CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201101437

Total Synthesis of (−)-Brevenal: A Streamlined Strategy for Practical Synthesis of Polycyclic Ethers

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Abstract: We describe a streamlined strategy for the practical synthesis of *trans*-fused polycyclic ethers and its application to a concise total synthesis of (−)-brevenal, a new pentacyclic polyether natural product with intriguing biological activities. The B-, D-, and E-rings were constructed by TEMPO/$PhI(OAc)_2$-mediated oxidative lactonization of the corresponding 1,6-diols, with minimal need for manipulation of oxygen functionalities. The B- and E-ring lactones were appropriately functionalized by Suzuki–Miyaura coupling of lactone-derived enol phosphates and subsequent stereoselective hydroboration. The A-ring was formed by our mixed thioacetalization methodology. The AB- and DE-ring fragments were assembled through Suzuki–Miyaura coupling, and the C-ring was forged in the same manner as that for the A-ring. More than two grams of the pentacyclic polyether core of (−)-brevenal have been synthesized by the synthetic route developed in this study.

Keywords: cross-coupling · natural products · oxacycles · oxidation · polyethers

Introduction

Secondary metabolites of marine organisms represent potential collections of molecular probes useful for elucidation of important biological functions as well as new lead compounds with distinct biological modes of action in drug discovery.[1] Marine polycyclic ether natural products, chiefly produced by dinoflagellates, are a unique class of marine metabolites, sharing a common ladder-shaped *trans*-fused polycyclic ether structural motif and exhibiting a broad range of biological activities with high potencies.[2] Among the family of marine polycyclic ethers, brevetoxin B (**1**), isolated from the Florida red-tide-forming dinoflagellate *Karenia brevis* as a potent ichthyotoxic constituent, was the first member to be structurally elucidated by spectroscopic and X-ray crystallographic analyses.[3] Since then the isolation and structure determination of natural congeners, including brevetoxin A,[4] have been reported. The unprecedented highly complex polycyclic ether structure of brevetoxin B has served as a significant challenge to synthetic chemists and as a source of inspiration for the development of new synthetic methods and strategies.[5,6] Furthermore, brevetoxin B exhibits potent neurotoxicity by acting as an agonist of voltage-gated sodium channels (VGSCs) in excitable membranes; brevetoxin B specifically binds to site 5 in a VGSC and causes a shift of activation potential, induction of prolonged mean open times, and inhibition of channel inactivation.[7] The remarkably potent and specific binding ability of brevetoxin B should be useful for better understanding of the structure and functions of VGSCs at the molecular level.

Recently, Baden and co-workers identified the novel pentacyclic ether brevenal (**2**) from a laboratory culture of *K. brevis*.[8] The overall structure and relative stereochemistry of brevenal was originally proposed on the basis of extensive 2D NMR analysis. The complete stereostructure of **2**, however, was eventually established through our total synthesis, which resulted in the stereochemical reassignment of the C26 stereogenic center.[9] It has been reported that brevenal competitively inhibits the binding of tritiated dihydrobrevetoxin B ($[^3H]$PbTx-3) to VGSCs in a dose-dependent manner without showing neurotoxicity and acts as a natural brevetoxin antagonist in vivo.[8,10] Moreover, Abraham et al. have reported that brevenal significantly improves tracheal mucus clearance ability in an animal model of asthma, suggesting that brevenal might serve as a potential drug candidate for treatment of cystic fibrosis.[11] More recently, Mattei et al. have reported that brevenal is a potent inhibitor of catecholamine secretion induced by ciguatoxin (**3**) without affecting other secretagogue activities, such as nicotine- or barium-induced secretion of catecholamine.[12] Ciguatoxin is a secondary metabolite of the dinoflagellate *Gambierdiscus toxicus* responsible for ciguatera seafood poisoning[13] and, like brevetoxin B, exhibits potent neurotoxicity by binding to the VGSC receptor site 5.[14] Mattei et al. suggested that brevenal and its derivatives could be potentially useful for treatment of ciguatera.[12]

