FULL PAPER

Synthesis and Neurotrophic Activity Studies of *Illicium* Sesquiterpene Natural Product Analogs

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Abstract: Neurotrophic natural products hold potential as privileged structures for the development of therapeutic agents against neurodegeneration. However, only few studies have been conducted in order to investigate a common pharmacophoric motif and the structure-activity relationship. Here, an investigation of structurally more simple analogs of neurotrophic sesquiterpenes of the *illicium* family is presented. A concise synthetic route enables the preparation of the carbon framework of (±)-Merrilactone A and (±)-Anislactone A/B in gram-scale. Thereby providing access to a series of structural analogs by modification of the core structure, including variation of oxidation levels and alteration of functional groups. In total, 15 derivatives of the natural products have been synthesized and tested for their neurite outgrowth activity. Our studies indicate that the promising biological activity can be retained by structurally more simple natural product analogs, which are accessible by a straightforward synthetic route.

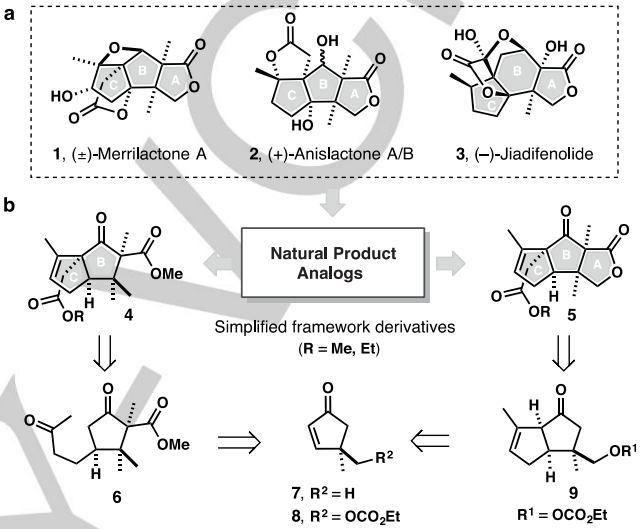

Figure 1. a Neurotrophic sesquiterpene natural products with their core structure (marked in grey). **b** Natural product analogs and retrosynthesis.

Introduction

The awe-inspiring structural diversity of natural products has always motivated organic chemists to investigate and develop new synthetic routes, methods and applications. Significant discoveries have been made by studying the chemical structure of these compound and their properties. In particular, the investigation of promising biological activities has resulted in an array of applications of natural products and their analogs as pharmaceuticals. Therefore, natural products are often used as a starting point for drug discovery, in which lead compounds undergo extensive optimization and structural variation. However, the complexity of natural products can often only be constructed *via* lengthy synthetic routes which may hamper drug discovery. One approach to circumvent this issue is to reduce the complexity of the natural products, while retaining the desired biological activity. Such strategies have been recently summarized by Gademann and co-workers who described the promising role of natural product based fragments in drug discovery. They highlighted examples where the structural complexity of natural products was reduced successfully.[1] Structurally more simple analogues, accessible *via* shorter synthetic routes, can greatly improve chemical tractability and can therefore overcome the limitations of lengthy chemical syntheses.

Since the discovery of several neurotrophic natural products which form part of the *illicium* family, e.g. Merrilactone A (**1**),[2] Anislactone A/B (**2**),[3] and Jiadifenolide (**3**)[4] (Figure 1a), these compounds have received remarkable attention from the synthetic community,[5] not least because of their challenging chemical structure and their promising biological activity.[2, 4, 6] The polycyclic small molecules are capable of promoting outgrowth in neuronal cultures.[7] Therefore, these privileged structures are considered to hold potential for the development of pharmaceuticals for the treatment of neurodegenerative diseases such as Parkinson's or Alzheimer's (AD).[8] In contrast to protein neurotrophins,[9] e.g. nerve growth factor (NGF) or brain-derived neurotrophic factor (BNDF), small-molecule neurotrophin-like

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compounds have been investigated because of their desirable pharmacokinetic properties and pharmacological advantages, i.e. low molecular weight, high serum stability and most importantly blood-brain-barrier permeability.[10] In the case of majucin-type sesquiterpenes, such as Jiadifenolide (**2**), several studies were conducted in order to determine a common pharmacophoric motif.[6a, c] These investigations led to the identification of several potent analogs and therefore have shown that certain synthetic derivatives can have activities comparable to the natural product.

