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Structure Determination of a Chloroenyne from *Laurencia majuscula* Using Computational Methods and Total Synthesis

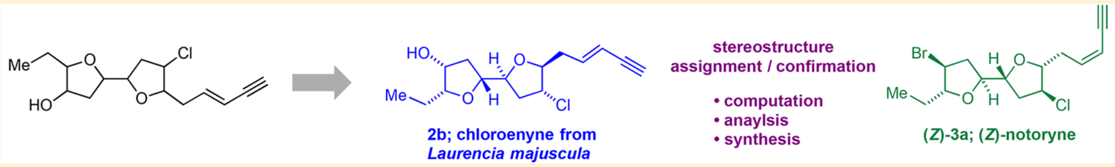
Erin D. Shepherd,[†] Bryony S. Dyson,[†] William E. Hak,[†] Quynh Nhu N. Nguyen,[†] Miseon Lee,[‡] Mi Jung Kim,[‡] Te-ik Sohn,[‡] Deukjoon Kim,[*,‡] Jonathan W. Burton,[*,†] and Robert S. Paton[*,†,§]

[†]Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford OX1 3TA, United Kingdom

[‡]The Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, Seoul 151-742, Korea

[§]Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States

Supporting Information



ABSTRACT: Despite numerous advances in spectroscopic methods through the latter part of the 20th century, the unequivocal structure determination of natural products can remain challenging, and inevitably, incorrect structures appear in the literature. Computational methods that allow the accurate prediction of NMR chemical shifts have emerged as a powerful addition to the toolbox of methods available for the structure determination of small organic molecules. Herein, we report the structure determination of a small, stereochemically rich natural product from *Laurencia majuscula* using the powerful combination of computational methods and total synthesis, along with the structure confirmation of notoryne, using the same approach. Additionally, we synthesized three further diastereomers of the *L. majuscula* enyne and have demonstrated that computations are able to distinguish each of the four synthetic diastereomers from the 32 possible diastereomers of the natural product. Key to the success of this work is to analyze the computational data to provide the greatest distinction between each diastereomer, by identifying chemical shifts that are most sensitive to changes in relative stereochemistry. The success of the computational methods in the structure determination of stereochemically rich, flexible organic molecules will allow all involved in structure determination to use these methods with confidence.

■ INTRODUCTION

Elucidating the structures of natural products that are available only in very small quantities is often exceptionally difficult, highlighted by the high number of structure revisions reported every year in the chemical literature.[1] Unequivocal establishment of molecular structure may be possible using single-crystal X-ray diffraction; however, for molecules that will not crystallize or that form poorly diffracting crystals, alternative methods must be used.[2] Nuclear magnetic resonance (NMR) spectroscopy remains one of the primary means of molecular structure determination. Comparison of computationally predicted NMR chemical shifts, coupling constants, and internuclear distances have also emerged as a powerful and reliable way to assess the likelihood of a putative structure being correct. NMR computations have thus been used to establish relative stereochemistry,[3] to confirm or reassign proposed natural product structures,[4] to characterize the identity of a side product,[5] and in conformational assignment of cyclic peptides.[6] However, this approach can become particularly challenging for molecules containing multiple stereogenic centers and with a high degree of conformational flexibility. In such cases, weighted ensemble averages must be considered in comparison against experimentally observed NMR parameters. In the case of complex structures such as baulamycin, hundreds and thousands of conformations may be relevant at room temperature.[7] Although elegant synthetic approaches have been developed to access multiple diastereomers of a target molecule,[8] the ability to predict the most plausible relative and absolute configuration of flexible natural product structures is desirable. Flexible, halogenated natural products epitomize this challenge and have been variously misassigned.[9]

Comparison of experimental NMR parameters, such as chemical shifts, against calculated values can reveal obvious discrepancies and raise doubts about a proposed structure.[4a] Furthermore, several measures have been used to quantify the "best match" from several putative structures with respect to an experimental spectrum. In particular, statistical parameters developed in the Goodman group, namely, CP3[10] and DP4,[11] use prior knowledge of the underlying empirical error distribution of computational predictions to assign statistical

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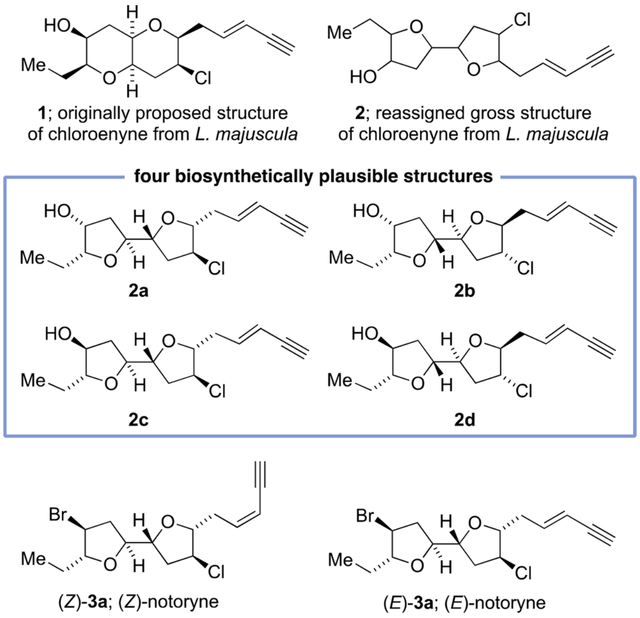
confidence values to a particular structural assignment. This has led to their widespread adoption in computational natural product assignments.[12] These metrics emphasize the importance of ensuring a narrow underlying prediction error as this allows greater significance to be attached to the differences between incorrect structures and experiment. More confident assignments can be made as a result. Empirical linear scaling, aided greatly through contributions from the Tantillo group and the CHESHIRE repository,[13] has contributed to this as have modified DP4 models and the use of different internal standards against which chemical shifts are referenced.[14] However, molecules with many accessible conformers can give rise to larger prediction errors,[3] making the use of these now standard tools more precarious. Herein, we report the full structure determination of a 2,2′-bifuranyl chloroenyne natural product isolated from *Laurencia majuscula* (**2**) using the powerful combination of biosynthetic postulates, density functional theory (DFT) calculations of NMR chemical shifts, and total synthesis. In addition, we report the synthesis of all four biosynthetically relevant diastereomers of **2** (**2a**−**d**) and show that comparison of the experimental ^{1}H and ^{13}C NMR data for any of these four diastereomers with the computed ^{1}H and ^{13}C NMR data for all 32 diastereomers of the natural product allows each specific biomimetic diastereomer to be identified. Finally, we report the structure confirmation of (*Z*)-notoryne as (*Z*)-**3a** using the above combined approach of quantum chemical calculations coupled with two distinct total syntheses.

Recently, we assigned the full structures of two 2,2′-bifuranyl natural products using the powerful combination of biosynthetic postulates, DFT calculations of NMR chemical shifts, and total synthesis. We used this combined approach to fully elucidate the structure of elatenyne[15] and to reassign the stereostructure of laurefurenynes A and B.[16] Previously, we demonstrated that the gross structure of a chloroenyne isolated from *Laurencia majuscula*, originally assigned as a pyrano[3,2-*b*]pyran (**1**)[17] on the basis of extensive NMR experiments and comparison with the NMR data of the dactomelynes[18] and of the originally assigned pyrano[3,2-*b*]pyran structure of elatenyne,[19] was actually a 2,2′-bifuranyl **2** (Chart 1).[15a,b] The 2,2′-bifuranyl **2** contains six stereocenters, with the full structure of the natural product being one of 32 possible diastereomers. We aimed to solve the complete stereostructure of this natural product using the combined approach which we had previously found successful, namely, biosynthetic postulates coupled with DFT calculations of NMR chemical shifts and total synthesis.

Clues from Biosynthesis. Algae of the genus *Laurencia* produce a vast array of structurally diverse C$_{15}$ halogenated natural products. Elatenyne,[19,20] notoryne (**3**),[21] laurendecumenyne B,[20,22] laurefurenynes A and B,[23] and the above chloroenyne from *L. majuscula* **2**[17] are currently the only 2,2′-bifuranyl natural products that have been isolated from *Laurencia* spp. Notoryne **3** was the first of these 2,2′-bifuranyls to be isolated, and its structure was determined through extensive chemical degradation and by comparison with chemical degradation products of laurencin.[21a] A plausible biosynthesis of notoryne **3a** was proposed by Suzuki and by Fukuzawa and Murai.[21a,24] For (3*Z*)-notoryne (*Z*)-**3a**, (3*Z*,12*E*,*R*,*R*)-laurediol **4a**[25] is converted into (3*Z*)-deacetyllaurencin **6a** via bromonium ion formation and cyclization (Figure 1a).[26]

Chart 1. Proposed Structures of Chloroenyne from *L. majuscula* (Relative Configurations) along with the Structures of (*Z*)- and (*E*)-Notoryne (Absolute Configurations)



1; originally proposed structure of chloroenyne from *L. majuscula*

2; reassigned gross structure of chloroenyne from *L. majuscula*

four biosynthetically plausible structures

2a **2b**

2c **2d**

(*Z*)-**3a**; (*Z*)-notoryne

(*E*)-**3a**; (*E*)-notoryne

Further bromoetherification of (3*Z*)-deacetyllaurencin **6a** gives the (3*Z*)-dibromide **8a**, prelaurefucin, via **7a**. Transannular displacement of bromide gives (3*Z*)-tricyclic oxonium ion **9a**, which on opening at C-7 with chloride gives (3*Z*)-notoryne (3*Z*)-**3a**. As we previously proposed for the biosynthesis of laurefurenynes A and B,[16a] displacement of bromide by water (or a water equivalent)[27] would give rise to **2a** as a potential stereostructure for the chloroenyne from *L. majuscula*. Based on this proposed biosynthesis of notoryne **3a**, we recently proposed a biosynthesis of elatenyne, laurendecumenyne B,[15d] and laurefurenynes A and B,[16a] which begins from a different diastereomer of the laurediols (**4b**)[25] and proceeds via the natural product bromofucin **8b**.[28] Here, laurediol **4b** undergoes bromoetherification to give a diastereomer of deacetyllaurencin **6b**, which undergoes further bromoetherification to give bromofucin **8b** (Figure 1b). Transannular displacement of bromide gives the oxonium ion **9b**, which on C-7 opening with chloride gives the notoryne diastereomer **3b**, (3*Z*)-laurendecumenyne B. Displacement of bromide by water (or a water equivalent)[27] gives diastereomer **2b** of the chloroenyne from *L. majuscula*. The laurediols exist naturally as unequal mixtures of (*R*,*R*), (*S*,*S*), (3*E*), (3*Z*), (12*E*), and (12*Z*)-diastereomers.[25] The (3*E*) and (12*Z*)-laurediols **4c** and **4d** are therefore also plausible starting points for the biosynthesis of the chloroenyne **2**, leading to stereostructures **2c** and **2d** (Figure 1c).[29] Based on our biosynthetic analysis, the structure of the chloroenyne from *L. majuscula* is plausibly, therefore, one of the four diastereomers **2a**, **2b**, **2c**, or **2d**, each of which could be produced from the above biogenetic schemes.[30] We then used quantum chemistry to predict the most likely stereostructure for **2**, based on computed ^{13}C and ^{1}H chemical shifts for each of the 32 possible diastereomers.[31]

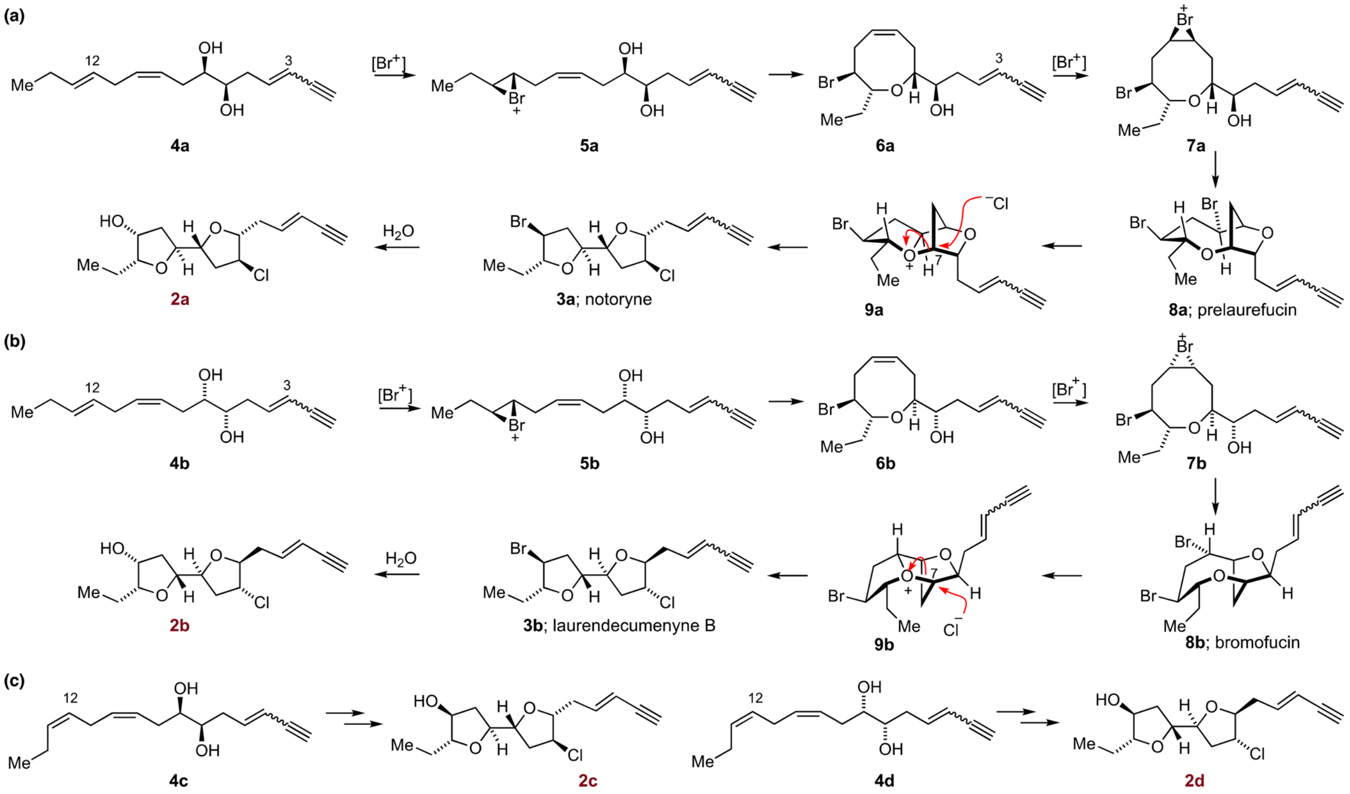


Figure 1. (a) Plausible biosynthesis of notoryne **3a** as proposed by Suzuki and by Fukuzawa and Murai along with the proposed biosynthesis of diastereomer **2a** of the chloroenyne from *L. majuscula*. (b) Proposed biosynthesis of diastereomer **2b** of the chloroenyne from *L. majuscula* via the natural products bromofucin **8b** and laurendecumeyne B **3b**. (c) Proposed stereostructures **2c** and **2d** of the chloroenyne from *L. majuscula* derived from the (12*Z*)-laurediols **4c** and **4d**.

RESULTS AND DISCUSSION

Computational Prediction. The specific challenges associated with the computational structural assignment of chloroenyne **2** (and related molecules) influenced the computational methods employed. First, each diastereomer is highly flexible. A Monte Carlo conformational search with the Merck Molecular Force Field (MMFF) was used to obtain the low-energy conformations within 10 kJ/mol of the lowest-energy structure of each diastereomer.[32] Across all of the diastereomers, there are 1277 conformers in this energy range that contribute to the predicted Boltzmann-weighted chemical shifts! Furthermore, the level of theory used for geometry optimization influences both the estimated populations and the computed chemical shifts of each conformation. Although MMFF geometries have been used in structure prediction,[31c,33] DFT optimization allows for more confident structural assignment as there is a narrower distribution of errors with respect to experimental chemical shifts.[16a,31c] As an illustration, for 82 molecules with 709 experimentally assigned ^{13}C chemical shifts, we verified that DFT optimizations led to a 2 ppm reduction in root-mean-square deviation (rmsd) compared to MMFF geometries, even though both sets of calculations used the same level of theory for shielding tensor calculation and empirical scaling (Figure S1). In this work, we optimized all structures with dispersion-corrected DFT, at the wB97XD/6-31G(d) level of theory[34] with CPCM (Conductor-like Polarizable Continuum Model) chloroform.[35] Conformer relative energies were checked against COSMO−DLPNO−CCSD(T)/cc-pVTZ single-point energies[36] for one diastereomer and showed a good level of agreement (R^2 = 0.90, rmsd = 3.1 kJ/mol) against this high accuracy method (Figure S2). Manual data processing is prohibitively difficult for so many conformations; a Python program was developed to automate all analysis given a collection of output files and a text file with experimental chemical shifts. Conformational Boltzmann weighting, empirical scaling, symmetry averaging, consideration of alternative assignments, and calculation of rmsd/MAD and DP4 for all structures are fully automated (Supporting Information shows example usage). We note that the DP4 workflow has now been automated (pyDP4) by Ermanis and Goodman.[12]

Halogenated natural products pose a further challenge due to the so-called heavy-atom light-atom (HALA) effect.[37] Relativistic spin−orbit contributions shift carbon atoms bonded to Cl, Br, or I to lower parts per million. In this work, we used the CHESHIRE database test set of molecules developed by Rablen, Bally, and Tantillo[13] to derive new, optimal scaling parameters for mPW1PW91/6-311G(d,p)//wB97XD/6-31G(d) GIAO shielding tensors for ^{13}C and ^{1}H nuclei (Figure S3). Several chlorine-containing compounds appear in this data set, from which we found an additive correction of 7.6 ppm applied to the shielding tensors of C−Cl atoms results in an rmsd no worse than if these atoms are excluded entirely. Such a correction (which is level of theory dependent) has also been used by Rzepa and Braddock.[38]

We analyzed the Boltzmann-weighted ^{13}C and ^{1}H chemical shifts for all 32 diastereomers at every position except the hydroxyl proton. The variability in computed shifts across the entire set of diastereomers (Figure 2) shows the extent to which each nucleus acts as a reporter for stereochemical changes. Larger standard deviations are obtained for positions

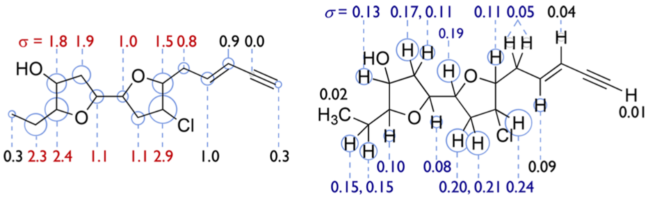


Figure 2. Standard deviations of computed ^{13}C and ^{1}H chemical shifts at each position over all 32 diastereomers of **2**. These values, illustrated by circle size, show the sensitivity of each shift to stereochemical changes. Values in black were excluded from experimental comparison.

which are inherently more sensitive to their relative stereochemistry. Stereostructure assignment can be made more confidently when these values are large in relation to the inherent accuracy of the computed chemical shifts versus experiment (i.e., by ensuring a higher signal-to-noise ratio).

Based on the work of Smith and Goodman,[11] standard deviations of 2.3 and 0.19 ppm for errors in ^{13}C and ^{1}H chemical shifts are representative of the underlying computational accuracy, although because previous calculations used MM geometries, these values are likely to be pessimistic for the DFT optimizations used here. For chloroenyne **2**, a handful of nuclei have low variability and are thus very poor reporters of stereochemical information. Consistent with chemical intuition, these are exocyclic positions remote from stereocenters. These nuclei were excluded from further analysis as they contribute minimally to stereochemical assignment. The inclusion of the halogenated carbon atom is important as this is the best stereochemical reporter from all of the ^{13}C shifts. This is important because halogenated carbons have been omitted previously from structural prediction due to the aforementioned challenges associated with the HALA.[15c] The ethyl $^{13}CH_2$ also provides one of the more diagnostic values. There are several protons which show a standard deviation larger than 0.19 ppm. This is consistent with the idea that structural differences in ^{1}H chemical shifts are more diagnostic than ^{13}C in relation to the underlying theoretical accuracy.[39] We compared predicted chemical shifts for each diastereomer against those of the natural product. The ^{13}C spectrum was fully assigned, whereas for three pairs of protons, the best possible (lowest rmsd) assignment was generated automatically for each structure. The rmsd values and DP4 metrics were generated using 10 ^{13}C and 14 ^{1}H chemical shifts (Figure 3). If one assumes that the underlying error distribution of n chemical shifts is Gaussian (in its original formulation, the DP4 metric assumes a t-distribution, although a Gaussian distribution was also proposed), the sum of squared errors obeys a χ^2-distribution with n degrees of freedom. The rmsd values can therefore be interpreted in a probabilistic fashion as is done for DP4: for example, incorrect structures can be rejected at the $p = 0.05$ significance level, where the rmsd falls above a critical value (Figure 3). Importantly, the statistical significance of differences between rmsd values is intrinsically linked to the number of chemical shifts being compared. Although rmsd, MAE, and R^2 measures have been used previously to compare the relative likelihood of structures being correct, the statistical confidence of these measures has not received much attention. Here, in addition to DP4 values, we show the 95% confidence intervals for rmsd values, above which structures are deemed to be unlikely candidates.

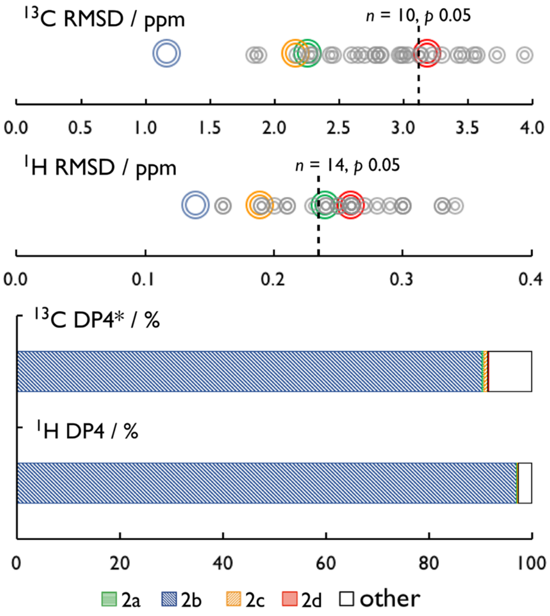


Figure 3. Comparison of computed ^{13}C and ^{1}H chemical shifts for 32 diastereomers of **2** against the natural product. The smallest rmsd values and largest DP4 probabilities point to biosynthetically predicted compound **2b**.

We found that one of the four biogenetically plausible structures (**2b**) was the best match for ^{13}C and ^{1}H experimental data, giving the smallest rmsd and largest DP4* values. The convergence of all four metrics, combined with biosynthetic arguments, overwhelmingly suggests the identity of the chloroenyne from *L. majuscula* as **2b**. In using the original t-distribution parameters (σ, υ) derived for MMFF-optimized geometries, we are being deliberately conservative: we expect a narrower error distribution using DFT optimizations that would penalize the less likely structures more severely. DP4 relies on individually scaling each structure against experiment, which can lead to a fortuitous improvement of incorrect structures, particularly for a small number of nuclei. Indeed, we found better predictive performance without individually scaling the ^{13}C shifts (indicated as DP4*).

