Stereocontrolled Synthesis of Unsaturated Halohydrins from Unsaturated Epoxides

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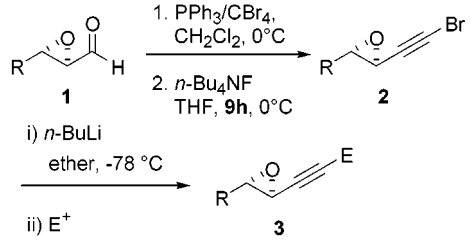
The regioselective opening of epoxides is a matter of continuous synthetic interest.[1] In our studies of syntheses of marine natural products[2] we considered enantiomerically enriched 1-alkyne-2,3-epoxides as possible alternative synthons[3] from suitable 2,3-epoxy alcohols[1] for the synthesis of substituted cyclic ethers.[4] On the other hand, halohydrins are frequently found in compounds isolated from marine sources.[5] They may also be synthesized by the opening of epoxides.[6]

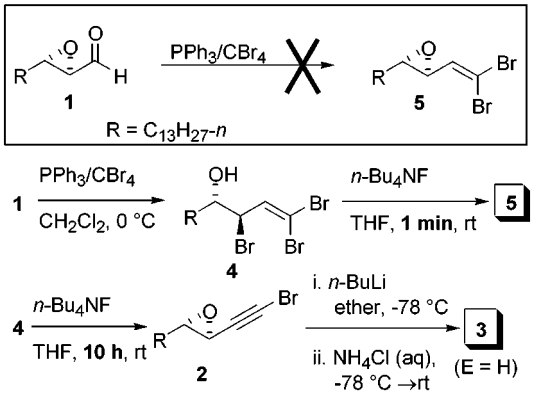
Syntheses of alkynes from aldehydes with homologation of one carbon, via 1,1-dibromo-1-alkenes, developed by McKelvie et al.[7] and further extended by Corey and Fuchs,[8] are unsuitable for the synthesis of the epoxyalkyne system since the strongly basic conditions of the method destroy the oxirane ring. Nicolaou et al.[9] have used *n*-Bu_4NF to give a terminal bromo-alkyne (Scheme 1) that could exchange bromine with electrophiles after treatment with *n*-BuLi.[10] The addition of Et_3N suppresses side reactions giving reproducible results in the transformation of aldehydes into 1,1-dibromo-1-alkenes.[10d−f]

When we submitted the epoxy aldehyde **1** (R = $C_{13}H_{27}$-*n*)[11] to PPh_3 and CBr_4,[12] the ensuing less polar product with *n*-Bu_4NF in THF gave almost instantly and cleanly

Scheme 1. Synthesis of 2,3-Epoxy-1-alkynes from 2,3-Epoxy Aldehydes



Scheme 2. Intermediates in the Formation of 3,4-Epoxy Alkynes



a substance **4** that was treated with *n*-BuLi at −78 °C. In the irresolvable product mixture we were unable to identify traces of the epoxy alkyne **3** (E = H). Interestingly, we found that simply with a longer treatment with *n*-Bu_4NF (ca. 10 h at room temperature) a substantial amount of **3** was obtained.

A detailed study of the process showed that aldehyde **1**, with PPh_3 and CBr_4, formed almost quantitatively the bromohydrin **4** (Scheme 2).[10d] Treatment of **4** with *n*-Bu_4NF afforded the epoxide **5** almost instantly. However, when the treatment with fluoride was extended for a longer period, the bromide elimination was almost completed, and a high yield of **2** was obtained. The consecutive treatment with *n*-BuLi at low temperature and immediate quenching with aqueous NH_4Cl provided the epoxy alkyne **3** (E = H) in good yield. In any case, we were unable to isolate **5** directly from **1** using the PPh_3/CBr_4 mixture.

The formation of the bromohydrin **4** is stereospecific and highly regioselective.[13] A few examples are outlined in Table 1. In all cases, except those where the allylic position is tetrasubstituted (entry 3), the allylic bromide was obtained with inversion of the configuration. The use of the epoxide of cinnamyl alcohol produced an inseparable mixture of products (entry 5). When the halohydrins **7** were treated with fluoride, only one diastereoisomer of **8** was obtained in each case. Additional bases, such as Et_3N (1 equiv), could also be used to perform the cyclization of the bromohydrins to the corresponding epoxides.[14]

COSY and HSQC experiments were necessary to determine the regioselectivity. We observed that the

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(11) Aldehydes **1** are easily available from the corresponding 2,3-epoxy alcohols via oxidation reactions. In this paper we used Swern's oxidation: Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482.
(12) The decomposition of 2,3-epoxy aldehydes when submitted to the PPh_3/CBr_4 mixture has been reported. See ref 10d.
(13) All the bromo-derivatives should be stored at low temperature (ca. −20 °C) since they are prone to decomposition.

