Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 9013–9018

TETRAHEDRON

Radical cyclization studies directed toward the synthesis of BMS-200475 'entecavir': the carbocyclic core

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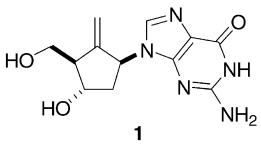
Received 9 January 2002; accepted 24 February 2003

Abstract—Two routes are presented for the conversion of D-diacetone glucose (**5a**) into a protected carbocyclic core of BMS-200475 (Entecavir). The reduction of two terminal epoxides with Cp_2TiCl to form carbon radicals and their cyclizations with a terminal acetylene and an α,β-unsaturated ester lead ultimately to allylic alcohol **11a**, a candidate for Mitsunobu coupling with guanine.

1. Introduction

BMS-200475 (Entecavir, **1**) is a synthetic carbocyclic nucleoside active at the nanomolar level against hepatitis B virus (HBV), a worldwide health problem.[1] The Bristol Myers–Squibb synthesis of **1** proceeded by asymmetric hydroboration of a substituted 1,3-cyclopentadiene followed by opening of an epoxide with a protected guanine.[2] Triol **2** presented itself as a viable candidate for the carbocyclic core of **1**, wherein installation of the purine base could be achieved via a Mitsunobu reaction on the allylic alcohol. To this end, triol **2** was perceived as arising from cyclization of a secondary radical, generated either from a cyclic thiocarbonate or an epoxide, with a terminal acetylene or α,β-unsaturated ester acceptor to form the designated bond of **2**. Starting from L-glucose, the thiocarbonate/ester route had been shown by Rokach[3] to lead successfully to lactone *ent*-**3**. Owing to the need to degrade lactone **3** to realize the exocyclic double bond of triol **2**, initial studies focused on the use of a terminal acetylene as the radical acceptor and a cyclic thiocarbonate as the initiator. While radical cyclization of this type initiated by *n*-Bu_3SnH had served us well in the past,[4] the attempted cyclization of **4** led to products of Schönberg rearrangement and the formation of vinyl stannanes. Moreover, compound **4** was prepared by an inefficient route from D-diacetone glucose. Accordingly, the epoxide/acetylene tandem offered the best hope.[5]



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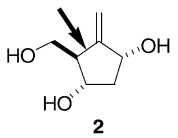

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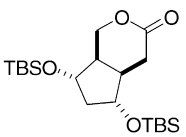

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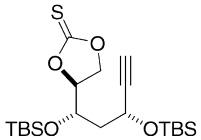

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2. Results and discussion

D-Diacetone glucose (**5a**, Scheme 1) was transformed into the known unsaturated acetonide **6a** by modification of the procedure of Deslongchamps.[6] Fu's catalytic *n*-Bu_3SnH protocol[7] was utilized for removal of the C_3–OH. Conversion of 1,2-diol **5c** into olefin **6a** was achieved using the Eastwood amide acetal procedure.[8] Acetonide hydrolyses mirrored the Rokach procedures.[3]

Efforts to convert the lactol **6b** into the terminal acetylene **7** with the Gilbert reagent, $[(MeO)_2POCHN_2]$, in the presence of strong base (t-C_4H_9OK) were unsuccessful. That this failure was not related to the quality of the reagent was demonstrated by the facile conversion of *p*-nitrobenzaldehyde into the corresponding aryl acetylene (60%). The milder alkaline conditions of the Ohira protocol[9] $[(MeO)_2POCN_2Ac$, K_2CO_3, MeOH; room temperature] afforded acetylenic diol **7** in excellent yield (Scheme 2). Bis-silylation of diol **7** and subsequent non-selective epoxidation occurred without incident. The presence of a mixture of

Keywords: radical cyclization; hepatitis B virus; thiocarbonate.
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† Taken in part from the PhD Thesis of MAS, Yale University, 2002.