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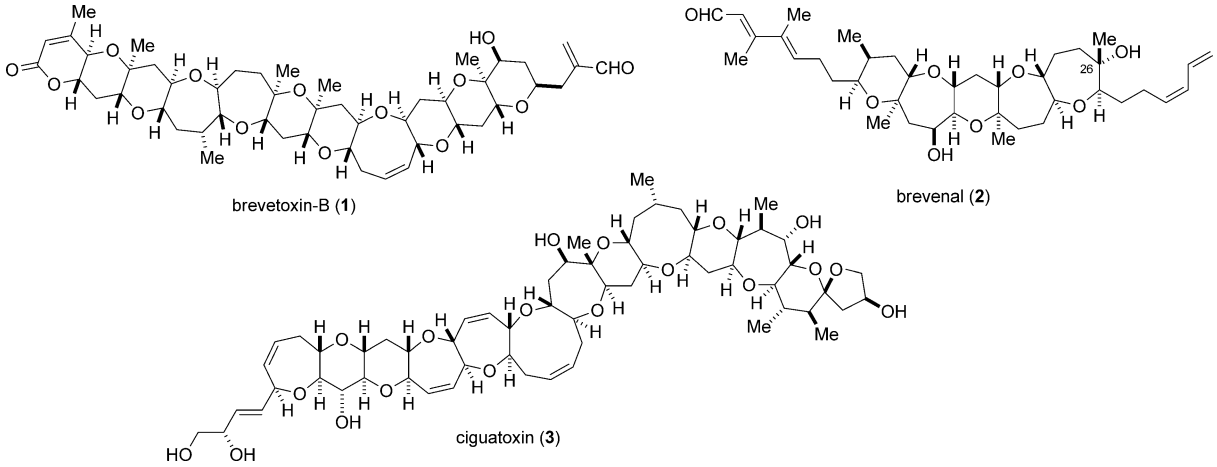
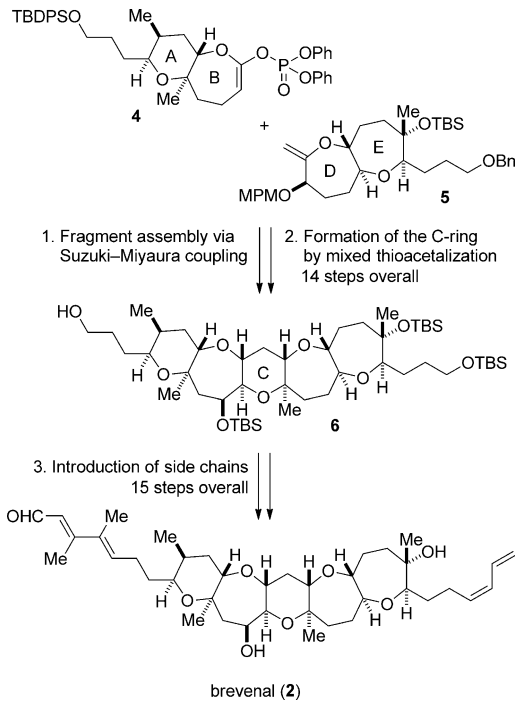
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201101437.



Because of its intriguing structure and promising biological profile, brevenal represents an attractive synthetic target for organic chemists.[15,16] In 2006 we reported the first total synthesis of (−)-brevenal,[9b] based on our developed Suzuki–Miyaura coupling/mixed-thioacetalization chemistry[17–19] as outlined in Scheme 1.

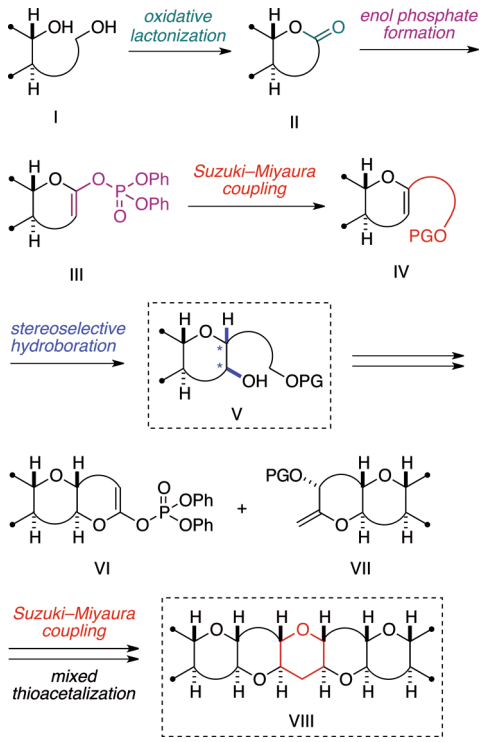


Scheme 1. Outline of our first-generation total synthesis of (−)-brevenal. Bn = benzyl, MPM = *p*-methoxyphenylmethyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

Assembly of the AB-ring enol phosphate **4** and the DE-ring exocyclic enol ether **5**, followed by construction of the central C-ring through mixed thioacetalization, delivered the pentacyclic ether **6**, and a sequential installation of the A- and E-ring side chains completed the total synthesis of **2** (50 steps from 2-deoxy-D-ribose, the longest linear sequence). Unfortunately, though, our first-generation synthesis could afford only a milligram-scale quantity of synthetic brevenal because of the lengthy linear sequences required for the synthesis of the AB- and DE-ring fragments and the low material throughput of the post-fragment coupling stage of the total synthesis. To address these problems, here we disclose a streamlined strategy for the practical synthesis of polycyclic ethers and its successful implementation in a concise total synthesis of (−)-brevenal.[20]

Results and Discussion

Synthetic plan: In designing the overall synthetic plan, we paid particular attention to minimizing the number of manipulations of oxygen-containing functional groups and attempted to formulate a streamlined strategy for the synthesis of polycyclic ethers based on six- and seven-membered rings (Scheme 2). TEMPO/PhI$(OAc)_2$-mediated oxidative lactonization of 1,5- and 1,6-diols has recently emerged as a powerful means for producing six- and seven-membered lactones, respectively.[21] Notably, this methodology does not require differentiation of primary and secondary hydroxy groups: oxidation takes place exclusively at the less hindered primary hydroxy group with concomitant lactonization, thanks to the unique reactivity of TEMPO/PhI$(OAc)_2$.[22] The diol **I** would thus be directly transformed into the lactone **II**. For the functionalization of the lactone **II**, we thought it would be suitable to utilize Suzuki–Miyaura coupling of the lactone-derived enol phosphate **III** and hydroboration of the resultant endocyclic enol ether **IV**, which should afford the cyclic ether **V** with simultaneous generation of two stereogenic centers in a stereocontrolled manner under substrate control. Significantly, only four steps would be required for the construction of the cyclic ether **V** from the simple diol **I**, and this sequence should allow for a practical synthesis of small cyclic ether fragments (e.g., **VI** and **VII**). Furthermore, as we had previously demonstrated,[17–19] convergent assembly of small cyclic ether

