Harnessing Glycal-Epoxide Rearrangements: The Generation of the AB, EF, and IJ Rings of Adriatoxin[**]

Clement Osei Akoto and
Department of Chemistry, University of Utah 315 South 1400 East, Salt Lake City, UT 84112 (USA) Fax: (+ 1) 801−581−8433

Jon D. Rainier[*]

[*]*Department of Chemistry, University of Utah 315 South 1400 East, Salt Lake City, UT 84112 (USA) Fax: (+ 1) 801−581−8433*

Keywords

enols; epoxidation; metathesis; rearrangement; titanium

The marine ladder toxin class of natural products has generated considerable interest from the synthetic and biomedical communities because of their fascinating structures and biological activities.[1,2] This group includes a target that has recently become of interest to us, adriatoxin (Scheme 1), a polyether toxin isolated by Fattorusso and coworkers from the digestive gland of the Adriatic mussel *Mytilus galloprovincialis*.[3-5] Synthetically, our fascination with adriatoxin came out of an interest in determining whether our recently described coupling protocol, which leads to the pairing of two subunits and the generation of two additional rings, would enable us to carry out a convergent synthesis of the ten-ring system from three bicyclic precursors representing the AB ring (**1**), the EF ring (**2**), and the IJ ring (**3**).[6] Biologically, that adriatoxin had been implicated in diarrhetic shellfish poisoning would allow us to continue our collaborative studies which have been focused on the ability of natural and non-natural polyethers to bind to ion channels.[7] In addition to this, that Shimizu has identified structurally related yessotoxin analogues as having exceptional cytotoxic activity against human cancer cell lines was also intriguing.[8]

We had hoped to utilize iterative C-glycoside technology to access the adriatoxin AB-ring subunit, starting from 2-deoxy-D-ribose (Scheme 2).[9] Conversion of this precursor into olefinic alcohol **5** required four steps and was carried out in a 64 % overall yield.[10] Esterification with butanoic acid derivative **6** and then olefinic ester cyclization, under our recently disclosed reduced-titanium reaction conditions, gave **8** in 70 % yield.[11] In contrast, the use of a more conventional two-step enol ether–olefin ring-closing metathesis sequence gave **8** in a 50 % overall yield from **7**.

Next, we needed to introduce an oxygen atom at C6 and to reduce C7 of **8**. In principle, these goals could be accomplished in a single flask by either subjecting the enol ether to a hydroboration/oxidation reaction or by the use of a 2,2-dimethyldioxirane (DMDO)/

---

diisobutylaluminum hydride protocol.[12] However, because of the presence of the C3 angular methyl group in **8** we felt that both of these procedures would generate the undesired stereochemistry at both C6 and C7.[13] Whereas we believed that this problem could be overcome by oxidizing the alcohol to the corresponding ketone, equilibrating the C7 stereocenter to the desired thermodynamically more stable isomer, and subsequently reducing the ketone, we sought a more direct solution. We realized that we might be able to take advantage of an epoxide rearrangement reaction that had, in the past, been problematic for us. [14] The reaction is outlined in Scheme 3 for **9** and involves a Lewis acid catalyzed pinacol-type rearrangement to give **10**. As illustrated, when the rearrangement was induced with allyl Grignard, it resulted in the generation of the corresponding tertiary alcohol (**11**). Of importance to our use of this reaction for the adriatoxin AB subunit was that **11** was isolated as a single diastereomer, implying that the rearrangement of **9** was stereoselective.

We recognized that if we were able harness the rearrangement in a synthetic context, that it might prove to be a useful solution for the adriatoxin A-ring problem and allow us to avoid the equilibration sequence mentioned above. That is, if the epoxidation of **8** was directed by the C3 angular methyl group and if the subsequent rearrangement was stereoselective per our previous results, the reaction would deliver the desired C7 stereochemistry along with a C6 ketone.

