JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

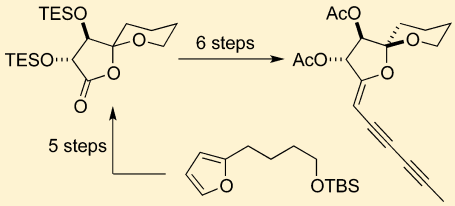
Synthesis of Stereoisomers of *Artemisia* and *Chrysanthemum* Bis(acetylenic) Enol Ether Spiroacetals

Boshen Wu, George C. Feast,† Amber L. Thompson,† and Jeremy Robertson*

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.

Supporting Information

ABSTRACT: An 11-step synthesis is described of two diastereomeric candidates for a bis(acetylenic) enol ether spiroacetal isolated from *Chrysanthemum boreale*. Key steps in the synthetic route include spiroacetal lactone alkylidenation and subseqent modified Cadiot−Chodkiewicz cross-coupling to install the bis(acetylenic) enol ether functionality. From NMR comparisons, neither of the candidates, whose structures were confirmed by single-crystal X-ray diffraction, correspond to the natural product, and a proposal for the correct structure is put forward.



INTRODUCTION

Plants of the genera *Artemisia* and *Chrysanthemum* (Asteraceae) produce, among other secondary metabolites, structurally intriguing bis(acetylenic) enol ether spiroacetals including "homo-tonghaosu" (**1**),[1] lactiflodiyne A (**2**),[2] and AL-1 (**3**)[3] (Figure 1). These three examples encapsulate the structural

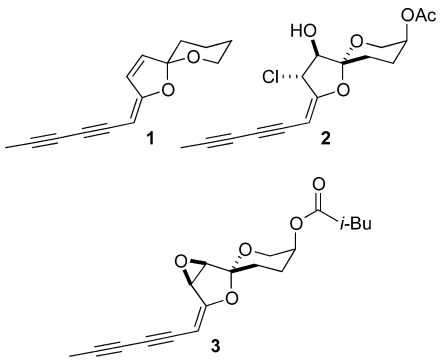


Figure 1. Representative *Artemisia* and *Chrysanthemum* bis(acetylenic) enol ether spiroacetals.

variations in the spiro[4.5] series; viz. mono-oxygenation in the tetrahydropyranyl ring and either alkene, epoxide, chlorohydrin, or (acylated) diol functionality in the hydrofuran ring. From a stereochemical perspective, variations are found in the geometry of the enol ether double bond, the relative stereochemistry of the spiro-center with respect to functionality in the five-membered ring and the axial/equatorial disposition of substituents in the tetrahydropyranyl ring. Some of these stereochemical aspects were addressed in Bohlmann's seminal work in this area,[4,5] with notable subsequent contributions by Marco and Hofer[6] and Ye.[2] To date, apart from homo-tonghaosu, which has been synthesized a number of times, total syntheses of natural products in this class have been achieved only by Mukai's research group.[7,8]

Our interest in this general area stemmed from a report of the isolation from *Chrysanthemum boreale* of diacetoxy variant *Z-cis*-**4** (Figure 2), referred to in this paper as CB-II.[9] The *Z*-

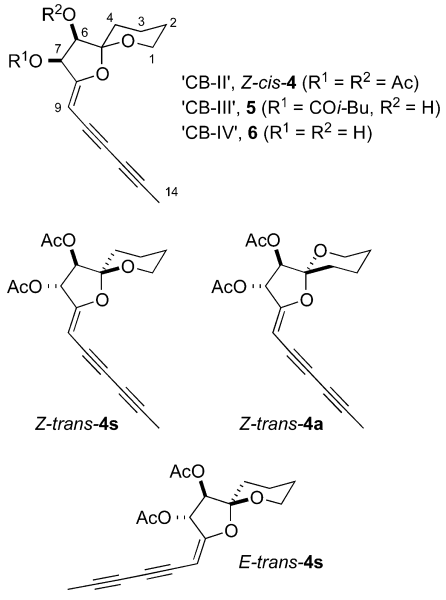
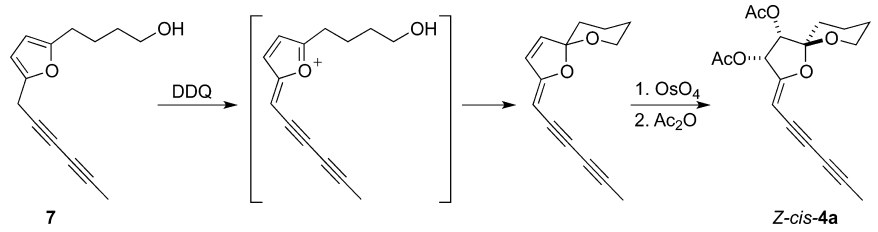


Figure 2. Originally proposed structures for CB-II and -III from *Chrysanthemum boreale* and diacetate stereoisomers discussed in this paper.[12]

stereochemistry reported for the enol ether double bond and the *cis*-disposition of the acetoxy substituents in the hydrofuran ring are particularly unusual because the only other *Z*-configured enol ethers in this class (except for "CB-III" (**5**) reported in the same paper) are homo-tonghaosu and its acetoxy and isovaleryloxy derivatives in the tetrahydropyranyl

Received: August 24, 2012
Published: October 31, 2012

Scheme 1



ring;[10] that is, natural products containing an alkene in the hydrofuran ring and which are prone to *E*-/*Z*- isomerization. In addition, all of the other reported hydrofuran-oxygenated examples have a *trans*-relative disposition of the substituents, formally derived by S_N2-mode opening at the allylic center of epoxides of the AL-1 type. In light of these interesting stereochemical aspects, and because the configuration of the spiro-center in CB-II had not been assigned, we completed a total synthesis of a candidate diastereomer *Z-cis*-**4a** based on DDQ-mediated oxidative activation and spirocyclization of 2-(4-hydroxybutyl)furan derivative **7** (Scheme 1).[11]

From that work it became apparent that the structure reported for CB-II required revision as, among other differences between the ^{1}H NMR data, the H-6/H-7 vicinal coupling constant (numbering, Figure 2) of our synthetic compound *Z-cis*-**4a** ($^3J \sim 4.5$ Hz) did not match the reported value ($^3J = 7.5$ Hz). Examination of molecular models showed that, irrespective of the relative spiro-center configuration, the dihedral angle between these coupling protons could not vary beyond about ±40°. Combined with an expectation that the acetoxy substituents would favor an approximate gauche rather than eclipsed relationship, it is unlikely that a *cis*-diacetate of this type could give rise to a significantly larger coupling constant than that observed for diacetate *Z-cis*-**4a**.[13]

This paper describes syntheses of the two spiro-diastereomers of CB-II in the *trans*-diacetate series (*Z-trans*-**4s** and *Z-trans*-**4a**, Figure 2), shows that neither is a correct match for CB-II, and proposes a structure for both CB-II and, by implication, CB-III.

RESULTS AND DISCUSSION

Initially, we expended considerable effort in attempting to convert *cis*-diol intermediates such as **8**–**10** (Figure 3) to the

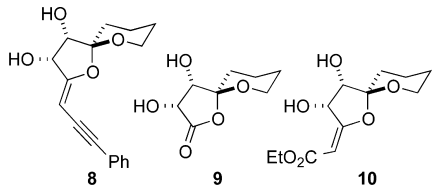


Figure 3. *cis*-Diol substrates investigated as potential precursors to *trans*-diols.

trans-diol/diacetate motif,[14] all to no avail, and we switched to a route in which the correct diol stereochemistry was established prior to spirocyclization. For this, furan derivative **11**[15] (Scheme 2) was oxidized efficiently according to Salomon's procedure, and the first-formed *Z*-ketoacid was isomerized as described[16] to the *E*-isomer **12**. We were unable to effect asymmetric dihydroxylation of this electron-deficient alkene and only Sharpless' conditions with citric acid[17] were effective in generating the racemic diol **13**. Silyl deprotection under acidic conditions led directly to spirocyclization and lactonization producing a pair of spiro-diastereomers **14** that were silylated (→ **15**) in readiness for introduction of the acetylenic side-chain.

