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Epimeric Face-Selective Oxidations and Diastereodivergent Transannular Oxonium Ion Formation Fragmentations: Computational Modeling and Total Syntheses of 12-Epoxyobtusallene IV, 12-Epoxyobtusallene II, Obtusallene X, Marilzabicycloallene C, and Marilzabicycloallene D

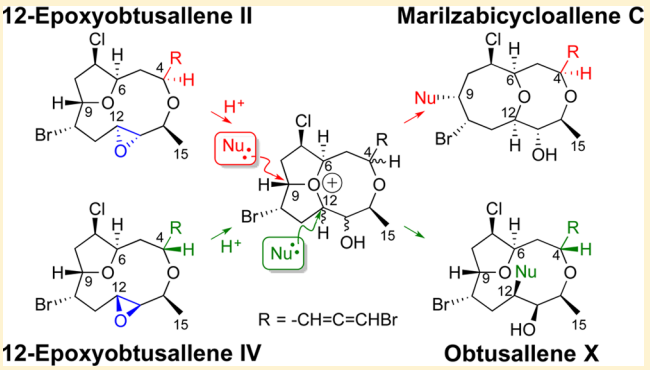
James Clarke,[†] Karl J. Bonney,[†] Muhammad Yaqoob,[†] Savade Solanki,[†] Henry S. Rzepa,[†] Andrew J. P. White,[†] David S. Millan,[‡] and D. Christopher Braddock*[,†]

[†]Department of Chemistry, Imperial College London, South Kensington, London, SW7 2AZ, U.K.

[‡]Sandwich Laboratories, Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ, U.K.

Supporting Information

ABSTRACT: The total syntheses of 12-epoxyobtusallene IV, 12-epoxyobtusallene II, obtusallene X, marilzabicycloallene C, and marilzabicycloallene D as halogenated C_{15}-acetogenin 12-membered bicyclic and tricyclic ether bromoallene-containing marine metabolites from *Laurencia* species are described. Two enantiomerically pure C_4-epimeric dioxabicyclo[8.2.1]-tridecenes were synthesized by *E*-selective ring-closing metathesis where their absolute stereochemistry was previously set via catalytic asymmetric homoallylic epoxidation and elaborated via regioselective epoxide-ring opening and diastereoselective bromoetherification. Epimeric face-selective oxidation of their $\Delta^{12,13}$ olefins followed by bromoallene installation allowed access to the oppositely configured 12,13-epoxides of 12-epoxyobtusallene II and 12-epoxyobtusallene IV. Subsequent exploration of their putative biomimetic oxonium ion formation−fragmentations reactions revealed diastereodivergent pathways giving marilzabicycloallene C and obtusallene X, respectively. The original configurations of the substrates evidently control oxonium ion formation and their subsequent preferred mode of fragmentation by nucleophilic attack at C_9 or C_{12}. Quantum modeling of this stereoselectivity at the ωB97X-D/Def2-TZVPPD/SCRF = methanol level revealed that in addition to direction resulting from hydrogen bonding, the dipole moment of the ion-pair transition state is an important factor. Marilzabicycloallene D as a pentahalogenated 12-membered bicyclic ether bromoallene was synthesized by a face-selective chloronium ion initiated oxonium ion formation−fragmentation process followed by subsequent bromoallene installation.



INTRODUCTION

Since the first report in the 1960s,[1] red algae of the family Rhodomelaceae, in particular of the genus *Laurencia*, have been found to give rise to fascinating structurally diverse non-terpenoid C_{15}-acetogenin (ACG) metabolites as halogenated monocyclic, bicyclic, and tricyclic ring ethers[2,3] where these metabolites can be usefully classified on the basis of the largest ether ring size present.[4] These complex structures have attracted much attention as synthetic target molecules,[5,6] and recent further efforts have also been directed at further elucidating[7] and unifying[8] their biosynthetic origins. The largest reported ether ring sizes in these C_{15}-ACGs are those compounds with 12-membered ether rings: the obtusallenes[9−15] and the more recently discovered marilzabicycloallenes.[16]

Despite much synthetic effort in the wider family, the total synthesis of any of these 12-membered cyclic ethers remains unreported. Obtusallene II (**1**) (Figure 1A) is considered to be the biogenetic precursor to the other obtusallenes and is, therefore, an interesting synthetic target.[17] What is more, obtusallenes II and IV (**2**), related as C_4-epimers (C_{15}-ACG numbering) and as enantiomeric *R* and *S* bromoallenes, respectively, have been hypothesized as the biogenetic precursors to marilzabicycloallenes A−D (**3**−**6**) (Figure 1A) via 12*S*,13*S*-configured onium ions **A** (X = OH, Cl; R = −CH=C=CHBr) and, hence, 12*R*-configured oxonium ions **B** in transannular oxonium ion formation−fragmentations with attack of the nucleophile at C_9 (Figure 1B).[16,18] Recently reported[15] 12*R*,13*R*-configured coisolates 12-epoxyobtusallene IV (**7**) and obtusallene X (**8**) are therefore evidently related metabolites (Figure 1C). Epoxide **7** is clearly related to olefin **2**

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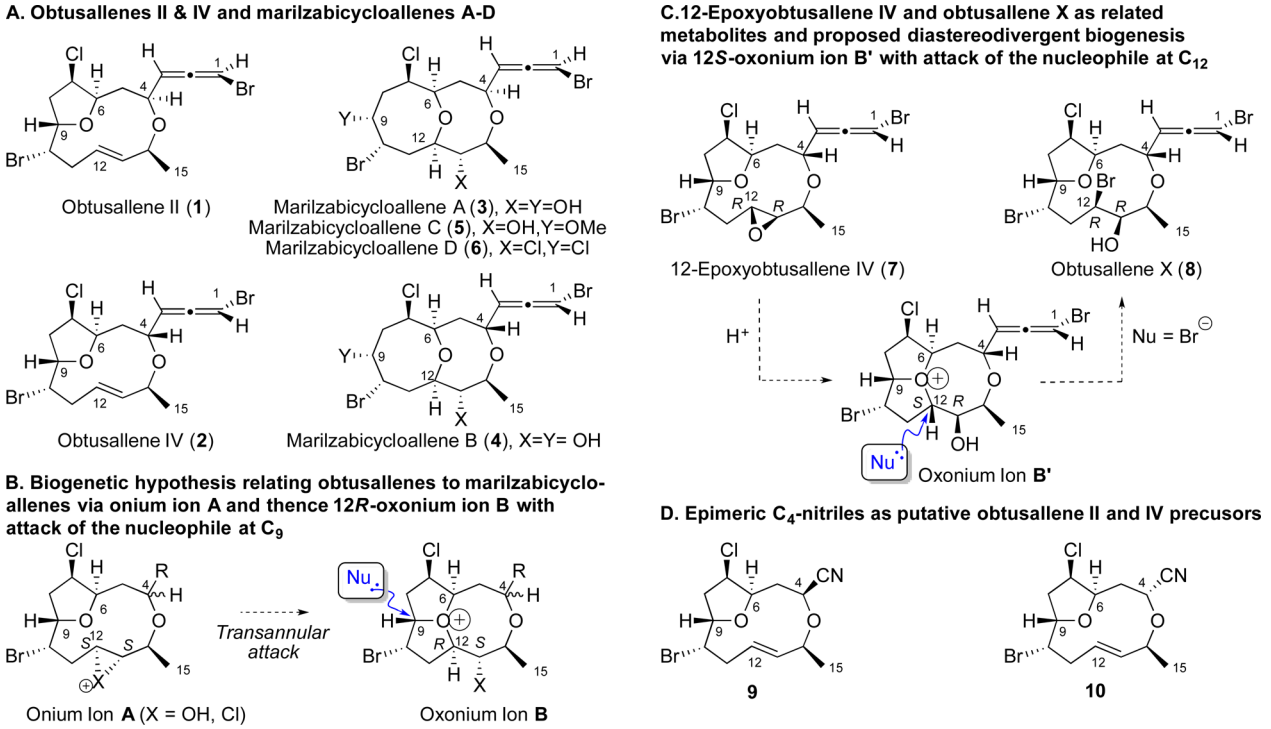


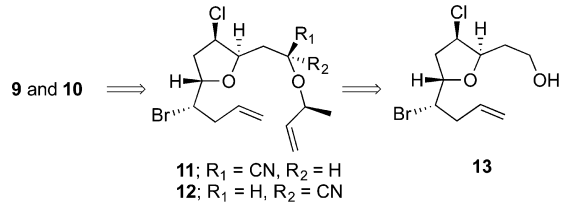
Figure 1. Structures and putative biogeneses of obtusallene and marilzabicycloallene C_{15}-ACGs.

by epoxidation of the *Re* face of the macrocyclic olefin.[19] On the basis of their absolute configurations at C_{12} and C_{13}, we propose that obtusallene X (**8**) arises biogenetically from 12-epoxyobtusallene IV (**7**) via diastereomeric 12*S*-oxonium ion **B′** in a transannular oxonium ion formation−fragmentation with a diastereodivergent nucleophilic attack at C_{12}. The signature overall double-stereochemical inversion at this position implicates the intermediacy of the oxonium ion. It is interesting to speculate whether these different oxonium ion formation−fragmentation metabolites are formed with inherent selectivity because they arise from different starting diastereomeric forms or whether the compounds are simply representative isolates of all possible fragmentations of such oxonium ions. Herein, in an experimental exploration of the above, we report on an asymmetric strategy for the synthesis of two bicyclic 12-membered ring ethers as C_4-epimeric nitrile epimers **9** and **10** (Figure 1, D) as putative synthetic precursors of obtusallene II and obtusallene IV. We demonstrate that the latter can serve as an advanced precursor for the synthesis of 12-epoxyobtusallene IV (**7**), thereby achieving the first total synthesis of a C_{15}-ACG with a 12-membered ether ring from *Laurencia* species. Moreover, we demonstrate face-selective oxidations of nitrile epimers **9** and **10**, thereby enabling remarkably selective and high-yielding diastereodivergent transannular oxonium ion formation−fragmentations for the total synthesis of obtusallene X (**8**) via 12*S*-oxonium ions of the type **B′** and marilzabicycloallenes C (**5**) and D (**6**) via 12*S*,13*S*-onium ions **A** (X = OH, Cl, respectively) and thus 12*R*-oxonium ions of type **B**.