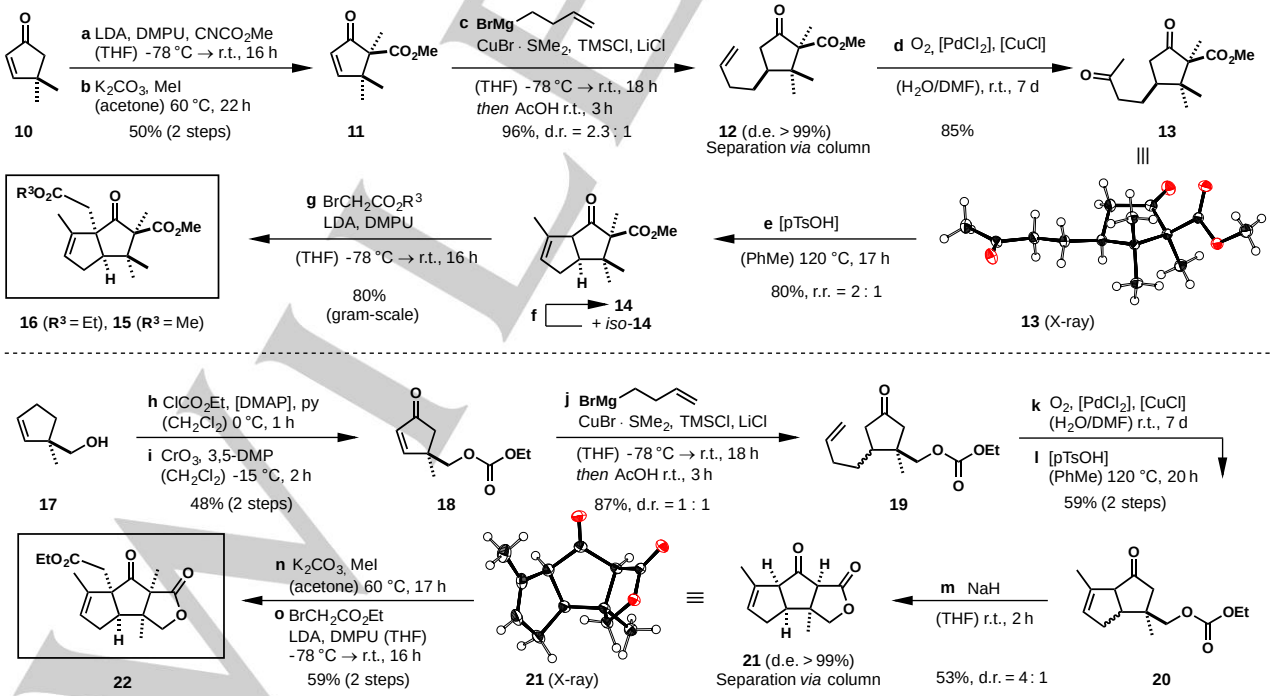
Although a great number of synthetic studies on Merrilactone A (**1**) and Anislactone A/B (**2**) have been performed, no systematic investigation on their structure-activity relationship is available. This might be due to the length of the syntheses reported. As a consequence, variations of the carbon frameworks of the natural products are not readily accessible. We realized that in order to overcome this limitation a synthetic route, which provides simple access to the core structure, was required. An efficient synthesis of the carbon framework would then allow for versatile modification and preparation of natural product derivatives.

Results and Discussion

We focused our studies on the structural core motif (see figure 1a, marked in grey), which consists of a highly substituted central ring structure surrounded by additional rings including a cyclopentane and a γ-lactone. Specifically, our aim was to synthesize structural simplified analogs, investigate their neurite outgrowth activity and ultimately learn about the structure-activity relationship. Importantly, we have placed the emphasis on synthesizing simplified analogs, i.e. carbon framework derivatives of (±)-**1** and (±)-**2**. Two rationally simplified structural derivatives **4** and **5** (Figure 1b) were designed by altering the oxidation state and by targeted disconnection of hydroxo functionalities, e.g. oxetane and lactone moieties. The synthetic strategy towards these two derivatives is based on the rapid construction of the polycyclic structure from readily available enones. Retrosynthetically, structure **4** (Figure 1b) can be traced back to cyclopentenone **7** *via* ring disconnection to diketone **6**. Analogously, lactone **5** is constructed from bicyclic ketone **9**. Here, the γ-lactone ring is attached by employing the pre-functionalized enone **8**.

