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Synthesis of Azide-alkyne Fragments for 'Click' Chemical Applications. Formation of Chiral 1,4-Disubstituted-(β-alkyl)-γ-1,2,3-triazole Scaffolds from Orthogonally Protected Chiral β-Alkyl-trialkylsilyl-γ-pentynyl Azides and Chiral β-Alkyl-γ-pentynyl-alcohols

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A library of chiral γ-pentynyl alcohols and γ-pentynyl azides was made using the SuperQuat auxiliary. Coupling of the free alkynes with the azides by Huisgen 1,3-dipolar cycloaddition provided chiral oligomeric 1,4-disubstituted-1,2,3-triazoles as possible peptidomimetic compounds.

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Introduction

Development of strategies to prepare novel peptidomimetic frameworks is a highly desirable and very active area in medicinal chemistry. Many recent developments have shown the usefulness of unnatural peptide-like frameworks towards many biological applications,[1] including those such as antimicrobial polymers (AMP),[2] cell-permeable peptides (CPP),[3] and anticancer agents.[4]

It has been shown that 'click' chemistry[5–7] provides a reliable pathway for accessing 1,2,3-triazolic scaffolds and oligomeric foldamers that may act as potential peptidomimetic compounds with defined secondary structure. Examples of 1,2,3-triazole scaffold development include the works of Arora et al.[8] and Martinelli et al.,[9] with the most recent applications in the biological evaluation of a set of chiral α-disubstituted-(1,4-disubstituted)-1,2,3-triazolamers as active-site inhibitors of HIV-1 protease.[10]

Recently, we reported the synthesis of chiral β^3-disubstituted-(1,4-disubstituted)-1,2,3-triazole oligomer scaffolds from chiral β^3-substituted homopropargyl alcohols **1** and chiral β^3-substituted trialkylsilyl-homopropargyl azides **2** as fragment building blocks, using the Huisgen Cu^0-catalyzed 1,3-dipolar cycloaddition as a key coupling step.[11] This work confirmed earlier observations, which showed that racemic α-disubstituted-(1,4-disubstituted)-1,2,3-triazole oligomer scaffolds could be generated in a stepwise and controlled manner in excellent yields from racemic α-propargyl alcohols **3** and racemic α-substituted trialkylsilyl-protected propargyl azides **4**, using the Cu^0-catalyzed Huisgen 1,3-dipolar cycloaddition.[12]

We anticipated that an expansion to the set of azide and alkyne fragments available within our fragment library may prove to be valuable when designing novel triazolamer peptidomimetics. In particular, it was decided that an additional carbon within the fragment backbone (chiral β-alkyl-γ-pentynyl azides and alcohols, Fig. 1) would provide greater structural diversity and flexibility within the triazolamer backbone chain and thus more conformational control when constructing these oligomers in a stepwise fashion.

Herein, we report the synthesis of chiral β-alkyl-γ-pentynyl-alcohols **5** and chiral β-alkyl-trialkylsilyl-protected-γ-pentynyl azides **6** using the 'SuperQuat' (SQ) group as a chiral auxiliary.[13–17] This method provides a novel synthetic strategy to access chiral β-alkyl-γ-pentynyl-alcohols **5** and chiral β-alkyl-trialkylsilyl-protected-γ-pentynyl azides **6** in an enantioselective manner. We also report the coupling of the two fragments in a Huisgen, Cu^0-catalyzed 1,3-dipolar cycloaddition reaction to generate chiral 1,4-disubstituted-(β-alkyl)-γ-1,2,3-triazole scaffolds.

Results and Discussion

The synthetic strategy outlined in Scheme 1 was applied to the two target molecules: chiral β-alkyl-γ-pentynyl-alcohols **5** and chiral β-alkyl-trialkylsilyl-protected-γ-pentynyl azides **6**. The intermediate chiral β-alkyl-trialkylsilyl-protected-γ-pentynyl-alcohol **7** can be generated via $LiBH_4$-mediated reductive SQ-removal of the alkylated SQ-adduct **8**. Alkylation of the SQ adduct **9** could then be achieved by enolization and introduction of an appropriate electrophile, and generation of the SQ adduct could be done via a simple coupling reaction of starting materials **10** and **11**.

Following literature procedures,[13,14] a methyl Grignard addition to (*S*)-methyl esters **12** and **13** in THF provided the (*S*)-dimethyl alcohols **14** and **15** (Scheme 2). This was followed by base-induced intramolecular ring closure in the presence of

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potassium *tert*-butoxide and THF to provide (*S*)-SQ compounds **11a** and **11b** in 58 and 77% overall yield respectively. The $[\alpha]_D$ values of compounds **11a**, **11b**, **12**–**15** correlated well when compared with literature values of the same compounds.[14,15]

Synthesis of the other starting material, 5-trimethylsilyl-pent-5-yn-1-oic acid **10**, was also performed following literature procedures.[18,19] Trimethylsilyl-protection of pent-5-yn-1-ol **17** using 3.0 equivalents of ^{n}BuLi and 6.0 equivalents of TMSCl in THF was followed by oxidation of **17** in the presence of pyridinium chlorochromate (PCC) and DMF (Scheme 2) and gave the desired acid **10** in 70% overall yield.

Coupling of 5-TMS-pent-5-yn-1-oic acid **10** to the (*S*)-*iso*-propyl- and (*S*)-benzyl-SQ auxiliaries **11a** and **11b** was performed via addition of 1.1 equivalents of pivaloyl chloride to the acid **10** in order to the form the mixed anhydride, followed by addition of the lithium oxazolidin-2-one salt of SQ auxiliaries **11a** or **11b** at −40° to −78°C (Scheme 2). Short reaction times (1 h), lower temperatures (−78°C) and a small excess of base (1.1 equiv. Et_3N and 1.2 equiv. ^{n}BuLi) were found to be optimal, with the (*S*)-benzyl (Bn) SQ adduct **9b** (5,5-dimethyl-(4*S*)-benzyloxazolidin-2-one) providing a higher yield (72%) than the (*S*)-^{i}Pr SQ adduct **9a** (5,5-dimethyl-(4*S*)-*iso*-propyloxazolidin-2-one, 56% yield).

The SQ adducts **9a** and **9b** now required asymmetric alkylation. There are no records of the asymmetric alkylation of these compounds; however, there are examples in the literature for the asymmetric alkylation of other *N*-acylated SQ adducts. *N*-Propionyl-5,5-dimethyl-4-substituted-SQ adducts have been shown to produce an enolate on treatment with a stoichiometric base such as lithium hexamethyldisilazide (LiHMDS).[15] Those enolates are known to react diastereoselectively depending on the bulkiness of the chiral substituent on the oxazolidin-2-one ring.[15] A greater level of diastereomeric control was achieved using *N*-propionyl-5,5-dimethyl-4-isopropyloxazolidin-2-one over *N*-propionyl-5,5-dimethyl-4-phenyloxazolidin-2-one. This precedent, along with the efficient scale-up procedures for the synthesis of the *N*-benzyloxazolidin-2-one **11b**,[14] guided the following alkylation reactions of adducts **9a** and **9b**.

Asymmetric alkylation was initiated using either the (*S*)-^{i}Pr or (*S*)-Bn SQ adduct **9a** or **9b**, along with a strong base (LiHMDS, lithium diisopropylamide (LDA), or KHMDS) and in the presence of an alkyl halide or alkyl triflate as the electrophile (Scheme 3, Table 1).

In the presence of alkyl halides as the electrophile, all attempts gave no reaction (entries 1–4, Table 1), with the exception of the (*S*)-^{i}Pr SQ adduct **8a** in the presence of LiHMDS and MeI (entry 5, Table 1). These conditions provided a modest amount (22%) of the major product **8d** (the (4*S*,2*S*)-diastereoisomer), along with trace amounts (3%) of a minor product (the (4*S*,2*R*)-diastereomer). The corresponding diastereoisomers were assigned based on literature stereoselectivity for similar model substrates,[17] NOESY analysis and energy minimization calculations of the major product (see Accessory Publication). It should be noted that no study or optimization of the use of the particular bases in Table 1 has been made.

