Perkin 1 Abstracts: Natural Product Synthesis

Robert Narquizian and Philip Kocienski
Department of Chemistry, University of Glasgow, Glasgow, UK G12 8QQ

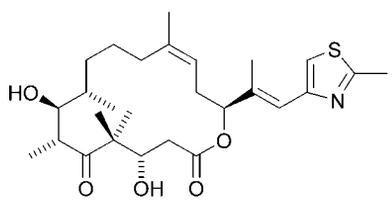
Perkin 1 Abstracts: Natural Product Synthesis aims to highlight syntheses that have been recently published. It includes brief descriptions of *biological activity* and *key steps*. A more comprehensive list of Natural Product syntheses and isolations can be found in *Natural Product Updates*

12,13-Desoxyepothilone B

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

Key steps: (a) aldol reaction; (b) Suzuki coupling; (c) asymmetric Noyori reduction of a β-keto ester; (d) Lewis acid catalysed diene-aldehyde cyclocondensation.

C. R. Harris, S. D. Kuduk, A. Balog, K. Savin, P. W. Glunz and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1999, **121**, 7050.

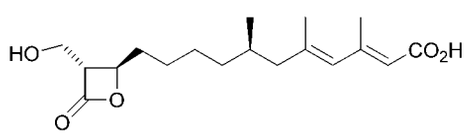


1233A

Biological activity: (a) cholesterol biosynthesis inhibitor; (b) inhibitor of enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) synthase; (c) antibiotic.

Key steps: (a) oxidative decomplexation of a (π-allyl)tricarbonyliron lactone complex; (b) Stille coupling.

R. W. Bates, E. Fernández-Megía, S. V. Ley, K. Rück-Braun and D. M. G. Tilbrook, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1917.

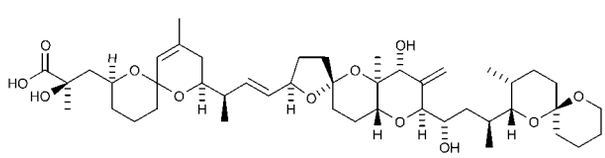


7-Deoxyokadaic acid

Biological activity: most potent known inhibitor of the tumor suppressor protein phosphatase-2A (PP-2A).

Key steps: (a) Sharpless asymmetric epoxidation; (b) Seebach's lactate enolate alkylation ('self-regeneration of stereogenic centres'); (c) *C*-glycosylation of an altropyranoside; (b) asymmetric reduction of an enone using Corey's oxazaborolidine method.

A. B. Dounay, R. A. Urbanek, S. F. Sabes and C. J. Forsyth, *Angew. Chem., Int. Ed.*, 1999, **38**, 2258.

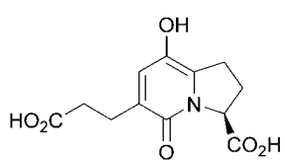


(–)-A58365A

Biological activity: enzyme inhibitor.

Key steps: [3+2]-cycloaddition reaction of a phenylsulfonyl-substituted pyrrolidine imide.

C. S. Straub and A. Padwa, *Org. Lett.*, 1999, **1**, 83.

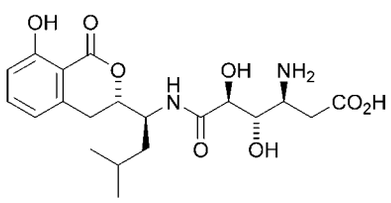


AI-77-B

Biological activity: gastroprotective activity without anticholinergic, antihistaminergic or central nervous depressive effects.

Key steps: (a) a CsF-mediated cyclisation of a phenolic propargyl ether to a benzofuran; (b) use of a benzofuran as a synthon for a salicylic acid. Both the dihydrocoumarin and the dihydroxyamino acid fragments were synthesised from D-ribose.

H. Kotsuki, T. Araki, A. Miyazaki, M. Iwasaki and P. K. Datta, *Org. Lett.*, 1999, **1**, 499.

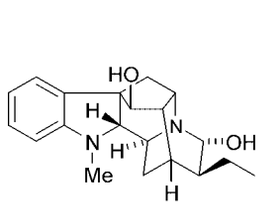


(+)-Ajmaline, alkaloid G and norsuaveoline

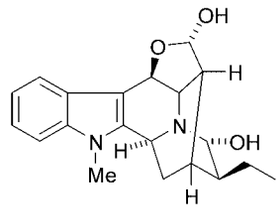
Biological activity: (+)-ajmaline is used for the treatment of cardiac arrhythmia.

