorganisms.

Key steps: (a) chelation controlled reduction using $Zn(BH_4)_2$; (b) Yamaguchi lactonisation; (c) Mitsunobu reaction.

Y. Kobayashi, B. G. Kumar and T. Kurachi, *Tetrahedron Lett.*, 2000, **41**, 1559.



Macrosphelide A: X =

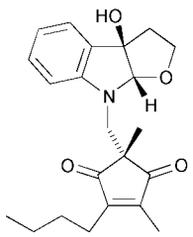
Macrosphelide B: X = O

(+)-Madindoline A and (–)-Madindoline B

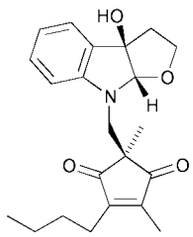
Biological activity: potent and selective inhibitor of interleukin 6.

Key steps: (a) Sharpless asymmetric epoxidation of tryptophol to give the 3a-hydroxyfuroindoline system; (b) creation of the single quaternary centre of the cyclopentene ring *via* an aldol reaction; (b) ring closing metathesis to create the cyclopentene ring.

T. Sunazuka, T. Hirose, T. Shirahata, Y. Harigaya, M. Hayashi, K. Komiyama and S. Omura, *J. Am. Chem. Soc.*, 2000, **122**, 2122.



(–)-Madindoline A



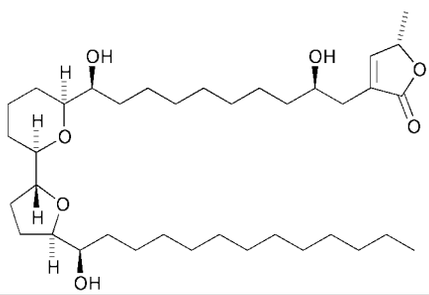
(+)-Madindoline B

(+)-Muconin

Biological activity: a potent and selective cytotoxin against PACA-2 (pancreatic cancer) and MCF-7 (breast cancer).

Key steps: (a) Pd(0)-mediated coupling of an alkyne with an iodoalkyne; (b) hydrogenation of a diyne using Wilkinson's catalyst.

W.-Q. Yang and T. Kitahara, *Tetrahedron*, 2000, **56**, 1451.

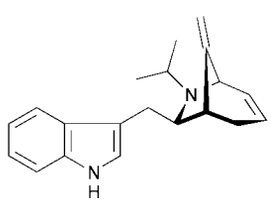


(±)-Peduncularine

Biological activity: isolated from the Tasmanian shrub *Aristotelia peduncularis*; biological activity not reported.

Key steps: [3 · 2] annulation of allylic silanes and chlorosulfonyl isocyanate.

C. W. Roberson and K. A. Woerpel, *Org. Lett.*, 2000, **2**, 621.

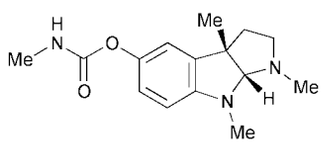


Physostigmine

Biological activity: (a) clinically useful anticholinergic drug; (b) analogues have shown promise as therapeutic agents for Alzheimer's disease; (c) the enantiomer protects against organophosphate poisoning.

Key steps: alkylative cyclisation using Corey–Kim reagent on tryptamine or tryptophan carbamates to construct the pyrrolo[2,3-*b*]indole skeleton.

M. Kawahara, A. Nishida and M. Nakagawa, *Org. Lett.*, 2000, **2**, 675.

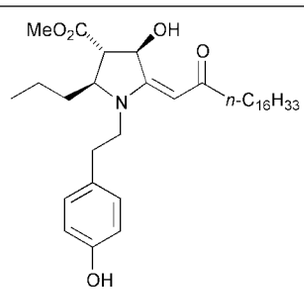


(2*S*,3*S*,4*R*)-Plakoridine A

Biological activity: cytotoxic against the murine lymphoma L1210 cell line.

Key steps: (a) diastereoselective Michael addition; (b) aldol condensation/deprotection/cyclisation to form pyrrolidinone moiety; (c) Eschenmoser sulfide contraction.