As it has been shown that more strongly activated electrophiles such as BnBr consistently provide better yields (70–80%) and excellent levels of stereoselectivity on similar substrates and under similar conditions,[17] it was decided to attempt the

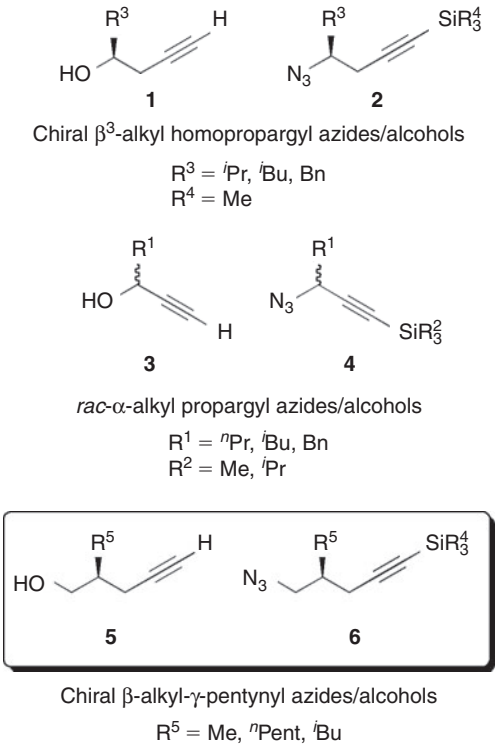
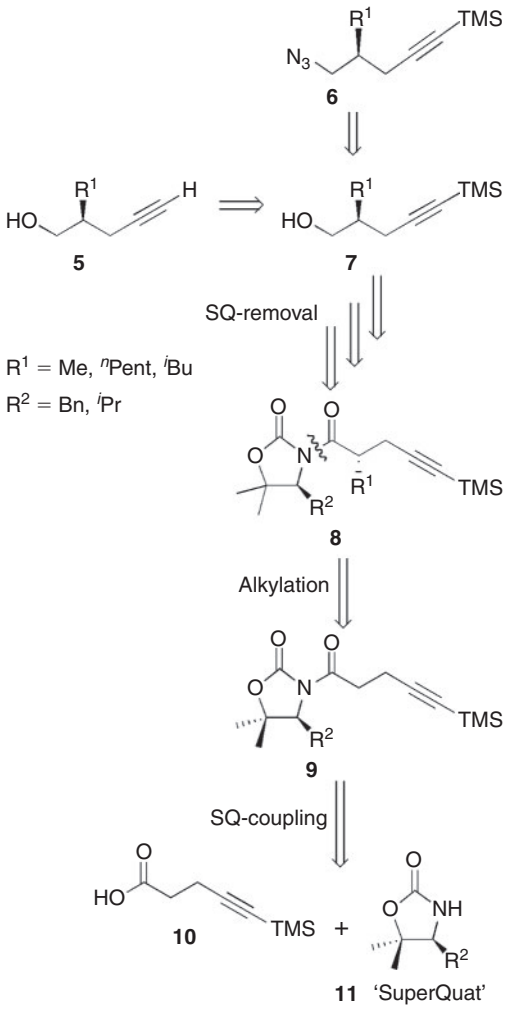
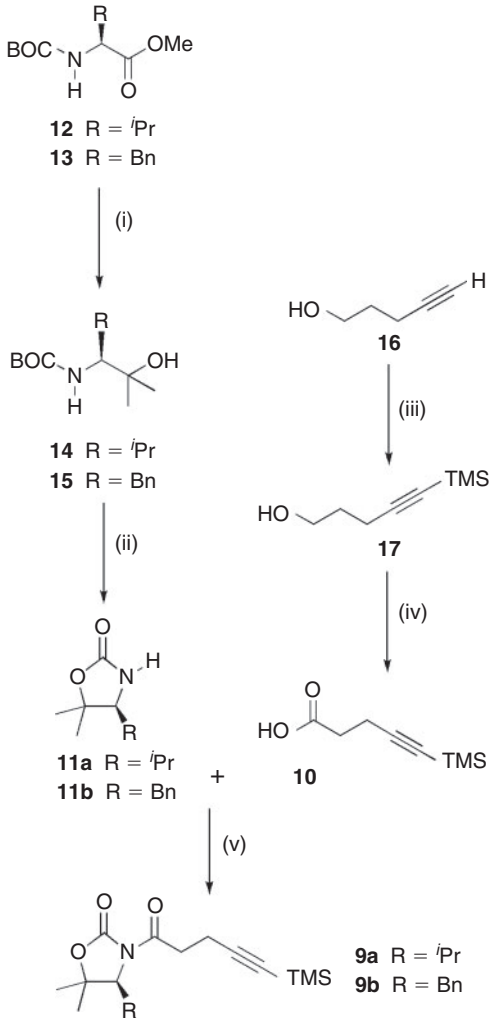


Fig. 1. Click chemistry azides and alkynes.



Scheme 1.

alkylation of (*S*)-SQ adducts **8a** and **8b** using alkyl triflates in the presence of a strong base in THF at −78°C (entries 6–15, Table 1). The triflates used in the present work were easily synthesized from the corresponding alcohols in the presence of pyridine and triflic anhydride,[20] could be purified by flash column chromatography and were all stable at 0°C for weeks.



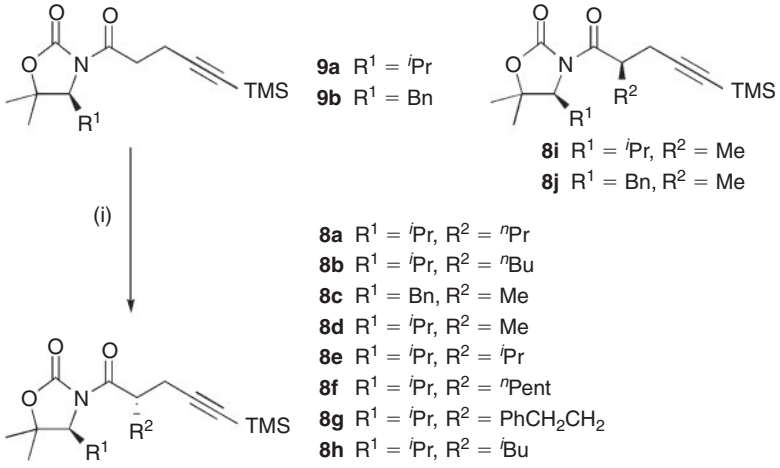
Scheme 2.

Methyl triflate provided the methyl-substituted (4*S*,2*S*)-diastereoisomer **8d** as the sole product in 61% yield when used in conjunction with the (*S*)-^{i}Pr SQ adduct **9a** (entry 7, Table 1). The (*S*)-Bn SQ adduct **9b** showed lower levels of diastereoselectivity, providing a 4:1 mixture of the methyl-substituted (4*S*,2*S*)- and (4*S*,2*R*)-diastereomers **8c**, respectively, with an overall yield of 46% (entry 6, Table 1). The stability of the other triflate electrophiles seemed to influence the yields of the reaction. Pentyl triflate, phenyl ethyl triflate, and ^{i}Bu-triflate all provided the desired (4*S*,2*S*)-diastereoisomers possessing a pentyl-substituent **8f** (entries 9–10, Table 1), phenyl ethyl-substituent **8g** (entry 11, Table 1), and an *iso*-butyl-substituent **8h** (entries 12–15, Table 1) exclusively, in 21–64% yields.

Removal of the SQ chiral auxiliary was performed by $LiBH_4$-mediated reduction, leading to the formation of the intermediate (*S*)-β-alkyl-trialkylsilyl-protected γ-pentynyl alcohols **7a**, **7b**, and **7c**. The reaction proceeded in 60–76% yields using 2.0–3.0 equivalents of $LiBH_4$ in Et_2O/H_2O, 100:1 (Scheme 4).