All of our biosynthetic and computational analysis provided compelling evidence that the correct structure for the chloroenyne from *L. majuscula* was represented by **2b**; however, proof of this could only come through total synthesis.[1,2b] Additionally, we decided to synthesize all four biosynthetically relevant diastereomers of the chloroenyne from *L. majuscula*, which would allow us to obtain NMR data for each diastereomer. With these data in hand, we could further test the computational methods; would it be possible computationally to correctly identify each of the four biosynthetically predicted diastereomers (**2a**−**d**) from the computed data of the 32 possible diastereomers of the chloroenyne from *L. majuscula*?

Synthesis. The proposed synthesis of the four biomimetically plausible diastereomers of the chloroenyne form *L. majuscula* (**2a**−**d**) presented us with the opportunity to modify and improve our modular route to 2,2′-bifuranyl natural products.[15d] The retrosynthetic synthetic route to diastereomers **2a** and **2c** is shown in Figure 4. Enynes **2a** and **2c** were to be readily derived from the 2,2′-bifuranyl **10**, which itself was to be derived from **11** and subsequently from diol **12** following a route analogous to that described in our recent

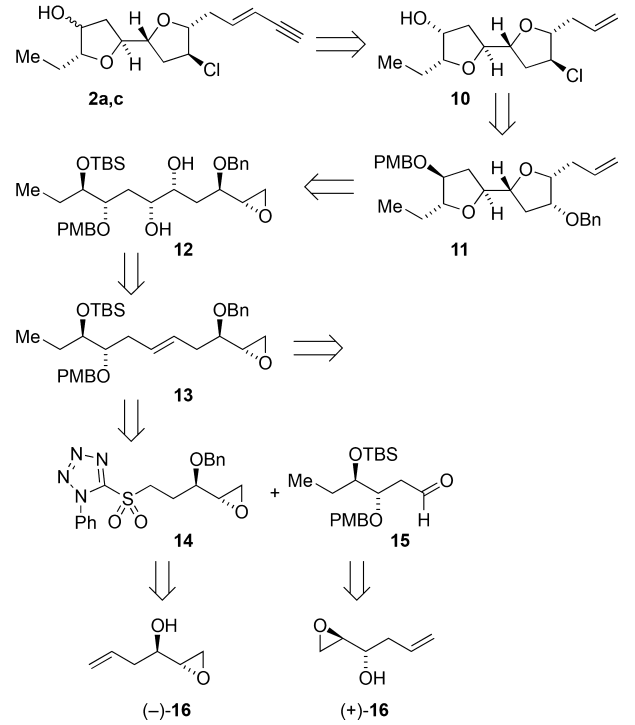
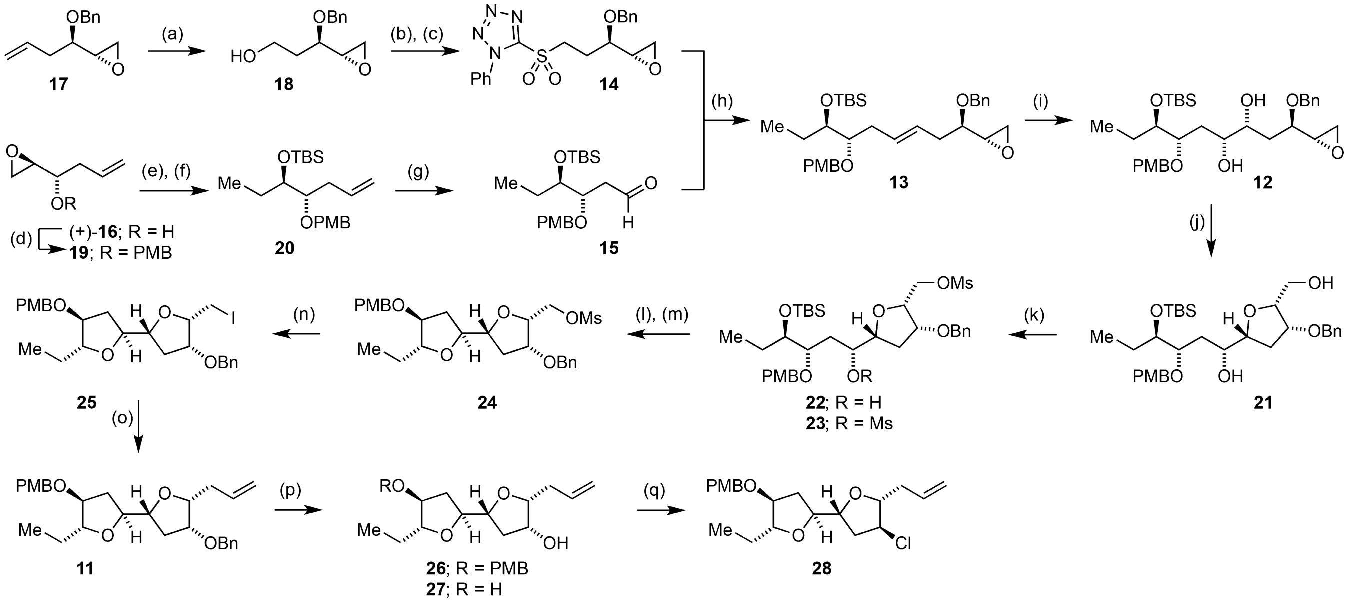


Figure 4. Retrosynthetic analysis of diastereomers **2a** and **2c**.

synthesis of elatenyne.[15d] Diol **12** was to be derived from alkene **13**, which was to be constructed by Julia−Kocienski olefination of aldehyde **15** with sulfone **14**.[40] The two coupling partners **14** and **15** were to be derived from protection of the known enantiomeric epoxy alkenes (+)-**16** and (−)-**16**. In the forward direction (Scheme 1), the known benzyl-protected epoxy alkene **17**, prepared according to the method of Crimmins,[41] was converted into alcohol **18** by ozonolysis with in situ reduction (PPh_3 then $NaBH_4$). Alcohol **18** was then converted into the corresponding tetrazole sulfone **14** by Mitsunobu reaction followed by oxidation.[40] Aldehyde **15** was readily prepared from alcohol (+)-**16**, which on PMB protection gave ether **19**.[15d] Copper-catalyzed ring opening of epoxide **19** with methylmagnesium bromide[41] followed by silyl protection gave alkene **20**. Ozonolysis of alkene **20** and reductive phosphine workup gave the required aldehyde **15**. Julia−Kocienski[40,42] coupling of sulfone tetrazole **14** with aldehyde **15** proceeded in good yield with >20:1 *E*/*Z*-selectivity to give alkene **13**.[43] Sharpless asymmetric dihydroxylation[44] of **13** using super-AD-mix *β*[45] gave the corresponding diols in 91% yield as a 6:1 mixture of *syn*-diastereomers; diol **12** could be isolated in pure form in 64% yield. Under acid catalysis, diol **12** underwent cyclization to give THF **21**. Formation of the second THF ring was achieved using a three-step procedure. Exposure of diol **21** to mesyl chloride and Hünig's base gave dimesylate **23** which, without purification, was treated with (±)-10-camphorsulfonic acid to remove the silyl-protecting group. Exposure of the resulting alcohol to potassium *tert*-butoxide gave 2,2′-bifuranyl **24** in 52% yield over three steps.

During optimization studies, the monomesylate **22** was isolated and characterized. Mosher ester formation using **22** allowed the sense of the Sharpless asymmetric dihydroxylation reaction to be confirmed.[46] As with the synthesis of elatenyne,[15d] forcing conditions (Bu_4NI, toluene, reflux) were

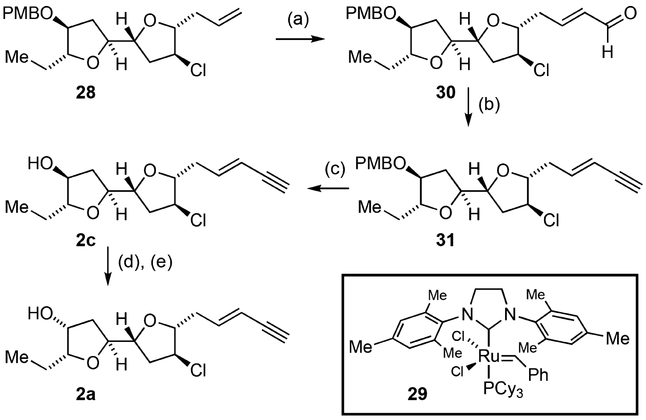
Scheme 1. Synthesis of Chloride 28[a]



[a]Reagents and conditions: (a) O_3/O_2, CH_2Cl_2, MeOH, −78 °C, then PPh_3, 30 min, then $NaBH_4$, −78 °C to rt, 2 h, 92%; (b) DIAD, PPh_3, THF, 0 °C, then **18**, then 1-phenyl-1*H*-tetrazole-5-thiol, rt, 16 h, 88%; (c) 3-chloroperbenzoic acid, CH_2Cl_2, rt, 72 h, 60%; (d) NaH, PMBBr, Bu_4NI, THF, −78 °C to rt, 16 h; (e) MeMgBr, CuI, THF, −20 °C, 1 h, 88% (two steps); (f) TBSCl, imidazole, DMF, 60 °C, 16 h, 99%; (g) O_3/O_2, CH_2Cl_2, −78 °C, then PPh_3, −78 °C to rt, 16 h, 98%; (h) **14**, DME, NaHMDS, −78 °C, 15 min, then add **15** in DME, −78 °C, 1 h, then warm to rt, 2 h, 80%; (i) $K_2OsO_4(OH)_4$, $K_3Fe(CN)_6$, $(DHQD)_2PHAL$, K_2CO_3, $MeSO_2NH_2$, *t*BuOH, water, rt, 24 h, 64% pure **12** (6:1 mixture of *syn*-diol diastereomers 91% total); (j) (±)-10-camphorsulfonic acid, CH_2Cl_2, 0 °C, 2 h, 86%; (k) MsCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 1 h; (l) (±)-10-camphorsulfonic acid, CH_2Cl_2, MeOH, rt, 24 h; (m) *t*-BuOK, *t*BuOH, 35 °C, 52% (three steps); (n) Bu_4NI, toluene, 110 °C, 16 h, 80%; (o) $CH_2{=}CHMgBr$, benzene, THF, 40 °C, 3 h, 57%; (p) Li, 4,4′-di-*tert*-butyl-1,1′-biphenyl, THF, −78 °C, 77%; (q) CCl_4, PPh_3, CH_2Cl_2, rt, 3 h, 78%.

required to convert the mesylate **24** into the corresponding iodide **25**. Iodide **25** underwent displacement with vinylmagnesium bromide in a mixed benzene/THF solvent system to give the allyl-substituted 2,2′-bifuranyl **11** in 57% yield.[47] Deprotection of the benzyl group in **11** in the presence of the PMB group was achieved by titrating LiDBB[48] into a THF solution of **11** to minimize formation of diol **27**. Attempted chlorination of alcohol **26** using triphenylphosphine with carbon tetrachloride as both reagent and solvent led to very little conversion of **26** into chloride **28**.[49] Appel reported a large solvent effect on the chlorination of alcohols using tertiary phosphines and carbon tetrachloride with the use of dichloromethane and acetonitrile, resulting in significant rate enhancements.[49] Conducting the chlorination of alcohol **26** using dichloromethane as solvent gave chloride **28** in 78% yield. Conversion of chloride **28** into the biosynthetically plausible diastereomers **2a** and **2c** required introduction of the (*E*)-enyne (Scheme 2). Previously the Oxford group have used a Wittig reaction with the ylide derived from (3-trimethylsilyl-2-propynyl)triphenylphosphonium bromide[15a,b,d] for the stereoselective synthesis of (*E*)-enynes from aldehydes; however, the diastereocontrol in these reactions was never above 9:1 *E*/*Z*. We therefore elected to use the recently developed methodology for (*E*)-enyne synthesis from alkenes reported by the Seoul group, which gives very high *E*-selectivity.[15d,16a,50] Cross-metathesis of alkene **28** with crotonaldehyde and Grubbs' second generation catalyst **29** gave the corresponding *α*,*β*-unsaturated aldehyde **30**, which was immediately exposed to lithiated trimethylsilyl diazomethane (Colvin−Ohira homologation) to give enyne **31**. Removal of the *para*-methoxy benzyl group[51] from **31** gave **2c**, the first of the enyne targets. Mitsunobu inversion[52] of the secondary alcohol in **2c** followed by ester methanolysis gave **2a**, the second of the biomimetically plausible diastereomers.

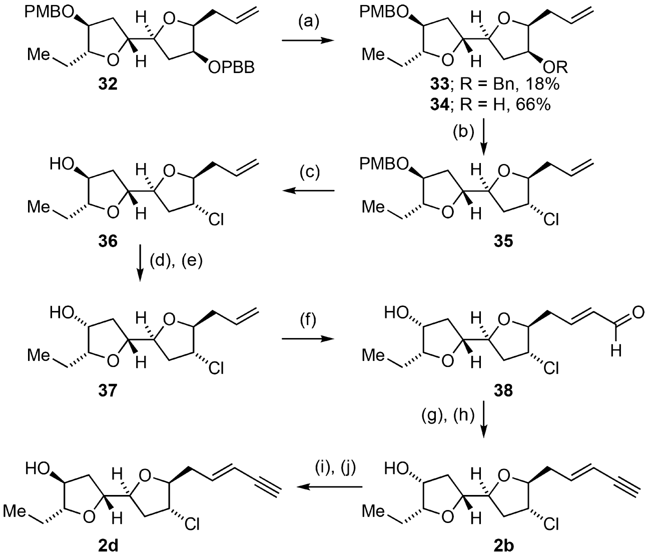
Scheme 2. Synthesis of Diastereomers 2a and 2c[a]



[a]Reagents and conditions: (a) crotonaldehyde, catalyst **29**, CH_2Cl_2, 40 °C, 1 h then Me_2SO, rt, 16 h, 88%; (b) (trimethylsilyl)diazomethane, *n*-BuLi, THF, add **30**, −78 °C to rt, 1 h 70%; (c) $BCl_3\cdot SMe_2$, CH_2Cl_2, rt, 5 min, 84%; (d) DIAD, PPh_3, THF, 0 °C, then **2c**, then 4-nitrobenzoic acid, rt; (e) K_2CO_3, MeOH, rt, 20 min, 25% two steps).

The synthesis of the final two biosynthetically plausible diastereomers of the chloroenyne from *L. majuscula* (enynes **2b** and **2d**) began from the known 2,2′-bifuranyl **32**, an intermediate in our recent synthesis of elatenyne (Scheme 3).[15d] Selective removal of the *para*-bromobenzyl group in the presence of the more electron-rich *para*-methoxy benzyl group was achieved using LiDBB[48] in the presence of a proton donor,[53] which gave the requisite alcohol **34** in 66% yield along with 18% of the benzyl ether **33**.[54] Chlorination of **34** as before[49] provided chloride **35** in 96% yield, which was readily deprotected under Lewis acidic conditions to give alcohol **36**.[51] Mitsunobu inversion of **36**[52] to give **37**, followed by enyne introduction, as before,[15d,50] gave the third biomimetic diastereomer **2b**. A further Mitsunobu reaction gave the fourth and final biomimetic diastereomer **2d**.[55]

Scheme 3. Synthesis of Diastereomers 2b and 2d[a]



[a]Reagents and conditions: (a) Li, 4,4′-di-*tert*-butyl-1,1′-biphenyl, bis(2-methoxyethyl)amine, THF, −78 °C, 18% of **33**, 66% of **34**; (b) CCl_4, PPh_3, CH_2Cl_2, rt, 3 h, 96%; (c) $BCl_3\cdot SMe_2$, CH_2Cl_2, rt, 5 min; 94%; (d) DIAD, PPh_3, THF, 0 °C, then **36**, then 4-nitrobenzoic acid, rt; (e) K_2CO_3, MeOH, rt, 30 min, 79% (two steps); (f) crotonaldehyde, catalyst **29**, CH_2Cl_2, 40 °C, 90 min; (g) (trimethylsilyl)diazomethane, *n*-BuLi, THF, add **37**, −78 to 0 °C; (h) Bu_4NF, THF, 0 °C, 5 min, 39% (three steps); (i) DIAD, PPh_3, THF, 0 °C, then **2b**, then 4-nitrobenzoic acid, rt; (j) K_2CO_3, MeOH, rt, 30 min.

Analysis. Having completed the total synthesis of all four of the biosynthetically relevant diastereomers of the chloroenyne from *L. majuscula* (**2a−d**), we were delighted to find that the ^1H and ^{13}C NMR data for diastereomer **2b** were in excellent agreement with that reported for the natural product.[17] Our synthesis of the chloroenyne from *L. majuscula* **2b** proceeds in 16 steps (longest linear sequence) from (+)-**16**. The optical rotation for our synthetic **2b** was in good agreement in terms of both sign and magnitude with that recorded for the natural product,[17] demonstrating that the absolute configuration of the chloroenyne from *L. majuscula* is as represented by **2b**. The chloroenyne from *L. majuscula* **2b** thus sits on the same proposed biosynthetic pathway as elatenyne,[15d] laurendecumenyne B,[15d] and laurefurenynes A and B,[16] proceeding from (3*E*/*Z*)-laurediols **4b** via the bromofucins **8b**.

The identification of the full stereostructure of the chloroenyne from *L. majuscula* as **2b** on the basis of DFT methods demonstrates the power and utility of these methods to aid in the structure determination of stereochemically rich organic molecules. The synthesis of the remaining three biosynthetically relevant diastereomers **2a**, **2c**, and **2d** provided us with the opportunity to further test the computational

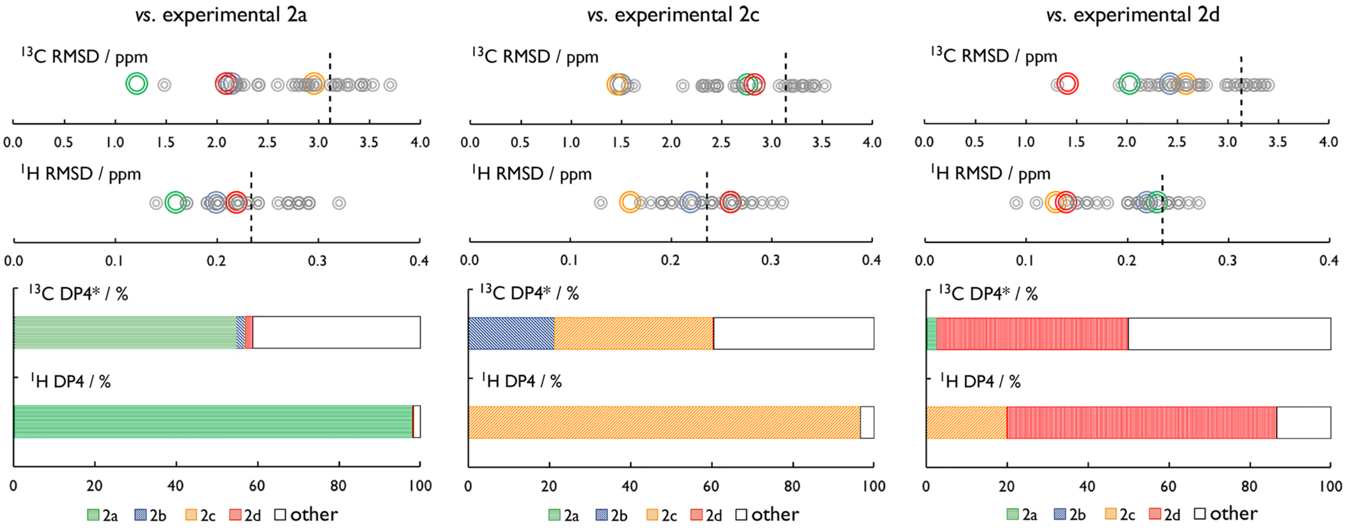
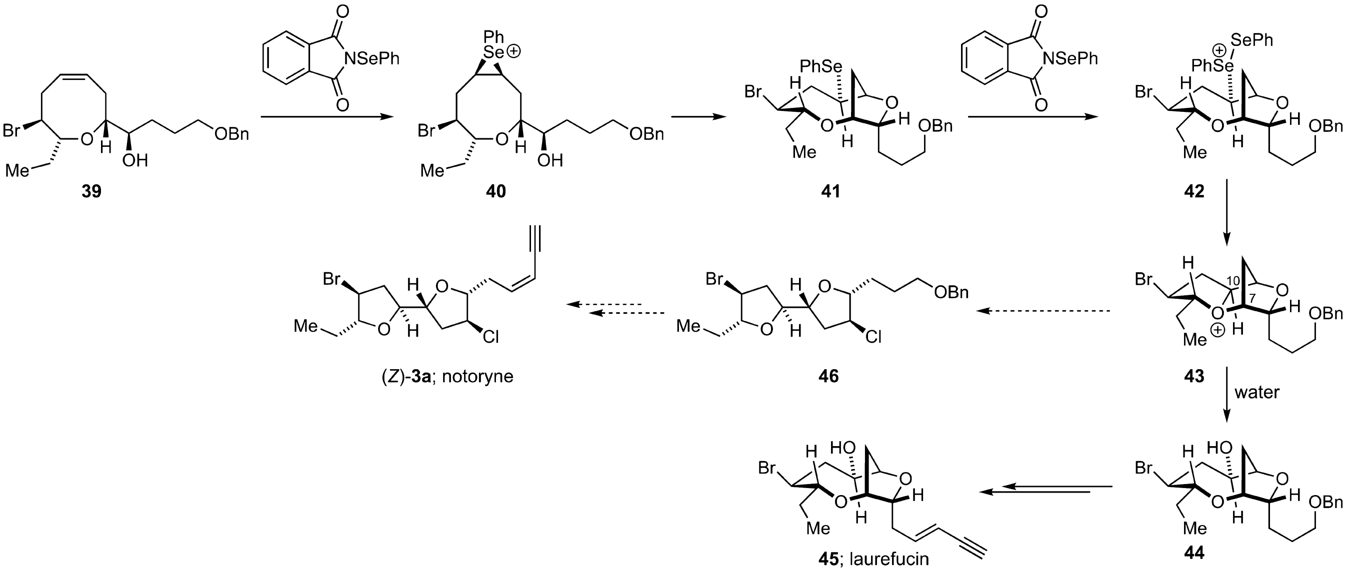


Figure 5. Comparison of computed ^{13}C and ^{1}H chemical shifts for 32 diastereomers of **2** against experimental spectra for **2a**, **2c**, and **2d**.