Key steps: (a) stereospecific Pictet-Spengler/Dieckmann process; (b) Barbier-Grignard reaction; (c) anionic oxy-Cope rearrangement.

J. Li, T. Wang, P. Yu, A. Peterson, R. Weber, D. Soerens, D. Grubisha, D. Bennett and J. M. Cook, *J. Am. Chem. Soc.*, 1999, **121**, 6998.



(+)-Ajmaline



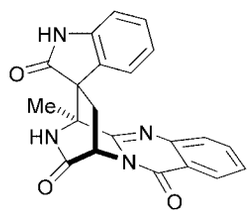
Alkaloid G

(–)-Alantrypinone

Biological activity: no biological activity reported.

Key steps: use of $[Me_3AlSPh]Li$ as a promoter of a 4-iminobenzoxazine to quinazolin-4-one rearrangement and as a reagent for the deprotection of an Fmoc-protected amino acid derivative.

D. J. Hart and N. Magomedov, *Tetrahedron Lett.*, 1999, **40**, 5429.

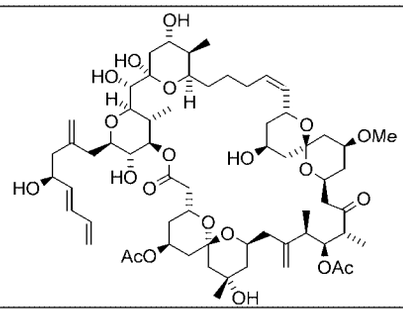


Altohyrtin C (Spongistatin 2)

Biological activity: (a) *in vitro* antitumor activity; (b) IC_{50} = 0.03 nM; (c) inhibits tubulin polymerisation.

Key steps: (a) regioselective macrolactonisation; (b) stereoselective Wittig coupling; (c) 1,5-*anti*, enolate-controlled methyl ketone aldol reaction to construct a spiroketal; (d) *anti* aldol reaction catalysed by Sn(II)-bis(oxazoline); (e) Lewis acid mediated addition of allylstannanes to anomeric epoxides; (f) anomeric sulfone acylation.

D. A. Evans, B. W. Trotter, P. J. Coleman, B. Côté, L. C. Dias, H. A. Rajapakse and A. N. Tyler, *Tetrahedron*, 1999, **55**, 8671.

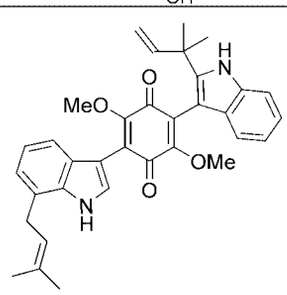


Asterriquinone B1

Biological activity: *in vivo* antitumor activity against Ehrlich carcinoma, ascites hepatoma AH13 and mouse P388 leukemia.

Key steps: (a) Vilsmeier formylation; (b) sodium methoxide catalysed rearrangement of a pyrandione to form demethylasterriquinone B1.

K. Lui, H. B. Wood and A. B. Jones, *Tetrahedron Lett.*, 1999, **40**, 5119.

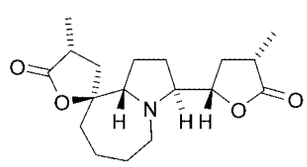


(+)-Croomine

Biological activity: isolated from *Stemonaceae* plants, whose extracts are used in traditional Chinese medicine for the treatment of pertussis, tuberculosis, and bronchitis.

Key steps: vinylogous Mannich reaction by nucleophilic addition of a 2-trialkylsilyloxy furan to a cyclic iminium salt.

S. F. Martin and K. J. Barr, *J. Am. Chem. Soc.*, 1996, **118**, 3299.

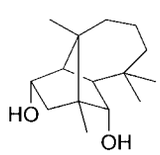


(±)-Culmorin

Biological activity: antifungal.

