

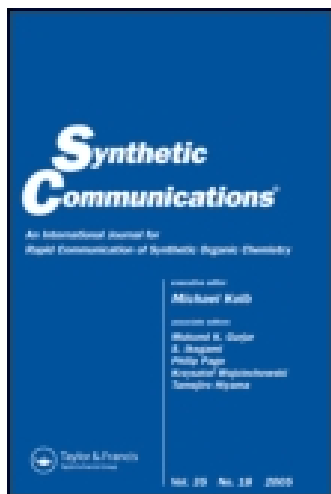
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Stereospecific Syntheses of Chiral Epoxides Bearing 1,4-Diyne or 1,4-Enyne Unit Via Alkylative Epoxide Rearrangement

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ABSTRACT

Stereospecific syntheses of a series of chiral epoxides bearing the 1,4-diyne or 1,4-enyne unit were achieved through alkylative epoxide rearrangement, which proceeded in two steps: 1) coupling of epoxy tosylate with alkynyltrifluoroborate; and 2) ring-closure of the resulting intermediate.

Key Words: Alkylative epoxide rearrangement; 1,4-Diyne; 1,4-Enyne; Chiral epoxides; Stereospecific synthesis.

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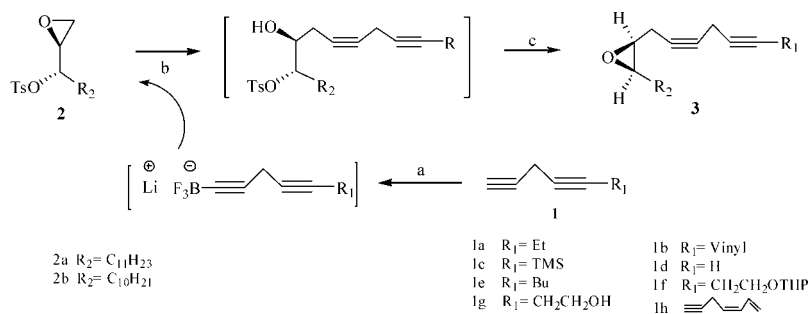
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Optically active epoxides are an important class of natural products encountered as sex pheromones of Lepidopteran pests^[1] and self-defensive substances against rice blast disease.^[2] Most reported syntheses of chiral epoxides involved Sharpless asymmetric epoxidation^[3] or Payne rearrangement.^[4] In pioneering studies,^[5] Bell and Ciaccio have demonstrated that alkylative epoxide rearrangement is a remarkably efficient method for the synthesis of internal epoxides. Noteworthy, the method has a strategic synthetic advantage over Payne rearrangement and complements Sharpless asymmetric epoxidation.^[5b] To our knowledge, however, alkylative epoxide rearrangement performed on 1,4-diyne or 1,4-enyne has not been defined with the exception of 1,4-heptdiyne due to their susceptibility to the basic conditions. As part of our current research program was directed toward the total synthesis of sex pheromonal components of *Hyphantria cunea* (Drug),^[6] we sought to explore a method for the synthesis of chiral epoxides bearing 1,4-diyne or 1,4-enyne unit. In the end, we attempted to extend the scope of an alkylative epoxide rearrangement process to a range of 1,4-diyne and 1,4-enynes. Herein, we present the results and the synthesis of chiral epoxides bearing the 1,4-diyne or 1,4-enyne unit.

As shown in Sch. 1, the alkylative epoxide rearrangement process proceeded in two steps. Alkynyltrifluoroborate salt, readily generated in situ by the addition of $\text{BF}_3 \cdot \text{OEt}_2$ to alkynyllithium of **1**, mediated the regioselective C-O ring cleavage of epoxy tosylate $(2S,3S)$ -**2** to afford the ring-opening intermediate, and this intermediate could be used directly in the next ring-closure reaction under the basic conditions to furnish **3**.

