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Ethynylogation approach in pharmacophore design: from alkynyl-to butadiynyl-carbinols *vs* antitumoral cytotoxicity

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ABSTRACT

Ethynylogation of a chiral lipidic dialkynylcarbinol (DAC), identified as a lead for cytotoxicity against HCT116 cancer cells, is shown to typify the butadiynyl-alkynylcarbinol (BAC) unit as a new pharmacophore. The enantiomers of the internal BAC have been synthesized with 72–75% yield and 85% ee through the use of a modified Carreira reaction shown here for the first time to be compatible with butadiyne and ynal substrates. One enantiomer of the internal BAC could be characterized by X-ray crystallography. In this particular case, the 'DAC to BAC' ethynylogation results in a slight enhancement of the eutomer potency with a preserved vanishing eudismic ratio (IC_{50} values from 102±14 nM to 42±12 nM for the (+) enantiomers).

1. Introduction

Owing to a unique tradeoff between availability and reactivity, the C≡C triple bond has long been widely exploited in organic synthesis,[1] but in spite of benchmark examples,[2] it has been more sporadically envisaged as pharmacophoric component in drug design. Addressing this point, a systematic approach is first formally proposed, and then tentatively illustrated on a particular example of bio-active molecules containing pre-existing triple bonds.

Current options in medicinal chemistry for the optimization of a chemical structure from a lead candidate consist in tailoring the assumed pharmacophoric unit, or decorating its periphery, by either isomerization, analogation, reduction/oxidation, C–H fluorination, CH_2-homologation (chain length variation), and general C–H substitution. Although the limit between the pharmacophore warhead and its ancillary environment can be somewhat arbitrary, the bond between them is analytically essential. Expanding this bond by insertion of any divalent motif will have much more than a simple elongation effect, and in particular modify the «chemical bulkiness» of the link and the relative orientations of the two moieties. With respect to the latter two criteria, the most neutral motif is certainly a C_2 unit, i.e., a –C≡C– acetylenic motif if the bond is a single bond.[3a–c] In this formal context, the proposed 'ethynylogation' approach[3d–g] has been put to test on a recently disclosed anti-tumor lead compound **1** for which the limits between the functional core, assumed to be the pharmacophore, and the periphery can be unambiguously delineated (Fig. 1).

The lead structure **1** derives from a family of natural acetylenic lipids occurring as secondary metabolites of marine sponges. Among these natural products, functional representatives embedding an alkenyl-alkynylcarbinol (AAC) fragment in their structure were first found to display numerous biological activities (antibiotic, antiviral, cytotoxic, enzyme inhibition, …).[4] More recently, a rational approach consisting in a systematic four-parameter structural variation from the naturally occurring C_{20} lipidic AAC (*S*)-(+)-**2**,[4a–b,4d] led to the discovery of a bio-inspired artificial pharmacophore, namely the terminal dialkynylcarbinol (DAC) unit of the C_{17} lipid **1** exhibiting a cytotoxicity against HCT116 tumor cells 100 times higher than **2** (IC_{50}=90 nM vs 10 μM; Fig. 1).[5] The

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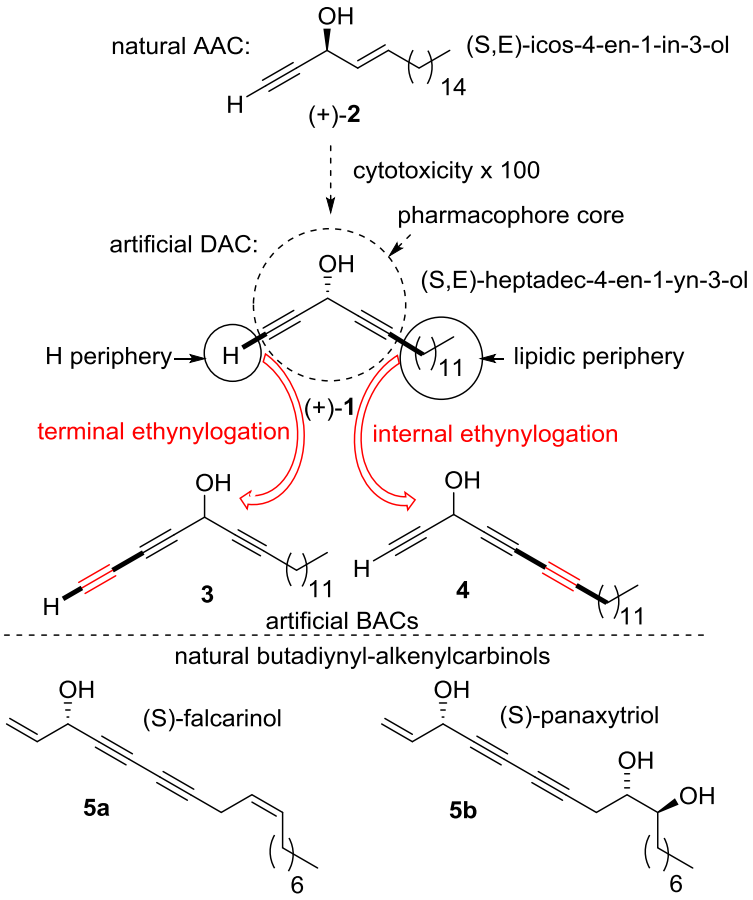


Fig. 1. Proposed ethynylogation approach for the design of the artificial BAC targets, and related natural products.

lead (+)-**1** differs from the reference product (+)-**2**, not only by the level of the internal unsaturation (C≡C instead of C=C), but also by the absolute configuration of the carbinol asymmetric center and by the length of the alkyl chain, these characteristics being independently optimal in (*S*)-(+)-**1**.[5a] Further standard modulations around the AAC and DAC motifs, like oxidation or substitution of the DAC center and *E*→*Z* isomerization or cyclomethylenation of the AAC double bond, led to lower cytotoxic activity.[5b] Insertion of an ethynyl unit at either ends of the DAC core, i.e., in the terminal *sp*C–H or in the internal *sp*C–$C_{12}H_{25}$ bonds, was thus envisaged according to the above-proposed ethynylogation approach, defining the butadiynyl-alkynylcarbinol (BAC) targets **3** and **4**, respectively.