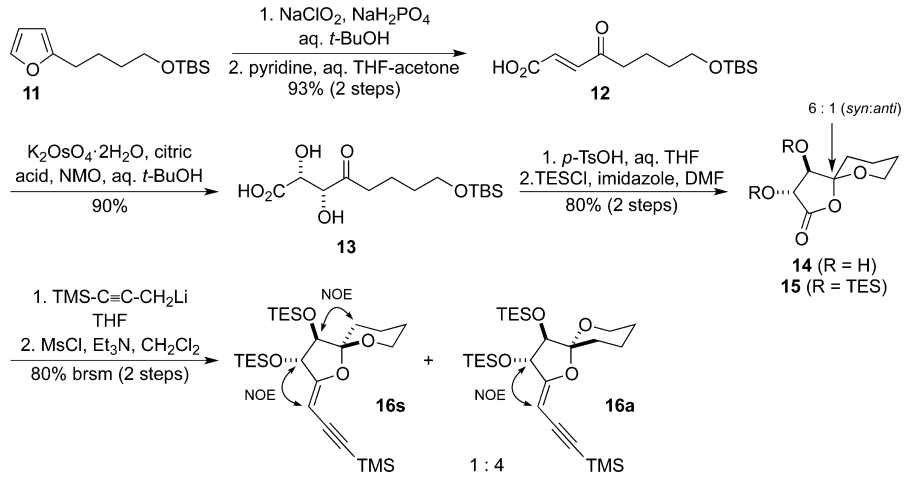
The stereochemical relationship between the tetrahydropyranyl oxygen and adjacent silyloxy substituent in these isomers was established by NOE experiments; see the Supporting Information. On the assumption that the spirocyclization proceeds under thermodynamic control, hydrogen bonding between the tetrahydropyranyl oxygen and the adjacent hydroxyl may be sufficient to account for the favored formation of diastereomer **14s**.

The conversion of the carbonyl group in [*m*,*n*]-spiroacetal lactones (*m*,*n* = 4 or 5) into an exocyclic alkene has not been described except in two papers reporting direct methylenation with Petasis reagent, Cp_2TiMe_2.[18] However, such transformations applied to simple lactones are reasonably well-known, and after failing to achieve a direct Wittig olefination with hexa-2,4-diyn-1-ylidenetriphenylphosphorane, we embarked upon a strategy comprising organometallic addition followed by dehydration of the so-formed lactol to deliver the enol ether. Application of conditions reported for propargyl addition to a glucurono-γ-lactone derivative,[19] in which the propargyl source is 3-lithio-1-trimethylsilylpropyne,[20] was successful so long as the reaction temperature and time were kept to a minimum. Thus, adding TMEDA to increase the rate of addition, and quenching the reaction at −78 °C within 5−10 min, led to clean product formation (45% isolated) with full recovery of unreacted lactone (55%) which was then recycled. Significantly longer reaction times led to unraveling of the spiroacetal and hydride transfer to deliver monocyclic lactol **17** (with unassigned stereochemistry) as outlined in Scheme 3. Dehydration of the diastereomeric mixture of lactols was easily achieved via the mesylate and the two spiro-epimers **16s** and **16a** were obtained efficiently. These isomers were separated and key NOE correlations allowed assignment of both the relative stereochemistry at the spiro-center and the *Z*-stereochemistry of the enol ether double bond in each compound (for details, see the Supporting Information). Interestingly, the major isomer at this stage possessed an *anti*-relationship between the tetrahydropyranyl oxygen and adjacent silyloxy group, presumably reflecting the ability of the intermediate lactol to attain a more stable *anti*-,*anti*-disposition of oxygen functionality by reversible ring-opening.

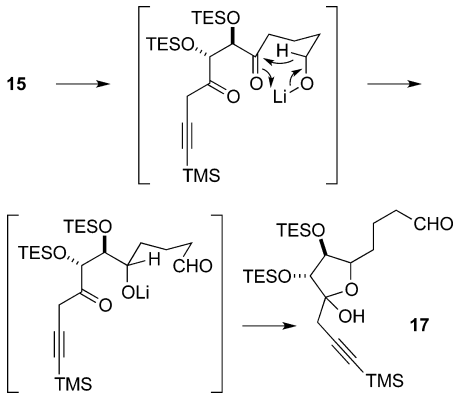
Each isomer was then subjected to a four-step sequence to complete syntheses of the CB-II candidate isomers *Z-trans*-**4s** and *Z-trans*-**4a** (Scheme 4). Selective deprotection[21] of the alkynylsilane set the scene for modified[22] Cadiot−Chodkiewicz cross coupling with 1-iodopropyne,[23] paralleling the end stages of Mukai's route to AL-2 and related molecules.[7] Final deprotection and double acetylation completed the sequences without epimerization at the spiro-center.

dx.doi.org/10.1021/jo301810d | J. Org. Chem. 2012, 77, 10623−10630

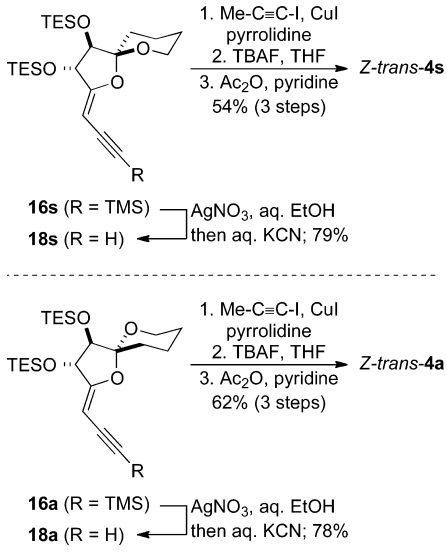
Scheme 2



Scheme 3



Scheme 4



Crystals suitable for single-crystal X-ray diffraction experiments[24] were grown of both isomers, thereby confirming the stereochemistry predicted on the basis of the NOE studies in intermediates **16s** and **16a**. The crystal structures explain an unexpected feature of the NMR data for these diacetates; viz. the critical H-6/H-7 coupling constant in isomer *Z-trans*-**4s** is 7.5 Hz, but in isomer *Z-trans*-**4a** this is reduced to 1.0 Hz. In *Z-trans*-**4s**, the *CH*(OAc)−*CH*(OAc) dihedral angle is 164° in a conformation that accommodates an antiperiplanar arrangement of the (C-6)−OAc and hydrofuranyl-O−(C-5) bonds, as well as a potential [(C-6)−H]σ−[tetrahydropyranyl-O−(C-5)]σ* interaction. On the other hand, in *Z-trans*-**4a**, the overall conformation is the same as that in *Z-trans*-**4s** but the hydrofuranyl H and AcO substituents are swapped resulting in a corresponding dihedral angle of 91°; here, the (C-6)−OAc bond is antiperiplanar with respect to both the (C-7)−OAc and tetrahydropyranyl-O−(C-5) bonds, and a [(C-6)−H]σ−[hydrofuranyl-O−(C-5)]σ* interaction is possible. In these two compounds and diacetate *Z-cis*-**4a**, for which crystal data are available, the H-6/H-7 coupling constant obtained in solution ($CDCl_3$ or CCl_4) and that calculated using the dihedral angle (ϕ), measured in the solid state, fits the Karplus equation $J(\phi) = 7.0\cos^2\phi - 0.10\cos\phi + 1.0$.

NMR Data Comparison with CB-II. Table 1 lists ^{1}H NMR data (coupling constants rounded to the nearest 0.5 Hz) for CB-II,[9] our three synthetic diacetates (*Z-trans*-**4s**, *Z-trans*-**4a**, and *Z-cis*-**4a**[11]), and *E-trans*-**4s** (Figure 2) isolated[6] by Marco from *Chrysanthemum lavandulifolium* and synthesized[7] by Mukai.

With these data viewed together certain trends emerge. (1) For the *Z*-compounds, the H-1 resonances are distinctly split into a td for the axial proton and a dd or d for the equatorial proton, whereas in Marco's compound *E-trans*-**4s** and CB-II both H-1 protons appear together at ∼3.7−3.8 ppm; (2) the H-6/H-7 coupling constant is not, in itself, diagnostic of the relative stereochemistry in the hydrofuran ring; however, it is notable that CB-II and both *Z*- and *E-trans*-**4s** all show J = 7.5 Hz; (3) of the two *CH*(OAc) protons, the chemical shift of H-7 is the more sensitive to stereochemistry, being notably shifted upfield in *Z-trans*-**4a** in which it is 1,3-*anti*-disposed to the tetrahydropyranyl oxygen (it is correspondingly *syn* in *Z-trans*-**4s**, *Z-cis*-**4a** and *E-trans*-**4s**); (4) the chemical shift of the olefinic proton H-9 in the *Z*- isomers, in which this proton is *trans*-disposed to the hydrofuran oxygen, is shifted upfield by between ∼0.2−0.5 ppm compared with that in CB-II and *E-trans*-**4s**; (5) the resonances for H-6, H-7, and H-9 show a consistent solvent dependence, appearing ∼0.02−0.13 ppm upfield in CCl_4 relative to the shifts in $CDCl_3$.

