Perkin 1 Abstracts: Natural Product Synthesis

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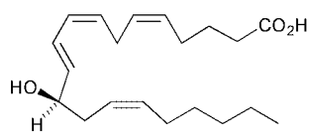
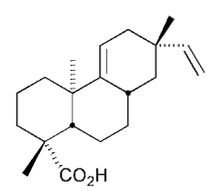
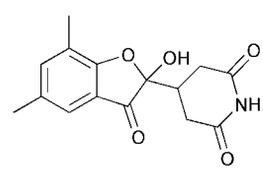
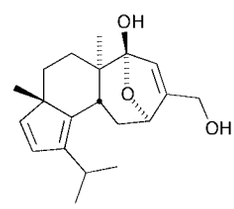
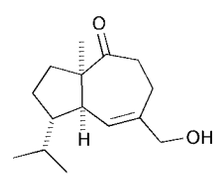
Perkin 1 Abstracts: Natural Product Synthesis aims to highlight syntheses that have been recently published. It includes brief descriptions of *biological activity* and *key steps*. A more comprehensive list of Natural Product syntheses and isolations can be found in *Natural Product Updates*.

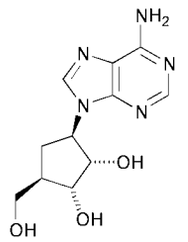
12(*R*)-Hydroxy-5(*Z*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoic acid *Biological activity*: implicated in angiogenesis, atherogenesis, coronary thrombosis, type 1 diabetes induction, inflammation, psoriasis and inhibition of apoptosis. *Key steps*: (a) Sharpless asymmetric dihydroxylation; (b) *trans*-selective Wittig reaction. X. Han and E. J. Corey, *Org. Lett.*, 2000, **2**, 2543.	
(–)-Acanthoic acid *Biological activity*: (a) isolated from the root bark of *Acanthopanax koreanum* Nakai; (b) antiinflammatory; (c) antifibrotic. *Key steps*: Diels–Alder cycloaddition. T. Ling, B. A. Kramer, M. A. Palladino and E. A. Theodorakis, *Org. Lett.*, 2000, **2**, 2073.	
Actiketal (RK-441S) *Biological activity*: (a) isolated from *Streptomyces pulveraceus* subsp. *epiderstagenes*; (b) antibiotic; (c) low cytotoxicity; (d) inhibitor of EGF-induced DNA formation in murine epithelial cell (100% at 1 μM); (e) inhibitor of Con A-induced blast formation in spleen cell (100% at 20 nM); (f) inhibitor towards the incorporation of [^{3}H]thymidine into epidermal growth factor-stimulated Balb/MK cells (IC_{50} 14.5 μM). *Key steps*: palladium-assisted oxidative coupling reaction of 5,7-dimethylbenzofuran and dimethyl glutaconate. H. Kiyota, Y. Shimizu and T. Oritani, *Tetrahedron Lett.*, 2000, **41**, 5887.	
Allocyathin B_3 *Biological activity*: (a) isolated from cultures of bird's nest fungi of the genus *Cyathus*; (b) biological activity not reported. *Key steps*: (a) radical cyclisation of a methyl propargyl acetal of an α-bromo ketone; (b) Pd-catalysed carbonylation of a vinyl triflate. D. E. Ward, Y. Gai and Q. Qiao, *Org. Lett.*, 2000, **2**, 2125.	
(+)-Aphanamol 1 *Biological activity*: (a) isolated as a minor toxic principal from the fruit peel of *Aphanamixis grandifolia*; (b) biological activity not reported. *Key steps*: (a) novel decarboxylative dehydration reaction; (b) Rh(I)-catalysed [5 + 2] cycloaddition of a vinylcyclopropane with a tetrasubstituted allene. P. A. Wender and L. Zhang, *Org. Lett.*, 2000, **2**, 2323.	

