On terminal alkynylcarbinols and derivatization thereof

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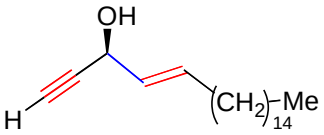
Abstract. The chemistry of three prototypes of secondary alkynylcarbinols (ACs), recently highlighted as challenging targets in anti-tumoral medicinal chemistry, is further documented by results on *n*-alkyl, alkynyl and alkenyl representatives. The *N*-naphthyl carbamate of an *n*-butyl-AC is thus characterized by X-ray crystallography. A novel dialkynylcarbinol (DAC) with synthetic potential is described, namely the highly dissymmetrical triisopropylsilyl-protected version of diethynylmethanol. The latter is shown to act as a dipolarophile in a selective Huisgen reaction with benzyl azide under CuAAC click conditions, giving an alkenyl-AC, where the alkene unsaturation is embedded in a 1,4-disubstituted 1,2,3-triazole ring, as confirmed by X-ray crystallography.

Introduction

Bio-inspired asymmetric secondary terminal alkynylcarbinols (ACs) substituted by various α-unsaturated units have been recently highlighted as relevant pharmacophores [1,2]. Natural lipidic alkenyl-ACs (AACs) extracted from marine sponges had indeed long been reported to exhibit significant *in vitro* anti-tumoral cytotoxicity [3]. Beyond total synthesis achievements [2,4], a systematic four-parameter variation study, then refined to a three-parameter one, was undertaken from the (*S*)-eicos-(4*E*)-en-1-yn-3-ol model extracted from *Cribrochalina vasculum* (**Figure 1**)[5].

(*S*)-eicos-(4*E*)-en-1-yn-3-ol, extracted from the marine sponge *Cribrochalina vasculum*:



$[\alpha]_D^{25}$ = +3.8° (c = 0.9, MeOH);
IC_{50} (murine P388: lung tumor) = 1.0 µg/mL

=> three-parameter pharmacophore study:

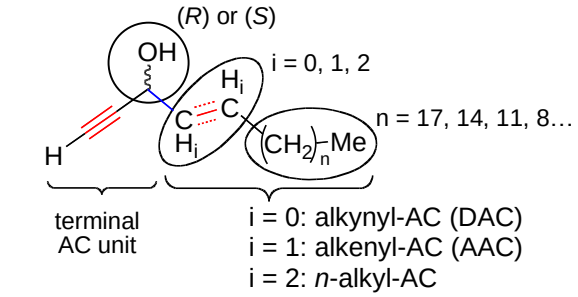


Figure 1. Natural anti-tumoral AAC (*top*), model for a systematic three-parameter pharmacophore study (*bottom*)

Derived structure-activity relationships indicate significant chirality effects, the eutomers being the unnatural enantiomers, with IC_{50} values *ca* one order of magnitude higher than those of the natural distomers [1]. Moreover, artificial lipidic alkynyl-ACs, i.e. dialkynyl-carbinols (DACs), proved to be the most potent pharmacophores, with anti-tumoral cytotoxicity IC_{50} values down to 60 nM on HCT116 cell lines [1].

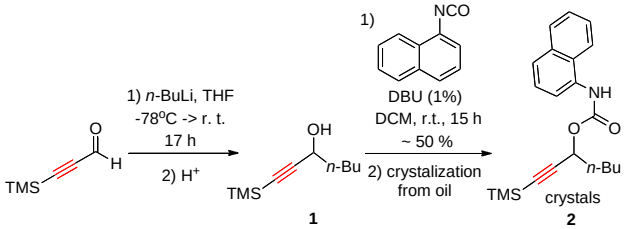
Further exploration of the chemical space by variation of the pharmacophore structure relies first on the availability of chemical data and synthesis tools. This is hereafter addressed through variations of the AC substituent according to the hybridization state of the first carbon atom, which can be either sp^3, sp^2, or *sp*.

Results and discussion

The disclosed insights into the chemistry of novel terminal AC prototypes are presented in the order: *n*-alkyl-ACs (sp^3), alkynyl-ACs (DACs, *sp*), and alkenyl-ACs (AACs, sp^2).

