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Substituent effects on the SmI_2/Pd(0)-promoted carbohydrate ring-contraction of 5-alkynylpyranosides

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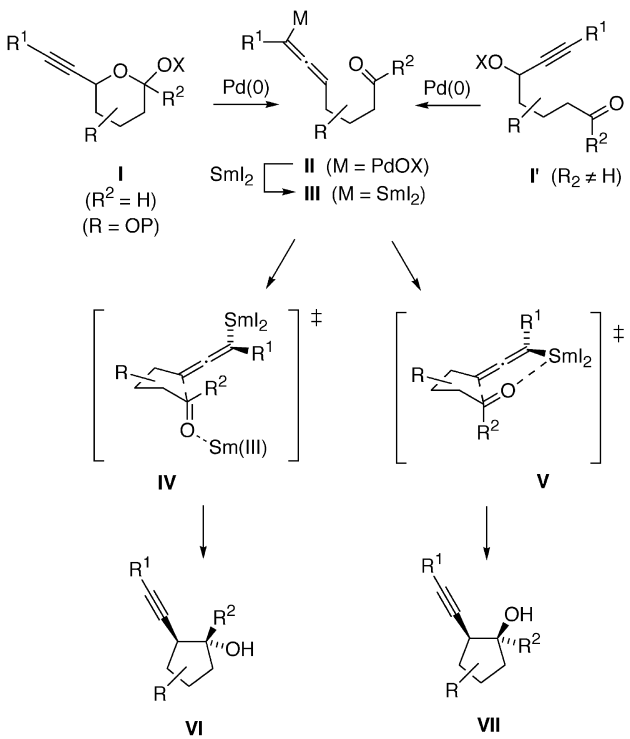
Abstract—The effect of substituents on the reactivity and stereoselectivity of the SmI_2/Pd(0)-promoted ring-contraction of 5-alkynylpyranosides has been examined using substrates substituted only at selected positions. While formation of 2-ethynylcyclopentanols takes place efficiently, an internal alkyne did not afford the expected product. The presence of peripheral alkoxy substituents leads to variable stereoselectivities that depend on the number and orientation of such groups. Thus, an isolated OBn substituent at C(3) (carbohydrate numbering) exerts a significant stereochemical control while additional substitution with the same group at C(4) either enhances or drastically reduces stereoselectivity depending on its orientation (α or β, respectively).

1. Introduction

We have reported a Pd-catalyzed SmI_2-mediated carbohydrate ring-contraction[1] that starting from substrates of type **I** leads to cyclopentanes of types **VI**, **VII** (Scheme 1).[2a] This transformation features the intramolecular propargylation of a carbonyl-tethered allenylsamarium **III** originated in the SmI_2 reduction of an allenylpalladium complex **II** derived from **I**. Useful levels of diastereoselectivity have already been realized using fully oxygenated glucose-, mannose- and galactose derivatives, where a general preference for a relative *trans*-relationship between the ethynyl- and hydroxyl-substituted stereogenic centers was generally observed. This preference is probably the result of a cyclization step proceeding through open- (**IV**, R^2=H) rather than cyclic (**V**, R^2=H)[3] TS's as a consequence of the dominant effect of the relatively strong Lewis-acidic character of the Sm(III)[4] salts present in the medium, that coordinate to the carbonyl group. The stereochemical picture is actually more complex as the absolute configuration of the above-mentioned stereogenic centers was found to be substrate- and catalyst-dependent. While it is apparent that substantial stereochemical scrambling takes place at the level of intermediates **II** and/or **III**,[5] other factors such as the steric and/or electronic effects of peripheral substituents (R=OP) are likely to also play a role. To have a better understanding of the intrinsic stereochemical preferences of these reactions without the incidence of the steric and/or electronic effects associated to stereocenters adjacent to the reactive sites, and to extend the scope of the method, we have now examined the corresponding reactions on selected substrates where some or all of the oxygenated ring-substituents (R=OP in structure **I**) have been removed. Additional impetus for this work came from literature reports showing that the sense and extent of diastereoselectivity in



Scheme 1.

Keywords: carbohydrate ring-contraction; allenylpalladium; intramolecular propargylation; samarium.
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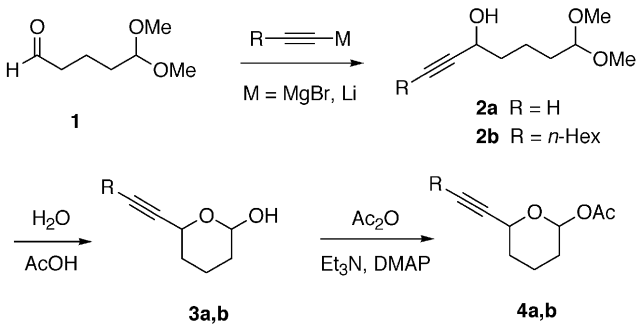
the related allylzirconium intramolecular carbonyl addition heavily depend on the presence and orientation of the substituent immediately adjacent to the nucleophilic center.[1b,g]

2. Results and discussion

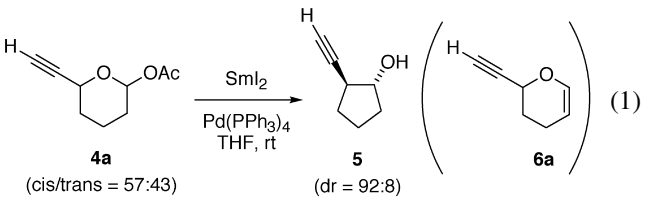
2.1. Non-carbohydrate substrates

Alkynylpyranosides **4** lacking all of the peripheral oxygen substituents were tested first. The presence of an alkyl substituent in the alkynyl portion of **4b** would also allow an assessment of the possibility of applying this chemistry to carbohydrate-derived substrates containing an internal alkyne. Substrates **4** were prepared according to Scheme 2. Thus, alkynylmetal addition to the known monoprotected dialdehyde **1**[6a] (prepared from cyclopentene according to the oxidative cleavage method of Schreiber[6]) afforded propargylic alcohols **2**. Hydrolysis of the acetal function in **2** and acetylation of the resulting lactols **3** led to the desired substrates **4**, that were obtained as nearly 1:1 diastereomeric mixtures.



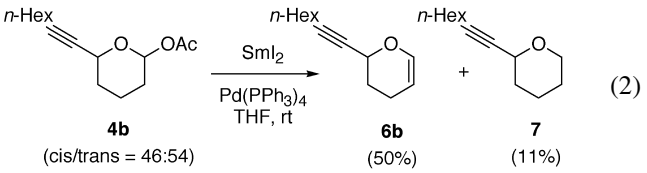
Scheme 2.

Treatment of **4a** with SmI_2 (3 equiv.) and catalytic (5 mol%) $Pd(PPh_3)_4$ at room temperature afforded cyclopentane **5** (Eq. (1)) as a 92:8 *trans*/*cis* mixture, according to GC–MS analysis on the crude product. After chromatographic purification **5**[7] was isolated in undetermined overall yield due to the volatility of this material. The ^1H NMR spectrum of the crude product also contained signals compatible with the presence of enol ether **6a** (~15% with respect to **5**). However, this product was not isolated and instead, small amounts of lactol **3a**, probably the result of hydrolysis of **6a**, were found during chromatographic purification of **5**. In any case, these results obtained with **4a**, a substrate devoid of structural constraints, evidence a high intrinsic preference for a ring closure that proceeds through a TS of type **IV**. This is in contrast to observations made on the related reaction starting from ketone substrates of type **I′** (R=H; R^2=Me), that led to a very poor diastereoselectivity under the same reaction conditions.[2c] It is also interesting to note that the reaction **4a→5** took only 1.5 h to go to completion at room temperature. In comparison, fully oxygenated carbohydrate-derived substrates **I** need much longer reaction times (24 h) or higher temperatures (40°C) to produce **VI**, **VII**.[2a] The lower reactivity of **I** (R=OP, R^2=H) with respect to **4a** could be due to the inductive electron-withdrawing character of the alkoxy substituents in the former substrate that disfavors development of oxocarbenium-like character at C(1) (carbohydrate numbering) during the ring opening leading to intermediate **II**. Alternatively, the substituent at C(4) in **I** could hinder the *anti* approach of the Pd(0) catalyst to the propargylic ether moiety to effect the required S_N2'-like displacement[8] of the leaving group in the oxidative addition leading to **II**.



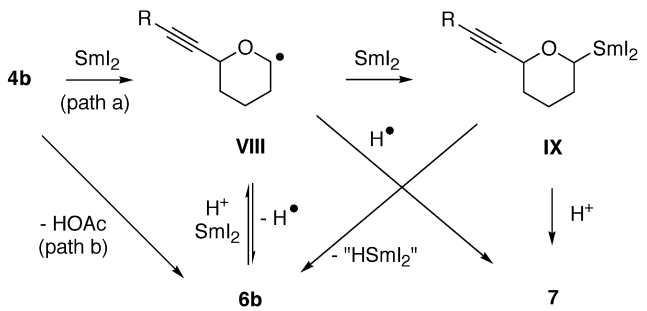
(1)

On the other hand, the internal alkyne **4b** displayed a completely different reactivity as no cyclopentane product analogous to **5** was found, and enol ether **6b** was obtained as major product together with smaller amounts of tetrahydropyran **7** (Eq. (2)).



