# *Perkin 1 Abstracts:* Natural Product Synthesis

**Duncan McArthur and Jacqueline Milne**

*Department of Chemistry, University of Glasgow, Glasgow, UK G12 8QQ*

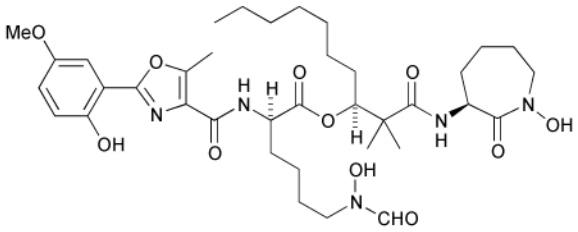
*Perkin 1 Abstracts: Natural Product Synthesis* aims to highlight syntheses that have been recently published. It includes brief descriptions of *biological activity* and *key steps*. A more comprehensive list of Natural Product syntheses and isolations can be found in *Natural Product Updates*.

## (–)-Amamistatin A

*Biological activity*: antiproliferative agent against several human cancer cell lines.

*Key steps*: (a) synthesis of a β-hydroxy acid *via* chiral oxazaborolidine-mediated aldol reaction; (b) oxazole ring constructed *via* cyclodehydration of an *N*-acylthreonine.

F. Yokokawa, K. Izumi, J. Omata and T. Shioiri, *Tetrahedron*, 2000, **56**, 3027.

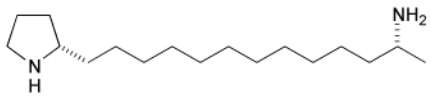



## (2*S*,12'*R*)-2-(12'-Aminotridecyl)pyrrolidine

*Biological activity*: defense alkaloid extracted from the bodies of adult Mexican bean beetles.

*Key steps*: (a) diastereoselective 1,2-addition of methyllithium to an aldehyde-SAMP-hydrazone; (b) reductive N-N bond cleavage.

D. Enders and C. Thiebes, *Synthesis*, 2000, **4**, 510.

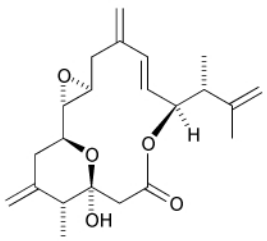



## (–)-Amphidinolide P

*Biological activity*: (a) isolated from strains of microscopic marine dinoflagellates; (b) the amphidinolide family show potent *in vitro* antitumour activity in NCI screens.

*Key steps*: (a) Sakurai allylation reaction; (b) Stille cross-coupling; (c) macrolactonisation by intramolecular transesterification.

D. R. Williams, B. J. Myers and L. Mi, *Org. Lett.*, 2000, **2**, 945.

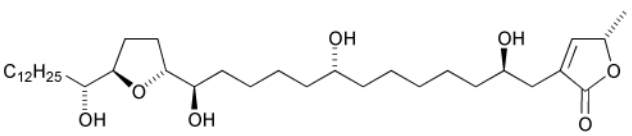



## Annonacin

*Biological activity*: (a) 9ASK (astrocytoma reversal) activity; (b) high cytotoxicity against KB cells (human nasopharyngeal carcinoma) and P388 cells (mouse leukemia).

*Key steps*: (a) highly convergent route starting from D-glucono-1,5-lactone, L-ascorbic acid and ethyl L-lactate; (b) coupling between a phosphonium salt and an epoxide; (c) Sharpless asymmetric dihydroxylation.

T.-S. Hu, Y.-L. Wu and Y. Wu, *Org. Lett.*, 2000, **2**, 887.

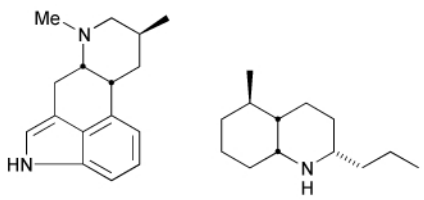



## (±)-Costaclavine and (±)-Pumiliotoxin C

*Biological activity*: not reported.

*Key steps*: (a) Pummerer reaction of imidosulfoxides bearing tethered alkenyl groups; (b) intramolecular dipolar cycloaddition of a mesoionic betaine intermediate.

