Perkin 1 Abstracts: Natural Product Synthesis

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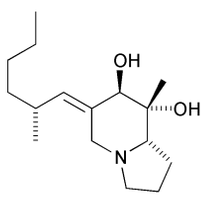
Perkin 1 Abstracts: Natural Product Synthesis aims to highlight syntheses that have been recently published. It includes brief descriptions of *biological activity* and *key steps*. A more comprehensive list of Natural Product syntheses and isolations can be found in *Natural Product Updates*.

(+)-Allopumiliotoxin 267A

Biological activity: nerve toxin isolated from the skin secretions of neotropical frogs of the family Dendrobatidae.

Key steps: (a) regio- and stereo-specific addition of an alkynyllithium to a 1-acylpyridinium salt of a trisubstituted pyridine; (b) axial acetoxylation of an indolizidinone with $Pb(OAc)_4$; (c) one-pot reduction using K-Selectride followed by $LiAlH_4$ to provide a diol.

D. L. Comins, S. Huang, C. L. McArdle and C. L. Ingalls, *Org. Lett.*, 2001, **3**, 649.

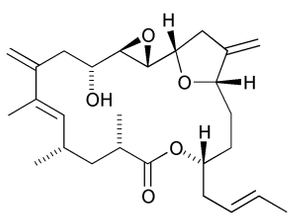


(+)-Amphidinolide K

Biological activity: antitumour agent isolated from the marine dinoflagellate *Amphidinium* sp. with extraordinary activity against a variety of NCI tumour cell lines.

Key steps: (a) asymmetric allylation reaction; (b) Stille coupling reaction using copper(I) thiophene-2-carboxylate as a co-catalyst to prepare a substituted diene.

D. R. Williams and K. G. Meyer, *J. Am. Chem. Soc.*, 2001, **123**, 765.

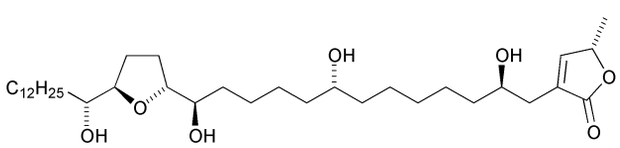


Annonacin

Biological activity: an annonaceous acetogenin isolated from the stem bark of *Annona densicoma*.

Key steps: (a) coupling between an epoxide and the lithium derivative of an alkyne in the presence of $BF_3{\bullet}Et_2O$ to afford an alkynol; (b) introduction of the butenolide moiety using an aldol condensation of a protected (*S*)-lactal.

T.-S. Hu, Q. Yu, Y.-L. Wu and Y. Wu, *J. Org. Chem.*, 2001, **66**, 853.

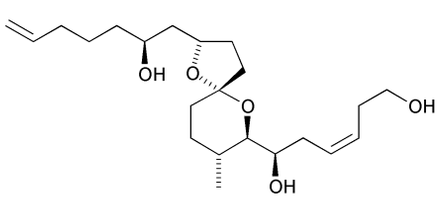


Attenol A

Biological activity: (a) isolated from the Chinese bivalve *Pinna attenuata*; (b) cytotoxic against P388 cells (IC_{50} = 24 μg ml^{-1}).

Key steps: (a) diastereoselective hydroboration; (b) Lindlar reduction; (c) acid-catalysed acetal formation.

K. Suenaga, K. Araki, T. Sengoku and D. Uemura, *Org. Lett.*, 2001, **3**, 527.

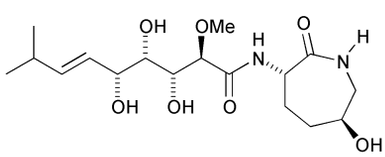


(+)-Bengamide E

Biological activity: inhibits MDA-MB-435 human breast carcinoma cells implanted as xenografts in athymic mice at well-tolerated doses.

Key steps: olefination reaction using a *gem*-dichromium reagent. (+)-Bengamide B was also synthesised.

