Communications

Neuritogenic Small Molecules

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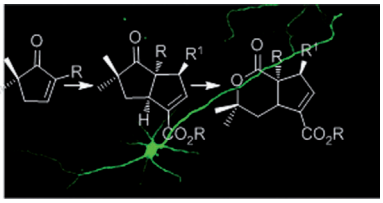

Neuroactive! An enantioselective, catalytic synthesis strategy provides rapid access to natural-product-inspired classes of neuritogenic compounds (see scheme). The goal is to find interesting chemical probes to shed light on neurodevelopmental processes and foster a better understanding of the complex biology and physiology of neuronal development and related neurodegenerative disorders.

VIP Neuritogenic Small Molecules

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Discovery of Neuritogenic Compound Classes Inspired by Natural Products**

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Dedicated to the Bayer company on the occasion of its 150th anniversary

The progressive degeneration and impaired restoration of neurons are hallmarks of neurodegenerative disorders for which neuroprotective and neurite-growth-promoting small molecules[1] are in high demand.[2] The characteristic structural scaffolds of classes of neuroprotective or neurotrophic natural products (NPs)[3] may define biologically prevalidated starting points in vast chemical structure space inspiring the design and synthesis of compound collections endowed with the same or similar kind of biological activity.[4] Different iridoid glycosides[5] and sesquiterpenoids[6] possess pronounced neuritogenic properties (for relevant examples see Figure 1a), and therefore their structural scaffolds may provide valuable targets for the synthesis of natural-product-inspired compound libraries endowed with neurite-growth-promoting activity.

Here we report the enantioselective synthesis[7] of an iridoid-inspired compound collection, its investigation in phenotypic assays monitoring modulations in neurite outgrowth from primary hippocampal neurons and motor neurons derived from mouse embryonal stem cells, and the discovery of two novel natural-product-inspired neuritogenic compound classes. The screen revealed two novel classes of natural-product-inspired neuritogenic compounds.

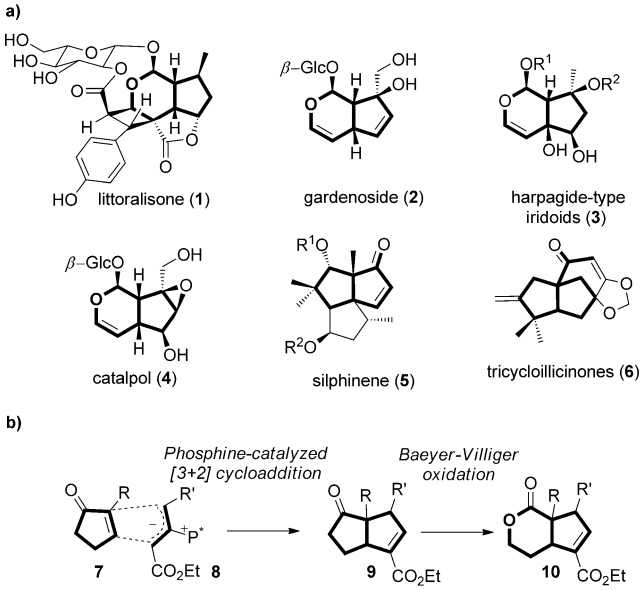

Figure 1. a) Natural products with neurobiological activities. b) Plan for the synthesis of two focused libraries based on the pentalenone (**9**) and the cyclopenta[*c*]pyranone scaffold (**10**).

We envisaged that the [3+2] cycloaddition of allene-derived zwitterions **8**[8] and cyclopentenones **7** catalyzed by a chiral phosphine[9] would provide pentalenones **9**, and that subsequent regioselective Baeyer–Villiger (BV) oxidation[10] would yield the iridoid-inspired scaffold **10** (Figure 1b). Cyclopentenones have not been employed previously in this zwitterionic annulation.[11]

While cyclopentenone **7** (R = H) did not undergo the cycloaddition, cyclopentenone **11a** reacted smoothly with the zwitterion derived from allene ester **12a** to yield the desired pentalenone ring system **13a** (Scheme 1).The additional carbonyl group embedded in **11a** enhances the reactivity of the cyclopentenone and provides an additional opportunity to increase the diversity of the final products (see below).

