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Digest Paper

Recent progress toward synthesis of chlorosulfolipids: total synthesis and methodology

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ABSTRACT

Chlorosulfolipids (CSLs) are an intriguing family of natural products featuring highly chlorinated linear hydrocarbon skeletons. Although CSLs were first isolated in 1962, chemical synthesis of CSLs was hampered because relevant methods for stereoselective construction of the polychlorinated motifs of CSLs were scarce. Since Carreira's first total synthesis of the CSL mytilipin A in 2009, several groups, including our own, have reported total syntheses of CSLs. As a result of these total syntheses, important progress has been made in the development of reliable synthetic methods for stereoselective polychlorination. In this digest, we summarize the total syntheses of CSLs by focusing on synthetic methods for stereoselective polychlorination of the organic frameworks of CSLs.

Contents

Introduction

Chlorosulfolipids (CSLs), first isolated from *Ochromonas danica* by Haines in 1962,[1a] are an unusual family of chlorine-rich lipids which include danicalipin A (**1**), mytilipins A–C (**7**, **9**, and **10**), and malhamensilipin A (**8**) (Fig. 1).[1] CSLs are unique in featuring hydrocarbon skeletons densely functionalized with chlorine atoms. Around 1970, studies concerning producers,[2] biological activities,[3] and biosyntheses of CSLs[4] were reported. For example, *O. danica* and *Poterioochromonas malhamensis* were identified as producers and toxicity against fish and invertebrates,[3a,b] growth inhibition of bacteria,[3c,d] and lysis of mammalian erythrocytes[3e–g] were revealed. After further investigations throughout the 1970s, research on CSLs largely subsided owing to the lack of availability of CSLs from natural resources and chemical access to CSLs.

In order to elucidate the mechanism of the biological activity of CSLs at the molecular level, the determination of stereochemistries of CSLs is essential. However, only planar structures of CSLs were known until the 2000s due to the lack of means to elucidate their complex stereochemistries, although the absolute configuration of the simplest CSL **6** was determined in 1969.[1c] More recently, in 1994, Gerwich and Slate reported the isolation and gross structure of malhamensilipin A (**8**), a protein tyrosine kinase (PTK) inhibitor found in cultured *P. malhamensis*.[5] Finally, in 2001, Ciminiello and Fattorusso isolated mytilipins A–C (**7**,[6] **9**,[7a] and **10**[7b]) and determined their relative and absolute configurations during their search on food poisoning from mussels in the Adrian Sea. In their structure elucidation, *J*-based configuration analysis (JBCA) developed by Murata[8] was successfully utilized to arrive at the relative stereochemistries. This structure determination study was the first application of JBCA to CSLs. With this publication as a turning

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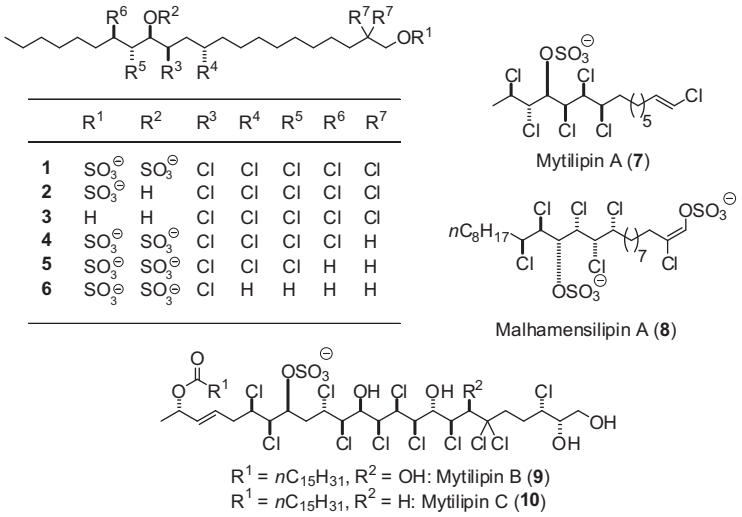


