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Synthesis of Azide-Alkyne Fragments for "Click" Chemical Applications. Part 2. Formation of Oligomers from Orthogonally Protected Chiral Trialkylsilylhomopropargyl Azides and Homopropargyl Alcohols

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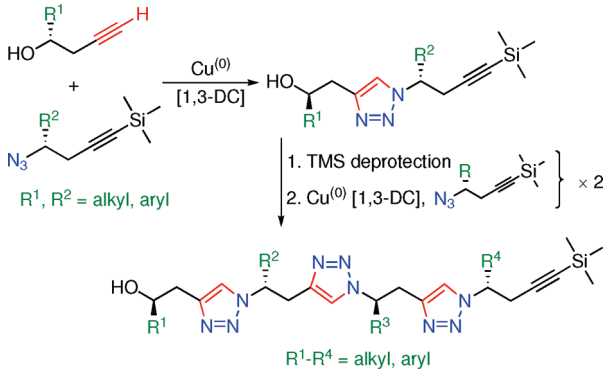

A small library of chiral, β^3-substituted homopropargyl alcohols and chiral β^3-substituted trimethylsilylhomopropargyl azides were generated starting from natural L-amino acids. The free alkynes and azides were then coupled, using a Huisgen 1,3-dipolar cycloaddition, to provide chiral oligomeric 1,4-disubstituted-1,2,3-triazoles as potential peptidomimetic compounds. The work is an extension to the previous synthesis of racemic, orthogonally protected 1,4-disubstituted-1,2,3-triazoles from the corresponding α-substituted propargyl alcohols and α-substituted trialkylsilylpropargyl azides.

Introduction

We previously developed a synthetic strategy for the preparation of simple azido-alkyne building blocks, and provided a platform for the development of oligomeric 1,4-disubstituted-1,2,3-triazole dimers and higher order oligomeric scaffolds, using Huisgen's $Cu^{(0)}$ mediated 1,3-dipolar cycloaddition (also known as "click" chemistry[1]) as a key reaction step.[2] It was shown that racemic α-substituted propargyl alcohols **3** could be efficiently generated in two steps, while racemic α-substituted trialkylsilylpropargyl azides **5** were easily synthesized in three steps. Both of these azido-alkyne building blocks were generated by using α-substituted trialkylsilylpropargyl alcohols **2** as a common intermediate (Scheme 1).

It was also shown that racemic α-substituted trialkylsilylpropargyl azide and α-substituted free-propargyl alcohol building blocks may be coupled via a copper(I)-catalyzed 1,3-dipolar cycloaddition [1,3-DC] to generate a range of alkyl-substituted, racemic 1,4-disubstituted-1,2,3-triazole dimers **6** (Scheme 2). Optimization of the reaction conditions for the [1,3-DC] showed that $Cu^{(0)}$ powder in the presence of ^{t}BuOH:H_2O 1:2 provided the highest yields of dimer. Furthermore, dimers **6** were extended to form oligomers in a controlled, stepwise fashion with use of $Cu^{(0)}$ powder in the presence of ^{t}BuOH:H_2O 1:2 to provide a range of racemic oligomers **7**. This extension step was found to have the greatest efficiency in the direction of the alkyne terminus, involving trimethylsilyl-deprotection of the dimer, followed by [1,3-DC] with the corresponding azide.

To assess the potential for these and other oligomeric 1,2,3-triazole scaffolds to act as structural peptidomimetics (we are referring to a "structural peptidomimetic" as a molecule capable of mimicking the structural and biological

(1) For selected reviews on "click" chemistry see: Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021. Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–1137. Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51–68.

(2) Montagnat, O. D.; Lessene, G.; Hughes, A. B. *Tetrahedron Lett.* **2006**, *47*, 6971–6974.

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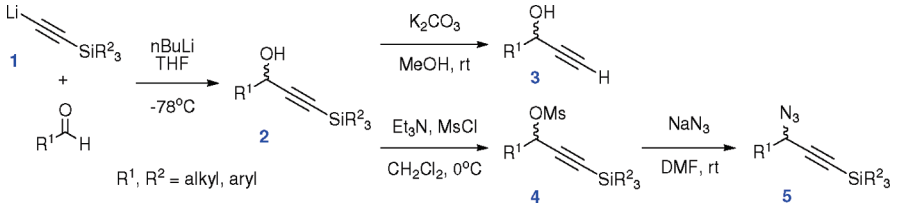
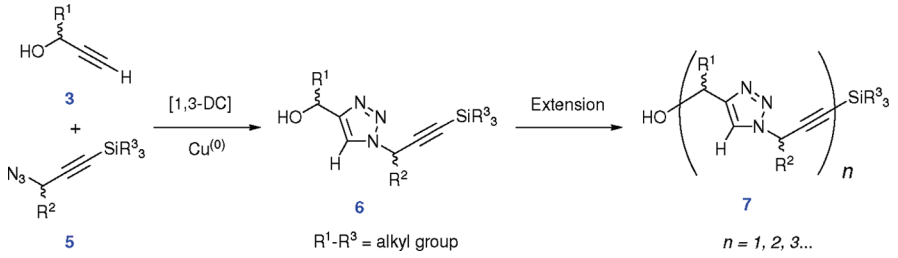
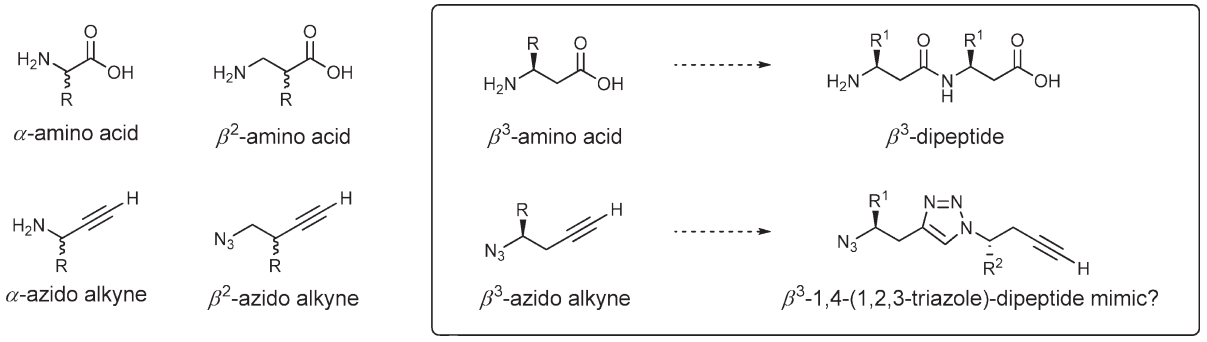
SCHEME 1. Synthesis of *rac*-α-Substituted Propargyl Alcohols and *rac*-α-Substituted Trialkylsilylpropargyl Azides[2]



SCHEME 2. Synthesis of Racemic 1,4-Disubstituted-1,2,3-triazole Dimers and Higher Order Oligomers



SCHEME 3. β^3-Azido Alkynes and Related 1,2,3-Triazole Oligomers Used to Mimic β^3-Amino Acids and Related β^3-Oligopeptides



action of a natural parent peptide, but lacking the hydrolytic sensitivity the natural parent peptide possesses), it was of interest to determine what secondary conformation(s) one or more of the 1,2,3-triazole oligomers would adopt in solution. Would these molecules be capable of reproducing defined conformations such as α-helices or β-sheets? Or would these molecules be too flexible, leading to a set of partially folded conformations or even a complete lack of secondary structure? Since an assessment of conformation could not be performed on the initial 1,4-disubstituted-1,2,3-triazole homotetramer (*rac*-HO-^{i}Bu-^{i}Bu-^{i}Bu-^{i}Bu-CCTMS[2]) (obtained as a mixture of diastereoisomers), we decided to prepare oligomers with defined chirality.