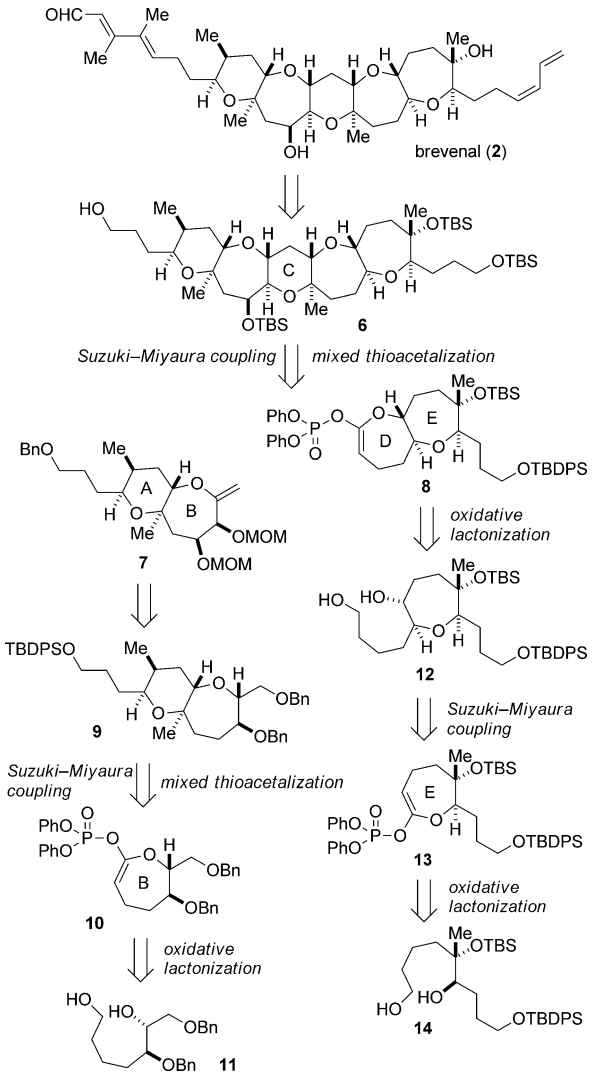


Scheme 2. Streamlined strategy for practical synthesis of polycyclic ethers; PG = protective group.

fragments by means of our Suzuki–Miyaura coupling/mixed-thioacetalization chemistry should give access to larger polycyclic ether arrays in a rapid and efficient manner (e.g., **VI** + **VII** → **VIII**). Overall, a practical synthesis of polycyclic ethers should be possible by exploitation of oxidative lactonization, Suzuki–Miyaura coupling, and mixed thioacetalization as key transformations.

With the above considerations in mind, we planned a second-generation total synthesis of (−)-brevenal as illustrated in Scheme 3. We envisioned the synthesis of the pentacyclic polyether core **6** by our Suzuki–Miyaura coupling/mixed-thioacetalization chemistry.[17] The assembly of the AB-ring exocyclic enol ether **7** and the DE-ring enol phosphate **8** through Suzuki–Miyaura coupling and subsequent construction of the C-ring by the mixed thioacetalization methodology developed in our laboratory[18] should thus deliver the pentacyclic ether **6** in a convergent fashion. The AB-ring fragment **7** would be derived from the bicyclic ether **9** through a series of functional group manipulations. According to the general strategy formulated in Scheme 2, the bicyclic ether **9** should be obtainable from the B-ring enol phosphate **10** by means of Suzuki–Miyaura coupling and subsequent formation of the A-ring by mixed thioacetalization, whereas the B-ring enol phosphate **10** should in turn be available from the 1,6-diol **11** through TEMPO/$PhI(OAc)_2$-mediated oxidative lactonization.

