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Illicium Sesquiterpenes: Divergent Synthetic Strategy and Neurotrophic Activity Studies

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Abstract: Majucin-type sesquiterpenes from *Illicium sp.*, such as jiadifenolide (**2**), jiadifenin (**3**), and (1*R*,10*S*)-2-oxo-3,4-dehydroxyneomajucin (**4**, ODNM), possess a complex caged chemical architecture and remarkable neurotrophic activities. As such, they represent attractive small-molecule leads against various neurodegenerative diseases. We present an efficient, enantioselective, and unified synthesis of **2**, **3**, and **4** and designed analogues that diverge from tetracyclic key intermediate **7**. The synthesis of **7** is highlighted by the use of an enantioselective Robinson annulation reaction (construction of the AB rings), a Pd-mediated carbomethoxylation reaction (construction of the C ring), and a one-pot oxidative reaction cascade (construction of the D ring). Evaluation of the neurotrophic activity of these compounds led to the identification of several highly potent small molecules that significantly enhanced the activity of nerve growth factor (NGF) in PC-12 cells. Moreover, efforts to define the common pharmacophoric motif suggest that substitution at the C-10 center significantly affects bioactivity, while the hemiketal moiety of **2** and **3** and the C-1 substitution might not be critical to the neurotrophic activity.

Keywords: cascade reactions · natural products · oxidation · sesquiterpene · total synthesis

Introduction

The discovery of nerve growth factor (NGF)[1] has fueled intensive research in the area of neurotrophins, a family of polypeptides that play an essential role in the development and maintenance of neurons in both the central and peripheral nervous system.[2] The binding of NGF to its cell surface receptor leads to a cascade of signaling pathways that promote axonal and dendritic branching. In turn, this activity allows the construction of a neural network that is critical during embryonic development and/or after neuronal injury. Importantly, alterations in neurotrophin levels have been implicated in various neurodegenerative[2,3] and psychiatric disorders.[4] Moreover, preclinical studies have suggested that administration of neurotrophins may lead to an effective treatment for various neurodegenerative disorders.[5] However, despite such potential, clinical trials with NGF and related polypeptides have been disappointing since these compounds cannot be delivered orally, they are rapidly degraded in the body and are inefficient in crossing the blood–brain barrier.[6] These problems, inherent with most protein-based therapies, have prompted the scientific community to explore nonpeptidyl small-molecule-based therapeutics.[7] In principle, these compounds could induce neurite outgrowth by enhancing the activity or inducing the biosynthesis of NGF and related neurotrophic factors.

Natural products, used in traditional medicine[8,9] or as neutraceuticals,[10] hold significant promise as tools for biological studies and as privileged structures for the development of new therapeutic agents against neurodegeneration. The *Illicium* species of plants exemplify such a dual potential. Spreading over eastern North America, Mexico, the West Indies, and eastern Asia, these plants are known for their distinctive star-shaped fruits and characteristic flavors.[11] Isolation of their chemical constituents has led to the identification of three distinct families of sesquiterpenes: the *seco*-prezizaanes, the anislactones, and the *allo*-cedranes.[11] Among them, the majucin-subfamily of *seco*-prezizaanes is particularly interesting since it contains compounds with potent neurotrophic activities. Members of this family include majucin (**1**),[12] jiadifenolide (**2**),[13] jiadifenin (**3**),[14] and (1*R*,10*S*)-2-oxo-3,4-dehydroxyneomajucin (**4**, ODNM)[15] (Figure 1). Central to their caged architecture is a highly substituted cyclohexane ring (B ring) that is surrounded by three additional rings including a cyclopentane (A ring) and a γ-lactone (C ring). Further functionalization at C-4 and C-10 forms a unique γ-lactone ring (E ring) as in the structure of **2**.[11] Initial biological studies have shown that compounds **2**–**4** significantly enhance neurite outgrowth in primary cultured rat cortical neurons or NGF-mediated

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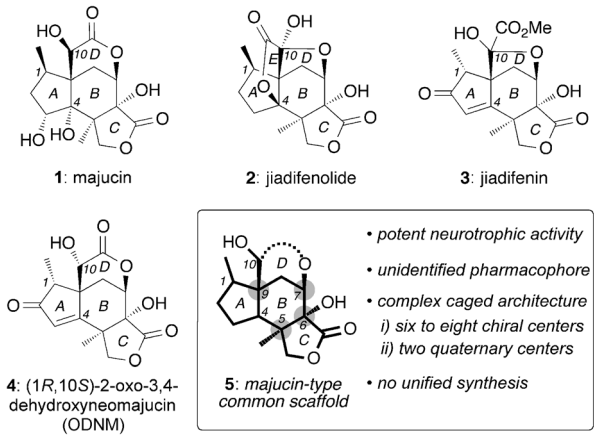


Figure 1. Structures of selected neurotrophic majucin-subtype *Illicium* sesquiterpenes and their common scaffold.

PC-12 cells at concentrations between 10 to 100 nM. This is particularly interesting since it suggests that these compounds rather than acting independently of NGF, enhance its activity. Among them, jiadifenolide is reportedly the most active compound inducing neurite outgrowth at 10 nM.[13]

