Perkin 1 Abstracts: Natural Product Synthesis

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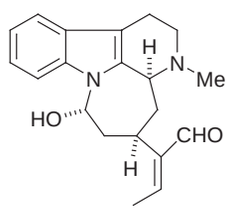
Perkin 1 Abstracts: Natural Product Synthesis aims to highlight syntheses that have been recently published. It includes brief descriptions of *biological activity* and *key steps*. A more comprehensive list of Natural Product syntheses and isolations can be found in *Natural Product Updates*

Akagerine

Biological activity: isolated from *Strychnos usambarensis*; activity not reported.

Key steps: ring closure *via* a Pummerer reaction.

M.-L. Bennasar, B. Vidal, B. A. Sufi and J. Bosch, *Chem. Commun.*, 1998, 2639.

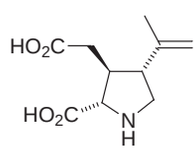


(+)-α-Allokainic Acid

Biological activity: (a) a neuroexcitatory amino acid; (b) conformationally restricted analogue of glutamate.

Key steps: (a) Nickel-catalysed cyclisation of a D-serine-derived alkynyl enone with trimethylaluminum; (b) palladium-catalysed reductive allylic carbonate transposition.

M. V. Chevliakov and J. Montgomery, *Angew. Chem. Int. Ed.*, 1998, **37**, 3144.

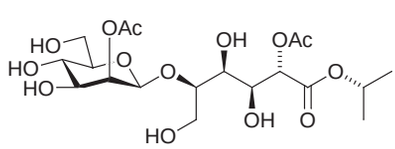


Caloporoside Disaccharide

Biological activity: The parent molecule Caloporoside is a novel inhibitor of phospholipase C. The related desacetyl caloporoside is a fungal metabolite that is reported to inhibit the binding of ^{35}S-labelled *t*-butylbicyclophosphorothionate to the $GABA_A$/benzodiazepine chloride channel receptor complex.

Key steps: direct and stereoselective formation of a β-mannosidic linkage using the sulfoxide method.

D. Crich and G. R. Barba, *Tetrahedron Lett.*, 1998, **39**, 9339.

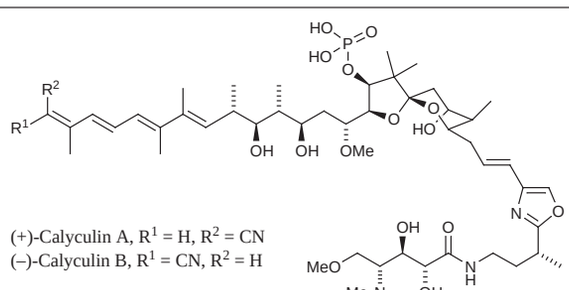


(+)-Calyculin A and (–)-Calyculin B

Biological activity: potent serine-threonine protein phoisphatase 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. J.-W. Duan, J. Barbosa, K. G. Hull, M. Iwashima, Y. Qiu, P. G. Spoors, E. Bertounesque and B. A. Salvatore, *J. Org. Chem.*, 1998, **63**, 7596.



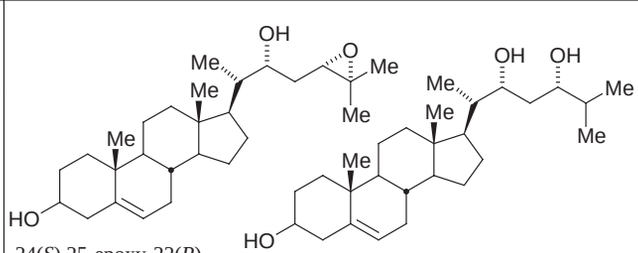
(+)-Calyculin A, R^1 = H, R^2 = CN
(–)-Calyculin B, R^1 = CN, R^2 = H

24(*S*),25-Epoxy-22(*R*)-hydroxycholesterol and 22(*R*),24(*S*)-Dihydroxycholesterol

Biological activity: bind to the ligand binding domain of LXRα and LXRβ with K_d values of *ca*. 1μM.