The oxidation of **8** using "acetone free" DMDO presumably gave **12** (not isolated; Scheme 4), [15] which was then directly subjected to Lewis acids in an attempt to induce the rearrangement. We focused on Mg salts and examined $MgBr_2 \cdot Et_2O$, an "aged" bottle of $MeMgCl$, and reagent grade $MgCl_2$. Pleasingly, because it was the simplest to use, the $MgCl_2$ worked best; upon exposure to $MgCl_2$, **12** rearranged to ketone **13** in 82 % yield. Extensive nOe experiments indicated that **13** had the desired adriatoxin C7 stereochemistry, thus confirming our earlier hypothesis regarding the stereoselectivity of the rearrangement.

Having successfully generated **13** we next focused our attention on the C6 center and the B ring. To accomplish these goals the ketone in **13** was reduced with $NaBH_4$ to obtain the desired equatorial alcohol (Scheme 5), which then underwent acid-mediated cyclization and elimination to give the adriatoxin B ring (**14**).[16] DMDO oxidation of **14** and propenyl magnesium chloride addition to the resulting epoxide provided a mixture of secondary alcohols **15** and **16**. The undesired diastereomer (**16**) was converted into **15** by using the three-step protocol mentioned earlier involving: 1) oxidation of the secondary alcohol, 2) equilibration of the C10 stereocenter, and 3) reduction of the ketone. The synthesis of AB subunit **15** was reasonably efficient in that it required 13 steps (15 % overall yield) and utilized D-ribose as the sole source of chirality.

Intrigued by the reaction to access ketone **13**, we examined the scope of the rearrangement reaction by exploring the effect of substitution in D-glucal model substrates [Eq. (1); TBDPS = *tert*-butyldiphenylsilyl]. In these studies we were somewhat disappointed to find that the epoxides from **17** and **18** gave no rearranged products, but instead gave only diols **19** and **20**.

$$O-O, CH_2Cl_2, \quad MgCl_2, THF$$

(1)

17: R = H
**18**: R = Me

19: R = H (82%)
20: R = Me (83%)
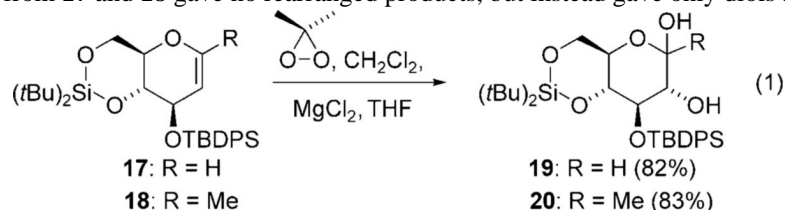
In contrast to the results from **17** and **18**, epoxides lacking substitution at the allylic position gave the ketones in high yield. Thus, when unsubstituted glycals **21** and **22** were subjected to

DMDO and subsequently reacted with $MgCl_2$ we isolated ketones **23** and **24**, respectively [Eq. (2)]. As with the rearrangement to **13**, each of these compounds was isolated as a single diastereomer. Although additional experiments on a broader range of substrates are needed, our results imply that less sterically hindered glycal epoxides are more likely to undergo the rearrangement reaction, and are consistent with previous results from our lab which described an inverse dependence between epoxide reactivity and the steric bulk of the allylic substituent. [17]

Seven-membered ring ketones can also be synthesized by using the epoxide rearrangement reaction. When **25** was subjected to DMDO and $MgCl_2$ we isolated enol **26** as a single diastereomer in 75% yield [Eq. (3)]. [18]

Our efforts to access the adriatoxin EF ring began with D-glyceraldehyde acetonide as a precursor to the E ring (Scheme 6). The addition of homoallyl grignard in the

21: R = Me
22: R = H

23: R = Me (90%)
24: R = H (88%)

(2)

25

(75%)