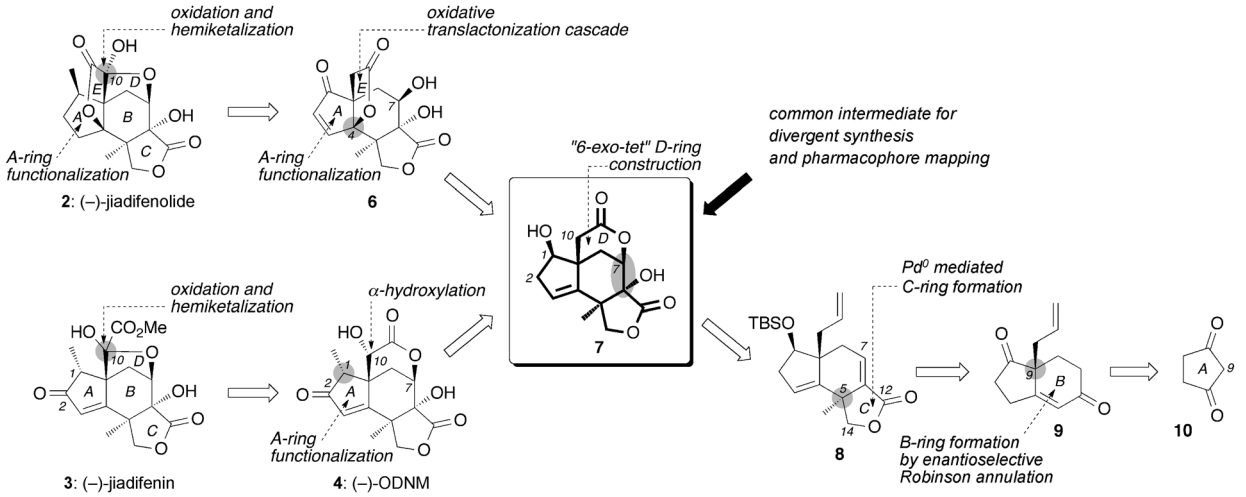
Due to the combination of a complex ring motif and significant therapeutic potential, these compounds represent attractive targets for synthetic and biological studies.[16] Despite various successful syntheses of similar sesquiterpenes, such as anisatin[17] and merrilactone,[18] synthetic efforts towards the majucin-subtype *seco*-prezizaane-type sesquiterpenes are rather limited.[19] To date, two impressive syntheses of jiadifenin (**3**) have been reported by the Danishefsky[20] and Zhai groups.[21] Intrigued by the synthetic challenge and medicinal potential of these compounds, we sought to develop a unified synthetic strategy. We hypothesized that such a divergent strategy would provide access to a library of related molecules for subsequent structure–activity relationship studies. Herein, we describe the strategy that led to the first enantioselective synthesis[22] of **2**, **3**, and **4** and related analogues. Biological evaluation of these compounds led to the identification of more potent neurotrophic agents and allowed us to propose a critical pharmacophoric motif.

Results and Discussion

Divergent retrosynthetic analysis: The key strategic bond disconnections toward a divergent synthesis of **2**–**4** and related analogues are shown in Scheme 1. We envisioned that these natural products could derive from "core" structure **7** by following late-stage modifications. Key to the conversion of **7** to (−)-jiadifenolide would be an oxidative translactonization reaction cascade that formed the E ring of **6** leading, after C-10 oxidation and hemiketalization, to **2**. On the other hand, hydroxylation at C-10 of **7** followed by further A-ring functionalization would produce ODNM (**4**). An oxidation and hemiketalization reaction would then form jiadifenin (**3**) from **4**. Furthermore, the divergent functionalization of **7** would produce a set of designed analogues.

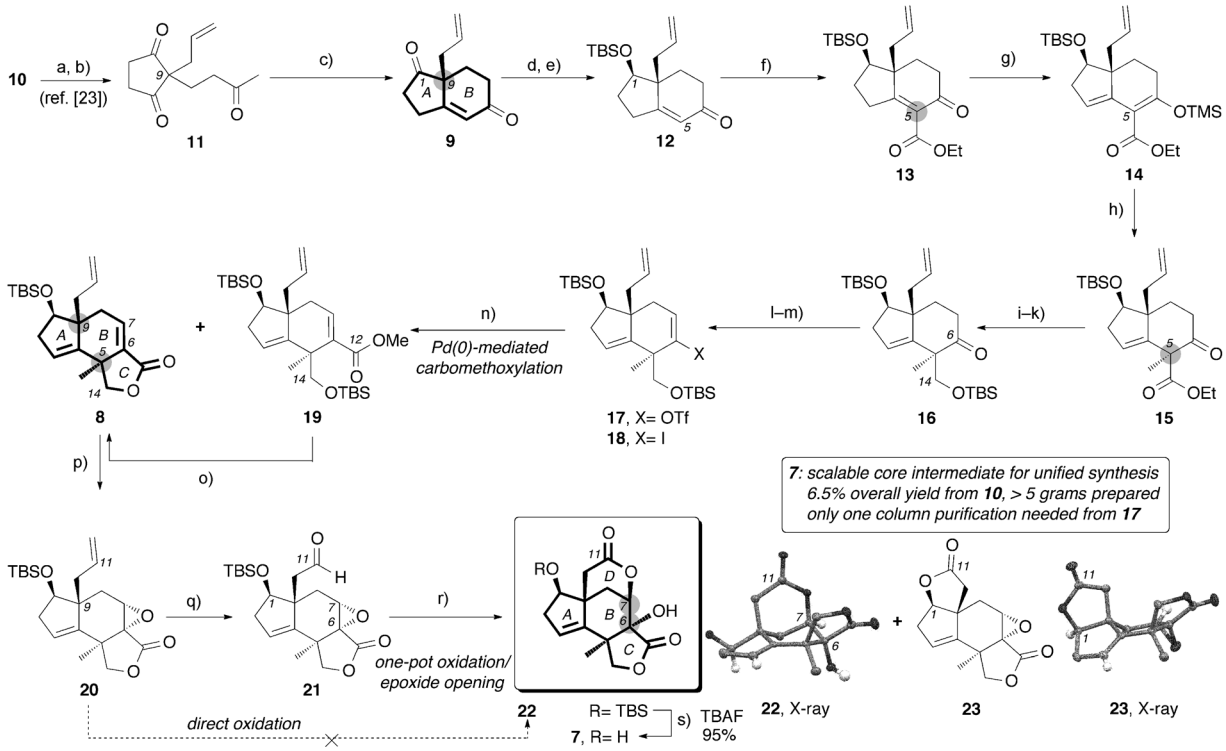
We theorized that the tetracyclic motif of **7** could be formed from compound **8** through a sequence of reactions among which the key step is a one-pot oxidation/"*6-exo-tet*" epoxide-opening cascade. In turn, the C ring lactone of **8** could arise from a Pd-catalyzed carbomethoxylation. This disconnection opens the possibility to construct compound **8** from a Hajos–Parrish-type enone **9**. Importantly, this compound could be produced from 1,3-cyclopentadione (**10**) by C-9 alkylation followed by an enantioselective Robinson annulation.

Scalable synthesis of core intermediate 7: Our synthesis of **7** commenced from commercially available dione **10**, which was readily converted to **11** in two steps and 63% combined yield.[23] Robinson annulation of **11** to **9** was accomplished by optimizing the Tu/Zhang conditions.[23c] At the onset of



Scheme 1. Unified retrosynthetic strategy for jiadifenolide, jiadifenin, and ODNM. TBS = *tert*-butyldimethylsilyl?.

