Perkin 1 Abstracts: Natural Product Synthesis

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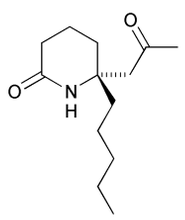
Perkin 1 Abstracts: Natural Product Synthesis aims to highlight syntheses that have been recently published. It includes brief descriptions of *biological activity* and *key steps*. A more comprehensive list of Natural Product syntheses and isolations can be found in *Natural Product Updates*.

(–)-Adalinine

Biological activity: (a) isolated from the secretion of the European two-spotted ladybird beetle, *Adalia bipunctata*; (b) biological activity not reported.

Key steps: (a) stereoselective Michael addition; (b) samarium iodide-promoted regioselective carbon-nitrogen bond cleavage reaction.

T. Honda and M. Kimura, *Org. Lett.*, 2000, **2**, 3925.

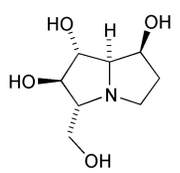


Australine

Biological activity: (a) isolated from the genera *Castanospermum* and *Alexa*; (b) glucosidase inhibitor; (c) antiviral; (d) retroviral.

Key steps: (a) enzymatic aldol reaction; (b) bis-reductive amination; (c) asymmetric epoxidation of a divinyl carbinol.

A. Romero and C.-H. Wong, *J. Org. Chem.*, 2000, **65**, 8264.

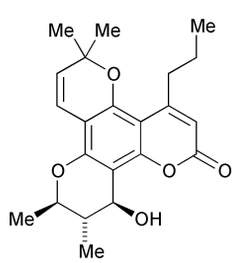


(+)-Calanolide A

Biological activity: (a) isolated from *Calophyllum lanigerum* var. *austrocoriaceum* (Guttiferae); (b) a potent anti HIV-1 active coumarin.

Key steps: (a) (–)-quinine-catalysed asymmetric intramolecular oxo-Michael addition; (b) MgI_2-mediated *syn-anti* isomerisation.

T. Tanaka, T. Kumamoto and T. Ishikawa, *Tetrahedron Lett.*, 2000, **41**, 10229.

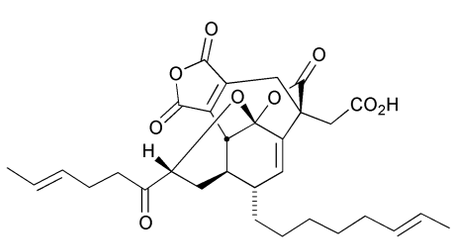


CP-262,114 and CP-225,917

Biological activity: (a) cholesterol lowering properties through inhibition of squalene synthase; (b) farnesyl transferase inhibitor.

Key steps: (a) Heck and aldol reactions on cyclohexenone to generate a 7-membered ring; (b) addition of a metallated dithiane to an aldehyde.

Q. Tan and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2001, **39**, 4509.

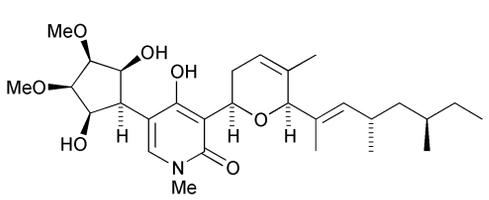


3′*O*,4′*O*-Dimethylfuniculosin

Biological activity: (a) isolated from the fermentation broth of *Penicillium funiculosium*; (b) potent antifungal agent; (c) modest antitumour agent; (d) *in vitro* activity against Herpes simplex virus (strain HF) and Newcastle disease virus.

Key steps: (a) asymmetric conjugate addition using a Yamamoto organocopper reagent to establish the 1,3-*anti*-dimethyl array; (b) Mosher asymmetric reduction; (c) Saegusa oxidation-cyclisation.

D. R. Williams, P. D. Lowder and Y.-G. Gu, *Tetrahedron Lett.*, 2000, **41,** 9397.

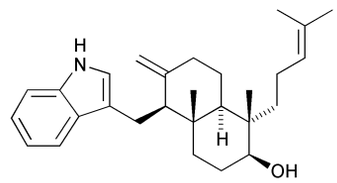


(+)-Emindole SA

Biological activity: (a) isolated from *Emericella striata*; (b) tremorgenic.