It has previously been shown that chiral β-peptide sequences as short as four residues are capable of folding into a stable 14-helical conformation.[3] As an extension to these previous findings, it was proposed that β^3-1,4-disubstituted-1,2,3-triazole scaffolds[4] may be suitable for mimicking the backbone structure of β-peptide chains (Scheme 3).

As a result of this proposal, it was decided to investigate the secondary structural organization of a chiral 1,4-disubstituted-1,2,3-triazole heterotetramer **10**, which could be constructed from the corresponding chiral β^3-substituted homopropargyl alcohols **8** and chiral β^3-substituted trimethylsilylhomopropargyl azides **9**, respectively (Scheme 4).

To achieve this, synthetic strategies were required to provide access to chiral β^3-substituted homopropargyl alcohols and chiral β^3-substituted trimethylsilyl-homopropargyl azides, respectively. Amino acids provide starting materials possessing a wide range of structural diversity at the β^3-substitution point. Furthermore, the side chain motifs present in the selection of naturally occurring amino acids are useful, as they can be matched to that of naturally occurring peptide chains, allowing for targeted investigation of backbone effects in newly synthesized β^3-substituted (1,4-disubstituted-1,2,3-triazole) oligomers.

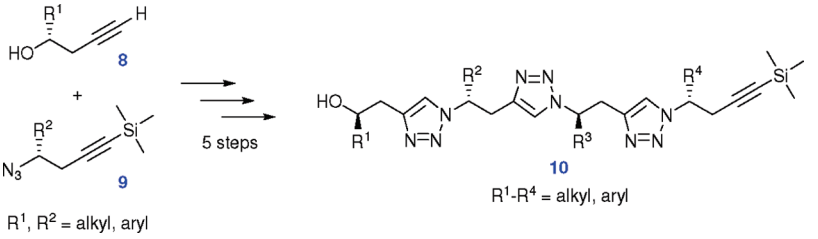
Results and Discussion

The synthesis of chiral β^3-substituted trimethylsilyl-homopropargyl alcohols was essential, as it was planned that these alcohols would be a common precursor to chiral β^3-substituted homopropargyl alcohols and chiral β^3-substituted trimethylsilyl-homopropargyl azides, respectively. A four-step synthetic scheme was devised starting from L-amino

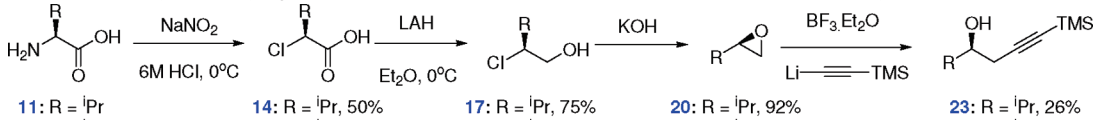
(3) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071–13072.

(4) A "*β^3-1,4-disubstituted-triazole scaffold*" is defined by repeating units of a 1,2,3-triazole ring, substituted with 2-carbon chains attached to N-1 and C-4 of the 1,2,3-triazole ring. Each 2-carbon chain is substituted with an R group, which is attached to the carbon positioned adjacent to N-1 of the 1,2,3-triazole ring.

SCHEME 4. 1,2,3-Triazole Tetramer 10 Made from β^3-Substituted Azido-Alkyne Units in Five Steps



SCHEME 5. Synthesis of (*R*)- and (*S*)-β^3-Substituted Trimethylsilylhomopropargyl Alcohols from (*S*)-α-Amino Acids



11: R = ^{i}Pr
12: R = ^{i}Bu
13: R = Bn

14: R = ^{i}Pr, 50%
15: R = ^{i}Bu 54%
16: R = Bn, 97%

17: R = ^{i}Pr, 75%
18: R = ^{i}Bu, 100%
19: R = Bn, 62%

20: R = ^{i}Pr, 92%
21: R = ^{i}Bu, 78%
22: R = Bn, 77%

23: R = ^{i}Pr, 26%
24: R = ^{i}Bu, 59%
25: R = Bn, 56%

acids. This involved diazotization, reduction, epoxide formation, and regioselective epoxide ring-opening with lithium trimethylsilyl acetylide ions (Scheme 5).

Diazotization was conducted on L-amino acids **11**−**13** with 1.6 equiv of sodium nitrite and 6 M HCl at 0 °C to give the chloroacids **14**−**16**, while reduction of the carboxylic acid was conducted with 1.2 equiv of LAH in Et_2O at 0 °C (Scheme 5). The conditions for diazotization provided a range of alkyl-substituted (*S*)-α-chloro acids **14**−**16**. The double S_N2 displacement occurs with complete retention of configuration and in excellent enantiomeric excess (ee >95%, enantiomeric excesses for compounds **14**−**16** were assessed based on comparison of experimental $[\alpha]_D$ values to literature $[\alpha]_D$ values).[5]

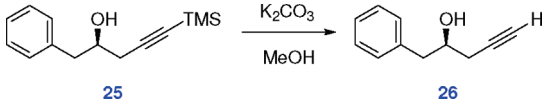
The conditions employed for LAH reduction provided the (*S*)-α-chloro alcohols **17**−**19**. The enantiomeric purities for alcohols **17**−**19** were not quoted in the literature;[6] however, subsequent comparison of $[\alpha]_D$ values for the (*R*)-epoxides **20**−**22** generated in the next reaction were compared to literature values and showed that high ee values were obtained.[6]

The third step, which also followed literature procedures,[6] involved the synthesis of (*R*)-monosubstituted epoxides **20**−**22**. These were generated from the corresponding chloroalcohols **17**−**19** upon exposure to aqueous KOH under reduced pressure (Scheme 5). Under these conditions, only the 4-alkyl-substituted regioisomers were obtained, possessing (*R*)-stereochemistry. These stereochemical assignments were based on literature precedents including stereoselectivity,[6] experimental $[\alpha]_D$ values, and the presence of only one diastereoisomer in the formation of triazole dimer **41** from alkyne **26** and azide **30** (see below Scheme 9).

Ring-opening of the (*R*)-monosubstituted epoxides **20**−**22** was conducted with 1.0 equiv of $BF_3 \cdot OEt_2$ and 1.0 equiv of lithium trimethylsilyl acetylide in THF at −78 °C. This gave the desired (*R*)- and (*S*)-β^3-substituted trimethylsilyl-homopropargyl alcohols **23**−**25** (Scheme 5).