The desired chiral β-alkyl-trialkylsilyl-γ-pentynyl azide and chiral β-alkyl-γ-pentynyl-alcohol fragments were prepared following the protocol previously described for the synthesis of *rac*-α-propargyl alcohols **3**, *rac*-α-substituted trialkylsilyl-protected propargyl azides **4**, chiral β^3-substituted homopropargyl alcohols **1** and chiral β^3-substituted trialkylsilyl-homopropargyl azides **2** respectively.[11,12] (*S*)-β-Alkyl-γ-pentynyl alcohol **5a** was generated quantitatively via trimethylsilyl-deprotection using 1.5 equivalents of K_2CO_3 in MeOH (Scheme 5), while trimethylsilyl-protected (*R*)-β-alkyl-γ-pentynyl azides **6a**, **6b**, and **6c** were synthesized via mesylation of the corresponding alcohols **7a**, **7b**, and **7c** using 1.5 equivalents of triethylamine and 1.3 equivalents of methanesulfonyl chloride in dichloromethane in 64–84% yield, followed by azide ion displacement of mesylates **18a**, **18b**, and **18c** with 3.0 equivalents of sodium azide in DMF (Scheme 4). The range of yields obtained for the formation of pentynyl azides **6a**–**6c** (44–77%) was found to be lower than for the formation of the propargyl azide fragments **4** (70–87%)[11] but higher than that of homopropargyl azide fragments **2** (43–53%)[12] respectively.

This was thought to be due to a combination of the inductive withdrawing effects of the alkyne and steric hindrance with the



Scheme 3. Alkylation of **9a** and **9b**. Reagents and conditions: (i) base, electrophile, THF, −78°C.

side chain of the mesylate substrate. The mesylates **19** are more deactivated to nucleophilic substitution than the mesylates **20** (Chart 1) owing to the extra carbon between the inductively withdrawing alkyne and the mesylate displacement site.

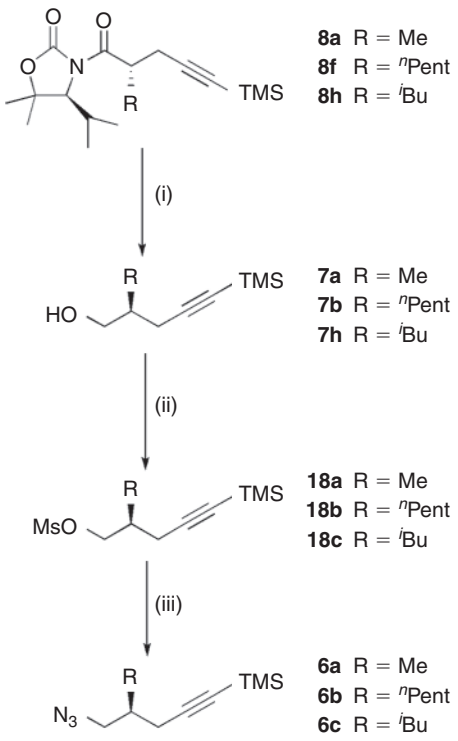
Generation of chiral 1,4-disubstituted-(β-alkyl)-γ-1,2,3-triazole scaffolds in a stepwise manner was attempted using fragments such as alkyne **5a** and azide **6c**. The Huisgen 1,3-dipolar cycloaddition of (4*S*)-^{i}Bu-trimethylsilyl-pent-1-yn-5-ol **5a** and (4*S*)-^{i}Bu-trimethylsilyl-1-ynyl-5-azide **6c** was conducted using Cu^0 in the presence of $^{t}BuOH/H_2O$, 2:1 (Scheme 5).

A good yield was obtained for dimeric triazolamer **21** (73%). This compared well with the efficiency of the generation of α-disubstituted-(1,4-disubstituted)-1,2,3-triazole dimer **24** (76%)[11] and chiral β^3-disubstituted-(1,4-disubstituted)-1,2,3-triazole dimer **25** (80%) (Chart 2).[12]

Trimethylsilyl-deprotection of **21** using 1.5 equivalents of K_2CO_3 in MeOH provided **22** in 81% yield, which is a lower yield than was observed in the conversion of silyl alkyne **7c** to acetylene **5a**. Cycloaddition of **5a** with azide **6c** afforded the pseudo-dimer **21** in 73% yield; however, efficiency of this cycloaddition step was found to decrease when generating the 1,4-disubstituted-(β-isobutyl)-γ-1,2,3-triazole trimer **23** (39%, Scheme 5). This may be as a result of several factors. Increased free rotation around the extended backbone chain may be generating a steric interaction between the copper acetylide and the azide, leading to lower yields. Alternatively, there is evidence in the literature suggesting that polytriazole compounds may act as tridentate ligands in the presence of Cu^I to form stable tricoordinate Cu^I complexes.[21] This has been shown to be true with Cu^I in the presence of bis(pyrazolyl)-methane ligands.[22]

Conclusion

In conclusion, it has been shown that chiral β-alkyl-trialkylsilyl-protected-γ-pentynyl azides and chiral β-alkyl-γ-pentynyl-alcohols may be constructed using asymmetric alkylation of a SQ substrate to install the chiral alkyl side chain. Furthermore, it has been shown that the aforementioned fragments may be sequentially coupled using the Cu^0-catalyzed Huisgen 1,3-dipolar cycloaddition to provide chiral 1,4-disubstituted-(β-alkyl)-γ-1,2,3-triazolamer scaffolds.

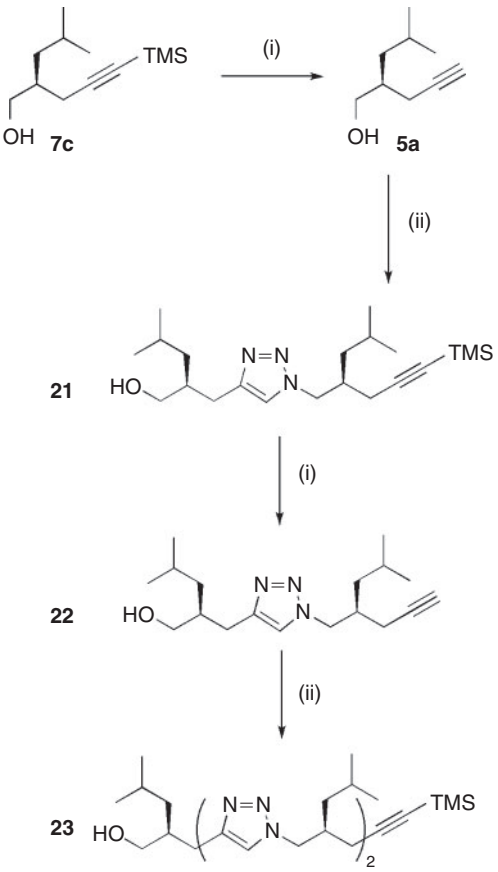


Scheme 4. Synthesis of azides **6a**–**6c**. Reagents and conditions: (i) $LiBH_4$, H_2O, Et_2O, 0°C; (ii) Et_3N, methanesulfonyl (Ms)Cl, CH_2Cl_2, room temperature (rt); (iii) NaN_3, DMF, THF, rt.