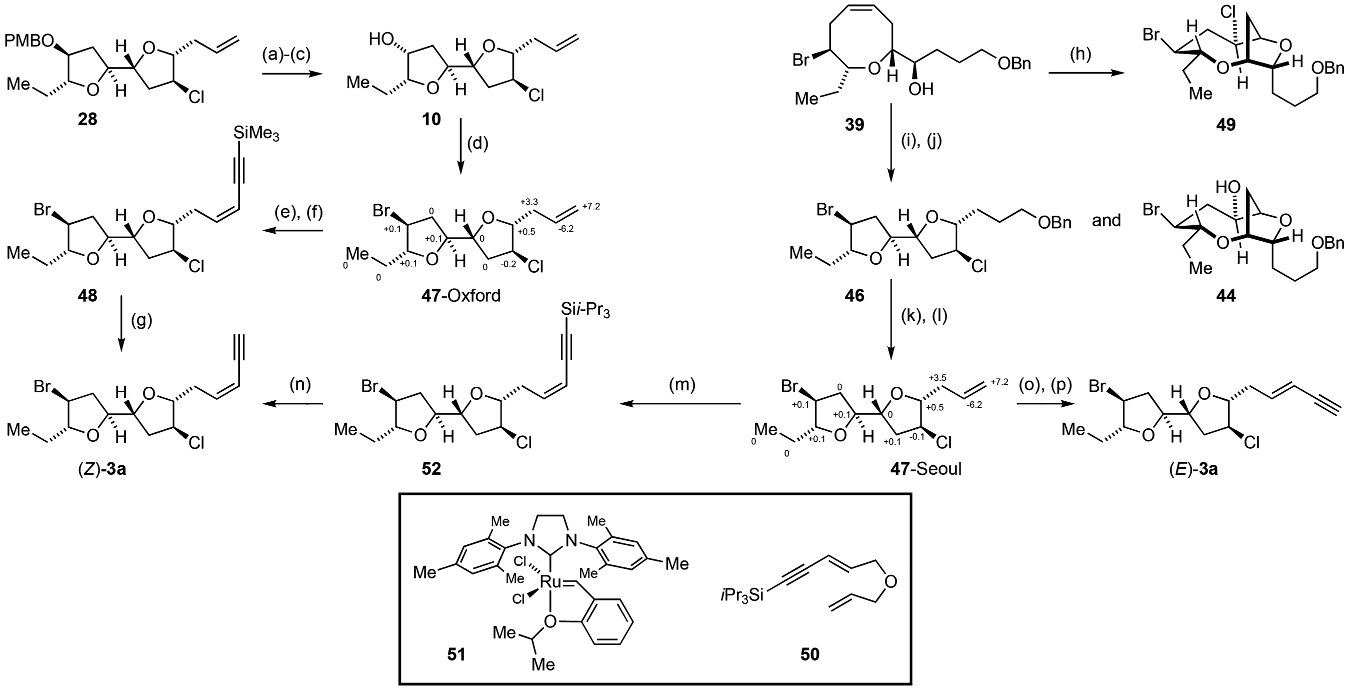
Scheme 4. Key Step in the Seoul Synthesis of Laurefucin, along with the Proposed Route to Notoryne



methods. We had acquired ^{1}H and ^{13}C NMR data for the chloroenynes **2a**, **2c**, and **2d**, which allowed us to determine whether it would be possible, computationally and correctly, to identify each of these diastereomers from the computed data of the 32 possible diastereomers of the chloroenyne from *L. majuscula*. We found the correct stereostructures identified among structures with the smallest rmsd values: the two structures with the lowest rmsd values contain the correct structure in all but one case (^{1}H of **2d**), where it is in the lowest four (Figure 5). ^{1}H DP4 values were more diagnostic, with the correct structure predicted with 60−98% confidence (compared to 40−55% for ^{13}C). The product of the DP4/DP4* values for both nuclei provide an unequivocal and, importantly, correct stereostructure prediction for all four diastereomers studied, including the natural product.

Notoryne. Notoryne (*Z*)-**3a** is the first halogenated 2,2′-bifuranyl natural product isolated from *Laurencia* spp.[56] The structure of (*Z*)-notoryne (*Z*)-**3a** was originally assigned by careful chemical degradation and comparison with chemical degradation products from laurefucin and laurencin, whose structures and absolute configurations were securely established through single-crystal X-ray analysis.[21] As noted above, a biosynthesis of notoryne **3** was first proposed by Suzuki and by Fukuzawa and Murai (Figure 1a).[21,24] Previously, the Oxford group had prepared the 2,2′-bifuranyl **28** (Scheme 1), with the necessary stereochemical arrangement for ready conversion into notoryne (*Z*)-**3a**. Additionally, the Seoul group had demonstrated a number of biomimetic syntheses of halogenated natural products from *Laurencia* spp., including the synthesis of the 2,2′-bifuranyl natural products (*Z*)- and (*E*)-elatenyne[15d] and laurendecumenyne B.[15d] In their synthesis of laurefucin,[50a] the Seoul group had prepared the bromooxocene **39**, which on treatment with *N*-phenylselenophthalimide (*N*-PSP) under aqueous acidic conditions gave rise to the [5.2.1]dioxabicyclic bromide **44** in quantitative yield (Scheme 4); the bromide was readily converted into the natural product laurefucin **45**. The formation of the [5.2.1]dioxabicyclic bromide **44** most likely follows the mechanism indicated. Here, seleniranium ion formation occurs from the oxocene **39**, giving **40**, which undergoes ether formation to yield the

Scheme 5. Oxford and Seoul Syntheses of Notoryne[a]



[a]Reagents and conditions: (a) $BCl_3 \cdot SMe_2$, CH_2Cl_2, rt, 5 min, 95%; (b) DIAD, PPh_3, THF, 0 °C, then 4-nitrobenzoic acid, rt, 74%; (c) K_2CO_3, MeOH, rt, 20 min, 91%; (d) CBr_4, PPh_3, toluene, 80 °C, 75 min, 75%; (e) O_3, CH_2Cl_2, −78 °C then PPh_3, −78 °C to rt, 15 h; (f) TMSC≡CCH2TBS, *t*BuLi, THF, −78 °C, 1 h, then $Ti(OiPr)_4$, 10 min, then add **47**, −78 °C, 30 min, rt, 30 min, 32% (two steps); (g) TBAF, THF, −20 °C, 5 min, quant.; (h) PhSeCl, *n*-hexane; (i) PhSeCl (3 equiv), activated silica gel, *n*-hexane, rt, 72 h; (j) CH_3CN/H_2O (9:1), rt, 24 h, 80% of **46**, 20% of **44**; (k) H_2, $Pd(OH)_2/C$, EtOH, 1 h, 95%; (l) *o*-nitrophenylselenocyanide, $(Oct)_3P$, THF, rt, 10 min, then H_2O_2, 0 °C to rt, 24 h, 85%; (m) **50**, catalyst **51**, benzene, 70 °C, 1.5 h, then additional **50** and **51**, 82% 3:1 *Z*/*E*; (n) TBAF, THF, 0 °C, 1 h, 95%; (o) crotonaldehyde, catalyst **29**, CH_2Cl_2, 40 °C, 1.5 h then Me_2SO, rt, 12 h; (p) (trimethylsilyl)diazomethane, LDA, THF, −78 to 0 °C, 2 h, 88% (two steps). *Note: The difference in the ^{13}C NMR chemical shifts between the synthetic compounds* **47** *prepared by the Oxford and Seoul groups and natural notoryne (Z)-***3a** *are shown adjacent to the relevant carbon atoms in structures* **47**.

selenide **41**. Activation of the selenide group in **41** by reaction with further *N*-PSP gives prelaurefucin surrogate **42**. Transannular C−O bond formation then occurs, giving the key oxonium ion **43**. Attack at C-10 by water with loss of a proton leads to the laurefucin precursor **44** that was readily transformed into the natural product **45**. Opening of the oxonium ion **43** at C-7 by chloride with inversion of configuration would yield the notoryne precursor **46** with the correct absolute configuration for synthesis of the natural product (*Z*)-**3a**. Given the previous preparation of the 2,2′-bifuranyl **28** and the oxocene **39**, we reasoned that synthesis of the natural product notoryne could be readily achieved by two independent routes (Scheme 5). The Oxford group began their synthesis from the previously prepared chloroalcohol **28**, which was readily converted into chloroalcohol **10** through deprotection, Mitsunobu inversion, and saponification. Bromination of alcohol **10** using the Hooz procedure[57] gave bromide **47**. The Seoul team prepared the same bromide beginning with their previously prepared oxocene **39**. After extensive experimentation, the Seoul team found that exposure of the oxocene alcohol **39** to phenylselenyl chloride in the presence of activated silica gel followed by treatment of the crude mixture with water in acetonitrile gave the 2,2′-bifuranyl chloride **46** along with alcohol **44**.[58] It is of note that in the absence of silica gel, the [5.2.1]-bicyclic chloride **49** was formed.[50a] In both the Oxford and Seoul syntheses, the chlorine-bearing carbon atoms could be identified using ^{13}C NMR chlorine-induced isotopic shift.[59] The Seoul group converted the benzyl-protected alcohol **46** into the corresponding alkene **47** using standard procedures. Comparison of the ^{13}C NMR chemical shifts of the 2,2′-bifuranyls **47** synthesized in Oxford and Seoul, with the corresponding chemical shifts for notoryne, indicated that the synthesized material had the same stereostructure as that of the natural product (Scheme 5). Completion of the synthesis of the natural products was accomplished by two independent routes. In Oxford, the terminal alkene in **47** was subject to ozonolysis followed by reductive workup to give the corresponding aldehyde (uncharacterized) that was subject to a Yamamoto−Petersen reaction[60] to give the (*Z*)-enyne **48** with high diastereoselectivity. Removal of the terminal silyl group was readily achieved on brief exposure of **48** to fluoride to give notoryne (*Z*)-**3a**. In Seoul, the (*Z*)-enyne was introduced directly from the terminal alkene **47** via a relay cross-metathesis using enyne **50** and catalyst **51**,[15d,50b,61] which gave the desired enyne **52** as a 3:1 mixture of *Z*/*E*-enynes in 82% combined yield.

Fluoride treatment of **52** gave notoryne (*Z*)-**3a**. The Oxford and Seoul ^1H and ^{13}C NMR data were in excellent agreement with each other and with the data reported by Suzuki.[21a,62] Additionally, the optical rotations of the synthetic materials confirm that the absolute configuration of the natural product is as represented by (*Z*)-**3a** as originally assigned by Suzuki. Additionally, the Seoul team synthesized (*E*)-notoryne (*E*)-**3a**[21b] from alkene **47**. Cross-metathesis of alkene in **47** using crotonaldehyde and the Grubbs−Hoveyda catalyst **29** gave the corresponding α,β-unsaturated aldehyde as a single *E*-isomer,[15d,50] which on Colvin−Ohira homologation gave (*E*)-notoryne (*E*)-**3a** in 88% overall yield from alkene **47**.[21b]

Having synthesized notoryne by two independent routes, we elected to further test the computational methods for prediction/confirmation of structure of these halogenated 2,2′-natural products. As with the previous 2,2′-bifuranyls from *Laurencia* spp. we have studied, notoryne (*Z*)-**3a** contains six stereocenters, resulting in 32 diastereomeric notorynes. We decided to challenge the computational method to see if it could predict the correct structure of notoryne from the pool of 32 diastereomeric notorynes.

Upon computing the Boltzmann-weighted chemical shifts for all 32 diastereomers, we found maximum variance to stereochemical changes occurs for carbon atoms directly attached to halogen atoms and the attached protons (Figure 6). As with earlier studies, the exocyclic positions offer little for predictive power and were excluded from further analysis. The stereostructure for notoryne, (*Z*)-**3a**, is clearly favored in the analysis of ^{13}C predictions, whereas from ^{1}H chemical shifts, it ranks in the top two structures. Again, the cumulative $^{1}H/^{13}C$ DP4 metric gives (*Z*)-**3a** as the single most likely stereostructure. The total synthesis and structure confirmation of notoryne (*Z*)-**3a** further demonstrates the utility of computational methods to not only predict but also confirm the structures of stereochemically rich, functionalized, and flexible organic molecules and natural products.

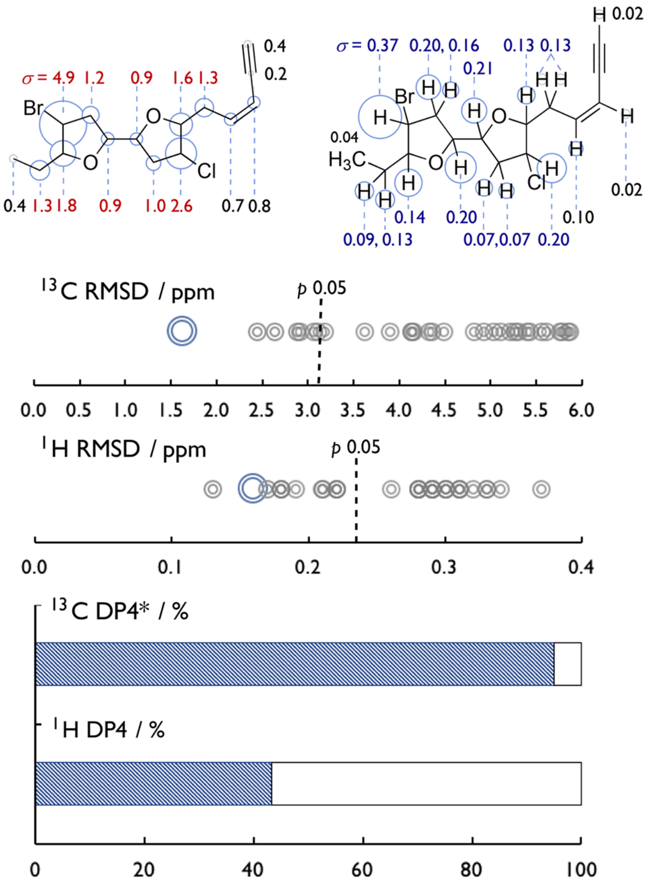


Figure 6. Comparison of computed ^{13}C and ^{1}H chemical shifts for 32 diastereomers against experimental spectra of notoryne. Data for (*Z*)-**3a** are shown as blue circles in rmsd and blue area in DP4*.

CONCLUSIONS

We have demonstrated that computational methods are able to predict the structure of a highly flexible chloroenyne natural product from *L. majuscula* containing six stereocenters from the 32 possible diastereomeric structures of the natural product. Moreover, we have synthesized three further "biomimetic" diastereomers of the natural product. Using the NMR data of these diastereomers, we have shown that the same computational methods can identify each diastereomer out of the set of 32 possible diastereomers. Key to these computational methods was to use the computed NMR chemical shift data only for those atoms that are good reporters of stereochemical information across all 32 diastereomers, that is, those atoms that show a large standard deviation in computed NMR chemical shift among the diastereomers. Furthermore, we applied both computational methods and synthesis to confirm the structure of notoryne, a further halogenated 2,2′-bifuranyl natural product isolated from *Laurencia* spp.

EXPERIMENTAL SECTION

General Procedures. Proton (^{1}H), carbon (^{13}C), and fluorine (^{19}F) NMR spectra were recorded on a Bruker AV 500 (500/125 MHz), Bruker AV 400 (400/100 MHz), or Bruker DPX 300 (300/75 MHz) spectrometer. Proton and carbon chemical shifts (δ) are quoted in parts per million and referenced to tetramethylsilane with residual protonated solvent as internal standard. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dd (double doublet), and so on. Coupling constants (J) are given in hertz and are rounded to the nearest 0.1 Hz. H and H′ refer to diastereotopic protons attached to the same carbon and imply no particular stereochemistry. All assignments are confined by $^{1}H-^{1}H$ COSY and $^{1}H-^{13}C$ HSQC experiments. Low-resolution mass spectra were recorded on a Fisons Platform spectrometer (ES). High-resolution mass spectra were recorded by the mass spectrometry staff at the Chemistry Research Laboratory, University of Oxford, using a Bruker Daltronics microTOF spectrometer (ES) or a Micromass GCT (FI). The m/z values are reported in Daltons with their percentage abundances and, where known, the relevant fragment ions in parentheses. High-resolution values are calculated to four decimal places from the molecular formula, with all found values being within a tolerance of 5 ppm. Infrared spectra were recorded on a Bruker Tensor 27 Fourier transform spectrometer, as a thin film on diamond ATR. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}). Optical rotations were measured using a PerkinElmer 241 polarimeter in a cell of 1 dm path length (l). TLC was performed on Merck DC-Alufolien 60F254 0.2 mm precoated plates and visualized using an acidic vanillin or basic potassium permanganate dip. Retention factors (R_f) are reported with the solvent system used in parentheses. Flash column chromatography was performed on Merck 60 silica (particle size 40−63 μm, pore diameter 60 Å), and the solvent system used is recorded in parentheses.

All nonaqueous reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen and employing standard techniques for handling air-sensitive materials. Solvents and commercially available reagents were dried and purified before use, as appropriate. In particular, DCM and THF were distilled from CaH_2 and stored over 3 Å molecular sieves. "Petrol" refers to the fraction of light petroleum ether boiling in the range of 40−60 °C unless otherwise stated. All water used experimentally was distilled, and the term "brine" refers to a saturated solution of sodium chloride in water.

(R)-3-(Benzyloxy)-3-((S)-oxiran-2-yl)propan-1-ol ***(18)***. Alkene **17** (3 g, 14.7 mmol) was dissolved in DCM/MeOH (1:1, 200 mL) and the stirred solution cooled to −78 °C. O_2 was sparged through the solution for 5 min followed by O_3/O_2 until a faint blue hue appeared. Then the reaction was sparged with O_2 for 5 min and PPh_3 was added (11.6 g, 44 mmol) and the reaction stirred at −78 °C for 30 min. To

the reaction mix was added $NaBH_4$ (1.6 g, 44 mmol), and the reaction was allowed to warm to rt over 2 h. The reaction was quenched with H_2O (100 mL) and then diluted with DCM (100 mL). The aqueous phase was separated and extracted with DCM (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was dry-loaded onto silica and purified by rapid flash column chromatography (2:1→ 1:1 petrol bp 30−40 °C/diethyl ether 1% NEt_3) to give the title compound as a colorless oil (2.81 g, 13.5 mmol, 92%): R_f 0.40 (1:1 petrol/diethyl ether); ν_{max}/cm^{-1} (thin film) 3434s br, 2875m; ^{1}H NMR (400 MHz C_6D_6) δ 7.06−7.23 (m, 5H, Ar*H*), 4.46 (d, *J* = 11.6 Hz, 1H, CH*H*′Ar), 4.23 (d, *J* = 11.6 Hz, 1H, C*H*H′Ar), 3.48−3.73 (m, 2H, C*H*$_2$OH), 3.24 (dt, *J* = 6.8, 5.6 Hz, 1H, C*H*OBn), 2.61 (ddd, *J* = 5.6, 3.8, 2.8 Hz, 1H, C*H*OCH$_2$), 2.35 (dd, *J* = 5.3, 2.6 Hz, 1H, CHOCH*H*′), 2.29 (dd, *J* = 5.4, 3.8 Hz, 1H, CHOC*H*H′), 1.75−1.60 (m, 3H, CO*H*, C*H*$_2$CH$_2$OH); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6) δ 139.0 (Ar), 128.2 (Ar), 128.0 (Ar), 127.8 (Ar), 76.9 (CHOBn), 72.4 (CH$_2$Ar), 59.5 (CH$_2$OH), 53.1 (CHOCH$_2$) 45.3 (CHOCH$_2$), 35.6 (CH$_2$CH$_2$OH); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{16}O_3Na$ 231.0992; found 231.0992; $[\alpha]_D^{25}$ +32.0 (*c* = 1.0 in CHCl$_3$).

5-(((R)-3-(Benzyloxy)-3-((S)-oxiran-2-yl)propyl)thio)-1-phenyl-1H-tetrazole. PPh$_3$ (4.23 g, 16.1 mmol) was dissolved in dry THF (50 mL) and cooled to 0 °C, and DIAD (3.2 mL, 16.1 mmol) was added dropwise to the solution and stirred at 0 °C for 15 min. Alcohol **18** (2.8 g, 13.4 mmol) was dissolved in dry THF (25 mL) and added dropwise to the reaction mixture followed by a wash with dry THF (5 mL), and the reaction was stirred at 0 °C for 15 min. 1-Phenyl-1*H*-tetrazole-5-thiol (3.12 g, 17.5 mmol) was added in one portion, and the reaction mixture was warmed to rt and stirred for 16 h. The reaction mixture was concentrated in vacuo and dry-loaded on silica. Purification by flash column chromatography (5:1 petrol/acetone) yielded the title compound as a colorless oil (4.37 g, 11.8 mmol, 88%): R_f 0.5 (5:1 petrol/acetone); ν_{max}/cm^{-1} (thin film) 2870; ^{1}H NMR (400 MHz CDCl$_3$) δ 7.54−7.58 (m, 5H, Ar*H*), 7.27−7.35 (m, 5H, Ar*H*), 4.70 (d, *J* = 11.4 Hz, 1H, C*H*H′Ar), 4.50 (d, *J* = 11.4 Hz, 1H, CH*H*′Ar), 3.56 (ddd, *J* = 13.3, 7.9, 5.4 Hz, 1H, C*H*OBn), 3.43−3.51 (m, 2H, C*H*$_2$SAr), 2.98 (ddd, *J* = 5.2, C*H*$_2$CH$_2$OH4.0, 2.8 Hz, 1H, C*H*OCH$_2$), 2.81 (dd, *J* = 5.0, 4.0 Hz, 1H, CHOC*H*H′), 2.75 (dd, *J* = 5.0, 2.8 Hz, 1H, CHOCH*H*′), 2.25 (dtd, *J* = 14.4, 7.6, 3.8 Hz, 1H, C*H*H′CH$_2$SAr), 2.13 (dddd, *J* = 14.4, 8.8, 7.6, 3.3 Hz, 1H, CH*H*′CH$_2$SAr); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 154.2 (Ar), 138.0 (Ar) 133.7 (Ar), 130.1 (Ar), 128.5 (Ar), 127.9 (Ar), 127.6 (Ar) 123.8 (Ar), 76.1 (CHOBn), 72.5 (CH$_2$Ar), 53.0 (CHOCH$_2$), 45.6 (CHOCH$_2$), 32.12 (CH$_2$CH$_2$SAr), 29.3 (CH$_2$SAr); MS (ESI-TOF) *m*/*z* 391 [M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{20}N_4O_2SNa$ 391.1199; found 391.1201; $[\alpha]_D^{25}$ +26.0 (*c* = 1.0 in CHCl$_3$).

