Pergamon

Tetrahedron Letters 41 (2000) 7677–7680

TETRAHEDRON LETTERS

Synthetic studies on brevetoxin-B. Part 2: Stereoselective synthesis of the EFG-ring system

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Received 13 July 2000; revised 3 August 2000; accepted 4 August 2000

Abstract

The EFG-ring system of brevetoxin-B, having an α-methyl group on the D-ring, was stereoselectively synthesized based on the stereoselective Michael addition of the α-methyl group, novel ring-expansion reaction, and 6-*endo*-cyclizations of the vinylepoxide and methylepoxide.

Keywords: brevetoxin-B; Michael addition; ring-expansion reaction; *endo*-cyclization.

In the preceding paper,[1] we reported the stereoselective synthesis of the ABC-ring system of brevetoxin-B (BTX-B). We now report the stereoselective synthesis of the EFG-ring system having an α-methyl group on the D-ring. Our synthesis of the EFG-ring system features the stereoselective Michael addition for the introduction of the α-methyl group on the D-ring, a novel ring-expansion reaction for the construction of the E-ring system, and the 6-*endo*-cyclizations for the construction of the F- and G-ring systems.

In the total synthesis of BTX-B, the stereoselective introduction of the α-methyl group on the D-ring should be one of the crucial problems.[2] We anticipated that the methyl group would be stereoselectively introduced to an α,β-unsaturated ester or δ-lactone by the Michael addition. The α,β-unsaturated ester **3** and δ-lactone **6** were thus synthesized from the diol **1**,[3] which is a key intermediate in our total synthesis of hemibrevetoxin B (Scheme 1). The starting material **1**, prepared from geranyl acetate, was converted into the alcohol **2** in three steps: (1) selective acetylation of the primary alcohol,[4] (2) protection of the secondary alcohol as the TBS ether and (3) alkaline hydrolysis of the acetate. The oxidation of **2** with TPAP[5] followed by the Wittig reaction provided the desired α,β-unsaturated ester **3a**, which was treated with TBAF to give the alcohol **3b**. On the other hand, after the oxidation of **2** with TPAP, the aldol reaction with the lithium enolate of ethyl acetate gave the ester **4**. Deprotection of the TBS group with TBAF, hydrolysis with LiOH and lactonization-acetylation with Ac_2O afforded **5**, which was treated with DBU to produce the desired α,β-unsaturated δ-lactone **6**.

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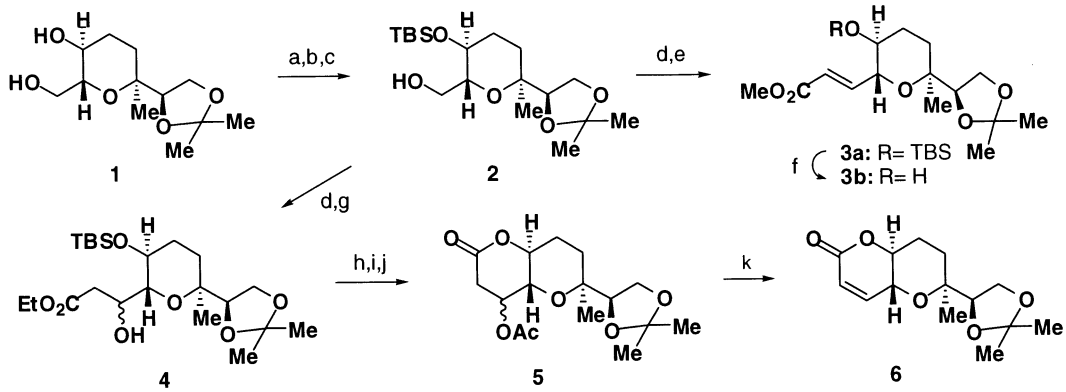
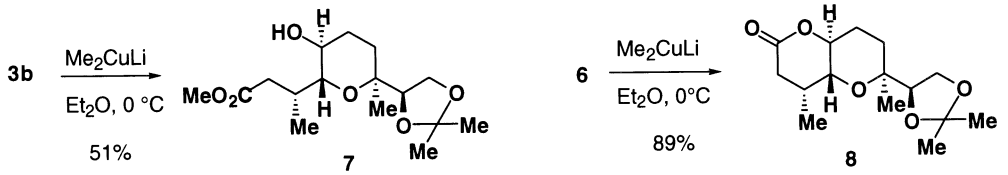
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01340-X



