Perkin 1 Abstracts: Natural Product Synthesis

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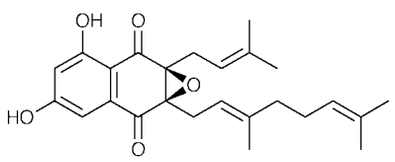
Perkin 1 Abstracts: Natural Product Synthesis aims to highlight syntheses that have been recently published. It includes brief descriptions of *biological activity* and *key steps*. A more comprehensive list of Natural Product syntheses and isolations can be found in *Natural Product Updates*.

(±)-A80915G

Biological activity: antibiotic.

Key steps: (a) Stille reactions; (b) Diels–Alder reactions using the Danishefsky–Brassard diene.

S. Takemura, A. Hirayama, J. Tokunaga, F. Kawamura, K. Inagaki, K. Hashimoto and M. Nakata, *Tetrahedron Lett.*, 1999, **40**, 7501.

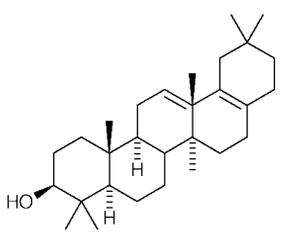


(+)-Aegiceradienol

Biological activity: not reported.

Key steps: (a) asymmetric epoxidation using the Noc-Lin catalyst; (b) a three component coupling involving a Brook rearrangment of the adduct of 2-propenyllithium and an acylsilane followed by alkylation with an allylic bromide; (c) epoxide initiated cationic cyclisation to generate 3 rings in one step; (d) generation of the pentacyclic ring system by intramolecular CuCl-mediated coupling of two alkenylstannanes. The title compound can be converted to β-amyrin and oleanolic acid.

A. X. Huang, Z. Xiong and E. J. Corey, *J. Am. Chem. Soc.*, 1999, **121**, 9999.

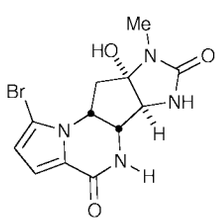


(±)-Agelastatin A

Biological activity: The natural product, isolated from the deep water marine sponge *Agelas dendomorpha*, displays *in vitro* activity against L1219 and KB tumour cells.

Key steps: (a) hetero Diels–Alder reaction of cyclopentadiene with N-sulfinyl methyl carbamate; (b) Sharpless–Kresze allylic amination with a sulfodiimide; (c) generation of two heterocyclic rings by Pd-catalysed addition of nitrogen nucleophiles onto a cyclopentene ring.

D. Stien, G. T. Anderson, C. E. Chase, Y.-h. Koh and S. M. Weinreb, *J. Am. Chem. Soc.*, 1999, **121**, 9574.

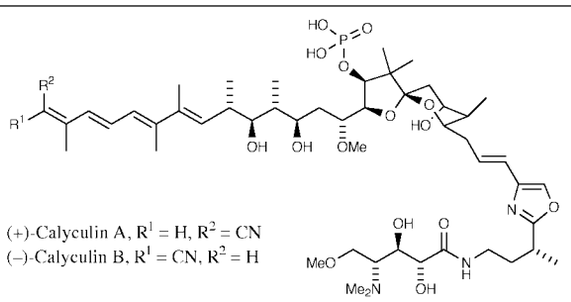


(+)-Calyculin A and (–)-Calyculin B

Biological activity: potent serine-threonine protein phosphatase inhibitors.

Key steps: (a) tetraene constructed sequentially from simple ethene derivatives *via* Pd catalysed coupling of an organozinc with a bromoalkene, then a Suzuki coupling and finally a Horner–Wadsworth–Emmons reaction; (b) cleavage of an oxirane with an alkenylcuprate. The unnatural antipodes were synthesised.

A. B. Smith, G. K. Friestad, J. Barbosa, E. Bertounesque, J. J.-W. Duan, K. G. Hull, M. Iwashima, Y. Qiu, P. G. Spoors and B. A. Salvatore, *J. Am. Chem. Soc.*, 1999, **121**, 10478.