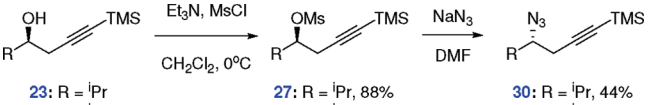
Only the β^3-substituted trimethylsilyl-homopropargyl alcohol regioisomers were obtained, possessing (*R*)- or (*S*)-stereochemistry depending on the side chain ((*S*)-^{i}Pr **23**, (*R*)-^{i}Bu **24**, (*R*)-Bn **25**). Optical purity was assessed based on experimental $[\alpha]_D$ values (see the Experimental Section) and the presence of only one diastereoisomer in the formation of 1,2,3-triazole dimer **41** from alkyne **26** and azide **30**. The yield for these reactions was found to be low for the smaller ^{i}Pr side chain (26%) and moderate for the larger ^{i}Bu and Bn side chains (59% and 56%, Scheme 5), respectively. This was to be expected, as the isopropyl group is the most sterically demanding group in the series and is likely to account for the low yield.

SCHEME 6. Synthesis of (*R*)-β^3-Benzyl Trimethylsilylhomopropargyl Alcohol 26



25 **26**

SCHEME 7. Synthesis of (*R*)- and (*S*)-β^3-Substituted Homopropargyl Alcohols 30−32



23: R = ^{i}Pr
24: R = ^{i}Bu
25: R = Bn

27: R = ^{i}Pr, 88%
28: R = ^{i}Bu, 78%
29: R = Bn, 100%

30: R = ^{i}Pr, 44%
31: R = ^{i}Bu, 43%
32: R = Bn, 53%

Deprotection of trimethylsilyl-homopropargyl alcohol **25** was conducted with 1.6 equiv of K_2CO_3 in MeOH (Scheme 6). This provided (*R*)-homopropargyl alcohol **26** in 98% yield. This alcohol **26** was then used to start the formation of the 1,2,3-triazole oligomeric chain (Scheme 9).

The chiral azides **30**−**32** were synthesized by using the same chemistry and under the same conditions as used for the generation of the racemic α-substituted trialkylsilylpropargyl azides;[2] alcohols **23**−**25** were mesylated by using methanesulfonyl chloride and triethylamine in dichloromethane at 0 °C, followed by azide ion displacement with sodium azide in DMF (Scheme 7).

The optimal reaction conditions for the generation of mesylates **27**−**29** used 1.5 equiv of Et_3N and 1.3 equiv of methanesulfonyl chloride in CH_2Cl_2 at 0 °C. These conditions provided excellent yields of the mesylates **27**−**29** in only 10 min reaction time (Scheme 7).

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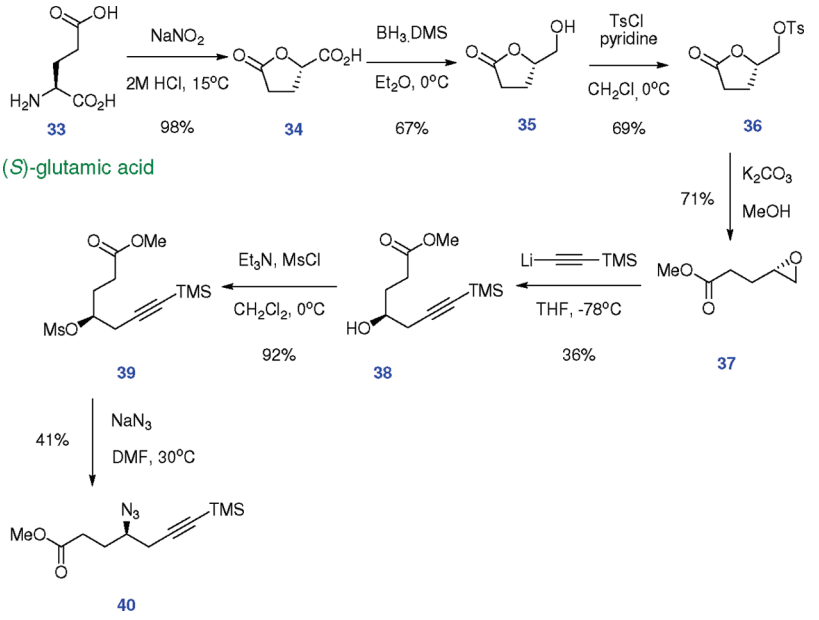
(6) Koppenhoefer, B.; Schurig, V. *Org. Synth.* **1988**, *66*, 160–172.

SCHEME 8. Synthesis of (*R*)-β^3-Methylbutanoyl Trimethylsilylhomopropargyl Azide 40



Despite successful generation of the aforementioned mesylates, lower yields were obtained for the azides **30**−**32** compared to the racemic α-substituted trialkylsilyl-propargyl azide synthesis.[2] No β^3-substituted trimethylsilyl-homopropargyl azides were detectable by TLC at 20 °C (also employing 2.0 equiv of sodium azide in DMF). These lower yields for the generation of compounds **30**−**32** were attributed to deactivation of the reaction center, due to an increase in the distance from the alkyne, and a subsequent decrease in electronic withdrawal by the mesylate leaving group. Reaction conditions were modified and increasing the reaction temperature from ∼20 °C to ∼40 °C resulted in activation of the mesylates toward substitution. Under these conditions, azide ion attack provided azides **30**−**32** in 43−53% yield (Scheme 7). Similarly to the stereochemical assignment of alcohols **23**−**25**, stereochemical assignment of azides **30**−**32** was based on experimental $[\alpha]_D$ values (see the Experimental Section) and the fact that only one diastereoisomer for each step in the formation of triazole oligomers (**41**−**45**) was observed (Scheme 9).

In addition to the desired azides, a highly polar chromophore (as determined by TLC) was obtained from each reaction in minor amounts and was found to be volatile under vacuum. ^{1}H NMR spectroscopy showed these compounds to be conjugated enynes, most likely produced by thermal elimination of the mesylate group from compounds **27**−**29**.

To circumvent the elimination, a *Mitsunobu* reaction was attempted on ^{i}Pr alcohol **23**, employing 1.5 equiv of PPh_3, diisopropyl azodicarboxylate (DIAD), and diphenylphosphoryl azide (DPPA) in THF at −50 °C to room temperature for 48 h. These conditions provided the desired azide in 40% yield; however, purification of the azide from the reaction mixture was found to be more difficult than that of previously attempted azide substitution reactions (NaN_3, DMF, rt) as a result of the solid triphenylphosphine oxide byproduct present. The enantiomeric excess of mesylates **27**−**29** and azides **30**−**32** was not determined;[7] however, it has been shown under similar conditions that conversion of chiral alcohols to mesylates followed by reaction with sodium azide in a polar aprotic solvent provides chiral azides with minimal racemization.[8]

As an extension to the introduction of chirality for the β^3-substituted azido-alkyne monomers, introduction of additional functionality in the side chain of the molecule was desired. A methyl ester was selected for several reasons. Methyl esters offer a form of acid protection, and can be generated from a range of functional groups including acids,[9] nitriles,[10] ketenes,[11] acid chlorides,[12] and anhydrides.[13] Deprotection of methyl esters can be achieved employing a range of conditions such as LiOH, $AlBr_3$, $(CH_3)_3SiOK$, lipases, and esterases.[14] Once deprotected, acids provide a versatile attachment point, allowing for modification of solubility profiles, attachment of reporter groups such as rhodamine and biotin,[15] or extension with other structural motifs such as alternative fragments and drug-like pharmacophores.