A. Padwa, T. M. Heidelbaugh and J. T. Kuethe, *J. Org. Chem.*, 2000, **65**, 2368.



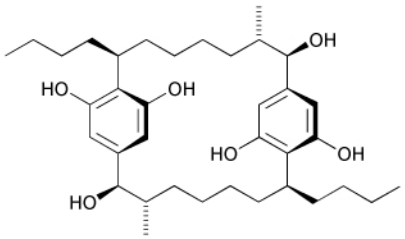

Costaclavine Pumiliotoxin C

### (–)-Cylindrocyclophane A

*Biological activity*: not reported.

*Key steps*: (a) double Horner–Emmons macrocyclic dimerisation; (b) double asymmetric hydroboration of trisubstituted alkenes using $IpcBH_2$.

T. R. Hoye, P. E. Humpal and B. Moon, *J. Am. Chem. Soc.*, 2000, **122**, 4982.

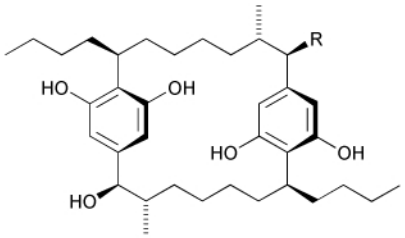



### (–)-Cylindrocyclophanes A and F

*Biological activity*: not reported.

*Key steps*: (a) reaction of a cyclobutenone with a siloxyalkyne to generate the resorcinol ring; (b) creation of the macrocycle by double metathesis using the Schrock Mo catalyst.

A. B. Smith, S. A. Kozmin, C. M. Adams and D. V. Paone, *J. Am. Chem. Soc.*, 2000, **122**, 4984.



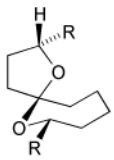

(–)-Cylindrocyclophane A (R = OH)
(–)-Cylindrocyclophane F (R = H)

### (2*S*,5*R*,7*S*)-2,7-Dimethyl-1,6-dioxaspiro[4.6]undecane and (2*S*,5*R*,7*S*)-2,7-Diethyl-1,6-dioxaspiro[4.6]undecane

*Biological activity*: pheromones produced by *Andrena haemorrhoa* and *Andrena wilkella* respectively.

*Key steps*: (a) baker's yeast reduction of two ketone groups to give secondary alcohols; (b) use of a nitro group as a latent ketone.

G. Bez, M. Sarma Bezbarua, A. K. Saikia and N. C. Barua, *Synthesis*, 2000, **4**, 537.



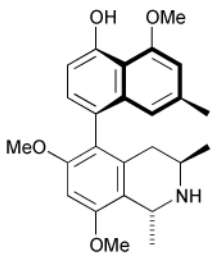

R = Me: (2*S*,5*R*,7*S*)-2,7-Dimethyl-1,6-dioxaspiro[4.6]undecane
R = Et: (2*S*,5*R*,7*S*)-2,7-Diethyl-1,6-dioxaspiro[4.6]undecane

### *O,O′*-Dimethylkorupensamine A and (–)-Steganone

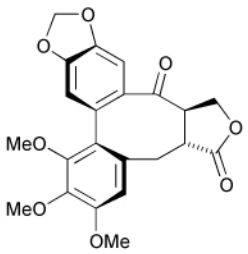
*Biological activity*: (a) Steganone has *in vivo* activity against P-338 leukemia in mice and *in vitro* activity against cells derived from human carcinoma of the nasopharynx; (b) *O,O′*-dimethylkorupensamine A is potentially active against malaria, HIV-1 and HIV-2.

*Key steps*: Pd(0)-mediated Suzuki–Miyaura cross-coupling of planar chiral (arene)chromium complexes with *o*-substituted arylboronic acids to give stereoselectively axially chiral mono $Cr(CO)_3$-complexes of biaryls.

K. Kamikawa, T. Watanabe, A. Daimon and M. Uemura, *Tetrahedron*, 2000, **56**, 2325.




*O,O′*-Dimethylkorupensamine A




(–)-Steganone

### (±)-Grimaldone

*Biological activity*: isolated from the central European liverwort *Mannia fragrans*.

*Key steps*: (a) Lewis-acid catalysed rearrangement of a diazo ketone; (b) intramolecular cyclopropanation of a diazo ketone.

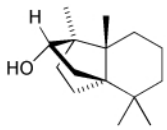
A. Srikrishna and D. B. Ramachary, *Tetrahedron Lett.*, 2000, **41**, 2231.


### (±)-Junicedranol

*Biological activity*: not reported.

*Key steps*: (a) anionic [1,3] rearrangement of an 8-methylenebicyclo[3.2.1]-oct-6-en-2-ol giving a cyclopentadiene derivative; (b) Diels–Alder reaction.