(2)

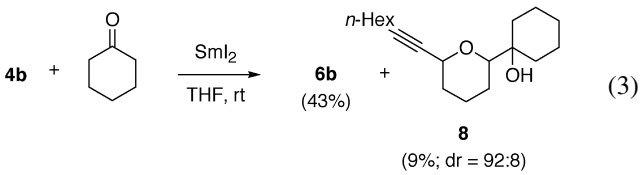
Therefore, it appears that the steric effect of the alkyl substituent at the alkynyl terminus retards the oxidative addition of the propargylic ether moiety to Pd(0) so that other competing reactions take over. While the formation of alkenes related to **6b** has been observed before,[2b] compounds of type **7** are unprecedented in these Pd(0)/SmI_2-promoted reactions. The formation of **7** appears to imply the intervention of anomeric radical **VIII** and/or organosamarium **IX** as intermediates (Scheme 3). Radical **VIII** could arise by direct reduction of the acetoxy ether function of **4b** by SmI_2 (path a), a process that has ample precedent in the corresponding reactions of glycosyl bromides, -chlorides, -phosphates and -pyridylsulfones.[9] Radical disproportionation[10] would then account for the formation of both **6b** and **7**. Alternatively, further reduction of **VIII** to organosamarium **IX**[9] followed by protonation or samarium hydride elimination[9a,11] could also lead to **7** and **6b**, respectively.



Scheme 3.

To test for the formation of **VIII** and **IX** from **4b**, this substrate was treated with cyclohexanone and SmI_2 under samarium Barbier conditions[12] at room temperature (Eq. (3)). Alkene **6b** was again obtained as major product, this time accompanied by the expected coupling product,

the alcohol **8**. While the formation of **8** supports the notion that radicals **VIII** are formed from **4b**, several considerations argue against **VIII** and **IX** being in the major path to **6b**. Thus, the ratio **6b**:**7** is too high for these compounds to originate exclusively in a disproportionation process. Furthermore, anomeric organosamariums analogous to **IX** are known to lead efficiently to coupling products with ketones rather than undergoing β-hydride elimination.[9] Therefore, the comparatively low yield of **8** with respect to **6b** indicates that the incidence of radicals **VIII** and/or organosamariums **IX** in these reactions is small, and points to the Lewis-acidic character of SmI_2, and Sm(III) formed thereof,[4] as responsible for formation of **6** via elimination of AcOH from **4** (path b, Scheme 3). Small amounts of **VIII** could then be formed by SmI_2 reduction of an oxonium ion generated from either **4b** or **6b**.

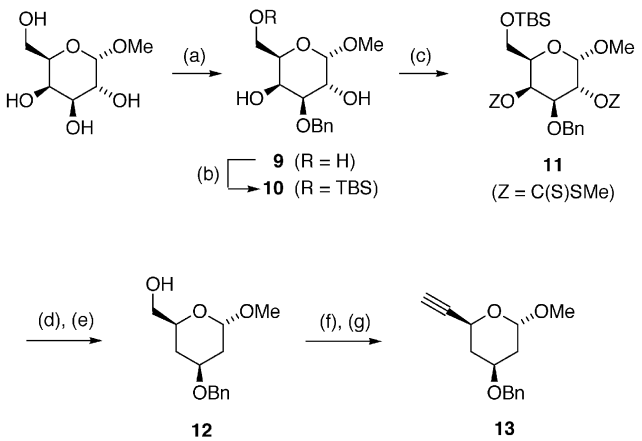


(3)

2.2. Carbohydrate-derived substrates

The tendency of the acetate leaving group to form alkenes by elimination of AcOH, together with the expected lower reactivity of substrates with alkoxy substituents (vide supra) advised the choice of the more robust methyl pyranosides, with a methoxy leaving group, for the reactions discussed next and involving partially oxygenated carbohydrate-derived substrates.

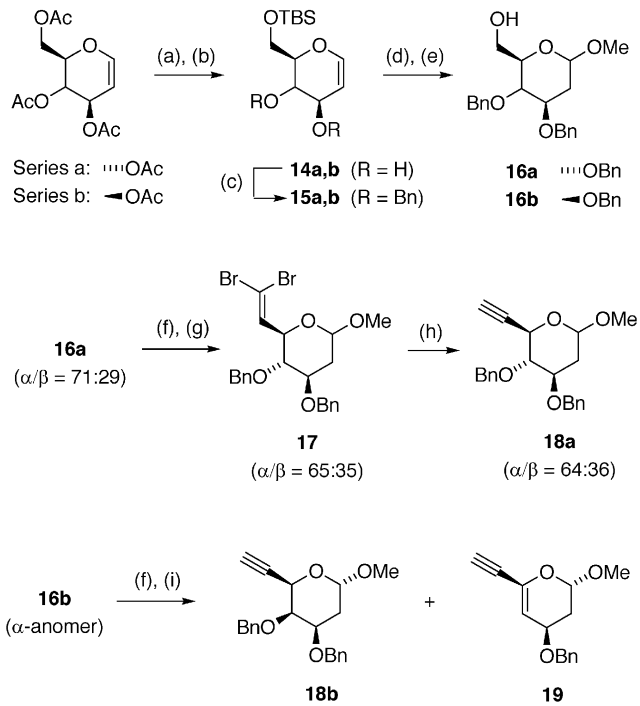
Substrate **13**, featuring a single protected hydroxyl group at a remote position from the carbons involved in cyclization, was prepared from commercial methyl α-D-galactopyranoside as shown in Scheme 4. Thus, selective monobenzylation at the C(3)-hydroxyl following David's method[13] and silylation of the primary alcohol function in the so formed



Scheme 4. (a) (i) Bu_2SnO, benzene, Dean–Stark; (ii) *n*-Bu_4NI, BnBr, reflux (49%). (b) TBSCl, Im, DMF, room temperature (87%). (c) (i) NaH, CS_2, THF, room temperature; (ii) MeI, room temperature (90%). (d) *n*-Bu_3SnH, AIBN, toluene, reflux. (e) *n*-Bu_4NF, THF, room temperature (34% for three steps from **10**). (f) (i) $(COCl)_2$, DMSO, −70°C; (ii) *i*-Pr_2EtN, −70°C→room temperature. (g) Dimethyl 1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, room temperature (65% for two steps from **12**).

triol **9** afforded diol **10**. This was subjected to the Barton–McCombie dehydroxylation protocol[14] to yield after desilylation the doubly dehydroxylated derivative **12**.[15] Swern oxidation using diisopropylethylamine[16] and direct ethynylation with dimethyl 1-diazo-2-oxopropylphosphonate[17] then afforded the required alkyne **13**.

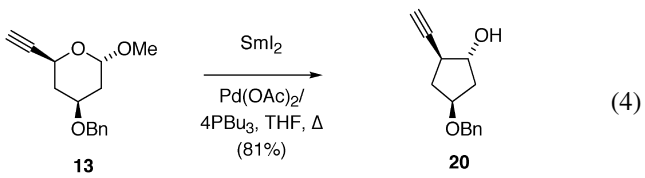
The synthesis of 2-deoxy substrates **18** and **19** is depicted in Scheme 5. Starting from either commercial tri-*O*-acetyl-D-glucal (series a) or tri-*O*-acetyl-D-galactal (series b), protecting group manipulation led to suitably protected triols **15** in 87 and 61% overall yields, respectively. Glycoside formation with triphenylphosphine hydrobromide/methanol[18] and desilylation afforded primary alcohols **16** (90 and 75% yields) as mixtures of anomers. Alcohol **16a** was obtained with a 71:29 α/β anomer ratio and was carried forward as a mixture, whereas for **16b** the initial 94:6 α/β anomer mixture could be separated and the synthesis was continued with the α-anomer alone. Alcohols **16** were then converted into alkynes **18a** and **18b**. Thus, Swern oxidation[16] was followed by either a modified Corey–Fuchs[19] procedure, using triethylamine in the dibromomethylenation step[20] and LDA[21] for the dehydrobromination, or by direct ethynylation[17] to afford alkynes **18a** and **18b** in 38% and 62% yields for these three- and two-step protocols, respectively. Enyne **19** was also obtained in 7% yield along with alkyne **18b**.



Scheme 5. (a) NaOMe, MeOH, room temperature. (b) TBSCl, Im, DMF, room temperature. (c) (i) NaH, THF, 0°C; (ii) BnBr, *n*-Bu_4NI, room temperature. (d) TPPHB, MeOH, CH_2Cl_2, room temperature. (e) *n*-Bu_4NF, THF, room temperature. (f) (i) $(COCl)_2$, DMSO, −45°C; (ii) *i*-Pr_2EtN, −45°C→room temperature. (g) PPh_3, CBr_4, Et_3N, CH_2Cl_2, 0°C. (h) LDA, THF, −78°C. (i) Dimethyl 1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, room temperature.

Results for the reactions of **13**, **18a** and **18b** with SmI_2/Pd(0) are collected in Eqs. (4)–(6). As expected based on previous experience, these acetals were inert to SmI_2/Pd(0) at room temperature. However, they reacted rapidly upon heating to

yield the expected cyclopentanes **20**–**22**. A combination of $Pd(OAc)_2$ and $P(n\text{-}Bu)_3$ in a 1:4 ratio was used as catalyst precursor since it had been found to give the best results with other carbohydrate-derived substrates.[2a] Not unexpectedly, the substrate with a single OBn substituent (**13**) displayed the highest reactivity, the reaction being complete in less than 5 min, whereas the presence of a second OBn in substrates **18** led to somewhat longer reaction times (~1–3 h) for high conversions. The reaction of **18a**, while proceeding rapidly in the initial stages, did not go to completion and some starting material was recovered. Interestingly, the anomeric ratio in the recovered material (α/β=22:78) was significantly different from the initial 64:36 α/β value. This observation suggests a higher reactivity of the α-anomer relative to the alternative β-configuration, and this could be due to stereoelectronic assistance provided by the endocyclic oxygen to departure of an axially oriented leaving group during ring-opening in the α-anomer.