Key steps: intramolecular double Michael addition between a cyclopentenone and an α,β-unsaturated ester to generate the tricyclic ring system in one operation.

K. Takasu, S. Mizutani, M. Noguchi, K. Makita and M. Ihara, *Org. Lett.*, 1999, **1**, 391.

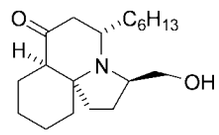


(–)-Cylindricine C

Biological activity: (a) bioactivity against brine shrimp in a bioassay and a DNA-repair-deficient yeast strain; (b) inhibits growth of murine leukemia and solid tumor cell lines.

Key steps: (a) $CrCl_2$ reduction of an azide to form the corresponding amine; (b) double Michael addition to create the tricyclic skeleton.

G. A. Molander and M. Rönn, *J. Org. Chem.*, 1999, **64**, 5183.

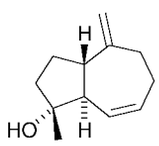


(+)-Dictamnol

Biological activity: not reported.

Key steps: Rhodium-catalysed [5 + 2] cycloaddition of an allene and a vinylcyclopropane.

P. A. Wender, M. Fuji, C. O. Husfeld, and J. A. Love, *Org. Lett.*, 1999, **1**, 137.

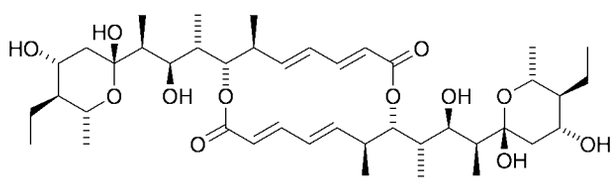


Elaiolide

Biological activity: (a) antimicrobial activity against several strains of Gram-positive bacteria; (b) anthelmintic activity against *Trichonomonas vaginalis*; (c) inhibitory activity against K^+-dependent adenosine triphosphatases.

Key steps: (a) Cu(I) thiophene-2-carboxylate promoted cyclodimerisation of a vinyl stannane; (b) two directional aldol coupling.

I. Paterson, H.-G. Lombart and C. Allerton, *Org. Lett.*, 1999, **1**, 19.

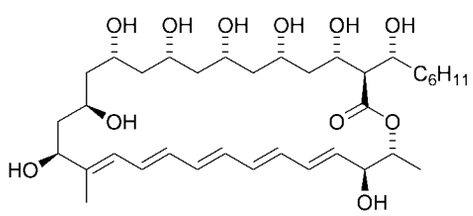


Filipin III

Biological activity: (a) polyene macrolide antibiotic; (b) used as a histochemical stain for cholesterol.

Key steps: (a) cyanohydrin acetonide alkylation and reductive decyanation sequence; (b) Yamaguchi's esterification; (c) intramolecular Horner-Emmons cyclisation.

T. I. Richardson and S. D. Rychnovsky, *Tetrahedron*, 1999, **55**, 8977.

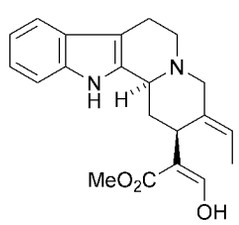


(+)-Geissoschizine

Biological activity: not reported.

Key steps: (a) vinylogous Mannich reaction; (b) radical decarboxylation *via* an acyl selenide.

S. F. Martin, K. X. Chen and C. T. Eary, *Org. Lett.*, 1999, **1**, 79.

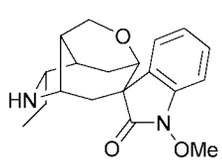


(+)-Gelsidine

Biological activity: not reported

Key steps: (a) iodide-promoted cyclisation of an allene onto a cyclic *N*-acyliminium ion; (b) Pd(0)-catalysed aminocarbonylation of an iodoalkene to give an α,β-unsaturated amide; (c) Heck cyclisation of an *o*-bromoanilide to generate the spirocyclic oxindole. The synthesis was accomplished in 21 steps from (*S*)-malic acid and gave the enantiomer of the natural product.

W. G. Beyersbergen van Henegouwen, R. M. Fieseler, F. J. P. T. Rutjes and H. Hiemstra, *Angew. Chem., Int. Ed.*, 1999, **38**, 2214.