1. n-*Alkyl-ACs: the "short" n-butyl derivative and a carbamate thereof*

The known *n*-butyl-AC **1** can be obtained by reaction of trimethylsilyl-propiolaldehyde [6] with *n*-BuLi or *n*-BuMgBr [7]. In view of possible analysis of scalemic samples by chiral HPLC [1], the racemic *n*-butyl-AC **1** was reacted with naphth-1-yl isocyanate to give the corresponding carbamate **2** in 50 % yield.



Scheme 1. Preparation of the *N*-naphthyl carbamate of the known *n*-butyl-AC **1** (see Figure 2). TMS = $SiMe_3$.

The isolated oil slowly gave crystals of **2** suitable for X-ray diffraction (XRD) analysis revealing rather classical geometrical features. A *cisoid* conformation of the (naphthtyl)N–C(O) bond of the carbamate unit, along with a quite acute O–C(O)–N bond angle, are however noticeable (**Figure 2**, **Table 1**). A quite large dihedral angle between the naphthyl and carbamate planes of 53.7° also indicates a weak conjugation between the two π systems.

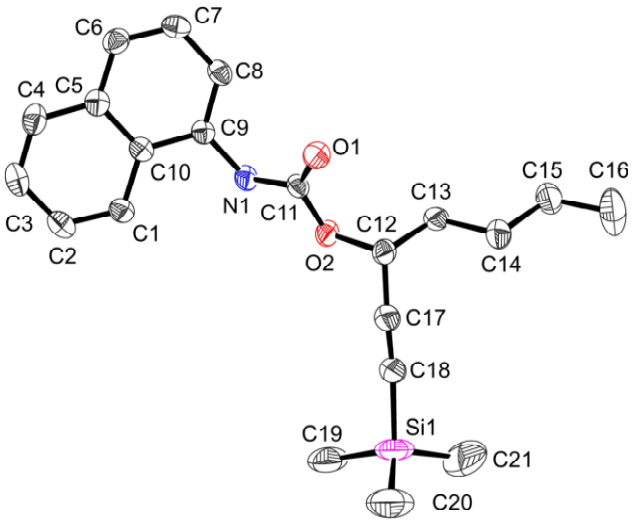
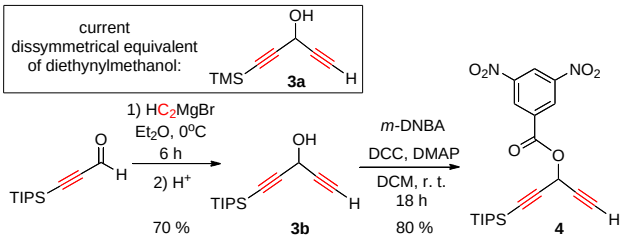


Figure 2. Molecular view of the X-ray crystal structure of the carbamate **2** (Scheme 1). For clarity, hydrogen atoms and disordered atoms are omitted (see Table 1 and CCDC n° 1038852). Selected bond lengths (Å) and bond angles (°) (disordered C18 atom): C12-O2 = 1.461(2), C12-C17 = 1.468(3), C13-C12 = 1.510(3), C17-C18'= 1.193(7) and C17-C18 = 1.224(6), C11-O1 1.214(3), C11-N1 = 1.342(3), O2-C12-C17 = 105.19(17), O2-C12-C13 = 110.37(18), C17-C12-C13 = 113.0(2), C12-C17-C18 = 171.3(4) and C12-C17-C18' = 171.6(4), N1-C11-O2 = 109.54(18).