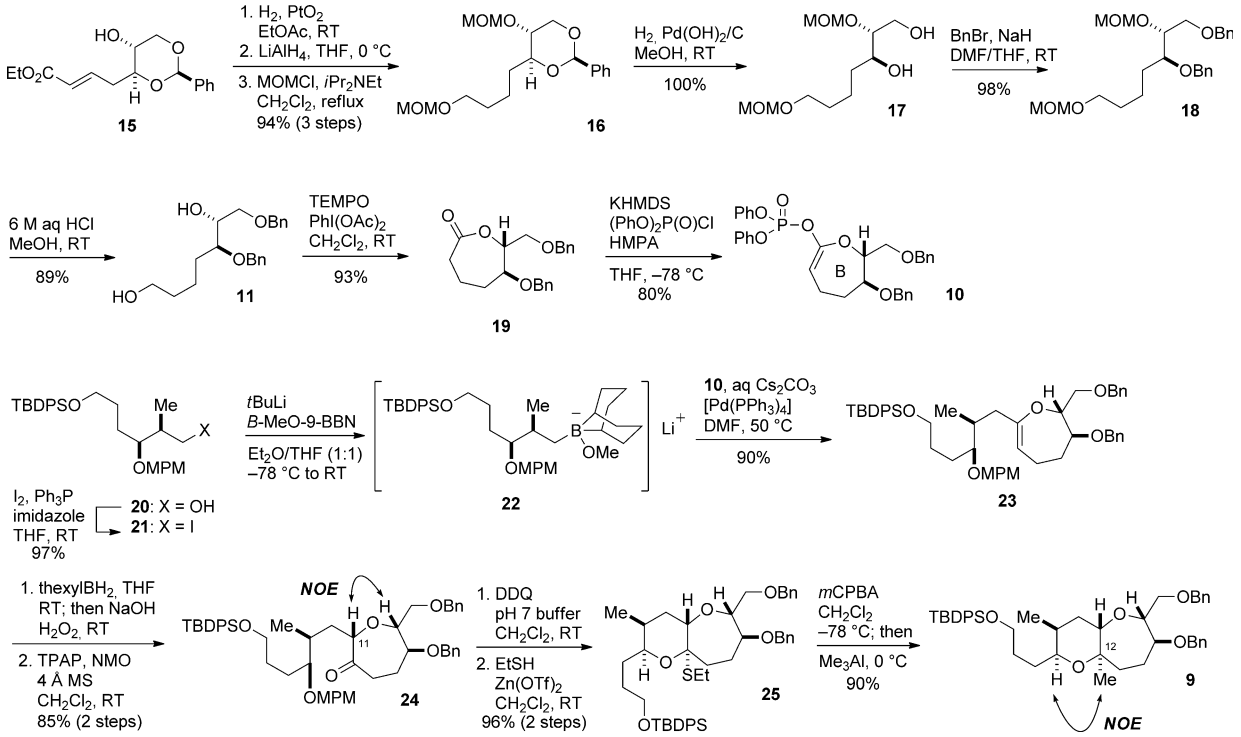
We also planned to apply our general strategy to the synthesis of the DE-ring fragment. The DE-ring enol phosphate **8** could thus be traced back to the 1,6-diol **12** through oxidative lactonization, and this should in turn be synthesizable from the E-ring enol phosphate **13** through Suzuki–Miyaura coupling with an appropriate alkylborane. The E-ring should be available from the 1,6-diol **14** by means of oxidative lactonization.[23]



Scheme 3. Synthesis plan for (−)-brevenal. MOM = methoxymethyl.

Accordingly, our synthetic plan for (−)-brevenal hinges on 1) TEMPO/$PhI(OAc)_2$-mediated oxidative lactonization for the construction of the B-, D-, and E-ring frameworks; 2) Suzuki–Miyaura coupling for the functionalization of the B- and E-rings and the convergent union of the AB- and DE-ring fragments; and 3) mixed thioacetalization for the formation of the A- and C-rings. Notably, all of these synthetic methodologies were developed in our laboratory.

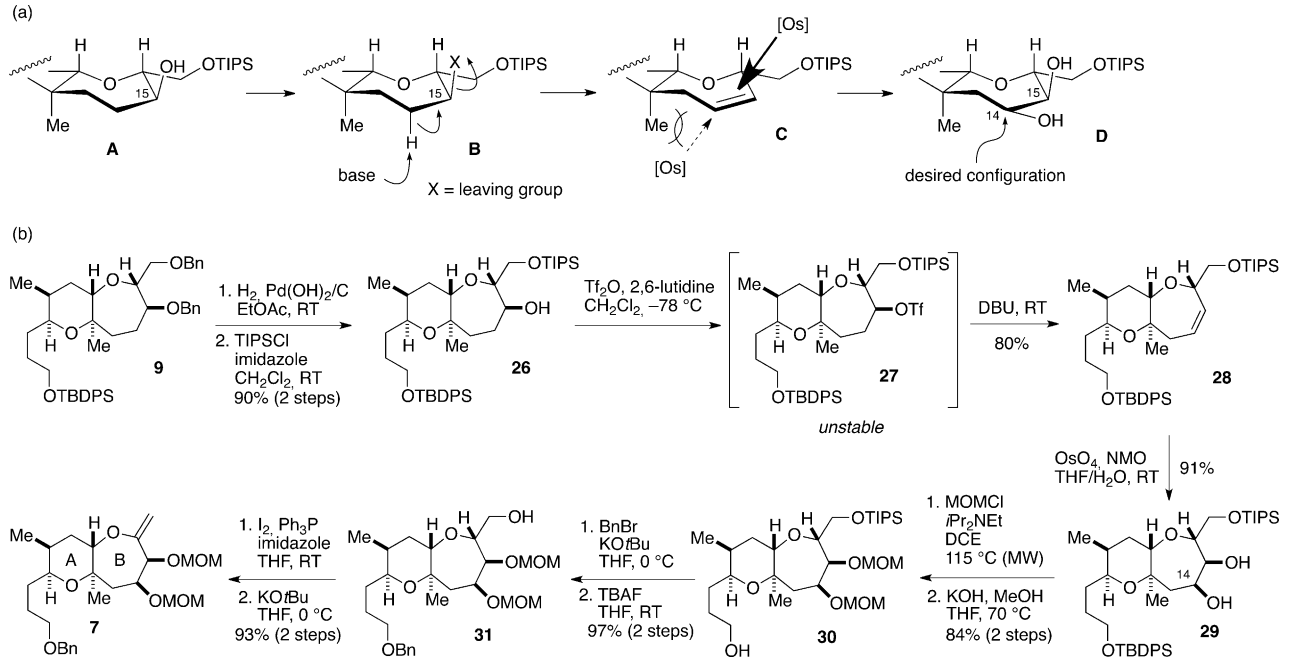
Synthesis of the AB-ring fragment: The synthesis of the AB-ring bicyclic ether **9** (Scheme 4) commenced with hydrogenation of the known unsaturated ester **15**, available in two steps from 2-deoxy-D-ribose.[24,25] Subsequent reduction of the derived ester with $LiAlH_4$ and protection of the resultant diol (MOMCl, iPr_2NEt) gave the bis-MOM ether **16**



Scheme 4. Synthesis of the bicyclic ether **9**. 9-BBN = 9-borabicyclo[3.3.1]nonyl, DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, DMF = *N*,*N*-dimethylformamide, HMPA = hexamethylphosphoramide, KHMDS = potassium bis(trimethylsilyl)amide, *m*CPBA = *m*-chloroperoxybenzoic acid, MS = molecular sieves, NMO = *N*-methylmorpholine *N*-oxide, NOE = nuclear Overhauser effect, TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl, Tf = trifluoromethanesulfonyl, TPAP = tetra-*n*-propylammonium perruthenate.

