Perkin 1 Abstracts: Natural Product Synthesis

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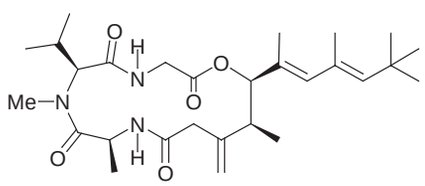
Perkin 1 Abstracts: Natural Product Synthesis aims to highlight syntheses that have been recently published. It includes brief descriptions of *biological activity* and *key steps*. A more comprehensive list of Natural Product syntheses and isolations can be found in *Natural Product Updates*

Antillatoxin

Biological activity: ichthyotoxic metabolite from the marine cyanobacterium *Lyngbya majuscula* (LD_{50} = 0.05 μg/mL).

Key steps: (a) Suzuki coupling reaction; (b) use of Evans' chiral auxiliary; (c) Stille-Horner olefination; (d) macrolactamisation.

F. Yokokawa and T. Shioiri, *J. Org. Chem.*, 1998, **63**, 8638.

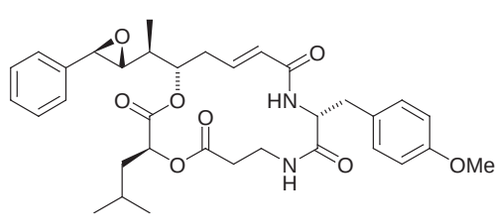


Arenastatin A

Biological activity: Potent cytotoxic activity; IC_{50} = 5 pg/ml in KB cells.

Key steps: (a) Stille coupling; (b) Takai reaction with iodoform; (c) Wittig reaction; (d) a diisopropylcarbodiimide mediated coupling of a hydroxy ester with an amino acid derivative.

J. D. White, J. Hong, and L. A. Robarge, *Tetrahedron Lett.*, 1998, **39**, 8779.

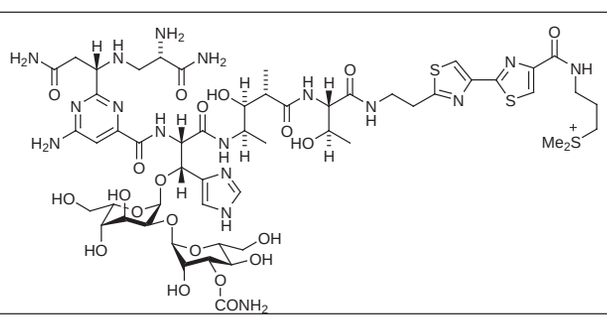


Bleomycin A_2

Biological activity: antibiotic and antitumour agent

Key steps: use of glycosyl trichloroacetimidates in the synthesis of the disaccharide unit.

K. Kitano, H. An, Y. Aoyagi, M. Overhand, S. J. Sucheck, W. C. Stevens, C. D. Hess, X. Zhou and S. M. Hecht, *J. Am. Chem. Soc.*, 1998, **120**, 11285.

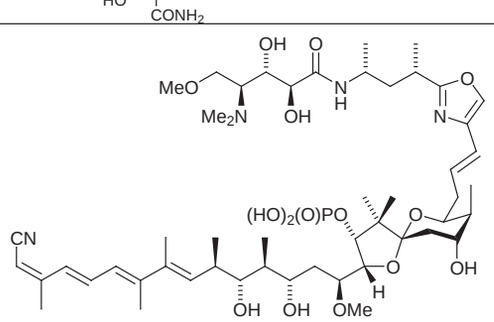


Calyculin C

Biological activity: serine/threonine phosphatase inhibitor.

Key steps: the reagent-controlled Brown crotylboration is subverted by remote protecting groups.

A. K. Ogawa and R. W. Armstrong, *J. Am. Chem. Soc.*, 1998, **120**, 12435.

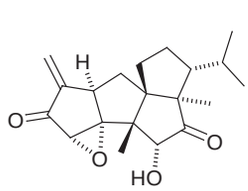


Crinipellin B

Biological activity: antibiotic active against gram-positive bacteria, yeasts, filamentous fungi, and Ehrlich carcinoma ascites cells.

Key steps: arene-alkene *meta*-photocycloaddition reaction.

P. A. Wender and T. M. Dore, *Tetrahedron Lett.*, 1998, **39**, 8589.

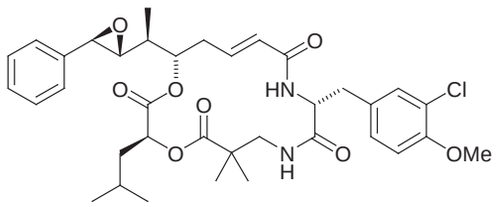


Cryptophycin 52

Biological activity: the cryptophycin macrolides exhibit a broad range of antitumour activity.