Following the same conceptual methodology of using chiral pool α-amino acids, (*S*)-glutamic acid **33** was used as a starting point for the generation of (*R*)-β^3-methylbutanoyl trimethylsilyl-homopropargyl azide **40** (Scheme 8).

(7) The enantiomeric excess of mesylates **27**−**29** and azides **30**−**32** was not determined due to the fact that subsequent analysis of diastereoisomer **41** with ^{1}H and ^{13}C NMR spectroscopy revealed no other diastereoisomers were present, and thus chiral purity had been maintained.

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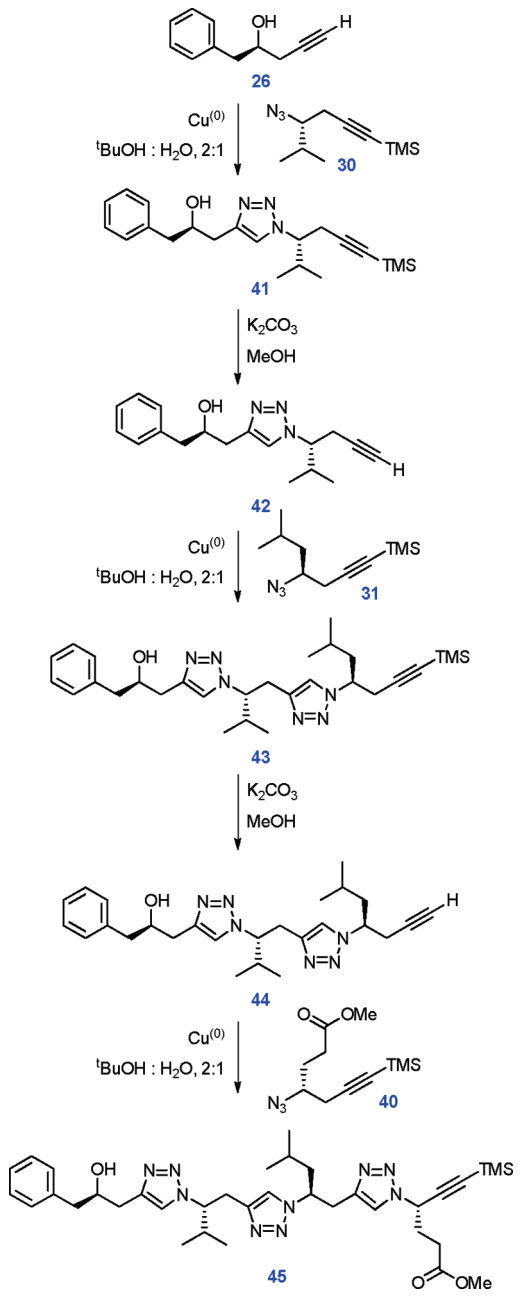
SCHEME 9. Synthesis of Chiral Heterotetramer 45 via Trimethylsilyl-Deprotection and [1,3-DC]



All of the synthetic steps up until epoxide **37** were conducted following literature procedures.[16−18] Diazotization of **33** in 2 M HCl at 15 °C provided the (4*S*)-(+)-4-carboxy-1,4-butyrolactone **34** in 98% yield. This was followed by reduction of the acid **34** with borane dimethyl sulfide complex (BMS) to provide the desired (4*S*)-4-hydroxymethyl-4-butyrolactone **35** in 67% yield. The hydroxymethyllactone was tosylated, using pyridine and toluenesulfonyl chloride at 0 °C to provide **36** in 69% yield. This set the molecule for K_2CO_3-induced ring-opening−ring-closing to give epoxide **37** in 71% yield. From the epoxide **37**, the same conditions were employed as were used in the synthesis of alcohols **23**−**25**, mesylates **27**−**29**, and azides **30**−**32**, providing the (4*S*)-alcohol **38**, the (4*S*)-mesylate **39**, and the (4*R*)-azide **40** in similar yields, respectively (36%, 92%, and 41% yields, respectively). Stereochemical assignment of alcohol **38** was based on comparison of the experimental $[\alpha]_D$ value to literature.[8] Stereochemical assignment of mesylate **39** and azide **40** was based on experimental $[\alpha]_D$ values and the presence of only one diastereoisomer in the formation of triazole tetramer **45**.

As shown in Scheme 2, previous synthesis and optimization of a range of racemic 1,4-disubstituted-1,2,3-triazole oligomer scaffolds from the corresponding *rac*-α-substituted propargyl alcohols and *rac*-α-substituted trialkylsilylpropargylazides provided the conditions to be employed in the generation of chiral 1,4-disubstituted-1,2,3-triazole scaffolds from the corresponding β^3-substituted homopropargylic substrates.[2] Sequential rounds of trimethylsilyl-deprotection with K_2CO_3 in MeOH were followed by [1,3-DC] with $Cu^{(0)}$ powder (40 mesh) in the presence of a 2:1 mixture by volume of ^{t}BuOH and H_2O (Scheme 9, Table 1).

TABLE 1. Conditions for the Synthesis of Chiral 1,4-Disubstituted-1,2,3-triazole Heterotetramer 45

entry	reagent	conditions (equiv)	product (yield %)
1	**25**	K_2CO_3 (2.0), MeOH, rt, 1 h	**26** (98)
2	**26**	**30** (1.0), $Cu^{(0)}$ (xs), ^{t}BuOH:H_2O, 2:1, rt, 20 h	**41** (80)
3	**41**	K_2CO_3 (2.3), MeOH, rt, 1 h	**42** (89)
4	**42**	**31** (1.0), $Cu^{(0)}$ (xs), ^{t}BuOH:H_2O, 2:1, rt, 1.5 h	**43** (89)
5	**43**	K_2CO_3 (2.0), MeOH, rt, 0.5 h	**44** (94)
6	**44**	**40** (1.0), $Cu^{(0)}$ (xs), ^{t}BuOH:H_2O, 2:1, rt, 2.5 h	**45** (80)

Deprotection of the (*R*)-Bn alcohol **25** (entry 1, Table 1) followed by [1,3-DC] with the (*R*)-^{i}Pr azide **30** provided the triazole dimer **41** in 80% yield (entry 2, Table 1; a full assignment of ^{1}H and ^{13}C NMR signals for all triazole oligomers **41**−**45** can be found in the Experimental Section or the Supporting Information). In this reaction, only one product was detected by TLC and ^{1}H and ^{13}C NMR spectroscopy, suggesting that the [1,3-DC] resulted in the generation of only one diastereoisomer.