Synthesis of the core structure (depicted in Scheme 1) starts with commercially available dimethylcyclopentenone (**10**) which was subjected to an α-methoxycarbonylation using Mander's reagent,[11] followed by methylation of the 1,3-dicarbonyl with methyl iodide. A 1,4-addition of the *in situ* formed cuprate gave rise to **12** in excellent yield (96%) and with a diastereoselectivity of 2.3:1. The two diastereomers could be separated *via* column chromatography. After Wacker-oxidation, the desired *syn*-configuration of diketone **13** was confirmed by X-ray crystal structure analysis. Attempts to close the cyclopentene ring failed under a variety of basic conditions. However, treatment with *p*-toluene sulfonic acid[12] provided bicyclic ketone **14**, along with conjugated *iso*-**14** (r.r. = 2:1), which could be recycled *via* acidic equilibration. Finally, α-alkylation with bromo alkyl acetate yielded structures **15** and **16** (R = Et or Me). The route described allows for the gram-scale access to diastereomerically pure carbon framework derivatives of the natural products.

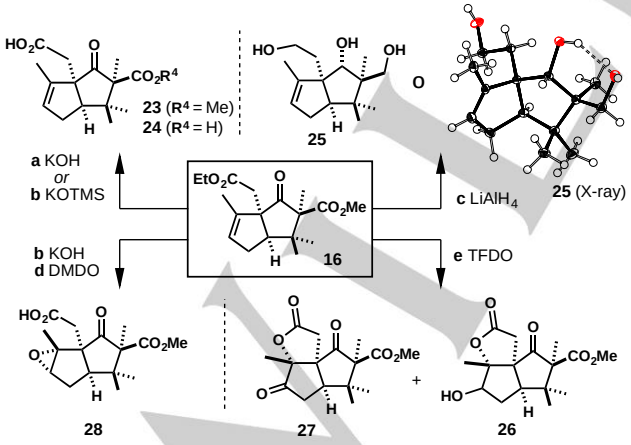
Furthermore, we were interested in structure derivatives carrying the intact eastern lactone ring. Thus, alcohol **17** was found to be a suitable starting point.[13] Functionalization with chloroformate and allylic oxidation with chromium(VI) oxide[14] gave enone **18** in 48% yield over two steps. 1,4-Addition, Wacker-oxidation and acidic cyclization provided deconjugated **20** exclusively. Notably,



Scheme 1. Synthesis of the carbon frameworks **15**, **16** and **22.** **f** [pTsOH] (PhMe) 120 °C, 17 h, quant., r.r. = 2 : 1. LDA = lithium diisopropylamide, DMPU = 4-dimethyl-aminopyridine, THF = tetrahydrofuran, TMSCl = trimethylsilylchloride, DMF = *N,N*-dimethylformamide, DMP = 3,5-dimethyl pyrazol.

the carbonate group survived these transformations, serving not only as a protecting group for the primary alcohol, but also as building block and precursor for the lactone moiety, which was introduced by treatment with sodium hydride. At this point, the diastereomers could be separated *via* column chromatography and the desired *syn*-configuration of bowl-shaped **21** was confirmed by X-ray crystal structure analysis. The 1,3-dicarbonyl compound allowed for two selective α-alkylations, first with potassium carbonate and methyl iodide and then using LDA and bromo ethyl acetate. The concise route provided access to the complete carbon framework structure **22**, which resembles the (±)-Merrilactone A core structure including the eastern lactone ring.

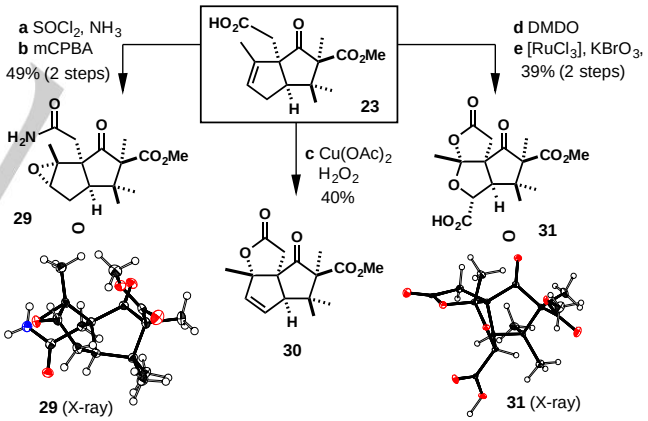
With the carbon framework in hand, we turned our attention to further modifications of the core structure (see Scheme 2). Saponification of diester **16** under standard conditions (KOH in aqueous media) allowed for selective hydrolysis of the sterically more accessible ester to yield monoacid **23**. However, the second ester group proved to be unreactive even under forcing conditions, presumably because of the steric bulk of the quaternary carbon center in α-position. Furthermore, in case of successful formation of the β-keto acid, isolation of the product was thwarted by spontaneous decarboxylation. Ultimately, diacid **24** was accessible by employing potassium trimethylsilanolate and subsequent facile hydrolysis of the silyl ester.[15] For the investigation of the core structure at different oxidation levels, we turned our attention to reductive modifications of the framework. Unfortunately, a selective reduction of the carbonyl functionalities proved to be challenging. Only mixtures of different oxidation states or decomposed material were obtained with a variety of reagents (including borohydrides, aluminum hydrides or Bouveault-Blanc conditions[16]). However, triol **25** was accessible by employing lithium aluminum hydride reduction with careful choice of the work-up method. The configuration of the secondary alcohol, pointing outside of the bowl shape structure, was unambiguously confirmed by X-ray crystal structure analysis.



