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Diastereoselective synthesis of the C29–C41 fragment of karlotoxin 2

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ABSTRACT

A highly diastereoselective synthesis of the C29–C41 fragment of karlotoxin 2 (KmTx2) is described by employing regio-selective epoxide opening, our own developed domino isomerization followed by C–O and C–C bond formation reaction and chelation-controlled Grignard reaction as key steps. The synthesis involves installation of seven stereocenters present in the C29–C41 fragment of karlotoxin 2.

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Karlotoxins are fascinating group of metabolites, isolated from *Karlodinium venificum* in Maryland.[1] Karlotoxin 2 (KmTx2) was obtained from cultured material of *K. Venificum* (ccmp 2064) actually collected from a fish-kill in Georgia.[2] Two families of karlotoxins have been described as belonging to the karlotoxin 1 (KmTx1) and karlotoxin 2 (KmTx2) groups. The main difference between these two groups is in carbon chain structure which is localized to the length of the lipophilic side chain. KmTx2 is two carbons shorter, whereas KmTx1 has 18 carbon chain and lipophilic arm length an important determinant for potency of both the karlotoxins. Karlotoxins shows similar activity to amphotericin B, and amphidinol 3 (AM3) (Fig. 1).

KmTx2 exhibits potent homolytic, cytotoxic, ichthyotoxic activity[1a] through the membrane and sterol binding.

KmTx2, which resembles the structural features of amphidinol 3, possesses 28 stereogenic centers, two immensely oxygenated tetrahydropyrans, a long irregular polyol system and with a chlorine atom.[3] Recently, we have developed a novel protocol that is tandem isomerization followed by C–O and C–C bond formation reaction for the synthesis of a *trans*-2,6-disubstiuted dihydropyran from δ-hydroxy α,β-unsaturated aldehyde and applied for a synthesis of a number of complex biologically active molecules.[4] As there is only one synthesis of C42–C63 fragment of karlotoxin 2 till date,[5] we intrigued to apply our own developed protocol for the synthesis of C29–C41 fragment of karlotoxin 2.

According to our retrosynthetic analysis, compound 3 could be prepared from **4**, following a chelation controlled Grignard reaction on aldehyde. Advance intermediate *trans*-2,6-disubstiuted dihydropyran **6** could be achieved from δ-hydroxy α,β-unsaturated aldehyde **5** following our own developed methodology. δ-Hydroxy α,β-unsaturated aldehyde **5** could be prepared from a known epoxide **7** which in turn could be synthesized starting from commercially available 1,4-butyne diol (**8**) (Scheme 1).

The synthesis was started with a known epoxy alcohol **7**, which was accessed starting from butyne-1,4-diol, following a three-step protocol[6] (Scheme 2). Oxidation of alcohol **7** with Dess–Martine periodinane[7] in CH_2Cl_2 at room temperature afforded a corresponding aldehyde that was immediately treated with $Ph_3P{=}CHCO_2Et$ in toluene at room temperature to obtain the α,β-unsaturated ester **9** in 76% yield over two steps as exclusive *E*-isomer. Regioselective opening of epoxy α,β-unsaturated ester under Lewis acid conditions with benzyl alcohol as a nucleophile in CH_2Cl_2 afforded the δ-hydroxy α,β-unsaturated ester **10** as a single isomer in 82% yield.[8]

DIBAL-*H* reduction of the ester at −78 °C provided the corresponding allyl alcohol **11** in 89% yield. Selective oxidation of allyl alcohol was carried out under 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) and [bis(acetoxy)iodo]benzene (BAIB) conditions[9] at room temperature in CH_2Cl_2 to furnish the δ-hydroxy α,β-unsaturated aldehyde **5** in 90% yield. Now, the stage is set to carry out our own developed iodine-catalyzed tandem isomerization followed by C–O and C–C bond formation reaction. Accordingly, compound **5** was treated with 10 mol % of molecular iodine and