2. Alkynyl-ACs: triisopropylsilylpenta-1,4-diyn-3-ol, a highly dissymmetrical equivalent of diethynylmethanol

The pharmacophoric value of lipidic DACs [1] calls for systematic efforts toward the investigation of their synthesis and reactivity. The chemistry of DACs, mostly tertiary, is largely documented for their use as basic synthons in the synthesis of hexaoxy-[6]pericyclynes serving as direct precursors of *carbo*-benzenes [8,9] or related acetylenic chromophores [10]. In the secondary DAC series, trimethylsilyl-penta-1,4-diyn-3-ol **3a** is a currently referenced dissymmetrical equivalent of diethynylmethanol (**Scheme 2**) [9,11]. To the best of the authors' knowledge, the more dissymmetrical and more robust triisopropylsilyl homologue **3b** has not been described hitherto. The latter has however been readily obtained as an oil in 70 % isolated yield by a Grignard reaction of ethynylmagnesium bromide with triisopropylsilylpropiolaldehyde (**Scheme 2**). In view determining structural features of the bulky DAC **3b** by derivatization to a crystalline solid, the 3,3-dinitrobenzoate ester **4** was targeted. The latter was obtained in 80 % yield by reaction of **3b** with *meta*-dinitrobenzoic acid (**Scheme 2**). The ester **4** was however isolated as a foam, from which sufficiently large single crystals could not be obtained, thus preventing structural determination by XRD analysis.

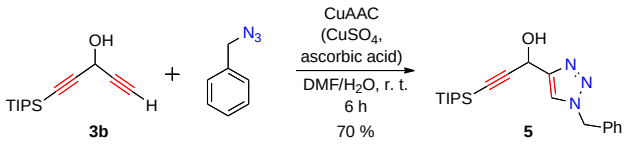


Scheme 2. Preparation of the disymmetrical equivalent of diethynylmethanol **3b** and *m*-dinitrobenzoate ester thereof. TIPS = Si^iPr_3; *m*-DNBA = *m*-dinitrobenzoic acid; DCC = dicyclohexylcarbodiimide; DMAP = 4-dimethylaminopyridine .

3. Alkenyl-ACs: a 1,2,3-triazolyl-carbinol

The reactivity of the above-disclosed dissymmetrical equivalent of diethynylmethanol was investigated in a Cu-catalyzed Huisgen alkyne-azide cycloaddition (CuAAC). With

benzyl azide, standard click conditions ($CuSO_4$ and ascorbic acid [12]) afforded the triazolyl-AC **5** with complete 1,4-stereoselectivity (**Scheme 3**), as previously observed from other dialkynylcarbinol dipolarophiles [13,14].



Scheme 3. Huisgen reaction of the DAC **3b** with benzyl azide under click conditions giving the 1,2,3-triazolyl-alkynylcarbinol **5** as a particular alkenyl-AC (Figure 3).

The triazolyl-AC **5** actually corresponds to a particular type of AAC, where the diaminoalkene unsaturation, embedded in a 1,2,3-triazole ring, is *trans*-substituted with respect to the carbinol center [15].

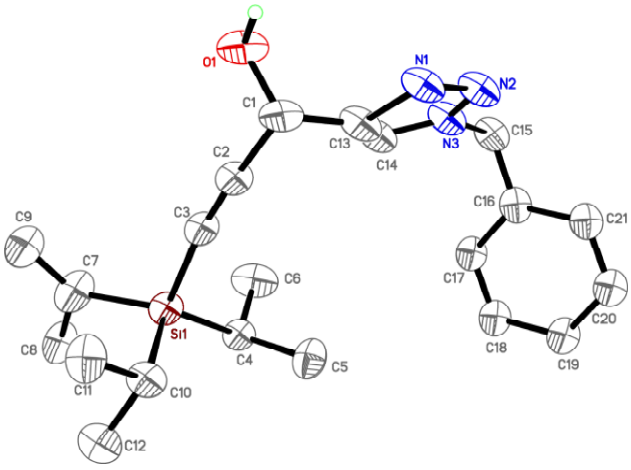


Figure 3. Molecular view of the X-ray crystal structure of the triazolyl-AC **5** (Scheme 3). For clarity, hydrogen atoms (except for that on O1) and disordered atoms are omitted (see Table 1 and CCDC no 1038853). Selected bond lengths (Å) and bond angles (°): C2-C3 = 1.194(7), C1-O1 = 1.425(7), C1-C2 = 1.486(7), C1-C13 = 1.464(12), C13-C14 = 1.381(16), O1-C1-C2 = 109.2(5), O1-C1-C13 = 115(2), C2-C1-C13 = 108.2(12), C1-C2-C3 = 176.2(6), C1-C13-C14 = 127.0(17).