Table 1. Alkylation of 9a and 9b
N/R, no reaction

Entry	R^1	Base [equiv.][A]	Electrophile [equiv.]	Time [h]	Yield [%]
1	^{i}Pr	LiHMDS (1.3)[B]	^{n}PrBr (3.0)	5	**8a** N/R
2	^{i}Pr	LDA (1.1)[B]	^{n}PrBr (3.0)	5	**8a** N/R
3	^{i}Pr	KHMDS (1.0)	^{n}BuI (4.0)	5	**8b** N/R
4	Bn	LiHMDS (2.0)[B]	MeI (4.0)	5	**8c** N/R
5	^{i}Pr	LiHMDS (2.0)[B]	MeI (4.0)	5	**8d** 22 (3)[F]
6	Bn	LiHMDS (1.2)[B]	MeOTf (2.0)	4	**8c** 36 (10)[F]
7	^{i}Pr	LiHMDS (1.2)[B]	MeOTf (2.0)	4	**8d** 61
8	^{i}Pr	LiHMDS (1.2)[B]	PentylOTf (2.0)[C]	4	**8f** 21
9	^{i}Pr	NaHMDS (1.2), DMPU (1.2)	PentylOTf (2.0)[C]	4	**8f** N/R
10	^{i}Pr	KHMDS (1.2)	PentylOTf (2.0)[C]	4	**8f** 48
11	^{i}Pr	KHMDS (1.2)	$PhCH_2CH_2OTf$ (2.0)[D]	4	**8g** 30
12	^{i}Pr	KHMDS (1.1)	^{i}BuOTf (2.0)[E]	4	**8h** 26
13	^{i}Pr	KHMDS (1.1)	^{i}BuOTf (3.8)[E]	4	**8h** 46
14	^{i}Pr	KHMDS (1.1)	^{i}BuOTf (4.0)[E]	4	**8h** 64
15	^{i}Pr	KHMDS (1.1)	^{i}BuOTf (5.0)[E]	4	**8h** 49

[A]All reactions were conducted in THF at −78°C.
[B]Prepared in situ from ^{n}BuLi and the corresponding amine at 0°C.
[C]Prepared from PentylOH, C_6H_6N, and $(Tf)_2O$ at 0°C. Purified by flash chromatography.
[D]Prepared from $PhCH_2CH_2OH$, C_6H_6N, and $(Tf)_2O$ at 0°C. Purified by flash chromatography.
[E]Prepared from ^{i}BuOH, C_6H_6N, and $(Tf)_2O$ at 0°C. Solvent was evaporated and the product used directly.
[F]Number in brackets gives yield of other diastereomer (compounds **8i** and **8j**).



Scheme 5. Preparation of triazolamers **21**–**23**. Reagents and conditions: (i) K_2CO_3, MeOH, room temperature; (ii) **6c**, Cu^0, ^{t}BuOH/H_2O 2:1.

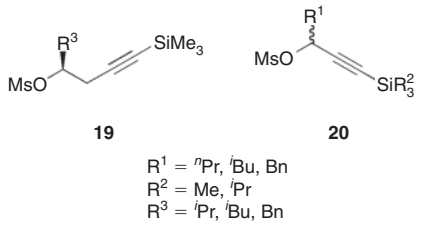


Chart 1.

Experimental

General experimental details and spectra for key intermediates can be found in the Accessory Publication.

*General Procedure for the Synthesis of Chiral SQ Adducts **9a** and **9b***

To a three-necked, argon-flushed 100-mL round-bottom flask fitted with an argon line, stopper and septum was added the acid **10** (1.16 g, 6.8 mmol) along with dry Et_2O (15 mL) and triethylamine (7.5 mmol, 1045 μL). The flask was cooled to −78°C and pivaloyl chloride (7.5 mmol, 885 μL) was added slowly via syringe. The mixture was left to stir at −78°C for 5 min, then warmed to 0°C and left to stir for 1 h (Solution A). Separately, (*S*)-^{i}Pr SQ **11a** (7.5 mmol, 1.18 g) was added to a three-necked, argon-flushed 50-mL round-bottom flask fitted with an argon line, stopper, and septum along with dry THF (5 mL) and cooled to −78°C. ^{n}BuLi (8.2 mmol, 5.13 mL of a 1.6 M solution in hexanes) was added via syringe over 5 min, to

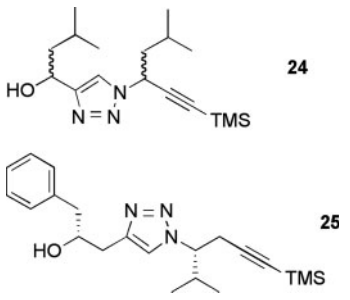


Chart 2.

allow for the formation of the anion of **11a** in situ (Solution B). After 10 min, Solution A was cooled to −78°C and cannulated onto Solution B and the mixture was left to stir for 15 min. The reaction mixture was then warmed to 0°C and left to stir for 45 min. The solution was quenched with sat. ammonium chloride (10 mL), extracted with Et_2O (2 × 30 mL), washed with H_2O (30 mL), brine (20 mL), dried with sodium sulfate, filtered, and concentrated under vacuum to leave a slightly pink oil. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane. In the same manner, intermediate **11b** generated adduct **9b**.

*4-(S)-iso-Propyl-5,5-dimethyl-3-(5-trimethylsilanyl-pent-4-ynoyl)-oxazolidin-2-one **9a***

The chiral SQ adduct **9a** was obtained as a colourless oil (1.52 g, 72%). $R_f = 0.63$ (20% ethyl acetate/hexane). $[\alpha]_D^{29}$ +25.9 (*c* 1.00 in $CHCl_3$). ν_{max}(NaCl)/cm^{-1} 2965, 2178, 1780, 1704, 1376, 844. δ_H (300 MHz, $CDCl_3$) 0.0 (s, 9H), 0.86 (d, 3H, *J* 6.8), 0.95 (d, 3H, *J* 7.0), 1.31, 1.44 (2 × s, 6H), 2.04–2.09 (m, 1H), 2.51 (dd, 1H, *J* 2.9 and 7.4), 2.53 (dd, 1H, *J* 2.5 and 7.1), 3.05 (dt, 1H, *J* 7.1 and 14.2), 3.19 (dt, 1H, *J* 7.4 and 14.1), 4.08 (d, 1H, *J* 3.2). δ_C (75 MHz, $CDCl_3$) −0.5, 14.8, 16.5, 20.8, 21.1, 28.3, 29.0, 34.3, 65.8, 82.4, 84.6, 104.7, 152.9, 171.6. *m*/*z* 310.1835; $C_{16}H_{28}NO_3Si$ requires M + H 310.1833.

*4-(S)-Benzyl-5,5-dimethyl-3-(5-trimethylsilanyl-pent-4-ynoyl)-oxazolidin-2-one **9b***

Compound **9b** was prepared by the same procedure as described for compound **9a**, employing (*S*)-Bn SQ **11b**. It was obtained as a colourless viscous oil (917 mg, 56%). $R_f = 0.35$ (10% ethyl acetate/hexane). $[\alpha]_D^{30}$ −7.4 (*c* 1.00 in $CHCl_3$). ν_{max}(NaCl)/cm^{-1} 3030, 2960, 2177, 1780, 1703, 1378, 1356, 1277, 1251, 1104, 844. δ_H (300 MHz, $CDCl_3$) 0.11 (s, 9H), 1.34 (d, 6H, *J* 6.1), 2.50–2.55 (m, 2H), 2.86 (dd, 1H, *J* 9.5 and 14.4), 3.11–3.16 (m, 3H), 4.48 (dd, 1H, *J* 3.9 and 9.5), 7.17–7.31 (m, 5H). δ_C (75 MHz, $CDCl_3$) −0.4, 14.6, 21.8, 28.1, 34.5, 34.8, 63.1, 81.9, 84.8, 104.7, 126.4, 128.2, 128.6, 136.4, 152.0, 171.0. *m*/*z* 358.1842; $C_{20}H_{28}NO_3Si$ requires M + H 358.1833.

