Diastereoselective Propargylation of α-Alkoxy Aldehydes with Propargyl Bromide and Zinc. A Versatile and Efficient Method for the Synthesis of Chiral Oxygenated Acyclic Natural Products

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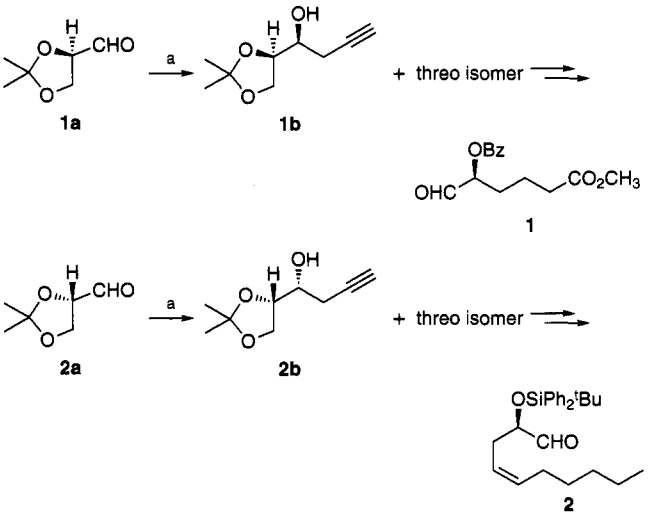
Introduction

The allylation of carbonyl compounds with organozinc reagents is of great synthetic interest because it offers mild reaction conditions and high stereoselectivity.[1] In 1990, Shono reported an improved procedure for allylation that employs allyl bromide and zinc dust in DMF instead of ether.[2] Recently Chan described a zinc-mediated allylation of α-alkoxy aldehyde in aqueous media and applied it successfully to the efficient synthesis of (+)-muscarine.[3] Relative to allylation, much less attention has been paid to propargylation with propargyl bromide and zinc.[1,4] In particular, the stereoselectivity of zinc-mediated propargylation of α-alkoxy aldehydes has not been well studied.[5] However, propargylation is of equal importance in organic synthesis because the propargyl group is a useful three-carbon building block and the propargylation products, homopropargyl alcohols, can be versatile intermediates for a variety of synthetic targets. Thus we have chosen to investigate this addition reaction.

Results and Discussion

In light of our synthetic interest in chiral oxygenated fatty acids, we sought a practical methodology for the construction of chiral homopropargylic alcohols (and then homoallylic alcohols) with an anti (erythro) selectivity from α-alkoxy aldehydes. 2,3-*O*-Isopropylideneglyceraldehyde was chosen as the first substrate, and Shono's allylation conditions were employed. The reaction proceeded successfully with good selectivity. Less than 5% of allenic product could be detected by NMR, and the anti/syn ratio of homopropargylic alcohol products was greater than 10:1. The configuration of the newly formed chiral center was confirmed by the synthesis of the C_1–C_6 segment **1** and the C_{11}–C_{20} segment **2** of leukotriene B_4 from the addition products of D-2,3-*O*-isopropylideneglyceraldehyde **1a** and L-2,3-*O*-isopropylideneglyceraldehyde (**2a**), respectively.[6]

This reaction could also be performed in a mixed solvent of DMF and ether or THF, but more than 50% ether or THF decreased the anti/syn selectivity. The successful application of propargylation with propargyl bromide and zinc in DMF (or in DMF–ether) motivated us to expand this methodology to a series of α-alkoxy aldehydes. The results are summarized in Table 1. Reactions of various substrates ranging from mono- to trioxygenated aldehydes provided good to excellent yields and selectivities except for entries 8 and 9. Some of the major products obtained from these reactions have already been used for the chiral syntheses of acyclic natural products.[7–11]



(a) Zn dust, propargyl bromide, DMF/THF (1:1), 40 °C, 12 h

The antiselectivity of propargylation suggests that the reactions do not occur via a chelation control transition state, which would lead to syn addition. In a polar reaction medium such as DMF, just as in an aqueous medium,[3] the chelation was disrupted and the major diastereoisomer was formed through a Felkin–Ahn transition state.[12] As the table shows, the anti/syn selectivity was usually higher if there was an oxygenated five-membered ring flanking the aldehyde group in the substrate (entries 1–7, 10, and 11). This might mean that strong steric congestion in the transition state favors anti selectivity. Presumably then, the simplest aldehyde **10a** resulted in lower selectivity due to the absence of this kind of bulky group in the transition state (entry 8). However, the lower selectivity in entry 9 is not as easily explained.