T. Uyehara, Y. Sato, H. Ishizuka, Y. Sakiyama, M. Ueno and T. Sato, *Tetrahedron Lett.*, 2000, **41**, 1939.

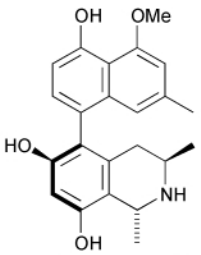


## Korupensamines A and B

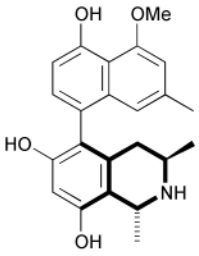
*Biological activity*: (a) antimalarial activities *in vitro* and *in vivo*; (b) synthetic and biogenetic precursors to anti-HIV homo-and heterodimeric naphthylisoquinolines.

*Key steps*: (a) Pd-catalysed biaryl synthesis; (b) Naphthalene ring constructed *via* a Stobbe condensation followed by an intramolecular Friedel–Crafts.

G. Bringmann, M. Ochse and R. Götz, *J. Org. Chem.*, 2000, **65**, 2069.



Korupensamine A



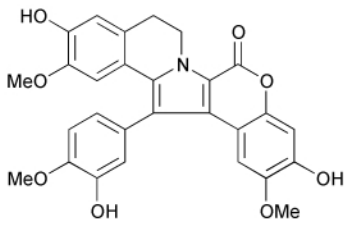
Korupensamine B

## Lamellarin L

*Biological activity*: (a) isolated from prosobranch mollusks and ascidians; (b) some alkaloids possessing the hexacyclic lamellarin system inhibit the growth of several tumour cell lines and revert the P-glycoprotein-mediated multidrug resistance (MDR) of tumour cells at very low concentrations.

*Key steps*: (a) one-pot reaction of an ethyl 3-arylpyruvate with a methyl 2-bromo-3-arylpyruvate in the presence of an arylethylamine to form the pyrrole moiety; (b) Pd(0)-catalysed Heck cyclisation.

C. Peschko, C. Winklhofer and W. Steglich, *Chem. Eur. J.*, 2000, **6**, 1147.

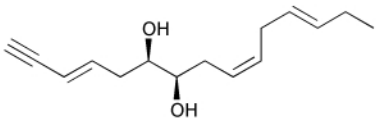



## *trans*-(+)-Laurediol

*Biological activity*: not reported.

*Key steps*: (a) Sharpless asymmetric dihydroxylation; (b) Wittig reaction.

T. Martín and V. S. Martín, *Tetrahedron Lett.*, 2000, **41**, 2503.

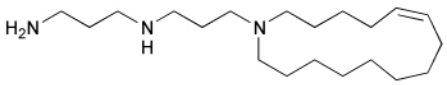



## Motuporamine C

*Biological activity*: *in vitro* cytotoxicity against a panel of human cancer cell lines.

*Key steps*: ring-closing alkyne metathesis.

A. Fürstner and A. Rumbo, *J. Org. Chem.*, 2000, **65**, 2608.

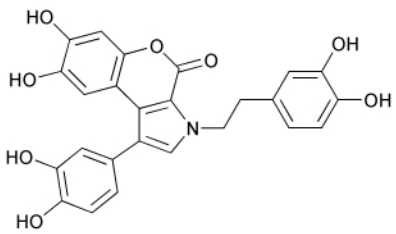



## Ningalin B

*Biological activity*: while lacking inherent cytotoxic activity, some ningalin B synthetic precursors, but not ningalin B itself, potently reverse multidrug resistance (MDR), resensitizing a resistant human colon cancer cell line (HTC116/VM46) to vinblastine and doxorubicin.

*Key steps*: heterocyclic azadiene Diels–Alder strategy (1,2,4,5-tetrazine → 1,2-diazine → pyrrole).

D. L. Boger, D. R. Soenen, C. W. Boyce, M. P. Hedrick and Q. Jin, *J. Org. Chem.*, 2000, **65**, 2479.

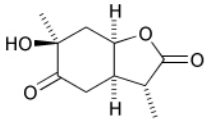



## Paeonilactone A

*Biological activity*: isolated from the root of *Paeonia Albiflora* Pallas that has been extensively used in Chinese and Japanese herbal medicine for the treatment of abdominal disorders.