(94%, three steps). The benzylidene acetal was removed by hydrogenolysis to provide the diol **17** (100%). Benzylation of **17** provided the bis-benzyl ether **18** (98%), and this was followed by cleavage of the MOM ethers under acidic conditions to deliver the diol **11** (89%). Oxidative lactonization of **11** with a catalytic amount of TEMPO and $PhI(OAc)_2$ as a stoichiometric oxidant proceeded smoothly under non-high-dilution conditions (CH_2Cl_2, 0.1 M substrate concentration, room temperature) to afford the B-ring lactone **19**[17b,c] in 93% yield, securing a scalable access to this important building block (>19 g in one batch).[26] Enolization of **19** with KHMDS in the presence of $(PhO)_2P(O)Cl$ gave the enol phosphate **10** in 80% yield. Suzuki–Miyaura coupling of **10** with the alkylborate **22**, generated in situ from the iodide **21** (derived from the alcohol **20**[9]), was carried out in the presence of $[Pd(PPh_3)_4]$ as the catalyst and aqueous Cs_2CO_3 as the base (DMF, 50 °C), which provided the endocyclic enol ether **23** in 90% yield. Stereoselective hydroboration of **23** with thexylborane and oxidative workup gave an alcohol as a single stereoisomer, which was oxidized with TPAP/NMO[27] to deliver the ketone **24** in 85% yield (two steps) as a single stereoisomer. The newly generated C11 stereogenic center was established by an NOE experiment as shown. Removal of the MPM group and subsequent mixed thioacetalization through the action of EtSH/Zn-$(OTf)_2$ afforded the *O*,*S*-acetal **25** in 96% yield (two steps). The C12 axial methyl group was stereoselectively introduced by a one-pot *m*CPBA oxidation/methylation procedure[9,28] (*m*CPBA, CH_2Cl_2, −78 °C; then excess Me_3Al, 0 °C), which furnished the AB-ring bicyclic ether **9** in 90% yield. The stereochemistry of the C12 stereogenic center was unambiguously confirmed by an NOE enhancement observed in **9**.

The bicyclic framework of the AB-ring having been completed, our next challenge was functionalization of the B-ring. To install the C14 hydroxy group, we envisioned a new method that makes use of the intrinsic conformational bias of seven-membered cyclic ethers, as summarized in Scheme 5a. Because the secondary hydroxy group in the oxepane **A** should be in a pseudoaxial orientation, transformation of the hydroxy group into a suitable leaving group (X) should facilitate a regioselective E2 elimination through the action of a base to provide the oxepene **C**. As a result of the conformation of **C**, dihydroxylation of **C** should exclusively occur from the sterically less hindered β face to afford the diol **D** with the correct configuration at the C14 stereogenic center. To test this idea, the bicyclic ether **9** was elaborated to the alcohol **26** in two steps involving debenzylation and selective silylation of the resulting primary hydroxy group (Scheme 5b). We examined several leaving groups for regioselective elimination of the C15 secondary hydroxy group and found that the corresponding mesylate[29] and monochloromesylate[30] were not sufficiently reactive toward base-mediated elimination, whereas the triflate **27** was very unstable and readily decomposed during attempted isolation. Eventually, a one-pot triflation/elimination protocol (Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; then DBU, room tem-