5-(((R)-3-(Benzyloxy)-3-((S)-oxiran-2-yl)propyl)sulfonyl)-1-phenyl-1H-tetrazole ***(14)****.* 5-(((*R*)-3-(Benzyloxy)-3-((*S*)-oxiran-2-yl)-propyl)thio)-1-phenyl-1*H*-tetrazole (4.3 g, 11.8 mmol) was dissolved in DCM (200 mL), and to the stirring solution was added *m*CPBA (7.2 g, 41.6 mmol), and the mixture was stirred at rt for 3 days. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL) and then with saturated aqueous $NaHCO_3$ (200 mL). The aqueous layer was separated and extracted with DCM (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification via flash column chromatography (DCM) gave the title compound as white needles (2.85 g, 7.1 mmol, 60%): R_f 0.52 (5:1 petrol/acetone); mp 90−92 °C; ν_{max}/cm^{-1} (thin film) 2918s, 1342s, 1150s; ^{1}H NMR (400 MHz CDCl$_3$) δ 7.56−7.70 (m, 5H, Ar*H*), 7.29−7.38 (m, 5H, Ar*H*), 4.69 (d, *J* = 11.6 Hz, 1H, C*H*H′Ar), 4.52 (d, *J* = 11.6 Hz, 1H, CH*H*′Ar), 3.93 (ddd, *J* = 14.9, 10.2, 5.3 Hz, 1H, CH*H*′SAr), 3.81 (ddd, *J* = 14.9, 10.3, 5.6 Hz, 1H, C*H*H′SAr), 3.47 (ddd, *J* = 8.3, 5.6, 4.3 Hz, 1H, C*H*OBn), 2.96 (ddd, *J* = 5.6, 3.8, 2.5 Hz, 1H, C*H*OCH$_2$), 2.82 (dd, *J* = 5.0, 3.8 Hz, 1H, CHOC*H*H′), 2.72 (dd, *J* = 5.0, 2.5 Hz, 1H, CHOCH*H*′), 2.37 (dddd, *J* = 14.4, 9.9, 5.6, 4.3 Hz, 1H, C*H*H′CH$_2$SAr) 2.24 (dddd, *J* = 14.4, 10.3, 8.3, 5.3 Hz, 1H, CH*H*′CH$_2$SAr); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 153.3 (Ar) 137.5 (Ar), 133.0 (Ar), 131.5 (Ar) 129.7 (Ar), 128.6 (Ar), 128.1 (Ar), 127.9 (Ar), 125.1 (Ar), 75.6 (CH$_2$Ar), 72.4 (CHOBn), 52.6 (CH$_2$SAr), 52.3 (CHOCH$_2$), 45.7(CHOCH$_2$), 25.5 (CH$_2$CH$_2$SAr); MS (ESI-TOF) *m*/*z* 423 [M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{20}N_4O_4SNa$ 423.1097; found 423.1089; $[\alpha]_D^{25}$ +14.5 (*c* = 1.0 in CHCl$_3$).

tert-Butyl-(((3R,4S)-4-((4-methoxybenzyl)oxy)hept-6-en-3-yl)-oxy)dimethylsilane ***(20)****.* The known alcohol (3*R*,4*S*)-4-(4-methoxybenzyloxy)hept-6-en-3-ol was readily prepared from the epoxy alcohol (+)-**16** via the *p*-methoxybenzyl ether **19** according to our previously reported route.[15d] (3*R*,4*S*)-4-(4-Methoxybenzyl-oxy)hept-6-en-3-ol thus prepared (3.3 g, 13.2 mmol) was dissolved in dry DMF (100 mL), then imidazole (1.97 g, 29.6 mmol) and TBSCl (2.98 g, 19.8 mmol) were added. The reaction mixture was heated to 60 °C for 16 h. The reaction was cooled to rt and then quenched with water (50 mL). The aqueous layer was separated and extracted with diethyl ether (3 × 75 mL). The combined organic layers were washed with water (3 × 50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (20:1 petrol bp 30−40 °C/diethyl ether) gave the title compound as a colorless oil (4.81 g, 13.0 mmol, 99%): R_f 0.62 (20:1 petrol/diethyl ether); ν_{max}/cm^{-1} (thin film) 3076m, 2957s, 2931s, 2857s, 1641m; ^{1}H NMR (400 MHz CDCl$_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.6 Hz, 2H, Ar*H*), 5.90 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*═CH$_2$), 5.10 (dq, *J* = 17.0, 1.7 Hz, 1H, CH= C*H*H), 5.05 (ddt, *J* = 10.0, 2.3, 1.1 Hz, 1H, CH= CH*H*) 4.59 (d, *J* = 11.3 Hz, 1H, C*H*H′Ar), 4.49 (d, *J* = 11.3 Hz, 1H, CH*H*′Ar), 3.81 (s, 3H, O*Me*), 3.69 (dt, *J* = 6.6, 4.3 Hz, 1H, C*H*OTBS), 3.41 (td, *J* = 6.0, 4.3 Hz, 1H, C*H*OPMB), 2.33 (dd *J* = 7.0, 6.0 Hz, 2H, C*H*$_2$CH = CH$_2$), 1.43−1.71 (m, 2H, CH$_3$C*H*$_2$), 0.92 (s, 9H, C*Me*$_3$), 0.90 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 0.07 (s, 3H, SiC*H*$_3$), 0.06 (s, 3H, SiC*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz CDCl$_3$) δ 159.0 (Ar), 136.0 (CH═CH$_2$), 131.1 (Ar), 129.3 (Ar), 116.4 (CH═CH$_2$), 113.6 (Ar), 81.4 (CHOPMB), 74.9 (CHOTBS), 72.0 (CH$_2$Ar), 55.3 (O*Me*), 35.6 (CH$_2$CH═CH$_2$), 26.0, (C*Me*$_3$), 25.5 (CH$_3$CH$_2$), 18.2 (SiC), 9.7 ((CH$_3$)$_3$C), −4.3 (SiCH$_3$), −4.5 (SiCH$_3$); MS (ESI-TOF) *m*/*z* 387 [M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{36}O_3SiNa$ 387.2326; found 387.2326; $[\alpha]_D^{25}$ −11.9 (*c* = 1.0 in CHCl$_3$).

(3S,4R)-4-((tert-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)-oxy)hexanal ***(15)****.* Alkene **20** (3.68 g, 10 mmol) was dissolved in DCM (300 mL), cooled to −78 °C, and sparged with O_2 for 2 min. O_3/O_2 was then bubbled through the stirred solution until a faint blue color appeared, and excess ozone was then sparged out with O_2 for 5 min before adding PPh$_3$ (7.9 g, 30 mmol). The reaction mixture was allowed to warm to rt over 16 h before being concentrated in vacuo and dry-loaded onto silica. Purification via rapid column chromatography (16:1 → 8:1 petrol/diethyl ether) yielded the title compound as a colorless oil (3.60 g, 9.8 mmol, 98%): R_f 0.63 (10:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 2931s, 2858s, 1725s; ^{1}H NMR (400 MHz CDCl$_3$) δ 9.80 (t, *J* = 2.0 Hz, 1H, C*H*O), 7.24−7.30 (m, 2H,Ar*H*), 6.86−6.92 (m, 2H, Ar*H*), 4.57 (d, *J* = 11.2 Hz, 1H, C*H*H′Ar), 4.45 (d, *J* = 11.2 Hz, 1H, CH*H*′Ar), 3.87 (dt, *J* = 7.4, 3.6 Hz, 1H, C*H*OPMB), 3.80 (s, 3H, O*Me*), 3.78 (dt, *J* = 7.0, 3.6 Hz, 1H, C*H*OTBS), 2.69 (ddd, *J* = 16.7, 7.0, 2.0 Hz, 1H, C*H*H′CHO), 2.56 (ddd, *J* = 16.7, 7.0, 2.0 Hz, 1H, CH*H*′CHO), 1.37−1.62 (m, 2H, CH$_3$C*H*$_2$), 0.91 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$), 0.90 (s, 9H, C*Me*$_3$), 0.08 (s, 3H, SiC*H*$_3$), 0.07 (s, 3H, SiC*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 202.0 (C═O), 159.2 (Ar), 130.2 (Ar), 129.4 (Ar), 113.8 (Ar), 76.8 (CHOPMB), 74.5 (CHOTBS), 71.6 (CH$_2$Ar) 55.3 (O*Me*), 44.4 (CH$_2$CO), 26.6 (CH$_3$CH$_2$), 25.9 (C(CH$_3$)$_3$), 18.2 (CH$_3$CH$_2$), 9.8 (C(CH$_3$)$_3$), −4.2 (SiCH$_3$), −4.6 (SiCH$_3$); MS (ESI-TOF) *m*/*z* 389 [M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + N]$^+$ calcd for $C_{20}H_{34}O_4SiNa$ 389.2119; found 389.2117; $[\alpha]_D^{25}$ −15.6 (*c* = 1.0 in CHCl$_3$).

(((3R,4S,9R,E)-9-(Benzyloxy)-4-((4-methoxybenzyl)oxy)-9-((S)-oxiran-2-yl)non-6-en-3-yl)oxy)(tert-butyl)dimethylsilane ***(13)****.* To a stirred solution of sulfone **14** (1.95 g, 4.88 mmol), in dry DME (60 mL) cooled to −78 °C, was added NaHDMS (3.42 mL, 2 M in THF, 6.83 mmol) dropwise. The reaction was stirred for 15 min, and a solution of aldehyde **15** (3.57g, 9.75 mmol) in DME (20 mL) was added dropwise over 15 min followed by a wash of DME (10 mL).

The reaction mixture was stirred at −78 °C for 1 h. The reaction was then warmed to rt and stirred for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) and then diluted with H_2O (20 mL) and EtOAc (50 mL). The aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (20:1 → 15:1 → 10:1 petrol/ethyl acetate) gave the title compound as a colorless oil (2.1 g, 3.9 mmol, 80%) and recovered aldehyde (1.2 g, 3.2 mmol): R_f 0.49 (10:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 2930s, 2856 m, 1613w; ^1H NMR (400 MHz $CDCl_3$) δ 7.24−7.36 (m, 7H, Ar*H*), 6.84−6.88 (m, 2H, Ar*H*), 5.54−5.67 (m, 2H, C*H*═C*H*), 4.63 (d, *J* = 11.8 Hz, 1H, C*H*H′Ar), 4.58, (d, *J* = 11.2 Hz, 1H, C*H*H′Ar), 4.53 (d, *J* = 11.8 Hz, 1H, CH*H*′Ar), 4.46 (d, *J* = 11.2 Hz, 1H, CH*H*′Ar), 3.80 (s, 3H, O*Me*), 3.68 (dt, *J* = 6.5, 4.3 Hz, 1H, C*H*OTBS), 3.37 (td, *J* = 5.9, 4.3 Hz, 1H, C*H*OPMB), 3.31 (dt, *J* = 6.7, 5.2 Hz, 1H, C*H*OBn), 2.97 (ddd, *J* = 5.2, 4.0, 2.8 Hz, 1H, C*H*OCH$_2$), 2.77 (dd, *J* = 5.3, 4.0 Hz, 1H, CHOC*H*H′), 2.73 (dd, *J* = 5.3, 2.8 Hz, 1H, CHOCH*H*′), 2.33−2.47 (m, 2H, CHOBnC*H*$_2$), 2.29 (m, 2H, CHOPMBC*H*$_2$), 1.58−1.69 (m, 1H, CH$_3$C*H*H), 1.45−1.55 (m, 1H, CH$_3$CH*H*), 0.92 (s, 9H, C*Me*$_3$) 0.91 (t, *J* = 8.4 Hz, 3H, C*H*$_3$CH$_2$), 0.06 (s, 3H, SiCH$_3$), 0.06 (s, 3H, SiCH$_3$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.0 (Ar), 138.5 (Ar), 131.1 (Ar), 130.4 (CH═CH), 129.3 (Ar), 128.3 (Ar), 127.6 (Ar) 127.2 (Ar) 127.2 (CH═CH) 113.6 (Ar), 81.7 (CHOPMB) 78.0 (CHOBn), 75.0 (CHOTBS), 72.2 (CH$_2$Ar), 72.0 (CH$_2$Ar), 55.3 (O*Me*), 53.2 (CHOCH$_2$), 45.6 (CHOCH$_2$), 36.1 (CHOBnCH$_2$), 34.1 (CHOPMBCH$_2$), 26.0 (C*Me*$_3$) 25.5 (CH$_3$CH$_2$), 18.2 (CMe$_3$), 9.8 (CH$_3$CH$_2$), −4.2 (SiCH$_3$), −4.5 (SiCH$_3$); MS (ESI-TOF) *m/z* 563 [M + Na]$^+$; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{32}H_{48}O_5SiNa$ 563.3163; found 563.3174; $[\alpha]_D^{20}$ −17.2 (*c* = 1.0 in $CHCl_3$).

(1R,3R,4R,6S,7R)-1-(Benzyloxy)-7-((tert-butyldimethylsilyl)oxy)-6-((4-methoxybenzyl)oxy)-1-((S)-oxiran-2-yl)nonane-3,4-diol (**12**). Alkene **13** (400 mg, 0.74 mmol), methanesulfonamide (211 mg, 2.22 mmol), (DHQD$_2$)PHAL (55.6 mg, 0.074 mmol), $K_3Fe(CN)_6$ (730 mg, 0.28 mmol), and K_2CO_3 (307 mg, 2.22 mmol) were dissolved in ^{t}BuOH/H_2O (8 mL:8 mL). $K_2OsO_4(OH)_2$ (2.73 mg, 7.4 μmol) was added and the reaction stirred for 24 h. Sodium sulfite (279 mg, 2.22 mmol) was added, and the reaction was stirred at rt for 30 min. H_2O (10 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were then washed with aqueous NaOH (10 mL, 0.1 M), and the aqueous layer was back extracted with EtOAc (15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography (3:1 petrol/ethyl acetate) gave the title compound as a partially separable mixture of colorless oils (377 mg total, 0.66 mmol 91% 6:1 3*R*,4*R*:3*S*,4*S* diastereomers from ^1H NMR analysis of the crude, from which 268 mg, 0.47 mmol, 64% could be obtained in pure form): R_f 0.38 (3:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 3471m, 2930s, 2859s; ^1H NMR (400 MHz C_6D_6) δ 7.15−7.47 (m, 7H, Ar*H*), 6.85−6.91 (m, 2H, Ar*H*), 4.72 (d, *J* = 11.5 Hz, 1H, C*H*H′Ar), 4.67 (d, *J* = 10.9 Hz, 1H, C*H*H′Ar), 4.54 (d, *J* = 11.5 Hz, 1H, CH*H*′Ar), 4.39 (d, *J* = 10.9 Hz, 1H, CH*H*′Ar), 4.26 (1H, br, O*H*), 4.06 (1H, br, C*H*OH), 3.82−3.87 (m, 2H, C*H*OH, C*H*OBn), 3.76 (ddd, *J* = 1.9, 4.9, 7.7 Hz, 1H, C*H*OTBS), 3.62 (ddd, *J* = 1.9, 3.0, 8.5 Hz, 1H, C*H*OPMB), 3.38 (s, 3H, O*Me*), 2.86 (ddd, *J* = 2.7, 3.8, 6.3 Hz, 1H, C*H*OCH$_2$), 2.81 (br s, 1H, O*H*), 2.56 (dd, *J* = 2.7, 5.5 Hz, 1H, CHOC*H*H′), 2.45, (dd, *J* = 3.8, 5.5 Hz, 1H, CHOCH*H*′), 2.02−2.16 (m, 2H, 2 × C*H*H′CHOH), 1.91 (ddd, *J* = 14.2, 9.5, 3.0 Hz, 1H, CHOPMBCH*H*′), 1.78 (ddd, *J* = 15.8, 3.5, 2.5 Hz, 1H, CHOBnCH*H*′), 1.64 (dq, *J* = 14.0, 7.6 Hz, 1H, CH$_3$C*H*H′), 1.42 (dqd, *J* = 14.0, 7.5, 4.9 Hz, 1H, CH$_3$CH*H*′), 1.11 (s, 9H, C*Me*$_3$), 0.97 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 0.25 (s, 3H, SiC*H*$_3$), 0.19 (s, 3H, C*H*$_3$); $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6) δ 159.9 (Ar), 139.4 (Ar), 130.4 (Ar), 130.0 (Ar), 128.5 (Ar), 127.6 (Ar), 128.5 (Ar), 114.2 (Ar), 82.3 (CHOBn), 76.0 (CHOPMB), 75.9 (CHOTBS), 73.2 (CHOH), 73.0 (CH$_2$Ar), 72.0 (CHOH), 71.0 (CH$_2$Ar), 54.7 (O*Me*), 53.6 (CHOCH$_2$), 45.2 (CHOCH$_2$), 37.3 (CHOPMBCH$_2$), 33.1 (CHOBnCH$_2$), 26.5 (CH$_3$CH$_2$), 26.2 (C*Me*$_3$), 18.5 (CMe$_3$), 10.9 (CH$_3$CH$_2$), −3.9 (Si*Me*), −4.6 (Si*Me*); HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{32}H_{50}O_7SiNa$ 597.3218; found 597.3221; $[\alpha]_D^{20}$ −4.0 (*c* = 1.0 in $CHCl_3$).

(1R,3S,4R)-1-((2R,4R,5R)-4-(Benzyloxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-4-((tert-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)hexan-1-ol (**21**). To a solution of diol **12** (1.3 g, 2.3 mmol) in DCM (18 mL) at 0 °C was added a solution of camphorsulfonic acid (10.6 mg, 0.05 mmol) in DCM (1.1 mL). The reaction was stirred for 2 h at 0 °C, and the cold reaction mixture was immediately purified by flash column chromatography (1:1 petrol/ethyl acetate) to give the title compound as a colorless oil (1.12 g, 2.0 mmol, 86%): R_f (5:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 3419br, 2930s, 2858s; ^1H NMR (400 MHz $CDCl_3$) δ 7.24−7.39 (m, 7H, ArH), 6.85−6.89 (m, 2H, ArH), 4.70 (d, *J* = 11.0 Hz, 1H, CHH′Ar), 4.62 (d, *J* = 11.9 Hz, 1H, CHH′Ar), 4.42 (d, *J* = 11.9 Hz, 1H, CHH′Ar), 4.41 (d, *J* = 11.0 Hz, CHH′Ar), 4.25 (q, *J* = 6.2 Hz, 1H, CHOBn), 3.95 (dt, *J* = 6.1, 4.5 Hz, 1H, CHORCHOH), 3.81−3.88 (m, 4H, CHOH, CHORCH$_2$OH), 3.80 (s, 3H, OMe), 3.75 (ddd, *J* = 7.1, 5.0, 2.0 Hz, 1H, CHOTBS), 3.64 (ddd, *J* = 8.1, 3.8, 2.0 Hz, 1H, CHOPMB), 2.80 (br, 1H, OH), 2.14 (ddd, *J* = 13.4, 7.0, 6.2 Hz, 1H, CHH′CHOBn), 2.00 (ddd, *J* = 13.4, 8.0, 6.2 Hz, 1H, CHH′CHOBn), 1.80 (dt, J= 14.8, 8.1 Hz, 1H, CHH′CHOPMB), 1.70 (dt, *J* = 14.8, 3.8 Hz, 1H, CHH′OPMB), 1.51−1.63 (m, 1H, CH$_3$CHH′), 1.40−1.50 (m, CH$_3$CHH′), 0.92 (t, *J* = 7.5 Hz, 3H, CH$_3$CH$_2$), 0.91 (s, 9H, CMe$_3$), 0.09 (s, 3H, SiCH$_3$), 0.08 (s, 3H, SiCH$_3$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.2 (Ar), 137.6 (Ar), 130.4 (Ar), 129.6 (Ar), 128.5 (Ar), 127.9 (Ar), 127.6 (Ar), 113.8 (Ar), 81.1(CHOPMB), 80.3 (CHORCHOH), 80.2 (CHORCH$_2$OH), 79.6 (CHOBn), 75.6 (CHOTBS), 71.6 (CHOH), 71.6 (CH$_2$Ar), 71.4 (CH$_2$Ar), 62.3 (CH$_2$OH), 55.3 (OMe), 33.4 (CH$_2$CHOBn), 33.0 (CH$_2$CHOPMB), 26.0 (CMe$_3$, CH$_3$CH$_2$), 18.2 (CMe$_3$), 10.6 (CH$_3$CH$_2$), −4.1 (SiCH$_3$), −4.7 (SiCH$_3$); HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{32}H_{50}O_7SiNa$ 597.3218; found 597.3240; $[\alpha]_D^{20}$ −13.0 (*c* = 1 in $CHCl_3$).

((2R,2′S,4R,4′S,5R,5′R)-4-(Benzyloxy)-5′-ethyl-4′-((4-methoxybenzyl)oxy)octahydro-[2,2′-bifuran]-5-yl)-methylmethanesulfonate (**24**). To a stirred solution of diol **21** (900 mg, 1.57 mmol) in DCM (30 mL) at 0 °C were added ethyldiisopropylamine (2.72 mL, 15.6 mmol) and MsCl (1 mL, 12.5 mmol) and stirred for 1 h before being quenched with saturated aqueous NH_4Cl (30 mL) and diluted with H_2O (30 mL) and DCM (30 mL). The aqueous layer was separated and extracted with DCM (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to give a crude oil (**23**). The crude oil was dissolved in DCM/MeOH (1:1, 30 mL); then CSA (363 mg, 1.57 mmol) was added, and the reaction was stirred for 24 h before being quenched by the addition of saturated aqueous $NaHCO_3$ (40 mL). The aqueous layer was separated and extracted with DCM (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to give a crude oil. The crude oil was then dissolved in ^{t}BuOH (20 mL) and warmed to 35 °C; ^{t}BuOK (527 mg, 4.71 mmol) was added and the reaction stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (30 mL). The aqueous layer was separated and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification via flash column chromatography (2:1 petrol/ethyl acetate) gave the title compound as a colorless oil (427 mg, 0.82 mmol, 52%): R_f 0.56 (2:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 2935m, 1356s, 1175s; ^1H NMR (400 MHz $CDCl_3$) δ 7.22−7.38 (m, 7H, Ar*H*), 6.88 (d, *J* = 8.6 Hz, 2H, Ar*H*), 4.61 (d, *J* = 11.8 Hz, 1H, C*H*H′Ar), 4.36 (d, *J* = 11.9 Hz, 1H, C*H*H′Ar), 4.32−4.52 (m, 5H, 2 × CH*H*′Ar, CHORC*H*$_2$OMs), 4.12−422 (m, 2H, C*H*OBn, C*H*OPMB), 4.00−4.09 (m, 2H, C*H*ORC*H*OR), 3.85−3.92 (m, 1H, EtC*H*OR), 3.81 (s, 3H, O*Me*), 3.00 (s, 3H, S*Me*), 2.21−2.30 (m, 2H, 2 × C*H*H′CHOR), 2.16 (dt, *J* = 13.1, 4.4 Hz, 1H, C*H*H′CHOBn), 2.00 (dt, *J* = 12.6, 4.4 Hz, 1H, CHOPMBCH*H*′), 1.48 (qn, *J* = 7.6 Hz, 2H, CH$_3$C*H*$_2$), 0.93 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.2 (Ar), 137.5 (Ar), 130.2 (Ar), 129.3 (Ar), 128.5 (Ar), 127.9 (Ar), 127.8 (Ar), 113.8 (Ar), 84.9 (EtCHOR), 82.4 (CHOPMB), 80.9 (CHOBn), 79.8 (CHORCHOR), 79.3 (CHORCHOR), 78.7 (CH$_2$OMs), 77.3

($CHORCH_2OMs$), 71.1 (CH_2Ar), 69.8 (CH_2Ar), 55.3 (O*Me*), 37.8 (SCH_3), 34.6 (CH_2), 34.1 (CH_2), 26.7 (CH_3CH_2), 10.1 (CH_3); MS (ESI-TOF) *m*/*z* 543 [M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{36}O_8SNa$ 543.2023; found 543.2022; $[\alpha]_D^{20}$ +4.0 (*c* = 1.0 in $CHCl_3$).

