Perkin 1 Abstracts: Natural Product Synthesis

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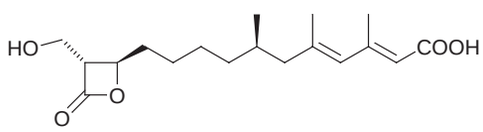
Perkin 1 Abstracts: Natural Product Synthesis aims to highlight syntheses that have been recently published. It includes brief descriptions of *biological activity* and *key steps*. A more comprehensive list of Natural Product syntheses and isolations can be found in *Natural Product Updates*

1233A

Biological activity: (a) antibiotic; (b) significant hypocholesterolemic activity; (c) potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A synthase (HMG-CoA synthase).

Key steps: β–lactone synthesis through an asymmetric [3+2] cycloaddition of oxazoline *N*-oxides.

O. Dirat, C. Kouklovsky and Y. Langlois, *J. Org. Chem.*, 1998, **63**, 6634.

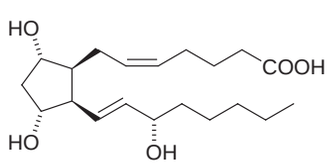


15-F_{2t}-isoprostane

Biological activity: (a) the kidney failure and death associated with severe liver disease is a consequence of the production and release of isoprostanes; (b) the effects of the title compound on the renal vasculature result from specific receptor binding.

Key steps: enzymatic resolution.

D. F. Taber and K. Kanai, *Tetrahedron*, 1998, **54**, 11767.

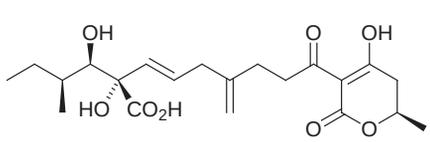


Alternaric Acid

Biological activity: highly specific inhibitor of fungal germination.

Key steps: (a) ruthenium-catalysed addition of a terminal alkene to a terminal alkyne generates the 1,4 diene unit; (b) Pd(0)-catalysed coupling of allyl tributylstannane with an α-bromoacrylate; (c) Sharpless asymmetric dihydroxylation.

B. M. Trost, G. D. Probst and A. Schoop, *J. Am. Chem. Soc.*, 1998, **120**, 9228.

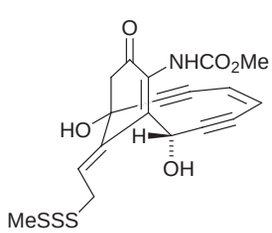


(±)-Calicheamicinone

Biological activity: the title compound, the aglycone of calicheamicin γ_1 isolated from the fermentation broth of *Micromonospora echinospora* sp. calichensis, exhibits potent antitumour activity.

Key steps: (a) generation of a highly functionalised cyclohexane *via* a Diels-Alder reaction; (b) enediyne synthesis *via* Pd(0)-catalysed coupling of two iodoalkyne units with (*Z*)-1,2-bis(trimethylstannyl)ethene.

D. J. L. Clive, Y. Bo, Y. Tao, S. Daignault, Y.-J. Wu and G. Meignan, *J. Am. Chem. Soc.*, 1998, **120**, 10332.

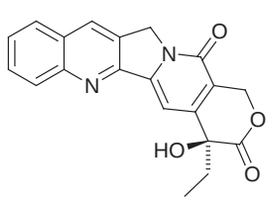


(±)-Camptothecin

Biological activity: anticancer activity.

Key steps: (a) intramolecular Michael addition; (b) Wittig reaction.

S. P. Chavan and M. S. Venkatraman, *Tetrahedron Lett.*, 1998, **39**, 6745.

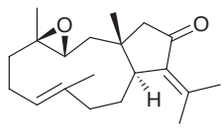


Claenone

Biological activity: (a) antimicrobial activity; (b) antiviral activity; (c) biogenetic and chemical precursors of dolastanes and fusicoccanes; (d) potent cytotoxiciy towards human prostate cancer WMF (GI_{50} 2.42 x 10^{-7}M) and RB cells (GI_{50} 3.06 x 10^{-7}M).

Key steps: (a) sequential Michael reaction of a cyclopentenone and a chiral α,β-unsaturated ester; (b) retroaldol reaction; (c) regio-selective macrocyclisation of a sulfone.

