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Enantioselective synthesis of *erythro*-4-deoxyglycals as scaffolds for target- and diversity-oriented synthesis: new insights into glycal reactivity†

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An efficient, enantioselective synthesis of *erythro*-4-deoxyglycals has been developed using asymmetric aldehyde allylation and tungsten-catalyzed alkynol *endo*-cycloisomerization as the key steps. These versatile synthetic scaffolds have been elaborated to a variety of products using stereoselective transformations that are complementary to those available using the corresponding *threo* glycals. This work has provided valuable insights into the relationships between glycal structure and reactivity. In addition, a new diene-forming side reaction during tungsten-catalyzed alkynol cycloisomerization has been discovered.

Introduction

Glycals are versatile building blocks with a broad range of applications in the synthesis of carbohydrates, polyketides, and other natural products.[1] Hence, they are also attractive scaffolds for diversity-oriented synthesis.[2–4] Recently, in the course of a project aimed at using stereochemical diversity to probe three-dimensional structure space, we required access to all four stereoisomeric 4-deoxyglycals **1**–**4** (Fig. 1). The *threo* stereoisomers (**1** and **2**) are readily synthesized by substrate-controlled stereoselective Luche reduction of the appropriate Danishefsky diene-derived dihydropyrone.[5] Surprisingly, however, the *erythro* stereoisomers (**3** and **4**) pose a much greater synthetic challenge. Herein we report our investigations of this deceptively simple problem and the effective solution we ultimately devised to provide synthetically useful quantities of *erythro*-4-deoxyglycals. We also describe stereoselective transformations of these scaffolds that are complementary to those available using the *threo* stereoisomers and demonstrate their utility as versatile synthons for stereoselective target- and diversity-oriented synthesis. In the course of this work, we have compared several alkynol *endo*-cycloisomerization reactions, discovered a new side reaction that can occur in the $W(CO)_6/Et_3N/h\nu$-catalyzed reaction, and gained valuable insights into the striking differences in glycal reactivity that arise from seemingly subtle differences in glycal structure.

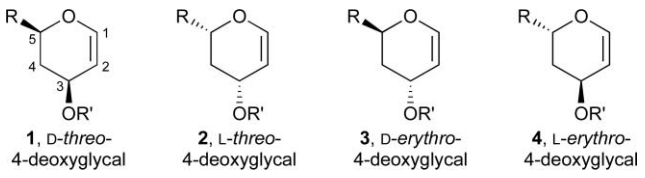

Fig. 1 Four stereoisomeric 4-deoxyglycal scaffolds for target- and diversity-oriented synthesis.

Results and discussion

Classical approaches

At the outset of these studies, we expected that the *erythro*-4-deoxyglycals could be accessed using any of a variety of well-precedented classical approaches. Thus, our initial efforts focused on 1,2-reduction of the dihydropyrone **5** (Fig. 2) with sterically demanding hydride reagents, based on the expectation that equatorial attack would provide the desired *erythro* product **7**. However, when **5** was treated with any of a variety of bulky hydride reagents,[6] the *threo* stereoisomer **6** was formed nearly exclusively. These results are in stark contrast to the stereoselectivity trends observed with bulky hydride reductions of cyclohexanones[7] and cyclohexenones.[8] This unusual stereoselectivity for dihydropyrone reduction may be rationalized by the reduced steric conflict along the axial trajectory (**5a**),[9] increased torsional strain associated with the transition state for equatorial attack,[10] stereoelectronic effects involving the ring oxygen,[11] and/or the availability of a competing reactive conformation (**5b**) in which the *C*5-methyl substituent is oriented axially.

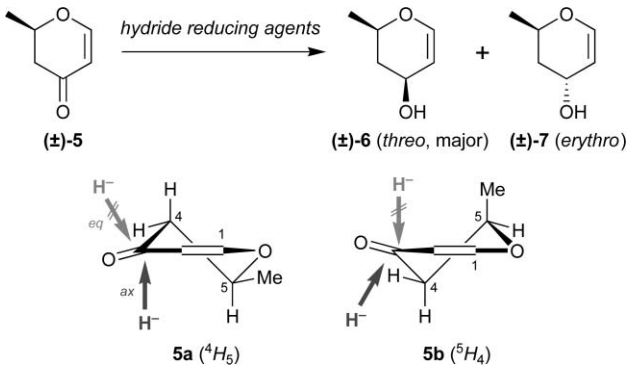

Fig. 2 Reductions of dihydropyrone **5** with bulky hydride reagents.

Since the *threo*-4-deoxyglycal **6** is readily available, we next turned our attention to inversion of its *C*3-hydroxyl group by either direct or indirect means. Not surprisingly, Mitsunobu inversion of **6** was thwarted by competing S_N2' displacement.[12] Interestingly, this was also the case for a *C*1-alkylated congener (not shown), which was synthesized using our recently

† Electronic supplementary information (ESI) available: experimental procedures and spectral data for compounds **25**–**35**. See http://www.rsc.org/suppdata/ob/b4/b417429a/

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reported *B*-alkyl Suzuki–Miyaura cross coupling approach to *C*1-alkylglycals.[13] These results indicate that electronic factors clearly dominate over steric constraints for these reactions of glycals.