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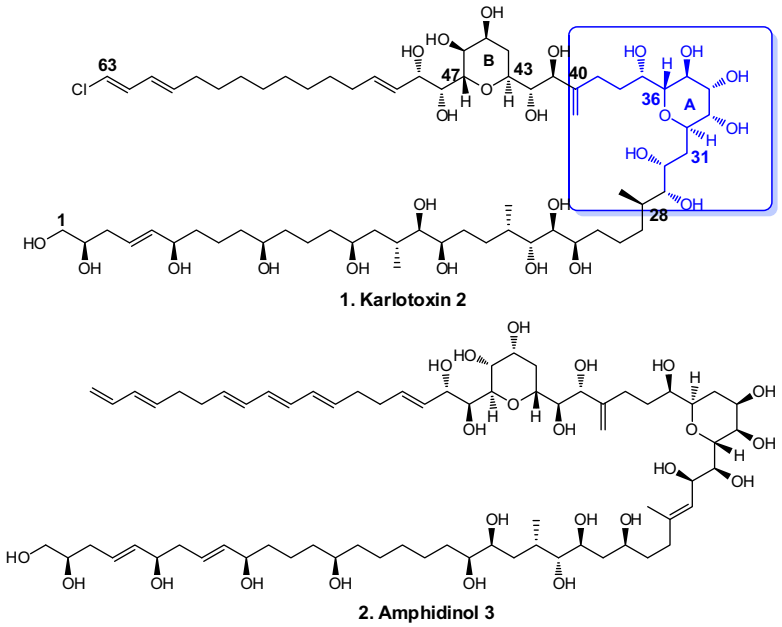
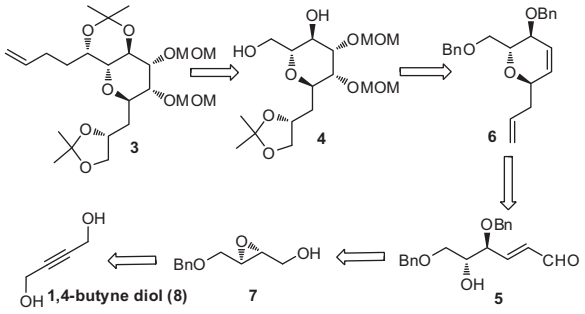
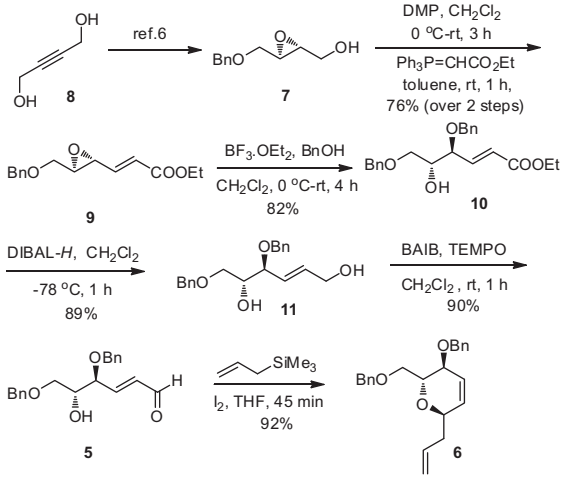


Figure 1. The proposed structures for KmTx2 and AM3.



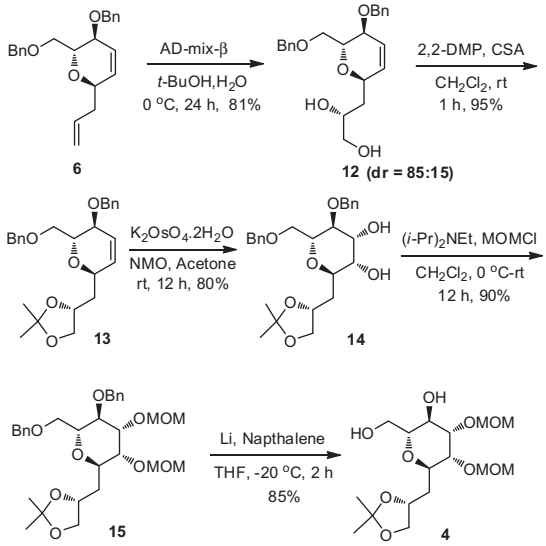
Scheme 1. Retrosynthetic analysis of KmTx2.



Scheme 2. Synthesis of dihydropyran **6**.

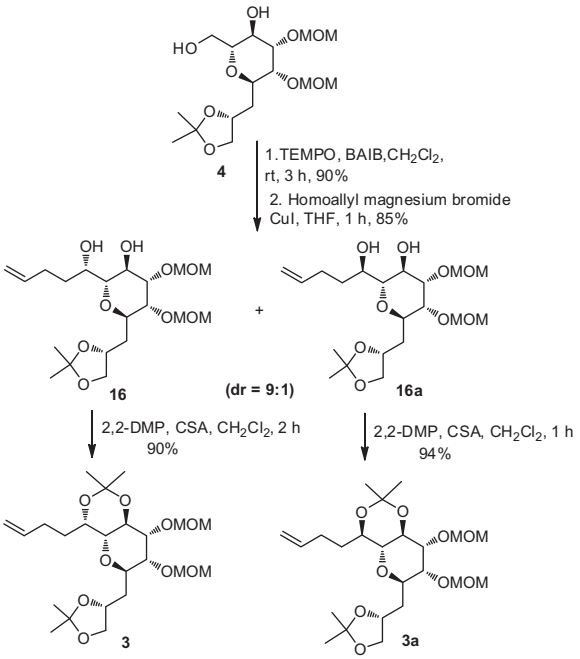
allyltrimethylsilane in THF at room temperature to obtain *trans*-2,6-disubstituted-3,6-dihydropyran **6** in 92% yield.