H. Miyaoka, Y. Isaji, Y. Kajiwara, I. Kunimune and Y. Yamada, *Tetrahedron Lett.*, 1998, **39**, 6503.

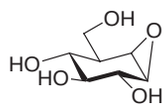


Cyclophellitol

Biological activity: (a) potent β-glucosidase inhibitor (IC_{50} against almond β-glucosidase : 0.8 μg ml^{-1}); (b) the stereoisomer *epi*-cyclophellitol displays potent α-glucosidase inhibitory activity.

Key steps: (a) $PdCl_2$-mediated Ferrier reaction to form the carbocyclic skeleton; (b) regioselective opening of an oxirane ring using Mes_2BCH_2Li.

H. Takahashi, T. Iimori and S. Ikegami, *Tetrahderon Lett.*, 1998, **39**, 6939.

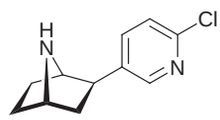


(±)-Epibatidine

Biological activity: (a) powerful analgesic that acts through a non-opioid mechanism; (b) two hundred times more potent than morphine.

Key steps: (a) Diels-Alder recation with Danishefsky's diene; (b) intramolecular nucleophilic displacement in a *trans*-1,4-methanesulfonyloxycyclohexylamide derivative.

A. Avenoza, J. H. Busto, C. Cativiela and J. M. Peregrina, *Synthesis*, 1998, 1335.

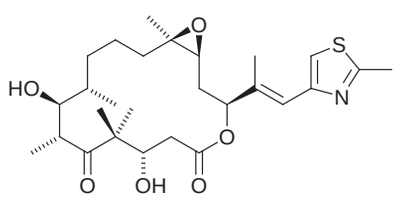


Epothilone B

Biological activity: potent microtubule binding, stabilizing abilities and antitumor properties; selective cytotoxicity against certain drug-resistant tumor cell lines.

Key steps: (a) Noyori asymmetric catalytic hydrogenation of a β-keto ester; (b) unusual *anti*-selective Mukaiyama directed aldol reaction involving a (*Z*)-lithium enolate to α-methylpent-4-enal.

A. Balog, C. Harris, K. Savin, X.-G. Zhang, T. C. Chou and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 1998, **37**, 2675.

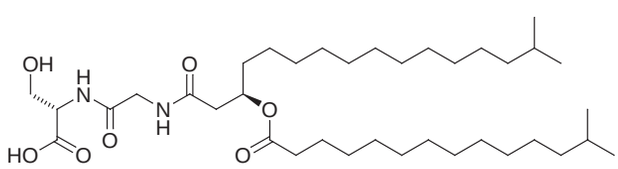


Flavolipin

Biological activity: (a) hemagglutination activity; (b) strongly stimulates macrophages to generate immunoregulatory substances; (c) potential nontoxic immunoactivator.

Key steps: established methods were used for the synthesis of the target.

M. Shiozaki, N. Deguchi, T. Mochizuki, T. Wakabayashi, T. Ishikawa, H. Haruyama, Y. Kawai and M. Nishijima, *Tetrahedron*, 1998, **54**, 11861.

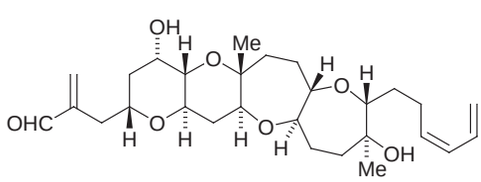


Hemibrevetoxin B

Biological activity: major marine toxin of the Florida red tide organism *Gymnodinium breve*.

Key steps: (a) two iterations of alkylation of an oxiranyl anion and 6-*endo* cyclisation to provide a 6,6,6-tricyclic ring system; (b) ring expansion using trimethylsilyl diazomethane.

Y. Mori, K. Yaegashi and H. Furukawa, *J. Org. Chem.*, 1998, **63**, 6200.

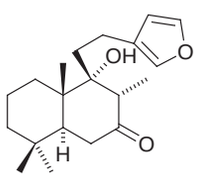


(±)-Hispanolone

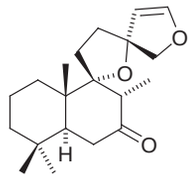
Biological activity: The natural product can be easily converted into prehispanolone which acts as a specific PAF (platelet activating factor) receptor antagonist.

Key steps: (±)-Wieland-Miescher ketone was used to prepare the product.

