Tetrahedron 65 (2009) 7597–7602

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Click à la carte: robust semi-orthogonal alkyne protecting groups for multiple successive azide/alkyne cycloadditions

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ARTICLE INFO

Article history:
Received 29 May 2009
Received in revised form 23 June 2009
Accepted 25 June 2009
Available online 30 June 2009

Keywords:
CuAAC
Click chemistry
Protective groups
Iterative cycloadditions

ABSTRACT

We herein describe an in-depth screening and systematic comparison of five classical silyl alkyne protective groups, to evaluate their potential in the context of multiple successive copper (I)-catalyzed alkyne–azide cycloadditions (CuAAC). We confirm the relative sensitivity of TMS, especially under CuAAC conditions. The relative robustness of its higher analogues, and the discovery of mild silver-catalyzed deprotection conditions selective for TES compared to DPS or TIPS allowed us to design a strategy allowing three successive CuAAC on a single scaffold, as we have illustrated by the synthesis of a tris-triazolo model compound.

1. Introduction

Cu(I) catalysis of the Huisgen 1,3-dipolar cycloaddition reaction[1] of organic azides and terminal alkynes (CuAAC) was introduced in 2001 by Meldal and Tornøe.[2] Metal catalysis has transformed this cycloaddition into an essentially quantitative and regioselective 'click' reaction, as realized independently in the Meldal and the Sharpless laboratories.[3,4] CuAAC is extremely robust, tolerant of an extensive variety of functional groups, and orthogonal to most other chemistries. The 1,4-disubstituted-1,2,3-triazole formed is chemically and biologically stable, and thus constitutes an excellent bio-compatible linker. This heterocycle is also a valuable pharmacophore, partly as a consequence of its bioisostery with trans secondary amide bonds.[5] This exquisite combination explains the considerable interest for this reaction in most fields of chemistry and the growing prevalence of commercially available substrates.

Since 2004, many groups have focused on the extension of the potential of CuAAC by developing methods for multiple successive cycloadditions. This has allowed access to unprecedentedly complex and diverse structures for applications in material sciences,[6,7] supramolecular chemistry,[8,9] or biomacromolecule mimics synthesis.[10–13] Most examples of iterative triazole formations involve the repetition of a two-stage process consisting of a CuAAC followed by the introduction of a 'fresh' azide or alkyne on the ligation product. In many cases, this functionalization is achieved through a poorly chemoselective reaction such as ester,[14] ether[6c] or amide[5a,11] formation, or conversion of an alkyl halide,[6a,15] sulfonate[16] or alcohol[10] into an azide group. All these strategies suffer from their incompatibility with many unprotected functional groups and thus do not exploit the full potential of 'click' CuAAC. The use of a chemoselective, copper-catalyzed diazo transfer reaction[17] to convert a primary amine into an azide[9a] is a more general approach, as it is compatible with most non-amine substrates.

In 2006, we introduced a universal methodology based on a temporary trimethylsilyl (TMS) alkyne masking group[16,18] that can be readily removed by treatment with silver[19] or fluoride salts. These mild and very chemoselective deprotection conditions are fully compatible with most organic functionalities. It potentially allows for the iterative ligation of any unprotected fragments through successive CuAAC/protiodesilylation steps. We were delighted to see that our strategy was quickly adopted by other groups, for the synthesis of complex [4]rotaxanes from simple fragments,[8b] pseudo glycopeptides[12] or triazole-linked DNA analogues.[13b] The Achilles' heel of this procedure is the slow Cu(I)-catalyzed decomposition of the TMS group, that can become prominent when heating the reaction mixture, employing stoichiometric copper loadings or long reaction times.[13b,16,18,20] van Hest[7a] and Limberg/Hecht[21] independently improved our procedure using a tri-*iso*-propylsilyl (TIPS) masking group, which is considerably more stable than TMS, but still labile to a mild fluoride treatment. While this manuscript was in preparation, Carell described a combination of both TMS and TIPS for successive conjugations of an oligonucleotide[22] and Flood reported the successful use of a 2-(2-hydroxypropyl) group that can be cleaved under harsh basic conditions.[23] To extend the high potential of our

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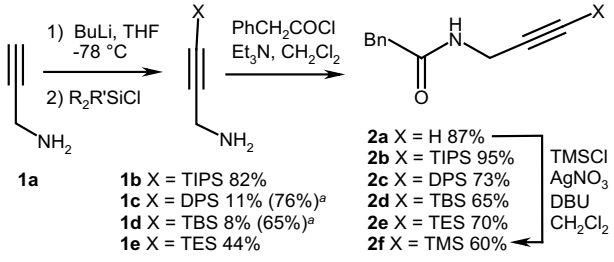
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.06.093

methodology, we decided to screen a range of commonly used alkyne protecting groups to check their compatibility with iterative CuAAC. Silyl groups are by far the most commonly used protection, and the only ones to date that can be cleaved under conditions mild enough to be compatible with a wide range of substrates.[24] Surprisingly, to the best of our knowledge a systematic comparison of the stabilities and deprotection conditions of the most common silyl alkyne protective groups has never been reported. Such an in-depth evaluation would be of a wide general interest, and will assist the design of orthogonal alkyne masking schemes by setting up rigorous conditions for selective cleavages. Beside the applications to iterative CuAAC, such orthogonalities could be valuable for other synthetic stategies involving multiple successive reactions of terminal alkynes, such as Sonogashira couplings[26] and Cadiot–Chodkiewicz[27] or Glaser-type reactions.[28]

2. Results and discussion

2.1. Synthesis of a range of silyl-protected alkynes

TMS is the most employed protective group, accounting for nearly 70% of the examples found in the literature.[29] We decided to compare it with TIPS (10%), triethylsilyl (TES), *tert*-butyldimethylsilyl (TBS) and *tert*-butyldiphenylsilyl (DPS), which we identified as the following four most commonly used alkyne protective groups. We synthesized the corresponding range of five silyl-protected alkynes **2b–f**. These model propargyl phenylacetamide structures were chosen for practical considerations concerning their syntheses, solubilities and TLC and HPLC detection. Propargylamine **1a** was converted into the *C*-silylated derivatives **1b-e** using standard procedures. Further reaction with phenylacetyl chloride furnished their respective phenylacetamides **2a–e**. A TMS group was cleanly installed on **2a** under mild silver(I)-catalyzed conditions[30] to give **2f** (Scheme 1).