Related natural products containing 1,3-butadiynylcarbinol motifs are the falcarinol **5a** (also known as panaxynol)[6] and panaxytriol **5b**,[7] found in dietary plants (carrots, celery, parsnip, ginseng) and used in traditional Asian medicines (*Panax ginseng*, *P. quinquefolium*, *P. notoginseng*).[8] The antiproliferative properties of falcarinol **5a** towards various cancer cell-lines were also investigated in a systematic manner,[9] and an apoptotic cell division inhibition pathway, associated with a proteolytic cleavage of PKCδ, a caspase-3 activation and a degradation of PARP, were evidenced on the HL60 cell-line.[10] Racemic falcarinol-like probes were also recently shown to act as irreversible inhibitors of ALDH2.[11] After a first report in 1999 on the synthesis of the two enantiomers of falcarinol from (*D*)-gluconolactone and (*D*)-xylose,[12] their asymmetric synthesis through a BINOL/Ti(O^iPr)$_4$-mediated asymmetric addition of an alkynylzinc reactant to an aldehyde substrate was recently described.[13]

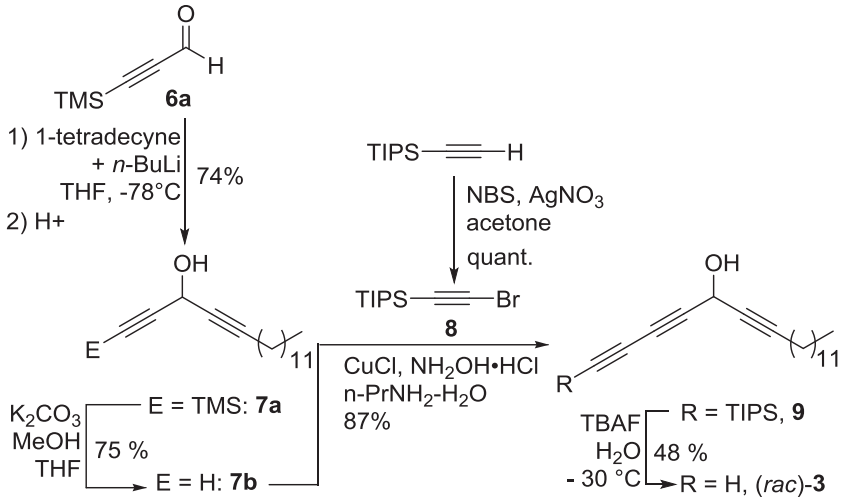
The (*S*)-**4** target is an isomer of the lipidic bishomologue of (*S*)-falcarinol **5a**, where the vinyl end of **5a** is dehydrogenated to an ethynyl terminus. Notably, H_2-saturation of the vinyl end of the most active enantiomer of a panaxytriol derivative was reported to induce a significant drop in cytotoxicity,[14] and the same effect was observed upon H_2-saturation of the ethynyl end of **1**.[5a] These results are in the same line as the enhancement of cytotoxicity upon increasing the *degree* of unsaturation from AAC to DAC, and a similar effect was expected upon increasing the *extent* of unsaturation from DAC to BAC.

2. Results and discussion

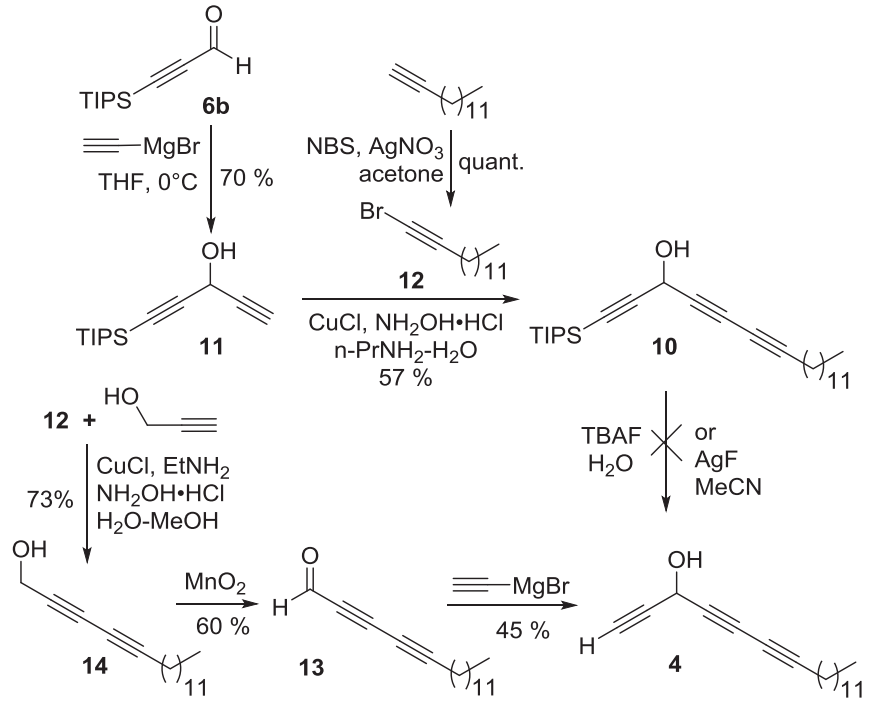
Synthesis of racemic samples of the BACs **3** and **4** was first accomplished by using a Cadiot-Chodkiewicz coupling to assemble the butadiynyl fragment from a non-functional bromoalkyne and a terminal DAC precursor, itself prepared by nucleophilic addition of a metal acetylide onto an aldehyde.