Unexpectedly, BV oxidation of **13a** yielded the undesired regioisomer **14** (Scheme 1), indicating that in the presence of an ester group, formation of the tertiary carbocation is still favored. Introduction of an α,α-dimethyl group, which favors the formation of a stabilized carbocation, and exchange of the

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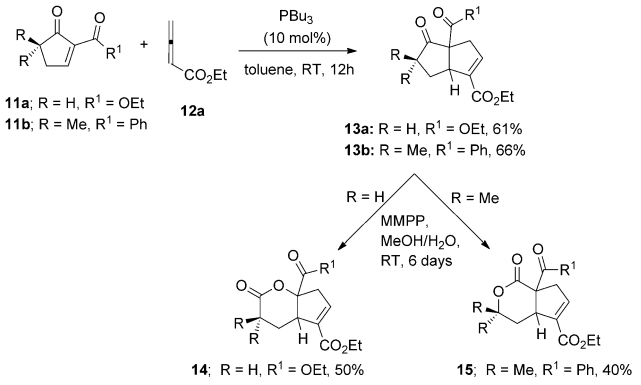


Scheme 1. Synthesis of target scaffolds.

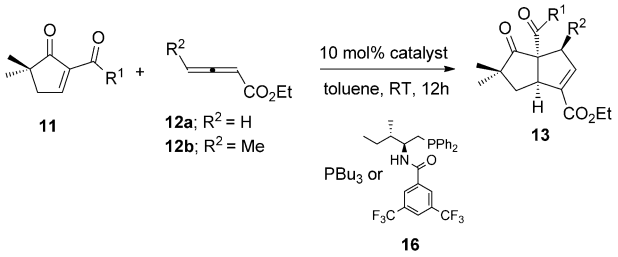
ester for a more strongly electron-withdrawing ketone efficiently changed the regioselectivity in the BV oxidation.[10] Thus, treatment of **13b** with magnesium bis(monoperoxyphthalate) hexahydrate (MMPP)[12] yielded the desired iridoid natural-product-inspired scaffold **15** (Scheme 1).

For the synthesis of the compound collection, cyclopentenone building blocks **11** (Table 1) (for their synthesis see the Supporting Information) were subjected to the [3+2] cycloaddition in the presence of either tri-*n*-butylphosphine or the enantiopure bidentate *N*-acylaminophosphine catalyst **16**[9d] (Table 1). Use of γ-methyl allene ester **12b** ($R^2 = Me$, entry 2) resulted in a good yield of a cyclopentenone product with an extra methyl group; product **13c** contains three contiguous stereogenic centers including an all-carbon quaternary center. The relative stereochemistry and the absolute configuration of the cycloadducts were ascertained by means of NOE experiments and modified Mosher ester analysis, respectively (for details, see the Supporting Information).

The asymmetric [3+2] annulation in the presence of organocatalyst **16** proceeded in high yield, and with high regio-, diastereo-, and enantioselectivity at room temperature (Table 1). The yields were significantly better than those obtained from the reactions with tri-*n*-butylphosphine (Table 1), and generally only one regioisomer was formed with high enantiomeric excess (for details see the Supporting Information). Decreasing the reaction temperature to −20 °C did not improve the enantioselectivity but lowered the yields.

The [3+2] annulation tolerates a variety of aryl and alkyl substituents appended to the keto group, including bulky, electron-deficient, and electron-rich aryl groups (Table 1, entries 1–13). The reaction also proceeded well with cyclopentenones bearing heterocyclic ketones (Table 1, entries 14–17). Also in these cases catalyst **16** afforded higher yields than tri-*n*-butylphosphine and provided high to excellent *ee* values. Cyclopentenone annulation products containing pyridyl ketones were difficult to handle and decomposed during the reaction and purification (Table 1, entries 18 and 19). Alkyl ketones reacted well in the annulation reaction (despite acidic α-protons) and yielded the bicyclic ring system in high yields (Table 1, entries 20–25). The highest enantiomeric excess was obtained for annulation adduct **13y** bearing a *tert*-butyl ketone (99 % *ee*; Table 1, entry 24). The broad scope, high

Table 1: Enantioselective [3+2] annulation of cyclopentenones **11** with allene-derived zwitterions.