Scheme 1. Synthesis of a range of silyl-protected alkynes. (a) The disappointing yields for **1c** and **1d** prompted us to use a multistep procedure adapted from Corriu.[25] See Experimental part for details.

2.2. Stability screening of silyl alkyne protecting groups

Compounds **2b–f** were first subjected to CuAAC-like conditions, using excess copper salts (Table 1, entry 1). The TMS derivative **2f** slowly decomposed into the terminal alkyne **2a**, fitting with what we[18] and others[13b,16,20] have already reported. In contrast, the higher analogues **2b–e** proved to be completely stable under similar conditions, demonstrating the potential of the TES, TBS, DPS and TIPS groups for multiple iterative triazole linkage formations. Compounds **2b–f** were then screened for their stability under a diverse range of common reaction conditions—e.g., oxidative, reductive, Lewis acid, Brønsted acid and base, and nucleophilic (Table 1, entries 2–6). Compounds **2b–e** were stable under all the conditions we tested, and the sensitivity of the TMS derivative **2f** was again demonstrated by it being partially cleaved by sodium borohydride in methanol (entry 2) or trifluoroacetic acid (entry 6).

We then screened different fluoride-mediated deprotection conditions. All the compounds **2b–f** were rapidly and quantitatively desilylated by treatment with excess tetra-*n*-butylbutylammonium fluoride (TBAF) in THF under anhydrous conditions (entry 7). As is well documented for silyl-based alcohol protecting groups, direct use of the commercially available TBAF trihydrate resulted in a considerable decrease in the reaction kinetics (entry 8). The TMS group (**2f**) was cleaved within two hours, and reactions slow down when increasing the steric hindrance around the silicon atom, ranging from 4 h for TES (**2e**) up to several days for TIPS (**2b**) or DPS (**2c**). Interestingly, buffering the inherent basicity of anhydrous fluoride anion by adding acetic acid to the reaction mixture led to clean deprotection within acceptable reaction times. This allows the use of such silyl-based alkyne masking groups for base-sensitive substrates (entry 9).

Table 1
Stability screening of the C–Si bond in compounds **2b–f**[a]

Conditions	% Cleaved C–Si bond				
	TIPS	DPS	TBS	TES	TMS
	2b	**2c**	**2d**	**2e**	**2f**
(1) Cu(I)[b] 2 equiv, aq ^{t}BuOH,[c] 20 h	0	0	0	0	38
(2) $NaBH_4$ 1 equiv, MeOH, 1 h	0	0	0	0	3
(3) *m*-CPBA 1 equiv, CH_2Cl_2, 20 h	0	0	0	0	0
(4) $BF_3{\cdot}Et_2O$ 1 equiv, CH_2Cl_2, 1 h	0	0	0	0	0
(5) Piperidine/DMF 2:8, 5 h	0	0	0	0	0
(6) TFA/CH_2Cl_2 1:1, 2 h	0	0	0	<1	10
(7) TBAF 3 equiv, THF,[d] 15 min	100	100	100	100	100
(8) TBAF·$3H_2O$ 3 equiv, THF[e]	100	100	100	100	100
(9) TBAF·AcOH 3 equiv, THF, 24 h	100	100	100	100	100[f]
(10) K_2CO_3 50 equiv, MeOH, 36 h	0	0	<1	>99	100
(11) Ag(I) 10 equiv, 8 h[g]	<1	<1	24	>99	100
(12) K_2CO_3 10 equiv, MeOH, 15 min	0	0	0	<1	>99
(13) Ag(I) 1 equiv, 48 h[g]	0	0	<1	47	>99

[a] All reactions were conducted at 0.01 M using standard quality solvents unless specified. RP-HPLC analyses were performed after an aqueous work up, see Supplementary data for details. Percentages refer to the detected amount of alkyne **2b**, other co-products never having been detected in more than trace amounts. '<1' refers to trace amounts of the desilylated product **2a** being detected.
[b] Cu(I) is generated in situ from $CuSO_4$ and Na ascorbate (1:2).
[c] ^{t}BuOH/H_2O 9:1.
[d] Anhydrous conditions.
[e] See text for details on reaction times.
[f] Reaction completed in 2 h.
[g] Solvent system: CH_2Cl_2/MeOH/H_2O 7:4:1.

