



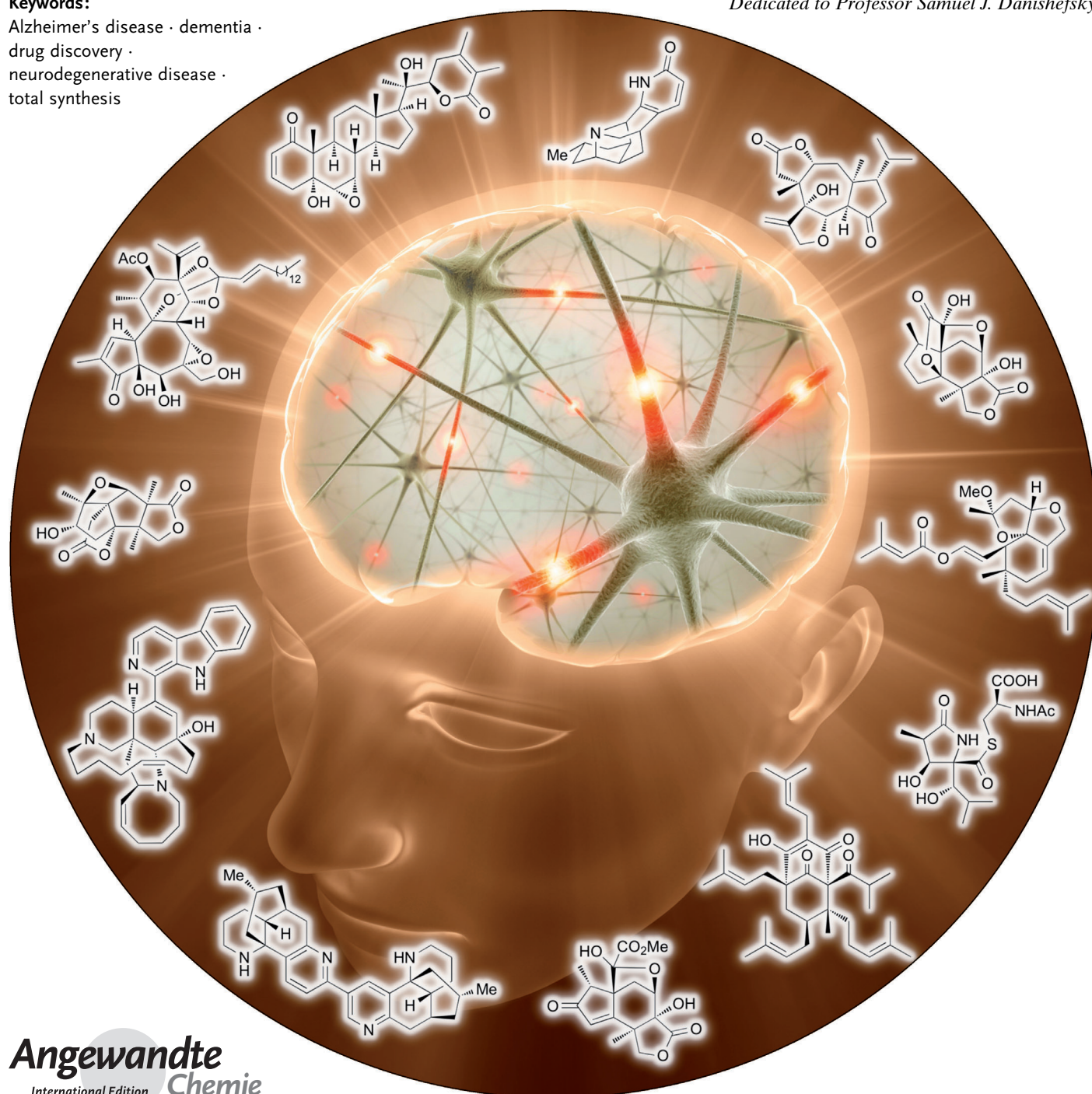
Neurotrophic Natural Products: Chemistry and Biology

Jing Xu, Michelle H. Lacoske, and Emmanuel A. Theodorakis*

Keywords:

Alzheimer's disease · dementia ·
drug discovery ·
neurodegenerative disease ·
total synthesis

Dedicated to Professor Samuel J. Danishefsky



Neurodegenerative diseases and spinal cord injury affect approximately 50 million people worldwide, bringing the total healthcare cost to over 600 billion dollars per year. Nervous system growth factors, that is, neurotrophins, are a potential solution to these disorders, since they could promote nerve regeneration. An average of 500 publications per year attests to the significance of neurotrophins in biomedical sciences and underlines their potential for therapeutic applications. Nonetheless, the poor pharmacokinetic profile of neurotrophins severely restricts their clinical use. On the other hand, small molecules that modulate neurotrophic activity offer a promising therapeutic approach against neurological disorders. Nature has provided an impressive array of natural products that have potent neurotrophic activities. This Review highlights the current synthetic strategies toward these compounds and summarizes their ability to induce neuronal growth and rehabilitation. It is anticipated that neurotrophic natural products could be used not only as starting points in drug design but also as tools to study the next frontier in biomedical sciences: the brain activity map project.

1. Introduction

Neurons are the basic building blocks of the nervous system, which includes the brain, the spinal cord, and the peripheral ganglia. Neurodegenerative disease (NDD) is a catchall term for heterogeneous and often sporadic disorders that are characterized by progressive nervous system dysfunction resulting from loss of neural structure and function as well as from neural death.^[1] Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis are notable examples of these disorders. On the other hand, spinal cord injury arises from extreme trauma to the spinal cord.^[2] Currently, neurodegenerative diseases and spinal cord injuries affect about 50 million people worldwide bringing the total annual healthcare cost to over 600 billion dollars.^[2a,3] Efforts to understand the progression of these diseases point to a series of molecular and cellular events, such as accumulation of misfolded proteins, protofibril formation, dysfunction of the ubiquitin-proteasome system, mitochondrial damage, oxidative stress, and synaptic failure.^[4] Nonetheless, the etiologies of these diseases still remain under investigation.

Typically, a neuron consists of a cell body, dendrites, and an axon. Although the selective pruning of exuberant neural projections is a fundamental mechanism for maintaining neural plasticity, aberrant axon degeneration, neuronal atrophy, and loss of synapses are a common scenario of acute injury or chronic NDDs.^[5] Currently, the therapies for NDDs and spinal cord injuries mainly relieve disease symptoms and control the damage. It is well-known that promoting the regeneration of neural axons, dendrites, and synapses within the adult nervous system would be a highly desirable therapeutic approach.^[6] Nonetheless, at present such therapeutic strategies have not yet been successful.^[2a,7]

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Neurotrophins are a family of proteins that regulate neuron survival, development, and function.^[8] Despite their overall promise, the advancement of neurotrophins as therapeutics has encountered significant problems,

likely because of their suboptimal pharmacological properties.^[9] These include poor serum stability, poor oral bioavailability, and limited penetration of the central nervous system (CNS).^[10,11] On the other hand, small molecules, such as dopamine, γ -aminobutyric acid (GABA), and acetylcholine (ACh), can overcome these limitations and were shown to play an important role in the management of NDDs.^[12] Nature has yielded a fascinating collection of small molecules that are able to mimic neurotrophins or modulate neural cellular signaling. Thus, therapeutic strategies based on neurotrophic small molecules could bypass the limitations of protein-based therapeutics and could lead to clinical applications.

In this Review we will introduce the representative neurodegenerative diseases and spinal cord injuries as well as the major neurotrophins. We will then highlight the main families of neurotrophic natural products, focusing in particular on compounds that have been shown to enhance neurite outgrowth, and will summarize approaches toward their chemical syntheses and biological profiles.

1.1. Neurodegenerative Diseases and Spinal Cord Injury

1.1.1. Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia and affects approximately 36 million people world-

[*] Dr. J. Xu, M. H. Lacoske, Prof. Dr. E. A. Theodorakis
Department of Chemistry and Biochemistry
University of California
San Diego, 9500 Gilman Drive, La Jolla, CA, 92093-0358 (USA)
E-mail: etheodor@ucsd.edu
Homepage: <http://theodorakisgroup.ucsd.edu>

wide.^[13] From a biological standpoint, pathogenic aggregation of amyloid- β (A β) and tau protein in the form of extracellular amyloid plaques and intracellular neurofibrillary tangles characterize this disease.^[3a] As these aggregations advance, the neurons gradually undergo dysfunction and cell death, thereby resulting in memory loss, cognitive deficit and ultimately death. Neuronal death in AD occurs mainly in the hippocampus and cerebral cortex.^[14] Currently, there are several hypotheses of pathological pathways of AD that include the cholinergic, the amyloid- β , and the tau protein hypotheses.^[15] The cholinergic hypothesis implicates decrease of acetylcholine levels as a significant factor in AD pathogenesis, based on the fact that the level of this neurotransmitter is significantly low in AD patients.^[15] The second hypothesis involves accumulation of A β aggregates, formed upon cleavage of amyloid precursor protein by two secretase enzymes, that form toxic oligomeric species and plaques in neuronal tissue, ultimately resulting in loss of cognitive function.^[7b] The third hypothesis attributes the pathology of AD to hyperphosphorylation of the microtubule-associated protein tau.^[13] These hypotheses have led to the evaluation of small-molecule-based inhibitors of cholinesterase,^[16] secretase,^[17] and tau aggregation.^[18] Although these compounds have shown symptom improvements or slowed disease progress, they are not capable of stopping, reversing, or curing AD.^[19]

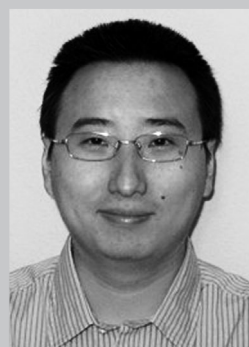
1.1.2. Parkinson's Disease

Parkinson's disease (PD) is considered to be one of the most common neurodegenerative diseases and affects approximately 1% of the population over 65 years of age.^[20] Death of dopamine-secreting neural cells (dopaminergic neurons) in the substantia nigra, has been proposed to occur

early in PD pathogenesis.^[21] The distinctive feature of PD that differentiates it from other NDDs is the development of intraneuronal proteinaceous cytoplasmic inclusions (referred to as Lewy bodies) in the affected brain area.^[22] Certain genetic mutations have been suggested to cause PD, such as mutations in genes for α -synuclein and ubiquitin C-terminal hydrolase like 1 (UCH-L1), parkin (PRKN), PINK1, and DJ-1.^[23] The encoded proteins from the above genes are thought to contribute significantly to the three major dysfunctions observed in PD, which are oxidative stress, mitochondrial failure, and proteasomal dysfunction.^[7e] The most common treatment of PD is targeting the dopamine receptors with various receptor agonists. Nevertheless, this strategy does not slow or stop the progressive neuron death and, more disturbingly, it produces several severe side effects.^[3b] Moreover, monoamine oxidase (MAO) inhibitors,^[24,25] catechol-O-methyl transferase (COMT) inhibitors,^[26] and amantadine^[27] are also used to manage the progression of PD.

1.1.3. Huntington's Disease

Huntington's disease (HD) is the most common genetic neurodegenerative disease and affects about 4 to 8 persons per 100 000 people.^[28] HD is characterized by progressive motor, cognitive, and psychiatric symptoms.^[29] At its early stage, HD affects the striatum and subsequently other areas of the brain.^[30] This disease is characterized by expansion of a cytosine-adenine-guanine (CAG) repeat in the coding area of the huntingtin gene located on chromosome 4. These CAG repeats are translated into a polyglutamine sequence in the N-terminal region of huntingtin (HTT) that interferes with the various regulatory processes of HTT and produces the defects associated with HD.^[7f,28] Currently available therapies only relieve HD symptoms.^[7f,28] For example, a small synthetic



Jing Xu received his BSc from Nanchang University (2000) and MSc from Tongji University (2004) working under the direction of Professor Ronghua Zhang. He received his PhD from Leipzig University with Professor Athanassios Giannis (2009). He then joined the group of Prof. Emmanuel A. Theodorakis at UCSD as a postdoctoral scientist. His research interests include the synthesis of bioactive natural products and their biological applications.



Emmanuel A. Theodorakis received his BSc in Chemistry from the University of Athens (Greece) and his MSc (D.E.A.) and PhD in Organic Chemistry from Paris XI University (France). His MSc studies were performed at the Institute of Chemistry of Natural Products (ICSN-CNRS) under the direction of Prof. H.-P. Husson, and his PhD studies at Texas A&M University under the direction of Sir Derek H. R. Barton. After postdoctoral research at TSRI with Prof. K. C. Nicolaou, in 1995 he joined the faculty at UCSD. His research focuses on the synthesis and biological studies of natural products and designed small molecules.



Michelle H. Lacoske received her BSc in chemistry from Stony Brook University, where she carried out undergraduate research with Prof. Nancy S. Goroff. She is currently a third-year graduate student at the University of California at San Diego under the direction of Prof. Emmanuel A. Theodorakis and is focusing on natural product synthesis.

molecule, tetrabenazine, is currently used to combat the chorea symptoms.^[31]

1.1.4. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) affects roughly 2 in 100 000 individuals annually.^[32] Pathologically, ALS is characterized by degeneration of the large pyramidal neurons in the motor cortex, loss of large motoneurons of the anterior horns in the spinal cord, and motor nuclei in the brainstem.^[33–35] The progressive degeneration of the motor neurons weakens the nervous and muscular system, resulting in paralysis, respiratory dysfunction, and eventually death.^[32] The cause of ALS remains unknown, although several specific gene mutations or immune responses associated with this disease have been suggested. For example, mutations in the gene encoding Cu/Zn superoxide dismutase (SOD1) have been implicated in certain cases of familial ALS.^[36] Recently, mutations of the TDP-43^[37] and FUS^[38] genes have also been linked to ALS. Current drug therapies of ALS^[7g] only help to alleviate the general symptoms, but do not target the disease itself. For example, riluzole is the only FDA approved drug for this condition which acts on ion channels.^[39] Moreover, encouraging phase II clinical data have been reported with dexpramipexole, a putative mitochondrial regulator.^[40] Nonetheless, these agents do not provide direct treatment of the motor neuron degeneration.

1.1.5. Spinal Cord Injury

Approximately 2.5 million people live with spinal cord injury (SCI), and more than 130 000 new injuries are reported annually.^[2a] Unlike NDDs, SCI is produced by direct trauma to the spinal cord, which commonly results in paralysis and death. Damage to the spinal cord results in the production of various growth inhibitors from the myelin and glial scars, which generate an undesirable environment for the regeneration of nerve cells.^[41,42] Potential therapeutic strategies include the control of glial scars, the inhibition of myelin-associated proteins, the use of neurotrophic factors and related small molecules, as well as cell replacements and transplantation of peripheral nerves, Schwann cells, and stem cells.^[7a,42a,43] Nevertheless, at present there is no effective method for fully regenerating healthy neuronal cells or regaining full mobility.^[41,42] Figure 1 shows a summary of neurodegenerative diseases and spinal cord injuries.