RESULTS AND DISCUSSION

Single enantiomer nitriles **9** and **10** were envisaged to be formed from epimeric acyclic dienes **11** and **12** via ring-closing metathesis, which in turn were expected to be accessible from bromochlorotetrahydrofuran **13** as a common intermediate (Scheme 1). We have previously reported the synthesis of (±)-**13**[18] which we have now adapted to an asymmetric

Scheme 1. Retrosynthesis of Nitriles 9 and 10



method utilizing Yamamoto's catalytic enantioselective homoallylic epoxidation method.[20] Accordingly, known enediyne **14**, prepared as previously described,[18] underwent transfer hydrogenation to (*Z*,*Z*)-doubly skipped triene **15** using a zinc−copper couple in a mixed solvent system of 2-propanol and water, avoiding over-reduction of the terminal alkene under these conditions (Scheme 2). Directed, catalytic asymmetric epoxidation of homoallylic alcohol **15** using Yamamoto's conditions and ligand **17** gave the desired epoxide **16**. The er of epoxide **16** was determined by conversion to its *O*-trityl derivative **18** followed by chiral HPLC analysis revealing an er of 91:9 (see the Supporting Information) and where the absolute configuration of the major enantiomer was assigned by anology to Yamamoto's work. The subsequent steps of regioselective epoxide ring opening (giving **19**), silyl protection of the primary alcohol (giving **20**), diastereoselective bromoetherification (giving **21**), and deprotection to bromochlorotetrahydrofuran **13** employed the previously reported conditions for the preparation of (±)-**13**[18] with minor modifications. With alcohol **13** in hand, it was oxidized to the corresponding aldehyde followed by immediate acetalization with the single enantiomer (*S*)-but-3-yn-2-ol under acidic catalysis to give acetal **22**. In this reaction, the addition of

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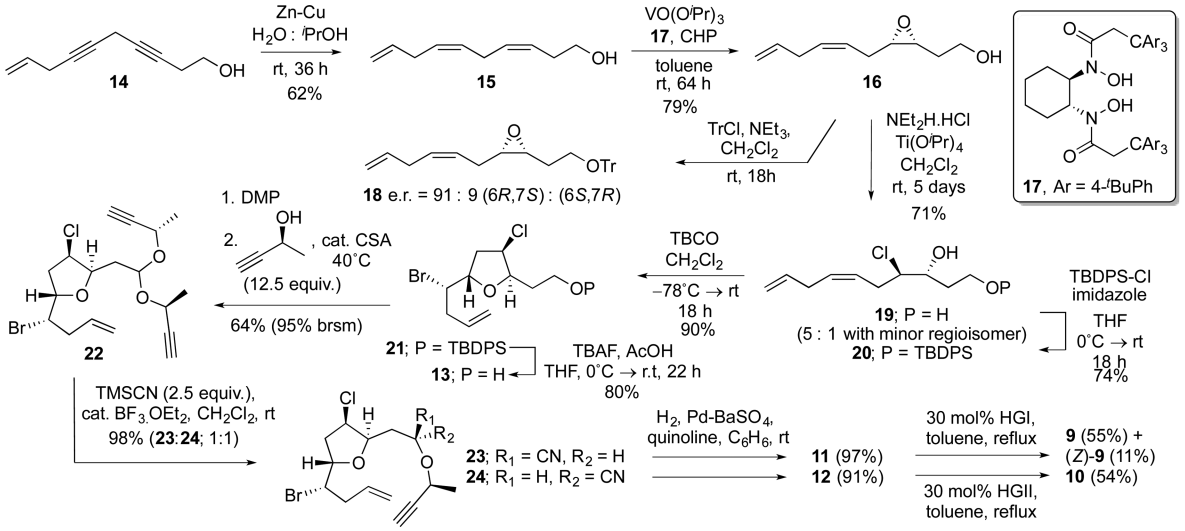
Scheme 2. Asymmetric Synthesis of Nitriles 9 and 10



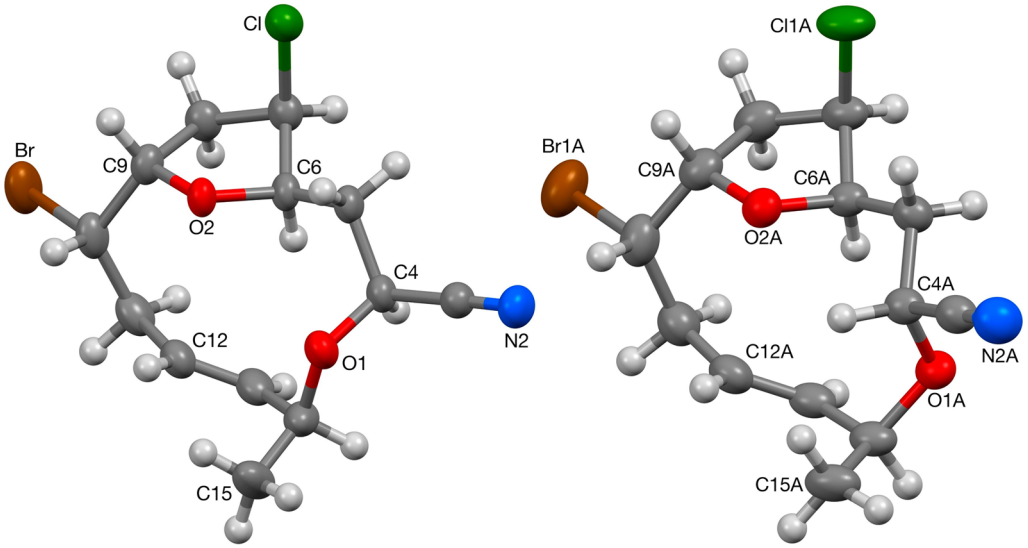


Figure 2. Crystal structure of **9** (50% probability ellipsoids) (left). Structure of one of the two independent molecules present in the crystal of **10** (50% probability ellipsoids) (right).

sodium borohydride as part of the workup procedure allowed recycling of unreacted material by recovery of alcohol **13**. Subsequent cyanation of the acetal with trimethylsilyl cyanide as catalyzed by boron trifluoride etherate[21] gave the separable cyanoethers **23** and **24** in excellent yield with essentially perfect stereodivergence (1:1 ratio), presumably via the intermediacy of a planar oxonium ion. Hydrogenation of each individual epimer gave acyclic dienes **11** and **12** in high yield. With these acyclic dienes in hand, we explored the proposed ring-closing metatheses to form *E*-macrocyclic epimers **9** and **10**. After much experimentation, and much to our delight, ring-closing metathesis using Hoveyda–Grubbs ruthenium benzylidene precatalyst[22a] for diene **11** and second-generation Hoveyda–Grubbs precatalyst[22b] for diene **12** in rigorously dry toluene at high dilution provided each of the desired *E*-macrocyclic nitrile epimers **9** and **10**, respectively, as the major product in good yields. In this chemistry, the incorporation of enantiomerically pure (*S*)-but-3-yn-2-ol into enantiomerically enriched (91:9) aldehyde **13** resulted in the formation of a minor diastereoisomer. The minor diastereoisomer was carried through in each subsequent step to acyclic dienes **11** and **12** as an inseparable entity. After RCM, both macrocycles **9** and **10** were purified as single diastereoisomers, meaning that these compounds are enantiomerically pure.

Single crystal X-ray crystallography of each epimer **9** and **10** unambiguously established their structures confirming all relative and absolute stereochemistries (Figure 2). These X-ray crystal structures were compared with the previously obtained X-ray structures of obtusallenes II (**1**)[11] and IV (**2**),[13] respectively. This comparison established three important details. First, the epimeric macrocycles of **9** and **10** map perfectly onto the macrocyclic solid-state structures of **1** and **2**, respectively (see the Supporting Information), showing that these compounds are excellent model compounds of the natural products. Second, in the solid state, each compound exposes its *Re* face of the C_{12}–C_{13} alkene where the *Si* face is blocked by the tetrahydrofuran. Thus, it is to be expected that 12*R*,13*R*-configured 12-epoxyobtusallene IV (**7**) could arise biogenetically by epoxidation of the exposed *Re* face of obtusallene IV (**2**). However, the proposed obtusallene-to-

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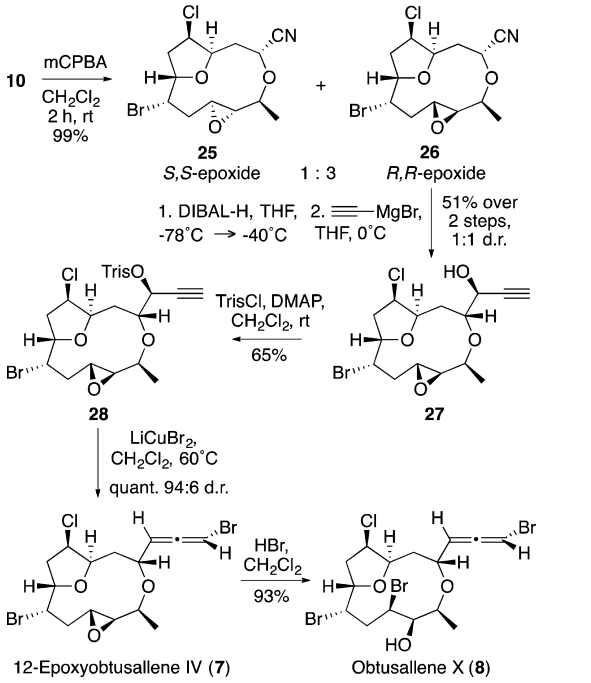
marilzabicycloallene interconversions require oxidation of the *Si* face of the olefins via 12*S*,13*S*-configured onium ions **A** (cf. Figure 1B). This apparent incongruity can be rationalized by noting that in solution obtusallenes II and IV have been shown to exist as interconverting alkene conformers, thereby exposing both *Re* and *Si* faces of the alkene.[12,14] This conformational interconversion manifests itself by broadened NMR signals for these compounds at room temperature. Epimeric nitriles **9** and **10** also display broadened NMR signals (see the Supporting Information) indicating that they behave in the same manner and are expected to expose both *Re* and *Si* faces of their alkenes in solution. As a third detail, we note that the X-ray crystal structures reveal that the two epimeric nitriles **9** and **10** have *different* local conformations around the $C_5-C_4-O-C_{14}$ torsion angle such that the nitrile group bisects the hydrogen atoms on C_5 in each case. Herein must lie the origin of their epimeric face-selective oxidative behavior (vide infra).

With epimeric nitriles **9** and **10** in hand, we planned to reduce each one to the corresponding aldehyde and then use well-established procedures[23] to install bromoallene functionalities leading to obtusallene II (**1**) and IV (**2**), respectively. Remarkably, there are no examples in the literature of the partial reduction of (allyloxy)acetonitriles, and DIBAL-H reduction of either nitrile proved to be unexpectedly troublesome and only minor quantities (ca. 10%) of the expected aldehydes could be obtained.[24] The use of model substrates[25] established that the allylic ether functional group in each is problematic, where the corresponding saturated or epoxidized model was converted to its aldehyde using DIBAL-H without incident. Accordingly, the attempted direct reduction of nitrile allylic ethers **9** and **10** with DIBAL-H was abandoned.