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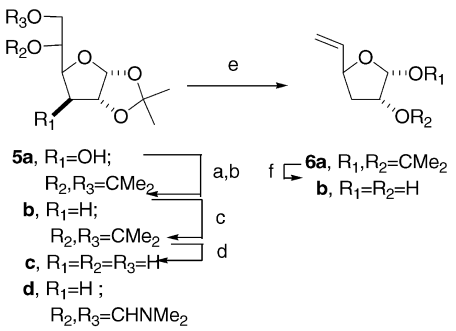
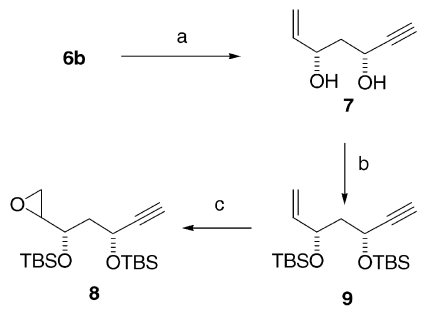
doi:10.1016/j.tet.2003.02.001



a) NaH, THF; CS_2; MeI. b) cat. AIBN, $(Bu_3Sn)_2O$, PMHS, *n*-BuOH, toluene, reflux (75%, 2 steps).
c) 30% aq. HOAc, 25 °C, 24h; 80%.
d) $(MeO)_2CHNMe_2$, toluene, reflux, 8h. e) Ac_2O, 120 °C, 12h (95%, 2 steps). f) 1:1 4% aq. H_2SO_4/THF, reflux, 4h; 80%.

Scheme 1.



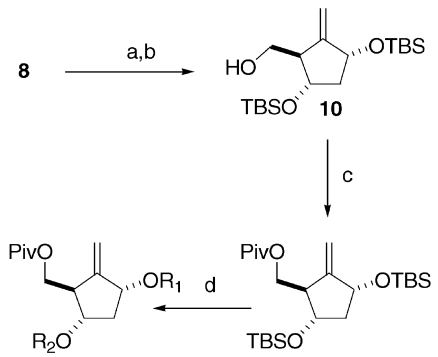
a) $(MeO)_2POCN_2COMe$; K_2CO_3/MeOH, rt; 84%.
b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0° - rt; 93%.
c) m-CPBA, CH_2Cl_2, rt; 91%.

Scheme 2.

epoxides was of no consequence because the offending stereogenic center was slated for removal in subsequent operations.

In their seminal paper on Ti(III)-mediated generation of β-alkoxy carbon radicals, RajanBabu and Nugent[10] reported the successful cyclization—albeit modest in yield[11]—of the parent compound of epoxyacetylene, bis-desilyloxy **8**.[12] Thus, inverse addition of a degassed 0.08 M THF solution of Cp_2TiCl to a degassed 0.02 M THF solution of epoxyacetylene **8** over 3 h at room temperature was followed by stirring of the solution for 8 h and eventual decomposition of the alkenyltitanium species with dilute aqueous H_2SO_4 to afford the desired methylene cyclopentane **10** in 82% yield with no sign of the *cis* isomer (Scheme 3).[13] Inverse addition was required to minimize deoxygenation to olefin **9**.

Two literature reports[14,15] describe the selective desilylation of secondary allylic silyl ethers with TBAF in the presence of secondary silyl ethers. Neither this reagent nor other fluoride-based reagents were successful in accomplishing this objective. Nakai[16] employed 80% acetic acid to effect this transformation in a prostaglandin model that was substituted the same way as **12** but contained an additional



a) Cp_2TiCl, degassed THF, inverse add'n., 11h, rt.
b) 10% aq. H_2SO_4, 5 min.; (82%, 2 steps).
c) Me_3CCOCl, pyr., cat. DMAP, rt; 92%.
d) 80% aq. HOAc, rt, 6h.

Scheme 3.

allylic silyl ether. In our hands and under these conditions, bis-silyl ether **12** afforded allylic alcohol **11a** in 38% yield, 54% based upon consumed reactant. The modest yield of allylic alcohol **11a** notwithstanding, set the stage for introduction of the nucleoside base. However, recent reports[17,18] describing a one step degradation of δ-valerolactols to homoallylic alcohols prompted an investigation of the epoxide/ester route.

The Ti(III)-induced cyclization of epoxides **14** (Scheme 4) mirrored the thiocarbonate radical cyclization conducted by Rokach[3] in the enantiomeric series derived from L-glucose. The cyclization afforded directly lactone **3** (32%), a mixture of hydroxy esters **16** (40%), and olefin **13b** (11%). Partial lactonization of the hydroxyester afforded an additional 19% of lactone **3** from hydroxy ester **16a**. The residue appeared to be a single hydroxy ester, presumably *trans* isomer **16b**. The *cis*-lactone **15** was not detected.