The synthesis of (*rac*)-**3** started with the addition of tetradecynyllithium to trimethylsilylpropynal **6a** giving the silylated DAC **7a**, followed by K_2CO_3-promoted desilylation leading to the terminal DAC **7b**, with 55% yield over two steps (Scheme 1).[5b] A Cadiot-Chodkiewicz coupling of **7b** with the bromoalkyne **8**,[15] prepared by bromination of triisopropylsilylacetylene with NBS in the presence of $AgNO_3$,[16] afforded the silylated BAC **9** in 87% yield.[17] Desilylation of **9** with TBAF at −30 °C afforded (*rac*)-**3** with 48% yield.

A similar method was used for the synthesis of (*rac*)-**4**, in which the butadiynyl fragment lies in the internal position. The silylated carbinol **10** was thus obtained in two steps and 40% yield from the silylated propynal **6b** (Scheme 2): the intermediate DAC **11** was first obtained by addition of ethynylmagnesium bromide to **6b**,[18] and the butadiynyl fragment of **10** was then formed by a Cadiot-



Scheme 1. Synthesis of the racemic BAC (*rac*)-**3**.



Scheme 2. Attempt at synthesis and synthesis of the racemic BAC (*rac*)-**4**.

Chodkiewicz coupling of **11** with the bromoalkyne **12**,[17] the latter being prepared by $AgNO_3$-promoted bromination of 1-tetradecyne with NBS.[16,19] However, proto-desilylation of **10** using TBAF or silver fluoride failed to produce the BAC target **4**.

The access to **4** was thus envisaged through another strategy, relying on the addition of ethynylmagnesium bromide to the butadiynal **13** (Scheme 2). The synthesis of **13** required first the use of a Cadiot-Chodkiewicz coupling between the bromoalkyne **12** and propargyl alcohol, giving the butadiynol **14** with 73% yield.[20] After oxidation of **14** to **13**, the final addition afforded the targeted racemic BAC (*rac*)-**4** with 45% yield.

The cytotoxicity of racemic mixtures of the regioisomeric BACs **3** and **4** was first evaluated on the human colon carcinoma HCT116 cancer cell-line previously used to assess the biological activity of alkynylcarbinol pharmacophores.[5] MTT cell viability assays evidenced that the activity is much higher for the racemic BAC (*rac*)-**4** containing the butadiynyl fragment at the internal position, with an IC_{50} of *ca.* 120 nM, comparable to that of the parent DAC in the scalemic series (*S*)-**1** (90 nM) (Table 1).

Asymmetric synthesis of the enantiomers of **4** was undertaken through the 'modified Carreira method' that proved efficient for the enantioselective preparation of DACs.[5] Instead of TIPS, a TMS protecting group of the terminal triple bond was selected for its possible removal under neutral conditions (using silver nitrate),[21] and two possible retrosynthetic disconnections were considered (Scheme 3). The disconnection 1, requiring the use of a Carreira reaction of the diynal **13** with trimethylsilylacetylene, failed to produce the silylated BAC **15**, likely because of the instability of **13** under these conditions. The disconnection 2, involving the a priori more stable trimethylsilylpropynal **6a** was then addressed.[22]

Table 1
Evaluation of the cytotoxicity against HCT116 cancer cells of the DAC **1** and the BACs **3** and **4**. Cells were seeded in 96-well plates and treated with concentrations ranging from 5 nM to 10 μM; after 72 h, the number of live cells was evaluated by standard MTT test (SD)

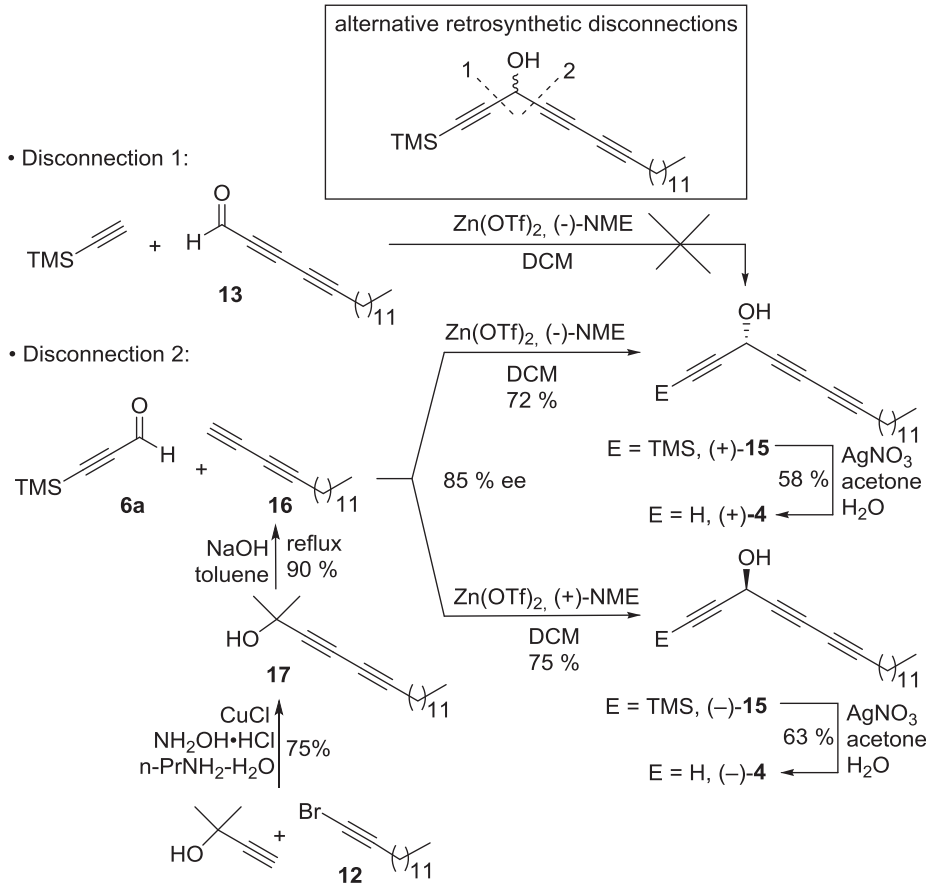
Derivative	IC_{50} [nM]
(*S*)-(+)-**1**	102 (±14)[a,b]
(*rac*)-**3**	10,000
(*rac*)-**4**	120
(*S*)-(+)-**4**	42 (±12)[a]
(*R*)-(−)-**4**	1500