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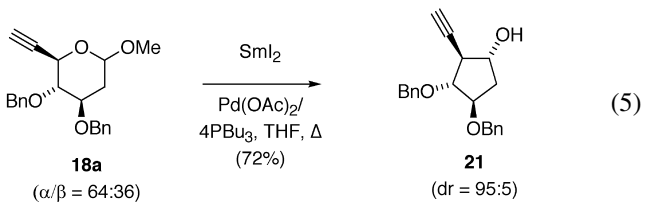

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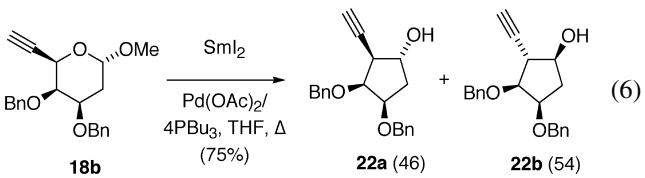


(6)

Cyclopentanes **20**–**22** were obtained in all cases as mixtures of diastereoisomers that were either separated or enriched in the major isomer. The stereochemistry of the individual diastereoisomers was unambiguously determined with the aid of n.O.e. experiments. A summary of relevant n.O.e. data is given in Chart 1. In line with the stereochemical result obtained for **4a**, products **20**–**22** were formed with a very predominant *trans* relationship between the alkynyl and free hydroxyl substituents. Cyclopentane **20** was obtained in a 85:15 ratio with another isomer of unknown stereochemistry (Eq. (4)). Therefore, it is seen that a single remote substituent at C(3) (carbohydrate numbering) in the cyclizing chain is enough to provide a good stereochemical control during cyclization. The particular *trans*-isomer obtained as major product displayed a *syn* relationship between the ethynyl and 4-OBn groups. The same trend was observed when, additionally, an α-OBn substituent was incorporated at C(4) of **18a**, and this in fact resulted in an enhanced stereochemical control as the major diastereomer **21** amounted to 95% of the isomer mixture (Eq. (5)). However, the corresponding β-OBn substituted **18b** afforded a nearly 1:1 mixture of the two possible *trans*-

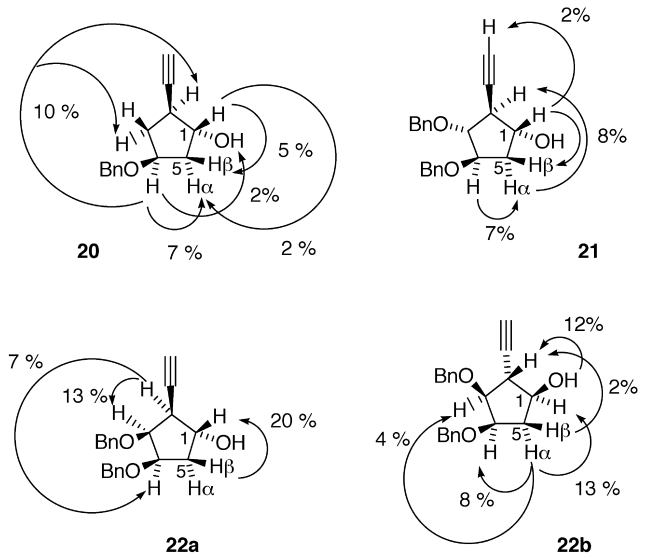
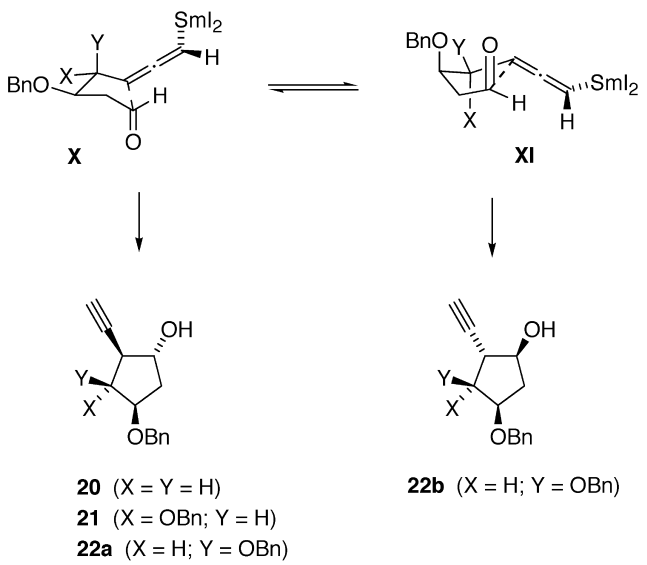


Chart 1. Summary of relevant n.O.e. data for compounds **20**–**22**.

products (relative to ethynyl and free hydroxyl groups) in cyclopentane **22** (Eq. (6)).

A model that fits the stereochemical tendencies observed in the formation of **20**–**22** (and more highly substituted products obtained under similar conditions)[2a] is suggested in Scheme 6. Thus, under high temperature conditions that favor rapid interconversion between the two allene configurations,[5] allenylsamariums **III** could form the observed products through anticlinal conformations **X** and **XI**.[3] Formation of **20** and **21** then would take place predominantly from the more stable conformation **X**. On the other hand, starting from **18b** (Y=OBn), the pseudoaxial Y substituent could destabilize[1b,g] **X** relative to **XI** and reduce the energy gap between them, thus resulting in nearly equal amounts of **22a** and **22b** being produced.



Scheme 6.

3. Conclusions

The SmI_2/Pd(0)-promoted carbohydrate ring-contraction of 5-ethynylpyranosides has been extended to substrates with limited peripheral functionality. This has unraveled important reactivity and stereochemical details of the reaction. Thus, the α-configuration at the anomeric center is found to be desirable for high reactivity whereas substitution at the alkynyl terminus has a very detrimental effect on the outcome of the reaction. A single OBn substituent at C(3) (carbohydrate numbering) is found to exert a significant control over the absolute configuration at the alkynyl- and free hydroxyl-bearing carbons in the resulting *trans*-2-ethynylcyclopentanol products. Additional substitution with another α-OBn group at C(4) enhances this stereocontrol, but the presence of an analogous β-OBn group leads to nearly equal proportions of both *trans*-isomers, probably as a result of conformational and configurational interconversion between intermediate allenylsamariums.

4. Experimental

4.1. General

All reactions involving air- and moisture-sensitive materials were performed using standard bench-top techniques.[22] Tetrahydrofuran and toluene were freshly distilled from sodium/benzophenone and, for reactions with SmI_2 and *n*-Bu_3SnH, they were deoxygenated prior to use. Acetic anhydride, dichloromethane, dimethylsulfoxide, dimethylformamide, pyridine, triethylamine and diisopropylamine were distilled from CaH_2. Methanol was dried by treatment with Mg–I_2 and distillation. Carbon tetrabromide was purified by sublimation. SmI_2 (ca 0.1 M in THF) was prepared as reported[23] from Sm metal and diiodomethane. *n*-Tributylphosphine (Fluka, 95%) was used from a Sure-Seal bottle. Flash column chromatography[24] was performed on silica gel (230–400 mesh). HPLC purifications were carried out with a LiChrosorb Si60 column (7 μm, 25×2.5 cm) using a refraction index detector. Routine ^1H and ^{13}C NMR spectra were obtained at 250 and 62.9 MHz, respectively, using $CDCl_3$ as solvent and internal reference (δ 7.26 for ^1H and δ 77.0 for ^{13}C). IR data include only characteristic absorptions. Mass spectra were obtained at 70 eV. GC–MS analysis were performed at 70–210°C (20°C/min) with a stationary phase of methylphenylsilicone (0.25 μm, 30 m×0.25 mm). In Kugelrohr distillations the boiling point refers to the external oven air temperature.

4.1.1. 7,7-Dimethoxyhept-1-yn-3-ol (2a).[25] Cyclopentene (13.0 mL, 142 mmol) was dissolved in CH_2Cl_2/CH_3OH (5:1, 564 mL) at −78°C and a mixture of ozone/oxygen (0.6 A, 70–100 L/h) was bubbled through the solution until this had turned into a light blue (~3 h). Ar was then bubbled through the solution at −78°C until colorless, *p*-TsOH (2.30 g, 12.1 mmol) was added, and the solution was allowed to reach room temperature. After 90 min solid $NaHCO_3$ (2.43 g, 29 mmol) was added, and the mixture was stirred for 15 min. Dimethyl sulfide (23 mL, 313 mmol) was added, and the mixture was further stirred at room temperature for 12 h. The solution was evaporated to a volume of ca. 20–25 mL and the residue was partitioned between CH_2Cl_2 (90 mL) and water (60 mL). The aqueous layer was extracted with CH_2Cl_2 (2×80 mL), and the combined organic layers were dried (Na_2SO_4). The residue after evaporation was purified by Kugelrohr distillation (60–70°C, 0.5 mm Hg) to yield 13 g of a 3.2:1 mixture of 5,5-dimethoxypentanal (**1**)[6a] and 2,6-dimethoxytetrahydropyran[26] that without further purification was dissolved under in THF (320 mL). To this solution at 0°C under Ar was added ethynylmagnesium bromide (0.5 M in THF, 320 mL, 160 mmol). The reaction mixture was allowed to reach room temperature, stirred for 14 h and quenched with saturated NH_4Cl (150 mL) at 0°C. The layers were separated, and the aqueous layer was extracted with EtOAc (2×170 mL). The combined organic extracts were washed with brine (30 mL) and dried (Na_2SO_4). The residue after evaporation was purified by flash chromatography (30% EtOAc/hexanes) to yield the propargylic alcohol **2a** (6.26 g, 30% for two steps) as an oil: ^1H NMR δ 1.46–1.76 (m, 6H), 2.44 (d, J=2.0 Hz, H-7, overlapped with OH signal, total 2H), 3.30 (s, 6H, OCH_3), 4.36 (apparent t, H-1; overlapped with m at 4.34–4.38, H-5; 2H); ^{13}C NMR δ 20.2, 31.9, 37.2, 52.6, 61.9, 72.8, 84.8, 104.3. These data coincide with those given in the literature for the same compound.[25]