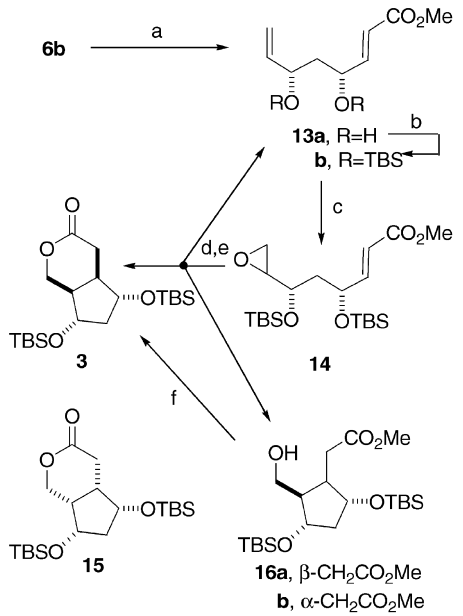
Brief exposure of lactol **17** (Scheme 5) to $Pb(OAc)_4$/$Cu(OAc)_2$ as described by Rigby, led to the methylene-cyclopentane **18** rapidly and efficiently. Saponification afforded alcohol **10**, identical with the sample prepared in Scheme 3. The stereochemistry of alcohol **10** follows from the known structure *ent*-**3** and from n.o.e studies performed on both lactone **3** and allylic alcohol **11a**.

Although our studies on installation of the guanine base using the Mitsunobu procedure are incomplete at this time, the successful coupling of a 4-methylene-3-furanol with 2-amino-6-chloropurine by Jeong and Yoo[19] using this procedure holds promise for the successful synthesis of Entecavir.

3. Experimental

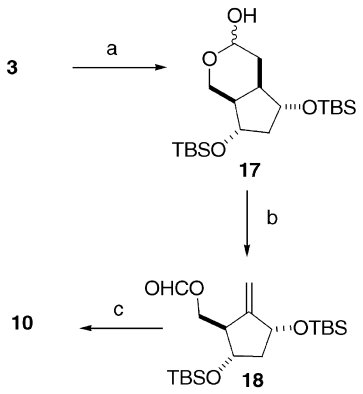
3.1. General

Solvents and reagents were used as received from commercial sources without further purification. When



a) $Ph_3P{=}CHCO_2Me$, THF, rt, 18h. b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0.5h, 0 °C. c) MCPBA, CH_2Cl_2, rt, 24h. d) Cp_2TiCl, THF, N_2, inverse add'n., 15h (4h add'n), rt. e) 10% H_2SO_4, rt, 5 min. f) p-TsOH, DMAP, THF, rt, 18h.

Scheme 4.



a) DIBALH, CH_2Cl_2, - 78°C, 2h; 85%. b) $Pb(OAc)_4$, cat. $Cu(OAc)_2$, cat. pyr., C_6H_6, reflux, 10 min; 95%. c) K_2CO_3, MeOH, rt; 81%.

Scheme 5.

necessary, reagents were purified by vacuum distillation under a nitrogen atmosphere. In the case of solvents, tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl under a N_2 atmosphere. Benzene, toluene, dichloromethane (CH_2Cl_2) and acetonitrile (CH_3CN) were distilled from calcium hydride under a N_2 atmosphere. Flash chromatography was performed using EM Science (E. Merck) 230–400 mesh, Baker 40 μm (J. T. Baker Inc.), SA 40 μm (Scientific Adsorbents Inc. or Silicycle). Melting points are uncorrected.

3.1.1. Vinyl acetonide 6a. A solution of diol **5c** (2 g, 9.8 mmol) and DMF dimethyl acetal (4 mL, 29.4 mmol) in freshly distilled toluene (10 mL) under N_2 was heated at reflux for 8 h. The reaction mixture was cooled and the solvent removed in vacuo. Acetic anhydride (10 mL) was added to the yellowish-brown residue of **5d** and the mixture was heated at 120°C for an additional 12 h. The dark brown solution was cooled, diluted with Et_2O and washed successfully with water, 1N aq. NaOH, water and brine. The organic solution was dried over $MgSO_4$, filtered and concentrated in vacuo to furnish a dark residue. Flash chromatography (30% EtOAc/hexane) furnished 1.61 g (95% yield) of vinylacetonide **6a** as a pale yellow oil: IR ($CDCl_3$): 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, s), 1.59 (3H, s), 1.63 (1H, m), 2.18 (1H, dd, J=4.3, 9.1 Hz), 4.65 (1H, m), 4.75 (1H, t, J=4.3 Hz), 5.19 (1H, dd, J=1.3, 7.8 Hz), 5.35 (1H, dd, J=1.3, 15.9 Hz), 5.85 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 140.05, 136.68, 117.56, 111.35, 105.73, 80.86, 78.95, 69.37, 39.72, 27.00, 26.45; HRMS (FAB) m/z found: 171.0657, [calcd for $C_9H_{15}O_3$ (M+H): 171.0657].