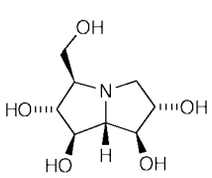
(+)-Calyculin A, R^1 = H, R^2 = CN
(–)-Calyculin B, R^1 = CN, R^2 = H

(+)-Casuarine

Biological activity: inhibitor of glucosidase I (72% inhibition at 5μg mL^{-1}).

Key steps: tandem [4 + 2]–[3 + 2] nitroalkene cycloaddition involving a nitroalkene, a chiral vinyl ether and a vinyl silane.

S. E. Denmark and A. R. Hurd, *Org. Lett.*, 1999, **1**, 1311.

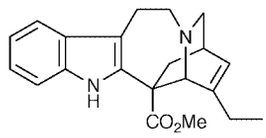


(±)-Catharanthine

Biological activity: presumed biological precursor of the antitumour alkaloids vinblastine and vincristine.

Key steps: radical-mediated cyclisation of a 2-alkenylthioanilide to afford an indole using a phosphorus-based radical-reducing agent.

M. T. Reding and T. Fukuyama, *Org. Lett.*, 1999, **1**, 973.

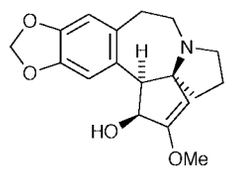


(–)-Cephalotaxine

Biological activity: 2-Alkyl-2-hydroxysuccinate esters of the title compound isolated from evergreen plum yews of the genus *Cephalotaxus* have antileukemic activity.

Key steps: The spirocycle and the 7-membered ring are created by two successive Pd-catalysed reactions.

L. F. Tietze and H. Schirok, *J. Am. Chem. Soc.*, 1999, **121**, 10264.

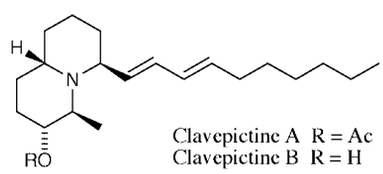


(–)-Clavepictine A and (+)-Clavepictine B

Biological activity: antimicrobial, antifungal, and antitumour activity.

Key steps: (a) diastereoselective α-lithiation of an *N*-Boc piperidine followed by alkylation; (b) diastereoselective Ag(I)-promoted cyclisation of a γ-aminoallene.

J. D. Ha and J. K. Cha, *J. Am. Chem. Soc.*, 1999, **121**, 10012.

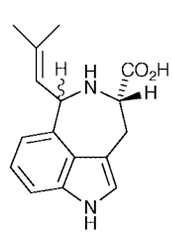


Clavicipitic acid

Biological activity: not reported.

Key steps: (a) enzymatic kinetic resolution; (b) Heck reaction.

Y. Yokoyama, H. Hikawa, M. Mitsuhashi, A. Uyama and Y. Murakami, *Tetrahedron Lett.*, 1999, **40**, 7803.

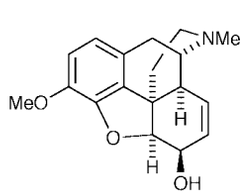


(+)-Codeine

Biological activity: (a) analgesic; (b) euphoriant.

Key steps: (a) asymmetric hydrogenation of a benzylidenesuccinate using a chiral rhodium catalyst; (b) insertion of an α-keto carbene into a tertiary C-H bond to generate a pentacycle.

J. D. White, P. Hrncair, and F. Stappenbeck, *J. Org. Chem.*, 1999, **64**, 7871.

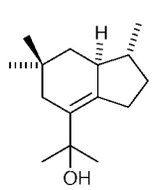


(+)-Conocephalenol

Biological activity: not described.

Key steps: (a) radical additions of tertiary radicals to enones; (b) intramolecular aldol cyclisation under acidic conditions.