Key steps: stereoselective production of a homoallylic alcohol from an aldehyde and a crotylboron reagent.

U. P. Dhokte, V. V. Khau, D. R. Hutchison and M. J. Martinelli, *Tetrahedron Lett.*, 1998, **39**, 8771.

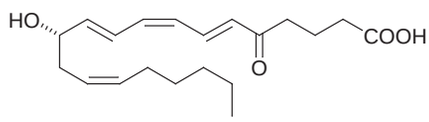


5-Oxo-12(*S*)-hydroxy-6(*E*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoic acid (5-oxo-12-HETE)

Biological activity: the title compound and its 8,9-*trans*-isomer are the result of a transcellular metabolism between neutrophils and platelets.

Key steps: Wittig condensation of a tris(3-methoxyphenyl)phosphonium bromide and an aldehyde to construct the 8,9-*cis* double bond.

S. P. Khanapure, W. S. Powell and J. Rokach, *J. Org. Chem.*, 1998, **63**, 8976.

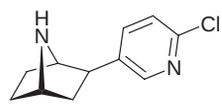


Epibatidine

Biological activity: potent non-opioid analgesic activity.

Key steps: cycloaddition of an *N*-protected pyrrole with ethynyl *p*-tolyl sulfone to prepare the azabicyclo[2.2.1] skeleton.

G. M. P. Giblin, C. D. Jones and N. S. Simpkins, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3689.

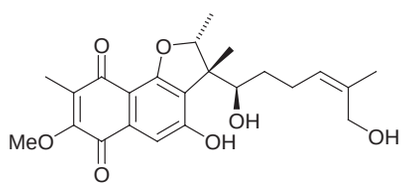


Furoquincocin A

Biological activity: cytotoxic activity against HeLa S3 and B16 melanoma cells.

Key steps: (a) 1,2-shift of a Co-complexed alkyne unit to generate a quaternary centre triggered by electrophilic cleavage of an oxirane; (b) Pd-catalysed cyclisation of a homopropargylic alcohol to give a dihydrofuran; (c) generation of a dihydrofuranonaphthalene ring by electrophilic cyclisation of an anhydride onto a dihydrofuran. Furoquinocins B, D and H were also synthesised.

T. Saito, T. Suzuki, M. Morimoto, C. Akiyama, T. Ochiai, K. Takeuchi, T. Matsumoto and K. Suzuki, *J. Am. Chem. Soc.*, 1998, **120**, 11633.

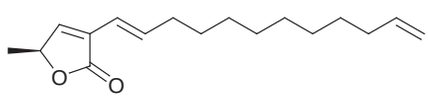


(+)-Hamabiwalactone B

Biological activity: isolated from the roots of the Japanese plant *Litsea Japonica*; the biological activity is not reported.

Key steps: Stille coupling of a stannylfuranone and an iodoalkene.

A. M. E. Richecoeur and J. B. Sweeney, *Tetrahedron Lett.*, 1998, **39**, 8901.

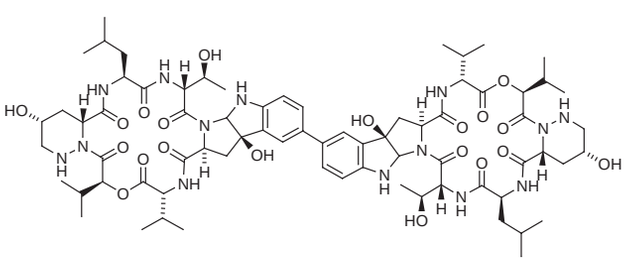


Himastatin

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. J. Kamenecka and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 1998, **37**, 2995.

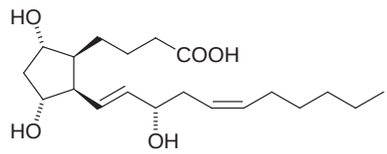


$iPF_{2\alpha}$-V

Biological activity: the synthetic title compound was used to identify its existence in urine : first proof of the existence of group V *in vivo*.

Key steps: Diels-Alder reaction.

Z. Pudukulathan, S. Manna, S.-W. Hwang, S. P. Khanapure, J. A. Lawson, G. A. FitzGerald and J. Rokach, *J. Am. Chem. Soc.*, 1998, **120**, 11953.