Epoxidation of nitrile **10** was then explored with a view toward accessing 12*R*,13*R*-configured 12-epoxyobtusallene IV (**7**) as a known natural product by subsequent selective nitrile reduction and installation of the requisite bromoallene. In the event, epoxidation of unsaturated nitrile **10** provided epoxides **25** and **26** in quantitative isolated yield in a 1:3 ratio, where the major product is the 12*R*,13*R*-configured epoxide (Scheme 3). As per the discussion above, this demonstrates that both *Re* and *Si* faces of the alkene in epimer **10** are accessible in solution, and for this epimer, the *Re* face is evidently subject to faster oxidation. Pleasingly, subsequent DIBAL-H reduction of epoxy nitrile **26** now proceeded smoothly, corroborating our findings from the earlier model studies. Bromoallene installation[23] was subsequently achieved via magnesium acetylide addition to the newly formed aldehyde to provide separable epimeric alcohols. The required alcohol **27** was converted to trisylate **28**, and copper-mediated S_N2' bromide incorporation provided 12-epoxyobtusallene IV (**7**).[15,26] To test the proposed relationship of 12-epoxyobtusallene IV (**7**) to obtusallene X (**8**) (cf. Figure 1C) it was treated with HBr in dichloromethane solution. Much to our delight, obtusallene X (**8**)[15] was produced in essentially quantitative yield.[27] This experiment thereby supports its probable biogenesis via transannular formation of 12*S*-oxonium ion **B′** and reinversion of configuration by attack of the nucleophile at C_{12}. We recognized also that deoxygenation of 12-epoxyobtusallene IV (**7**) would provide synthetic access to obtusallene IV (**2**). However, despite successful deoxygenation in model studies with a representative chlorobromoepoxide, attempted deoxygenation of 12-epoxyobtusallene IV (**7**) under the same conditions was unsuccessful.[28] Finally, the formation of 12*S*,13*S*-epoxide **25** in the epoxidation of alkene **10** also has biogenetic significance. Marilzabicycloallene B (**4**) is proposed to arise from the 12*S*,13*S*-epoxide of obtusallene IV via oxonium ion **B** (cf. Figure 1B, X = OH, R = 4*R*-(*S*)-CH═C═CHBr).[16] This is the first experimental evidence that such an 12*S*,13*S*-epoxide can be accessed in the obtusallene IV skeleta.[29] However, we elected to explore the obtusallene-to-marilzabicycloallene rearrangements in the obtusallene II manifold instead (vide infra).

Scheme 3. Synthesis of 12-Epoxyobtusallene IV and Obtusallene X



In contrast to the behavior of nitrile **10**, epoxidation of epimeric nitrile **9** under the same conditions gave 12*S*,13*S*-epoxide **29** as effectively the only component in essentially quantitative yield (Scheme 4). Evidently, for this epimer, *Si* face oxidation is now favored. We suggest that for this epimer 12*S*,13*S*-epoxide formation results in a compound with minimal transannular strain. With a 12*S*,13*S*-epoxide of the obtusallene II framework in hand, we elected to explore the proposed obtusallene-to-marilzabicycloallene rearrangements (cf. Figure 1B). Much to our delight, on treatment with catalytic acid in methanolic solvent, 12*S*,13*S*-epoxide **29** was found to rearrange smoothly to bicyclo[5.5.1]tridecane nitrile **30** in essentially quantitative yield, thus validating the proposed transannular oxonium ion formation−fragmentation as mediated by a protonated epoxide where 12*R*-oxonium ion **B** (cf. Figure 1B, X = OH, R = 4*S*-CN) undergoes preferential nucleophilic attack (NuH = MeOH) at C_9. Alternatively, DIBAL-H reduction of epoxy nitrile **29** followed by magnesium acetylide addition gave alcohol **31** along with its inseparable minor epimer, and bromoallene installation to give epoxide **32** was subsequently completed using an adaption of the established methods.[23] To our further delight, fully elaborated bromoallene epoxide **32** was also found to rearrange cleanly with catalytic acid in methanolic solvent to provide marilzabicycloallene C (**5**)[16,26] in essentially quantitative yield. Not only does this demonstrate the further validity of the proposed obtusallene-to-marilzabicycloallene biogenetic pathway (cf. Figure 1B, X = OH, R = 4*S*-(*R*)-CH═C═CHBr), it also implicates epoxide

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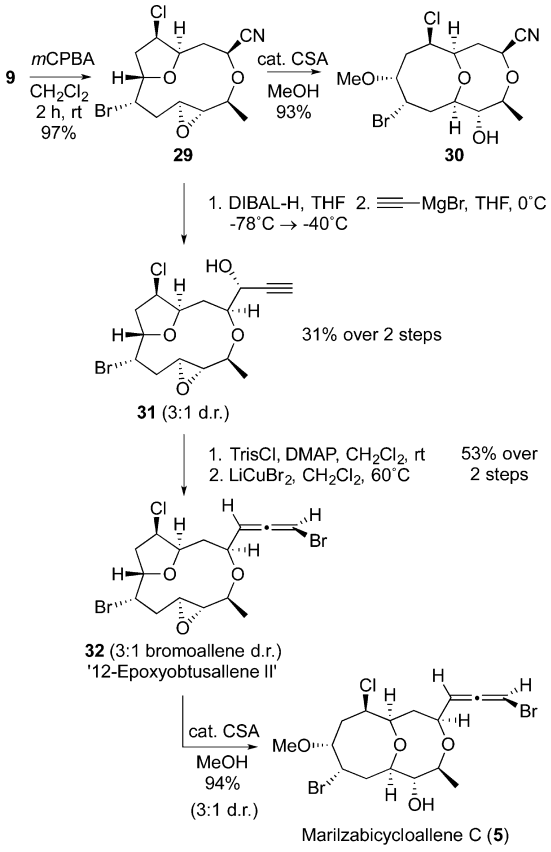
Scheme 4. Synthesis of Marilzabicycloallene C



32, which we name 12-epoxyobtusallene II, as a yet to be discovered natural product from *Laurencia* species.[30]

The experimentally demonstrated diastereodivergent selectivity observed for the position of nucleophilic attack in the above studies is intriguing and requires comment. There is obviously the initial question of epimeric face selectivity in the epoxidation of alkenes **9** and **10**, but once in place the configuration of any 12*S*,13*S* or 12*R*,13*R* epoxide necessarily control the configurations of the resulting respective oxonium ion 12*R*-**B** versus 12*S*-**B′** by stereospecific transannular epoxide ring opening.[31] For each trisubstituted oxonium ion[32] there are actually three possible positions of nucleophilic attack, C_6,[33] C_9, and C_{12} ,where the nucleophile must approach with the normal backside stereoelectronic constraints of S_N2-type substitution. For both oxonium ions **B** and **B′** inspection of the structures reveals that each one of these carbons is classified as secondary. Each one is also flanked by one methylene unit (C_5, C_8, and C_{11}, respectively) and one secondary carbon each bearing a heteroatom (C_7-Cl, C_{10}-Br, and C_{13}-OH). We chose to focus on oxonium ion 12*R*-**B** for a more detailed computational analysis of the possible factors controlling the regiochemical outcome.

Three different types of model were constructed, initially for X = OH, R = 4*S*-Me. The first involved inspecting the wave function of the reactant oxonium cation 12*R*-**B** itself. The conformational space of the larger 8-ring is complex; a partial exploration of this space showed the conformation of the reasonably related oxonium cation[34] for which a crystal structure is known, which coincided with the lowest energy conformation computed for 12*R*-**B** at the ωB97X-D/Def2-TZVPPD level using a self-consistent reaction field solvent model (cpcm, solvent = methanol). Both this conformation and computational method were used for the subsequent studies.[35] We also included in the study a reactant-based model as both a positively charged oxonium cation and with a model non-interacting counterion BF_4^- as a neutral ion pair.

NBO (natural bond orbital) localization of the wave function for both models allowed the relative energies of the three C−O σ* accepting orbitals to be compared (Figure 3). For the ion pair, the NBO energies increased in the order C_9 0.230 > C_{12} 0.241 > C_6 0.245 hartree, indicating the optimal position for nucleophilic attack is predicted by this approach to be at the best electron-accepting position, C_9. The corresponding energies for 12*R*-B as just a cation were C_9 0.198 > C_6 0.207 > C_{12} 0.225 hartree, again predicting nucleophilic attack at the C_9−O bond and coinciding with the actual outcome.

The next evolution of our reaction model was to compute the properties of transition states for reactions of a variety of nucleophiles interacting directly with the oxonium cation 12*R*-**B** (R = 4*S*-Me). With X = OH, we used clusters of both one MeOH and two MeOH, the latter interacting via hydrogen bonding and also anionic MeO^- and Br^- nucleophiles as ion pairs (Table 1).[36] In every case, the transition state of lowest free energy corresponded to attack at C_{12}, promoted by the directing influence of the adjacent hydroxyl group at C_{13}. When X = Cl, this effect was attenuated, and now the lowest free energy transition state emerged at C_6. Finally, we added a noninteracting counterion BF_4^- to the transition-state model, locating the counterion in the same pocket for all three transition states. Now, C_9 and C_6 emerged as both lower than C_{12}. The promotion of the C_9 position was because the dipole moment of this transition state was significantly lower than the

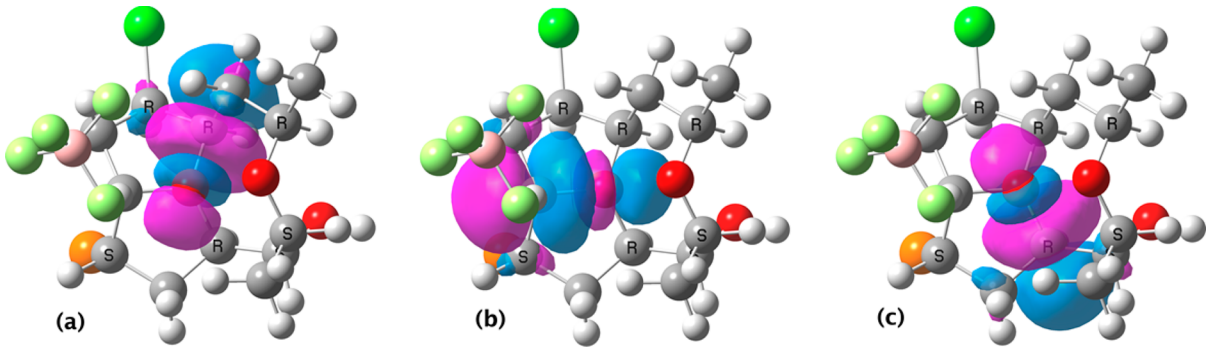


Figure 3. Representation of the NBOs computed for the C−O σ* accepting orbitals for the 12*R*-**B** ion pair using BF_4^- as the counterion for (a) C_6, (b) C_9, and (c) C_{12}. Interactive versions of these figures are available.[36]