J. Cossy, S. Bouzbouz and A. Hakiki, *Tetrahedron*, 1999, **55**, 11289.

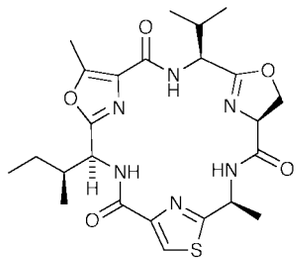


Dolastatin I

Biological activity: cytotoxicity.

Key steps: oxazoline, oxazole and thiazole rings generated by cyclodehydration of standard amino acids.

H. Kigoshi and S. Yamada, *Tetrahedron*, 1999, **55**, 12301.

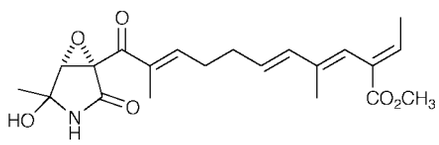


Epolactaene

Biological activity: potent neurite outgrowth activity in a human neuroblastoma cell line SH-SY5Y.

Key steps: fluoride anion-catalysed aldol-type reaction of (–)-α-trimethylsilyl angelica lactone epoxide with a tetraene aldehyde.

K. Kuramochi, S. Nagata, H. Itaya, K.-i. Takao and S. Kobayashi, *Tetrahedron Lett.*, 1999, **40**, 7371.

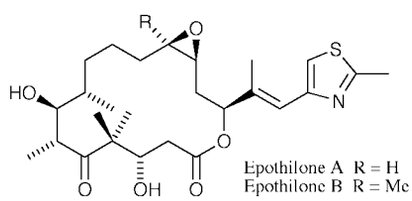


(–)-Epothilone A and (–)-Epothilone B

Biological activity: potent microtubule binding, stabilizing abilities and antitumour properties; selective cytotoxicity against certain drug-resistant tumour cell lines.

Key steps: (a) Pd-catalysed coupling to generate a trisubstituted alkene; (b) ring closing metathesis (epothilone A) to generate macrocycle; (c) macrolactonisation to generate macrocycle (epothilone B)

D. Schinzer, A. Bauer, O. M. Böhm, A. Limberg and M. Cordes, *Chem. Eur. J.*, 1999, **5**, 2483; D. Schinzer, A. Bauer and J. Schieber, *Chem. Eur. J.*, 1999, **5**, 2492.

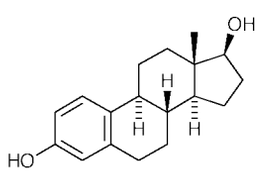


(+)-Estradiol

Biological activity: potent estrogen.

Key steps: novel benzannulation sequence involving (a) [6π+4π] cycloaddition of a (η^6-thiepine 1,1-dioxide)tricarbonylchromium(0) complex with a highly substituted diene; (b) Ramberg–Bäcklund reaction.

J. H. Rigby, N. C. Warshakoon and A. J. Payen, *J. Am. Chem. Soc.*, 1999, **121**, 8237.

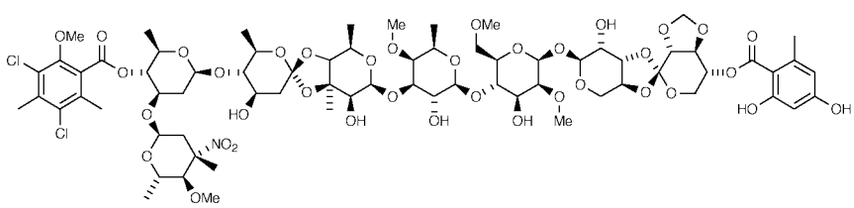


Everinomycin 13,384-1

Biological activity: antibiotic active against drug-resistant bacteria.

Key steps: (a) glycosidations mediated by PhS and PhSe glycosides; (b) tin-acetal mediated 1-1′ disaccharide formation and 1,2-diol differentiation; (c) hindered ester formation with acyl fluorides; (d) Sinaÿ orthoester synthesis.