This propensity of glycals to undergo attack at the *C*1 position brought our attention to an indirect approach to *C*3 inversion (Fig. 3). A thiophenol Ferrier–sigmatropic rearrangement sequence has been used to convert 3,4,6-tri-*O*-acetyl-D-glucal (**8**) to 3,6-di-*O*-acetyl-D-allal (**11**).[14,15] Unfortunately, exposure of our *threo*-4-deoxyglycal substrate **13** to the reported Ferrier conditions ($BF_3 \cdot OEt_2$) resulted in rapid decomposition. Interestingly, the use of $SnCl_4$ resulted in direct substitution at the *C*3 position by thiophenol (**12**) but allylic substitution at the *C*1 position by 4-methoxyphenol (**14**). Such nucleophile-dependent regioselectivity has been rationalized by the hard–soft acid–base principle.[16] In this vein, we tested the harder nucleophile *S*-(trimethylsilyl)thiophenol, which favors *C*1 attack on *C*4-substituted glycals.[17] However, this did not alter the undesirable *C*3 regioselectivity for our 4-deoxyglycal substrate **13**. These results highlight the striking differences in reactivity that arise from the absence of a *C*4-substituent in 4-deoxyglycals.

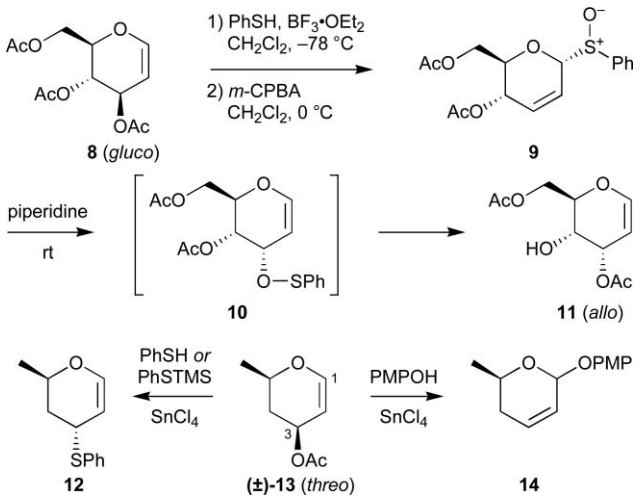


Fig. 3 Net *C*3-inversion of 3,4,6-tri-*O*-acetyl-D-glucal **8** and related reactions of *threo*-4-deoxyglycal **13**.

Alkynol cycloisomerization approaches

Having explored the classical approaches, we turned to an alternative strategy involving *endo*-cycloisomerization of an appropriately functionalized linear alkynol precursor (Fig. 4). Tungsten-catalyzed alkynol cycloisomerizations have been developed extensively by McDonald,[18–21] building upon earlier work with molybdenum-catalyzed reactions.[22] More recently, rhodium- and ruthenium-catalyzed cycloisomerizations have

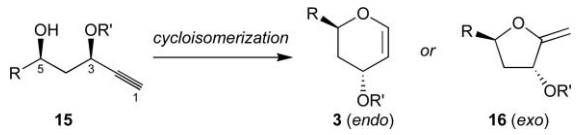


Fig. 4 *Endo*- and *exo*-cycloisomerizations of 3,5-dihydroxyalkynes.

been described by Trost.[23,24] Although multistep synthesis of the alkynol precursor would be required, we recognized that an enantioselective synthesis could be achieved by drawing upon the vast arsenal of methodologies that have been developed in the context of polyketide synthesis.

It should be noted that it was not clear at the outset of our studies whether or not the key cycloisomerization reaction would be successful. Trost had reported a single example of 4-deoxyglycal synthesis as a mixture of *threo* and *erythro* diastereomers using rhodium-catalyzed cycloisomerization.[23] Moreover, while our work was in progress, Wipf reported a strong influence of alkynol stereochemistry upon the regiochemical outcome of $W(CO)_6$/DABCO/*hν*-catalyzed cycloisomerization.[25] Notably, substrates with our required stereochemical configuration (**15**) favored *exo*-cycloisomerization (**16**) unless non-coordinating protecting groups were used at the *C*3 position. Furthermore, the practical utility of the reaction was limited by low yields (15–49%).