Key steps: Lewis acid-promoted polyene cyclisation.

J. D. Rainier and A. B. Smith III, *Tetrahedron Lett.*, 2000, **41**, 9419.

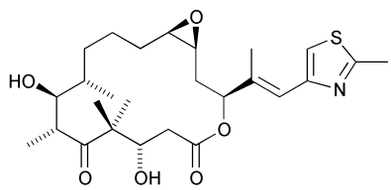


Epothilone A

Biological activity: induces tubulin polymerisation and microtubule stabilisation.

Key steps: (a) Lewis acid mediated electrophilic substitution of a chiral crotylsilane by an aldehyde; (b) kinetic resolution of an allylic alcohol using a lipase.

B. Zhu and J. S. Panek, *Org. Lett.*, 2000, **2**, 2575.

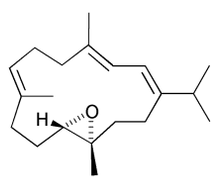


(+)-11,12-Epoxy-11,12-dihydrocembrene-C

Biological activity: (a) isolated from the Australian tropical marine soft coral *Sinularia grayi*; (b) oxidative metabolite.

Key steps: (a) intramolecular McMurray coupling; (b) Sharpless asymmetric epoxidation.

Z. Liu, W. Z. Li, L. Peng, Y. Li and Y. Li, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4250.

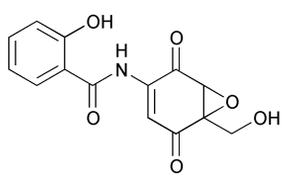


(±)-Epoxyquinomycin B

Biological activity: anti-inflammatory.

Key steps: oxidation of an anilide to a *p*-quinone with IBX.

K. C. Nicolaou, K. Sugita, P. S. Baran and Y.-L. Zhong, *Angew. Chem., Int. Ed.*, 2001, **40**, 207.

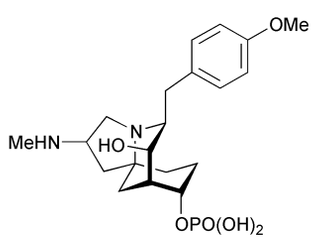


FR901483

Biological activity: immunosuppressant.

Key steps: (a) oxidative azaspiroannulation, (b) aldol cyclisation.

G. Scheffer, H. Seike and E. J. Sorenson, *Angew. Chem., Int. Ed.*, 2001, **39**, 4593.

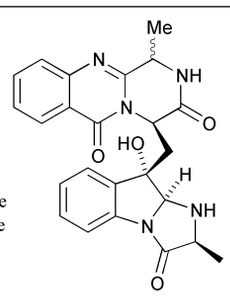


(–)-Fumiquinazoline A and B

Biological activity: (a) isolated from a strain of *Aspergillus fumigatus* from the gastrointestinal tract of the fish *Pseudolabrus japonicus*; (b) moderately cytotoxic.

Key steps: (a) Pd-catalysed cyclisation of an iodoindole carbamate to construct the imidazoindolone moiety; (b) dehydrative cyclisation of a diamide followed by rearrangement through an amidine to construct the quinazolone moiety.

B. B. Snider and H. Zeng, *Org. Lett.*, 2000, **2**, 4103.



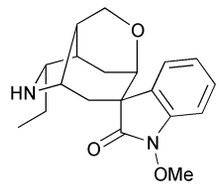
Fumiquinazoline A : α-Me
Fumiquinazoline B : β-Me

ent-Gelsedine

Biological activity: (a) isolated from Carolina jasmine (*Gelsemium sempervirens*); (b) biological activity not reported.

Key steps: iodide-promoted intramolecular reaction of an allene with an *N*-acyliminium ion intermediate to yield a bicyclic vinyl iodide.

W. G. Beyersbergen van Henegouwen, R. M. Fieseler, F. P. J. T. Rutjes and H. Hiemstra, *J. Org. Chem.*, 2000, **65**, 8317.

