5-Bromopentadienal: a Versatile Intermediate for the Synthesis of Functionalized Polyenic Compounds

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5-Bromopentadienal **1b** (n = 2), easily obtained from the potassium glutaconaldehyde salt, is used as precursor of ω-bromoheptatrienal **1d**, ω-bromomethoxyhexatriene **2**, diene diols **4**, diene diones **5**, 1,6-dibromohexa-1,3,5-triene **6** and 1,8 triene diol **8**, of controlled configuration.

ω-Halogenopolyenals **1** can be considered as versatile intermediates owing to the presence of the two reactive terminal functions. However, only a few members of this class of compounds are known: 3-halogenopropenals[1] and 5-chloropentadienal **1a**.[1b]† Here we report a short synthesis of such compounds **1** (n = 2,3) and some properties of 5-bromopentadienal **1b**.

5-Halogenopentadienals **1a–c** (n = 2, X = Cl, Br, I) were prepared from the potassium salt of glutaconaldehyde (itself obtained from commercial 1-pyridinium sulfonate),[2] by reaction with thionyl chloride, triphenylphosphine bromide and triphenylphosphine iodide, respectively (Scheme 1). The halogenoaldehydes **1a–c** are isolated with good yields (67–72%) as stereoisomers 2*E*,4*E* and 2*E*,4*Z* (**1a**, 2*E*,4*E* : 2*E*,4*Z* 50 : 50; **1b**, 75 : 25; **1c**, 55 : 45). The two stereoisomers of **1b** and **1c** were quantitatively separated by flash chromatography or crystallization.‡

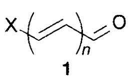
This procedure has the advantage of cheap and easy-to-handle starting materials, and permits the synthesis of halogenoaldehydes **1a–c** on a gram scale.

Condensation of ω-bromodienal **1b** (2*E*,4*E* : 2*E*,4*Z* 75 : 25) with 2-lithio-1-trimethylsiloxyethylene[3] leads to ω-bromotrienal **1d** (two isomers: all *trans* and 2*E*,4*E*,6*Z*), whereas reaction with methoxymethylene triphenylphosphorane allows the formation of 6-bromo-1-methoxyhexatriene **2** (four stereoisomers), precursor of a powerful trivinylogation reagent (Scheme 2).§

The reaction of BuLi with bromoenal **1b** (2*E*,4*E*) occurred selectively on the carbonyl function leading to the bromodienol **3a**, which was transformed easily into the dienediol **4a** by bromine—lithium exchange followed by condensation with benzaldehyde. Moreover, the transformation of **1b** into **4a** was performed in the same pot with a global yield of 55% *versus* 49% for the two-step procedure. The dienediol **4a** was oxidized with MnO_2 under very mild conditions into the 1,6-dienedione **5a** with different terminal substituents, with an 84% yield (Scheme 3).¶ Such 1,6-dienediones are important natural products[4] and intermediates in the field of carotenoids.[5]

The same type of reaction starting from **1b** (2*E*,4*Z*) enables one to obtain the diene-1,6-diol **4b** and diene-1,6-diketone **5b** without modification of the dienic configuration (Scheme 4).¶

Finally, the condensation of bromomethylene triphenylphosphorane with **1b** (2*E*,4*E*) led to the expected 1,6-dibro-



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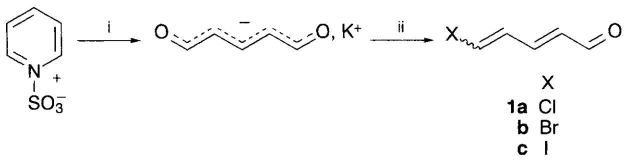
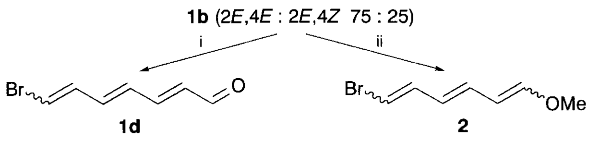
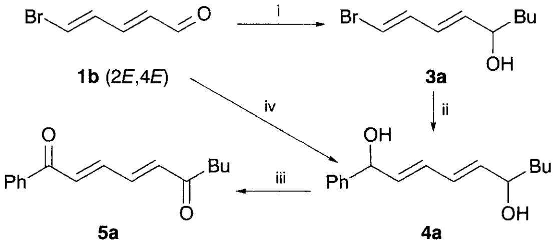


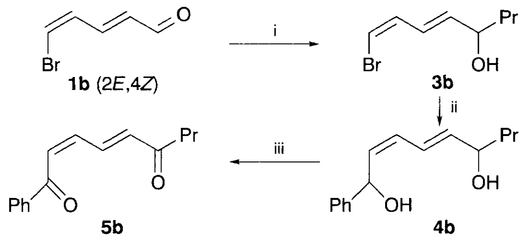
Scheme 1 *Reagents and conditions*: i, 4.1 equiv. KOH, 7.3 mol dm^{-3}, −20 °C, 1 h; then room temp., 4 h, 62%; ii, X = Cl : 1.5 equiv. $SOCl_2$, CH_2Cl_2, 0 °C then room temp., 12 h, 67%; X = Br or I: 1 equiv. Ph_3P, X_2, CH_2Cl_2, 0 °C then room temp., 12 h, X = Br, 72%; 72 h, X = I, 71%