Thus, we began by synthesizing the requisite alkynol precursors **22** (Fig. 5). We designed these substrates to maintain the spacing of oxygen functionalities found in polyketide natural products. We also envisioned that the orthogonally protected *C*7-hydroxyl might provide an attachment point for future applications in solid phase synthesis. Enantioselective allylation of aldehyde **17**[26,27] with Leighton's allylsilane reagent[28] provided convenient, efficient access to the homoallylic alcohol **18**, which was then converted to aldehyde **19**.[29] We next had the opportunity to evaluate several recently developed diastereoselective alkyne addition reactions.[30] Unfortunately, in our hands, attempted couplings of **19** with trimethylsilylacetylene using $Zn(OTf)_2$/*N*-methylephedrine[31] led to recovered starting material, consistent with a recent report involving related substrates.[32] Reactions at higher temperatures or with Et_2Zn/$Ti(O\textit{i}\text{-}Pr)_4$/BINOL[33] led to β-elimination of **19** to give the corresponding α,β-enone. We thus turned to direct addition of lithium trimethylsilylacetylide, which afforded modest substrate-controlled diastereoselectivity favoring the desired propargylic alcohol **20** (3 : 2 dr). Protecting group manipulations then provided cycloisomerization substrates **22**. Large scale material throughput was conveniently achieved using this route (8.0 g of alkynol **22a** in 30% overall yield from aldehyde **17**).[34] Notably, the minor alkynol diastereomer **21** was also readily separated chromatographically from **20** and carried on to **22** *via* standard Mitsunobu inversion protocols (not shown).

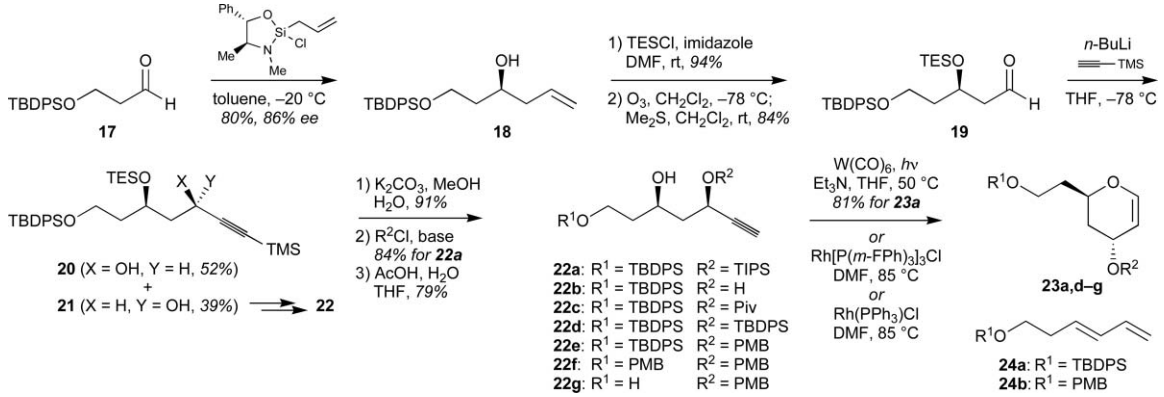


Fig. 5 Enantioselective synthesis of protected alkynol substrates **22** and *endo*-cycloisomerization reactions to form *erythro*-4-deoxyglycals **23**.

We were now in position to investigate the key alkynol cycloisomerization reaction. Unfortunately, in our hands, attempted cycloisomerizations of **22a,e–g** using $Rh[P(m\text{-}FPh)_3]_3Cl$ or $Rh(PPh_3)_3Cl$ yielded only trace amounts (<10%) of the corresponding glycals **23a,e–g**, despite their close similarity to the previously reported example.[23] However, after extensive experimentation with various substrates, we were gratified to find that exposure of **22a** to $W(CO)_6/Et_3N/h\nu$[20] provided the desired *erythro*-4-deoxyglycal **23a** in good yield with no evidence of competing *exo*-cycloisomerization.[25,35]

Several important observations were made in the course of these investigations. First, replacement of Et_3N with DABCO, which is now more commonly used as the base,[18,20] resulted in markedly slower reaction rates and no improvement in yields. Second, attempted tungsten-catalyzed cycloisomerizations of **22b–e** resulted in the formation of an unexpected truncated diene **24a**. This diene was the exclusive product for **22b** and **22c**, and a major product for **22d** (1 : 1 with **23d**) and **22e** (1 : 0.04 : 1.2 with **23e** and the corresponding *exo*-glycal). Similarly, reaction of the doubly PMB-protected alkynol **22f** yielded the corresponding diene **24b** (2.3 : 1 : 1 ratio with **23f** and the corresponding *exo*-glycal).

A possible mechanism for this side reaction involves normal cycloisomerization, followed by elimination of the axially-oriented *C*3-substituent, alkene isomerization, and [4 + 2]-cycloreversion (Fig. 6). Formation of this diene has not been reported previously, perhaps due to the decreased propensity for elimination of the corresponding *threo* stereoisomers (see below), decreased acidity of substrates having substituents at the *C*4 position, and volatility of dienes corresponding to substrates lacking our bulky sidechains.