3.1.2. Hemiacetal 6b. To a stirred solution of vinyl acetonide **6a** (6.7 g, 39.4 mmol) in THF (70 mL) at room temperature was added 4% aq. H_2SO_4 (70 mL). The solution was heated at reflux for 4 h. The solution was cooled and neutralized by portionwise addition of anhydrous Na_2CO_3. The mixture was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to provide a thick brown residue. The residue was crystallized from hot EtOAc to provide (4.1 g, 80% yield) of hemiacetal **6b** as a yellow solid: ^1H NMR (400 MHz, $CDCl_3$) δ 1.93 (1H, m), 2.12 (1H, m), 2.94 (1H, br), 3.75 (1H, br), 4.31 (1H, m), 4.75 (1H, m), 5.13–5.43 (3H, m), 5.88 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) 139.10, 138.31, 116.74, 116.50, 116.08, 103.17, 97.22, 81.17, 72.02, 69.14, 45.39, 39.32, 38.39, 28.08, 27.36, 13.96; LRMS (FI) $(M)^+$ 130.1.

3.1.3. α,β-Unsaturated ester 13b. A solution of hemiacetal **6b** (640 mg, 4.92 mmol) and methyl (triphenylphosphoranylidene) acetate (2.47 g, 7.38 mmol) in freshly distilled THF (50 mL) was stirred at room temperature for 24 h. The solution was concentrated in vacuo and the solid residue was dissolved in EtOAc. Flash chromatography (50% EtOAc/hexane) furnished crude unsaturated ester **13a** as a yellow solid contaminated with Ph_3PO. This material (900 mg) was used directly in the next step.

A solution of crude diol **13a** (900 mg, 4.83 mmol) was dissolved in freshly distilled CH_2Cl_2 (48 mL) and 2,6-lutidine (1.7 mL) was added. The solution was cooled to 0°C. Cold TBSOTf (TBDMSOTf) (2.8 mL, 12.1 mmol) was added over 5 min and the solution was stirred at 0°C for 30 min. The reaction mixture was diluted with CH_2Cl_2, warmed to room temperature and washed with water and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude oil was purified by flash chromatography (2% EtOAc/hexane) to furnish 1.68 g (84% yield) of disilyl ether **13b** as a yellow oil: IR ($CDCl_3$): 1725 and 1621 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (1H, dd, J=5.0, 15.4 Hz, C_3–H), 6.00 (1H, dd, J=15.7, 1.0 Hz, C_2–H), 5.82 (1H, ddd, J=17.2, 10.4,

6.3 Hz, C_7–H), 5.15 (1H, d, J=17.2 Hz, $C_{8(trans)}$–H), 5.11 (1H, d, J=10.4 Hz, $C_{8(cis)}$–H), 4.43 (1H, m), 4.24 (1H, m), 3.75 (3H, s), 1.86 (1H, m), 1.65 (1H, m), 0.93 (9H, s), 0.90 (9H, s), 0.11 (3H, s), 0.10 (3H, s), 0.07 (3H, s), 0.04 (3H, s); ^{13}C NMR (125.75 MHz, $CDCl_3$) 167.50, 151.40, 141,.42, 119.76, 114.97, 71.12, 69.21, 51.92, 46.70, 26.32, 26.24, 18.56, 18.53, −3.75, −4.03, −4.43, −4.44; LRMS (FAB, M+) 414.2600; HRMS (FAB) *m/z* found: 413.2544, [calcd for $C_{21}H_{41}O_4Si_2$ (M−H): 413.2543].