Scheme 2. Synthetic pathways starting from diester **16** to different derivatives of the natural product framework. **a** KOTMS (THF) r.t., 4–6 d, 85–95%; **b** KOH, H_2O (MeOH) 70°C, 2 h, 90%; **c** LAH, (THF) –78 C → r.t., 18 h, 73%; **d** DMDO, (ac) r.t., 2 h, quant.; **e** TFDO (TFac) –20 °C, 17 h, 64% (1:1). KOTMS = potassium trimethylsilanolate, DMDO = dimethyldioxirane, TFDO = trifluoromethyl(methyl)dioxirane; TFac = 1,1,1-trifluoroacetone.

Apparently, direction of the hydride by the primary β-alcohol group or preorganization by the hydrogen bonding (visible in the product's solid state structure) must have allowed for the hydride attack from the sterically more hindered concave side. In order to further vary the functionality of the olefin containing ring, we examined the epoxidation of ester **16** with TFDO. Surprisingly, the reaction yielded not the epoxide, but a mixture of lactones **26** and **27**. These Anislactone-type cyclic structures were presumably formed by opening of the epoxide intermediate. The alcohol group formed was then further oxidized to the ketone under the reaction conditions. Notably, the use of milder DMDO yielded the desired epoxide **28,** after saponification.

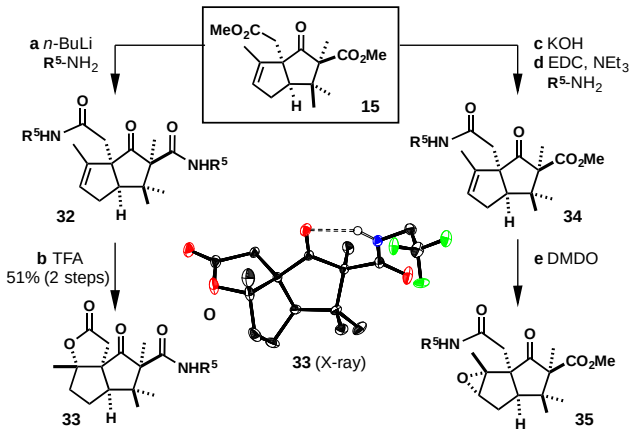
As depicted in Scheme 3, conversion of monoacid **23** with thionyl chloride, followed by reaction with aqueous ammonia and subsequent epoxidation with *m*-CPBA yielded amide **29** in 49% yield over two steps. X-ray structure analysis confirmed the structure and unequivocally proved the convex orientation of the epoxide. Carboxylic acid **23** was also exposed to oxidative conditions in order to increase the oxidation level of the carbon framework. Treatment with copper(II) acetate and hydrogen peroxide[17] yielded allylic lactone **30**—an unprecedented product for these reaction conditions. Even more surprising was the formation of oxidation product **31** in the reaction of the epoxidized acid with ruthenium(II) chloride and potassium bromate.[18] The product was apparently formed by carbon−carbon bond scission of the epoxide, subsequent oxidations and acetalization. Fortunately, a single crystal suitable for X-ray crystallography was obtained, which allowed structure elucidation of the unexpected product.



Scheme 3. Synthesis of epoxy amide **29**, and unexpected oxidation products **30** and **31**. **a** $SOCl_2$, NH_3 (CH_2Cl_2) 50 °C, 2 h, 74%; **b** *m*CPBA (CH_2Cl_2) r.t., 18 h, 83%; **c** $Cu(OAc)_2$, H_2O_2 (MeCN/H_2O) r.t. 1.4 h, 40%; **d** DMDO (ac) r.t., 2 h, quant.; **e** [$RuCl_3$], $KBrO_3$, [py] (MeCN/H_2O) 60°C, 17 h, 39% (2 steps). *m*CPBA = *meta*-chloroperbenzoic acid, DMDO = dimethyldioxirane.

Additionally, amide derivatives of ester **15** were investigated (Scheme 4). After saponification, the amide group[19] was introduced by coupling with EDC. Also in this case, the alkene could be epoxidized under mild conditions using DMDO. As it turned out, synthesis of diamide **32** was surprisingly challenging, presumably because of the steric hindrance of the α-quaternary carbon center. All attempts to convert diacid **24** to the diamide failed to give difunctionalized product. However, after having tested a variety of conditions, it was found that direct treatment of

the ester **15** with deprotonated amine allowed for conversion of both ester groups. By employing trifluoroacetic acid, diamide **32** could be further transformed to Anislactone-type structure **33**, which was confirmed by X-ray structure analysis.