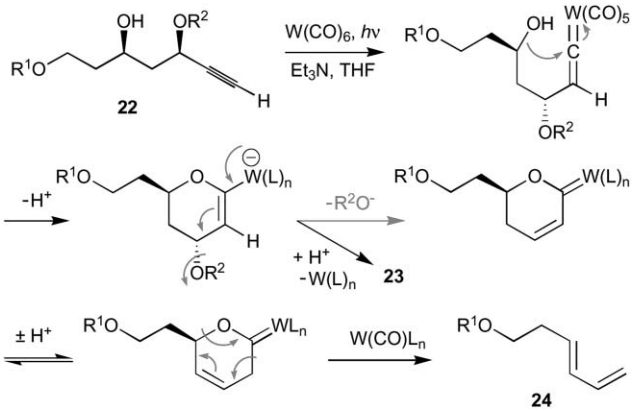


Fig. 6 A possible mechanism for formation of truncated diene **24**.

Taken together, our results underscore the major influence of protecting groups and stereochemical configuration upon the efficiency and outcome of alkynol cycloisomerization reactions.

Stereoselective reactions of the *erythro*-4-deoxyglycal

Having secured access to synthetically useful quantities of *erythro*-4-deoxyglycal **23a**, we were in a position to explore the reactivity of this novel glycal. In particular, this stereoisomer provides the opportunity to carry out stereoselective reactions of the glycal double bond that are complementary to those available using the corresponding *threo* stereoisomer. Selective reactivity at the β-face of the double bond is likely contingent upon a favored reactive conformation in which the large *C*3-OTIPS substituent is axially disposed (**23a**′, Fig. 7).[36]

Thus, we carried out a number of exploratory reactions to probe the reactivity of **23a** and to illustrate its potential synthetic utility in both target- and diversity-oriented synthesis (Fig. 8). We were gratified to find that epoxidation of **23a** with dimethyldioxirane[37] provided the β-epoxide **25** as a single diastereomer. Subsequent methanolysis led to quantitative formation of the α-D-*arabino*-4-deoxyglycoside **26**. Likewise, treatment of **25** with allylmagnesium chloride provided the corresponding α-allyl *C*-glycoside **27** (80% yield). Hydroboration–oxidation of **23a** using thexylborane proceeded stereoselectively to give the β-*C*2-alcohol **28** (74% isolated yield). In contrast, the use of BH_3 led to a 2 : 1 ratio of **28** and its α-*C*2-epimer while 9-BBN and dicyclohexylborane were unreactive.

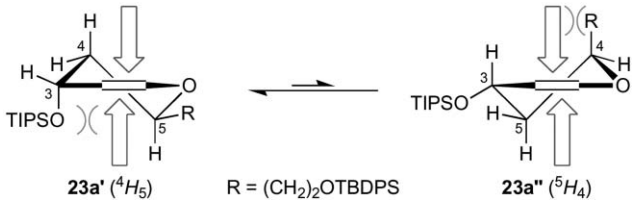


Fig. 7 Half-chair conformations of the *erythro*-4-deoxyglycal **23a** and steric influences upon double bond reactivity.

Interestingly, attempted direct methanolysis of the glycal double bond under mild acidic conditions ($PPh_3 \cdot HBr$) led to a 3 : 1 : 3.3 mixture of β-methyl *erythro*-2,4-dideoxyglycoside **30**, its α-anomer (not shown), and the α-glycoside Ferrier rearrangement product **31** (51% combined yield of **30** and **31**). Notably, exposure of the corresponding *threo*-4-deoxyglycal to identical conditions did not result in any Ferrier rearrangement. These results are also consistent with axial orientation of the *C*3-OTIPS substituent, which would be stereoelectronically predisposed to Ferrier-type elimination. Furthermore, these observations lend support to our proposed mechanism for diene formation during the cycloisomerization reaction (Fig. 6). Similarly, $Sc(OTf)_3$-catalyzed condensation of **23a** with salicylaldehyde[38] resulted in highly regio- and stereoselective formation of tricycle **29**, albeit in low yield, presumably *via* the intermediacy of a Ferrier-type elimination.

The *erythro*-4-deoxyglycal **23a** was also converted to *C*1-substituted glycals **32a,b** *via* previously described cross coupling-based routes.[13,39] Hydroboration–oxidation proceeded from the β-face of the glycal double bond with complete stereoselectivity to provide the corresponding α-D-*arabino*-4-deoxy-*C*-glycosides **33a,b** in good yields. Interestingly, acid-catalyzed alcoholysis of the *C*1-substituted glycal **32a** provided the α-methyl ketoglycoside **35a** (50% yield), corresponding to a double substitution at both the *C*1 and *C*3 positions. We postulate that, in contrast to the case with the parent unsubstituted glycal **23a**, an initial Ferrier-type elimination is followed by MeOH attack at the *C*3 position, leading to the 3-methoxyglycal intermediate **34a**. Indeed, in the *C*1-phenylglycal series (**32b**), the 3-methoxyglycal **34b** was isolated (24% yield) and found to be in equilibrium with the doubly substituted product **35b**.

