Perkin 1 Abstracts: Natural Product Synthesis

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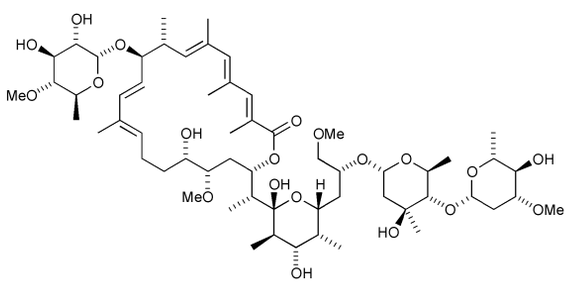
Perkin 1 Abstracts: Natural Product Synthesis aims to highlight syntheses that have been recently published. It includes brief descriptions of *biological activity* and *key steps*. A more comprehensive list of Natural Product syntheses and isolations can be found in *Natural Product Updates*.

Apoptolidine

Biological activity: (a) selective induction of apoptosis in rat glia cells transformed with adenovirus E1A oncogene; (b) inhibition of mitochondrial F_0F_1-ATPase

Key steps: (a) addition of a metallated dithiane to an aldehyde; (b) Stille coupling; (c) sulfoxide-based glycosidation; Yamaguchi macrolactonisation.

K. C. Nicolaou, Y. Li, K. C. Fylaktakidou, H. J. Mitchell, H.-X. Wei and B. Weyershausen, *Angew. Chem., Int. Ed.*, 2001, **40**, 3849; K. C. Nicolaou, Y. Li, K. C. Fylaktakidou, H. J. Mitchell and K. Sugita, *Angew. Chem., Int. Ed.*, 2001, **40**, 3854.

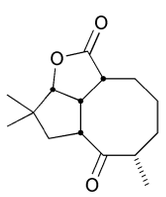


(±)-Asteriscanolide

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

Key steps: (a) intermolecular Pauson–Khand cycloaddition; (b) ring-closing metathesis.

M. E. Krafft, Y. Y. Cheung and K. A. Abboud, *J. Org. Chem.*, 2001, **66**, 7443.

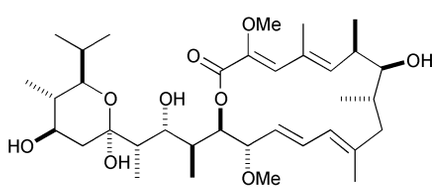


(–)-Bafilomycin A_1

Biological activity: vacuolar ATPase inhibitor.

Key steps: (a) carboalumination of a terminal alkyne; (b) Stille coupling; (c) diastereoselective conjugate addition of Me_2CuLi to enolate esters flanked by a stereogenic centre.

S. Hanessian, J. Ma and W. Wang, *J. Am. Chem. Soc.*, 2001, **123**, 10200.

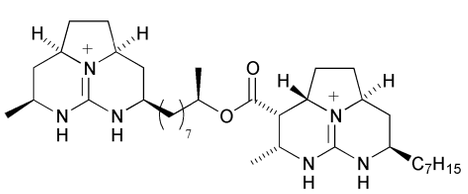


Batzelladine F

Biological activity: (a) isolated from a red Jamaican sponge; (b) induces dissociation of protein tyrosine kinase $p56^{lck}$ from CD4.

Key steps: two tethered Biginelli condensation reactions.

F. Cohen and L. E. Overman, *J. Am. Chem. Soc.*, 2001, **123**, 10782.

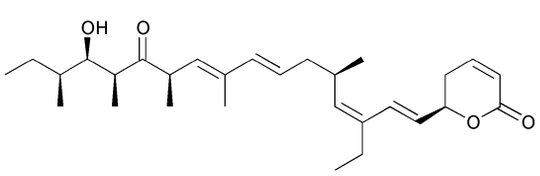


(–)-Callystatin A

Biological activity: (a) isolated from *Callyspongia truncata*; (b) inhibitor of tumour growth.

Key steps: (a) Heck coupling reaction; (b) Wittig olefination; (c) stereoselective aldol reaction.