*((2R,3R,5R)-3-(Benzyloxy)-5-((1R,3S,4R)-4-((tert-butyldimethylsilyl)oxy)-1-hydroxy-3-((4-methoxybenzyl)oxy)hexyl)tetrahydrofuran-2-yl)methylmethanesulfonate (**22**).* The title compound was isolated as a side product in the synthesis of **24**: R_f 0.63 (2:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 3540br, 2931m, 1356s, 1174s; ^{1}H NMR (400 MHz $CDCl_3$) δ 7.25−7.37 (m, 7H, ArH), 6.88 (d, *J* = 8.1 Hz, 2H, ArH), 4.69 (d, *J* = 11.0 Hz, 1H, CHH′Ar), 4.57 (d, *J* = 11.7 Hz, 1H, CHH′Ar), 4.43−4.46 (m, 2H, CH_2OMs), 4.41 (d, *J* = 11.1 Hz, 1H, CHH′Ar), 4.36 (d, *J* = 11.7 Hz, 1H, CHH′Ar), 4.19 (q, *J* = 5.3 Hz, 1H, $CHORCH_2OMs$), 4.12 (q, *J* = 5.3 Hz, 1H, CHOBn), 3.91 (q, *J* = 5.0 Hz, 1H, CHOHCHOR), 3.80 (s, 4H, OMe, OH), 3.75 (ddd, *J* = 7.3, 4.9, 2.0 Hz, 1H, CHOTBS), 3.62 (td, *J* = 6.0, 2.0 Hz, 1H, CHOPMB), 2.99 (s, 3H, SMe), 2.07−2.18 (m, 1H, CHHCHOBn), 1.98 (ddd, *J* = 13.1, 7.6, 4.4 Hz, 1H, CHHCHOBn), 1.71−1.75 (m, 2H, $CH_2CHOPMB$), 1.50−1.61 (m, 1H, CH_3CHH), 1.49−1.39 (m, 1H, CH_3CHH), 0.92 (t, *J* = 7.6 Hz, 3H, CH_3CH_2), 0.91 (s, 9H, CMe_3), 0.09 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.2 (Ar), 137.4 (Ar), 130.4 (Ar), 129.6 (Ar) 128.5 (Ar), 128.0 (Ar), 127.7 (Ar), 113.8 (Ar), 80.9 (CHORCHOH), 80.8 (CHOPMB), 80.6 (CHOBn), 78.7 ($CHORCH_2OMs$), 78.4 (CH_2OMs), 75.5 (CHOTBS), 71.4 (CH_2Ar), 71.0 (CHOH), 69.4 (CH_2Ar), 55.3 (OMe), 37.5 (CH_2CHOBn), 32.6 ($CH_2CHOPMB$), 26.1 (CH_3CH_2), 26.0 (CMe_3), 18.2 (CMe_3), 10.9 (CH_3CH_2), −4.1 (SiMe), −4.7 (SiMe); MS (ESI-TOF)*m*/*z* 675 [M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{33}H_{52}O_9SiSNa$ 675.2994; found 675.2990; $[\alpha]_D^{20}$ −55.6 (*c* = 1.0 in $CHCl_3$).

*(2R,2′S,4R,4′S,5S,5′R)-4-(Benzyloxy)-5′-ethyl-5-(iodomethyl)-4′-((4-methoxybenzyl)oxy)octahydro-2,2′-bifuran (**25**).* TBAI (3 g, 8.2 mmol) and mesylate **24** (420 mg, 0.82 mmol) were dissolved in dry toluene (6 mL) and heated to 110 °C for 16 h with vigorous stirring. The reaction mixture was cooled to rt, and then filtered through a sinter washing with diethyl ether (100 mL). The filtrate was concentrated in vacuo and purified by flash column chromatography (8:1 petrol/ethyl acetate) to give the title compound as a colorless oil (360 mg, 0.65 mmol, 80%) and recovered SM (40 mg, 0.08 mmol, 9%): R_f 0.47 (10:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 2961m; ^{1}H NMR (400 MHz $CDCl_3$) δ 7.23−7.39 (m, 7H, Ar*H*), 6.86−6.90 (m, 2H, ArH), 4.63 (d, *J* = 11.4 Hz, 1H, C*H*H′Ar), 4.49 (d, *J* = 11.4 Hz, 1H, C*H*H′Ar), 4.43 (d, *J* = 11.4 Hz, 1H, CH*H*′Ar), 4.38 (d, *J* = 11.4 Hz, 1H, CH*H*′Ar), 4.17 (td, *J* = 4.6, 2.8 Hz, 2H, CHORC*H*OR), 4.08−4.15 (m, 2H, C*H*OBnC*H*OR), 3.99 (td, *J* = 7.3, 5.0 Hz, 1H, C*H*ORCHOR), 3.88 (td, *J* = 6.6, 3.7 Hz, 1H, C*H*OPMB), 3.81 (s, 3H, OMe), 3.79 (dt, *J* = 6.4, 3.5 Hz, 1H), 3.41 (dd, *J* = 9.4, 8.3 Hz, 1H, C*H*H′I), 3.28 (dt, *J* = 9.3, 5.8 Hz, 1H, CH*H*′I), 2.18−2.33 (m, 3H, $C\mathit{H}_2CHOBn$, C*H*H′CHOPMB), 2.03 (ddd, *J* = 13.2, 7.3, 3.0 Hz, 1H, CH*H*′CHOPMB), 1.52−1.42 (m, 2H, $CH_3C\mathit{H}_2$), 0.93 (t, *J* = 7.0 Hz, 3H, $C\mathit{H}_3$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.2 (Ar), 138.0 (Ar), 130.2 (Ar), 129.3 (Ar), 128.3 (Ar), 127.9 (Ar), 127.7 (Ar), 113.8 (Ar), 84.8 (EtCHOR), 83.0 (CHOBn), 82.5 (CHOPMB), 81.3 ($CHORCH_2I$), 80.1 (CHORCHOR), 78.6 (CHORCHOR), 71.3 (CH_2Ar), 70.8 (CH_2Ar), 55.3 (O*Me*), 34.6 (CH_2CHOBn), 34.1 ($CH_2CHOPMB$), 26.7 (CH_3CH_2), 10.1 (CH_3), 2.2 (CH_2I); MS (ESI-TOF) *m*/*z* 575 [M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{33}O_5INa$ 575.1265; found 575.1283; $[\alpha]_D^{20}$ −16.5 (*c* = 1.0 in $CHCl_3$).

*(2R,2′S,4R,4′S,5R,5′R)-5-Allyl-4-(benzyloxy)-5′-ethyl-4′-((4-methoxybenzyl)oxy)octahydro-2,2′-bifuran (**11**).* Iodide **25** (360 mg, 0.65 mmol) was dried by being azeotroped with dry benzene three times and then dissolved in dry benzene (13 mL) and warmed to 40 °C. Vinylmagnesium bromide (13 mL, 1 M in THF, 13 mmol) was added and the reaction stirred for 3 h. The reaction mixture was cooled to 0 °C and then quenched with dropwise addition of saturated aqueous NH_4Cl (20 mL) and diluted with H_2O (10 mL) and EtOAc (10 mL). The aqueous layer was separated and extracted (3 × 30 mL EtOAc). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (50:1 → 25:1 DCM/ethyl acetate) gave the title compound as a colorless oil (166 mg, 0.37 mmol, 57%): R_f 0.45 (10:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 2933m; ^{1}H NMR (400 MHz $CDCl_3$) δ 7.23−7.39 (m, 7H, Ar*H*), 6.86−6.90 (m, 2H, Ar*H*), 5.86 (ddt, *J* = 17.0, 10.2, 7.7 Hz, 1H, $C\mathit{H}{=}CH_2$), 5.12 (dq, *J* = 17.0, 2.0 Hz, 1H, CH═C*H*H′), 5.04 (ddt, *J* = 10.2, 2.0, 1.2 Hz, 1H, CH═CH*H*′), 4.62 (d, *J* = 11.9 Hz, 1H, C*H*H′Ar), 4.49 (d, *J* = 11.9 Hz, 1H, C*H*H′Ar), 4.38 (d, *J* = 11.9 Hz, 2H, CH*H*′Ar), 3.93−4.03 (m, 2H, C*H*OBn, CHORC*H*OR), 3.88 (td, *J* = 6.5, 3.9 Hz, 1H, EtC*H*OR), 3.81 (s, 3H, O*Me*), 3.76−3.80 (m, 3H, C*H*OPMB, C*H*ORCHOR, CHOBnC*H*OR), 2.42−2.57 (m, 2H, $C\mathit{H}_2CH{=}CH_2$), 2.18−2.34 (m, 2H, 2 × C*H*H′CHOR), 2.11 (ddd, *J* = 13.7, 4.9, 2.3 Hz, 1H, CH*H*′CHOPMB), 2.06 (dt, *J* = 13.4, 5.2 Hz, 1H, CH*H*′CHOBn), 1.45−1/52(m, 2H, $CH_3C\mathit{H}_2$), 0.93 (t, *J* = 7.5 Hz, 3H, $C\mathit{H}_3$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.2 (Ar) 138.4 (Ar), 135.4 ($CH{=}CH_2$), 130.3 (Ar), 129.3 (Ar), 128.3 (Ar), 127.6 (Ar), 127.5 (Ar), 116.6 ($CH{=}CH_2$), 113.8 (Ar), 84.6 (EtCHOR), 82.5, 82.3, 80.4 (CHOPMB, *CH*ORCHOR, CHORCHOPMB), 80.0, 78.8 (CHORCHOR, CHOBn), 70.8 (CH_2Ar), 70.7 (CH_2Ar), 55.3 (O*Me*), 34.8 ($CH_2CHOPMB$), 34.6 (CH_2COBn), 33.9 ($CH_2CH{=}CH_2$), 26.7 (CH_3CH_2), 10.1 (CH_3); MS (ESI-TOF) *m*/*z* 475 [M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{36}O_5Na$ 475.2455; found 475.2440; $[\alpha]_D^{20}$ −6.4 (*c* = 1.0 in $CHCl_3$).

*(2R,2′S,4R,4′S,5R,5′R)-5-Allyl-5′-ethyl-4′-((4-methoxybenzyl)oxy)octahydro-[2,2′-bifuran]-4-ol (**26**).* To a stirring solution of ether **11** (150 mg, 0.33 mmol) in THF (12 mL) at −78 °C was added dropwise LiDBB (2 mL of a solution of LIDBB prepared by sonicating DBB (1.0 g, 3.7 mmol) and lithium (26 mg, 3.7 mmol) in THF (4 mL) for 2 h). Reaction progress was monitored by TLC every 0.4 mL of LiDBB solution. When no starting material was detected, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), diluted with EtOAc (10 mL), and warmed to rt. The aqueous layer was separated and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (5:1 petrol/ethyl acetate) gave the title compound as a colorless oil (92 mg, 2.5 mmol, 77%): R_f 0.34 (5:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 3413br, 2934; ^{1}H NMR (400 MHz $CDCl_3$) δ 7.23−7.28 (m, 2H, Ar*H*), 6.87−6.91 (m, 2H, Ar*H*), 5.88 (ddt, *J* = 17.4, 10.2, 7.0 Hz, 1H, $C\mathit{H}{=}CH_2$), 5.16 (dq, *J* = 17.4, 1.5 Hz, 1H, CH═C*H*H′), 5.07 (ddt, *J* = 10.2, 2.1, 1.5 Hz, 1H, CH═CH*H*′), 4.46 (d, *J* = 11.4 Hz, 1H, C*H*H′Ar), 4.43 (d, *J* = 11.4 Hz, 1H, CH*H*′Ar), 4.23 (ddd, *J* = 9.4, 7.1, 1.8 Hz, 1H, C*H*ORCHOR), 4.16−4.08 (m, 2H, CHORC*H*OR, O*H*), 4.00 (br s, 1H, C*H*OH), 3.91 (dt, *J* = 7.7, 5.2 Hz, 1H, EtC*H*OR), 3.79−3.83 (m, 4H, O*Me*, C*H*OPMB), 3.66 (td, *J* = 7.0, 2.4 Hz, 1H, C*H*ORCHOH), 2.54−2.37 (m, 2H, $C\mathit{H}_2CH{=}CH_2$), 2.30 (dt, *J* = 12.7, 6.9 Hz, 1H, C*H*H′CHOPMB) 2.21 (ddd, 1H, *J* = 14.0, 10.0, 5.2 Hz, C*H*H′CHOH), 2.14 (td, *J* = 14.0, 3.9 Hz, CH*H*′CHOH), 1.59−1.51 (3H, m, CH*H*′CHOPMB, $CH_3C\mathit{H}_2$), 0.96 (t, *J* = 7.5 Hz, 3H, $C\mathit{H}_3$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3 (Ar), 135.2 ($CH{=}CH_2$), 129.9 (Ar), 129.2 (Ar), 116.7 ($CH{=}CH_2$), 133.9 (Ar), 85.0 (EtCHOR), 83.8 (CHORCHOH), 81.8 (CHOPMB), 79.7 (CHORCHOR), 78.5 (CHORCHOR), 71.5 (CH_2Ar), 70.9 (CHOH), 55.3 (O*Me*), 34.9 ($CH_2CHOPMB$), 34.2 (CH_2CHOH), 33.6 ($CH_2CH{=}CH_2$), 26.4 (CH_3CH_2), 10.3 (CH_3); MS (ESI-TOF) *m*/*z* 385 [M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{30}O_5Na$ 385.1985; found 385.1987; $[\alpha]_D^{20}$ +18.9 (*c* = 1.0 in $CHCl_3$).

*(2R,2′S,4R,4′S,5R,5′R)-5-Allyl-5′-ethyloctahydro-[2,2′-bifuran]-4,4′-diol (**27**).* Isolated as a side product during the synthesis of **26**: R_f 0.40 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3394br, 2935m; ^{1}H NMR (500 MHz $CDCl_3$) δ 5.87 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, $C\mathit{H}{=}CH_2$), 5.18 (dq, *J* = 17.0, 1.6 Hz, 1H, CH═C*H*H′), 5.09 (ddt, *J* = 10.0, 2.1 1.6 Hz, 1H, CH═CH*H*′), 4.26 (ddd, *J* = 8.6, 7.3, 1.8 Hz, 1H, C*H*ORCHOR), 4.12−4.17 (m, 2H, CHORC*H*OR, $CH_2C\mathit{H}OH$), 4.07 (dt, *J* = 6.3, 4.3 Hz, 1H, $C\mathit{H}OHCH_2$), 3.82 (ddd, *J* = 9.2, 6.3, 4.3 Hz, 1H, EtC*H*OR), 3.73 (td, *J* = 6.9, 2.7 Hz, 1H, CHOHC*H*OR), 2.49 (tq, *J* = 6.9, 1.6 Hz, 2H, $C\mathit{H}_2CH{=}CH_2$),

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2.25–2.33 (m, 2H, 2 × CHOHC*H*H′), 1.88 (dd, *J* = 14.0, 4.5 Hz, 1H, CHOHCH*H*′), 1.80 (ddd, *J* = 13.3, 7.3, 4.5 Hz, 1H, CH*H*′CHOH), 1.42–1.55 (m, 2H, CH$_3$C*H*$_2$), 0.98 (t, *J* = 7.4 Hz, 3H, C*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 134.6 (CH=CH$_2$), 117.1 (CH=CH$_2$), 88.3 (EtCHOR), 83.4 (CHORCH$_2$CH=CH$_2$), 79.4 (CHORCHOR), 78.6 (CHORCHOR), 75.0 (CHOHCH$_2$), 71.3 (CH$_2$CHOH) 35.6 (CH$_2$), 35.4 (CH$_2$), 33.3 (CH$_2$CH=CH$_2$), 26.1 (CH$_3$CH$_2$), 10.2 (CH$_3$); MS (ESI-TOF) *m*/*z* 265 [M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for C$_{13}$H$_{22}$O$_4$Na 265.1410; found 265.1413; $[\alpha]_D^{20}$ +5.9 (*c* = 0.2 in CHCl$_3$).

*(2R,2′S,4S,4′S,5R,5′R)-5-Allyl-4-chloro-5′-ethyl-4′-((4-methoxybenzyl)oxy)octahydro-2,2′-bifuran (**28**).* To a stirred solution of alcohol **26** (86 mg, 0.24 mmol) and PPh$_3$ (186 mg, 0.70 mmol) in DCM (6 mL) was added CCl$_4$ (1.5 mL). The reaction mixture was stirred for 3 h, and the yellow reaction mixture was loaded straight onto the column. Purification by flash column chromatography (DCM → 5:1 petrol/ethyl acetate) gave the title compound as a colorless oil (70 mg, 0.18 mmol, 78%); *R*$_f$ 0.89 (5:1 petrol/ethyl acetate); ν$_{max}$/cm^{-1} (thin film) 2933m; ^{1}H NMR (400 MHz CDCl$_3$) δ 7.26 (d, *J* = 8.3 Hz, 2H, Ar*H*), 6.89 (d, *J* = 8.3 Hz, 2H, Ar*H*), 5.85 (ddt, *J* = 17.2, 10.1, 6.8 Hz, 1H, C*H*=CH$_2$), 5.25–4.77 (m, 2H, CH=C*H*$_2$), 4.49 (d, *J* = 11.4 Hz, 1H, C*H*H′Ar), 4.40 (d, *J* = 11.4 Hz, 1H, CH*H*′Ar), 4.22 (q, *J* = 6.6 Hz, 1H, CHORC*H*OR), 4.00–4.06 (m, 2H, C*H*ORC*H*Cl), 3.94 (q, *J* = 6.6 Hz, 1H, C*H*ORCHOR), 3.85–3.90(m, 1H, EtC*H*OR), 3.81 (O*Me*), 3.78–3.82 (m, 1H, C*H*OPMB), 2.19–2.43 (m, 5H, C*H*$_2$CHOBn, C*H*H′CHOPMB, C*H*$_2$CH=CH$_2$), 1.93 (dt, *J* = 12.3, 6.6 Hz, 1H, CH*H*′CHOPMB), 1.49 (qn, *J* = 7.6 Hz, 2H, CH$_3$C*H*$_2$), 0.93 (t, *J* = 7.6 Hz, 3H, C*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 159.2 (Ar), 133.6 (CH=CH$_2$), 130.2 (Ar), 129.2 (Ar), 117.8 (Ar), 113.8 (CH=CH$_2$), 113.7 (Ar), 86.2 (CHORCHCl), 84.8 (EtCHOR), 82.2 (CHOPMB), 80.1 (CHORCHOR), 79.3 (CHORCHOR), 71.0 (CH$_2$Ar), 59.2 (CHCl), 55.3 (O*Me*), 38.1 (CH$_2$CH=CH$_2$), 37.9 (CH$_2$CHCl), 34.6 (CH$_2$CHOPMB), 26.6 (CH$_3$CH$_2$), 10.1 (CH$_3$); MS (ESI-TOF) *m*/*z* 403 [^{35}M + Na]$^+$, 405 [^{37}M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for C$_{21}$H$_{29}$O$_4$^{35}ClNa 403.1647; found 403.1635; $[\alpha]_D^{20}$ +55.9 (*c* = 1.0 in CHCl$_3$).

*(E)-4-((2R,2′S,4S,4′S,5R,5′R)-4-Chloro-5′-ethyl-4′-((4-methoxybenzyl)oxy)octahydro-[2,2′-bifuran]-5-yl)but-2-enal (**30**).* To a stirred solution of alkene **28** (62 mg, 0.16 mmol) in dry degassed DCM (4.5 mL) were added crotonaldehyde (134 μL, 114 mg, 1.6 mmol) and Grubbs' second generation catalyst (14 mg, 16 μmol). The reaction mixture was stirred for 1.5 h at 40 °C and then cooled to rt and quenched with the addition of DMSO (0.1 mL) and stirred for 16 h. The mixture was concentrated in vacuo and purification by flash column chromatography (5:1 petrol ethyl acetate) gave the title compound as a colorless oil (58 mg, 14 mmol, 88%): *R*$_f$ 0.25 (5:1 petrol/ethyl acetate); ν$_{max}$/cm^{-1} (thin film) 2934m, 1691s; ^{1}H NMR (400 MHz CDCl$_3$) δ 9.52 (d, *J* = 7.8 Hz, 1H, C*H*O), 7.25 (d, *J* = 12.4 Hz, 2H, Ar*H*), 6.86–6.93 (m, 3H, Ar*H*, CH$_2$C*H*=CH), 6.21 (ddt, *J* = 15.7, 7.8, 1.3 Hz, 1H, C*H*CHO), 4.47 (d, *J* = 11.4 Hz, 1H, C*H*H′Ar), 4.41 (d, *J* = 11.4 Hz, 1H, CH*H*′Ar), 4.24 (td, *J* = 6.9, 5.4 Hz, 1H, CHORC*H*OR), 4.05 (ddd, *J* = 7.2, 5.8, 4.5 Hz, 1H, C*H*ORCHCl), 4.01–3.96 (m, 2H, C*H*Cl, C*H*ORCHOR), 3.88 (td, *J* = 6.7, 4.0 Hz, 1H, EtC*H*OR), 3.79–3.83 (m, 1H, C*H*OPMB), 3.81 (s, 3H, O*Me*), 2.72 (dddd, *J* = 14.3, 8.1, 5.8, 1.3 Hz, 1H, C*H*H′CH=CH), 2.58 (dt, *J* = 14.3, 5.8 Hz, 1H, CH*H*′CH=CH), 2.46 (dt, *J* = 13.9, 6.0 Hz, 1H, C*H*H′CHCl), 2.30–2.19 (m, 2H, CH*H*′CHCl, CH*H*′CHOH), 1.83 (ddd, *J* = 13.1, 6.0, 4.6 Hz, 1H, C*H*H′CHOPMB), 1.48 (qn, *J* = 7.6 Hz, 2H, CH$_3$C*H*$_2$), 0.93 (t, *J* = 7.6 Hz, 3H, C*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 193.8 (CHO), 159.3 (Ar), 153.1 (CH=CHCHO), 135.1 (CH=CHCHO), 130.0 (Ar), 129.2 (Ar), 113.8 (Ar), 85.0 (CHORCHCl), 84.7 (EtCHOR), 82.1 (CHOPMB), 80.4 (CHORCHOR), 78.9 (CHORCHOR), 71.1 (CH$_2$Ar), 58.8 (CHCl), 55.3 (O*Me*), 37.3 (CH$_2$CHCl), 36.3 (CH$_2$CH=CH), 34.4 (CH$_2$CHOPMB), 26.5 (CH$_3$CH$_2$), 10.2 (CH$_3$); MS (ESI-TOF) *m*/*z* 431 [^{35}M + Na]$^+$, 433 [^{35}M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for C$_{22}$H$_{29}$O$_5$^{35}ClNa 431.1596; found 431.1585; $[\alpha]_D^{20}$ +22.8 (*c* = 1.0 in CHCl$_3$).