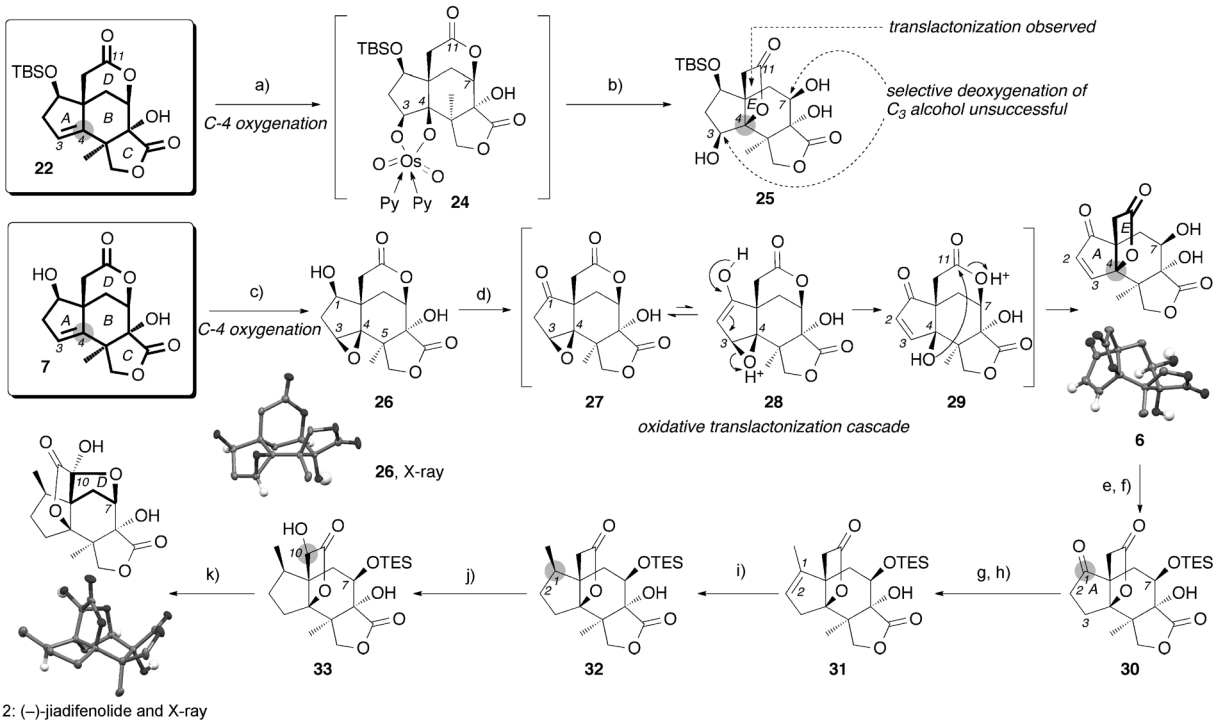
the study, we found that treatment of **11** with 30% D-prolinamide/PPTS at 80°C over 12 h afforded **9** in 74% yield and 70% *ee*. On the other hand, at room temperature this reaction needed up to 60 days to completely consume the starting material, thus yielding enantiomerically pure (−)-**9** (> 99% *ee*). To balance reaction efficiency with acceptable enantioselectivity we choose to perform this annulation at 40°C over 14 days producing **9** in 70% yield and 90% *ee* (50-gram scale). Chemoselective hydride reduction of the C-1 ketone followed by TBS protection[24] yielded enone **12** (92% combined yield). Stiles' reagent (MMC, $MeO_2CMgOMe$)[25] selectively introduced a sensitive carboxylic acid group at C-5, which was subsequently esterified by using Meerwein's salt ($Et_3O^+BF_4^-$) to form β-keto ester **13**.[26] This procedure provides a safer alternative to the commonly used diazomethane-based esterification of a "Hajos-Parrish-type" β-keto acid.[27] Construction of the C-5 quaternary center was accomplished by forming the extended enolate **14** (TMSOTf/lutidine)[28] and methylating the "pre-activated" C-5 center of **14** by using TBAF/MeI conditions, thereby producing compound **15** as a single diastereomer (43% combined yield from **12**). Construction of the C ring would require incorporation of a carboxyl group at C-6 and lactonization with the pendant C-14 hydroxyl group. With this in mind, **15** was converted to the silyl-ether **16** through a sequence of three steps that included: 1) global reduction with $LiAlH_4$, 2) selective TBS-protection of the primary C-14 hydroxyl group, and 3) IBX oxidation of the secondary C-6 hydroxyl group (85% over 3 steps). Treatment of **16** with McMurry reagent ($PhNTf_2$)[29] yielded enol triflate **17**, which underwent a Pd^0-mediated carbomethoxylation[30] under a carbon monoxide atmosphere (1 bar) to produce uncyclized compound **19** (60%) together with a small amount of lactone **8** (23%). Without purification, this mixture was treated with TFA to cleanly produce the desired lactone **8** (69% overall yield from **16**). Similarly, compound **8** can be made from vinyl iodide **18**, albeit in a slightly lowered overall yield (60% from **16**; Scheme 2).



Scheme 2. Scalable synthesis of tetracyclic scaffold **7**: a) *N,O*-bis(trimethylsilyl)acetamide (1.0 equiv), allyl acetate (1.0 equiv), [$PdCl_2$(allyl)] (0.01 equiv), DPPE (0.05 equiv), NaOAc (0.03 equiv), 70°C, 40 h; b) methyl vinyl ketone (2.0 equiv), H_2O/AcOH (67:1), 100°C, 4 h, 63% from **10**; c) D-prolinamide (0.3 equiv), PPTS (0.3 equiv), MeCN (80°C, 12 h: 75%, 70% *ee*; 40°C, 14 d: 74%, >90% *ee*; RT, 60 d, 70%, >99% *ee*); d) $NaBH_4$ (0.25 equiv), EtOH, 0°C, 1 h; e) TBSCl (2.0 equiv), NH_4NO_3 (3.0 equiv), DMF, RT, 12 h, 92% from **9**; f) Stiles' reagent (methyl methoxymagnesium carbonate, 4.0 equiv), DMF, 130°C, 3 h, then $Et_3O^+BF_4^-$ (1.0 equiv), iPr_2NEt (1.5 equiv), CH_2Cl_2, 0°C, 5 min; g) TMSOTf (1.3 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, 0°C to RT, 1 h; h) TBAF (1.0 equiv), MeI (10 equiv), THF, −78°C to RT, 3 h, 43% from **12**; i) $LiAlH_4$ (7.5 equiv), THF, 0°C to RT, 1 h; j) TBSCl (1.1 equiv), imidazole (2.0 equiv), CH_2Cl_2, 0°C, 30 min; k) IBX (3.0 equiv), DMSO, 80°C, 1 h, 85% from **15**; l) KHMDS (5.0 equiv), $PhNTf_2$ (3.0 equiv), THF, −78°C, 1 h, 95% (**17**); m) NH_2NH_2 (3.0 equiv), Et_3N (4.0 equiv), EtOH, 50°C, 5 h, then I_2 (10 equiv), DBU (6.0 equiv), Et_2O, 0°C, 80% (**18**); n) CO (1 atm.), [$Pd(PPh_3)_4$] (0.01 equiv), MeOH/DMF (1:3), Et_3N (3.0 equiv), 50°C, 2 h; from **17**: 60% (**19**) and 22% (**8**); from **18**: 61% (**19**) and 23% (**8**); o) TFA (3.0 equiv), CH_2Cl_2, RT, 5 h, 85%; p) H_2O_2 (10 equiv), 3 M NaOH, THF, 0°C to RT, 5 h, 99%; q) OsO_4 (0.01 equiv), $NaIO_4$ (4.0 equiv), 2,6-lutidine (2.0 equiv), 1,4-dioxane/H_2O (3:1), RT, 12 h, 99%; r) Jones reagent (6.0 equiv), acetone, 0°C, 30 min, 70% of **22** and 20% of **23**; s) TBAF (2.0 equiv), THF, RT, 30 min, 95% (**22**), 20% (**23**). The TBS group of **22** and some hydrogen atoms in the X-ray structure were omitted for clarity. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DPPE = 1,2-bis(diphenylphosphino)propane, IBX = 2-iodoxybenzoic acid, PPTS = pyridinium *p*-toluenesulfonate.

