Crystallographic analysis of $\mathbf{5}\cdot 12\,NO_3$: colorless prisms of $\mathbf{5}\cdot 12\,NO_3$ were grown by diffusion of diethyl ether into a solution of the complex in water/methanol for two weeks at room temperature. A single crystal of dimensions $0.40\times 0.20\times 0.10$ mm was coated with a sealing material and mounted on a glass fiber. All measurements were made on a Rigaku RAXIS II imaging plate area detector with graphite-monochromated $Mo_{K\alpha}$ radiation. The data were collected at 173 K. Crystal data for $\mathbf{5}\cdot 12\,NO_3$: $C_{84}H_{96}N_{48}O_{36}Pd_6\cdot 4\,H_2O$, $M_r = 3064.44$, triclinic, space group $P\bar{1}$, $a = 20.17(1)$, $b = 22.73(1)$, $c = 19.17(1)$ Å, $\alpha = 95.68(5)$, $\beta = 98.70(2)$, $\gamma = 113.47(2)^\circ$, $V = 7845(8)$ Å^3, $\rho_{calcd} = 1.297$ g cm^{-3}, $Z = 2$, $F(000) = 3080$, $\mu(Mo_{K\alpha}) = 7.51$ cm^{-1}, $\lambda(Mo_{K\alpha}) = 0.71070$ Å; 18566 reflections measured, 15736 observed ($I > 3.50\sigma(I)$); number of variables 1460; $R1 = 0.133$; $wR2 = 0.179$.[13]

Received: March 24, 1998 [Z 11631 IE]
German version: *Angew. Chem.* **1998**, *110*, 2192 – 2196

Keywords: metallacycles · molecular recognition · N ligands · palladium · supramolecular chemistry

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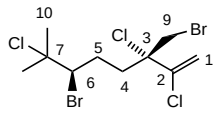
[13] Further details on the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository numbers CSD-408575, CSD-408576, and CSD-408577.

Total Synthesis of (±)-Halomon by a Johnson – Claisen Rearrangement**

Thierry Schlama, Rachid Baati, Véronique Gouverneur, Alain Valleix, John R. Falck, and Charles Mioskowski*

The antitumor agent halomon (**1**) has generated enormous interest owing to its unique mode of action that allows it to display differential cytotoxicity against various tumor cell lines.[1] Details of its discovery and structural characterization have been reported;[2] however, further elucidation of its atypical biological activity has been hampered by the limited amount of naturally occuring halomon that can be extracted from the red alga *Portieria hornemannii* and by the synthetic challenge posed in creating such a polyhalogenated molecule. A total synthesis is, consequently, needed to establish the basis for generating a wide range of analogues to expedite the structure and activity assessment of this novel class of anticancer agents.



1 halomon

The clearest chemical challenge posed by a total synthesis of **1** is the fashioning of the chlorinated tertiary carbon atom C_3 bearing the α-chlorovinyl group. A further complication is the regiospecificity in the introduction of the bromine and chlorine atoms on C_6 and C7, respectively. Herein, we disclose the first total synthesis of halomon featuring as key steps two novel chemical transformations to address these synthetic problems.

Current methodologies for the construction of tertiary chlorinated carbons such as C_3 involve either β-elimination of

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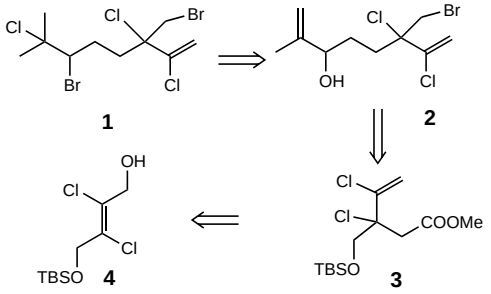
[**] This work was financially supported by Rhône – Poulenc (fellowship to T.S.), National Institutes of Health (NIHGM.31278 to J.R.F.), and NATO (CRG.971096 to C.M.). We are grateful to Dr. M. Boyd of the National Cancer Institute for a generous gift of natural halomon.

  1433-7851/98/3715-2085 $ 17.50+.50/0

a polyhalogenated compound[3] or chlorination of the corresponding allene.[4] Unfortunately, both these methods involve precursors that are not readily accessible, and they also suffer from very low selectivities and yields. In our retrosynthetic plan (Scheme 1), we reasoned that such a tertiary chlorinated carbon atom can be formed by a [2,3]- or [3,3]-sigmatropic rearrangement of a dichlorinated alkene. This approach also provides a general method for generating different halogenated analogues by varying the substitution of the starting alkene. We chose a route with compounds **2** and **3** as intermediates in the total synthesis of halomon.