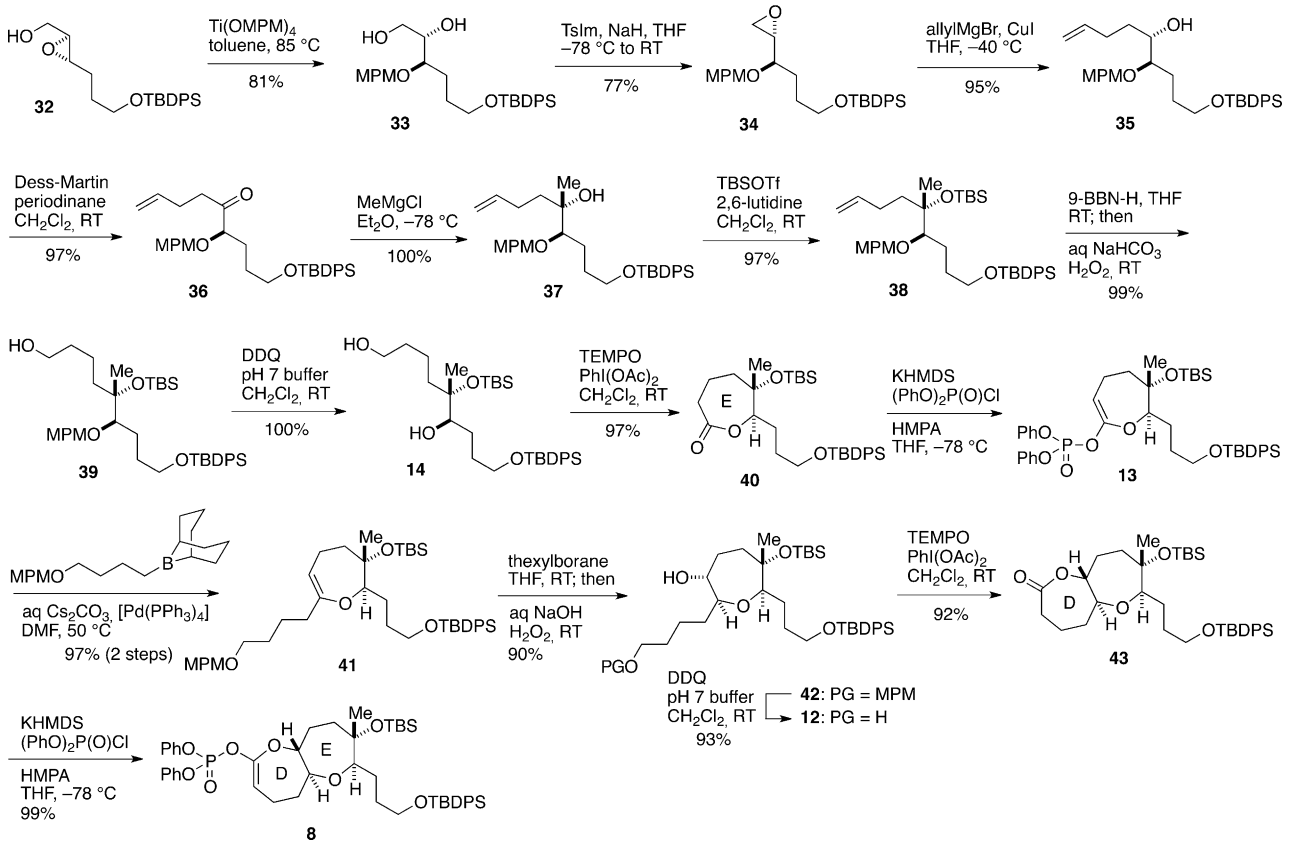


Scheme 5. a) Elimination/dihydroxylation sequence for the stereoselective introduction of the C14 hydroxy group. b) Synthesis of the AB-ring fragment **7**. DBU = diazabicyclo[5.4.0]undec-7-ene, DCE = 1,2-dichloroethane, MW = microwave, TBAF = tetra-*n*-butylammonium fluoride, TIPS = triisopropylsilyl.

perature) was devised to address this problem, cleanly giving the olefin **28** in 80% yield. As anticipated, dihydroxylation of **28** with OsO_4/NMO exclusively furnished the diol **29** (91%) as a single stereoisomer. We have thus successfully introduced the C14 hydroxy group with complete stereochemical control. The stereochemical outcome of the dihydroxylation was confirmed by an NOE experiment on the corresponding acetonide derivative (see the Supporting Information). Protection of the diol **29** with MOMCl/iPr$_2$NEt[31] under microwave irradiation conditions, followed by selective cleavage of the TBDPS group under basic conditions (KOH, MeOH/THF, 70°C), gave the alcohol **30** (84%, two steps). Benzylation of **30** and subsequent desilylation with TBAF led to the alcohol **31** (97%, two steps), which was transformed into the AB-ring exocyclic enol ether **7** in 93% yield (two steps) by iodination under standard conditions and base treatment (KOtBu, THF, 0°C).

Synthesis of the DE-ring fragment: The synthesis of the DE-ring enol phosphate **8** (Scheme 6) started from the known epoxy alcohol **32**,[32] readily prepared from butane-1,4-diol in four steps. Regioselective ring-opening of the epoxide with Ti(OMPM)$_4$ (toluene, 85°C)[33] delivered the 1,2-diol **33** in 81% yield. Direct formation of the terminal epoxide **34** from the 1,2-diol **33** was effected by Kishi's protocol,[34] through treatment with *N*-(*p*-toluenesulfonyl)imidazole in the presence of NaH (THF, −78°C to room temperature, 77%). Copper-catalyzed allylation of **34** regioselectively opened the terminal epoxide to provide the secondary alcohol **35** in 95% yield. Oxidation of **35** with Dess–Martin periodinane[35] gave the ketone **36** (97%), chelation-controlled methylation of which with methylmagnesium chloride (Et_2O, −78°C)[36] afforded the tertiary alcohol **37** in quantitative yield as a single stereoisomer, as judged by ^{1}H NMR analysis (600 MHz). Protection of the resulting hydroxy group as its TBS ether gave the silyl ether **38** (97%). Hydroboration of the terminal olefin in **38** with 9-BBN-H gave the alcohol **39** after oxidative workup (99%). Cleavage of the MPM ether with DDQ led quantitatively to the diol **14**. Upon treatment of the diol **14** with TEMPO/PhI(OAc)$_2$ in CH_2Cl_2 (0.1 M substrate concentration) at room temperature, oxidative lactonization took place smoothly to deliver the seven-membered lactone **40**, representing the E-ring, in 97% yield.