Possessing a readily functionalizable ABC ring system with two quaternary centers, lactone **8** provided a solid scaffold for further chemical modifications (Scheme 2). The next task was the installation of the C-6–C-7 *trans*-diol moiety and the construction of the D-ring lactone. To this end, the electronically deficient C-6=C-7 double bond was stereoselectively epoxidized under alkaline hydrogen peroxide conditions to generate epoxide **20** in 99% yield. This epoxidation proceeded selectively from the α-face in a substrate-controlled manner. Oxidative cleavage of the terminal double bond of **20** proceeded best by an osmium-catalyzed dihydroxylation and in situ cleavage of the resulting diol with $NaIO_4$. The corresponding aldehyde **21** was treated under Jones conditions to form the corresponding carboxylic acid. Concomitant activation of the neighboring epoxide led, in a one-pot reaction cascade, to lactone **22** (70% yield). The absolute stereochemistry of **22** was unambiguously confirmed by single-crystal X-ray analysis.[31] In addition to **22** we also isolated a small amount (20%) of a desilylated compound, as suggested by ^{1}H NMR spectroscopic analysis. This byproduct was shown to be lactone **23**, the structure of which was confirmed by X-ray analysis.[31] This compound might arise from concomitant cleavage of the C-1 silyl ether under acidic Jones conditions and lactonization of the resulting hydroxyl group with the C-11 carboxylic acid. Another possibility is the rapid desilylation of the C-1 hydroxy moiety resulting in the attack on the C-11 formyl group to form the corresponding lactol followed by oxidation to give this side product. Attempts to convert **23** to **22** were unsuccessful. Deprotection of the TBS group of **22** by using TBAF then afforded the crucial di-lactone **7**, the "core intermediate" for the divergent synthesis. Notably, only one column purification was needed for the conversion of triflate **17** to **7** (6 steps). More importantly, the synthesis of **7** from commercially available 1,3-cyclopentadione was readily reproducible and scalable (>5 g prepared), thus providing a robust platform for further investigations.

Total synthesis of (−)-jiadifenolide (2): With sufficient amounts of **7** in hand, we sought to establish a strategy for the oxygenation at C-4. At the onset of these studies, we treated **22** with catalytic OsO_4 but could not detect any dihydroxylation product (Scheme 3), presumably due to the steric hindrance of the trisubstituted double bond. Interestingly, treatment of **22** with stoichiometric amounts of OsO_4 in the presence of pyridine produced a moderately stable osmium–pyridine complex **24**[32] that upon treatment under reductive conditions (sodium thiosulfate) yielded a C-3–C-4 *cis*-diol. To our surprise, we observed a rapid and irreversible translactonization between the C-4 and C-11 functionali-