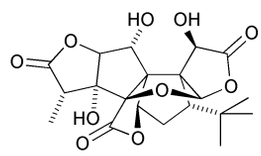


(±)-Ginkolide B

Biological activity: potent platelet activating factor (PAF) antagonist.

Key steps: (a) intramolecular photocycloaddition of a cyclopentenone with a furan generates a tetracyclic cyclobutane; (b) cyclobutane cleavage generates two adjacent spirocyclic centres.

M. T. Crimmins, J. M. Pace, P. G. Nantermet, A. S. Kim-Meade, J. B. Thomas, S. H. Watterson and A. S. Wagman, *J. Am. Chem. Soc.*, 2000, **122**, 8453.

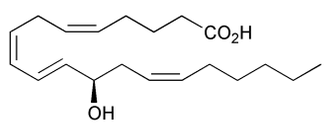


12(*R*)-HETE

Biological activity: (a) formed *via* the cytochrome P-450 pathway; (b) present in high concentration in psoriasis lesions.

Key steps: (a) Jacobsen hydrolytic kinetic resolution of racemic TES-glycidol with salen-Co catalyst; (b) regioselective Swern oxidation of a primary TES ether.

A. Rodríguez, M. Nomen, B. W. Spur, J. J. Godfroid and T. H. Lee, *Tetrahedron*, 2001, **57**, 25.

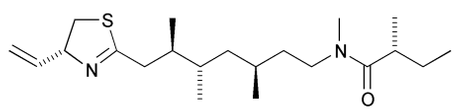


(+)-Kalkitoxin

Biological activity: (a) isolated from the marine cyanobacterium *Lyngbya majuscula*; (b) ichthyotoxic to *Carassius auratus* (LC_{50} 700 nM); (c) toxic to *Artemia salina* (LC_{50} 170 nM); (d) inhibits cell division in a fertilised sea urchin embryo assay (IC_{50} ~25 nM); (e) neurotoxic activity against a primary cell culture of rat neurons (LC_{50} 3.86 nM).

Key steps: (a) Horner–Emmons reaction; (b) asymmetric conjugate addition.

M. Wu, T. Okino, L. M. Nogle, B. L. Marquez, R. T. Williamson, N. Sitachitta, F. W. Berman, T. F. Murray, K. McGough, R. Jacobs, K. Colsen, T. Asano, F. Yokokawa, T. Shioiri and W. H. Gerwick, *J. Am. Chem. Soc.*, 2000, **122**, 12041.

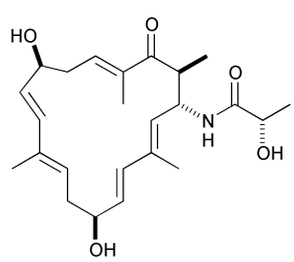


Lankacyclinol

Biological activity: antitumour activity against L1210 leukemia, B16 melanoma and solid lymphosarcoma cells.

Key steps: (a) asymmetric crotylboration; (b) ring closing metathesis; (c) modified Julia olefination to generate a diene; (d) intramolecular Horner–Wadsworth–Emmons olefination to generate the macrocyclic ring.

D. R. Williams, G. S. Cortez, S. L. Bogen and C. M. Rojas, *Angew. Chem., Int. Ed.*, 2001, **39**, 4612.

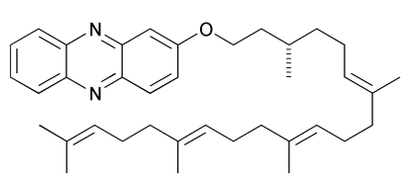


(*S*)-Methanophenazine

Biological activity: (a) isolated from the cytoplasmic membranes of *Methanosarcina mazei* Gö1; (b) an electron carrier in the enzyme catalysed heterodisulfide reduction with either H_2 or $F_{420}H_2$.

Key steps: Pd(0)-catalysed cross coupling of an organozinc reagent and a vinyl iodide.