After conversion of the lactone **40** into the enol phosphate **13** (KHMDS, (PhO)$_2$P(O)Cl, HMPA, THF, −78°C), Suzuki–Miyaura coupling with an alkylborane derived from 4-(4-methoxybenzyl)but-1-ene and 9-BBN-H was effected under optimized conditions ([Pd(PPh$_3$)$_4$], aqueous Cs_2CO_3, DMF, 50°C) to afford the endocyclic enol ether **41** in 97% yield for the two steps. Hydroboration of **41** with thexylborane proceeded in a highly stereoselective manner to provide the secondary alcohol **42** in 90% yield as a single stereoisomer after alkaline peroxide workup; subsequent removal of the MPM group with DDQ gave the diol **12** (93%). Oxidative lactonization of **12** with TEMPO/PhI(OAc)$_2$ (CH_2Cl_2, 0.1 M substrate concentration, room temperature) cleanly furnished the seven-membered lactone **43** (92%), the spectroscopic data and specific rotation value of which matched those of the authentic material, which we had previously prepared.[20] Finally, treatment of **43** with KHMDS in the presence of (PhO)$_2$P(O)Cl (HMPA, THF,



Scheme 6. Synthesis of the DE-ring fragment **8**. TsIm = *N*-(*p*-toluenesulfonyl)imidazole.

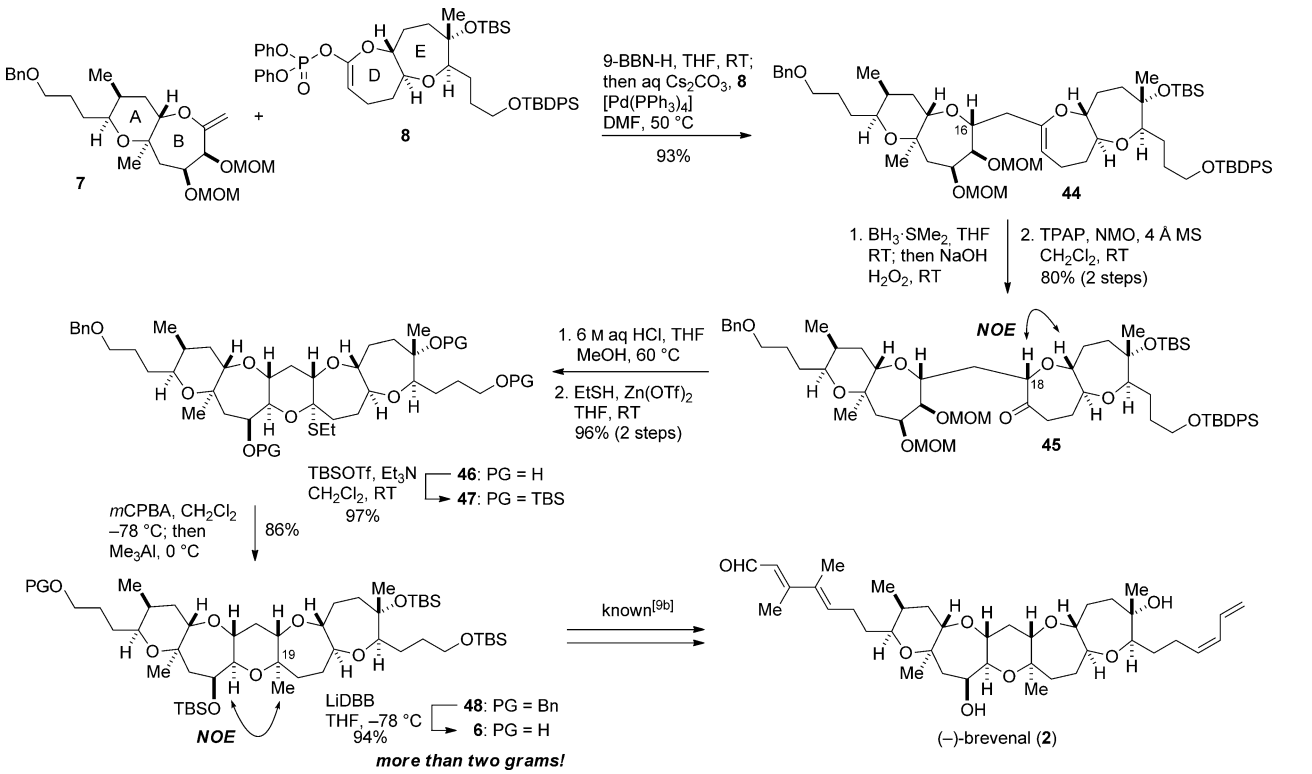
−78 °C) delivered the DE-ring enol phosphate **8** almost quantitatively.

Construction of the pentacyclic polyether core and completion of the total synthesis: The coupling of the AB-ring exocyclic enol ether **7** and the DE-ring enol phosphate **8** was efficiently achieved through Suzuki–Miyaura chemistry (Scheme 7). Hydroboration of **7** with 9-BBN-H generated the corresponding alkylborane, which was treated in situ with **8** under optimized conditions ($[Pd(PPh_3)_4]$, aqueous Cs_2CO_3, DMF, 50 °C) to afford the endocyclic enol ether **44** in 93% yield as a single stereoisomer.[37] Stereoselective hydroboration of **44** with $BH_3{\cdot}SMe_2$ followed by oxidative workup gave an inseparable 5:1 mixture of diastereomeric secondary alcohols, which was oxidized with TPAP/NMO to provide the ketone **45** in 80% yield (two steps) after removal of the minor C18 epimer by flash chromatography on silica gel. The C18 stereogenic center of **45** was confirmed by an NOE experiment as shown.

