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Synthetic studies on brevetoxin-B. Part 3: Stereoselective synthesis of the IJK-ring system

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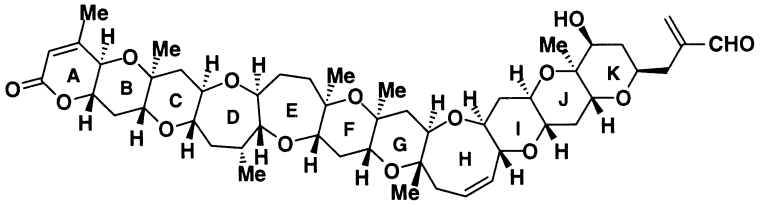
Abstract

The IJK-ring system of brevetoxin-B was stereoselectively synthesized based on the 6-*endo*-cyclizations of a hydroxy methylepoxide and a hydroxy styrylepoxide, and the direct introduction of the C-4 unit as the side chain.

Keywords: brevetoxin-B; *endo*-cyclization; styrylepoxide; allyl *C*-glycosidation.

In the preceding two papers,[1,2] we reported the stereoselective synthesis of the ABC- and EFG-ring systems of brevetoxin-B (BTX-B) (**1**). We now report the stereoselective synthesis of the IJK-ring system of BTX-B (**1**). Our synthesis of the IJK-ring system features 6-*endo*-cyclizations of a hydroxy methylepoxide and styrylepoxide for the construction of the J- and I-ring systems, respectively, and direct introduction of a C-4 unit as the side chain on the K-ring.



Brevetoxin B (1)

Since the structure of the J-ring is identical with that of the B-ring, the tetrahydropyran **2**,[1] the key intermediate in the synthesis of the ABC-ring system, was chosen as the starting material for

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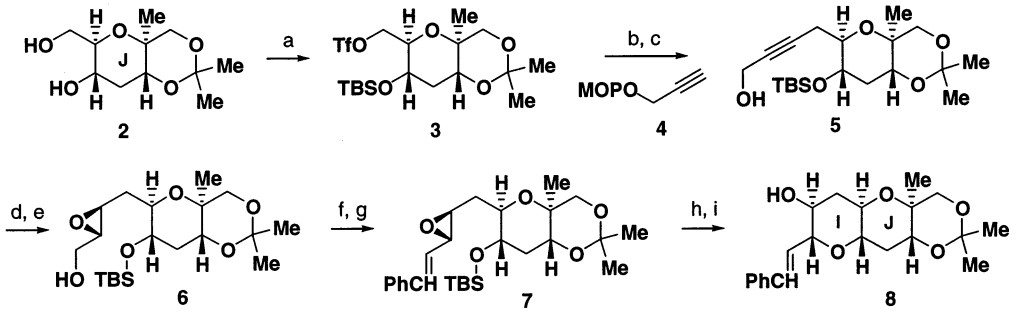
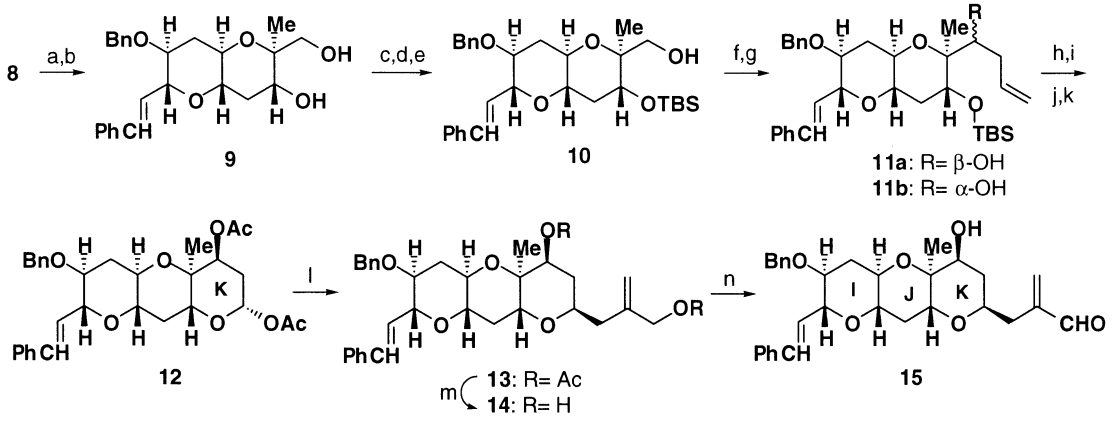
the construction of the IJK-ring system. First, the construction of the I-ring system was investigated using the 6-*endo*-cyclization of hydroxy styrylepoxide (Scheme 1).[3] The treatment of the diol **2** with triflic anhydride followed by TBSOTf[4] gave the triflate **3**. The reaction of **3** with the methoxypropylidene (MOP) ether **4**,[5] prepared from propargyl alcohol, in the presence of *n*-BuLi in THF–DMPU at −20°C[6] and subsequent deprotection of the MOP group with PPTS[7] afforded propargylic alcohol **5** in 76% yield from **2**. The reduction of **5** with Red-Al® gave the (*E*)-allylic alcohol, which was subjected to the Sharpless asymmetric epoxidation[8] with *t*-BuOOH in the presence of (+)-DET and Ti(O*i*-Pr)$_4$ in CH_2Cl_2 to give the β-epoxide **6**. The oxidation of the alcohol **6** with TPAP[9] followed by the Wittig reaction using $Ph_3P{=}CHPh$ gave the styrylepoxide **7**. After deprotection of the TBS group with TBAF, the cyclization of **7** was examined. The regio- and stereoselective 6-*endo*-cyclization of the resulting hydroxy styrylepoxide was performed by treatment with NaH in DMSO[3] to give the six-membered ether **8**, corresponding to the IJ-ring, in 92% yield from **7**. The cyclization with CSA, as an acidic activator, in CH_2Cl_2 produced **8** in 62% yield. Thus, in this case, base conditions gave better results for the 6-*endo*-cyclization.