The next task was to perform the regioselective oxidation of terminal double bond, which was achieved by following Sharpless asymmetric dihydroxylation[10] using AD-mix-β to obtain **12** (dr = 85:15), and the diastereomers were easily separated by silica gel column chromatography in 81% yield. Protection of the resulting diol **12** as its isopropylidine derivative **13** was achieved using a catalytic amount of camphorsulfonic acid (CSA) with dimethoxypropane (2,2-DMP) in 95% yield. Compound **13** was then treated with $K_2OsO_4{\cdot}2H_2O$ and *N*-methylmorpholine-*N*-oxide (NMO) at room temperature in acetone to obtain compound **14** as a major diastereomer (95:5) with 80% yield.[11] The resulting diol was protected as its methoxymethyl ethers with methoxy methyl chloride (MOMCl) and *N*,*N*-diisopropylethylamine (DIPEA) in CH_2Cl_2 at 0 °C to afford compound **15** in 90% yield.



Scheme 3. Synthesis of 1,3-diol compound **4**.

Having prepared fully functionalized tetrahydropyran **15**, the next task was to extend the side chain as well as to install the stereocenter present at C-37. Accordingly, benzyl groups were removed with lithium in the presence of naphthalene in freshly distilled THF at −20 °C to obtain diol **4** in 85% yield (Scheme 3).[12]



Scheme 4. Synthesis of the C29–C41 fragment.

Primary alcohol was selectively oxidized with TEMPO/BAIB in CH_2Cl_2 to afford aldehyde, which was immediately purified by flash chromatography on silica gel and treated with homoallyl magnesium bromide in the presence of a catalytic amount of CuI at −78 °C in anhydrous THF to obtain 1,3-diols **16** and **16a** (9:1) in 85% yield.[13] The selectivity was intrigued due to chelation controlled 1,3-induction by an internal addition of nucleophile (Scheme 4).[14]

At this stage, the Rychnovsky method[15] was utilized to assign geometry of the newly created stereogenic center. For the same, compound **16** and **16a** were converted to its respective acetonide derivatives **3** and **3a** by treating with 2,2-DMP and a catalytic amount of CSA in CH_2Cl_2 at room temperature in 90% and 94% yields, respectively. In ^{13}C NMR spectra, methyl groups for compound **3** resonated at δ = 24.7 and 24.8 ppm and quaternary carbon at 100.2 ppm indicated a 1,3-*trans* relationship, where as for compound **3a** methyl groups resonated at δ = 20.0 and 29.5 ppm and quaternary carbon at 99.6 ppm, which confirmed the *cis*-nature of 1,3-diol.

In summary, we have synthesized the C29–C41fragment of karlotoxin 2 in a concise manner utilizing regioselective epoxide opening, our own developed domino isomerization followed by C–O and C–C bond formation reaction as the key steps in good overall yield (14 longest linear sequence starting from epoxy alcohol with 15.5% overall yield). Further progress toward the synthesis of karlotoxin 2 and various related natural products using tandem isomerization followed by C–O and C–C bond formation reaction will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.051.

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15. *Spectral data of compound* **3**: $[\alpha]_D^{25}$ −39.6 (*c* 0.3, $CHCl_3$); IR (neat): υ_{max} 2915, 2857, 2359, 2342, 1453, 1219, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.81 (m, 1H), 5.06–4.90 (m, 2H), 4.81–4.57 (m, 4H), 4.22–3.95 (m, 5H), 3.93–3.74 (m, 2H), 3.62–3.44 (m, 2H), 3.40 (s, 3H), 3.36 (s, 3H), 2.36–1.91 (m, 4H), 1.84–1.67 (m, 2H), 1.43 (s, 3H), 1.38(s, 3H), 1.33(s, 3H), 1.31(s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4, 114.7, 108.8, 100.2, 96.5, 95.9, 77.1, 76.8, 75.7, 73.6, 73.4, 70.7, 70.0, 69.6, 69.5, 66.9, 55.5, 55.4, 32.7, 30.2, 28.3, 27.1, 26.9, 25.8, 23.7; ESI-HRMS: *m*/*z* calcd for $C_{23}H_{40}O_9Na$ $[M+Na]^+$ 483.2570, found 483.2543.