The propargylation reaction could also be performed in the presence of an unprotected hydroxyl group, as in entries 9, 10, and 11. In these cases, the major diastereoisomer was also erythro (anti attack), which was confirmed by 2D-NMR studies of the acetal.

All of the reactions were carried out at room temperature with no special precautions against air and moisture, and all of the solvents were used without purification. The ease of these propargylation reactions bodes well for their utility in the asymmetric syntheses of oxygenated acyclic natural products.

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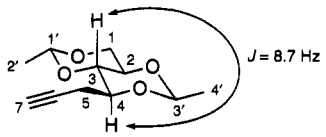
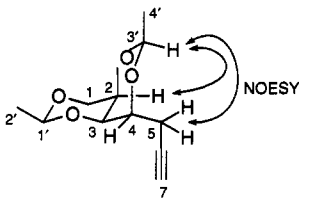


14

acetal of entry 9 product **11b**



15

acetal of entry 10 product **12b**

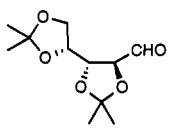
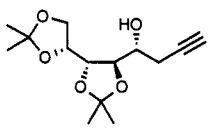
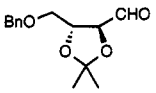
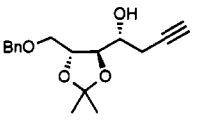
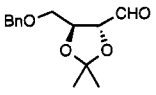
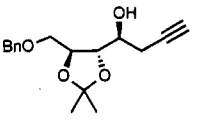
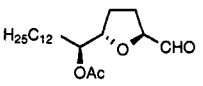
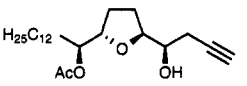
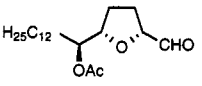
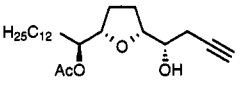
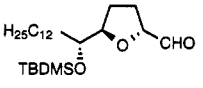
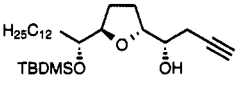
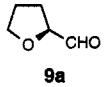
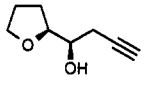
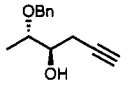
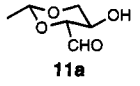
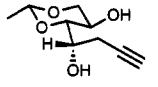
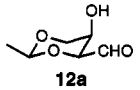
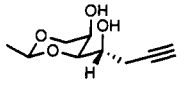
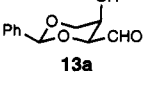
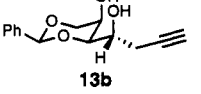
Experimental Section

General. Melting points are uncorrected. ^1H NMR spectra were measured with a Bruker AMX-300 or AMX-600 spectrometer. Column chromatography was performed on silica gel H (400 mesh). Microanalyses were carried out by the Microanalytical Laboratory at Shanghai Institute of Organic Chemistry.

Typical Procedure. The aldehyde (or freshly prepared from the alcohol) (1 mmol) and propargyl bromide (2 mmol) were dissolved in a mixed solvent (DMF–ether, 1:1, 4 mL). To this well-stirred solution was added activated zinc dust (washed with 2% HCl, water, and dried in vacuum) (3 mmol) slowly at room temperature. After 2–5 min, the exothermic reaction brought itself to reflux. The whole reaction mixture was stirred for 5–10 h at room temperature until TLC indicated that the reaction was finished. Usual aqueous workup and the following column chromatography on silica gel gave the pure product.

(2*S*,5*S*)-2-[(1*S*)-1-Acetoxytridecyl]-5-[(1*R*)-1-hydroxy-3-butynyl]tetrahydrofuran (6b) and (2*S*,5*S*)-2-[(1*S*)-1-Acetoxytridecyl]-5-[(1*S*)-1-hydroxy-3-butynyl]tetrahydrofuran (6c). DMSO (267 mg, 3.42 mmol) in dry CH_2Cl_2 (2.0 mL) was added to a solution of $(COCl)_2$ (150 μL, 1.71 mmol) in dry CH_2Cl_2 (5.0 mL) at −60 °C under an N_2 atmosphere and sitrring was continued for additional 15 min. (2*S*,5*S*)-2-[(1*S*)-1-Acetoxytridecyl]tetrahydrofuran-5-carbinol (390 mg, 1.14 mmol) in dry