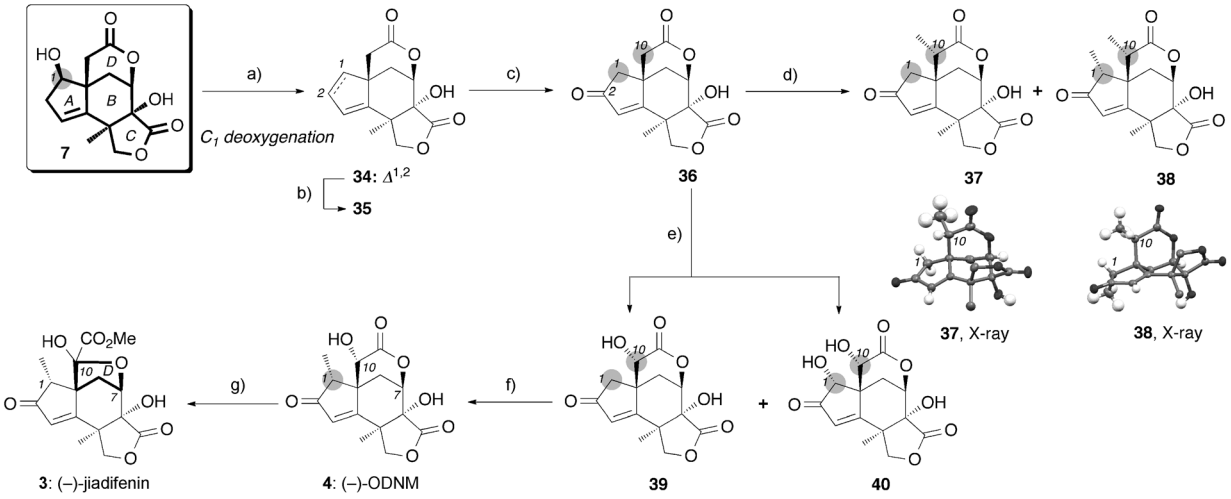


Scheme 3. Total synthesis of (−)-jiadifenolide (**2**) from core intermediate **7**: a) OsO_4 (1.0 equiv), THF/pyridine (2:1), RT, 30 min, 90%; b) $Na_2S_2O_3$ (10 equiv), MeOH/H_2O (3:1), 60 °C, 1 h, 87%; c) *m*CPBA (4.0 equiv), THF, 50 °C, 3 h, 80%; d) Dess–Martin periodinane (2.0 equiv), acetone, RT, 2 h, 38% from **7**; e) H_2 (6 atm.), 10% Pd/C (0.05 equiv), MeOH, RT, 24 h; f) TESOTf (2.0 equiv), 2,6-lutidine (4.0 equiv), THF, 0 °C to RT, 30 min, 90% for 2 steps; g) KHMDS (1.5 equiv), Comins reagent (*N*-(5-chloro-2-pyridyl)triflimide, 1.1 equiv), THF, −78 °C to RT, 1.5 h; h) $AlMe_3$ (20 equiv), [$Pd(PPh_3)_4$] (0.5 equiv), THF, RT, 2 h, 57% from **30**; i) H_2 (90 atm.), PtO_2 (0.2 equiv), MeOH, RT, 24 h; j) NaHMDS (4.0 equiv), (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (Davis oxaziridine, 5.0 equiv), THF, −78 °C to RT, 1.5 h; k) Jones reagent (5.0 equiv), acetone, 0 °C, 15 min, 33% for 3 steps. Some hydrogen atoms were omitted for X-ray structure clarity. *m*CPBA = *meta*-chloroperoxybenzoic acid, KHMDS = potassium hexamethyl disilazide, TESOTf = triethylsilyl trifluoromethanesulfonate.

ties that formed **25** containing the E-ring structure of the target molecule (78% from **22**). The resulting C-3 and C-7 secondary hydroxyl groups of **25** were found to be difficult to differentiate. Nonetheless, the tendency of the C-4 hydroxyl group to translactonize suggested a suitable way to construct the E ring of jiadifenolide. With this in mind, compound **7** was treated with *m*CPBA to produce epoxide **26** as a single diastereomer in 80% yield.[31] We postulated that the selectivity arises from a combination of steric hindrance of the C-5 methyl group and the directing effect of the C-1 hydroxyl group.[33] Treatment of **7** with Dess—Martin periodinane initiated the desired oxidative translactonization cascade converting epoxide **26** to lactone **6** in 48% yield. The moderate yield of this reaction might be due to the poor solubility of **26**. Although none of the cascade intermediates could be isolated, a mechanistic rationale for this critical transformation could involve: 1) oxidation of the C-1 hydroxyl group to form ketone **27**, 2) opening of the pendant epoxide under acidic conditions to form **29**, and 3) irreversible translactonization of the C-4 hydroxyl group of **29** to produce **6**. X-ray analysis of **6** proved unambiguously that the desired E ring of jiadifenolide has been formed.[31]

The last task toward **2** would be the installation of the C-1 methyl group and the formation of the D-ring hemiketal. To this end, enone **6** was converted to ketone **30** by hydrogenation under Pd/C conditions and subsequent silylation of the C-7 hydroxyl group (90% over 2 steps). The requirement of up to 6 bars pressure of H_2 to saturate the C-2=C-3 double bond of **6** indicated a significant steric hindrance of the A ring. Therefore, not surprisingly, direct methylenation attempts to install the C-15 carbon atom at the C-1 center (Wittig reaction, Peterson reaction,[34] titanium-[35] or zinc-based[36] reagents) proved to be ineffective. Gratifyingly, a Pd^0-catalyzed cross-coupling reaction[37] provided a solution to this challenge. Thus, chemoselective triflation of the C-1 ketone of **30** by using Comins reagent [*N*-(5-chloro-2-pyridyl)triflimide][38] followed by treatment with trimethylaluminum/$[Pd(PPh_3)_4]$[39] cleanly yielded compound **31** (57% over two steps). In turn, the C-1=C-2 double bond of **31** was selectively hydrogenated from the ⟨-face (PtO_2, H_2, 90 bar, 24 h) to produce the desired C-1 methylated compound **32**. It should be noted that under a higher pressure of H_2 (>110 bar) the hydrogenation was mildly accelerated but we observed concomitant desilylation of the C-7 triethylsilyl ether.[40] The last functionalization at the C-10 center was inspired by Danishefsky's synthesis of jiadifenin.[20] ⟨-Hydroxylation with the Davis oxaziridine[41] produced ⟨-hydroxy lactone **33** (stereochemistry not assigned). Ultimately, the ⟨-hydroxyl group of **33** was oxidized under Jones conditions to produce, after concurrent desilylation of the C-7 silyl ether, (−)-jiadifenolide (**2**) in one-pot (33% yield over 3 steps). The isolated sample of synthetic **2** was found to be identical in all aspects with naturally occurring jiadifenolide.[13] The absolute stereochemistry of **2** was also confirmed by X-ray analysis.[31]

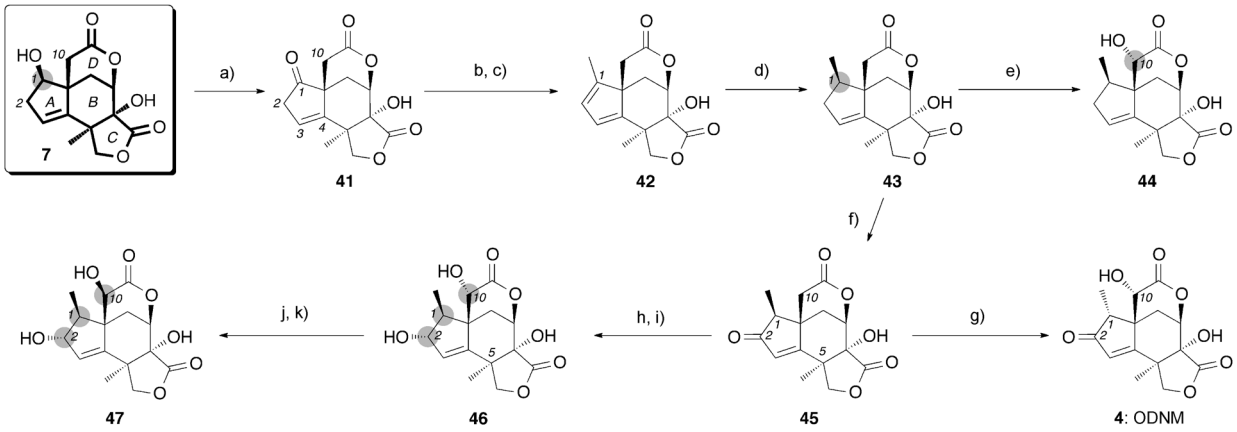
Total synthesis of (−)-jiadifenin (3) and (−)-ODNM (4): Initial attempts to perform a C-1 radical deoxygenation of **7**[42] en route to the synthesis of **3** were unsuccessful (Scheme 4). However, treatment of **7** with Martin sulfurane[43] under dehydrating conditions led to diene **34**, which was directly and selectively reduced under Pd/C-catalyzed hydrogenation to give compound **35** in 72% combined yield. Various reagents and methods, involving selenium-, chromium-, palladium-, and rhodium-based oxidants, were tested to oxidize the C-2 allylic center, but proved to be insufficient.[44] Eventually, we were able to isolate small amounts of enone **36** (~10%) by using $Mn_3O(OAc_3)_9$/*tert*-butylhydroperoxide (TBHP)[45]