F. R. Kinder, S. Wattanasin, R. W. Versace, K. W. Bair, J. Bontempo, M. A. Green, Y. J. Lu, H. R. Marepalli, P. E. Phillips, D. Roche, L. D. Tran, R. Wang, L. Waykole, D. D. Xu and S. Zabludoff, *J. Org. Chem.*, 2001, **66**, 2118.

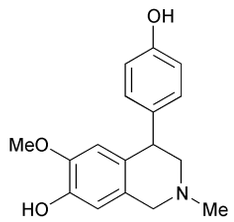


Cherylline

Biological activity: not reported.

Key steps: formation of a δ-lactam by a Pd-catalysed intramolecular coupling of an aryl halide and an amide-enolate.

T. Honda, H. Namiki and F. Satoh, *Org. Lett.*, 2001, **3**, 631.

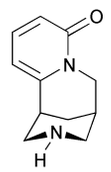


(±)-Cytisine

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: intramolecular Heck cyclisation of activated glutarimide-derived ketene aminals to construct the tricyclic carbon skeleton.

J. W. Coe, *Org. Lett.*, 2000, **2**, 4205.

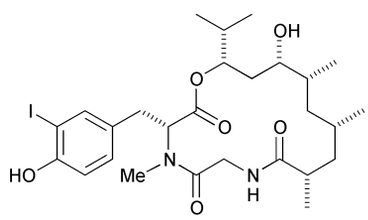


(–)-Doliculide

Biological activity: (a) isolated from the Japanese sea hare *Dolabella auricularia* (Aplysiidae); (b) potent antitumour agent; (c) cytotoxic against HeLa-S_3 cells (IC_{50} = 1 ng ml^{-1}).

Key steps: asymmetric cyclopropanation followed by electrophilic cleavage to install the methyl groups on the polyketide chain.

A. K. Ghosh and C. Liu, *Org. Lett.*, 2001, **3**, 635.

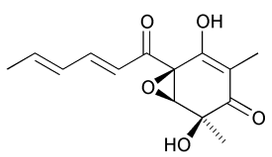


(±)-Epoxysorbicillinol

Biological activity: not reported.

Key steps: 1,3-dipolar cycloaddition between an α-diazo ketone and a propiolate ester.

J. L. Wood, B. D. Thompson, N. Yusuff, D. A. Pflum and M. S. P. Matthäus, *J. Am. Chem. Soc.*, 2001, **123**, 2097.

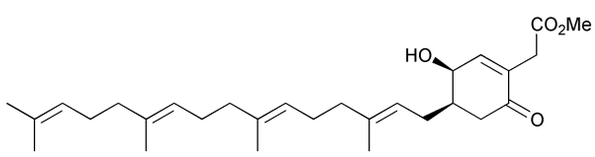


(+)-Eunicenone A

Biological activity: not reported.

Key steps: (a) asymmetric Diels–Alder reaction of achiral components using a chiral catalyst; (b) Cu(I)-catalysed allylic substitution using a silylcuprate; (c) Pd(0)-catalysed methoxycarbonylation of a 1,2-epoxy-1,3-diene; (d) 1,3-diene synthesis involving a Pd(0)-catalysed coupling of an iodoalkene and an alkenylzirconium reagent.

T. W. Lee and E. J. Corey, *J. Am. Chem. Soc.*, 2001, **123**, 1872.

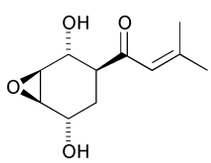


(–)-Eutipoxide B

Biological activity: (a) secondary metabolite of the phytopathogenic fungus *Eutypa lata*; (b) biological activity not reported.

Key steps: (a) base-catalysed asymmetric Diels–Alder reaction with 3-hydroxy-2-pyrone and chiral acrylates; (b) stereoselective reduction of carbonyl group using $NaBH(OAc)_3$; (c) chemoselective Swern oxidation.

H. Shimizu, H. Okamura, T. Iwagawa and M. Nakatani, *Tetrahedron*, 2001, **57**, 1903.

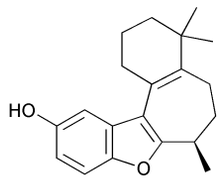


(+)-Frondosin B

Biological activity: interleukin-8 receptor antagonist.