On balance, these NMR trends suggest a close match between the data for CB-II and Marco's compound *E-trans*-**4s**, although the different solvents used (CCl_4 and $CDCl_3$) make a

dx.doi.org/10.1021/jo301810d | J. Org. Chem. 2012, 77, 10623−10630

Table 1. Comparison ^{1}H NMR Data (in CCl_4 unless Stated Otherwise)

proton	CB-II[9]	*Z-trans*-**4s**	*Z-trans*-**4a**	*Z-cis*-**4a**[11]	*E-trans*-**4s**[6]
H-1	3.73 (2H, t, J = 5.0 Hz)	3.80 (br d, J = 11.0 Hz) 3.98 (td, J = 11.0, 3.0 Hz) 3.83 (dd, J = 12.0, 4.5 Hz)[a] 3.96 (td, J = 12.0, 3.0 Hz)[a]	3.77 (br d, J = 11.5 Hz) 3.99 (td, J = 11.5, 3.5 Hz) 3.78 (dd, J = 11.5, 4.5 Hz)[a] 3.98 (td, J = 11.5, 3.5 Hz)[a]	3.76 (br d, J = 10.5 Hz) 3.97 (td, J = 10.4, 4.0 Hz) 3.67−3.79 (m)[a] 3.83−3.97(m)[a]	3.82 (2H, m)[a] 3.83 (2H, m)[a,b]
H-(2−4)	1.50−1.90 (6H, m)	1.60−1.89 (6H, m) 1.50−1.86 (6H, m)[a]	1.53−1.87 (6H, m) 1.52−2.00 (6H, m)[a]	1.50−1.82 (6H, m) 1.55−2.05 (6H, m)[a]	1.50−1.60 (2H, m)[a] 1.60−1.80 (4H, m)[a] 1.60−1.80 (6H, m)[a,b]
H-6	4.99 (d, J = 7.5 Hz)	5.00 (d, J = 7.5 Hz) 5.13 (d, J = 7.5 Hz)[a]	4.99 (s) 5.11 (d, J = 1.5 Hz)[a]	5.08 (d, J = 5.0 Hz) 5.20 (d, J = 5.0 Hz)[a]	5.16 (d, J = 7.5 Hz)[a] 5.14−5.17 (2H, m)[a,b]
H-7	6.07 (dd, J = 7.5, 2.0 Hz)	5.85 (d, J = 7.5 Hz) 5.98 (dd, J = 7.5, 2.0 Hz)[a]	5.40 (s) 5.52 (t, J = 1.5 Hz)[a]	5.93 (dd, J = 5.0, 2.0 Hz 6.01 (dd, J = 5.0, 2.0 Hz)[a]	6.25 (dd, J = 7.5, 2.0 Hz)[a] 6.25 (dd, J = 8.0, 1.0 Hz)[a,b]
H-9	5.03 (dq, J = 2.0, 1.0 Hz)	4.61 (s) 4.70 (dq, J = 2.0, 1.0 Hz)[a]	4.79 (s) 4.88 (∼quin, J = 1.25 Hz)[a]	4.52 (s) 4.59−4.63 (m)[a]	5.14 (dq, J = 2.0, 1.0 Hz)[a] see H-6[a,b]
H-14	1.97 (3H, d, J = 1.0 Hz)	2.02 (3H, s) 2.00 (3H, d, J = 1.0 Hz)[a]	2.03 (3H, s) 2.00 (3H, d, J = 1.0 Hz)[a]	1.97 (3H, s) 2.00 (3H, d, J = 1.0 Hz)[a]	1.96 (3H, d, J = 1.0 Hz)[a] 1.96 (3H, s)[a,b]
OAc	2.08 (3H, s) 2.10 (3H, s)	2.08 (3H, s) 2.12 (3H, s) 2.10 (3H, s)[a] 2.15 (3H, s)[a]	2.10 (3H, s) 2.12 (3H, s) 2.11 (3H, s)[a] 2.12 (3H, s)[a]	2.04 (3H, s) 2.09 (3H, s) 2.07 (3H, s)[a] 2.10 (3H, s)[a]	2.15 (6H, s)[a] 2.15 (3H, s)[a,b] 2.16 (3H, s)[a,b]

[a]In $CDCl_3$. [b]From ref 7.

firm conclusion impossible.[25] If CB-II is, in fact, *E-trans*-**4s** then the glycol **6** "CB-IV" (Figure 2) obtained[9] by hydrolysis of CB-II (and CB-III) should be reassigned to *E-trans*-**6s**, which was reported recently from *Ajania przewalskii* (Asteraceae).[26] In fact, the reported NMR data differ (Table 2), and on this basis

Table 2. Selected ^{1}H NMR Data (in $CDCl_3$)

proton	CB-IV[9]	*E-trans*-**6s**[26]
H-6	3.80 (d, J = 6.5 Hz)	3.95 (br s)
H-7	4.84 (dd, J = 6.5, 2.0 Hz)	4.59 (br s)
H-9	5.08 (dq, J = 2.0, 1.0 Hz)	5.17 (br s)
H-14	1.96 (3H, d, J = 1.0 Hz)	1.96 (3H, s)

and in view of the originally proposed structure for CB-IV, Zhu reasonably concluded that these glycols are different.[26] However, we have found that glycols in this class show concentration-dependent ^{1}H NMR shifts, particularly for the H-6, H-7 and H-9 resonances, and these data, therefore, offer no illumination of the situation.[25]

CONCLUSION

This paper has described the synthesis of two further candidate structures for CB-II, a bis(acetylenic) spiroacetal isolated from *Chrysanthemum boreale*. These syntheses are short, at 11 steps from **11**, and efficient (23% for *Z-trans*-**4s**, 26% for *Z-trans*-**4a** overall). Neither of these candidates provides a match for the data published for CB-II, and unambiguous confirmation of the identity of CB-II must await resynthesis[27] of Marco's compound *E-trans*-**4s** and, if necessary, the remaining diastereomers. So far, we have been unable to isomerize *Z-trans*-**4s** and *Z-trans*-**4a** or precursors **16s** and **16a** to the corresponding *E*-enol ethers, but this remains an attractive possibility.[28]

EXPERIMENTAL SECTION

General Methods. Infrared spectra were recorded using neat samples on an FT-IR spectrometer as thin films on NaCl plates or directly on a diamond ATR module; peaks are reported in wavenumbers (cm^{-1}) and their intensities as broad (br), strong (s), medium (m), and weak (w) as appropriate. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at the frequencies stated and in the specified solvents. Chemical shifts (δ) are reported in parts per million downfield of tetramethylsilane with respect to standard reference peaks. Assignments in NMR listings are made on the basis of chemical shift and coupling constant data in combination with COSY, HMQC, HSQC, HMBC, NOE, and NOESY data as necessary. Coupling constants (J) are quoted to the nearest 0.5 Hz. High resolution mass spectra (HRMS) were obtained using electrospray ionization (ESI) and a time-of-flight (TOF) analyzer.

5-[4-(*tert*-Butyldimethylsilyloxy)butyl]-5-hydroxyfuran-2(5*H*)-one (S1).[16] To a stirred solution of [4-*tert*-butyldimethylsilyloxy)butyl]furan **11** (2.00 g, 7.86 mmol) in *tert*-butyl alcohol and water (5:1, 40 mL) were added $NaH_2PO_4{\cdot}H_2O$ (1.74 g, 12.6 mmol) and $NaClO_2$ (2.27 g, 25.1 mmol). The resulting mixture was stirred at rt for 4 h and then diluted with water (150 mL) and extracted with chloroform (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (petroleum ether/ether/acetic acid, 80:20:1) furnished the title compound **S1** as a pale yellow oil (2.22 g, 98%): R_f 0.37 (petroleum ether/ethyl acetate, 80:20); IR (neat) 3385br, 2955s, 2931s, 2859s, 1770s, 1256m, 1102s, 835s, 776m; ^{1}H NMR (400 MHz, $CDCl_3$) 0.04 (6H, s, $Si(CH_3)_2$), 0.88 (9H, s, $C(CH_3)_3$), 1.42−1.71 (4H, m, H-2′, H-3′), 1.90−2.06 (2H, m, H-1′), 3.62 (2H, t, J = 6.0 Hz, H-4′), 4.20−4.30 (1H, br, OH), 6.09 (1H, d, J = 5.5 Hz, H-3), 7.21 (1H, d, J = 5.5 Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) −5.3 ($Si(CH_3)_2$), 18.3 ($C(CH_3)_3$), 20.2 (C-2′), 25.9 ($C(CH_3)_3$), 31.8 (C-3′), 36.9 (C-1′), 62.9 (C-4′), 108.0 (C-5), 123.1 (C-3), 154.2 (C-4),

dx.doi.org/10.1021/jo301810d | J. Org. Chem. 2012, 77, 10623−10630

170.3 (C-2); HRMS (ESI$^+$) calcd for $C_{14}H_{26}NaO_4Si^+$ (M + Na$^+$) 309.1493, found 309.1498.