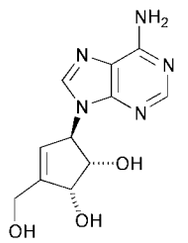
(–)-Aristeromycin and (–)-neplanocin A

Biological activity: antiviral agents owing to inhibition of *S*-adenosyl homocysteine hydrolase

Key steps: Pd(0)-catalysed enantioselective allylic amination of *cis*-3,5-dibenzoyloxycyclopent-2-ene.

B. M. Trost, R. Madsen, S. D. Guile and B. Brown, *J. Am. Chem. Soc.*, 2000, **122**, 5947.


(–)-Aristeromycin

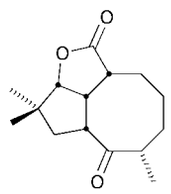

(–)-Neplanocin A

(±)-Asteriscanolide

Biological activity: (a) isolated from *Asteriscus aquaticus*; (b) biological activity not reported.

Key steps: (a) cobalt-mediated Pauson–Khand [2+2+1] cycloaddition; (b) ring-closing metathesis.

M. E. Krafft, Y.-Y. Cheung and C. A. Juliano-Capucao, *Synthesis*, 2000, **7**, 1020.

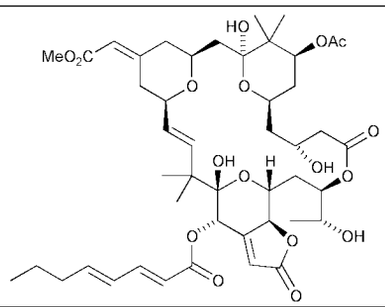


Bryostatin 3

Biological activity: (a) isolated from the marine bryozoa *Bugula neritina Linnaeus* and *Amathia convuluta*; (b) powerful antineoplastic activity; (c) activates protein kinase C without tumour promotion.

Key steps: stereoselective Horner–Wadsworth–Emmons reaction involving a novel BINOL-derived phosphonoacetate.

K. Ohmori, Y. Ogawa, T. Obitsu, Y. Ishikawa, S. Nishiyama and S. Yamamura, *Angew. Chem., Int. Ed.*, 2000, **39**, 2290.

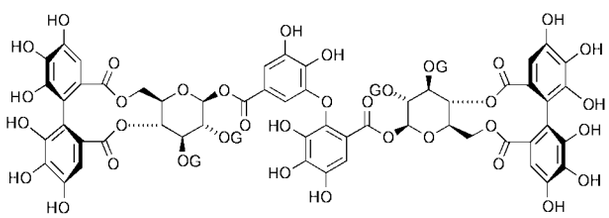


Coriariin A

Biological activity: tumour remissive properties possibly due to a host-mediated immunostimulatory response.

Key steps: (a) acylation of an electron-rich glucopyranosyl trichloroacetimidate with a sensitive dehydrogalloyl diacid; (b) double oxidative cyclisation to form the two biaryl linkages.

K. S. Feldman and M. D. Lawlor, *J. Am. Chem. Soc.*, 2000, **122**, 7396.

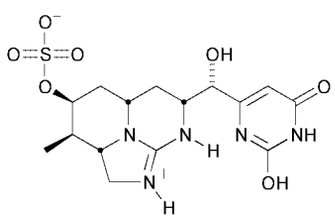

G = 3,4,5-trihydroxybenzoyl (galloyl)

(±)-Cylindrospermopsin

Biological activity: (a) isolated from the cyanobacterium *Cylindrospermopsis raciborskii*; (b) causative agent of hepatoenteritis.

Key steps: intramolecular nucleophilic displacement to generate the tetrahydropyrimidine ring.