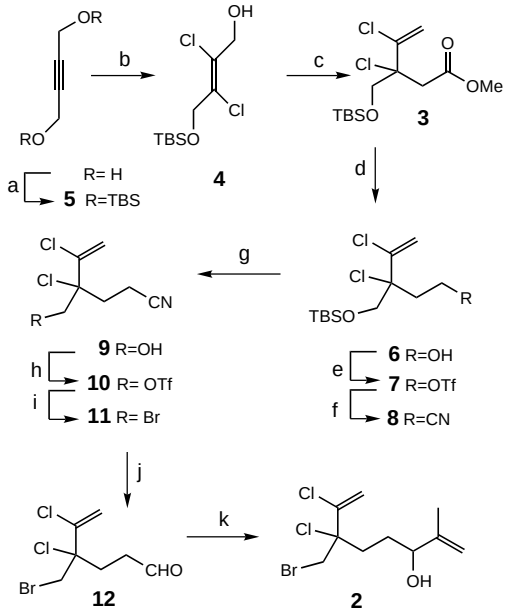


Scheme 1. Retrosynthesis of halomon (**1**). TBS = *t*BuMe$_2$.

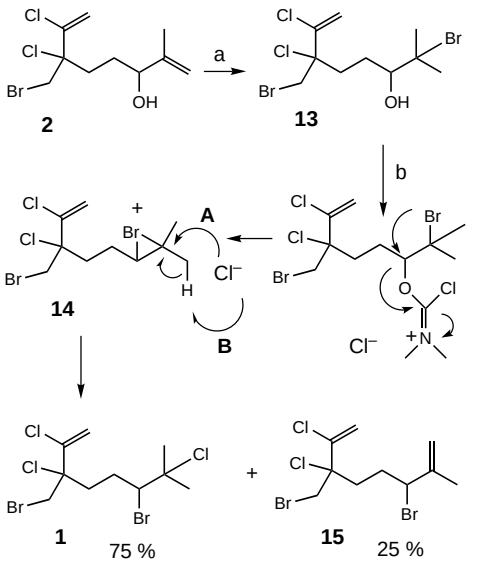
To commence the synthesis, the readily available but-2-yne-1,4-diol was bissilylated quantitatively giving **5**. This product was then chlorinated with concomitant monodesilylation with one equivalent of $Et_4N^+Cl_3^-$, a new reagent developed in this laboratory,[5] to give the *trans*-dichlorinated alkene **4** (Scheme 2). An extensive investigation was then undertaken to validate the rearrangement step of compound **4**. All attempts to promote Cope, Stevens, Claisen, or Ireland–Claisen rearrangements were unsuccessful.[6] However, the rearrangement was accomplished using Johnson–Claisen acidic conditions.[7] When the reaction was carried out for five days with methyl orthoacetate and propionic acid in refluxing toluene, the desired rearranged compound **3** was isolated in 30% yield. The absence of solvent and the use of *p*-toluenesulfonic acid instead of propionic acid resulted in an improved yield (55%) and a shorter reaction time (less than 24 hours).[8]

Compound **3** was then transformed into the intermediate compound **2** by an eight-step procedure. Ester **3** was reduced with $LiAlH_4$,[9] and the resultant primary alcohol **6** was converted into **8** in 88% overall yield, via the triflate **7**[10] with tetraethylammonium cyanide.[11] The silyloxy group of nitrile (**8**) was transformed first to an alcohol (**9**), then to a triflate (**10**), and finally into the corresponding bromide (**11**).[12] The aldehyde **12** was obtained by a controlled reduction of the cyanide group with Dibal-H at $-78\,^\circ C$. After an extensive investigation of a variety of protocols, we finally established that the reaction of the sensitive aldehyde **12** with three equivalents of isopropenylmagnesium bromide and three equivalents of hexaethylguanidinium chloride proceeded smoothly to give the allyl alcohol **2** in 87% yield after chromatography on silica gel. Grignard addition in the absence of the guanidinium salt never exceeded 20% yield.[13]

The completion of the synthesis is outlined in Scheme 3. Addition of $Et_4N^+HBr_2^-$ to the allylic alcohol **2** resulted in regiospecific hydrobromination of the nonchlorinated double



Scheme 2. a) TBSCl (2 equiv), imidazole, CH_2Cl_2, $0\,^\circ C$, 100%; b) $Et_4N^+Cl_3^-$ (1 equiv), CH_2Cl_2, $0\,^\circ C$, 59%; c) $CH_3C(OCH_3)_3$, TsOH, $170\,^\circ C$, 55%; d) $LiAlH_4$ (4 equiv), THF, $0\,^\circ C$, 93%; e) Tf_2O, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, $0\,^\circ C$, crude product; f) $Et_4N^+CN^-$ (10 equiv), 95%; g) TsOH, MeOH, reflux, 7 h, 95%; h) Tf_2O, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, $0\,^\circ C$, 89%; i) $Et_4N^+CN^-$ (10 equiv), $0\,^\circ C$, 98%; j) DIBAL-H, THF, $-78\,^\circ C$, 90%; k) isopropenylmagnesium bromide (3 equiv), hexaethylguanidinium chloride (3 equiv), THF, $0\,^\circ C$, 87%. TsOH = *p*-toluenesulfonic acid, Tf_2O = trifluoromethanesulfonic acid anhydride, DIBAL-H = diisobutylaluminium hydride.