D. Ma and H. Sun, *Tetrahedron Lett.*, 2000, **41**, 1947.

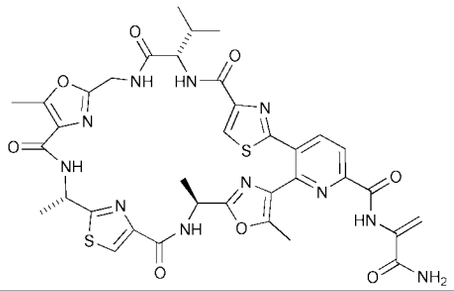


(+)-Promothiocin A

Biological activity: antibiotic isolated from *Streptomyces* sp. SF2741.

Key steps: (a) modified Bohlmann–Rahtz pyridine synthesis; (b) oxazole construction *via* Rh-catalysed carbenoid N–H insertion followed by cyclodehydration; (c) Hantzsch thiazole synthesis.

M. C. Bagley, K. E. Bashford, C. L. Hesketh and C. J. Moody, *J. Am. Chem. Soc.*, 2000, **122**, 3301.

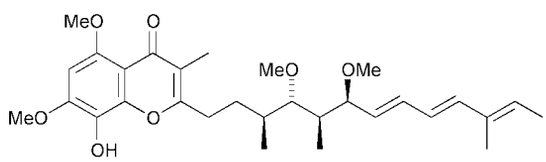


(+)-Stigmatellin A

Biological activity: powerful inhibitor of electron transport in mitochondria and chloroplasts.

Key steps: (a) asymmetric alkylation of a SAMP hydrazone; (b) titanium-mediated *syn*-aldol reaction; (c) hydroxy-directed diastereoselective reduction of a β-hydroxy ketone; (d) Baker–Venkataraman rearrangement to form the chromone.

D. Enders, G. Geibel and S. Osborne, *Chem. Eur. J.*, 2000, **6**, 1302.

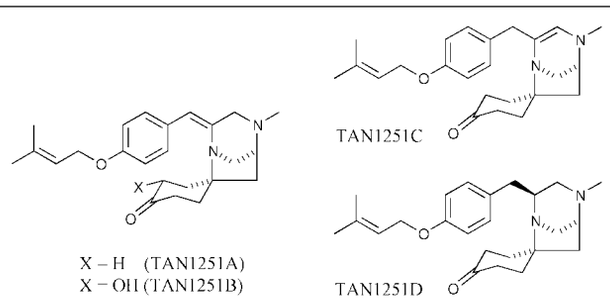


(+)-TAN1251A, (+)-TAN1251B, (+)-TAN1251C, and (+)-TAN1251D

Biological activity: (a) muscarinic antagonists; (b) related to the potent immunosuppressant FR901483.

Key steps: 1,3-dipolar cycloaddition of a nitrone and ethyl acrylate.

B. B. Snider and H. Lin, *Org. Lett.*, 2000, **2**, 643.

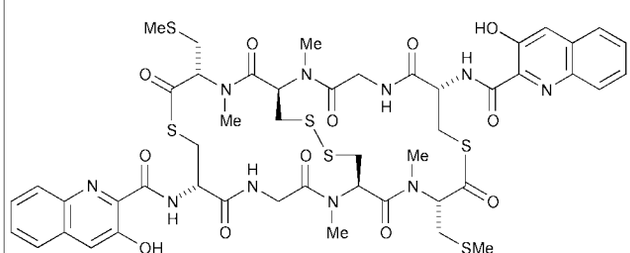


(–)-Thiocoraline

Biological activity: potent antitumour agent isolated from *Micromonospora* sp L-13-ACM2-092 which unwinds double stranded DNA

Key steps: (a) late stage introduction of the chromophore; (b) symmetrical tetrapeptide coupling; (c) macrocyclisation of a 26-membered octadepsipeptide; (d) generation of the dithiol ester linkage under racemisation free conditions.

D. L. Boger and S. Ichikawa, *J. Am. Chem. Soc.*, 2000, **122**, 2956.

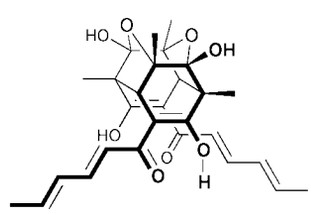


(±)-Trichodimerol, Bisorbibutenolide, Bisorbicillanol

Biological activity: inhibits tumour necrosis factor α (TNF-α); a lead compound for the treatment of septic shock.

Key steps: two-step Michael addition–ketalisation sequence involving an oxidised form of sorbicillin.