26

(3)
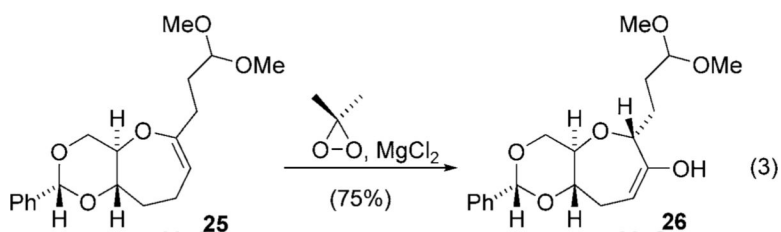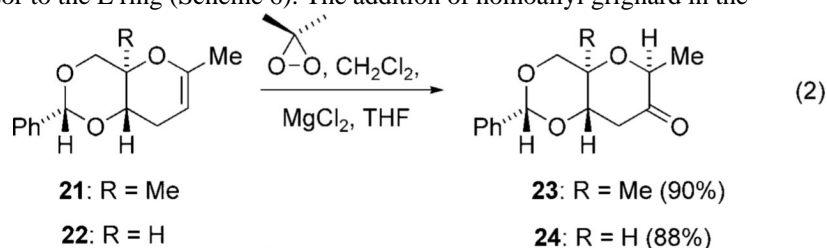
presence of $ZnCl_2$ gave alcohol **27**. [19] Methanolysis of the acetonide and benzylidene acetal formation gave cyclization precursor **30** after esterification with acetal **29**. Olefinic ester cyclization gave the adriatoxin E-ring subunit (**31**) in 65% yield.

Oxidation and reduction of the enol ether in **31** was carried out using DMDO and iBu$_2$AlH (Scheme 7). Additional oxidation of the resulting secondary alcohol gave ketone **32**. Notably, the reaction of **31** with DMDO and iBu$_2$AlH was stereoselective and ketone **32** existed as its keto tautomer. In contrast, diastereomeric substrate **26** existed as the enol tautomer [Eq. (3)]. Conversion of **32** into the corresponding tertiary alcohol and cyclization/elimination gave **33** in good yield. [16]

Two comments on the generation of **33** are worth noting. First, we had hoped that the C19 angular methyl group would ultimately dictate the stereochemistry at C23 (see below). Thus, we were relieved that the formation of the C19 tertiary alcohol was stereoselective. Second, whereas we have examined a number of related cyclization/elimination reactions, [16] the cyclization to obtain **33** was the first in which a ketal was employed, and we were pleased that the expected endocyclic enol ether was the only isomer obtained from this reaction.

For the generation of the C23 stereocenter and the completion of the adriatoxin F ring, we planned to employ a Claisen rearrangement from an in situ generated allyl enol ether (see **36**, Scheme 8). Whereas Claisen rearrangements to give C-glycosides are well precedented, [20] the proposed reaction is somewhat unique in that the oxygen atom linking the two alkenes is not in the allylic position on the pyran ring. To the best of our knowledge there is only one other

related reaction and it was accomplished by us during our gambierol work.[21] Oxidation of **33** with *m*CPBA in methanol gave **34** in 88% yield and then allyl ether formation gave rearrangement precursor **35**.

With the stage set for the rearrangement to the C23 stereocenter, we subjected **35** to PPTS, pyridine, and heat, and isolated ketone **37** in 92% yield and as a greater than 10:1 mixture of diastereomers (Scheme 8). Presumably, the path to **37** proceeds through allyl enol ether **36** and, as mentioned above, a stereoselective Claisen rearrangement. Having successfully generated **37**, all that remained to obtain EF-ring precursor **38** was the reduction of the ketone, and this was accomplished in 94% yield using NaBH$_4$. Our synthesis of the EF-ring precursor required 13 steps (11% overall yield) utilizing ᴅ-glyceraldehyde acetonide as the precursor to the remaining chiral centers.

Our synthesis of the IJ subunit is illustrated in Scheme 9. From ᴅ-glucal derived C-glycoside **39**,[22] vinyl ether formation and enol ether–olefin ring-closing metathesis, using the second generation Grubbs catalyst (**40**), gave **41**. The *m*CPBA oxidation of the enol ether resulted in a 5.5:1 mixture of anomeric acetals, both of which had the desired stereochemistry at C36. Here, we opted to invert the C32 stereocenter to that required for the synthesis of adriatoxin.[23] This inversion was accomplished in three steps: hydrogenolysis of **42** and then oxidation of the resulting alcohol gave **43**; reduction of the ketone in **42** with L-Selectride gave the IJ subunit to adriatoxin as **44**.[24] The synthesis of IJ-precursor **44** was efficient in that it required 12 steps (17% overall yield) from ᴅ-glucal.