2.3. Semi-orthogonal deprotections

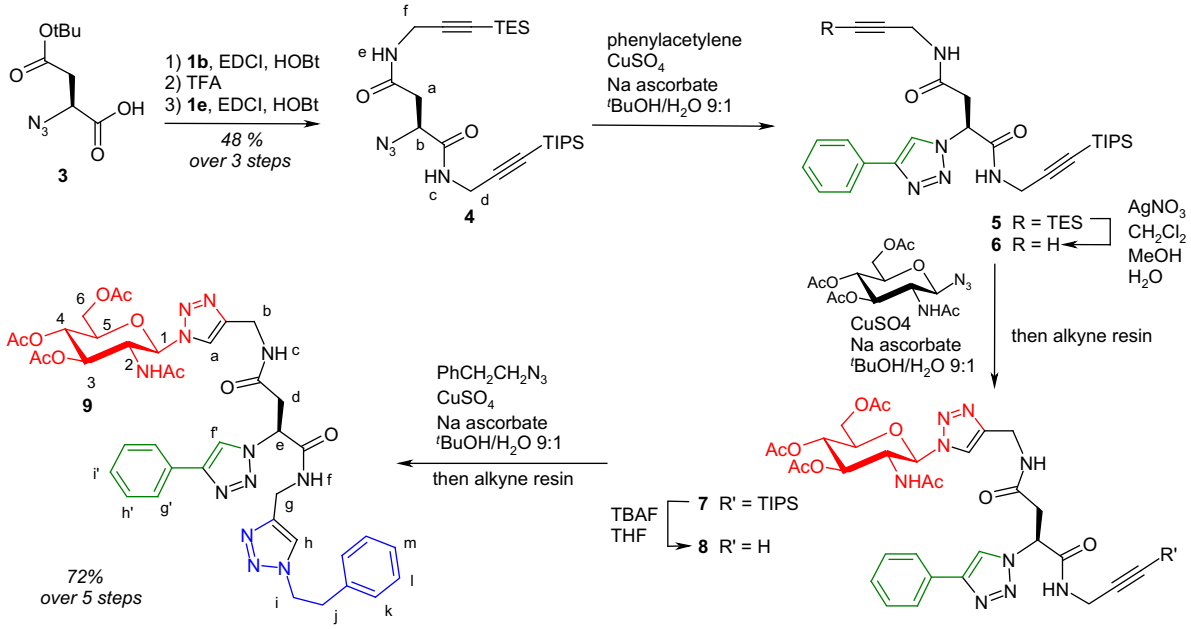
Though the selective cleavage of an alkyne/TMS versus other trialkylsilyl groups is well documented, much less is known about a possible selectivity between higher analogues. We found extremely difficult to set up rigorous conditions for selective TBAF cleavage of TES compared to TIPS, TBS or DPS, essentially due to the hypersensitivity of the fluoride anion to its environment. Screening for other conditions, excellent selectivities were obtained using excess potassium carbonate in methanol (entry 10).[31] We have also demonstrated the possible use of silver salts for TES versus TIPS or DPS cleavage (entry 11). This constitutes a valuable alternative for base-sensitive substrates. Finally, we have tested comparable conditions for TMS versus TES deprotection (entry 13), that led to poor selectivity.

2.4. Proof of concept for multiple successive CuAAC using a combination of silyl protecting groups

These screening results suggest the TIPS/TES or DPS/TES protecting schemes as ideal for demanding, multiple successive CuAAC applications. In order to test the potential of these combinations, we synthesized a simple scaffold (**4**) combining a free azide and both TES- and TIPS-protected alkynes, from the readily available aspartic acid derivative **3**[32] (Scheme 2). Compound **4** was reacted with phenylacetylene under standard CuAAC conditions to quantitatively give the corresponding triazole **5**. Excess alkyne was

removed by evaporation, then treatment with silver (I) salts furnished the mono-deprotected intermediate **6** in excellent yield and purities. Only trace amounts of the bis-deprotected compound (<1%, based on the integration of the HPLC peaks) were detected in the crude reaction mixture, consistent with our optimization study. Cu(I)-catalyzed reaction with an excess of β-1-azido-3,4,6-tri-*O*-acetyl-*N*-acetyl-D-glucosamine[33] gave the corresponding bis-triazolo compound **7**. Excess azide was removed by further reaction with an excess of an alkyne supported on a water-compatible PEGA® resin followed by filtration. Deprotection of the remaining silyl protecting group, TIPS, was performed using TBAF in THF to give **8**. A final cycloaddition reaction with homobenzyl azide[34] finally led to the tris-triazolo derivative **9** in a satisfactory purity. Short-path silica gel column chromatography purification finally yielded pure **9** in an excellent 72% overall yield from **4**.

were prepared according to literature procedures. Amino PEGA® 800 resin (0.4 mmol/g) was purchased from polymer laboratories. Flash column chromatographies were carried out using Kiesegel C60 (Merck, Germany) as the stationary phase, and TLC were performed on precoated silica gel plates (0.25 mm thick, $60F_{254}$, Merck, Germany) and observed under UV light at 254 nm. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV500 instrument, at a constant temperature of 25 °C. Chemical shifts are reported in parts per million from low to high field and referenced to TMS. Optical rotations were measured at 20 °C with a Perkin-Elmer model 141 polarimeter. Electrospray mass spectrometry (ESI-MS) analyses were performed on a triple quadrupole mass spectrometer (Quattro II, Micromass, Manchester, UK). MALDI-TOF mass spectrometry was performed on an Autoflex instrument (Bruker Daltonics, Bremen, Germany) and HRMS was performed on a Q-Tof micro (Waters).



Scheme 2. Synthesis of the tris-triazolo model compound **9** through three successive CuAAC on a single scaffold **3**.

3. Conclusion

In conclusion, this study has revisited the use of silyl protecting groups for terminal alkynes, within the context of their use as temporary masking groups to enable multiple successive CuAAC. A systematic screening of their stability towards a wide range of common reagents confirmed the problematic sensitivity of TMS, especially under CuAAC conditions. The relative robustness of its higher analogues, and the discovery of mild silver-catalyzed deprotection conditions selective for TES compared to DPS or TIPS allowed us to design a strategy allowing three successive CuAAC on a single scaffold, as we have illustrated by the synthesis of a tris-triazolo model compound **9**.