U. Beifuss and M. Tietze, *Tetrahedron Lett.*, 2000, **41**, 9759.

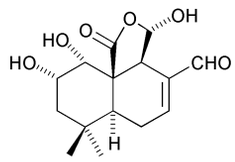


(–)-Mniopetal E

Biological activity: (a) isolated from the fermentation broth of a Canadian *Mniopetalum* sp. 87256; (b) inhibits the reverse transcriptase of HIV-1.

Key steps: (a) Horner–Emmons reaction; (b) intramolecular Diels–Alder reaction; (c) transformation of γ-lactone moiety to the γ-hydroxy-γ-lactone.

Y. Suzuki, R. Nishimaki, M. Ishikawa, T. Murata, K.-I. Takao and K.-I. Tadano, *J. Org. Chem.*, 2000, **65**, 8595.

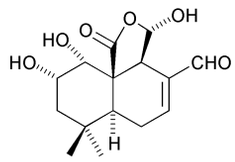


(–)-Mniopetal E

Biological activity: (a) isolated from the fermentation broth of a Canadian *Mniopetalum* sp. 87256; (b) inhibits the reverse transcriptase of HIV-1.

Key steps: (a) lithium phenyl selenide induced Baylis–Hillman reaction; (b) intramolecular asymmetric Diels–Alder reaction using a menthol chiral auxiliary; (c) a new variant of the Parikh–Doering oxidation.

J. Jauch, *Synlett*, 2001, 87.

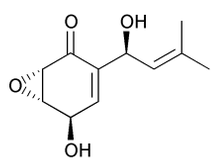


Panepoxydone

Biological activity: (a) secondary metabolite isolated from the basidiomycete *Panus conchatus*; (b) potent NF-κB inhibitor.

Key steps: (a) stereoselective reduction of ketone; (b) deprotection of a TBS group employing TREAT-HF.

J. B. Shotwell, S. Hu, E. Medina, M. Abe, R. Cole, C. M. Crews and J. L. Wood, *Tetrahedron Lett.*, 2000, **41**, 9639.

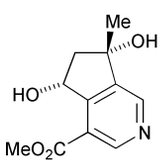


(–)-Plectrodorine

Biological activity: (a) isolated from the aerial parts of *Plectronia odorata* (Rubiaceae); (b) biological activity not reported.

Key steps: construction of the cyclopenta[*c*]pyridine skeleton by an intramolecular oxazole-olefin Diels–Alder reaction.

M. Ohba, R. Izuta and E. Shimizu, *Tetrahedron Lett.*, 2000, **41**, 10251.

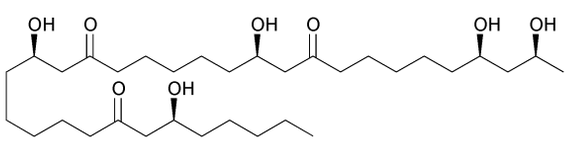


PM-Toxin B

Biological activity: (a) produced by the fungal pathogen *Phyllosticta maydis*; (b) corn host-specific pathotoxin.

Key steps: (a) cross-aldol coupling of four key segments; (b) organoselenium-mediated regioselective reductive cleavage of three α,β-epoxy ketone units.

M. Hosaka, H. Hayakawa and M. Miyashita, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4227.

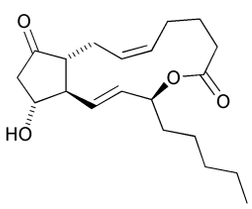


(–)-Prostaglandin E_2-1,15-lactone

Biological activity: (a) produced by the marine nudibranch *Tethys fimbria*; (b) plays an important role in the chemical defence mechanism of *T. fimbria*; (c) ichtyotoxin against the mosquito fish *Gambusia affinis* at concentrations of 1-10 μg mL^{-1}

Key steps: (a) macrocyclisation *via* ring-closing alkyne metathesis; (b) Lindlar reduction.

A. Fürstner, K. Grela, C. Mathes and C. W. Lehmann, *J. Am. Chem. Soc.*, 2000, **122**, 11799.

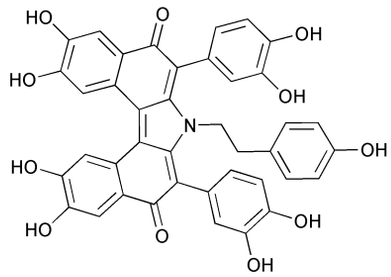


Purpurone

Biological activity: (a) isolated from an Indopacific sponge of the genus *Iotrochota*; (b) potent ATP-citrate lyase inhibitor (IC_{50}=25 μg mL^{-1}).