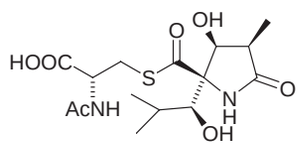


(+)-Lactacystin

Biological activity: (a) first non-protein neurotrophic factor; (b) displays neurotrophic activity to induce differentiation and neuritogenesis in a mouse neuroblastoma cell line (Neuro 2A cells) by irreversible inhibition of the 20S proteasome peptidase.

Key steps: (a) diastereoselective crotylboration of an aldehyde; (b) intramolecular mercurioamidation of an allylic trichloroacetimidate to introduce the three contiguous chiral centers of methyl, hydroxy, and amino substituents.

S. H. Kang, H.-S. Jun and J.-H. Youn, *Synlett*, 1998, 1045.

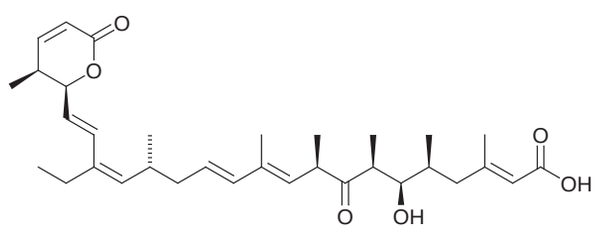


Leptomycin B

Biological activity: (a) antifungal antibiotic that inhibits a step for the initiation of DNA synthesis at the end of the G1 and G2 phase; (b) specifically binds chromosome maintenance region 1 (CRM1) protein and inhibits nuclear export signal (NES)-mediated transport of Rev and U snRNA protein.

Key steps: (a) Wittig reaction; (b) Evans' aldol reaction.

M. Kobayashi, W. Wang, Y. Tsutsui, M. Sugimoto and N. Murakami, *Tetrahedron Lett.*, 1998, **39**, 8291.

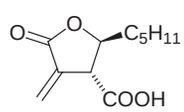


(–)-Methylenolactocin

Biological activity: (a) antibacterial; (b) antitumor.

Key steps: synthesis of α-methylene butyrolactones *via* tungsten-π-allyl complexes.

M. Chandrasekharam and R.-S. Liu, *J. Org. Chem.*, 1998, **63**, 9122.

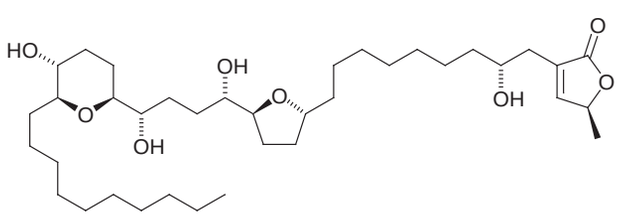


(–)-Mucocin

Biological activity: (a) antitumour agent; (b) inhibits oxygen uptake in rat liver mitochondria; (c) blocks the mitochondrial complex I (NADH-ubiquinone oxidoreductase) and inhibits the plasma membrane NADH oxidase.

Key steps: Sharpless asymmetric dihydroxylations and epoxidations were used to transform cyclododecatriene to the product in 20 steps

P. Neogi, T. Doundoulakis, A. Yazbak, S. C. Sinha, S. C. Sinha and E. Keinan, *J. Am. Chem. Soc.*, 1998, **120**, 11279.

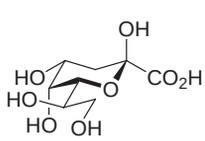


(+)-3-Deoxy-D-*manno*-2-octulosonic acid or (+)-KDO

Biological activity: not reported.

Key steps: (a) hydrolysis of a vinylogous urethane functionality; (b) stereoselective reduction of the resulting β-keto-lactone; (c) stereoselective dihydroxylation of the vinyl chain of a δ-lactone; (d) addition of α-ethoxyvinyllithium to a lactone carbonyl to produce the aldulosonic acid residue in the title compound upon ozonolysis.

R. H. Schlessinger and L. H. Pettus, *J. Org. Chem.*, 1998, **63**, 9089.

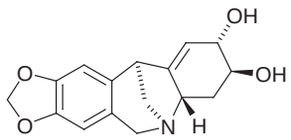


(±)-Pancracine

Biological activity: not reported.

Key steps: a 5-*exo*-*trig* radical cyclisation of *N*-(2-cyclohexenyl)-α–aryl-α-(phenylthio)acetamide.