*General Procedure for the Alkylation of Chiral SQ Adducts **9a** and **9b***

To a flame-dried, argon-filled 5-mL round-bottom flask fitted with a stopper, argon line and septum was added hexamethyldisilazane (2.0 mmol, 452 μL) and dry THF (1 mL). The flask was cooled to 0°C and ^{n}BuLi (2.0 mmol, 1.3 mL of a 1.6 M solution in hexanes) was added via syringe and the mixture was left to stir at 0°C for 30 min (Solution A). Separately, a flame-dried, argon-filled 25-mL round-bottom flask fitted with a stopper, argon line, and septum was injected with compound **9a** (1.0 mmol, 300 mg in 1 mL dry THF) via syringe and cooled to

−78°C (Solution B). Solution A was cannulated onto solution B and the reaction mixture was left to stir at −78°C for 1 h. The appropriate electrophile (methyl iodide, 4.0 mmol, 249 μL) was added slowly via syringe at −78°C and the mixture was left to stir at −78°C. After 5 h, the solution was warmed to −40°C and quenched with sat. NH_4Cl (3 mL), then it was left to warm to room temperature (rt). The reaction mixture was extracted with Et_2O (2 × 20 mL), washed with H_2O (15 mL), brine (15 mL), dried with sodium sulfate, filtered, and concentrated at reduced pressure to leave a yellow residue. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane to afford the compound **8d**.

4-(S)-Benzyl-5,5-dimethyl-3-(2-(S)-methyl-5-trimethylsilanyl-pent-4-ynoyl)-oxazolidin-2-one ***8c***

Compound **8c** was obtained as a major diastereoisomer using the same procedure as described for compound **8d**. The reaction was conducted in the presence of (*S*)-Bn SQ and with methyl triflate as the electrophile. Compound **8c** was obtained as a colourless viscous oil (111 mg, 36%). $R_f = 0.38$ (10% ethyl acetate/hexane). $[\alpha]_D^{29}$ +3.5 (*c* 2.00 in CH_2Cl_2). δ_H (300 MHz, $CDCl_3$) 0.09 (s, 9H), 1.18 (d, 3H, *J* 6.9), 1.35 (s, 3H), 1.36 (s, 3H), 2.34 (dd, 1H, *J* 7.1 and 16.8), 2.51 (dd, 1H, *J* 7.0 and 16.9), 2.88 (dd, 1H, *J* 9.0 and 14.3), 3.03 (dd, 1H, *J* 4.4 and 14.3), 3.87 (sextet, 1H, *J* 7.0), 4.49 (dd, 1H, 4.5 and 9.0), 7.18–7.28 (m, 5H). δ_C (300 MHz, $CDCl_3$) 0.3, 17.2, 22.0, 23.5, 28.2, 35.3, 37.7, 63.4, 82.1, 85.8, 104.2, 126.7, 128.5, 129.0, 136.6, 152.1, 175.2. *m*/*z* 372.2000; $C_{21}H_{30}NO_3Si$ requires M + H 372.1995.

A separate fraction was identified as the minor diastereomer **8j**.

4-(S)-Benzyl-5,5-dimethyl-3-(2-(R)-methyl-5-trimethylsilanyl-pent-4-ynoyl)-oxazolidin-2-one ***8j***

Compound **8j** was obtained as a minor diastereoisomer in the formation of compound **8c**, when conducted in the presence of (*S*)-Bn SQ and methyl triflate as the electrophile. Compound **8j** was obtained as a colourless oil (34 mg, 10%). δ_H (300 MHz, $CDCl_3$) 0.10 (s, 9H), 1.19 (d, 3H, *J* 6.9), 1.36 (s, 3H), 1.37 (s, 3H), 2.36 (dd, 1H, *J* 7.1 and 16.9), 2.54 (dd, 1H, *J* 6.9 and 16.8), 2.83 (dd, 1H, *J* 10.0 and 14.5), 3.18 (dd, 1H, *J* 3.2 and 14.5), 3.90 (sextet, 1H, *J* 7.0), 4.50 (dd, 1H, 4.2 and 9.2), 7.20–7.26 (m, 5H).

4-(S)-iso-Propyl-5,5-dimethyl-3-(2-(S)-methyl-5-trimethylsilanyl-pent-4-ynoyl)-oxazolidin-2-one ***8d***

Compound **8d** was obtained as a major diastereoisomer in the form of a colourless oil (70 mg, 22%). $R_f = 0.46$ (10% ethyl acetate/hexane). $[\alpha]_D^{23}$ +46.2 (*c* 1.89 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 2969, 2177, 1779, 1703, 1249. δ_H (300 MHz, $CDCl_3$) 0.07 (s, 9H), 0.91 (d, 3H, *J* 6.8), 0.97 (d, 3H, *J* 6.9), 1.29 (d, 3H, *J* 6.9), 1.36 (s, 3H), 1.48 (s, 3H), 2.10 (doublet of septets, 1H, *J* 3.3 and 6.8), 2.33 (dd, 1H, *J* 16.8 and 6.9), 2.55 (dd, 1H, *J* 7.4 and 16.8), 3.92 (sextet, *J* 7.0), 4.14 (d, 1H, *J* 3.3). δ_C (75 MHz, $CDCl_3$) 0.00, 16.9, 18.0, 21.3, 21.5, 23.4, 28.6, 29.5, 37.9, 66.2, 82.8, 85.7, 104.5, 153.1, 175.8. *m*/*z* 324.1995; $C_{17}H_{30}NO_3Si$ requires M + H 324.1989.

A separate fraction was identified as the minor diastereomer **8i**.

4-(S)-iso-Propyl-5,5-dimethyl-3-(2-(R)-methyl-5-trimethylsilanyl-pent-4-ynoyl)-oxazolidin-2-one ***8i***

Compound **8i** was obtained as a minor diastereoisomer in the formation of compound **8d**, when conducted in the presence of (*S*)-^{i}Pr SQ and methyl iodide as the electrophile. Compound **8i** was obtained as a clear viscous oil (8 mg, 3%). δ_H (300 MHz, $CDCl_3$) 0.10 (s, 9H), 0.95 (d, 3H, *J* 6.8), 1.03 (d, 3H, *J* 7.0), 1.20 (d, 3H, *J* 6.8), 1.35 (s, 3H), 1.49 (s, 3H), 2.11 (doublet of septets, 1H, *J* 2.9 and 6.8), 2.50 (dd, 1H, *J* 16.9 and 6.2), 2.64 (dd, 1H, *J* 7.1 and 16.9), 3.97 (sextet, *J* 6.7), 4.17 (d, 1H, *J* 3.0).

4-(S)-iso-Propyl-5,5-dimethyl-3-(2-(S)-pentyl-5-trimethylsilanyl-pent-4-ynoyl)-oxazolidin-2-one ***8f***

Compound **8f** was prepared by the same procedure as described for compound **8d**, employing pentyl triflate (prepared as described in the literature[20]). It was obtained as a colourless viscous oil (56 mg, 21%). It was also prepared using the same procedure as described for compound **8d**, employing potassium hexamethyldisilazide as a base, and was obtained then as a colourless viscous oil (220 mg, 48%). $R_f = 0.63$ (10% ethyl acetate/hexane). $[\alpha]_D^{30}$ +36.4 (*c* 1.68 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 2961, 2176, 1780, 1698, 1249, 1171. δ_H (300 MHz, $CDCl_3$) 0.06 (s, 9H), 0.83 (t, 3H, *J* 6.2), 0.92 (d, 3H, *J* 6.8), 0.99 (d, 3H, *J* 7.0), 1.15–1.33 (m, 6H), 1.37 (s, 3H), 1.47 (s, 3H), 1.48–1.60 (m, 3H), 2.11 (doublet of septets, 1H, *J* 3.0 and 6.9), 2.38 (dd, 1H, *J* 5.5 and 16.8), 2.51 (dd, 1H, *J* 8.9 and 16.8), 3.99–4.08 (m, 1H), 4.17 (d, 1H, *J* 2.9). δ_C (75 MHz, $CDCl_3$) −0.0, 13.9, 16.9, 21.2, 21.5, 22.2, 22.4, 26.2, 28.8, 29.6, 31.6, 32.6, 42.3, 66.3, 82.3, 85.5, 104.6, 153.2, 175.5.

