Pergamon

Tetrahedron 54 (1998) 7735–7748

TETRAHEDRON

# Effect of Cyclohexenonic Long Chain Fatty Alcohols on Neurite Outgrowth. Study on Structure-Activity Relationship

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Received 30 March 1998; accepted 28 April 1998

**Abstract**: Four series of long chain fatty alcohols bearing a cyclohexenone moiety in addition to a ω-alkanol side chain were synthesized using "Umpolung" reactivity strategy. Their effect on neurite outgrowth was evaluated by means of fetal rat neurons in culture. The length of the ω-hydroxy side chain is a crucial factor for biological activity. 

## INTRODUCTION

The normal development of the vertebrate nervous system entails the death of 30-70% of the neurons originally generated in most neuronal populations [1]. This naturally occurring cell death is regulated by specific neurotrophic factors for exemple NGF (Nerve Growth Factor), BDNF (Brain Derived Neurotrophic Factor), NT-3 (Neurotrophin-3), NT-4/5 (Neurotrophin-4/5), FGF (Fibroblast Growth Factor)[2] etc. They are produced in limited amounts by target cells, such as glial cells and promote neuronal survival and differentiation. These factors may potentially lead to a viable therapy to alter the pathogenesis of neurodegenerative diseases. However, these high molecular weight polypeptides are not able to cross several biological barriers, in particular the blood brain barrier, and consequently they can not be active therapeutic agents for the treatment of neurodegenerative diseases.

To overcome these difficulties, it has been suggested that small lipids which are able to mimick the biological activity of these naturally-occurring protein neurotrophic factors, to stimulate their production or to enhance their activity[3] would be ideal targets for research.

Recently, several examples of low-molecular weight compounds exhibiting neurotrophic properties have been reported. Some of these act indirectly by inducing the synthesis and the release of NGF. They are derivatives of catecholamines[4], of benzoquinones[5], hericenone[6], fellutamide[7], dictyophorine[8] and erinacine[9]. The others act directly on neurons and promote a neuronal differentiation effect by inducing neurite outgrowth. These are molecules such as lactacystin[10,11], epolactaene[12] and also extend to sesquiterpene-neoligans[13], SR 57746A[14], 1,3,3 tricyano-2-amino-1-propene[15] and PS-990[16].

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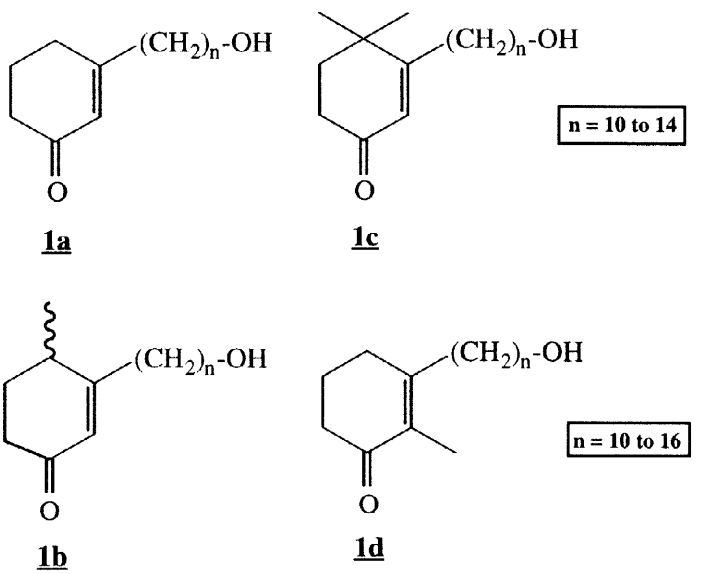
0040-4020/98/$19.00 
*PII:* S0040-4020(98)00406-2

Our initial research has lead to the demonstration of the neurotrophic activity of n-hexacosanol[17], a $C_{26}$ primary alcohol and of analogues of perhydroretinol[18]. Indeed these substances are able to promote the survival and the differentiation of rat central nervous system neurons in culture[19,20]. At $10^{-7}$-$10^{-8}$M, they induce markedly neurite outgrowth and appearance of multipolarity on treated neurons.

These fatty alcohols contain a large hydrophobic side chain and a small primary hydroxy group. We have postulated the necessary presence of a receptor or a carrier for these molecules mainly because of the specificity of the effect. Indeed in the straight chain series, the $C_{26}$ hexacosanol is the most potent compound while the $C_{28}$ octacosanol is only slighty active and the $C_{24}$ tetracosanol and the $C_{30}$ triacontanol are inactive. Furthemore, in the perhydroretinol series, compounds containing a $C_{11}$ side chain are the most active.

In addition to a hydrophobic effect, another interaction is due to the presence of the alcoholic function. At this point we now focused our attention on a series of long chain fatty alcohols bearing a ketone group. This second polar group may act as a second binding site and this new interaction leads to a more potent effect. In this paper, we report the synthesis of 4 series of long chain fatty alcohols bearing a cyclohexenonic function and an ω-alkanol containing 10 to 16 carbon atoms. These compounds are derivatives of cyclohexenone (compounds **1a**), of 4-methyl-cyclohexenone (compounds **1b**), of 4,4-dimethyl-cyclohexenone (compounds **1c**) and of 2-methyl-cyclohexenone (compound **1d**) **(scheme 1).** The preliminary data of their neurotrophic activity showed that compounds **1b** and **1d** with a $C_{14}$ side chain are the most potent. These molecules are labelled as **1b** (n=14) and **1d** (n=14).




Scheme 1 : The 4 series of cyclohexenonic alcohols differred by the presence of methyl groups in the cyclohexenonic ring.