*Key steps*: (a) Pd(II)-catalysed 1,4-oxylactonisation of a conjugated diene; (b) copper(I)-catalysed cross-coupling reaction between dienyltriflates with Grignard reagents.

C. Jonasson, M. Rönn and J.-E. Bäckvall, *J. Org. Chem.*, 2000, **65**, 2122.

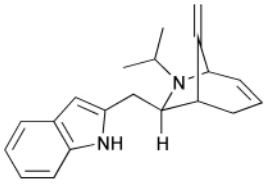


## Peduncularine

*Biological activity*: (a) isolated from the Tasmanian shrub *Aristotelia peduncularis*; (b) biological activity not reported.

*Key steps*: (a) Diels–Alder reaction; (b) intramolecular amidyl radical cyclisation of a hydroxyamic acid based radical with a pendant olefin to generate a functionalised 6-azabicyclo[3.2.1]octane ring.

X. Lin, D. Stien and S. M. Weinreb, *Tetrahedron Lett.*, 2000, **41**, 2333.

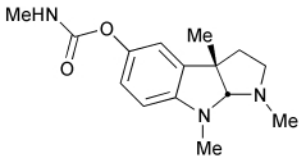



## Physostigmine

*Biological activity*: analogues of the natural product show promise for the treatment of Alzheimer's disease.

*Key steps*: alkylative cyclisation of 1,3-dimethylindole with (*Z*)-aziridine catalysed by $Sc(OTf)_3$ and TMSCl.

M. Nakagawa and M. Kawahara, *Org. Lett.*, 2000, **2**, 953.

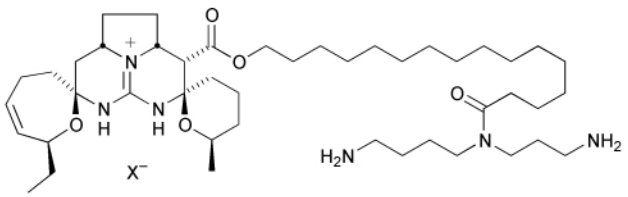



## (–)-Ptilomycalin A

*Biological activity*: antitumour agents.

*Key steps*: tethered Biginelli condensation of a β-keto ester with a ureidoaminal to create the guanidine nucleus. Crambescidin 657, its methyl ester and crambescidin 800 were also synthesised. An accompanying paper describes syntheses of 13,14,15-isocrambescidin 800 and 13,14,15-isocrambescidin 657.

D. S. Coffey, A. I. McDonald, L. E. Overman, M. H. Rabinowitz and P. A. Renhowe, *J. Am. Chem. Soc.*, 2000, **122**, 4893.

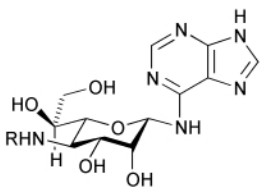



## Spicamycin Amino Nucleoside

*Biological activity*: Spicamycin was isolated from the culture broth of *Streptomyces alanosinicus* as a potent differentiation inducer of HL-60 human promyelocytic leukemia cells.

*Key steps*: coupling of a glycosylamine with 6-chloropurine in the presence of $Pd_2(dba)_3$ and (+)- BINAP to construct the *N*-glycoside linkage.

T. Suzuki, S. Tanaka, I. Yamada, Y. Koashi, K. Yamada and N. Chida, *Org. Lett.*, 2000, **2**, 1137.

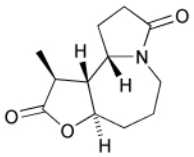



## (–)-Stemoamide

*Biological activity*: Members of the *Stemona* species have been used in Chinese traditional medicine to manage respiratory disorders and as antihelminthics and antiparasitics.

*Key steps*: intramolecular Diels–Alder/*retro*-Diels–Alder reaction of an alkyne and an oxazole generated the 7-membered ring and a butenolide presursor in one step. The synthesis was accomplished in 9 steps (4% yield overall).

P. A. Jacobi and K. Lee, *J. Am. Chem. Soc.*, 2000, **122**, 4295.




## (–)-Triptolide

*Biological activity*: (a) antitumor; (b) antiinflammatory; (c) immunosuppressive; (d) antifertile.

*Key steps*: lanthanide triflate-catalysed asymmetric oxidative radical cyclisation mediated by $Mn(OAc)_3$.

D. Yang, X.-Y. Ye and M. Xu, *J. Org. Chem.*, 2000, **65**, 2208.