PERKIN 1 ABSTRACTS

Perkin 1 Abstracts: Natural Product Synthesis

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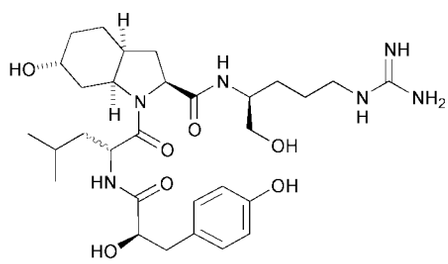
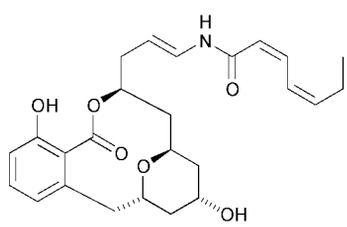
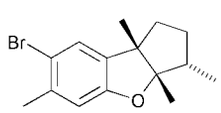
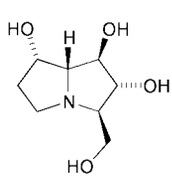
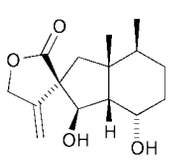
Perkin 1 Abstracts: Natural Product Synthesis aims to highlight syntheses that have been recently published. It includes brief descriptions of *biological activity* and *key steps*. A more comprehensive list of Natural Product syntheses and isolations can be found in *Natural Product Updates*.

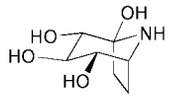
(+)-Aeruginosin 298-A *Biological activity*: (a) isolated from the blue-green freshwater algae *Microcystis aeruginosa*; (b) thrombin inhibitor (IC_{50} = 0.5 μM). *Key steps*: (a) tyrosine oxidation-rearrangement; (b) BF_3•OEt_2-catalysed organocuprate addition to (*R*)-benzylglycidol. P. Wipf and J.-L. Methot, *Org. Lett.*, 2000, **2**, 4213.	
Apicularen A *Biological activity*: (a) cytostatic activity against nine human cancer cell lines (IC_{50}~0.1–3 ng mL^{-1}); (b) initiates several abnormal effects including the formation of mitotic spindles with multiple spindle poles and clusters of bundled actin from the cytoskeleton. *Key steps*: addition of 1-lithiohexa-1,3-diene to an α,β-unsaturated isocyanate. A. Bhattacharjee, O. R. Seguil and J. K. De Brabander, *Tetrahedron Lett.*, 2001, **42**, 1217.	
(±)-Aplysin *Biological activity*: (a) extracted from the *Aplysia* sea hare; (b) believed to scavenge reactive halogens from the marine environment; (c) anti-feedant. *Key steps*: (a) Willgerodt–Kindler oxidation; (b) diastereoselective sulfur-mediated radical cyclisation of a diene. D. C. Harrowven, M. C. Lucas and P. D. Howes, *Tetrahedron*, 2001, **57**, 791.	
(+)-Australine *Biological activity*: (a) isolated from *Castanospermum australe*; (b) specific inhibitor of fungal amyloglucosidase and glycoprotein-processing glucosidase 1; (c) inhibits HIV-induced synostia formation in JM cells. *Key steps*: (a) ring-closing metathesis; (b) stereoselective epoxidation of an azacyclooctene; (c) transannular cyclisation. J. D. White and P. Hrnciar, *J. Org. Chem.*, 2000, **65**, 9129.	
(–)-Bakkenolide III *Biological activity*: (a) isolated from *Petasites japonicus* Maxim. and *Petasites formosanus* Kitamura; (b) significant inhibitory activity toward Hep G2, Hep G2,2,15 and P-388 tumour cell lines. *Key steps*: (a) SmI_2-promoted chemoselective double reduction of an epoxy ketone; (b) retroaldol-aldol reaction. O. Hamelin, Y. Wang, J.-P. Deprés and A. E. Greene, *Angew. Chem., Int. Ed.*, 2000, **39**, 4314.	

(+)-Calystegine B_2

Biological activity: (a) isolated from *Solanum tuberosum* and the roots of *Calystegia sepium*; (b) inhibitor of rat liver β-glucosidase and human lysosomal α-galactosidase A (α-Gal A) (IC_{50} – 30 μM).

Key steps: triple domino zinc-mediated reductive ring-opening, imine formation and allylation reaction of 6-iodoglucopyranose.