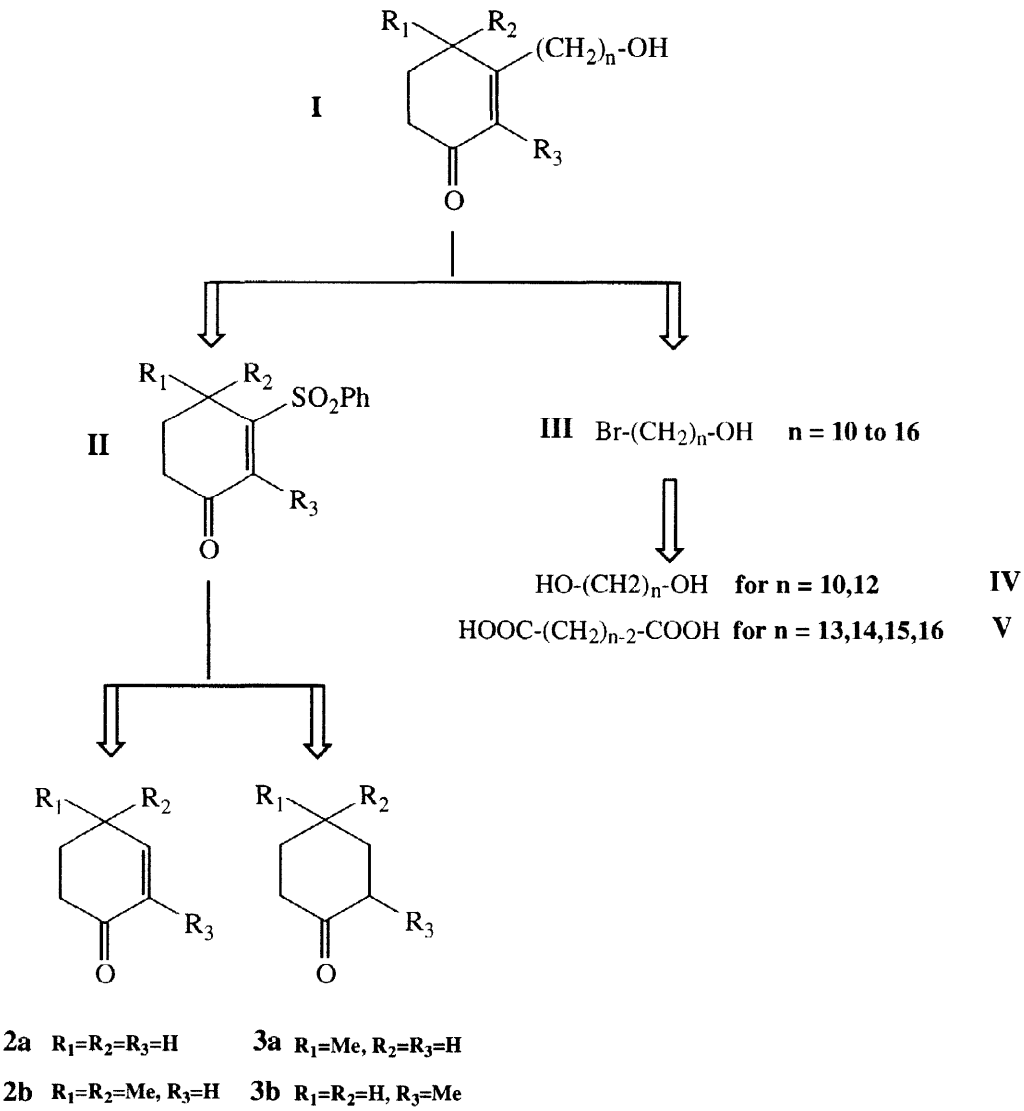
## RESULT AND DISCUSSION

Four series of long chain fatty alcohols **1a** to **1d** were synthesized by coupling an ω-alkanol side chain to different cyclohexenones. As we wished to introduce the alkanol side chain by means of a nucleophilic displacement it was necessary to "invert" the polarity of the cyclohexenone moiety in the synthetic strategy.

**1a** to **1d** were synthesized in the same manner. The starting materials were respectively **2a,3a,2b** and **3b (scheme 2)**.

## A) Synthesis of 1a, 1b, 1c, 1d long chain fatty alcohols

**Scheme 2**



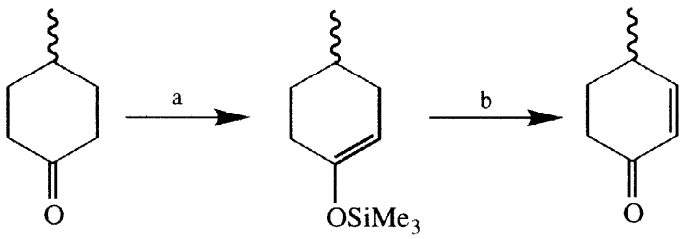

**Scheme 2** shows the retrosynthetic analysis for the preparation of **1a**, **1b**, **1c**, **1d** series. **I** can be broken up into the sulfone **II** and the side chain **III**.

Synthesis of cyclohexenones

**2a** and **2b** are commercially available products but 4-methyl-2-cyclohexen-1-one and 2-methyl-2-cyclohexen-1-one have to be synthesized from **3a** and **3b** respectively (**scheme 3,4**).

As shown in **scheme 3**, enol silane **4a** was formed using lithium diisopropylamide and trimethylsilyl chloride. The formation of the double bond was achieved using a catalytic amount of $Pd(OAc)_2$ in DMSO under a dioxygen atmosphere [21] to give **5a**. It was be tested at present state as racemics.

**Scheme 3**



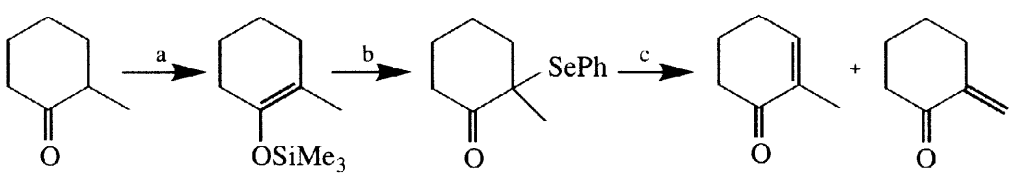

**3a** **4a** **5a**

**Reagents :** a) 1) LDA, -78°C,1h, 2) $Me_3SiCl$, -78°C, 1h (96%) ; b) $Pd(OAc)_2$ cat, DMSO, $O_2$, r.t., 6h (72%).

However, this latter technique was not appropriate for the preparation of 2-methyl-2-cyclohexen-1-one **6b** which was synthesized as shown in **scheme 4.**

Enol silane **4b** was prepared with diisopropylamide magnesium bromide and trimethylsilyl chloride. **4b** was subsequently reacted with phenyl selenium chloride followed by oxidation and elimination of selenium using hydrogen peroxide. **6b** and **7b** were obtained with a ratio of 95/5 (**scheme 4**).

**Scheme 4**




**3b** **4b** **5b** **6b** **7b**

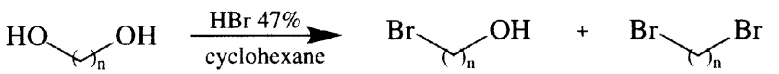
95 / 5

**Reagents :** a) 1) $(iPr)_2NMgBr$, $Et_2O$, r.t., 12h, 2) $Me_3SiCl$, $Et_3N$, HMPA, r.t., 3h (85%) ; b) PhSeCl, THF, -78°C, 10 min (85%) ; c) $H_2O_2$, $CH_2Cl_2$, pyridine, 0°C, 1h (98%).

Synthesis of ω-bromoalcohols

11-Bromo-undecanol is commercially available while 10-bromodecanol and 12-bromododecanol were synthesized from the corresponding diols by means of monobromation in a mixture of HBr-cyclohexane. The bromoalcohols were obtained in over 80% yield and the dibromoalkane in 10% yield (**scheme 5**).

**Scheme 5**



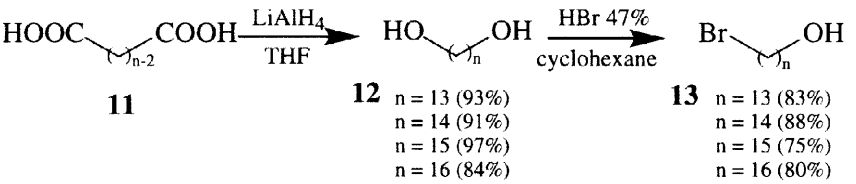

**8**

**9** n = 10 (88%) n = 10 (9%)

**10** n = 12 (82%) n = 12 (14%)

The $C_{13}$,$C_{14}$,$C_{15}$ and $C_{16}$ bromoalcohols were synthesized in two steps from the corresponding diacids. The first step consisted of a reduction of the diacids to the diols with lithium aluminium hydride and the second step was the monobromination. (**scheme 6**).