[a] The given statistical errors were calculated from six different MTT tests performed in strictly identical conditions.
[b] The IC_{50} value of 90 nM earlier reported for (*S*)-(+)-**1** (see ref. 5a) is within the given margin of error.

The lipidic butadiyne nucleophile **16** was prepared in two steps and 68% yield from the bromoalkyne **12** and 2-methylbut-3-yn-2-ol, via the diynol **17**, through a Cadiot-Chodkiewicz coupling and a retro-Favorskii reaction using procedures previously described for other substrates.[15] The asymmetric addition of the 1,3-diyne **16** to the ynal **6a** under the modified Carreira conditions afforded the TMS-protected BACs (+)-**15** and (−)-**15** with 72% and 75% yields, respectively.[23] It is noteworthy that this is the first example of application of the Carreira reaction, which is known to be highly substrate-dependent,[24] to butadiyne and ynal substrates. Protodesilylation of (+)-**15** and (−)-**15** was first attempted with the K_2CO_3–MeOH combination, but these basic conditions proved inefficient, giving only polymerization products instead. Under neutral conditions, however, treatment of (+)-**15** and (−)-**15** with $AgNO_3$ led to the ultimate BAC targets (+)-**4** and (−)-**4** with 58% and 63% yields, respectively,[19] and an enantiomeric excess of 85%, as determined by chiral supercritical fluid chromatography (SFC) using an IA-3 column (default value: depending on the experiment, an ee up to 89% has been measured). The BAC products were found remarkably stable, a sample of (+)-**4** remaining unchanged after storage over several months at −20 °C, either in solution or in the dry state. It can also be stored for a few weeks at room temperature in the solid state without degradation (and without a loss of biological activity against HCT116 cells).

Single crystals of the *levo* product obtained by slow evaporation of a dichloromethane solution proved suitable for X-ray diffraction analysis, which confirmed the chemical structure of (−)-**4** (Fig. 2).[25,26] Because the compound contains no heavy atom and the X-ray diffraction analysis was performed using Mo-Kα radiation, the absolute configuration of the carbinol center cannot be reliably ascertained. Nevertheless, the (*R*) configuration is represented on the basis of the general rules of asymmetric induction for the Carreira method: having used (+)-NME as chiral auxiliary, a (*S*) configuration can be predicted for (−)-**15**, and thus a (*R*) configuration for (−)-**4**.

The cytotoxicity of the scalemic BACs was evaluated towards the HCT116 cell-line, and compared with that of the reference DAC (*S*)-(+)-**1** exhibiting an IC_{50} of 90 nM.[5a] In Table 1 are listed the IC_{50} values measured for the racemic samples of the BACs **3** and **4**, and for the enantio-enriched samples of (*S*)-(+)-**4** and (*R*)-(−)-**4**. As mentioned above, the internal BAC ethynylogue (*rac*)-**4** is two order of magnitude more active than the external regioisomer (*rac*)-**3**. The compared cytotoxicity of the (*S*) and (*R*) enantiomers of **4**, isolated in 85% ee, once again evidenced the dramatic influence of the absolute configuration of the carbinol center.[5] The much higher



Scheme 3. Retrosynthesis and synthesis of the two enantiomers of the BAC **4**. The depicted absolute configurations correspond to those predicted by the Noyori's asymmetric induction model admitted for the Carreira's method.

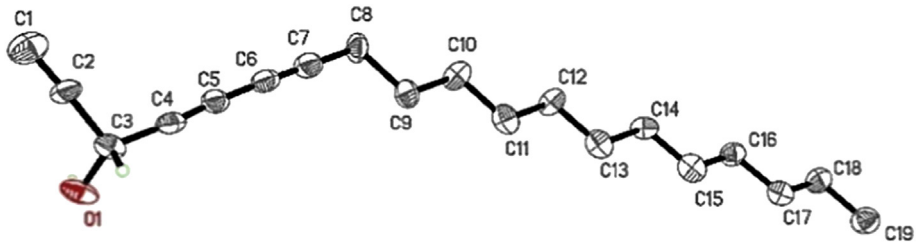


Fig. 2. Molecular view of the BAC **4** from X-ray diffraction analysis of a single crystal of the *levo* enantiomer (−)-**4**.[24] Thermal ellipsoids represent 50% probability. H atoms are omitted for clarity (except for that on asymmetric carbon C3 and on O1 atom) (see SD).