K. C. Nicolaou, G. Vassilikogiannakis, K. B. Simonsen, P. S. Baran, Y.-L. Zhong, V. P. Vidali, E. N. Pitsinos and E. A. Couladouros, *J. Am. Chem. Soc.*, 2000, **122**, 3071.

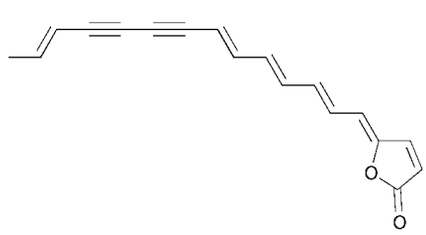


Xerulin

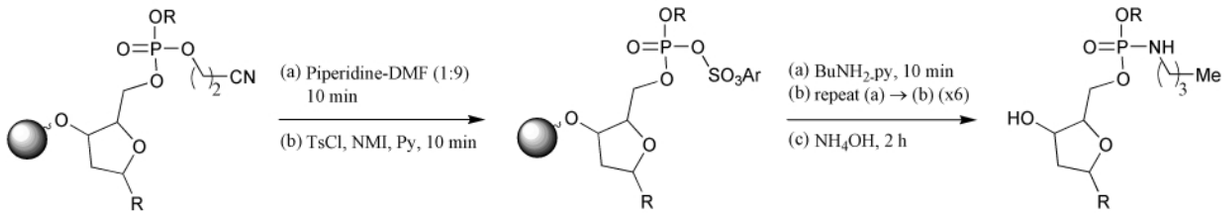
Biological activity: inhibitor of cholesterol biosynthesis.

Key steps: (a) improved synthesis of (*E*)-iodobromoethylene; (b) direct terminal alkyne synthesis using ethynylzinc bromide without silyl protection–deprotection; (c) double metal-catalysed alkenyl–alkenyl coupling with *in situ* generated alkenylzirconium derivatives catalysed by Pd and Zn; (d) Pd-catalysed conjugated diyne synthesis *via* 1-haloenynes; (e) Pd-catalysed ene-yne–cross coupling–carboxymetalation tandem process.

E.-i. Negishi, A. Alimardanov and C. Xu, *Org. Lett.*, 2000, **2**, 65.



Amidate linkages in oligonucleotides



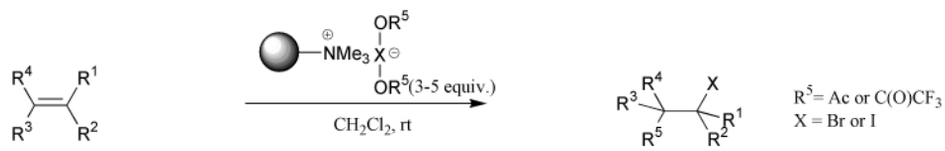
resin not specified

P. W. Davis and S. A. Osgood, *Bioorg. Med. Chem. Lett.*,1999, **9**, 2691.

1 example (yield 98%, HPLC purity 97%).

Polymer-supported acyl hypohalite equivalents for 1,2-haloacetoxylations of alkenes, alkynes and alkoxyallenes

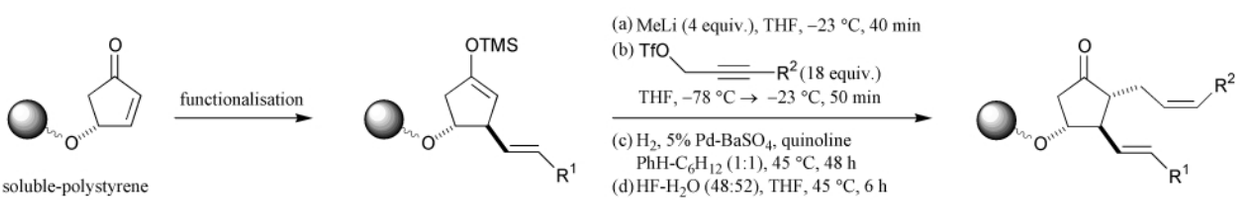
Reagent



H. Monenschein, G. Sourkouni-Argirusi, K. M. Schubothe, T. O'Hare and A. Kirshning, *Org. Lett.*, **1**, 2101.

13 examples (yields 12-93%) and 8 examples of 1,2-haloacetoxylations of alkynes & alkoxyallenes using the illustrated reagents (yields 57-83%). Preparation of the illustrated reagents from polystyrene-bound halides is also reported.