3.1.4. Epoxy esters 14. Freshly distilled CH_2Cl_2 (37 mL) was added to a mixture of disilyl ether **13b** (1.5 g, 3.62 mmol) and 67% *m*-chloroperoxybenzoic acid (*m*CPBA) (0.59 g, 5.43 mmol) and the resultant mixture was stirred at room temperature for 24 h. The reaction mixture was washed with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (15% EtOAc/hexane) to furnish 1.5 g (97% yield) of epoxides **14** as a colorless oil: IR ($CDCl_3$): 1727 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (1H, m), 6.00 (1H, m), 4.55 (1H, m), 3.74 (3H, s), 3.62–2.52 (4H, m), 1.92–1.68 (2H, m), 0.90 (18H, m), 0.07 (12H, m); ^{13}C NMR (125.75 MHz, $CDCl_3$) 167.35, 167.26, 150.84, 150.52, 120.47, 120.22, 71.99, 68.95, 68.93, 68.85, 56.18, 55.00, 51.99, 51.96, 45.48, 45.32, 44.12, 43.10, 26.26, 26.22, 26.18, 18.56, 18.51, −3.79, −3.84, −4.12, −4.18, −4.46, −4.47, −4.53, −4.78; HRMS *m/z* found: 431.2453, [calcd for $C_{21}H_{43}O_5Si_2$ (M+H): 431.2465].

3.1.5. δ-Valerolactone 3. Generation of Cp_2TiCl: to a solution of titanocene dichloride (0.4 g, 1.61 mmol) in freshly distilled THF (20 mL) under N_2 was added activated zinc dust (0.32 g, 4.84 mmol) [activated zinc was prepared by washing 20 g of commercially available zinc dust [CAUTION; pyrophoric] with 60 mL of 4N HCl followed by thorough washing with water, dry acetone and drying in vacuo]. The resultant dark orange solution was stirred for 1 h, during which time the heterogeneous solution turned a deep lime green. Stirring was discontinued and the residual zinc was allowed to settle. The resulting green solution of Cp_2TiCl was 0.08 M.

The resulting green solution (8.75 mL) was added dropwise via syringe pump over 4 h to a stirred solution of epoxides **15** (0.1 g, 0.23 mmol) in freshly distilled THF (11.5 mL) at room temperature under a N_2 atmosphere. The reaction mixture was stirred for an additional 15 h. The intermediate bis-titanium(IV) species was decomposed by adding 10% aq. H_2SO_4 (20 mL). The mixture was allowed to stir for 5 min, after which the solution was diluted with EtOAc and the organic layer separated. The aqueous portion was extracted with EtOAc. The combined organic layers were washed with saturated aq. $NaHCO_3$ and dried ($MgSO_4$). After filtration and concentration in vacuo, the crude residue was purified by flash chromatography (15% EtOAc/hexane) to afford lactone **3** (37 mg, 51% yield) as a clear white solid, as well as esters **16** (21 mg, 21%) and alkene **13b** (12 mg, 11%). Lactone **3**: mp 95.7–97.0°C; $[\alpha]_D^{20}$=+24.1° (c=0.29, CH_3OH); IR ($CDCl_3$): 1743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 (2H, m), 3.96 (1H, m), 3.62 (2H, m), 2.50 (2H, m), 2.34 (1H, m), 2.05 (1H, m), 1.64 (1H, q, J=11.2 Hz), ^{13}C NMR (125.75 MHz, $CDCl_3$) 173.16, 75.21, 71.66, 67.98, 44.66, 43.49, 41.91, 32.55, 26.05, 25.92, 18.10, 18.08, −4.24, −4.30, −4.59, −4.60; HRMS *m/z* found: 401.2542, [calcd for $C_{20}H_{41}O_4Si_2$ $(M+1)^+$: 401.2543]. Esters **16**: IR ($CDCl_3$): 3517 and 1735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.2 (1H, m), 4.0 (1H, m), 3.8–3.5 (5H, m), 2.7–1.5 (7H, m), 0.9 (18H, m), 0.01 (12H, m); LRMS (FAB), $(M+1)^+$ 433.5; HRMS *m/z* found: 433.2806, [calcd for $C_{21}H_{45}O_5Si_2$ (M+H): 433.2806].