potency of the (*S*) enantiomer with respect to the (*R*) counterpart is consistent with the systematic trend observed in the DAC series.[5a] The cytotoxicity of (*S*)-(+)-**4**, with an IC_{50} value of 40 nM, is slightly higher than that of the reference DAC (*S*)-(+)-**1**. The IC_{50} value of (+)-**1** and (+)-**4** being in the same range, for the sake of comparison, the uncertainties were calculated from six different MTT tests: the respective statistical errors of ±14 nM and ±12 nM show that the tests exhibit a reliable level of reproducibility, and confirm that the BAC (+)-**4** is definitely more active than the DAC (+)-**1**. The significance of the ethynylogation effect is also supported by pointing out that the enantiomeric enrichment of the sample of (+)-**4** is lower (85% ee) than that of (+)-**1** (91% ee).[5a] Furthermore, the cytotoxicity enhancement from (+)-**1** to (+)-**4** cannot be simply assigned to an effect of the two-carbon increase of the chain length: it has indeed been previously shown that elongation or truncation of the lipidic chain of (+)-**1** results in higher IC_{50} values.[5b]

3. Conclusion

The observed slight enhancement of cytotoxicity upon internal ethynylogation of the DAC (+)-**1** to the BAC (+)-**4** is a factual result, yielding the most active cytotoxic compound against HCT116 cancer cells at disposal to date in the lipidic alkynylcarbinols series. The results also provide a preliminary support to the relevance of the proposed ethynylogation approach, which has however to be appraised with other molecules before being possibly considered as generally useful in pharmacophore design. In passing, the enantioselective synthesis of (+)-**4** and (−)-**4** illustrates further and extend the scope of the modified Carreira procedure for asymmetric addition of terminal alkynes to ynals. The vanishing eudismic ratio of the BAC **4** (<40/1500) surpasses the trend established in the AAC and DAC series.[5] The triple bond inserted between the DAC pharmacophore and its lipidic periphery defines a BAC chemical functionality which can be in turn considered as a pharmacophore by itself, while repelling the limit with the lipidic chain by two C–C bonds. In principle, ethynylogation of the new pharmacophore limit might be applied again, and so sequentially until facing the stability limit of such bio-inspired polyynes. On the other hand, considering the lipidic BAC (+)-**4** as a new lead molecule for cytotoxicity, further optimization would consist in a systematic variation of the lipidic chain length, which was shown to be of paramount importance in the DAC series.[5a] Comparative biological evaluation of DACs and BACs against other cancer cell-lines, beyond HCT116, is also planned. Results in these directions will be communicated in due course.

4. Experimental section

4.1. General experimental details

The following solvents and reagents were dried and freshly distilled prior to use: CH_2Cl_2 (from CaH_2), Et_2O, THF (from sodium/benzophenone). All the reagents were used as commercially available. Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F254 pre-coated plates. TLC-plates were observed under UV light and/or revealed with a 10% phosphomolybdic acid ethanolic solution. Column chromatographies were carried out with silica gel 60 Å, 70–230 mesh. NMR spectroscopic data were obtained with instruments working at 300 or 400 MHz for ^1H nuclei. The following instruments were used: ^1H and ^{13}C NMR: Bruker Avance 300 or Avance 400 spectrometers. High-resolution mass spectra (HRMS) were performed by Desorption Chemical Ionization with methane gas (DCI (CH_4)) using a TOF mass analyzer. IR analyses were run on an ATR Perkin–Elmer Spectrum 100 FT-IR spectrometer. Optical rotations were measured on a Jasco P-2000 polarimeter. Chiral SFC: Acquity UPC^2 System by Waters and SFC PIC Lab Analytic by Pic Solution with column Chiralpak IA-3 (4.6×100 mm). Chemical shifts (δ) are given in ppm relative to the residual solvent peak; *J* values are given in Hz. $[\alpha]_D$ values are given in deg $dm^{-1}cm^{-3}g^{-1}$.

4.2. Experimental procedures and characterizations

*4.2.1. Nonadeca-1,3,6-triyn-5-ol (**3**).* To a solution of **9** (50 mg, 0.117 mmol) in THF (2 mL) containing one drop of water, at −30 °C, was added 1M TBAF solution in THF (350 μL, 0.349 mmol, 3 equiv). The mixture was stirred for 30–45 min, and quenched with a saturated aqueous solution of NH_4Cl. After extraction with Et_2O, the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (pentane/Et_2O 10:1) to give **3** as an oil (15 mg, 48%). ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J*=6.70 Hz, 3 H), 1.21–1.41 (m, 18 H), 1.53 (pseudo-quint, *J*=7.17 Hz, 2 H), 2.16 (d, *J*=7.86 Hz, 1 H), 2.23 (td, *J*=5.10, 2.50 Hz, 2 H, overlap with the signal at 2.24 ppm), 2.24 (d, *J*=1.20 Hz, 1 H, overlap with the signal at 2.23 ppm), 5.14 (dtd, *J*=7.86, 2.50, 1.20 Hz, 1 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 14.1, 18.7, 22.7, 28.2, 28.9, 29.1, 29.3, 29.5, 29.6, 29.6, 29.7, 31.9, 52.6, 67.2, 68.2, 69.3, 73.2, 76.0, 87.0; IR (neat): ν=3274, 2918, 2870, 2848, 2316, 2290, 2256, 2223, 1739, 1490, 1465, 1428, 1405, 1376, 1346, 1330, 1305, 1291, 1156, 1117, 1083, 1049, 1031, 1005, 995, 890, 813, 789, 755, 721, 697, 663, 641, 601, 582, 560 cm^{-1}; HRMS-DCI (CH_4): *m/z* $[M+H]^+$ calcd for $C_{19}H_{29}O$: 273.2218, found: 273.2238.