W. S. Cheung and H. N. C. Wong, *Tetrahedron Lett.*, 1998, **39**, 6521.



Hispanolone



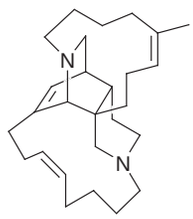
Prehispanolone

Keramaphidin B

Biological activity: the target is one of the manzamine alkaloids.

Key steps: a very low yield (0.2-0.3%) of the target involving intramolecular Diels-Alder cycloaddition of an alkene to a dihydropyridine lends support to Baldwin's hypothesis for the biosynthesis of the manzamines.

J. E. Baldwin, T. D. W. Claridge, A. J. Culshaw, F. A. Heupel, V. Lee, D. R. Spring, R. C. Whitehead, R. J. Boughtflower, I. M. Mutton and R. J. Upton, *Angew. Chem. Int. Ed.*, 1998, **37**, 2661.

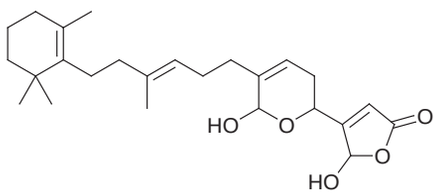


Manoalide

Biological activity: (a) irreversible PLA_2 inhibitor; (b) functions as a nonsteroidal anti-inflammatory drug (NSAID).

Key steps: $Me_3Al/AlCl_3$-mediated hetero-Diels-Alder addition of 2-silyloxy-1,3-dienes to a 3-formylated butenolide.

J. Coombs, E. Lattmann and H. M. R. Hoffmann, *Synthesis*, 1998, 1367.

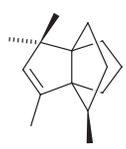


(±)-Modhephene

Biological activity: not reported.

Key steps: a tandem transannulation – cyclisation sequence from a cyclooctenyl substituted α-ketenyl radical intermediate.

B. DeBoeck and G. Pattenden, *Tetrahedron Lett.*, 1998, **39**, 6975.

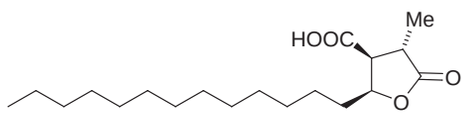


(±)-Nephromopsinic acid

Biological activity: not reported.

Key steps: introduction of the γ-chain *via* a mixed Kolbe electrolysis.

A. Forster, J. Fitremann and P. Renaud, *Tetrahedron Lett.*, 1998, **39**, 7097.

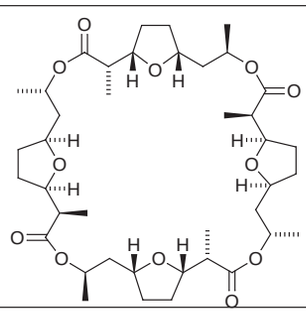


Nonactin

Biological activity: not reported.

Key steps: use of a versatile synthon with two silyl groups 1,2-related on a functionalised 6-carbon chain.

I. Fleming and S. K. Ghosh, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2733.

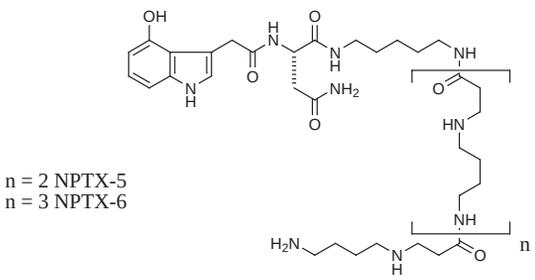


NPTX-5 and NPTX-6, Joro Spider *(Nephila clavata)* Toxins

Biological activity: the toxins show potent and specific blocking of glutaminergic neurotransmission and can be employed as tools for understanding excitatory amino acid neurotransmission and related pharmacology.

Key steps: iterative use of a key azide compound.

H. Saito, E. Yuri, M. Miyazawa, Y. Itagaki, T. Nakajima and M. Miyashita, *Tetrahedron Lett.*, 1998, **39**, 6479.

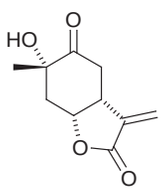


Paeonilactone B

Biological activity: not reported.

Key steps: SmI_2-mediated cascade reaction of methylenecyclopropane derivatives.