M. Kalesse, M. Quitschalle, C. P. Khandavalli, and A. Saeed, *Org. Lett.*, 2001, **3**, 3107.

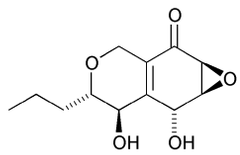


(–)-Cycloepoxydon

Biological activity: (a) isolated from fermentations of a deuteromycete strain; (b) inhibits degradation of IκBα, thereby inhibiting activation of NF-κB; (c) inhibits tumour necrosis factor (TNF)-induced NF-κB DNA binding in mouse 3T3 cells.

Key steps: (a) *endo*-cyclisation of an epoxy alcohol; (b) reagent-controlled asymmetric nucleophilic epoxidation of a quinone monoketal.

C. Li, E. A. Pace, M.-C. Liang, E. Lobkovsky, T. D. Gilmore and J. A. Porco, *J. Am. Chem. Soc.*, 2001, **123**, 11308.

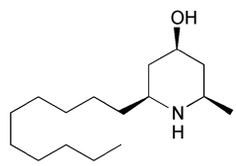


Dendrobate alkaloid (+)-241D

Biological activity: (a) isolated from the skin extracts of dendrobate frogs; (b) racemate inhibits binding of [^{3}H]perhydrohistrionicotoxin to nicotinic receptor channels of electroplax membranes; (c) blocks the action of acetylcholine through noncompetitive blockage of the nicotinic receptor-channel complex.

Key steps: intramolecular Mannich reaction of an δ-amino β-keto ester with an aldehyde, forming a polysubstituted piperidine.

F. A. Davis, B. Chao and A. Rao, *Org. Lett.*, 2001, **3**, 3169.

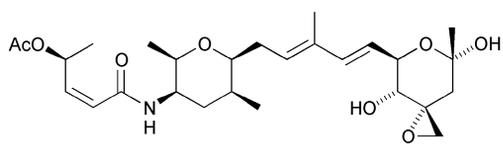


FR901464

Biological activity: (a) induces G_1 and G_2/M phase arrest in tumour cells; (b) causes changes in chromatin structure; (c) strongly differentiated transcriptional regulation.

Key steps: (a) chiral pool synthesis beginning with L-threonine, ethyl (*S*)-lactate and 2-deoxy-D-glucose; (b) Horner-Wadsworth-Emmons olefination of a thiolactone; (c) Julia olefination to generate a conjugated diene.

M. Horigome, H. Motoyoshi, H. Watanabe and T. Kitahara, *Tetrahedron Lett.*, 2001, **42**, 8207.

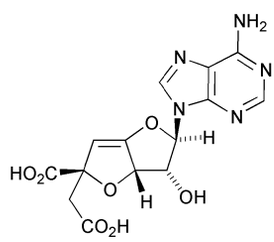


Griseolic acid B

Biological activity: (a) isolated from a cultured broth of *Streptomycetes griseoaurantiacus*; (b) exhibits nanomolar inhibition of cyclic AMP.

Key steps: π-face-dependent radical cyclisation.

S. Knapp, M. R. Madduru, Z. Lu, G. J. Morriello, T. J. Emge and G. A. Doss, *Org. Lett.*, 2001, **3**, 3583.

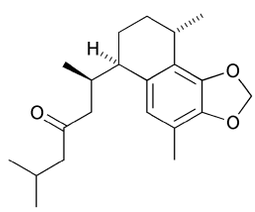


11-*epi*-Helioporin B

Biological activity: not reported.

Key steps: stereoselective nucleophilic *endo* addition to an arene-$Cr(CO)_3$ complex.

F. Dehmel and H.-G. Schmalz, *Org. Lett.*, 2001, **3**, 3579.

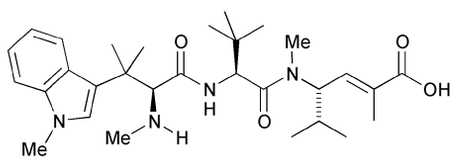


(–)-Hemiasterlin

Biological activity: (a) isolated from marine sponges; (b) cytotoxic; (c) antimitotic.

Key steps: (a) asymmetric Strecker synthesis; (b) coupling of two sterically hindered amino acid residues exploiting the high reactivity of a 2-benzothiazolylsulfonyl-protected amino acid chloride.