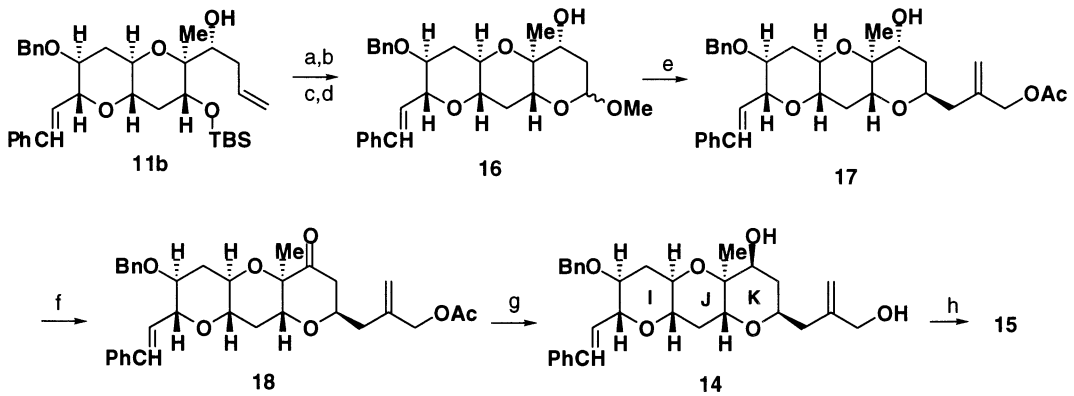


Scheme 1. (a) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78°C, then TBSOTf, −78 ~ 0°C; (b) **4**, *n*-BuLi, THF-DMPU (6:1), −20°C; (c) PPTS, MeOH, 0°C, (76% from **2**); (d) Red-Al®, Et_2O, rt (88%); (e) *t*-BuOOH, (+)-DET, Ti(O*i*-Pr)$_4$, MS-4A, CH_2Cl_2, −20°C (93%); (f) TPAP, NMO, MS-4A, CH_2Cl_2, rt; (g) $Ph_3P^+CH_2PhCl^-$, NaHMDS, THF, 0°C (64% from **6**); (h) TBAF, THF, rt; (i) NaH, DMSO, 0°C ~ rt (92% from **7**)

The construction of the K-ring system and introduction of the C-4 unit as the side chain were then investigated (Scheme 2). The alcohol **8** was converted into the alcohol **10** in five steps via **9**: (1) protection of the hydroxyl group as the benzyl ether, (2) deprotection of the acetonide, (3) acetylation of the primary alcohol, (4) silylation of the secondary alcohol and (5) methanolysis of the acetate. The oxidation of **10** with TPAP[9] followed by the Grignard reaction using allylmagnesium chloride in THF at −78°C gave the desired β-alcohol **11a** and its α isomer **11b** in 65 and 21% yields, respectively. Both isomers **11a** and **11b** were converted into the same diol **14**, a precursor of the α,β-unsaturated aldehyde **15** corresponding to the IJK-ring, as shown in Schemes 2 and 3, respectively.