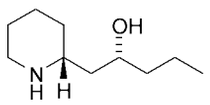


(–)-Halosaline

Biological activity: not reported.

Key steps: domino metathesis reaction using Grubbs' ruthenium catalyst.

R. Stragies and S. Blechert, *Tetrahedron*, 1999, **55**, 8179.

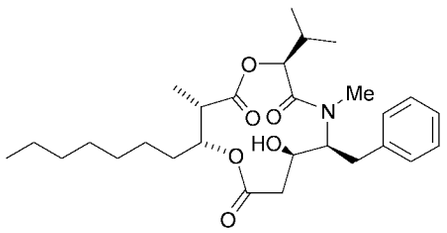


Hapalosin

Biological activity: reverses multidrug resistance (MDR) activity.

Key steps: (a) reductive amination of an epoxyketone using tetramethylammonium triacetoxyborohydride to form the corresponding *trans* aminoepoxide; (b) macrolactamisation.

M. Haddad, C. Botuha and M. Larchevêque, *Synlett*, 1999, 1118.

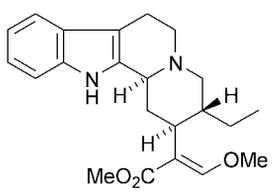


Hirsutine

Biological activity: strong inhibitory effect against the influenza A virus (subtype H3N2) with an EC_{50} = 0.40-0.57 μg ml^{-1}.

Key steps: domino Knoevenagel-hetero-Diels–Alder reaction.

L. F. Tietze and Y. Zhou, *Angew. Chem., Int. Ed.*, 1999, **38**, 2045.

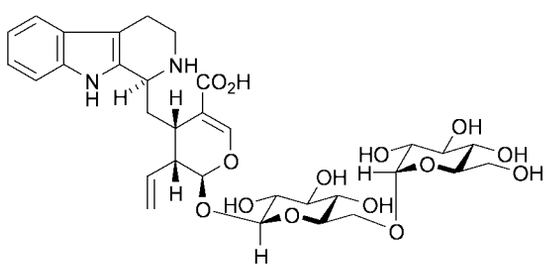


Hunterioside

Biological activity: extracted from a Thai medicinal plant, *Hunteria zeylanica*.

Key steps: standard carbohydrate transformations.

O. Ohmori, H. Takayama and N. Aimi, *Tetrahedron Lett.*, 1999, **40**, 5039.

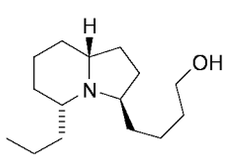


Indolizidine 239CD

Biological activity: isolated from poison frogs of the species *Dendrobates histrionicus*.

Key steps: treatment of a (2-azaallyl)stannane with HF•pyridine generates a nonstabilised *N*-substituted azomethine ylide which undergoes stereoselective dipolar cycloaddition with phenyl vinyl sulfone to produce a *trans*-2,5-dialkylpyrrolidine.

R. B. Clark and W. H. Pearson, *Org. Lett.*, 1999, **1**, 349.

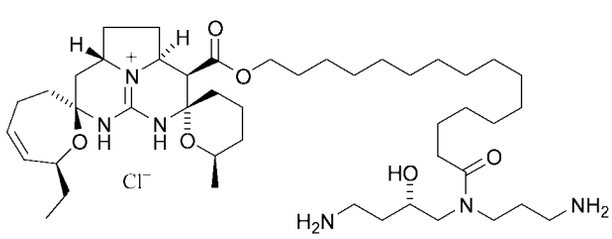


13,14,15-Isocrambescidin 800

Biological activity: a cytotoxic metabolite from the bright red sponge *Crambe crambe*.

Key steps: (a) TADDOL-mediated asymmetric addition of diethylzinc to an ynal; (b) tethered Biginelli reaction of a guanidine aminal with a β-keto ester.

D. C. Coffey, A. J. McDonald, L. E. Overman and F. Stappenbeck, *J. Am. Chem. Soc.*, 1999, **121**, 6944.

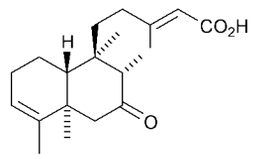


(–)-7-Oxokolavenic acid and (–)-Methyl solidagonate

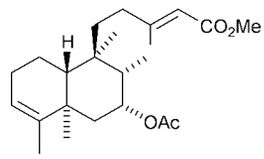
Biological activity: insect antifeedant.