C. Xie, M. T. C. Runnegar and B. B. Snider, *J. Am. Chem. Soc.*, 2000, **122**, 5017.

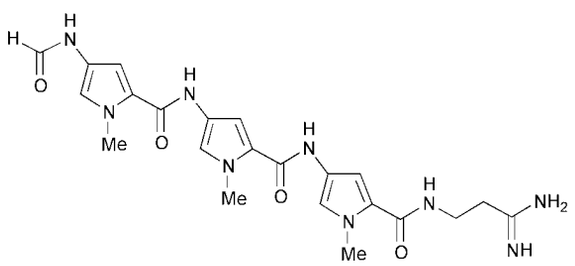


Distamycin A

Biological activity: DNA binding affinity.

Key steps: standard solution phase amide synthesis was used to synthesise distamycin A as well as a library of 2640 analogues. Compounds with 1000 times greater cytotoxicity than distamycin A were discovered.

D. L. Boger, B. E. Fink and M. P. Hedrick, *J. Am. Chem. Soc.*, 2000, **122**, 6382.

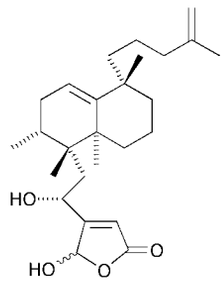


(±)-Dysidiolide

Biological activity: dysidiolide is a cdc25A protein phosphatase inhibitor and exhibits micromolar activity against A-549 human lung carcinoma and P388 murine leukemia cancer cell lines.

Key steps: (a) two radical deoxygenation reactions; (b) Eschenmoser–Claisen rearrangement to generate a quaternary carbon.

E. Piers, S. Caillé and G. Chen, *Org. Lett.*, 2000, **2**, 2483.

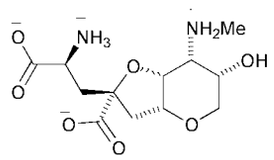


(–)-Dysiherbaine

Biological activity: selective agonist of non-*N*-methyl-D-aspartate type glutamate receptors in the central nervous system.

Key steps: (a) Sharpless asymmetric epoxidation of a symmetrical divinyl carbinol; (b) Jackson's protocol for the Pd(0)-catalysed coupling of the organozinc reagent derived from *N*-methoxycarbonyl-β-iodoalanine with a vinyl triflate.

H. Masaki, J. Maeyama, K. Kamada, T. Esumi, Y. Iwabuchi and S. Hatakeyama, *J. Am. Chem. Soc.*, 2000, **122**, 5216.

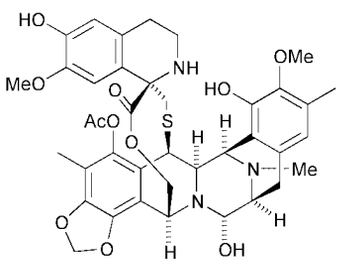


Ecteinascidin 743

Biological activity: antitumour agent.

Key steps: a synthesis of the title compound is described from cyanosafracin B which is available on kilogram scale by fermentation of *Pseudomonas fluorescens*.

C. Cuevas, M. Pérez, M. J. Martín, J. L. Chicharro, C. Fernández-Rivas, M. Flores, A. Francesch, P. Gallego, M. Zarzuelo, D. de la Calle, J. García, C. Polanco, I. Rodríguez and I. Manzanares, *Org. Lett.*, 2000, **2**, 2545.

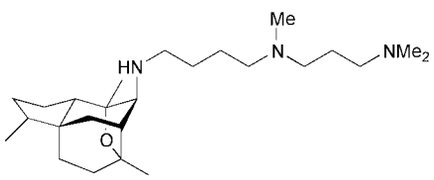


(±)-Hispidospermidin

Biological activity: phospholipase C inhibitor

Key steps: The carbocyclic rings were constructed using (a) an aldol reaction, (b) a Robinson annulation and (c) intramolecular carbomercuration involving addition of an enol silane to an alkyne.

A. J. Frontier, S. Raghavan and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2000, **122**, 6151.

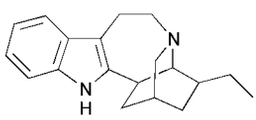


(–)-Ibogamine

Biological activity: not reported.