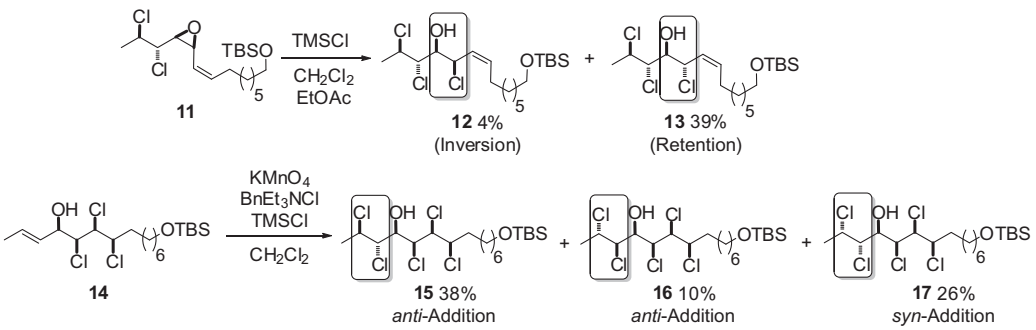
Figure 1. Chlorosulfolipids (CSLs).

point, use of JBCA became widespread for the elucidation of the relative stereochemistries of CSLs. In 2009, the absolute configuration of danicalipin A (**1**) was determined. Vanderwal and Gerwick achieved the total synthesis of **1** in racemic form and assigned the relative stereochemistries of synthetic **3** using JBCA. Additionally, a sample of natural **3** obtained by Haines more than 30 years ago was subjected to the modified Mosher's method[9] to determine the absolute stereochemistries of **1** and **3**.[10] Concurrently, Okino isolated CSLs **1**–**6** from cultured *O. danica* and elucidated their absolute configurations by a combination of JBCA and the modified Mosher's method.[11] These two reports reached the same conclusions. Moreover, Okino evaluated toxicities of **1**–**6** with brine shrimp (*Artemia salina*), with **1**, **2**, **4**–**6** showing similar toxicities and **3** showing less toxicity. This result seems to indicate that the number of chlorine atoms in CSLs does not affect their toxicity toward brine shrimp.

Because of their intriguing and unprecedented structures, CSLs have attracted a great deal of attention from synthetic organic chemists. After the first total synthesis of racemic **7**[12] by Carreira in 2009, a milestone for the chemical synthesis of CSLs, the following total syntheses of CSLs were reported from four groups: **9**[13] by Carreira, **1**,[10] **7**,[14] and **8**[15] by Vanderwal, **1**[16] and **7**[17] by Yoshimitsu, and **1**[18] by us. From a synthetic point of view, it is necessary for the efficient construction of the polychlorinated frameworks of CSLs to stereoselectively install chloride(s) into a chlorinated scaffold. However, unexpected stereoselectivities were often found in this type of transformation. For example, Carreira planned the synthesis of *syn*-chlorohydrin **12** from *cis*-epoxide **11** (Scheme 1).[12a] Although it is usually known that this type of S_N2 reaction by chloride anion occurs at the allylic position with stereochemical inversion, epoxide ring opening of **11** with TMSCl[19] afforded the unexpected *anti*-chlorohydrin **13** with retention as a major product along with a trace amount of the expected *syn*-chlorohydrin **12** with inversion. Yoshimitsu attempted the synthesis of *anti*-1,2-dichloride **15** through stereospecific *anti*-1,2-dichlorination reaction of *E*-olefin **14**.[17] However, 26% of unanticipated *syn*-1,2-dichloride **17** was formed along with anticipated *anti*-1,2-dichlorides **15** (38%) and **16** (10%). The anchimeric participation of chlorides in these polychlorinated systems most likely causes the unusual stereoselectivities. This review summarizes recent total syntheses of CSLs. Special emphasis is placed on synthetic methodologies[20] for stereoselective introduction of chlorides into organic frameworks of CSLs.[21]

Carreira's synthesis

The first in a series of syntheses of CSLs, Carreira reported the first total synthesis of racemic mytilipin A (**7**) in 2009.[12a] The synthetic details are shown in Schemes 2 and 3. When commercially available ethyl sorbate (**18**) was reacted with Et_4NCl_3, stereospecific *anti*-1,2-dichlorination exclusively took place at the δ, γ-double bond, which is more electron rich than the α,β-double bond, giving racemic *anti*-1,2-dichloride **19** in 68% yield. Reduction of the ester, TBS protection, diastereoselective dihydroxylation with OsO_4 (dr = 5.6:1, for facial selectivity, see: Scheme 7), and epoxide ring closure via triflation afforded *cis*-epoxide **20**. Epoxide



Scheme 1. Unusual stereoselectivities in total syntheses.