M. Ikeda, M. Hamada, T. Yamashita, F. Ikegami, T. Sato and H. Ishibashi, *Synlett*, 1998, 1246.

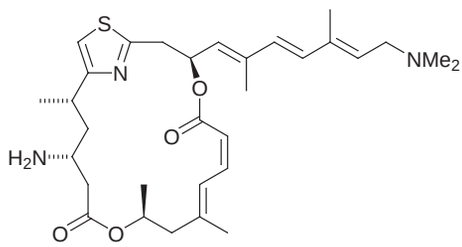


(–)-Pateamine

Biological activity: immunosuppressant

Key steps: (a) asymmetric aldol reactions using thiazolidinethione auxiliaries; (b) Noyori asymmetric catalytic hydrogenation of a β-keto ester; (c) Stille coupling to generate a diene; (d) asymmetric cuprate addition to an *N*-enoyloxazolidinone; (e) macrolactonisation *via* intramolecular attack of a hydroxy group on a β-lactam.

D. Romo, R. M. Rzasa, H. A. Shea, K. Park, J. M. Langenhan, L. Sun, A. Akhiezer and J. O. Liu, *J. Am. Chem. Soc.*, 1998, **120**, 12237.

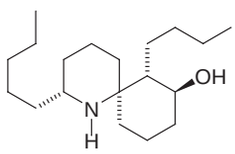


(–)-Perhydrohistrionicotoxin

Biological activity: has been used in studies of the mechanisms involved in transsynaptic transmission of neuromuscular impulses.

Key steps: photochemical reactions of chiral 2,3-dihydro-4(1*H*)-pyridone.

D. L. Comins, Y.-m. Zhang and X. Zheng, *Chem. Commun.*, 1998, 2509.

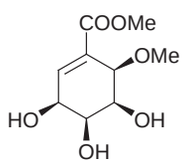


(+)-Pericosine B

Biological activity: antitumour agent with ED_{50} = 4μg/ml in the P388 lymphocytic leukaemia test system.

Key steps: Hydroxy-directed dihydroxylation using osmium tetroxide and an amine promoter.

T. J. Donohoe, K. Blades, M. Helliwell, M. J. Waring and N. J. Newcombe, *Tetrahedron Lett.*, 1998, **39**, 8755.

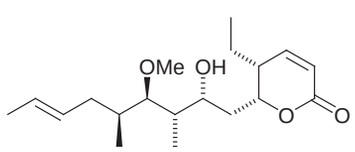


(–)-Pironetin

Biological activity: (a) immunosuppressive activity on the responses of T and B lymphocytes to mitogens; (b) potent plant growth regulator.

Key steps: skeleton formed *via* coupling of a dithiane and an epoxide.

H. Watanabe, H. Watanabe and T. Kitahara, *Tetrahedron Lett.*, 1998, **39**, 8313.

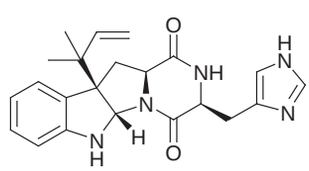


Roquefortine D

Biological activity: isolated from a culture of *Penicillium roqueforti*; its biological activity is not reported.

Key steps: (a) introduction of a reverse prenyl group *via* a selenide-mediated cyclisation-prenylation; (b) use of a photocleavable *o*-nitrobenzyl group in the protection of the histidine side chain.

W.-C. Chen and M. M. Joullié, *Tetrahedron Lett.*, 1998, **39**, 8401.

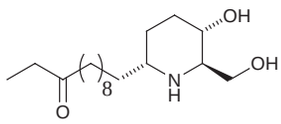


(+)-Prosopinine and (–)-Deoxoprosophylline

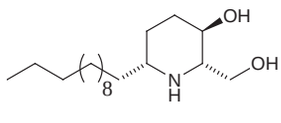
Biological activity: (a) antibiotic; (b) anesthetic.

Key steps: Rh-BIPHEPHOS complex-catalysed cyclohydrocarbonylation.

I. Ojima and E. S. Vidal, *J. Org. Chem.*, 1998, **63**, 7999.



(+)-Prosopinine



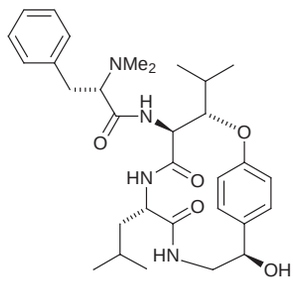
(–)-Deoxoprosophylline

Sanjoinine G1

Biological activity: (a) isolated from the seeds of *Zizphus Vulgaris* var. *spinosus* (Sanjoin); (b) the biologial activity is not reported.

Key steps: (a) an S_NAr reaction with 4-fluorobenzonitrile to form a key alkyl-aryl ether linkage; (b) macrocyclisation using a modified Schmidt protocol that involves an activated pentafluorophenyl ester.