Key steps: (a) Friedel–Crafts reaction to construct the 7-membered ring; (b)cationic cyclisation of a vinylogous benzofuran to generate a 6-membered ring; (c) Diels–Alder reaction. Two routes to the racemic product are reported as well as a scalemic route that established the absolute configuration

M. Inoue, M. W. Carson, A. J. Frontier and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2001, **39**, 1878.

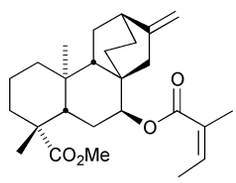


(±)-Gummiferolic acid, methyl ester

Biological activity: plant growth regulator.

Key steps: homoallyl–homoallyl radical rearrangement to generate the bicyclo[2.2.2]octane ring system.

M. Toyota, M. Yokota and M. Ohara, *J. Am. Chem. Soc.*, 2001, **123**, 1856.

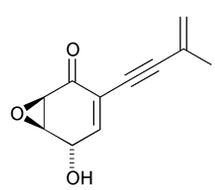


(+)-Harveynone

Biological activity: phytotoxin isolated from the tea gray blight fungus *Pestalotiopsis theae*.

Key steps: Stille cross-coupling.

M. T. Barros, C. D. Maycock and M. R. Ventura, *Chem. Eur. J.*, 2000, **6**, 3991.

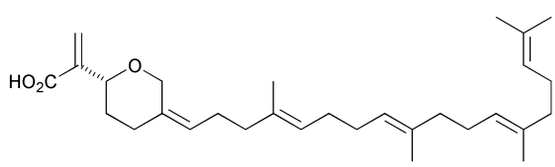


(*R*)-Hippospongic acid A

Biological activity: (a) isolated from the marine sponges *Hippospongia* sp. and *Rhopaloeides* sp. (b) inhibits gastrulation of starfish embryos (IC_{50} = 14 μM).

Key steps: (a) stereoselective reduction of an α-hydroxy ketone with baker's yeast; (b) photosensitised oxidation of a diene to an endoperoxide using hematoporphyrin as a sensitiser; (c) stereoselective epoxidation/epoxide opening sequence.

H. Hioki, H. Ooi, M. Hamano, Y. Mimura, S. Yoshio, M. Kodama, S. Ohta, M. Yanai and S. Ikegami, *Tetrahedron*, 2001, **57**, 1235.

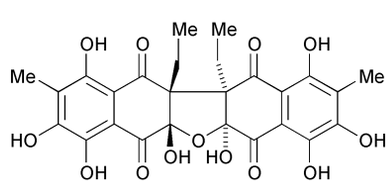


Hybocarpone

Biological activity: (a) isolated from mycobiont cultures derived from the lichen *Lecanora hybocarpa*; (b) potent cytotoxic activity against the murine mastocytoma P815 cell line (IC_{50} = 0.15 mg ml^{-1}).

Key steps: CAN-induced single-electron transfer dimerisation-hydration cascade.

K. C. Nicolaou and D. Gray, *Angew. Chem., Int. Ed.*, 2001, **40**, 761.

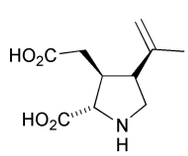


(–)-α-Kainic acid

Biological activity: (a) neurotransmitter; (b) antiworming agent.

Key steps: (a) metal-promoted enantioselective ene-reaction; (b) chemo- and stereoselective zirconium-mediated Strecker reaction.

Q. Xia and B. Ganem, *Org. Lett.*, 2001, **3**, 485.

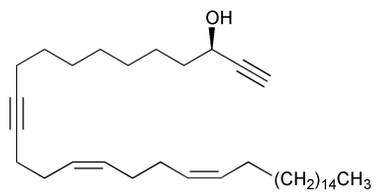


Lembehyne A

Biological activity: (a) isolated from the marine sponge *Haliclona* sp.; (b) induces neuritogenesis in PC12 cells (2 μg ml^{-1}) and Neuro2A cells (0.1 μg ml^{-1}) without nerve growth factor.