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Table 1. Computed Reaction Free Energy Barriers (kcal/mol^{-1}) for Obtusallene-Derived Oxonium and Chloronium Cations and Ion Pairs[a]

nucleophile	@C6	@C9	@C12
	Nucleophilic Attack on Oxonium Cation 12*R*-**B**		
MeOH	21.9,[c] bfd2[b]	23.2, bjqc	21.3, bfcr
		32.1,[d] bfcs	0.0, bj96;[e] 2.0, bj99[f]
2MeOH		26.4, bjnj	18.8, bjmw
			0.0, bnhz[e]
Br^-	18.0 (16.1),[g] bfcj	17.5 (14.5),[g] bfck	14.7 (11.1),[g] bfcm
			0.0, bnrd[e]
MeO^-	21.1 (15.5),[g] bfcn	18.6 (15.5),[g] bfcp	10.9 (11.0),[g] bfcq
			0.0, bnh6[e]
	Nucleophilic Attack on Chloronium Cation		
MeOH	16.8, bj8z	17.9, bj95	18.4, bj82
			0.0, bn5n[e]
	Nucleophilic Attack on Oxonium Cation/BF_4^- Model Ion Pair		
MeOH	20.0 (24.5),[g] bksg	20.3 (15.0),[g] bj97	20.5 (26.5),[g] bj98
			0.0, bnhq[e]

[a]See ref 36 for an interactive FAIR data version of this table. [b]Digital object identifier (DOI) for managed research data, resolved as, e.g. http://doi.org/bfd2. See also ref 35. [c]Activation free energies as $\Delta G^{\ddagger}_{298}$ for a ωB97XD/Def2-TZVPPD/SCRF = methanol model. [d]Alternative conformation for 8-membered ring. [e]Reactant. [f]Product. [g]Dipole moment, D.

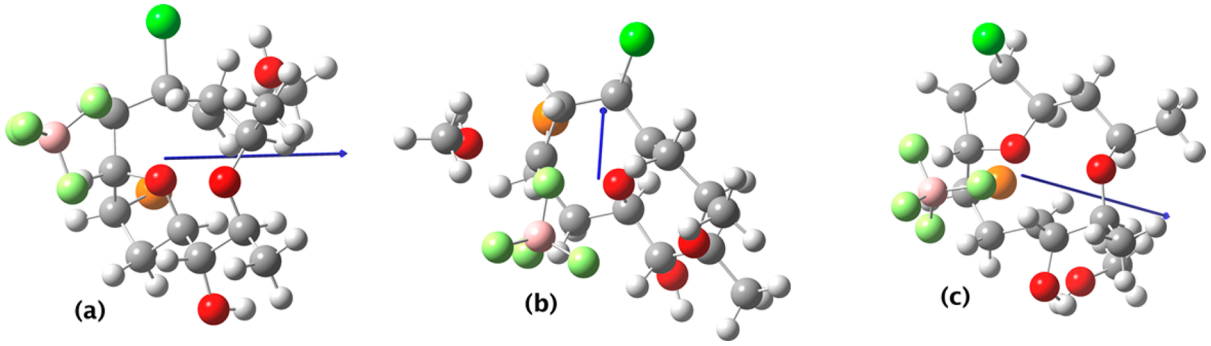

Figure 4. Computed dipole moment vectors for the computed transition states for nucleophilic attack by methanol at the (a) C_6, (b) C_9, and (c) C_{12} positions of 12*R*-**B**.

other two isomers, resulting in stabilization from lower charge separation (Figure 4).

This was also true for the other two ion-pair models using anionic MeO^- and Br^- as nucleophiles, where the transition state with the lowest dipole moment/charge separation was also the lowest in free energy.

Two principle conclusions can be drawn from these results. First, this model is an unusually complex one due to factors such as the conformational flexibility of the larger 8-membered ring, the hydrogen-bonding interactions possible with the incoming nucleophile, and the possibility of positional diversity of the counterion associated with the oxonium cation. A complete stochastic nondynamic exploration of each of these variables is not possible for a system of this size, and we cannot claim to have reduced each of these to the global lowest energy structures. Nevertheless, one interesting conclusion that can be drawn is that the reaction of an ion pair with a nucleophile may be strongly influenced by the charge-separation/dipole moment of the resulting highly ionic transition states. This is in addition to the more obvious structural features such as steric interactions or local hydrogen bonding. Thus, the regiochemical outcome of such reactions may well be determined by a complex blend of these various effects, with perhaps no one effect dominating. Certainly, the simpler analysis based purely on just the properties of the reactant oxonium cation should be considered as far too simplistic, even though in this specific case it predicts the "correct" outcome, for probably the wrong reasons.

Having demonstrated that a group VI onium ion from a preformed epoxide can drive these transannular rearrangements, we undertook to attempt the use of a group VII onium ion generated *directly from* olefin **9** to do so. With marilzabicycloallene D (**6**) as the intended target, we were delighted to find that the combination of catalytic quantities of TMG[37] and stoichiometric quantities of NCS and TMSCl[38] in dichloromethane effected the transformation of olefin **9** into trichlorobromide bicyclo[5.5.1]tridecane **33** in excellent isolated yield (Scheme 5). Evidently, the *Si* face of epimer **9** is again subject to kinetically controlled oxidation, now as the 12*S*,13*S*-chloronium ion **A** (cf. Figure 1B, X = Cl, R = 4*S*-CN), followed by stereospecific transannular oxonium ion 12*R*-**B** formation by chloronium ion ring-opening. As per the previously observed fragmentations of 12*R*-**B** oxonium ions (vide supra), the same remarkable selectivity for the C_9-position is observed, presumably for the same reasons, but now with chloride anion functioning as the nucleophile. Subsequent DIBAL-H reduction of the nitrile, which proceeded without complication, and installation of the bromoallene[23] via alcohol **34** provided marilzabicycloallene D (**6**).[16,26]

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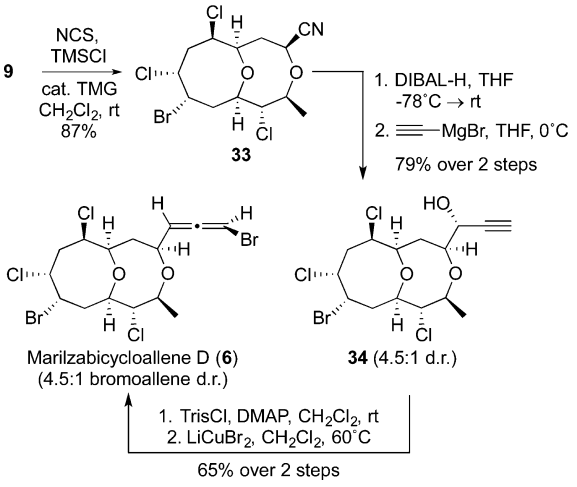
Scheme 5. Synthesis of Marilzabicycloallene D



Thus, we have accomplished the total synthesis of 12-epoxyobtusallene IV (**7**) and 12-epoxyobtusallene II (**32**) (as a yet to be discovered natural product from *Laurencia* species) as the first C_{15}-ACGs with 12-membered ether rings. To the best of our knowledge, these also constitute the first total syntheses of any tricyclic ethers of this class of C_{15}-ACGs. We also report the total synthesis of obtusallene X (**8**), marilzabicycloallene C (**5**), and marilzabicyclocallene D (**6**) via consideration, proposition, and exemplification of their biogeneses via oxonium ion formation−fragmentation reactions. These studies show that these metabolites are not simply representative isolates of all possible formation−fragmentations of such oxonium ions but rather are produced by inherently selective pathways. A density functional mechanistic exploration of one of these pathways involving ring opening of an intermediate ion-pair complex suggests that a major factor in the selectivity may be the dipole moment magnitude at the transition state.

EXPERIMENTAL SECTION

General Information. Quinoline was dried over Na_2SO_4 and distilled from and stored over Zn dust. Triethylamine was dried over $CaSO_4$ prior to distillation under nitrogen and was subsequently stored over 4 Å molecular sieves. TBCO was prepared according to the method of Matveeva.[39] Asymmetric epoxidation ligand **17** was prepared according to the method of Yamamoto.[20b] All other reagents were obtained from commercial sources and used as received. All reactions were performed in anhydrous solvents unless used in combination with H_2O. CH_2Cl_2, THF, and Et_2O were dried by passing through a column of alumina beads. Toluene was distilled from sodium and benzophenone immediately before use. MeOH, EtOH, MeCN, and glacial AcOH were used as received. Extraction solvents and chromatography eluents were used as received. MeOH and CH_2Cl_2 were HiPerSolv grade, EtOH was AnalaR grade, and *n*-hexane, Et_2O, EtOAc, and petroleum spirit 40−60 °C were GPR grade. Benzene was purchased and used as received. Reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen unless otherwise stated. Air- and moisture-sensitive reagents were transferred by syringe or cannula. Molecular sieves (4 Å) were dried by repeatedly heating under vacuum and flushing with nitrogen. Reaction temperatures other than room temperature were recorded as aluminum heating block or bath temperatures. Temperatures below room temperature were achieved by an ice/NaCl bath or acetone/dry ice bath. Brine refers to a saturated aqueous solution of NaCl. Column chromatography was performed on silica gel, particle size 33−70 μm or 40−63 μm. Analytical TLC was performed on Kieselgel 60 F254 precoated aluminum-backed plates which were visualized by ultraviolet light (254 and 350 nm) and/or chemical staining using potassium permanganate or an acidified solution of vanillin. Fourier transform IR spectra were recorded as neat samples using an ATR-IR spectrometer. ^{1}H NMR spectra were recorded at 400 or 500 MHz. $^{13}C\{^1H\}$ NMR spectra were recorded at 101 or 126 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (J) are quoted in hertz (Hz). All NMR spectra were acquired at room temperature unless otherwise stated. Low-resolution MS were performed using ESI, EI, or CI methods and ToF or magnetic sector analysis. Chiral analytical HPLC was performed on a 25 cm × 4.6 mm ChiralPak AD or ODH column. All solvents for HPLC were HiPerSolv grade and used as received.