4-(S)-Isopropyl-5,5-dimethyl-3-(2-(S)-phenethyl-5-trimethylsilanyl-pent-4-ynoyl)-oxazolidin-2-one ***8g***

Compound **8g** was prepared by the same procedure as described for compound **8d**, employing phenylethyl triflate (prepared as described in the literature[23]). It was obtained as a colourless oil (715 mg, 30%). $R_f = 0.49$ (10% ethyl acetate/hexane). $[\alpha]_D^{29}$ +23.0 (*c* 1.77 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3027, 2996, 2175, 1777, 1698, 843. δ_H (300 MHz, $CDCl_3$) 0.10 (s, 9H), 0.96 (d, 3H, *J* 6.8), 1.04 (d, 3H, *J* 7.0), 1.40 (s, 3H), 1.50 (s, 3H), 1.79–2.20 (m, 3H), 2.45–2.71 (m, 4H), 4.09–4.20 (m, 1H), 4.21 (d, 1H, *J* 2.9). δ_C (75 MHz, $CDCl_3$) 0.3, 16.8, 21.1, 21.5, 22.1, 28.6, 29.5, 33.1, 34.4, 42.1, 66.4, 82.6, 85.8, 104.2, 125.9, 128.2, 128.3, 141.4, 153.1, 174.8. *m*/*z* 414.2459; $C_{24}H_{36}NO_3Si$ requires M + H 414.2464.

3-(2-(S)-Isobutyl-5-trimethylsilanyl-pent-4-ynoyl)-4-(S)-isopropyl-5,5-dimethyl-oxazolidin-2-one ***8h***

Compound **8h** was prepared by the same procedure as described for compound **8d**, employing *iso*-butyl triflate (prepared as described in the literature[24]). It was obtained as a colourless viscous oil (961 mg, 64%). $R_f = 0.41$ (10% ethyl acetate/hexane). $[\alpha]_D^{25}$ +49.2 (*c* 2.42 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 2960, 2176, 1780, 1698, 843. δ_H (300 MHz, $CDCl_3$) −0.06 (s, 9H), 0.79–0.82 (m, 9H), 0.84 (d, 3H, *J* 7.0), 1.16–1.25 (m, 1H), 1.28 (s, 3H), 1.37 (s, 3H), 1.45–1.60 (m, 2H), 2.00–2.08 (m, 1H), 2.23 (dd, 1H, *J* 5.1 and 16.7), 2.36 (dd, 1H, *J* 9.1 and 16.7), 4.04–4.14 (m, 2H). δ_C (75 MHz, $CDCl_3$) −0.2, 16.6, 21.0, 21.3, 22.3, 22.4, 22.7, 25.6, 28.6, 29.3, 40.1, 41.8, 66.0, 82.1, 85.4, 104.2, 152.8, 175.4. *m*/*z* 366.2455; $C_{20}H_{36}NO_3Si$ requires M + H 366.2459.

General Procedure for the Synthesis of Chiral β-Alkyl-trialkylsilyl-protected γ-Pentynyl Alcohols ***7a–7c***

To a 10-mL round-bottomed flask was added compound **8d** (0.56 mmol, 209 mg) along with Et_2O (12 mL) and H_2O (1.69 mmol, 30 μL), and the flask was cooled to 0°C. Lithium borohydride (1.69 mmol, 37 mg) was added in small portions over the course of 15 min, and the heterogeneous mixture was

left to stir vigorously at 0°C. The reaction was monitored by TLC. After 1 h, the reaction mixture was quenched with NH_4Cl solution (4 mL), extracted with Et_2O (3×10 mL), and the organic extracts were pooled. The organic layer was dried with sodium sulfate, filtered, and concentrated on the rotary evaporator to leave a milky residue. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane.

2-(R)-Methyl-5-trimethylsilanyl-pent-4-yn-1-ol **7a**

Compound **7a** was obtained as a colourless oil (66 mg, 69%). $R_f = 0.34$ (20% ethyl acetate/hexane). ν_{max} (NaCl)/cm^{-1} 3349, 2960, 2174, 1250, 1037, 842. δ_H (300 MHz, $CDCl_3$) 0.12 (s, 9H, $Si(CH_3)_3$), 0.97 (d, 3H, *J* 6.8, CH_3), 1.69 (s, 1H, OH), 1.86 (octet, 1H, *J* 6.4, H2), 2.23 (d, 2H, *J* 1.0, H3), 3.55 (d, 2H, *J* 6.1, C*H*$_2$OH). δ_C (75 MHz, $CDCl_3$) −0.3 ($Si(CH_3)_3$), 15.8 (C5), 23.5 (C3), 34.7 (C4), 66.9 (CH_2OH), 85.8 (C1), 105.1 (C2). *m*/*z* 171.1201; $C_9H_{19}OSi$ requires M + H 171.1200.

2-(R)-Pentyl-5-trimethylsilanyl-pent-4-yn-1-ol **7b**

Compound **7b** was prepared from compound **8f** using the same procedure as described for compound **7a**. It was obtained as a colourless oil (84 mg, 60%). $R_f = 0.63$ (20% ethyl acetate/hexane). $[\alpha]_D^{26}$ +8.2 (*c* 1.24 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3335, 2958, 2174, 1249, 988, 842, 760. δ_H (300 MHz, $CDCl_3$) 0.1 (s, 9H), 0.84 (t, 3H, *J* 6.4), 1.18–1.32 (m, 8H), 1.62–1.70 (m, 1H), 2.11 (s, 1H), 2.22 (dd, 1H, *J* 6.6 and 17.1), 2.31 (dd, 1H, *J* 5.6 and 17.0), 3.55 (dd, 1H, *J* 7.0 and 10.9), 3.61 (dd, 1H, *J* 4.8 and 10.8). δ_C (75 MHz, $CDCl_3$) 0.0, 14.0, 21.7, 22.5, 26.5, 30.2, 31.9, 39.8, 65.3, 86.1, 105.6. *m*/*z* 227.1834; $C_{13}H_{27}OSi$ requires M + H 227.1826.

*2-(R)-*iso*-Butyl-5-trimethylsilanyl-pent-4-yn-1-ol* **7c**

Compound **7c** was prepared from compound **8h** using the same procedure as described for compound **7a**. It was obtained as a colourless oil (1.12 g, 76%). $R_f = 0.66$ (20% ethyl acetate/hexane). $[\alpha]_D^{25}$ +8.0 (*c* 1.36 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3347, 2957, 2174, 1250, 1029, 842. δ_H (300 MHz, $CDCl_3$) 0.1 (s, 9H), 0.84 (d, 3H, *J* 6.2), 0.86 (d, 3H, *J* 6.1), 1.05–1.23 (m, 2H), 1.55–1.68 (m, 1H), 1.70–1.84 (m, 1H), 2.20 (dd, 1H, *J* 6.5 and 17.1), 2.08 (s, 1H), 2.30 (dd, 1H, *J* 5.4 and 17.1), 3.52 (dd, 1H, *J* 6.8 and 10.8), 3.60 (dd, 1H, *J* 4.5 and 10.8). δ_C (75 MHz, $CDCl_3$) 0.0, 21.9, 22.5, 23.0, 25.1, 37.5, 39.7, 65.5, 86.1, 105.6. *m*/*z* 213.1670; $C_{12}H_{25}OSi$ requires M + H 213.1669.

General Procedure for the Synthesis of Chiral β-Alkyl-trialkylsilyl-protected γ-Pentynyl Mesylates **18a–18c**

The chiral alcohol **7a** (65 mg, 0.4 mmol) was dissolved in dry CH_2Cl_2 (1 mL) and cooled to 0°C. Triethylamine (0.6 mmol, 79 μL) was added in one portion followed by methanesulfonyl chloride (0.5 mmol, 39 μL). The reaction mixture was left to stir at 0°C. After 20 min, the solution was diluted with CH_2Cl_2 (30 mL), washed with H_2O (20 mL), brine (20 mL), dried with sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel, using ethyl acetate/hexane as the eluent.