R. J. Boffey, M. Santagostino, W. G. Whittingham and J. D. Kilburn, *Chem. Commun.*, 1998, 1875.

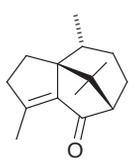


(–)-Patchoulenone

Biological activity: (a) *in vitro* activity (EC_{50} $1.08.10^{-4}$ M) against malarial parasite *Plasmodium falciparum*; (b) strong anti-fungal activity against *Rhizoctonia solani* and *Saprolegnia asterophora*; (c) significant toxicity in a brine shrimp bioassay.

Key steps: microbial oxidation of toluene.

M. Banwell and M. McLeod, *Chem. Commun.*, 1998, 1851.

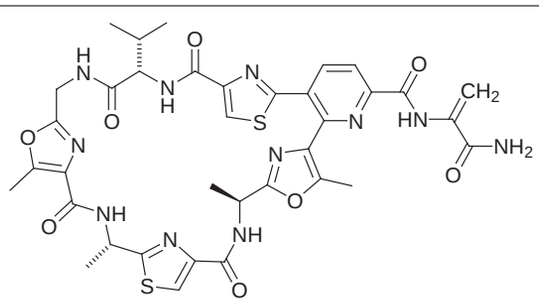


Promothiocin A

Biological activity: inhibits protein synthesis in bacteria.

Key steps: (a) rhodium(II) acetate catalysed reaction of *N*-protected amino acid amides with methyl 2-diazo-3-oxobutanoate resulting in an insertion of the metallocarbenoid into the amide N–H bond; (b) conversion of an alanine-derived oxazole into an oxazole-thiazole-pyridine fragment using a method based on the Bohlmann-Rahtz pyridine synthesis; (c) macrolactamisation following Schmidt's protocol.

C. J. Moody and M. C. Bagley, *Chem. Commun.*, 1998, 2049.

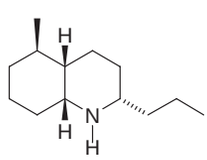


(–)-Pumiliotoxin C

Biological activity: (a) component of the toxic skin secretions of certain neotropical frogs; (b) acts as a reversible blocker of the nicotinic acetylcholine receptor channel.

Key steps: use of an acetylenic sulfone as the synthetic equivalent of an alkene dipole in a cycloaddition sequence.

T. G. Back and K. Nakajima, *J. Org. Chem.*, 1998, **63**, 6566.

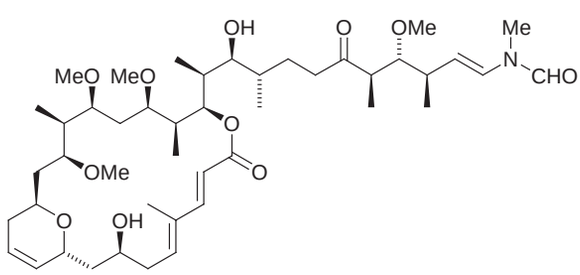


Scytophycin C

Biological activity: (a) cytotoxixc agent; (b) antifungal; (c) inhibits cytokinesis in cultured mammalian cells; (d) inhibits actin polymerisation; (e) induces the depolymerisation of F-actin *in vitro*; (f) circumvents P-glycoprotein mediated multi-drug resistance in tumor cells and maintain their antiproliferative effects.

Key steps: (a) asymmetric crotylboration; (b) boron mediated aldol reaction; (c) $Ba(OH)_2$-promoted HWE reaction; (d) Mukaiyama aldol reaction; (e) P_2O_5-promoted condensation to install the *N*-methyl vinylformamide moiety.

I. Paterson, K.-S. Yeung, C. Watson, R. A. Ward and P. A. Wallace, *Tetrahedron*, 1998, **54**, 11935 and 11955.

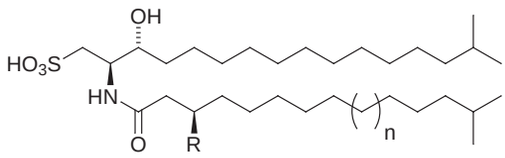


Sulfobacin A and B

Biological activity: (a) act as von Willebrand factor receptor antagonists; (b) Sulfobacin A is also reported to be a DNA polymerase α inhibitor

Key steps: L-cysteine was used as the starting material.

