

The Manganese-Mediated Regioselective Chlorination of Allenes in Synthetic Approaches Towards the Spongistatins and Halomon Natural Products

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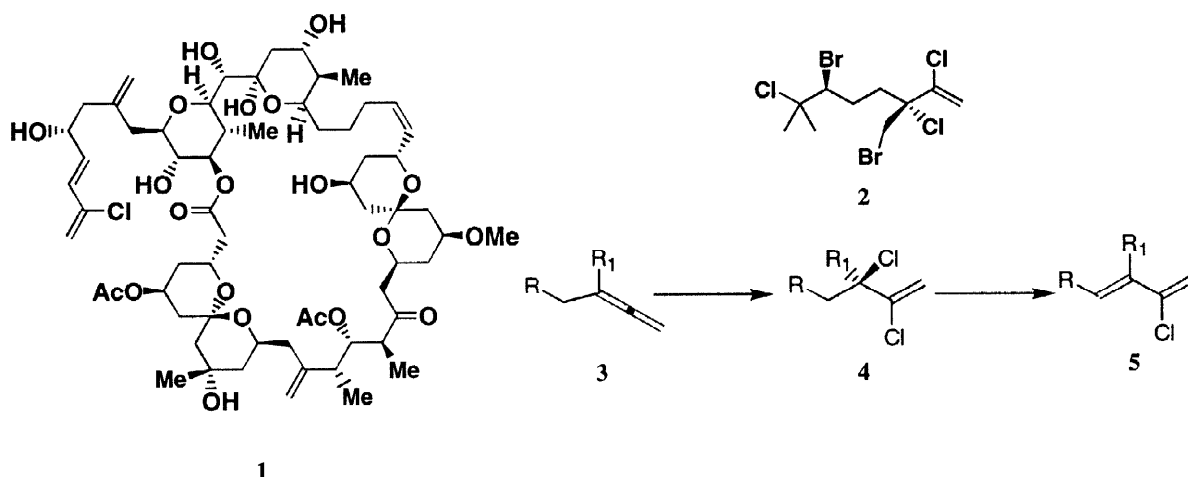
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Abstract

The first examples for the chlorination of allenes using manganese reagents generated from potassium permanganate and benzyl triethylammonium chloride in the presence of the chlorine donors oxalyl chloride or chlorotrimethylsilane are reported with the aim of developing useful synthetic routes to the spongistatin and halomon marine natural products. © 1998 Elsevier Science Ltd. All rights reserved.

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During our studies towards the synthesis of the potent antitumour marine natural products spongistatin 1 [1] **1** and halomon [2] **2** we recognised that the regioselective chlorination of terminal allenes **3** would give 2,3-dichlorobut-1-ene derivatives **4**. Elimination of HCl would furnish the chlorodiene **5**. The regioselective chlorination of terminal allenes would therefore provide useful



synthetic methodology in approaches to the synthesis of these natural products and their analogues. The recent publication of the first total synthesis of spongistatin 1 by Kishi and co-workers [3] was the first to address the preparation of the chloro diene moiety. The synthesis of halomon related monoterpenes was reported by Jung and Parker [4]. We wish to report the first examples of manganese mediated chlorinations of allenes in this letter.

Chlorination of some simple allenes has been reported by Poutsma [5], however, this method seemed to be inefficient due to rearrangement and condensation by-products resulting from the proposed cationic intermediates. The 1,2-addition of chlorine to terminal allenes has been reported using stoichiometric quantities of $\text{PdCl}_2(\text{PhCN})_2$ by Bäckvall and Jonasson [6].

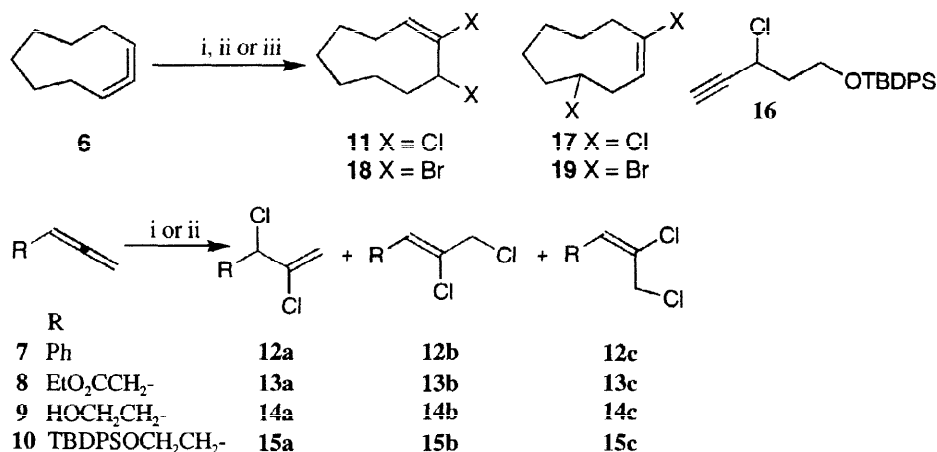
Marko and Richardson [7] have reported a novel manganese reagent for the stereospecific chlorination of olefins and have postulated the intermediacy of a non-cationic organomanganese species [8], which we anticipated would overcome the problems caused by the cationic intermediates in the chlorination of allenes. As no examples for the chlorination of allenes using this reagent have been reported we decided to examine the synthetic utility of the reagent in the preparation of 2,3-dichlorobut-1-enes **4** and 2-chlorodienes **5**.

