Notes

A Very Concise and Stereoselective Synthesis of 3-Substituted *cis*-Hex-3-ene-1,5-diyne and Corresponding Epoxydiyne

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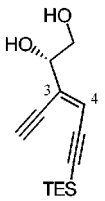
Chromoprotein enediyne antitumor agents such as kedarcidin,[1] C1027,[2] and neocarzinostatin,[3] incorporate highly unstable enediyne and epoxydiyne chromophores. As key intermediates, the substructures *cis*-hex-3-ene-1,5-diyne **1** and corresponding epoxydiyne **2** are valuable targets in the total synthesis of such complex chromophores.[4−6] Although several synthetic routes to **1**, **2** and their equivalents have been developed,[7] the 3,4-(*E*/*Z*) stereoselectivity is occasionally low[6a] or the routes are rather lengthy.[8] Furthermore, the common ketone intermediate **3** used for these syntheses is not stable, particularly toward silica gel. In this paper, we describe a concise and stereocontrolled route to **1** and **2** that circumvents the use of labile **3**.



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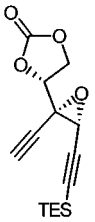

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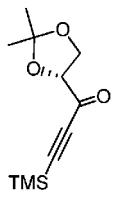
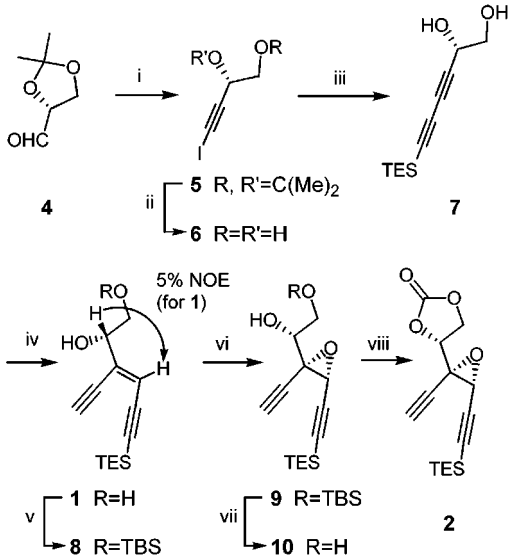


3

Very recently, Fallis[9] reported a facile method to prepare a *cis*-enediyne by the direct addition of an ethynyl Grignard reagent to 2,4-pentadiynol. Although the reported yield was low (36%), this magnesium-mediated carbometalation was very attractive due to its conciseness. Thus, we planned to apply this method to the synthesis of **1** and **2**.

Scheme 1



[a] Reagents: (i) CHI_3, Ph_3P, *t*-BuOK (1 equiv), rt, 15 min; then *t*-BuOK (5 equiv), −78 °C, 84%; (ii) 15% HCl/MeOH, rt, 93%; (iii) triethylsilylacetylene, CuI, 0 °C, 81%; (iv) ethynylmagnesium bromide (6 equiv), THF, reflux, 76%; (v) TBSCl, 4-*N*,*N*-(dimethylamino)pyridine, Et_3N, 86%; (vi) $Ti(O\textit{i}\text{-}Pr)_4$, D-(−)-diethyl tartrate, t-BuOOH, molecular sieves 4A, −23 °C, 82%; (vii) HF/pyridine, THF (1:10), rt; (viii) 1,1-carbonyldiimidazole, 88% (two steps).

Synthesis of the chiral diynediol **7** commenced from the readily available glyceraldehyde derivative **4** (Scheme 1). According to a one-pot procedure,[10] the aldehyde **4** was converted to the alkynyl iodide **5** using triphenylphosphine, triiodomethane, and t-BuOK in good yield. Hydrolytic removal of the acetonide group followed by

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coupling with triethylsilylacetylene gave **7**.[11] As the key step, compound **7** was refluxed in THF with ethynylmagnesium bromide (6 equiv) and solely gave the desired compound **1** in 76% yield with the (*E*)-geometry as confirmed by NOE experiments. Selective protection of the primary alcohol as a *tert*-butyldimethylsilyl (TBS) ether and subsequent Sharpless asymmetric epoxidation at −23 °C produced the α-epoxide **9** in 82% yield. Careful removal of the TBS group using HF/pyridine in THF (1:10) at room temperature gave **10** without affecting the triethylsilyl (TES) group on the terminal alkyne. Last, protection of the resulting diol **10** with 1,1-carbonyldiimidazole (CDI) afforded the desired cyclic carbonate **2** in 88% overall yield.