H. Takikawa, S.-e. Muto, D. Nozawa, A. Kayo and K. Mori, *Tetrahedron Lett.*, 1998, **39**, 6931.



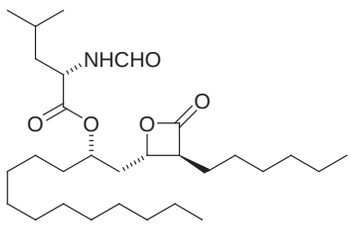
Sulfobacin A R = OH, n = 3
Sulfobacin B R = H, n = 1

(–)-Tetrahydrolipstatin

Biological activity: esterase inhibitor

Key steps: (a) stereoselective alkylation of a β-silyl ester; (b) hydroboration of an allylsilane.

I. Fleming and N. J. Lawrence, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2679.

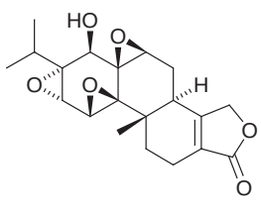


Triptolide

Biological activity: (a) potent antileukemic activity; (b) potent antitumor activity; (c) inhibits lymphocyte proliferation and interleukin-2 production.

Key steps: (a) radical cyclisation of an acyclic precursor mediated by $Mn(OAc)_3$ using Snider method; (b) triepoxide construction.

D. Yang, X.-Y. Ye, M. Xu, K.-W. Pang, N. Zou and R. M. Letcher, *J. Org. Chem.*, 1998, **63**, 6446.

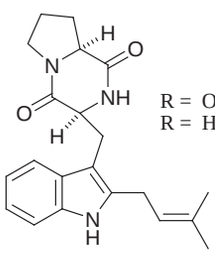


Tryprostatin A and B

Biological activity: completely inhibit cell cycle progression of tsFT210 cells in the G2/M phase at a final concentration of 50 μg mL^{-1} and 12.5 μg mL^{-1} (tryprostatine A and B respectively).

Key steps: (a) alkylation with the Schöllkopf chiral auxiliary; (b) synthesis of both enantiomers of tryprostatin A and B *via* alkylation of the corresponding 2-lithioindole derivatives.

S. Zhao, T. Gan, P. Yu and J. M. Cook, *Tetrahedron Lett.*, 1998, **39**, 7009.



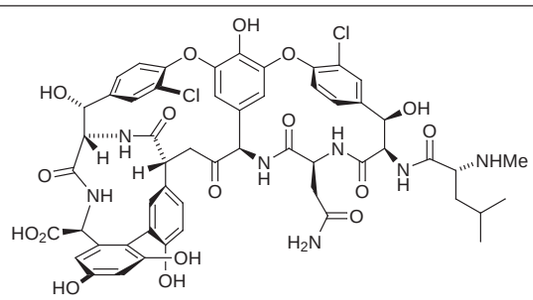
R = OMe, Tryprostatin A
R = H, Tryprostatin B

Vancomycin Aglycone

Biological activity: the glycoside is used for the treatment of methicillin resistant *Staphylococcus aureus* infections.

Key steps: (a) asymmetric synthesis of amino acids *via* nucleophilic amination of *N*-acyl oxazolidinone enolates; (b) biaryl ether synthesis *via* phenolate addition-elimination to *o*-fluoronitroarenes.

D. A. Evans, M. R. Wood, B. W. Trotter, T. I. Richardson, J. C. Barrow and J. L. Katz, *Angew. Chem. Int. Ed.*, 1998, **37**, 2700.



Vancomycin Aglycone

Biological activity: the glycoside is used for the treatment of methicillin resistant *Staphylococcus aureus* infections.
Key steps: novel biaryl ether synthesis via phenolate addition-elimination to *o*-bromoaryl triazene.

K. C. Nicolaou, S. Natarajan, H. Li, N. F. Jain, R. Hughes, M. E. Solomon, J. M. Ramanjulu, C. N. C. Boddy and M. Takayanagi, *Angew. Chem. Int. Ed.*, 1998, **37**, 2708; K. C. Nicolaou, N. F. Jain, S. Natarajan, R. Hughes, M. E. Solomon, H. Li, J. M. Ramanjulu, M. Takayanagi, A. E. Koumbis and T. Bando, *ibid.*, 1998, **37**, 2714; K. C. Nicolaou, M. Takayanagi, N. F. Jain, S. Natarajan, A. E. Koumbis, T. Bando and J. M. Ramanjulu, *ibid.*, 1998, **37**, 2717.