Key steps: (a) reaction of an arsonium ylide and an aldehyde to give an *E*-α,β-enone; (b) C_α-O reductive cleavage of an epoxide using samarium iodide; (c) Wittig coupling; (d) prenylbarium addition to an aldehyde; (e) hydroxy-directed epoxidation.

E. J. Corey and M. J. Grogan, *Tetrahedron Lett.*, 1998, **39**, 9355.



24(*S*),25-epoxy-22(*R*)-hydroxycholesterol

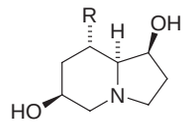
22(*R*), 24(*S*)-dihydroxycholesterol

(+)-7-Deoxy-6-epicastanospermine, (–)-7,8-Dideoxy-6-epicastanospermine and (–)-*N*-Acetylslaframine

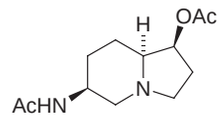
Biological activity: (a) (+)-7-Deoxy-6-epicastanospermine is a known inhibitor of amyloglucosidase and yeast α-glucosidase; (b) the related (–)-slaframine has a potential use in the treatment of diseases arising from cholinergic dysfunctions.

Key steps: stereoselective intramolecular iodocyclisation of trichloroacetimidates generated from *cis*-olefinic allylic alcohols.

S. H. Kang, J. S. Kim and J.-H. Youn, *Tetrahedron Lett.*, 1998, **49**, 9047.



R = OH (+)-7-Deoxy-6-epicastanospermine
R = H (–)-7,8,Dideoxy-6-epicastanospermine



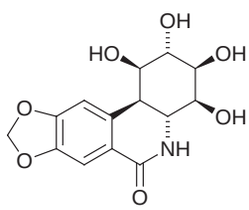
(–)-*N*-Acetylslaframine

(+)-7-Deoxypancratistatin

Biological activity: not reported.

Key steps: (a) cyclisation of an aryl radical onto an *N*-aziridinylimine; (b) removal of both an acetonide and an unusually robust TBS protecting groups using BF_3•OEt_2 in dichloromethane.

G. E. Keck, T. T. Wager, and S. F. McHardy, *J. Org. Chem.*, 1998, **63**, 9164.

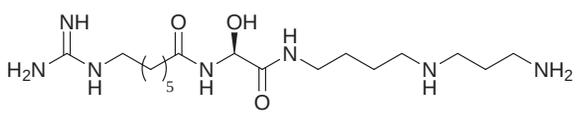


(–)-15-Deoxyspergualin

Biological activity: has been marketed in Japan for the control of corticoresistant acute renal graft rejection.

Key steps: (a) conversion of an azido group to a primary amine by action of PPh_3/H_2O which allows a selective conversion in the presence of benzyloxy and benzyloxycarbonyl groups; (b) use of the Pearlman's catalyst in the final deprotection step; (c) total synthesis of the title compound in 9 steps, 7.5% overall yield, and ee 99.5%.

P. Durand, P. Richard and P. Renault, *J. Org. Chem.*, 1998, **63**, 9723.

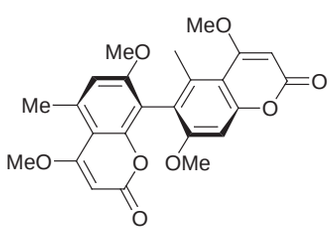


Desertorin C

Biological activity: not reported.

Key steps: (a) Mitsunobu reactions; (b) copper-mediated intramolecular oxidative coupling to form a biphenol derivative from a D-threitol derivative.

R. V. Kyasnoor and M. V. Sargent, *Chem Commun.*, 1998, 2713.

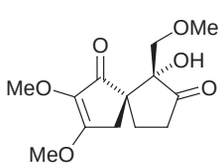


Dimethyl gloiosiphone A

Biological activity: isolated from the algae *Gloiosiphonia verticillaris*, which exhibits antimicrobial activity against several *Staphyloccus*, *Bacillus* and *Salmonella* species.

Key steps: an α-carbonyl radical spirocyclisation.

C.-K. Sha and W.-Y. Ho, *Chem Commun.*, 1998, 2709. See also: Y. Hashizume, S. Maki, M. Ohashi and H. Niwa, *Synlett*, 1998, 1357.