Conclusion

We have developed an efficient, enantioselective synthesis of *erythro*-4-deoxyglycals *via* a tungsten-catalyzed alkynol *endo*-cycloisomerization. We have also carried out a variety of stereoselective reactions of these *erythro*-4-deoxyglycals to probe their reactivity and to demonstrate their utility as versatile synthetic intermediates for target- and diversity-oriented synthesis. Notably, the products have the appropriate stereochemical configuration for applications in the target-oriented synthesis of polyketide natural products such as the apicularens,[40] latrunculins,[41] spongistatins,[42,43] salicylihalimides,[44] and compactin.[45] Efforts to use the *erythro*- and *threo*-4-deoxyglycals as stereoisomeric scaffolds for diversity-oriented synthesis are ongoing and will be reported in due time. In the course of this work, we have also discovered a new side reaction that occurs during tungsten-catalyzed cycloisomerization and compared various cycloisomerization reactions. Our studies highlight the striking effects upon glycal reactivity that can result from the absence of a *C*4-substituent or the presence of axially-oriented *C*3-substituents.

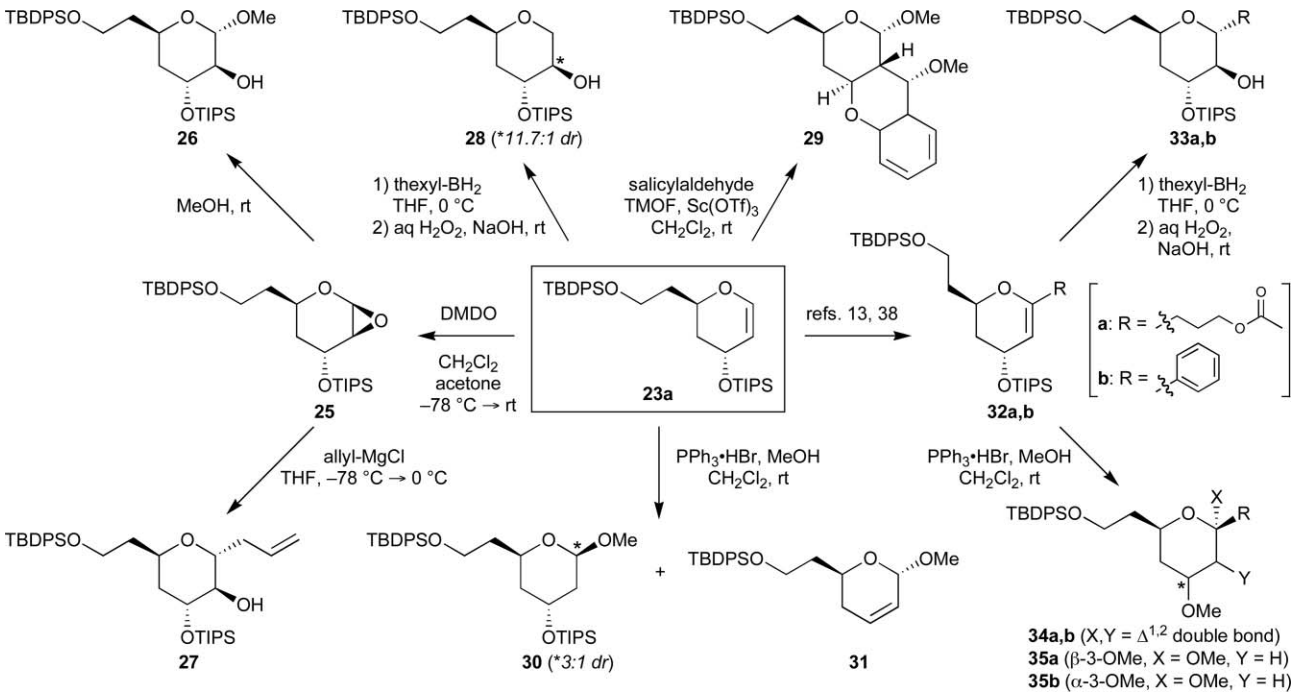


Fig. 8 Stereoselective reactions probing the reactivity of the *erythro*-4-deoxyglycal **23a** and illustrating its potential synthetic utility as a versatile scaffold for target- and diversity-oriented synthesis.