Scheme 2. (a) BnBr, n-Bu_4NI, NaH, THF, 0°C ~ rt (96%); (b) CSA, MeOH, rt (94%); (c) AcCl, 2,4,6-collidine, CH_2Cl_2, −78°C; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C; (e) K_2CO_3, MeOH, rt (85% from **9**); (f) TPAP, NMO, MS-4A, CH_2Cl_2, rt; (g) allylMgCl, THF, −78°C (**11a** 65% and **11b** 21% from **10**); (h) TBAF, THF, rt (91%); (i) OsO_4, NMO, aq. t-BuOH (1:1), rt; (j) $NaIO_4$, aq. THF, rt (91%, 2 steps); (k) Ac_2O, pyridine, rt (99%); (l) CH_2=C(CH_2OAc)CH_2TMS, TMSOTf, MeCN, 0°C (98%); (m) K_2CO_3, MeOH, rt (95%); (n) MnO_2, Et_2O, rt (81%)



Scheme 3. (a) TBAF, THF, rt (98%); (b) OsO_4, NMO, aq. t-BuOH (1:1), rt; (c) $NaIO_4$, aq. THF, rt (80%, two steps); (d) Dowex® (50W-X2), MeOH, rt (75%); (e) CH_2=C(CH_2OAc)CH_2TMS, TMSOTf, MeCN, 0°C (82%); (f) PCC, MS-4A, benzene, 80°C (80%); (g) L-Selectride®, THF, −78°C, then MeOH (85%); (n) MnO_2, Et_2O, rt (81%)

After deprotection of the TBS group in **11a** with TBAF, dihydroxylation of the olefin with OsO_4–NMO followed by $NaIO_4$ treatment produced a hemiacetal, which was acetylated to give the diacetate **12** (Scheme 2). The direct introduction of a C-4 unit as the side chain of the K-ring was then carried out. The reaction of **12** with CH_2=C(CH_2OAc)CH_2TMS in the presence of TMSOTf in MeCN at 0°C exclusively produced the desired β-substituted compound **13** as a single isomer in 98% yield.[3b,10] The stereochemistry of **13** was determined by ^1H NMR analysis and an NOE experiment. Methanolysis of the diacetate **13** with K_2CO_3 gave the allyl alcohol **14**, which was oxidized with MnO_2 in ether to give the α,β-unsaturated aldehyde **15** in 81% yield. The product **15** corresponds to the IJK-ring system of BTX-B (**1**).

On the other hand, the isomeric α-alcohol **11b** was also converted into the diol **14** via the ketone **18** (Scheme 3).[3b] The α-alcohol **11b** was converted into the acetal **16** in four steps: (1) desilylation, (2) oxidation of the olefin to a diol, (3) oxidative cleavage of the diol to an

aldehyde, and (4) hemiacetalization. The treatment of **16** with CH_2=CH(CH_2OAc)CH_2TMS in the presence of TMSOTf also gave the β-substituted compound **17** in 82% yield as the single product. After oxidation of **17** with PCC, reduction of the resulting ketone **18** with L-Selectride® exclusively took place from the α-side to give the β-alcohol **14**, accompanied by cleavage of the acetate. The diol **14** was oxidized with MnO_2 to the desired aldehyde **15**, which was identical with the aldehyde **15** from **11a**.

In summary, the IJK-ring system **15** of BTX-B (**1**) was efficiently synthesized based on the 6-*endo*-cyclization of the methyl epoxide and styrylepoxide, and formation of the hemiacetal followed by direct introduction of a C-4 unit as the side chain of the K-ring. We have accomplished the stereoselective syntheses of the ABC-, EFG-, and IJK-ring systems of BTX-B (**1**). Further studies toward the total synthesis of BTX-B are now in progress in our laboratory.

Acknowledgements

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