Key steps: (a) enantioselective and regioselective *endo* Diels–Alder reaction catalysed by (*S*)-BINOL $TiCl_2$; (b) Beckmann rearrangement; (c) Fischer indolisation reaction.

J. D. White and Y. Choi, *Org. Lett.*, 2000, **2**, 2373.

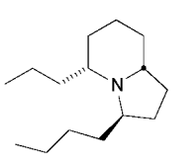


(–)-Indolizidine 223AB

Biological activity: (a) isolated from the skin of the neotropical dart-poison frogs of the genus *Dendrobates*; (b) biological activity not reported.

Key steps: two consecutive radical cyclisation reactions of β-aminoacrylate substrates.

E. Lee, E. J. Jeong, S. J. Min, S. Hong, J. Lim, S. K. Kim, H. J. Kim, B. G. Choi, and K. C. Koo, *Org. Lett.*, 2000, **2**, 2169.

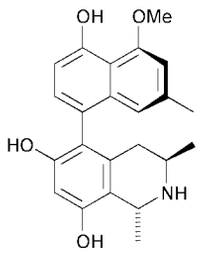


(–)-Korupensamine A

Biological activity: antimalarial.

Key steps: Pd(0)-catalysed Suzuki–Miyaura coupling of a planar chiral tricarbonylchromium-complexed bromoarene with a naphthylboronic acid.

T. Watanabe, M. Shakadou and M. Uemura, *Synlett*, 2000, 1141.

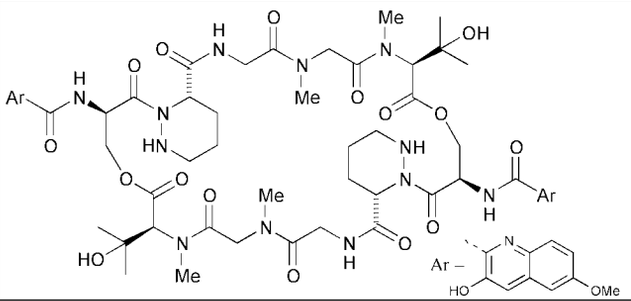


Luzopeptin E2

Biological activity: inhibit HIV reverse transcriptase at non-cytotoxic concentrations.

Key steps: closure of the 32-membered ring by macrolactamisation using a carbodiimide. (EDCI).

M. A. Ciufolini, D. Valognes and N. Xi, *Angew. Chem., Int. Ed.*, 2000, **39**, 2493.

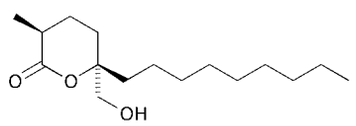


(+)-Malyngolide

Biological activity: (a) isolated from the alga *Lyngbya majuscula* Gomont; (b) antibiotic against pathogenic species belonging to genera such as *Staphylococcus*, *Mycobacterium*, *Pseudomonas* and other related genera.

Key steps: (a) Felkin–Anh diastereoselective allylation of a polyoxygenated ketone; (b) ring closing metathesis reaction employing Grubbs catalyst; (c) allylic oxidation of a dihydropyran with CrO_3 3,5-DMP complex to form an α,β-unsaturated δ-lactone.

M. Carda, E. Castillo, S. Rodríguez and J. A. Marco, *Tetrahedron Lett.*, 2000, **41**, 5511.

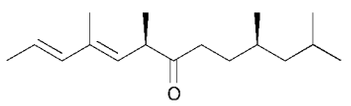


Matsuone

Biological activity: (a) isolated from the Japanese pine scale *Matsucoccus matsumurae* and the red pine scale *Matsucoccus resinosae*; (b) female sex pheromone.

Key steps: coupling of a Weinreb amide and a Grignard reagent.