K. C. Nicolaou, H. J. Mitchell, R. M. Rodriguez, K. C. Fylaktakidou and H. Suzuki, *Angew. Chem., Int. Ed.*, 1999, **38**, 3345.

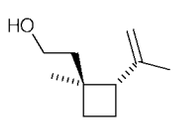


(±)-Franagol

Biological activity: isolated from the roots of *Artemisia fragans* Willd.

Key steps: $TiCl_4$ promoted [2+2] cycloaddition of allyl-*tert*-butyldiphenylsilane and methyl methacrylate.

H.-J. Knölker, G. Baum, O. Schmitt, and G. Wanzl, *Chem. Commun.*, 1999, 1737.

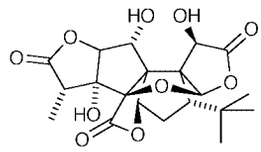


(±)-Ginkolide B

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.*, 1999, **121**, 10249.

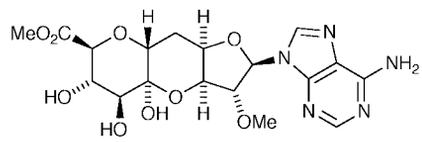


(+)-Herbicidin B

Biological activity: inhibits the growth of *Xanthomonas oryzae* which causes leaf blight.

Key steps: SmI_2-promoted aldol type *C*-glycosidation reaction with 1-phenylthio-2-ulose derivatives as precursors to ulose-1-enolates.

S. Ichikawa, S. Shuto and A. Matsuda, *J. Am. Chem. Soc.*, 1999, **121**, 10270.

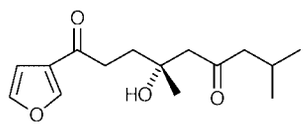


(+)-Hydroxymyoporone

Biological activity: (a) stress metabolite produced by sweet potatoes infected with *Fusarium solani*; (b) possesses a strong lung toxic effect.

Key steps: asymmetric allylation of a methyl ketone in the presence of a norpseudoephedrine derivative and catalytic amount of TfOH.

L. F. Tietze, C. Wegner and C. Wulff, *Chem. Eur. J.*, 1999, **5**, 2885.

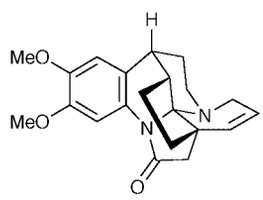


(±)-Isoschizogamine

Biological activity: isolated from the shrub *Schizozygia caffaeoides*; biological activity not reported.

Key steps: conjugate addition of a bicyclic imine to an arylidenemalonic ester to give a tricyclic lactam.

J. L. Hubbs and C. H. Heathcock, *Org. Lett.*, 1999, **1**, 1315.

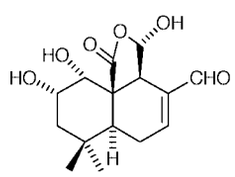


(–)-Mniopetal E

Biological activity: (a) inhibitory activity against RNA-directed DNA-polymerases (RT) of human immunodeficiency virus (HIV)-1 and moloney murine leukemia viruses; (b) antimicrobial and cytotoxic properties.

Key steps: stereoselective intramolecular Diels–Alder reaction for the construction of the octahydronaphthalene core structure.

Y. Suzuki, R. Nishimaki, M. Ishikawa, T. Murata, K.-i. Takao and K.-i. Tadano, *Tetrahedron Lett.*, 1999, **40**, 7835.

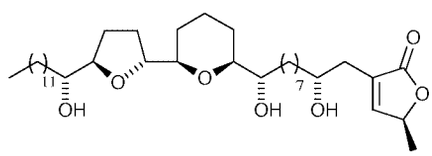


(+)-Muconin

Biological activity: potent and selective *in vitro* cytotoxic against pancreatic and breast tumour cell lines.

Key steps: Pd(0)-mediated crossed diyne coupling.

W.-Q. Yang and T. Kitahara, *Tetrahedron Lett.*, 1999, **40**, 7827.