**Scheme 6**




**11**

**12** n = 13 (93%)
n = 14 (91%)
n = 15 (97%)
n = 16 (84%)

**13** n = 13 (83%)
n = 14 (88%)
n = 15 (75%)
n = 16 (80%)

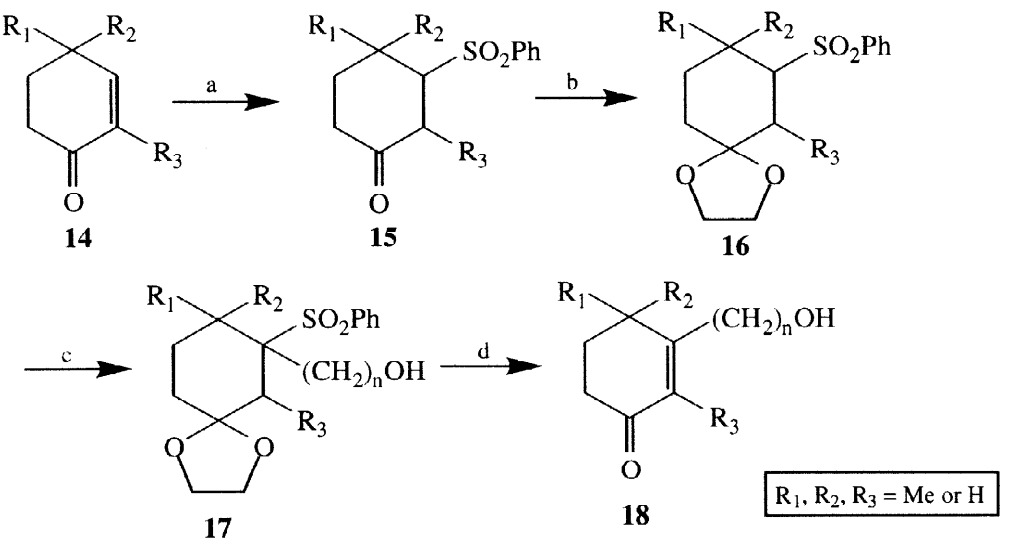
Coupling between cyclohexenones and the side chain

As shown in **scheme 7**, to reverse the polarity of the differents cyclohexenones we used a phenyl sulfonyl group which allowed the formation and the stabilisation of a carbanion in the α position.

In an aqueous medium, **14** reacted with benzenesulfinic acid sodium salt to give sulfone **15**[22]. The carbonyl function of the latter was protected by the formation of the ketal **16**. The carbanion was generated using n-butyllithium in the presence of HMPA and reacted with the unprotected ω-bromoalcohols. **17** was obtained in 84-98%.yield.

The desulfonylation-deketalization was accomplished in one step by treating **17** with p-TsOH (5% mol/equiv) in chloroform/acetone 5/1 at 50°C [23].**18** was obtained in 58-90%.yield

**Scheme 7**




**14** **15** **16** **17** **18**

**Reagents :** a) $PhSO_2Na$, HCl, $H_2O$, r.t., 24h ; b) HO-$(CH_2)_2$-OH, pTsOH, benzene, reflux, 4h ; c) 1) nBuLi, THF, HMPA, -78°C to r.t., 1h, 2) Br-$(CH_2)_n$-OH, THF, -78°C to -20°C, 2h ; d) $CHCl_3$-acetone (5-1), pTsOH, 50°C, 24h.

## B) Effect of different cyclohexenonic fatty alcohols on primary neuronal cultures

To investigate the differentiation effect of cyclohexenonic fatty alcohols, we undertook studies of the two most typical criteria of neuronal differentiation. We quantified the enhancement of neurite outgrowth and analysed the modification of morphology of treated neurons. It is well known that a high percentage of long neurites and of neuron multipolarity is associated with a high degree of differentiation.

Fatty alcohols **1a** which do not contain methyl group on cyclohexenonic ring do not enhance neurite outgrowth. Moreover, they are toxic at $10^{-5}$M.

**Table 1**, shows the comparative effect of cyclohexenonic fatty alcohols that we have synthesized. Neurite outgrowth is induced by fatty alcohols bearing a side chain containing at least 12 carbon atoms. Compounds **1b** and **1d** with a methyl group at C-4 and C-2 are the most potent. And among these, the most active carry a $C_{14}$ side chain. With a slightly longer $C_{15}$ side chain, the activity disappears completely and moreover is replaced by a neurotoxicity

| COMPOUNDS | | ACTIVITY |
|---|---|---|
| CONTROL | | 0 |
| bFGF | | + + |
| **1a** | **(n = 11)** | - - |
| | **(n = 12)** | - - |
| | **(n = 13)** | - |
| | **(n = 14)** | - |
| **1b** | **(n = 10)** | + |
| | **(n = 11)** | + |
| | **(n = 12)** | +++ |
| | **(n = 13)** | ++++ |
| | **(n = 14)** | ++++ |
| | **(n = 15)** | 0 |
| | **(n = 16)** | 0 |
| **1c** | **(n = 10)** | 0 |
| | **(n = 11)** | ++ |
| | **(n = 12)** | +++ |
| | **(n = 13)** | +++ |
| | **(n = 14)** | +++ |
| **1d** | **(n = 10)** | + |
| | **(n = 11)** | 0 |
| | **(n = 12)** | ++ |
| | **(n = 13)** | +++ |
| | **(n = 14)** | ++++ |
| | **(n = 15)** | - - |
| | **(n = 16)** | - - |

**Table 1**

Effect of different ketonic long chain fatty alcohols on neurite outgrowth : At least two independent experiments were performed for each treatment. The compound dissolved in EtOH was added to the culture medium after seeding at $10^{-8}$ M. Plus signs indicate a significant difference in the percentage of cells exhibiting a bipolar morphology as well as neurites two times longer than in control. An additional plus sign indicates that the differentiated cells exhibited a predominantly multipolarity as well as neurites more than two times longer than the control. Minus signs indicate a toxic effect with decrease of neuron population.

Fatty alcohols **1b(n=14)** and **1d(n=14)** enhance neurite outgrowth and induce appearance of multipolarity at $10^{-8}$M.

To investigate the potency of neurite outgrowth in treated neurons, we classified the neurons according to the total length of their neurites. Five types of neurons were taken under consideration. As shown in **Figure 1**, in the control culture, 90% of the neurons bear a neurite shorter than 208μm (types 1 and 2). In culture treated by **1b (n=14)** and **1d (n=14)**, over 24% of neurites are longer than 208μm (types 3, 4 and 5). The effect of bFGF is less potent than that of fatty alcohols.

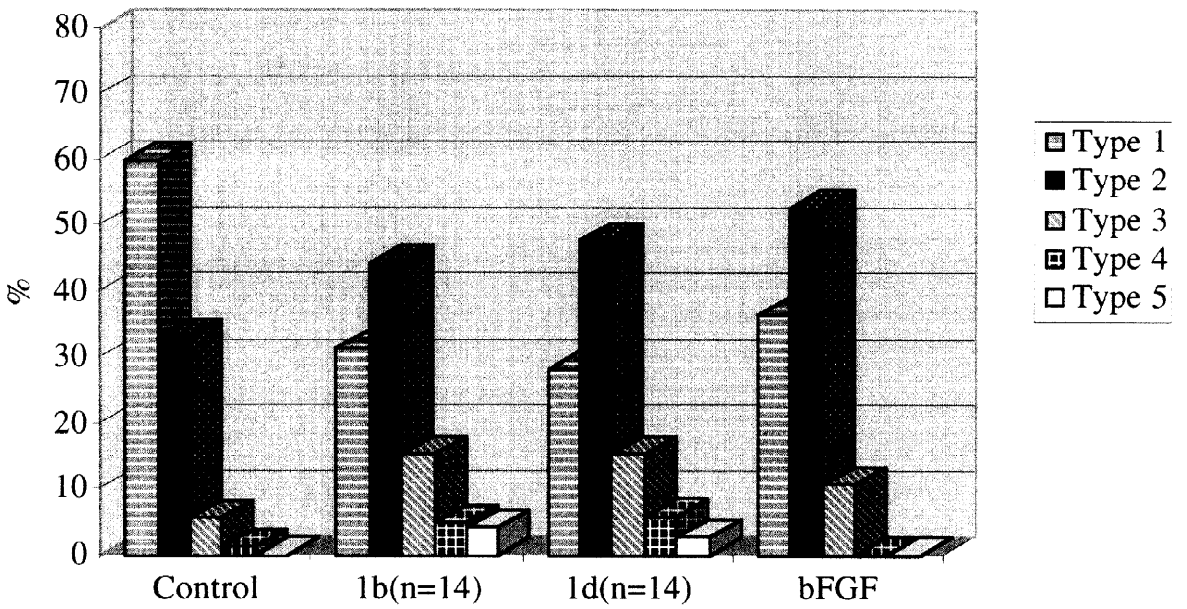



**Figure 1 : Neurite outgrowth induced by cyclohexenonic long chain fatty alcohols :**
Neurons are classified according to the total lenght of their neurite : type 1 = less than 104 μm; type 2 : between 104 and 208 μm; type 3 = between 208 and 311 μm; type 4 = between 311 and 415 μm and type 5 over 415 μm. The figure shows the % of these different types of neurons after treatment with the 2 most potent cyclohexenonic derivatives : **1b (n = 14)** and **1d (n = 14)** in comparison with control culture and with the effect of bFGF in the same conditions. The total of neurons of all types represents 100%. The length of neurites was measured by NIH Image.