Deprotection of **41** (entry 3, Table 1) and [1,3-DC] of triazole dimer **42** with (*S*)-^{i}Bu azide **31** provided the triazole trimer **43** in 89% yield (entry 4, Table 1). Deprotection of **43** (entry 5, Table 1) followed by [1,3-DC] of triazole trimer **44** with (*R*)-azide **40** provided the desired triazole heterotetramer **45** in 80% yield (entry 6, Table 1). From this reaction, it can be seen that the [1,3-DC] maintains a high level of efficiency, even in the presence of a subunit possessing side-chain functionalization. A single diastereoisomer was obtained from each reaction step as determined by experimental $[\alpha]_D$ values and ^{1}H and ^{13}C NMR spectroscopy.

In comparison with the racemic homotetramer **47**,[2] improvements were seen for the synthesis of the 1,4-disubstituted-1,2,3-triazole heterotetramer **45** in three areas: overall

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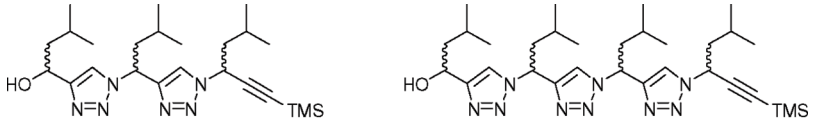


46 47

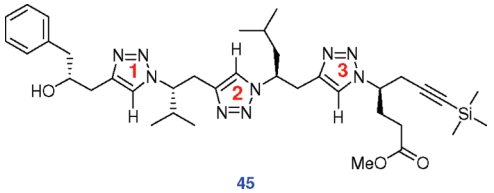
FIGURE 1. Racemic 1,4-disubstituted-1,2,3-triazole homotetramer **47**.

yield of tetramer, average yield for the [1,3-DC], and reaction time profile for the [1,3-DC].

First, the overall yield of the triazole heterotetramer **45** synthesis was higher, with 47% overall yield over 6 steps compared to 38% for the 1,4-disubstituted-1,2,3-triazole tetramer **47** synthesis. Second, the average yield of the [1,3-DC] reaction for the heterotetramer **45** was also much improved, with 83% average yield (57% overall) compared to 75% (42% overall) for the triazole tetramer **47** synthesis. Third, the time taken for the [1,3-DC] reaction to reach completion was considerably reduced, with only 1.5 and 2.5 h required for completion of the trimer **43** and tetramer **45** [1,3-DC] reactions, respectively (average, 8 h over three [1,3-DC] steps), compared to 17 and 15 h for the corresponding trimer **46** and tetramer **47** [1,3-DC] reactions, respectively (Figure 1).[2]

These three improvements were rationalized by three variations in the corresponding fragment structure. First, the position of the acetylene function relative to the hydroxyl groups within each fragment type was considered. The acetylene group is connected two carbon atoms away from the secondary hydroxyl group in the β^3-substituted fragment(s), but only one carbon away from the secondary hydroxyl group in the α-substituted fragment(s). It is conceivable that this structural difference leads to an improvement in yield/reaction time for the β^3-substituted fragment, as [1,3-DC] reactions are deactivated by the close proximity of electron donating groups to the 1,3-dipolarophile (in this case, the acetylene function).[19] Second, the position of the acetylene functions relative to the side chain within each fragment type was considered. The acetylene function is β to the alkyl-substituted side chain in the β^3-substituted fragment(s), but α to the hydrophobic side chain in the α-substituted fragment(s). This is expected to lead to a lower level of steric congestion around the reaction center for the β^3-substituted fragment(s), and therefore an improvement in the reaction rate and yield for the β^3-substituted 1,4-disubstituted-1,2,3-triazole oligomer scaffold. Third, the nature of the side chain identity was considered. A range of alkyl-substituted side chains and one hydrophilic side chain were employed in the structure of the heterotetramer **45**, whereas only the isobutyl group was employed in the structure of the homotetramer **47**.[20]

Conformational analysis of heterotetramer **45** was conducted by performing a molecular mechanics calculation at the Victorian Partnership for Advanced Computing (VPAC), in addition to 2D NMR studies to ensure complete characterization. NOESY/ROESY NMR studies were conducted (see the Supporting Information) in order to inform of any close-range through-space interactions between side chain residues and so give an indication of any secondary conformation(s) of the heterotetramer **45**.



45

FIGURE 2. A 2D representation of chiral heterotetramer **45** (1,2,3-triazole rings indicated by red numbers).

A local energy minimization was determined from a 2D representation of heterotetramer HO-(*R*)-Bn-(*R*)-^{i}Pr-(*S*)-^{i}Bu-(*R*)-Glu(OMe)-C≡CTMS **45** via a two-step process. First, an initial geometry optimization was performed on the 2D structure (Figure 2) to generate a Chem3D structure with a geometrically defined starting point.[21] Second, the Chem3D structure was optimized to a *.pdb file using the SCHRODINGER/maestro molecular mechanics suite through VPAC. The optimized *.pdb file was then visualized with RasMol 2.7 (Figure 3).

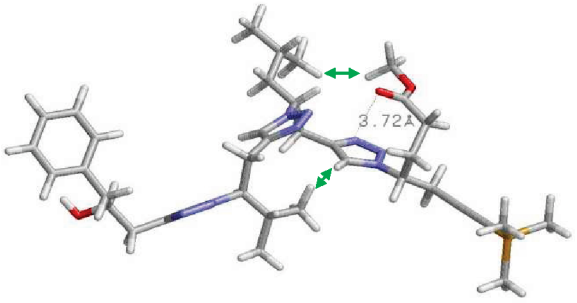


FIGURE 3. The energy-minimized structure of chiral heterotetramer **45** produced in RasMol 2.7 (expected NOE enhancements have been indicated by green arrows).

This structure (Figure 3) showed that the (*R*)-methyl glutamate side chain sits perpendicular to triazole ring-**3**, with a distance of 3.72 Å from the vinylic proton of triazole ring-**3** to the carbonyl group of the glutamate side chain. It also showed that triazole ring-**3** adopts a cis conformation (side chains are on the *same* side, relative to the 1,2,3-triazole ring) relative to the (*S*)-^{i}Bu and (*R*)-Glu(OMe) side chains whereas triazole rings-**1** and -**2** both adopt a trans conformation (side chains are on the *opposite* side, relative to the 1,2,3-triazole ring) relative to the (*R*)-Bn, (*R*)-^{i}Pr, and (*S*)-^{i}Bu side

(19) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, 1st ed. John Wiley & Sons Inc.: New York, 1984; Vol. 1.

(20) Assessment of overall efficiency for the synthesis of a β^3-substituted homotetramer possessing only isobutyl side chains would determine if this variation is a contributing factor.

