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Preparation of chiral propargylic alcohols from α,β-unsaturated esters

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Abstract—A series of chiral propargylic alcohols with high enantiomeric excess was prepared by asymmetric dihydroxylation of α,β-unsaturated esters, conversion of the diols to 4-(chloromethyl)-1,3-dioxolane intermediates, and base-induced elimination.

Chiral propargylic alcohols are widely used synthons for many natural products.[1] Among the methods for preparing chiral propargylic alcohols are addition of organometallic reagents to α,β-acetylenic aldehydes in the presence of chiral ligands,[2] enantioselective aldol additions to α,β-ynals,[3] asymmetric reduction of α,β-ynones,[4] enzymatic resolution,[5] base-mediated double elimination of substrates [1-chloro-2,3-epoxy[6] and 4-(chloromethyl)-1,3-dioxolane[7]], elimination of chiral vinyl sulfoxides,[8] alkynylation of aldehydes catalyzed by a chiral ligand,[9] and reductive cleavage of α,β-alkynyl acetals.[10] However, some of these methods provide low enantiomeric excess (ee), especially for the synthesis of long-chain propargylic alcohols. For example, Alpine-Borane reduction of a long-chain ynone gave the *E* analog of **1a** in only 60–65% ee.[11] Furthermore, when we used ynone reduction ($LiAlH_4$ in the presence of Darvon alcohol[4a] or (*R*)-Alpine-Borane[4b]) to prepare **1c** (an important synthon for ceramide synthesis), an unsatisfactory optical purity (<80% ee) was obtained. Since it is well known that α,β-unsaturated esters are excellent substrates for the asymmetric dihydroxylation (AD) reaction (giving high yield and very high ee),[12] we have developed a new method for the preparation of 4-(chloromethyl)-1,3-dioxolane intermediates from α,β-unsaturated esters. These dioxolane intermediates are easily converted to chiral propargylic alcohols via double elimination. The configuration at C-3 of the product is established during the AD reaction and remains intact in this reaction sequence. We demonstrate here the utility of this method by preparing a series of representative propargylic alcohols **1a–e** (Scheme 1) in high chiral purity.

The Horner–Wadsworth–Emmons (HWE) reaction of aldehydes with a phosphonate reagent provides α,β-unsaturated esters.[13] Compounds **2a**,[14] **2c**,[15] and **2d** were prepared via HWE reaction of the aldehydes with $(i\text{-PrO})_2P(O)CH_2CO_2Et$. Compound **2e** was synthesized as previously described.[16]

Compound **1a** is the *Z* analog of eicos-(4*E*)-en-1-yn-3-ol. The *E* isomer, which was isolated from a marine sponge, has been synthesized;[11,17] it exhibits immunosuppressive and antitumor activities.[18] Analog **1a**, which may be useful for establishing structure–function relationships, was obtained in geometrically pure form by the reaction sequence illustrated in Scheme 2. The AD reaction of α,β-unsaturated esters **2b–e** provided diols **3b–e** in high yield (~90%). However, diol **3a** was obtained in low yield under the normal AD reaction conditions. The yield of **3a** was markedly improved (to 80%) by supplementation of the reaction mixture with additional osmium reagent ($K_2OsO_4{\cdot}2H_2O$) and chiral ligand [$(DHQ)_2$-PHAL]. After conversion of diol **3a** to acetonide ester **4a**, reduction with DIBAL-H provided alcohol **5a** in 92% yield (two steps from **3a**). Reduction of **5a** with Lindlar catalyst in MeOH provided cis compound **6a**, which was converted to chloride **7a** (NCS, Ph_3P).[19] (*Z*)-Alcohol **1a** was obtained by treatment of **7a** with *n*-BuLi in the presence of HMPA[7] (81% yield, 96% ee).[20] Application of the method used to prepare alcohol **1a** also afforded **1b–e** with high ee (Scheme 1).[21]

Keywords: asymmetric dihydroxylation; propargyl secondary alcohols.