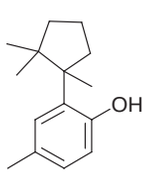


α-Herbertenol

Biological activity: (a) shows antifungal activity; (b) the related herbertenediol and mastigophorene show anti-lipid peroxidation activity and interesting neurotrophic properties.

Key steps: (a) synthesis of a 1,5-diketone involving the addition of dihydropyranone to an organolithium reagent; (b) titanium(0)-mediated intramolecular pinacolic coupling reaction.

D. C. Harrowven and J. C. Hannam, *Tetrahedron Lett.*, 1998, **39**, 9573.

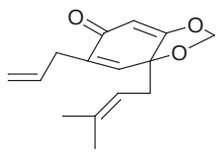


Illicinone and Tricycloillicinone

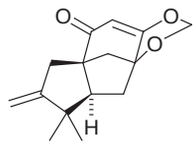
Biological activity: (a) members of the class of "small molecule" neurotrophic factors; (b) exhibit their effects through increased choline acetyltransferase (ChAT) activity, resulting in enhanced sprouting during the development of neurons in a primary culture of fetal rat cerebral tissues.

Key steps: sequential aromatic Claisen rearrangements.

T. R. R. Pettus, X.-T. Chen and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1998, **120**, 12684.



Illicinone



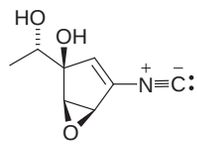
Tricycloillicinone

(–)-Isonitrin B

Biological activity: antibiotic.

Key steps: construction of a cyclopentene ring by insertion of an alkenylidene carbene into C-H bond of a secondary alcohol.

D. F. Taber, H. Yu, C. D. Incarvito and A. L. Rheingold, *J. Am. Chem. Soc.*, 1998, **120**, 13285.

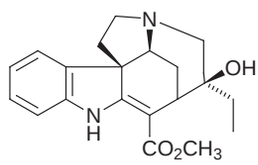


(–)-Lochneridine

Biological activity: not reported.

Key steps: (a) Horner-Emmons condensation; (b) modified Grignard reaction.

M. E. Kuehne and F. Xu, *J. Org. Chem.*, 1998, **63**, 9434.

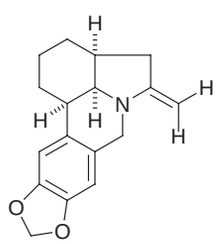


(–)-γ-Lycorane

Biological activity: no useful pharmacological properties.

Key steps: a Bu_3SnH-mediated-5-*endo*-*trig* radical cyclisation of *N*-vinylic α-halo amides.

M. Ikeda, S. Ohtani, T. Sato, and H. Ishibashi, *Synthesis*, 1998, 1803.

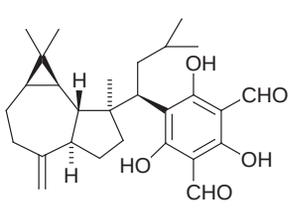


(–)-Macrocarpal C

Biological activity: some Macrocarpals show a wide range of biological activities such as (a) inhibitory activity of HIV reverse transcriptase; (b) antibacterial activity against cariogenic and periodontopathic bacteria.

Key steps: highly stereoselective coupling reaction of a silyldienol ether with a biomimetic benzyl cation species which was generated from novel hexasubstituted benzene chronium tricarbonyl complexes.

T. Tanaka, H. Mikamiyama, K. Maeda, C. Iwata, Y. In and T. Ishida, *J. Org. Chem.*, 1998, **63**, 9782.

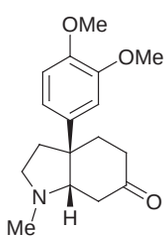


(–)-Mesembrine

Biological activity: no significant biological activity.

Key steps: (a) stereoselective alkylation of a dianion derived from a C_2 symmetric imidazoline allowing efficient formation of a quaternary benzylic centre; (b) cleavage of a phenylsulfonyl protecting group under Birch conditions.