S. Kurosawa, M. Takenaka, E. Dunkelblum, Z. Mendel and K. Mori, *ChemBioChem*, 2000, 1, 56.

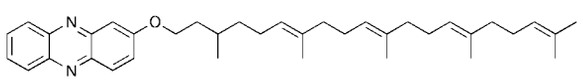


Methanophenazine

Biological activity: (a) isolated from membranes of *Methanosarcina mazei* Gö1; (b) mediates electron transport between membrane-bound enzymes.

Key steps: (a) Pd(0)-catalysed coupling of an organozinc compound and a vinyl iodide; (b) etherification of a mesylate and 2-hydroxyphenazine.

U. Beifuss, M. Tietze, S. Bäumer and U. Deppenmeier, *Angew. Chem., Int. Ed.*, 2000, **39**, 2470.

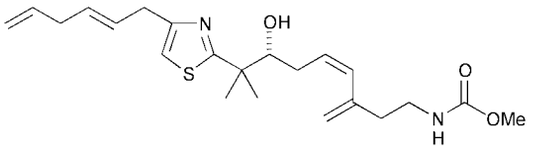


(–)-Mycothiazole

Biological activity: (a) isolated from *Spongia mycofijiensis*; (b) anthelmintic activity *in vitro*; (c) highly toxic to mice.

Key steps: (a) dehydrogenation of a thiazolidine to a thiazole using chemical manganese dioxide; (b) Nagao acetate aldol reaction of a chiral 1,3-thiazolidine-2-thione with an aldehyde; (c) construction of the conjugated diene by lithium and copper(I) mediated Stille coupling.

H. Sugiyama, F. Yokokawa and T. Shioiri, *Org. Lett.*, 2000, **2**, 2149.

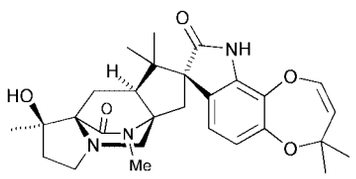


(–)-Paraherquamide A

Biological activity: (a) isolated from *Penicillium paraherquei*; (b) anthelminthic and antinematodal; (c) potential for treatment of intestinal parasites in animals.

Key steps: (a) intramolecular S_N2' alkylation of an enolate generates the 2,4-diazabicyclo[2.2.2]octane ring system; (b) oxidative rearrangement of an indole generates the spiro oxindole.

R. M. Williams, J. Cao and H. Tsujishima, *Angew. Chem., Int. Ed.*, 2000, **39**, 2540.

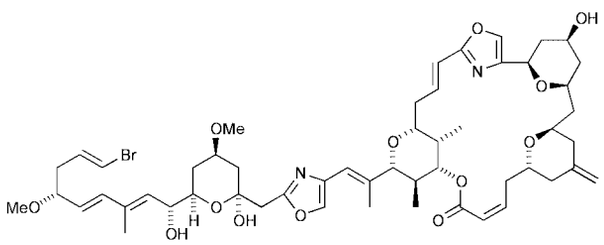


Phorboxazole B

Biological activity: Phorboxazole B isolated from an Indian Ocean sponge is a potent antimitotic agent which halts progression of the cell cycle during S phase.

Key steps: (a) Cu(II)-catalysed enantioselective aldol reaction using a Pybox ligand; (b) Sn(II)-catalysed enantioselective aldol reaction using a Box ligand; (c) modified Julia olefination.

D. A. Evans, V. J. Cee, T. E. Smith, D. M. Fitch and P. S. Cho, *Angew. Chem., Int. Ed.*, 2000, **39**, 2533; D. A. Evans and D. M. Fitch, *Angew. Chem., Int. Ed.*, 2000, **39**, 2536.