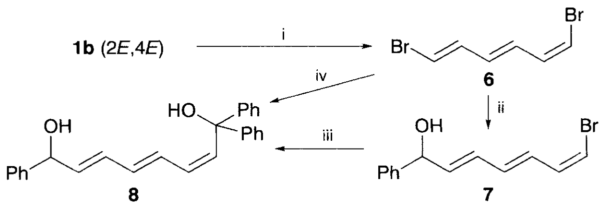
Scheme 2 *Reagents and conditions*: i, 2-lithio-1-trimethylsiloxyethylene, Et_2O, −70 °C, 0.8 equiv. **1b**, Et_2O, 5 min; −70 to 0 °C, 1 h; −70 °C, 1 mol dm^{-3} HCl then room temp., 2 h, 61%; ii, 1.2 equiv. $Ph_3P^+CH_2OMe$, Cl^-, THF, −50 °C, 1.2 equiv. Bu^tOK, 1 h; 1 equiv. **1b**, THF, −50 to 0 °C; 0 °C, 1 h; $NaHCO_3$ (5% *m*/*v*), 86%



Scheme 3 *Reagents and conditions*: i, 1.5 equiv. BuLi, Et_2O, −20 °C, 3 h; NH_4Cl (10% *m*/*v*) then room temp., 77%; ii, 2.8 equiv. Bu^tLi, Et_2O, −78 °C, 1 h; 1.8 equiv. PhCHO, Et_2O, room temp., 1 h; NH_4Cl (10% *m*/*v*), 64%; iii, 10 equiv. MnO_2, Et_2O, room temp., 12 h, 81%; iv, 1.5 equiv. BuLi, Et_2O, −20 °C, 3 h; −78 °C, 1.8 equiv. Bu^tLi, 1.5 h; 1.8 equiv. PhCHO, Et_2O, room temp., 1 h; NH_4Cl (10% *m*/*v*), 55%



Scheme 4 *Reagents and conditions*: i, 1.5 equiv. *n*PrMgBr, Et_2O, −20 °C, 3 h; NH_4Cl (10% *m*/*v*) then room temp., 74%; ii, as for ii in Scheme 3, 68%; iii, as for iii in Scheme 3, 83%



Scheme 5 *Reagents and conditions*: i, 1.2 equiv. $Ph_3P^+CH_2Br$, Br^-, THF, −50 °C, 1.2 equiv. Bu^tOK, 1 h; 1 equiv. **1b** (2*E*,4*E*), THF, −50 to 0 °C; 0 °C, 1 h; $NaHCO_3$ (5% *m*/*v*), then crystallization in pentane, 0 °C, 66% (1*E*,3*E*,5*Z*); ii, 1.8 equiv. Bu^tLi, Et_2O, −78 °C, 1.5 h; 0.8 equiv. PhCHO, Et_2O, room temp., 1 h; NH_4Cl (10% *m*/*v*), 72%; iii, 2.8 equiv. Bu^tLi, Et_2O, −78 °C, 1.5 h; 0.8 equiv. Ph_2CO, Et_2O, room temp., 1 h; NH_4Cl (10% *m*/*v*), 51%; iv, 1.8 equiv. Bu^tLi, Et_2O, −78 °C, 1.5 h; 0.8 equiv. PhCHO, Et_2O, 0 °C, 1 h; −78 °C, 1.8 equiv. Bu^tLi, Et_2O, −78 °C, 1.5 h; 0.8 equiv. Ph_2CO, Et_2O, 0 °C, 1 h; NH_4Cl (10% *m*/*v*), 29% (not optimized)

mohexa-1,3,5-triene **6** (1*E*,3*E*,5*Z*: 1*E*,3*E*,5*E* 80 : 20). The bromine–lithium exchange from the separated major isomer of **6** (1*E*,3*E*,5*Z*) occurs exclusively on the bromine atom of the *E* double bond, giving, after condensation with benzaldehyde, the bromoalcohol **7**. A second bromine–lithium exchange from **7** followed by condensation with benzophenone led to the diol **8** which was also obtained from **6** in a one-pot reaction (Scheme 5). It is noteworthy that the central pattern of **8** (2*E*,4*E*,6*Z*) is the same as that of leukotriene LTB4.‖

Further studies with haloaldehydes **1** and dibromohexatriene **6** are in progress.[6]

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Footnotes

† 5-Chloropentadienal **1a** has been obtained by reaction of phosgene with the sodium salt of glutaconaldehyde.[1b] Some homologous compounds with substituents on the polyenic chain have been reported.[7]

‡ Pure bromopentadienal **1b** (2*E*,4*E*) and pure bromopentadienal **1b** (2*E*,4*Z*) slowly equilibrate in $CDCl_3$ to a 1 : 1 mixture of the two isomers.

§ The lithio derivative of **2** obtained after bromine–lithium exchange allows the transformation of carbonyl compounds into trienals in one step, with an all-*trans* configuration when starting from aldehydes, whatever the configuration of the starting bromoenol ether **2**.[8]

¶ Whereas the *E*,*E* configuration of **3a**–**5a** and the *Z*,*E* configuration of **3b**–**5b** are well established, the diastereoisomeric composition of intermediate diols **4a** and **4b** was not determined.

‖ Many syntheses of LTB4 have been reported since the first synthesis by Corey *et al.*,[9,10] but none of them had the three double bonds being introduced at once.

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