1.2. Neurotrophins and Cell Signaling

Neurotrophins are a class of small proteins that act on cell membrane receptors that elicit cell growth, differentiation, and survival.^[8] Well-known neurotrophins include nerve growth factor (NGF), brain-derived growth factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5).^[45] Each neurotrophin binds selectively to its tyrosine kinase receptor (Trk) and nonselectively to a 75 kDa neurotrophin receptor (p75^{NTR}; Figure 2). Trk signaling occurs through two

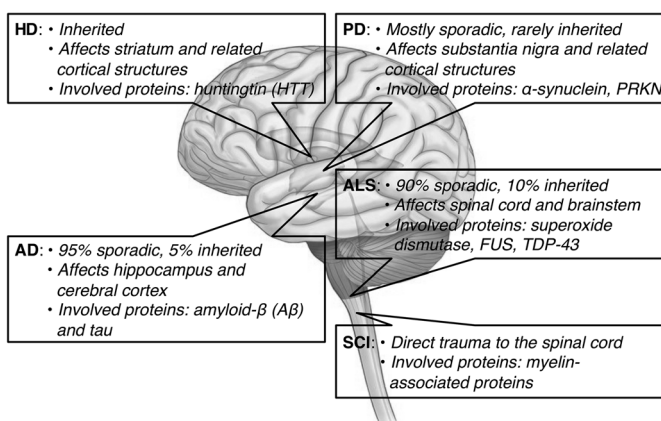


Figure 1. Summary of neurodegenerative diseases (NDDs; AD = Alzheimer's Disease, ALS = amyotrophic lateral sclerosis, HD = Huntington's Disease, PD = Parkinson's Disease) and spinal cord injury (SCI).^[44]

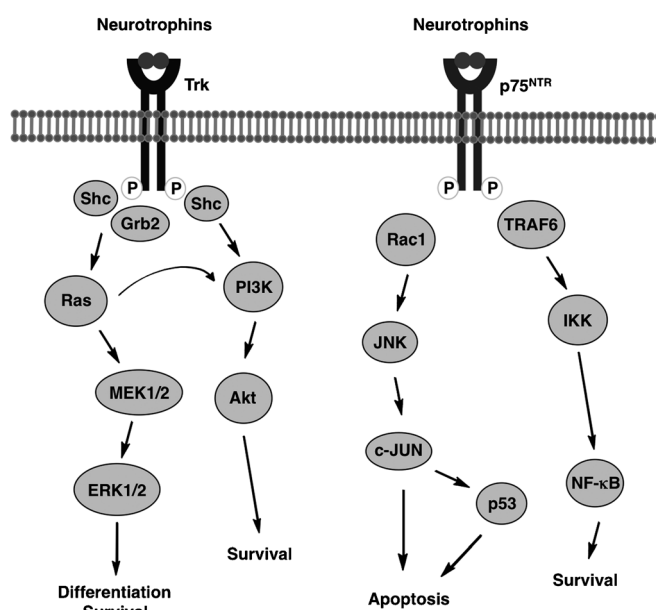


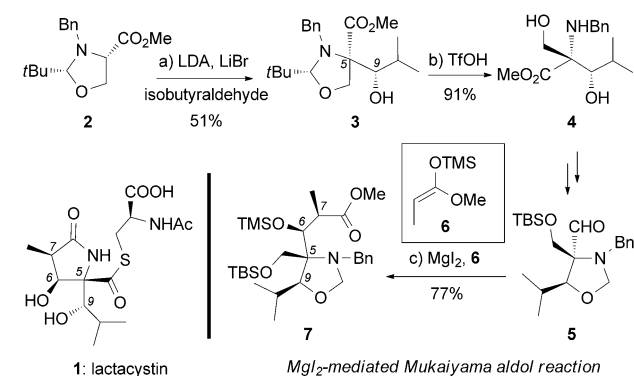
Figure 2. Neurotrophin signaling pathways.

major pathways: the mitogen-activated protein kinase (MAPK) pathway and the phosphoinositide 3-kinase (PI3) pathway. These pathways regulate the fate of neurotrophin signaling in terms of cell survival and cell differentiation.^[46] On the other hand, neurotrophin binding to p75^{NTR} can trigger neuron apoptosis.^[47]

2. Neurotrophic Natural Products

2.1. Lactacystin

From a historical standpoint, lactacystin (**1**, Scheme 1) is the first nonprotein neurotrophic natural product. Isolated by the Omura research group from a culture broth of *Streptomyces* sp., **1** was shown to exhibit significant neuritogenic activity at a concentration of 1.3 μ M in mouse neuroblastoma



Scheme 1. Part of the total synthesis of (+)-lactacystin by Corey et al.^[52] Bn = benzyl, LDA = lithium diisopropylamide, TBS = *tert*-butyldimethylsilyl, TfOH = trifluoromethanesulfonic acid, TMS = trimethylsilyl.

cell line Neuro 2A.^[48] Specifically, cells treated with lactacystin for one day displayed a predominantly bipolar (two-neurite-bearing) morphology, in which two neurites project at opposite sites of the cell body. Upon longer exposure (3–4 days) the cells displayed a multipolar (multiple-neurite-bearing) morphology, while the neurites became increasingly branched. Lactacystin was found to increase intracellular cAMP levels at a time point that coincides with the development of maximal bipolar morphology, but did not affect protein kinase C (PKC) and did not inhibit proteinases such as thrombin and the plasminogen activator. The lactacystin-induced neurite outgrowth appears to be dependent upon microtubule assembly, actin polymerization, and *de novo* protein synthesis.^[49,50]

The promising biological profile of lactacystin (**1**) and its interesting γ -lactam thioester motif triggered numerous biological and synthetic efforts.^[51] The first total synthesis of (+)-lactacystin was accomplished by Corey et al. one year after its isolation.^[52] The C5–C9 *trans*-aminol moiety of key intermediate **3** was achieved through an aldol reaction between oxazolidine **2** and isobutyraldehyde (Scheme 1). Another key synthetic step was a MgI₂-mediated Mukaiyama aldol reaction^[53] between oxazolidine aldehyde **5** and the TMS enolate **6** that produced the desired C6 and C7 stereocenters in **7**. Subsequent to this pioneering synthesis by Corey et al., several additional syntheses and formal syntheses of **1** were reported.^[54]

Studies on the structure–activity relationships on lactacystin have been reported by Corey, Schreiber, and co-workers^[49a] as well as by the Omura and Smith research groups.^[54d,55] Biological investigation of lactone **8**, referred to as *clasto*-lactacystin β -lactone (formally the product of elimination of *N*-acetylcysteine), unveiled that this bicyclic motif represents the active form of lactacystin (Figure 3).^[49a,50c] Certain synthetic analogues, such as **9** and **10**, were found to be about ten times more active than lactacystin.^[49a,54d,55] On the other hand, the dihydroxy acid **11** was inactive, even at a concentration of 100 μ M.^[49a] Furthermore, it has been shown that the C6 hydroxy group, the C7 methyl group, and the hydroxyisobutyl side chain are essential for the neurotrophic activity.

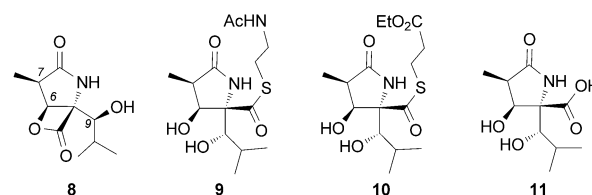


Figure 3. Selected lactacystin analogues.

Important information regarding the mechanism of action of lactacystin was disclosed by Schreiber and co-workers.^[49a] Working with Neuro 2A and MG-63 osteosarcoma cells, these authors found that **1** inhibits cell-cycle progression at both the G₀/G₁ and G₂/M phases of the cell cycle. Based on structure–activity relationship screening studies, the authors suggested that the mode of action of **1** could involve acylation of a cellular target through attack of the β -lactone by a nucleophilic group on the target molecule and subsequent opening of the β -lactone ring.^[49a] To identify the target of lactacystin, the authors synthesized radiolabeled versions of **1** and used them as covalent affinity labels.^[50a] This strategy allowed identification of the 20S proteasome as the main observed target of **1**. In particular, the N-terminal threonine residue of the mammalian proteasome subunit X (also known as MB1) was found to be esterified on its side-chain hydroxy group by **1**.^[50a] This acylation results in inhibition of several proteasome peptidase activities that are critical to protein degradation, cellular differentiation, and apoptosis. In turn, these findings point to a connection between proteasome inhibition and neuronal differentiation. Fellutamide B (**12**; Figure 4),

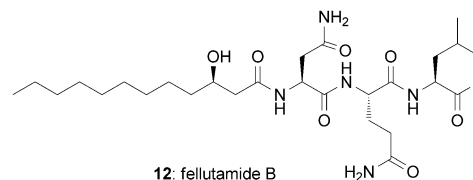


Figure 4. Structure of fellutamide B (**12**).

a marine fungal metabolite,^[56,57] provides further evidence in support of this connection; this compound binds to the 20S proteasome at a distinct site, which results in inhibition of its hydrolytic activity^[58] and at a concentration of 10 μ M induces synthesis of NGF in fibroblasts and cultured brain cells.^[59] Perhaps more importantly, these findings suggest that controlled inhibition of proteasome activity by small molecules represents a promising therapeutic approach against various diseases,^[59,60] including NDDs.^[61]

2.2. Illicium Sesquiterpenes

The *Illicium* family of natural products has attracted considerable attention^[62] since several of its members possess potent neurotrophic activities. These include merrillactone A (**13**),^[63] jiadifenin (**14**),^[64] jiadifenolide (**15**),^[65] (1*R*,10*S*)-2-

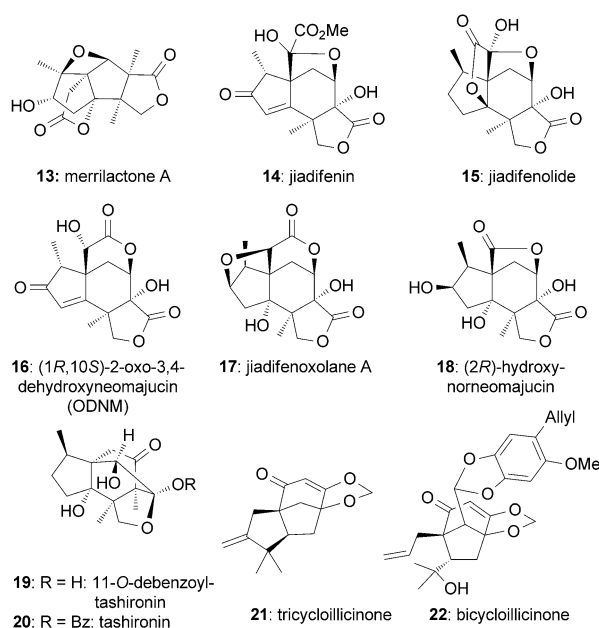
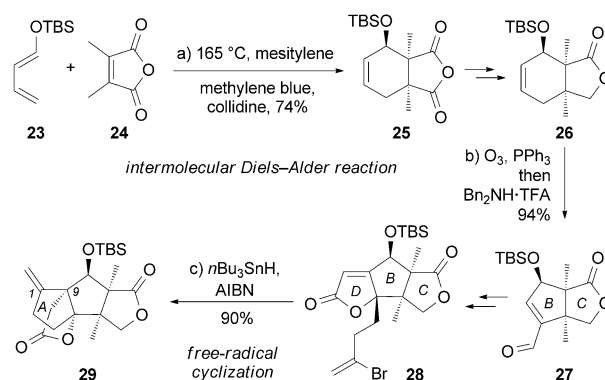


Figure 5. Representative neurotrophic *Illicium* sesquiterpenes.

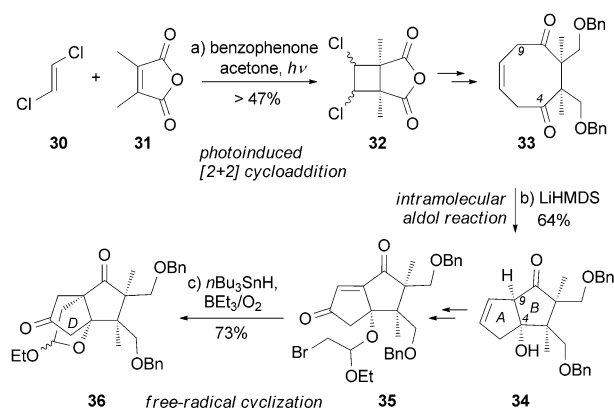
oxo-3,4-dehydroxyneomajucin (**16**, ODNM),^[66] jiadifenoxolane A (**17**),^[65] (2*R*)-hydroxynorneomajucin (**18**),^[67] 11-*O*-debenzoyltashironin (**19**),^[68] tricycloillicinone (**21**),^[69] and bicycloillicinone (**22**)^[70] (Figure 5). In addition to their complex caged architectures, several natural products of this family were shown to promote neurite outgrowth at low nanomolar to low micromolar concentration in primary cultures of cortical neurons of fetal rats.

Isolated from *Illicium merrillianum*, a plant indigenous to China and Myanmar, merrilactone A (**13**) was found to promote neurite outgrowth in primary cultures of cortical neurons of fetal rats at concentrations ranging from 0.1 to 10 μM .^[63a] A pioneering synthesis of **13** was reported by the Danishefsky research group that allowed synthetic access to several *Illicium* natural products (Scheme 2).^[71] This approach builds upon an intermolecular Diels–Alder reaction between **23** and **24**^[72] to afford **25**. A subsequent ozonolysis of **26** produced the corresponding dialdehyde, which underwent an intramolecular aldol condensation to yield **27**, which contains the BC ring system of the natural product.^[73] After formation of the D ring, an impressive AIBN/*n*Bu₃SnH-induced free-radical cyclization^[74] allowed formation of the A ring of **29** from vinyl bromide **28**.

The synthesis of merrilactone by Inoue, Hirama et al. is highlighted by an intramolecular aldol reaction that forms the AB ring system in **34** from diketone **33** (Scheme 3).^[75] The latter compound was obtained from cyclic anhydride **32** which, in turn, was assembled from a [2+2] photocycloaddition between *trans*-1,2-dichloroethene (**30**) and **31**. The D ring of **36** was formed by an intramolecular radical cyclization of alkyl bromide **35**. Interestingly, in subsequent studies, the authors reported that both enantiomers of **13** are equally active in primary cultures of cortical neurons of fetal rats.^[75c]

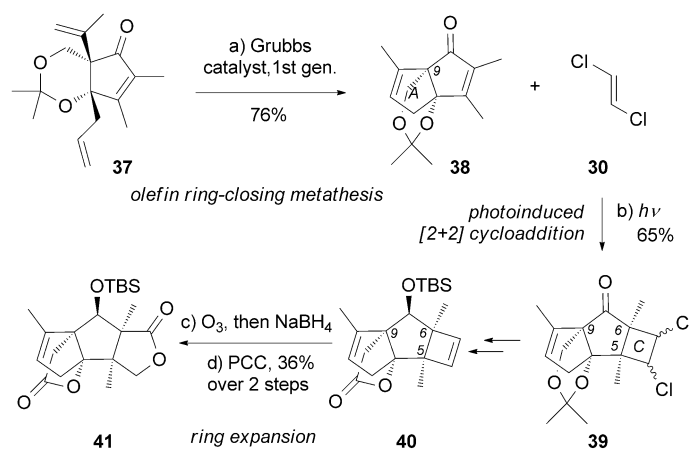


Scheme 2. Part of the total synthesis of merrilactone A (**13**) by Danishefsky and co-workers.^[71] AIBN = azobis(isobutyronitrile), TFA = trifluoroacetic acid.



Scheme 3. Part of the total synthesis of merrilactone A (**13**) by Inoue, Hiramama and co-workers.^[75] LiHMDS = lithium hexamethyldisilazide.

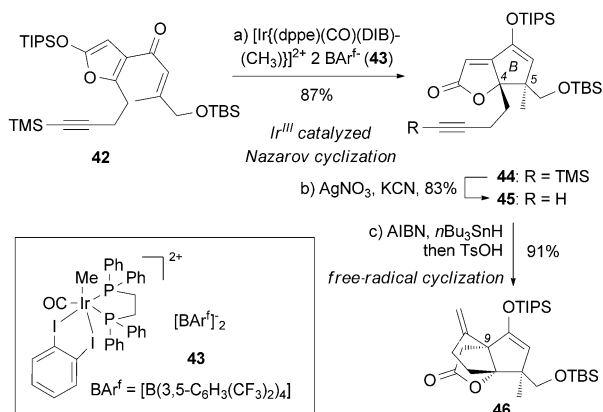
The synthesis of ($\pm$)-**13**^[76] by Mehta and Singh relied on a ring-closing metathesis (RCM)^[77] to build the A ring and a [2+2] photocyclization to furnish the C-ring framework (Scheme 4). The cyclobutene motif of **40** was then subjected



Scheme 4. Part of the total synthesis of (±)-merrilactone A (**13**) by Mehta and Singh.^[76] PCC = pyridinium chlorochromate.

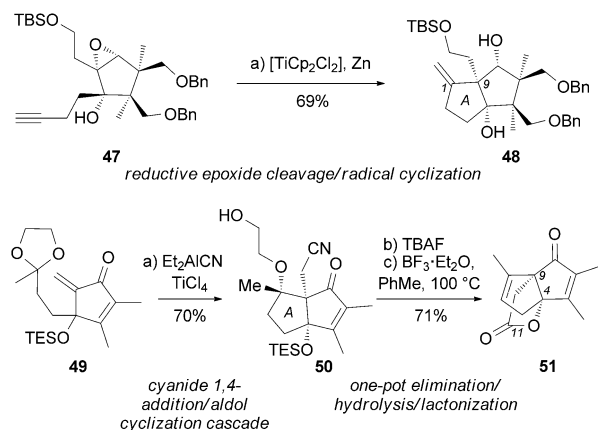
to a ring-expansion strategy that proceeded through ozonolysis and lactol oxidation to afford advanced intermediate **41**.