Methanesulfonic Acid 2-(R)-Methyl-5-trimethylsilanyl-pent-4-ynyl Ester **18a**

Compound **18a** was obtained as a colourless oil (75 mg, 78%). $R_f = 0.66$ (20% ethyl acetate/hexane). $[\alpha]_D^{29}$ −5.5 (*c* 1.24 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 2961, 2174, 1358, 1250, 1177, 964, 843. δ_H (300 MHz, $CDCl_3$) 0.1 (s, 9H), 1.02 (d, 3H, *J* 6.8), 2.07 (octet, 1H, *J* 6.4), 2.27 (d, 2H, *J* 6.1), 2.97 (s, 3H), 4.1 (d, 2H, *J* 6.1). δ_C (75 MHz, $CDCl_3$) −0.1, 15.7, 23.2, 32.2, 37.0, 72.8, 87.0, 103.5. *m*/*z* 249.0981; $C_{10}H_{21}O_3SSi$ requires M + H 249.0975.

Methanesulfonic Acid 2-(R)-Pentyl-5-trimethylsilanyl-pent-4-ynyl Ester **18b**

Compound **18b** was prepared by the same procedure as described for compound **18a** and was obtained as a colourless oil (70 mg, 64%). $R_f = 0.63$ (20% ethyl acetate/hexane). $[\alpha]_D^{26}$ +1.5 (*c* 1.16 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 2957, 2174, 1359, 1250, 1778, 956, 843. δ_H (300 MHz, $CDCl_3$) 0.11 (s, 9H), 0.85 (t, 3H, *J* 6.8), 1.20–1.38 (m, 8H), 1.90 (septet, 1H, *J* 5.8), 2.27 (dd, 1H, *J* 6.4 and 17.2), 2.36 (dd, 1H, 5.5 and 17.2), 2.98 (s, 3H), 4.14 (dd, 1H, *J* 6.6 and 9.7), 4.21 (dd, 1H, *J* 4.9 and 9.7). δ_C (75 MHz, $CDCl_3$) −0.0, 13.9, 21.2, 22.4, 26.1, 29.7, 31.6, 36.9, 37.0, 71.4, 87.0, 103.6. *m*/*z* 305.1620; $C_{14}H_{29}O_3SSi$ requires M + H 305.1601.

*Methanesulfonic Acid 2-(R)-*iso*-Butyl-5-trimethylsilanyl-pent-4-ynyl Ester* **18c**

Compound **18c** was prepared by the same procedure as described for compound **18a** and was obtained as a colourless viscous oil (572 mg, 84%). $R_f = 0.63$ (20% ethyl acetate/hexane). $[\alpha]_D^{23}$ −0.3 (*c* 5.48 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 2958, 2175, 1359, 1250, 1178, 949, 843. δ_H (300 MHz, $CDCl_3$) 0.89 (s, 9H), 0.85 (d, 3H, *J* 6.5), 0.87 (d, 3H, *J* 6.5), 1.18 (ddd, 1H, *J* 7.2, 6.7, and 13.9), 1.26 (ddd, 1H, *J* 7.2, 6.7, and 13.9), 1.62 (nonet, 1H, *J* 6.8), 1.92–2.04 (m, 1H), 2.24 (dd, 1H, *J* 6.4 and 17.2), 2.34 (dd, 1H, *J* 5.4 and 17.2), 4.11 (dd, 1H, *J* 6.7 and 9.7), 4.20 (dd, 1H, *J* 4.6 and 9.7). δ_C (75 MHz, $CDCl_3$) −0.1, 21.3, 22.3, 22.7, 24.9, 34.7, 36.9, 38.9, 71.6, 87.0, 103.6. *m*/*z* 291.1449; $C_{13}H_{27}O_3SSi$ requires M + H 291.1445.

General Procedure for the Synthesis of Chiral β-Alkyl-trialkylsilyl-protected γ-Pentynyl Azides **6a–6c**

The mesylate **18a** (72 mg, 0.29 mmol) was dissolved in dry DMF (1 mL) and to this solution was added sodium azide (0.87 mmol, 57 mg) and the mixture was stirred vigorously at rt. The reaction was monitored by TLC. After 72 h, the reaction mixture was diluted with Et_2O (15 mL), washed with H_2O (15 mL), brine (10 mL), dried with sodium sulfate, filtered, and concentrated under vacuum to leave a yellow oil. The oil was purified by column chromatography on silica gel, using ethyl acetate/hexane as the eluent.

(5-Azido-4-(R)-methyl-pent-1-ynyl)trimethylsilane **6a**

Compound **6a** was obtained as a yellow oil (20 mg, 57%). $R_f = 0.49$ (5% ethyl acetate/hexane). ν_{max} (NaCl)/cm^{-1} 2959, 2176, 2100, 1733, 1457, 1250, 1037, 843. δ_H (300 MHz, $CDCl_3$) 0.14 (s, 9H), 1.01 (d, 3H, *J* 6.7), 1.92 (octet, 1H, *J* 6.5), 2.25 (d, 2H, *J* 6.0), 3.20–3.33 (m, 2H). δ_C (75 MHz, $CDCl_3$) −0.3, 16.8, 24.1, 32.6, 55.9, 86.3, 103.8.

(4-(R)-Azidomethyl-6-methyl-non-1-ynyl) trimethylsilane **6b**

Compound **6b** was prepared by the same procedure as described for compound **6a** and was obtained as a colourless oil (24 mg, 44%). $R_f = 0.76$ (5% ethyl acetate/hexane). ν_{max} (NaCl)/cm^{-1} 2960, 2176, 2099, 1249, 843. δ_H (300 MHz,

$CDCl_3$) 0.14 (s, 9H), (t, 3H, *J* 7.0), 1.24–1.35 (m, 8H), 1.73 (septet, 1H, *J* 6.1), 2.24 (dd, 1H, *J* 6.5 and 17.1), 2.32 (dd, 1H, *J* 5.6 and 17.1), 3.31 (dd, 1H, *J* 2.1 and 12.2), 3.36 (dd, 1H, *J* 1.4 and 12.2). δ_C (75 MHz, $CDCl_3$) −0.3, 14.0, 22.3, 22.5, 26.3, 31.1, 31.8, 37.6, 54.5, 86.6, 104.3. *m*/*z* 252.1894; $C_{13}H_{26}N_3Si$ requires M + H 252.1896.

(4-(R)-Azidomethyl-6-methyl-hept-1-ynyl) trimethylsilane ***6c***

Compound **6c** was prepared by the same procedure as described for compound **6a** and was obtained as a colourless oil (356 mg, 77%). $R_f = 0.39$ (100% hexane). $[\alpha]_D^{25}$ −1.5 (*c* 1.57 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 2971, 2178, 2101, 1252, 845. δ_H (300 MHz, $CDCl_3$) 0.13 (s, 9H), 0.86 (d, 3H, *J* 4.7), 0.88 (d, 3H, *J* 6.5), 1.16 (ddd, 1H, *J* 6.8, 7.1, and 13.8), 1.25 (ddd, 1H, *J* 6.5, 7.3, and 13.8), 1.61 (nonet, 1H, *J* 6.7), 1.75–1.87 (m, 1H), 2.22 (dd, 1H, *J* 6.4 and 17.1), 2.31 (dd, 1H, *J* 5.4 and 17.1), 3.30 (dd, 1H, *J* 6.5 and 12.1), 3.35 (dd, 1H, *J* 5.4 and 12.1). δ_C (75 MHz, $CDCl_3$) 0.1, 22.4, 22.9, 25.1, 35.3, 40.5, 54.7, 86.7, 104.2. *m*/*z* 238.1739; $C_{12}H_{24}N_3Si$ requires M + H 238.1739.