E. Vedejs and C. Kongkittingam, *J. Org. Chem.*, 2001, **66**, 7355.

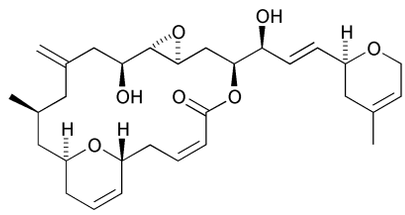


(–)-Laulimalide

Biological activity: cytotoxicity against several human tumour cell lines with IC_{50} 10–50 ng/ml.

Key steps: (a) ring closing metathesis to generate both dihydropyran rings; (b) Julia-Kocienski olefination; (c) reaction of a metallated sulfone with ICH_2MgCl to generate exocyclic methylene; (d) intramolecular Sharpless kinetic resolution.

J. Mulzer and E. Öhler, *Angew. Chem. Int. Ed.*, 2001, **40**, 3842.

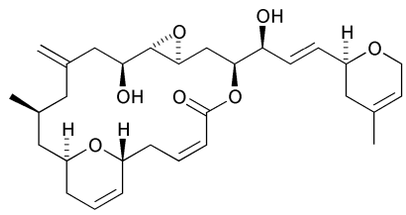


(–)-Laulimalide

Biological activity: (a) isolated from the Pacific sponges *Hyatella* sp. and *Spongia mycofijiensis*, and the Okinawan sponge *Fasciospongia rimosa*; (b) potent microtubule-stabilising anticancer agent with activity against numerous cancer cell lines (IC_{50} values in the low nanomolar range).

Key steps: (a) Jacobsen's hetero-Diels–Alder reaction; (b) diastereoselective aldol coupling using chiral boron enolate methodology; (c) Mitsunobu macrolactonisation; (d) Sharpless asymmetric epoxidation reaction.

I. Paterson, C. D. Savi, and M. Tudge, *Org. Lett.*, 2001, **3**, 3149.

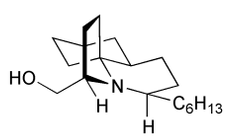


(±)-Lepadiformine

Biological activity: (a) isolated from the tunicate *Clavelina lepadiformis*; (b) exhibits moderate *in vitro* cytotoxic activity against several tumour lines.

Key steps: stereoselective intramolecular spirocyclisation of an allylsilane and an *N*-acyliminium ion.

P. Sun, C. Sun and S. M. Weinreb, *Org. Lett.*, 2001, **3**, 3507.

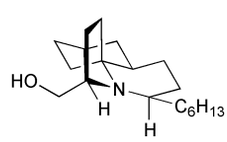


(±) Lepadiformine

Biological activity: (a) isolated from the tunicate *Clavelina lepadiformis*; (b) exhibits moderate *in vitro* cytotoxic activity against several tumour lines.

Key steps: (a) intermolecular cycloaddition of a 2-amidoacrolein with the dimethyl acetal of hepta-4,6-dienal; (b) Mitsunobu ring-closing reaction to form an aziridine; (c) diastereoselective addition of an organoytterbium reagent to an aldehyde.

T. J. Greshock and R. L. Funk, *Org. Lett.*, 2001, **3**, 3511.

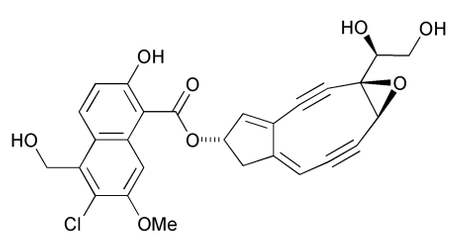


N1999-A2

Biological activity: (a) antibacterial; (b) antitumour; (c) cleaves DNA in a base-specific manner.

Key steps: Sonogashira coupling.

S. Kobayashi, S. Ashizawa, Y. Takahashi, Y. Sugiura, M. Nagaoka, M. J. Lear and M. Hirama, *J. Am. Chem. Soc.*, 2001, **123**, 11294.

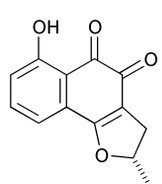


(–)-Nocardione A

Biological activity: (a) isolated from the culture broth of *Nocardia* sp. TP-A0248; (b) tyrosine phosphatase inhibitor; (c) antifungal; (d) cytotoxic.