*4.2.2. Racemic nonadeca-1,4,6-triyn-3-ol (**4**).* To a solution of the aldehyde **13** (20 mg, 0.081 mmol) in THF (5 mL) under stirring at 0 °C was added dropwise ethynylmagnesium bromide (162 μL, 0.081 mmol). The reaction mixture was stirred for 1 h at 0 °C and 1 h at room temperature before treatment with a saturated aqueous NH_4Cl solution. After extractions with E_2O (3×1 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by silica gel chromatography (R*f*=0.2, pentane/Et_2O 20:1) to give **4** as a colorless oil (10 mg, 45%). ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J*=6.53 Hz, 3 H), 1.23–1.45 (m, 18 H), 1.54 (pseudo-quin, *J*=7.10 Hz, 2 H), 2.29 (t, *J*=6.91 Hz, 2 H), 2.59 (d, *J*=2.05 Hz, 1 H), 5.16

(br s, 1 H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 14.1, 19.3, 22.7, 28.0, 28.8, 29.1, 29.3, 29.5, 29.6 (3C), 31.9, 52.4, 64.0, 70.2, 71.1, 73.2, 80.0, 83.4; IR (neat): ν=3313, 3289, 3230, 2955, 2922, 2847, 2257, 2123, 1719, 1498, 1464, 1422, 1371, 1290, 1276, 1230, 1220, 1127, 1023, 990, 970, 881, 724, 711, 699, 666, 649, 565, 558 cm^{-1}; HRMS-DCI (CH_4): *m/z* $[M+H]^+$ calcd for $C_{19}H_{29}O$: 273.2218, found: 273.2221. Chiral SFC analysis: Chiralpak IA 3 μm (4.6×100 mm), SC CO_2+15% MeOH (gradient), 4 mL/min, 40 °C, 130 bar, UV 240 nm, t_R 3.93 (*R*), 4.08 (*S*) min.

*4.2.3. (+)-Nonadeca-1,4,6-triyn-3-ol ((+)-**4**).* To a solution of (+)-**15** (57 mg, 0.166 mmol) in acetone (3 mL) was added $AgNO_3$ (2.8 mg, 0.016 mmol, 0.1 equiv) and one drop of water. The mixture was stirred for 4 h (followed by TLC), and then quenched with a saturated aqueous NaCl solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was purified by silica gel chromatography (pentane/Et_2O 15:1) to give (+)-**4** as a white solid (26 mg, 58%). The analytical data for (+)-**4** are identical to those of the racemate **4** excepted the optical rotation $[\alpha]_D^{20}$ +7.5 (*c*=2.24, $CHCl_3$). Chiral SFC analysis: Chiralpak IA 3 μm (4.6×100 mm), SC CO_2+15% MeOH (gradient), 4 mL/min, 40 °C, 130 bar, UV 240 nm, t_R 3.93 (*R*), 4.08 (*S*) min.

*4.2.4. (−)-Nonadeca-1,4,6-triyn-3-ol ((−)-**4**).* The BAC (−)-**4** was prepared from (−)-**15** using the procedure described for the (+)-**4** enantiomer. It was obtained as a white solid (32 mg, 63%). Analytical data for (−)-**4** are identical to those of the racemate **4** excepted the optical rotation. $[\alpha]_D^{20}$ −8.8 (*c*=2.84, $CHCl_3$). Chiral SFC analysis: Chiralpak IA 3 μm (4.6×100 mm), SC CO_2+15% MeOH (gradient), 4 mL/min, 40 °C, 130 bar, UV 240 nm, t_R 3.93 (*R*), 4.08 (*S*) min.

*4.2.5. 1-[tris(Propan-2-yl)silyl]nonadeca-1,3,6-triyn-5-ol (**9**).* CuCl (1.75 mg, 0.0176 mmol) was added to a *n*-propylamine solution (0.55 mL, 30% v/v in water) at 0 °C. After stirring for 5 min, hydroxylamine hydrochloride (0.7 mg, 0.0102 mmol) was added, inducing the disappearance of the blue color of the mixture. A solution of the terminal alkyne **7b** (100 mg, 0.4032 mmol) in THF (0.1 mL) was then added, and the mixture stirred at 0 °C for 15 min. Finally, a solution of the bromoalkyne **8** (125 mg, 0.4757 mmol) in THF (0.1 mL) was added dropwise, and the mixture stirred at 0 °C for 4 h (TLC monitoring). The reaction was quenched with a saturated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with diethylether (3×1 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (pentane/Et_2O 15:1) to give **9** as a pale yellow oil (150 mg, 87%). ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J*=6.40 Hz, 3 H), 1.09 (s, 21 H), 1.22–1.45 (m, 18 H), 1.46–1.57 (m, 2 H), 2.16 (d, *J*=7.68 Hz, 1 H), 2.23 (td, *J*=7.10, 2.18 Hz, 2 H), 5.16 (dt, *J*=7.68, 2.05 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): 11.2, 14.1, 18.5, 18.7, 22.7, 28.2, 28.9, 29.1, 29.4, 29.5, 29.6 (2C), 29.7, 31.9, 52.8, 69.3, 73.3, 76.2, 86.2, 86.8, 88.6. IR (neat): ν=3369, 2923, 2854, 2727, 2209, 2154, 2106, 1715, 1650, 1615, 1463, 1379, 1367, 1292, 1242, 1071, 1016, 996, 919, 882, 721, 678, 663, 618, 602, 595 cm^{-1}; HRMS-DCI (CH_4) *m/z* $[M+H]^+$ calcd for $C_{28}H_{49}OSi$: 229.3553, found: 229.3560.