4.1.2. 1,1-Dimethoxytridec-6-yn-5-ol (2b). *n*-Butyllithium (1.6 M in hexanes, 22 mL, 36.16 mmol) was added to a solution of 1-octyne (6.40 mL, 43.4 mmol) in THF (105 mL) at −78°C under Ar, and the resulting solution was stirred at the same temperature for 30 min. A solution of **1** (prepared as described above, 6.37 g of mixture, 33.0 mmol of **1**) in THF (97 mL) was then added, and the reaction mixture was allowed to reach room temperature and worked-up as described above for **2a**. The crude product was purified by flash chromatography (25% EtOAc/hexanes) to yield the propargylic alcohol **2b** (6.22 g, 34% for two steps from cyclopentene) as an oil: ^1H NMR δ 0.80 (t, J=6.7 Hz, 3H, H-12), 1.18–1.63 (m, 16H), 2.11 (td, J=6.9, 1.8 Hz, 2H, H-8), 2.67 (br s, $W_{1/2}$=7.1 Hz, 1H, OH), 3.23 (s, 6H, OCH_3), 4.23–4.32 (m, 2H, H-1 and H-5); ^{13}C NMR δ 13.8, 18.5, 20.2, 22.3, 28.3, 28.5, 31.1, 31.9, 37.7, 52.3, 62.1, 81.2, 85.1, 104.3; IR (neat) ν 3650–3100 (m, br, O–H), 2205 (w, C≡C) cm^{-1}.

4.1.3. 6-Ethynyltetrahydropyran-2-yl acetate (4a). A solution of **2a** (2.08 g, 12.1 mmol) in acetic acid/water (1:1, 27 mL) was stirred and refluxed for 1 h. After cooling, the solution was made neutral with saturated K_2CO_3 (30 mL), water (70 mL) was added and the aqueous layer was extracted with EtOAc (4×200 mL). The combined organic extracts were washed with brine (16 mL) and dried (Na_2SO_4). Purification by flash chromatography (25% EtOAc/hexanes) afforded the lactol **3a** (1.02 g, 67%) as a 2.1:1 diastereomeric mixture: ^1H NMR δ 1.50–1.93 (m, 6H), 2.44 and 2.46 (2d, J=2.8 Hz, 1H, H-2′), 3.23–3.27 (m, OH, major isomer), 3.58–3.60 (m, OH, minor isomer), 4.24 (dt, J=10.3, 2.8 Hz, H-6, minor isomer), 4.72–4.82 (m), 5.30 (br d, H-2, major isomer). A solution of the crude lactol **3a** [prepared from **2a** (2.05 g, 11.9 mmol)] in Et_3N (2.50 mL, 17.5 mmol) was treated with Ac_2O (2.24 mL, 23.8 mmol) and DMAP (459 mg, 3.68 mmol) at room temperature for 17 h. The solution was diluted with diethyl ether (100 mL) and poured over ice/water (~10 mL). The

aqueous layer was extracted with ether (3×50 mL). The combined organic layers were washed successively with 1 M HCl (10 mL), 1 M NaOH (10 mL) and H_2O (5 mL), and dried (Na_2SO_4). The crude product was purified by flash chromatography (10% EtOAc/hexanes) to yield the acetate **4a** (1.34 g, 89% for two steps from **2a**) as a 1.3:1 *cis*/*trans* mixture: ^{1}H NMR δ 1.52–2.02 (m, 6H), 2.03 and 2.04 (2s, 3H, OCOCH_3), 2.41 and 2.43 (2d, J=2.2 Hz, 1H, H-2′), 4.33–4.39 (m, H-6, *cis*-**4a**), 4.58 (br d, J=7.9 Hz, $W_{1/2}$=13.6 Hz, H-6, *trans*-**4a**), 5.68–5.72 (dd, J=7.1, 2.9 Hz, H-2, *cis*-**4a**), 6.12 (br s, $W_{1/2}$=5.9 Hz, H-2, *trans*-**4a**); ^{13}C NMR δ 19.0, 20.8, 22.5, 29.4, 30.2, 32.0, 32.2, 62.7, 65.6, 72.2, 73.3, 81.8, 82.0, 91.1, 92.5, 166.4, 166.6; IR (neat) ν 3290 (m, ≡C–H), 2120 (w, C≡C), 1755 (s, C=O) cm^{-1}; LRMS (EI) *m*/*z* (%) 167 (M−1, 3), 125 (20), 111 (12), 109 (91), 107 (28), 97 (14), 86 (14), 80 (41), 79 (base), 77 (16), 68 (16), 65 (11); HRMS calcd for $C_9H_{11}O_3$ (M−H) 167.0708, found 167.0710.

4.1.4. 6-(Oct-1-ynyl)tetrahydropyran-2-yl acetate (4b). Lactol **3b** was first prepared from **2b** following the procedure described above for **3a**. The crude product could be purified by flash chromatography (20% EtOAc/hexanes) to yield **3b** (59%) as a 1.9:1 mixture of diastereoisomers: ^{1}H NMR δ 0.86 (t, J=6.5 Hz, 3H, H-8′), 1.20-1.84 (m, 14H), 2.10–5.57 (m, 2H, H-3′), 3.10–3.60 (m, 1H, O*H*), 4.17–4.20 (m, H-6, minor isomer), 4.35–4.77 (m), 5.25–5.29 (m, H-2, major isomer). Alternatively, the crude lactol **3b** was treated with Et_3N, Ac_2O and DMAP as described above for **4a** to yield after flash chromatography (6% EtOAc/hexanes) acetate **4b** (53% yield for two steps from **2b**) as a 1.2:1 *trans*/*cis* diastereomeric mixture: ^{1}H NMR δ 0.86 (t, J=6.7 Hz, 3H, H-8′), 1.24–1.95 (m, 14H), 2.07 (s, 3H, OCOCH_3), 2.18 (tt, J=7.0, 2.4 Hz, 2H, H-3′), 4.30–4.35 (m, H-6, *cis*-**4b**), 4.62 (dm, J=8.5 Hz, H-6, *trans*-**4b**), 5.69 (dd, J=7.9, 2.7 Hz, H-2, *cis*-**4b**) 6.17 (br s, $W_{1/2}$=5.5 Hz, H-2, *trans*-**4b**); ^{13}C NMR δ 13.7, 17.4, 18.4, 18.4, 20.0, 20.8, 22.2, 28.0, 28.2, 28.9, 31.0, 31.3, 31.4, 62.6, 66.4, 78.2, 85.1, 85.7, 91.6, 93.3, 168.9; IR (neat) ν 3600–3200 (m, O–H), 2240 (w, C≡C), 1760 (s, C=O) cm^{-1}; LRMS (EI) *m*/*z* (%) 251 (M−1, 7), 209 (16), 207 (18), 191 (10), 138 (11), 137 (base), 113 (14), 105 (16), 99 (18), 95 (14), 93 (11), 91 (13), 85 (10), 81 (18), 79 (19), 77 (12), 71 (40), 69 (17), 67 (31); HRMS calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1718.

4.1.5. Methyl 3-*O*-benzyl-α-D-galactopyranoside (9). Methyl α-D-galactopyranoside monohydrate (13.50 g, 64 mmol) and dibutyltin oxide (15.84 g, 64 mmol) were heated in benzene (250 mL) with azeotropic separation of water (Dean–Stark) for 16 h. Tetrabutylammonium iodide (23.32 g, 64 mmol) and benzyl bromide (16.0 mL, 128 mmol) were added to the cooled solution and the mixture was refluxed for 4 h. Solvent evaporation afforded a crude product that was purified by flash chromatography (EtOAc) to yield **9** (8.82 g, 49%): ^{1}H NMR δ 2.31 (d, J=7.8 Hz, 1H, O*H*), 2.61 (d, J=4.6 Hz, 1H, O*H*), 2.85 (s, 1H, O*H*), 3.40 (s, 3H, OCH_3), 3.61 (dd, J=9.6, 3.2 Hz, 1H, H-3), 3.69–4.03 (m, 4H, H-2, H-5 and H-6), 4.06 (br s, $W_{1/2}$=7.9 Hz, 1H, H-4), 4.71 (s, 2H, OCH_2Ph), 4.83 (d, J=3.8 Hz, 1H, H-1), 7.25–7.37 (m, 5H, Ar); ^{13}C NMR δ 55.3, 62.6, 67.9, 68.2, 69.3, 72.0, 78.0, 99.5, 127.8, 128.0, 128.5, 137.6; IR (neat) ν 3200–3500 (m, OH), 1050 (s, C–O–C) cm^{-1}; $[\alpha]_D^{20}$=+141.43° (*c*=3.21, $CHCl_3$); LRMS (EI) *m*/*z* (%) 284 (M), 92 (9), 91 (base); HRMS calcd for $C_{14}H_{20}O_6$ 284.1260, found 284.1252.