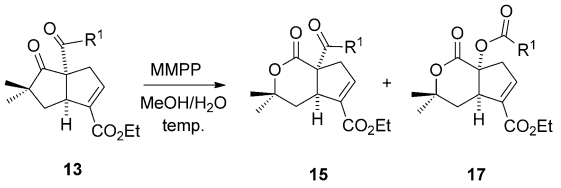
Entry	Prod.	R^1	R^2	Yield [%] PBu_3/**16**	*ee* [%]
1	**13b**	Ph	H	66/72	95
2	**13c**	Ph	Me	54/76	90
3	**13d**	1-naphthyl	H	61/69	94
4	**13e**	4-PhC_6H_4	H	64/71	93
5	**13f**	3,5-$tBu_2C_6H_3$	H	59/77	92
6	**13g**	3,4-$BrFC_6H_3$	H	54/70	97
7	**13h**	3,4-$BrFC_6H_3$	Me	51/73	90
8	**13i**	3-(4-ClC_6H_4)C_6H_4	H	68/81	95
9	**13j**	3-(4-ClC_6H_4)C_6H_4	Me	85/90	92
10	**13k**	4-(BnO)C_6H_4	H	58/71	94
11	**13l**	4-(BnO)C_6H_4	Me	65/70	91
12	**13m**	3,5-$MeOC_6H_3$	H	65/80	93
13	**13n**	3,5-$MeOC_6H_3$	Me	61/75	91
14	**13o**	2-benzofuryl	H	60/66	96
15	**13p**	2-benzofuryl	Me	53/71	88
16	**13q**	4-(2-methyloxazolyl)	H	58/56	98
17	**13r**	4-(2-methyloxazolyl)	Me	60/55	81
18	**13s**	4-pyridyl	H	33/–	–
19	**13t**	4-pyridyl	Me	28/–	–
20	**13u**	isopropyl	H	70/90	96
21	**13v**	isopropyl	Me	76/92	91
22	**13w**	cyclohexyl	H	70/88	96
23	**13x**	cyclohexyl	Me	79/94	91
24	**13y**	*t*-butyl	H	74/89	99
25	**13z**	*t*-butyl	Me	75/88	92

yields, and enantioselectivity of the asymmetric [3+2] annulations of zwitterions **8** with cyclic olefins are unprecedented .

For the BV oxidation of ketones **13** to the desired lactones **15** the best results were obtained with four equivalents of MMPP in methanol/water (1:1) at room temperature.[12] Under these conditions the desired lactone **15** ($R^1 = Ph$) was obtained in 40 % yield after six days at room temperature together with the doubly oxidized product **17** ($R^1 = Ph$) (Table 2, entry 1). At higher reaction temperature the doubly oxidized products **17** were formed in higher yields (Table 2, entries 6 and 8). In general, the BV oxidation proceeded without formation of further undesired products and yielded the desired lactones incorporating aromatic, heteroaromatic, and alkyl ketones in moderate to high yields (Table 2).

For the synthesis of a focused collection of analogues the functional groups embedded in or appended to the bicyclic scaffolds were subjected to various transformations. Dihydroxylation of the olefin in **13** and **15** proceeded smoothly and with complete diastereoselectivity providing highly substituted diols **18** and **20**, respectively, in excellent yields. Selective acylation of the secondary alcohol in **18** was successfully achieved providing ester **19.** Olefin epoxidation

Table 2: BV oxidation of bicyclic adducts **13** to gove lactones **15** and **17**.

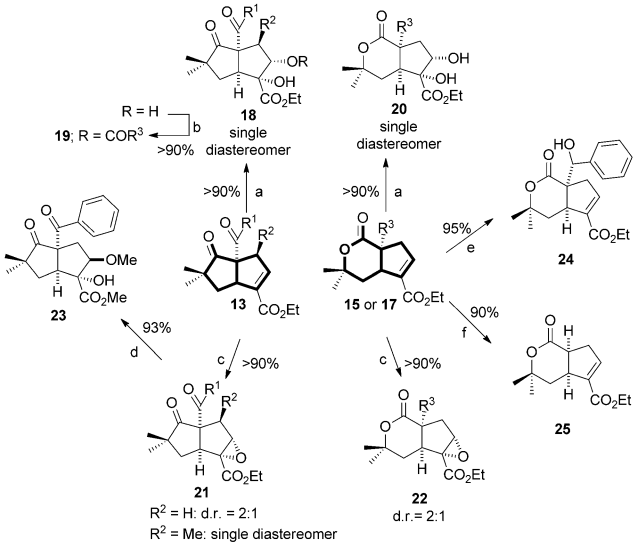


13 **15** **17**

Entry	R^1	Conv. [%]	**15** Yield [%]	**17** Yield [%]
1	Ph	60[a]	40	20
2	1-naphthyl	49[b]	49	–
3	3,5-$tBu_2C_6H_3$	66[b]	52	14
4	3,4-$BrFC_6H_3$	85[a]	62	23
5	3-(4-C_6H_4)C_6H_4	53[a]	53	–
6	3-(4-C_6H_4)C_6H_4	80[b]	–	80
7	3,5-$MeOC_6H_3$	70[a]	70	–
8	3,5-$MeOC_6H_3$	80[b]	50	30
9	4-(2-methyloxazolyl)	78[c]	78	–
10	isopropyl	32[b]	32	–
11	cyclohexyl	37[b]	37	–