Table 1. Propargylation of α-Alkoxy Aldehydes

no.	aldehyde	yield[a]	major product	anti/syn	note
1	 **3a**	86	 **3b**	12	utilization of the major product, see refs 7, 8
2	 **4a**	91[b]	 **4b**	30	utilization of the major product, see refs 9, 10
3	 **5a**	81[b]	 **5b**	30	utilization of the major product, see refs 9, 10
4	 **6a**	65[b]	 **6b**	8.3	utilization of the major product, see ref 11
5	 **7a**	64[b]	 **7b**	9.8	
6	 **8a**	62[b]	 **8b**	9.6	
7	 **9a**	63[b]	 **9b**	7.3[c]	
8	 **10a**	79[b]	 **10b**	2.6[c]	
9	 **11a**	74	 **11b**	3.3	
10	 **12a**	89		11.7	
11	 **13a**	92	 **13b**	10.5	

[a] Isolated yield. [b] For two steps, from the alcohol. [c] Determined by NMR.

CH_2Cl_2 (3.0 mL) was added dropwise. Et_3N (1.1 mL, ~8 mmol) was injected after 1 h, and the whole mixture was warmed to room temperature and stirred for 0.5 h. Then it was diluted with ether (10 mL) and washed with brine (5 mL × 2), dried (Na_2SO_4), and concentrated. The crude aldehyde **6a** was dried in vacuum prior to use.

To the well-stirred solution of the crude aldehye and propargyl bromide (270 mg, 2.27 mmol) in a 1:1 mixed solvent of DMF–ether (6 mL) was then added activated zinc dust (225 mg, 3.46 mmol). The whole mixture was stirred at room temperature for 4.5 h. Then the mixture was diluted with ether (20 mL), and the solid was filtered. The filtrate was washed with satd aqueous NH_4Cl (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. Chromatography on silica gel (petroleum ether–EtOAc, 7:1) gave an erythro product (**6b**) (247 mg, 57% two steps) and a threo product (**6c**) (30 mg, 6.9%) as clear oils. Data for **6b**: $[\alpha]^{20}_D$ −19.7 (*c* 0.42, $CHCl_3$). IR (neat): 3450, 3300, 2100, 1740 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): 4.83 (1H, ddd, J = 6.3, 4.5, 1.9 Hz), 4.07 (1H, ddd, J = 3.7, 6.6, 7.4 Hz), 3.98 (1H, ddd, J = 6.2, 7.8, 1.8 Hz), 3.93 (1H, ddd, J = 3.7, 6.9, 6.9 Hz), 2.45 (1H, ddd, J = 2.7, 6.7, 10.1 Hz), 2.30 (1H, ddd, J = 2.7, 7.1, 9.7 Hz), 2.10 (3H, s), 2.00 (1H, t, J = 2.4 Hz), 1.70–2.05 (4H, m), 1.57 (3H, m), 1.26 (20H, m), 0.88 (3H, t, J = 7.2 Hz) ppm. EIMS (*m*/*z*): 381 (MH^+), 362 ($M^+ - H_2O$), 337 (M^+ − Ac), 321 (M^+ − AcO), 303, 169, 139. Data for **6c**: $[\alpha]^{20}_D$ −13.3 (*c* 0.11, $CHCl_3$). IR (neat): 3450, 3300, 2100, 1740 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): 4.87 (1H, ddd, J = 2.3, 7.7, 7.8 Hz), 4.02 (1H, m), 3.98 (1H, m), 3.64 (1H, m), 2.42 (2H, dd, J = 6.5, 2.7 Hz), 2.09 (3H, s), 2.03 (1H, t, J = 2.7 Hz), 1.65–2.00 (4H, m), 1.55 (3H, m), 1.26 (20H, m), 0.88 (3H, t, J = 7.2 Hz) ppm. EIMS (*m*/*z*): 381 (MH^+), 362 ($M^+ - H_2O$), 337 (M^+ − Ac), 321 (M^+ − AcO), 303, 299, 281, 169, 139.