To study the ability of fatty alcohols to promote the appearance of multipolarity, we quantified neurons with a special morphology for example: neurons bearing neurites longer than 141μm, neurons with a long neurite and many collaterals, as well as stellate shaped multipolar neurons. As shown in **Figure 2**, only 10% of control neurons belong to one of these 3 groups while 50% of fatty alcohol treated neurons are endowed with special morphology. Once again, the effect of bFGF is weaker than that of fatty alcohols.

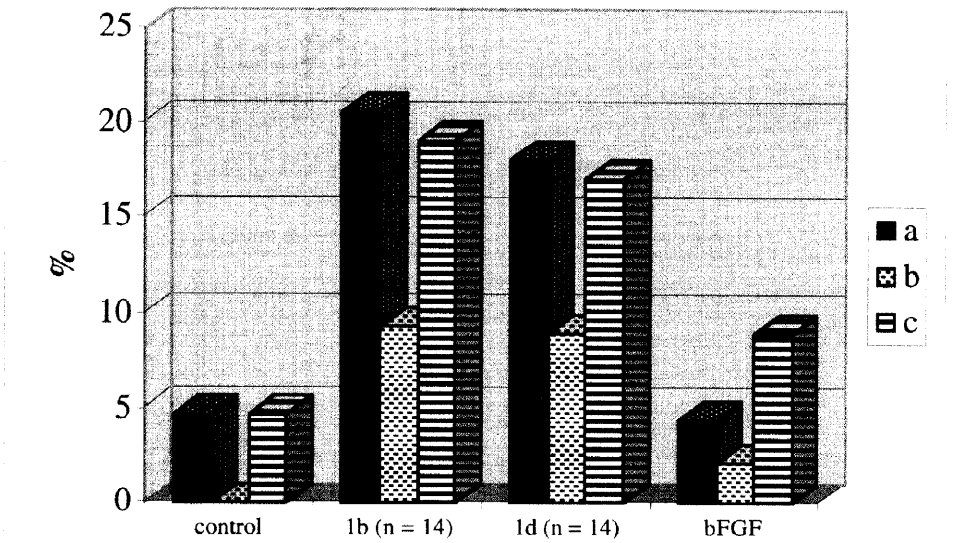



**Figure 2 : % of special neurons after treatment with cyclohexenonic long chain fatty alcohols.**
Neurons are divided into 3 types according to their special morphology a) neurons with at least one long neurite > 141 µm, b) neurons with one long neurite > 141 µm and bearing >2 collaterals, c) stellate-shaped multipolar neurons. Ketonic compounds **1b (n = 14)** and **1d (n = 14)** induce more of these special types of neurons which represent a high degree of differentiation.

Our data shed light on a structural requirement which is crucial for the neurotrophic activity of long chain fatty alcohols. The presence of a methyl group in the cyclohexenonic ring plays an important role. Indeed compounds **1a** which contain no methyl group are inactive.

The crucial role played by the length of the side chain appears in every series of fatty alcohols that we have investigated. In the straight chain series, the $C_{26}$ hexacosanol is the most active while the $C_{28}$ octacosanol is only slightly active and the $C_{30}$ triacontanol and the $C_{24}$ tetracosanol are totally inactive. In the perhydroretinol series, compounds bearing a $C_{11}$ side chain are by far the most neurotrophic. And in the cyclohexenonic series , which is described in the present publication, an ω-tetradecanol side chain induces the most potent differentiation effect in comparison to a longer or a shorter side chain.

## EXPERIMENTAL SECTION

Tetrahydrofuran (THF) was distilled from sodium/benzophenone under argon prior to use. Dichloromethane, methanol and benzene were distilled from calcium hydride. Pyridine was distilled from potassium hydroxide. Hexamethylphosphoramide (HMPA) was distilled from calcium hydride and stored over 3Å molecular sieves under argon. All reactions involving moisture sensitive reactants were executed under an argon atmosphere using oven dried and/or flame dried glassware.

$^1$H NMR spectra were recorded on Bruker SY 200 (200 MHz) and AM 400 (400 MHz) spectrometers as solutions in deuterochloroform ($CDCl_3$). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to $CHCl_3$ (7.26 ppm) as internal standard. Splitting patterns are designated as s, singlet ; d, doublet ; t, triplet ; q, quartet ; qn, quintuplet ; m, multiplet ; br, broad. Coupling constants are given in hertz (Hz). $^{13}$C NMR spectra were recorded on Bruker SY 200 (50 MHz) and AM 400 (75 MHz) spectrometers as solutions in $CDCl_3$. Chemical shifts are reported in parts per million (ppm, δ) downfield from TMS and are referenced to the center line of $CDCl_3$ (77.0 ppm) as internal standard (*, ° : interchangable assignments). The attribution of the different carbons (C, CH, $CH_2$, $CH_3$) was determined by $^{13}$C to $^1$H polarisation transfer (DEPT). IR spectra were recorded on sodium chloride using Perkin-Elmer 881 FT-IR spectrometer and are reported in wave numbers ($cm^{-1}$). UV spectra were obtained in acetonitrile solution using a Kontron-Uvikon 810 UV-Vis spectrometer. Mass spectra (MS) were measured on a TRIO 2000 apparatus by direct introduction (an ionisation potential of 70 eV was used, m/z relative intensities (in %) are noted in round brackets) or coupled to a GC DB5 column (J.W). GC chromatograms were obtained by dissolving the sample in ethyl acetate, using a Carlo-Erba apparatus and a SE 30 column. Microanalyses were performed by the Service Central de Microanalyse du CNRS (Strasbourg). Routine monitoring of reactions were performed using 60 $F_{254}$ silica gel TLC plates (Merck), which were dipped in a solution of vanillin (1 g) in $EtOH/H_2SO_4$ (95/5) and heated on a hot plate. Flash chromatography was conducted using 60 $F_{254}$ silica gel (Merck) with the indicated solvent.

***4-Methyl-1-(trimethylsilyloxy)-1-cyclohexene 4a***

Synthesis of lithium diisopropylamide (LDA)

To a solution of N,N-diisopropylamine (7 ml, 49.6 mmol, 1.5 eq.) in 20 ml of THF was added dropwise a solution of n-BuLi (1.4M, 35.4 ml, 49.6 mmol, 1.5 eq) at -78°C.The solution was stirred at 0°C for 30 min.