Procedure for the Synthesis of 2-(R)-iso-Butyl-pent-4-yn-1-ol ***5a***

The trimethylsilyl-pentynyl alcohol **7a** (300 mg, 1.4 mmol) was dissolved in dry MeOH (2 mL) and to this was added anhydrous K_2CO_3 (2.1 mmol, 292 mg) in one portion. The reaction mixture was left to stir at rt. After 1.5 h, the reaction mixture was diluted with Et_2O (30 mL), washed with H_2O (15 mL), brine (15 mL), dried with magnesium sulfate, filtered, and evaporated at reduced pressure to leave a yellow oil. ^{1}H NMR spectroscopy of the oil showed the desired product was obtained in high purity and it was used without any further purification.

2-(R)-iso-Butyl-pent-4-yn-1-ol ***5a***

Compound **5a** was obtained as a yellow oil (198 mg, 100%). $R_f = 0.46$ (20% ethyl acetate/hexane). ν_{max} (NaCl)/cm^{-1} 3314, 3311, 2956, 1468, 1024, 629. δ_H (300 MHz, $CDCl_3$) 0.87 (d, 3H, *J* 6.5), 0.89 (d, 3H, *J* 6.5), 1.12–1.28 (m, 2H), 1.65 (octet, 1H, *J* 6.8), 1.73–1.87 (m, 1H), 1.95 (t, 1H, *J* 2.7), 2.22 (ddd, 1H, *J* 2.7, 6.4, and 16.9), 2.32 (ddd, 1H, *J* 2.7, 5.3, and 16.9), 3.55–3.68 (m, 2H). δ_C (75 MHz, $CDCl_3$) 20.3, 22.5, 22.9, 25.1, 37.2, 39.5, 65.2, 69.6, 82.6. *m*/*z* 141.1279; $C_9H_{16}O$ requires M + H 141.1274.

General Procedure for the Synthesis of Chiral 1,4-Disubstituted-(β-iso-butyl)-γ-1,2,3-triazole Oligomers ***21*** *and* ***23***

The acetylene **5a** (170 mg, 1.21 mmol) was added to a 25-mL round-bottom flask along with the azide **6c** (1.21 mmol, 288 mg), *tert*-butanol (2.7 mL), H_2O (1.3 mL), and excess Cu^0 powder (40-mesh, 1.0 g). The mixture was left to stir at rt overnight. After 24 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and flushed through a plug of Celite. The filtrate was washed with H_2O (20 mL), brine (20 mL), dried with magnesium sulfate, filtered, and concentrated at reduced pressure to leave a yellow oil. The oil was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane.

2-[1-(2-(R)-iso-Butyl-5-trimethylsilanyl-pent-4-ynyl)-1H-[1,2,3]triazol-4-ylmethyl]-4-(R)-methyl-pentan-1-ol ***21***

Compound **21** was obtained as a colourless oil (334 mg, 73%). $R_f = 0.31$ (30% ethyl acetate/hexane). $[\alpha]_D^{28}$ −21.3 (*c* 1.96 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3353, 2955, 2174, 1467, 1367, 1249, 1049, 1019, 840, 759. δ_H (300 MHz, $CDCl_3$) 0.01 (s, 9H), 0.67–0.76 (m, 12H), 0.89–1.22 (m, 4H), 1.44–1.54 (m, 2H), 1.73–1.86 (m, 1H), 1.90–2.13 (m, 3H), 2.63 (d, 2H, *J* 6.1), 3.26 (dd, 1H, *J* 6.6 and 11.1), 3.40 (dd, 1H, *J* 4.1 and 11.1), 3.52 (s, 1H), 4.17 (d, 2H, *J* 6.2), 7.27 (s, 1H). δ_C (75 MHz, $CDCl_3$) −0.2, 21.6, 21.8, 22.5, 22.6, 22.8, 24.6, 24.9 (2), 26.7, 35.5, 38.0, 39.7, 39.8 (2), 52.7, 63.9, 87.3, 103.1, 122.5, 145.5. *m*/*z* 378.2935; $C_{21}H_{40}N_3OSi$ requires M + H 378.2935.

2-(1-{2-[1-(2-(R)-iso-Butyl-5-trimethylsilanyl-pent-4-ynyl)-1H-[1,2,3]triazol-4-ylmethyl]-4-(R)-methyl-pentyl}-1H-[1,2,3]triazol-4-ylmethyl)-4-(R)-methyl-pentan-1-ol ***23***

Compound **23** was prepared by the same procedure as described for compound **21** and was obtained as a colourless, viscous oil (96 mg, 39%). $R_f = 0.33$ (60% ethyl acetate/hexane). $[\alpha]_D^{23}$ −19.7 (*c* 1.55 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3393, 2956, 2176, 1465, 1250, 1052, 843. δ_H (300 MHz, $CDCl_3$) 0.15 (s, 9H), 0.77–0.85 (m, 18H), 0.95–1.33 (m, 6H), 1.62 (nonet, 3H, *J* 6.7), 1.82–1.95 (m, 1H), 2.05–2.20 (m, 3H), 2.31–2.43 (m, 1H), 2.55 (d, 2H, *J* 5.8), 2.68 (dd, 1H, *J* 6.9 and 14.6), 2.76 (dd, 1H, *J* 5.4 and 14.9), 3.35 (dd, 1H, *J* 6.5 and 11.1), 3.48 (dd, 1H, *J* 3.9 and 11.1), 3.58 (s, 1H), 4.21 (d, 2H, *J* 6.2), 4.27 (d, 2H, *J* 6.4), 7.41 (s, 1H), 7.63 (s, 1H). δ_C (75 MHz, $CDCl_3$) 0.0, 21.8, 22.0, 22.2, 22.8, 22.9, 23.0, 24.8, 24.8, 24.9, 25.1, 26.7, 27.0, 35.8, 36.8, 38.0, 40.0, 40.1, 40.4, 52.7, 52.9, 64.5, 87.7, 103.2, 123.1, 123.2, 144.1, 145.4. *m*/*z* 543.4222; $C_{30}H_{55}N_6OSi$ requires M + H 543.4201.

Procedure for the Trimethylsilyl-deprotection of Chiral 1,4-Disubstituted-(β-iso-butyl)-γ-1,2,3-triazole Oligomer ***22***

The trialkylsilyl-protected cycloadduct **21** (274 mg, 0.7 mmol) was added to a 25-mL round-bottom flask along with MeOH (3 mL) and K_2CO_3 (0.9 mmol, 120 mg) and the mixture was left to stir at rt. After 1.5 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and the organic phase was washed successively with H_2O (15 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 residue was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane.

2-[1-(2-(R)-iso-Butyl-pent-4-ynyl)-1H-[1,2,3]triazol-4-ylmethyl]-4-(R)-methyl-pentan-1-ol ***22***

Compound **22** was obtained as a yellow oil (180 mg, 81%). $R_f = 0.28$ (40% ethyl acetate/hexane). $[\alpha]_D^{22}$ −18.2 (*c* 1.79 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3315, 3312, 2954, 1467, 1367, 1218, 1051. δ_H (300 MHz, $CDCl_3$) 0.70–0.82 (m, 12H), 0.90–1.31 (m, 4H), 1.46–1.66 (m, 2H), 1.76–1.89 (m, 1H), 1.90–2.18 (m, 3H), 2.67 (d, 2H, *J* 5.8), 3.30 (dd, 1H, *J* 6.4 and 10.2), 3.44 (dd, 1H, *J* 2.6 and 10.6), 3.89 (s, 1H), 4.22 (d, 2H, *J* 6.1), 7.32 (s, 1H). δ_C (75 MHz, $CDCl_3$) 20.2, 21.8, 22.5, 22.6, 22.8, 24.7, 24.9, 26.8, 35.4, 38.0, 39.7, 39.8, 52.6, 64.0, 70.9, 80.3, 122.6, 145.5. *m*/*z* 306.2536; $C_{18}H_{32}N_3O$ requires M + H 306.2540.

Accessory Publication

General experimental procedures and spectroscopic data for selected compounds are available on the Journal's website.

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