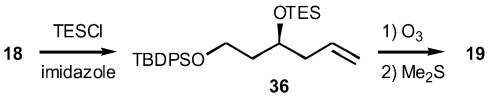
Experimental

Materials and methods

Reagents were obtained from Aldrich Chemical (www.sigma-aldrich.com) or Acros Organics (www.fishersci.com) and used without further purification. Optima grade solvents were obtained from Fisher Scientific (www.fishersci.com), degassed with Ar, and purified using a solvent drying system as described,[46] unless otherwise indicated. Reactions were performed in flame-dried glassware under positive Ar pressure with magnetic stirring. Cold baths were generated as follows: 0 °C, wet ice/water; −78 °C, dry ice/acetone. Photolysis reactions were carried out in a Rayonet photoreactor at 300 nm. Flash chromatography was performed on E. Merck 60 230–400 mesh silica gel. Optical rotations were recorded on a JASCO model DIP-370 digital polarimeter. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by using potassium permanganate or cerium ammonium molybdenate stains. IR spectra were recorded neat on NaCl plates with a Perkin–Elmer model 1600 FTIR spectrometer with peaks reported in cm^{-1}. NMR spectra were recorded on Bruker DRX500 or AMX400 instruments at 24 °C in $CDCl_3$ unless otherwise indicated. Chemical shifts are expressed in ppm relative to TMS (^1H, 0 ppm) or solvent signals: $CDCl_3$ (^{13}C, 77.0 ppm), C_6D_6 (^1H, 7.16 ppm; ^{13}C, 128.0 ppm) or d_6-acetone (^{13}C, 206.2 ppm). Coupling constants are expressed in Hz. Mass spectra were obtained at the MSKCC Analytical Core Facility on a PE SCIEX API 100 mass spectrometer by electrospray (ESI) ionization.

(3*S*)-1-(*tert*-Butyldiphenylsilyloxy)hex-5-en-3-ol (18)

A solution of aldehyde **17**[26,27] (15.6 g, 49.9 mmol, 1.0 equiv.) in anhydrous toluene (30 mL) was added to a cooled (0 °C) solution of (4*S*,5*S*)-2-allyl-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazasilolidine[28] (18.6 g, 69.4 mmol, 1.4 equiv.) in anhydrous toluene (200 mL). The mixture was transferred to a freezer (−20 °C) for 3 h. 1 N aq. HCl (150 mL) and EtOAc (100 mL) were then added and the mixture was warmed to rt and stirred for 15 min. The aqueous layer was extracted with EtOAc (2 ×) then the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (elution with 95 : 5 hexanes–EtOAc) to yield alcohol **18** as a clear oil (14.1 g, 80%). The ee of **18** was determined to be 86% by analysis of its Mosher ester. The reaction was also completed on a 29 mg scale in 73% yield and 88% ee. Spectral data were in agreement with the literature.[29]



(3*R*)-5-(*tert*-butyldiphenylsilyloxy)-3-(triethylsilyloxy)pentanal (19)

The alcohol **18** was converted to aldehyde **19** in two steps as previously described.[29] For analytical scale synthesis, olefin **36** and aldehyde **19** were purified by flash chromatography as usual. For preparative scale synthesis, 14.1 g of alcohol **18** was converted to 18.7 g of crude aldehyde **19** (84% overall yield based on NMR analysis of the crude product), which was carried on to **20** without further purification (see below).

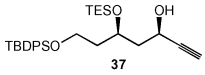
(3*R*,5*R*)-7-(*tert*-Butyldiphenylsilyloxy)-5-(triethylsilyloxy)-1-(trimethylsilyl)hept-1-yn-3-ol ((−)-20) and (3*S*,5*R*)-7-(*tert*-Butyldiphenylsilyloxy)-5-(triethylsilyloxy)-1-(trimethylsilyl)-hept-1-yn-3-ol ((−)-21)

n-BuLi (2.5 M in hexane, 1.99 mmol, 1.3 equiv.) was added dropwise to a cooled (−78 °C) solution of TMS acetylene (270 μL, 1.99 mmol, 1.3 equiv.) in anhydrous THF (4.5 mL). The reaction mixture was stirred at −78 °C for 1 h then treated over 5 min with a solution of the aldehyde **19** (722 mg, 1.53 mmol, 1.0 equiv.) in anhydrous THF (3.5 mL). After an additional 20 min at −78 °C, the reaction was quenched with H_2O. The aqueous layer was extracted with Et_2O (3 ×) and the combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford a 59 : 41 mixture of **20** and **21**. The crude material was purified by flash chromatography (elution with 93 : 7 hexanes–EtOAc) to yield propargylic alcohols **20** (454 mg, 52%) and **21** (342 mg, 39%) as clear oils. For preparative scale synthesis, 18.7 g of crude aldehyde **19** (see above) was converted to alcohol **20**, which was purified by flash chromatography: (10.4 g, 46% overall yield over 3 steps **18** → **20**).

20: $[\alpha]_D^{25} = -8.7$ (*c* 0.5, $CHCl_3$). TLC: R_f 0.11 (9 : 1 hexanes–EtOAc). IR (NaCl, film): 2955, 2871, 1422, 1249, 1111, 1087,

1009, 841, 739, 703. ^{1}H-NMR (400 MHz): δ 7.63 (m, 4H), 7.39 (m, 6H), 4.52 (m, 1H), 4.14 (m, 1H), 3.69 (m, 2H), 2.80 (d, 1H, $J = 3.9$), 1.89–1.70 (m, 4H), 1.04 (s, 9H), 0.95 (t, 9H, $J =$ 7.9), 0.50 (q, 6H, $J = 7.9$), 0.16 (s, 9H). ^{13}C-NMR (100 MHz): δ 135.8, 135.0, 133.9, 129.9, 127.9, 106.9, 89.3, 69.2, 62.0, 60.6, 44.2, 40.9, 27.1, 19.3, 7.1, 5.3. ESI-MS *m/z*: (pos.) 569.4 [M + H]$^+$, 591.3 [M + Na]$^+$; (neg.) 567.3 [M − H]$^-$.