P. I. Dalko, V. Brun, and Y. Langlois, *Tetrahedron Lett.*, 1998, **39**, 8979.

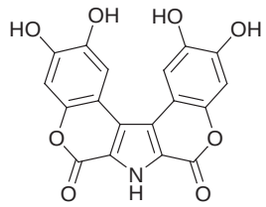


Ningalin A

Biological activity: Members of this class of marine natural products reverse multidrug resistance at noncytotoxic concentrations more effectively than verapamil, resensitising resistant malignant colon cancer cells to treatment

Key steps: (a) heterocyclic azadiene Diels-Alder reaction involving a 1,2,4,5-tetrazine; (b) reductive cleavage of 1,2-diazine adducts with zinc to give a pyrrole ring. Lamellarin O, lukianol A and permethyl storniamide A were also synthesised.

D. L. Boger, C. W. Boyce, M. A. Labroli, C. A. Sehon and Q. Jin, *J. Am. Chem. Soc.*, 1999, **121**, 54.

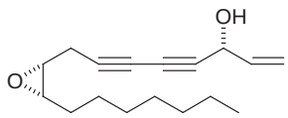


Panaxydol

Biological activity: potential anti-tumour agent isolated from *Panax ginseng* C. A. Meyer.

Key steps: a Cadiot-Chodkiewicz reaction.

W. Lu, G. Zheng, Haji, A. Aisa and J. Cai, *Tetrahedron Lett.*, 1998, **39**, 9521.

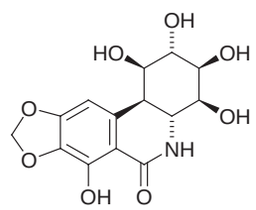


(+)-Pancratistatin

Biological activity: antitumour agent.

Key steps: β-azidonation reaction using iodosylbenzene and $TMSN_3$.

P. Magnus and I. K. Sebhat, *Tetrahedron*, 1998, **54**, 15509.

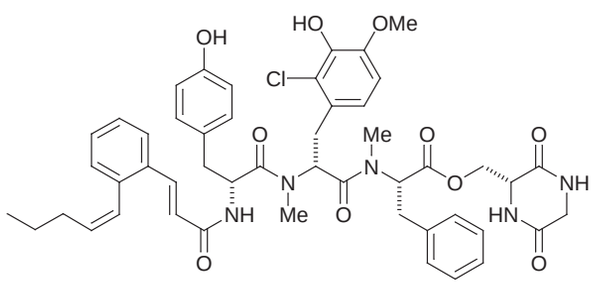


(–)-Pepticinnimin E

Biological activity: protein farnesyl transferease inhibitor.

Key steps: modified tyrosine derivative synthesised using the Schöllkopf lactim ether method.

K. Hinterding, P. Hagenbuch, J. Rétey and H. Waldmann, *Chem. Eur. J.*, 1999, **5**, 227.

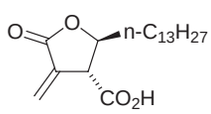


(±)-Protolichesterinic Acid and (±)-Rocellaric Acid

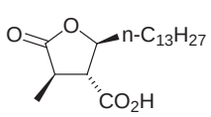
Biological activity: not reported.

Key steps: stereoselective formation of a homoallylic alcohol is achieved with the use of a tungsten-π-allyl complex.

M.-J. Chen and R.-S. Liu, *Tetrahedron Lett.*, 1998, **39**, 9465.



protochesterinic acid



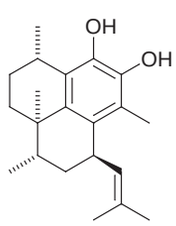
rocellaric acid

(–)-Pseudopterosin A and E Aglycone

Biological activity: antiinflammatory agent.

Key steps: (a) lipase-catalysed esterification of a mixture of alcohols generated from nonstereoselective hydroboration of (*S*)-(–)-limonene; (b) construction of the aromatic ring by Robinson annulation followed by MnO_2-mediated aromatisation; (c) the remaining ring was constructed by electrophilic aromatic substitution using an allyl carbocation.

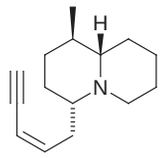
E. J. Corey and S. E. Lazerwith, *J. Am. Chem. Soc.*, 1998, **120**, 12777.