Key steps: Friedel–Crafts alkylation in the presence of acidic alumina.

C. Peschko and W. Steglich, *Tetrahedron Lett.*, 2000, **41**, 9477.

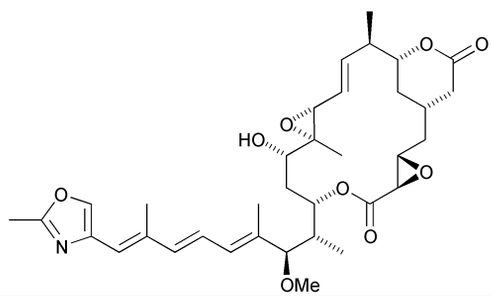


Rhizoxin D

Biological activity: potent antitumor agent including activity against vincristine- and adriamycin-resistant cells; antifungal and antibiotic activity.

Key steps: (a) two Julia olefinations; (b) Horner–Wadsworth–Emmons macrocyclisation; (c) catalytic asymmetric allylation.

G. E. Keck, C. A. Wager, T. T. Wager, K. A. Savin, J. A. Covel, M. D. McLaws, D. Krishnamurthy and V. J. Cee, *Angew. Chem., Int. Ed.*, 2001, **40**, 231.

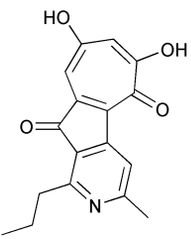


Rubrolone Aglycon

Biological activity: not reported.

Key steps: (a) intramolecular Diels–Alder reaction involving 4π participation of an *O*-alkyl α,β-unsaturated oxime; (b) *exo* selective Diels–Alder reaction of a cyclopropenone ketal; (c) electrocyclic rearrangement.

D. L. Boger, S. Ichikawa and H. Jiang, *J. Am. Chem. Soc.*, 2000, **122**, 12169.

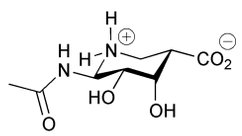


Siastatin B

Biological activity: (a) isolated from a *Streptomyces* culture; (b) sialidase inhibitor.

Key steps: (a) bromo-β-lactonisation; (b) *N*-acyliminium azidation.

S. Knapp and D. Zhao, *Org. Lett.*, 2000, **2**, 4037.

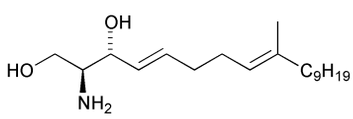


(4*E*,8*E*)-9-Methylsphinga-4,8-dienine

Biological activity: not reported.

Key steps: construction of the 1,5-diene unit *via* a S_N2'-type homoallylic coupling reaction between a thioether-stabilised allylic copper reagent and an allylic mesylate.

X.-Z. Wang, Y.-L. Wu, S. Jiang and G. Singh, *J. Org. Chem.*, 2000, **65**, 8146.

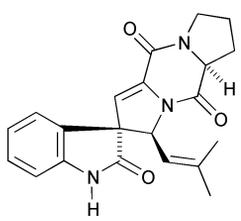


(–)-Spirotryprostatin B

Biological activity: inhibits G2/M phase progression of the mammalian cell cycle at micromolar concentrations.

Key steps: intramolecular Heck reaction to generate the spiroindolone ring system.

L. E. Overman and M. D. Rosen, *Angew. Chem., Int. Ed.*, 2000, **39**, 4596.

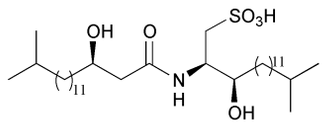


Sulfobactin A

Biological activity: (a) isolated from the culture broth of *Chryseobacterium* sp. (*Flavobacterium* sp.) NR 2993; (b) an inhibitor of the binding of von Willebrand factor to the GPIb/IX receptors (IC_{50s} = 0.47 μM); (c) an inhibitor of DNA polymerase α.