Key steps: ene reactions.

M. Kato, H. Kosugi, T. Ichiyanagi, T. Suzuki, A. Kodaira, P. Drechsel and H. Hagiwara, *Tetrahedron Lett.*, 1999, **40**, 5377.



(–)-7-Oxokolavenic acid



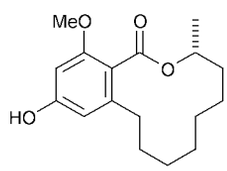
(–)-Methyl solidagonate

(*R*)-(+)-Lasiodiplodin and Zeranol

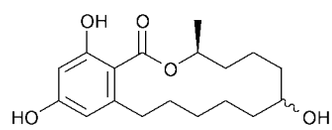
Biological activity: (a) inhibitors of prostaglandin biosynthesis; (b) antileukemic activity.

Key steps: (a) ring closing metathesis; (b) Stille coupling; (c) Suzuki coupling.

A. Fürstner, G. Seidel and N. Kindler, *Tetrahedron*, 1999, **55**, 8215.



(*R*)-(+)-Lasiodiplodin



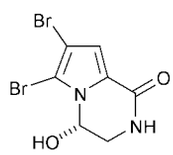
Zeranol

(±)-Longamide

Biological activity: not reported.

Key steps: regioselective pyrrolic N_1 intramolecular cyclisation.

S. Marchais, A. A. Mourabit, A. Ahond, C. Poupat and P. Potier, *Tetrahedron Lett.*, 1999, **40**, 5519.

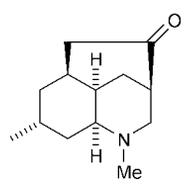


(+)-Luciduline

Biological activity: isolated from *Lycopodium lucidulum*.

Key steps: (a) intramolecular Diels-Alder; (b) retro-Mannich ring opening; (c) novel tandem cationic alkylation / reductive cyclisation reaction.

D. L. Comins, C. A. Brooks, R. S. Al-Awar and R. R. Goehring, *Org. Lett.*, 1999, **1**, 229.

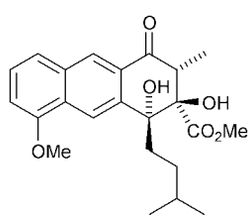


(±)-Methyl rishirilide B

Biological activity: (a) $(\alpha)_2$-macroglobulin inhibitor; (b) potentially useful for the treatment and/or prevention of thrombosis.

Key steps: (a) construction of a hydroanthracenone intermediate through condensation of a phenylsulfonyl isobenzofuranone with a functionalised cyclohex-2-en-1-one; (b) introduction of the vicinal *trans*-hydroxy groups in the densely functionalised ring A *via* a one-pot procedure that involved oxidation of enolate anions with the Davis reagent.

F. M. Hauser and Y.-j. Xu, *Org. Lett.*, 1999, **1**, 334.

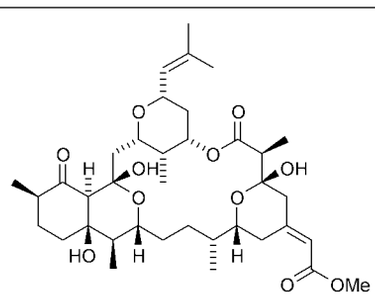


(+)-Miyakolide

Biological activity: not reported.

Key steps: (a) β-ketoamide aldol reaction in fragment linkage; (b) intramolecular [3–2] cycloaddition of a nitrile oxide onto an alkyne to generate the macrocycle; (c) transannular aldol reaction of a 1,3,7-triketone containing macrocycle followed by hemiketalisation to form the oxydecalin ring system.

D. A. Evans, D. H. B. Ripin, D. P. Halstead and K. R. Campos, *J. Am. Chem. Soc.*, 1999, **121**, 6816.

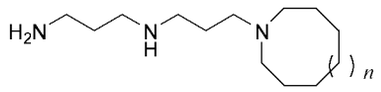


Motuporamines A and B

Biological activity: cytotoxic against a panel of human solid tumor cell lines.

