derived from ligand **2**, with its bulky mesityl groups, cannot achieve a C_2-symmetric conformation in the enantioselectivity-determining step. Thus, a possible explanation for the low enantioselectivity of **2** might be that it adopts a *syn* conformation (Figure 1 **B**).

The use of asymmetric Lewis acid catalysts bearing sulfonamido-based ligands is becoming more prevalent. In several of these systems, it is likely that the coordination of the sulfonyl oxygen atoms to the metal center plays an important role in defining the chiral environment of the catalyst,[15–17] as it does with the titanium bis(sulfonamide) system. The experiments outlined here will be useful in understanding transfer of asymmetry in these, and other, systems (full experimental details can be found in the Supporting Information).

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A Three-Step Synthesis of Halomon

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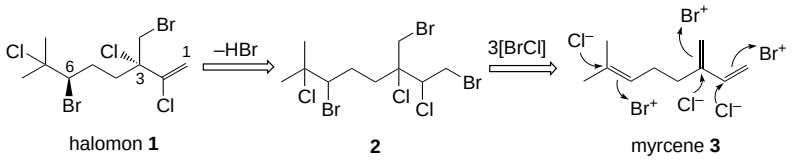
Halomon (**1**), which was isolated from the red algae *Portieria hornemannii*,[1] is a member of a novel class of antitumor agents with selective cytotoxicity against various tumor cell lines (see Scheme 1).[2] Detailed studies on the biological activity of **1** have been hampered due to its limited accessibility. Halomon (**1**) is a small molecule that can be easily synthesized; however, the presence of five halogen atoms on the acyclic carbon chain has created a number of difficulties for regio- and stereocontrolled synthesis.[3, 4] We report herein a very short and straightforward synthesis of **1**.

A close inspection of the structural features of **1** indicates a Markovnikov-type arrangement of Cl^- and Br^+ on the myrcene skeleton.[1] We expected that **1** could be synthesized by three successive Markovnikov-type bromochlorinations of myrcene (**3**) followed by elimination of hydrogen bromide from the intermediate **2** (Scheme 1). Tetraalkylammonium dichlorobromate (R_4NBrCl_2) should be the reagent of choice for this halogenation.[5] Myrcene (**3**) was first treated with excess Bu_4NBrCl_2 to obtain **2**, but this resulted in formation of a complex mixture. A stepwise bromochlorination reaction was then investigated. When **3** was treated with one equivalent of Bu_4NBrCl_2 in CH_2Cl_2 at 0 °C, the trisubstituted double bond of **3** instead of the conjugate diene was bromochlorinated to yield **4** (Table 1) in an excellent example of Markovnikov selectivity (> 43:1) (Scheme 2).[6, 7] This exclusive formation of **4** is remarkable because 2-methyl-2-butene was reported to give a 2.4:1 mixture of regioisomers under similar reaction conditions.[5b] It is likely that in the present case the attack of chloride ion on the less substituted C6 center of a bromonium-like intermediate could be hindered by the long and branched alkenyl substituent at C6. Therefore, the electronically favored attack of chloride ion on the more substituted C7 would become overwhelming. The regioselectivity of reactions of alkenes with Bu_4NBrCl_2 was found to be sensitive to the steric effect of the alkyl substituents.[5b] The high selectivity for **3** was not affected by temperature (−78 °C or 0 °C) nor by alkyl substituents on



Scheme 1. Retrosynthetic scheme for the synthesis of halomon (**1**) from myrcene (**3**).