Prostanoids

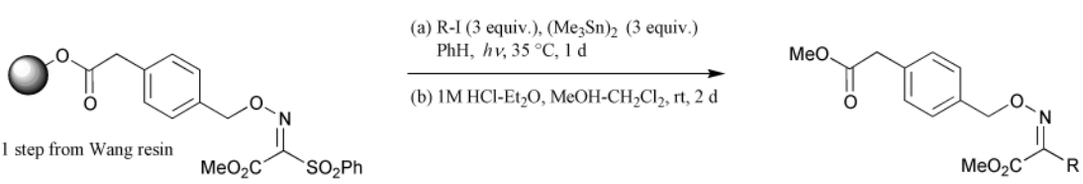


soluble-polystyrene

K. Joo Lee, A. Angulo, P. Ghazal and K. D. Janda, *Org. Lett.*, **1**, 1859.

Preparation and biological evaluation of a 16-member library is reported (yields 26-38%).

Radical reaction of phenylsulfonyl oxime ethers: synthesis of α–amino-esters

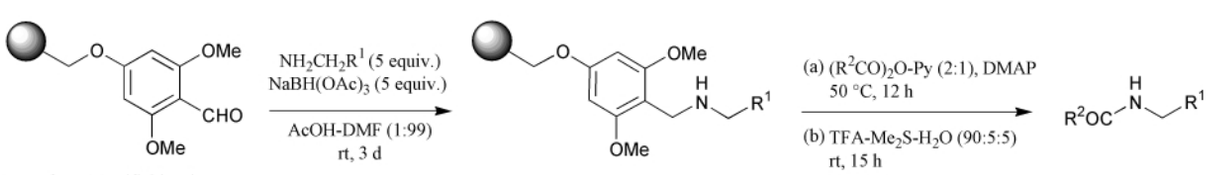


1 step from Wang resin

G.-H. Jeon, J.-Y. Yoon, S. Kim and S. Soo Kim, *Synlett*, 2000, 128.

6 examples (yields 22-50%). Solution-phase reduction of 3 of the illustrated oxime ethers to give the corresponding α–amino-esters is also reported (yields 65-73%).

Phenylalkylamide derivatives: melatoninergic ligands for human mt_1 and MT_2 receptors

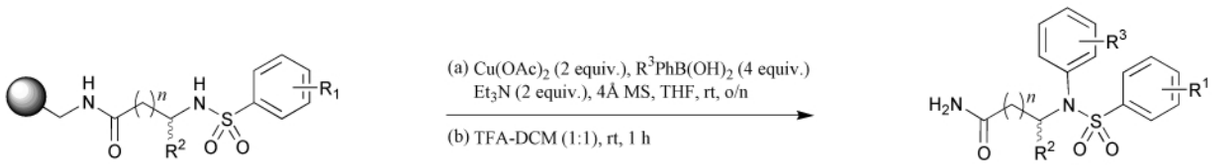


1 step from Merrifield resin

C. Pégurier, S. Curtet, J-P. Nicolas, J. A. Boutin, P. Delagrange, P. Renard and M. Langlois, *Bioorg. Med. Chem.*, 2000, **8**, 163.

Preparation and biological evaluation of a 108-member library is reported.

_N_-Arylation of sulfonamides

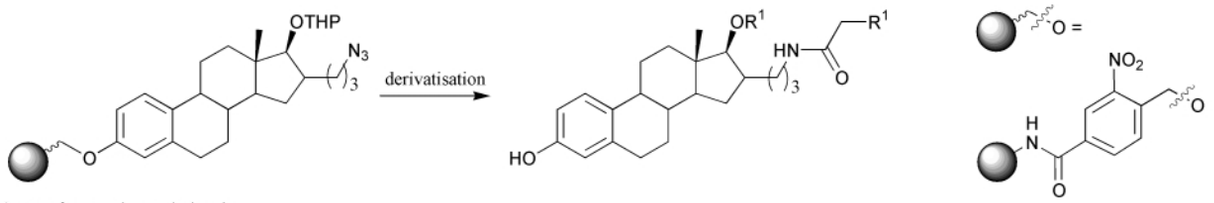


4 steps from Fmoc-PAL-PS resin

A. P. Combs and M. Rafalski, *J. Comb. Chem.*, 2000, **2**, 29.

13 examples (yields 0, 43-81%)