(21) The conformation of the initial 2D structure was based on the rationale that the side chain substituents of the oligomeric, 1,4-disubstituted-1,2,3-triazole backbone chain would be oriented trans to each other, while the 1,2,3-triazole rings of the backbone chain would also be oriented trans to each other. As such, only one local energy minimum was calculated.

chains, respectively. It was concluded from this calculation that indirect NOE (Nuclear Overhauser Effect) enhancements could be expected between one of the isobutyl CH_3 groups and the methylglutamate CH_3 group, as well as between one of the isopropyl CH_3 groups and the triazole ring-**3** hydrogen. It was also concluded that the ordered secondary conformation the heterotetramer **45** adopted did not resemble any of the known secondary structural motifs found in biological systems such as α-helices or β-sheets (or even motifs found in nonbiological systems, such as the zigzag conformation seen in the (*S*)-tetrabenzyl-1,2,3-triazole tetramer **SC6** in the studies of Arora).[22]

To complement this in silico study, we fully assigned the ^{1}H NMR spectrum of the tetramer **45** (for a full ^{1}H and ^{13}C assignment of all 1,4-disubstituted-1,2,3-triazole oligomers **41**−**45**, see the Experimental Section). This chemical shift assignment was followed by an assessment of its conformation in solution by NOESY and ROESY 2D-NMR analysis. Initial characterization involved ^{1}H and ^{13}C NMR assignments made from ^{1}H, ^{13}C, DEPT, HSQC, and mCOSY spectra. These experiments were conducted on a 300 MHz spectrometer, using three different solvents: *d*-chloroform ($CDCl_3$), d_6-benzene (C_6D_6), and d_6-acetone ($(CD_3)_2CO$) (see the Supporting Information for a table of complete assignments).

From the results, the following conclusions were made:

The most well-resolved ^{1}H spectrum was obtained in d_6-acetone, followed by *d*-chloroform and then d_6-benzene. *d*-Chloroform was found to be the best solvent for characterization, as individual proton signals contained the least amount of spectral overlap, and both ^{1}H and ^{13}C NMR spectra produced only one set of peaks, indicating that a single conformation was present in this solvent.

Tetramer **45** may exist as two conformers in d_6-acetone: ^{1}H/^{13}C-HSQC spectra of **45** showed several cross-peaks that corresponded to two C signals in the ^{13}C spectrum but only one H signal in the ^{1}H NMR spectrum. In addition, some of the carbon peaks in the ^{13}C spectrum were split into two peaks of slightly different chemical shift. Neither of these phenomena was observed in *d*-chloroform and d_6-benzene, suggesting that in d_6-acetone, tetramer **45** interacts with the solvent in a way that causes constrained rotation of a section of the molecule. It is unlikely that these phenomena would occur as a result of a mixture of diastereoisomers. All precursors to tetramer **45** produced a single set of ^{1}H NMR peaks (300 MHz, $CDCl_3$) and a single spot by TLC analysis. Tetramer **45** also produced a single spot by TLC analysis.

The chiral α-protons from each residue were all shifted downfield in different solvents in the following order: $CDCl_3 < C_6D_6 < (CD_3)_2CO$. This was to be expected, as acetone provides the greatest amount of deshielding as a result of its large relative polarity (dielectric constant: $K_{d_6\text{-acetone}} = 20.7$, $K_{d\text{-chloroform}} = 4.8$, $K_{d_6\text{-benzene}} = 2.3$) and benzene is slightly more deshielding relative to *d*-chloroform due to the interaction of the π-electrons with the residue α-protons.

The 1,2,3-triazole vinylic ^{1}H-signals were shifted downfield by ∼0.3 ppm relative to each other starting from the alkyne-trimethylsilyl terminus and toward the hydroxyl terminus. This variation was found to be greater than seen in the racemic homotetramer **47**, which varied by ∼0.2 ppm across all three 1,2,3-triazole vinylic ^{1}H-signals.[2] Furthermore, the chemical shift of all 1,2,3-triazole vinylic ^{1}H-signals in heterotetramer **45** was found to follow the same trend as had been seen for the chiral α-proton signals across the same three solvents ($CDCl_3 < C_6D_6 < (CD_3)_2CO$). The widest distribution of chemical shift for 1,2,3-triazole vinylic ^{1}H-signals in a single solvent was for *d*-chloroform, occurring across ∼0.7 ppm compared to ∼0.6 and ∼0.3 ppm for d_6-benzene and d_6-acetone, respectively. This suggests that in d_6-acetone, all of the 1,2,3-triazole vinylic protons are in a more similar chemical environment relative to each other than for the other two solvents. This phenomenon may occur as a result of relative dipole alignment of the 1,2,3-triazole rings in the tetramer backbone (it has previously been shown that the secondary structure of similar tetrameric foldamers possessing 1,2,3-triazole rings as backbone subunits is defined by the dipole−dipole interactions between adjacent triazole rings).[22]

Variable-temperature (VT) experiments showed that the ^{1}H NMR signals for side chain groups did not shift across the temperature range of 300−315 K. This was found to be true for all three solvents. There may be several reasons for this effect. The molecule may be unstructured in solution over the tested temperature range and possess a high degree of rotational freedom, resulting in a signal-averaged ^{1}H NMR spectrum and one set of peaks. A mixture of diastereoisomers may be present, which would also result in ^{1}H signal averaging. However, this was discounted based on the previous analysis of ^{13}C NMR signals for heterotetramer **45** across three solvents, as well as TLC analysis. Alternatively, it may be the case that the temperature range tested was not broad enough to cause a major conformational change of the tetramer **45** and result in significant shifting of the ^{1}H NMR signals for side chain groups.

NOESY and ROESY experiments were conducted on chiral tetramer **45** in order to assess the spatial orientation of side chain residues. These were obtained on a 400 MHz NMR spectrometer, using *d*-chloroform as solvent (see the Supporting Information for NOESY and ROESY spectra of compound **45**).

The NOESY spectrum showed that under these conditions ($CDCl_3$, ∼200 mM, 300 K), many NOE enhancements were present; however, all of these were determined to be direct NOE enhancements. No through-space interactions were identified, including the expected NOE enhancements (obtained from computational modeling) between one of the isobutyl CH_3 groups and the methyl of the glutamate CH_3 group, as well as between one of the isopropyl CH_3 groups and the triazole ring-**3** hydrogen. The ROESY spectrum supported these findings, showing that in spite of many direct ROE enhancements, indirect ROE enhancements representing through-space interactions were absent.

These two sets of studies (computational and NMR instrumental) allowed the conclusion that the heterotetramer **45** exists in *d*-chloroform in a linear conformation without any secondary structural motifs (such as α-helices and β-sheets) present. This result was not surprising for two reasons. First, heterotetramer **45** was not *designed* for the purpose of folding into a specific secondary structural motif. Second, it is very rare to see short, peptidic and nonpeptidic oligomers less than five residues in length fold into ordered, stable

(22) Angelo, N. G.; Arora, P. S. *J. Am. Chem. Soc.* **2005**, *127*, 17134–17135.

secondary structural motifs such as α-helices (some exceptions to this include the design of the unnatural tetrapeptide Boc-(*S*)-γ-Ala-(*S*)-γ-Val-(*S*)-γ-Ala-(*S*)-γ-Val-TMSE by Hanessian and co-workers,[23] which was found to form a stable, right-handed 2.6_1 helix in d_5-pyridine, the design of Boc-$(ACHC)_4$-CO_2Bn by Apella and co-workers,[3] which was found to adopt a 14-helical conformation in the solid state, and the design of the 1,2,3-triazole tetramer: Boc-(*S*)-Lys(Cbz)-(*S*)-Lys(Cbz)-(*S*)-Bn-(*S*)-Bn-CO_2Me by Angelo and Arora,[22] which was found to adopt a zigzag structure reminiscent of β-strand conformations). Further investigations with these β-type 1,2,3-triazole oligomers are required to determine if *any* stable secondary structures can be formed, and if so, what minimum residue length and additional structural factors (such as the nature of side chains, hydrogen bond donors/acceptors, electron donating/withdrawing groups, etc.) control the nature of these conformation(s).