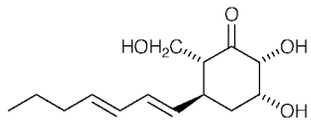


Palitantin

Biological activity: precursor of frequentin which shows antifungal and antibiotic activities.

Key steps: (a) *cis*-dihydroxylation using OsO_4; (b) 1,4-addition of a cyanocuprate to a cyclohexenone.

G. Harcau, M. Koiwa, T. Hanazawa and F. Sato, *Tetrahedron Lett.*, 1999, **40**, 7493.

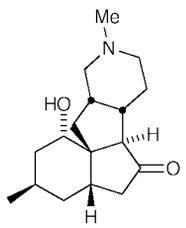


(+)-Paniculatine

Biological activity: not reported.

Key steps: (a) Cu(I)-catalysed conjugate addition of a homopropargylic Grignard reagent to a cyclohexenone; (b) α-carbonyl radical-initiated tandem cyclisation to generate the two 5-membered rings.

C.-K. Sha, F.-K. Lee and C.-J. Chang, *J. Am. Chem. Soc.*, 1999, **121**, 9875.

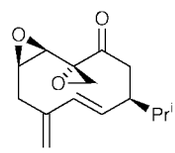


(–)-Periplanone-B

Biological activity: sex attractant pheromone of the American cockroach.

Key steps: (a) chromium(II)-mediated preparation of an (*E*)-alkenylstannane from an aldehyde; (b) Intramolecular Stille cross coupling; (c) alkene-selective ring closing metathesis.

D. M. Hodgson, A. M. Foley, L. T. Boulton, P. J. Lovell and G. N. Maw, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2911.

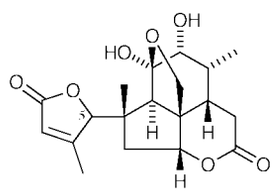


5(*R*)- and 5(*S*)-Polyandrane

Biological activity: not reported.

Key steps: (a) quinone Diels–Alder reaction; (b) ring contraction *via* a photochemical Wolff rearrangement.

D. P. Walker and P. A. Gricco, *J. Am. Chem. Soc.*, 1999, **121**, 9891.

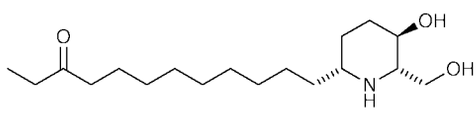


(–)-Prosophylline

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

Key steps: (a) modified Speckamp protocol requiring a Lewis acid promoted allylsilane addition to an acyliminium ion intermediate; (b) Wittig reaction.

S. D. Koulocheri and S. A. Haroutounian, *Tetrahedron Lett.*, 1999, **40**, 6869.

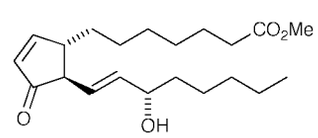


Prostaglandin-J_1

Biological activity: potent activity against Sendai 37RC virus (IC_{50} = 0.5 μM).

Key steps: (a) Suzuki coupling; (b) 1,4-addition of a higher order cyanocuprate to an enone.

S. M. Roberts, M. G. Santoro and T. Guyot, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2437.

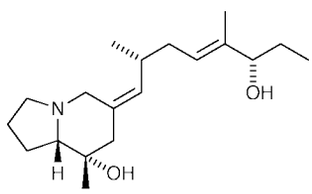


Pumiliotoxins A and 225F

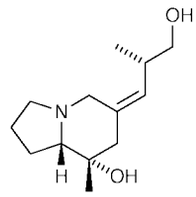
Biological activity: neurotoxins.

Key steps: (a) synthesis of a scalemic allenylsilane by substitution of a propargylic mesylate with a silylcuprate; (b) construction of a homopropargylic alcohol by hafnium(IV) chloride-mediated addition of a scalemic allenylsilane to a methyl ketone; (c) regioselective hydrostannylation of a homopropargylic alcohol; (d) synthesis of a trisubstituted alkene by Pd(0)-catalysed carbonylation of an iodoalkene; (e) Pd(0)-catalysed cross coupling of an homoallylzinc with an iodoalkene to generate a trisubstituted alkene.