Estradiol derivatives

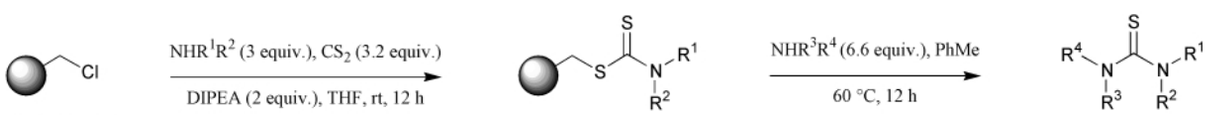


2 steps from aminomethyl resin

M. R. Tremblay and D. Poirier, *J. Comb. Chem.*, 2000, **2**, 48.

3 examples (yields 20-31%) and 1 other example of estradiol preparation (yield 31%). Preparation of Steroidal precursors and the use of 4 other less efficient linker strategies are also reported.

Traceless synthesis of _N,N'_-substituted thioureas

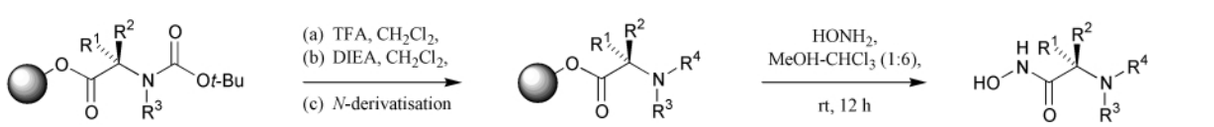


Merrifield resin

L. Gomez, F. Gellibert, A. Wagner and C. Mioskowski, *J. Comb. Chem.*, 2000, **2**, 75.

12 examples (yields 33-97%, HPLC purity >90%).

Nucleophilic displacement of resin-bound carboxylates with hydroxylamine

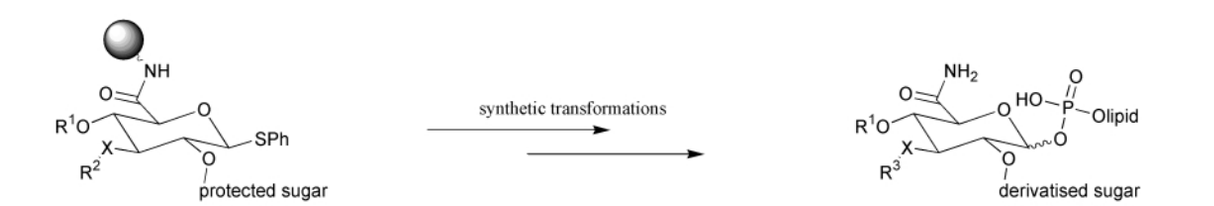


1 step from oxime resin

E. Thouin and W. D. Lubell, *Tetrahedron Lett.*, 2000, **41**, 457.

9 examples (yields 48->99%, NMR or HPLC purity 77-96%).

Disaccharide antibacterial agents

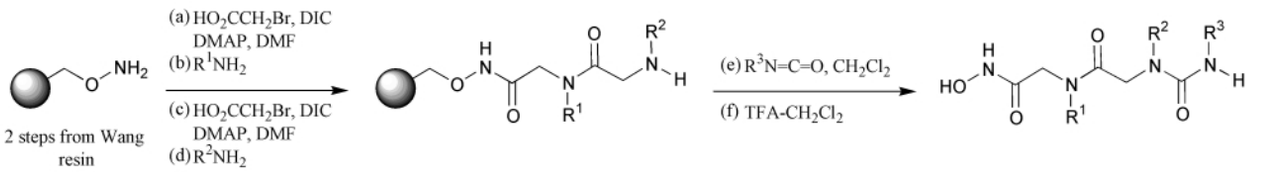


1 or 2 steps from Aminoethyl-photolinker AM resin

M. J. Sofia *et al*, *J. Med. Chem.*, 1999, **42**, 3193.

Preparation and biological evaluation of a 1300-member library are reported.