Conclusion

In this paper, the synthesis of β^3-substituted homopropargyl alcohols and chiral β^3-substituted trimethylsilyl-homopropargyl azides has been described in order to increase the diversity of our set of small azido-alkyne precursors. It was shown alkyl-substituted α-amino acids provide a chiral pool for the synthesis of these fragments, using β^3-substituted trimethylsilyl-homopropargyl alcohols as a common synthetic intermediate. One pure chiral 1,4-disubstituted-1,2,3-triazole heterotetramer **45** was fully characterized and investigated for the presence of organized secondary structure. NOESY/ROESY NMR along with computational modeling studies showed that this heterotetramer existed in a linear conformation in solution. Further modeling studies are required to be conducted on alternative, enantiomerically pure 1,4-disubstituted-1,2,3-triazole oligomers in order to assess if these molecules are capable of adopting ordered secondary conformation(s) in solution.

Experimental Section

General Procedure for the Synthesis of Chiral β^3-Substituted Trimethylsilyl-Homopropargyl Alcohols 23−25. Preparation of (*S*)-2-Methyl-6-trimethylsilanylhex-5-yn-3-ol, 23. The epoxide **20** was synthesized immediately before use and stored at −20 °C. To a flame-dried, argon-filled, 25 mL three-necked round-bottomed flask fitted with a stopper, septum, and argon line was added dry THF (2.0 mL) and trimethylsilylacetylene (3.1 mmol, 442 μL) at −78 °C. ^{n}BuLi (1.9 mL of a 1.6 M solution in hexanes, 3.1 mmol) and boron trifluoride etherate (3.1 mmol, 397 μL) were added at −78 °C and the mixture was left to stir for 0.5 h. The epoxide **20** was then added (270 mg, 3.1 mmol) at −78 °C and the reaction mixture was left to stir for 2 h. The reaction mixture was then quenched with saturated NH_4Cl solution (4 mL) and diluted with Et_2O (20 mL), washed with H_2O (15 mL) and brine (15 mL), dried with sodium sulfate, filtered, and concentrated on a rotary evaporator to leave a yellow oil. The crude oil was purified by column chromatography on silica gel, using 10% ethyl acetate/hexane as the eluant, to afford (*S*)-2-methyl-6-trimethylsilanylhex-5-yn-3-ol **23** as a clear oil (149 mg, 26%). R_f 0.52 (10% ethyl acetate/hexane); $[\alpha]_D$ +17.3 (*c*, 0.75 in CH_2Cl_2); IR (NaCl) ν_{max} 3409, 2961, 2176, 1250, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, T = 330 K) δ 0.10 (s, 9H, $Si(CH_3)_3$), 0.87 (d, 3H, J = 10.1 Hz, H6), 0.90 (d, 3H, J = 10.0 Hz, H6′), 1.72 (octet, 1H, J = 6.2 Hz, H5), 2.01 (s, 1H, OH), 2.41 (2 × dd, 2H, J = 16.8 and 7.4 Hz, H3), 3.38−3.42 (m, 1H, H4); ^{13}C NMR (75 MHz, $CDCl_3$) −0.4 ($Si(CH_3)_3$), 17.2, 18.3 (C6, C6′), 25.8 (C3), 32.2 (C5), 74.2 (C4), 86.8 (C1), 103.3 (C2).

General Procedure for the Synthesis of Chiral β^3-Substituted Trimethylsilyl-Homopropargyl Mesylates 27−29. Preparation of (*S*)-2-Methyl-6-(trimethylsilyl)hex-5-yn-3-yl Methanesulfonate, 27. The alcohol **23** (133 mg, 0.72 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL) and the solution was cooled to 0 °C. Triethylamine (1.08 mmol, 150 μL) was added via syringe along with methanesulfonyl chloride (0.94 mmol, 58 μL) in one portion. After 0.25 h, the reaction mixture was diluted with Et_2O (20 mL), washed with H_2O (15 mL) and brine (15 mL), dried with sodium sulfate, filtered, and evaporated under reduced pressure to leave a yellow residue. The crude residue was purified by column chromatography on silica gel, using 10% ethyl acetate/hexane as the eluant, to afford (*S*)-2-methyl-6-(trimethylsilyl)hex-5-yn-3-yl methanesulfonate **27** as a clear residue (156 mg, 88%). R_f 0.54 (10% ethyl acetate/hexane); IR (NaCl) ν_{max} 2960, 2180, 1362, 1251, 1176, 914, 844 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.52 (s, 9H, $Si(CH_3)_3$), 1.36 (2 × d, 6H, J = 6.7 and 6.7 Hz, H6, H6′), 2.45−2.56 (m, 1H, H5), 3.01 (2 × dd, 2H, 17.4 and 5.7 Hz, H3), 3.45 (s, 3H, H_3CSO_3), 4.95 (q, 1H, J = 5.5 Hz, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.5 ($Si(CH_3)_3$), 16.7, 17.8 (C6, C6′), 23.1 (C3), 31.1 (C5), 38.3 (H_3CSO_3), 85.0 (C4), 87.3 (C1), 101.4 (C2).

General Procedure for the Synthesis of Chiral β^3-Substituted Trimethylsilyl-Homopropargyl Azides 30−32. Preparation of (*S*)-(4-Azido-5-methylhex-1-ynyl)trimethylsilane, 30. The mesylate **27** (559 mg, 2.18 mmol) was dissolved in dry DMF (13.6 mL) along with sodium azide (283 mg, 4.36 mmol) and the mixture was stirred at 40 °C. After 40 h, the reaction mixture was diluted with Et_2O (40 mL), washed with H_2O (2 × 20 mL) and brine (20 mL), dried with sodium sulfate, filtered, and concentrated under reduced pressure to leave a dark yellow oil. The crude oil was purified by column chromatography on silica gel, using hexane as the eluant, to afford (*S*)-(4-azido-5-methylhex-1-ynyl)trimethylsilane **30** as a slightly yellow oil (456 mg, 44%). R_f 0.55 (100% hexane); $[\alpha]_D$ −4.5 (*c*, 1.78 in CH_2Cl_2); IR (NaCl) ν_{max} 2964, 2901, 2180, 2124, 2100, 1250, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 9H, $Si(CH_3)_3$), 0.90, 0.93 (2 × d, 6H, J = 9.5 Hz, H6, H6′), 1.84 (octet, 1H, J = 6.3 Hz, H5), 2.43−2.49 (m, 2H, H3), 3.26 (q, 1H, J = 5.9 Hz, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.2 ($Si(CH_3)_3$), 17.5, 19.4 (C6, C6′), 24.0 (C3), 31.7 (C5), 67.2 (C4), 87.5 (C1), 102.6 (C2); HRMS *m*/*z* for $C_{10}H_{20}N_3Si$ $[M + H]^+$ calcd 210.1421, found 210.1425.