Synthesis of 4a

To a solution of 4-methylcyclohexan-1-one **3a** (4 ml, 33 mmol, 1 eq.) in 10 ml of THF was added the preceeding solution at -78°C. The mixture was stirred at -78°C for 1 h, and trimethylsilyl chloride (6.5 ml, 1.5 eq) was added. After stirring at room temperature for 1 h the solution was poured into a solution of $NaHCO_3$ and extracted with ether.The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by distillation under vacuo to obtain a liquid **4a** (5.83 g, 96%). **TLC** : (hexane-AcOEt : 8-2) Rf = 0.8 ; **GC** : 30°C (7 min) --> 150°C *(15°C/min)* --> 280°C *(20°C/min)* 11.1 min, 96% ; **$^1$H NMR** (200 MHz), δ : 0.17 (s , 9H, Si-$(CH_3)_3$) ; 0.94 (d, J = 6.2 Hz, 3H, H-7) ; 1.2-1.43 (m, 1H, H-4) ; 1.57-1.76 (m, 4H, H-3,6) ; 1.88-2.14 (m, 2H, H-5) ; 4.8-4.83 (m, 1H, H-2) ; **$^{13}$C NMR** (50 MHz), δ : 0.3 (Si-$(CH_3)_3$) ; 21.2 (C-7) ; 28.3 (C-4) ; 29.6 (C-5) ; 31.3 (C-6) ; 32.3 (C-3) ; 103.5 (C-2) ; 150.1 (C -1) ; **IR** (NaCl) : 3052, 3021 (w, =C-H) ; 2954, 2926 (s, C-H) ; 1670 (s, C=C) ; 1457 (m) ; 1371 (m) ; 1252 (s) ; 1190 (s) ; 1046 (m) ; 892 (s) ; 844 (s).

***4-Methyl-2-cyclohexen-1-one 5a***

To a solution of **4a** (3.53 g, 19.2 mmol, 1 eq.) in dry DMSO (70 ml) was added palladium (II) acetate (432 mg, 0.1 eq.). The mixture was stirred under oxygen for 6 h, then water was added at 0°C, the solution was filtrated on celite$^R$ and extrated with ether. The organic layer was concentrated in vacuo and the residue dissolved in a mixture of hexane-water. The solution was extracted with hexane, washed with brine, dried with $MgSO_4$ and concentrated in vacuo to give a liquid (1.52 g, 72%). **TLC** : (hexane-AcOEt : 8-2) Rf = 0.35 ; **GC** : 30°C (7 min) --> 150°C *(15°C/min)* --> 280°C *(20°C/min)* 5 min ; **$^1$H NMR** (200 MHz), δ : 1.15 (d, J = 7.1 Hz, 3H, H-7) ; 1.56-1.76 (m, 1H, H-5a) ; 2.1 (dq, $J_{gem}$ = 13.3 Hz, $^3$J = 4.9 Hz, 1H, H-5e) ; 2.26-2.48 (m, 2H, H-6) ; 2.49-2.62 (m, 1H, H-4) ; 5.94 (dd, $^3$J = 10.1 Hz, $^4$J = 2.5 Hz, 1H, H-2) ; 6.79 (ddd, $^3$J = 10.1 Hz, $^3$J = 2.7, $^4$J = 1.5 Hz, 1H, H-3) ; **$^{13}$C NMR** (50 MHz), δ : 20.1 (C-7) ; 29.6 (C-5) ; 30.9 (C-4) ; 36.8(C-6) ; 128.4 (C-2) ; 156.2 (C-3) ; 199.7 (C -1) ; **IR** (NaCl) : 3025 (w, =C-H) ; 2958, 2932 (s, C-H) ; 1683 (s, C=O) ; 1617 (w, C=C) ; 1458 (m) ; 1391, 1375 (m) ; 1251 (s) ; 1094, 1053, 1016 (m) ; 828 (s) ; 750 (m).

***2-Methyl-1-(trimethylsilyloxy)-1-cyclohexene 4b***

Preparation of BMDA (Bromide magnesium diisopropyl amide).

To a solution of diisopropylamine (4.4 ml, 30.9 mmol, 1.25 eq.) in ether (160 ml) was added dropwise a solution of methylmagnesium bromide (3M in ether, 9.8 ml, 29.6 mmol, 1.2 eq.) at room temperature. The suspension was stirred at this temperature for 12 h.

Synthesis of **4b**

To the previous solution was added slowly 2-methylcyclohexan-1-one **3b** (3ml, 24.7 mmol, 1eq.) in ether (60ml). After 15 min, trimethylsilyl chloride (9.4ml, 74.1 mmol, 3 eq.), distilled trimethylamine (11.2ml, 80.4 mmol, 3.25 eq) and distilled hexamethylphosphoramide (2.2ml, 0.5 eq) were added. After stirring at room temperature for 3 h, the mixture was poured cautiously into an aqueous solution of $NaHCO_3$ (2N) at 0°C, then extracted with ether (3 times), washed with brine, dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by distillation under reduced pressure (0.5 mm Hg) to give a colorless liquid (3.88 g, 85%). **TLC** : (hexane-AcOEt : 8-2) Rf = 0.7 ; **GC** : 30°C (7 min) --> 150°C *(15°C/min)* --> 280°C *(20°C/min)* 11.3 min, 97% ; **$^1$H NMR** (200 MHz), δ : 0.16 (s , 9H, Si-$(CH_3)_3$) ; 1.44-1.70 (m, 4H, H-4, 5) ; 1.54 (s br, 3H, H-7) ; 1.88-2.06 (m, 4H, H-3, 6) ; **$^{13}$C NMR** (50 MHz), δ : 0.7 (Si-$(CH_3)_3$) ; 16.3 (C-7) ; 23 (C-4) ; 23.8 (C-5) ; 30.1 (C-6*) ; 30.3 (C-3*) ; 111.7 (C-2) ; 142.9 (C-1) ; **IR** (NaCl) : 2933 (s, C-H) ; 1716 (s, C=C) ; 1450, 1377, 1350 (m) ; 1252, 1184, 1171 (s) ; 919, 886 (m) ; 844 (s) ; **MS** (EI) : 184 ($M^+$, 49) ; 169 (M-$CH_3$ ,91) ; 155 (21) ; 141 (50) ; 75 (82) ; 73 ($SiMe_3$, 100) ; 45 (25).

***2-Methyl-2-(phenylselenyl)-cyclohexan-1-one 5b***

To a solution of ether **4b** (3.05 g, 16.5 mmol, 1 eq.) in THF (20 ml) was added dropwise PhSeCl (Aldrich, 3.17 g, 1eq) in THF (40 ml) at -78°C. After stirring for 10 min, the mixture was quenched with water and extracted with ether (3 times). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, then with brine, dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by chromatography over silica gel (hexane-AcOEt : 98-2 as eluent) to give an oil (3.7 g, 85%). **TLC** : (hexane-AcOEt : 9-1) Rf = 0.3 ; **GC** : 30°C (7 min) --> 150°C *(15°C/min)* --> 280°C *(20°C/min)* 17.2 min, >99% ; **$^1$H NMR** (200 MHz), δ : 1.36 (s, 3H, H-7) ; 1.62-1.84 (m, 2H, H-4) ; 1.87-1.98 (m, 1H, H-6e) ; 2-2.2 (m, 2H, H-5) ; 2.24-2.38 (m, 2H, H-3) ; 3.42 (ddd, $J_{gem}$ = 14.9 Hz, $^3$J = 13.8 Hz, $^3$J = 6.2 Hz, 1H, H-6a) ; 7.23-7.38 (m, 3H, H ar.-3', 4') ; 7.43-7.48 (m, 2H, H ar.-2') ; **$^{13}$C NMR** (50 MHz), δ : 22.3 (C-4) ; 24.8 (C-7) ; 27.0 (C-5) ; 37.1 (C-3) ; 40.7 (C-6) ; 55.2 (C-2) ; 126.6 (C ar.-1') ; 128.8 (C ar.-2'*) ; 129.1 (C ar.-4') ; 137.4 (C ar.-3'*) ; 207.5 (C-1).