In summary, described herein is our synthetic strategy toward the diarrhetic shellfish poison, adriatoxin, which includes the use of a glycal-epoxide rearrangement to obtain the AB subunit, a Claisen rearrangement to access the EF subunit, and the use of C-glycoside-forming chemistry to obtain the IJ subunit. This work expands the scope of glycal epoxide chemistry by introducing epoxide rearrangements as a viable synthetic reaction. Our future efforts will be focused on the coupling of the subunits, the completion of the synthesis of adriatoxin, and the study of its ability to interact with biological receptors.

References

1. For a recent review on the synthesis of polycyclic ethers, see: Nakata T. Chem. Rev 2005;105:4314. [PubMed: 16351046]

2. For a recent review that discusses ion channel binding of ladder toxins, see: Nicholson GM, Lewis RJ. Mar. Drugs 2006;4:82.

3. Ciminiellow P, Fattorusso E, Forino M, Magno S, Poletti R, Viviani R. Tetrahedron Lett 1998;39:8897.

4. With the exception of the terminal K ring, adriatoxin shares a core skeleton with yessotoxin, see: Murata M, Kumagai M, Lee JS, Yasumoto T. Tetrahedron Lett 1987;28:5869.

5. For synthetic efforts to adriatoxin, see: a Hiramatsu N, Mori Y. Heterocycles 2006;69:437. b Kadota I, Ueno H, Yamamoto Y. Tetrahedron Lett 2003;44:8935. c Mori Y, Takase T, Noyori R. Tetrahedron Lett 2003;44:2319. d Mori Y, Nogami K, Hayashi H, Noyori R. J. Org. Chem 2003;68:9050. [PubMed: 14604380] e Suzuki K, Nakata T. Org. Lett 2002;4:3943. [PubMed: 12599498]

6. Johnson HWB, Majumder U, Rainier JD. J. Am. Chem. Soc 2005;127:848. [PubMed: 15656618]

7. a Cuypers E, Abdel-Mottaleb Y, Kopljar I, Rainier JD, Raes AL, Snyders DJ, Tytgat J. Toxicon 2008;51:974. [PubMed: 18313714] b Cuypers E, Yanagihara A, Rainier JD, Tytgat J. Biochem. Biophys. Res. Commun 2007;361:214. [PubMed: 17659256] c LePage KT, Rainier JD, Johnson HWB, Baden DG, Murray TF. J. Pharmacol. Exp. Ther 2007;361:214. d Cao Z, George J, Gerwick WH, Baden DG, Rainier JD, Murray TF. J. Pharmacol. Exp. Ther 2008;326:604. [PubMed: 18448863]

8. Konishi M, Yang X, Li B, Fairchild CR, Shimizu Y. J. Nat. Prod 2004;67:1309. [PubMed: 15332847]

9. Allwein SP, Cox JM, Howard BE, Johnson HWB, Rainier JD. Tetrahedron 2002;58:1997.

10. Nicolaou KC, Nugiel DA, Couladouros E, Hwang C-K. Tetrahedron 1990;46:4517.

11. Iyer K, Rainier JD. J. Am. Chem. Soc 2007;129:12604. [PubMed: 17900112]

12. Majumder U, Cox JM, Johnson HWB, Rainier JD. Chem. Eur. J 2006;12:1736.

13. Alternatively, superhydride reduction of the glycal epoxide from 8 would potentially deliver the desired stereochemistry at C(7), see: Inoue M, Yamashita S, Tatami A, Miyazaki K, Hirama M. J. Org. Chem 2004;69:2797. [PubMed: 15074930]