F.-D. Boyer and I. Hanna, *Tetrahedron Lett.*, 2001, **42**, 1275.

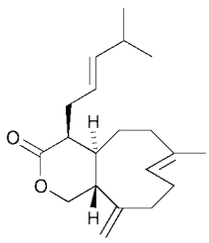


Coraxeniolide-A

Biological activity: (a) isolated from a pink coral, *Corallium* sp.; (b) member of a class of diterpenes called the xenicanes which exhibit biological properties ranging from cytotoxicity to antitumour activity.

Key steps: stereospecific Grob fragmentation to construct nine-membered ring.

D. Renneberg, H. Pfander and C. J. Leumann, *J. Org. Chem.*, 2000, **65**, 9069.

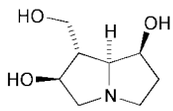


(–)-Croalbinecine

Biological activity: not reported.

Key steps: (a) ester-imine condensation; (b) ring-closing metathesis.

J.-B. Ahn, C.-S. Yun, K. H. Kim and D.-C. Ha, *J. Org. Chem.*, 2000, **65**, 9249.

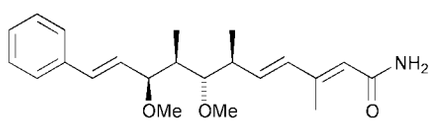


(+)-Crocacin C

Biological activity: (a) isolated from the myxobacterial strains of *Chondromyces crocatus* and *Chondromyces pediculatus*; (b) antifungal; (c) cytotoxic.

Key steps: (a) Horner–Wadsworth–Emmons olefination; (b) Ti(IV)-mediated diastereoselective aldol reaction using a oxazolidine-2-thione-based chiral auxiliary; (c) Sharpless asymmetric epoxidation; (d) lithium dimethylcuprate opening of an epoxide ring.

T. K. Chakraborty and S. Jayaprakash, *Tetrahedron Lett.*, 2001, **42**, 497.

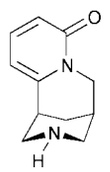


(±)-Cytisine

Biological activity: (a) high affinity partial agonist at neuronal nicotinic receptors (EC_{50} – 1 μM); (b) important probe in nicotinic acetylcholine receptor research; (c) potential therapeutic agent in the treatment of addiction, provided efficacy can be improved.

Key steps: (a) formation of an unsymmetrically substituted biaryl pyridine system by either an "*in situ*" Stille or a Suzuki coupling; (b) selective reduction (H_2/PtO_2) of one pyridyl ring; (c) cyclisation of a 3,5-*cis*-piperidine to form the diazabicyclo[3.3.1]nonane framework.

B. T. O'Neill, D. Yohannes, M. W. Bundesmann and E. P. Arnold, *Org. Lett.*, 2000, **2**, 4201.

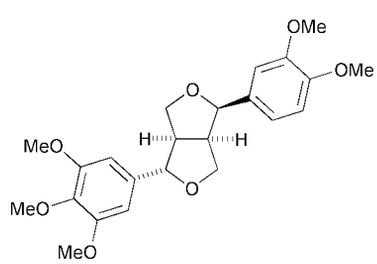


(±)-Epimagnolin A

Biological activity: (a) isolated from the flower buds of *Magnolia fargesii*; (b) growth inhibitor of the larvae of *Drosophila melanogaster*.

Key steps: rhodium(II) acetate catalysed diastereoselective C–H insertion of an α-diazo-γ-butyrolactone.

R. C. D. Brown, C. J. R. Bataille and J. D. Hinks, *Tetrahedron Lett.*, 2001, **42**, 473.

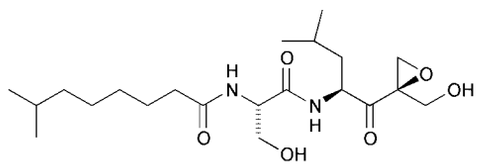


(+)-Epopromycin B

Biological activity: (a) isolated from a *Streptomycete*; (b) inhibitor of the cell-wall synthesis of plant protoplasts.

Key steps: (a) addition of a vinyllithium to an aldehyde; (b) DCC coupling.

M. R. Dobler, *Tetrahedron Lett.*, 2001, **42**, 215.

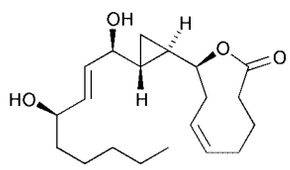


Halicholactone

Biological activity: lipoxygenase inhibitor isolated from the marine sponge *Halichondoria okadai*.