*4.2.6. 1-[tris(Propan-2-yl)silyl]nonadeca-1,4,6-triyn-3-ol (**10**).* CuCl (1.85 mg, 0.0186 mmol), was added to a solution of *n*-propylamine (0.58 mL of 30% v/v in water) at 0 °C. After stirring for 5 min, hydroxylamine hydrochloride (0.8 mg, 0.0108 mmol) was added, inducing the disappearance of the blue color of the mixture. A solution of the terminal alkyne **11** (100 mg, 0.4255 mmol) in THF (0.1 mL) was added under stirring at 0 °C for 15 min. A solution of the bromoalkyne **12** (137 mg, 0.5028 mmol) in THF (0.1 mL) was then added dropwise, and the resulting mixture was stirred at 0 °C for 4 h (TLC monitoring). The mixture was treated with a saturated aqueous NH_4Cl solution (5 mL) and the aqueous layer was extracted with diethyl ether (3×1 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (pentane/Et_2O 25:1) to give **10** as a clear yellow oil (104 mg, 57%). ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J*=6.70 Hz, 3 H), 1.09 (s, 21 H), 1.21–1.45 (m, 18 H), 1.54 (pseudo-quintet, *J*=7.00 Hz, 2 H), 2.25–2.35 (m, 3 H), 5.16 (d, *J*=7.00 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 11.1, 14.1, 18.5, 19.3, 22.7, 28.1, 28.8, 29.1, 29.3, 29.5, 29.6 (3C), 31.9, 53.0, 64.2, 69.5, 71.9, 82.9, 86.7, 102.9; IR (neat): ν=3390, 2923, 2855, 2725, 2257, 2232, 2178, 1709, 1624, 1462, 1383, 1367, 1291, 1262, 1228, 1101, 1037, 1017, 996, 919, 882, 805, 717, 676, 611, 579, 566, 559 cm^{-1}; HRMS-DCI (CH_4) *m/z* $[M+H]^+$ calcd for $C_{28}H_{49}OSi$: 229.3553, found: 229.3565.

*4.2.7. Heptadeca-2,4-diyn-1-ol (**14**).* To a stirred solution of propargyl alcohol (23 mg, 0.42 mmol), ethylamine (0.15 mL of 70% w/w solution in water) and 1-bromo-1-tetradecyne **12** (100 mg, 0.366 mmol) in MeOH (5 mL), was added freshly prepared CuCl (1 mg, 0.01 mmol). After the reaction mixture turned to a yellowish green color, hydroxylamine hydrochloride (7 mg, 0.1 mmol) was added, inducing an immediate change of the color which became yellow. The reaction was monitored by TLC (pentane/Et_2O 10:1) and reached completion after 20 h. Then, the mixture was filtered through a short pad of Celite®, and the filtrate was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc, washed with water and saturated brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel (pentane/Et_2O 10:1) to give **14** as a white solid 76 mg (73%). The obtained physical data were in agreement with literature.[20]

*4.2.8. Heptadeca-2,4-diynal (**13**).* To a solution of **14** (50 mg, 0.201 mmol) in dichloromethane (5 mL) under stirring at 0 °C was added MnO_2 (336 mg, 4 mmol, 20 equiv) in one portion. The resulting mixture was stirred at this temperature for 1 h, and at rt for 2 h before being filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure to give **13** as a pale yellow oil (60%, 29 mg). ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J*=7.20 Hz, 3 H), 1.18–1.47 (m, 18 H), 1.59 (quin, *J*=8.20 Hz, 2 H), 2.40 (t, *J*=7.04 Hz, 2 H), 9.20 (s, 1 H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 14.1, 19.8, 22.7, 27.7, 28.8, 29.0, 29.3, 29.4, 29.6 (2C), 29.7, 31.9, 63.7, 72.4, 80.7, 93.2, 176.1; IR (neat): ν=2922, 2852, 2733, 2477, 2230, 2131, 1727, 1660, 1551, 1464, 1423, 1380, 1260, 1237, 1075, 1021, 947, 910, 856, 803, 771, 722, 697, 580, 567, 556 cm^{-1};HRMS-DCI (CH_4) *m/z* $[M+H]^+$ calcd for $C_{17}H_{27}O$: 247.2062, found: 247.2074.

*4.2.9. 2-Methyl-3,5-octadecadiyn-2-ol (**17**).*[27] CuCl (6 mg, 0.064 mmol), was added to a solution of *n*-propylamine (2 mL of 30% v/v in water) at 0 °C. After stirring for 5 min, hydroxylamine hydrochloride (2.6 mg, 0.038 mmol) was added, inducing the disappearance of the blue color of the solution. 2-Methyl-3-butyn-2-ol (166 μL, 145 mg, 1.72 mmol) was then added and the mixture was stirred at 0 °C for 15 min. A solution of the bromoalkyne **12** (554 mg, 2.03 mmol) in THF (0.1 mL) was then added dropwise, and the resulting mixture was stirred at 0 °C for 4 h (TLC monitoring). The mixture was treated with a saturated aqueous NH_4Cl solution (5 mL) and the aqueous layer was extracted with diethyl ether (3×1 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (pentane/Et_2O 10:1) to give **17** as a colorless oil 390 mg (82%). R*f*=0.3, pentane/Et_2O=10:1. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J*=6.4 Hz, 3H), 1.20–1.45 (m, 18H), 1.47–1.60 (m, 10H), 1.89 (s, 1H), 2.27 (t, *J*=7.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR

(75 MHz, $CDCl_3$): δ 14.1, 19.3, 22.7, 28.3, 28.9, 29.2, 29.7 (3C), 31.2 (2C), 32.0, 64.5, 65.5, 67.4, 80.0, 81.6. IR (neat): ν=3361, 2981, 2922, 2853, 2252, 1713, 1465, 1423, 1363, 1328, 1261, 1153, 956, 895, 795, 721, 597, 553, 464 cm^{-1}; HRMS-DCI (CH_4) m/z $[M+H]^+$ calcd for $C_{19}H_{33}O$:277.2531, found: 277.2531.