Reaction conditions: [a] 6 days, RT; [b] 6 days, 50 °C; [c] 3 days, RT.

in **13**, **15**/**17** smoothly provided **21** and **22**, respectively in excellent yields (see the Supporting Information for details). Compounds **13** apparently favored a completely stereoselective epoxidation (**21**, Scheme 2). Epoxide ring-opening in **21** was performed with methanol as the nucleophile under mildly acidic conditions leading to **23**. DibalH reduction of the keto group in **15** provided the iridoid scaffold **24** incorporating a secondary alcohol. Interestingly, upon attempted formation of an acetal, scaffold **15** underwent decarboxylation to yield the product **25** in excellent yield (Scheme 2).



Scheme 2. Functionalization of the bicyclic scaffolds. Reaction conditons: a) OsO_4, NMO, THF/H_2O, RT; b) R^3COCl or R^3CO_2H, RT; c) *m*CPBA, RT; d) *p*TSA, MeOH, 45 °C, 3 days; e) DibalH, −78 °C; f) *p*TSA, $(CH_2OH)_2$, RT. NMO = *N*-methylmorpholine *N*-oxide, *m*CPBA = *meta*-chloroperbenzoic acid, *p*TSA = *para*-toluenesulfonic acid, DibalH = diisobutylaluminum hydride.

The compound collection was screened for neurite-outgrowth-promoting activity in tests employing primary neurons. Although more sensitive and technically more demanding to manipulate and assay, the use of primary neuronal cultures of hippocampi from E18/E19 Sprague Dowley rats was preferred over frequently employed model cell lines, in particular PC12 cells that have a tumorigenic origin.[13]

During the first days in cell culture, individual neuronal processes emanating from hippocampal neurons can be visualized in their entirety, thus allowing a direct observation of, for example, growing neurites, axons, and the degree of branching. Initially the primary neurons were treated with racemic molecules as DMSO solutions at 10 μM and 1 μM concentration for two days; then the cells were fixed and stained with a membrane dye, and the overall membrane formation was quantified by spectrophotometric readout at 550 nm (see the Supporting Information for details). Enhanced fluorescence relative to that of the DMSO control thus provides a direct measurement of the enhanced neurite outgrowth induced by the compounds.

Gratifyingly, the screen identified compounds **18b** and **17b** as interesting hits that substantially enhanced the overall formation of neuronal membranes. Neurons with an enhanced overall membrane signal can have very different morphology which cannot be discriminated without a specific analysis which dissects dendritic branching. In order to visualize the complexity of the neuronal network developed as a consequence of compound treatment, the mean total length of the neurites should be judged against the mean total number of neurites (Figure S1 in the Supporting Information). Thus, the enantiomers **17b** and racemic (±)-**18b** were subjected to further indepth analysis. Quantitative analysis of confocal images acquired after exposure for five days revealed that (±)-**18b** (1 μM) significantly induced the formation of more complex neuronal networks (Figure 2). Racemic (±)-**18b** enhanced the mean total neurite length per cell primarily because it generates a higher number of neurites per cell than BDNF does (Figure 2a,b). The enantiomers of **17b** displayed remarkable differences in neurotrophic activity. While (*R*,*R*)-**17b** enhanced the mean single neurite length by twofold relative to the DMSO control (Figure 2c,d), enantiomeric (*S*,*S*)-**17b** was cytotoxic as indicated by membrane blebbing (see Figure S2 in the Supporting Information).