4.1.6. Methyl 3-*O*-benzyl-6-*O*-(*tert*-butyldimethylsilyl)-α-D-galactopyranoside (10). A solution of **9** (8.67 g, 30.5 mmol), imidazole (4.34 g, 64.1 mmol) and *tert*-butyldimethylsilyl chloride (5.06 g, 33.6 mmol) in DMF (140 mL) was stirred at room temperature for 12 h. The mixture was diluted with diethyl ether (400 mL), and the resulting solution was washed with H_2O (2×150 mL). The aqueous layers were back-extracted with diethyl ether (2×130 mL), and the combined organic layers were dried (Na_2SO_4). The crude after evaporation was purified by flash chromatography (50% EtOAc/hexanes) to yield **10** (10.60 g, 87%): ^{1}H NMR δ 0.07 (s, 6H, Si–CH_3), 0.89 (s, 9H, *t*-Bu), 2.22 (d, J=7.8 Hz, 1H, O*H*), 2.63 (s, 1H, O*H*), 3.40 (s, 3H, OCH_3), 3.60 (dd, J=9.7, 3.2 Hz, 1H, H-3), 3.70 (apparent t, J=5.8 Hz, 1H, H-5), 3.78 (dd, J=10.3, 5.6 Hz, 1H, H-6), 3.86 (dd, J=10.2, 6.2 Hz, 1H, H-6), 4.01 (ddd, J=9.6, 7.9, 3.9 Hz, 1H, H-2), 4.05 (br s, $W_{1/2}$=7.1 Hz, 1H, H-4), 4.72 (s, 2H, OCH_2Ph), 4.80 (d, J=3.9 Hz, 1H, H-1), 7.29–7.40 (m, 5H, Ar); ^{13}C NMR δ −5.5, 18.2, 25.8, 55.1, 62.6, 66.8, 68.5, 69.9, 71.9, 78.5, 99.3, 127.8, 127.9, 128.5, 137.9; IR (neat) ν 3450 (m, OH), 1080 (s, C–O–C) cm^{-1}; $[\alpha]_D^{20}$=90.25° (*c*=3.61, $CHCl_3$); LRMS (EI) *m*/*z* (%) 398 (M), 117 (17), 91 (73), 91 (base), 91 (58), 75 (12), 75 (13); HRMS calcd for $C_{20}H_{34}O_6Si$ 398.2124, found 398.2114.

4.1.7. Methyl 3-*O*-benzyl-6-*O*-(*tert*-butyldimethylsilyl)-2,4-bis-*O*-(methylsulfanylthiocarbonyl)-α-D-galactopyranoside (11). A mixture of **10** (150.0 mg, 0.38 mmol), NaH (60% dispersion in mineral oil, 80.0 mg, 2.0 mmol) and imidazole (10 mg) in THF (12 mL) was stirred at room temperature for 0.5 h. Carbon disulfide (4 mL) was added and the resulting yellow suspension was stirred for 7 h, after which CH_3I (0.11 mL, 1.8 mmol) was added. The mixture was further stirred for 12 h, diluted with diethyl ether (70 mL), and the solution was washed with H_2O (30 mL) and saturated NH_4Cl (30 mL). The aqueous layers were back-extracted with diethyl ether (60 mL), and the combined organic layers were dried (Na_2SO_4). The crude after evaporation was purified by flash chromatography (10% EtOAc/hexanes) to yield **11** (0.197 g, 90%) as an oil: ^{1}H NMR δ 0.07 (s, 6H, SiCH_3), 0.89 (s, 9H, *t*-Bu), 2.56 (s, 3H, SCH_3), 2.59 (s, 3H, SCH_3), 3.40 (s, 3H, OCH_3), 3.61–3.74 (m, 2H, H-6), 4.04 (t, J=6.3 Hz, 1H, H-5), 4.20 (dd, J=10.3, 3.1 Hz, 1H, H-3), 4.53 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.75 (d, J=12.0 Hz, 1H, OC*H*Ph), 5.21 (d, J=3.4 Hz, 1H, H-1), 5.94 (dd, J=10.3, 3.5 Hz, 1H, H-2), 6.55 (br s, $W_{1/2}$=2.8 Hz, 1H, H-4), 7.26–7.32 (m, 5H, Ar); ^{13}C NMR δ −5.5, 18.2, 19.0, 19.3, 25.6, 55.4, 61.6, 70.2, 72.3, 73.6, 76.7, 78.4, 96.4, 127.6, 127.8, 128.3, 137.6, 216.0, 216.1; IR (neat) ν 1200 (m, C=S), 1050 (m, C–O–C) cm^{-1}; $[\alpha]_D^{20}$=+83.33° (*c*=1.14, $CHCl_3$).

4.1.8. Methyl 3-*O*-benzyl-2,4-dideoxy-α-D-*threo*-hexapyranoside (12).[15] Starting from **10** (9.49 g, 23.86 mmol) the above procedure was followed to obtain a partially purified **11** (13.95 g) after flash chromatography. To a refluxing solution of this material and AIBN (80 mg) in toluene (250 mL) was added *n*-Bu_3SnH (48 mL, 18.12 mmol) and the mixture was stirred while heated

under reflux. After 16 and 24 h of total reaction time further portions of AIBN (0.5 and 0.4 g) and *n*-Bu_3SnH (8 and 4 mL) were added. Refluxing was continued until a total reaction time of 36 h. After solvent evaporation the residue was subjected to flash chromatography eluting first with hexanes to remove non-polar material and then with EtOAc to collect the polar fraction. The latter was evaporated and the residue (8.07 g) was redissolved in THF (200 mL). To this solution at 0°C was added tetrabutylammonium fluoride (1 M in THF, 44 mL, 44 mmol), and the mixture was stirred at room temperature for 12 h and then quenched with saturated NH_4Cl (70 mL). The layers were separated, the aqueous layer was extracted with EtOAc (3×100 mL) and the combined organic layers were dried (Na_2SO_4). The crude after evaporation was purified by flash chromatography (20% and then 40% EtOAc/hexanes) to yield **12** (2.05 g, 34% for three steps from **10**) as an oil: ^{1}H NMR δ 1.38 (q, J=11.9 Hz, 1H, H-4α), 1.57 (ddd, J=12.5, 11.3, 3.4 Hz, 1H, H-2β), 1.99 (dt, J=12.3, 2.4 Hz, 1H, H-4β), 2.21 (ddd, J=12.7, 2.0, 2.4 Hz, 2H, H-2α, OH), 3.32 (s, 3H, OCH_3), 3.58–3.63 (m, 2H, H-6), 3.70–4.01 (m, 2H, H-3 and H-5), 4.54 (s, 2H, OCH_2Ph), 4.90 (d, J=3.2 Hz, 1H, H-1), 7.24–7.35 (m, 5H, Ar); ^{13}C NMR δ 33.5, 36.4, 54.6, 65.7, 68.4, 69.9, 70.5, 99.1, 127.5, 128.3, 138.4; IR (neat) ν 3447 (m, OH), 1050 (s, C–O–C) cm^{-1}. These spectroscopic data coincide with those reported in the literature for the same compound.[15]

4.1.9. Methyl 3-*O*-benzyl-2,4,6-trideoxy-α-D-*threo*-hept-6-ynopyranoside (13). To a solution of oxalyl chloride (0.64 mL, 7.32 mmol) in CH_2Cl_2 (33 mL) at −70°C under Ar, was added a solution of DMSO (1.1 mL, 14.9 mmol) in CH_2Cl_2 (30 mL). After 15 min a solution of **12** (1.50 g, 5.95 mmol) in CH_2Cl_2 (30 mL) was added, and the resulting mixture was stirred for 2 h at −70°C. Diisopropylethylamine (5.18 mL, 29.7 mmol) was then added, and the mixture was allowed to reach room temperature over a period of 2 h. The solution was diluted with CH_2Cl_2 (120 mL), successively extracted with saturated $NaHCO_3$ (3×50 mL) and water (2×50 mL), and dried (Na_2SO_4). Removal of the solvent in vacuo afforded a residue that was dissolved in benzene and evaporated (three times) to yield the corresponding aldehyde.[15] Without further manipulation, this was dissolved in dry methanol (65 mL), and to this solution was added anhydrous K_2CO_3 (1.64 g, 11.9 mmol) followed by a solution of dimethyl 1-diazo-2-oxopropylphosphonate[17a] (1.40 g, 7.32 mmol) in methanol (20 mL). The mixture was stirred for 3 h, it was diluted with diethyl ether (200 mL), and the solution was washed with saturated $NaHCO_3$ (60 mL) and dried (Na_2SO_4). The crude after evaporation was purified by flash chromatography (10% EtOAc/hexanes) to yield alkyne **13** (0.95 g, 65%, for two steps from **12**) as an oil: ^{1}H NMR δ 1.63 (ddd, J=12.3, 11.5, 3.6 Hz, 1H, H-2β), 1.73 (q, J=11.9 Hz, 1H, H-4β), 2.17 (ddd, J=12.7, 2.4, 2.0 Hz, 1H, H-2α), 2.31 (dt, J=12.5, 2.0 Hz, 1H, H-4α), 2.46 (d, J=2.0 Hz, 1H, H-7), 3.38 (s, 3H, OCH_3), 3.85 (m, 1H, H-3), 4.40–4.61 (m, 3H, OCH_2Ph, H-5), 4.90 (d, J=3.2 Hz, 1H, H-1,), 7.25–7.39 (m, 5H, Ar); ^{13}C NMR δ 36.0, 38.1, 55.1, 58.4, 69.8, 69.9, 72.6, 82.3, 99.4, 127.4, 127.5, 127.6, 138.3; IR (neat) ν 3288 (m, ≡C–H), 2123 (w, C≡C), 1048 (s, C–O–C) cm^{-1}; $[\alpha]_D^{20}$=+122.5° (c=0.7, $CHCl_3$); LRMS (EI) m/z (%) 246 (M), 91 (base); HRMS calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1256.