(*E*)-8-[(*tert*-Butyldimethylsilyl)oxy]-4-oxooct-2-enoic Acid (12).[16] To a stirred solution of butenolide **S1** (4.50 g, 15.7 mmol) in a mixture of THF, water, and acetone (5:4:1, 3 mL) was added pyridine (12.6 μL, 0.157 mmol) at rt. The resulting mixture was stirred at rt for 2 h, and then the solvent was removed. Flash chromatography (petroleum ether/ether/acetic acid, 80:20:1) furnished the title compound **12** as a colorless oil (4.27 g, 95%): R_f 0.27 (petroleum ether/ether/acetic acid, 80:20:1); IR (neat) 3197br, 2955s, 2931s, 2858s, 1699s, 1256s, 1103s, 837s, 777m; ^{1}H NMR (500 MHz, $CDCl_3$) 0.05 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $C(CH_3)_3$), 1.52−1.58 (2H, m, H-7), 1.71 (2H, app. quin, J = 7.5 Hz, H-6), 2.69 (2H, t, J = 7.5 Hz, H-5), 3.63 (2H, t, J = 6.0 Hz, H-8), 6.67 (1H, d, J = 16.0 Hz, H-3), 7.13 (1H, d, J = 16.0 Hz, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) −5.3 ($Si(CH_3)_2$), 18.3 ($C(CH_3)_3$), 20.2 (C-6), 25.9 ($C(CH_3)_3$), 32.0 (C-7), 41.4 (C-5), 62.7 (C-8), 129.6 (C-2), 141.0 (C-3), 170.0 (C-1), 199.4 (C-4); HRMS (ESI$^+$) calcd for $C_{14}H_{27}O_4Si^+$ (M + H$^+$) 287.1673, found 287.1676.

(2*R,3*R**)-8-[(*tert*-Butyldimethylsilyl)oxy]-2,3-dihydroxy-4-oxooctanoic Acid (13).** To a stirred solution of acid **12** (670 mg, 2.34 mmol) and citric acid (338 mg, 1.76 mmol) in a mixture of *tert*-butyl alcohol and water (1:1, 5 mL) was added $K_2OsO_4{\cdot}2H_2O$ (43 mg, 0.117 mmol) followed by NMO solution (50% aq solution, 580 μL, 2.81 mmol). The resulting mixture was stirred for 100 min and then concentrated. Flash chromatography (methanol/dichloromethane/acetic acid, 10:90:3) furnished the *title compound* **13** as a pale brown oil (673 mg, 90%) which was used without purification: R_f 0.29 (petroleum ether/ether/acetic acid, 80:20:1); IR (neat) 3420br, 2954s, 2931s, 2887m, 2859m, 1720s, 1255s, 1101s, 837s, 813s; ^{1}H NMR (500 MHz, $CDCl_3$) 0.05 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $C(CH_3)_3$), 1.50−1.59 (2H, m, H-6), 1.66−1.76 (2H, m, H-7), 2.55−2.73 (2H, m, H-5), 3.60−3.67 (2H, m, H-8), 4.53−4.64 (1H, app. s, H-2), 4.64−4.74 (1H, app. s, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) −5.4 ($Si(CH_3)_2$), 18.3 ($C(CH_3)_3$), 19.9 (C-7), 25.9 ($C(CH_3)_3$), 31.9 (C-6), 37.7 (C-5), 62.8 (C-8), 71.4 (br, C-3), 77.3 (br, C-2), 175.4 (br, C-1), 208.1 (br, C-4); HRMS (ESI$^+$) calcd for $C_{14}H_{28}NaO_6Si^+$ (M + Na$^+$) 343.1547, found 343.1540.

(3*R,4*R**,5*S**)-3,4-Dihydroxy-1,6-dioxaspiro[4.5]decan-2-one (14s) and (3*R**,4*R**,5*R**)-3,4-Dihydroxy-1,6-dioxaspiro-[4.5]decan-2-one (14a).** To a stirred solution of crude dihydroxy acid **13** (200 mg, 0.624 mmol) in a mixture of THF (6 mL) and water (11.5 μL, 0.638 mmol) was added *p*-toluenesulfonic acid monohydrate (60 mg, 0.315 mmol) at rt; some precipitation occurred. The resulting suspension was stirred at rt for 3 h and then concentrated. Flash chromatography (dichloromethane/ethyl acetate/acetic acid, 66:33:1) furnished the *title compound* **14** as a mixture of two diastereomers **14s** and **14a** (6:1, respectively) and as a white solid (94 mg, 83%): R_f 0.44 (methanol/dichloromethane/acetic acid, 10:90:3); IR (neat) 3406br, 2951m, 1784s, 1644w, 1234m, 1148m, 1097s, 935m, 883m; ^{1}H NMR (500 MHz, d_6-acetone) 1.58−2.03 (6H, m, H-8, H-9, H-10), 3.81−3.85 (3H, m, H-4, H-7), 4.43 (1H, dd, J = 9.0, 5.0 Hz, H-3), 4.48 (1H, d, J = 9.0 Hz, (C-4)OH), 5.12 (1H, d, J = 5.0 Hz, (C-3)OH); ^{13}C NMR (125 MHz, d_6-acetone) data for **14s** 19.5 (C-9), 25.1 (C-8), 31.0 (C-10), 63.8 (C-7), 73.2 (C-3), 79.9 (C-4), 103.4 (C-5), 174.1 (C-2); data for **14a** 18.9 (C-9), 25.4 (C-8), 29.1 (C-10), 64.5 (C-7), 74.7 (C-3), 81.1 (C-4), 106.7 (C-5), 172.8 (C-2); HRMS (ESI$^+$) calcd for $C_8H_{12}NaO_5^+$ (M + Na$^+$) 211.0577, found 211.0577.

(3*R,4*R**,5*S**)-3,4-Bis[(triethylsilyl)oxy]-1,6-dioxaspiro[4.5]-decan-2-one (15s) and (3*R**,4*R**,5*R**)-3,4-Bis[(triethylsilyl)oxy]-1,6-dioxaspiro[4.5]decan-2-one (15a).** To a stirred solution of diol **14** (a mixture of diastereomers **14s** and **14a**, 51 mg, 0.271 mmol) in anhydrous DMF (0.3 mL) at 0 °C was added imidazole (111 mg, 1.63 mmol) followed by chlorotriethylsilane (137 μL, 0.814 mmol). The resulting mixture was warmed to rt and stirred for 3 h, and then water (5 mL) and ether (5 mL) were added. The aqueous layer was extracted with ether (3 × 5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography (petroleum ether/ether, 97:3) furnished the *title compounds* (**15s**, 96 mg, 85%) and (**15a**, 18 mg, 16%) as colorless oils. **Data for 15s**: R_f 0.42 (petroleum ether/ether, 95:5); IR (neat) 3418br, 2956s, 2789s, 1802s, 1651w, 1458m, 1239m, 1171s, 1103s; ^{1}H NMR (500 MHz, $CDCl_3$) 0.65−0.77 (12H, m, 2 × $Si(CH_2CH_3)_3$), 0.96−1.04 (18H, m, 2 × $Si(CH_2CH_3)_3$), 1.57−1.93 (6H, m, H-8, H-9, H-10), 3.85−3.92 (3H, m, H-4, H-7), 4.56 (1H, d, J = 8.5 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) 4.9 and 5.0 (2 × $Si(CH_2CH_3)_3$), 6.7 (2 × $Si(CH_2CH_3)_3$), 18.7 (C-9), 24.3 (C-8), 30.8 (C-10), 63.4 (C-7), 73.7 (C-3), 80.2 (C-4), 102.9 (C-5), 173.1 (C-2); HRMS (ESI$^+$) calcd for $C_{20}H_{40}NaO_5Si_2^+$ (M + Na$^+$) 439.2306, found 439.2303. **Data for 15a**: R_f 0.60 (petroleum ether/ether, 95:5); IR (neat) 3406br, 2955s, 2878s, 1798s, 1459m, 1416m, 1238m, 1166s; ^{1}H NMR (500 MHz, $CDCl_3$) 0.63−0.76 (12H, m, 2 × $Si(CH_2CH_3)_3$), 0.96−1.02 (18H, m, 2 × $Si(CH_2CH_3)_3$), 1.51−2.00 (6H, m, H-8, H-9, H-10), 3.82 (1H, dd, J = 11.5, 4.5 Hz, H-7$_{eq}$), 3.98 (1H, td, J = 11.5, 3.0 Hz, H-7$_{ax}$), 4.04 (1H, d, J = 8.5 Hz, H-4), 4.23 (1H, d, J = 8.5 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) 4.7 and 4.8 (2 × $Si(CH_2CH_3)_3$), 6.6 (2 × $Si(CH_2CH_3)_3$), 18.0 (C-9), 24.5 (C-8), 28.7 (C-10), 64.1 (C-7), 75.3 (C-3), 81.6 (C-4), 105.7 (C-5), 171.5 (C-2); HRMS (ESI$^+$) calcd for $C_{20}H_{40}NaO_5Si_2^+$ (M + Na$^+$) 439.2306, found 439.2305.