(2*R*,5*R*)-2-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]trideyl]-5-[(1*S*)-1-hydroxy-3-butynyl]tetrahydrofuran (8b) and (2*R*,5*R*)-2-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]tridecyl]-5-[(1*R*)-1-hydroxy-3-butynyl]tetrahydrofuran (8c). To a well-stirred solution of the crude aldehye **8a** prepared from the corresponding alcohol (86 mg, 0.21 mmol) as above and propargyl bromide (50 mg, 0.42 mmol) in a 1:1 mixed solvent of DMF–ether (3 mL), was then added activated zinc dust (40 mg, 0.62 mmol). The whole mixture was stirred at room temperature for 5 h. Then the mixture was diluted with ether (10 mL), and the excess zinc was filtered. The filtrate was washed with satd aqueous NH_4Cl (6 mL) and brine (6 mL). The organic layer was dried (Na_2SO_4) and concentrated. Chromatography on silica gel (petroleum ether–EtOAc, 50:1 to 30:1) gave the threo product **8c** (6 mg, 6.4% two steps) and the erythro product **8b** (58 mg, 62%) as clear oils. Data for **8b**: $[\alpha]^{20}_D$ +12.2 (*c* 2.05, $CHCl_3$). IR (neat): 3400, 3300, 2920, 2860, 1465, 1250, 1060, 838, 778 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 3.96 (1H, ddd, J = 5.4, 5.8, 8.4 Hz), 3.92 (1H, m), 3.82 (1H, dt, J = 6.2, 5.4 Hz), 3.55 (1H, m), 2.43 (2H, dd, J = 6.4, 2.7 Hz), 2.02 (1H, t, J = 2.7 Hz), 1.60–1.96 (6H, m), 1.26 (20H, m), 0.90 (9H, s), 0.88 (3H, t, J = 7.0 Hz), 0.07 (3H, s), 0.05 (3H, s) ppm. EIMS (*m*/*z*): 413 (M^+ − $CH_2C{\equiv}CH$), 395 (M^+ − Bu^t), 377, 351, 337, 313 (100.00), 285, 257, 143, 115, 75. Data for **8c**: $[\alpha]^{20}_D$ −10.3 (*c* 0.25, $CHCl_3$). IR (neat): 3450, 3300, 2920, 2860, 1465, 1250, 1080, 835, 778 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 3.99 (1H, ddd, J = 5.8, 5.8, 7.8 Hz), 3.90 (1H, ddd, J = 6.0, 6.1, 8.2 Hz), 3.60 (1H, dt, J = 6.2, 4.9 Hz), 3.56 (1H, m), 2.41 (2H, dd, J = 6.2, 2.7 Hz), 2.01 (1H, t, J = 2.7 Hz), 1.60–1.98 (6H, m), 1.26 (20H, m), 0.90 (9H, s), 0.88 (3H, t, J = 6.8 Hz), 0.08 (3H, s), 0.06 (3H, s) ppm. EIMS (*m*/*z*): 437 (M^+ − CH_3), 413 (M^+ − $CH_2C{\equiv}CH$), 395 (M^+ − Bu^t), 383, 377, 337, 313 (100.00), 257, 115, 75.

(2*R*,3*R*,4*R*)-1,3-*O*-Ethylidenehept-6-yne-1,2,3,4-tetrol (11b) and (2*R*,3*R*,4*S*)-1,3-*O*-Ethylidenehept-6-yne-1,2,3,4-tetrol (11c). To a stirred solution of the aldehyde (dimer) **11a** (1.46 g, 10 mmol) and propargyl bromide (2.23 mL, 25 mmol) in DMF–Et_2O (1:1, 20 mL) was slowly added zinc dust (1.97 g, 30 mmol). An exothermic reaction started within a few minutes, and the reflux was allowed to continue until most of compound **11a** had been consumed. Then, the reaction mixture was poured into satd aqueous NH_4Cl. Usual workup and chromatography yielded the erythro product **11b** (1.06 g) and the corresponding threo product **11c** (0.32 g), total yield 74%. Physical data for compound **11b**: mp 96–97 °C. $[\alpha]^{20}_D$ −40.1 (*c* 0.9, $CHCl_3$). IR (KBr): 3400, 3290, 2100, 1405, 1160, 1100, 1045, 900 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 1.31 (3H, d, J = 5.0 Hz), 2.11 (1H, t, J = 2.6 Hz), 2.51 (1H, ddd, J = 2.6, 6.8, 16.9 Hz), 2.70 (1H, ddd, J = 2.6, 3.8, 16.9 Hz), 2.85 (2H, br s), 3.37 (2H, m), 3.80 (1H, m), 3.92 (1H, m), 4.15 (1H, dd, J = 5.3, 10.9 Hz), 4.67 (1H, q, J = 5.0 Hz) ppm. EIMS (*m*/*z*): 185 (M^+ − 1), 171 (M^+ − CH_3), 125 ($M^+ + 1 - H_2O - CH_3CHO$), 117, 103, 99, 73, 45 (100). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.48; H, 7.77. Physical data for the threo product **11c**: mp 94–96 °C. $[\alpha]^{20}_D$ −33.7 (*c* 0.8, $CHCl_3$). IR (KBr): 3300, 3290, 2100, 1405, 1380, 1155, 1090, 900 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 1.33 (3H, d, J = 5.0 Hz), 2.06 (1H, t, J = 2.7 Hz), 2.45 (2H, br s), 2.56 (2H, m), 3.42 (1H, m), 3.53 (1H, dd, J = 2.3, 9.4 Hz), 3.88 (1H, m), 4.06 (1H, dt, J = 2.3, 6.9 Hz), 4.15 (1H, m), 4.73 (1H, q, J = 5.0 Hz) ppm. EIMS (*m*/*z*): 186 (M^+), 125 ($M^+ + 1 - H_2O - CH_3CHO$), 117, 103, 88, 74, 72 (100), 67. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.10; H, 7.69.