Our initial experiments in alkylative epoxide rearrangement involved the use of 1,4-heptdiyne **1a**, with which the coupling of $(2S,3S)$ -**2a** proceeded



Scheme 1. Coupling of various 1,4-diyne and 1,4-enyne with $(2S,3S)$ -**2** via alkylative epoxide rearrangement. Reagents and conditions: a) *n*-BuLi, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, -78°C , 30 min; b) **2**, THF, -78°C , 3 h; c) K_2CO_3 , CH_3OH , rt., 30 min.

smoothly and afforded the desired chiral epoxide product **3a** (Fig. 1) in 69% yield. In sharp contrast, the coupling of (2*S*,3*S*)-**2a** with **1b** under the similar conditions had proven abortive. Repeated attempts to modify the procedure by numerous experimental variations in base, reaction solvent, and temperature failed to furnish the product. Analysis showed that introduction of an electron-withdrawing vinyl group lead to isomerization of molecules, mainly due to deprotonation of a methylene between two triple bonds. To probe the effects of structural variations of 1,4-diyne on the course of coupling, we synthesized five additional 1,4-diyne (**1c**, **1d**, **1e**, **1f**, **1g**) and utilized them in alkylative epoxide rearrangement. As a result, **1e**, **1f**, and **1g** were coupled with (2*S*,3*S*)-**2a** to afford the desired products **3e**, **3f**, and **3g**, respectively. The TMS-protected 1,4-pentadiyne **1c** failed, and 1,4-pentadiyne **1d** bearing two terminal triple bonds afforded the mixture of two isomerizing products (**3d1**, **3d2**), which demonstrated their susceptibility to the basic conditions. In addition, 1,4-enyne **1h** was synthesized and employed in the alkylative epoxide rearrangement process. To our delight, **1h** was stable enough to endure the basic conditions and coupled with **2b** to furnish **3h** in 67% yield.

In summary, we have examined the scope of alkylative epoxide rearrangement utilizing 1,4-diyne or 1,4-enynes in the reaction, through which a series of chiral epoxides bearing 1,4-diyne or 1,4-enyne unit were successfully synthesized.

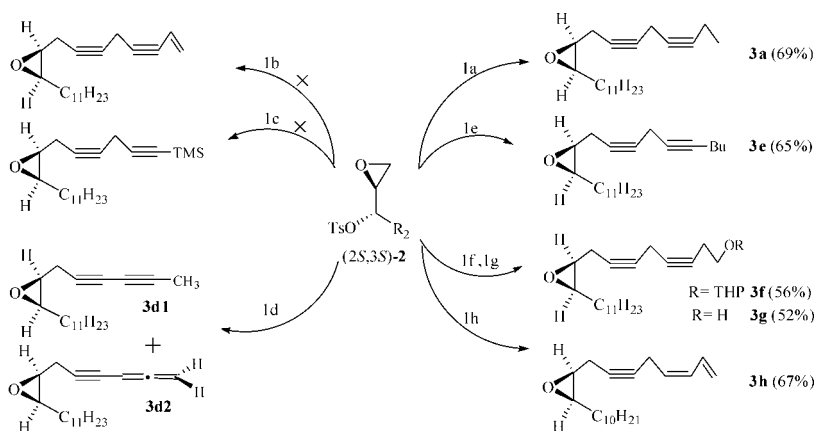


Figure 1. Results for the synthesis of chiral epoxides via alkylative epoxide rearrangement.