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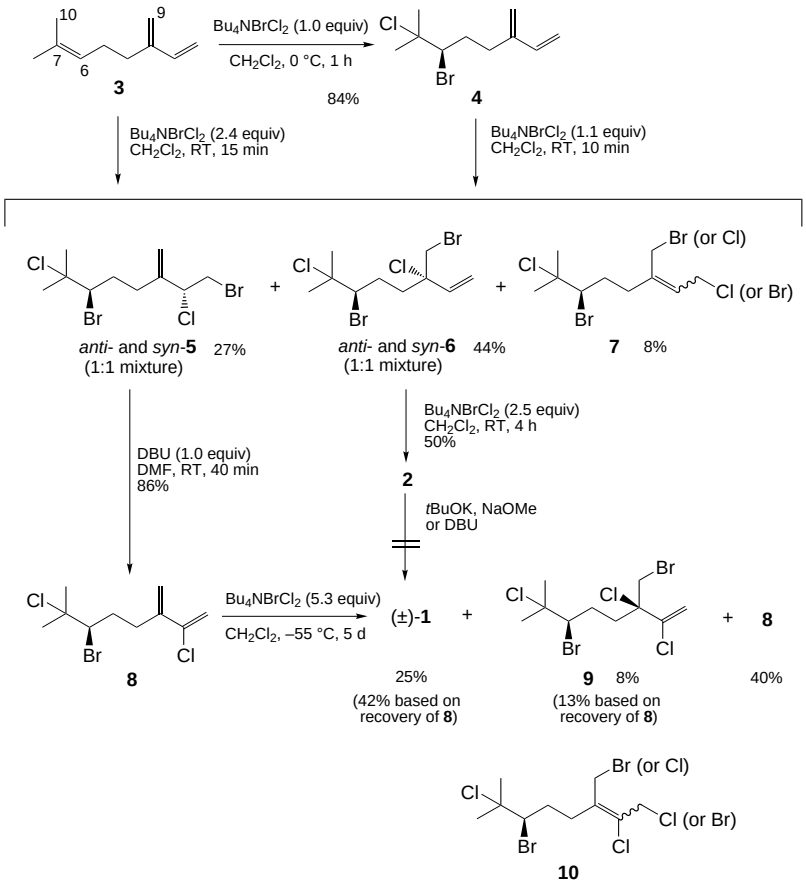
Table 1. 500 MHz ^{1}H NMR data of intermediates (**4**–**6**, and **8**) in $CDCl_3$.[a]

Carbon	**4**	**5**[b]	*anti*-**6**	*syn*-**6**	**8**[c]
1	5.29 (br d, J = 17.3 Hz, 1H)	3.71 (dd, J = 10.0, 6.0 Hz, 1H)	5.35 (d, J = 10.5 Hz, 1H)	5.36 (d, J = 11.0 Hz, 1H)	5.26 (br s, 1H)
	5.08–5.12 (m, 1H)	4.61 (dd, J = 10.0, 6.0 Hz, 1H)	5.49 (d, J = 17.3 Hz, 1H)	5.49 (d, J = 16.5 Hz, 1H)	5.45 (br s, 1H)
2	6.38 (dd, J = 17.3, 10.5 Hz, 1H)	3.66 (t, J = 6.0 Hz, 1H)	5.98 (dd, J = 17.3, 10.5 Hz, 1H)	5.98 (dd, J = 17.5, 11.0 Hz, 1H)	
4, 5	1.89–1.98 (m, 1H)	1.94–2.25 (m, 1H)	1.86–2.10 (m, 2H)	1.86–2.10 (m, 2H)	1.90–2.02 (m, 1H)
	2.33 (qd, J = 8.5, 7.5 Hz, 1H)	2.28–2.36 (m, 1H)	2.44–2.56 (m, 2H)	2.44–2.56 (m, 2H)	2.34–2.62 (m, 2H)
	2.49 (qdd, J = 9.0, 7.5, 1.5 Hz, 1H)	2.46–2.54 (m, 1H)			2.62–2.84 (m, 1H)
	2.67 (ddd, J = 13.5, 9.3, 4.6 Hz, 1H)	2.56–2.63 (m, 1H)			
6	4.07 (dd, J = 11.0, 1.5 Hz, 1H)	4.11 (dd, J = 11.5, 1.5 Hz, 1H)	4.05 (dd, J = 11.0, 1.0 Hz, 1H)	4.01 (dd, J = 11.3, 1.8 Hz, 1H)	4.04 (dd, J = 11.0, 1.2 Hz, 1H)
8, 10	1.67 (s, 3H)	1.70 (s, 3H)	1.69 (s, 3H)	1.69 (s, 3H)	1.66 (s, 3H)
	1.78 (s, 3H)	1.81 (s, 3H)	1.80 (s, 3H)	1.80 (s, 3H)	1.78 (s, 3H)
9	5.08–5.12 (m, 2H)	5.19 (br s, 1H)	3.68 (d, J = 10.5 Hz, 1H)	3.68 (d, J = 10.5 Hz, 1H)	5.53 (br s, 1H)
		5.30 (br s, 1H)	3.72 (d, J = 10.5 Hz, 1H)	3.72 (d, J = 10.5 Hz, 1H)	5.66 (br s, 1H)