Quinolizidine 217A

Biological activity: extracted from the skin of certain poisonous frogs and toads.

Key steps: cyclisation of an azide onto an ester-bearing alkene provided a 3,4,5,6-tetrahydropyridine that was reduced in a stereoselectively to produce a *cis*-2,6-disubstituted piperidine.

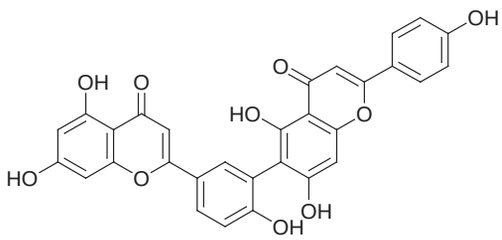


W. H. Pearson and H. Suga, *J. Org. Chem.*, 1998, **63**, 9910.

Robustaflavone

Biological activity: potent nonnucleoside inhibitor of hepatitis B virus (HBV) replication.

Key steps: (a) formation of an apigenin 3'-boronate using a palladium-catalysed exchange of the corresponding 3'-iodide with a diboron reagent; (b) Suzuki coupling.

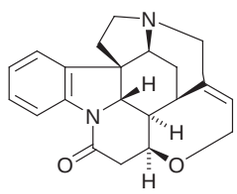


D. E. Zembower and H. Zhang, *J. Org. Chem.*, 1998, **63**, 9300.

(–)-Strychnine

Biological activity: poison.

Key steps: (a) Horner-Emmons condensation; (b) synthesis *via* the Wieland-Gumlich aldehyde.

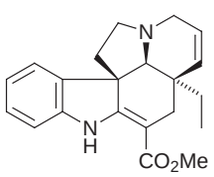


M. E. Kuehne and F. Xu, *J. Org. Chem.*, 1998, **63**, 9427.

(±)-Tabersonine

Biological activity: no biolological activity reported.

Key steps: the 12-step synthesis (30% yield overall) was based on (a) a regioselective Diels-Alder reaction using a 1-amino-3-siloxy-1,3-butadiene; (b) intramolecular olefin metathesis to construct the *cis*-hexahydroquinoline ring; (c) indole synthesis *via* regiospecific *ortho*-nitrophenylation of enol silane.

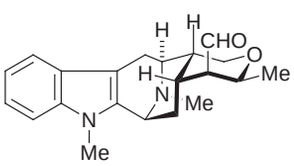


S. A. Kozmin and V. H. Rawal, *J. Am. Chem. Soc.*, 1998, **120**, 13523.

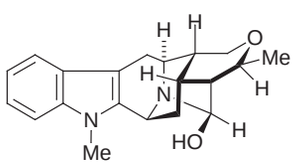
Talcarpine and Talpinine

Biological activity: isolated from the stem bark of *Pleicarpa talbotii* Wernham.

Key steps: (a) Pictet-Spengler reaction; (b) Dieckmann cyclisation; (c) anionic oxy-Cope rearrangement.



Talcarpine



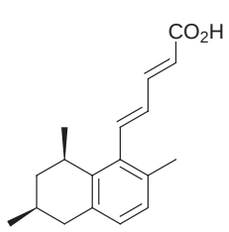
Talpinine

P. Yu and J. M. Cook, *J. Org. Chem.*, 1998, **63**, 9160.

Tanzawaic Acid A (GS-1302-3)

Biological activity: (a) isolated from *Pencillium citrium* SCRC-SA125; (b) has been patented as an antimicrobial agent.

Key steps: (a) Suzuki-Tsuchihashi's reductive pinacol rearrangement; (b) use of Liebeskind's tin scavenger in a Stille coupling with a highly hindered aryl triflate.

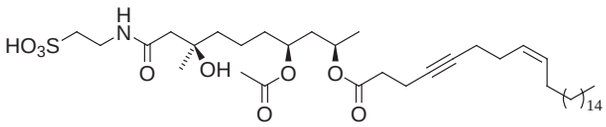


H. Arimoto, K. Nishimura, M. Kuramoto and D. Uemura, *Tetrahedron Lett.*, 1998, **39**, 9513.

Taurospongin A

Biological activity: potent inhibitor of both DNA polymerase β and HIV reverse transcriptase.