Formation of the B ring of **44** by a Nazarov cyclization^[78] constitutes the key step of the total synthesis of ($\pm$)-**13** reported by Frontier and co-workers.^[79] Ir^{III} complex **43**^[80] was pivotal for the success of this cyclization.^[81] After removal of the TMS group, alkyne **45** was subjected to an AIBN/*n*Bu₃SnH-induced free-radical cyclization to afford the critical C9 quaternary center in **46** (Scheme 5).



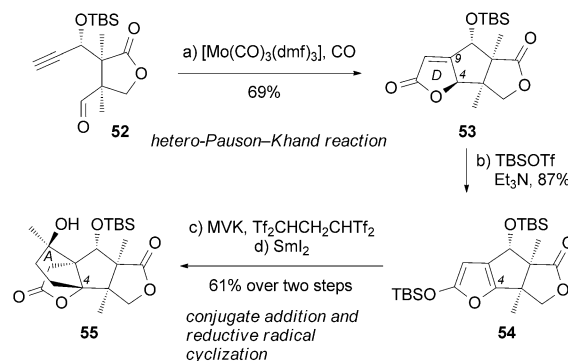
Scheme 5. Part of the total synthesis of ($\pm$)-merrillactone A (**13**) by Frontier and co-workers.^[79] dppe = 1,2-bis(diphenylphosphino)ethane, DIB = *o*-diiodobenzene, TIPS = triisopropylsilyl, TsOH = *p*-toluenesulfonic acid.

Recently, the Greaney research group reported two interesting synthetic strategies toward ($\pm$)-merrillactone A (**13**).^[82] Key to the first-generation synthesis was a Cp₂TiCl₂/Zn-triggered reductive epoxide cleavage followed by radical cyclization, which furnished the A ring of **48** containing the C9 quaternary center. The second-generation synthesis was based on a cyanide 1,4-addition/aldol reaction cascade^[83] that constructed the A ring and the C9 quaternary center. Intermediate **50** then underwent a one-pot elimination/hydrolysis/lactonization upon treatment with a Lewis acid and heating (Scheme 6).



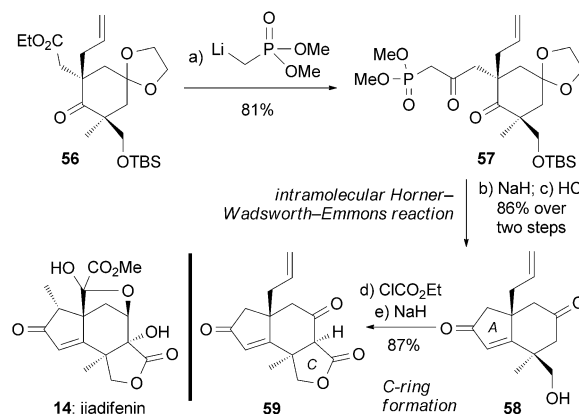
Scheme 6. Total synthesis of ($\pm$)-merrillactone A (**13**) by Greaney and co-workers.^[82] Cp = cyclopentadienyl, TBAF = tetrabutylammonium fluoride, TES = triethylsilyl.

More recently, an interesting synthesis of ($\pm$)-**13** was described by the Zhai research group,^[84] in which a hetero-Pauson–Khand reaction^[85] was employed to convert alkyne **52** into the D-ring lactone motif in the presence of [Mo(CO)₃-(DMF)₃]/CO (Scheme 7). Subsequently, the A-ring framework of **55** was constructed through a sequence of reactions that included formation of the extended enol silyl ether **54**, conjugate addition of **54** to methyl vinyl ketone (MVK), and SmI₂-mediated reductive radical cyclization.^[86]



Scheme 7. Part of the total synthesis of ($\pm$)-merrillactone A (**13**) by Zhai and co-workers.^[84] MVK = methyl vinyl ketone.

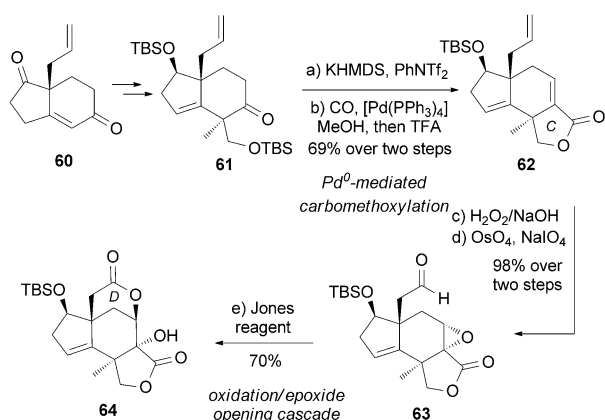
Jiadifenin (**14**) and ODNM (**16**) were isolated from the East-Asian plants *Illicium jiadifengpi*^[64] and *Illicium majus*,^[66] respectively. **14** was shown to promote neurite outgrowth in primary cultures of cortical neurons of fetal rats at a concentration of 0.1 μ M. The first synthesis of ($\pm$)-**14** was elegantly accomplished by Danishefsky and co-workers (Scheme 8).^[87]



Scheme 8. Part of the total synthesis of ($\pm$)-jiadifenin (**14**) by Danishefsky and co-workers.^[87]

Central to the strategy was an intramolecular Horner–Wadsworth–Emmons reaction that formed the A ring of **58**. Subsequent formation of the C ring led to construction of key intermediate **59**.

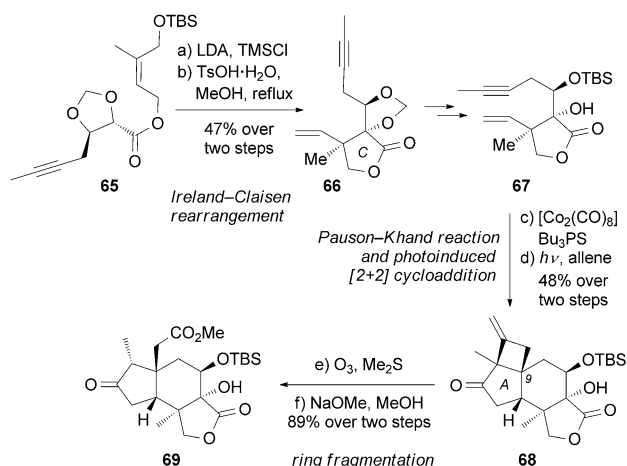
Recently, the Theodorakis research group reported an enantioselective synthesis of (–)-jiadifenin (**14**) from **60**, which was obtained by an organocatalyzed^[88] asymmetric



Scheme 9. Part of the total synthesis of (–)-jiadifenin (**14**) by Theodorakis and co-workers.^[89]

Robinson annulation.^[89] Palladium-mediated carbomethoxylation^[90] followed by an oxidation/epoxide opening cascade was used to build the C/D ring system of **64**, an advanced intermediate toward **14** (Scheme 9).

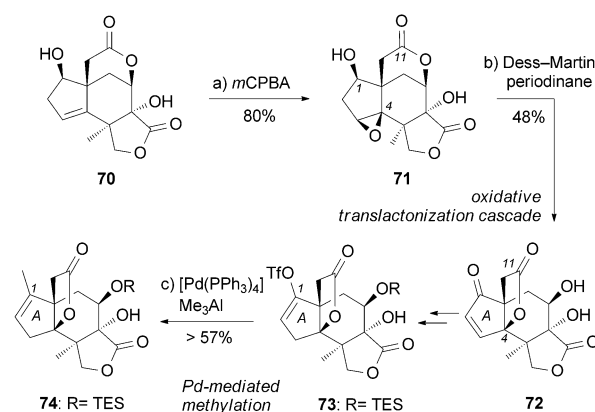
Another enantioselective route toward (–)-**14** was recently reported by the Zhai research group (Scheme 10).^[91] Critical to this strategy was an Ireland–Claisen rearrangement^[92] to form the C ring of **66** followed by a Pauson–Khand reaction^[85] to construct the A ring. Subse-



Scheme 10. Part of the total synthesis of (–)-jiadifenin (**14**) by Zhai and co-workers.^[91]

quently, an interesting photoinduced [2+2] cycloaddition between a pendant enone and an allene motif was used to install the C9 quaternary center in a diastereoselective manner. The cyclobutane moiety was then cleaved through a base-assisted ring fragmentation to afford advanced intermediate **69**.

The pentacyclic sesquiterpenoid jiadifenolide (**15**) was isolated from pericarps of *Illicium jiadifengpi*.^[65] Remarkably, **15** exhibited neurite outgrowth at concentrations as low as 10 nM, thus ranking as one of the most potent neurotrophic small molecules. Theodorakis and co-workers reported an



Scheme 11. Part of the total synthesis of (–)-jiadifenolide (**15**) by Theodorakis and co-workers.^[93] mCPBA = *m*-chloroperbenzoic acid.

enantioselective synthesis of (–)-**15** that is highlighted by an unusual oxidative transactonization cascade (Scheme 11).^[93] Treatment of allylic alcohol **70** with *m*CPBA afforded epoxide **71** in a diastereoselective manner.^[94] **71** was then treated with Dess–Martin periodinane to produce the corresponding C1 ketone, which underwent epoxide opening followed by a C4 transactonization to furnish the desired five-membered lactone **72**. Further functionalization of the A ring furnished triflate **73**, which underwent a Pd-mediated methylation to install the C1 methyl group in **74**. This compound represents a fully functionalized framework of jiadifenolide.

The above strategies paved the way to evaluate structure–activity relationship issues of jiadifenin (Figure 6). Notably, the Danishefsky^[87] and Theodorakis research groups^[95] have

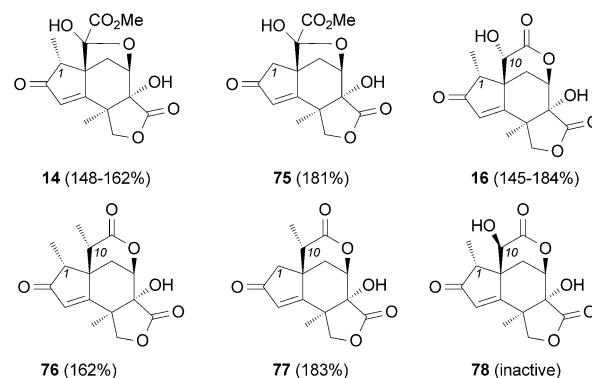
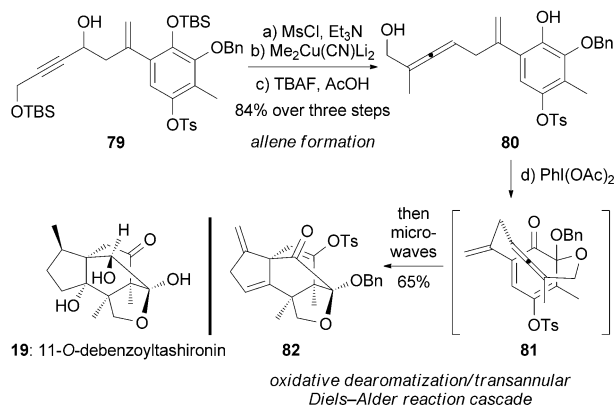


Figure 6. Representative structure–activity relationship studies on jiadifenin and analogues. The numbers in parenthesis indicate the extent of neurite outgrowth compared to a control; inactive indicates less than 110% neurite outgrowth as compared to control.

independently performed such studies on the jiadifenin structural motif and have identified several compounds, such as **75**, ODNM (**16**), **76**, and **77**, which are more potent than the parent natural products in promoting neurite outgrowth. The neurotrophic effects were evaluated by measuring the stimulation of NGF-mediated neurite outgrowth in PC-12 cells.^[96,97] These studies suggest that: a) removal of the

C1 methyl group increases the neurotrophic activity of the jiadifenin motif, as shown by comparing **14** with **75**, and **76** with **77**; and b) the α substitution at the C10-position is critical for the activity (Figure 6). These compounds are likely to upregulate NGF signaling rather than mimicking NGF.^[87, 89, 184]

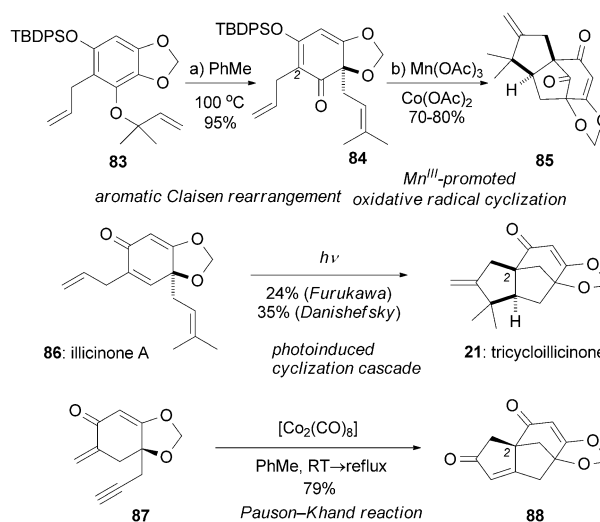
11-*O*-Debenzoyltashironin (**19**, Scheme 12) and its benzoate ester (tashironin, **20**) were isolated from pericarps of *Illicium merrillianum*.^[68, 98] **19** was found to induce neurite



Scheme 12. Part of the total synthesis of 11-*O*-debenzoyltashironin (**19**) by Danishefsky and co-workers.^[99]

outgrowth in cortical neurons of fetal rats at concentrations of as low as 0.1 μ M, while **20** was inactive in this assay. Danishefsky and co-workers reported an impressive total synthesis of ($\pm$)-**19**.^[99] The key step of their approach is a remarkable oxidative dearomatization/transannular Diels-Alder reaction cascade. This transformation was achieved using PhI(OAc)₂ followed by a microwave-assisted intramolecular Diels-Alder reaction.^[100] The enantioselective construction of propargyl alcohol **79** led to an asymmetric synthesis of **19**.^[101] A synthesis of 11-*O*-methyldebenzoyltashironin has also been reported by the Mehta research group.^[102]

Tricycloillicinone (**21**) and bicycloillicinone (**22**) were isolated from the extracts of *Illicium tashiroi* by Fukuyama et al.^[69, 70] Interestingly, these compounds have been shown to enhance choline acetyltransferase (ChAT) activity at concentrations as low as 30 μ M.^[69, 70] There is significant evidence that ChAT upregulation induces neurite outgrowth.^[103] Specifically, it has been shown that the level of acetylcholine (ACh) is low in AD patients, thus suggesting that upregulation of ChAT represents a possible strategy for the treatment of AD.^[104] In 1998, Danishefsky and co-workers reported the first total synthesis of **21**.^[105] Highlights of their strategy include an aromatic Claisen rearrangement followed by a Mn^{III}-promoted oxidative radical cyclization (Scheme 13).^[106] Heating protected phenol **83** in toluene produced the rearranged cyclohexadienone **84** in nearly quantitative yield. In turn, **84** was oxidized by Mn^{III} in the presence of Co^{II} as a co-oxidant to afford a resonance-stabilized radical^[107] at C2, which underwent a cyclization cascade to yield the cyclic core of **85**. A biomimetic trans-



Scheme 13. Part of the total syntheses of tricycloillicinone (**21**) by Danishefsky et al.^[105] and Terashima and Furuya.^[110] TBDPS = *tert*-butyldiphenylsilyl.

formation of **21** from its likely biosynthetic precursor illicinone A (**86**) was initially described by Furukawa et al.^[108] and later optimized by Danishefsky and co-workers.^[109] A synthesis of *ent*-**21** has also been reported by the Terashima research group^[110] by using a Pauson-Khand reaction^[85] to generate the challenging C2 quaternary center (conversion of **87** into **88**). In addition, Danishefsky and co-workers have reported the synthesis of bicycloillicinone aldehyde.^[105b]

2.3. Lycopodium Alkaloids

Several members of the *Lycopodium* alkaloids,^[111] such as huperzine A (**89**),^[112] lyconadins (**90** and **91**),^[113] complanadine A (**94**)^[114] and B (**95**),^[115] and nankakurine A (**92**) and B (**93**), display highly promising neurotrophic profiles (Figure 7).^[116]

Huperzine A (**89**) was originally isolated from the Chinese plant *Huperzia serrate* by Liu et al. in 1986.^[112] Huperzi-

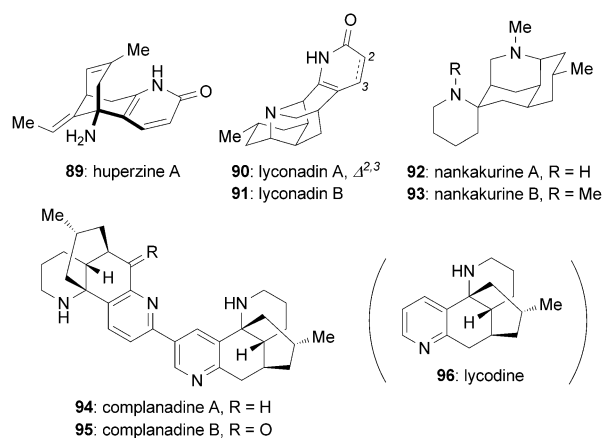
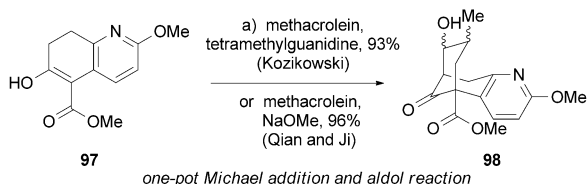


Figure 7. Neurotrophic *Lycopodium* alkaloids.