S. P. East, F. Shao, L. Williams and M. M. Joullié, *Tetrahedron*, 1998, **54**, 13371.

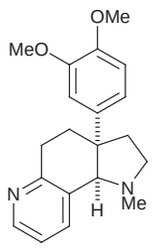


(+)-Sceletium A-4

Biological activity: not reported.

Key steps: three different methods for producing the enantiomerically pure intermediate 2-(3,4-dimethoxyphenyl)cyclohex-2-en-1-ol.

O. Yamada and K. Ogasawara, *Tetrahedron Lett.*, 1998, **39**, 7747.

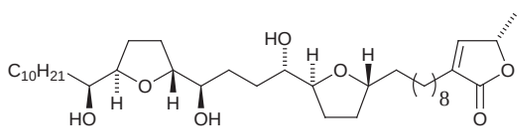


Squamostatin-D

Biological activity: cytotoxicity toward human tumor cell lines.

Key steps: (a) enantioselective addition of chiral oxygenated allylic tin and indium reagents to aldehydes; (b) addition of a functionalised organozinc reagent to an aldehyde in the presence of a chiral bis-sulfonamide-titanium catalyst.

J. A. Marshall and H. Jiang, *J. Org. Chem.*, 1998, **63**, 7066.

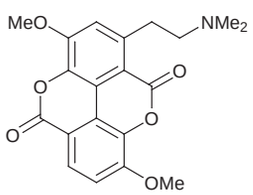


Taspine

Biological activity: (a) active ingredient in the sap of the *Croton lechleri* tree used by the Jivaro Indians of Peru to promote wound healing and to treat various maladies; (b) anti-inflammatory; (c) anti-ulcer; (d) cytotoxic activity; (e) inhibits viral DNA polymerase.

Key steps: (a) Ullmann coupling reaction ; (b) Stille coupling.

T. R. Kelly and R. L. Xie, *J. Org. Chem.*, 1998, **63**, 8045.

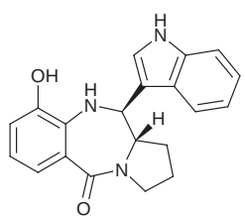


Tilivalline

Biological activity: cytotoxicity toward mouse leukemia L1210.

Key steps: (a) modified Curtius reaction; (b) stereoselective introduction of indole.

T. Nagasaka and Y. Koseki, *J. Org. Chem.*, 1998, **63**, 6797.

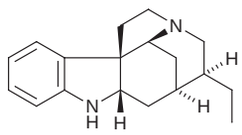


Tubifolidine

Biological activity: not reported.

Key steps: (a) asymmetric Michael addition using the heterobimetallic asymmetric catalyst (ALB-KO-*t*-Bu-MS 4Å); (b) one pot construction of the tetracyclic synthetic intermediates from the tricyclic intermediates using DDQ.

S. Shimizu, K. Ohori, T. Arai, H. Sasai and M. Shibasaki, *J. Org. Chem.*, 1998, **63**, 7547.

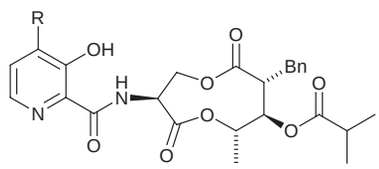


UK-2A and UK-3A

Biological activity: (a) strongly inhibit the growth of various types of yeast and filamentous fungi; (b) show very weak cytotoxic activity against several kinds of mammalian cells.

Key steps: (a) Evans aldol reaction; (b) an intramolecular Mitsunobu reaction.

M. Shimano, N. Kamei, T. Shibata, K. Inoguchi, N. Itoh, T. Ikari and H. Senda, *Tetrahedron*, 1998, **54**, 12745.



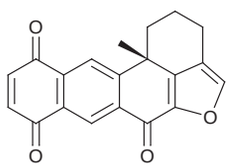
UK-2A : R = OMe
UK-3A : R = H

(+) -Xestoquinone

Biological activity: not reported.

Key steps: cascade-type asymmetric Heck reaction. Investigations carried out into the effect of the amount of silver salt required to produce the product in high yield and ee.

F. Miyazaki, K. Uotsu and M. Shibasaki, *Tetrahedron*, 1998, **54**, 13073.



(*S*)-Zearalenone

Biological activity: not reported.

Key steps: solid phase synthesis for the formation of macrocycles by a novel cyclorelease mechanism that employs the Stille coupling.

K. C. Nicalaou, N. Winssinger, J. Pastor and F. Murphy, *Angew. Chem. Int. Ed.*, 1998, **37**, 2534.