In light of the encouraging neurite-growth-enhancing effects on primary hippocampal neurons we investigated whether the compound collection also contains members that modulate the differentiation and development of motor neurons derived from mouse embryonal stem cells (ESCs). Compounds endowed with such properties are potentially relevant for applications in regenerative medicine and their discovery is challenging. Glial cell line derived neurotrophic factor (GDNF), which is important for neuronal development, neurogenesis, and neuronal survival[14] and in neurodegenerative disorders,[15] was used as a positive control. The neuronal complexity resulting after the treatment with the compounds (10 μM) was quantitatively analyzed by measuring parameters for neuronal cells that characterize mean and total neurite length, neurite branching, mean and total neurite

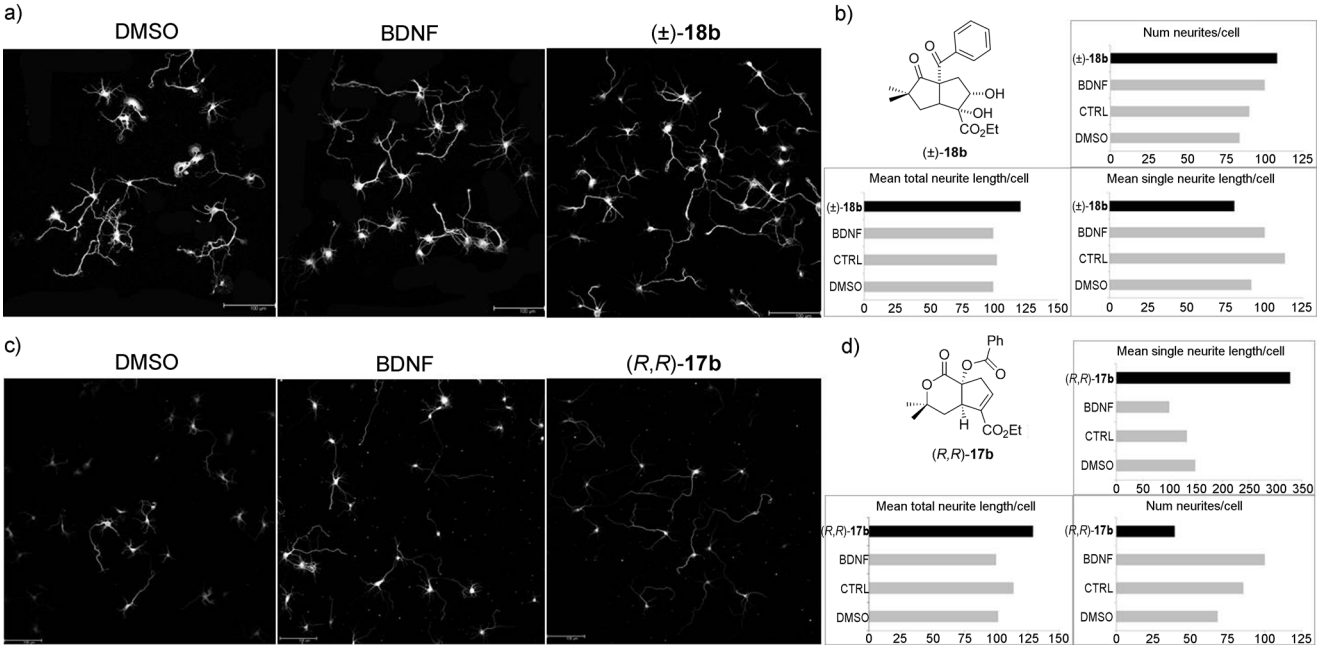


Figure 2. Neurite-outgrowth-promoting activity on primary cultured rat hippocampal neurons and quantification of morphological changes. a) Morphology of neurons treated with DMSO (negative control; 1:10000 dilution), BDNF (positive control), and racemic **18b** (1 μM); b) comparative effect of **18b** on the number and length of neurites; c) morphology of neurons treated with DMSO (negative control; 1:1000 dilution), BDNF (positive control), and enantiopure (*R*,*R*)-**17b** (10 μM); d) comparative effect of (*R*,*R*)-**17b** on the number and length of neurites.; scale bar: 100 μm. BDNF = brain-derived neurotrophic factor, DMSO = dimethylsulfoxide, CTRL = control, untreated cells.