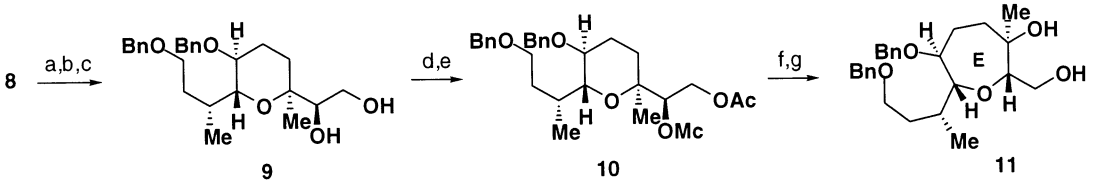
Scheme 1. (a) AcCl, 2,4,6-collidine, CH_2Cl_2, −78°C; (b) TBSCl, imidazole, DMF, rt; (c) K_2CO_3, MeOH, rt (92% from **1**); (d) TPAP, NMO, MS-4A, CH_2Cl_2, rt; (e) $Ph_3P{=}CHCO_2Me$, toluene, 100°C (85% from **2**); (f) TBAF, THF, rt (77%); (g) EtOAc, LDA, THF, −78°C (84% from **2**); (h) TBAF, THF, rt; (i) LiOH, aq. THF, 0°C; (j) Ac_2O, pyridine, rt (78% from **4**); (k) DBU, benzene, rt (88%)

The Michael reactions of **3a**, **3b** and **6** with Me_2CuLi were then examined (Scheme 2). The reaction of the α,β-unsaturated ester **3a** with Me_2CuLi in Et_2O at 0°C gave no adduct, while **3b** stereoselectively afforded the desired α-methyl adduct **7** as the sole product, although the yield was moderate (51%). On the other hand, the Michael reaction of **6** under the same conditions proceeded smoothly with complete stereoselection and in high yield, giving the desired **8** (89%). The stereoselective Michael additions would take place via coordination of the reagent and the hydroxyl group in **3b**, and via axial attack of the reagent in **6**.



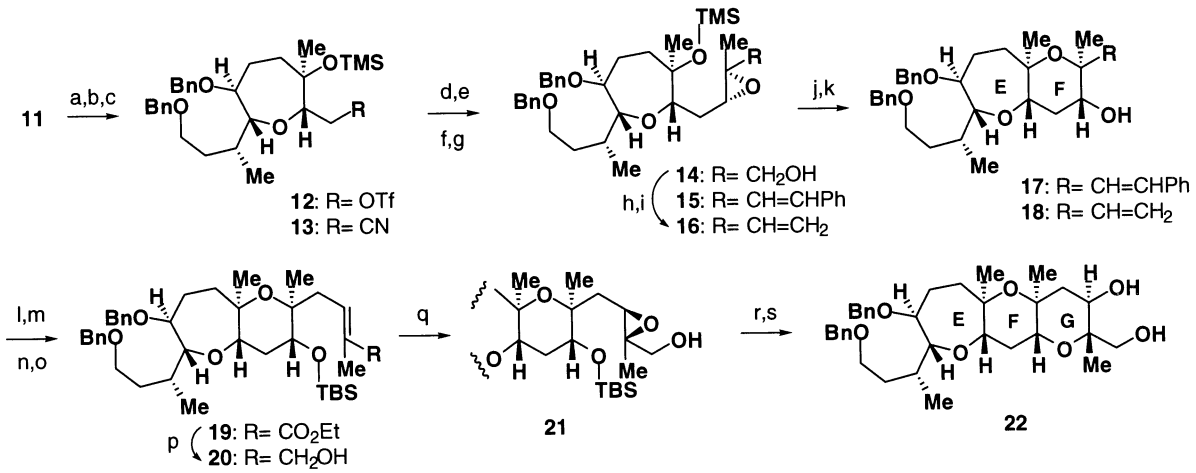
Scheme 2.

Having accomplished the introduction of the α-methyl group on the D-ring with complete stereoselection, we then examined the construction of the E-ring system based on our ring-expansion reaction using a chloromethanesulfonate (monochlate) (Scheme 3).[6] The reduction of **8** with $LiAlH_4$, protection of the resulting diol as the benzyl ether, and deprotection of the acetonide afforded the diol **9**. Selective protection of the alcohols in **9** with AcCl-2,4,6-collidine[4] followed by $ClCH_2SO_2Cl$ (McCl)-2,6-lutidine gave the required monochlate **10**. Upon treatment with $Zn(OAc)_2$ in AcOH–H_2O (1:1) at reflux, the ring-expansion of **10** took place to give the seven-membered ether, which was treated with K_2CO_3 in methanol to give the oxepane **11**, corresponding to the E-ring, in 88% yield from **9**.