*(3Z,6Z)-Deca-3,6,9-trien-1-ol (**15**).* Freshly prepared zinc−copper couple (1.32 kg) was added to a solution of dec-9-ene-3,6-diyn-1-ol (**14**) (33 g) in water (1.0 L) and 2-propanol (65 mL) at room temperature. After being stirred for 24 h, the mixture was diluted with additional water and stirred for a further 12 h. The suspension was filtered through a sintered funnel and washed with diethyl ether. The layers were separated and the organics dried over Na_2SO_4 and subsequently filtered. The solvent was removed in vacuo and the crude mixture subjected to column chromatography (petroleum spirit/ethyl acetate 9:1−4:1) to provide product **15** (21 g, 62% over three steps) as a colorless oil: R_f 0.40 (petroleum spirit/ethyl acetate 2:1). All other data as previously reported.[18]

*(3R,4S,6Z)-3,4-Epoxydodeca-6,9-dien-1-ol (**16**).* Vanadyl(V) isopropoxide (0.33 mL, 1.38 mmol, 0.01 equiv) was added to a solution of bishydroxamic acid **17** (2.89 g, 2.75 mmol, 0.02 equiv) in toluene (140 mL) at room temperature and stirred for 24 h. Cumene hydroperoxide (30 mL, 206 mmol, 1.5 equiv) was added followed by a solution of (3*Z*,6*Z*)-deca-3,6,9-trien-1-ol (**15**) (20.9 g, 138 mmol, 1.0 equiv) in toluene (140 mL). The reaction mixture was stirred for 12 days at room temperature after which it was quenched with Na_2SO_3 solution (1 L). The aqueous was extracted with ethyl acetate (3 × 600 mL), the combined organics were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The crude mixture was subjected to column chromatography (100% petroleum spirit, to petroleum spirit/ethyl acetate 1:1) to provide epoxide **16** (18.2 g, 79%) as a pale red oil: R_f 0.25 (petroleum spirit/ethyl acetate 1:1); $[\alpha]^{25}_D$ +12.7 (*c* 0.30, CH_2Cl_2). All other data as previously reported.[18]

*(3R,4S,6Z)-3,4-Epoxydodeca-6,9-dien-1-yl Trityl Ether (**18**).* Triethylamine (0.06 mL, 0.45 mmol, 1.5 equiv) and trityl chloride (125 mg, 0.45 mmol, 1.5 equiv) were added to a solution of (3*R*,4*S*,6*Z*)-3,4-epoxydodeca-6,9-dien-1-ol (**16**) (51 mg, 0.3 mmol, 1.0 equiv) in dichloromethane (10 mL) at room temperature and stirred for 18 h at room temperature. The mixture was washed with aqueous ammonium chloride (10 mL) and brine (10 mL), the organics were then dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The crude mixture was purified by column chromatography (petroleum spirit/ethyl acetate 98:2, to 95:5) to provide the title compound **18** (20 mg, 16%) as a colorless oil: R_f 0.37 (petroleum spirit/ethyl acetate, 10:1); $[\alpha]^{25}_D$ +6.1 (*c* 0.45, CH_2Cl_2); IR (neat) 3056, 3019, 2975, 2925, 2873, 1637, 1490, 1448, 1218, 1072, 1031, 900, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.46 (m, 6H), 7.34−7.31 (m, 6H), 7.28−7.24 (m, 3H), 5.83 (ddt, J = 16.3, 10.0, 6.1 Hz, 1H), 5.60−5.49 (m, 2H), 5.09−5.00 (m, 2H), 3.30 (t, J = 6.4 Hz, 2H), 3.17−3.13 (m, 1H), 3.01−2.96 (m, 1H), 2.82 (br t, J = 6.3 Hz, 2H), 2.41−2.34 (m, 1H), 2.28−2.20 (m, 1H), 1.94−1.81 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.1, 136.4, 129.4, 128.7, 127.8, 127.0, 125.3, 115.0, 86.7, 61.1, 56.3, 54.9, 31.7, 28.7, 26.3; MS (ESI$^+$) m/z 433 (M + Na)$^+$; HRMS (ESI$^+$, TOF) m/z [M + Na]$^+$ calcd for $C_{29}H_{30}O_2Na$ 433.2144, found 433.2152; HPLC (OD-H), *n*-hexane/EtOH = 99:1, injection volume = 10 μL, flow rate = 0.5 mL/min, column oven temperature = 20 °C, t_R = 15.9 min (major) (3*R*,4*S*), t_R = 14.9 min (minor) (3*S*,4*R*); e.r. 91:9.

*(3R,4R,6Z)-4-Chlorodeca-6,9-diene-1,3-diol (**19**).* According to the reported procedure for the racemate,[18] diethylamine hydrochloride (20.8 g, 189 mmol, 5.3 equiv) and titanium(IV) isopropoxide (15.8 mL, 54 mmol, 1.5 equiv) were added to a solution of (3*R*,4*S*,6*Z*)-3,4-epoxydeca-6,9-dien-1-ol (**16**) (6.0 g, 36 mmol, 1.0 equiv) in dichloromethane (720 mL) at room temperature. After the solution

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was stirred for 5 days, saturated tartaric acid (800 mL) was added and the precipitate was filtered off using a sinter and washed thoroughly with dichloromethane (300 mL). The aqueous was extracted with dichloromethane (3 × 200 mL), and the combined organics were washed with sodium bicarbonate (400 mL) and brine (400 mL). The organics were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The crude mixture was subjected to column chromatography (petroleum spirit/ethyl acetate 2:1) to provide the title compound **19** an inseparable mixture of the two chlorohydrin regioisomers (5.2 g, 71%) in a 5:1 ratio as a colorless oil: R_f 0.21 (petroleum spirit/ethyl acetate 1:1); $[\alpha]^{21}_D$ +9.4 (*c* 0.55, CH_2Cl_2). All other data as previously reported.[18]

*(3R,4R,6Z)-1-(tert-Butyldiphenylsilanyloxy)-4-chlorodeca-6,9-dien-3-ol (**20**).* By a modification of the reported procedure for the racemate,[18] imidazole (4.14 g, 61 mmol, 2.4 equiv) and TBDPS-Cl (6.58 mL, 25 mmol, 1.0 equiv) were added sequentially to a solution of (3*R*,4*R*,6*Z*)-4-chlorodeca-6,9-diene-1,3-diol (**19**) (5.20 g, 25 mmol, 1.0 equiv) in THF (180 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The mixture was diluted with ethyl acetate (600 mL) and washed with water (500 mL) and brine (500 mL). The organics were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The crude mixture was subjected to column chromatography (petroleum spirit/ethyl acetate 20:1) to provide product **20** (8.29 g, 74%) as a colorless oil: R_f 0.46 (petroleum spirit/ethyl acetate 9:1); $[\alpha]^{23}_D$ +6.1 (*c* 0.95, CH_2Cl_2). All other data as previously reported.[18]

*(2R,3R,5S)-5-((S)-1-Bromobut-3-enyl)-2-(2-(tert-butyldiphenylsilyloxy)ethyl)-3-chlorotetrahydrofuran (**21**).* By a modification of the reported procedure for the racemate,[18] TBCO (1.11 g, 2.7 mmol, 1.2 equiv) was added to a solution of (3*R*,4*R*,6*Z*)-1-(*tert*-butyldiphenylsilanyloxy)-4-chlorodeca-6,9-dien-3-ol (**20**) (1.00 g, 2.3 mmol, 1.0 equiv) in dichloromethane (60 mL) at −78 °C. The reaction mixture was allowed to warm slowly to room temperature and stirred for a period of 18 h. The mixture was subsequently diluted with ethyl acetate (100 mL) and washed with sodium bicarbonate (50 mL) and brine (50 mL). The organics were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The crude mixture was purified by column chromatography (petroleum spirit/ethyl acetate 25:1) to provide product **21** (1.06 g, 90%) as a pale yellow-brown oil: R_f 0.51 (petroleum spirit/ethyl acetate 9:1); $[\alpha]^{23}_D$ −1.5 (*c* 0.52, CH_2Cl_2). All other data as previously reported.[18]

*2-[(2R,3R,5S)-5-[(1S)-1-Bromobut-3-en-1-yl]-3-chlorotetrahydrofuran-2-yl]ethanol (**13**).* By a modification of the reported procedure for the racemate,[18] TBAF (1.0 M in THF, 25.6 mL, 26.1 mmol, 3.0 equiv) was added dropwise to a solution of (2*R*,3*R*,5*S*)-5-((*S*)-1-bromobut-3-enyl)-2-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-3-chlorotetrahydrofuran (**21**) (4.52 g, 8.7 mmol, 1.0 equiv) and AcOH (2.4 mL, 43.5 mmol, 5.0 equiv) in THF (270 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 3 h. A further portion of AcOH (2.4 mL, 43.5 mmol, 5.0 equiv) was added, and additional TBAF (1.0 M in THF, 25.6 mL, 26.1 mmol, 3.0 equiv) was added after cooling to 0 °C. The reaction mixture was allowed to slowly warm to room temperature over a period of 18 h. It was diluted with ethyl acetate (500 mL) and washed with sodium bicarbonate (250 mL). The aqueous portion was extracted with ethyl acetate (3 × 200 mL), and the organics were subsequently combined and washed with brine (400 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the crude mixture purified by column chromatography (petroleum spirit/ethyl acetate 2:1) to provide product **13** (1.97 g, 80%) as a pale yellow oil: R_f 0.38 (petroleum spirit/ethyl acetate 1:1); $[\alpha]^{24}_D$ +4.3 (*c* 1.01, CH_2Cl_2). All other data as previously reported.[18]

*(2R,3R,5S)-2-[2,2-Bis[(2S)-but-3-yn-2-yloxy]ethyl]-5-[(1S)-1-bromobut-3-en-1-yl]-3-chlorooxolane (**22**).* To a stirred solution of alcohol **13** (495 mg, 1.75 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added Dess−Martin periodinane (1.48 g, 75% active, 2.62 mmol, 1.5 equiv). The white suspension was allowed to warm to room temperature and stirred for 30 min until TLC (*n*-hexane/EtOAc 2:1) showed completion of the reaction. The mixture was passed through a silica plug, eluting with *n*-hexane/EtOAc 2:1, and the solvent was removed in vacuo to give a light yellow oil (498 mg). This material was carried through to the next step without further purification.