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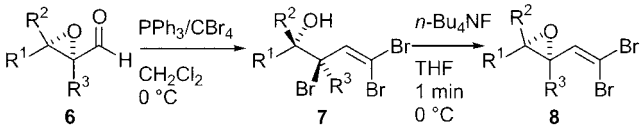
Table 1. Examples of Formation of 1,1-Dibromo-1-alkene-3-bromo-4-hydrins and 1,1-Dibromo-1-alkene-3,4-epoxides from 2,3-Epoxy Aldehydes



6 **7** **8**

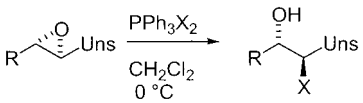
entry	6	**7** (%)[a]	**8** (%)[a]
1	$R^1 = C_{13}H_{27}$-*n* $R^2 = H$ $R^3 = H$	83	90
2	$R^1 = (CH_2)_4OTBDPS$ $R^2 = H$ $R^3 = H$	82	91
3	$R^1 = C_6H_{13}$-*n* $R^2 = H$ $R^3 = CH_3$	—[b]	—[b]
4	$R^1 = C_6H_{13}$-*n* $R^2 = CH_3$ $R^3 = H$	83	91
5	$R^1 = Ph$ $R^2 = H$ $R^3 = H$	—	—

[a] Yield obtained after chromatographic purification. [b] Without Et_3N the reaction gave an unresolvable mixture. When this reagent was used, the epoxide was the obtained compound

chemical shift in ^1H NMR experiments corresponding to the hydroxylic group remained almost unaffected under concentration changes. We speculated with the formation of a hydrogen bond with the vicinal halide.[15] The assignment of the signal corresponding to such a proton was essential for the structural determination and was clearly stablized by acetylating the corresponding halohydrins.[16]

The fact that the bromohydrins were obtained by attack of the bromide in the allylic position prompted us to speculate over the possibility of using Ph_3P/Br_2 as a convenient reagent to obtain bromohydrins regioselectively from unsaturated epoxides.[17] As shown in Table 2, the reaction is quite general in terms of the kind of unsaturation, nucleophilic (entry 2) and electrophilic (entry 1) olefins and alkynes (entry 3) being valid. Interestingly, the procedure was also valid to form chlorohydrin when commercially available Ph_3PCl_2 was used (entry 5).[18] As above, the use of the epoxide of cinnamyl alcohol yielded an irresolvable mixture (entry 4). The reaction was also stereospecific for both bromine and chlorine since the treatment of the halohydrin with *n*-Bu_4NF or Et_3N yielded the starting enantiomeric

Table 2. Synthesis of Halohydrins from Unsaturated Epoxides



9 **10**

entry	**9**	**10** (%)
1	$R = C_{13}H_{27}$-*n* Uns = CH=$CHCO_2CH_3$-(*E*)	82[a] (X = Br)
2	$R = C_{13}H_{27}$-*n* Uns = $CH=CH_2$	91[a] (X = Br)
3	$R = C_{13}H_{27}$-*n* Uns = C≡CH	89[a] (X = Br)
4	R = Ph Uns = CH=$CHCO_2CH_3$-(*E*)	—[a]
5	$R = C_{13}H_{27}$-*n* Uns = CH=$CHCO_2CH_3$-(*E*)	82[b] (X = Cl)

[a] The reagent was prepared by mixing Ph_3P and Br_2. [b] Using commercially available Ph_3PCl_2.

epoxides. However, when an equimolecular mixture of PPh_3/I_2 was used, the opening reaction was also completely regioselective, but a 1:1 mixture of the epimeric mixture at the halide position was obtained even at temperature lower than −20 °C.[19]

Although it is known that the use of Zn with Ph_3P/CBr_4 prevents the formation of Ph_3PBr_2 by formation of $ZnBr_2$,[8,10d] in our case even after adding a stoichiometric amount of that metal a substantial amount of the bromohydrin **4** was produced. Actually we observed that the treatment of **9** ($R = C_{13}H_{27}$-*n*; Uns = $CH=CH_2$) with $ZnBr_2$ produced a considerable amount of the corresponding bromohydrin, albeit slowly. Analogously, although it is recommended to use at least 2 equiv of PPh_3 for each equivalent of CBr_4 to avoid the formation of Br_2,[8] we observed that even using a 1.5:1 ratio (PPh_3:CBr_4) the formation of the corresponding bromohydrin was complete.

In summary, we have described new insights into a known reaction, rendering it more reliable and reproducible. In addition, we have developed a new procedure for the stereocontrolled synthesis of enantiomerically enriched unsaturated halohydrins. The application of such methodology to the synthesis of halogenated marine compounds is under study in our laboratory and will be published in due course.