Key steps: reductive amination using sodium triacetoxyborohydride.

J. E. Balwin, H. R. Vollmer and V. Lee, *Tetrahedron Lett.*, 1999, **40**, 5401.



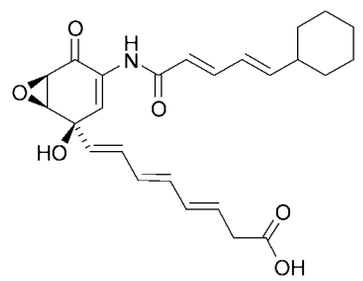
Motuporamine A $n = 6$
Motuporamine B $n = 7$

(±)-Nisamycin

Biological activity: antibiotic.

Key steps: (a) Zr-Zn transmetallation; (b) Stille coupling.

P. Wipf and P. D. G. Coish, *J. Org. Chem.*, 1999, **64**, 5053.

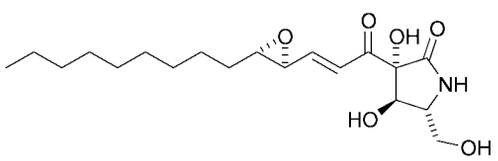


(+)-Pramanicin

Biological activity: moderate activity against a variety of fungi and especially towards the acapsular form of *Cryptococcus neoformans*, which is responsible for meningitis in AIDS patients.

Key steps: (a) conjugate addition of a silylzincate to a γ-lactam followed by an aldol reaction; (b) $Ni(Acac)_2$-catalysed hydroxylation of a β-dicarbonyl; (c) Fleming-Tamao oxidation of an aminosilane. The synthetic product is the enantiomer of the natural product.

A. G. M. Barrett, J. Head, M. L. Smith, N. S. Stock, A. J. P. White and D. J. Williams, *J. Org. Chem.*, 1999, **64**, 6005.

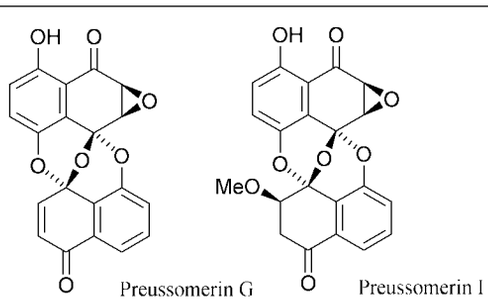


(±)-Preussomerins G and I

Biological activity: inhibitors of Ras farnesyl transferase, an enzyme associated with the regulation of tumor growth.

Key steps: "ring-chain tautomerisation" – nucleophilic 1,6-addition of a phenoxide to the oxygen end of a quinone carbonyl group.

S. Chi and C. H. Heathcock, *Org. Lett.*, 1999, **1**, 3.



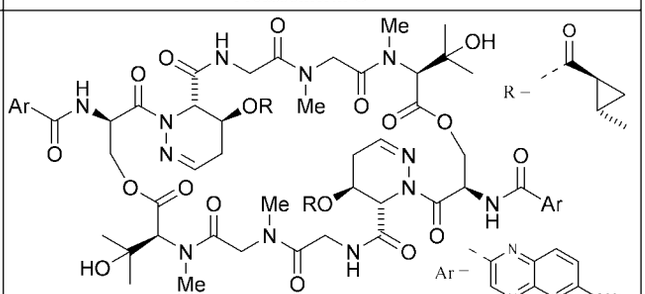
Preussomerin G Preussomerin I

Quinoxapeptin A–C

Biological activity: inhibit HIV-1 and HIV-2 reverse transcriptase at non-cytotoxic concentrations.

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

D. L. Boger, M. L. Ledeboer, M. Kume and Q. Jin, *Angew. Chem., Int. Ed.*, 1999, **38**, 2424.



Saframycin A

Biological activity: antitumor activity.

Key steps: use of 1-fluoro-3,5-dichloropyridinium triflate to oxidise a phenolic ring to a 1,4-benzoquinone unit while simultaneously cleaving a methoxymethyl ether of a different phenolic ring to the corresponding phenol.

E. J. Martinez and E. J. Corey, *Org. Lett.*, 1999, **1**, 75.