4. Experimental section

4.1. General

Unless stated otherwise, all reagents and anhydrous solvents were purchased from Aldrich Chemicals and used without further purification. The azido acid **3**,[32] *N*,*N*-bis(trimethylsilyl)propargylamine[25] and β-1-azido-3,4,6-tri-*O*-acetyl-*N*-acetyl-D-glucosamine[33]

4.2. 3-(Triisopropylsilyl)prop-2-yn-1-amine (1b)

A solution of propargylamine (864 mg, 16 mmol) in anhydrous THF (40 mL) was cooled to −78 °C. *n*-BuLi (6.4 mL, 2.5 M in hexanes, 16 mmol, 1.0 equiv) was added dropwise. The solution was allowed to stir for 15 min at −78 °C, then was warmed to 0 °C and TIPS-Cl was added dropwise (4 mL, 19 mmol, 1.2 equiv). The reaction mixture was stirred for 2 h at rt then quenched with an aqueous $NaHCO_3$ saturated solution (15 mL). The aqueous layer was extracted with EtOAc (3×20 mL), the combined organic fractions were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was then purified by flash chromatography on silica gel (eluent: petroleum ether/EtOAc 95:5 then 1:1) to give **1b** as an orange oil (2.73 g, 82%). ^1H NMR (500 MHz, $CDCl_3$): δ 3.44 (s, 2H, CH_2), 1.76–1.28 (m, 21H, ^iPr). ^{13}C NMR (125 MHz, $CDCl_3$): δ 109.4 (C), 82.7 (C), 32.7 (CH_2), 18.8 (CH_3), 11.5 (CH). ESI-HRMS: M=212.1827 (calcd for $C_{12}H_{26}NSi$, 212.1835).

4.3. General procedure for the synthesis of propargylamines 1c and 1d

A solution of *N*,*N*-bis(trimethylsilyl)propargylamine[25] (500 mg, 2.5 mmol) in anhydrous THF (5 mL) was cooled to −78 °C, *n*-BuLi

was added dropwise (1 mL, 2.5 M in hexanes, 2.5 mmol, 1.0 equiv). The solution was allowed to stir at −78 °C for 15 min, then was warmed to 0 °C and a solution of TBS-Cl for **1c** or DPS-Cl for **1d** (3 mmol, 2 equiv) in anhydrous THF (2 mL) was added dropwise. The reaction mixture was stirred for 2 h at rt then quenched with a 1 M aqueous HCl solution (15 mL). The aqueous layer was extracted with EtOAc (3×5 mL) then its pH was adjusted to 9–10 with an aqueous $NaHCO_3$ saturated solution. The aqueous layer was extracted with EtOAc (3×10 mL), the combined organic fractions were dried over Na_2SO_4, filtered and concentrated in vacuo to give pure **1c** or **1d** without the need of any further purification.

*4.3.1. 3-(tert-Butyl(diphenyl)silyl)prop-2-yn-1-amine (**1c**)*

Pale oil (559 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80–7.37 (m, 10H, Ph), 3.62 (s, 2H, CH_2), 1.00 (s, 9H, ^{t}Bu). ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.8 (C), 133.6 (C), 129.7 (CH), 127.9 (CH), 111.5 (C), 82.1 (C), 32.8 (CH_2), 27.3 (CH_3), 18.6 (C). ESI-HRMS: M=294.1668 (calcd for $C_{19}H_{24}NSi$, 294.1678).

*4.3.2. 3-(tert-Butyl(dimethyl)silyl)prop-2-yn-1-amine (**1d**)*

Pale oil (276 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.45 (s, 2H, CH_2), 0.94 (s, 9H, ^{t}Bu), 0.10 (s, 6H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 108.1 (C), 84.9 (C), 32.6 (CH_2), 26.2 (CH_3), 16.7 (C), −4.4 (CH_3). ESI-HRMS: M=170.1351 (calcd for $C_9H_{20}NSi$, 170.1365).

4.4. 3-(Triethylsilyl)prop-2-yn-1-amine (1e)

A solution of propargylamine (368 mg, 6.7 mmol) in anhydrous THF (10 mL) was cooled to −78 °C. *n*-BuLi (2.6 mL, 2.5 M in hexanes, 6.7 mmol, 1.0 equiv) was added dropwise. The solution was allowed to stir for 15 min at −78 °C, then was warmed to 0 °C and TESCl (1.34 mL, 8 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred for 2 h at rt then quenched with an aqueous NH_4Cl solution (15 mL). After removal of THF by evaporation under vacuum, the aqueous slurry was diluted with 20 mL of a 1 M HCl solution. The aqueous phase was then extracted with EtOAc (3×10 mL) then pH was adjusted to 10 with an aqueous $NaHCO_3$ saturated solution. The aqueous layer was extracted with EtOAc (3×10 mL), the combined organic fractions were dried over Na_2SO_4, filtered and concentrated in vacuo to give **1e** as an orange oil (187 mg, 44%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.45 (s, 2H, CH_2NH$_2$), 0.99 (t, 9H, $J_{CH3-CH2}$=8.0 Hz, CH_3), 0.60 (q, 6H, CH_2CH$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 108.6 (C), 84.1 (C), 32.6 (CH_2), 7.6 (CH_3), 4.6 (CH_2). ESI-HRMS: M=170.1356 (calcd for $C_9H_{20}NSi$, 170.1365).