In summary, an efficient and completely selective method to synthesize the chiral (*E*)-enediyne **1** and (*E*)-epoxydiyne **2** has been established by application of carbometalation methodology to the extended propargylic chiral diol **7**.

Experimental Section

NMR spectra were recorded in $CDCl_3$ or CD_3OD and chemical shifts are reported in parts per million relative to TMS using residual partially or nondeuterated solvent as reference. IR spectra were recorded as films or using KBr pellets on a FTIR spectrometer. All solvents were dried over molecular sieves before use, and reagents were used directly without further purification. Air- and moisture-sensitive reactions were carried out under an argon atmosphere in anhydrous conditions. All reactions were monitored by TLC on 0.25 mm Merck Kieselgel TLC plate (60F-254) using UV light, ethanolic *p*-anisaldehyde solution with heating for visualization. Merck Kieselgel 60 (230−400 mesh) was used for flash chromatography.

1-Iodo-2-[(1*S*)-1,2-isopropylidenedioxyethyl]ethyne (5). To a solution of iodoform (60.5 g, 0.154 mol) in THF (500 mL) was added triphenylphosphine (44.4 g, 0.169 mol) and then *t*-BuOK (14.5 g, 0.129 mol) at room temperature. After stirring for 2 min, the brown suspension was cooled to 0 °C, and a solution of **4** (16.0 g, 0.123 mol) in 100 mL of THF was added. Stirring was continued for another 15 min, and then the mixture was cooled to −78 °C and another portion of *t*-BuOK (68.9 g, 0.614 mol) was added. The reaction temperature was kept at this temperature for 30 min and then quenched with brine, filtered through Celite, and the organic layer was separated. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent, the residue was purified by flash chromatography on silica (hexane/EtOAc, 20:1) to give compound **5** as a pale yellow oil (26.2 g, 84%): $[\alpha]^{29}_D$ +30.0 (*c* 1.13, $CHCl_3$); IR (film) 2185 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.83(t, 1H, J = 6.4 Hz), 4.15 (dd, 1H, J = 8.0, 6.4 Hz), 3.94 (dd, 1H, J = 8.0, 6.4 Hz), 1.49 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 110.5, 91.7, 69.8, 66.7, 26.1, 25.9, 3.7; HRMS (EI) *m*/*z* 251.9641, Calcd for $C_7H_9IO_2$ (M^+) required 251.9647.

(2*S*)-4-Iodo-3-butyne-1,2-diol (6). To a solution of **5** (23.9 g, 94.7 mmol) in 80 mL of MeOH was added 15% aqueous HCl (8 mL) and the solution stirred at room temperature for 6 h until TLC showed completion. The reaction solution was diluted with EtOAc and carefully neutralized with aqueous saturated $NaHCO_3$. The organic layer was separated and the aqueous layer further extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration, solvent evaporation, and purification of the residue by flash chromatography (hexane/EtOAc, 5:1 to 1:1) gave compound **6** as a white amorphous solid (18.6 g, 93%): $[\alpha]^{29}_D$ +12.5 (*c* 0.3, EtOH); IR (KBr) 3229, 2172 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 4.4 (t, 1H, J = 7.2 Hz), 3.54 (dd, 2H, J = 7.2, 2.4 Hz); ^{13}C NMR (50 MHz, CD_3OD) δ 93.9, 67.4, 65.5, 6.24; HRMS (EI) *m*/*z* 211.9335, Calcd for $C_4H_5IO_2$ (M^+) required 211.9334.