(3*R,4*R**)-3,4-Bis[(triethylsilyl)oxy]-2-[3-(trimethylsilyl)prop-2-yn-1-yl]-1,6-dioxaspiro[4.5]decan-2-ol (S2).** To a stirred solution of 1-(trimethylsilyl)propyne (41 μL, 0.277 mmol) and TMEDA (42 μL, 0.280 mmol) in anhydrous, degassed THF (1.1 mL) at −78 °C was added BuLi (1.6 M in hexanes, 173 μL, 0.277 mmol). After the solution was stirred for 1 h, a solution of lactone **15s** (96 mg, 0.230 mmol) in anhydrous, degassed THF (5.8 mL) was added. The mixture was stirred at −78 °C for 10 min, and then acetic acid (0.3 mL) was added to quench the reaction. Ether (15 mL) and water (15 mL) were added, and the layers were separated. The aqueous layer was extracted with ether (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$) then concentrated. Flash chromatography (petroleum ether/ether, 80:20) furnished the *title compound* **S2** as a mixture of four diastereomers (dr not determined) and as a colorless oil (54 mg, 44%, 98% brsm): R_f 0.58 (petroleum ether/ether, 70:30); IR (neat) 3418br, 2957s, 2915s, 2879m, 2181w, 1461m, 1249m, 1124s, 1091s, 978m, 844m; ^{1}H NMR (500 MHz, $CDCl_3$) 0.14−0.17 (9H, m, $Si(CH_3)_3$), 0.64−0.74 (12H, m, 2 × $Si(CH_2CH_3)_3$), 0.96−1.03 (18H, m, 2 × $Si(CH_2CH_3)_3$), 1.46−1.95 (6H, m, H-8, H-9, H-10), 2.62−2.82 (2H, m, H-1′), 3.60−4.31 (5H, m, H-3, H-4, H-7, OH); ^{13}C NMR (125 MHz, $CDCl_3$) −0.08, 0.02, and 0.04 ($Si(CH_3)_3$), 4.92, 4.95, 5.00, and 5.15 (2 × $Si(CH_2CH_3)_3$), 6.75, 6.80, 6.82, and 6.90 (2 × $Si(CH_2CH_3)_3$), 18.9, 19.2, and 19.3 (C-9), 24.9 (2 peaks), 25.1 and 25.2 (C-8), 28.3 and 31.0 (C-1′), 29.6 (2 peaks) and 29.7 (C-10), 61.9, 62.0 (2 peaks) and 62.2 (C-7), 78.4, 78.7, 82.7, and 83.0 (C-3), 82.5 (2 peaks, C-4), 86.0, 86.2, and 86.4 (C-3′), 99.9, 100.4, 102.1, 102.4, 102.6, 102.7 (2 peaks), 102.9, 104.2, 104.3, 105.5, and 105.7 (C-2, C-5, C-2′); HRMS (ESI$^+$) calcd for $C_{26}H_{52}NaO_5Si_3^+$ (M + Na$^+$) 551.3015, found 551.3016.

(3*R,4*R**,5*S**,*Z*)-3,4-Bis[(triethylsilyl)oxy]-2-[3-(trimethylsilyl)prop-2-yn-1-ylidene]-1,6-dioxaspiro[4.5]decane (16s) and (3*R**,4*R**,5*R**,*Z*)-3,4-Bis[(triethylsilyl)oxy]-2-[3-(trimethylsilyl)-prop-2-yn-1-ylidene]-1,6-dioxaspiro[4.5]decane (16a).** To a stirred solution of lactol **S2** (a mixture of four diastereomers, 91 mg, 0.172 mmol) in dichloromethane (5 mL) at 0 °C was added triethylamine (192 μL, 1.38 mmol) and then methanesulfonyl chloride (53.4 μL, 0.688 mmol). The resulting mixture was stirred at rt for 100 min, and then ether (5 mL) and $NaHCO_3$ solution (satd aq, 5 mL) were added. The aqueous layer was extracted with ether (3 × 5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography (petroleum ether/ether, 95:5) furnished the *title compounds* (**16s**, 14 mg, 16%) and (**16a**, 56 mg, 64%) both as colorless oils. **Data for 16s**: R_f 0.62 (petroleum ether/ether, 95:5); IR (neat) 3406br, 2956s, 2879s, 2136m, 1666m, 1458m, 1416m, 1247m, 1155m, 1128m, 972m, 848m, 743m; ^{1}H NMR (500 MHz, $CDCl_3$) 0.20 (9H, s, $Si(CH_3)_3$), 0.63−0.73 (12H, m, 2 × $Si(CH_2CH_3)_3$), 0.95−1.03 (18H, m, 2 × $Si(CH_2CH_3)_3$), 1.55−2.02 (6H, m, H-8, H-9, H-10), 3.72 (1H, d, J = 8.0 Hz, H-4), 3.81 (1H, dd, J = 11.5, 4.0 Hz, H-7$_{eq}$), 3.95 (1H, td, J = 11.5, 3.5 Hz, H-7$_{ax}$), 4.64 (1H, d, J = 2.0 Hz, H-1′), 4.73 (1H, dd, J = 8.0, 2.0 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) 0.16 ($Si(CH_3)_3$), 5.1 and 5.2 (2 ×

dx.doi.org/10.1021/jo301810d | J. Org. Chem. 2012, 77, 10623−10630

$Si(CH_2CH_3)_3$), 6.8 and 6.9 (2 × $Si(CH_2CH_3)_3$), 19.0 (C-9), 24.7 (C-8), 31.2 (C-10), 62.7 (C-7), 76.1 (C-3), 79.0 (C-1′), 81.3 (C-4), 97.4 (C-3′), 100.2 (C-2′), 103.3 (C-5), 166.5 (C-2); HRMS (ESI^+) calcd for $C_{26}H_{50}NaO_4Si_3^+$ (M + Na^+) 533.2909, found 533.2910. **Data for 16a**: R_f 0.79 (petroleum ether/ether, 95:5); IR (neat) 3385br, 2957s, 2879m, 2135w, 1665w, 1457m, 1247w, 1155m, 1116s, 1077m; ^1H NMR (500 MHz, $CDCl_3$) 0.20 (9H, s, $Si(CH_3)_3$), 0.61−0.69 (12H, m, 2 × $Si(CH_2CH_3)_3$), 0.94−1.00 (18H, m, 2 × $Si(CH_2CH_3)_3$), 1.50−1.97 (6H, m, H-8, H-9, H-10), 3.77 (1H, dd, J = 11.5, 4.5 Hz, H-7_{eq}), 3.86 (1H, d, J = 7.5 Hz, H-4), 4.03 (1H, td, J = 11.5, 3.0 Hz, H-7_{ax}), 4.38 (1H, dd, J = 7.5, 1.5 Hz, H-3), 4.61 (1H, d, J = 1.5 Hz, H-1′); ^{13}C NMR (125 MHz, $CDCl_3$) 0.17 ($Si(CH_3)_3$), 4.9 and 5.0 (2 × $Si(CH_2CH_3)_3$), 6.7 and 6.8 (2 × $Si(CH_2CH_3)_3$), 18.3 (C-9), 24.9 (C-8), 28.8 (C-10), 63.5 (C-7), 76.9 (C-3), 78.9 (C-1′), 82.3 (C-4), 97.2 (C-3′), 100.4 (C-2′), 107.1 (C-5), 166.2 (C-2); HRMS (ESI^+) calcd for $C_{26}H_{50}NaO_4Si_3^+$ (M + Na^+) 533.2909, found 533.2907.

(3*R,4*R**,5*S**,*Z*)-3,4-Bis[(triethylsilyl)oxy]-2-(prop-2-yn-1-ylidene)-1,6-dioxaspiro[4.5]decane (18s).** To a stirred solution of spiroacetal **16s** (66 mg, 0.129 mmol) in absolute ethanol (2.2 mL) at 0 °C was added a solution of $AgNO_3$ (88 mg, 0.518 mmol) in water (2.2 mL). A white suspension formed immediately. The mixture was stirred for 1 h in the dark and was then diluted with dichloromethane (20 mL) and transferred into a rapidly stirred solution of KCN (202 mg, 3.10 mmol) in water (44 mL). After 2 min, the mixture was extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (petroleum ether/ether, 97:3) furnished the *title compound* **18s** as a colorless oil (44 mg, 78%): R_f 0.76 (petroleum ether/ether, 95:5); IR (neat) 3316m, 2956s, 2878s, 2104w, 1670m, 1459m, 1238m, 1201m, 1155m, 1127m, 1048m; ^1H NMR (500 MHz, $CDCl_3$) 0.63−0.74 (12H, m, 2 × $Si(CH_2CH_3)_3$), 0.96−1.04 (18H, m, 2 × $Si(CH_2CH_3)_3$), 1.54−2.06 (6H, m, H-8, H-9, H-10), 3.06 (1H, d, J = 1.5 Hz, H-3′), 3.72 (1H, d, J = 8.0 Hz, H-4), 3.81 (1H, dd, J = 11.5, 4.5 Hz, H-7_{eq}), 3.94 (1H, td, J = 11.5, 3.0 Hz, H-7_{ax}), 4.59 (1H, t, J = 1.5 Hz, H-1′), 4.74 (1H, dd, J = 8.0, 1.5 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) 5.1 and 5.3 (2 × $Si(CH_2CH_3)_3$), 6.8 and 6.9 (2 × $Si(CH_2CH_3)_3$), 19.0 (C-9), 24.6 (C-8), 31.1 (C-10), 62.7 (C-7), 76.1 (C-3), 77.8 (C-1′), 78.8 (C-2′), 80.2 (C-3′), 81.2 (C-4), 103.5 (C-5), 166.6 (C-2); HRMS (ESI^+) calcd for $C_{23}H_{42}NaO_4Si_2^+$ (M + Na^+) 461.2514, found 461.2511.