4.5. General procedure for the syntheses of propargyl phenylacetamides 2a–e

To an ice cooled solution of propargylamine derivatives **1a**–**e** (2.3 mmol) and ^{i}Pr$_2$NEt (618 μL, 3.5 mmol, 1.5 equiv) in CH_2Cl_2 (25 mL) was added phenylacetyl chloride (472 μL, 3.5 mmol, 1.5 equiv) dropwise and the solution was allowed to stir at rt for 2 h. After completion of the reaction (TLC), the solution was diluted with EtOAc and washed consecutively with an aqueous $NaHCO_3$ saturated solution (2×10 mL) and brine (2×10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was then purified by flash chromatography on silica gel (petroleum ether/EtOAc) to furnish the desired product.

*4.5.1. 2-Phenyl-N-[prop-2-ynyl]acetamide (**2a**)*

White amorphous solid (77%). Spectrometric data were found to be identical to literature data.[35]

*4.5.2. 2-Phenyl-N-[3-(triisopropylsilyl)prop-2-ynyl] acetamide (**2b**)*

White amorphous solid (95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H, Ph), 5.48 (br t, 1H, NH), 4.06 (d, 2H, J_{CH2-NH}=5.0 Hz, CH_2NH), 3.61 (s, 2H, CH_2Ph), 1.03 (s, 21H, ^{i}Pr). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5 (C), 134.7 (C), 129.6 (CH), 129.4 (CH), 129.3 5 (CH), 129.1 (CH), 127.7 (CH), 103.0 (C), 84.9 (C), 43.8 (CH_2), 30.7 (CH_2), 18.7 (CH_3), 11.3 (CH). ESI-HRMS: M=330.2256 (calcd for $C_{20}H_{32}NOSi$, 330.2253).

4.5.3. 2-Phenyl-N-[3-(tert-butyl(diphenyl)silyl)prop-2-ynyl]acetamide (2c)

White amorphous solid (73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73–7.71 (m, 5H, Ph), 7.43–7.27 (m, 10H, 2Ph), 5.61 (br t, 1H, NH), 4.21 (d, 2H, J_{CH2-NH}=5.0 Hz, CH_2NH), 3.64 (s, 2H, CH_2Ph), 1.05 (s, 9H, ^{t}Bu). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5 (C), 135.7 (CH), 134.6 (C), 133.0 (C), 129.7 (CH), 129.6 (CH), 129.4 (CH), 128.9 5 (CH), 127.9 (CH), 127.7 (CH), 105.3 (C), 84.1 (C), 43.7 (CH_2), 30.7 (CH_2), 27.1 (CH_3), 18.7 (C). ESI-HRMS: M=412.2104 (calcd for $C_{27}H_{30}NOSi$, 412.2097).

*4.5.4. 2-Phenyl-N-[3-(tert-butyl(dimethyl)silyl)prop-2-ynyl]acetamide (**2d**)*

White amorphous solid (65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.26 (m, 5H, Ph), 5.48 (br t, 1H, NH), 4.04 (d, 2H, J_{CH2-NH}=5.0 Hz, CH_2NH), 3.60 (s, 2H, CH_2Ph), 0.90 (s, 9H, ^{t}Bu), 0.07 (s, 6H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5 (C), 134.7 (C), 129.6 (CH), 129.3 (CH), 127.7 (CH), 101.8 (C), 87.0 (C), 43.8 (CH_2), 30.6 (CH_2), 26.2 (CH_3), 16.6 (C), −4.6 (CH_3). ESI-HRMS: M=288.1784 (calcd for $C_{17}H_{26}NOSi$, 288.1784).

*4.5.5. 2-Phenyl-N-[3-(triethylsilyl)prop-2-ynyl] acetamide (**2e**)*

White amorphous solid (70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H, Ph), 5.52 (br t, 1H, NH), 4.05 (d, 2H, J_{CH2-NH}=5.0 Hz, CH_2NH), 3.60 (s, 2H, CH_2Ph), 0.952 (t, 9H, $J_{CH3-CH2}$=8.0 Hz, CH_3), 0.57 (q, 6H, $J_{CH2-CH3}$=8.0 Hz, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5 (CH), 134.7 (CH), 129.6 (CH), 129.2 (CH), 127.6 (CH), 102.4 (C), 86.1 (C), 43.8 (CH_2), 30.6 (CH_2), 7.5 (CH_3), 4.4 (CH_2). ESI-HRMS: M=288.1791 (calcd for $C_{17}H_{26}NOSi$, 288.1784).

4.6. 2-Phenyl-*N*-[3-(trimethylsilyl)prop-2-ynyl] acetamide (2f)

To a suspension of $AgNO_3$ (23 mg, 0.144 mmol, 0.1 equiv) in CH_2Cl_2 (5 mL) were consecutively added *N*-propargylphenylacetamide **2a** (250 mg, 1.44 mmol), chlorotrimethysilane (258 μL, 1.73 mmol, 1.2 equiv) and DBU (258 μL, 1.73 mmol, 1.2 equiv) and the solution was allowed to stir under reflux for 24 h. The solution was diluted with CH_2Cl_2 and washed consecutively with a saturated aqueous solution of $NaHCO_3$ (3×5 mL), a 1 M HCl solution (3×5 mL) and water (1×5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/EtOAc 9:1) to afford the product **2f** as a white solid (210 mg, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.28 (m, 5H, Ph), 5.50 (br t, 1H, NH), 4.04 (d, 2H, J_{CH2-NH}=5.5 Hz, CH_2NH), 3.59 (s, 2H, CH_2Ph), 0.15 (s, 9H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5 (C), 134.6 (C), 129.6 (CH), 129.2 (CH), 127.6 (CH), 101.2 (C), 88.6 (C), 43.9 (CH_2), 30.5 (CH_2), −0.1 (CH_3). ESI-HRMS: M=246.1318 (calcd for $C_{14}H_{20}NOSi$, 246.1314).