Key steps: (a) kinetic resolution of a terminal epoxide with a (salen)Cr catalyst and $TMSN_3$; (b) asymmetric catalytic transfer hydrogenation of ynones.

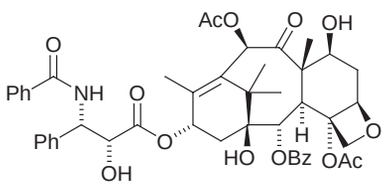


H. Lebel and E. N. Jacobsen, *J. Org. Chem.*, 1998, **63**, 9624.

(–)-Taxol

Biological activity: antitumour agent

Key steps: several innovative variants of the aldol reaction pioneered by Mukaiyama are strategically deployed to construct the target.

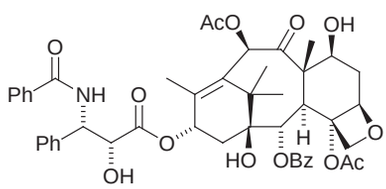


T. Mukaiyama, I. Shiina, H. Iwadare, M. Saitoh, T. Nishimura, N. Ohkawa, H. Sakoh, K. Nishimura, Y. Tani, M. Hasegawa, K. Yamada and K. Saitoh, *Chem. Eur. J.*, 1999, **5**, 121.

(–)-Taxol

Biological activity: antitumour agent

Key steps: (a) cyclooctane ring generated by an intramolecular directed aldol reaction; (b) introduction of the C-19 angular methyl group by reductive cleavage of a cyclopropyl ketone.

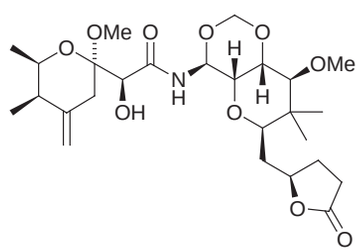


K. Morihira, R. Hara, S. Kawahara, T. Nishimori, N. Nakamura, H. Kusama and I. Kuwajima, *J. Am. Chem. Soc.*, 1998, **120**, 12980.

Theopederin D

Biological activity: (a) potent antitumor agent (IC_{50} = 1.0 nM against P388 murine leukaemia); (b) antiviral.

Key steps: (a) Mukaiyama aldol reaction; (b) the trioxabicyclo[4.4.0]decane ring was created by reaction of a methoxymethyl ether with a silyloxirane induced by phosphorus pentoxide; (c) Curtius rearrangement.

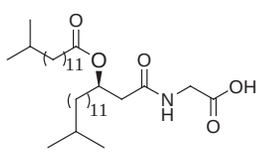


P. J. Kocienski, R. Narquizian, P. Raubo, C. Smith, and F. T. Boyle, *Synlett*, 1998, 1432.

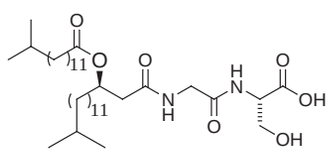
Topostins B567 and D654 (WB-3559D, Flavolipin)

Biological activity: inhibitors of mammalian DNA topoisomerase I.

Key steps: (a) asymmetric hydrogenation of a β-keto ester using (*R*)-BINAP ruthenium bromide; (b) peptide coupling using diethyl phosphorocyanidate (DEPC, $(EtO)_2P(O)CN$).



Topostin B567



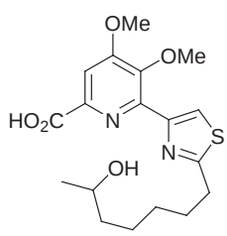
Topostin D654

T. Shioiri, Y. Terao, N. Irako and T. Aoyama, *Tetrahedron*, 1998, 15701.

WS75624 B

Biological activity: potent inhibitor of endothelin-converting enzyme (ECE); IC_{50} = 0.03 μg/mL.

Key steps: palladium(0)-catalysed cross-coupling of an organozinc reagent with an aryl bromide.



S.-T. Huang and D. M. Gordon, *Tetrahedron Lett.*, 1998, **39**, 9335.