Key steps: (a) Lewis acid-mediated regio- and stereo-selective nucleophilic substitution of an ester iron carbonyl complex; (b) stereoselective [2,3]-sigmatropic rearrangement; (c) modified Simmons–Smith cyclopropanation; (d) ring-closing metathesis.

Y. Baba, G. Saha, S. Nakao, C. Iwata, T. Tanaka, T. Ibuka, H. Ohishi and Y. Takemoto, *J. Org. Chem.*, 2001, **66**, 81.

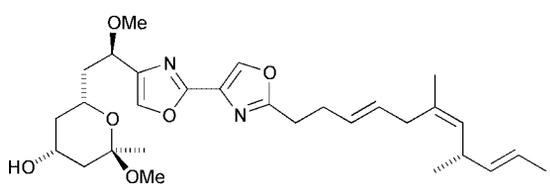


(–)-Hennoxazole A

Biological activity: (a) isolated from the marine sponge *Polyfibrospongia* sp.; (b) active against herpes simplex virus type 1 (IC_{50} = 0.6 μg mL^{-1}); (c) peripheral analgesic.

Key steps: (a) diastereoselective Mukaiyama aldol reaction; (b) formation of a nonconjugated diene *via* S_N2 displacement of an allylic bromide with a vinyllithium; (c) Takai's $CrCl_2$-mediated iodoolefination to yield a (*E*)-vinyl iodide; (d) palladium-catalysed cross coupling of the vinyl iodide with MeMgBr.

F. Yokokawa, T. Asano and T. Shioiri, *Org. Lett.*, 2000, **2**, 4169.

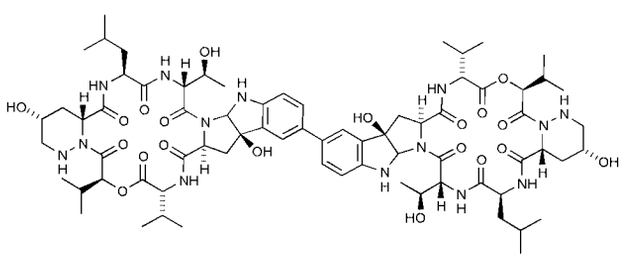


Himastatin

Biological activity: (a) antibiotic against Gram positive bacteria; (b) antitumour agent.

Key steps: (a) pyrroloindoline synthesis *via* oxidative cyclisation of a tryptophan derivative with dimethyl dioxirane; (b) biaryl synthesis *via* Stille coupling.

T. M. Kamenecka and S. J. Danishefsky, *Chem. Eur. J.*, 2001, **7**, 41.

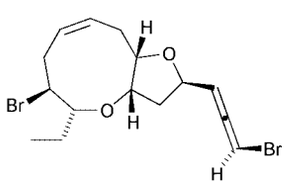


(–)-Isolaurallene

Biological activity: not reported

Key steps: (a) asymmetric α-alkylation of an α-alkoxyethanoyloxazolidinone; (b) Sharpless asymmetric epoxidation; (c) ring closing metathesis.

M. T. Crimmins and K. A. Emmitte, *J. Am. Chem. Soc.*, 2001, **123**, 1533.

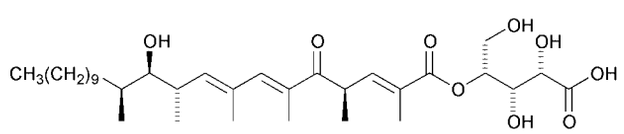


(–)-Khafrefungin

Biological activity: antifungal that inhibits the biosynthesis of inositol phosphorylceramide.

Key steps: tin(II)-mediated asymmetric aldol reactions using homochiral diamine promoters.

T. Wakabayashi, K. Mori and S. Kobayashi, *J. Am. Chem. Soc.*, 2001, **123**, 1372.

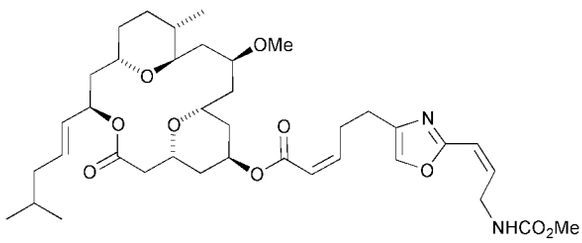


Leucascandrolide A

Biological activity: (a) isolated from the sponge *Leucascandra caveolata*; (b) *in vitro* cytotoxicity against KB and P388 cancer cell lines; (c) potent antifungal, inhibiting the growth of *Candida albicans*.