Key steps: (a) asymmetric aldol reaction of the Schiff base derived from a glycine ester and (+)-2-hydroxypinan-3-one; (b) an Noyori asymmetric hydrogenation.

T. Shioiri and N. Irako, *Tetrahedron*, 2000, **56**, 9129.

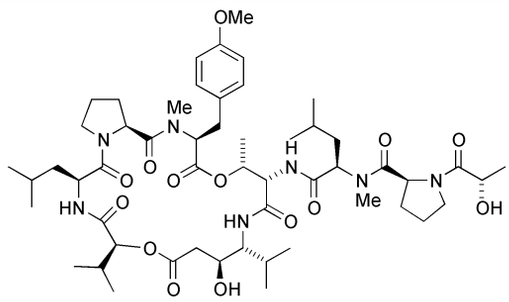


(–)-Tamandarin B

Biological activity: metabolite of an unidentified didemnid ascidian found on a shallow-water reef.

Key steps: (a) diastereoselective ketone reduction; (b) condensation of an activated pentafluorophenyl ester with the lithium enolate of methyl acetate; (c) HATU-promoted cyclisation; (d) DEPBT-promoted coupling reaction.

M. M. Joullié, P. Portonovo, B. Liang and D. J. Richard, *Tetrahedron Lett*., 2000, **41**, 9373.

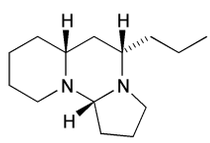


Tetraponerine T4

Biological activity: (a) isolated from the venom of the New Guinean ant *Tetraponera* sp.; (b) major constituent of the contact poison that attacks the nervous system of ants.

Key steps: (a) Pd-catalysed domino allylation; (b) Ru-catalysed ring rearrangement, in which a carbocycle is transformed into a heterocycle product by an intramolecular ring-opening–ring-closing domino metathesis.

R. Stragies and S. Blechert, *J. Am. Chem. Soc.*, 2000, **122**, 9584.

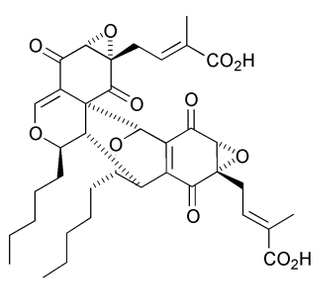


(±)-Torreyanic Acid

Biological activity: cytotoxic to tumour cells and 5-10 times more potent in cell lines that are sensitive to protein kinase C.

Key steps: biomimetic synthesis featuring a [4+2] dimerisation of diastereoisomeric 2*H*-pyran monomers.

C. Li, E. Lobkovsky and J. A. Porco, *J. Am. Chem. Soc.*, 2000, **22**, 10484.

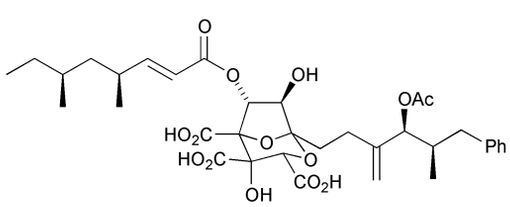


(+)-Zaragozic acid A

Biological activity: potent inhibitor of squalene synthase.

Key steps: acetal [1,2] Wittig rearrangement.

K. Tomooka, M. Kikuchi, K. Igawa, M. Suzuki, P.-H. Keong and T. Nakai, *Angew. Chem., Int. Ed.*, 2001, **39**, 4502.



(+)-Zaragozic acid C

Biological activity: potent inhibitor of squalene synthase.

Key steps: (a) double Sharpless asymmetric dihydroxylation reaction of a diene; (b) dithiane monosulfoxide anion mediated coupling reaction; (c) acid-mediated simultaneous acetonide deprotection–dithiane removal–ketalisation; (d) triple oxidation to install the tricarboxylic acid.

A. Armstrong, P. A. Barsanti, L. H. Jones and G. Ahmed, *J. Org. Chem.*, 2000, **65**, 7020.