To a stirred solution of the crude aldehyde (498 mg) in (2*S*)-but-3-yn-2-ol (1.75 mL, 22.3 mmol) at room temperature was added CSA (51.9 mg, 0.223 mmol, 0.13 equiv), and the yellow solution was heated to 40 °C. After 1 h, $NaBH_4$ (704 mg, 1.74 mmol) was added, followed by THF (3 mL). After a further 30 min at 40 °C, water (5 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 5 mL), dried over Na_2SO_4, filtered, and the solvent was removed in vacuo to give a colorless oil (699 mg). Column chromatography (*n*-hexane/EtOAc 4:1) gave the title compound **22** (450 mg, 1.11 mmol, 64% over two steps, 95% brsm) as a colorless oil: R_f 0.61 (*n*-hexane/EtOAc 2:1); IR (neat) 3296, 2924, 1736, 1091, 1040 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 5.87 (ddt, *J* = 17.0, 10.2, 6.9 Hz, 1H), 5.21−5.13 (m, 2H), 5.09 (t, *J* = 5.8 Hz, 1H), 4.63 (qd, *J* = 6.5, 1.8 Hz, 1H), 4.57 (dd, *J* = 4.7, 2.9 Hz, 1H), 4.51−4.40 (m, 2H), 4.29 (td, *J* = 6.8, 2.8 Hz, 1H), 4.01 (ddd, *J* = 8.6, 5.4, 3.1 Hz, 1H), 2.72 (ddd, *J* = 9.7, 7.7, 6.4 Hz, 2H), 2.54 (ddd, *J* = 14.3, 9.7, 4.8 Hz, 1H), 2.46 (d, *J* = 2.0 Hz, 1H), 2.42 (d, *J* = 2.0 Hz, 1H), 2.36 (dd, *J* = 13.6, 5.9 Hz, 1H), 2.18 (ddd, *J* = 13.6, 7.3, 6.1 Hz, 1H), 2.02 (dt, *J* = 13.8, 6.1 Hz, 1H), 1.46 (d, *J* = 5.7 Hz, 3H), 1.45 (d, *J* = 5.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 134.8, 118.1, 98.1, 84.2, 84.0, 79.3, 78.6, 73.0, 72.9, 62.8, 62.3, 61.7, 58.0, 41.1, 40.0, 36.7, 22.6, 22.0; MS (ES^+, TOF) 425 $[M + Na]^+$; HRMS (ES^+, TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{24}O_3Na^{35}Cl^{79}Br$ 425.0495, found 425.0509. Starting alcohol **13** (180 mg, 0.635 mmol, 36%) ws also obtained as a colorless oil.

*(2S)-3-[(2R,3R,5S)-5-[(1S)-1-Bromobut-3-en-1-yl]-3-chlorooxolane-2-yl]-2-[(2S)-but-3-yn-2-yloxy]propanenitrile ((S)-**23**) and (2R)-3-[(2R,3R,5S)-5-[(1S)-1-Bromobut-3-en-1-yl]-3-chlorooxolane-2-yl]-2-[(2S)-but-3-yn-2-yloxy]propanenitrile ((R)-**24**).* According to a modified procedure,[21] to a stirred solution of acetal **22** (280 mg, 0.694 mmol) in CH_2Cl_2 (1 mL) at room temperature were added trimethylsilyl cyanide (217 μL, 1.73 mmol, 2.5 equiv) and $BF_3.OEt_2$ (12 μL, 0.0972 mmol, 0.14 equiv). The orange solution was stirred for 2 h until TLC (*n*-hexane/EtOAc 9:1) showed completion of the reaction. The reaction was quenched with water (1 mL) and stirred for a further 15 min. The mixture was extracted with CH_2Cl_2 (3 × 3 mL), dried over Na_2SO_4, and filtered and the solvent removed in vacuo to give an orange oil (350 mg). Column chromatography (*n*-hexane/EtOAc 9:1) gave nitrile (*S*)-**23** (130 mg, 0.360 mmol, 52%) as a colorless oil: R_f 0.29 (*n*-hexane/EtOAc 9:1); $[\alpha]^{28}_D$ −13.3 (*c* 0.42, CH_2Cl_2); IR (neat) 3296, 2992, 2945, 2116, 1645, 1439, 1375, 217, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.22−5.12 (m, 2H), 4.73 (t, *J* = 7.0 Hz, 1H), 4.58−4.54 (m, 1H), 4.53−4.42 (m, 2H), 4.41 (ddd, *J* = 8.2, 5.5, 3.0 Hz, 1H), 4.01 (ddd, *J* = 8.6, 5.8, 3.0 Hz, 1H), 2.73 (ddd, *J* = 8.1, 6.3, 4.9 Hz, 2H), 2.58 (ddd, *J* = 14.3, 9.5, 4.9 Hz, 1H), 2.55 (d, *J* = 2.0 Hz, 1H), 2.44−2.33 (m, 2H), 2.18 (ddd, *J* = 13.8, 7.2, 5.6 Hz, 1H), 1.50 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 134.6, 118.2, 117.6, 81.4, 78.8, 78.6, 75.1, 65.0, 64.0, 62.1, 57.4, 40.9, 39.9, 35.4, 21.7; MS (CI^+, NH_3) *m*/*z* 377, 379, 381 $[M + NH_4]^+$; HRMS (CI^+, magnetic sector) *m*/*z* $[M + NH_4]^+$ calcd for $C_{15}H_{23}N_2O_2{}^{35}Cl^{79}Br$ 377.0631, found 377.0635. Nitrile (*R*)-**24** (116 mg, 0.321 mmol, 46%) was also obtained as a colorless oil: R_f 0.22 (*n*-hexane/EtOAc 9:1); $[\alpha]^{28}_D$ +2.1 (*c* 0.60, CH_2Cl_2); IR (neat) 3298, 2986, 2935, 1645, 1439, 1312, 1267, 1217, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93−5.75 (m, 1H), 5.25−5.08 (m, 2H), 4.59−4.31 (m, 5H), 3.99 (td, *J* = 7.1, 2.7 Hz, 1H), 2.72 (td, *J* = 7.1, 1.5 Hz, 2H), 2.63−2.52 (m, 1H) 2.60 (d, *J* = 2.2 Hz, 1H), 2.38 (dd, *J* = 14.0, 6.3 Hz, 1H), 2.30−2.09 (m, 2H), 1.49 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 134.5, 118.7, 118.4, 81.6, 78.4, 77.7, 75.3, 67.3, 63.9, 62.3, 58.3, 41.6, 40.7, 36.7, 21.7; MS (CI^+, NH_3) *m*/*z* 377, 379, 381 $[M + NH_4]^+$; HRMS (CI^+, magnetic sector) *m*/*z* $[M + NH_4]^+$ calcd for $C_{15}H_{23}N_2O_2{}^{35}Cl^{79}Br$ 377.0631, found 377.0633.

*(2S)-3-[(2R,3R,5S)-5-[(1S)-1-Bromobut-3-en-1-yl]-3-chlorooxolan-2-yl]-2-[(2S)-but-3-en-2-yloxy]propanenitrile (**11**).* To a solution of nitrile (*S*)-**23** (140 mg, 0.388 mmol) and quinoline (79.8 μL, 0.675 mmol) in benzene (9.70 mL) was added 5% $Pd/BaSO_4$ (41.3 mg, 0.0194 mmol, 5 mol %). The flask was then flushed with hydrogen and the atmosphere maintained with hydrogen filled balloons. The black

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suspension was stirred vigorously for 30 min until TLC (*n*-hexane/EtOAc 3:1) showed completion of the reaction. The reaction mixture was passed through a plug of silica, eluting with *n*-hexane/EtOAc 2:1. The solvent was removed in vacuo to give a yellow oil (170.2 mg). Column chromatography (*n*-hexane/EtOAc 10:1) gave diene **11** (136.5 mg, 0.376 mmol, 97%) as a colorless oil: R_f 0.57 (*n*-hexane/EtOAc 3:1); $[\alpha]^{28}_D$ −37.5 (*c* 0.37, CH_2Cl_2); IR (neat) 2980, 1646, 1433, 1375, 1244, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddt, *J* = 17.0, 10.1, 6.8 Hz, 1H), 5.61 (ddd, *J* = 17.5, 10.1, 8.2 Hz, 1H), 5.36−5.26 (m, 2H), 5.18−5.12 (m, 2H), 4.50 (dd, *J* = 4.8, 3.2 Hz, 1H), 4.43 (ddd, *J* = 9.5, 6.2, 3.1 Hz, 1H), 4.40−4.33 (m, 2H), 4.14 (app. p, *J* = 6.4 Hz, 1H), 4.00 (ddd, *J* = 8.6, 5.7, 3.0 Hz, 1H), 2.72−2.68 (m, 2H), 2.55 (ddd, *J* = 14.2, 9.5, 4.9 Hz, 1H), 2.36 (dd, *J* = 13.9, 6.2 Hz, 1H), 2.27 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.13 (ddd, *J* = 13.6, 7.8, 5.0 Hz, 1H), 1.30 (d, *J* = 6.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 137.6, 134.6, 119.2, 118.2, 118.2, 78.9, 78.8, 77.2, 63.4, 62.4, 57.3, 40.9, 39.9, 35.6, 21.3; MS (CI^+, NH_3) *m*/*z* 379, 381, 383 $(M + NH_4)^+$; HRMS (CI^+, magnetic sector) *m*/*z* $[M + NH_4]^+$ calcd for $C_{15}H_{25}N_2O_2{}^{35}Cl^{79}Br$ 379.0788, found 379.0784.

*(2R)-3-[(2R,3R,5S)-5-[(1S)-1-Bromobut-3-en-1-yl]-3-chlorooxolan-2-yl]-2-[(2S)-but-3-en-2-yloxy]propanenitrile (**12**).* To a solution of nitrile (*R*)-**24** (102 mg, 0.283 mmol) and quinoline (58.1 μL, 0.492 mmol) in benzene (7.00 mL) was added 5% $Pd/BaSO_4$ (30.0 mg, 0.0141 mmol, 5 mol %). The flask was then flushed with hydrogen and the atmosphere maintained with hydrogen-filled balloons. The black suspension was stirred vigorously for 30 min until TLC (*n*-hexane, EtOAc 3:1) showed completion of the reaction. The reaction mixture was passed through a plug of silica, eluting with EtOAc. The solvent was removed in vacuo to give a yellow oil (162 mg). The oil was redissolved in EtOAc (∼5 mL) and washed with 1 M HCl (3 × 3 mL). The solvent was removed in vacuo again to give a yellow oil (111 mg). Column chromatography (*n*-hexane/EtOAc 10:1) gave the diene **12** (93.0 mg, 0.256 mmol, 91%) as a colorless oil: R_f 0.35 (*n*-hexane/EtOAc 3:1); $[\alpha]_D{}^{26}$ +33.3 (*c* 0.30, CH_2Cl_2); IR (neat) 2980, 2875, 1643, 1314, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93−5.81 (m, 2H), 5.34−5.21 (m, 2H), 5.20−5.13 (m, 2H), 4.49 (dd, *J* = 4.9, 2.9 Hz, 1H), 4.45−4.34 (m, 3H), 4.14−4.11 (m, 1H), 4.00 (td, *J* = 7.1, 2.7 Hz, 1H), 2.73 (tt, *J* = 7.1, 1.3 Hz, 2H), 2.59 (ddd, *J* = 14.2, 9.5, 4.9 Hz, 1H), 2.39 (dd, *J* = 13.9, 6.3 Hz, 1H), 2.22 (ddd, *J* = 14.2, 9.7, 3.2 Hz, 1H), 2.16−2.08 (m, 1H), 1.30 (d, *J* = 6.3 Hz, 1H), $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.7, 134.5, 119.2, 118.3, 117.5, 79.0, 78.4, 77.8, 63.4, 62.4, 58.2, 41.6, 40.7, 36.8, 20.2; MS (CI^+, NH_3) *m*/*z* 379, 381, 383 $(M + NH_4)^+$; HRMS (CI^+, magnetic sector) *m*/*z* $[M + NH_4]^+$ calcd for $C_{15}H_{25}N_2O_2{}^{35}Cl^{79}Br$ 379.0788, found 379.0789.