EXPERIMENTAL

General Methods

^1H NMR spectra were recorded on a Bruker AMX-400 spectrometer using TMS as internal standard. All the coupling constants are reported in Hz. ^{13}C NMR spectra were recorded on the same instrument, and chemical shifts were measured relative to residual solvent resonances [δ (CDCl_3) = 77.0]. The IR spectra were determined by Bruker Tensor 27 spectrometer. Mass spectra were recorded with Agilent-5973N instrument. High-resolution mass spectra were obtained on a Micromass UK GCT-MS instrument with EI ionization methods. The optical rotations were determined for solutions in CHCl_3 at 25°C by using a Perkin-Elmer Model 241-Mc automatic polarimeter. Melting points were determined on a Yanagimoto apparatus and were uncorrected. Compounds (2*S*,3*S*)-**2a** and (2*S*,3*S*)-**2b** were prepared according to the reported methods.^[7] 1,4-Diyne and 1,4-enyne **1a–1h** were synthesized based on the general procedures described in the literature.^[8] Anhydrous THFs were freshly distilled under N_2 from Na/benzophenone. Purification of products was performed by flash column chromatography on silica gel (200–300 mesh).

Typical Procedure for the Preparation of Chiral Epoxides Bearing 1,4-Diyne or 1,4-Enyne Unit Via Alkylative Epoxide Rearrangement

(*Z*,9*S*,10*R*)-**9,10-Epoxyicosa-1,3-dien-6-yne (3h)**. To a solution of **1h** (276 mg, 3 mmol) in 15 mL of anhydrous THF was added dropwise at -78°C a solution of 2.5 M *n*-BuLi in hexane (1 mL, 2.5 mmol) by syringe. The resulting dark green solution was stirred for 15 min, and then $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.31 mL, 2.5 mmol) was added via syringe. After another 15 min, a solution of **2b** (368 mg, 1 mmol) in 4 mL of THF was added also by syringe, and the reaction mixture was stirred for 3 h at -78°C . After addition of 10 mL of saturated aqueous NH_4Cl , the aqueous layer was extracted with ether (10 mL \times 2). The combined organic layer was dried over anhydrous Na_2SO_4 , and the concentration afforded a brown residue. This crude sample was redissolved in anhydrous methanol (10 mL), and 400 mg anhydrous K_2CO_3 was added with vigorous stirring at room temperature. After 30 min, reaction mixture was filtered. Concentration of the filtrate and purification by flash chromatography (Hexane : ether, 10 : 1) afforded the product **3h** (200 mg, 67% in two steps) as a colorless oil, which solidified at room temperature. $[\alpha]_{\text{D}}^{25} = 20.5$ ($C = 1$, CHCl_3); IR (neat) ν 3086, 3030,

2925, 2285 (weak), 1645, 1595 cm^{-1} ; ^1H NMR (CDCl_3) δ 6.63 (ddd, $^3J_{\text{trans}} = 16.8$, $^3J_{\text{cis}} = 10.2$, $^3J = 10.7$, 1H, $\text{CH}=\text{CHCH}=\text{CH}_2$), 6.04 (t, $^3J = ^3J_{\text{cis}} = 10.7$, 1H, $\text{CH}=\text{CHCH}=\text{CH}_2$), 5.44 (dt, $^3J_{\text{cis}} = 10.7$, $^3J = 7.2$, 1H, $\text{CH}=\text{CHCH}=\text{CH}_2$), 5.24 (d, $^3J_{\text{trans}} = 16.8$, 1H, $\text{CH}=\text{CHCH}=\text{CHH}$), 5.16 (d, $^3J_{\text{cis}} = 10.2$, 1H, $\text{CH}=\text{CHCH}=\text{CHH}$), 3.06 ~ 3.12 (m, 3H, $\text{HC}\equiv\text{CCH}_2\text{C}=\text{CH}$, oxirane CH), 2.95 (dt, $J = 4.2$, 5.5, 1H, oxirane CH), 2.52 ~ 2.58 (ddt, $^2J = 17$, $^3J = 5.5$, $^5J = 2.7$, 1H, $\text{C}\equiv\text{CCHHCH}(\text{O})\text{CH}$), 2.22 ~ 2.28 (ddt, $^2J = 17$, $^3J = 7.2$, $^5J = 2.5$, 1H, $\text{C}\equiv\text{CCHHCH}(\text{O})\text{CH}$), 1.56 (br, m, 2H, $\text{CH}(\text{O})\text{CHCH}_2$), 1.26 (br, s, 16H, $(\text{CH}_2)_8$), 0.88 (t, $J = 6.6$, 3H, CH_3); ^{13}C NMR (CDCl_3) δ 131.3, 130.2, 126.5, 118.5, 79.8, 75.4, 57.1, 55.2, 31.9, 29.7, 29.6, 29.5, 29.3, 27.5, 26.5, 22.7, 18.8, 17.6, 14.1; MS (m/z) 288 (M^+ , 1), 273 (2), 259 (2), 161 (11), 147 (31), 133 (37), 107 (87), 91 (100), 79 (65), 67(44); HRMS (m/z) calc. for $\text{C}_{20}\text{H}_{32}\text{O}$ 288.2453, found 288.2450.