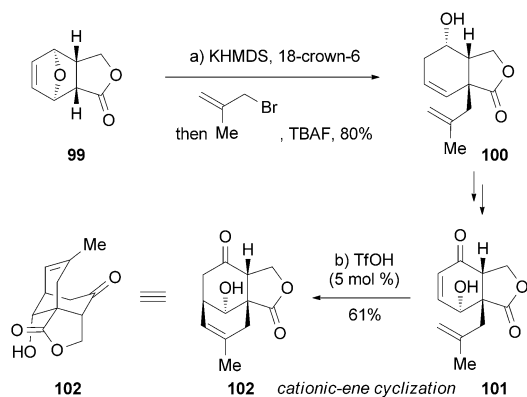
ne A has been found to potently inhibit acetylcholinesterase (AChE)^[117] and effectively cross the blood–brain barrier with no signs of cytotoxicity and minimal side effects.^[118] Both NGF and P75^{NTR} levels increased in the presence of **89** in studies performed in PC-12 cells.^[119,120] Huperzine A was shown to prevent oxidative damage in SHSY5Y cells, presumably as a result of its ability to increase NGF production.^[121] Studies in mice demonstrated that huperzine A, administered at 0.2 mg kg^{−1}, increases the concentration of various proteins, including NGF, BDNF, and phosphorylated MAPK.^[122] Interestingly, **89** was also reported to promote hippocampal neurogenesis in vitro and in vivo.^[120] Moreover, **89** is an approved drug in China to treat cognitive deficiencies associated with AD, and is being offered as a herbal supplement in the USA.^[123] The pharmacology and therapeutic potential of huperzine A has recently been reviewed.^[124]

The total synthesis of (±)-**89** was independently accomplished by Kozikowski and Xia^[125] as well as Qian and Ji^[126] by using an almost identical strategy to construct the huperzine A core. Specifically, a one-pot Michael addition/aldol reaction of **97** with methacrolein formed the desired carbon bridge of **98** (Scheme 14).

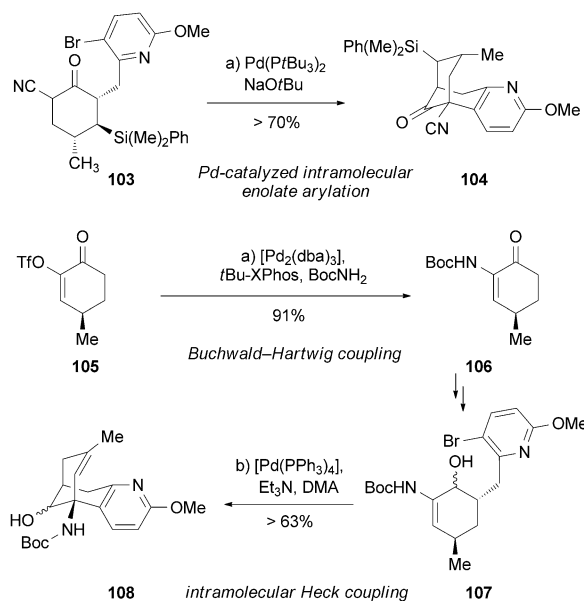


Scheme 14. Part of the total syntheses of (±)-huperzine A (**89**) by Xia and Kozikowski as well as Qian and Ji.^[125,126]

The Fukuyama research group has also reported a synthesis of (−)-**89**^[127] (Scheme 15). Key to this strategy was a TfOH-catalyzed cationic ene cyclization that produced tricyclic lactone **102**. Precursor **100** could be constructed from readily available **99** in one step.



Scheme 15. Part of the total synthesis of (−)-huperzine A (**89**) by Fukuyama and co-workers.^[127]



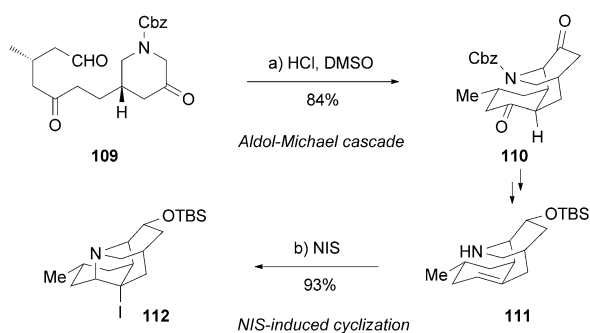
Scheme 16. Part of the total syntheses of (−)-huperzine A (**89**) by Herzon and co-workers and Lin and co-workers.^[129,131] Boc = *tert*-butoxycarbonyl.

The growing pharmacological interest in (−)-huperzine A (**89**) prompted two efficient syntheses of this molecule by using palladium-catalyzed coupling reactions as a key step (Scheme 16).^[128] Specifically, Herzon and co-workers reported a scalable synthesis of huperzine A^[129] that relies on a modified intramolecular Heck coupling of α -cyanoketone **103** to assemble the carbon bridge of **104**.^[130] Lin and co-workers also disclosed a synthesis of **89**^[131] by using a Buchwald–Hartwig coupling reaction^[132] between enol triflate **105** and Boc-NH₂ to form enamine **106**. A subsequent intramolecular Heck reaction^[133] of **107** led to the bridged motif of **108**. Several other syntheses and formal syntheses of huperzine A (**89**) have also been reported.^[134]

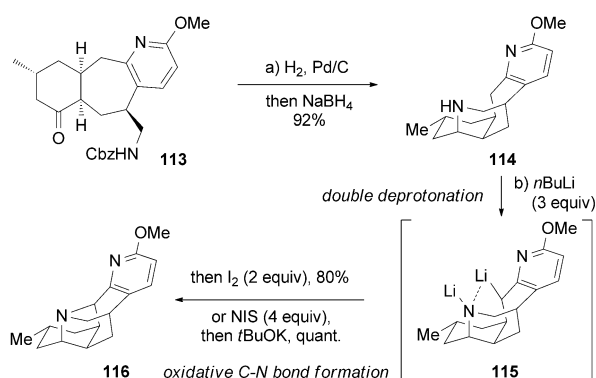
Lyconadins (**90** and **91**)^[113] and complanadins (**94** and **95**)^[114,115,135] are particularly attractive small molecules since they enhance the mRNA expression of NGF in human glial cells.^[113b,115] In addition, **90** displayed modest cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cells,^[113a] while **94** exhibited modest cytotoxicity against murine lymphoma L1210 cells.^[114]

From a structural point of view, lyconadins possess a pyridinone-fused tetracyclic caged framework, which constitutes the central synthetic challenge for **90**. The Smith research group reported the first total synthesis of (+)-**90** and (−)-**91** (Scheme 17).^[136] The tricyclic intermediate **110** was crafted by an aldol/1,4-addition reaction cascade from aldehyde **109**. After a few synthetic steps, amine **111** underwent a NIS-induced cyclization to furnish the tetracyclic motif **112**.

One year later, the Sarpong research group reported the synthesis of (±)- and (+)-**90**.^[137] Double deprotonation of **114** formed dianion **115**, which was oxidized with iodine to form the critical C–N bond of **116**. This bond formation can also be accomplished by an NIS-mediated S_N2 reaction (Scheme 18).



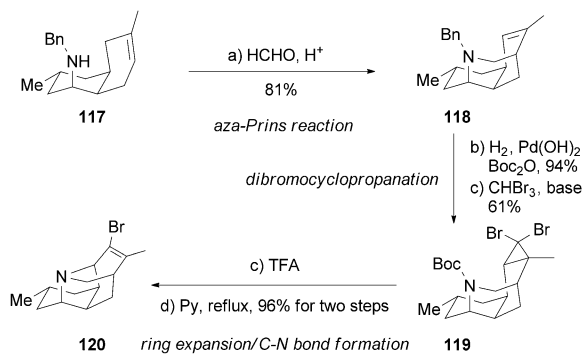
Scheme 17. Part of the total synthesis of (+)-lyconadin A (**90**) and (–)-B (**91**) by Beshore and Smith.^[136] Cbz = carboxybenzyl, NIS = *N*-iodosuccinimide.



Scheme 18. Part of the total synthesis of lyconadin A (**90**) by Sarpong and co-workers.^[137]

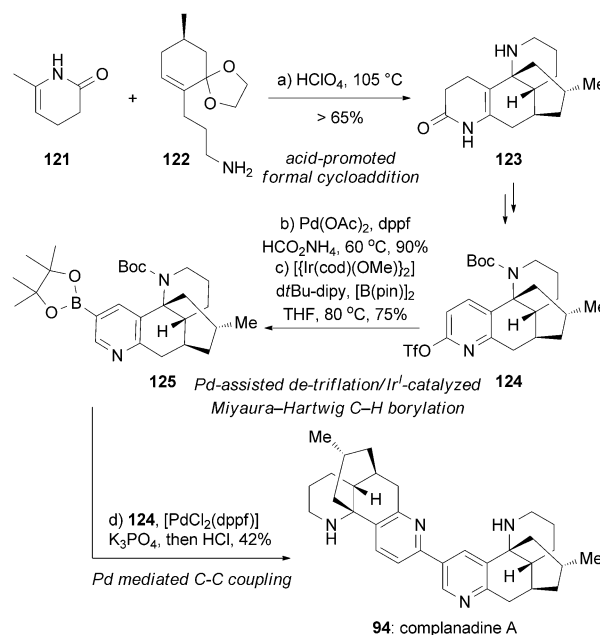
Another interesting synthesis of (+)-**90** and (–)-lyconadins B and C was reported by the Fukuyama research group (Scheme 19)^[138] The authors utilized dibromocyclopropane **119** as the key motif, which was prepared from amine **117** by an aza-Prins reaction followed by a dibromocyclopropanation. Subsequently, **119** underwent an acid-promoted ring expansion to produce the tetracyclic core of **120**.

Complanadine A (**94**) is an unsymmetric dimer of lycodine (**96**),^[139] while complanadine B (**95**) can be considered as a pseudodimer of **96**. Independent studies by the Sarpong and



Scheme 19. Part of the total syntheses of lyconadins by Fukuyama and co-workers.^[138] Py = pyridine.

Siegel research groups have yielded two intriguing strategies for the synthesis of (+)-complanadine A. In the former study, Fischer and Sarpong started the synthesis^[140] from tetracyclic compound **123** following the procedure developed by Schumann and Naumann (Scheme 20).^[141] The authors converted

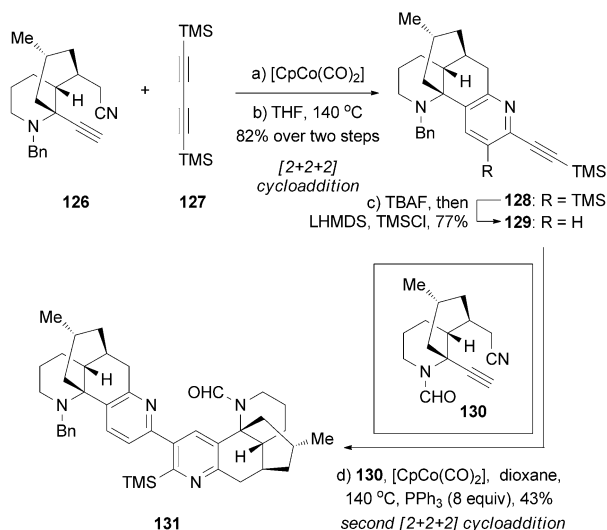


Scheme 20. Part of the total synthesis of (+)-complanadine A (**94**) by Fischer and Sarpong.^[140] [B(pin)]₂ = diboron pinacolato ester, dppe = 1,1'-bis(diphenyl phosphino) ferrocene, dtBu-dipy = di-*tert*-butyl-bipyridine.

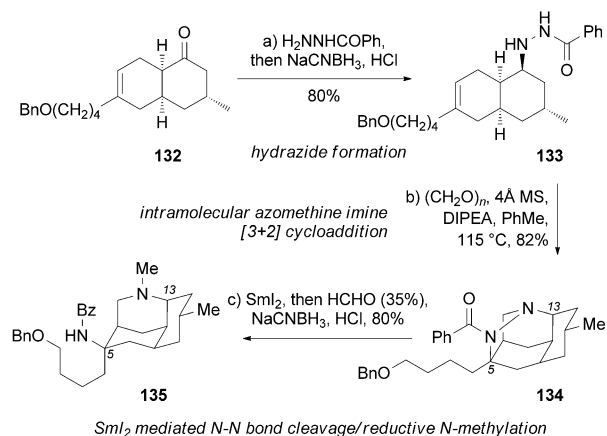
triflated lycodine derivative **124** into boronic ester **125** under reductive detriflation conditions, followed by an Ir^I-catalyzed Miyaura–Hartwig C–H borylation.^[142] Pd-based cross-coupling between **125** and triflate **124**, followed by cleavage of the Boc group, produced (+)-**94**. A synthesis of complanadine B (**95**) has also been reported by similar strategies.^[143]

In parallel, the Siegel research group reported a synthesis of (+)-**94** (Scheme 21).^[144] Key to this strategy was a [2+2+2] cycloaddition of **126** with **127** to produce lycodine analogue **129**. This compound was then coupled with **130** to yield complanadine precursor **131**. Notably, it was found that both the presence of PPh₃ and the formyl motif of **130** were essential for the regioselectivity of the second cycloaddition. More recently, Tsukano and co-workers reported a synthesis of (–)-complanadine A and B^[145] by a Pd-catalyzed coupling^[146] of *N*-oxolycodine with α-bromolycodine.^[147]

Nankakurine A (**92**), another *Lycopodium* natural product, was reported to possess neurotrophic activity in human astrocytoma cells.^[116b] **92** was isolated from *Lycopodium hamiltonii* in 2004,^[116a] and its originally proposed structure was revised two years later.^[116b] The Overman research group reported the first synthesis of (+)-nankakurine A (**92**) and B (**93**), thereby establishing their absolute configurations (Scheme 22).^[148] Critical to the synthetic strategy was an intramolecular azomethine imine [3+2] cycloaddition of **133** that installed the two nitrogen atoms at C5 and C13 in



Scheme 21. Part of the total synthesis of (+)-complanadine A (**94**) by Siegel and co-workers.^[144]

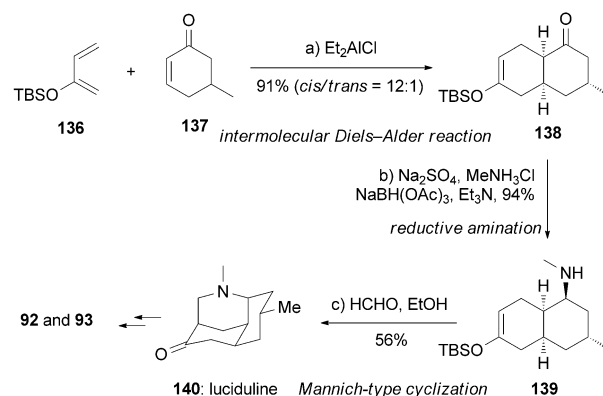


Scheme 22. Part of the total syntheses of (+)-nankakurines by Overman and co-workers.^[148]

a stereoselective manner. Reductive cleavage of the N–N bond in **134** released the free amine at C13, which was reductively methylated to form **135**.