S. Hirashima, S. Aoyagi and C. Kibayashi, *J. Am. Chem. Soc.*, 1999, **121**, 9873.



(+)–Pumiliotoxin A



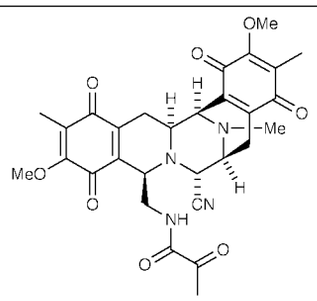
(–)–Pumiliotoxin 225F

(–)-Saframycin A

Biological activity: antitumour agent.

Key steps: directed condensation of α-amino aldehyde precursors.

A. G. Myers and D. W. Kung, *J. Am. Chem. Soc.*, 1999, **121**, 10828.

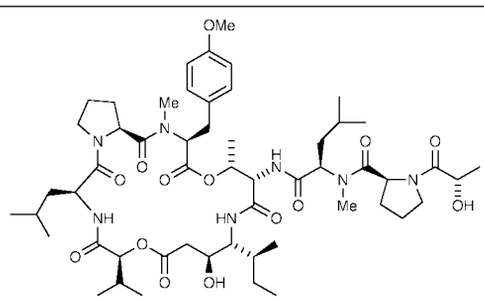


(–)-Tamandarin A

Biological activity: *in vitro* activity against pancreatic carcinoma (ED_{50} = 1.5–2 ng mL^{-1}).

Key steps: (a) usual peptide chemistry; (b) macrolactamisation.

B. Liang, P. Portnovo, M. D. Vera, D. Xiao and M. M. Joullié, *Org. Lett.*, 1999, **1**, 1319.

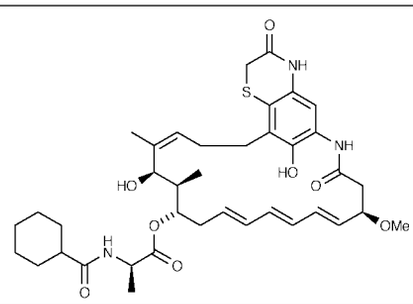


(+)-Thiazinotrienomycin E

Biological activity: the title compound is a *Streptomyces* metabolite with significant *in vitro* cytotoxicity against a variety of human tumour cell lines.

Key steps: (a) Kocienski modified Julia protocol to elaborate the triene unit; (b) Mukaiyama macrolactamisation.

A. B. Smith and Z. Wan, *Org. Lett.*, 1999, **1**, 1491.

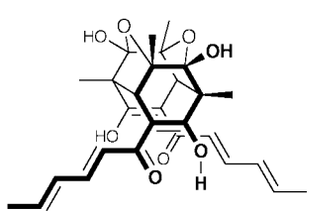


(–)-Trichodimerol

Biological activity: inhibits production of tumour necrosis factor α.

Key steps: (a) spontaneous dimerisation of a chiral hydroxydienone involving first an intermolecular Michael addition followed by an intramolecular Michael addition; (b) resolution of the racemic hydroxydienone by chiral HPLC.

D. Barnes-Seeman and E. J. Corey, *Org. Lett.*, 1999, **1**, 1503.



(–)-Wodeshiol

Biological activity: not reported.

Key steps: (a) asymmetric reduction of an enone with an oxazoborolidine; (b) homo-coupling of an alkenylstannane to give a diene catalysed by a mixture of Pd(0), Cu(I) and Cu(II); (c) $VO(acac)_2$-catalysed directed hydroxylation of an allylic alcohol; (d) double acid catalysed ring closure of an epoxy alcohol to generate the two tetrahydrofuran rings.

X. Han and E. J. Corey, *Org. Lett.*, 1999, **1**, 1871.