Scheme 4. Total synthesis of (−)-jiadifenin (**3**) and (−)-ODNM (**4**) from core intermediate **7**: a) Martin sulfurane (6.0 equiv), THF, RT, 2 h; b) H_2 (1.1 atm.), 10% Pd/C (0.3 equiv), MeOH, 30 min, 72% from **8**; c) *t*BuOOH (10 equiv), $Mn_3O(OAc)_9$ (0.2 equiv), EtOAc, 3 Å MS, 40 °C, 16 h, 65%; d) LDA (5.0 equiv), MeI (3.0 equiv), THF, −78 to −10 °C, 1.5 h, 50% of **39** and 25% of **40**; e) NaHMDS (3.0 equiv), (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (1.0 equiv), THF, −78 °C, 30 min, 61% of **41** and 19% of **42**; f) LDA (5.0 equiv), MeI (1.2 equiv), HMPA (1.2 equiv), THF, −78 to −10 °C, 5 h, 38% (60% brsm); g) Jones reagent (15 equiv), acetone, RT, 20 min, then MeOH, 15 min, 45%. Some hydrogen atoms were omitted for X-ray structure clarity. HMPA = hexamethylphosphoramide, LDA = lithium diisopropylamide.

under the reported conditions (72 h, RT). Gratifyingly, this oxidation occurred much faster by raising the reaction temperature (24 h, 40 °C) increasing significantly the yield of **36** to 65 %. Next in line was projected to be a chemoselective C-1 methylation of **36** followed by α-hydroxylation at the C-10 position. However, all methylation attempts suggested that the C-10 position is more reactive, leading exclusively to monomethylated product **37**. When excess base and methyl source (such as LDA and MeI) were applied, the C-10 and C-1 dimethylated product **38** was isolated, which suggested that the significantly less hindered C-10 carbon atom was competing for the methylation.[31] Based on these findings, we decided to invert the functionalization sequence. Enone **36** was initially α-hydroxylated with the Davis oxaziridine to afford the hydroxy lactone **39** (61 % yield) together with dihydroxylated product **40** (19 % yield). Subsequently, the C-1 methylation was performed by subjecting **39** to the LDA/MeI/HMPA conditions to produce (−)-ODNM (**4**) in 38 % yield (60 % brsm, based on recovered starting material). The following transformation proceeded under Jones conditions with methanolic workup leading to the isolation of jiadifenin (**3**) in 45 % yield. Both synthetic **4** and **3** were found to have identical spectroscopic and analytical properties with those of the natural products.[14,20,21]

Synthesis of designed analogues: Examination of the chemical structures of the *Illicium* natural products indicates that subtle variations at carbon atoms C-1, C-2, and C-10 play a significant role in the neurotrophic activities of these compounds. For instance, ODNM was found to be one of the most potent neurotrophic natural products (as low as 100 nM), whereas the 10-*epi*-ODNM and the 1,10-*diepi*-ODNM were devoid of any activity.[14] Synthetically, the first challenge proved to be the creation of the β-substituted C-1 methyl moiety. After several unsuccessful attempts (DBU, LDA, or *t*BuOK) to invert the C-1 stereochemistry of ODNM, we were prompted to develop an alternative route that could install the C-1 methyl moiety before constructing the C-2 enone motif. To this end, the C-1 hydroxyl group of **7** was oxidized under PCC conditions (0.5 h, RT) to afford ketone **41** in 65 % yield (Scheme 5). It should be noted that the Swern oxidation was ineffective while Dess–Martin-periodinane or IBX oxidations led to complete migration of the C-3=C-4 double bond to give the corresponding enone. Treatment of **41** under 2,6-bis(*tert*-butyl)-4-methylpyridine/Tf_2O conditions selectively formed the corresponding C-1 triflate that was subsequently subjected to $AlMe_3$/[Pd-$(PPh_3)_4$][39] conditions to produce diene **42**. Partial hydrogenation of **42** gave rise to compound **43** possessing the desired C-1 methyl moiety, albeit with moderate yield (23 % over 3 steps). Allylic oxidation by using the manganese-based conditions ($Mn_3O(OAc)_9$/TBHP)[45] was able to effectively deliver enone **45** without any C-1 epimerization (60 % yield). We then attempted a Davis-based α-hydroxylation at the C-10 center of **45**. To our surprise, we isolated (−)-ODNM (**4**) as the only product in 59 % yield. The formation of **4** under these conditions can be explained by considering that the C-1 methyl group of **45** undergoes a rapid epimerization during the C-10 hydroxylation. To overcome this issue, we first reduced the C-2 carbonyl group under Luche conditions. Interestingly, this reduction was selectively accomplished from the top face of the enone motif, presumably due to the steric hindrance of the adjacent C-5 stereocenter. The resulting allylic alcohol was then converted to **46** upon treatment with NaHMDS and the Davis oxaziridine (40 % combined yield). The C-10 stereochemistry could be further modified by a two-step sequence with a Dess–Martin periodinane-based global oxidation followed by stereoselective reduction with $NaBH_4$ to produce **47** (40 %



Scheme 5. Synthesis of designed analogues from core intermediate **7**: a) PCC (2.0 equiv), Celite, CH_2Cl_2, RT, 30 min, 65 %; b) Tf_2O (2.0 equiv), DTBMP (3.0 equiv), THF, 0 °C to RT, 12 h; c) $AlMe_3$ (10 equiv), [$Pd(PPh_3)_4$] (0.3 equiv), THF, RT, 1 h; d) H_2 (3 atm.), Pd/C (10 % w/w), MeOH, 3 h, 23 % from **43**; e) NaHMDS (2.5 equiv), (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (1.1 equiv), THF, −78 °C, 30 min, 57 %; f) *t*BuOOH (10 equiv), $Mn_3O(OAc)_9$ (0.2 equiv), EtOAc, 3 Å MS, 40 °C, 16 h, 60 %; g) NaHMDS (3.0 equiv), (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (1.0 equiv), THF, −78 °C, 30 min, 59 %; h) $NaBH_4$ (3.0 equiv), $CeCl_3 \cdot 7H_2O$ (3.0 equiv), THF/MeOH (3:1), −78 to −50 °C, 30 min; i) NaHMDS (2.5 equiv), (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (1.1 equiv), THF, −78 °C, 10 min, 40 % for 2 steps; j) Dess–Martin periodinane (2.0 equiv), THF, RT, 2 h; k) $NaBH_4$ (3.0 equiv), MeOH, −20 °C, 1 h, 40 % for 2 steps. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, PCC = pyridinium chlorochromate.

combined yield). In a similar fashion, analogue **44** was prepared from lactone **43** by using the Davis oxaziridine (57% yield). The stereochemistries of new compounds **44**, **46**, and **47** have been assigned based on 2D NOESY analyses.