*(2R,2′S,4S,4′S,5R,5′R)-4-Chloro-5′-ethyl-4′-((4-methoxybenzyl)oxy)-5-((E)-pent-2-en-4-yn-1-yl)octahydro-2,2′-bifuran (**31**).* To a solution of (diazomethyl)trimethylsilane (50 μL, 2 M in ether, 0.1 mmol) in THF at −78 °C was added BuLi (62 μL, 1.6 M in hexanes, 0.1 mmol) dropwise. The reaction mixture was stirred for 30 min before being transferred rapidly to a solution of enal **30** (4.2 mg, 10 μmol) in THF (0.5 mL) at −78 °C. The reaction was stirred at −78 °C for 1 h before warming to 0 °C for a further 1 h. The reaction was quenched with acetic acid (0.1 mL) and then saturated aqueous NaHCO$_3$ (10 mL). The aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (MgSO$_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (16:1 petrol/ethyl acetate) gave the title compound as a colorless oil (2.9 mg, 7 μmol, 70%): *R*$_f$ 0.78 (8:1 petrol/ethyl acetate); ν$_{max}$/cm^{-1} (thin film) 2930; ^{1}H NMR (400 MHz CDCl$_3$) δ 7.26 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.89 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.27 (dt, *J* = 15.7, 7.0 Hz, 1H, CH$_2$C*H*=CH), 5.58 (dq, *J* = 15.7, 2.0 Hz, 1H, CH$_2$CH=C*H*), 4.49 (d, *J* = 11.4 Hz, 1H, C*H*H′Ar), 4.41 (d, *J* = 11.4 Hz, 1H, CH*H*′Ar), 4.21 (q, *J* = 6.8 Hz, 1H, CHORC*H*OR), 3.92–4.01 (m, 3H, C*H*ORC*H*Cl, C*H*ORCHOR), 3.88 (td, *J* = 7.3, 4.0 Hz, 1H, EtC*H*OR), 3.81 (s, 3H, O*Me*), 3.78–3.82 (m, 1H, C*H*OPMB), 2.83 (d, *J* = 2.0 Hz, 1H, CC*H*), 2.47 (dddd, *J* = 13.4, 6.8, 4.8 Hz, 1.5, 1H, C*H*H′CHCl), 2.33–2.40 (m, 2H, C*H*$_2$CH=CH), 2.19–2.30 (m, 2H, 2 × CH*H*′CHX), 1.90 (ddd, *J* = 13.2, 6.6, 5.0 Hz, 1H, CH*H*′CHOPMB), 1.48 (qn, *J* = 7.3 Hz, 2H, CH$_3$C*H*$_2$), 0.93 (t, *J* = 7.3 Hz, 3H, C*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 159.2 (Ar), 141.0 (CH$_2$CH=CH), 130.1 (Ar), 129.3 (Ar), 113.8 (Ar), 111.6 (CH$_2$CH=CH), 85.5 (CHORCHCl), 84.9 (EtCHOR), 82.2 (CHOPMB), 82.0 (CCH), 80.2 (CHORCHOR), 79.1 (CHORCHOR), 77.2 (CCH), 71.1 (CH$_2$Ar), 58.9 (CHCl), 55.3 (O*Me*), 37.9 (CH$_2$CHCl), 36.7 (CH$_2$CH=CH), 34.5 (CH$_2$CHOPMB), 26.6 (CH$_3$CH$_2$), 10.2 (CH$_3$); MS (ESI-TOF) *m*/*z* 427 [^{35}M + Na]$^+$, 429 [^{35}M + Na] $^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for C$_{23}$H$_{29}$O$_4$^{35}ClNa 427.1647; found 427.1634; $[\alpha]_D^{20}$ +34.2 (*c* = 1.0 in CHCl$_3$).

*(2S,2′R,4S,4′S,5R,5′R)-4′-Chloro-5-ethyl-5′-((E)-pent-2-en-4-yn-1-yl)octahydro-[2,2′-bifuran]-4-ol (**2c**).* To a stirred solution of ether **31** (21 mg, 50 μmol) in DCM (5 mL) was added BCl$_3$.DMS (120 μL, 2 M in DCM, 0.24 mmol). The reaction was stirred for 5 min and then quenched with saturated aqueous NaHCO$_3$ (5 mL). The mixture was then extracted with DCM (3 × 10 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (3:1) petrol/ethyl acetate) gave the title compound as a colorless oil (12 mg, 42 μmol, 84%); *R*$_f$ 0.60 (3:1 petrol/ethyl acetate); ν$_{max}$/cm^{-1} (thin film) 3420br, 3294m (CH), 2964m; ^{1}H NMR (400 MHz CDCl$_3$) δ 6.22 (dt, *J* = 15.4, 7.4 Hz, 1H, CH$_2$C*H*=CH), 5.59 (dq, *J* = 15.4, 2.0 Hz, 1H, CH$_2$CH=C*H*), 4.39 (ddd, *J* = 9.1, 6.8, 4.0 Hz, 1H, CHORC*H*OR), 4.16 (dt, *J* = 9.1, 3.5 Hz, 1H, C*H*ORCHOR), 4.07 (dt, *J* = 6.8, 5.4, Hz, 1H, CHClC*H*OR), 4.03 (dt, *J* = 6.1, 2.0 Hz, 1H, C*H*Cl), 3.97 (ddd, *J* = 7.8, 5.4, 4.3 Hz, 1H, C*H*OH), 3.86 (td, *J* = 6.9, 1.8 Hz, 1H, EtC*H*OR), 3.13 (br, 1H, O*H*), 2.84 (d, *J* = 2.0 Hz, 1H, CC*H*), 2.51 (dddd, *J* = 14.4, 7.4, 5.3, 2.0 Hz, 1H, C*H*H′CH=CH), 2.41 (dddd *J* = 14.4, 7.4, 5.3, 2.0 Hz, 1H, CH*H*′CH=CH), 2.30 (ddd, *J* = 13.9, 9.1, 6.1 Hz, 1H, C*H*H′CHOH), 2.19 (ddd, *J* = 13.9, 6.8, 4.0 Hz, 1H, C*H*H′CHCl), 2.08 (ddd, *J* = 13.9, 8.9, 7.8 Hz, 1H, CH*H*′CHCl), 1.76 (ddd, *J* = 13.9, 4.2, 2.0 Hz, CH*H*′CHOH), 1.39 (2H, qn, *J* = 7.6 Hz, CH$_3$C*H*$_2$), 0.95 (3H, t, *J* = 7.6 Hz, 1H, C*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 140.1 (CH$_2$CH=CH), 112.3 (CH$_2$CH=CH), 88.9 (EtCHOR), 86.0 (CHORCHCl), 81.7 (CCH), 79.8 (CHORCHOR), 78.2 (CHORCHOR), 77.2 (CCH), 74.8 (CHOH), 58.3 (CHCl), 38.2 (CH$_2$CHCl), 36.6 (CH$_2$CH=CH), 34.3 (CH$_2$CHOH), 26.0 (CH$_3$CH$_2$), 10.2 (CH$_3$); MS (ESI-TOF) *m*/*z* 307 [^{35}M + Na]$^+$, 309 [^{35}M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for C$_{15}$H$_{21}$O$_3$^{35}ClNa 307.1071; found 307.1070; $[\alpha]_D^{20}$ +53.4 (*c* = 1.0 in CHCl$_3$).

*(2S,2′R,4R,4′S,5R,5′R)-4′-Chloro-5-ethyl-5′-((E)-pent-2-en-4-yn-1-yl)octahydro-[2,2′-bifuran]-4-ol (**2a**).* Alcohol **2c** (2 mg, 7 μmol) and PPh$_3$ (20.2 mg, 77 μmol) were dissolved in THF (0.3 mL) and cooled to 0 °C. DIAD (15.6 μL, 77 μmol), was added dropwise and

the reaction stirred for 30 min before the addition of 4-nitrobenzoic acid (13 mg, 77 μmol). The reaction was then warmed to rt and stirred for 2 h before being concentrated in vacuo. Purification by short silica plug (DCM) gave the intermediate ester mixed with DIADH$_2$. The mixture was then dissolved in MeOH (0.2 mL), and cooled to 0 °C and K$_2$CO$_3$ (5.5 mg, 40 μmol) was added. The reaction was stirred for 30 min, then diluted with H$_2$O (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then dried (MgSO$_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography gave the title compound as a colorless oil (0.5 mg, 2 μmol, 25%): R_f 0.62 (3:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 3455m, 3291m, 2969m; ^{1}H NMR (500 MHz CDCl$_3$) δ 6.25 (dt, *J* = 15.8, 7.3 Hz, 1H, CH$_2$C*H*=CH), 5.58 (dq, *J* = 15.8, 2.2 Hz, 1H, CH$_2$CH=C*H*), 4.30 (br m, 1H, C*H*OH), 4.15−4.23 (m, 2H, C*H*ORC*H*OR), 3.98−4.03 (m, 2H, C*H*ORC*H*Cl), 3.73 (td, *J* = 7.0, 2.8 Hz, 1H, EtC*H*OR), 2.83 (d, *J* = 2.2 Hz, 1H, CC*H*), 2.47 (dddd, *J* = 12.3, 7.3, 5.0, 2.2 Hz, 1H, C*H*H′CH=CH), 2.37 (dddd, *J* = 12.3, 7.3, 6.3, 2.2 Hz, 1H, CH*H*′CH=CH), 2.28−2.17 (m, 2H, C*H*$_2$CHCl), 2.10 (dd, *J* = 13.6, 6.3 Hz, 1H, C*H*H′CHOH), 1.94 (ddd, *J* = 13.6, 9.1, 4.6 Hz, 1H, CH*H*′CHOH), 1.70 (dq, *J* = 13.6, 7.6 Hz, 1H, CH$_3$C*H*H′), 1.61 (dq, *J* = 13.6, 7.6 Hz, 1H, CH$_3$CH*H*′), 0.99 (t, *J* = 7.6 Hz, 3H, C*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 140.8 (CH$_2$CH=CH), 117.8 (CH$_2$CH=CH), 85.7 (CHORCHCl), 84.7 (EtCHOR), 81.9 (CCH), 80.3 (CHORCHOR), 78.3 (CHORCHOR), 77.2 (CCH), 72.6 (CHOH), 58.8 (CHCl), 37.9 (CH$_2$CHOH), 37.9 (CH$_2$CHCl), 36.7 (CH$_2$CH=CH), 22.0 (CH$_3$CH$_2$), 10.5 (CH$_3$); MS (ESI-TOF) *m*/*z* 307 [^{35}M + Na] $^+$, 309 [^{35}M + Na] $^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for C$_{15}$H$_{21}$O$_3$^{35}ClNa 307.1071; found 307.1070; $[\alpha]_D^{20}$ +66.0 (*c* = 0.05 in CHCl$_3$).

*(2S,2′R,4S,4′S,5S,5′R)-5-Allyl-5′-ethyl-4′-((4-methoxybenzyl)oxy)-octahydro-[2,2′-bifuran]-4-ol (**34**).* To a solution of (2*S*,2′*R*,4*S*,4′*S*,5*S*,5′*R*)-5-allyl-4-((4-bromobenzyl)oxy)-5′-ethyl-4′-((4-methoxybenzyl)oxy)octahydro-2,2′-bifuran **32** (50 mg, 94 μL) and bis(methoxyethyl)amine (44 μL, 39 mg, 0.3 mmol) in THF (4 mL) at −78 °C was titrated a solution of LiDBB (ca. 1 mL of a solution prepared by sonicating DBB (0.75 g, 2.8 mmol), lithium (20 mg, 2.8 mmol) in THF (3 mL) for 2 h). The reaction progress was monitored by TLC. When no more starting material was detected, the reaction was quenched by the addition of saturated aqueous NH$_4$Cl and diluted with EtOAc and then allowed to warm to rt. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were dried (MgSO$_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (5:1 petrol/ethyl acetate) gave the title compound as a colorless oil (23 mg, 62 μmol, 66%) and benzyl-protected intermediate **33** (8 mg, 17 μmol, 18%). Data for **34**: ν_{max}/cm^{-1} (thin film) 3437br, 2960m, 2934m; R_f 0.38 (5:1 petrol/ethyl acetate); ^{1}H NMR (500 MHz C$_6$D$_6$) δ 7.15 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.81 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.07(ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH$_2$), 5.20 (dq, *J* = 17.0, 2.0 Hz, 1H, CH=C*H*H′), 5.08 (ddt, *J* = 10.0, 2.0 Hz, 1H, CH=CH*H*′), 4.46 (ddd, *J* = 10.8, 5.7, 2.0 Hz, 1H, C*H*ORCHOR), 4.19 (d, *J* = 11.6 Hz, 1H, C*H*H′Ar), 4.14 (d, *J* = 11.6 Hz, 1H, CH*H*′Ar), 3.89−3.93 (m, 3H, EtC*H*OR, CHORC*H*OR, C*H*OH), 3.76 (d, *J* = 10.7 Hz, 1H, O*H*), 3.55 (td, *J* = 7.0, 2.8 Hz, 1H, C*H*ORCHOH), 3.40−3.44 (m, 1H, C*H*OPMB), 3.31 (s, 3H, O*Me*), 2.67−2.78 (m, 2H, C*H*$_2$CH=CH$_2$), 1.78 (ddd, *J* = 13.6, 10.2, 5.3 Hz, 1H, C*H*H′CHOH), 1.70 (dd, *J* = 13.6, 2.8 Hz, 1H, CH*H*′CHOH), 1.65 (ddd, *J* = 13.2, 5.5, 2.0 Hz, 1H, C*H*H′CHOPMB), 1.44 (dq, *J* = 14.6, 7.3 Hz, 1H, CH$_3$C*H*H′), 1.26−1.33 (m, 1H, CH$_3$CH*H*′), 1.12 (ddd *J* = 13.2, 10.3, 6.5 Hz, 1H, CH*H*′CHOMPB), 0.83 (t, *J* = 7.4 Hz, 3H, C*H*$_3$); ^{13}C{1H} NMR (125 MHz C$_6$D$_6$) δ 159.8 (Ar), 136.0 (CH=CH$_2$), 130.7 (Ar), 129.3 (Ar), 127.5 (Ar), 116.6 (CH=CH$_2$) 114.1 (Ar), 86.3 (EtCHOR), 84.0 (CHORCHCl), 82.2 (CHOPMB), 79.9 (CHORCHOR), 78.9 (CHORCHOR), 71.4 (CHOH), 70.8 (CHOH), 54.8 (O*Me*), 34.9 (CH$_2$CHOH), 34.8 (CH$_2$CHOPMB), 34.5 (CH$_2$CH=CH$_2$), 27.4 (CH$_3$CH$_2$), 10.4 (CH$_3$); MS (ESI-TOF) *m*/*z* 385 [M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for C$_{21}$H$_{30}$O$_5$Na 385.1985; found 385.1985; $[\alpha]_D^{20}$ +38.1 (*c* = 1.0 in CHCl$_3$).

*(2S,2′R,4R,4′S,5S,5′R)-5-Allyl-4-chloro-5′-ethyl-4′-((4-methoxybenzyl)oxy)octahydro-2,2′-bifuran (**35**).* Alcohol **34** (24 mg, 66 μmol) was dissolved in DCM/CCl$_4$ (2.4 mL/0.6 mL) and PPh$_3$ (72.5 mg, 396 μmol) was added and the reaction stirred for 2.5 h. Direct purification of the reaction mixture via flash column chromatography (DCM → 5:1 petrol/ethyl) gave the title compound as a colorless oil (24 mg, 64 μmol, 96%): R_f 0.89 (6:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 2916m, 2930m, 2876m; ^{1}H NMR (500 MHz C$_6$D$_6$) 7.19 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar*H*), 5.78 (ddt, *J* = 16.5, 10.0, 7.0 Hz, 1H, C*H*=CH$_2$), 4.96−5.01 (m, 1H, CH=C*H*$_2$), 4.27 (d, *J* = 11.5 Hz, 1H, C*H*H′Ar), 4.21 (d, *J* = 11.5 Hz, 1H, CH*H*′Ar), 4.00−4.13 (m, 3H, C*H*ORC*H*OR, CHClC*H*OR), 3.96 (ddd, *J* = 7.0, 6.0, 3.0 Hz, 1H, EtC*H*OR), 3.77 (dt, *J* = 7.0, 5.0 Hz, 1H, C*H*Cl), 3.55 (ddd, *J* = 6.5, 3.0, 2.5 Hz, 1H, C*H*OPMB), 3.30 (s, 3H, O*Me*), 2.06−2.17 (m, 4H, C*H*$_2$CH=CH$_2$, C*H*$_2$CHCl), 2.04 (ddd, *J* = 13.4, 6.0, 2.5 Hz, 1H, C*H*H′CHOPMB), 1.57 (ddd, *J* = 13.4, 9.0, 6.5 Hz, 1H, CH*H*′CHOPMB), 1.32−1.48 (m, 2H, CH$_3$C*H*$_2$), 0.90 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$); ^{13}C{^{1}H} NMR (125 MHz C$_6$D$_6$) δ 159.8 (Ar), 134.1 (CH=CH$_2$), 130.9 (Ar), 129.4 (Ar), 127.5 (Ar), 117.4 (CH=CH$_2$), 114.1 (Ar), 86.7 (CHORCHCl), 85.9 (EtCHOR), 82.8 (CHOPMB), 80.8 (CHORCHOR), 80.4 (CHORCHOR), 70.9 (CH$_2$Ar), 59.8 (CHCl), 54.8 (O*Me*), 38.9 (CH$_2$CHCl), 38.3 (CH$_2$CH=CH$_2$), 35.7 (CH$_2$CHOPMB), 27.8 (CH$_3$CH$_2$), 10.5 (CH$_3$); MS (ESI-TOF) *m*/*z* 403 [^{35}M + Na]$^+$, 405 [^{37}M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for C$_{21}$H$_{29}$O$_4$^{35}ClNa 403.1647; found 403.1638; $[\alpha]_D^{20}$ +8.1 (*c* = 1.0 in CHCl$_3$).

*(2R,2′S,4S,4′R,5R,5′S)-5′-Allyl-4′-chloro-5-ethyloctahydro-[2,2′-bifuran]-4-ol (**36**).* Chloride **35** (24 mg, 66 μmol) was dissolved in DCM (6 mL) and BCl$_3$·DMS (165 μL, 2 M in DCM, 0.33 mmol) was added dropwise. The reaction was stirred for 5 min and then quenched by the addition of saturated aqueous NaHCO$_3$ (4 mL). The mixture was then extracted with DCM (3 × 10 mL). The combined organic layers were then dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo. Purification via flash column chromatography (4:1 petrol/ethyl acetate) gave the title compound as a colorless oil (16 mg, 62 μmol, 94%): R_f 0.34 (5:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 3423br (OH), 2965m, 1437w, 1067s; ^{1}H NMR (400 MHz CDCl$_3$) δ 5.83 (ddt, *J* = 17.0, 9.9, 7.0 Hz, 1H, C*H*=CH$_2$), 5.13 (d, *J* = 17.0 Hz, 1H, CH=C*H*H′), 5.11 (d, *J* = 9.9 Hz, 1H, CH=CH*H*′), 4.06−4.15 (m, 3H, C*H*OH, C*H*ORC*H*OR), 4.00−4.06 (m, 2H, C*H*ClC*H*OR), 3.68 (td, *J* = 6.6, 2.8 Hz, 1H, EtC*H*OR), 2.30−2.40 (m, 2H, C*H*$_2$CH=CH$_2$), 2.17−2.29 (m, 2H, C*H*$_2$CHCl), 1.85−1.98 (m, 2H, C*H*$_2$CHOH), 1.74 (br s, 1H, O*H*), 1.44−1.57 (m, 2H, CH$_3$C*H*$_2$), 0.96 (t, *J* = 7.4 Hz, 3H, C*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 133.5 (CH=CH$_2$), 117.9 (CH=CH$_2$), 88.2 (EtCHOR), 86.4 (CHORCHCl), 80.0 (CHORCHOR), 79.2 (CHORCHOR), 75.7 (CHOH), 59.2 (CHCl), 38.0 (CH$_2$CH=CH$_2$), 38.0 (CH$_2$CHCl), 37.6 (CH$_2$CHOH), 27.1 (CH$_3$CH$_2$), 10.2 (CH$_3$); MS (ESI-TOF) *m*/*z* 283 [^{35}M + Na]$^+$, 285 [^{37}M + Na]$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for C$_{13}$H$_{21}$O$_3$^{35}ClNa 283.1071; found 283.1073; $[\alpha]_D^{20}$ −38.6 (*c* = 1.0 in CHCl$_3$).

(2R,2′S,4R,4′R,5R,5′S)-5′-Allyl-4′-chloro-5-ethyloctahydro-[2,2′-bifuran]-4-yl 4-nitrobenzoate. Alcohol **36** (15.5 mg, 60 μmol) and PPh$_3$ (156 mg, 600 μmol) were dissolved in THF (0.8 mL) and cooled to 0 °C. DIAD (120 μL, 600 μmol) was added dropwise, and the reaction was stirred for 30 min before the addition of 4-nitrobenzoic acid (99.6 mg, 600 μmol). The reaction was then warmed to rt and stirred for 2 h before being concentrated in vacuo. Purification via flash column chromatography (DCM) gave the title compound as a colorless oil (20 mg, 49 μmol, 81%): R_f 0.43 (8:1 petrol/acetone); ν_{max}/cm^{-1} (thin film) 2972w, 1724s (CO), 1528s, 1350m; ^{1}H NMR (400 MHz CDCl$_3$) δ 8.31 (d, *J* = 9.1 Hz, 2H, Ar*H*), 8.20 (d, *J* = 9.1 Hz, 2H, Ar*H*), 5.77 (ddt, *J* = 17.0, 10.0, 7.1 Hz, 1H, C*H*=CH$_2$), 5.54 (ddd, *J* = 6.5, 3.6, 1.6 Hz, 1H, C*H*OPNB), 5.07 (dd, *J* = 17.0, 1.2 Hz, 1H, CH=C*H*H′), 5.05 (dd, *J* = 10.0, 1.2 Hz, 1H, CH=CH*H*′), 4.24 (dt, *J* = 7.5, 6.1 Hz, 1H, CHORC*H*OR), 4.01−4.11 (m, 2H, C*H*ClC*H*OR), 3.97 (dt, *J* = 8.3, 6.0 Hz, 1H, C*H*ORCHOR), 3.81 dd, *J* = 7.4, 6.1, 3.5 Hz, 1H, EtC*H*OR), 2.57 (ddd, *J* = 14.9, 8.5, 6.5 Hz, 1H, C*H*H′CHOPNB), 2.22−2.38 (m, 4H,

$CH_2CH{=}CH_2$, CH_2CHCl), 2.02 (ddd, J = 14.8, 6.0, 1.7 Hz, 1H, $CHH'CHOPNB$), 1.63−1.85 (m, 2H, CH_3CH_2), 0.99 (t, J = 7.4 Hz, 3H, CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.0 (C=O), 150.7 (Ar), 135.4 (Ar), 133.3 ($CH{=}CH_2$), 130.7 (Ar), 123.7 (Ar), 118.0 ($CH{=}CH_2$), 86.4 (CHORCHCl), 83.7 (EtCHOR), 79.6 (CHORCHOR), 79.0 (CHORCHOR), 75.9 (CHOPNB), 59.1 (CHCl), 38.2 ($CH_2CH{=}CH_2$), 37.9 (CH_2CHCl), 35.9 ($CH_2CHOPNB$), 22.2 (CH_3CH_2), 10.6 (CH_3); MS (ESI-TOF) m/z 432 [$^{35}M + Na^+$], 434 [$^{37}M + Na^+$]; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{24}NO_6{}^{35}ClNa$ 432.1184; found 432.1184; $[\alpha]_D^{20}$ −12.4 (c = 1.0 in $CHCl_3$).