4.1.10. 1,5-Anhydro-3,4-di-*O*-benzyl-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-D-*arabino*-hex-1-enitol (15a). A solution of **14a**[15] (18.2 g, 69.9 mmol) in THF (55 mL) was added to a slurry of NaH (60% dispersion in mineral oil, 10.5 g, 262 mmol) in THF (150 mL) at 0°C. The mixture was allowed to reach room temperature and stirred for 1.5 h. Benzyl bromide (18.1 mL, 152.0 mmol) and tetrabutylammonium iodide (900 mg, 2.43 mmol) were added, and the mixture was stirred at room temperature for 7 h and then quenched at 0°C with saturated NH_4Cl (150 mL). The aqueous layer was extracted with diethyl ether (2×150 mL), and the combined organic phases were washed with brine (20 mL) and dried (Na_2SO_4). The residue after evaporation was purified by flash chromatography (hexanes, then 5% EtOAc/hexanes and finally 7% EtOAc/hexanes) to yield **15a** (27.9 g, 93%) as a colorless oil: ^{1}H NMR δ 0.07 and 0.08 (2s, 6H, SiCH_3), 0.91 (s, 9H, SiC(CH_3)$_3$), 3.88–4.00 (m, 4H, H-6, H-4 and H-5), 4.19–4.22 (m, 1H, H-3), 4.58 (d, J=11.7 Hz, 1H, OC*H*Ph), 4.66 (d, J=11.7 Hz, 1H, OC*H*Ph), 4.75 (d, J=11.1 Hz, 1H, OC*H*Ph), 4.84 (dd, J=6.0, 2.6 Hz, H-2) and 4.87 (d, J=11.1 Hz, OC*H*Ph) (total 2H), 6.39 (dd, J=6.0, 1.3 Hz, 1H, H-1), 7.27–7.37 (m, 10H, Ar); ^{13}C NMR δ −5.4, −5.2, 18.3, 25.9, 61.6, 70.6, 73.9, 74.1, 75.8, 78.0, 99.7, 127.6, 127.7, 127.9, 128.4, 138.3, 144.7; IR (neat) ν 1647 (m, C=C), 1102 (s, Si–O) cm^{-1}.

4.1.11. Methyl 3,4-di-*O*-benzyl-2-deoxy-D-*arabino*-hexopyranoside (16a). To a solution of **15a** (6.27 g, 14.2 mmol) in CH_2Cl_2 (80 mL) were added methanol (1.80 mL, 44.4 mmol) and triphenylphosphine hydrobromide (250 mg, 0.70 mmol). The mixture was stirred at room temperature for 20 min and diluted with CH_2Cl_2 (100 mL). The solution was washed with saturated $NaHCO_3$ (2×100 mL) and brine (50 mL), and dried (Na_2SO_4). The residue after evaporation was dissolved in THF (54 mL) and treated with tetrabutylammonium fluoride (1.0 M in THF, 18.0 mL, 18.0 mmol) for 2 h. Saturated NH_4Cl (50 mL) was then added. The aqueous layer was extracted with EtOAc (3×75 mL), and the combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). The residue after evaporation was purified by flash chromatography (40% EtOAc/hexanes) to yield **16a** (4.58 g, 90%) as a 71:29 α/β anomer mixture: ^{1}H NMR δ 1.58 (m, H-2β, α-**16a**), 1.67 (ddd, J=13.1, 11.3, 3.6 Hz, H-2β, β-**16a**), 2.01 (br s, $W_{1/2}$=13.5 Hz, 1H, O*H*), 2.31 (ddd, J=13.1, 5.1, 1.1 Hz, H-2α, α-**16a**, overlapped with signals of the same proton of β-**16a**, total 1H), 3.31 (s, OCH_3 α-**16a**, overlapped with signals of β-**16a**), 3.44–3.75 (m), 3.80 (dd, J=5.4, 3.5 Hz, 1H of α-**16a**), 3.87 (dd, J=4.7, 3.0 Hz, 1H of β-**16a**, overlapped with signals of other protons of β-**16a**), 4.01 (ddd, J=11.3, 8.6, 5.1 Hz, H-3, α-**16a**), 4.41 (dd, J=9.7, 1.9 Hz, H-1, β-**16a**), 4.82 (dm, H-1, α-**16a**), 4.61–4.74 (m, 3H, OCH_2Ph), 4.97 (d, J=11.1 Hz, 1H, OC*H*Ph), 7.27–7.39 (m, 10H, Ar); ^{13}C NMR δ 35.3, 36.5, 54.5, 56.7, 62.1, 71.0, 71.4, 71.6, 74.8, 75.0, 75.1, 77.3, 77.9, 78.0, 79.0, 98.4, 100.8, 127.5, 127.7, 127.8, 128.0, 128.0, 128.3, 128.4, 138.1, 138.3, 138.5; IR (neat) ν 3464 (m, OH) cm^{-1}; LRMS (EI) m/z (%) 267 (M−91, 44), 235 (30), 161 (21), 143 (12) (129 (45), 113 (17), 111 (21), 107 (16), 105 (37), 99 (12), 92 (27), 91 (base), 77 (12), 69 (11); HRMS calcd for $C_{21}H_{26}O_5$ 358.1780, found 358.1794.

4.1.12. Methyl 3,4-di-*O*-benzyl-7,7-dibromo-2,6,7-trideoxy-D-*arabino*-hept-6-enopyranoside (17). To a solution

of oxalyl chloride (350 μL, 4.04 mmol) in CH_2Cl_2 (25 mL) at −45°C under argon, was added DMSO (580 μL, 8.18 mmol). After 10 min a solution of **16a** (1.18 g, 3.30 mmol, 71:29 α/β anomer mixture) in CH_2Cl_2 (9 mL) was added, and the resulting mixture was stirred for 1 h 20 min. Diisopropylethylamine (2.88 mL, 16.50 mmol) was then added, and the mixture was allowed to reach room temperature over a period of 30 min. The mixture was extracted with saturated $NaHCO_3$ (3×5 mL) and water (2×5 mL). The organic layer was diluted with CH_2Cl_2 (25 mL), washed with saturated $CuSO_4$ (5 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo afforded a residue that was dissolved in benzene and evaporated (three times) to yield the corresponding aldehyde (1.14 g) [^{1}H NMR δ 1.63–1.74 (m, 1H, H-2), 2.16–2.30 (m, 1H, H-2), 3.34 (s, OC*H*$_3$ α-anomer), 3.51 (s, OC*H*$_3$ β-anomer), 3.46–3.92 (m), 4.02–4.12 (m), 4.18 (d, *J*=9.5 Hz), 4.52–4.69 (m), 4.80–4.94 (m), 7.32–7.33 (m, 10H, Ar), 9.72 and 9.75 (2s, 1H, C*H*O)]. Without further manipulation, this aldehyde was used in the next step as follows. To a solution of Ph_3P (3.52 g, 13.44 mmol) in CH_2Cl_2 (13 mL) at room temperature was added dropwise a solution of CBr_4 (2.19 g, 6.61 mmol) in CH_2Cl_2 (9.5 mL). The resulting orange slurry was stirred 40 min at the same temperature and then Et_3N (2.20 mL, 15.78 mmol) was added. After cooling the resulting purple slurry to 0°C, the crude aldehyde (1.14 g) in CH_2Cl_2 (16 mL) was added dropwise. The mixture was allowed to reach room temperature and was stirred at that temperature for 2 h. The solvents were partially evaporated until 3–5 mL remained, and the resulting residue was filtered through silica gel (1 cm, ∅=6.8 cm) that had been previously saturated with Et_3N. The solid residue was washed with the minimum volume of CH_2Cl_2 and then with 25% EtOAc/hexanes (100 mL). The combined filtrate and washings were filtered and the solvents were evaporated. The crude product was purified by flash chromatography (10% EtOAc/hexanes) to yield dibromoolefin **17** (0.802 g, 48% for two steps from **16a**) as a 65:35 α/β anomer mixture: ^{1}H NMR δ 1.54–1.71 (m, 1H, H-2α), 2.24–2.36 (m, 1H, H-2β), 3.28–3.37 (m, 1H), 3.37 and 3.49 (2s, 3H, OC*H*$_3$), 3.68 (ddd, *J*=11.5, 8.5, 5.0 Hz, 1H, β-**17**), 3.94–4.04 (m, 1H), 4.36 (t, *J*=9.1 Hz, H-5, α-**17**), 4.40 (dd, *J*=9.7, 2.0 Hz, H-1, β-**17**), 4.61–4.71 (m, 3H, OC*H*$_2$Ph), 4.76 (dm, *J*=2.6 Hz, H-1 α-**17**), 4.84 (d, *J*=11.0 Hz, 1H, OC*H*Ph), 6.32 (d, *J*=8.8 Hz, H-6, α-**17**), 6.39 (d, *J*=8.2 Hz, H-6, β-**17**), 7.27–7.40 (m, 10H, Ar); ^{13}C NMR δ 35.5, 36.5, 55.0, 56.8, 71.3, 71.8, 72.1, 75.0, 75.0, 75.1, 76.8, 78.4, 80.5, 80.9, 95.0, 95.4, 98.5, 100.7, 127.6, 127.7, 127.8, 127.9, 128.4, 128.5, 135.7, 136.2, 137.8, 138.0, 138.1, 138.4; IR (neat) ν 1723 (m), 1636 cm^{-1}.