14. Rainier JD, Allwein SP, Cox JM. J. Org. Chem 2001;66:1380. [PubMed: 11312970]

15. Ferrer M, Gibert M, Sánchez-Baeza F, Messeguer A. Tetrahedron Lett 1996;37:3585.

16. Rainier JD, Allwein SP. Tetrahedron Lett 1998;39:9601.

17. Roberts SW, Rainier JD. Org. Lett 2005;7:1141. [PubMed: 15760159]

18. That 23, 24, and 26 were isolated as single diastereomers implies a stereoselective epoxidation. For a discussion of the reaction of DMDO with cyclic enol ethers, see: Orendt AM, Roberts SW, Rainier JD. J. Org. Chem 2006;71:5565. [PubMed: 16839135]

19. Clark JS, Kettle JG. Tetrahedron Lett 1997;38:127.

20. For reviews, see: a Arjona O, Gomez AM, Lopez JC, Plumet J. Chem. Rev 2007;107:1919. [PubMed: 17488060] b Martin Castro AM. Chem. Rev 2004;104:2939. [PubMed: 15186185]

21. Cox JM, Rainier JD. Org. Lett 2001;3:2919. [PubMed: 11529790]

22. Clark JS, Kimber MC, Robertson J, McErlean CSP, Wilson C. Angew. Chem 2005;117:6313.Angew. Chem. Int. Ed 2005;44:6157.

23. The stereochemistry at C32 was instrumental in setting the C33 and C34 stereocenters, see: reference [17] and Majumder U, Cox JM, Rainier JD. Org. Lett 2003;5:913. [PubMed: 12633104]