Evaluation of neurotrophic activity and pharmacophore mapping: Earlier studies by the Danishefsky group[20] established that certain synthetic analogues have activities comparable to jiadifenin, further justifying the studies toward the identification of a common pharmacophoric motif. Our synthetic approach gave access to several highly active natural products and a library of designed analogues that can be used to map the unexplored neurotrophic pharmacophore. Our first task was to validate the biological profile of synthetic jiadifenolide (**2**), jiadifenin (**3**), and ODNM (**4**) with regard to NGF-mediated neurite outgrowth in PC-12 cells. This cell line undergoes neuronal differentiation into neuron-like cells with elongated neurite outgrowth in response to NGF. As such, it has been broadly applied to study NGF activity.[20,46] The ability of synthetic natural products **2**–**4** to promote neurite outgrowth was measured both in the presence and absence of NGF. In the presence of NGF (50 ng mL^{-1}), a significant increase of neuronal differentiation could be observed upon 72 h of incubation

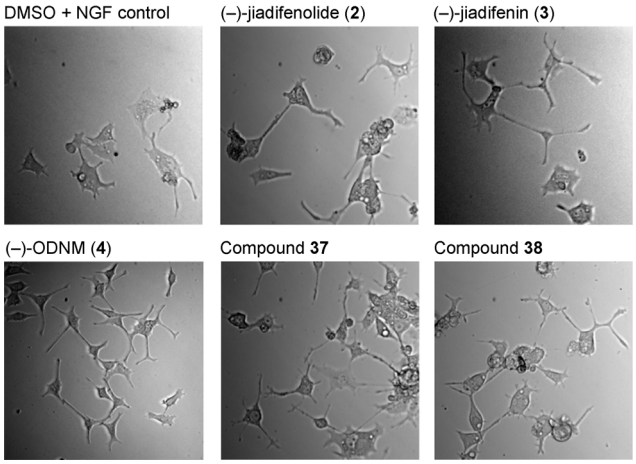


Figure 2. Neurite outgrowth studies with selected synthetic compounds in PC-12 cells. All compounds were dissolved in 1% DMSO (v/v) and tested at a concentration of 0.3 μM in the presence of 50 ng mL^{-1} of NGF; 1% DMSO (v/v) in the presence of 50 ng mL^{-1} of NGF was used as a control.

(Figure 2). Specifically, the neurite length outgrowth induced by **2**, **3**, and **4** (at 0.3 μM) was 166, 148, and 145%, respectively, (relative to DMSO+NGF control). No outgrowth was observed in the absence of NGF, in agreement with previous findings.[20] This supports the notion that these compounds operate by enhancing the action of NGF rather than functioning independently.[20] Interestingly, our synthetic (−)-jiadifenin displayed similar activity with the one previously reported for racemic jiadifenin.[20] Similar observations have been reported in merrilactone A studies.[18k]

We then evaluated the in vitro neurotrophic activity of the synthetic analogues in PC-12 cells. The results related to neurite outgrowth and the percentage of cells with neurites are summarized in Figures 3 and 4. The most active ana-

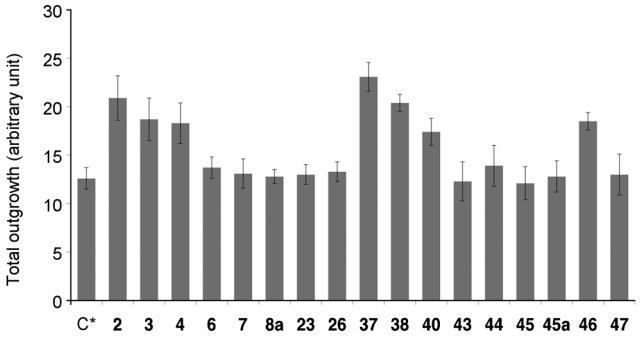


Figure 3. Length of neurite outgrowth. All compounds were dissolved in 1% DMSO (v/v) and tested at concentration of 0.3 μM in the presence of 50 ng mL^{-1} of NGF. C*=control: 50 ng mL^{-1} of NGF and 1% DMSO (v/v).

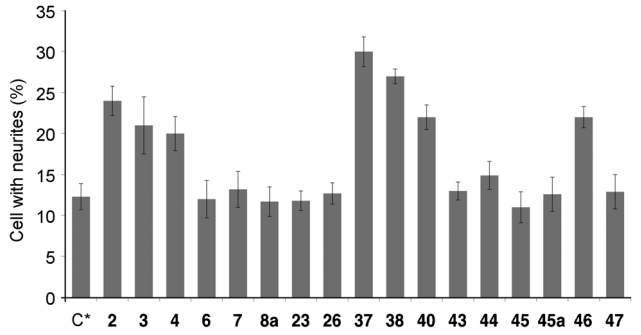
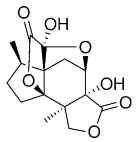
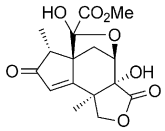
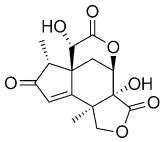
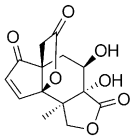
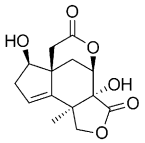
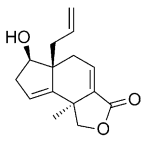
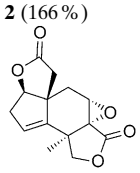
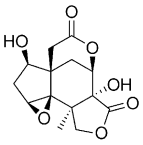
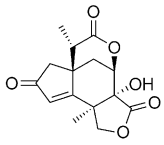
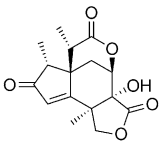
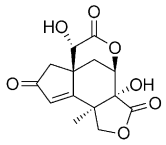
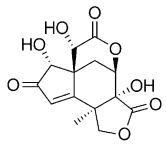
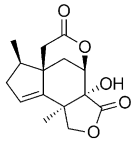
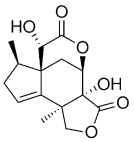
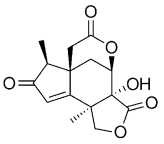
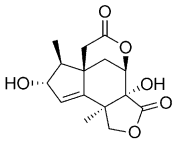
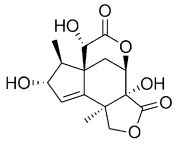
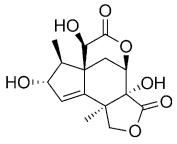


Figure 4. Percentage of cells with neurites. All compounds were dissolved in 1% DMSO (v/v) and tested at a concentration of 0.3 μM in the presence of 50 ng mL^{-1} of NGF. C*=control: 50 ng mL^{-1} of NGF and 1% DMSO (v/v).