4.1.13. Methyl 3,4-di-*O*-benzyl-2,6,7-trideoxy-D-*arabino*-hept-6-ynopyranoside (18a). A solution of LDA (~0.43 M in THF, 7.7 mL, 3.31 mmol) was added dropwise to a solution of **17** (0.760 g, 1.50 mmol) in THF (3.3 mL) at −78°C. Additional portions of LDA solution were added until disappearance of the dibromoolefin as judged by TLC. After addition of H_2O (10 mL), the mixture was allowed to reach room temperature. The layers were separated, the aqueous layer was extracted with EtOAc (3×20 mL), and the combined organic extracts were dried (Na_2SO_4). The residue obtained after evaporation of the solvents was purified by flash chromatography (15% EtOAc/hexanes) to yield **18a** (0.422 g, 80%) as a 64:36 α/β anomer mixture: ^{1}H NMR δ 1.63–1.76 (m, 1H, H-2), 2.20–2.31 (m, 1H, H-2), 2.49 (d, *J*=2.3 Hz, H-7, α-**18a**), 2.52 (d, *J*=2.3 Hz, H-7, β-**18a**), 3.35 (s, OC*H*$_3$ α-**18a**), 3.49–3.57 (m), 3.86 (ddd, *J*=11.5, 8.8, 5.0 Hz, H-3, α-**18a**), 4.00 (dd, *J*=9.2, 2.0 Hz, 1H of β-**18a**), 4.35 (dd, *J*=9.6, 1.9 Hz, 1H), 4.63 and 4.68 (AB system, *J*=11.2 Hz, 2H, OC*H*$_2$Ph), 4.82 (d, *J*=2.8 Hz, H-1, α-**18a**), 4.87 (d, *J*=10.5 Hz, 1H, OC*H*Ph), 4.95 (d, *J*=10.5 Hz, 1H, OC*H*Ph), 7.29–7.41 (m, 10H, Ar); ^{13}C NMR δ 35.3, 36.5, 55.0, 56.8, 62.0, 65.9, 71.9, 72.2, 73.1, 73.6, 75.4, 75.5, 76.0, 77.7, 80.8, 81.6, 81.9, 82.1, 98.6, 100.8, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 128.3, 128.3, 128.3, 128.4, 138.0, 138.1, 138.1, 138.4; IR (neat) ν 3282 (m, ≡C–H) cm^{-1}; LRMS (EI) *m*/*z* (%) 261 (M−91, 12), 229 (6), 175 (10), 123 (7), 105 (9), 101 (5), 99 (12), 92 (10), 91 (base), 77 (4), 65 (6); HRMS calcd for $C_{22}H_{24}O_4$ 352.1675, found 352.1687.

4.1.14. Methyl 3,4-*O*-dibenzyl-2,6,7-trideoxy-α-D-lyxo-hept-6-ynopyranoside (18b). Prepared from **16b**[27] as described above for **13**. The crude product was purified by flash chromatography (10% EtOAc/hexanes) to yield enyne **19** (7%) followed by alkyne **18b** (62%, for two steps from **16b**) as transparent oils. Data for **18b**: ^{1}H NMR δ 1.93 (dd, *J*=12.7, 4.6 Hz, 1H, H-2α), 2.25 (td, J=12.6, 3.6 Hz, 1H, H-2β), 2.46 (d, *J*=2.3 Hz, 1H, H-7), 3.37 (s, 3H, OC*H*$_3$), 3.84 (ddd, J=11.9, 4.6, 2.6 Hz, 1H, H-3), 3.91 (br s, $W_{1/2}$=7.5 Hz, 1H, H-4), 4.47–4.53 (m, 3H, H-5, OC*H*$_2$Ph), 4.91–4.96 (m, 3H, H-1, OC*H*$_2$Ph), 7.29–7.50 (m, 10H, Ar); ^{13}C NMR δ 30.6, 55.3, 62.2, 70.3, 73.3, 73.6, 74.5, 75.0, 80.6, 99.2, 127.3, 127.5, 127.6, 128.1, 128.3, 128.4, 138.2, 138.5; IR (neat) ν 3280 (m, ≡C–H), 2120 (w, C≡C), 1120 (s, C–O–C), 1050 (s, C–O) cm^{-1}; $[\alpha]_D^{20}$=+121.0° (*c*=1.38, $CHCl_3$); LRMS (EI) *m*/*z* (%) 352 (M), 105 (13), 104 (35), 91 (base), 77 (12); HRMS calcd for $C_{22}H_{24}O_4$ 352.1675, found 352.1679. Data for methyl 1,5-anhydro-3-*O*-benzyl-2,4,6,7-tetradeoxy-α-L-*glycero*-hept-4-en-6-ynopyranoside (**19**): ^{1}H NMR δ 1.93–2.11 (m, 2H, H-2), 2.93 (s, 1H, H-7), 3.54 (s, 3H, OC*H*$_3$), 4.14 (dd, *J*=9.3, 5.6 Hz, 1H, H-3), 4.53 and 4.58 (AB system, *J*=11.7 Hz, 2H, OC*H*$_2$Ph), 5.00 (dd, *J*=6.1, 3.0 Hz, 1H, H-1), 5.52 (d, *J*=3.8 Hz, 1H, H-4), 7.34–7.36 (m, 5H, Ar); ^{13}C NMR δ 32.8, 56.5, 67.2, 70.0, 76.1, 78.3, 99.3, 109.5, 127.6, 127.7, 128.4, 135.4, 138.0; IR (neat) ν 3265 (m, ≡C–H), 2095 (w, C≡C), 1630 (C=C), 1130 (s, C–O–C), 1040 (s, C–O) cm^{-1}; $[\alpha]_D^{20}$=+255.24° (*c*=1.01, $CHCl_3$); LRMS (EI) *m*/*z* (%) 244 (M), 105 (15), 91 (base), 77 (13); HRMS calcd for $C_{15}H_{16}O_3$ 244.1099, found 244.1098.

4.2. General procedure for reactions with SmI_2/Pd(0)

Preparation of Pd(0) catalyst solutions: $Pd(Ph_3P)_4$ was prepared using the literature procedure[28] and directly dissolved in admixture with the substrate. A THF solution of $Pd(OAc)_2$/4(*n*-Bu_3)P was prepared by adding (*n*-Bu_3)P (80 μL, 0.30 mmol) to a solution of $Pd(OAc)_2$ (15 mg, 0.07 mmol) in THF (4 mL). An immediate color change from orange to yellow was observed. A portion of this solution was immediately added to a solution of the substrate (**4**, **13**, **18**) in THF to obtain a final molar ratio of substrate to catalyst of about 19:1. In a typical experiment, to a solution of SmI_2[23] (1.88 mmol) in THF (19 mL) under Ar was added a solution of substrate **4**, **13**, **18**

(0.63 mmol) and the Pd(0) catalyst (0.03 mmol) in THF (4 mL). The resulting solution was stirred at room temperature (**4**) or in an oil bath at 75–80°C (**13**, **18**) until TLC indicated the total disappearance of the starting material or no further evolution was observed. After cooling, saturated K_2CO_3 (15 mL) was added. The layers were separated, the aqueous layer was extracted with Et_2O (4×20 mL), and the combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The residue after evaporation was purified as specified for the individual cases to afford cyclopentanes **5**, **20**–**22**.

4.2.1. *trans*-2-Ethynylcyclopentanol[7] (5). Obtained from **4a** using $Pd(PPh_3)_4$ as catalyst in 1.5 h. The crude product (a 92:8 *trans*/*cis* mixture as determined by GC–MS) was purified by flash chromatography (25% EtOAc/hexanes) to yield **5** as a volatile oil: GC–MS t_R=6.8 and 7.1 min; ^{1}H NMR δ 1.51–1.78 (m, 4H), 1.93–2.10 (m, 3H), 2.48–2.59 (m, 2H), 4.15–4.21 (m, 1H, H-1); ^{13}C NMR δ 21.6, 30.7, 33.3, 39.1, 69.5, 79.0, 86.3. These spectroscopic data coincide with those described in the literature for the same compound.[7]

4.2.2. (1*R*,2*S*,4*S*)-4-Benzyloxy-2-ethynylcyclopentanol (20). Obtained from **13** in 81% yield after a reaction time of 6 min. The crude product was purified by flash chromatography (30% EtOAc/hexanes) to yield the title compound in a 85:15 mixture with another isomer. Repeated flash chromatography enriched this mixture to a 97:3 ratio. Data for the major (1*R*,2*S*,4*S*)-isomer (**20**): ^{1}H NMR δ 1.76–1.91 (m, 2H, H-5α, H-3α), 2.08 (br s, $W_{1/2}$=10.3 Hz, 1H, O*H*), 2.13–2.25 (m, 2H, ≡C–*H*, H-5β), 2.42–2.59 (m, 2H, H-3β, H-2), 4.06–4.10 (m, 1H, H-4), 4.39 (dd, *J*=14.3, 7.1 Hz, 1H, H-1), 4.47 (s, 2H, OC*H*$_2$Ph), 7.30–7.35 (m, 5H, *Ar*); ^{13}C NMR δ 37.3, 39.8, 69.7, 70.7, 76.2, 76.3, 85.1, 127.3, 127.4, 128.1, 138.0; IR (neat) ν 3380 (m, OH), 3285 (s, ≡C–H), 2100 (w, C≡C) cm^{-1}; $[\alpha]_D^{20}$=−42.6° (*c*=0.61, $CHCl_3$); LRMS (EI) *m*/*z* (%) 215 (M−1, 23), 123 (25), 108 (20), 107 (45), 106 (27), 105 (base), 91 (60), 79 (18), 77 (29); HRMS calcd for $C_{14}H_{16}O_2$ 216.1150, found 216.1141.