21: $[a]_D^{25} = -6.4$ (*c* 1.0, $CHCl_3$). TLC: R_f 0.34 (9 : 1 hexanes–EtOAc). IR (NaCl, film): 3436, 2955, 2872, 1467, 1420, 1384, 1249, 1096, 1008, 844, 738, 697. ^{1}H-NMR (400 MHz): δ 7.64 (m, 4H), 7.40 (m, 6H), 4.59 (m, 1H), 4.37 (m, 1H), 3.68 (m, 2H), 3.41 (d, 1H, $J = 5.5$), 1.92–1.63 (m, 4H), 1.06 (s, 9H), 0.95 (t, 9H, $J = 7.9$), 0.61 (q, 6H, $J = 8.0$), 0.15 (s, 9H). ^{13}C-NMR (100 MHz): δ 136.3, 135.6, 133.6, 127.8, 127.5, 127.0, 106.7, 88.8. 60.4, 27.1, 26.8, 26.6, 19.1, 5.0. ESI-MS *m/z*: (pos.) 569.2 [M + H]$^+$, 591.3 [M + Na]$^+$; (neg.) 567.3 [M − H]$^-$, 603.3 [M + Cl]$^-$.

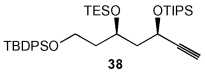


37

(3*R*,5*R*)-7-(*tert*-Butyldiphenylsilyloxy)-5-(triethylsilyloxy)hept-1-yn-3-ol (37)

A cooled (0 °C) solution of **20** (10.3 g, 18.1 mmol) in MeOH (180 mL, Optima grade) was treated with H_2O (9.8 mL) and K_2CO_3 (5.0 g, 36.2 mmol). The mixture was stirred at 0 °C for 10.5 h then the MeOH was evaporated to afford a white solid. The solid was dissolved in Et_2O, washed with H_2O (3 ×), washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield propargylic alcohol **37** as a white solid (9.41 g, 91% based on NMR analysis of the crude product) that was carried on without further purification in preparative scale synthesis. An analytical sample was purified by flash chromatography for spectral characterization.

TLC: R_f: 0.24 (4 : 1 hexanes–EtOAc). IR (NaCl, film): 3307, 2950, 2881, 1461, 1427, 1104, 1006, 816, 735, 695. ^{1}H-NMR (400 MHz): δ 7.66 (m, 4H), 7.40 (m, 6H), 4.52 (m, 1H), 4.20 (m, 1H), 3.70 (m, 2H), 2.81 (d, 1H, $J = 4.0$), 2.44 (d, 1H, $J = 2.1$), 1.91–1.68 (m, 4H), 1.03 (s, 9H), 0.92 (t, 9H, $J = 7.9$), 0.60 (q, 6H, $J = 7.9$). ^{13}C-NMR (100 MHz): δ 135.8, 135.0, 133.8, 129.9, 127.9, 85.0, 73.1, 69.0, 61.3, 60.6, 44.2, 40.8, 27.1, 19.4, 7.1, 5.3. ESI-MS *m/z*: (pos.) 497.3 [M + H]$^+$, 519.3 [M + Na]$^+$; (neg.) 495.3 [M − H]$^-$, 531.0 [M + Cl]$^-$.



38

(3*R*,5*R*)-7-(*tert*-Butyldiphenylsilyloxy)-5-(triethylsilyloxy)-3-(triisopropylsilyloxy)hept-1-yne (38)

Triisopropylsilyl chloride (73 μL, 0.34 mmol, 1.5 equiv.) was added dropwise to a solution of the propargylic alcohol **37** (113.1 mg, 0.23 mmol, 1.0 equiv.) and imidazole (31.3 mg, 0.46 mmol, 2.0 equiv.) in anhydrous DMF (2.3 mL, Sureseal bottle). After 22 h at rt the reaction mixture was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 ×) and the combined extracts were washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (elution with 98 : 2 hexanes–EtOAc) to yield alkyne **38** as a clear oil (125.5 mg, 84%). For preparative scale synthesis, 9.4 g of crude alcohol **37** was converted to 14.0 g of crude alkyne **38**, which was carried on without further purification (see below).