Key steps: (a) asymmetric reduction reaction with Alpine-borane; (b) alkyne formation with dimethyl-1-diazo-2-oxopropylphosphonate.

N. Murakami, T. Nakajima, and M. Kobayashi, *Tetrahedron Lett.*, 2001, **42**, 1941.

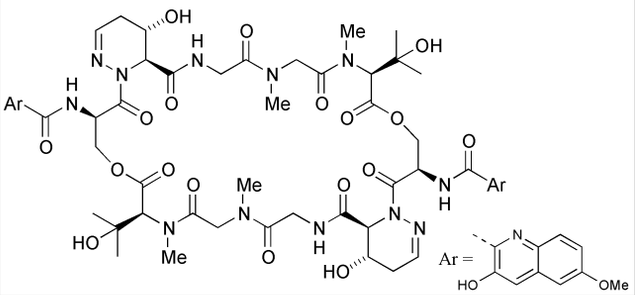


Luzopeptin C

Biological activity: potent inhibitor of HIV replication at non-cytotoxic levels in human T-cells *in vitro*.

Key steps: macrocyclisation reaction *via* activation of a pentapeptide monomer.

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

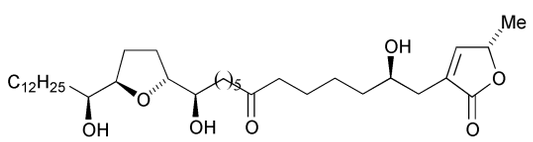


Mosin B

Biological activity: (a) isolated from the bark of *Annona squamosa*; (b) selective cytotoxic activity against the human pancreatic tumour cell line PACA-2.

Key steps: (a) asymmetric desymmetrisation of a σ-symmetric diol; (b) Nozaki–Hiyama–Kishi reaction.

N. Maezaki, N. Kojima, A. Sakamoto, C. Iwata and T. Tanaka, *Org. Lett.*, 2001, **3**, 429.

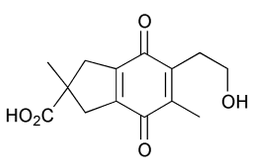


(±)-Puraquinonic Acid

Biological activity: (a) fungal metabolite produced by cultures of *Mycena pura*; (b) induces differentiation of HL-60 cells (human promyelocytic leukemia); (c) potential lead compound in the design of drugs to treat leukemia.

Key steps: Nazarov cyclisation.

D. L. J. Clive, M. Sannigrahi and S. Hisaindee, *J. Org. Chem.*, 2001, **66**, 954.

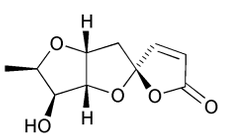


(+)-Pyrenolide D

Biological activity: cytotoxic towards HeLa cells

Key steps: oxidative ring contraction of a glycal with dimethoxyiodosylbenzene generated *in situ* to give a tetrahydrofuran ring.

K. M. Engstrom, M. R. Mendoza, M. Navarro-Villalobos and D. Y. Gin, *Angew. Chem., Int. Ed.*, 2001, **40**, 1128.

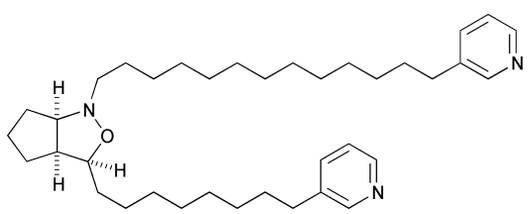


Pyrinodemin B

Biological activity: (a) isolated from *Amphimedon* sp. (b) cytotoxic.

Key steps: (a) two Pd(0)-catalysed cross coupling reactions; (b) stereoselective intramolecular 1,3-dipolar cycloaddition of a nitrone and an alkene.

B. B. Snider and B. Shi, *Tetrahedron Lett.*, 2001, **42**, 1639.

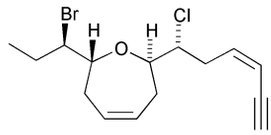


(+)-Rogioloxepane A

Biological activity: (a) isolated from *L. microcladia*; (b) biological activity not reported.