Key steps: construction of the dihydrofuran ring *via* a ring closing Mitsunobu reaction.

Y. Tanada and K. Mori, *Eur. J. Org. Chem.*, 2001, 4313.

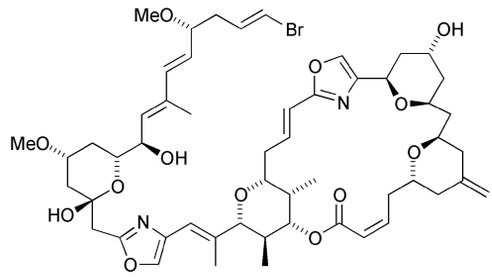


(+)-Phorboxazole

Biological activity: antimitotic agent; arrests the cell cycle at the S phase and does not affect tubulin.

Key steps: (a) Petasis-Ferrier rearrangement to construct two *cis*-tetrahydropyran rings; (b) two Stille couplings: one to construct the conjugated diene and the other to append an alkene to an oxazole ring.

A. B. Smith, K. B. Minbiole, P. R. Verhoest and M. Schelhaas, *J. Am. Chem. Soc.*, 2001, **123**, 10942.

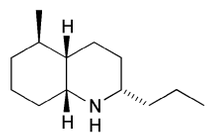


(±)-Pumiliotoxin C

Biological activity: (a) isolated from skin extracts of the Panamanian poisonous frog *Dendrobates pumilio*; (b) biological activity not reported.

Key steps: formation of a quinoline by the reaction of a ketoalkyne with a titanium-nitrogen complex prepared from molecular nitrogen.

M. Akashi, Y. Sato and M. Mori, *J. Org. Chem.*, 2001, **66**, 7873.

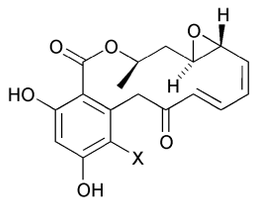


Radiciclol and Monocillin I

Biological activity: Suppresses the transformed phenotype caused by various oncogenes such as *src*, *ras* and *raf via* inhibition of the Hsp90 molecular chaperone.

Key steps: (a) metallated dithiane alkylation; (b) ring-closing metathesis.

R. M. Garbaccio, S. J. Stachel, D. K. Baeschlin and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2001, **123**, 10903.



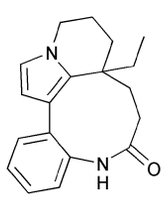
X = Cl Radiciclol
X = H Monocillin I

(±)-Rhazinilam

Biological activity: (a) isolated from a number of plant sources such as *Rhazya stricta* Decaisne, *Melodinus australis* and *Kopsia singapurensis*; (b) mimics the cellular effects of paclitaxel.

Key steps: conversion of a lactam into an annulated pyrrole derivative *via* the formation of a thiophenyl imino ether.

P. Magnus and T. Rainey, *Tetrahedron*, 2001, **57**, 8647.

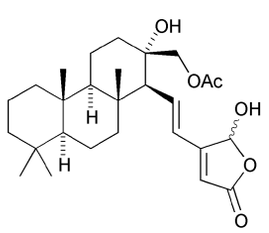


(–)-Spongianolide A

Biological activity: (a) isolated from the marine sponge *Spongia* sp.; (b) inhibits proliferation of the mammary tumour cell line MCF-7 (IC_{50} = 0.5–1.4 μM); (c) inhibits proliferation of protein kinase C (PKC) (IC_{50} = 20–30 μM).

Key steps: tin tetrachloride mediated olefin cyclisation.

N. Furuichi, T. Hata, H. Soetjipto, M. Kato, and S. Katsumura, *Tetrahedron*, 2001, **57**, 8425.



(±)-Thielocin A1β

Source: culture broths of ascomycetes *Thielavia terricola* RF-143.

Biological activity: inhibitor of human secretory phospholipase A_2.

Key steps: reaction of a cyclohexadienone with a quinone methide to create the linear tricyclic ring system.

Y. Genisson, P. C. Tyler, R. G. Ball and R. N. Young, *J. Am. Chem. Soc.*, 2001, **123**, 11381.