***2-Methyl-2-cyclohexen-1-one 6b***

Hydrogen peroxide $H_2O_2$ (30 % in water, 14.7 ml, 10 eq.) was added dropwise at 0°C to a solution of ketone **5b** in pyridine (2.1 ml, 2 eq) and $CH_2Cl_2$ (50 ml). After 1h, the solution was refluxed for 5 min, then HCl 2N was added and the mixture was extracted with ether (3 times). The organic layer was dried with $MgSO_4$, filtered and evaporated. The residue was purified by distillation under reduced pressure to give a colorless liquid (1.4 g, 98%).

**TLC** : (hexane-AcOEt : 8-2) Rf = 0.35 ; **GC** : 30°C (7 min) --> 150°C *(15°C/min)* --> 280°C *(20°C/min)* Retention time: α, β-unsaturated ketone **6b** : 6.7min (5%); cyclohexenone **5b** :7.3min (95%) ; **$^1$H NMR** (200 MHz), δ : 1.76 (dd, $^4J$ = 3.4 Hz, $^5J$ = 2 Hz, 3H, H-7) ; 1.97 (q, J = 6.4 Hz, 2H, H-5) ; 2.26-2.36 (m, 2H, H-4) ; 2.42 (t, J = 6.4 Hz, 2H, H-6) ; 6.74 (m, 1H, H-3) ; **$^{13}$C NMR** (50 MHz), δ : 15.7 (C-7) ; 23.1 (C-5) ; 25.8 (C-4) ; 38.1 (C-6) ; 135.4 (C-2) ; 145.3 (C-3) ; 199.8 (C-1).

***10-Bromo-decan-1-ol 9***

To a solution of 1,10-decandiol (10 g, 57 mmol) in cyclohexane (150 ml) was added HBr (47% in water, 150 ml). After stirring at reflux for 6h, the solution was extracted with hexane (3 times), washed with saturated $NaHCO_3$ (4 times) and brine, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography on silica-gel, eluting with hexane-AcOEt (95-5 to 70-30) to give a colorless oil (12 g, 88%). **TLC** : (hexane-AcOEt : 6-4) Rf = 0.4 ; **GC** : 40-280°C (15°/min) 8.5 min, >99% ; **$^1$H NMR** (200 MHz), δ : 1.28 (s br, 12H, H-3 to H-8) ; 1.57 (qn, $^3J$ = 6.7 Hz, 2H, H-2) ; 1.86 (qn, $^3J$ = 6.8 Hz, 2H, H-9) ; 3.41 (t, $^3J$ = 6.8 Hz, 2H, H-10) ; 3.65 (t, $^3J$ = 6.6 Hz, 2H, H-1) ; **$^{13}$C NMR** (50 MHz), δ : 25.5 (C-3) ; 28.1 (C-8) ; 28.5 (C-7) ; 29.4 (C-4 to C-6) ; 32.7 (C-2, 10) ; 33.8 (C-9) ; 62.9 (C-1).

***1,13-Tridecanediol 12***

To a suspension of $LiAlH_4$ (>97%, 0.93 g, 24.6 mmol, 2 eq.) in dry THF (60 ml) was added 1,11-undecanedioic acid (94%, 3 g, 12.3 mmol, 1 eq.) disolved in dry THF (150 ml) at 0°C under argon. The solution was stirred at room temperature for 2h, poured into a solution of sodium potassium tartrate at 0°C and extracted with ether. The organic layer was washed with brine, dried with $MgSO_4$ and concentrated *in vacuo* to give a white solid (12.47 g, 93%). **TLC** : (hexane-AcOEt : 7-3) Rf = 0.35 ; **$^1$H NMR** (200MHz), δ : 1.28 (s br, 18H, H-3 to H-11) ; 1.56 (qn, $^3J$ = 6.6 HZ, 4H, H-2, 12) ; 3.64 (t, $^3J$ = 6.6 Hz, 4H, H-1, 13) ; **$^{13}$C NMR** (50MHz, pyridine), δ : 26.5 (C-3, 11) ; 29.9 (C-4 to C-10) ; 33.7 (C-2, 12) ; 62.1 (C-1,13).

**Experimental section for synthesis of 1a (n=10)**

***3-(Phenylsulfonyl)-cyclohexan-1-one 15***

Benzenesulfinic acid sodium salt (10.25 g , 62.5 mmol , 1 eq.) was added to a solution containing cyclohexenone **14** (5 ml, 50 mmol, 1 eq.) and 30 ml of water. Then a solution of HCl 1N was added dropwise (60 ml). The reaction mixture was stirred at room temperature for 24 h and the solid formed was removed by filtration, washed with water, isopropanol and cold ether. After recrystallization in isopropanol , a white solid was obtained (5.74g, 97%)). **m.p.** : 83-85°C ; **TLC** : (hexane-AcOEt : 6-4) Rf = 0,2 ; **GC** : 40°C --> 280°C (15°C/min) 11.6 min, >99% ; **$^1$H NMR** (200 MHz), δ : 1.53-1.77 (m, 2H, H-5) ; 2.1-2.45 (m, 4H, H-4, 6) ; 2.6 (d, J = 9.1Hz, 2H, H-2) ; 3.2-3.4 (m, 1H, H-3) ; 7.5-7.7 (m, 3H, H ar.-3', 4') ; 7.8-7.9 (m, 2H, H ar.-2') ; **$^{13}$C NMR** (50 MHz), δ : 23.2 (C-5*) ; 23.5 (C-4*) ; 40.1 (C-6°) ; 40.2 (C-2°) ; 62.1 (C-3) ; 128.8 (C ar.-2') ; 129.3 (C ar.-3') ; 134 (C ar.-4') ; 136.5 (C ar.-1') ; 206.2 (C -1) ; **IR** (KBr) : 3053 (w, =C-H) ; 2966, 2926 (m, C-H) ; 1708 (s, C=O) ; 1582 (w, C=C) ; 1450 (m) ; 1304 (s, $SO_2$) ; 1288 (s) ; 1228 (m) ; 1198 (m) ; 1159 (s, $SO_2$) ; 1138 (s) ; 1084 (m) ; 1062 (m) ; 912 (m) ; 765 (m) ; 728 (s, C-H ar.) ; 693 (m) ; 661, 605, 540 (m) ; **UV** (acetonitrile) : $\lambda_{max}$ : 222 nm (ε 3740), λ : 258 (ε 640), 264 (ε 905), 271 (ε 777) ; **MS** (EI) : 238.1 ($M^+$, 0,3) ; 143 ($PhSO_2H_2$, 0,2) ; 141 ($PhSO_2$, 0.3) ; 125 (PhSO, 0.4) ; 120,1 ($(CH_2)_4SO_2$, 0.4) ; 110 (PhSH, 0.3) ; 97 (M-$PhSO_2$ ,100) ; 96 (cyclohexène, 17) ; 77 (Ph, 19) ; 69,1 ($(CH_2$-$)_3$-CH=$CH_2$, 63.2) ; 55,1 ($(CH_2$-$)_2$-CH=$CH_2$, 22) ; **microanalysis (%)** : calculated for $C_{12}H_{14}O_3S$ (238.3) C : 60.5, H : 5.9 ; found C : 60.4, H : 5.7.