Hydroxamate/urea-based gelatinase inhibitors

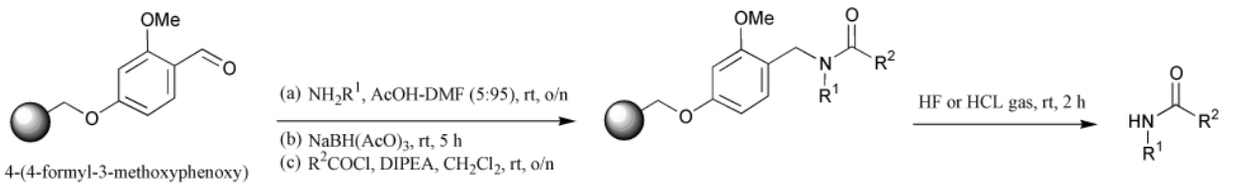


2 steps from Wang resin

Y. Zhang, D. Li, J. C. Houtman, D. T. Witiak, J. Seltzer, P. J. Bertics and C. T. Lauhon, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2823.

Preparation and biological evaluation of >1000 compounds is reported.

Gaseous HF and HCL cleavage of amino acids

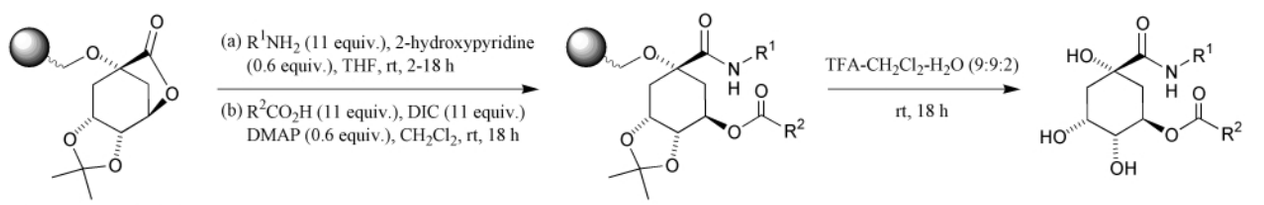


4-(4-formyl-3-methoxyphenoxy) butyryl resin

A. Kerschen, A. Kanizsai, I. Botros and V. Krchnák, 1999, *J. Comb. Chem.*, **1**, 480.

11 examples (yields 92->99%, HPLC purity 95-99%). 10 Wang resin-bound Fmoc amino acids are also cleaved using gaseous acid (yields 11-88%).

D-(–)-Quinic acid derivatives

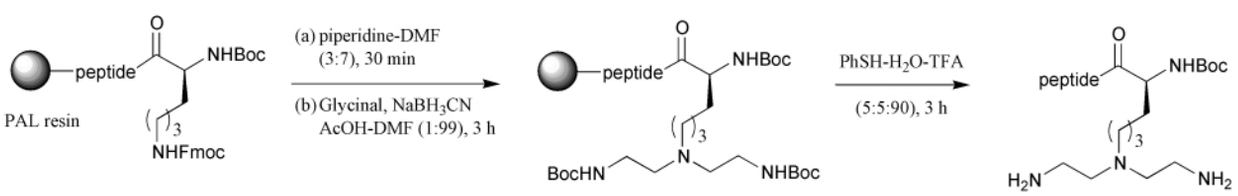


1 step from brominated Wang resin

C. W. Phoon and C. Abell, *J. Comb. Chem.*, 1999, **1**, 485.

10 examples (yields 62-92%, HPLC purity 84-99%). Preparation of 8 quinic acid derivatives *via* 2 similar routes is also reported (yields 63-84%, HPLC purity 91-97%).

Synthesis of an antimicrobial peptide using an unnatural amino acid as a building block

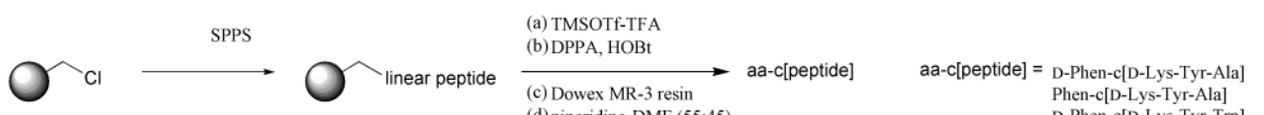


PAL resin

J. Eun Oh and K. Hyeung Lee, *Bioorg. Med. Chem.*, 1999, **7**, 2985.

Preparation and biological evaluation of a small library of peptides are reported.

Analogues of the opioid peptide YKFA



Merrifield resin

DPPA = diphenylphosphoryl azide

J. E. Burden, P. Davis, F. Porreca and A. F. Spatola, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 3441.

Synthesis and biological activities of 4 analogues of YKFA, in which the usual Tyr^1-Phe^3 combination found in the opioid peptides has been transposed, are reported.