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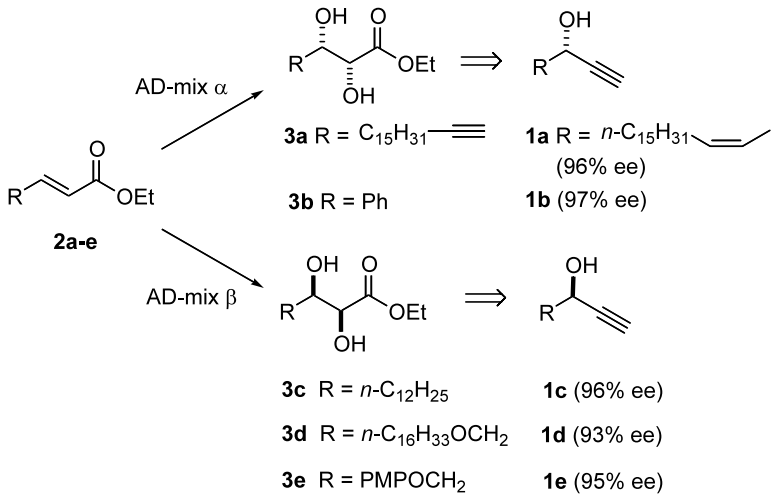
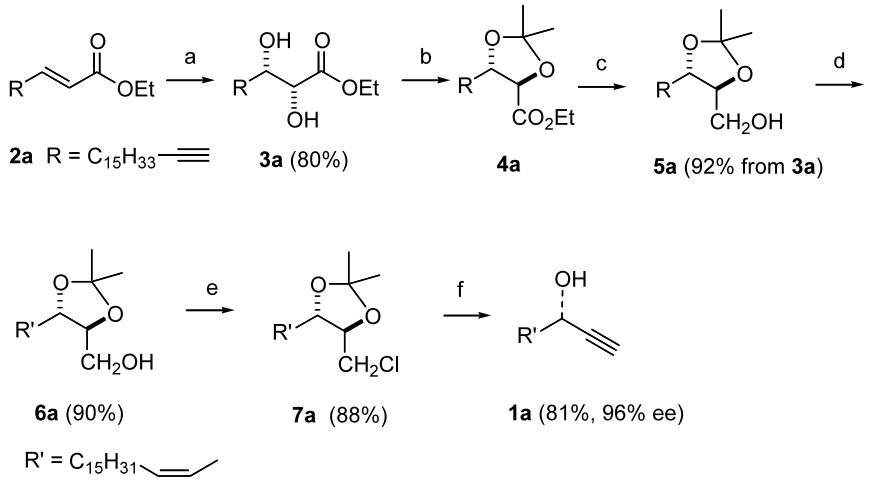


Scheme 1. Outline of the preparation of chiral alcohol **1** from ester **2**.



Scheme 2. Representative example of the conversion of ester **2a** to alcohol **1**. *Reagents and conditions*: (a) AD-mix-α (more $K_2OsO_4{\cdot}2H_2O$ and $(DHQ)_2$-PHAL were added), $MeSO_2NH_2$, *t*-BuOH/H_2O 1:1, rt; (b) $Me_2C(OMe)_2$, *p*-TsOH, CH_2Cl_2, rt; (c) DIBAL-H, THF, 0°C–rt; (d) H_2, Pd-$CaCO_3$ (cat.), MeOH, rt; (e) NCS, Ph_3P, CH_2Cl_2, 0°C–rt; (f) *n*-BuLi, HMPA, THF, –42°C–rt.

In summary, we have developed an efficient method that affords both *R* and *S* propargylic alcohols in high ee. AD reaction of an α,β-unsaturated ester with either AD-mix α or β, followed by acetonide formation, DIBAL-H reduction, conversion of the resultant primary alcohol to 4-(chloromethyl)-1,3-dioxolane, and elimination with *n*-BuLi in the presence of HMPA gave chiral propargylic alcohols **1a**–**e** in high ee.

Acknowledgements

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21. **Compound 1a**: mp 32.5–33.0°C, $[\alpha]_D^{25}$ +76.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J=6.4$ Hz), 1.10–1.60 (m, 26H), 2.03 (s, 1H), 2.11 (m, 2H), 2.49 (d, 1H, $J=2.2$ Hz), 5.14 (m, 1H), 5.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 27.6, 29.2, 29.3, 29.4, 29.5, 29.6, 27.7, 32.0, 58.0, 72.9, 84.1, 128.7, 134.1; HR-MS [DEI, M^+] m/z calcd for $C_{20}H_{36}O$ 292.2766, found 292.2761. **Compound 1b**: $[\alpha]_D^{25}$ −28.0 (*c* 1.0, $CHCl_3$) (lit.[8] $[\alpha]_D^{21}$ −26.7 (*c* 1.5, $CHCl_3$); Fluka catalog: $[\alpha]_D^{20}$ −28 (*c* 3.2, $CHCl_3$)). **Compound 1c**: mp 40.0–41.0°C; $[\alpha]_D^{25}$ +2.60 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J=6.6$ Hz), 1.20–1.60 (m, 20H), 1.72 (m, 2H), 2.41 (br s, 1H), 2.44 (d, 1H, $J=3.7$ Hz), 4.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 25.1, 29.3, 29.5, 29.62, 29.69, 29.7, 32.0, 37.6, 62.3, 72.8, 85.1; HR-MS [DCI, MH^+] m/z calcd for $C_{15}H_{29}O$ 225.2218, found 225.2211. **Compound 1d**: mp 46.0–47.0°C; $[\alpha]_D^{25}$ +6.96 (*c* 2.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J=6.6$ Hz), 1.20–1.40 (m, 26H), 1.57 (m, 2H), 2.44 (d, 1H, $J=2.2$ Hz), 2.57 (d, 1H, $J=4.8$ Hz), 3.52 (m, 3H), 3.60 (m, 1H), 4.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 26.0, 29.3, 29.45, 29.53, 29.60, 29.62, 29.69, 29.7, 31.9, 61.4, 71.8, 73.6, 74.0, 81.7; HR-MS [DCI, MNH_4^+] m/z calcd for $C_{20}H_{42}NO_2$ 328.3216, found 328.3216. **Compound 1e**: mp 50.0–51.0°C (lit.[5a] mp 52–53°C); $[\alpha]_D^{25}$ +28.6 (*c* 1.0, $CHCl_3$). The NMR spectra of **1b** and **1e** were in full accordance with the literature data.