Cheng and Waters reported a short synthesis of (±)-**92** and (±)-**93** (Scheme 23).^[149] Amine **139** was derived from an intermolecular Diels–Alder reaction between **136** and **137** followed by reductive amination of the resulting ketone **138**. Upon treatment with formaldehyde, a Mannich-type cyclization produced luciduline (**140**), a known precursor of nankakurines.^[150]

In a recent study, Overman and co-workers reported that **92** and **93** showed no effect on neurite outgrowth in rat hippocampus H-19 cells,^[148b] which stands in contrast to the previously reported results.^[116b] Certainly, further biological investigation of these intricate *Lycodium* alkaloids would be necessary to unveil their biological potential.



Scheme 23. Part of the total syntheses of (±)-nankakurines by Cheng and Waters.^[149]

2.4. Cyathane Diterpenoids

Isolated from fungi, sponges, and fruiting plants, cyathane diterpenes possess a variety of bioactivities including antimicrobial activity and cytotoxicity against certain tumor cells.^[151] In addition, erinacines,^[152] scabronines,^[153] and cyrneines^[154] were found to induce NGF synthesis in 1321N1 human astrocytoma cells and mouse astroglial cells as well as promote neurite outgrowth in PC-12 cells at low micromolar concentrations. From a chemical point of view, the cyathane natural product family possess a skeleton with 20 carbon atoms (**141**) and a 5-6-7 fused tricyclic ring system (Figure 8). Since the first report on this class in 1971,^[155] the family of cyathane diterpenoids has prompted intensive synthetic and biological studies.^[151]

Erinacines A–F (**142–147**; Figure 8) were isolated from the cultured mycelia of *Hericium erinacium* by Kawagishi et al.^[152] These cyathane xylosides are able to stimulate NGF secretion in mouse astroglial cells, albeit at rather high concentrations (1–5 mM). The *in vivo* effect of erinacine A (**142**) was also studied. Specifically, rats treated with **142** showed an increase in the levels of both noradrenaline and homovanillic acid, and displayed enhanced NGF secretions in both the locus coeruleus and hippocampus.^[156] Moreover, erinacine E is a selective agonist of κ -opioid receptors,^[157] which are present on the peripheral terminals of primary afferent neurons. It has been reported that activation of these receptors reduces hyperalgesia in a rat model of inflammation.^[158]

An efficient synthesis of (+)-erinacine A (**142**), was reported by the Snider research group (Scheme 24).^[159] Key to this strategy was an intramolecular carbonyl–ene reaction^[160] of **157** that furnished erinacine A aglycon (**158**). The synthesis of **158**, also known as allocyathin B₂, has also been reported by various research groups.^[161]

Nakada and co-workers recently disclosed a divergent synthesis of (–)-erinacines B (**143**)^[162] and E (**146**)^[161e,163] by using **161** as the common intermediate (Scheme 25). The tricyclic motif of **161** was constructed through a sequence of three steps that included: a) carbomethoxylation of ketone **159** with Mander's reagent,^[164] b) cyclopropanation, and c) SmI₂-assisted ring expansion. Interestingly, the D ring of

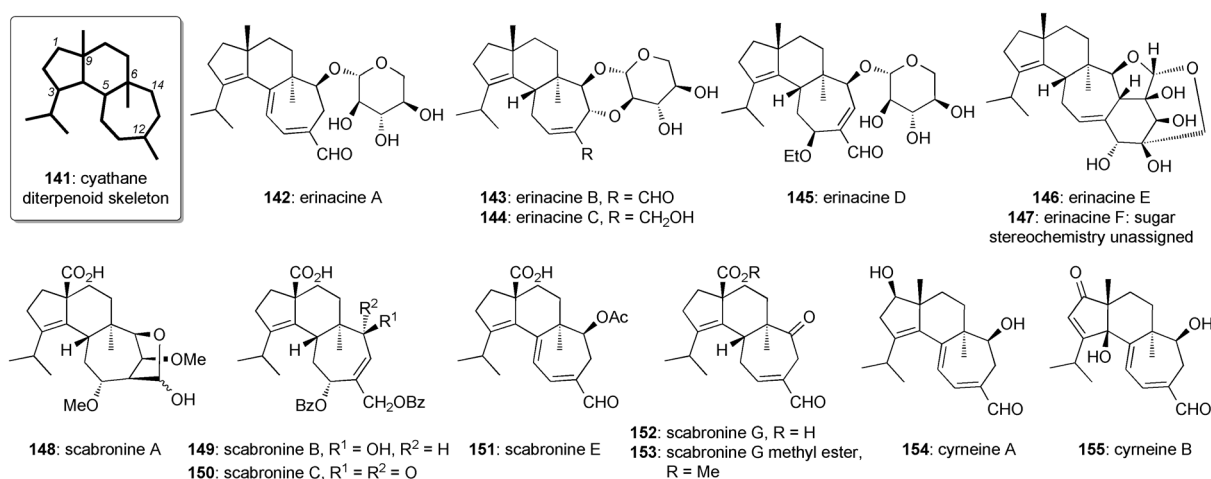
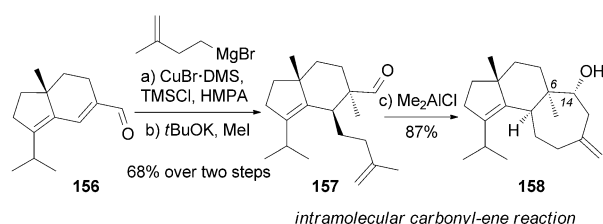
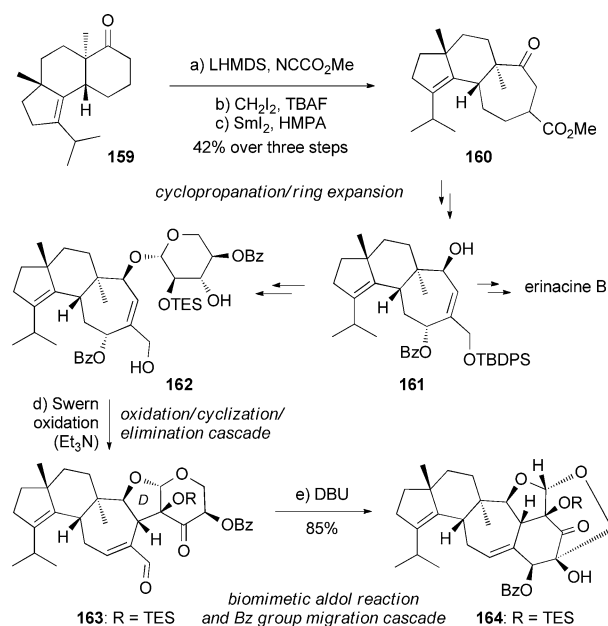


Figure 8. Neurotrophic cyathane diterpenoids.



Scheme 24. Part of the total synthesis of (+)-erinacine A (**142**) by Snider et al.^[159] DMS = dimethylsulfide, HMPA = hexamethylphosphoramide.



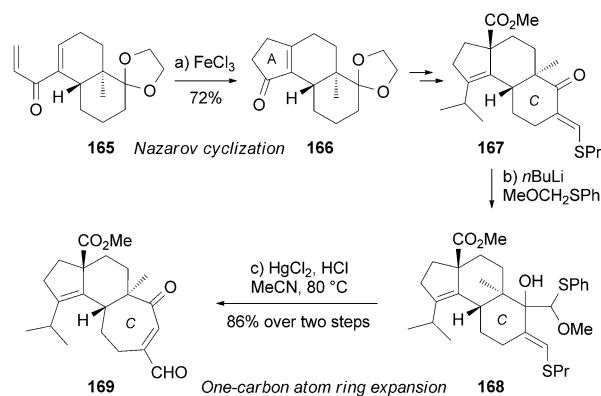
Scheme 25. Part of the total syntheses of (-)-erinacine B (**143**) and (-)-E (**146**) by Watanabe and Nakada.^[162, 163] Bz = benzoyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

163 could be constructed during a Swern oxidation of diol **162**, presumably through the presence of triethylamine. In turn, a well-designed biomimetic intramolecular aldol reaction^[163] of **163** followed by a 1,2-migration of a benzoyl group

(Scheme 25) produced the motif **164**, thus paving the way for the synthesis of erinacine E (**146**).

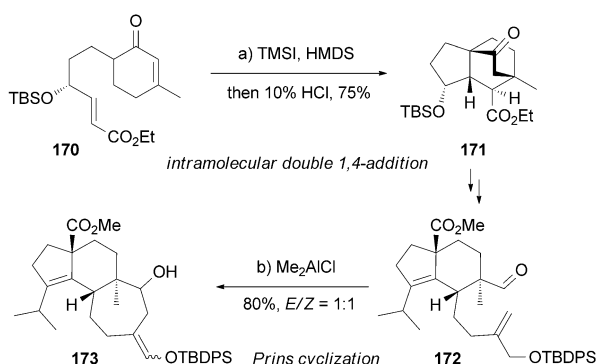
Scabronines A–C (**148–150**), E (**151**), and G (**152**) were isolated from the mushroom *Sarcodon scabrosus*.^[153] Compounds **148** and **152** potentially induce NGF synthesis in 1321N1 human astrocytoma cells in a concentration-dependent manner.^[153b,c] It was also found that **148** and **152** enhanced NGF mRNA by 3.2-fold and 3.6-fold, respectively, in the same cell line.^[153c] However, it was observed that the concentration of NGF synthesized in response to these compounds was not sufficient to induce differentiation of PC-12 cells. Based on this finding, the authors suggested that other neurotrophic growth factors might be involved in the PC-12 cell differentiation process.^[153c]

The Danishefsky research group initiated a synthesis of (-)-scabronine G (**152**)^[165] from enone **165**, which is available from the Wieland–Miescher ketone (Scheme 26).^[166] Nazarov



Scheme 26. Part of the total synthesis of (-)-scabronine G (**152**) by Danishefsky and co-workers.^[165]

cyclization^[78] of **165** produced the A-ring motif of **166** which was transformed into **167** over several steps. **167** was then subjected to lithiated (methoxymethyl)phenyl sulfide to afford alcohol **168**. Treatment of **168** with HgCl₂ under acidic conditions facilitated the desired one-carbon-atom



Scheme 27. Part of the total synthesis of (–)-scabronine G (**152**) by Kanoh, Iwabuchi et al.^[168] HMDS = hexamethyldisilazane.

expansion of the C ring to furnish conjugated cycloheptenone **169**, which was then converted into **152**.^[167]

In 2011 another synthesis of (–)-scabronine G (**152**) was reported by the Kanoh, Iwabuchi et al. (Scheme 27).^[168] Key to this synthesis was an intramolecular double 1,4-addition of **170** under TMSI/HMDS conditions, which afforded the bridged tricyclic scaffold of **171**. Another critical step was a Lewis acid induced Prins cyclization of **172** to construct the seven-membered ring of **173**.^[159] More recently, the Nakada research group reported a divergent synthesis of (–)-scabronines A (**148**) and G (**152**).^[169]

In addition, the scabronine G methyl ester (**153**) was synthesized from **152** and biologically evaluated by the Nakahata research group.^[170] This compound displayed stronger neurite outgrowth activity and NGF-synthesis-inducing activity than scabronine G in 1321N cells and PC-12 cells (in the **153**-conditioned 1321N cell medium). Similar activities have been reported by Danishefsky and co-workers.^[165] Furthermore, the synthetic analogue **169** was found to possess a 30 % greater neurite-outgrowth activity than **153**.^[165] Additional studies on the effect of **153** on NGF synthesis in 1321N cells were reported by Nakahata and co-workers.^[170] These authors suggested that the **153**-induced NGF synthesis is mediated by the activation of PKC- ζ , an isoform of protein kinase C.^[170]

Interestingly, scabronine M (**174**) significantly inhibited NGF-induced neurite outgrowth in PC-12 cells without showing any cytotoxicity at the concentrations tested (Figure 9).^[171] Gao and co-workers suggested that this activity might be due to suppressing the phosphorylation of TrkA and ERK. Moreover, the epoxide motif of **174** was proposed to be the reason for the potent inhibition of neurite outgrowth.

Cyrneines A (**154**) and B (**155**) were isolated from the mushroom *Sarcodon cyrneus* in 2006.^[154] Both compounds induced moderate neurite outgrowth in PC-12 cells at high micromolar concentrations without significant toxicity.^[154] It was reported that **154** upregulates the transcription factors activator protein-1 (AP-1) and NF- κ B. Moreover, the activity of Rac-1, a small GTPase protein

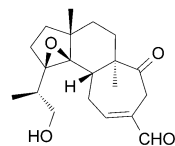
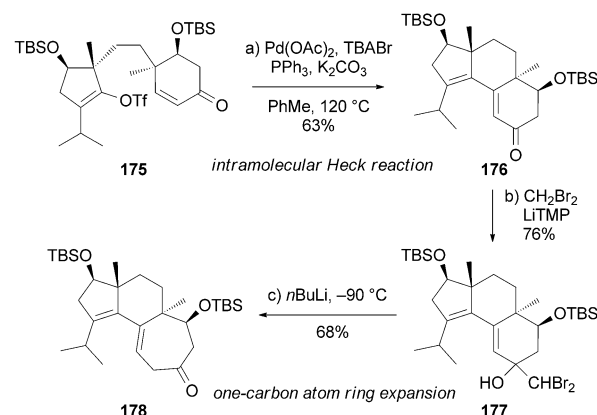


Figure 9. Structure of scabronine M (**174**).

that regulates actin dynamics, was increased, while expression of a dominant-negative Rac-1 mutant significantly inhibited the **154**-induced neurite outgrowth in PC-12 cells. Based on these findings, it was suggested that **154** promotes neurite outgrowth through a Rac-1-dependent mechanism.^[172]

The Gademann research group recently reported a total synthesis of (+)-cyrneine A (**154**) starting from commercially available (*R*)-carvone.^[173] Critical to this strategy is an intramolecular Heck coupling reaction that constructed the tricyclic core of **176**. Treatment of **176** with lithiated dibromomethane followed by lithium/halogen exchange resulted in a one-carbon-atom ring expansion to form the desired tricyclic motif of **178** (Scheme 28).



Scheme 28. Part of the total synthesis of (+)-cyrneine A (**154**) by Gademann and co-workers.^[173] TBABr = tetrabutylammonium bromide, TMP = 2,2,6,6-tetramethylpiperidine.

2.5. Trichothecanes

Isolated from the fruiting bodies of *Paecilomyces tenuipes*, the trichothecanes paecilomycine A (**179**)^[174] and spirotenuipeines A (**180**) and B (**181**)^[175] display significant neurotrophic profiles (Figure 10). Paecilomycine A was reported to

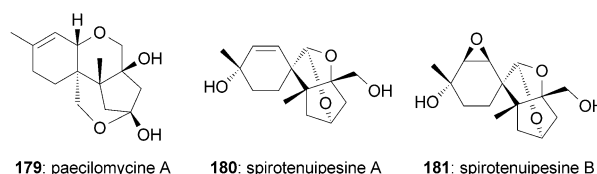
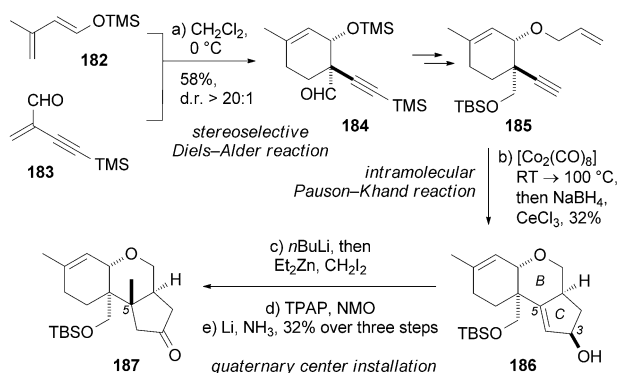


Figure 10. Neurotrophic trichothecanes.

stimulate the synthesis of neurotrophic factors, since 1321N medium cultured with **179** (10 nM) was found to promote the differentiation of PC-12 cells.^[174] The reported potency of **179** was about 1000 times higher than that of scabronine G (**152**) in the same NGF-stimulation assay. The related spirotenuipeine A (**180**) and B (**181**) were also shown to induce the biosynthesis of neurotrophic factors in 1321N cells, albeit at a higher concentration (1 μ M).^[175]

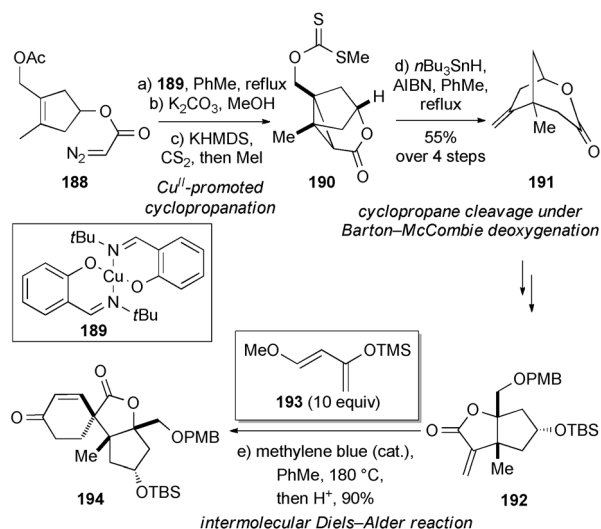
Min and Danishefsky reported an efficient synthesis of (±)-**179** starting with a stereoselective Diels–Alder reaction



Scheme 29. Part of the total synthesis of (±)-paecilomycine A (**179**) by Min and Danishefsky.^[176] NMO = *N*-methylmorpholine *N*-oxide, TPAP = tetrapropylammonium perruthenate.