*(1R,3S,5S,6E,9S,10S,12R)-9-Bromo-12-chloro-5-methyl-4,13-dioxabicyclo[8.2.1] tridec-6-ene-3-carbonitrile (**9**) and (1R,3S,5S,6Z,9S,10S,12R)-9-Bromo-12-chloro-5-methyl-4,13-dioxabicyclo[8.2.1] tridec-6-ene-3-carbonitrile (**Z-9**).* Toluene (160 mL) was refluxed in a Dean−Stark apparatus for 1 h. The flask was removed from the hot plate and allowed to cool before diene **11** (20 mg, 0.055 mmol) and Hoveyda−Grubbs I catalyst[22a] (10.0 mg, 30 mol %) were added. The flask was covered with aluminum foil, and the orange solution was returned to reflux for 22 h. The flask was removed from the hot plate and allowed to cool before di(ethylene glycol) vinyl ether (6 μL) was added. The solvent was removed in vacuo to give a brown oil. Column chromatography (toluene) gave the *E*-macrocycle **9** (10.1 mg, 55%) as white crystals: R_f 0.13 (toluene); mp 136−140 °C; $[\alpha]^{28}_D$ +6.2 (*c* 0.64, CH_2Cl_2); IR (neat) 2979, 2929, 1443, 1378, 1311, 1268, 1088 cm^{-1}; ^1H NMR (400 MHz, 298 K, $CDCl_3$) δ 6.03−5.87 (m, 1H), 5.68−5.30 (m, 1H), 4.59−4.47 (m, 1H), 4.42 (td, *J* = 4.9, 2.3 Hz, 1H), 4.03 (dq, *J* = 8.7, 6.3 Hz, 1H), 2.90−2.64 (m, 2H), 2.46−2.33 (m, 1H), 2.30−2.11 (m, 3H), 1.33 (d, *J* = 6.3 Hz, 3H); ^1H NMR (400 MHz, 323 K, $CDCl_3$) δ 5.95 (dt, *J* = 14.5, 7.0 Hz, 1H), 5.55 (dd, *J* = 15.4, 9.3 Hz, 1H), 4.52 (dd, *J* = 6.5, 4.9 Hz, 1H), 4.48 (t, *J* = 4.6 Hz, 1H), 4.41 (td, *J* = 4.9, 2.3 Hz, 1H), 4.28−4.12 (m, 2H), 4.02 (dq, *J* = 8.7, 6.4 Hz, 1H), 2.77 (dd, *J* = 7.7, 4.2 Hz, 2H), 2.41 (ddd, *J* = 13.7, 9.5, 6.5 Hz, 1H), 2.29−2.19 (m, 2H), 2.15 (ddd, *J* = 15.3, 4.9, 2.7 Hz, 1H), 1.33 (d, *J* = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, 323 K, $CDCl_3$) δ 133.1, 130.6, 119.3, 81.0, 79.1, 76.4, 66.9, 59.9, 51.4, 41.6, 40.4, 38.3, 21.1; MS (CI^+, NH_3) *m*/*z* 334, 336, 338 $[M + H]^+$; HRMS (CI^+, magnetic sector) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{18}NO_2{}^{35}Cl^{79}Br$ 334.0209, found 334.0210. Crystal data for **9**: $C_{13}H_{17}BrClNO_2$, *M* = 334.64, monoclinic, $P2_1$ (no. 4), *a* = 8.87379(10) Å, *b* = 4.83007(5) Å, *c* = 16.63090(14) Å, β = 90.2687(8)°, *V* = 712.810(12) $Å^3$, *Z* = 2, D_c = 1.559 g cm^{-3}, μ(Cu Kα) = 5.612 mm^{-1}, *T* = 173 K, colorless blocks, Oxford Diffraction Xcalibur PX Ultra diffractometer; 2699 independent measured reflections (R_{int} = 0.0261), F^2 refinement, R_1(obs) = 0.0196, wR_2(all) = 0.0431, 2400 independent observed absorption-corrected reflections [$|F_0| > 4\sigma(|F_0|)$, $2\theta_{max}$ = 143°], 164 parameters. The absolute structure of **9** was determined by a combination of *R*-factor tests [$R_1{}^+$ = 0.0196, $R_1{}^-$ = 0.0338] and by use of the Flack parameter [x^+ = 0.000(13), x^- = 1.013(13)]. CCDC: 1455995. *Z*-macrocycle *Z*-**9** (2.0 mg, 11%) was isolated as a white solid: R_f 0.22 (toluene); mp 133−135 °C; $[\alpha]_D{}^{28}$ +8.0 (*c* 0.54, CH_2Cl_2); IR (neat) 2971, 2934, 2899, 1660, 1447, 1378, 1292, 1270, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.58 (dd, *J* = 10.9, 9.1 Hz, 1H), 5.51 (td, *J* = 10.5, 6.1 Hz, 1H), 4.60 (dq, *J* = 8.9, 6.2 Hz, 1H), 4.47 (dt, *J* = 11.5, 5.7 Hz, 1H), 4.40 (dt, *J* = 10.1, 6.8 Hz, 1H), 4.33 (t, *J* = 8.0 Hz, 1H), 4.22 (d, *J* = 9.2 Hz, 1H), 3.98 (ddd, *J* = 12.5, 3.6, 1.3 Hz, 1H), 3.15 (td, *J* = 12.7, 10.5 Hz, 1H), 2.57 (dtd, *J* = 13.4, 7.2, 3.7 Hz, 2H), 2.37 (ddd, *J* = 15.4, 11.4, 9.5 Hz, 1H), 2.15−2.04 (m, 2H), 1.38 (d, *J* = 6.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 135.3, 128.4, 119.6, 77.8, 77.2, 73.5, 65.0, 55.6, 53.9, 38.2, 35.4, 35.0, 19.8; MS (CI^+, NH_3) *m*/*z* 351, 353, 355 $(M + NH_4)^+$; HRMS (ESI$^+$, TOF) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{18}NO_2{}^{35}Cl^{79}Br$ 334.0209, found 334.0202.

*(1R,3R,5S,6E,9S,10S,12R)-9-Bromo-12-chloro-5-methyl-4,13-dioxabicyclo[8.2.1]tridec-6-ene-3-carbonitrile (**10**).* Toluene (160 mL) was refluxed in a Dean−Stark apparatus for 1 h. The flask was removed from the hot plate and allowed to cool before diene **11** (20 mg, 0.055 mmol) and Hoveyda−Grubbs II catalyst[22b] (10.4 mg, 30 mol %) were added. The flask was covered with aluminum foil, and the orange solution was returned to reflux for 18 h. The flask was removed from the hot plate and allowed to cool before di(ethylene glycol) vinyl ether (6 μL) was added. The solvent was removed in vacuo to give a brown oil. Column chromatography (toluene) gave the *E*-macrocycle **10** (10.0 mg, 54%) as white crystals: R_f 0.13 (toluene); mp 144 °C; $[\alpha]_D{}^{18}$ +18.4 (*c* 0.46, CH_2Cl_2); IR (neat) 2932, 2253, 1665, 1449, 1386, 1091, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90−5.77 (m, 1H), 5.72−5.59 (m, 1H), 4.72 (td, *J* = 8.1, 5.4 Hz, 1H), 4.54−4.44 (m, 2H), 4.43−4.38 (m, 1H), 4.37−4.29 (m, 1H), 3.92−3.77 (m, 1H), 2.93−2.84 (m, 1H), 2.55−2.35 (m, 3H), 1.95−1.89 (m, 2H), 1.42 (d, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 129.7, 126.6, 119.6, 78.3, 75.3, 71.8, 61.4, 56.6, 49.2, 38.9, 37.6, 36.3, 13.5; MS (CI^+, NH_3) *m*/*z* 334, 336, 338 $(M + H)^+$; HRMS (CI^+, magnetic sector) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{18}NO_2{}^{35}Cl^{79}Br$ 334.0209, found 334.0212. Crystal data for **10**: $C_{13}H_{17}BrClNO_2$, *M* = 334.64, orthorhombic, $P2_12_12_1$ (no. 19), *a* = 9.90540(9) Å, *b* = 16.30560(13) Å, *c* = 17.66934(16) Å, *V* = 2853.84(4) $Å^3$, *Z* = 8 (two independent molecules), D_c = 1.558 g cm^{-3}, μ(Cu Kα) = 5.607 mm^{-1}, *T* = 173 K, colorless tablets, Oxford Diffraction Xcalibur PX Ultra diffractometer; 5605 independent measured reflections (R_{int} = 0.0374), F^2 refinement, R_1(obs) = 0.0310, wR_2(all) = 0.0746, 5086 independent observed absorption-corrected reflections [$|F_0| > 4\sigma(|F_0|)$, $2\theta_{max}$ = 145°], 325 parameters. The absolute structure of **10** was determined by a combination of *R*-factor tests [$R_1{}^+$ = 0.0310, $R_1{}^-$ = 0.0422] and by use of the Flack parameter [x^+ = 0.000(15)]. CCDC 1455996.