*(2R,2′S,4R,4′R,5R,5′S)-5′-Allyl-4′-chloro-5-ethyloctahydro-[2,2′-bifuran]-4-ol (**37**).* (2*R*,2′*S*,4*R*,4′*R*,5*R*,5′*S*)-5′-allyl-4′-chloro-5-ethyloctahydro-[2,2′-bifuran]-4-yl 4-nitrobenzoate (20 mg, 49 μmol) was dissolved in MeOH (2 mL) and cooled to 0 °C, and K_2CO_3 (40 mg, 290 μmol) was added. The reaction was stirred for 30 min and then diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (4:1 petrol/ethyl acetate) gave the title compound as a colorless oil (13 mg 48 μmol, 98%): R_f 0.32 (5:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 3461br (OH), 2968m, 1430m, 1050s; ^1H NMR (400 MHz $CDCl_3$) δ 5.82 (ddt, J = 17.0, 10.0, 6.8 Hz, 1H, $CH{=}CH_2$), 5.17 (dd, J = 17.0, 1.5 Hz, 1H, $CH{=}CHH'$), 5.15 (dd, J = 10.0, 1.5 Hz, 1H, $CH{=}CHH'$), 4.44 (ddd, J = 9.1, 6.8, 2.6 Hz, 1H, CHORCHOR), 4.16 (dt, J = 9.8, 2.6 Hz, 1H, CHORCHOR), 4.11−4.14 (m, 1H, CHORCHCl), 3.99−4.04 (m, 2H, CHOH, CHCl), 3.54 (tdfz, J = 6.9, 2.5 Hz, 1H, EtCHOR), 3.24 (br s, 1H, OH), 2.33−2.47 (m, 2H, $CH_2CH{=}CH_2$), 2.25 (ddd, J = 14.0, 9.8, 5.5 Hz, 1H, $CHH'CHOH$), 2.15 (ddd, J = 13.8, 6.8, 3.7 Hz, 1H, $CHH'CHCl$), 2.00 (ddd, J = 13.8, 9.6, 7.8 Hz, 1H, $CHH'CHCl$), 1.81 (dd, J = 14.0, 3.3 Hz, 1H, $CHH'CHOH$), 1.65−1.74 (m, 2H, CH_3CH_2), 0.97 (t, J = 7.6 Hz, 3H, CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 132.7 ($CH{=}CH_2$), 118.6 ($CH{=}CH_2$), 86.6 (CHORCHCl), 85.7 (EtCHOR), 79.0 (CHORCHOR), 77.9 (CHORCHOR), 70.9 (CHOH), 58.4 (CHCl), 38.2 (CH_2CHCl), 37.6 ($CH_2CH{=}CH_2$), 34.7 (CH_2CHOH), 21.8 (CH_3CH_2), 10.5 (CH_3); MS (ESI-TOF) m/z 283 [$^{35}M + Na^+$], 285 [$^{37}M + Na^+$]; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{13}H_{21}O_3{}^{35}ClNa$ 283.1071; found 283.1072; $[\alpha]_D^{20}$ −40.2 (c = 1.0 in $CHCl_3$).

*(2R,2′S,4R,4′R,5R,5′S)-4′-Chloro-5-ethyl-5′-((E)-pent-2-en-4-yn-1-yl)octahydro-[2,2′-bifuran]-4-ol, L. majuscula Enyne (**2b**).* To a stirred solution of alkene **37** (12 mg, 46 μmol) (62 mg, 0.16 mmol) in dry degassed DCM (1.4 mL) were added crotonaldehyde (38 μL, 0.46 mmol) and Grubbs' second generation catalyst (3.9 mg, 4.6 μmol). The reaction mixture was stirred for 1.5 h at 40 °C and then cooled to rt and quenched with the addition of DMSO (30 μL) and stirred for 16 h. The mixture was concentrated in vacuo and purified by flash column chromatography (5:1 petrol ethyl acetate) to give the intermediate enal (**38**) (12.6 mg), which was used immediately in the next reaction: MS (ESI-TOF) m/z 311 [$^{35}M + Na^+$], 313 [$^{37}M + Na^+$]; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{14}H_{21}O_4{}^{35}ClNa$ 311.1021; found 311.1026.

To a solution of (diazomethyl)trimethylsilane (230 μL, 2 M in ether, 0.46 mmol) in THF (1 mL) at −78 °C was added BuLi (288 μL, 1.6 M in hexanes, 0.46 mmol) dropwise. The reaction mixture was stirred for 30 min before a solution of the intermediate enal **38** was added as a solution in THF (0.5 + 0.5 mL) at −78 °C. The reaction was stirred at −78 °C for 1 h before being warmed to 0 °C for a further 1 h. The reaction was quenched with acetic acid (0.1 mL) and then saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (20:1 petrol/ethyl acetate) gave the OTMS-protected version title compound (m/z 379 M + Na^+, 100), which was then dissolved in THF (1 mL) and cooled to 0 °C, and TBAF (0.13 mL, 1 M in THF, 0.13 mmol) was added and the reaction stirred for 5 min. The reaction was quenched with saturated aqueous NH_4Cl (1 mL). The aqueous layer was separated and extracted with EtOAc (3 × 8 mL). Purification by flash column chromatography (5:1 petrol/ethyl acetate) gave the title compound as a colorless oil (5 mg, 18 μmol, 39%): R_f 0.40 (5:1: petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 3461br (OH), 3296m (CH), 2968m, 1442m, 1066s; ^1H NMR (500 MHz $CDCl_3$) δ 6.22 (dt, J = 15.9, 7.4 Hz, 1H, $CH_2CH{=}CH$), 5.59 (dddd, J = 15.9, 2.2, 1.6, 1.5 Hz, 1H, $CH_2CH{=}CH$), 4.41 (ddd, J = 9.1, 6.8, 2.6 Hz, 1H, CHORCHOR), 4.11 (ddd, J = 9.8, 3.3, 2.6 Hz, 1H, CHORCHOR), 4.08 (ddd, J = 6.5, 5.6, 5.4 Hz, 1H, CHORCHCl), 4.05 (br m, 1H, CHOH) 3.96 (ddd, J = 7.8, 5.4, 4.2 Hz, 1H, CHCl), 3.54 (dt, J = 6.9, 2.5 Hz, 1H, EtCHOR), 3.00 (br s, 1H, OH), 2.83 (d, J = 2.2 Hz, 1H), 2.40−2.53 (m, 2H, $CH_2CH{=}CH$), 2.25 (ddd, 1H, J = 14.0, 9.8, 5.5 Hz, $CHH'CHOH$), 2.18 (ddd, J = 13.8, 6.8, 4.2 Hz, 1H, $CHH'CHCl$), 2.05 (ddd, J = 13.8, 9.1, 7.8 Hz, 1H, $CHH'CHCl$), 1.78 (dd, J = 14.0, 3.3 Hz, 1H, $CHH'CHOH$), 1.70 (qn, J = 7.5 Hz, 2H, CH_3CH_2), 0.98 (t, J = 7.5 Hz, 1H, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 139.9 ($CH_2CH{=}CH$), 112.4 ($CH{=}CH_2$), 86.0 (CHORCHCl), 85.7 (EtCHOR), 81.7 (CCH), 79.2 (CHORCHOR), 77.9 (CHORCHOR), 77.2 (CCH), 71.0 (CHOH), 58.2 (CHCl), 38.1 (CH_2CHCl), 36.5 ($CH_2CH{=}CH_2$), 35.1(CH_2CHOH), 21.7 (CH_3CH_2), 10.5 (CH_3); MS (ESI-TOF) m/z 307 [$^{35}M + Na^+$], 309 [$^{37}M + Na^+$]; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{21}{}^{35}ClO_3Na$ 307.1071; found 307.1066; $[\alpha]_D^{20}$ −51.9 (c = 0.45 in $CHCl_3$), lit. $[\alpha]_D^{22}$ −67.8 (c = 0.09 in $CHCl_3$).

*(2R,2′S,4S,4′R,5R,5′S)-4′-chloro-5-ethyl-5′-((E)-pent-2-en-4-yn-1-yl)octahydro-[2,2′-bifuran]-4-ol (**2d**).* Alcohol **2b** (2 mg, 7 μmol) and PPh_3 (20.2 mg, 77 μmol) were dissolved in THF (0.3 mL) and cooled to 0 °C. DIAD (15.6 μL, 77 μmol) was added dropwise, and the reaction was stirred for 30 min before the addition of 4-nitrobenzoic acid (13 mg, 77 μmol). The reaction was then warmed to rt and stirred for 2 h before being concentrated in vacuo. Purification by short silica plug (DCM) gave the intermediate ester mixed with $DIADH_2$. The mixture was then dissolved in MeOH (0.2 mL) and cooled to 0 °C, and K_2CO_3 (5.5 mg, 40 μmol) was added. The reaction was stirred for 30 min, diluted with H_2O (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by column chromatography (3:1 petrol/ethyl acetate) gave the title compound as a colorless oil (1.8 mg, 7 μmol, 90%): R_f 0.62 (3:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 3444br (OH), 3291m (CH), 2966m, 1442m, 1066s; ^1H NMR (500 MHz $CDCl_3$) δ 6.25 (dt, J = 16.2, 7.4 Hz, 1H, $CH_2CH{=}CH$), 5.57 (d t, J = 16.2, 1.8 Hz, 1H, $CH{=}CH$), 4.08−4.15 (m, 3H, CHORCHOR, CHOH), 3.97−4.02 (m, 2H, CHClCHOR), 3.70 (td, J = 6.7, 3.1 Hz, 1H, CHEt), 2.83 (d, J = 1.8 Hz, 1H, CCH), 2.43−2.49 (m, 2H, $CHH'CH{=}CH$), 2.34−2.40 (m, 1H, $CHH'CH{=}CH$), 2.26−2.32 (m, 1H, $CHH'CHCl$), 2.19 (ddd, J = 13.4, 6.4, 4.7 Hz, 1H, $CHH'CHCl$), 1.95 (ddd, J = 13.3, 5.9, 2.7 Hz, 1H, $CHOHCHH'$), 1.86 (ddd, J = 13.2, 8.8, 6.2 Hz, 1H, $CHOHCHH'$), 1.46−1.56 (m, 2H, CH_2Me), 0.97 (t, J = 7.4 Hz, 3H, Me); $^{13}C\{^1H\}$ NMR (125 MHz $CDCl_3$) δ 140.9 ($CH_2CH{=}CH$), 111.7 ($CH{=}CH$), 88.2 (CHEt), 85.7 (CHClCHOR), 81.9 (CCH), 79.9, (CHORCHOR), 79.1 (CHORCHOR), 76.6 (CCH), 75.7 (CHOH), 58.9 (CHCl), 37.8 (CH_2CHCl), 37.6 ($CHOHCH_2$), 36.8 ($CH_2CH{=}CH$), 27.0 (CH_2Me), 10.2 (Me); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{21}ClO_3Na$ 307.1071; found 307.1070; $[\alpha]_D^{20}$ −31.3 (c = 0.16 in $CHCl_3$).

Notoryne: Oxford Route. *(2S,2′R,4S,4′S,5R,5′R)-5′-Allyl-4′-chloro-5-ethyloctahydro-[2,2′-bifuran]-4-ol.* To a stirred solution of ether **28** (35 mg, 0.09 mmol) in DCM (9 mL) was added $BCl_3\cdot SMe_2$ (0.23 mL, 2 M in DCM, 0.45 mmol), and the reaction was stirred for 5 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (6 mL) and the stirred vigorously for 10 min. The aqueous layer was separated and extracted with DCM (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography (3:1 petrol/ethyl acetate) gave the title compound as a colorless oil (22 mg, 86 μmol, 95%): R_f 0.56 (3:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 3432br (OH), 2964s, 1642w,1438w, 1074s, 921m; ^1H NMR (500 MHz $CDCl_3$) δ 5.82 (ddt, J = 17.2, 10.1, 6.8 Hz, 1H, $CH{=}CH_2$), 5.17 (dd, J = 17.2, 1.6 Hz, 1H, $CH{=}CHH'$), 5.14 (dd, J

= 10.1, 1.6 Hz, 1H, CH=CH*H*′), 4.42 (ddd, *J* = 9.3, 6.4, 2.6 Hz, 1H, CHORC*H*OR), 4.19 (dt, *J* = 9.3, 3.1 Hz, 1H, C*H*ORCHOR), 4.12 (dt, *J* = 6.6, 5.3 Hz, 1H, C*H*ORCHCl), 3.99−4.04 (m, 2H, C*H*Cl, C*H*OH), 3.88 (td, *J* = 7.4, 1.0 Hz, 1H, EtC*H*OR), 3.43 (br s, 1H, O*H*), 2.41−2.47 (m, 1H, C*H*HCH=CH$_2$), 2.33−2.39 (m, 1H, CH*H*CH=CH$_2$), 2.28 (ddd, *J* = 13.9, 6.4, 3.8 Hz, 1H, C*H*H′CHOH), 2.18 (ddd, *J* = 13.9, 6.4, 2.6 Hz, 1H, C*H*H′CHCl), 2.04 (ddd, *J* = 13.9, 9.3, 8.0 Hz, 1H, CH*H*′CHCl), 1.78 (ddd, *J* = 13.9, 3.4, 1.6 Hz, 1H, CH*H*′CHOH), 1.38 (qn, *J* = 7.4 Hz, 2H, CH$_3$C*H*$_2$), 0.95 (t, *J* = 7.4 Hz, 3H, C*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 132.8 (CH=CH$_2$), 118.5 (CH=CH$_2$), 89.1 (EtCHOR), 86.7 (CHORCHCl), 79.7 (CHORCHOR), 78.2 (CHORCHOR), 74.8 (CHOH), 58.5 (CHCl), 38.3 (CH$_2$CHCl), 37.6 (CH$_2$CH=CH$_2$), 33.8 (CH$_2$CHOH), 26.1 (CH$_3$CH$_2$), 10.2 (CH$_3$); MS (ESI-TOF) *m*/*z* 283 [^{35}M + Na$^+$], 285 [^{37}M + Na$^+$]; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for C$_{13}$H$_{21}$NO$_3$^{35}ClNa 283.1071; found 283.1072; $[\alpha]_D^{20}$ +60.4 (*c* = 1.0 in CHCl$_3$).

(2S,2′R,4R,4′S,5R,5′R)-5′-Allyl-4′-chloro-5-ethyloctahydro-[2,2′-bifuran]-4-yl 4-nitrobenzoate. To a stirred solution of (2*S*,2′*R*,4*S*,4′*S*,5*R*,5′*R*)-5′-allyl-4′-chloro-5-ethyloctahydro-[2,2′-bifuran]-4-ol (16 mg, 62 μmol) and PPh$_3$ (78 mg, 0.3 mmol) in THF (0.9 mL) at 0 °C was added DIAD (60 μL, 60 μg, 0.3 mmol). The reaction mixture was stirred for 30 min at 0 °C, during which time a white precipitate formed. 4-Nitrobenzoic acid (50 mg, 0.3 mmol) was added in one batch, and the reaction was stirred for 1 h. The reaction was then concentrated in vacuo and purified by flash column chromatography (DCM) to give the title compound as a colorless oil (19 mg, 46 μmol, 74%): R_f 0.45(8:1 petrol/acetone); ν_{max}/cm^{-1} (thin film) 2967w, 1725s, 1529s, 1348w, 1274s, 1103m; ^{1}H NMR (400 MHz CDCl$_3$) δ 8.30 (dd, *J* = 7.0, 1.9 Hz, 2H, Ar*H*), 8.22 (dd, *J* = 7.0, 1.9 Hz, 2H, Ar*H*), 5.83 (ddt, *J* = 17.0, 10.0, 6.7 Hz, 1H, C*H*=CH$_2$), 5.63 (t, *J* = 3.4 Hz, 1H, C*H*OPNB), 5.13 (dd, *J* = 17.0, 0.9 Hz, 1H, CH=C*H*H′), 5.12 (dd, *J* = 10.0, 0.9 Hz, 1H, CH=CH*H*′), 4.22−4.30 (m, 2H, C*H*ORC*H*OR), 4.05−4.09 (m, 2H, C*H*ClC*H*OR), 4.02 (td, *J* = 7.1, 3.4 Hz, 1H, EtC*H*OR), 2.32−2.39 (m, 2H, C*H*$_2$CH=CH$_2$), 2.20−2.28 (m, 4H, C*H*$_2$CHOPNB, C*H*$_2$CHCl), 1.57−1.80 (m, 2H, CH$_3$C*H*$_2$), 0.97 (t, *J* = 7.5 Hz, 3H, C*H*$_3$); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 164.0 (C=O), 150.7 (Ar), 135.3 (Ar), 133.3 (CH=CH$_2$), 130.8 (Ar), 123.6 (Ar), 118.0 (CH=CH$_2$), 86.5 (CHORCHCl), 83.4 (EtCHOR), 80.0, 78.8 (CHORCHOR), 76.6 (CHOPNB), 59.0 (CHCl), 38.1 (CH$_2$), 37.9 (CH$_2$CH=CH$_2$), 35.6 (CH$_2$), 22.6 (CH$_3$CH$_2$), 10.5 (CH$_3$); MS (ESI-TOF) *m*/*z* 432 [^{35}M + Na$^+$], 434 [^{37}M + Na$^+$]; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for C$_{20}$H$_{24}$NO$_6$^{35}ClNa 432.1184; found 432.1185; $[\alpha]_D^{20}$ −4.0 (*c* = 1.0 in CHCl$_3$).

*(2S,2′R,4R,4′S,5R,5′R)-5′-Allyl-4′-chloro-5-ethyloctahydro-[2,2′-bifuran]-4-ol (**10**).* To a stirred solution of (2*S*,2′*R*,4*R*,4′*S*,5*R*,5′*R*)-5′-allyl-4′-chloro-5-ethyloctahydro-[2,2′-bifuran]-4-yl 4-nitrobenzoate (19 mg, 46 μmol) in MeOH (1 mL) was added K$_2$CO$_3$ (39 mg, 132 mmol), and the reaction was stirred for 30 min. The mixture was diluted with H$_2$O (3 mL) and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (MgSO$_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (3:1 petrol/ethyl acetate) gave the title compound as a colorless oil (11 mg, 42 μmol, 91%): R_f (0.54 3:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 3247br (OH), 2932s, 1642w, 1434w, 1055s, 1013m, 924s; ^{1}H NMR (500 MHz CDCl$_3$) δ 5.83 (ddt, *J* = 17.1, 10.3, 7.0 Hz, 1H, C*H*=CH$_2$), 5.14 (dd, *J* = 17.1, 1.5 Hz, 1H, CH=C*H*H′), 5.11 (dd, *J* = 10.3, 1.5 Hz, 1H, CH=CH*H*′), 4.28−4.31 (m, 1H, C*H*OH), 4.16−4.22 (m, 2H, C*H*ORC*H*OR), 4.02−4.07 (m, 2H, C*H*ClC*H*OR), 3.73 (td, *J* = 7.3, 2.8 Hz, 1H, EtC*H*OR), 2.28−2.42 (m, 2H, C*H*$_2$CH=CH$_2$), 2.16−2.24 (m, 2H, C*H*$_2$CHCl), 2.10 (ddd, *J* = 13.0, 5.6, 1.0 Hz, 1H, C*H*H′CHOH), 1.97 (ddd, *J* = 13.0, 8.7, 4.7 Hz, 1H, CH*H*′CHOH), 1.57−1.74 (m, 2H, CH$_3$C*H*$_2$), 1.45 (d, *J* = 5.3 Hz, 1H, O*H*), 0.99 (t, *J* = 7.5 Hz, 3H, C*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 133.4 (CH=CH$_2$), 117.9 (CH=CH$_2$), 86.4 (CHORCHCl), 84.6 (EtCHOR), 80.3 (CHORCHOR), 78.4 (CHORCHOR), 72.7 (CHOH), 59.1 (CHCl), 38.1 (CH$_2$CHCl), 37.9 (CH$_2$CH=CH$_2$, CH$_2$CHOH), 22.0 (CH$_3$CH$_2$), 10.4 (CH$_3$); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for C$_{13}$H$_{21}$O$_3$ClNa 283.1071; found 283.1071; $[\alpha]_D^{20}$ +6.8 (*c* = 1.0 in CHCl$_3$).

*(2R,2′S,4S,4′S,5R,5′R)-5-Allyl-4′-bromo-4-chloro-5′-ethyloctahydro-2,2′-bifuran (**47**-Oxford).* To a stirred solution of alcohol **10** (14 mg, 57 μmol) in toluene (2.4 mL) were added PPh$_3$ (78 mg, 0.3 mmol) and CBr$_4$ ((99 mg, 0.3 mmol), which was then purified by sublimation, dissolved in DCM, filtered through deactivated alumina, and dried in a desiccator over KOH for 16 h), and the mixture was heated to 80 °C for 75 min. The reaction mixture was cooled to rt and then diluted with DCM (1 mL) and loaded directly onto a column. Purification by flash column chromatography (DCM) gave the title compound as a colorless oil (14 mg, 43 μmol, 75%): R_f 0.82 (5:1 petrol/ethyl acetate); ν_{max}/cm^{-1} (thin film) 2964m, 1456m, 1262m, 1067s; ^{1}H NMR (500 MHz CDCl$_3$) δ 5.83 (ddt, *J* = 17.0, 10.1, 6.9 Hz, 1H, C*H*=CH$_2$), 5.15 (dd, *J* = 17.0, 1.6 Hz, 1H, CH=C*H*H′), 5.12 (dd, *J* = 10.1, 1.6 Hz, 1H, CH=CH*H*′), 4.24 (dt, *J* = 7.2, 5.5 Hz, 1H, CHORC*H*OR), 4.03−4.07 (m, 2H, C*H*Cl, C*H*ORCHCl), 3.97 (ddd, *J* = 8,2, 6.9, 5.5 Hz, 1H, C*H*ORCHOR), 3.91 (td, *J* = 7.5, 4.0 Hz, 1H, EtC*H*OR), 3.86 (td, *J* = 8.7, 7.3 Hz, 1H, C*H*Br), 2.66 (dt, *J* = 13.1, 6.9 Hz, 1H, C*H*H′CHBr), 2.31−2.40 (m, 2H, C*H*$_2$CH=CH$_2$), 2.24−2.26 (m, 2H, C*H*$_2$CHCl), 2.18 (dt, *J* = 13.6, 8.0 Hz, 1H, CH*H*′CHBr), 1.76 (dqd, *J* = 13.8, 7.5, 3.8 Hz, 1H, CH$_3$C*H*H′), 1.50 (dqn, *J* = 13.8, 7.5 Hz, 1H, CH$_3$CH*H*′), 1.01 (t, *J* = 7.5 Hz, 3H, C*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 133.3 (CH=CH$_2$), 118.0 (CH=CH$_2$), 87.1 (EtCHOR), 86.4 (CHORCHCl), 79.9 (CHORCHOR), 78.9 (CHORCHOR), 58.9 (CHCl), 47.3 (CHBr), 39.3 (CH$_2$CHCl), 38.0 (CH$_2$CHBr), 37.8 (CH$_2$CH=CH$_2$), 25.4 (CH$_3$CH$_2$), 10.0 (CH$_3$); MS (ESI-TOF) *m*/*z* 345 [M + Na$^+$], 347[M + Na$^+$]; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for C$_{13}$H$_{20}$O$_2$^{35}Cl^{79}BrNa 345.0227; found 345.0235; $[\alpha]_D^{20}$ +29.5 (*c* = 1.0 in CHCl$_3$).

*((Z)-5-((2R,2′S,4S,4′S,5R,5′R)-4′-Bromo-4-chloro-5′-ethyloctahydro-[2,2′-bifuran]-5-yl)pent-3-en-1-yn-1-yl)trimethylsilane (**48**).* A mixture of ozone and oxygen was gently bubbled through a stirred solution of **47**-Oxford (5 mg, 15 μmol) in DCM (3 mL) at −78 °C until the solution became pale blue (approximately 2 min). The excess ozone was purged from the solution by bubbling oxygen through for a further 5 min. Triphenylphosphine (20 mg, 75 μmol) was added, and the reaction mixture was allowed to warm to rt over 15 h. The reaction mixture was dry-loaded onto silica and rapidly purified by flash column chromatography (5:1 petrol bp 30−40 °C/diethyl ether) to give the corresponding aldehyde as a colorless oil (4.4 mg, 13.6 μmol, 91%) that was used in the subsequent transformation without characterization.