Scheme 4. Synthesis of amide derivatives. R^5 = CH_2CF_3. **a** *n*-BuLi, R^5-NH_2 (THF) –78°C, 2 h; **b** TFA (CH_2Cl_2) r.t., 40 h, 51% (2 steps); **c** KOH, H_2O (MeOH) 70°C, 2 h; **d** EDC, R-NH_2, [DMAP], NEt_3 (CH_2Cl_2) r.t., 16 h, 29% (2 steps); **e** DMDO, (ac) r.t., 14 h, quant.. TFA = trifluoroacetic acid, EDC = 3-(ethyl-iminomethyleneamino)-*N*,*N*-dimethylpropan-1-amine, DMDO = dimethyl-dioxirane.

In order to investigate the activity profile, we analyzed the effect of the prepared compounds on neuronal cells. Previous studies have shown that natural products of the *illicium* family and their structural analogs were capable of promoting NGF-mediated neurite outgrowth in neuronal cells (rat PC12 cells and primary cell cultures).[6c, 20] To explore the scope and species-independence of the neurotrophic activity of *illicium* sesquiterpenes, we here used mouse N2a cells—an established model for neurite outgrowth.[21a-c] We first validated the biological activity of a natural *illicium* sesquiterpene (synthetic Jiadifenolide **3**[5v][22]) in this model and found that it potently enhanced serum deprivation-induced neurite outgrowth (140% compared to DMSO) with the strongest effect at a concentration of 1000 nM (Figure 2 and data not shown). This magnitude of neurite outgrowth stimulations is comparable to the effect size of other neurotrophic agents in N2a cells[21a-c] as well as the effect of Jiadifenolide in other neurotrophic assays.[6c, 20] It is noteworthy that N2a cells are not responsive to classical neurotrophins such as BDNF, suggesting that the neurotrophic effect of Jiadifenolide is independent of these mechanisms.

Since our synthetic approach has provided access to a variety of framework analogs, we next explored the biological profile of the synthetic derivatives. Figure 2 shows a graphical representation of the results of the biological activity study with the relative neurite outgrowth of the N2a cells in comparison to the control run (DMSO). An overview of the selected compounds and their activities is given in Table 1.

Figure 3 depicts representative images of selected N2a cells after neurite outgrowth in the presence of selected compounds. The prolonged dendrites are visible in case of neurotrophically active compounds (Figure 3b,c,d) relative to the control (Figure 3a, DMSO). Several compounds such as **15**, **23** and **30** were identified that were almost as potent as (–)-Jiadifenolide, while being structurally highly simplified. A SAR analysis suggests that structural variations at the northern carboxy group are tolerated (methyl ester **15** or acid **23**), while modifications of the western olefin reduce (compounds **27** and **31**) or abolish activity (compounds **26** and **28**). Likewise, derivatization of the eastern ester moiety abrogated activity (compare **23**→**24** and **16**→**22**).

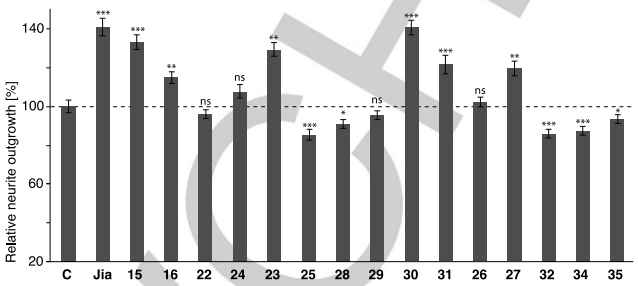
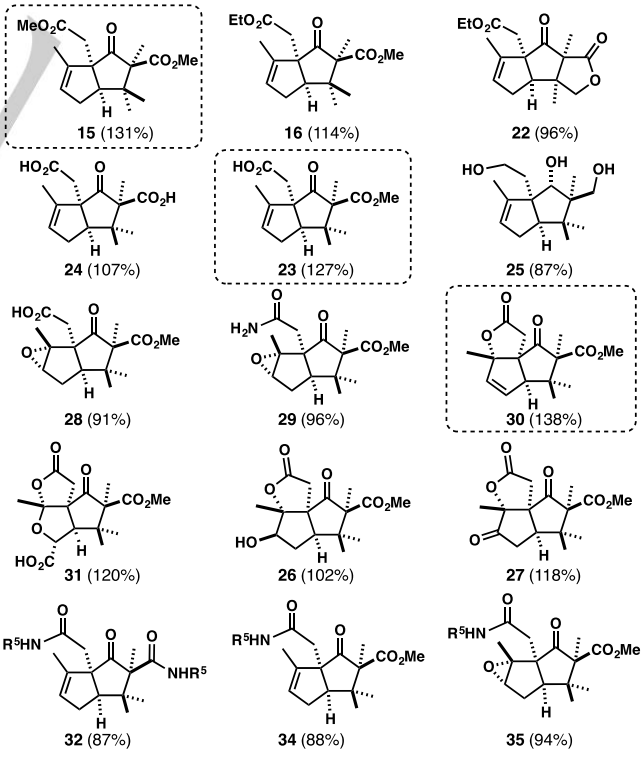