(2*R*,3*R*,4*R*)-1,3:2,4-Di-*O*-ethylidenehept-6-yne-1,2,3,4-tetrol (14). A solution of alcohol **11b** (40 mg, 0.22 mmol), acetal (0.062 mL, 0.43 mmol), and *p*-toluenesulfonic acid monohydrate (5 mg) in DMF (2 mL) was stirred for 6 h at 40 °C under N_2, then diluted with Et_2O and washed successively with satd $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silics gel to give compund **11** (49 mg, 69%): mp 66–68 °C. $[\alpha]^{20}_D$ −51.4 (*c* 0.1, $CHCl_3$). IR (KBr): 3290, 2100, 1415, 1130, 1095, 935, 890, 640 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): 1.32 (3H, d, J = 5.1 Hz), 1.36 (3H, d, J = 5.1 Hz), 2.01 (1H, t, J = 2.9 Hz, 7-H), 2.46 (1H, ddd, J_{57} = 2.9 Hz, J_{45} = 6.7 Hz, J_{55} = 17.2 Hz, 5−H), 2.66 (1H, ddd, J_{45} = 2.9 Hz, J_{57} = 2.9 Hz, J_{55} = 17.2 Hz, 5-H), 3.33 (1H, dd, J_{23} = 8.1 Hz, J_{34} = 8.7 Hz, 3-H), 3.57 (2H, m, J_{12} = 3.3, 8.7 Hz, J_{11} = 10.6 Hz, 1-H), 3.71 (1H, ddd, J_{45} = 2.9 Hz, J_{45} = 6.7 Hz, J_{34} = 8.7 Hz, 2-H), 4.11 (1H, ddd, J_{12} = 3.2 Hz, J_{23} = 8.1 Hz, J_{12} = 8.7 Hz, 2-H), 4.77 (1H, q, J = 5.1 Hz), 4.90 (1H, q, J = 5.1 Hz) ppm. Irradiation of resonance at δ 4.11 resulted in collapse of the mutiplets at δ 3.57 and 3.33, giving essentially two doublets (J_{11} = 10.6 Hz) and a doublet (J_{34} = 8.7 Hz), respectively. Irradiation of the resonance at δ 3.71 resulted in collapse of the mutiplets at δ 3.33 and 2.66, giving essentially a doublet (J_{23} = 8.1 Hz) and double doublet (J_{57} = 2.9 Hz, J_{55} = 17.2 Hz), respectively. Irradiation of the resonance at δ 3.57 resulted in collapse of the mutiplets at δ 4.22, giving essentially a doublet (J_{23} = 8.1 Hz). Irradiation of the resonance at δ 3.32 resulted in collapse of the mutiplets at δ 4.42 and 3.71, giving essentially a double doublet (J_{12} = 3.2 and 8.7 Hz) and a double doublet (J_{45} = 2.6 and 6.7 Hz), respectively. EIMS (*m*/*z*): 211 (M^+ − 1), 197 (M^+ − CH_3), 173 (M^+ − C_3H_3), 129, 125, 100, 87 (100), 67.

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Supplementary Material Available: Physical data for compounds **4b**, **5b**, **7b**, **7c**, **9b** and **9c**, **10b** and **10c**, **12b**, **12c**, **13b**, **13c**, and **15** as well as reproductions of ^1H NMR spectra of compounds **6b**, **7b**, **7c**, **8b**, **8c**, **14**, and **15** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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