3.1.6. Lactols 17. A solution of lactone **3** (7.0 mg, 0.017 mmol), dissolved in freshly distilled CH_2Cl_2 (0.3 mL) was cooled to −78°C. A solution of diisobutylaluminum hydride (DIBALH) (1.0 M in hexane, 19 μL, 0.019 mmol) was added dropwise and the resultant solution was allowed to stir at −78°C for 1 h. The reaction was quenched by adding precooled methanol (10 μL) and the mixture was allowed to stir at 0°C for another 10 min. Water (0.1 mL) was added and the mixture diluted with CH_2Cl_2. The layers were separated and the aqueous portion was extracted further with CH_2Cl_2. The combined organic extracts was dried over $MgSO_4$, filtered, and concentrated in vacuo to yield the lactols **17** (6 mg, 85% yield) as a yellow oil: IR ($CDCl_3$): 3560 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (1H, q, J=3.3 Hz), 4.69 (1H, m), 4.2–3.5 (7H, m), 2.82 (1H, d, J=5.3 Hz), 2.5–1.3 (2H, m), 0.89 (18H, s), and 0.06 (12H, brd. s); ^{13}C NMR (100.5 MHz, $CDCl_3$) 95.65, 91.78, 76.69, 76.14, 72.74, 72.58, 64.24, 59.02, 44.77, 44.70, 44.68, 44.48, 39.83, 33.28, 29.93, 26.25, 18.46, 18.43, −4.07, −4.21, −4.25, −4.30; LRMS (FAB, Fragment: 385.2); HRMS *m/z* found: 403.2701, [calcd for $C_{20}H_{43}O_4Si_2$ (M+H): 403.2700].

3.1.7. Formate 18. A mixture of lactols **17** (4.1 mg, 0.01 mmol), $Pb(OAc)_4$ (7.1 mg, 0.016 mmol), $Cu(OAc)_2$ (0.36 mg, 0.0018 mmol), and pyridine (0.97 μL, 0.012 mmol) in freshly distilled benzene (1.5 mL) was heated at reflux. After 10 min the reaction mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (15% EtOAc/hexane) to afford formate **18** as a colorless oil (3.9 mg, 95%): IR ($CDCl_3$): 1723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (1H, s), 5.19 (1H, t, J=2.5 Hz), 5.04 (1H, t, J=2.4 Hz), 4.36 (2H, m), 4.25 (1H, m), 3.94 (1H, m), 2.77 (1H, m), 2.26 (1H, m), 1.63 (1H, m), 0.93 (9H, s), 0.88 (9H, s), 0.11 (3H, s), 0.10 (3H, s), 0.08 (3H, s), 0.06 (3H, s); ^{13}C NMR (100.5 MHz, $CDCl_3$) 161.50, 151.73, 109.14, 72.39, 70.62, 63.91, 50.30, 44.22, 26.25, 26.13, 18.60, 18.30, −3.99, −4.13, −4.35, −4.48; HRMS *m/z* found: 401.2542, [calcd for $C_{20}H_{41}O_4Si_2$ (M+H): 401.2543.

3.1.8. Alcohol 10 via lactone 3. To a solution of formate **18** (4.0 mg, 0.01 mmol) in dry methanol (1 mL) was added anhydrous K_2CO_3 (2.0 mg, 0.014 mmol) at room temperature. The reaction mixture was allowed to stir 1 min. The solution was concentrated in vacuo, the residue dissolved in brine and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield 3.0 mg (81%) of primary alcohol **10** as a yellow oil: $[\alpha]_D^{20}$=−72.7° (c=0.055, CH_3OH); IR ($CDCl_3$): 3520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (1H, t, J=2.5 Hz), 5.03 (1H, t, J=2.5 Hz), 4.33 (1H, m), 4.02 (1H,

dt, J=8.1, 7.8 Hz), 3.79 (2H, m), 2.65 (1H, m), 2.25 (1H, m), 1.64 (1H, m), 1.58 (1H, br), 0.93 (9H, s), 0.90 (9H, s), 0.12–0.09 (12H); ^{13}C NMR (125.75 MHz, $CDCl_3$) 152.19, 108.45, 72.46, 71.07, 63.01, 53.27, 43.97, 26.06, 25.96, 18.40, 18.11, −4.06, −4.31, −4.55, −4.62; LRMS (FAB, M+) 372.10; HRMS m/z found: 371.2436, [calcd for $C_{19}H_{39}O_3Si_2$ $(M-H)^+$: 371.2438].