(*endo/exo* > 20:1) between diene **182** and dienophile **183** (Scheme 29).^[176] Product **184** was then converted into alkyne **185**. An intramolecular Pauson–Khand reaction^[85] followed by Luche reduction of the resulting enone produced alcohol **186**. Diastereoselective cyclopropanation of **186** followed by ring opening by an oxidation/reduction sequence afforded the desired C5 quaternary center. Inspired by this approach, the Mehta research group also reported a formal synthesis of **179**.^[177]

The Danishefsky research group has also achieved the synthesis of (±)-spirotenuipesine A (**180**) and B (**181**) (Scheme 30).^[178] In this approach the tricyclic motif of **190** was formed through a Cu^{II}-promoted intramolecular cyclopropanation.^[179] This was followed by a radical deoxygenation under Barton–McCombie conditions, which also cleaved the strained cyclopropane ring of **190** to afford **191**.^[180] Another key step involved the construction of enone **194** by a Diels–Alder reaction between **192** and Danishefsky diene **193**.^[181]



Scheme 30. Part of the total syntheses of (±)-spirotenuipesine A (**180**) and B (**181**) by Danishefsky and co-workers.^[178] PMB = *p*-methoxybenzyl.

2.6. Manzamine Alkaloids

Isolated from marine sponges of the genera *Haliclona* and *Pellina*, the manzamine family is comprised of various structurally complex indole alkaloids.^[182] Among them, manzamine A (**195**)^[183] displays a broad biological profile that includes anticancer, antibacterial, insecticidal, antimalarial, anti-inflammatory, and anti-HIV activities.^[184] In addition, manzamines A (**195**), E (**197**), F (**198**), and 8-hydroxymanzamine A (**196**) were shown to exhibit potent neurotogenic activities in Neuro 2A cells at concentrations as low as 1 μM (Figure 11).^[185] Furthermore, it was proposed that **195** could act through the same mechanism reported for lactacystin (**1**).^[185]

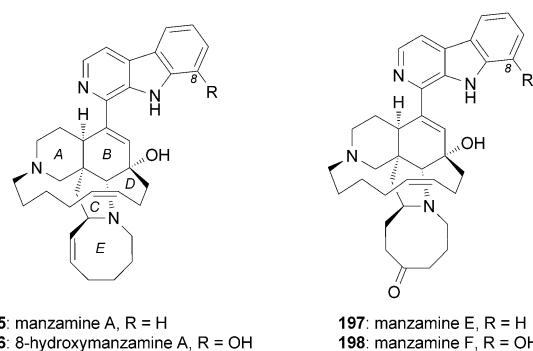
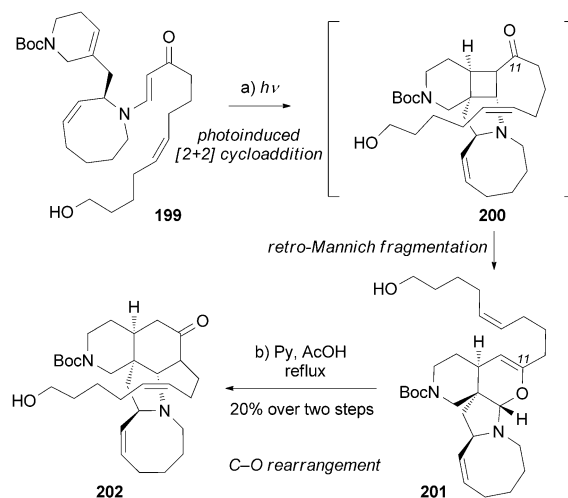


Figure 11. Neurotrophic manzamine natural products.

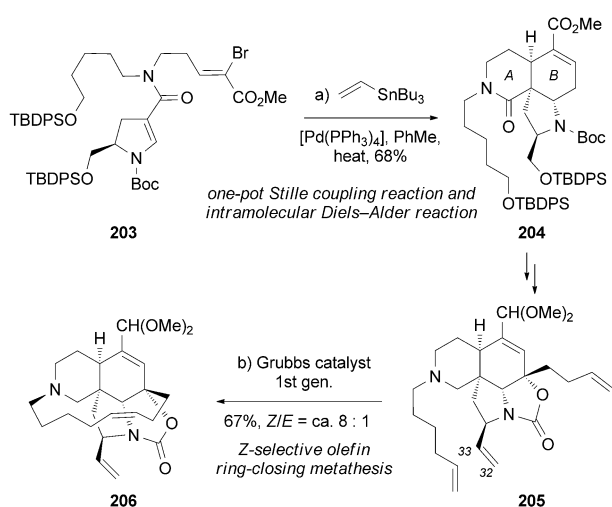
The complex chemical architecture and exciting biological profile of manzamine alkaloids attracted considerable attention from the synthetic community.^[182a–c] Winkler and Axten accomplished the first total synthesis of (+)-**195** in 1998 (Scheme 31).^[186] The construction of the tetracyclic core of **201** was elegantly initiated through a photoinduced [2+2] intramolecular cycloaddition between the enone moiety and



Scheme 31. Part of the total synthesis of (+)-manzamine A (**195**) by Winkler and Axten.^[186]

the tetrahydropyridine motif of **199**. The transiently formed cyclobutane ring of **200** underwent a retro-Mannich fragmentation, and the resulting iminium ion was trapped by the C11 enol to form amination **201**. The corresponding C→O rearrangement furnished the crucial tetracyclic motif **202** in pyridine/AcOH at elevated temperature.

Martin and co-workers also reported an efficient synthesis of (+)-**195**.^[187] The AB ring system of **195** was constructed through a one-pot Stille coupling^[188] between vinyl bromide **203** and vinyltributylstannane. This reaction produced in situ the corresponding diene, which underwent an intramolecular Diels–Alder cyclization to form **204**. In turn, the macrocyclic ring of **206** was built through the assistance of a Z-selective (ca. 8:1) ring-closing metathesis (RCM) reaction^[189] of the two terminal alkenes of **205**. Interestingly, the C32/C33 terminal alkene of **205** did not interfere with the formation of this 13-membered ring (Scheme 32).

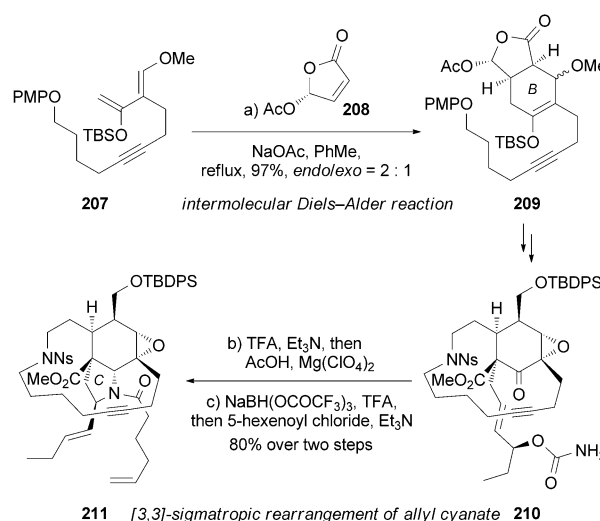


Scheme 32. Part of the total synthesis of (+)-manzamine A (**195**) by Martin et al.^[187]

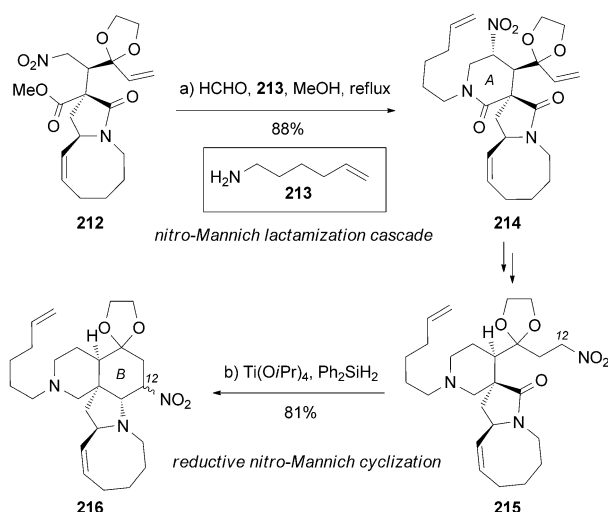
Another interesting synthesis of (+)-**195** was reported by the Fukuyama research group.^[184] An intermolecular Diels–Alder reaction between the Danishefsky-diene-like motif **207** and chiral butenolide **208** provided the B ring of **209**. Subsequently, a well-designed [3,3] sigmatropic rearrangement of allyl cyanate **210** furnished the desired pyrrolidine motif of **211**. Notably, the stereochemistry of the preformed macrocycle dictated the stereoselectivity during the subsequent chemical steps (Scheme 33).

An alternative synthesis of (+)-**195** was recently accomplished by Dixon and co-workers.^[190] Highlights of this synthesis include: a) a three-component nitro-Mannich lactamization cascade between **212**, formaldehyde, and amine **213** to form the A-ring motif in **214**; and b) a novel reductive nitro-Mannich cyclization between the C12 alkyl nitrate and the five-membered lactam moiety of **215** in the presence of $\text{Ti}(\text{O}i\text{Pr})_4/\text{Ph}_2\text{SiH}_2$ to generate the B ring of **216** (Scheme 34).

In addition to its neurotrophic activities, **195** was found to be a potent non-ATP competitive inhibitor of GSK-3 β , a serine-threonine kinase known to phosphorylate the micro-



Scheme 33. Part of the total synthesis of (+)-manzamine A (**195**) by Fukuyama and co-workers.^[184] PMP = *p*-methoxyphenyl.



Scheme 34. Part of the total synthesis of (+)-manzamine A (**195**) by Dixon and co-workers.^[190]

tubule-associated protein tau in mammalian cells.^[191] It has been found that overexpression of GSK-3 leads to abnormally hyperphosphorylated tau protein, which can no longer bind to microtubules but instead are free and available to undergo filament assembly.^[192] Such hyperphosphorylation is believed to be an early event in various neuropathological conditions including brain impairment, learning/memory deficits, depression, AD, and ALS. Thus, inhibiting the abnormally upregulated GSK-3 activity has become an important strategy for NDD treatment.^[192] A potential binding site of **195** to GSK-3 was reported.^[193]

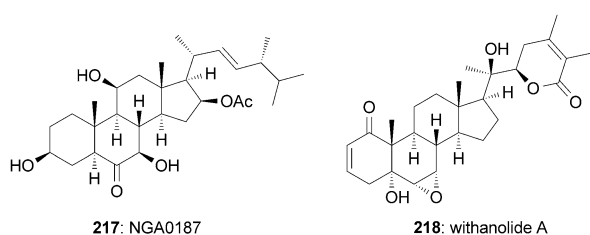
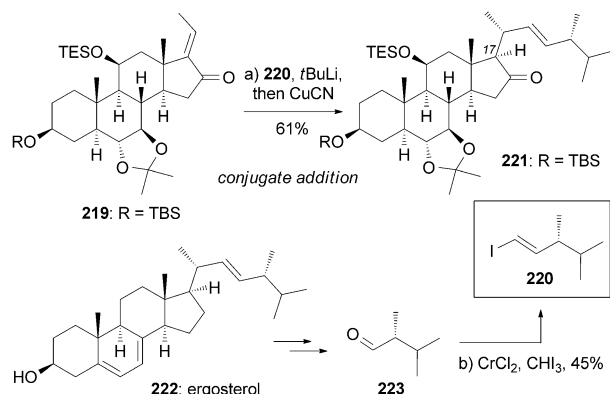


Figure 12. Representative neurotrophic steroids.

2.7. Steroids

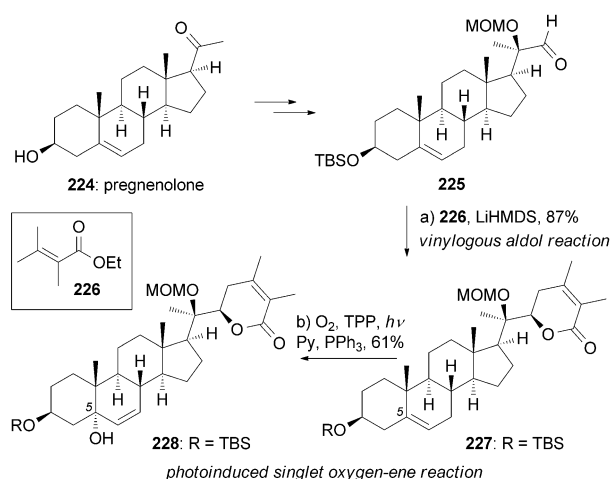
Various steroids, such as NGA0187 (**217**) and withanolide A (**218**), display interesting neurotrophic activities (Figure 12). NGA0187 was isolated from *Acremonium* sp. TF-0356^[194] and is considered to be the first neurotrophic steroid.^[10b,195] It was found that **217** induces neurite outgrowth in PC-12 cells at a concentration of 30–60 μM .^[194,195] The Danishefsky research group reported a synthesis of (+)-**217** starting from adrenosterone (Scheme 35).^[195] The strategy is



Scheme 35. Part of the total synthesis of (+)-NGA0187 (**217**) by Danishefsky and co-workers.^[195]

highlighted by a conjugate addition of the lithium-copper complex of **220** to enone **219** to produce advanced intermediate **221**. Interestingly, **220** was obtained in an enantiomerically pure form from oxidative cleavage of the side chain of ergosterol (**222**). Moreover, several C17 side chain truncated analogues of **217** have been synthesized and evaluated. These analogues have shown no appreciable activities, which suggests that the C17 side chain may play a critical role in the neurotrophic activity of NGA0187.^[195]

Withanolide A (**218**) and related steroids were isolated from the roots of *Withania somnifera* and have shown potent neurite outgrowth activities in human neuroblastoma SH-SY5Y cells at 1 μM .^[196] The Gademmann research group designed a synthesis of (+)-**218** starting from pregnenolone (**224**; Scheme 36).^[197] Crucial steps of this approach include: a) a vinylogous aldol reaction between aldehyde **225** and the lithium enolate of **226** to afford lactone **227**; and b) an elegant singlet oxygen-ene reaction^[198] to produce the C5 tertiary alcohol of **228**. The singlet oxygen was generated in situ from



Scheme 36. Part of the total synthesis of (+)-withanolide A (**218**) by Gademmann and co-workers.^[197] MOM = methoxymethyl, TPP = meso-tetraphenylporphyrin.

oxygen under irradiation with a Na lamp in the presence of meso-tetraphenylporphyrin (TPP) as the sensitizer.