Compounds **3a**, **3e**, **3f**, and **3g** were prepared in the same manner to that described above.

(9S,10R)-9,10-Epoxyhenicos-3,6-diyne (3a). A colorless oil that solidified at room temperature (208 mg, 69%), $[\alpha]_{\text{D}}^{25} = 22.5$ ($\text{C} = 1$, CHCl_3), lit. $[\alpha]_{\text{D}}^{23} = 52.2$ ($\text{C} = 3.6$, CCl_4)^{5b}; IR (neat) ν 2920, 2210 (weak) cm^{-1} ; ^1H NMR (CDCl_3) δ 3.09 ~ 3.14 (m, 3H, $\text{C}\equiv\text{CCH}_2\text{C}\equiv\text{C}$, oxirane CH), 2.95 (dt, $J = 4.5$, 5.5, 1H, oxirane CH), 2.25 and 2.56 (2m, 2H, $\text{C}\equiv\text{CCH}_2\text{CH}(\text{O})\text{CH}$), 2.18 (qt, $^3J = 7.5$, $^5J = 2.3$, 2H, $\text{C}\equiv\text{CCH}_2\text{CH}_3$), 1.51 (br, m, 2H, $\text{CH}(\text{O})\text{CHCH}_2$), 1.26 (br, s, 18H, $(\text{CH}_2)_9$), 1.12 (t, $J = 7.5$, 3H, $\text{CH}_3\text{CH}_2\text{C}\equiv\text{C}$), 0.88 (t, $J = 6.9$, 3H, CH_3); ^{13}C NMR (CDCl_3) δ 81.9, 76.6, 75.2, 73.2, 60.0, 54.9, 31.8, 29.6, 29.5, 29.3, 27.5, 26.4, 22.6, 19.5, 18.7, 14.0, 13.8, 12.3, 9.6; MS (m/z) 302 (M^+ , 0.8), 301 (2), 287 (4), 273 (9), 147 (86), 133 (100), 119 (60), 105 (80), 91 (94), 67 (72); HRMS (m/z) calc. for $\text{C}_{21}\text{H}_{34}\text{O}$ 302.2601, found 302.2608.

(11S,12R)-11,12-Epoxytricos-5,8-diyne (3e). A colorless oil that solidified below room temperature (214 mg, 65%), $[\alpha]_{\text{D}}^{25} = 23.3$ ($\text{C} = 1$, CHCl_3); IR (neat) ν 2930, 2213 (weak) cm^{-1} ; ^1H NMR (CDCl_3) δ 3.09 ~ 3.13 (m, 3H, $\text{C}\equiv\text{CCH}_2\text{C}\equiv\text{C}$, oxirane CH), 2.94 (dt, $J = 4.6$, 5.4, 1H, oxirane CH), 2.25 and 2.55 (2m, 2H, $\text{C}\equiv\text{CCH}_2\text{CH}(\text{O})\text{CH}$), 2.15 (tt, $^3J = 7.0$, $^5J = 2.4$, 2H, $\text{C}\equiv\text{CCH}_2\text{CH}_2$), 1.51 (br, m, 2H, $\text{CH}(\text{O})\text{CHCH}_2$), 1.26 (br, s, 22H, $(\text{CH}_2)_{11}$), 0.89 (m, 6H, $(\text{CH}_3)_2$); ^{13}C NMR (CDCl_3) δ 80.7, 76.8, 75.3, 73.8, 57.1, 55.1, 31.9, 30.8, 29.6, 29.5, 29.4, 29.3, 27.5, 26.5, 22.7, 21.9, 18.7, 18.4, 14.1, 13.6, 9.7; HRMS (m/z) calc. for $\text{C}_{23}\text{H}_{38}\text{O}$ 330.2923, found 330.2922.