3.1.9. Acetylene 9. To a stirred mixture of hemiacetal **6b** (2.13 g, 16 mmol) and anhydrous K_2CO_3 (9.05 g, 65 mmol) in dry methanol (180 mL) maintained at room temperature (N_2 atmosphere) was added via cannulation a solution of diazophosphonate (3.77 g, 19.6 mmol, $(MeO)_2POCN_2Ac$) in methanol (20 mL). The bright yellow solution was stirred at room temperature for 14 h. The solution was decanted and concentrated in vacuo. The residue was dissolved in brine, continuously extracted with EtOAc, and the combined EtOAc layers dried over $MgSO_4$. Filtration and concentration in vacuo afforded diol **7** (0.32 g, 84% yield) as a yellow semi-solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.0 (2H, m), 2.54 (1H, d, J=2.0 Hz), 3.00–2.60 (2H, br. s), 4.43 (1H, m), 4.68 (1H, m), 5.18 (1H, dt, J=10.4 Hz), 5.31 (1H, dt, J=17.2 Hz), 5.90 (1H, ddd, J=17.2, 10.4, 6.5 Hz). The diol prepared by this procedure was subjected to silylation without purification.

To a flask containing crude diol **7** (2.0 g, 15.9 mmol) under a N_2 atmosphere was added freshly distilled CH_2Cl_2 (166 mL) and anhydrous 2,6-lutidine (5.56 mL, 47.7 mmol). The solution was cooled to 0°C and TBSOTf (TBDMSOTf) (9.13 mL, 39.8 mmol) was added dropwise over 5 min. The reaction mixture was stirred at 0°C for an additional 30 min and then diluted with CH_2Cl_2, warmed to room temperature and washed with water and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude oil was purified by flash chromatography (2% EtOAc/hexane) to furnish 5.23 g (93% yield) of disilyl ether **9** as a colorless oil: IR (solution cell, NaCl): 3301 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (1H, ddd, J=17.2, 10.4, 6.5 Hz), 5.18 (1H, d, J=17.2 Hz), 5.06 (1H, d, J=10.4 Hz), 4.48 (1H, m), 4.31 (1H, m), 2.44 (1H, d, J=2.0 Hz), 1.93 (1H, m), 1.80 (1H, m), 0.92 (9H, s), 0.91 (9H, s), and 0.15 (3H, s), 0.12 (3H, s), 0.08 (3H, s), and 0.04 (3H, s); ^{13}C NMR (100.5 MHz, $CDCl_3$) 141.26, 114.49, 85.41, 72.96, 71.07, 60.65, 47.14, 26.02, 25.96, 18.40, 18.31, −4.40, −4.77, −4.89, −5.05; HRMS (FAB) m/z 353.2333, [calcd for $C_{19}H_{37}O_2Si_2$ (M^+): 353.2332].

3.1.10. Epoxide 8. To a solution of *m*-chloroperoxybenzoic acid (1.53 g, 6.1 mmol; 69% pure) in freshly distilled CH_2Cl_2 (72 mL) under a N_2 atmosphere was added a solution of vinyl acetylene **9** (1.45 g, 4.1 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 36 h. The reaction mixture was diluted with CH_2Cl_2, washed with saturated aq. $NaHCO_3$, brine, and dried over $MgSO_4$. After filtration and concentration in vacuo, the residue was subjected to flash chromatography (2% EtOAc/hexane) to afford epoxyacetylene **8** (1.36 g, 91% yield) as a pale yellow oil: IR ($CDCl_3$): 3301 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (0.5H, m), 3.84 (0.5H, m), 3.00 (1H, m), 2.44 (1H, m), 2.02–1.82 (2H, m), 0.93–0.90 (18H, m), 0.16–0.08 (12H, m); ^{13}C NMR (125.75 MHz, $CDCl_3$) 85.06, 84.92, 73.37, 73.33, 72.46, 68.65, 63.32, 60.51, 56.02, 54.79, 45.10, 44.73, 44.17, 43.50, 26.04, 26.01, 25.96 (×2), 18.39 (×2), 18.30, 18.27, −4.12, −4.15, −4.45, −4.47, −4.84, −4.89 (×2), −5.08; HRMS (FAB) m/z 371.2436, [calcd for $C_{19}H_{39}O_3Si_2$ (M+1): 371.2438].