It has been demonstrated that **218** significantly induces axonal/dendritic regeneration and synaptic reconstruction in the impaired mouse brain and damaged rat cortical neurons.^[196b] However, conflicting results precluded a clearer view of the mechanism of action of **218**.^[197a,199]

Certain steroids, such as β -estradiol, were shown to induce neurite outgrowth through the MAPK pathway (Figure 2)^[200] and enhance synaptophysin expression via membrane estrogen receptor and p44 MAP kinase.^[201] In addition to **217** and **218**, several other steroids,^[202] such as deoxygedunin,^[203] allopregnanolone,^[204] and S19159,^[205] have been reported to possess neurotrophic activities.^[206] The signaling mechanisms of these steroids are likely similar to that of β -estradiol.^[196b,206]

2.8. Polyprenylated Acylphloroglucinols

Polyprenylated acylphloroglucinols (PPAPs) possess an intricate polycyclic structure and a broad range of important bioactivities.^[207] Hyperforin (**229**) and garsubellin A (**230**) are two representative samples (Figure 13). The neurite outgrowth effects of hyperforin (**229**) have been well documented.^[208] On the other hand, garsubellin A (**230**), isolated from the wood of *Garcinia subelliptica*, was proposed to

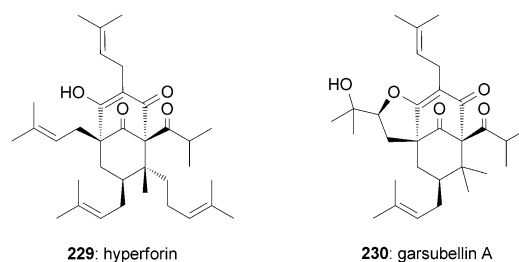


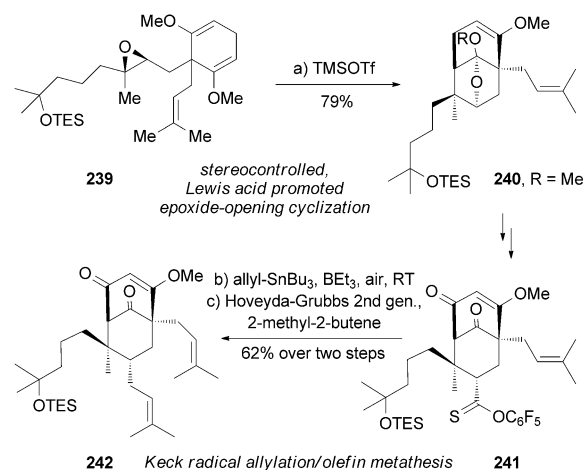
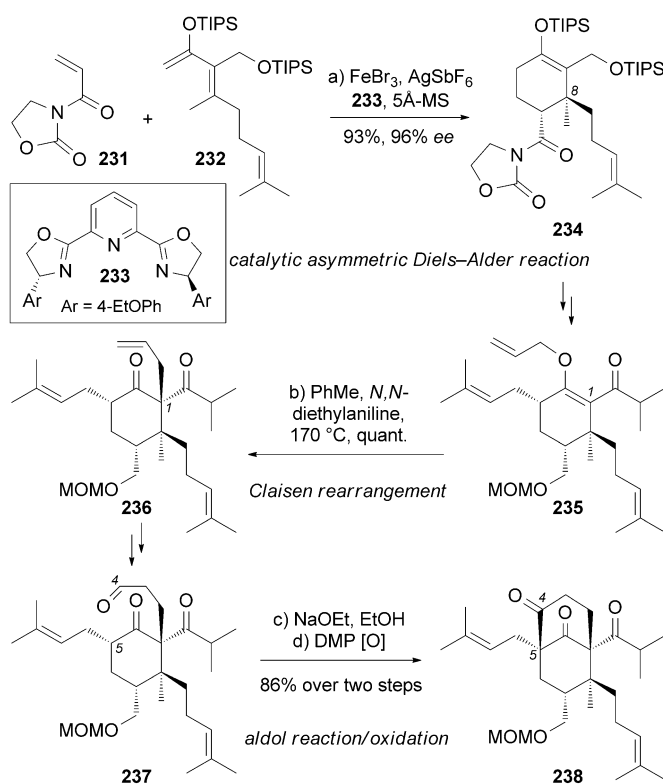
Figure 13. Representative neurotrophic PPAPs.

display potent neurotrophic activities by enhancing choline acetyltransferase (ChAT) activity in P10 septal neurons of cultures rats (154 % relative to control).^[209]

Hyperforin (**229**) was isolated from the herb St. John's wort (*Hypericum perforatum*) in 1971.^[210] In addition to other important bioactivities,^[211] **229** was shown to induce promising neurological effects. For example, the antidepressant activity of **229** was attributed to its ability to inhibit neuronal uptake of various neurotransmitters.^[208a–f] Furthermore, **229** is known to induce neurite outgrowth (10 μ M)^[208g] by directly and selectively activating a member of the canonical transient receptor potential (TRPC) family of ion channels.^[208g,212] Moreover, **229** was reported to affect the processing of the amyloid precursor protein (APP)^[213] and to prevent formation of the amyloid- β (A β) deposit, A β neurotoxicity, and spatial memory impairments.^[214] In addition, **229** stimulates the expression of TrkB, the selective BDNF receptor.^[215]

A total synthesis of (–)-**229** was accomplished by Kanai, Shibasaki, and co-workers.^[216] This approach stems from a catalytic asymmetric Diels–Alder reaction^[217] between dienophile **231** and diene **232** promoted by an Fe^{III} complex with PyBOX ligand **233** (Scheme 37). Claisen rearrangement^[92] of allyl enol ether **235** installed the C1 quaternary center of **236**. The C5 quaternary center of **238** was set through an intramolecular aldol reaction of **237**.

Shair and co-workers reported an efficient approach of (+)-**229** (Scheme 38).^[218] Key to the hyperforin core **240** was the use of a TMSOTf-mediated epoxide-opening cyclization cascade. During this cyclization, the chair transition state is

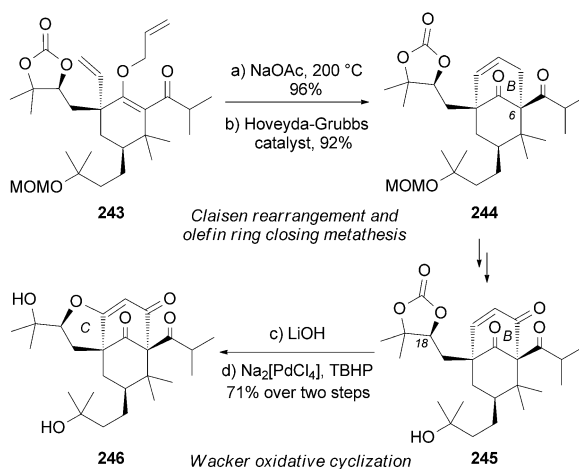


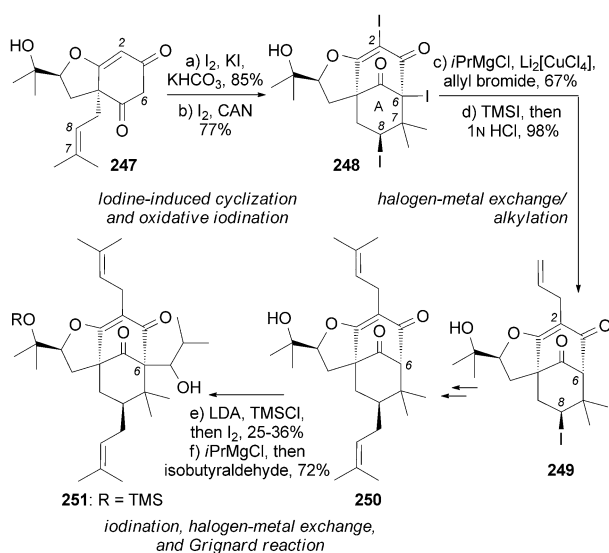
Scheme 38. Part of the total synthesis of (+)-hyperforin (**229**) by Shair and co-workers.^[218]

favorable over the boat conformation, which offers perfect stereocontrol. Another key step involves a Keck radical allylation under allyl-SnBu₃/BEt₃/air conditions. This step was followed by olefin metathesis using the Hoveyda-Grubbs second-generation catalyst^[189c] in the presence of 2-methyl-2-butene to yield advanced intermediate **242**. More recently, the Nakada research group reported a total synthesis of (±)-**229**.^[219]

Kanai, Shibasaki, and co-workers also reported a total synthesis of (±)-garsubellin A (**230**).^[220] The B ring of this compound was set through a Claisen rearrangement^[92] of **243** followed by a ring-closing metathesis. Cleavage of the carbonate group in **245** and a subsequent Wacker-type oxidative cyclization^[221] gave rise to the tricyclic motif of **246** (Scheme 39).

In the total synthesis of (±)-**230** by Danishefsky and co-workers the A ring was formed by an iodine-induced cyclization between the C6 center and the C7–C8 olefin of **247** (Scheme 40).^[222] A subsequent oxidative iodination^[222] installed the vinyl iodide motif in **248** that, upon metalation and





Scheme 40. Part of the total synthesis of (±)-garsubellin A (**230**) by Siegel and Danishefsky.^[222] CAN = cerium(IV) ammonium nitrate.

allylation, allowed installation of the C2 side chain. A similar sequence was implemented for the conversion of **250** into **251**.

A formal synthesis of (±)-garsubellin A (**230**) was accomplished by the Simpkins research group.^[224]

2.9. Tricholomalides

Tricholomalides A–C (**252–254**) were isolated from the mushroom *Tricholoma* sp. and were found to promote neurite outgrowth in PC-12 cell lines at concentrations of 100 μM (Figure 14).^[225] A total synthesis of (±)-**252** and (±)-**253** was reported by Danishefsky and co-workers, thus allowing revision of the C2 configuration (Scheme 41).^[226] The bicyclic

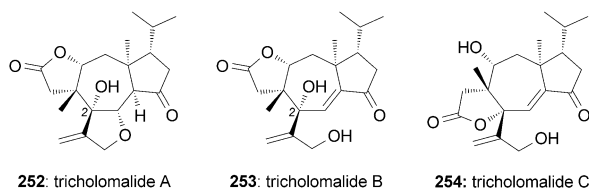
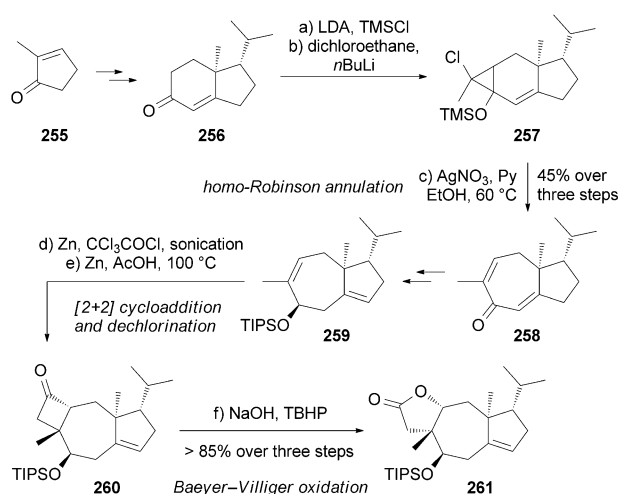


Figure 14. Neurotrophic tricholomalides.

motif of **258** was produced through a homo-Robinson annulation.^[226b] Compound **259** was then subjected to a [2+2] cycloaddition followed by dechlorination to afford the tricyclic motif of **260**. Subsequently, the cyclobutanone motif of **260** underwent a Baeyer–Villiger oxidation^[227] under basic TBHP conditions to yield lactone **261**.



Scheme 41. Part of the total syntheses of (±)-tricholomalides by Danishefsky and co-workers.^[226] TBHP = *tert*-butylhydrogen peroxide.

2.10. Neovibsanines

Neovibsanin A (**262**) and B (**263**) were isolated from the leaves of the poisonous plants *Viburnum awabuki* (Figure 15).^[228] Both compounds were reported to induce NGF-mediated neurite outgrowth in PC-12 cells at 40 μM.^[229]

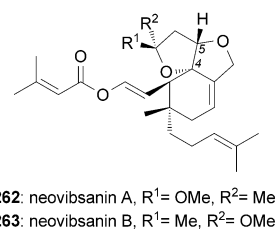
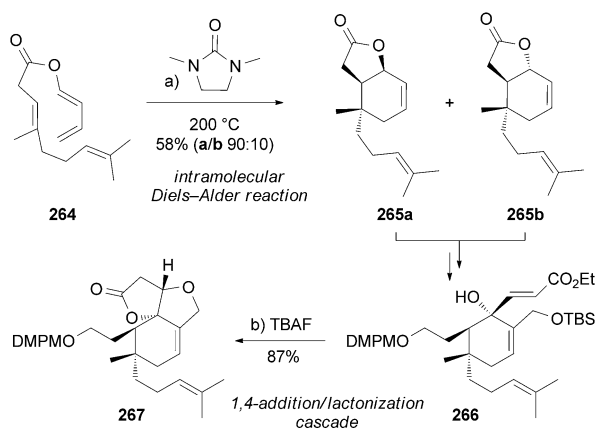


Figure 15. Neurotrophic neovibsanines.

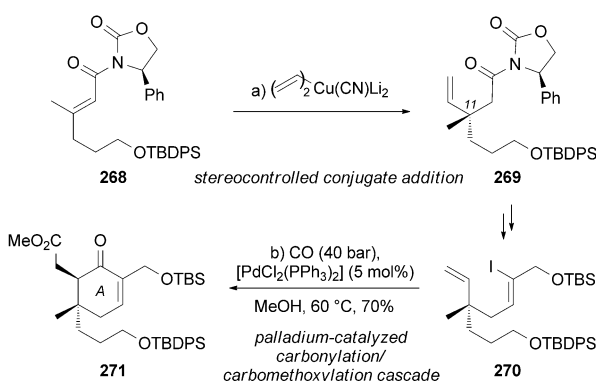
The first total synthesis of (±)-neovibsanin B (**263**) was accomplished by Imagawa, Nishizawa et al.^[229b] This synthesis is based on the formation of lactone **265** through an intramolecular Diels–Alder reaction^[72] to yield a mixture of two isomers **265a** and **265b**, which were both carried forward (Scheme 42). A conjugate addition/lactonization cascade reaction was used to convert **266** into **267**. The neurotrophic activity of the racemic **263** was evaluated in PC-12 cells and its activity was found to be comparable to that of enantiomerically pure **263**.^[229b]

An enantioselective synthesis of (+)-neovibsanin B (**263**) was accomplished by Esumi, Fukuyama et al.^[229c] The strategy features a stereocontrolled conjugate vinylation of chiral oxazolidinone **268** to form the C11 quaternary center (Scheme 43). This reaction was followed by a Pd⁰-mediated carbonylation/carbomethoxylation cascade reaction to furnish the A ring of **271**.

Moreover, the Williams research group reported the synthesis of (±)-4,5-bis-*epi*-neovibsanin A and B.^[230] These



Scheme 42. Part of the total synthesis of (±)-neovibsanin B (**263**) by Imagawa, Nishizawa et al.^[229b] DMPM = 3,4-dimethoxybenzyl.



Scheme 43. Part of the total synthesis of (+)-neovibsanin B (**254**) by Esumi, Fukuyama et al.^[229c]

compounds were also shown to promote NGF-mediated neurite outgrowth in PC-12 cells at 40 μM . More recently, a fluorescently labeled and structurally simplified neovibsanin analogue was observed to accumulate around the outer edge prominences of the PC-12 cells.^[231]

2.11. Miscellaneous Natural Products

In addition to the above-mentioned natural products, nature has produced other fascinating small molecules that possess various levels of architectural complexity, yet they share a similar level of exciting neurotrophic activity. Representative examples of such natural products are shown in Figure 16.