At this stage it was necessary to remove the MOM ethers for the formation of the C-ring. Treatment of **45** with aqueous HCl (6 M) in THF/MeOH cleanly cleaved both the MOM ethers and the silyl ethers to give an equilibrating mixture of the corresponding tetraol-ketone and hemiacetal almost quantitatively,[38] and this was converted into the *O*,*S*-acetal **46** by mixed thioacetalization in 96% yield (two steps). After protection of the hydroxy groups with TBSOTf/Et_3N to give the tris-silyl ether **47** (97%), the C19 axial methyl group was stereoselectively installed by the one-pot *m*CPBA oxidation/methylation protocol, giving rise to the pentacyclic ether **48** in 86% yield. The newly generated C19 stereogenic center was confirmed by an NOE experiment. Debenzylation of **48** with LiDBB[39] (THF, −78 °C) afforded the primary alcohol **6** in 94% yield, while also successfully intercepting with our previous total synthesis of (−)-brevenal.[9b] The spectroscopic data and specific rotation value for **6** synthesized in this study were in full accordance with those of the authentic sample.[9b,20] It was significant that we were able to synthesize the key intermediate **6** in quantities of over two grams, showcasing the feasibility of our strategy for practical synthesis of polycyclic ethers.

Conclusion

We have described a newly designed streamlined strategy for the practical synthesis of polycyclic ethers and its successful application to a concise total synthesis of (−)-brevenal. TEMPO/$PhI(OAc)_2$-mediated oxidative lactonization of 1,6-diols enabled the efficient construction of the B-, D-, and E-ring frameworks in their lactone forms with minimal



Scheme 7. Synthesis of the pentacyclic polyether core **6** and completion of the total synthesis. DBB = 4,4′-di-*tert*-butylbiphenyl.

transformations of oxygen functionalities. The B- and E-ring lactones were suitably functionalized through Suzuki–Miyaura coupling of lactone-derived enol phosphates and subsequent stereoselective hydroboration. The A-ring was constructed by our developed mixed thioacetalization methodology. Finally, the AB- and DE-ring fragments were coupled through Suzuki–Miyaura chemistry, and the C-ring was constructed by mixed thioacetalization to complete the total synthesis of (−)-brevenal. This synthesis took place in only 34 steps (longest linear sequence) from the commercially available 2-deoxy-D-ribose, thus being much more efficient than our previous synthesis (50 steps, longest linear sequence). Significantly, more than two grams of the pentacyclic ether core of (−)-brevenal have been synthesized by these practical synthetic methodologies, thereby paving the way to a variety of unnatural analogues of this promising therapeutic lead compound. We believe that our strategy should be generally applicable to the synthesis of marine polycyclic ether natural products.

Acknowledgements

We thank Y. Suga from our laboratory for his contribution to the early stage of this work. This work was supported in part by Grant-in-Aids for Challenging Exploratory Research (No. 21651090) and Scientific Research (A) (No. 21241050) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan and from the Japan Society for the Promotion of Sciences (JSPS). M.E. was a recipient of a predoctoral fellowship from JSPS.

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[23] In the preliminary communication (Ref. [20]), the E-ring was synthesized based on SmI_2-induced cyclization of a β-alkoxyacrylate developed by Nakata and co-workers.[6b,c] However, we found that scale-up of the cyclization was quite laborious and not easy; a significant amount of SmI_2 solution was necessary due to the low solubility of SmI_2 in THF (usually around 0.1 M concentration) and care should be taken to keep the solvent degassed.

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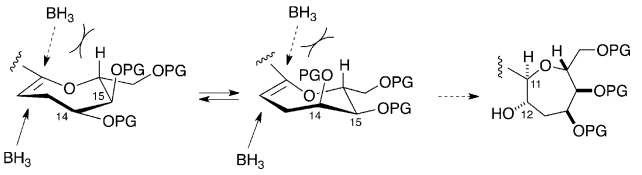
[25] A referee has pointed out that D-ribose may serve as a good starting material for the B-ring, because both the C14 and C15 hydroxy groups of (−)-brevenal are already present. However, it appears that a problem would arise during the course of the formation of the A-ring. Due to the intrinsic conformational property of seven-membered cyclic ethers, either the C14 or C15 hydroxy groups (in their protected forms) would be pseudoaxially oriented, making the β face of the B-ring sterically crowded as shown below. Accordingly, hydroboration of a B-ring endocyclic enol ether would proceed from the less hindered α face of the molecule to yield a secondary alcohol with wrong configurations at the C11 and C12 stereogenic centers. A similar observation has been described in a recent report by Takamura et al. (Ref. [15b]) To avoid such an undesirable outcome, we decided to start our synthesis of the B-ring from 2-deoxy-D-ribose and postponed the introduction of the C14 hydroxy group until completion of the AB-ring framework. Our result (i.e., **23** to **24**, Scheme 4) is in sharp contrast to the observation made by Takamura and supports the above consideration.



[26] Although we previously reported the synthesis of lactone **19** by means of Yamaguchi lactonization (J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993) of the corresponding hydroxy acid, scale-up of the process was impractical due to the need of the so-called "pseudo high-dilution technique" as well as the high cost of the Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride).

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[30] T. Shimizu, T. Ohzeki, K. Hiramoto, N. Hori, T. Nakata, *Synthesis* **1999**, 1373–1385.

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Received: May 11, 2011
Revised: August 8, 2011
Published online: November 3, 2011