4.2.3. (1*R*,2*S*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-ethynylcyclopentanol (21). Prepared from **18a** in 61% yield (72% yield based on recovered starting material) after a reaction time of 3 h. The crude product was purified by flash chromatography (20% EtOAc/hexanes) and HPLC (35% EtOAc/hexanes, 10 mL/min, t_R=25 min). The product was characterized from an inseparable 95:5 diastereomeric mixture: ^{1}H NMR δ 1.94–2.05 (m, 1H, H-5), 2.11–2.25 (m, 1H, H-5), 2.26–2.40 (m, 1H, O*H*), 2.27 (d, *J*=2.38 Hz, 1H, H-2′), 2.67–2.74 (m, 1H, H-2), 4.01–4.07 (m, 2H, H-3 and H-4), 4.32 (dd, *J*=14.0, 6.9 Hz, 1H, H-1), 4.50 (s, 2H, OC*H*$_2$Ph), 4.64 (d, *J*=11.7 Hz, 1H, OC*H*Ph), 4.76 (d, *J*=11.7 Hz, 1H, OC*H*Ph), 7.27–7.38 (m, 10H, Ar); ^{13}C NMR δ 38.2, 44.6, 71.3, 71.4, 72.0, 75.4, 82.0, 83.8, 88.1, 127.6, 127.7, 127.8, 128.3, 137.7, 137.9; IR (neat) ν 3420, 3292, 2116 cm^{-1}; $[\alpha]_D^{20}$=−10.5° (*c*=0.95, $CHCl_3$); LRMS (EI) *m*/*z* (%) 231 (M−91, 23), 143 (4), 107 (10), 105 (13), 92 (11), 91 (base), 77 (4), 65 (5); HRMS (FAB) calcd for $C_{21}H_{21}O_3$ (M−H) 321.1569, found 321.1487.

4.2.4. (3*S*,4*R*)-3,4-Bis(benzyloxy)-2-ethynylcyclopentanol (22). Obtained from **18b** in 75% yield after a reaction time of 1 h. The crude product was purified by flash chromatography (32% EtOAc/hexanes) to yield **22** as a 54:46 diastereomeric mixture. The isomers were separated by HPLC (32% EtOAc/hexanes, 8 mL/min). Data for the (1*S*,2*R*)-isomer (**22b**): t_R=31 min; ^{1}H NMR δ 1.92–1.99 (m, 1H, H-5β), 2.14–2.20 (m, 1H, H-5α), 2.23 (d, *J*=2.6 Hz, 1H, C≡C*H*), 2.90 (d, *J*=9.7 Hz, 1H, O*H*), 3.03 (t, *J*=3.2 Hz, 1H, H-2), 3.89 (dd, *J*=6.3, 4.0 Hz, 1H, H-3), 4.02–4.08 (m, 1H, H-4), 4.12–4.21 (m, 1H, H-1), 4.58–4.77 (m, 4H, OC*H*$_2$Ph), 7.32–7.37 (m, 10H, Ar); ^{13}C NMR δ 37.8, 43.9, 71.5, 71.9, 72.1, 77.0, 78.5, 84.1, 84.9, 127.7, 128.3, 137.8, 138.0; IR (neat) ν 3420 (m, OH), 3290 (m, ≡C–H), 2100 (w, C≡C), 1120 (s, C–O–C), 1060 (s, C–O) cm^{-1}; $[\alpha]_D^{20}$=−33.33° (*c*=0.75, $CHCl_3$); LRMS (EI) *m*/*z* (%) 322 (M), 232 (14), 231 (93), 107 (43), 105 (17), 92 (16), 91 (base); HRMS calcd for $C_{21}H_{22}O_3$ 322.1569, found 322.1575. Data for the (1*R*,2*S*)-isomer (**22a**): t_R=43 min; ^{1}H NMR δ 1.89 (ddd, *J*=12.9, 7.9, 4.3 Hz, 1H, H-5α), 2.19 (s, *J*=9.5 Hz, 1H, OH), 2.26 (d, *J*=2.6 Hz, 1H, C≡C*H*), 2.27–2.40 (m, 1H, H-5β), 2.65 (ddd, *J*=6.9, 4.3, 2.5 Hz, 1H, H-2), 4.01–4.12 (m, 2H, H-3, H-4), 4.49 and 4.54 (AB system, *J*=12.1 Hz, 2H, OC*H*$_2$Ph), 4.57–4.62 (m, 1H, H-1), 4.84 and 4.89 (AB system, *J*=12.1 Hz, 2H, OC*H*$_2$Ph), 7.26–7.47 (m, 10H, Ar); ^{13}C NMR δ 37.2, 43.1, 71.5, 71.9, 73.1, 75.8, 78.8, 79.8, 82.4, 127.5, 127.5, 127.9, 128.2, 128.3, 138.2, 138.5; IR (neat) ν 3400 (m, OH), 3290 (m, ≡C–H), 2100 (w, C≡C), 1130 (s, C–O–C), 1060 (s, C–O) cm^{-1}; $[\alpha]_D^{20}$=+9.82° (*c*=0.55, $CHCl_3$); LRMS (EI) *m*/*z* (%) 322 (M), 231 (22), 107 (17), 105 (23), 91 (base); HRMS calcd for $C_{21}H_{22}O_3$ 322.1569, found 322.1583.

4.2.5. Reaction of 4b with SmI_2/$Pd(PPh_3)_4$. The general procedure was followed with $Pd(PPh_3)_4$ as catalyst at room temperature for 4 h. The crude product was subjected to flash chromatography (1% EtOAc/hexanes) to yield in order of elution **6b** (50%) and **7** (11%). Data for 2-(oct-1-ynyl)-3,4-dihydro-2*H*-pyran (**6b**): The characterized sample was obtained after additional purification by HPLC (1% EtOAc/hexanes, 8 mL/min; t_R=17 min); ^{1}H NMR δ 0.88 (t, *J*=6.7 Hz, 3H, H-8′), 1.26–1.57 (m, 9H), 1.82–2.17 (m, 5H), 2.21 (td, *J*=7.0, 1.9 Hz, 2H, H-3′), 4.59–4.65 (m, 1H, H-2), 4.67–4.73 (m, 1H, H-5), 6.31 (dt, *J*=6.1, 1.4 Hz, 1H, H-6); ^{13}C NMR δ 14.0, 18.5, 18.7, 22.5, 28.5, 28.7, 31.3, 65.2, 78.4, 85.7, 100.7, 142.7; IR (neat) ν 3060 (w, =C–H), 2240 (w, C≡C), 1650 (m, C=C) cm^{-1}; LRMS (EI) *m*/*z* (%) 192 (M, 6), 191 (36), 179 (15), 165 (5), 162 (7), 137 (91), 137 (11), 133 (8), 123 (12), 121 (12), 121 (13), 119 (17), 117 (10), 110 (15), 109 (13), 108 (14), 107 (33), 105 (23), 97 (14), 96 (10), 95 (41), 94 (14), 93 (56), 30 (92), 91 (60), 83 (26), 81 (56), 80 (28), 79 (96), 79 (13), 77 (46), 70 (34), 69 (45), 68 (15), 67 (base), 66 (19), 65 (28); HRMS calcd for $C_{13}H_{18}O$ (M−H) 191.1436, found 191.1438. Data for 2-(oct-1-ynyl)tetrahydropyran (**7**): The characterized sample was obtained after additional purification by HPLC (4% EtOAc/hexanes, 8 mL/min; t_R=25 min); ^{1}H NMR δ 0.88 (t, *J*=6.7 Hz, 3H, H-8′), 1.26–1.86 (m, 14H), 2.21 (td, *J*=6.7, 1.9 Hz, 2H, H-3′), 3.45–3.55 (m, 1H, H-6), 3.94–4.00 (m, 1H, H-6), 4.20–4.24 (m, 1H, H-2); ^{13}C NMR δ 14.0, 18.7, 21.9, 22.5, 25.7, 28.5, 28.6, 29.6, 31.3, 32.5, 66.6, 67.3, 79.1, 85.8; LRMS (EI) *m*/*z* (%) 194 (M, 15), 193 (base), 165 (6), 151 (7), 137 (71), 124 (27), 111 (20), 109

(16), 107 (10), 98 (27), 95 (17), 93 (16), 91 (16), 81 (27), 80 (16), 79 (28), 77 (13), 71 (15), 69 (18), 67 (47), 65 (10); HRMS calcd for $C_{13}H_{20}O$ (M−H) 193.1592, found 193.1597.

4.2.6. Reaction of 4b with SmI_2 and cyclohexanone. To a stirred solution of SmI_2 (~0.1 M in THF, 12.4 mL, 1.24 mmol) at room temperature under Ar was added a solution of **4b** (140 mg, 0.55 mmol) and cyclohexanone (60 μL, 0.58 mmol) in THF (5 mL). The mixture was stirred for 2.5 h and worked-up as indicated in the general procedure. The crude product was subjected to flash chromatography (1% and then 6% EtOAc/hexanes) to yield in order of elution **6b** (43 mg, 43%) and **8** (14 mg, 9%, 92:8 diastereomeric mixture as measured by GC–MS). Data for 1-[6-(oct-1-ynyl)tetrahydropyran-2-yl]cyclohexanol (**8**): ^{1}H NMR δ 0.89 (t, *J*=6.6 Hz, 3H, H-8′), 1.2–1.9 (m, 24H), 2.00 (s, 1H, O*H*), 2.22 (td, *J*=6.8, 1.9 Hz, 2H, H-3′), 3.70 (dd, *J*=11.4, 2.2 Hz, 1H, H-2), 4.76 (br s, $W_{1/2}$=8.7 Hz, 1H, H-6); ^{13}C NMR δ 14.0, 18.7, 19.2, 21.7, 22.6, 24.4, 26.0, 28.5, 28.7, 30.8, 31.3, 32.4, 34.6, 65.7, 72.3, 76.3, 78.4, 87.3; IR (neat) ν 3600–3300 (O–H), 2230 (w, C≡C) cm^{-1}. GC–MS t_R=18.6 and 19.5 min; LRMS (EI) *m/z* (%) 291 (M−1, 1), 275 (3), 235 (1), 209 (2), 194 (4), 192 (4), 176 (3), 165 (2), 147 (2), 125 (3), 124 (28), 123 (4), 121 (2), 106 (7), 99 (base), 98 (7), 97 (5), 95 (8), 95 (8), 93 (7), 91 (7), 81 (30), 80 (16), 79 (13), 77 (5), 69 (5), 67 (11); HRMS calcd for $C_{19}H_{32}O_2$ 292.2402, found 292.2392.

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