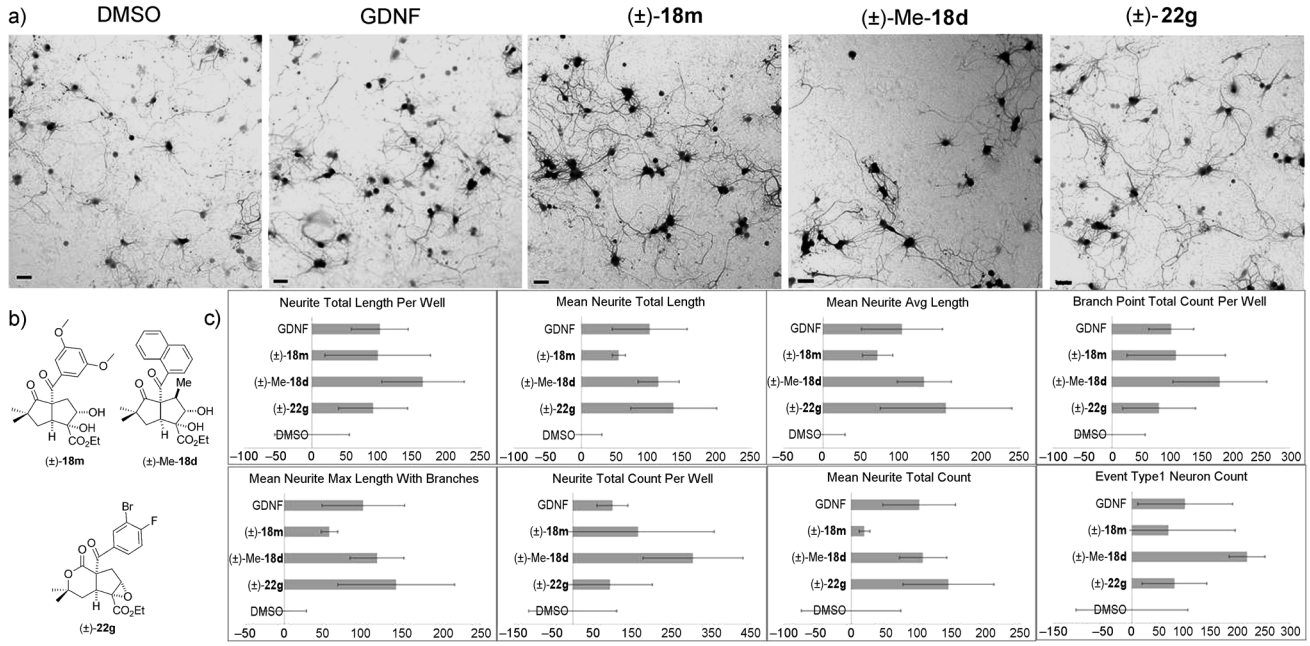


Figure 3. Neurite-outgrowth-promoting activity and quantification of morphological changes for ESC-derived motor neurons. a) Morphology of neurons treated with 10 μM of compounds (2 days), DMSO, and GDNF (negative and positive controls, respectively); b) chemical structures of active molecules; c) eight different parameters analyzed for differentiation, scale bar: 40 μm. Error bars show standard deviation ($n = 4$). *P* values were determined following two-tailed Student's *t*-test. For all the individual morphological changes analyzed, $P < 0.05$ was observed (except in the case of branch point total count for **18m** and **18d**) using DMSO versus compound and GDNF control (data not shown). A *P* value of < 0.05 was considered significant.

count, and survival (event type 1 neuron count) of neurons (Figure 3).

Several compounds induced neuronal outgrowth as early as after two days of treatment. Interestingly, (*R*,*R*)-**17b**, which was active on primary hippocampal neurons, also induced neuronal outgrowth and differentiation of ESC-derived motor neurons (see Figure S3 in the Supporting Information). The most remarkable results were obtained with the racemic pentalenones **18m** and **18d** and the iridoid-inspired epoxide **22g**. The neuronal complexity induced by **18m** emerged mainly because of extensive neurite branching observed for an enhanced number of total neurites. In contrast to **18m**, which induced shorter axons attached to their somas (event type 1 neuron count), **18d** decorated with a naphthyl ketone and an additional methyl substitution on the pentandiol ring scored better than GDNF in increasing the neurite length, branching, and number per wells (Figure 3a–c). The iridoid-inspired epoxide **22g** induced the highest degree of neuronal complexity in ESC-derived motor neurons. While it increased the total and mean neurite length 1.5-fold as compared to that after treatment with GDNF alone, the number of neurites per well and the type 1 neuron count were increased by more than twofold.

In conclusion, we have developed a concise, enantioselective synthesis of natural-product-inspired compound collections endowed with neurotrophic properties which may yield interesting chemical probes to shed new light on neurodevelopmental processes and foster a better understanding of the complex biology and physiology of neuronal development and related neurodegenerative disorders.

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