4.7. (*S*)-2-Azido-*N*-4-(3-triethylsilyl-prop-2-ynyl)-*N*-1-(3-triisopropylsilyl-prop-2-ynyl)-succinamide (4)

To an ice cooled solution of 2-azido-4-*tert*-butoxy-4-oxobutanoic acid **3**[32] (500 mg, 2.32 mmol), **1b** (737 mg, 3.48 mmol, 1.5 equiv), HOBt (532 mg, 3.48 mmol, 1.5 equiv) and ^{i}Pr$_2$NEt (810 μL, 4.64 mmol, 2 equiv) in CH_2Cl_2 (5 mL) was added EDCI portionwise (668 mg, 3.48 mmol, 1.5 equiv) and the solution was allowed to stir overnight. The solution was then diluted with EtOAc and washed consecutively with a 1 M HCl solution (3×5 mL), a saturated aqueous solution of $NaHCO_3$ (3×5 mL), and water (1×5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by

flash chromatography on silica gel (eluent: petroleum Ether/EtOAc 8:2) to afford *tert*-butyl (S)-3-azido-4-oxo-4-{[3-(triisopropylsilyl)-prop-2-ynyl]amino}butanoate as a yellowish oil (210 mg, 60%). $[\alpha]_D^{20}$ −21.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.63 (s, 1H, Hc), 4.40 (dd, 1H, J_{CH-CH}=3.5 Hz, J_{CH-CH}=9.0 Hz, Hb), 4.14 (dd, 1H, J_{CH-CH}=17.7 Hz, J_{CH-NH}=5.3 Hz, Hd_1), 4.10 (dd, 1H, J_{CH-CH}=17.7 Hz, J_{CH-NH}=5.3 Hz, Hd_2), 3.06 (dd, 1H, J_{CH-CH}=17.5 Hz, J_{CH-CH}=3.5 Hz, Ha_1), 2.62 (dd, 1H, J_{CH-CH}=17.5 Hz, J_{CH-CH}=9.0 Hz, Ha_2), 1.49 (s, 18H, ^{i}Pr), 1.07 (s, 9H, ^{t}Bu). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5 (C), 168.0 (C), 102.2 (C), 85.6 (C), 82.2 (C), 60.6 (CH), 38.6 (CH_2), 30.7 (CH_2), 28.2 (CH_3), 18.7 (CH_3), 11.1 (CH). ESI-HRMS: M=431.2438 (calcd for C20H36 N_4O_3Si, 431.2454).

To *tert*-butyl (*S*)-3-azido-4-oxo-4-{[3-(triisopropylsilyl) prop-2-ynyl]amino}butanoate (137 mg, 0.332 mmol) was slowly added 3 mL TFA at 0 °C and the solution was allowed to stir at 0 °C for 5 min. TFA was then removed in vacuo at 0 °C to afford (*S*)-3-azido-4-oxo-4-{[3-(triisopropylsilyl)prop-2-ynyl] amino}butanoic acid as a yellowish oil (117 mg, 100%). $[\alpha]_D^{20}$ −37.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72 (t, 1H, J_{CH2-NH}=5.0 Hz, Hc), 4.46 (dd, 1H, J_{CH-CH2}=3.5 Hz, J_{CH-CH2}=9.0 Hz, Hb), 4.16 (dd, 1H, J_{CH2-NH}=18.0 Hz, J_{CH2-NH}=5.0 Hz, Hd_1), 4.10 (dd, 1H, J_{CH2-NH}=18.0 Hz, J_{CH2-NH}=5.0 Hz, Hd_2), 3.19 (dd, 1H, J_{CH2-CH}=18.0 Hz, J_{CH2-CH}=3.5 Hz, Ha_1), 2.75 (dd, 1H, J_{CH2-CH}=18.0 Hz, J_{CH-CH2}=9.0 Hz, Ha_2), 1.07 (s, 18H, ^{i}Pr). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9 (C), 167.9 (C), 101.9 (C), 85.9 (C), 60.1 (CH), 37.1 (CH_2), 30.9 (CH_2), 18.7 (CH_3), 11.3 (CH). ESI-HRMS: M=353.2008 (calcd for $C_{16}H_{29}N_4O_3Si$, 353.2009).

To an ice cooled solution of (*S*)-3-azido-4-oxo-4-{[3-(triisopropylsilyl)prop-2-ynyl]amino}butanoic acid (88 mg, 0.25 mmol), **1e** (62.7 mg, 0.37 mmol, 1.5 equiv), HOBt (56.6 mg, 0.37 mmol, 1.5 equiv), and ^{i}Pr$_2$NEt (87 μL, 0.5 mmol, 2 equiv) in CH_2Cl_2 (5 mL) was added EDCI portionwise (71 mg, 0.37 mmol, 1.5 equiv) and the solution was allowed to stir at rt overnight. The solution was then diluted with EtOAc and washed consecutively with a 1 M HCl solution (3×5 mL), a saturated aqueous solution of $NaHCO_3$ (3×5 mL), and water (1×5 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/EtOAc 8:2) to afford **4** as a yellowish oil (100 mg, 80%). $[\alpha]_D^{20}$ +3.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80 (br t, 1H, J_{CH2-NH}=5.0 Hz, Hc), 6.04 (br t, 1H, He), 4.47 (dd, 1H, J_{CH-CH2}=4.0 Hz, J_{CH-CH2}=8.0 Hz, Hb), 4.18–4.05 (m, 4H, Hg, Hd), 3.00 (dd, J_{CH2-CH}=15.5 Hz, J_{CH2-CH}=4.0 Hz, Ha_1), 2.56 (dd, 1H, *J*=15.5 Hz, J_{CH-CH2}=8.0 Hz, Ha_2), 1.80 (s, 18H, ^{i}Pr), 0.98 (t, 9H, $J_{CH3-CH2}$=15.5 Hz, CH_3CH_2), 0.60 (q, 6H, CH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6 (C), 168.4 (C), 102.1 (C), 101.8 (C), 86.6 (C), 85.7 (C), 60.2 (CH), 38.8 (CH_2), 18.8 (CH_3), 11.3 (CH), 7.6 (CH_3), 4.4 (CH_2). ESI-HRMS: M=504.3184 (calcd for $C_{25}H_{46}N_5O_2Si_2$, 504.3190).

