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Karlotoxin synthetic studies: concise synthesis of a C(42–63) B-ring tetrahydropyran fragment

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Abstract

Starting from natural D-mannose, a C(42–63) B-ring tetrahydropyran fragment in karlotoxin 2 has been prepared via a common THP intermediate in a concise manner. *E*-selective Julia–Kocienski olefination efficiently assembled a C(51–63) chlorodiene subunit and a C(42–50) tetrahydropyran segment.

Keywords

Polyketide; Karlotoxin; Tetrahydropyran; D-Mannose; Julia-Kocienski olefination

Karlotoxins (KmTxS) are a family of linear polyketides isolated from a toxic phytoplankton, the dinoflagellate *Karlodinium micrum*.¹ These toxins are believed to possess hemolytic, cytotoxic, and ichthyotoxic activities.² Recent study also demonstrated that the toxins possess a unique, strong binding affinity to cholesterol,³ which is one of the major components of lipid rafts. Since the lipid rafts, a cholesterol-rich membrane domain, have important clinical implications in major human diseases such as cancer, HIV (human immunodeficiency virus), TB (tubercle bacillus), and neurological disorders, the study of KmTx–cholesterol interactions may help to reveal further mechanistic aspects for the chemopreventive and drug design.⁴ The scarcity of this class of natural products is the key limitation to further biological evaluation. Indeed, more than 50 years of isolation efforts by a number of researchers globally has provided only several 1–10 mg batches of toxin to date

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at <http://>

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which has been utilized to characterize in vitro pharmacology and the structure of the molecule.

Recently, the absolute configuration of KmTx2 (**1**), the first complete structure determination among the congeners, was successfully assigned by our groups (Figure 1).⁵ The KmTx2 reveals unique structural features, including highly oxygenated C(30–49) bis-tetrahydropyran core fragment, in conjunction with a long, irregular C(1–31) polyol arm as well as a C(50–63) lipophilic chlorotriene unit, with a total of 28 stereogenic centers. Such potent biological activities as well as novel molecular complexity of the toxins engaged our interest in the synthesis of KmTx2 and the analogues.

Interestingly, the KmTx2 shares structural similarities to amphidinol 3 (AM3)⁶ and their bis-tetrahydropyran core units nearly identical with exception of a few substitution patterns. Importantly the absolute configuration of these two fragments is opposite and still remains uncertain.⁷ Although several synthetic groups have been actively involved in the synthesis of AM3,^{8–13} the recent structure revisions in 2008^{13a} and 2013^{13c} unfortunately hinder their progress. Thus, the synthesis of KmTx2 would also serve to confirm the proposed absolute configuration as well as supply the toxin for further biological study.

Our retrosynthetic plan disconnects KmTx2 into three major fragments: two THP fragments (A and B) and a polyol chain fragment. Further disconnections of both THPs lead to a known common THP intermediate (**3**) that can be readily prepared from natural D-mannose.^{14a} In this report, we describe a concise stereoselective approach leading to a C(42–63) B-ring THP segment (**2**) employing Julia–Kocienski olefination as a key reaction (Scheme 1). Note: during the preparation of this manuscript, a partly similar approach to construct the *ent*-THP fragment of AM3 from D-mannose has been reported by Reymond and Cossy.^{11f}

To begin, based on the literature procedures,¹⁴ the common THP intermediate **3** was prepared from D-mannose in a five-step reaction series. For subsequent construction of the B-ring THP framework (Scheme 2), a free hydroxyl group in **3** was removed by standard Barton–McCombie deoxygenation¹⁵ which led to **4** (71% over 2 steps). A Pd(II)-catalyzed alkene isomerization of **4** followed by ozonolytic cleavage of the internal alkene provided corresponding aldehyde. Treatment of the crude aldehyde with sulfone **7** under Julia–Kocienski olefination conditions afforded desired α,β -unsaturated ester **6** (63% over 3 steps); however, the (*E*)-selectivity was mediocre (*E*:*Z* = ~2:1) and the *E*/*Z* mixture was difficult to separate. To avoid this drawback, following the ozonolysis the aldehyde was treated with a Horner–Wadsworth–Emmons (HWE) reagent and (*E*)- α,β -unsaturated ester **5** was predominantly obtained in 89% yield over 3 steps. Following DIBAL reduction of the ester, the resulting alcohol was protected by a benzyl group. Pure *E*-isomer **6** was provided in high yield (94% over 2 steps).

Sharpless asymmetric dihydroxylation of **6** using AD mix- α and subsequent acetonide protection of diol gave **8** (Scheme 3). The stereoconfiguration of **8** was confirmed by leading to the enantiomer of Crimmins' AM3 THP intermediate **9** which was spectroscopically identical to the literature values except the sign of the optical rotation {**9**: $[\alpha]_D^{20} = -3.75^\circ$ (*c* = 0.40, CH₂Cl₂), lit: $[\alpha]_D^{23.5} = +3.76^\circ$ (*c* = 3.3, CH₂Cl₂)}.¹² Reductive debenzoylation of **8** with lithium di-*tert*-butylbiphenylide (LiDBB)¹⁶ afforded alcohol **10** in 95% yield.

The preparation of the side chain fragment (C51–C63) was readily accomplished (Scheme 4). The starting chlorodiene **11** was prepared from a commercially available undec-10-yn-1-ol based on two-step literature procedures (lit: 50%).¹⁷ Since the degree of *E*-selectivity in Julia olefination is often substrate dependent and unpredictable,^{8b,9b} both aldehyde **12** and

sulfone **13** were accordingly prepared. DMP oxidation of **11** gave aldehyde **12** in 83% yield. One-pot Mitsunobu reaction of **11** with 1-phenyl-1*H*-tetrazolyl sulfone (PTSH) followed by molybdate-promoted oxidation afforded sulfone **13** in 91%.

Likewise, THP alcohol **10** was also converted into sulfone **14** (68%) and aldehyde **15** (Scheme 5). Those fragments were finally assembled by the Julia-Kocienski reaction. Although both approaches (routes A and B) afforded desired olefination product (*E*)-**2** as a major isomer (up to *E*:*Z* = ~3:1), route B (40%, 2 steps) provided higher yield of **2** than route A (17%, 3 steps). (*E*)-**2** and (*Z*)-**2** were only separable by HPLC.

As an alternative to construct the C50–C51 double bond, olefin metathesis and Wittig reactions were then examined. Unfortunately, the metathesis approach was unsuccessful and also, as expected, the standard Wittig olefination exclusively gave the undesired *Z*-isomer of **2** in 74% yield (Scheme 6). The Schlosser modification of the Wittig reaction often produces an *E*-isomer from an unstabilized ylide,¹⁸ but, due to the technical complexity in small scale operations, our attempt failed.

In summary, a C(42–63) B-ring THP fragment (**2**) of KmTx2 was concisely prepared from a readily available common THP intermediate **3** in a 12-step reaction series (11% overall yield, 83% per step). The Julia–Kocienski olefination, particularly between an aldehyde **15** and a sulfone **13**, effectively afforded **2**. Further investigations towards the synthesis of karlotoxins are currently underway in our laboratories.

Supplementary Material

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Figure 1.
Karlotoxin 2 (**1**)

Scheme 1.
Retrosynthetic analysis of KmTx 2

Scheme 2.
Synthesis of **6**

Scheme 3.
Synthesis of **10**

Scheme 4.
Synthesis of chlorodiene fragments

Scheme 5.
Julia-Kocienski olefination

Scheme 6.
Wittig reaction