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(2*S*)-6-Triethylsilyl-3,5-hexadiyne-1,2-diol (7). To an ice cooled mixture of **6** (2.20 g, 10.4 mmol) and triethylsilyl acetylene (2.34 mL, 18.7 mmol) were added pyrrolidine (15 mL) and then CuI (0.19 g, 1 mmol) under an argon atmosphere. After stirring at 0 °C for 30 min, the reaction was quenched with saturated NH_4Cl solution and extracted with ether. The combined organic layers were washed with brine and then dried over $MgSO_4$. Filtration, evaporation, and purification of the residue by flash chromatography (hexane/EtOAc, 3:1) gave compound **7** as a brown oil (1.87 g, 81%): $[\alpha]^{28}_D$ +28.1 (*c* 0.9, $CHCl_3$); IR (film) 3392, 2106 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.51 (dd, 1H, J = 6.2, 4.0 Hz), 3.73 (dd, 2H, J = 6.2, 4.0 Hz), 0.99 (t, 9H), 0.65 (q, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 87.9, 85.8, 74.5, 66.0, 63.4, 7.2, 3.9; HRMS (EI) *m*/*z* 224.1229, Calcd for $C_{12}H_{20}O_2Si$ (M^+) required 224.1233.

(2*S*,3*E*)-3-Ethynyl-6-triethylsilyl-3-hexen-5-yne-1,2-diol (1). To a solution of **7** (3.88 g, 17.3 mmol) in dry THF (50 mL) was added ethynylmagnesium bromide (0.5 M solution in THF, 207 mL, 103 mmol) at room temperature under argon. The resulting brown solution was heated at reflux for 36 h. The reaction was then allowed to cool to room temperature and then aqueous NH_4Cl solution added. The organic layer was separated and the aqueous layer extracted with ether. The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration, evaporation, and purification of the residue by flash chromatography (hexane/EtOAc, 2.5:1) gave compound **1** as a brown oil (3.29 g, 76%): $[\alpha]^{23}_D$ +29.6 (*c* 0.33, $CHCl_3$); IR (film) 3306, 2108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.19 (d, 1H, J = 1.4 Hz), 4.33 (m, 1H), 3.82 (dd, 1H, J = 11.2, 3.8 Hz), 3.73 (dd, 1H, J = 11.2, 3.8 Hz), 3.45 (s, 1H), 1.00 (t, 9H), 0.65 (q, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 133.7, 117.9, 102.6, 101.2, 86.7, 79.6, 73.9, 65.4, 7.4, 4.3; HRMS (EI) *m*/*z* 250.1388, Calcd for $C_{14}H_{22}O_2Si$ (M^+) required 250.1389.

(2*S*,3*E*)-1-*tert*-Butyldimethylsilyloxy-3-ethynyl-6-triethylsilyl-3-hexen-5-yn-2-ol (8). To a solution of **1** (1.21 g, 4.80 mmol) in CH_2Cl_2 (20 mL) were added *tert*-butyldimethylchlorosilane (0.804 g, 5.28 mmol) and *N*,*N*-(dimethylamino)pyridine (29.3 mg, 0.24 mmol). The solution was cooled to 0 °C, triethylamine (1.2 mL, 8.64 mmol) added, and the reaction stirred at room temperature for 10 h. After dilution with ether, the reaction was quenched with saturated aqueous NH_4Cl, the organic layer separated, and the aqueous layer extracted with ether. The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration, evaporation, and purification of the residue by flash chromatography (hexane/EtOAc, 30:1) gave compound **8** as a pale yellow oil (1.45 g, 83%): $[\alpha]^{26}_D$ +16.5 (*c* 0.88, $CHCl_3$); IR (film) 3310, 2109 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.19 (t, 1H, J = 1.0 Hz), 4.02 (m, 1H), 3.85 (dd, 1H, J = 9.8, 3.4 Hz), 3.60 (dd, 1H, J = 9.8, 3.4 Hz), 3.40 (s, 1H), 1.01 (t, 9H), 0.90 (s, 9H), 0.64 (q, 6H), 0.09 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 133.6, 117.5, 102.9, 100.5, 86.1, 79.9, 73.5, 65.8, 25.8, 7.4, 7.3, 4.3, 4.2, −5.4; HRMS (EI) *m*/z 364.2248, Calcd for $C_{20}H_{36}O_2Si_2$ (M^+) required 364.2254.