Key steps: (a)Yb(OTf)$_3$-catalysed oxymercuration; (b) regioselective Rh(I)-catalysed hydroformylation; (c) intramolecular alkoxycarbonylation according to the Semmelhack protocol; (d) macrolactonisation according to the Yonemitsu-modified Yamaguchi protocol.

K. R. Hornberger, C. L. Hamblett and J. L. Leighton, *J. Am. Chem. Soc.*, 2000, **122**, 12894.

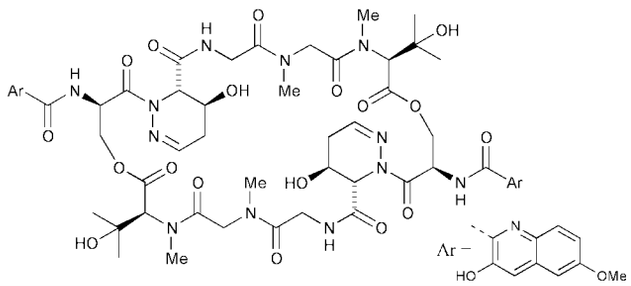


Luzopeptin C

Biological activity: potent inhibitor of HIV replication.

Key steps: self-assembly of the macrocycle *via* activation of a pentapeptide monomer.

D. Valognes, P. Belmont, N. Xi and M. A. Ciufolini, *Tetrahedron Lett.*, 2001, **42**, 1907.

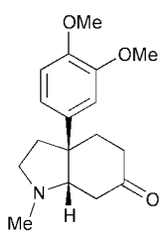


(–)-Mesembrine

Biological activity: (a) isolated from the Mesembryanthemaceae family (*Sceletium tortuosum*); (b) inhibitor of serotonin uptake; (c) lead compound for the preparation of antidepressants.

Key steps: (a) highly stereoselective conjugate addition employing a chiral oxazolidinone auxiliary; (b) intramolecular alkylidene C–H insertion.

D. F. Taber and T. D. Neubert, *J. Org. Chem.*, 2001, **66**, 143.

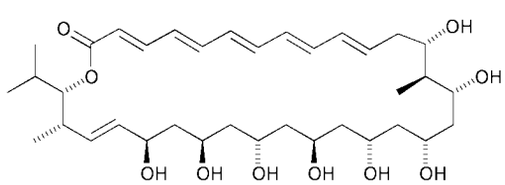


Mycoticin A

Biological activity: not reported.

Key steps: (a) intermolecular cross metathesis reaction between a terminal alkene and acrolein diethyl acetal; (b) asymmetric allylboration; (c) intramolecular oxymercuration followed by Rh-catalysed carbonylation of the alkylmercurial. This is a formal total synthesis intersecting with an advanced intermediate previously prepared by Schreiber *et al.*, *J. Am. Chem. Soc.*, 1993, **115**, 3360.

S. D. Dreher and J. L. Leighton, *J. Am. Chem. Soc.*, 2001, **123**, 341.

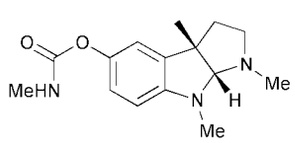


(–)-Physostigmine

Biological activity: not reported.

Key steps: (a) Fischer indole synthesis; (b) retro-Diels–Alder reaction.

K. Tanaka, T. Taniguchi and K. Ogasawara, *Tetrahedron Lett.*, 2001, **42**, 1049.

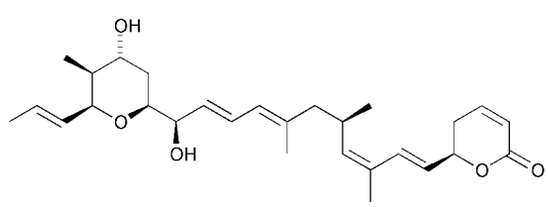


(+)-Ratjadone

Biological activity: (a) isolated from *Sorangium cellulosum* (So ce360); (b) high cytotoxicity in cultured mouse cell lines (L929) (IC_{50} – 50 pg mL^{-1}); (c) growth inhibitor of the HeLa cell line (KB3.1) at 40 pg mL^{-1}; (d) antifungal (MIC – 0.04–0.6 μg mL^{-1}).