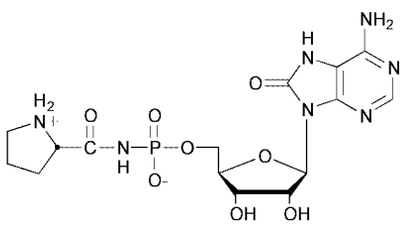


Phosmidosine A

Biological activity: (a) isolated from the fermentation broth of *Streptomyces* sp. strain RK-16; (b) antitumour activity; (c) significant growth inhibitory activities against various human cancer cell lines in the range of 8.8–190 μM.

Key steps: construction of the *N*-acyl phosphoramidate linkage by condensation of a 5′-*O*-phosphoramidite derivative with a prolinamide derivative in the presence of 5-(3,5-dinitrophenyl)-1*H*-tetrazole.

T. Moriguchi, N. Asai, T. Wada, K. Seio, T. Sasaki and M. Sekine, *Tetrahedron Lett.*, 2000, **41**, 5881.

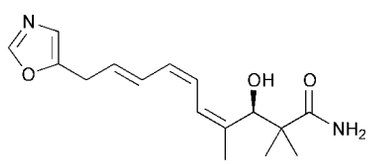


Phthoxazolin A

Biological activity: (a) potent herbicide; (b) low cytotoxicity to animal cells.

Key steps: (a) Heck coupling; (b) deboronation-iodination sequence with inversion of alkene stereochemistry; (c) Stille coupling.

N. Hénaff and A. Whiting, *Tetrahedron*, 2000, **56**, 5193.

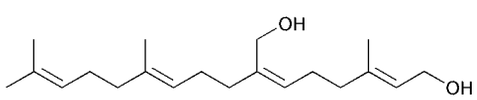


Plaunotol

Biological activity: (a) major component of the Thai folk medicinal plant *Plau-noi*; (b) antipeptic ulcer activity, (c) antibacterial activity against *Helicobacter pylori*.

Key steps: highly *Z*-selective trisubstituted Wittig olefination of aliphatic α-acetal ketones in the presence of a potassium base and 18-crown-6.

K. Tago, M. Arai and H. Kogen, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2073.

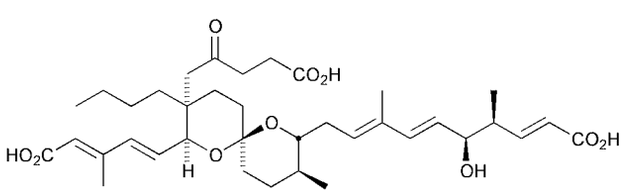


Reveromycin A

Biological activity: (a) isolated from the genus *Streptomyces*; (b) inhibitor of mitogenic activity induced by the epidermal growth factor in a mouse epidermal keratinocyte; (c) exhibit morphological reversion of src^{ts}-NRK cells; (d) antiproliferative against human tumour cell lines; (e) antifungal; (f) selective inhibitor of protein synthesis in eukaryotic cells.

Key steps: (a) stereocontrolled construction of the 6,6-spiroketal system; (b) succinylation of the *tert*-alcohol.

T. Shimizu, T. Masuda, K. Hiramoto, and T. Nakata, *Org. Lett.*, 2000, **2**, 2153.

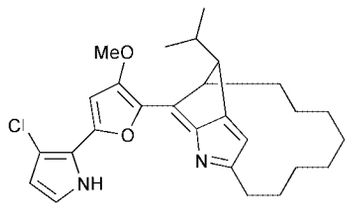


Roseophilin

Biological activity: antitumour agent.

Key steps: (a) Pt-catalysed enyne metathesis *via* a formal [2 + 2] cycloaddition to a cyclobutene followed by conrotatory ring opening; (b) installation of the isopropyl group using a Cu(I)-catalysed opening of a vinyl epoxide with i-PrMgCl; (c) Paal–Knorr reaction to install the pyrrole.