4.8. Synthesis of 9 from 4 through three successive cycloadditions

Compounds **5**–**8** were not purified by chromatography nor fully characterized. See the HPLC traces from the crude reaction mixtures in Supplementary data.

*4.8.1. (S)-2-(4-Phenyl-[1,2,3]triazol-1-yl)-N-4-(3-triethyl silyl-prop-2-ynyl)-N-1-(3-triisopropylsilyl-prop-2-ynyl)-succinamide (**5**)*

To a solution of **4** (96 mg, 0.19 mmol) and phenylacetylene (59 mg, 0.29 mmol, 1.5 equiv) in *tert*-butanol (1.9 mL) under an argon athmosphere was added a solution of sodium ascorbate (38 mg, 0.19 mmol, 1 equiv) in water (0.2 mL) and a solution of $CuSO_4$ (24 mg, 0.095 mmol, 0.5 equiv) in water (0.2 mL) consecutively and the solution was allowed to stir for 16 h. The solution was then diluted with EtOAc and washed consecutively with a 1 M HCl solution (3×5 mL), a saturated aqueous solution of $NaHCO_3$ (3×5 mL), and a saturated solution of aqueous EDTA (1×5 mL). The organic phase was filtered, dried over $MgSO_4$ and concentrated in vacuo to remove excess phenylacetylene (TLC) and afford the desired product **5**.

*4.8.2. (S)-2-(4-Phenyl-[1,2,3]triazol-1-yl)-N-4-prop-2-ynyl-N-1-(3-triisopropylsilyl-prop-2-ynyl)-succinamide (**6**)*

Crude **5** (assumed 0.19 mmol) in CH_2Cl_2/MeOH/H_2O (7:4:1) (14 mL) was added a solution of silver nitrate (327 mg, 1.9 mmol, 10 equiv) in the same solvent mixture (5 mL). The resulting mixture was then stirred at rt for 8 h. An aqueous saturated solution of NH_4Cl (5 mL/mmol) was added. The resulting mixture was then extracted three times with CH_2Cl_2 (5 mL/mmol). The combined organic layers were dried over $MgSO_4$, filtered, filtered over Celite and concentrated in vacuo.

*4.8.3. (S)-N-4-(1-[2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranose]-[1,2,3]triazol-4-ylmethyl)-2-(4-phenyl-[1,2,3]triazol-1-yl)-N-1-(3-triisopropylsilyl-prop-2-ynyl)-succinamide (**7**)*

To a solution of **6** (assumed 0.19 mmol) and β-1-azido-3,4,6-tri-*O*-acetyl-*N*-acetyl-D-glucosamine[33] (106 mg, 1.5 equiv) in *tert*-butanol (1.8 mL) under an argon athmosphere was added a solution of sodium ascorbate (38 mg, 0.19 mmol, 1 equiv) in water (0.2 mL) and a solution of $CuSO_4$ (24 mg, 0.095 mmol, 0.5 equiv) in water (0.2 mL) consecutively. The solution was allowed to stir for 4 h at rt. An alkyne-derivatized resin, prepared through standard HATU/DIEA/DMF coupling of pentynoic acid with amino PEGA® 800 (substitution: 0.4 mmol/g) was added (667 mg, 0.57 mmol/g, 0.19 mmol, 1 equiv) and the reaction mixture stirred for 16 h at rt. The solution was filtrated, then diluted with EtOAc and washed consecutively with a 1 M HCl solution (3×5 mL), a saturated aqueous solution of $NaHCO_3$ (3×5 mL), and a saturated solution of aqueous EDTA (1×5 mL). The organic phase was filtered, dried over $MgSO_4$ and concentrated in vacuo to afford the crude desired product **7**.

*4.8.4. (S)-N-4-(1-[2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranose]-[1,2,3]triazol-4-ylmethyl)-2-4-(phenyl-[1,2,3]triazol-1-yl)-N-1-prop-2-ynyl-succinamide (**8**)*

To a solution of **7** (assumed 0.19 mmol) in anhydrous THF (1.5 ml) was added a solution of TBAF trihydrate (90 mg, 0.29 mmol, 1.5 equiv) in anhydrous THF (0.4 ml) and the mixture was allowed to stir 16 h at rt. The solution was diluted with a 0.1 M HCl solution (5 mL) then extracted with a $CHCl_3$/^{i}PrOH (3:1) mixture (5×3 mL). The organic phase was filtered, dried over $MgSO_4$ and concentrated in vacuo. Crude **8** was directly engaged in the next step.