The 1,4-disubstitution pattern has been confirmed by XRD analysis of a single crystal of **5** (**Figure 3**, **Table 1**). It can also be noted that the C-C(OH)-C carbinol angle is more acute in **5** than in the *n*-butyl-AC carbamate **2** (*ca* 108° *vs ca* 113°), and that the mean plane of the (disordered) triazole ring is almost perpendicular to the C(triazole)–C–OH plane (dihedral angle of *ca* 87°).

Conclusions

The disclosed results provide complementary information on the chemistry of the sp^3, *sp* and sp^2 series of *C*-substituted secondary terminal ACs. Although quite standard in terms of chemical structure, the triisopropylsilyl-penta-1,4-diyn-3-ol DAC **3b**, described here for the first time, is a more dissymmetrical and more robust equivalent of diethynylmethanol than the classical trimethylsilyl homologue **3a**: **3b** can therefore be considered as a potential key synthon for the versatile preparation of generic ACs with improved selectivity with respect to **3a**.

Experimental section.

General.

The following solvents were dried and distilled prior to use: THF and diethyl ether (Et_2O) over sodium/benzophenone, dichloromethane (DCM) over CaH_2. All other solvents, like petroleum ether (PE), and reagents were used as commercially available. 3-(Trimethylsilyl)- and 3-(triisopropylsilyl)-propiolaldehydes were

prepared using known procedures [6]. 1-(Trimethylsilyl)hept-1-yn-3-ol **1** was prepared by reaction of trimethylsilyl-propiolaldehyde with *n*-BuLi (instead of *n*-BuMgBr)[7]. Analytical thin-layer chromatography (TLC) was performed with Merck silica gel 60 F_{254} pre-coated plates. Chromatograms were observed under UV light and/or visualized by heating plates dipped in 10 % phosphomolybdic acid in EtOH, or in a $KMnO_4$ aqueous solution (for the triazole **5**). Column chromatography was carried out with SDS 35-70 mm flash silica gel. NMR spectra were recorded in $CDCl_3$ solutions on a Bruker Advance 300 instrument. ^1H and ^{13}C chemical shifts (δ) are given in ppm with positive values to high frequency relative to the tetramethylsilane resonances determined from the residual solvent peaks. Coupling constants *J* are given in Hertz. Mass spectrometry (MS) was performed on a ThermoQuest TSQ 7000 instrument, and high-resolution MS (HRMS) on a Thermo-Finnigan MAT 95 XL instrument. IR analyses were run on a Thermo-Nicolet Diamond ATR (4 cm^{-1} of resolution, 16 scans) equipped with a DTGS detector.

Experimental procedures and characterizations.

1-(Trimethylsilyl)hept-1-yn-3-yl-*N*-(naphthalen-1-yl) carbamate (**2**). Naphth-1-yl isocyanate (152 mg, 0.9 mmol, 1.5 equiv.) and DBU (9 mg, 0.06 mmol, 0.1 equiv.) in DCM were added to a solution of trimethylsilylhept-1-yn-3-ol **1** (110 mg, 0.6 mmol, 1 equiv.) in DCM (0.5 mL). After stirring overnight, water was added and the mixture extracted with DCM. After standard treatment of the combined organic layers, the crude product was purified by chromatography over silica gel (pentane/ Et_2O = 8/2) to give the carbamate **2** as a viscous oil (158 mg, 50 %), which crystallized with time.

1-[Tris(propan-2-yl)silyl]penta-1,4-diyn-3-ol (**3b**)**.** Ehynylmagnesium bromide (1 mL, 0.5 M in THF, 0.52 mmol, 1.1 equiv.) was added to a solution of 3-[tris(propan-2-yl)silyl]prop-2-ynal (100 mg, 0.47 mmol) in THF (10 mL) at 0°C, and the reaction mixture was stirred for 6 h at 0°C. After addition of saturated aqueous NH_4Cl, the mixture was partitioned with brine and Et_2O and the aqueous phase extracted with Et_2O. After standard treatment of the combined organic layers, chromatography of the crude product though silica gel (pentane/Et_2O = 15/1) gave **3b** as a colorless oil (78 mg, 70 %).