(3*R,4*R**,5*R**,*Z*)-3,4-Bis[(triethylsilyl)oxy]-2-(prop-2-yn-1-ylidene)-1,6-dioxaspiro[4.5]decane (18a).** To a stirred solution of spiroacetal **16a** (264 mg, 0.517 mmol) in absolute ethanol (8.8 mL) at 0 °C was added a solution of $AgNO_3$ (352 mg, 2.07 mmol) in water (8.8 mL). A white suspension formed immediately. The mixture was stirred for 1 h in the dark and was then diluted with dichloromethane (100 mL) and transferred into a rapidly stirred solution of KCN (808 mg, 12.4 mmol) in water (176 mL). After 2 min, the mixture was extracted with dichloromethane (3 × 100 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (petroleum ether/ether, 97:3) furnished the *title compound* **18a** as a colorless oil (175 mg, 77%): R_f 0.87 (petroleum ether/ether, 95:5); IR (neat) 3316w, 2955s, 2878s, 2103w, 1668m, 1458m, 1114s; ^1H NMR (500 MHz, $CDCl_3$) 0.63−0.70 (12H, m, 2 × $Si(CH_2CH_3)_3$), 0.94−1.02 (18H, m, 2 × $Si(CH_2CH_3)_3$), 1.54−1.98 (6H, m, H-8, H-9, H-10), 3.05 (1H, d, J = 2.5 Hz, H-3′), 3.77 (1H, dd, J = 11.5, 4.5 Hz, H-7_{eq}), 3.86 (1H, d, J = 7.0 Hz, H-4), 4.04 (1H, td, J = 11.5, 3.0 Hz, H-7_{ax}), 4.39 (1H, dd, J = 7.0, 1.5 Hz, H-3), 4.55−4.56 (1H, m, H-1′); ^{13}C NMR (125 MHz, $CDCl_3$) 4.9 and 5.0 (2 × $Si(CH_2CH_3)_3$), 6.7 and 6.8 (2 × $Si(CH_2CH_3)_3$), 18.3 (C-9), 24.8 (C-8), 28.8 (C-10), 63.4 (C-7), 76.8 (C-3), 77.7 (C-1′), 78.9 (C-2′), 80.1 (C-3′), 82.2 (C-4), 107.4 (C-5), 166.4 (C-2); HRMS (ESI^+) calcd for $C_{23}H_{42}NaO_4Si_2^+$ (M + Na^+) 461.2514, found 461.2505.

1-Iodopropyne (S3).[23] To a stirred solution of 1-(trimethylsilyl)-propyne (250 μL, 1.69 mmol) in freshly distilled acetone (12 mL) at rt was added *N*-iodosuccinimide (490 mg, 2.18 mmol) and $AgNO_3$ (340 mg, 2.00 mmol). After the solution was stirred for 1 h in the dark, the white precipitate was filtered, and the filtrate was diluted with water (40 mL) and petroleum ether (40 mL). The layers were separated; the aqueous layer was extracted with petroleum ether (3 × 40 mL), and the combined organic layers were dried ($MgSO_4$) and then concentrated carefully. The volatile iodoalkyne (90 mg, 32%), an oil, was used in the coupling step (with **18s**) without purification. For coupling with **18a**, the iodoalkyne was obtained in 31% yield (346 mg) from 1-(trimethylsilyl)propyne (1.0 mL, 6.75 mmol), *N*-iodosuccinimide (1.96 g, 8.71 mmol), and $AgNO_3$ (1.36 g, 8.00 mmol) in acetone (48 mL). Data as reported.

(3*R,4*R**,5*S**,*Z*)-3,4-Bis[(triethylsilyl)oxy]-2-(hexa-2,4-diyn-1-ylidene)-1,6-dioxaspiro[4.5]decane (S4s).** To a stirred solution of alkyne **18s** (22 mg, 50.1 μmol) and freshly prepared iodoalkyne **S3** (90 mg, 0.542 mmol) in degassed pyrrolidine (2.5 mL) at rt was added CuI (3.0 mg, 15.8 μmol). The solution became green immediately. After being stirred for 1.5 h, the reaction mixture became yellow and was diluted with water (10 mL). The mixture was extracted with ether (3 × 15 mL), and the combined organic extracts were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (petroleum ether/ether, 97:3) furnished the *title compound* **S4s** as a pale yellow oil (17 mg, 70%): R_f 0.50 (petroleum ether/ether, 95:5); IR (neat) 2955s, 2916s, 2878s, 2144w, 1661m, 1458m, 1238m, 1200m, 1155s, 1126s, 1112s, 970m, 946m; ^1H NMR (500 MHz, $CDCl_3$) 0.63−0.73 (12H, m, 2 × $Si(CH_2CH_3)_3$), 0.95−1.03 (18H, m, 2 × $Si(CH_2CH_3)_3$), 1.51−1.85 (6H, m, H-8, H-9, H-10), 1.99 (3H, d, J = 1.0 Hz, H-6′), 3.70 (1H, d, J = 8.0 Hz, H-4), 3.80 (1H, dd, J = 11.5, 4.5 Hz, H-7_{eq}), 3.92 (1H, td, J = 11.5, 3.5 Hz, H-7_{ax}), 4.60 (1H, dq, J = 2.0, 1.0 Hz, H-1′), 4.73 (1H, dd, J = 8.0, 2.0 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) 4.7 (C-6′), 5.1 and 5.3 (2 × $Si(CH_2CH_3)_3$), 6.8 and 6.9 (2 × $Si(CH_2CH_3)_3$), 18.9 (C-9), 24.5 (C-8), 31.1 (C-10), 62.7 (C-7), 65.1 (C-4′), 69.9 (C-2′), 76.3 (C-3), 77.2 (C-3′), 77.9 (C-1′), 79.3 (C-5′), 81.2 (C-4), 103.7 (C-5), 168.2 (C-2); HRMS (ESI^+) calcd for $C_{26}H_{44}NaO_4Si_2^+$ (M + Na^+) 499.2670, found 499.2660.

(3*R,4*R**,5*R**,*Z*)-3,4-Bis[(triethylsilyl)oxy]-2-(hexa-2,4-diyn-1-ylidene)-1,6-dioxaspiro[4.5]decane (S4a).** To a stirred solution of alkyne **18s** (88 mg, 0.201 mmol) and freshly prepared iodoalkyne **S3** (346 mg, 2.08 mmol) in degassed pyrrolidine (10.1 mL) at rt was added CuI (11.5 mg, 60.4 μmol). The solution turned green immediately. After being stirred for 1.5 h, the reaction mixture became yellow and was diluted with water (50 mL). The mixture was extracted with ether (3 × 50 mL), and the combined organic extracts were washed with water (50 mL), brine (50 mL), then dried ($MgSO_4$) and concentrated. Flash chromatography (petroleum ether/ether, 97:3) furnished the *title compound* **S4a** as a pale yellow oil (68 mg, 71%): R_f 0.61 (petroleum ether/ether, 95:5); IR (neat) 2956s, 2917s, 2878s, 2144w, 1660m, 1458m, 1240m, 1155s, 1114s, 973m, 946m; ^1H NMR (500 MHz, $CDCl_3$) 0.62−0.69 (12H, m, 2 × $Si(CH_2CH_3)_3$), 0.95−1.00 (18H, m, 2 × $Si(CH_2CH_3)_3$), 1.51−1.95 (6H, m, H-8, H-9, H-10), 1.99 (3H, d, J = 1.0 Hz, H-6′), 3.76 (1H, dd, J = 11.5, 4.5 Hz, H-7_{eq}), 3.85 (1H, d, J = 7.0 Hz, H-4), 4.04 (1H, td, J = 11.5, 3.0 Hz, H-7_{ax}), 4.38 (1H, dd, J = 7.0, 2.0 Hz, H-3), 4.57 (1H, dq, J = 2.0, 1.0 Hz, H-1′); ^{13}C NMR (125 MHz, $CDCl_3$) 4.7 (C-6′), 4.8 and 5.0 (2 × $Si(CH_2CH_3)_3$), 6.7 and 6.8 (2 × $Si(CH_2CH_3)_3$), 18.2 (C-9), 24.8 (C-8), 28.7 (C-10), 63.5 (C-7), 65.2 (C-4′), 70.0 (C-2′), 77.1 (C-3′), 77.2 (C-3), 77.8 (C-1′), 79.1 (C-5′), 82.1 (C-4), 107.7 (C-5), 167.9 (C-2); HRMS (ESI^+): calcd for $C_{26}H_{44}NaO_4Si_2^+$ (M + Na^+) 499.2670, found 499.2662.