*4.2.10. (+)-1-(Trimethylsilyl)nonadeca-1,4,6-triyn-3-ol ((+)-**15**).* A flask was charged with $Zn(OTf)_2$ (664 mg, 1.83 mmol, 4 equiv), (−)-*N*-methylephedrine (328 mg, 1.83 mmol, 4 equiv) was purged with argon for 15 min. Anhydrous CH_2Cl_2 (10 mL) and triethylamine (248 μL, 1.83 mmol, 4 equiv) were then added, and the resulting mixture was vigorously stirred for 2 h at rt. Then, a solution of the diyne **16** (400 mg, 1.83 mmol, 4 equiv) in CH_2Cl_2 (0.5 mL) was added in one portion. After stirring 1 h, the aldehyde **6a** (68 μL, 0.4575 mmol, 1 equiv) was added and the mixture was stirred overnight at rt. A saturated aqueous NH_4Cl solution was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (pentane/Et_2O 15:1) to give (+)-**15** as a clear oil 114 mg (72%). $[\alpha]_D^{20}$ +8.3 (c=7.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.19 (s, 9H), 0.89 (t, J=6.27 Hz, 3H), 1.20–1.45 (m, 20H), 1.54 (quin, J=6.98 Hz, 2H), 2.23–2.35 (m, 3H), 5.14 (d, J=7.68 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ −0.4, 14.1, 19.3, 22.7, 28.0, 28.8, 29.0, 29.3, 29.4, 29.6, 29.6, 29.6, 31.9, 52.9, 64.2, 69.7, 71.6, 83.1, 90.2, 100.7; IR (neat): ν=3357, 2955, 2923, 2853, 2669, 2257, 2179, 1710, 1622, 1465, 1424, 1409, 1376, 1292, 1250, 1228, 1115, 1036, 1010, 929, 898, 841, 760, 719, 700, 649, 623, 610, 563 cm^{-1}; HRMS-DCI (CH_4) m/z $[M+H]^+$ calcd for $C_{22}H_{37}OSi$:345.2614, found: 345.2610. A 89% ee was deduced from the value measured for (+)-**4** by chiral SFC analysis.

*4.2.11. (−)-**1**-(Trimethylsilyl)nonadeca-1,4,6-triyn-3-ol ((−)-**15**).* It was obtained from the diyne **16** and the aldehyde **6a** as a colorless oil (120 mg, 75%) using (+)-*N*-methylephedrine according to the procedure described for the (+)-**15** enantiomer. The obtained analytical data for (−)-**15** were identical to those described for the (+)-**15** enantiomer, excepted for the optical rotation. $[\alpha]_D^{20}$ −8.15 (c=6.75, $CHCl_3$). A 85% ee was deduced from the one measured by chiral SFC analysis of (−)-**4**.

*4.2.12. Hexadeca-1,3-diyne (**16**).*[27] To solution of **17** (300 mg, 1.085 mmol) in toluene (10 mL) was added powdered sodium hydroxide (176 mg, 4.4 mmol), and the resulting mixture was refluxed for 1 h. After complete consumption of the starting material (TLC monitoring), the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (pentane/Et_2O 10:1) to give **16** as a pale oil 213 mg (90%). R*f*=0.5, pentane/Et_2O=10:1. ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J=7.0 Hz, 3H), 1.24–1.46 (m, 18H), 1.62–1.48 (m, 2H), 1.98 (t, J=1.2 Hz, 1H), 2.27 (td, J=7.0, 1.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 14.2, 19.2, 22.8, 28.2, 29.0, 29.2, 29.5, 29.6, 29.8 (3C), 32.1, 64.5, 64.9, 68.7, 78.5. IR (neat): ν=3312, 2922, 2852, 2298, 2226, 1465, 1425, 1377, 1323, 1208, 721, 608 cm^{-1}.

4.3. Biological evaluation

4.3.1. MTT test (MTT=(3-[4,5-diMethylThiazol-2-yl]-2,5-diphenyl Tetrazolium bromide). The drugs' cytotoxicity was determined by standard MTT tests on HCT116 cells. In brief, 10.000 HCT116 cells were distributed in 96 flat bottom well plates in 100 μL of DMEM 10% FCS and 1 μL of DMSO containing the drugs dilutions were then added to each well. For each drug, triplicates of concentrations ranging from 10 μM to 5 nM were carried out, by means of 7 successive three fold dilutions of a 1 mM stock solution. Controls always included medium alone, DMSO alone and dilutions of the reference drug (+)-**1** (IC_{50} around 100 nM). Plates were then placed in a CO_2 tissue culture incubator for 72 h before the MTT test was performed. This was done by adding 10 μL of MTT stock solution (12 μM, 5 mg/ml in PBS, Sigma) to each well and incubating the plate for 90 min at 37 °C. 100 μL isopropanol, 0.1 M HCl were then added to each well, and the plates were returned to 37 °C for 90 min before reading the OD at 570 nM.

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Supplementary data

Supplementary (Experimental details, procedures and characterizations for new compounds, NMR spectra, chiral SFC chromatograms, crystallographic data, MTT tests for biological evaluations.) data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2016.09.001.

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