*4.8.5. N-4-(1-[2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranose]-[1,2,3]triazol-4-ylmethyl)-N-1-(1-phenethyl-1H-[1,2,3]triazol-4-ylmethyl)-2-(S)-(4-phenyl-[1,2,3]triazol-1-yl)-succinamide (**9**)*

To a solution of **8** (assumed 0.19 mmol) and (2-azidoethyl)benzene (42 mg, 0.29 mmol, 1.5 equiv) in *tert*-butanol (1.8 mL) under an argon athmosphere was added a solution of sodium ascorbate (38 mg, 0.19 mmol, 1 equiv) in water (0.2 mL) and a solution of $CuSO_4$ (24 mg, 0.095 mmol, 0.5 equiv) in water (0.2 mL) consecutively. The solution was allowed to stir for 4 h at rt. Alkyne-derivatized resin was added (667 mg, 0.57 mmol/g, 0.19 mmol, 1 equiv) and the reaction mixture stirred for 16 h at rt. The solution was filtrated, then diluted with EtOAc (25 mL) and washed consecutively with a 1 M HCl solution (5 mL), a saturated aqueous solution of $NaHCO_3$ (5 mL), and a saturated solution of aqueous EDTA (5 mL). The organic phase was filtered, dried over $MgSO_4$ and concentrated to afford the crude desired product. Short path flash chromatography on silica gel (eluent: gradient of MeOH in CH_2Cl_2, from 5% to 12%) finally furnished the pure tris-triazolo compound **9** as a white amorphous solid (117 mg, 72%). $[\alpha]_D^{20}$ −19.9 (*c* 0.8, $CHCl_3$/MeOH 1:1). ^{1}H NMR (500 MHz, $(CD_3)_2SO$): (53:47 mixture of two rotamers) δ 9.01 (br t, 1H, J_{CH2-NH}=5.0 Hz, Hc or Hf), 8.63 (br t, 1H,

J_{CH2-NH}=5.0 Hz, Hf or Hc), 8.58 (s, 1H, Hf′), 8.07 (d, 1H, J_{H2-NH}= 9.0 Hz, NHAc), 8.049 (s, 0.53H, Hh_M or Ha_M), 8.035 (s, 0.47H, Hh_m or Ha_m), 7.86 (br d, 2H, $J_{Hg'-Hh'}$=7.5 Hz, Hg′), 7.85 (s, 1H, Ha or Hh), 7.45 (br dd, 2H, $J_{Hh'-Hi'}$ ~ $J_{Hh'-Hg'}$=7.5 Hz, Hh′), 7.34 (t, 1H, Hi′), 7.25 (br t, 2H, J_{Hl-Hk}=J_{Hl-Hm}=7.0 Hz, Hl), 7.19 (t, 1H, Hm), 7.17 (br d, 2H, Hk), 6.083 (d, 0.53H, J_{H1-H2}=9.5 Hz, $H1_M$), 6.078 (d, 0.47H, J_{H1-H2}= 9.5 Hz, $H1_m$), 5.72 (br dd, 1H, J_{He-Hd}=7.5 Hz, He), 5.352 (dd, 0.53H, J_{H3-H4} ~ J_{H3-H2}=9.5 Hz, $H3_M$), 5.347 (dd, 0.47H, J_{H3-H4} ~ J_{H3-H2}= 9.5 Hz, $H3_m$), 5.065 (dd, 0.53H, J_{H4-H5}=9.5 Hz, $H4_M$), 5.059 (dd, 0.47H, J_{H4-H5}=9.5 Hz, $H4_m$), 4.55 (br t, 1H, J_{Hi-Hj}=7.0 Hz, Hi), 4.57–4.48 (m, 1H, H2), 4.35–4.16 (m, 3H, Hb or Hg, H5), 4.31 (br t, 2H, Hg or Hb), 4.128 (dd, 0.53H, J_{H6a-H5}=5.0 Hz, $J_{H6a-H6b}$=12.0 Hz, $H6a_M$), 4.122 (dd, 0.47H, J_{H6a-H5}=5.0 Hz, $J_{H6a-H6b}$=12.0 Hz, $H6a_m$), 4.01 (br dd, 1H, J_{H6b-H5}=7.0 Hz, H6b), 3.17 (br dd, 1H, $J_{Hda-Hdb}$=16.0 Hz, Hda), 3.12–3.06 (m, 1H, Hdb), 3.11 (t, 2H, Hj), 2.01 (s, 3H, AcO), 1.97 (s, 3H, AcO), 1.94 (s, 3H, AcO), 1.58 (s, 3H, AcNH). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ 170.0 (C), 169.6 (C), 169.51 and 169.50 (CO), 169.3 (C), 168.0 and 167.9 (CO), 167.10 and 167.08 (CO), 146.1 (C), 144.8 (C), 144.0 (C), 137.6 (C), 130.6 (C), 128.9 (CH), 128.6 (CH), 128.4 (CH), 127.9 (CH), 126.6 (CH), 125.1 (CH), 122.8 (CH), 121.65 and 121.57 (CH), 121.05 (CH), 120.99 (CH), 84.6 (CH), 73.4 (CH), 72.4 (CH), 68.0 (CH), 61.8 (CH_2), 59.6 (CH), 52.2 (CH), 50.4 (CH_2), 36.9 (CH_2), 35.7 (CH_2), 34.7 (CH_2), 34.1 (CH_2), 22.4 (CH_3), 20.5 (CH_3), 20.4 (CH_3), 20.3 (CH_3). ESI-HRMS: M=855.3546 (calcd for $C_{40}H_{47}N_{12}O_{10}$, 855.3538).

Acknowledgements

I.E.V. thanks the Région Centre Council for a PhD fellowship. This work was supported by grants from ARC Grand-Ouest, Fondation pour la Recherche Médicale (comité du Loiret) and La Ligue Contre le Cancer (comité du Loiret). We are grateful to Guillaume Gabant (CBM) and Bertand Legeret (CRMP, Aubière) for recording the MS spectra and to Hervé Meudal for recording the NMR spectra. We thank Dr. Drew Thomson for proofreading the manuscript.

Supplementary data

Detailed experimental procedures for the reactions listed in Table 1, kinetic curves from the selective deprotections depicted in Part **2.4**, copies of the ^{1}H and ^{13}C HPLC traces for crude **5**–**9**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.093.

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