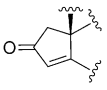
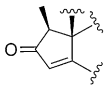
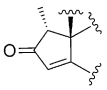
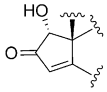
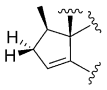
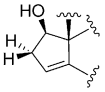
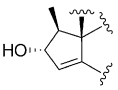
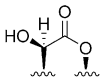
logue was found to be enone **37**, which enhanced neurite outgrowth by more than 180%. Notably, **37** contains a methyl group at C-10 and a carbonyl group at C-2 and shows superior activity in comparison to the natural products. This suggests that the hemiketal functionality of **2** and **3** might be not essential to the neurotrophic activity. The C-1 methylated analogue **38** also exhibits excellent activity, promoting neurite outgrowth by 162%. Interestingly, compounds lacking a C-10 substituent, such as **43** and **45**, have dramatically reduced neurotrophic activity. The C-1 and C-10 bis(hydroxylated) analogue **40** was found to be active (138%), although less active than the bis(methylated) compound **38** (162%). A comprehensive summary of these results is shown in Tables 1 and 2. The pharmacophore mapping (Table 2) suggests that all the C-10 β-substituted compounds are inactive (Table 2, row 2), while all compounds that possess a C-10 α-substituted moiety have shown moderate to excellent neurotrophic activities (Table 2, rows 3 and 4). Interestingly, α-methyl substitution at C-10 increases the activity (compounds **37** and **38**) relative to the related α-hy-

Table 1. Neurite outgrowth studies of *illicium* natural products and analogues.[a]

 **2** (166 %)	 **3** (148 %)	 **4** (145 %)	 **6** (109 %)	 **7** (104 %)	 **8a**[b] (103 %)
 **23** (104 %)	 **26** (106 %)	 **37** (183 %)	 **38** (162 %)	 **39** (121 %)[20]	 **40** (138 %)
 **43** (94 %)	 **44** (110 %)	 **45** (96 %)	 **45a** (104 %)	 **46** (147 %)	 **47** (103 %)

[a] All compounds were dissolved in 1 % DMSO (v/v) and tested at a concentration of 0.3 μM in the presence of 50 ng mL^{-1} of NGF; 1 % DMSO (v/v) in the presence of 50 ng mL^{-1} of NGF as the control. [b] Prepared from **8** upon treatment with TBAF in THF at RT for 1 h.

Table 2. Pharmacophore mapping.[a]

							
	**36**, inactive[b][20]	–	**48**, inactive[20]	–	**45**, inactive	**7**, inactive	**45a**, inactive
	–	**49**, inactive[14]	**50**, inactive[14]	–	–	–	**47**, inactive
	**39**, active[b]	–	**4**, active	**40**, active	**44**, active	–	**46**, active
	**37**, active	–	**38**, active	–	–	–	–

[a] Due to the highly substrate-controlled diastereoselectivity profile, some compounds are only available with certain stereochemistry on the C-10 and C-1 positions. [b] "Inactive" indicates less than 110% of neurite outgrowth, as compared to control; "active" indicates equal to or greater than 110% of neurite outgrowth, as compared to control.

droxylated compounds (**39** and **40**). Moreover, C-10 nonsubstituted compounds were found to all be inactive (Table 2, row 1). The pharmacophore mapping efforts thus suggest that an α-substituent at C-10 is essential to the neurotrophic activity of this family. Two pairs of compounds support this conclusion: the C-10 α-substituted compounds **4** and **46** exhibit good to excellent activities while their C-10 β-substituted diastereomers **50**[14,15] and **47** are essentially inactive. This conclusion may also explain why many *Illicium* natural product family members possess highly similar structures with ODNM (**4**) but are devoid of neurotrophic activities. We also assume that the potent activity of jiadifenolide (**1**) and jiadifenin (**2**) might have benefited from their suitable oriented C-10 hemiketalic hydroxyl group.

Conclusion

Jiadifenolide (**2**), jiadifenin (**3**), and (1*R*,10*S*)-2-oxo-3,4-dehydroxyneomajucin (**4**, ODNM), three highly neurotrophic *Illicium* natural products, have been synthesized in a divergent manner. Key to the synthesis is an enantioselective Robinson annulation reaction[47] that produces the AB ring system **9**. Functionalization at the periphery of the B ring produces the C-ring lactone, while a one-pot oxidation and epoxide-opening reaction cascade form tetracyclic motif **7**. Compound **7** represents the branching point for the synthesis of the natural-product targets and designed analogues. Evaluation of the neurotrophic activities of these compounds in PC-12 cells leads to identification of simplified analogues **37** and **38** that induce more than 160 % neurite

outgrowth at 0.3 μM by enhancing the activity of NGF. In addition, pharmacophore mapping studies suggest that the substituent at the C-10 center plays a critical role in the neurotrophic activity. On the other hand, the hemiketal moiety of **2** and **3**, and the substitution at C-1 might not be important to the bioactivity. The designed strategy along with the pharmacophore mapping studies may pave the way for the rational design of potent agents against neurodegenerative diseases.

Acknowledgements

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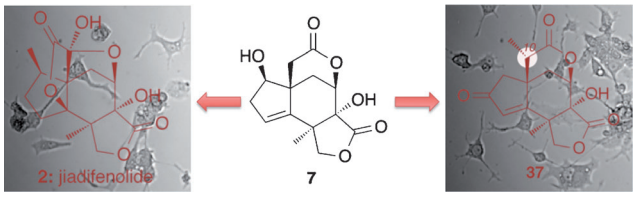
***Illicium* Sesquiterpenes: Divergent Synthetic Strategy and Neurotrophic Activity Studies**



Enantioselective synthesis: A unified strategy toward the synthesis of several *illicium* natural products is reported (see scheme). Key steps include an enantioselective Robinson annulation reaction and a one-pot oxidative lactonization cascade. The synthetic strategy allows access to various potent analogues. Structure–activity studies revealed that the C-10 stereocenter significantly affected the neurotrophic activity.