24. Mitsunobu inversion of the C32 alcohol from 42 was slow and gave low yields of the desired alcohol.
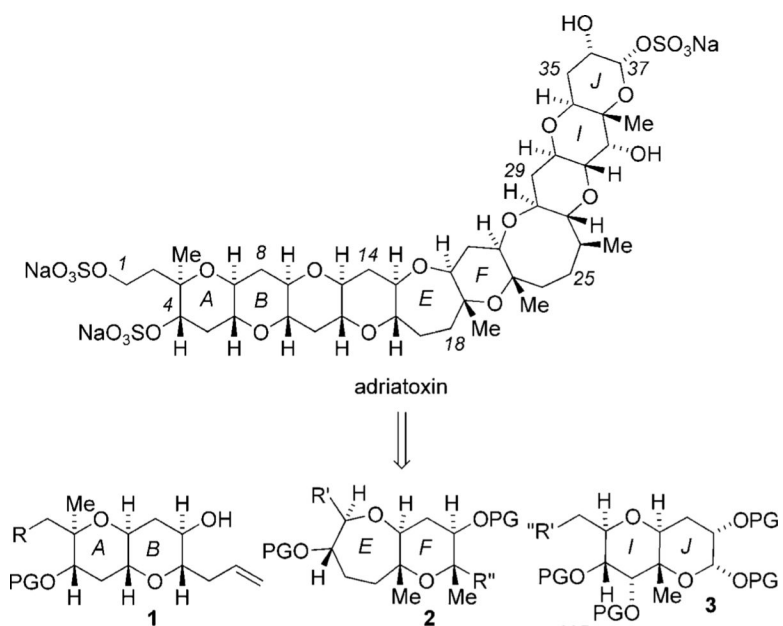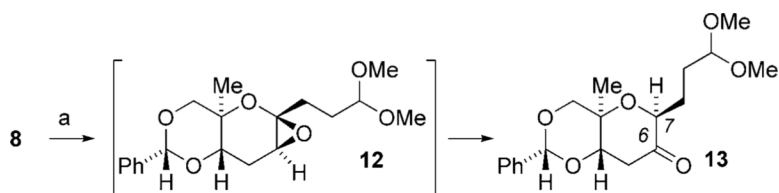
Scheme 1.
Retrosynthetic analysis of adriatoxin. P = protecting group.
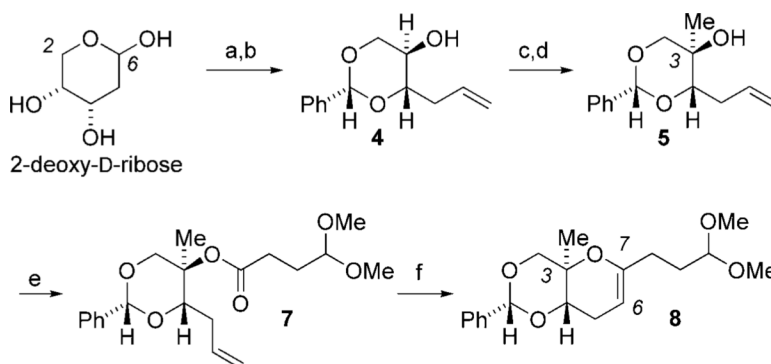
Scheme 2.
Synthesis of glycal **8**. Reagents and conditions: a) Ph$_3$PMeBr, THF, *t*BuOK; b) PhCH
(OMe)$_2$, CSA (80% over two steps); c) (COCl)$_2$, DMSO, Et$_3$N, −78 °C; d) MeMgBr, Et$_2$O,
−78 °C (80% over two steps); e) HO$_2$CCH$_2$CH$_2$CH(OMe)$_2$ (**6**), DCC, DMAP, CH$_2$Cl$_2$ (80%);
f) TiCl$_4$, TMEDA, Zn, PbCl$_2$, THF, CH$_2$Cl$_2$,CH$_3$CH$_2$Br$_2$ (70%). CSA = (+)-camphorsulfonic
acid, DMSO = dimethylsulfoxide; DCC = dicyclohexylcarbodiimide; DMAP = 4-
(dimethylamino)pyridine; TMEDA = N,N,N′,N′-tetramethyl-1,2-ethanediamine.
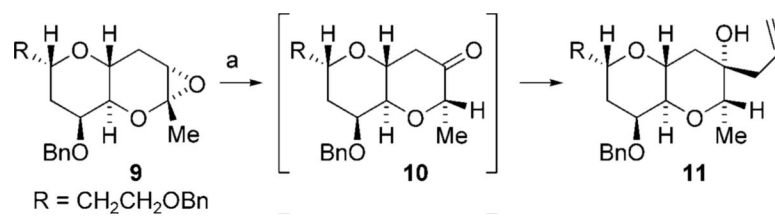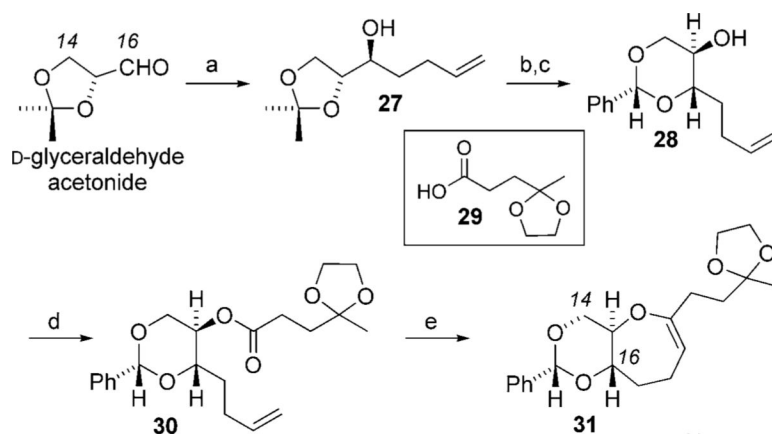
Scheme 3.
Glycal epoxide rearrangement of **9**. Reagents and conditions: a) propenyl magnesium chloride, THF, 0 °C to RT (70%).
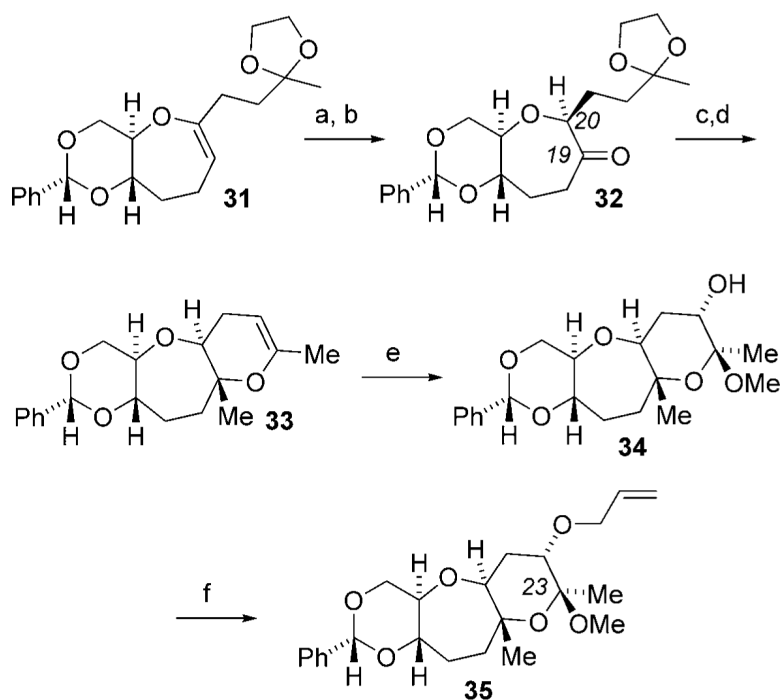