Figure 2. Relative neurite outgrowth of N2a-cells with selected compounds (at 1000 nM concentration) in comparison to control (C, DMSO). Jia = **3**, (–)-Jiadifenolide, concentration: 1000 nM. Data represent averages of three independent runs (analysis of >25 cells for each run). Error bars indicate ± s.e.m. ***P ≤ 0.001, **P ≤ 0.01, *P < 0.05, ns = not significant.

The inactivity of **22** was surprising since this eastern lactone motif (ring A in Figure 1) is present in Merrilactone A and bioactive Jiadifenolide analogs.[6c] Furthermore, the distinct neurite outgrowth by lactone **30** (138%) is remarkable, considering that

Table 1. Overview of carbon framework derivatives and neurite outgrowth.

Compound (neurite outgrowth)[a]	
C, DMSO (100%)	**3**, (–)-Jiadifenolide (140%)



R^5 = CH_2CF_3, a) Relative neurite outgrowth [%] in comparison to control (DMSO)

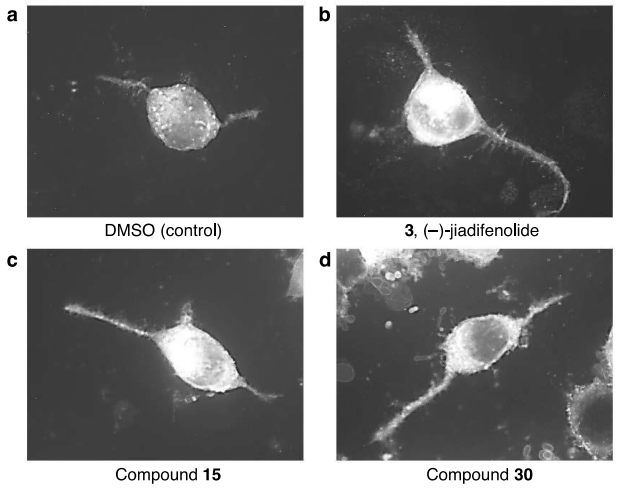


Figure 3. Representative images of N2a-cells after cell differentiation and neurite outgrowth. **a** DMSO (control); **b** (–)-Jiadifenolide (reference); **c** compound **15**; **d** compound **30** (all at 1000 nM concentration).

the structure shows a high degree of similarity to the Anislactone structure, especially in light of the position of the γ-lactone moiety. Although it has been shown that Merrilactone A can be readily converted to the related natural product,[5a] to the best of our knowledge the biological activity of Anislactone A/B has not yet been validated. The results presented confirm that the natural product Merrilactone A can be structurally simplified while retaining biological activity. The most active derivatives (**15**, **23**, **30**) are accessible in 6–8 synthetic steps with high yields from commercial starting materials. This compares favorably to the 17–26 steps required for the total syntheses of (±)-Merrilactone A reported.

Conclusions

In conclusion, a series of structural analogs derived from the neurotrophic *illicium* sesquiterpene natural products (±)-Merrilactone A and (±)-Anislactone A/B has been synthesized. The concise synthetic route relies on the rapid construction of the carbon skeleton and enables the gram-scale preparation of the diastereomerically pure framework structure. Therefore, access is provided to further modified and functionalized analogs. In total, a library of 15 framework derivatives has been prepared, enabling the analysis of the structure-activity relationship. Our study identifies promising structural derivatives, i.e. simplified natural product analogs, which are accessible in only 6–8 synthetic steps and still promote neurite outgrowth (138% compared to control). These results will aid biochemical studies aimed towards elucidating the molecular mechanism and relevant targets underlying the neurotrophic activity of the *illicium* sesquiterpenes and analogs thereof. The simplified compounds could also facilitate the development of new pharmaceuticals for the treatment of neurodegenerative diseases.