Experimental Section

Materials and Methods. NMR spectra were measured at 400 or 300 MHz (^1H) and 75 MHz (^{13}C), and chemical shifts are reported relative to internal Me_4Si ($\delta = 0$). Optical rotations were determined for solutions in chloroform or carbon tetrachloride. Melting points are reported in degrees Celsius and are uncorrected. Column chromatography was performed on Merck silica gel, 60 Å and 400−500 mesh. Compounds were visualized by use of UV light and/or 2.5% phosphoromolybdic acid in ethanol stain with heating. All solvents were purified by standard techniques.[20] Reactions requiring anhydrous conditions were performed under argon. Anhydrous magnesium sulfate was used for drying solutions.

General Method To Prepare 1,1-Dibromo-1-alkene-3-bromo-4-hydrins. Preparation of (3*R*,4*S*)-1,1,3-Tribromo-1-heptadecen-4-ol (4). Aldehyde **1** was prepared from the

(14) When Et_3N was added to the Ph_3P/CBr_4 mixture,[10d] it was possible to detect by TLC the formation of the bromohydrins **7** that evolve almost simultaneously to the epoxide **8**.

(15) Blander, M.; Frurip, D. J.; Curtiss, L. A. *J. Am. Chem. Soc.* **1978**, *100*, 79−86.

(16) See Supporting Information.

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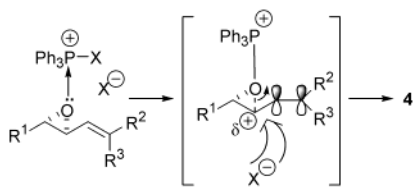
(18) This result suggests that even when using Ph_3P/CBr_4 the active species is Ph_3PBr_2. A plausible mechanism for the epoxide opening would imply an electrophilic activation of the C−O bond of the epoxide by a positive phosphorus (see ref 17):



(19) The treatment of such a mixture with TBAF yielded a 1:1 mixture of both *cis*- and *trans*-epoxides.

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known [(3*S*,2*S*)-3-tridecyloxiran-2-yl]methan-1-ol[21] by Swern oxidation[11] and used without any purification as described below.

To a stirred solution of crude aldehyde **1** (500 mg, 1.97 mmol) in CH_2Cl_2 (20 mL) was added triphenylphosphine (2.87 g, 10.8 mmol) under nitrogen at 0 °C. The mixture was additionally stirred for 10 min, and CBr_4 (1.78 g, 5.31 mmol) was added, whereupon the mixture turned dark red. The mixture was stirred for 1 h after which time TLC showed complete reaction. Then, the mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure. The resulting brown residue was purified by silica gel flash chromatography affording de 1,1-dibromo-4-hydroxy-3-bromoalkene **4** (810 mg, 83% yield) as a colorless oil: $[\alpha]^{25}_D = +99.9$ (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 5.1$ Hz, 3H), 1.25−1.55 (m, 24H), 2.26 (br s, 1H), 3.87 (m, 1H), 4.76 (dd, $J = 7.7$, 2.0 Hz, 1H), 6.79 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 22.7 (t), 25.8 (t), 29.5 (t), 31.9 (t), 33.7 (t), 57.7 (d), 74.2 (d), 95.6 (s), 133.9 (d). IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 2923, 2852, 2360, 2341, 1457. MS (FAB) *m*/*z* (relative intensity) 412 $(M - Br)^+$ (3), 317 (6), 212 (7). Anal. Calcd for $C_{17}H_{31}Br_3O$: C, 41.57; H, 6.36. Found: C, 41.29; H, 6.24.

General Method To Prepare 3,4-Epoxy-1,1-dibromo-1-alkenes. Preparation of (3*S*,4*S*)-3,4-Epoxy-1,1-dibromoheptadec-1-ene (5). To a stirred solution of **4** (486 mg, 0.99 mmol) in dry THF (10 mL) was added *n*-Bu_4NF (1.98 mL, 1 M in THF, 1.98 mmol) under nitrogen at 0 °C. The mixture was stirred for 1 min, diluted with water, and extracted with Et_2O. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual yellow oil was purified by silica gel flash chromatography to yield the 3,4-epoxy-1,1-dibromo-1-alkene **5** (365 mg, 90%) as a white solid: mp 34−36 °C; $[\alpha]^{25}_D = -15.2$ (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 6.5$ Hz, 3H), 1.25−1.62 (m, 24H), 2.91 (m, 1H), 3.33 (dd, $J = 7.7$, 1.9 Hz, 1H), 6.12 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 22.7 (t), 25.7 (t), 29.5 (t), 31.6 (t), 31.9 (t), 57.5 (d), 59.4 (d), 92.9 (s), 136.0 (d). IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 2924, 2853, 2360. MS (FAB) *m*/*z* (relative intensity) 411 $(M + 1)^+$ (18), 410 $(M)^+$ (5), 331 $(M - Br)^+$ (11), 199 (19). Anal. Calcd for $C_{17}H_{30}Br_2O$: C, 49.77; H, 7.37. Found: C, 49.41; H, 7.32.