^1H NMR (300 MHz): δ = 1.09 (s, 21H), 2.55 (s, 1H), 2.56 (s, 1H), 5.14 (s, 1H); ^{13}C NMR (75 MHz): δ = 11.2, 18.6, 52.5, 72.6, 81.1, 86.5, 103.6; IR (neat): ν = 3312, 2943, 2892, 2866, 2177, 2125, 1463, 1384, 1367, 1289, 1044, 1017, 997, 919, 881, 672, 657, 591, 562, 504 cm^{-1}; MS (DCI, NH_3): *m/z* (%): 254.2 (90) $[M+NH_4]^+$, 236.2 (10) $[M]^+$.

1-[Tris(propan-2-yl)silyl]penta-1,4-diyn-3-yl 3,5-dinitrobenzoate (**4**)**.** To a solution of 1-[tris(propan-2-yl)silyl]penta-1,4-diyn-3-ol **3b** (100 mg, 0.42 mmol) in DCM (10 mL) were added successively: DCC (105 mg, 0.51 mmol,

1.1 equiv.), DMAP (17 mg, 0.14 mmol, 0.3 equiv.) and *m*-DNBA (108 mg, 0.51 mmol, 1.1 equiv.). After stirring at r.t. for 18 h, the mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with DCM (2 x10 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue over silica gel (R_f = 0.4, pentane/ Et_2O = 10/1), gave ester **4** as a colorless foam (145 mg, 80 %).

^{1}H NMR (400 MHz): δ = 1.08 (s, 21H), 2.69 (d, J = 4 Hz, 1H), 6.34 (d, J = 4 Hz, 1H), 9.20 (m, 3H), 9.26 (m, 2H); ^{13}C NMR (101 MHz): δ = 11.2, 18.6, 55.9, 75.1, 76.6, 90.4, 98.4, 123.0, 129.9, 133.1, 148.9, 161.0; IR (neat): ν = 3395, 3297, 3288, 3103, 2944, 2892, 2866, 2252, 2229, 2139, 2074, 1745, 1629, 1598, 1547, 1461, 1385, 1344, 1328, 1316, 1294, 1260, 1155, 1073, 1018, 978, 921, 883, 857, 820, 796, 769, 729, 721, 681, 645, 624, 607, 583, 562 cm^{-1}; MS (DCI, NH_3): *m/z* (%): 430.2 (100) $[M]^+$, 210.9 (100), 181.0 (5).

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-3-[tris(propan-2-yl)silyl]prop-2-yn-1-ol (**5**)**.** To a solution of 1-[tris(propan-2-yl)silyl]penta-1,4-diyn-3-ol **3b** (100 mg, 0.42 mmol, 1 equiv.) and benzyl azide (56 mg, 0.42 mmol, 1 equiv.) in DMF (8 mL) were added $CuSO_4$•$5H_2O$ (0.1 g), ascorbic acid (0.1 g), and H_2O (1 mL). The mixture was then stirred at r.t. until the terminal alkyne has disappeared (TLC monitoring, over nearly 6 h). Saturated aqueous NH_4Cl (10 mL) and Et_2O (10 mL) were added, and the organic phase was separated, washed with brine (2 x10 mL), and dried over $MgSO_4$. Purification by column chromatography (R_f = 0.5, Et_2O/pentane = 2/1) afforded the 1,2,3-triazolylcarbinol **5** as a white solid (108 mg, 70 %).