3.1.11. Alcohol 10 via acetylene 8. A 0.08 M solution of Cp_2TiCl (17.2 mL, 1.38 mmol) (vide supra) was added dropwise via syringe pump over 3 h to a stirred solution of epoxyacetylene **8** (0.17 g, 0.46 mmol) dissolved in freshly distilled THF (23 mL) at room temperature under an N_2 atmosphere. The reaction mixture was stirred for an additional 8 h and the intermediate bis-titanium(IV) intermediate was decomposed by the addition of 10% aq. H_2SO_4 (10 mL). After stirring for 5 min, the solution was extracted thoroughly with EtOAc. The bright orange aqueous portion was extracted further with EtOAc. The combined organic layers were washed with saturated aq. $NaHCO_3$ and dried ($MgSO_4$). After filtration and concentration in vacuo, the crude residue was purified by flash chromatography (15% EtOAc/hexane) to afford 0.12 g (82% yield) of alcohol **10** as a viscous light yellow liquid, whose spectral data was identical with the sample of **10** prepared above.

3.1.12. Pivaloate ester 12. To a solution of anhydrous pyridine (10 mL) and alcohol **10** (0.37 g, 1.0 mmol) under a N_2 atmosphere and cooled to 0°C was added DMAP (2.5 mg, 0.02 mmol) followed by dropwise addition of pivaloyl chloride (0.25 mL, 2.0 mmol). After stirring the mixture for 18 h at room temperature, water (0.5 mL) was added and the mixture was stirred vigorously for 6 h. Ether was added to the mixture and the solution washed with 1N aq. HCl, saturated $NaHCO_3$, and water. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (2% EtOAc/hexanes) to furnish the pivaloate ester **12** (42 mg, 92%) as a clear oil: IR ($CDCl_3$): 1752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (1H, t, J=2.3 Hz), 5.02 (1H, t, J=2.4 Hz), 4.35 (2H, m), 4.05 (1H, m), 3.94 (1H, m), 2.71 (1H, m), 2.24 (1H, m), 1.65 (1H, q, J=10.2 Hz), 1.20 (9H, s), 0.93 (9H, s), 0.89 (9H, s), 0.11 (3H, s), 0.10 (3H, s), 0.07 (3H, s), and 0.06 (3H, s); HRMS (FAB) m/z found: 455.3012, [calcd for $C_{24}H_{47}O_4Si_2$ (M−H): 455.3012].

3.1.13. Allylic alcohol 11a. A solution of disilyl ether **12** (48.1 mg, 0.105 mmol) in 80% aq. acetic acid (5 mL) was stirred at room temperature for 6 h, in which time TLC analysis showed the optimum ratio of desired product **11a** to starting material **12**. The solution was neutralized with 50% aq. NaOH, saturated with NaCl, and continuously extracted with EtOAc. The combined organic extracts were concentrated in vacuo and the crude residue was purified by flash chromatography (15% EtOAc/hexane) to furnish 13.6 mg (38% yield, 54% based on recovered pivaloate **12**) of the desired allylic alcohol **11a** as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (1H, s), 5.22 (1H, t, J=1.6 Hz), 4.40 (1H, m), 4.22 (1H, m), 3.96 (2H, m), 2.92 (1H, m), 2.72 (1H, d, J=10.0 Hz), 2.11 (1H, m), 1.86 (1H, m), 1.22 (9H, s), 0.90 (9H, s), and 0.11 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 178.87, 153.32, 113.26, 75.26, 75.03, 65.24, 51.93, 42.67, 39.23, 27.65, 26.25, 18.32, −4.37, −4.40; HRMS (FAB) m/z found: 365.2123, [calcd for $C_{18}H_{34}O_4SiNa$ (M+Na): 365.2123]. Additionally, 2.6 mg (11% yield) of the diol **11b** was also isolated: ^{1}H NMR (400 MHz, $CDCl_3$)

δ 5.41 (1H, t, J=1.2 Hz), 4.52 (1H, m), 4.16 (2H, m), 4.02 (1H, m), 2.97 (1H, m), 2.23 (1H, m), 1.87–1.94 (3H, m), and 1.22 (9H, s).

Acknowledgements

We thank Dr Weihong Zhang for her early contributions to this research. M.A.S. is grateful for a Dox Fellowship and a Heyl Dissertation Fellowship.

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