1-Phenyl-pent-4-yn-2-(*R*)-ol, 26. The trimethylsilylbutynyl alcohol **25** (336 mg, 1.4 mmol) was dissolved in dry MeOH (2 mL) and to this was added anhydrous K_2CO_3 (2.1 mmol, 299 mg) in one portion. The reaction mixture was left to stir at rt. After 1 h, the reaction mixture was diluted with Et_2O (30 mL), washed with H_2O (15 mL) and brine (15 mL), dried with magnesium sulfate, filtered, and evaporated at reduced pressure to leave **26** as a yellow oil (194 mg, 98%). ^1H NMR spectroscopy of the oil showed the desired product was obtained and it was then used in the next reaction without further purification. R_f 0.46 (20% ethyl acetate/hexane); R_f 0.23 (10% ethyl acetate/hexane); $[\alpha]_D$ +2.2 (*c*, 0.50 in CH_2Cl_2); IR (NaCl) ν_{max} 3395, 3294, 3028, 2915, 1261, 1075, 1047, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.09 (t, 1H, J = 2.7 Hz, H1), 2.16 (s, 1H, OH), 2.37 (ddd, 1H, J = 2.7, 5.8, and 8.5 Hz, H3), 2.39 (ddd, 1H, J = 2.6, 5.0, and 7.6 Hz, H3′), 2.82 (dd, 1H, J = 7.4 and 13.6 Hz, H5), 2.92 (dd, 1H, J = 5.6 and 13.6 Hz, H5′), 3.97 (quintet, 1H, J = 5.7 Hz, H4), 7.22−7.34 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1 (C3), 42.1 (C5), 70.5 (C4), 70.8 (C1), 80.4 (C2),

(23) Hanessian, S.; Luo, X.; Schaum, R.; Michnick, S. *J. Am. Chem. Soc.* **1998**, *120*, 8569–8570.

126.3, 128.3, 129.1 (aryl CH), 137.4 (aryl C); HRMS m/z for $C_{11}H_{12}O$ $[M + H]^+$ calcd 160.0888, found 160.0885.

General Procedure for the Synthesis of Chiral β^3-Substituted 1,4-Disubstituted-1,2,3-triazole oligomers 41, 43, and 45. Preparation of (*R*)-1-(1-((*R*)-2-Methyl-6-(trimethylsilyl)hex-5-yn-3-yl)-1*H*-1,2,3-triazol-4-yl)-3-phenylpropan-2-ol, 41. The acetylenyl alcohol **26** (115 mg, 0.7 mmol) was dissolved in ^{t}BuOH:H_2O 2:1 (1400 μL) and to this mixture was added azide **30** (100 mg, 0.5 mmol) along with excess $Cu^{(0)}$ powder (500 mg, 40 mesh). The reaction was stirred vigorously at 0 °C for 1.5 h, then it was allowed to warm to rt. After 19 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and flushed through a plug of Celite, dried over sodium sulfate, and concentrated at reduced pressure to leave a viscous yellow residue, which started to crystallize on standing. The crude residue was purified by column chromatography on silica gel, eluting with 30% ethyl acetate/hexane, to afford the triazole **41** as a white solid (141 mg, 80%). R_f 0.35 (30% ethyl acetate/hexane); mp 84−85 °C; $[\alpha]_D$ −25.0 (c, 1.0 in CH_2Cl_2); IR (NaCl) ν_{max} 3392, 3028, 2963, 2180, 1250, 1054, 844 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9H, $Si(CH_3)_3$), 0.68 (d, 3H, J = 6.7 Hz, $CH(CH_3)_2$), 0.95 (d, 3H, J = 6.7 Hz, $CH(CH_3)_2$), 2.14−2.27 (m, 1H, $CH(CH_3)_2$), 2.66−2.89 (m, 6H, CH_2Ph, β^1CH_2, β^2CH_2), 3.44 (s, 1H, OH), 4.04−4.19 (m, 1H, α^1CH), 4.21−4.28 (m, 1H, α^2CH), 7.11−7.23 (m, 5H, ArH), 7.46 (s, 1H, δ^1CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.4 ($Si(CH_3)_3$), 18.5, 19.3 ($CH(CH_3)_2$), 24.1 (β^2C), 31.7 ($CH(CH_3)_2$), 32.1 (β^1C), 43.0 (CH_2Ph), 65.6 (α^2C), 71.6 (α^1C), 88.0 (δ^2C), 101.4 (γ^2C), 121.1 (δ^1C), 126.0, 128.1, 129.2 (aryl CH), 138.2 (aryl C), 144.2 (γ^1C).

General Procedure for the Deprotection of Chiral β^3-Substituted 1,4-Disubstituted-1,2,3-triazole Oligomers 42 and 44. Preparation of (*R*)-1-(1-((*R*)-2-Methylhex-5-yn-3-yl)-1*H*-1,2,3-triazol-4-yl)-3-phenylpropan-2-ol, 42. The TMS-protected cycloadduct **41** (266 mg, 0.6 mmol) was added to a 25 mL round-bottomed flask along with MeOH (1.5 mL) and K_2CO_3 (199 mg, 1.4 mmol) and the mixture was left to stir at rt. After 1 h, the reaction mixture was diluted with Et_2O (20 mL) and the organic phase was washed successively with H_2O (20 mL) and brine (15 mL). The organic layer was dried with sodium sulfate, filtered, and evaporated at reduced pressure to leave a yellow residue. The crude residue was purified by column chromatography on silica gel, eluting with 40% ethyl acetate/hexane to provide the acetylene **42** as a clear residue (191 mg, 89%). R_f 0.34 (40% ethyl acetate/hexane); $[\alpha]_D$ −35.4 (c, 1.0 in $CHCl_3$); IR (NaCl) ν_{max} 3300, 3296, 3027, 2966, 1428, 1050, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (d, 3H, J = 6.7 Hz, $CH(CH_3)$), 1.00 (d, 3H, J = 6.7 Hz, $CH(CH_3)_2$), 1.96 (t, 1H, J = 2.6 Hz, δ^2CH), 2.22−2.34 (m, 1H, $CH(CH_3)_2$), 2.68−2.94 (m, 6H, CH_2Ph, β^1CH_2, β^2CH_2), 3.17 (s, 1H, OH), 4.12−4.19 (m, 1H, α^1CH), 4.21−4.28 (m, 1H, α^2CH), 7.15−7.28 (m, 5H, ArH), 7.49 (s, 1H, δ^1CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 19.4 ($CH(CH_3)_2$), 22.9 (β^2C), 31.8 ($CH(CH_3)$), 32.2 (β^1C), 43.1 (CH_2Ph), 65.6 (α^2C), 71.5 (α^1C), 71.7 (δ^2C), 79.0 (γ^2C), 121.3 (δ^1C), 126.3, 128.3, 129.3 (aryl CH), 138.2 (aryl C), 144.4 (γ^1C).

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Supporting Information Available: Experimental procedures, characterization data, ^{1}H and ^{13}C spectra for all new compounds, as well as HSQC, mCOSY, ROESY and NOESY spectra for selected 1,4-disubstituted-1,2,3-triazoles. This material is available free of charge via the Internet at http://pubs.acs.org.