***1,1-(Ethylenedioxy)-3-(phenylsulfonyl)-cyclohexane 16***

To a solution of ketone **15** (5.3g 22.3 mmol,1eq.) in dry benzene(60ml),were added 1,2-ethanediol (0.3 ml, 1.2 eq.) and anhydrous paratoluenesulfonic acid (200 mg). The mixture was stirred under reflux for 4h, then a solution of $NaHCO_3$ 2M was added and the mixture was extracted with ethylacetate (3 times). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The solid was recrystallized in ether to obtain of white crystals (6.1g, 97%). **m.p.** : 93-95°C ; **TLC** : (hexane-AcOEt : 6-4) Rf = 0.26 ; **GC** : 40°C --> 280°C *(15°C/min)* : 12.8 min, >99% ; **$^1$H NMR** (200 MHz), δ : 1.3-1.6 (m, 3H, H-5, 4a) ; 1.61 (t, J = 12.5 Hz, 1H, H-2a) ; 1.65-1.73 (m, 1H, H-4e) ; 1.75-2.05 (m, 2H, H-6) ; 2.12 (ddt, $J_{gem}$ = 12.5 Hz, $^3J$ = 3.5 Hz, $^4J$ = 2.5 Hz, 1H, H-2e) ; 3.21 (tt, $^3J$ = 12.5 Hz, $^3J$ = 3.5 Hz, 1H, H-3) ; 3.84-3.99 (m, 4H, O-$CH_2$-$CH_2$-O) ; 7.5-7.7 (m, 3H, H ar.-3', 4') ; 7.8-7.9 (m, 2H, H ar.-2') ; **$^{13}$C NMR** (50 MHz), δ : 21.8 (C-5) ; 24.5 (C-4) ; 33.9 (C-2*) ; 34.1 (C-6*) ; 61.3 (C-3) ; 64.4 (O-$\underline{C}H_2$-$\underline{C}H_2$-O) ; 107.9 (C-1) ; 128.9 (C ar.-2'°) ; 129 (C ar.-3'°) ; 133.6 (C ar.-4') ; 136.9 (C ar.-1') ; **IR** (KBr) : 3060 (w, =C-H) ; 2968,2938, 2894 (m,C-H) ; 1583 (w, C=C) ; 1448 (m) ; 1301 (s,$SO_2$) ; 1267 (m) ; 1158 (s, $SO_2$) ; 1144 (s) ; 1082 (s) ; 1023 (s) ; 939 (m) ; 916 (m) ; 838 (m) ; 749 (s, C-H ar.) ; 718 (s) ; 689 (s) ; **UV** (acetonitrile) : $\lambda_{max}$ : 221 nm (ε 4970), λ : 258 (ε 710), 264 (ε 1010), 271 (ε 861) ; **MS** (CI, $NH_3$) : 300.2 ($MNH_4^+$, 100) ; 283.1 ($MH^+$, 27) ; 256.1 (8) ; 141.1 (M-$SO_2$Ph, 83) ; **microanalysis (%)** : calculated for $C_{14}H_{18}O_4S$ (282.2) C : 59.82, H : 6.32 ; found : C : 59.6, H : 6.4.

***1,1-(Ethylenedioxy)-3-(10-hydroxydecyl)-3-(phenylsulfonyl)-cyclohexane 17***

To a solution of sulfone **16** (565 mg, 2 mmol, 3eq.) and triphenylmethane (4 mg) in 5 ml of THF was added dropwise a solution of nBuLi (2 ml, 4.1 eq.) under argon at -78°C. After 10 min, the mixture was stirred at room temperature for 1 h and HMPT (1 ml) was added.It was then recooled at -78°C and a solution of bromoalcohol **9** (159 mg, 0.67 mmol, 1eq.) in 2 ml of THF was added slowly. The mixture was stirred for 2 h at -20°C and poured into a solution of saturated $NH_4Cl$ (40 ml). The solution was extracted with ether and the organic layer was washed with water and brine, dried with $MgSO_4$ and concentrated. The residue was purified by chromatography over silica gel and eluted with hexane-AcOEt 8-2 to 6-4 to obtain a colorless oil (265 mg, 90%). **TLC** : (hexane-AcOEt : 6-4) Rf = 0.14 ; **$^1$H NMR** (200 MHz), δ : 1.26 (s br, 14H, H-8 to H-14) ; 1.57 (qn br, $^3$J = 6.5 Hz, 2H, H-15) ; 1.6-1.94 (m, 8H, H-4, 5, 6, 7) ; 1.98 (s, 2H, H-2) ; 3.64 (t, J = 6.5 Hz, 2H, H-16) ; 3.86-3.92 (m, 4H, O-$CH_2$-$CH_2$-O) ; 7.5-7.7 (m, 3H, H ar.-3', 4') ; 7.81-7.87 (m, 2H, H ar.-2') ; **$^{13}$C NMR** (50 MHz), δ : 19 (C-5) ; 23.8 (C-14) ; 25.7 (C-7) ; 28.4 (C-4) ; 29.5 (C-10 to C-13) ; 30.2 (C-8) ; 30.5 (C-9) ; 32.7 (C-15) ; 34.5 (C-6) ; 35.7 (C-2) ; 62.9 (C-16) ; 63.8 et 64.8 (O-$CH_2$-$CH_2$-O) ; 67.4 (C-3) ; 108.5 (C-1) ; 128.7 (C ar.-3'*) ; 130.3 (C ar.-2'*) ; 133.5 (C ar.-4') ; 135.8 (C ar.-1') ; **IR** (NaCl) : 3510 (m br, O-H) ; 3063 (w, =C-H) ; 2926, 2853 (s, C-H) ; 1585 (w, C=C) ; 1447 (m) ; 1286, 1140 (s, $SO_2$) ; 1096, 1083 (m, O-$CH_2$) ; 723, 693 (m) ; **UV** (acetonitrile) : $\lambda_{max}$ : 218 nm (ε 8600), λ : 258 (ε 1050), 265 (ε 1300), 271 (ε 1150) ; **MS** (IC-$NH_3$) : 456.3 ($MNH_4^+$, 36) ; 439.2 ($MH^+$, 3.5) ; 299.3 ($MH_2$-$SO_2Ph$, 33) ; 297.2 (M-$SO_2Ph$, 100) ; 141 ($SO_2Ph$, 10) ; 98.9 ($C_6H_{11}O$, 28).

**Coupling with the other bromoalcohols**

See procedure described for compound **17**

**Physical chemical deltails of 11 to 14 Carbon side chains**

| product, (n) | Formula (Yield %) | MW | Rf.* | Analysis |
|---|---|---|---|---|
| (11) | $C_{25}H_{40}O_5S$ (97) | 452 | 0.14 | **MS**(CI,$NH_3$) : 470.3 ($MNH_4^+$, 39) ; 453.2 ($MH^+$, 3) ; 313.3 ($MH_2$-$SO_2Ph$, 41) ; 311.2 (M-$SO_2Ph$, 100) ; 141 ($SO_2Ph$, 13) ; 98.9 ($C_6H_{11}O$, 31).<br><br>**Microanalysis** (%) :<br>calculated C : 66.34 H : 8.91<br>found C : 66.4 H : 8.7. |
| (12) | $C_{26}H_{42}O_5S$ (96) | 466 | 0.17 | **MS**(CI-$NH_3$) : 484.2 ($MNH_4^+$, 36) ; 467.2 ($MH^+$, 2) ; 327.3 ($MH_2$-$SO_2Ph$, 27) ; 325.3 (M-$SO_2Ph$, 100) ; 256.1 (33) ; 141 ($SO_2Ph$, 14) ; 98.9 ($C_6H_{11}O$, 31). |
| (13) | $C_{27}H_{44}O_5S$ (96) | 480 | 0.17 | **Microanalysis** (%) :<br>calculated C : 67.48 H : 9.23 ;<br>found C : 67.5 H : 8.9. |
| (14) | $C_{28}H_{46}O_5S$ (95) | 494 | 0.20 | **Microanalysis** (%) :<br>calculated C : 67.98 H : 9.37 ;<br>found C : 67.4 H : 9.1. |