B. M. Trost and G. A. Doherty, *J. Am. Chem. Soc.*, 2000, **122**, 18021.

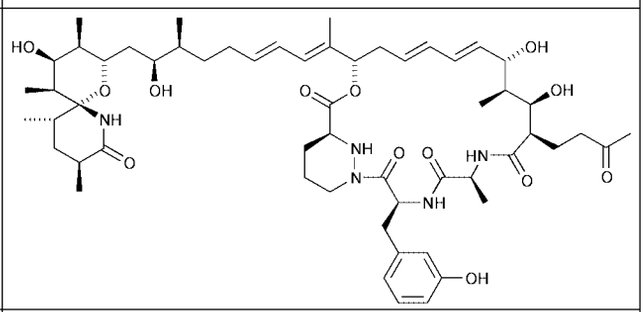


Sanglifehrin A

Biological activity: immunosuppressant.

Key steps: double Stille coupling to generate the two conjugated diene units.

K. C. Nicolaou, F. Murphy, S. Barluenga, T. Ohshima, H. Wei, J. Xu, D. L. F. Gray and O. Baudoin, *J. Am. Chem. Soc.*, 2000, **122**, 3830.

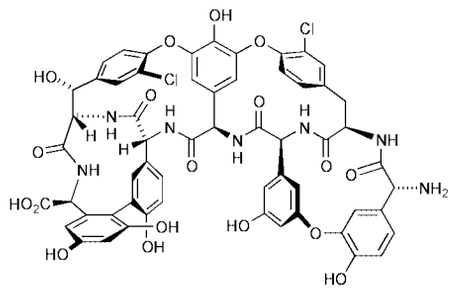


Teicoplanin aglycone

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, S. Miyazaki, H. Strittmatter, J.-H. Weng, Y. Mori, O. Rogel, S. L. Castle and J. J. McAtee, *J. Am. Chem. Soc.*, 2000, **122**, 7146.

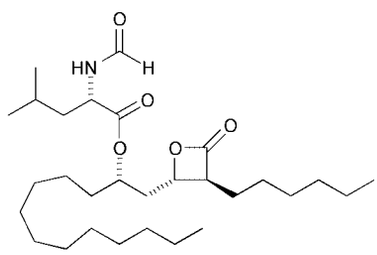


(–)-Tetrahydrolipstatin

Biological activity: potent inhibitor of pancreatic lipase—used clinically as an anti-obesity drug (Xenical).

Key steps: (a) titanium-mediated *anti*-selective aldol coupling using *N*-tosyl-1-aminoindan-2-ol as a chiral auxiliary; (b) nitro-aldol reaction; (c) diastereoselective reduction of a β-hydroxy ketone to an *anti*-1,3-diol.

A. K. Ghosh and S. Fidanze, *Org. Lett.*, 2000, **2**, 2405.

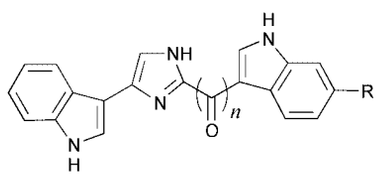


Topsentin A and Nortopsentins B and D

Biological activity: (a) deep-sea sponge metabolites; (b) antitumour, antiviral and antiinflammatory.

Key steps: (a) hydrogenation of an acyl cyanide over Pd/C to form an oxotryptamine; (b) regiospecific bromination of 3-cyanoindole (Nortopsentin B only).

F. Y. Miyake, K. Yakushijin and D. A. Horne, *Org. Lett.*, 2000, **2**, 2121.



R = H, *n* = 1 Topsentin A
R = Br, *n* = 0 Nortopsentin B
R = H, *n* = 0 Nortopsentin D

(+)-Vellosimine

Biological activity: isolated from *Geissospermum vellosii* and from various species of *Rauwolfia* (employed in traditional Chinese medicine against neuralgia, migraine and hypertension).

Key steps: (a) asymmetric Pictet–Spengler reaction; (b) stereocontrolled intramolecular palladium (enolate-mediated) coupling.

T. Wang and J. M. Cook, *Org. Lett.*, 2000, **2**, 2057.