(2*R*,3*S*,4*R*)-1-*tert*-Butyldimethylsilyloxy-3,4-epoxy-3-ethynyl-6-triethylsilyl-hex-5-yn-2-ol (9). A suspension of freshly activated powdered molecular sieves 4A (3.0 g) in dry CH_2Cl_2 (60 mL) was cooled to −23 °C, and then titanium(IV) isoproxide (2.71 mL, 9.18 mmol) and D-(−)-diethyl tartrate (1.79 mL, 10.5 mmol) were added. After the mixture was stirred at this temperature for 10 min, a solution of compound **8** (2.58 g, 7.07 mmol) in CH_2Cl_2 (20 mL) and *tert*-butyl hydroperoxide (~3.0 M in CH_2Cl_2, 14 mL, 42 mmol) was added and the mixture stirred at −23 °C for 6 days. After this time, the reaction was diluted with ether and quenched with aqueous sodium thiosulfate. The precipitate was filtered off and washed with ether, the organic layer separated, and the aqueous layer extracted with ether. The combined organic layers were washed with brine and dried over $MgSO_4$, filtered, and concentrated to a residue which was purified by flash chromatography (hexane/EtOAc, 20:1) to give compound **9** as a pale yellow oil (2.18 g, 82%): $[\alpha]^{28}_D$ +40.3 (*c* 1.1, $CHCl_3$); IR (film) 3460, 3331, 2190, 2160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.93 (d, 2H, J = 4.0 Hz), 3.86 (m, 1H), 3.71 (s, 1H), 2.49 (s, 1H), 1.00 (t, 9H), 0.91 (s, 9H), 0.63 (q, 6H), 0.1 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 99.8, 90.0, 77.9, 75.6, 71.1, 63.2, 57.8, 48.7, 25.8, 18.2, 7.3, 4.1, −5.4, −5.2; HRMS (EI) *m*/*z* 380.2205, Calcd for $C_{20}H_{36}O_3Si_2$ (M^+) required 380.2203.

(2*R*,3*S*,4*R*)-3,4-Epoxy-3-ethynyl-6-triethylsilyl-5-hexyne-1,2-diyl Carbonate (2). A solution of **9** (0.76 g, 2.0 mmol) in THF (5 mL) was cooled to 0 °C, HF/pyridine (70%, 0.5 mL) added, and the reaction temperature allowed to slowly reach room temperature. After 6 h, the reaction was diluted with EtOAc and quenched with aqueous NH_4Cl. The organic layer was separated and the aqueous layer extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent, the residue was dissolved in THF (5 mL) and 1,1-carbonyldiimidazole (0.49 g, 3.0 mmol) added. The solution was stirred at room temperature for 1 h, diluted with EtOAc, and quenched with saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration and evaporation of solvent, the residue was purified by flash chromatography (hexane/EtOAc, 8:1) to give compound **2** as a pale yellow oil (0.51 g, 88% for two steps): $[\alpha]^{28}_D$ +41.1 (*c* 1.11, $CHCl_3$); IR (film) 2129, 1824 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.67 (dd, 1H, J = 8.8, 7.0 Hz), 4.66 (dd, 1H, J = 8.8, 7.0 Hz), 4.38 (dd, 1H, J = 7.4, 6.4 Hz), 3.65 (s, 1H), 2.61 (s, 1H), 1.01 (t, 9H), 0.65 (q, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.7, 97.6, 77.8, 75.7, 74.1, 66.5, 56.8, 51.2, 7.3, 3.9; HRMS (EI) *m*/*z* 292.1128, Calcd for $C_{15}H_{20}O_4Si$ (M^+) required 292.1131.

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