(3*R,4*R**,5*S**,*Z*)-2-(Hexa-2,4-diyn-1-ylidene)-1,6-dioxaspiro-[4.5]decane-3,4-diol (*Z*-*trans*-6s).** To a stirred solution of bis(silyl ether) **S4s** (10 mg, 21.0 μmol) in THF (0.4 mL) at 0 °C was added TBAF solution (1.0 M in THF, 52.5 μL, 52.5 μmol). The resulting mixture was warmed to rt and stirred for 1 h. Water (5 mL) and ether (5 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with ether (3 × 5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. Preparative TLC (dichloromethane/methanol, 95:5) furnished the *title compound Z-trans*-**6s** as a colorless oil (5.0 mg, 96%): R_f 0.37 (dichloromethane/methanol, 95:5); IR (neat) 3398br, 2926s, 2162w, 2182w, 2143w, 1738s, 1662s, 1367s, 1259m, 1131s, 1109s; ^1H NMR (500 MHz, $CDCl_3$) 1.54−2.05 (6H, m, H-8, H-9, H-10), 2.00 (3H, d, J = 1.0 Hz, H-6′), 2.25−2.73 (2H, br s, 2 × OH), 3.63 (1H, d, J = 7.5 Hz, H-4), 3.81 (1H, app. d, J = 11.0 Hz, H-7_{eq}), 3.98 (1H, td, J = 11.0,

3.5 Hz, H-7_{ax}), 4.63 (1H, d, J = 7.5 Hz, H-3), 4.77 (1H, app. s, H-1′); ^{13}C NMR (125 MHz, $CDCl_3$) 4.7 (C-6′), 18.5 (C-9), 24.5 (C-8), 30.5 (C-10), 63.2 (C-7), 64.9 (C-4′), 69.1 (C-2′), 76.5 (C-3), 77.8 (C-3′), 79.2 (C-1′), 79.7 (C-5′), 80.8 (C-4), 103.5 (C-5), 168.7 (C-2); HRMS (ESI$^+$) calcd for $C_{14}H_{16}NaO_4^+$ (M + Na^+) 271.0941, found 271.0942.

(3*R,4*R**,5*R**,*Z*)-2-(Hexa-2,4-diyn-1-ylidene)-1,6-dioxaspiro-[4.5]decane-3,4-diol (*Z-trans*-6a).** To a stirred solution of bis(silyl ether) **S4a** (60 mg, 0.126 mmol) in THF (2.5 mL) at 0 °C was added TBAF solution (1.0 M in THF, 0.3 mL, 0.30 mmol). The resulting mixture was warmed to rt and stirred for 1 h. Water (10 mL) and ether (15 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with ether (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$) then concentrated. Flash chromatography (dichloromethane/methanol, 95:5) furnished the *title compound Z-trans*-**6a** as a colorless oil (31 mg, 99%): R_f 0.34 (dichloromethane/methanol, 95:5); IR (neat) 3398br, 2950s, 2192m, 2142m, 1739s, 1656s, 1367s, 1217s, 1136s, 1093s, 747s; ^{1}H NMR (500 MHz, $CDCl_3$) 1.62−2.04 (6H, m, H-8, H-9, H-10), 2.00 (3H, d, J = 1.0 Hz, H-6′), 2.86 (1H, d, J = 11.5 Hz, (C-3)OH), 3.73−3.78 (2H, m, H-7_{eq}), (C-4)OH), 3.93 (1H, dd, J = 5.5, 1.5 Hz, H-4), 4.01 (1H, td, J = 11.0, 4.0 Hz, H-7_{ax}), 4.24 (1H, ddd, J = 11.5, 1.5, 1.0 Hz, H-3), 4.91 (1H, dq = quin, J = 1.0 Hz, H-1′); ^{13}C NMR (125 MHz, $CDCl_3$) 4.7 (C-6′), 18.5 (C-9), 24.6 (C-8), 27.4 (C-10), 62.9 (C-7), 64.9 (C-4′), 69.2 (C-2′), 77.6 (C-3), 78.2 (C-3′), 79.4 (C-4), 80.1 (C-5′), 82.8 (C-1′), 110.1 (C-5), 168.7 (C-2); HRMS (ESI$^+$) calcd for $C_{14}H_{16}NaO_4^+$ (M + Na^+) 271.0941, found 271.0941.

(3*R,4*R**,5*S**,*Z*)-3,4-Diacetoxy-2-(hexa-2,4-diyn-1-ylidene)-1,6-dioxaspiro[4.5]decane (*Z-trans*-4s).** To a stirred solution of diol *Z-trans*-**6s** (5.0 mg, 20.1 μmol) in pyridine (1 mL) at rt was added acetic anhydride (19 μL, 0.201 mmol). The reaction mixture was stirred for 14 h at rt, diluted with ether (10 mL), and washed with $CuSO_4$ solution (satd aq, 3 × 5 mL). The combined aqueous extracts were extracted with ether (3 × 10 mL), and the combined organic extracts were dried ($MgSO_4$) and then concentrated. Preparative TLC (petroleum ether/ethyl acetate, 80:20) furnished the *title compound Z-trans*-**4s** as a pale yellow solid (5.0 mg, 72%): R_f 0.37 (petroleum ether/ethyl acetate, 80:20); IR (neat) 2954m, 2917s, 2849s, 2145w, 1748s, 1665m, 1371m, 1239s, 1115m, 1074m, 1047m; ^{1}H NMR (500 MHz, $CDCl_3$) (numbered according to Figure 2 and Table 1) 1.50−1.86 (6H, m, H-2, H-3, H-4), 2.00 (3H, d, J = 1.0 Hz, H-14), 2.10 and 2.15 (2 × 3H, 2 × s, 2 × $COCH_3$), 3.83 (1H, dd, J = 12.0, 4.5 Hz, H-1_{eq}), 3.96 (1H, td, J = 12.0, 3.0 Hz, H-1_{ax}), 4.70 (1H, dq, J = 2.0, 1.0 Hz, H-9), 5.13 (1H, d, J = 7.5 Hz, H-6), 5.98 (1H, dd, J = 7.5, 2.0 Hz, H-7); ^{1}H NMR (500 MHz, CCl_4) (numbered according to Figure 2 and Table 1) 1.60−1.89 (6H, m, H-2, H-3, H-4), 2.02 (3H, s, H-14), 2.08 and 2.12 (2 × 3H, 2 × s, 2 × $COCH_3$), 3.80 (1H, br d, J = 11.0 Hz, H-1_{eq}), 3.98 (1H, td, J = 11.0, 3.0 Hz, H-1_{ax}), 4.61 (1H, s, H-9), 5.00 (1H, d, J = 7.5 Hz, H-6), 5.85 (1H, d, J = 7.5 Hz, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) 4.7 (C-6′), 18.7 (C-9), 20.8 (2 peaks) (2 × $COCH_3$), 24.2 (C-8), 30.7 (C-10), 63.2 (C-7), 64.8 (C-4′), 68.3 (C-2′), 74.3 (C-3), 77.4 (C-4), 78.5 (C-3′), 80.2 (C-5′), 81.7 (C-1′), 104.5 (C-5), 162.2 (C-2), 170.1 and 170.4 (2 × $COCH_3$); HRMS (ESI$^+$) calcd for $C_{18}H_{20}NaO_6^+$ (M + Na^+) 355.1152, found 355.1142.

(3*R,4*R**,5*R**,*Z*)-3,4-Diacetoxy-2-(hexa-2,4-diyn-1-ylidene)-1,6-dioxaspiro[4.5]decane (*Z-trans*-4a).** To a stirred solution of diol *Z-trans*-**6a** (30 mg, 0.121 mmol) in pyridine (7.5 mL) at rt was added acetic anhydride (115 μL, 1.21 mmol). The reaction mixture was stirred for 14 h at rt, diluted with ether (50 mL), and washed with $CuSO_4$ solution (satd aq, 3 × 20 mL). The combined aqueous extracts were extracted with ether (3 × 50 mL), and the combined organic extracts were dried ($MgSO_4$) and then concentrated. Flash chromatography (petroleum ether/ethyl acetate, 80:20) furnished the *title compound Z-trans*-**4a** as a pale yellow solid (35 mg, 87%): R_f 0.42 (petroleum ether/ethyl acetate, 80:20); IR (neat) 3016m, 2970m, 2143w, 1741s, 1659m, 1367m, 1230s, 1217s, 1103m, 1078m, 1048m; ^{1}H NMR (500 MHz, $CDCl_3$) (numbered according to Figure 2 and Table 1) 1.52−2.00 (6H, m, H-2, H-3, H-4), 2.00 (3H, d, J = 1.0 Hz, H-14), 2.11 and 2.12 (2 × 3H, 2 × s, 2 × $COCH_3$), 3.78 (1H, dd, J = 11.5, 4.5 Hz, H-1_{eq}), 3.98 (1H, td, J = 11.5, 3.5 Hz, H-1_{ax}), 4.88 (1H, dq ∼ quin, app. J = 1.25 Hz, H-9), 5.11 (1H, d, J = 1.5 Hz, H-6), 5.52 (1H, t, J = 1.5 Hz, H-7); ^{1}H NMR (500 MHz, CCl_4) (numbered according to Figure 2 and Table 1) 1.53−1.87 (6H, m, H-2, H-3, H-4), 2.03 (3H, s, H-14), 2.10 and 2.12 (2 × 3H, 2 × s, 2 × $COCH_3$), 3.77 (1H, br d, J = 11.5 Hz, H-1_{eq}), 3.99 (1H, td, J = 11.5, 3.5 Hz, H-1_{ax}), 4.79 (1H, s, H-9), 4.99 (1H, s, H-6), 5.40 (1H, s, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) 4.7 (C-6′), 18.7 (C-9), 20.6 and 20.9 (2 × $COCH_3$), 24.5 (C-8), 29.7 (C-10), 62.9 (C-7), 64.8 (C-4′), 68.7 (C-2′), 75.5 (C-3), 78.6 (C-4), 78.8 (C-3′), 80.3 (C-5′), 83.7 (C-1′), 109.1 (C-5), 164.3 (C-2), 169.2 and 170.0 (2 × $COCH_3$); HRMS (ESI$^+$) calcd for $C_{18}H_{20}NaO_6^+$ (M + Na^+) 355.1152, found 355.1143.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds; selected NOE(SY) data; ORTEP representations of compounds *Z-trans*-**4s** and *Z-trans*-**4a**; X-ray data for *Z-trans*-**4s** and *Z-trans*-**4a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jeremy.robertson@chem.ox.ac.uk.