Key steps: (a) amberlyst-15 induced intramolecular 6-*exo* ring closure to form tetrahydropyran ring; (b) hetero-Diels–Alder reaction catalysed by the chiral Lewis acid generated from (–)-BINOL and Ti(O*i*Pr)$_4$; (c) Wittig olefination; (d) intermolecular Heck reaction.

M. Christmann, U. Bhatt, M. Quitschalle, E. Claus and M. Kalesse, *Angew. Chem., Int. Ed.*, 2000, **39**, 4364.

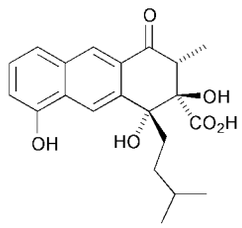


(±)-Rishirilide B

Biological activity: antithrombotic activity through inhibition of α_2-macroglobulin.

Key steps: intermolecular [4 + 2] cycloaddition of a cyclohexenone to a quinonedimethide.

J. G. Allen and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2001, **123**, 351.

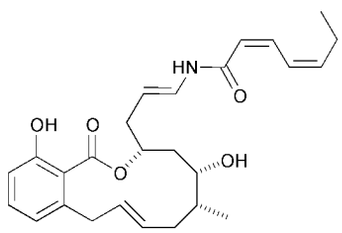


(+)-Salicylihalamide A

Biological activity: (a) isolated from the marine sponge *Haliclona* sp.; (b) antineoplastic; (c) belongs to a potentially new mechanistic class of antitumour compounds.

Key steps: (a) Mitsunobu esterification; (b) *trans*-selective ring-closing olefin metathesis; (c) Curtius rearrangement.

Y. Wu, L. Esser and J. K. De Brabander, *Angew. Chem., Int. Ed.*, 2000, **39**, 4308; Y. Wu, O. R. Seguil and J. K. De Brabander, *Org. Lett.*, 2000, **2**, 4241.

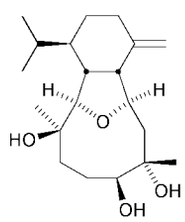


Sclerophytin A

Biological activity: (a) antineoplastic; (b) cytotoxic.

Key steps: (a) hydroxy-directed asymmetric epoxidation using $VO(acac)_2$/*t*-BuO_2H; (b) photochemical isomerisation.

F. Gallou, D. W. C. MacMillan, L. E. Overman, L. A. Paquette, L. D. Pennington and J. Yang, *Org. Lett.*, 2001, **3**, 135.

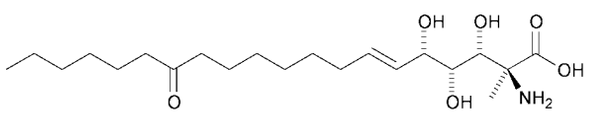


Sphingofungin F

Biological activity: (a) isolated from the fermentation broth of *Poecilomyces variotii*; (b) inhibitor of *Serinepalmitoyl transferase*.

Key steps: (a) Sharpless asymmetric epoxidation; (b) Lewis acid-catalysed intramolecular epoxide-opening reaction with an *N*-nucleophile.

D.-G. Liu, B. Wang and G.-Q. Lin, *J. Org. Chem.*, 2000, **65**, 9114.



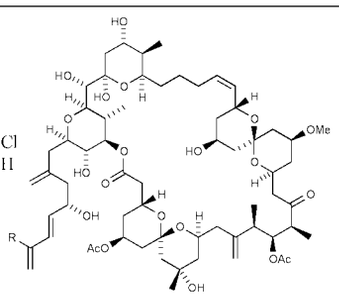
Spongistatins 1 and 2

Biological activity: antitumour agent.

Key steps: key fragment linkage reactions include Julia olefination and dithiane alkylation reactions.

A. B. Smith, V. A. Doughty, L. Z. Q. Lin, M. D. McBriar, A. M. Boldi, W. H. Moser, N. Murase, K. Nakayama and M. Sabukawa, *Angew. Chem., Int. Ed.*, 2001, **40**, 191; A. B. Smith, Q. Lin, V. A. Doughty, L. Zhuang, M. D. McBriar, J. K. Kerns, C. S. Brook, N. Murase and K. Nakayama, *Angew. Chem., Int. Ed.*, 2001, **40**, 196.

Spongistatin 1 R = Cl
Spongistatin 2 R = H



(–)-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, S. Ichikawa, W. C. Tse, M. P. Hedrick and Q. Jin, *J. Am. Chem. Soc.*, 2001, **123**, 561.