Panaxyltriol (**272**) is an active component of red Ginseng^[232] and its chemical synthesis has been reported by several research groups.^[233] Among them, Danishefsky and co-workers have shown that **272** promotes NGF-induced neurite outgrowth in PC-12 cells at a concentration of 60 μM .^[234] Talaumidin (**273**) is a tetrahydrofuran neolignan that was isolated from the roots of *Aristolochia arcuata*.^[235] It promotes neurite outgrowth of cultured rat cortical neurons at a concentration of 1–30 μM and exhibits neuroprotective

effects.^[235] As a consequence of its promising biological profiles, various synthetic studies of **273** have been reported.^[236] 14-Norpseurotin (**274**)^[237] was isolated from the marine-derived fungus *Aspergillus sydowi* PFW 1-13 and was reported to induce neurite outgrowth of PC-12 lines at concentrations of 10 μM .^[238] A member of the flavonoid family, 7,8-dihydroxyflavone (**275**), was recently found to be a selective TrkB agonist through Erk1/2 and Akt activation.^[239] Moreover, its neuroprotective effects^[239,240] and optimized analogues^[241] have been recorded. In addition, several other natural flavonoids have been reported to possess activities to promote neurite outgrowth or neurogenesis.^[242] Aspermytin A (**276**) was isolated from a marine-derived fungus *Aspergillus* sp. and was found to display neurotrophic effects in PC-12 cells at a concentration of 50 μM .^[243] A synthesis of **267** has been reported by the Shishido research group.^[244] Gelsemiol (**277**)^[245] was isolated from the Paraguayan plant *Verbena littoralis* H. B. K. and was shown to promote NGF-mediated neurite outgrowth in PC-12 cells at concentrations between 100 and 300 μM . Gademann and co-workers have reported an efficient synthesis of **277**.^[246]

Various protein kinase C (PKC) activators, such as phorbol ester (PMA, **278**)^[247] and bryostatin 1 (**279**),^[248] were found to significantly promote neurite outgrowth in PC-12 cell lines^[249] and primary culture of chicken dorsal root ganglion (DRG) neurons.^[250] Other notable neurotrophic PMA natural analogues include kirkinine (**280**),^[250] kirkinine B, mezerein, and synaptoplep factor K7.^[250c] Pioneering syntheses of phorbol and related daphnane natural products have been reported by the research groups of Wender^[251] and Cha.^[252] In addition, multiple impressive syntheses of bryostatin 1 (**270**)^[253] and its natural analogues have been reported by the research groups of Keck,^[253] Masamune,^[254] Evans,^[255] Nishiyama/Yamamura,^[256] Manaviyar,^[257] Trost,^[258] Kri-sche,^[259] and Wender.^[260]

Caryolanemagnolol (**281**) and clovanemagnolol (**282**) were isolated from *Magnolina obovata* and have been found to enhance neurite outgrowth as well as increase ChAT activity at a concentration of 0.1 μM .^[261] Studies conducted by Siegel and co-workers have led to a bioinspired synthesis of **281** and **282**.^[262] The authors also confirmed the potent neurotrophic activity of **272** in embryonic hippocampal and cortical neurons at concentrations of 10 nM.^[262b] A member of the caged *Garcinia* xanthenes,^[263] gambogic amide (**283**), has shown significant neurotrophic activity at a low nanomolar concentration by binding to and activating TrkA, thereby promoting its dimerization and autophosphorylation.^[264] In addition, **283** also exhibited neuroprotective effects.^[264]

The clerodane diterpenoid^[265] ptychonal (**284**) was isolated from *Ptychopetalum olacoides* as a mixture of the hemiacetal and aldehyde form.^[266] This equilibrium mixture was shown to exhibit neurite outgrowth promoting activities on NGF-mediated PC-12 cells at concentrations ranging from 0.1 to 10.0 μM . The neurotrophic metabolite epolactaene (**285**) was isolated from the fungal strain *Penicillium* sp. BM 1689-P.^[267] **285** was shown to promote neurite outgrowth in a human neuroblastoma cell line (SH-SY5Y) at concentrations ranging from 10 μM to 25 μM .^[267,268] As a result of its promising biological activity, various syntheses have been

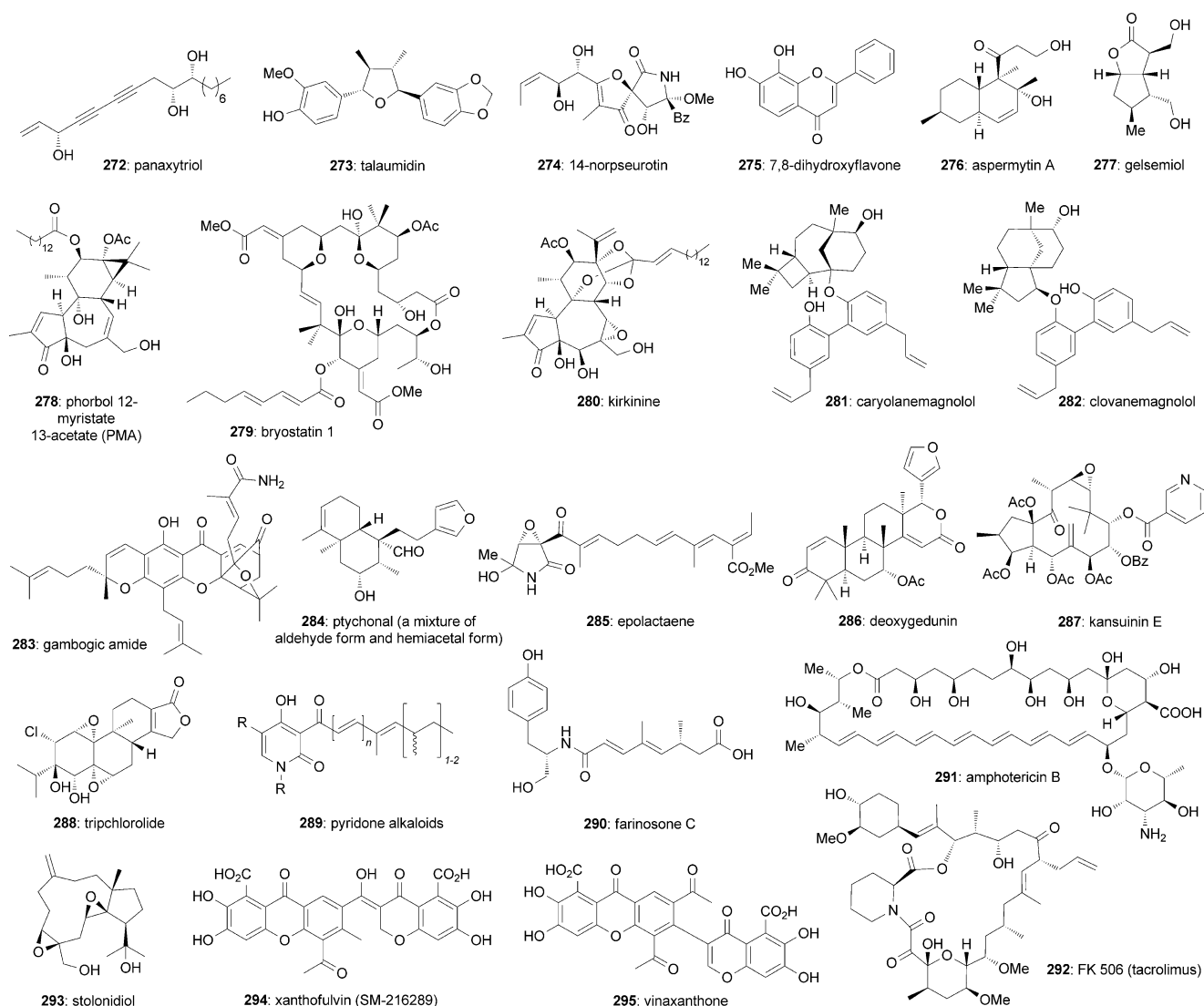


Figure 16. Other selected neurotrophic natural products.

reported.^[269] Deoxygedunin (**286**), a natural product isolated from Indian neem trees (*Azadirachta indica*), was found to act as a BDNF mimic and exhibited TrkB activation in rat hippocampal neurons at nanomolar concentrations.^[203] Kansuinin E (**287**),^[270] a macrocyclic jatrophane diterpene,^[270,271] was found to promote neurotrophic activity, presumably through TrkA activation.^[271c] A related study has also suggested that activation of cyclooxygenase plays an essential role in NGF synthesis.^[271b] Triphchlorolide (**288**), an immunosuppressive extract of Chinese herb *Tripterygium wilfordii* Hook F, was reported to induce neurotrophic activity in embryonic mesencephalic neurons of rats and displayed neuroprotective effects in dopaminergic neurons from 1 pM to 10 nM. **288** was reported to stimulate BDNF mRNA expression.^[272] Moreover, its neuroprotective properties have been evaluated in several studies.^[272,273] The neurological activity of **288** might be similar to another immunosuppressant FK506 (tacrolimus).^[274]

A series of pyridone alkaloids (**289**),^[275] such as tenellins,^[276] bassianins,^[276a–c] farinosones,^[277] and militarinones,^[278]

share a common chemical skeleton and promising neurotrophic activities. In 1982, the Williams research group reported an efficient synthesis of tenellin.^[279] More recently, a divergent synthesis of various neurotrophic pyridone alkaloids was reported by Gademann and co-workers.^[275d,280] The related farinosone C (**290**)^[277] also promotes neurite outgrowth in NGF-mediated PC-12 cell lines at a concentration of 50 μM .^[281] The authors reported a synthesis of **290** and have disclosed that L-tyrosinolamide represents its pharmacophore.^[281] Studies in PC12 cells suggest that certain militarinones induce persistent neuritic differentiation by elevating the intracellular cAMP levels that, in turn, affect TrkA receptor signaling.^[278c] Such persistent activation of the PI3/Akt and MEK/ERK pathways was shown to upregulate p53 and induce the release of AIF from mitochondria, ultimately resulting in cell apoptosis in Neuro 2a mouse neuroblastoma cells. Based on these findings, the authors concluded that the effect of militarinones depends on the basal expression of p53; specifically these compounds induce apoptosis in cells with high p53 expression but prompt

neuritic differentiation in cells where the p53 levels are low.^[278e]

Various macrolides, such as amphotericin B (**291**) and FK506 (tacrolimus, **292**), exhibit remarkable neurotrophic profiles. **291** was originally isolated from the filamentous bacterium *Streptomyces nodosus*^[282–284] and is often used as an antifungal agent.^[285] The exciting neurological activity of **291** was recently revealed.^[286] This compound was shown to promote neurite outgrowth in rat postnatal cerebellar neurons and rat embryonic cortical neurons. It was also found to prevent the activities of the major myelin- and glial-associated inhibitors, which are the crucial factors that suppress neuron regeneration upon spinal cord injury.^[286] A stereoselective synthesis of **291** has been reported by Nicolaou et al.^[287] A recent mechanistic study suggested that **291** antagonizes CNS inhibitors to promote axon growth through the activation of the Akt pathway, which suppresses the activity of GSK-3 β .^[286]

FK506 (tacrolimus, **292**) was isolated from *Streptomyces tsukubaensis* in 1987.^[288] In addition to its remarkable function in the immune system, **292** has also shown intriguing neuroprotective and neurotrophic activities, including promotion of neurite outgrowth in PC-12 cells and peripheral neurons.^[289] **292** was shown to induce functional improvements of peripheral nerve damage and spinal cord injury.^[274] Furthermore, it was reported that **292** promotes the proliferation of cultured Schwann cells and NGF secretion at a concentration of 10 nM.^[290] In addition, **292** was reported to promote NGF-induced neurite outgrowth through the MAP kinase pathway.^[291] The neuroprotective potential of **292** following CNS injury has been evaluated.^[274] Although the detailed mechanism remains unclear, it is noted that binding to two members of the immunophilin family, FKBP-12 and FKBP-52, are critical for its neuroprotective effects.^[292] Since CNS injury is associated with the activation of the immune response, it is suggested that the immunosuppressive activity of **292** could induce the observed neuroprotective effects.^[274e] Indeed, it has been shown that immunophilin ligands possess neurotrophic activities.^[292,293] Therefore, it is reasonable to find that several natural or synthetic analogues of **292**, such as rapamycin^[289,294] and FK1706,^[295] promote neurite outgrowth in PC-12 cells (rapamycin, 1 nM) and human neuroblastoma SH-SY5Y cells (FK1706, 1 nM). Several total syntheses of **292** have been accomplished by Merck,^[296] Schreiber and co-workers,^[297] and Ireland et al.^[298] In addition, the research groups of Danishefsky,^[299] Sih,^[300] and Smith^[301] have completed formal total syntheses. The synthetic efforts toward **292** have been reviewed by Nakata^[302] and Ley and co-workers.^[303]

Stolonidiol (**293**) was isolated from the Okinawan marine soft coral *Clavularia* sp.^[103a,304] Aside from its potent cytotoxicity to P388 leukemia cells, **293** was reported to possess significant ChAT activity in primary cultured basal forebrain cells and clonal septal SN49 cells at a concentration of 0.3 μ M.^[103a] A synthesis of stolonidiol was reported by Yamada and co-workers.^[305] Xanthofulvin (SM-216289, **294**) and vinaxanthone (**295**) were isolated from the cultured broth of a fungus *Penicillium* sp. SPF-3059.^[306] Significantly, these two compounds were found to strongly inhibit the activity of semaphorin3A (Sema3A), an inhibitor of axonal regeneration, with no observable cytotoxicity. Studies in animals

validated the clinical promise of **294**.^[307] These findings may pave the way for the development of agents to treat injured spinal cords. Recently, Siegel and co-workers have reported an impressive synthesis of **294** and **295**.^[308]

3. Conclusions and Perspectives

It is widely accepted that natural products have evolved to perform, often in synergy, a wide array of functions that are beneficial to the producing organism. In fact, they are considered to be “privileged structures”^[309] which, upon subtle changes aimed to improve their pharmacokinetic and pharmacodynamic profile, can lead to the development of new medicines.^[310] For example, natural products and their structural relatives still comprise more than 50 % of the drugs used clinically.^[311] Equally important is the role of natural products as tools in chemical biology, where the aims are to develop new bioassays, to characterize cell signaling pathways, and to chemically evaluate biological events.

Neurodegenerative diseases is a generic term applied to a variety of conditions that arise from a chronic breakdown and deterioration of the nerve cells, in particular those of the central nervous system.^[312] Most commonly, these diseases manifest in elderly people and in industrialized societies, where the life expectancy is long, and they impose severe strains on the social welfare systems. Preventive approaches against neurodegeneration require consideration of various genetic and epidemiological studies that are not easy to correlate. In addition, such approaches are difficult to implement in the case of a traumatic event, such as spinal cord injury. Research into the underlying cause of neurodegeneration is far from complete and no cures for these diseases have been found. The current approach is to produce symptomatic relief or correct neurotransmitter deficiencies and enzymatic breakdown.^[2a,7]

Neurotrophins have been identified as promoters of neuronal survival, development, and function, including synapse formation and remodeling of the synaptic network.^[8] The importance of these molecules is underscored by the severe neurological effects observed in animals in which neurotrophins or their receptors have been deleted.^[313] Despite their unambiguous importance in biology and physiology, drug development approaches based on neurotrophins have encountered several problems associated with oral availability, insufficient delivery to the brain, and high manufacturing cost.^[314] Natural products and related molecules with neurotrophic activity can, in principle, overcome these obstacles.^[10,11,315] In fact, several compounds are currently in clinical trials for neurodegenerative diseases.^[316] A recent example is bryostatin 1 (**279**),^[317,318] which, in turn, highlights the importance of developing robust synthetic strategies that can be used to evaluate and optimize the biological properties of the parent structure.^[319]

The synthetic strategies reviewed above offer confidence that the privileged motifs of various neurotrophic natural products can be constructed in the laboratory. Constant advances in the area of synthetic methods promise to further improve these strategies, particularly as they relate to

efficiency, flexibility, and overall cost. Apart from certain notable exceptions that have been discussed in this Review, the chemical biology of neurotrophic natural products has not been explored methodically. This could be due to the complexity of pathways that account for neural degeneration and the difficulties related to conducting biological experiments in primary neural cells. The readily available PC-12 cell line offers an attractive and reliable alternative to the primary cell cultures.^[96] On the other hand, several key proteins that regulate neuronal growth have been identified as potential targets for therapeutic intervention against neurodegeneration. In addition, advances in high-throughput screening,^[320] cellular phenotype imaging,^[321] stem cell technology, and regenerative medicine promise to facilitate and accelerate such studies.^[322] It is critical to take advantage of this progress on all fronts and push the frontiers of chemical neurobiology further. This task is particularly important and timely due to the recently announced Brain Activity Map (BAM) project.^[323] Reminiscent of the Human Genome Project, this initiative will attempt to reconstruct the entire neural activity in the brain. With such an ambitious goal in mind, chemical neurotrophins are expected to play a critical role in the chemical evaluation of neural circuit remodeling, cognitive functions, and behavior.

Financial support from the National Institutes of Health (CA 133002) is gratefully acknowledged. We also thank the U.S. Department of Education for a Fellowship to M.H.L. through GAANN grant P200A120223. We thank the National Science Foundation for instrumentation grants CHE9709183 and CHE0741968. We also thank Dr. Lynnie Trzoss, Weng K. Chang, and Prof. William C. Mobley for contributions to the research described in this Review, and Professors Jerry Yang and Carlos A. Guerrero (UCSD) for useful comments.

Received: March 17, 2013

Published online: December 18, 2013

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