Author Contributions

†G.C.F and A.L.T. obtained the X-ray diffraction data.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the China Oxford Scholarship Fund, the Overseas Research Students Award Scheme, and Jesus College, Oxford, for funding. We are very grateful to the following from the University of Oxford: Phillip Unsworth for preliminary studies and Drs. Tim Claridge and Barbara Odell for supporting NMR spectroscopy.

■ REFERENCES

(1) This compound has been isolated from a variety of sources over the past 50 years, but the designation as "homo-tonghaosu" first appeared in: Chen, L.; Yin, B.-L.; Xu, H.-H.; Chiu, M.-H.; Wu, Y.-L. *Chin. J. Chem.* **2004**, *22*, 92−99.

(2) Ma, L.; Ge, F.; Tang, C.-P.; Ke, C.-Q.; Li, X.-Q.; Althammer, A.; Ye, Y. *Tetrahedron* **2011**, *67*, 3533−3539.

(3) (a) Nakamura, Y.; Ohto, Y.; Murakami, A.; Jiwajinda, S.; Ohigashi, H. *J. Agric. Food Chem.* **1998**, *46*, 5031−5036. (b) Nakamura, Y.; Kawamoto, N.; Ohto, Y.; Torikai, K.; Murakami, A.; Ohigashi, H. *Cancer Lett.* **1999**, *140*, 37−45.

(4) (a) Bohlmann, F.; Herbst, P.; Arndt, C.; Schönowsky, H.; Gleinig, H. *Chem. Ber.* **1961**, *94*, 3193−3216 and subsequent papers. See also: (b) Bohlmann, F.; Burkhardt, T.; Zdero, C. *Naturally Occurring Acetylenes*; Academic Press: London, 1973.

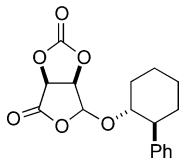
(5) The stereochemical aspects of this class of molecules, including the potentially confusing use of "*cis*-" and "*trans*-" to describe *E*- and *Z*-enol ether geometries, respectively, are well summarized in: Birnecker, W.; Wallnöfer, B.; Hofer, O.; Greger, H. *Tetrahedron* **1988**, *44*, 267−276.

(6) (a) Marco, J. A.; Sanz, J. F.; Jakupovic, J.; Huneck, S. *Tetrahedron* **1990**, *46*, 6931−6938. (b) Wurz, G.; Hofer, O.; Sanz-Cervera, J. F.; Marco, J. A. *Liebigs Ann. Chem.* **1993**, 99−101.

(7) (a) Miyakoshi, N.; Mukai, C. *Org. Lett.* **2003**, *5*, 2335−2338. (b) Miyakoshi, N.; Aburano, D.; Mukai, C. *J. Org. Chem.* **2005**, *70*, 6045−6052.

(8) Synthetic approaches: (a) Toshima, H.; Aramaki, H.; Ichihara, A. *Tetrahedron Lett.* **1999**, *40*, 3587−3590. (b) Wensley, A. M.; Hardy, A. O.; Gonsalves, K. M.; Koviach, J. L. *Tetrahedron Lett.* **2007**, *48*, 2431−2434.

(9) Matsuo, A.; Uchio, Y.; Nakayama, M.; Hayashi, S. *Tetrahedron Lett.* **1974**, 1885−1888.
(10) See, for example: (a) Bohlmann, F.; Arndt, C.; Starnick, J. *Tetrahedron Lett.* **1963**, 1605−1610. (b) Bohlmann, F.; Arndt, C.; Bornowski, H.; Kleine, K.-M.; Herbst, P. *Chem. Ber.* **1964**, *97*, 1179−1192. (c) Bohlmann, F.; Rode, K.-M. *Chem. Ber.* **1966**, *99*, 2416−2418. (d) Bohlmann, F.; Zdero, C. *Chem. Ber.* **1975**, *108*, 735−738.
(11) Robertson, J.; Naud, S. *Org. Lett.* **2008**, *10*, 5445−5448.
(12) Compound numbers followed with **s** possess *syn*- stereochemistry between the tetrahydropyranyl ring oxygen and the neighboring functionality in the hydrofuran ring, in this case, the acetoxy group; the corresponding *anti*- diastereomers are designated in the compound numbers by **a**.
(13) In constrained systems such as the cyclic carbonate shown below, the corresponding H−C−C−H dihedral angle is close to 15° (molecular modelling), and consequently, the coupling constant is higher, J = 7.0 Hz: Fishlock, L. *Chemistry Part II Thesis*, University of Oxford, 2005.



(14) For example: monoacylation followed by inversion of the remaining hydroxyl via the triflate; Pd(0)-catalyzed epimerization of the allylic acetate; formation of the epoxide followed by hydrolysis; base-mediated epimerization of *O*-protected derivatives; selective oxidation−reduction sequences. (a) Naud, S.; Robertson, J. Unpublished results. (b) Smith, G. *Chemistry Part II Thesis*, University of Oxford, 2009. (c) Unsworth, P. *Chemistry Part II Thesis*, University of Oxford, 2010.
(15) Sun, M.; Deng, Y.; Batyreva, E.; Sha, W.; Salomon, R. G. *J. Org. Chem.* **2002**, *67*, 3575−3584.
(16) Annangudi, S. P.; Sun, M.; Salomon, R. G. *Synlett* **2005**, 1468−1470.
(17) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421−433.
(18) (a) DeShong, P.; Rybczynski, P. J. *J. Org. Chem.* **1991**, *56*, 3207−3210. (b) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1995**, *36*, 2393−2396.
(19) Fernández-González, M.; Alonso, R. *J. Org. Chem.* **2006**, *71*, 6767−6775.
(20) Corey, E. J.; Kirst, H. A. *Tetrahedron Lett.* **1968**, 5041−5043.
(21) Schmidt, H. M.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 1138−1142. See also ref 20.
(22) Alami, M.; Ferri, F. *Tetrahedron Lett.* **1996**, *37*, 2763−2766.
(23) (a) Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed.* **1984**, *23*, 727−729. (b) Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485−486.
(24) Single-crystal diffraction data were collected using a Nonius Kappa CCD: Otwinowski, Z.; Minor, W. Processing of X-ray Diffraction Data Collected in Oscillation Mode. *Methods Enzymol.* **1997**, *276*, 307−326. Solved with SuperFlip: Palatinus, L.; Chapuis, G. J. *Appl. Crystallogr.* **2007**, *40*, 786−790. Refined using CRYSTALS: Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487. Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Crystallogr.* **2010**, *43*, 1100−1107. Crystallographic data (excluding structure factors) for *Z-trans*-**4s** and *Z-trans*-**4a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 897797 and 897798, respectively) and can be obtained via www. ccdc.cam.ac.uk/data_request/cif.
(25) No original sample of *E-trans*-**4s** remains for testing this proposal (Professor Alberto Marco, University of Valencia, personal communication); furthermore, no sample of genuine glycol *E-trans*-**6s** (ref 26) remains available (Professor Ying Zhu, Lanzhou University, personal communication).
(26) Zhu, Y.; Zhang, L.-X.; Zhao, Y.; Huang, G.-D. *Food Chem.* **2010**, *118*, 228−238.
(27) No sample of synthetic *E-trans*-**4s** remains for acquisition of ^{1}H NMR data in CCl_4 (Professor Chisato Mukai, Kanazawa University, personal communication).
(28) Attempts to effect *Z*-/*E*-isomerization, using *Z-cis*-**4a**, *Z-trans*-**4s**, or **16a**, resulted either in no observable isomerization or substrate decomposition; methods included: cat. camphorsulfonic acid; cat. *para*-toluenesulfonic acid; cat. methanesulfonic acid; cat. trifluoromethanesulfonic acid; cat. HI; cat. oxalic acid; cat. I_2; cat. I_2, $h\nu$; and $h\nu$.