Scheme 3. (a) $LiAlH_4$, Et_2O, 0°C ~ rt; (b) BnBr, *n*-Bu_4NI, NaH, THF, 0°C ~ rt; (c) CSA, MeOH, rt (93% from **8**); (d) AcCl. 2,4,6-collidine, CH_2Cl_2, −78°C; (e) McCl, 2,6-lutidine, CH_2Cl_2, 0°C; (f) $Zn(OAc)_2$, aq. AcOH, reflux; (g) K_2CO_3, MeOH, rt (88% from **9**)

Next, the construction of the F-ring system, which has 1,3-diaxial dimethyl groups on the tetrahydropyran ring, was examined (Scheme 4). The oxepane **11** was converted into the epoxy alcohol **14** via carbon elongation and the Sharpless asymmetric epoxidation (AE).[7] The treatment of **11** with triflic anhydride followed by TMSOTf[8] gave the triflate **12**, which was treated with NaCN and then TMSOTf[9] to give the nitrile **13**. The nitrile **13** was then converted into an epoxy alcohol **14** in four steps: (1) DIBAH reduction, (2) the Wittig reaction using $Ph_3P{=}C(Me)CO_2Et$, (3) DIBAH reduction and (4) the Sharpless AE[7] using (–)-DIPT. After deprotection of the TMS group, the direct cyclization of **14** with PPTS[10] gave the undesired 5-*exo*-cyclized compound, as anticipated, due to the steric hindrance of the dimethyl groups. We then examined the cyclization using epoxides having a styryl[11] or vinyl group,[12] which should activate the 6-*endo*-cyclization. The oxidation of **14** with TPAP followed by the Wittig reactions with $Ph_3P{=}CHPh$ and $Ph_3P{=}CH_2$ afforded the styryl and vinyl epoxides, **15** (82%) and **16** (87%), respectively. After deprotection of the TMS group in **15** and **16** with TBAF, treatment of the resulting alcohols with PPTS produced the 6-*endo*-cyclization to give the desired 2,3-*trans*-tetrahydropyrans **17** and **18**, corresponding to the F-ring, in 55 and 88% yield, respectively. Although the 6-*endo*-cyclization of the styrylepoxides usually gave a higher yield than that of the vinylepoxides, this is the only exception that we have examined so far.



Scheme 4. (a) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78°C, then TMSOTf, −78°C; (b) NaCN, DMSO, 35°C; (c) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C (72% from **11**); (d) DIBAH, CH_2Cl_2, −78°C; (e) $Ph_3P{=}C(Me)CO_2Et$, toluene, 100°C (96% from **13**); (f) DIBAH, toluene, −78°C (93%); (g) *t*-BuOOH, (–)-DIPT, $Ti(O\textit{i}\text{-}Pr)_4$, MS-4A, CH_2Cl_2, −20°C (85%); (h) TPAP, NMO, MS-4A, CH_2Cl_2, rt; (i) $Ph_3P^+MeBr^-$, NaHMDS, THF, 0°C (87% from **14**); (j) TBAF, THF, rt; (k) PPTS, CH_2Cl_2, 0°C (88% from **16**); (l) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C; (m) $BH_3{\cdot}THF$, THF, 0°C ~ rt, then aq. NaOH, H_2O_2 (67% from **18**); (n) TPAP, NMO, MS-4A, CH_2Cl_2, rt; (o) $Ph_3P{=}C(Me)CO_2Et$, toluene, 100°C (93% in 2 steps); (p) DIBAH, toluene, −78°C (87%); (q) MCPBA, CH_2Cl_2, 0°C (93%); (r) TBAF, THF, 40°C; (s) CSA, CH_2Cl_2, 0°C (72% from **21**)

Finally, the construction of the G-ring system was carried out. The protection of the alcohol **18** with TBSOTf and subsequent hydroboration/oxidation afforded an alcohol, which was subjected to TPAP-oxidation followed by the Wittig reaction using $Ph_3P{=}C(Me)CO_2Et$ to give the ester **19**. The reduction of **19** with DIBAH followed by MCPBA treatment stereoselectively gave the β-epoxide **21**.[13] After deprotection of the TBS group in **21**, treatment of the resulting

alcohol with CSA stereoselectively effected the 6-*endo*-cyclization without any activation to give the *trans*-fused six–six–seven-membered ether **22** in 72% yield. The cyclic product **22** corresponds to the EFG-ring system of BTX-B.

In summary, the EFG-ring system having an α-methyl group on the D-ring was synthesized with complete stereoselection based on the stereoselective Michael addition of the methyl group, the ring-expansion of a tetrahydropyran to an oxepane, and the 6-*endo*-cyclizations of the vinylepoxide and methylepoxide.

Acknowledgements

This work was supported in part by Special Project Funding for Basic Science (Multibioprobe) from RIKEN. The authors thank Dr. H. Koshino for the NMR spectral measurements, Ms. K. Kobayashi for the X-ray crystallographic analysis, and Ms. K. Harata for the mass spectral measurements.

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