Scheme 4.
Pinacol rearrangement of **12**. Reagents and conditions: a) DMDO, CH$_2$Cl$_2$, −60 °C to 0 °C; MgCl$_2$, −60 °C to RT (82%).
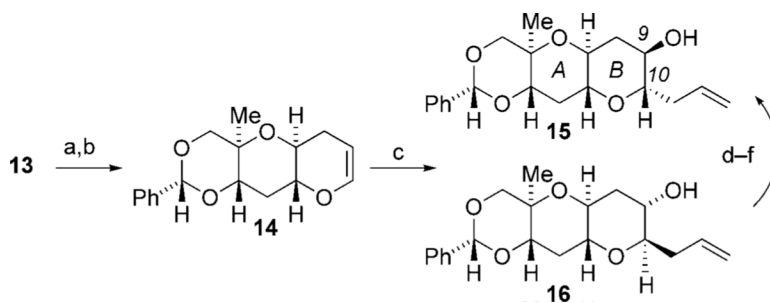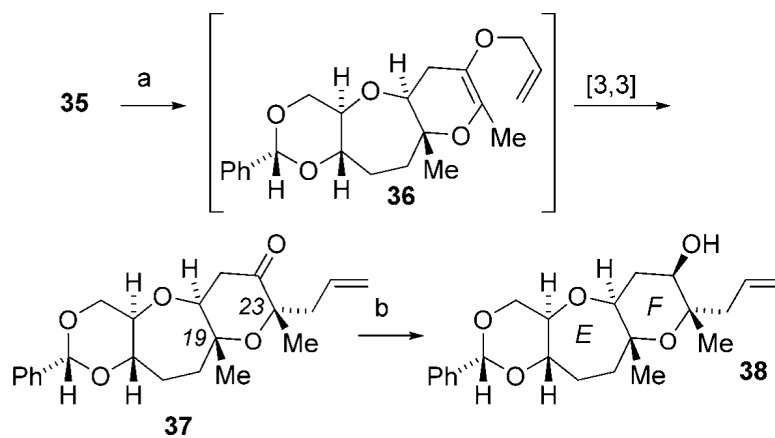
Scheme 5.
Synthesis of adriatoxin AB-precursor **15**. Reagents and conditions: a) NaBH$_4$, MeOH, −65 °C to RT (95%); b) PPTS, PhCl, pyridine, 135 °C (86%); c) DMDO, CH$_2$Cl$_2$, −60 °C to RT; propenyl magnesium bromide, THF, −60 °C to RT (75%, 2.3:1 ratio of **15/16**); d) SO$_3$·pyridine, DMSO, CH$_2$Cl$_2$,0 °C to RT; e) DBU, PhCH$_3$, 110 °C; f) NaBH$_4$, MeOH, −65 °C to RT (60% over three steps). PPTS = pyridinium *para*-toluenesulfonate; DBU = 1,8-diazabicycloundec-7-ene.
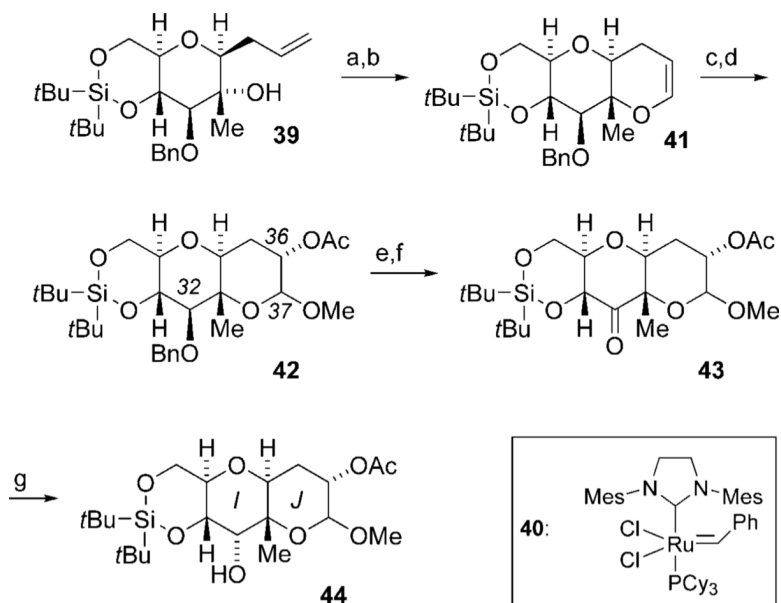
Scheme 6.
Synthesis of adriatoxin E-ring precursor **31**. Reagents and conditions: a) butenyl magnesium bromide, $ZnCl_2$, Et_2O, −90 °C (87%, 6:1); b) PPTS, MeOH, 65 °C (89%); c) $PhCH(OMe)_2$, CSA (82%); **29**, DCC, DMAP, CH_2Cl_2 (85%); d) $TiCl_4$, TMEDA, Zn, $PbCl_2$, THF, CH_2Cl_2, CH_3CHBr_2, 60 °C (65%).