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Keywords: Natural Products • Neurotrophic • Biological Activity • Synthesis • Sesquiterpenes

CCDC ###### contains the supplementary crystallographic data for this paper (compounds **13**, **21**, **25**, **29** and **33**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/structures.

References

[1] E. A. Crane and K. Gademann, *Angew Chem Int Ed Engl* **2016**, *55*, 3882–3902.
[2] J. Huang, R. Yokoyama, C. Yang and Y. Fukuyama, *Tetrahedron Letters* **2000**, *41*, 6111–6114.
[3] I. Kouno, K. Mori, N. Kawano and S. Sato, *Tetrahedron Letters* **1989**, *30*, 7451–7452.
[4] M. Kubo, C. Okada, J. M. Huang, K. Harada, H. Hioki and Y. Fukuyama, *Org Lett* **2009**, *11*, 5190–5193.
[5] a) J.-M. Huang, C.-S. Yang, M. Tanaka and Y. Fukuyama, *Tetrahedron* **2001**, *57*, 4691–4698; b) V. B. Birman and S. J. Danishefsky, *Journal of the American Chemical Society* **2002**, *124*, 2080–2081; c) M. Inoue, T. Sato and M. Hirama, *J Am Chem Soc* **2003**, *125*, 10772–10773; d) K. Harada, H. Kato and Y. Fukuyama, *Tetrahedron Letters* **2005**, *46*, 7407–7410; e) J. Iriondo-Alberdi, J. E. Perea-Buceta and M. F. Greaney, *Org Lett* **2005**, *7*, 3969–3971; f) G. Mehta and S. R. Singh, *Tetrahedron Letters* **2005**, *46*, 2079–2082; g) Z. Meng and S. J. Danishefsky, *Angew Chem Int Ed Engl* **2005**, *44*, 1511–1513; h) M. Inoue, T. Sato and M. Hirama, *Angew Chem Int Ed Engl* **2006**, *45*, 4843–4848; i) G. Mehta and S. R. Singh, *Angew Chem Int Ed Engl* **2006**, *45*, 953–955; j) K. Harada, H. Ito, H. Hioki and Y. Fukuyama, *Tetrahedron Letters* **2007**, *48*, 6105–6108; k) W. He, J. Huang, X. Sun and A. J. Frontier, *J Am Chem Soc* **2007**, *129*, 498–499; l) M. Inoue, N. Lee, S. Kasuya, T. Sato, M. Hirama, M. Moriyama and Y. Fukuyama, *J. Org. Chem.* **2007**, 3065–3075; m) W. He, J. Huang, X. Sun and A. J. Frontier, *J Am Chem Soc* **2008**, *130*, 300–308; n) L. Shi, K. Meyer and M. F. Greaney, *Angew Chem Int Ed Engl* **2010**, *49*, 9250–9253; o) J. Xu, L. Trzoss, W. K. Chang and E. A. Theodorakis, *Angew Chem Int Ed Engl* **2011**, *50*, 3672–3676; p) N. Nazef, R. D. Davies and M. F. Greaney, *Org Lett* **2012**, *14*, 3720–3723; q) J. Chen, P. Gao, F. Yu, Y. Yang, S. Zhu and H. Zhai, *Angew Chem Int Ed Engl* **2012**, *51*, 5897–5899; r) L. Trzoss, J. Xu, M. H. Lacoske and E. A. Theodorakis, *Beilstein J Org Chem* **2013**, *9*, 1135–1140; s) D. A. Siler, J. D. Mighion and E. J. Sorensen, *Angew Chem Int Ed Engl* **2014**, *53*, 5332–5335; t) I. Paterson, M. Xuan and S. M. Dalby, *Angew Chem Int Ed Engl* **2014**, *53*, 7286–7289; u) Y. Shen, L. Li, Z. Pan, Y. Wang, J. Li, K. Wang, X. Wang, Y. Zhang, T. Hu and Y. Zhang, *Org Lett* **2015**, *17*, 5480–5483; v) H. H. Lu, M. D. Martinez and R. A. Shenvi, *Nat Chem* **2015**, *7*, 604–607; w) J. Gomes, C. Daeppen, R. Liffert, J. Roesslein, E. Kaufmann, A. Heikinheimo, M. Neuburger and K. Gademann, *J Org Chem* **2016**, *81*, 11017–11034.
[6] a) D. A. Carcache, Y. S. Cho, Z. Hua, Y. Tian, Y. M. Li and S. J. Danishefsky, *J Am Chem Soc* **2006**, *128*, 1016–1022; b) D. Urabe and M. Inoue, *Tetrahedron* **2009**, *65*, 6271–6289; c) L. Trzoss, J. Xu, M. H. Lacoske, W. C. Mobley and E. A. Theodorakis, *Chemistry* **2013**, *19*, 6398–6408.
[7] For recent reviews see: a) J. Xu, M. H. Lacoske and E. A. Theodorakis, *Angew Chem Int Ed Engl* **2014**, *53*, 956–987; b) R. A. Shenvi, *Nat Prod Rep* **2016**, *33*, 535–539.
[8] a) P. M. Joyner and R. H. Cichewicz, *Nat Prod Rep* **2011**, *28*, 26–47; b) P. Williams, A. Sorribas and M. J. Howes, *Nat Prod Rep* **2011**, *28*, 48–77.
[9] a) M. V. Sofroniew, C. L. Howe and W. C. Mobley, *Annu Rev Neurosci* **2001**, *24*, 1217–1281; b) E. J. Huang and L. F. Reichardt, *Annu Rev Neurosci* **2001**, *24*, 677–736; c) M. V. Chao, *Nat Rev Neurosci* **2003**, *4*, 299–309.