Key steps: (a) three stereoselective epoxidation/epoxide opening sequences; (b) stereo- and regioselective cyclisation of a hydroxy epoxide promoted by $(Bu_3Sn)_2O/Zn(OTf)_2$ to construct the α,ω-*trans*-disubstituted oxepine skeleton.

R. Matsumura, T. Suzuki, H. Hagiwara, T. Hoshi and M. Ando, *Tetrahedron Lett.*, 2001, **42**, 1543.

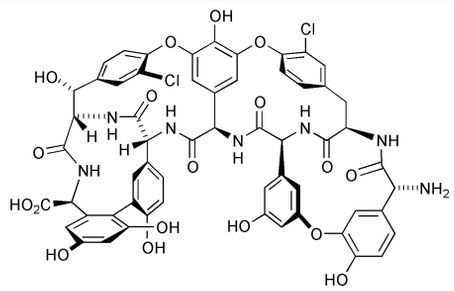


Teicoplanin aglycone

Biological activity: antibiotic with greater potency and lower toxicity than vancomycin.

Key steps: (a) nucleophilic substitution macrocyclisation using an *o*-fluoronitroarene to generate a 16-membered biaryl ether ring; (b) macrolactamisation to construct a 12-membered biaryl ether ring.

D. L. Boger, S. H. Kim, Y. Mori, J.-H. Weng, O. Rogel, S. L. Castle and J. J. McAtee, *J. Am. Chem. Soc.*, 2001, **123**, 1862.

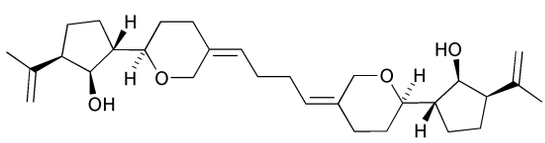


(+)-Testudinariol A

Biological activity: (a) isolated from the skin and mucus of the marine mollusc *Pleurobrancus testudinarius*; (b) ichthyotoxic against *Gambusia affinis*; (c) potential defensive allomone of *P. testudinarius*.

Key steps: (a) (*E*)-selective Horner–Wadsworth–Emmons olefination; (b) intramolecular Michael-type cyclisation; (c) stereoselective ene reaction using Me_2AlCl; (d) (*Z*)-selective olefination of a ketone using a chiral phosphonoacetate.

H. Takikawa, M. Yoshida and K. Mori, *Tetrahedron Lett.*, 2001, **42**, 1527.

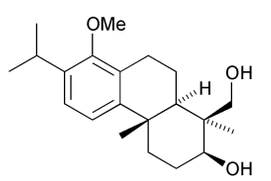


(+)-Triptocallol

Biological activity: isolated from tissue cultures of *Tripterygium wilfordii*.

Key steps: $Mn(OAc)_3$ mediated asymmetric radical cyclisation of a β-keto ester employing a chiral auxiliary.

D. Yang, M. Xu and M.-Y. Bian, *Org. Lett.*, 2001, **3**, 111.

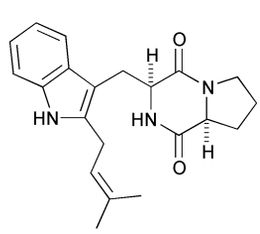


Tryprostatin B

Biological activity: (a) isolated from *Aspergillus fumingatus*; (b) prevents the interaction between microtubule-associated proteins with the carboxy-terminal domain of tubulin.

Key steps: acid-induced cyclization with concomitant cleavage of a solid phase silyl linker.

B. Wang, L. Chen and K. Kim, *Tetrahedron Lett.*, 2001, **42**, 1463.



Yersiniabactin

Biological activity: (a) siderophore produced by the Gram-negative coccoid bacterium *Yersinia enterocolitica*; (b) biological activity not reported.

Key steps: cyclisation reaction of a β-hydroxythioamide using Burgess reagent to form a thiazoline with retention of stereochemistry.

A. Ino and A. Murabayashi, *Tetrahedron*, 2001, **57**, 1897.