^{1}H NMR (400 MHz): δ = 1.03 (s, 21H), 2.76 (d, J = 4 Hz, 1H), 5.52 (s, 2H), 5.68 (d, J = 4 Hz, 1H), 7.27 (m, 2H), 7.37 (m, 3H), 7.49 (s, 1H); ^{13}C NMR (101 MHz): δ = 11.1, 18.5, 29.7, 54.4, 57.5, 88.1, 107.2, 121.4, 128.3, 128.9, 129.2, 134.1; IR (neat): ν = 3290, 3067, 3034, 2942, 2892, 2865, 2176, 1704, 1545, 1497, 1462, 1383, 1366, 1280, 1226, 1160, 1122, 1045, 996, 976, 919, 883, 822, 800, 769, 723, 678, 601, 592, 577, 532 cm^{-1}; MS (DCI, NH_3): *m/z* (%): 370.1 (100) $[MH]^+$, 367.8 (5), 326.1 (5), 188.0 (1), 108.0.

Crystallography.

X-ray intensity data of crystals of **2** and **5** were collected were collected at 193(2) K on a Bruker-AXS APEX II QUAZAR diffractometer equipped with a 30W air-cooled microfocus source, using MoKα radiation (λ = 0.71073Å). The data were integrated with SAINT, and an empirical absorption correction with SADABS was applied [16]. The structures were solved by direct methods (SHELXS-97) and refined using the least-squares method on F^2 [17]. All non-H atoms were refined with anisotropic displacement parameters. The H atoms were refined isotropically at calculated positions using a riding model. The hydroxyl H atom of **5**

was located in difference Fourier maps and included in the subsequent refinement without using restraints. Data are listed in Table 1.

CCDC-1038852 (**2**) and CCDC-1038853 (**5**) contain the supplementary crystallographic data, which can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Crystallographic data and structural refinement parameters for **2** and **5**.

	2	**5**
Chemical formula	$C_{21}H_{27}NO_2Si$	$C_{21}H_{31}N_3OSi$
*M*r	353.53	369.58
Crystal system	monoclinic	triclinic
Space group	*P* 2_1/c	*P* $\bar{1}$
a [Å]	7.7295(6)	8.043(2)
b [Å]	30.407(2)	11.428(3)
c [Å]	9.0824(7)	12.777(3)
α [°]	90	96.854(13)
β [°]	95.688(4)	101.838(10)
γ [°]	90	103.855(12)
V [Å^3]	2124.1(3)	1098.3(5)
Z	4	2
Reflections collected	28188	14592
Independent reflections	4072 [R(int) = 0.0403]	3556 [R(int) = 0.1855]
ρ_{calc} [g cm^{-3}]	1.105	1.118
μ ($Mo_{K\alpha}$) [mm^{-1}]	0.123	0.121
Crystal size (mm^3)	0.22 x 0.18 x 0.02	0.24 x 0.04 x 0.02
GOF on F²	1.068	0.964
R (I > 2σ(I))	0.0548	0.0851
*w*R² (all data)	0.1671	0.2446
Largest difference peak and hole [eÅ^{-3}]	0.374 and -0.510	0.204 and -0.219

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[14] M. Oukessou, *Alcynyl-TriAzolylCarbinols N-glycosylés* (*N-Glycoslated Alkynyl-TriazolylCarbinols*), Ph. D. dissertation, Université Paul Sabatier-Toulouse 3, in co-tutelle with the Université Sidi Mohamed Ben Abdellah, Fès, January 31st, 2014.

[15] This formal consideration had prompted investigations of biological activities of related N-glycosyl lipidic 1,2,3-triazolyl-alkynylcarbinol for the purpose of comparison with disubstituted AACs inspired from the natural eicos-(4*E*)-en-1-yn-3-ol (**Figure 1**) [5,14]. As no effect was detected on HCT 116 cells (IC_{50} > 50 μM), 1,2,3-triazolyl-alkynyl-carbinols cannot be considered as "AAC pharmacophores" for cytotoxicity. Nevertheless, lipidic N-glycosyl-1,2,3-triazolyl-alkenyl-carbinol parents were found to behave as inhibitors of a sphingosine kinase ($IC_{50} \approx 1$ μM on SK1): L. Brizuela, O. Cuvillier, M. Oukessou, Y. Genisson, R. Chauvin, *unpublished results*.

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