Allenes **6** and **7** were prepared from the corresponding dibromocyclopropanes using the method of Skattebøl [9]. Allenes **8** and **9** were prepared in an improved yield by the method of Dauben and Shapiro [10], silyl ether **10** was prepared by standard methodology. The five allenes were chlorinated according to the original method of Marko and Richardson using oxalyl chloride as the chlorine donor, and by their improved method employing chlorotrimethylsilyl chloride [11].

The results are summarised, Table 1. The cyclic allene **6** gave one major product **11** whilst the terminal allenes **7** to **10** gave all the three possible products **12a-c** to **15a-c** respectively. In addition for allene **10** we isolated the terminal alkyne **16** by column chromatography as 28% of the product. No evidence for the hydride shift rearrangement product **17** was detected for the chlorination of **6**, which suggested that an organomanganese intermediate was present in the reaction pathway and not a free carbocation. This contrasts to the formation of **19** in the bromination of **6** to give **18** and **19** [12].

The major products from the terminal allenes **7** to **10** were **12a** to **15a** resulting from the chlorination of the internal double bond, and were accompanied by the geometric isomers **12-15 b** and **c** resulting from chlorination of the terminal double bond. Each of the three regioisomers **12-15 a-c** were obtained in varying ratios and were identified by their characteristic coupling patterns for the allylic chloride signals. Two one proton doublets in **12-15a** around 5.4 and 5.6 ppm, each with a coupling of 2 Hz for the terminal olefinic protons, and in **13-15a** a doublet of doublets around 5.0 ppm with a coupling of 6 to 8 Hz for the allylic proton were characteristic of these structures.

In contrast **12-15 b** & **c** showed a distinct vinylic proton triplet between 6 to 7 ppm with coupling constants in the region of 7 Hz and a singlet around 4.5 ppm for the terminal allylic protons. The



Reagents and Conditions: i, Benzyl triethylammonium chloride, KMnO₄, (COCl)₂, -40°C, ii, Benzyl triethylammonium chloride, KMnO₄, TMSCl, 0 to 20°C, iii, Ref. 10

Table 1. Yields and product ratios for the chlorination of allenes.

Allene	Cl Donor	Time/ hr	Prod	Yield ^a / %	Product ratio ^b		
					a	b	and c
6 	TMSCl	2	11	72	1	-	-
	OxalylCl	2		92	1	-	-
7 	TMSCl	0.5	12	68	6	3	1
	OxalylCl	0.5		78	2	1	1
8 	TMSCl	1.5	13	82	18	2	1
	OxalylCl	18		87	5	4	1
9 	TMSCl	1	14	87	12	2	1
	OxalylCl	12		18	5	3	1
10 	TMSCl	1	15	87	5	3	1
	OxalylCl	16		92	3	3	2

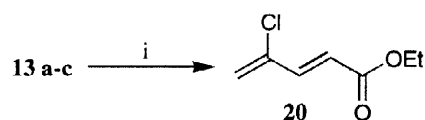
^aOverall yield of mixtures.

^bBased on GLC and NMR analysis. Structures were assigned from the proton NMR spectra and GLC-MS studies of isolated products. Satisfactory NMR, IR and Mass spectral data were obtained.

formation of tetrachlorinated compounds were not detected by NMR or GLC-MS analysis.

In general, use of chlorotrimethylsilane as the chlorine donor gave the better regioselectivity towards the internal double bond of the allenes compared with oxalyl chloride. Our results gave the opposite regioselectivity compared to the method reported by Backvall and Jonasson who obtained only the isomer corresponding to **12-15 b** (R = *n*-Bu).

A mixture of **13 a-c** was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane to give *E*-ethyl-4-chloropentadieneoate **20** in 94% yield as a single geometric



Reagents and Conditions: 1, DBU, CH_2Cl_2 ,
(94 %)

isomer with a coupling constant of 15 Hz across the central double bond. This completed a new and synthetically useful route to compounds containing a terminal 2-chlorodiene functionality.

In conclusion we have shown that the manganese reagents have permitted a regiocontrolled chlorination of terminal allenes. In addition, we have also demonstrated improved regio-control for the chlorination of cyclic allenes. Studies are in progress to apply this new methodology in natural product synthesis.

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