General Method To Prepare 3,4-Epoxy-1-bromo-1-alkynes. Preparation of (3*S*,4*S*)-3,4-Epoxy-1-bromoheptadec-1-yne (2). To a stirred solution of **4**[22] (324 mg, 0.66 mmol) in dry THF (7 mL) was added *n*-Bu_4NF (1.32 mL, 1 M in THF, 1.32 mmol) under nitrogen at 0 °C. The mixture was allowed to reach room temperature and stirred for 10 h. Then the mixture was submitted to reflux for 20 min in order to complete the conversion (ca. 10%). The reaction mixture was cooled at room temperature, diluted with water, and extracted with Et_2O. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual yellow oil was purified by silica gel flash chromatography to yield the epoxy bromoalkyne **2** (176 mg, 81%) as a white solid: mp 34−36 °C; $[\alpha]^{25}_D = -7.6$ (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 6.3$ Hz, 3H), 1.25−1.55 (m, 24H), 3.1 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 22.7 (t), 25.5 (t), 29.5 (t), 31.6 (t), 31.9 (t), 44.1 (s), 45.8 (d), 60.3 (d), 76.8 (s). IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 2924, 2854, 2360, 1457. MS (FAB) *m*/*z* (relative intensity) 329 $(M)^+$ (2), 314 (8), 211 (11). Anal. Calcd for $C_{17}H_{29}BrO$: C, 62.00; H, 8.88. Found: C, 61.64; H, 8.56.

General Method To Prepare 3,4-Epoxy-1-alkynes. Preparation of (3*S*,4*S*)-3,4-Epoxyheptadec-1-yne (3). To a stirred solution of **2** (176 mg, 0.53 mmol) in dry ether (5 mL) was added dropwise *n*-BuLi (0.31 mL, 1.9 M in hexane, 0.57 mmol) under nitrogen at −78 °C. Immediately, the reaction was quenched with saturated aqueous NH_4Cl solution and the aqueous layer extracted with ether. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography affording **3** (119 mg, 89%) as a colorless oil: $[\alpha]^{25}_D = +1.8$ (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 6.1$ Hz, 3H), 1.25−1.56 (m, 24H), 2.29 (d, $J = 1.5$ Hz, 1H), 3.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 22.7 (t), 25.5 (t), 29.5 (t), 31.6 (t), 31.9 (t), 44.8 (d), 60.4 (d), 71.6 (s), 80.5 (s). IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 2924, 2090, 1645. MS (FAB) *m*/*z* (relative intensity) 249 $(M - 1)^+$ (3), 233 (7), 225 (6). Anal. Calcd for $C_{17}H_{30}O$: C, 81.54; H, 12.08. Found: C, 81.39; H, 11.78.

General Method To Prepare Unsaturated Halohydrins. Preparation of (3*R*,4*S*)-3-Bromo-1-heptadecyn-4-ol (10). To a stirred solution of triphenylphosphine (148 mg, 0.57 mmol) in dry CH_2Cl_2 (3 mL) was added bromine (91 mg, 0.57 mmol) under nitrogen at 0 °C. The mixture was stirred for 15 min after which time a solution of **3** (119 mg, 0.47 mmol) in dry CH_2Cl_2 (2 mL) was added. The mixture was stirred for 15 min, and the reaction was quenched with water. The aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography yielding the bromohydrin **10** (138 mg, 88%) as a colorless oil: $[\alpha]^{25}_D = -4.0$ (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 5.0$ Hz, 3H), 1.25−1.72 (m, 24H), 2.19 (d, $J = 4.5$ Hz, 1H), 2.71 (d, $J = 1.8$ Hz, 1H), 3.77 (m, 1H), 4.56 (dd, $J = 2.8$, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 22.7 (t), 25.6 (t), 29.5 (t), 31.9 (t), 33.7 (t), 43.0 (d), 74.2 (d), 79.1 (s). IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 2923, 2853, 1465. MS (FAB) *m*/*z* (relative intensity) 331 $(M)^+$ (2), 307 (3), 279 (12), 147 (11). Anal. Calcd for $C_{17}H_{31}BrO$: C, 61.62; H, 9.43. Found: C, 61.33; H, 9.15.

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Supporting Information Available: ^{1}H and ^{13}C NMR data for all the new compounds. In addition, specific rotations for chiral compounds and HSQC and COSY experiments for all halohydrins. This material is available free of charge at http://pubs.acs.org.

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(22) The epoxide **5** can also be used.