2-((9S,10R)-9,10-Epoxyhenicos-3,6-diynoxy)-tetrahydro-2H-pyran (3f). A colorless oil (225 mg, 56%), $[\alpha]_{\text{D}}^{25} = 14.2$ ($\text{C} = 1$, CHCl_3); IR (neat) ν 2930, 2220 (weak), 1120, 1030 cm^{-1} ; ^1H NMR (CDCl_3) δ 4.64 (t, $J = 2.8$, 1H, OCHO), 3.53 and 3.85 (2m, 4H, $(\text{OCH}_2)_2$), 3.09 ~ 3.14 (m, 3H, $\text{C}\equiv\text{CCH}_2\text{C}\equiv\text{C}$, oxirane CH), 2.95 (dt, $J = 4.5$, 5.5, 1H, oxirane CH), 2.25

and 2.55 (2m, 2H, C≡CCH₂CH(O)CH), 2.45 (m, 2H, C≡CCH₂CH₂OTHP), 1.5 ~ 1.8 (m, 8H, CH(O)CHCH₂, (CH₂)₃), 1.26 (br, s, 18H, (CH₂)₉), 0.88 (t, J = 6.4, 3H, CH₃); ¹³C NMR (CDCl₃) δ 98.7, 75.4, 75.1, 71.8, 68.5, 65.7, 62.2, 57.1, 55.0, 31.9, 30.5, 29.7, 29.6, 29.5, 29.4, 29.3, 27.5, 26.4, 25.4, 22.6, 20.1, 19.4, 18.7, 14.1, 9.7; HRMS (m/z) calc. for C₂₆H₄₂O₃ 402.3134, found 402.3136.

(9S,10R)-9,10-Epoxyhenicos-3,6-diyne-1-ol (3g). A white solid (165 mg, 52%), mp 48 ~ 50°C; [α]_D²⁵ = 23.5 (C = 1, CHCl₃); IR (KBr) ν 3393, 2930, 2280 (weak) cm⁻¹; ¹H NMR (CDCl₃) δ 3.71 (t, J = 6.2, 2H, CH₂OH), 3.15 (m, 2H, C≡CCH₂C≡C), 3.11 (dt, J = 5.5, 1.6, 1H, oxirane CH), 2.95 (dt, J = 4.5, 5.5, 1H, oxirane CH), 2.29 and 2.52 (2m, 2H, C≡CCH₂CH(O)CH), 2.45 (tt, ³J = 6.2, ⁵J = 2.3, 2H, C≡CCH₂CH₂OH), 1.51 (m, 2H, CH(O)CHCH₂CH₂), 1.26 (br, s, 18H, (CH₂)₉), 0.88 (t, J = 6.6, 3H, CH₃); ¹³C NMR (CDCl₃) δ 77.1, 76.3, 76.2, 75.7, 61.1, 57.1, 55.0, 31.9, 29.6, 29.5, 29.4, 29.3, 27.5, 26.4, 23.1, 22.7, 18.7, 14.1, 9.8; HRMS (m/z) calc. for C₂₁H₃₄O₂ 318.2559, found 318.2553.

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