[a] Chemical shifts referenced to tetramethylsilane. [b] Signals of *anti* and *syn* diastereomers are not separated. [c] Measured by 200 MHz ^{1}H NMR spectroscopy.



Scheme 2. Synthesis of halomon ((±)-**1**) and its congener **9** from myrcene (**3**).

ammonium salt reagents such as Me_4NBrCl_2 and $(octyl)_4NBrCl_2$.

Bromochlorination of the conjugate diene **4** using 1.1 equivalents of Bu_4NBrCl_2 proceeded smoothly at room temperature and yielded the 1,2-adducts **5** and **6** in 27 and 44% yields, respectively, which were separable by HPLC.[6] In addition, a small amount (8%) of the 1,4-adduct **7**[8] was produced (Scheme 2). Both **5** and **6** are 1:1 diastereomeric mixtures based on NMR spectral data (Table 1). The NMR spectrum of the *anti* diastereomer in **6** was identical with that of the natural product.[1, 2b] We then attempted a bis-bromochlorination of **3** using 2.4 equivalents of Bu_4NBrCl_2 at room temperature. The mixture of **5** (21%), **6** (42%), and **7** (9%) was obtained in a one-pot reaction from **3**.

The terminal vinyl compound **6** was bromochlorinated regioselectively with Bu_4NBrCl_2 in CH_2Cl_2 at room temperature to yield **2** in 50% yield (Scheme 2).[9] The planned regioselective elimination of hydrogen bromide from **2**, however, was not successful under any conditions investigated.

We next focused our attention on the *exo*-methylene compound **5**, which was expected to undergo the dehydrobromination more readily at the C1–C2 position because of the presence of an allylic hydrogen atom at C2. Treatment of **5** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature yielded **8** (Table 1) in good yield, while elimination with *t*BuOK produced a mixture (Scheme 2).[10] Since the diene **8** is not stable, like 2-chloromyrcene,[11] it was subjected to a final bromochlorination immediately after flash chromatography. Excess Bu_4NBrCl_2 was necessary to completely consume **8**, because **8** was less reactive than **4**, as expected. A mixture of **1** and **9** was produced in 20% combined yield, when two equivalents of Bu_4NBrCl_2 were used at room temperature for 10 min. However, 1,4-adduct **10**[8] was simultaneously formed (24%), and the total material balance was low probably because of the instability of **8** under the reaction conditions. After a considerable number of trials, we established optimal conditions to suppress the formation of **10**. The

reaction with 5.3 equivalents of Bu_4NBrCl_2 at $-55\,^{\circ}C$ under an argon atmosphere gave halomon (**1**: 25%; 42% based on recovery of **8**) and the diastereomer (**9**: 8%) together with recovered **8** (40%). The racemic halomon ((±)-**1**) was separated by reversed-phase HPLC (Cosmosil 5PYE; CH_3CN/water 60/40); its ^1H and ^{13}C NMR spectra[2a] are identical with those of natural halomon.[12] Furthermore, pure natural enantiomer (+)-**1** was isolated by HPLC using DAICEL CHIRALPAK AD-RH (CH_3CN/water 54/46) as colorless needles (from EtOH): m.p. 56.0–57.2 °C; $[\alpha]_D^{25} = +42.6$ ($c = 1.0$, CH_2Cl_2); ref.[2a] m.p. 49–50 °C; $[\alpha]_D$ +206 ($c = 1.08$, CH_2Cl_2). The structure of synthetic (+)-**1** was unambiguously confirmed by X-ray crystallographic analysis. Optically pure synthetic (−)-**1**, which was also isolated, exhibited $[\alpha]_D^{25} = -40.2$ ($c = 0.75$, CH_2Cl_2). Therefore, the reported large value of $[\alpha]_D$ for natural halomon[2a] appears to arise from some impurity.