[10] F. Longo, T. Yang, J. Knowles, Y. Xie, L. Moore and S. Massa, *Current Alzheimer Research* **2007**, *4*, 503–506.
[11] S. R. Crabtree, W. L. A. Chu and L. N. Mander, *Synlett* **1990**, *1990*, 169–170.
[12] G. Mehta and K. Pallavi, *Tetrahedron Letters* **2006**, *47*, 8355–8360.
[13] S. Pichlmair, M. de Lera Ruiz, K. Basu and L. A. Paquette, *Tetrahedron* **2006**, *62*, 5178–5194.
[14] W. G. Salmond, M. A. Barta and J. L. Havens, *The Journal of Organic Chemistry* **1978**, *43*, 2057–2059.
[15] E. D. Laganis and B. L. Chenard, *Tetrahedron Letters* **1984**, *25*, 5831–5834.
[16] L. Bouveault and G. Blanc, *Bull. Soc. Chim. France* **1904**, *31*, 666–672.
[17] C. M. Rasik and M. K. Brown, *Angew Chem Int Ed Engl* **2014**, *53*, 14522–14526.
[18] E. McNeill and J. Du Bois, *J Am Chem Soc* **2010**, *132*, 10202–10204.
[19] The trifluoroethyl amide group was employed as a directing group for C–H functionalization J. Richers, M. Heilmann, M. Drees and K. Tiefenbacher, *Org Lett* **2016**, *18*, 6472–6475.
[20] M. Shoji, M. Nishioka, H. Minato, K. Harada, M. Kubo, Y. Fukuyama and T. Kuzuhara, *Biochem Biophys Res Commun* **2016**, *470*, 798–803.
[21] a) S. Gaali, A. Kirschner, S. Cuboni, J. Hartmann, C. Kozany, G. Balsevich, C. Namendorf, P. Fernandez-Vizarra, C. Sippel, A. S. Zannas, R. Draenert, E. B. Binder, O. F. Almeida, G. Ruhter, M. Uhr, M. V. Schmidt, C. Touma, A. Bracher and F. Hausch, *Nat Chem Biol* **2015**, *11*, 33–37; b) S. Pomplun, Y. Wang, A. Kirschner, C. Kozany, A. Bracher and F. Hausch, *Angewandte Chemie International Edition* **2015**, *54*, 345-348; c) S. Gaali, X. Feng, A. Hähle, C. Sippel, A. Bracher and F. Hausch, *Journal of Medicinal Chemistry* **2016**, *59*, 2410-2422.
[22] A sample of synthetic (–)-Jiadifenolide was kindly provided by Prof. Ryan Shenvi.

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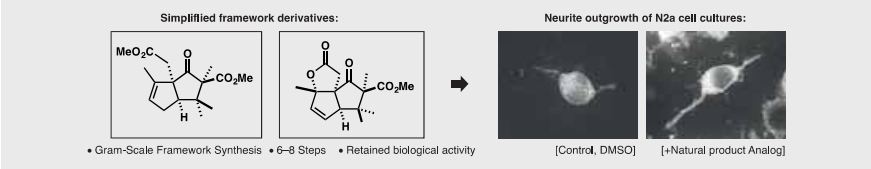

*Johannes Richers, Alexander Pöthig, Eberhardt Herdtweck, Claudia Sippel, Felix Hausch and Konrad Tiefenbacher**
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Synthesis and Neurotrophic Activity Studies of Illicium Sesquiterpene Natural Product Analogs

Access to a series of structural analogs of the *illicium* sesquiterpene natural products (±)-Merrilactone A and (±)-Anislactone A/B is enabled by an efficient synthetic route. The derivatives can be prepared in 6–8 steps while retaining the biological activity as shown in neurite outgrowth studies.