Scheme 7.
Synthesis of adriatoxin EF-precursor **35**. Reagents and conditions: a) DMDO, *i*Bu$_2$AlH, CH$_2$Cl$_2$, −78 °C (80%); b) SO$_3$·pyridine, Et$_3$N, DMSO (85%); c) MeMgBr, −78 °C (92%, 5:1); d) PPTS, PhCl, pyridine, 135 °C (75%); e) *m*CPBA, MeOH, −78 °C to RT (88%); f) 3-bromo-1-propene, *n*Bu$_4$NI, DMF, 0 °C to 65 °C (85%). *m*CPBA = 3-chloroperbenzoic acid.

Scheme 8.
Synthesis of adriatoxin EF-precursor **38**. Reagents and conditions: a) PPTS, PhCH$_3$, pyridine, 100 °C to 120 °C (92%, > 10:1); b) NaBH$_4$, MeOH −65 °C to RT (94%).

Scheme 9.
Synthesis of adriatoxin IJ-precursor **44**. Reagents and conditions: a) Hg(OC(O)CF$_3$)$_2$, ethyl vinyl ether; b) **40** (20 mol%), PhH (60% over 2 steps); c) *m*-CPBA, MeOH, −63 °C to RT (75%, 5.5:1); d) Ac$_2$O, DMAP, NEt$_3$, CH$_2$Cl$_2$ (96%); e) H$_2$, Pd(OH)$_2$/C (90%); f) SO$_3$·pyridine, DMSO, CH$_2$Cl$_2$, NEt$_3$ (90%); g) L-Selectride, THF, −78 °C (90%). Mes = 2,4,6-trimethylphenyl; Ac$_2$O = acetic anhydride; L-Selectride = lithium tri-*sec*-butylborohydride.