Scheme 3. a) $Et_4N^+HBr_2^-$, CH_2Cl_2, $0\,^\circ C$, 97%; b) $Cl_2C{=}NMe_2^+Cl^-$, CH_2Cl_2, $0\,^\circ C$.

bond to afford the desired bromohydrin **13** in almost quantitative yield (97%).[14] Surprisingly, treatment of the bromohydrin **13** with one equivalent of dichlorophosgeniminium chloride (Viehe's salt)[15] gave halomon (**1**) directly[16] in 75% yield with simultaneous formation of the allyl bromide **15** (25%). This unusual transformation probably involves

  1433-7851/98/3715-2086 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1998**, *37*, No. 15

neighboring-group participation of the bromine positioned on C_7 through the three-membered bromonium intermediate **14**. The chloride counterion could act either as a nucleophile to furnish halomon (path A) or as a weak base to yield the allyl bromide **15** (path B). To our knowledge, this complete 1,2-shift of the bromine atom of a bromohydrin in the presence of a chlorinating reagent has no precedent in the literature.[17] This transformation appears to be a general method for rearranging bromohydrins.

The four stereoisomers of **1** were separated by HPLC (see Experimental Section). The 6*R*,3*S* and 6*S*,3*R* diastereoisomers eluted prior to the 6*R*,3*R* and 6*S*,3*S* diastereoisomers. The 6*R*,3*R* and 6*S*,3*S* enantiomers were separated by HPLC on a chiral column. Comparisons with natural halomon allowed us to assign unambiguously the stereochemistry of both signals. All four stereoisomers will be tested for biological activity.

In summary, the first total synthesis of halomon (**1**) has been accomplished in 13 steps from but-2-yne-1,4-diol with an overall yield of 13%. The following significant new findings were made: 1. The Johnson–Claisen [3,3]-sigmatropic rearrangement of a dichlorinated alkene for the construction of a tertiary chlorinated carbon;[18] 2. the hexaethylguanidinium chloride mediated addition of Grignard reagents to sensitive aldehydes; and 3. a new rearrangement of bromohydrins for the regiospecific introduction of the bromine and chlorine atoms on C_6 and C_7, respectively. The versatility of the methods developed herein can be adapted to produce enantiomerically pure halomon[19] as well as a variety of analogues to investigate fully the potential of this novel anticancer agent.

Experimental Section

3: A solution of alcohol **4** (147 mg), trimethyl orthoacetate (1 mL), and a catalytic amount of *p*-toluenesulfonic acid (7 mg) was heated in a sealed tube until the starting material had disappeared. After dilution of the reaction mixture with dichloromethane, the crude mixture was washed successively with water, 5% $NaHCO_3$, and then brine, and dried over $MgSO_4$. The solvent was removed in vacuo. The crude oil was purified by column chromatography (SiO_2, hexane/ethyl acetate (95/5)) to yield **3** (93 mg, 55%).

1: Dichlorophosgeniminium chloride (0.11 mmol) was added in one portion to a solution of alcohol **13** (0.1 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C. After the mixture was stirred for 6 hours at 0 °C and 10 h at room temperature, the solvent was removed in vacuo and the crude oil purified by column chromatography (SiO_2, hexane) to yield halomon (**1**, 75%) contaminated with **15** (25%). HPLC (Zorbax SBC18 column, methanol/water (75/25)): Diastereoisomers 6*R*,3*S* and 6*S*,3*R* eluted prior to diastereoisomers 6*R*,3*R* and 6*S*,3*S*. Separation of the 6*R*,3*S* and 6*S*,3*R* enantiomers: OJ-R column, acetonitrile/water (55/45).

Received: January 28, 1998 [Z11415IE]
German version: *Angew. Chem.* **1998**, *110*, 2226–2228

Keywords: antitumour agents · halomon · natural products · rearrangements · total synthesis

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[19] New asymmetric [3,3]-sigmatropic rearrangements are under current investigation in our laboratory.

  1433-7851/98/3715-2087 $ 17.50+.50/0