TLC: R_f: 0.59 (9 : 1 hexanes–EtOAc). IR (NaCl, film): 3296, 2950, 2869, 1461, 1427, 1237, 1104, 1058, 1006, 885, 822, 735, 695. ^{1}H-NMR (400 MHz): δ 7.67 (d, 4H, $J = 6.9$), 7.40 (m, 6H), 4.61 (m, 1H), 4.19 (m, 1H), 3.70 (m, 2H), 2.40 (d, 1H, $J =$ 1.8), 1.91–1.69 (m, 4H), 1.13–1.02 (m, 30H), 0.92 (t, 9H, $J =$ 7.9), 0.59 (q, 6H, $J = 7.9$). ^{13}C-NMR (100 MHz): δ 135.8, 134.1, 129.7, 127.8, 85.7, 73.2, 67.1, 61.3, 60.6, 46.5, 41.1, 27.0, 19.3, 18.2, 12.4, 7.2, 5.3. ESI-MS *m/z*: (pos.) 653.6 [M + H]$^+$, 675.3 [M + Na]$^+$; (neg.) 687.4 [M + Cl]$^-$.

(3*R*,5*R*)-1-(*tert*-Butyldiphenylsilyloxy)-5-(triisopropylsilyloxy)-hept-6-yn-3-ol ((+)-22a)

Acetic acid (1.1 mL) was added to a solution of alkyne **38** (122.9 mg, 0.19 mmol) in THF (0.4 mL, Optima grade) and water (0.4 mL). After 1.5 h at rt the mixture was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extractedwith Et_2O (3 ×) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by flash chromatography (elution with 95 : 5 hexanes–EtOAc) to yield alcohol **22a** as a clear oil (80.6 mg, 79%). For preparative scale synthesis, 14.0 g of crude alkyne **38** (see above) was converted to alcohol **22a**, which was purified by flash chromatography (8.0 g, 81% overall yield over 3 steps **20** → **22a**).

$[a]_D^{25} = +4.2$ (*c* 1.0, $CHCl_3$). TLC: R_f: 0.35 (9 : 1 hexanes–EtOAc). IR (NaCl, film): 2934, 2862, 1462, 1426, 1105, 881, 820, 736, 699. ^{1}H-NMR (400 MHz): δ 7.66 (m, 4H), 7.41 (m, 6H), 4.72 (m, 1H), 4.18 (m, 1H), 3.85 (m, 2H), 3.27 (d, 1H, $J =$ 2.7), 2.45 (d, 1H, $J = 2.0$), 1.97 (m, 1H), 1.82 (m, 1H), 1.72 (m, 2H), 1.20–1.13 (m, 30H). ^{13}C-NMR (100 MHz): δ 135.8, 133.5, 130.0, 128.0, 85.4, 73.2, 68.7, 62.6, 61.8, 46.1, 39.3, 27.0, 19.3, 18.2, 12.5. ESI-MS *m/z*: (pos.) 561.4 [M + Na]$^+$; (neg.) 537.3 [M − H]$^-$.

(2*R*,4*R*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-4-(triisopropylsilyloxy)-3,4-dihydro-2*H*-pyran ((+)-23a)

A solution of the alkynol **22a** (116.1 mg, 0.22 mmol, 1.0 equiv.) in anhydrous THF (0.6 mL) was added to $W(CO)_6$ (19.0 mg, 0.054 mmol, 0.25 equiv.) and the mixture was treated with distilled Et_3N (135 μL, 0.97 mmol, 4.5 equiv.). The mixture was irradiated without cooling for 8 h. The solvent was evaporated to give a yellow mixture of oil and solid. The crude material was purified by flash chromatography (elution with 99 : 1 hexanes–EtOAc) to yield *erythro*-4-deoxyglycal **22a** as a clear oil (94.3 mg, 81%). For preparative scale synthesis, the reaction was carried out with three parallel batches of alkynol **22a** (158.1, 203.0, and 249.0 mg), which were then combined and purified to afford 479.8 mg of glycal **23a** (79%).

$[a]_D^{25} = +68.8$ (*c* 1.0, $CHCl_3$). TLC: R_f: 0.33 (9 : 1 hexanes–EtOAc). IR (NaCl, film): 2941, 2864, 2360, 1636, 1241, 1111, 1088, 997, 882, 735, 701. ^{1}H-NMR (400 MHz): δ 7.64 (d, 4H, $J =$ 6.8), 7.39 (m, 6H), 6.39 (d, 1H, $J = 6.1$), 4.88 (t, 1H, $J = 4.9$), 4.28–4.17 (m, 2H), 3.81 (m, 2H), 1.81 (m, 3H), 1.60 (m, 1H), 1.03 (m, 30H). ^{13}C-NMR (100 MHz): δ 145.9, 135.8, 134.3, 134.1, 129.8, 127.8, 104.1, 68.4, 60.6, 60.3, 38.7, 38.5, 27.1, 19.4, 18.4, 12.6. ESI-MS *m/z*: (pos.) 539.3 [M + H]$^+$, 561.4 [M + Na]$^+$; (neg.) 573.5 [M + Cl]$^-$.

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