* TLC: hexane-AcOEt : 6-4

**3-(10-Hydroxydecyl)-2-cyclohexen-1-one 18**

To a solution of sulfone **17** (193 mg, 0.44 mmol) in chloroform (3 ml) and acetone (0.6 ml) was added paratoluenesulfonic acid (20 mg). The mixture was stirred at 50°C for 24 h. A solution of saturated $NaHCO_3$ was added (10 ml) and the solution was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified on silica gel (eluting with hexane-AcOEt 8-2 to 6-4) to obtain a colorless oil (86 mg, 77%). **TLC**: (hexane-AcOEt : 6-4) Rf = 0.33 ; **GC** : 80 °C (1 min) --> 150 °C *(15 °C/min)* --> 280°C (5°C/min) 16.6 min, >99% ; **$^1$H NMR** (200 MHz), δ : 1.28 (s br, 14H, H-8 to H-14) ; 1.44-1.59 (m, 2H, H-15) ; 1.97 (qn, J = 6.4 Hz, 2H, H-5) ; 2.1-2.4 (m, 6H, H-4, 6, 7) ; 3.64 (t, J = 6.4 Hz, 2H, H-16) ; 5.87 (s, 1H, H-2) ; **$^{13}$C NMR** (50 MHz), δ : 22.6 (C-5) ; 25.6 (C-14) ; 26.8 (C-4) ; 29.3 (C-8 to C-13) ; 32.6 (C-15) ; 37.2 (C-7) ; 37.9 (C-6) ; 62.7 (C-16) ; 125.5 (C-2) ; 166.9 (C-3) ; 200.1 (C-1) ; **IR** (NaCl) : 3446 (m br, O-H) ; 3058 (w, =C-H) ; 2926, 2854 (s, C-H) ; 1665 (s, C=O) ; 1624 (m, C=C ) ; 1446 (m) ; 1301 (m) ; 1152, 1125, 1078 (m, O-

$CH_2$) ; 728, 693 (m) ; **UV** (acetonitrile) : $\lambda_{max}$ : 232 nm (ε 16050) ; **MS**(EI) : 252.1 ($M^+$, 9) ; 222.1 (8) ; 124 (12) ; 123 ($C_8H_{11}O$, 93) ; 110 (100) ; 97 ($C_6H_9O$, 65) ; 95 ($C_6H_7O$, 22) ; 82 (64) ; 81 (13) ; 79 (12) ; 66.9 (26) ; 55 (23) ; **microanalysis** (%) : calculated for $C_{16}H_{28}O_2$ (252.4) C : 76.14, H : 11.18 ; found: C : 75.8, H : 10.9.

**Elimination for the other analogues**
See procedure described for product **17**

| Product (n) | Formula (yield %) | MW | Rf.* | Analysis |
|---|---|---|---|---|
| (11) | $C_{17}H_{30}O_2$ (58) | 266 | 0.2 | **m.p;. : 34-35°C** **GC°** : Retention time: 18.4 min (purity > 99%) **MS**(EI) : 266.1 ($M^+$, 9) ; 248.1 (M-$H_2O$, 2) ; 236.1 (8) ; 124 (11) ; 123 ($C_8H_{11}O$, 83) ; 109.9 (100) ; 97 (56) ; 95 ($C_6H_7O$, 25) ; 82 (51) ; 81 (13) ; 79 (12) ; 69 (7) ; 66.9 (23) ; 55 (21). **Microanalysis** (%) : calculated C : 76.64 H : 11.35 found C : 76.4 H : 11.6 |
| (12) | $C_{18}H_{32}O_2$ (60) | 280 | 0.24 | **m.p.: 35-36°C.** : **GC°** : Retention time: 20.1 min (purity > 99%) **MS**(EI ) : 280.3 ($M^+$, 12) ; 262.1 (M-$H_2O$, 3) ; 250.1 (7) ; 150.9 ($C_{10}H_{15}O$, 5) ; 136.9 ($C_9H_{13}O$, 4) ; 124 (10) ; 123 ($C_8H_{11}O$, 84) ; 110 (100) ; 97 (51) ; 95 ($C_6H_7O$, 22) ; 82 (46) ; 81 (10) ; 78.9 (10) ; 66.9 (20) ; 55 (22). **Microanalysis** (%) : calculated C : 77.07 H : 11.50 found C : 77.1 H : 11.5 |
| (13) | $C_{19}H_{34}O_2$ (93) | 294 | 0.26 | **m.p.:42-43°C.** : **GC°** : Retention time: 21.7 min (purity > 99%) **MS** (EI) : 294.2 ($M^+$, 8) ; 276.1 (M-$H_2O$, 2) ; 264.1 (5) ; 151 ($C_{10}H_{15}O$, 5) ; 136.9 ($C_9H_{13}O$, 4) ; 124 (9) ; 123 ($C_8H_{11}O$, 77) ; 111 (8) ; 109.9 (100) ; 97 (46) ; 95 ($C_6H_7O$, 20) ; 82 (36) ; 81.1 (10) ; 78.9 (8) ; 66.9 (18) ; 55 (21). **Microanalysis** (%) : calculated C : 77.50 H : 11.64 found C : 77.4 H : 11.5 |
| (14) | $C_{20}H_{36}O_2$ (90) | 308 | 0.28 | **m.p.:44-45°C.** : **GC°** :Retention time: 23.3 min (purity > 99%) **MS**(EI) : 308.1 ($M^+$, 10) ; 290.3 (M-$H_2O$, 3) ; 278.4 (6) ; 150.9 ($C_{10}H_{15}O$, 5) ; 137 ($C_9H_{13}O$, 3) ; 124 (8) ; 123 ($C_8H_{11}O$, 77) ; 111 (8) ; 119.9 (100) ; 97 (44) ; 95 ($C_6H_7O$, 19) ; 82 (30) ; 81.1 (8) ; 78.9 (7) ; 66.9 (18) ; 55 (20). **Microanalysis** (%) : calculated C : 77.87 H : 11.76 found C : 77.6 H : 11.4 |

* TLC : hexane-AcOEt : 6-4
° GC : 80 °C (1 min) --> 150 °C *(15 °C/min)* --> 280°C *(5°C/min)*

**Preparation of the cultures for studies of differentiation effects**

The neurotrophic activities were investigated on neurons in primary culture which derived from fetal rat cerebral hemispheres (14 day-old) and the cultures were performed as described by Borg and al[24] with modifications. The dissociated cells were seeded at a density of $1.5x10^5$ cells per 35 mm polylysine-coated Petri dish. They were then preincubated for 3h in a medium supplemented with 20% fetal calf serum, in 3 ml of a chemically defined culture medium (DMEM supplemented with insulin, transferrin, progesterone, sodium selenite and putrescine). Each compound was dissolved in ethanol and added after seeding at different concentrations ranging from $10^{-5}$ to $10^{-9}$ M. Cells were cultured without medium change for 3 days. Cultures were, then, fixed with 2% glutaraldehyde in Phosphate Buffer Saline ($2.9x10^{-2}$ M, pH = 7.4) and stained with Coomasie Brilliant Blue. Neurons were observed and photographed under a light microscope. Control cultures were treated with ethanol only. Neurite outgrowth was quantified by the software 'NIH Image" and mean values were calculated from measuring seven photographs per tested compound.

## Acknowlegements

We are grateful to Dr Monique Sensenbrener and to Professor Guy Ourisson for advice and valuable discussion. The study was partly supported by a grant from Meiji Milk Products Co.Ltd (Japan).

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