To a solution of 3-(*tert*-butyldimethylsilyl)-1-trimethylsilanylpropyne (135 mg, 0.63 mmol) in dry THF (1 mL) at −78 °C was added dropwise *tert*-butyllithium (0.37 mL, 1.7 M in pentane, 0.63 mmol), and this solution was stirred at −78 °C for 1 h. A solution of titanium(IV) isopropoxide (0.19 mL, 180 mg, 0.63 mmol) in dry THF (0.5 mL) was added dropwise to the reaction mixture; the resulting solution was stirred for 10 min, and then 1.94 mL was removed and discarded. To the remaining 0.12 mL (36 μmol) was added dropwise a solution of the aldehyde prepared above in dry THF (0.5 mL + 0.5 mL rinse). The reaction mixture was stirred at −78 °C for 30 min, and then the cooling bath was removed and the reaction mixture stirred at rt for 30 min. The reaction mixture was then poured into a separating funnel containing 0.1 M aqueous HCl (2 mL), and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried (MgSO$_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (50:1 petrol bp 30−40 °C/diethyl ether) gave the title compound as a colorless oil (2 mg, 4.8 μmol, 32% from **47**-Oxford, >30:1 (*Z*):(*E*) from crude ^{1}H NMR analysis and characterized as such a mixture): ν_{max}/cm^{-1} (thin film) 2963; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.02 (dt, *J* = 10.9, 7.5 Hz, 1HCH$_2$C*H*=CH), 5.63 (dt, *J* = 10.9, 1.3 Hz, 1H, CH$_2$CH=C*H*), 4.25 (td, *J* = 7.3, 5.6 Hz, 1H, CHClCH$_2$C*H*O), 4.13−4.08 (m, 2H, C*H*CH$_2$CH=CH, C*H*Cl), 3.97 (ddd, *J* = 8.3, 6.7, 5.5 Hz, 1H, CHBrCH$_2$C*H*O), 3.91 (td, *J* = 7.5, 4.0 Hz, 1H, C*H*Et), 3.86 (dt, *J* = 8.7, 7.3 Hz, 1H, C*H*Br), 2.66 (dt, *J* = 13.2, 6.7 Hz, 1H, CHBrC*H*H), 2.69−2.63 (m, 1H, C*H*HCH=CH), 2.61−2.55 (m, 1H, CH*H*CH=CH), 2.29–2.22 (m, 2H, CHClC*H*$_2$), 2.18 (dt, *J* = 13.2, 8.3 Hz, 1H, CHBrCH*H*), 1.75 (dqd, *J* = 13.9, 7.4, 4.0 Hz, 1H, C*H*HCH$_3$), 1.49 (dqn, *J* = 14.0, 7.4 Hz, 1H, CH*H*CH$_3$), 1.00 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$), 0.20 (s, 9H, Si(C*H*$_3$)$_3$); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 139.3 (CH$_2$CH=CH), 112.4 (CH$_2$CH=CH), 101.6 (C≡C), 100.0 (C≡C), 87.3 (CHEt), 86.5 (CHCH$_2$CH=CH), 80.3 (CHClCH$_2$CH), 79.1 (CHBrCH$_2$CH), 59.4 (CHCl), 47.5 (CHBr), 39.5 (CHBrCH$_2$), 38.3 (CHClCH$_2$), 34.6 (CH$_2$CH=CH), 25.6 (CH$_2$CH$_3$), 10.2 (CH$_2$CH$_3$), 0.11 (Si(CH$_3$)$_3$); $[\alpha]_D^{25}$ +37.5 (*c* = 0.16 in CHCl$_3$).

*(2S,2′R,4S,4′S,5R,5′R)-4-Bromo-4′-chloro-5-ethyl-5′-((Z)-pent-2-en-4-yn-1-yl)octahydro-2,2′-bifuran, (Z)-notoryne ((Z)-**3a**).* To a stirred solution of **48** (2 mg, 4.8 μmol) in THF (1 mL) at −20 °C was added TBAF (20 μL of a 2.0 M solution in THF, 40 μmol), and stirring was continued for 5 min. The reaction mixture was quenched by the addition of aqueous ammonium chloride (3 mL), and the aqueous phase was extracted with ether (3 × 5 mL). The combined organic extracts were dried (Na$_2$SO$_4$). Purification by flash chromatography (30:1 petrol bp 30–40 °C/diethyl ether) gave the title compound as a colorless oil (1.7 mg, 4.8 μmol, quant.): ν_{max}/cm^{-1} (thin film) 3294, 1728, 1460, 1289, 1071, 966; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.08 (dtd, *J* = 10.9, 7.5, 0.9 Hz, 1H, CH$_2$C*H*=CH), 5.60 (ddt, *J* = 10.9, 2.7, 1.4 Hz, 1H, CH$_2$CH=C*H*), 4.25 (td, *J* = 7.3, 5.6 Hz, 1H, CHClCH$_2$C*H*O), 4.11–4.07 (m, 2H, C*H*CH$_2$CH=CH, C*H*Cl), 3.98 (ddd, *J* = 8.3, 6.8, 5.6 Hz, 1H, CHBrCH$_2$C*H*O), 3.91 (td, *J* = 7.5, 3.9 Hz, 1H, C*H*Et), 3.86 (dt, *J* = 8.8, 7.3 Hz, 1H, C*H*Br), 3.12 (dd, *J* = 2.2, 0.9 Hz, 1H, CC*H*), 2.66 (dt, *J* = 13.1, 7.0 Hz, 1H, CHBrC*H*H), 2.69–2.64 (m, 1H, CH*H*CH=CH), 2.60 (dddd, *J* = 14.6, 7.4, 6.0, 1.4 Hz, 1H, C*H*HCH=CH), 2.29–2.24 (m, 2H, CHClC*H*$_2$), 2.17 (dt, *J* = 13.2, 8.5 Hz, 1H, CHBrCH*H*), 1.75 (dqd, *J* = 14.0, 7.5, 3.9 Hz, 1H, C*H*HCH$_3$), 1.49 (dqn, *J* = 14.0, 7.4 Hz, 1H, CH*H*CH$_3$), 1.00 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 139.9 (CH$_2$CH=CH), 111.1 (CH$_2$CH=CH), 87.2 (CHEt), 86.1 (CHCH$_2$CH=CH), 82.3 (HC≡C), 80.1 (CHClCH$_2$CH), 79.9 (HC≡C), 78.9 (CHBrCH$_2$CH), 59.3 (CHCl), 47.3 (CHBr), 39.3 (CHBrCH$_2$), 38.1 (CHClCH$_2$), 34.4 (CH$_2$CH=CH), 25.4 (CH$_2$CH$_3$), 10.2 (CH$_2$CH$_3$); HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{15}H_{20}{}^{79}Br^{35}ClNaO_2$ 369.0227; found 369.0231, calcd for $C_{15}H_{20}{}^{79/81}Br^{37/35}ClNaO_2$ 371.0206; found 371.0203; $[\alpha]_D^{25}$ +19.2 (*c* = 0.125 in CHCl$_3$) {lit.[21a] $[\alpha]_D$ = +40.3 (*c* 1.03 CHCl$_3$)}.

Notoryne: Seoul Route. *General Procedures.* Proton (^{1}H) and carbon (^{13}C) NMR spectra were obtained on a JEOL JNM-LA300 (300/75 MHz), Bruker AV 400 (400/100 MHz), Bruker AMX 500 (500/125 MHz), Bruker Avance 600 (600/150 MHz), or Bruker Avance 900 (900/225 MHz) spectrometer. Chemical shifts are reported in parts per million units with Me$_4$Si or CHCl$_3$ as the internal standard. All reactions were routinely carried out under an inert atmosphere of dry nitrogen or argon. Reactions were checked by thin layer chromatography (Kieselgel 60 F254, Merck). Spots were detected by viewing under a UV light and by colorizing with charring after immersion in a *p*-anisaldehyde solution or phosphomolybdic acid solution. In an aqueous workup, all organic solutions were dried over anhydrous sodium sulfate and filtered prior to rotary evaporation at water pump pressure. The crude compounds were purified by column chromatography on a silica gel (Kieselgel 60, 70-230 mesh, Merck). Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. All solvents were purified and dried by standard techniques just before use. THF and Et$_2$O were freshly distilled from sodium and benzophenone. Methylene chloride, toluene, and benzene were purified by refluxing with CaH$_2$. Hexanes and ethyl acetate were purified by simple distillation.

*(2R,2′S,4S,4′S,5R,5′R)-5-(3-(Benzyloxy)propyl)-4′-bromo-4-chloro-5′-ethyloctahydro-2,2′-bifuran (**46**).* To a stirred mixture of bromo alcohol **39** (21.9 mg, 0.055 mmol), activated silica gel, and PhSeCl (21.13 mL, 0.005 M) was added anhydrous hexane (4 mL). After being stirred under an argon atmosphere at room temperature for 72 h, the mixture was filtered and concentrated in vacuo. To the resulting mixture was added CH$_3$CN/H$_2$O (9:1) solution (3 mL) to convert inseparable chloro ether **49** to hydroxy ether **44**. The resulting yellow solution was allowed to stand at room temperature for 24 h. The reaction mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with saturated brine, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 15/1) to afford tetrahydrofuran **46** (18.5 mg, 80%) as a colorless oil: R_f 0.67 (*n*-hexane/ethyl acetate, 4/1); $[\alpha]_D^{25}$ = +37.5 (*c* 0.805, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37–7.32 (m, 5H), 4.50 (s, 2 H), 4.21 (ddd, *J* = 6.5, 6.5, 7.1 Hz, 1H), 4.00–3.78 (m, 5H), 3.54–3.46 (m, 2H), 2.64 (ddd, *J* = 7.0, 7.0, 13.3 Hz, 1H), 2.28–2.24 (m, 2H), 2.20–2.13 (m, 1H), 1.83–1.67 (m, 4H), 1.65–1.45 (m, 2H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 138.5, 128.4, 127.6, 127.5, 87.12, 87.0, 79.9, 79.1, 72.9, 69.9, 59.9, 47.4, 39.3, 38.4, 30.5, 26.0 25.4 10.0 ; IR (neat) 2925, 2872, 1453, 1295, 1072, 923 cm^{-1}; HRMS (FAB-TOF) *m/z* [M + H]$^+$ calcd for $C_{20}H_{29}O_3{}^{79}Br^{35}Cl$ 431.0983; found 431.0982.

3-((2R,2′S,4S,4′S,5R,5′R)-4′-Bromo-4-chloro-5′-ethyloctahydro-[2,2′-bifuran]-5-yl)propan-1-ol. To a stirred solution of bistetrahydrofuran **46** (21.9 mg, 0.051 mmol) in THF (21.13 mL, 0.005 M) was added Pd(OH)$_2$ (4.38 mg, 20 wt % of Pd). The mixture was stirred under hydrogen atmosphere at room temperature for 1 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/ethyl acetate, 2/1) to afford the title alcohol (8.7 mg, 95%) as a colorless oil: R_f 0.33 (*n*-hexane/ethyl acetate, 2/1); $[\alpha]_D^{25}$= +48.4 (*c* 1.01, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.26 (ddd, *J* = 7.0, 7.0, 5.6 Hz, 1 H), 4.01–3.95 (m, 3H), 3.91 (ddd, *J* = 7.5, 7.5, 4.1 Hz, 1H), 3.90–3.84 (m, 1H), 3.73–3.63 (m, 2H), 2.66 (ddd, *J* = 6.6, 6.6, 13.6 Hz, 1H), 2.31 (ddd, *J* = 7.2, 7.2, 13.6 Hz, 1H), 2.23 (dddd, *J* = 13.6, 6.7, 4.5 Hz, 1H), 2.12 (ddd, *J* = 8.4, 8.4, 13.6 Hz, 1H), 1.83–1.66 (m, 4H), 1.60–1.46 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 87.3, 87.2, 80,0. 78.7, 62.5, 60.0, 47.2, 39.3, 37.7, 30.3, 29.4, 25.4, 9.97 ; IR (neat) 3408, 2936, 1648, 1295, 1060, 971, 923 cm^{-1}; HRMS (FAB-TOF) *m/z* [M + H]$^+$ calcd for $C_{13}H_{23}{}^{79}Br^{35}ClO_3$ 341.0514; found 341.0514.

*(2R,2′S,4S,4′S,5R,5′R)-5-Allyl-4′-bromo-4-chloro-5′-ethyloctahydro-2,2′-bifuran (**47**-Seoul).* To a solution of alcohol 3-((2*R*,2′*S*,4*S*,4′*S*,5*R*,5′*R*)-4′-bromo-4-chloro-5′-ethyloctahydro-[2,2′-bifuran]-5-yl)propan-1-ol (20.2 mg, 0.059 mmol) in dry THF (5.9 mL, 0.05 M) were added *o*-nitrophenylselenocyanide (66.98 mg, 0.045 mmol) and tri-*n*-octylphosphine (0.263 mL, tech. 90%, 0.045 mmol) at room temperature under N$_2$. The resulting mixture was stirred at room temperature for 10 min. The reaction mixture was cooled to 0 °C, and 30% H$_2$O$_2$ (0.1 mL) was added. The resulting mixture was stirred at the same temperature for 30 min, allowed to warm to room temperature, and stirred for an additional 24 h. The reaction mixture was neutralized with saturated aqueous NaHCO$_3$ (1 mL) and diluted with diethyl ether (4 mL). The layers were separated, and the aqueous layer was extracted with Et$_2$O (2 × 4 mL). The combined organic layers were washed with saturated brine, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 25/1) to afford terminal olefin **47**-Seoul (16.2 mg, 85%) as a colorless oil: R_f 0.61 (*n*-hexane/ethyl acetate, 1/1); $[\alpha]_D^{25}$= +66.8 (*c* 0.395, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.83 (dddd, *J* = 7.0, 7.0, 10.3, 17.2 Hz, 1H), 5.15–5.10 (m, 2H), 4.26–4.22 (m, 1H), 4.05–3.98 (m, 2H), 3.96 (ddd, *J* = 6.5, 6.5, 7.4 Hz, 1H), 3.91 (ddd, *J* = 4.0, 7.5, 7.5 Hz, 1H), 3.89–3.84 (m, 1H), 2.64 (ddd, *J* = 7.0, 7.0, 13.7 Hz, 1H), 2.39–2.30 (m, 2H), 2.25–2.23 (m, 2H), 2.17 (ddd, *J* = 8.6, 8.6, 13.4 Hz, 1H), 1.75 (ddddd, *J* = 4.0, 7.5, 7.5, 7.5, 14.7 Hz, 1H), 1.49 (ddddd, *J* = 7.4, 7.4, 7.4, 7.4, 14.6 Hz, 1H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 133.3, 118.0, 87.1, 86.4, 79.9, 78.9, 59.0, 47.3, 39.3, 38.1, 37.8, 25.4, 10.0; IR (neat) 2966, 2923, 1642, 1294, 1069, 920 cm^{-1}; HRMS (FAB-TOF) *m/z* [M + H]$^+$ calcd for $C_{13}H_{21}O_2ClBrNa$ 323.0408; found 323.0406.

*((Z)-5-((2R,2′S,4S,4′S,5R,5′R)-4′-Bromo-4-chloro-5′-ethyloctahydro-[2,2′-bifuran]-5-yl)pent-3-en-1-yn-1-yl)triisopropylsilane (**52**).* To a solution of terminal olefin **47**-Seoul (13.5 mg, 0.038 mmol) in dry benzene (3.64 mL) were added enyne **50** (52 mg, 0.083 mmol) in

benzene (1.0 mL) and Grubbs' catalyst **51** (15.0 mg, 0.053 mmol) in benzene (0.2 mL) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 70 °C for 1.5 h. Addition of enyne (17.3 mg, 0.062 mmol) in benzene (0.1 mL) and Grubbs' catalyst (4.2 mg, 0.0067 mmol) in benzene (0.1 mL) was repeated three times every 1.5 h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, toluene) to afford enyne as a 3:1 mixture (by ^{1}H NMR analysis) of TIPS-(*Z*)- and TIPS-(*E*)-enynes (17.2 mg, 82%) as a colorless oil: R_f 0.40 (*n*-hexane/ethyl acetate, 10/1) (for TIPS-(*Z*)-enyne **52**) $[\alpha]_D^{25}$= +33.4 (*c* 0.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (ddd, *J* = 7.5, 7.5, 10.9 Hz, 1 H), 5.67 (d, *J* = 10.9 Hz, 1 H), 4.26−4.22 (m, 1H), 4.13−4.08 (m, 2 H), 3.97−3.94 (m, 1H), 3.91 (ddd, *J* = 4.0, 7.5, 7.5, 1H), 3.86−3.82 (m, 1H), 2.72−2.57 (m, 3H), 2.24−2.22 (m, 2 H), 2.18 (ddd, 8.5, 8.5, 13.2 Hz, 1H), 1.75 (ddddd, *J* = 4.0, 7.4, 7.4, 7.4, 14.8 Hz, 1 H), 1.50 (ddddd, *J* = 7.4, 7.4, 7.4, 7.4, 14.8 Hz, 1H), 1.09−1.01 (m, 3H), 1.05 (s, 18H) 1.00 (t, *J* = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 138.6, 112.5, 103.1, 96.2, 87.1, 86.5, 80.2, 79.0, 59.3, 47.3, 39.3, 38.4, 34.7, 25.4, 18.7, 11.3, 10.0; IR (neat) 2942, 2146, 1260, 1071, 920 cm^{-1}; HRMS (FAB-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{41}{}^{79}Br^{35}ClO_2Si$ 503.1742; found 503.1768.

*(2S,2′R,4S,4′S,5R,5′R)-4-Bromo-4′-chloro-5-ethyl-5′-((Z)-pent-2-en-4-yn-1-yl)octahydro-2,2′-bifuran, (Z)-Notoryne ((Z)-**3a**).* To a cooled (0 °C) solution of (*Z*)-TIPS-enyne **52** (5.2 mg, 0.0103 mmol) in THF (0.2 mL) was added dropwise TBAF (0.02 mL, 1.0 M solution in THF, 0.0206 mmol). After the mixture was stirred at the same temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The resulting mixture was diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 7 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 4/1) to afford (*Z*)-notoryne (*Z*)-**3a** (3.4 mg, 94%) as a colorless oil: R_f 0.68 (*n*-hexane/ethyl acetate, 1/1); $[\alpha]_D^{25}$= +40.6 (*c* 0.16 $CHCl_3$) {lit.[21a] $[\alpha]_D$ = +40.3 (*c* 1.03 $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (dddd, *J* = 0.8, 7.5, 7.5, 10.9 Hz, 1H), 5.60 (dddd, *J* = 1.4, 1.4, 2.6, 10.9 Hz, 1H), 4.25 (ddd, *J* = 5.6, 7.1, 7.1 Hz, 1H), 4.12−4.06 (m, 2H), 3.97 (ddd, *J* = 5.6, 6.8, 8.2 Hz, 1H), 3.91 (ddd, *J* = 4.0, 7.6, 7.6 Hz, 1H), 3.86 (ddd, *J* = 7.3, 7.3, 8.7 Hz, 1H), 3.12 (d, *J* = 1.8 Hz, 1H), 2.70−2.55 (m, 3H), 2.32−2.23 (m, 2H), 2.17 (ddd, *J* = 8.4, 8.4, 13.2 Hz, 1H), 1.75 (ddddd, *J* = 3.7, 7.5, 7.5, 7.5, 14.3 Hz, 1H), 1.56−1.44 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 139.9, 111.1, 87.2, 86.2, 82.3, 80.1, 80.0, 79.0, 59.3, 47.3, 39.4, 38.2, 34.5, 25.5, 10.0; IR (neat) 3293, 2964, 1733, 1712, 1290, 1073, 967, 923 cm^{-1}; HRMS (EI) *m*/*z* $[M - C_2H_5]^+$ calcd for $C_{10}H_{15}{}^{79}Br^{35}ClO_2$ 280.9938; found 280.9935.

*(2S,2′R,4S,4′S,5R,5′R)-4-Bromo-4′-chloro-5-ethyl-5′-((E)-pent-2-en-4-yn-1-yl)octahydro-2,2′-bifuran, (E)-Notoryne ((E)-**3a**).* To a solution of terminal olefin **47**-Seoul (7.7 mg, 0.024 mmol) in dry CH_2Cl_2 (0.47 mL, 0.05 M) were added crotonaldehyde (0.015 mL, 0.19 mmol) and Grubbs' catalyst **29** (2.04 mg, 0.0024 mmol) at room temperature. After the mixture was stirred at 40 °C for 1.5 h, the reaction was quenched with DMSO (0.02 mL). The resulting mixture was stirred at room temperature for 12 h and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 6/1) to afford (*E*)-4-((2*R*,2′*S*,4*S*,4′*S*,5*R*,5′*R*)-4′-bromo-4-chloro-5′-ethyloctahydro-[2,2′-bifuran]-5-yl)but-2-enal (7.3 mg, 87%) as a colorless oil: R_f 0.37 (*n*-hexane/ethyl acetate, 4/1). To a cooled (−78 °C) solution of LDA (0.42 mL, 0.5 M solution in THF, 0.21 mmol) was added dropwise $TMSCH_2N_2$ (0.105 mL, 2.0 M solution in Et_2O, 0.021 mmol) under argon atmosphere. After the mixture was stirred at −78 °C for 30 min, (*E*)-4-((2*R*,2′*S*,4*S*,4′*S*,5*R*,5′*R*)-4′-bromo-4-chloro-5′-ethyloctahydro-[2,2′-bifuran]-5-yl)but-2-enal (7.3 mg, 0.021 mmol) in THF (0.42 mL, 0.05 M) was added dropwise at −78 °C. After the reaction mixture was stirred at −78 °C for 1 h, and then at 0 °C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 2 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 4/1) to afford (*E*)-notoryne (*E*)-**3a** (6.4 mg, 88%) as a colorless oil: R_f 0.69 (*n*-hexane/ethyl acetate, 4/1); $[\alpha]_D^{25}$ = +47.6 (*c* 0.225, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (ddd, *J* = 7.2, 7.2, 16.0 Hz, 1H), 5.57 (dd, *J* = 1.8, 16.0 Hz, 1H), 4.22 (ddd, *J* = 5.6, 7.0. 7.0 Hz, 1 H), 4.03−3.94 (m, 3H), 3.93−3.84 (m, 2H), 2.83 (d, *J* = 2 Hz, 1H), 2.66 (ddd, *J* = 13.2, 7.0, 7.0 Hz, 1H), 2.46 (dddd, *J* = 12.9, 6.5, 5.4, 1.6 Hz, 1H), 2.40−2.33 (m, 1H), 2.32−2.20 (m, 2H), 2.14 (dt, *J* = 13.3, 8.4 Hz, 1H), 1.75 (ddddd, *J* = 14.1, 7.5, 7.5, 7.5, 3.8 Hz, 1H), 1.55−1.44 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 140.7, 111.8, 87.3, 85.7, 81.9, 80.0, 78.8, one peak buried under $CDCl_3$ peak by HSQC, 58.7, 47.3, 39.4, 37.9, 36.6, 25.5, 10.0; IR (neat) 3294, 2963, 1731, 1712, 1295, 1072, 959, 925 cm^{-1}; HRMS (EI) *m*/*z* $[M - C_2H_5]^+$ calcd for $C_{10}H_{15}{}^{79}Br^{35}ClO_2$ 280.9938; found 280.9944.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02975.

Tables of comparative NMR data (PDF)

Computational methods, benchmarking, and calculated NMR parameters for all structures (PDF)

Copies of NMR spectra (PDF)

Notoryne xyz files (ZIP)

Chloroenyne xyz files (ZIP)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: deukjoon@snu.ac.kr.
*E-mail: jonathan.burton@chem.ox.ac.uk.
*E-mail: robert.paton@colostate.edu.

ORCID

Deukjoon Kim: 0000-0003-4079-8734
Robert S. Paton: 0000-0002-0104-4166

Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to the memory of Erin D. Shepherd—a brilliant chemist and an amazing individual.

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