Thus, we have achieved the total synthesis of halomon (**1**) in only three steps from myrcene. This synthesis indicates the possible biosynthesis pathway of **1**.[1] Further research directed towards a stereocontrolled and enantioselective total synthesis of halomon and its congeners is currently under way in our laboratory.

Experimental Section

5, **6**, **7**: Bu_4NBrCl_2 (0.94 g, 2.4 mmol) was added to a solution of **3** (0.17 mL, 1.0 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 15 min. The reaction mixture was diluted with diethyl ether (10 mL), washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was subjected to chromatography on silica gel (hexane) to yield an approximate 1:2 mixture of **5** and **6** (0.23 g, 0.63 mmol, 63%) together with **7** (34 mg, 0.090 mmol, 8%).

8: DBU (75 μL, 0.50 mmol) was added to a solution of a 0.6:1 mixture of **5** and **6** (0.59 g, 1.6 mmol) in DMF (15 mL), and the mixture was stirred at room temperature for 1.2 h. The reaction mixture was poured into a vigorously stirred mixture of ice–water (30 mL) and hexane (30 mL). The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography (SiO_2, hexane) of the products gave **8** (0.11 g, 0.39 mmol, 78% from **5**) and the recovered **6** (0.36 g, 97% recovery).

1: Bu_4NBrCl_2 (14 g, 36 mmol) was added to a solution of **8** (1.95 g, 6.8 mmol) in CH_2Cl_2 (60 mL) under an argon atmosphere at $-55\,^{\circ}C$, and the solution was allowed to stir at $-55\,^{\circ}C$ for five days. 2-Methyl-2-butene (7.8 mL, 74 mmol) was added to the reaction mixture at $-55\,^{\circ}C$ until the yellow color faded. The reaction mixture was diluted with hexane (60 mL), washed with water and brine, dried over Na_2SO_4, and the solvent was removed in vacuo. The product was purified by flash column chromatography (SiO_2, hexane) to yield a 3:1 mixture of **1** and **9** (0.93 g, 2.3 mmol, 33%) and the recovered **8** (0.79 g, 2.8 mmol, 40%). Compound **1** was separated from **9** by HPLC (Cosmosil 5PYE; CH_3CN/water 60/40); **9** eluted as a shoulder on the front-side of the peak of **1**. HPLC of (±)-**1** using DAICEL CHIRALPAK AD-RH (CH_3CN/water 54/46) gave the enantiomers; (−)-**1** was eluted prior to natural (+)-**1**.

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[6] The ratio was determined by HPLC analysis (Cosmosil 5C18-MS 4.6 × 150 mm, MeOH/H_2O 80/20, 1 mL min^{-1}).

[7] Acetonitrile was also usable, while the reaction became too sluggish in hexane, and side reactions occurred in DMF.

[8] Neither the positions of the added bromine and chlorine atoms nor the geometry of the double bond were determined.

[9] The presence of four diastereomers was revealed by NMR spectroscopy.

[10] Separation of **5** and **6** by HPLC was inconvenient. Therefore, the mixture of **5** and **6** was treated with DBU without separation to yield the diene **8** and the recovered **6**, which were easily separated by flash chromatography (see Experimental Section).

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Synthesis of a Triazatriangulenium Salt

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Stabilized carbenium ions such as the triarylmethyl, xanthyl, and acridinium cations are organic compounds of great scientific and commercial importance. Many of them are used as textile and laser dyes, as well as in various fluorescent probes and cellular stains for biological and diagnostic purposes.[1–3] Consequently, their thermodynamic and photophysical properties have been extensively studied, and great effort has been put into clarifying the relationship between structure and stability[4, 5] as well as into synthesizing new carbenium ions with very high stability.[6, 7] Aromatic nucleophilic substitution (S_NAr) with amines on *para*-methoxy- or *para*-chloro-substituted carbenium ions has proven a powerful tool in the preparation of a variety of new triaryl carbenium ions.[8–10] Until now no substitution of *ortho* groups in these ions has been described. Herein we report the synthesis of a novel and extremely stable trimethyl triaza-

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