*(1S,2S,4S,6S,7S,9R,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecane-9-carbonitrile (**25**) and (1S,2S,4R,6R,7S,9R,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecane-9-carbonitrile (**26**).* To a solution of *E*-macrocycle **10** (25.0 mg, 0.0747 mmol) in CH_2Cl_2 (830 μL) was added *m*-CPBA (25.8 mg, 75%, 0.112 mmol). The colorless solution was stirred for 2 h until TLC (*n*-hexane/Et_2O 2:1) showed completion of the reaction. The reaction was quenched with 10% Na_2SO_3 (1 mL) and stirred for an additional 5 min. The mixture was extracted with CH_2Cl_2 (3 × 3 mL), the organic layers washed with satd aq $NaHCO_3$ solution (2 × 5 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo to give a cloudy oil (37.8 mg). Column chromatography (*n*-hexane/Et_2O 2:1) gave

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epoxide **26** (19.0 mg, 0.0542 mmol, 73%) and epoxide **25** (6.8 mg, 0.0194 mmol, 26%) as colorless oils. Epoxide **26**: R_f 0.17 (*n*-hexane/EtOAc 2:1); IR 2926, 1681, 1262, 1090, 927 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.76 (dt, J = 9.8, 6.3 Hz, 1H), 4.60 (dd, J = 10.3, 3.1 Hz, 1H), 4.63−4.56 (m, 1H), 4.47 (ddd, J = 13.0, 6.0, 3.2 Hz, 1H), 4.43 (ddd, J = 4.4, 2.4, 1 Hz, 1H), 4.17 (dt, J = 10.8, 2.6 Hz, 1H), 3.13 (dd, J = 8.7, 2.1 Hz, 1H), 3.00 (dd, J = 3.6, 2.2 Hz, 1H), 2.63 (dd, J = 15.1, 3.0 Hz, 1H), 2.52 (dd, J = 14.5, 6.8 Hz, 1H), 2.43 (ddd, J = 14.4, 9.8, 4.4 Hz, 1H), 2.15−2.09 (m, 2H), 1.86 (ddd, J = 15.1, 12.5, 8.6 Hz, 1H), 1.17 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 119.1, 77.8, 77.7, 73.2, 61.0, 60.3, 58.1, 53.6, 46.3, 39.2, 36.6, 35.5, 9.9; HRMS (ES^+, TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{18}NO_3{}^{35}Cl^{79}Br$ 350.0153, found 350.0152. Epoxide **25**: R_f 0.16 (*n*-hexane/EtOAc 2:1); IR 2926, 1671, 1263, 1087, 948 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.65 (dd, J = 11.4, 3.4 Hz, 1H), 4.58 (dd, J = 6.3, 3.4 Hz, 1H), 4.54−4.45 (m, 2H), 4.31 (ddd, J = 7.2, 3.1, 1.6 Hz, 1H), 3.48−3.38 (m, 2H), 3.04 (dd, J = 8.7, 2.1 Hz, 1H), 2.99 (dt, J = 14.7, 6.3 Hz, 1H), 2.78 (ddd, J = 14.5, 7.2, 2.5 Hz, 1H), 2.54 (ddd, J = 14.8, 7.7, 1.2 Hz, 1H), 2.34 (ddd, J = 13.6, 9.9, 3.3 Hz, 1H), 2.14 (ddd, J = 14.1, 11.4, 4.4 Hz, 1H), 1.75 (ddd, J = 14.6, 8.3, 1.6 Hz, 1H), 1.59 (d, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 125.5, 79.4, 78.3, 76.4, 62.0, 61.1, 59.8, 57.3, 54.3, 43.0, 36.9, 35.1, 17.2; HRMS (ES^+, TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{18}NO_3{}^{35}Cl^{79}Br$ 350.0153, found 350.0147.

*(1S)-1-[(1S,2S,4R,6R,7S,9R,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecan-9-yl]prop-2-yn-1-ol (**27**).* To a stirred solution of epoxynitrile **26** (6.8 mg, 0.019 mmol) in THF (300 μL) at −78 °C was added DIBAL-H in THF (34 μL, 0.86 M, 0.029 mmol), and the colorless solution was warmed to 0 °C and stirred for 30 min until TLC (toluene/MeCN 9:1) showed completion of the reaction. The reaction was quenched with a 1 M aqueous citric acid solution (1 mL) and stirred for 15 min. The mixture was extracted with CH_2Cl_2 (3 × 3 mL), the organic layer was dried over Na_2SO_4, and the solvent removed in vacuo to give the desired aldehyde as white solid (6.8 mg) which was carried through to the next step without further purification. To a stirred solution of the crude aldehyde (6.8 mg) in THF (200 μL) at 0 °C was added ethynylmagnesium bromide in THF (57 μL, 0.5 M, 0.029 mmol), and the yellow solution was stirred for 30 min until TLC (*n*-hexane/EtOAc 1:1) showed completion of the reaction. The reaction was quenched with satd aq NH_4Cl (1 mL) and stirred for 5 min. The mixture was extracted with CH_2Cl_2 (3 × 3 mL), the organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo to give a yellow oil (10.8 mg). Column chromatography (*n*-hexane/EtOAc 2:1) gave compound *epi*-alcohol **27** (1.8 mg, 0.0047 mmol, 25%) and compound **27** (1.9 mg, 0.0050 mmol, 26%) as colorless oils. *epi*-Alcohol **27**: R_f 0.12 (*n*-hexane/EtOAc 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (dt, J = 9.6, 6.5 Hz, 1H), 4.56 (qd, J = 7.2, 3.2 Hz, 1H), 4.49 (ddd, J = 12.8, 5.7, 2.9 Hz, 1H), 4.43 (dd, J = 4.2, 2.4 Hz, 1H), 4.28−4.22 (m, 2H), 3.96 (ddd, J = 11.2, 4.7, 1.8 Hz, 1H), 3.14 (dd, J = 8.8, 2.2 Hz, 1H), 3.09 (t, J = 3.2, 2.3 Hz, 1H), 2.63 (dd, J = 14.9, 2.9 Hz, 1H), 2.51 (d, J = 2.2 Hz, 1H), 2.50 (dd, J = 11.8, 6.9 Hz, 1H), 2.43 (td, J = 9.8, 4.8 Hz, 1H), 2.23 (d, J = 6.0 Hz, 1H), 2.02 (ddd, J = 13.5, 10.8, 1.9 Hz, 1H), 1.89 (ddd, J = 15.4, 12.9, 9.1 Hz, 1H), 1.80 (ddd, J = 13.7, 11.2, 2.1 Hz, 1H), 1.12 (d, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 82.3, 78.8, 78.0, 74.7, 72.3, 70.3, 65.6, 62.5, 61.5, 54.3, 46.9, 38.8, 35.4, 33.1, 10.5. Alcohol **27**: R_f 0.07 (*n*-hexane/EtOAc 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (dt, J = 9.7, 6.3 Hz, 1H), 4.58 (qd, J = 7.3, 3.3 Hz, 1H), 4.49 (ddd, J = 12.6, 5.6, 2.9 Hz, 1H), 4.43 (dd, J = 4.3, 2.1 Hz, 1H), 4.38 (ddd, J = 5.4, 3.1, 2.3 Hz, 1H), 4.24 (dt, J = 10.9, 2.2 Hz, 1H), 4.01 (ddd, J = 11.3, 2.8, 1.7 Hz, 1H), 3.14 (dd, J = 8.8, 2.2 Hz, 1H), 3.09 (dd, J = 3.3, 2.3 Hz, 1H), 2.63 (dd, J = 14.9, 2.9 Hz, 1H), 2.54 (d, J = 2.2 Hz, 1H), 2.50 (dd, J = 14.4, 6.8 Hz, 1H), 2.43 (ddd, J = 14.3, 9.6, 4.4 Hz, 1H), 2.24 (d, J = 5.5 Hz, 1H), 1.99 (ddd, J = 14.2, 10.9, 1.9 Hz, 1H), 1.92−1.81 (m, 2H), 1.08 (d, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 81.1, 79.0, 78.0, 75.3, 72.3, 70.6, 66.0, 62.4, 61.5, 54.2, 46.9, 38.9, 35.4, 32.1, 10.5; HRMS (ES^+, TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{21}O_4{}^{35}Cl^{79}Br$ 379.0312, found 379.0316.

*(1S)-1-[(1S,2S,4R,6R,7S,9R,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecan-9-yl]prop-2-yn-1-yl 2,4,6-tris(propan-2-yl)benzene-1-sulfonate (**28**).* To alcohol **27** (5.0 mg, 0.013 mmol) was added a solution of TrisCl and DMAP in CH_2Cl_2 (440 μL, 0.038 M, 0.017 mmol of each). The colorless solution was stirred for 20 h, a further aliquot of TrisCl and DMAP in CH_2Cl_2 (200 μL, 0.038 M, 0.0076 mmol of each) was added, and stirring was resumed for 4 h until TLC (*n*-hexane/EtOAc 2:1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane/EtOAc 2:1. The solvent was removed in vacuo to give a white solid (12.6 mg). Column chromatography (*n*-hexane/EtOAc 7:1) gave the title compound **28** (5.5 mg, 0.0085 mmol, 65%) as a white solid: R_f 0.58 (*n*-hexane/EtOAc 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 2H), 5.07 (t, J = 2.5 Hz, 1H), 4.76 (dt, J = 9.7, 6.3 Hz, 1H), 4.51−4.44 (m, 2H), 4.39 (dd, J = 4.1, 2.2 Hz, 1H), 4.22 (dt, J = 11.0, 2.2 Hz, 1H), 4.18−4.10 (m, 3H), 3.11 (dd, J = 8.8, 2.2 Hz, 1H), 3.04 (dd, J = 3.1, 2.3 Hz, 1H), 2.90 (hept, J = 7.3 Hz, 1H), 2.62 (dd, J = 14.8, 2.9 Hz, 1H), 2.49 (dd, J = 14.5, 6.9 Hz, 1H), 2.42 (ddd, J = 14.3, 9.6, 4.4 Hz, 1H), 2.32 (d, J = 2.3 Hz, 1H), 1.93 (ddd, J = 12.6, 10.8, 1.7 Hz, 1H), 1.93−1.72 (m, 3H), 1.32−1.21 (m, 18H), 1.06 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.9, 150.8, 123.6, 110.0, 78.6, 78.0, 77.9, 77.2, 72.9, 72.4, 69.9, 62.2, 61.4, 54.1, 46.8, 38.9, 35.4, 34.3, 32.9, 29.7, 24.8, 24.6, 23.6, 23.6, 10.2; HRMS (ES^+, TOF) m/z $[M + H]^+$ calcd for $C_{30}H_{43}O_6S^{35}Cl^{79}Br$ 645.1652, found 645.1659.

*(1S,2S,4R,6R,7S,9R,11R,12R)-2-Bromo-9-[(S$_a$)-3-bromopropa-1,2-dien-1-yl]-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecane, 12-Epoxyobtusallene IV (**7**).* LiBr (11.4 mg, 0.131 mmol) and CuBr (18.8 mg, 0.131 mmol) were stirred at room temperature in CH_2Cl_2 (1.20 mL) for 1 h, during which time the salts dissolved and turned bright green. To a stirred solution of trisylate **28** (5.5 mg, 0.0085 mmol) in CH_2Cl_2 (300 μL) was added the $LiCuBr_2$ solution (235 μL, 0.109 M, 0.0256 mmol). The green solution was heated to 60 °C and stirred for 2.5 h, until TLC (*n*-hexane/EtOAc 2:1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane/EtOAc 2:1. The solvent was removed in vacuo to give a white solid (3.3 mg). Column chromatography (toluene) gave title compound **7** (3.8 mg, 0.0085 mmol, quant, 94:6 dr) as a white solid: R_f 0.52 (*n*-hexane/EtOAc 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dd, J = 5.7, 1.7 Hz, 1H), 5.37 (dd, J = 6.5, 5.7 Hz, 1H), 4.76 (dt, J = 9.7, 6.3 Hz, 1H), 4.54 (qd, J = 6.9, 3.7 Hz, 1H), 4.49 (ddd, J = 12.7, 5.9, 2.9 Hz, 1H), 4.45 (ddt, J = 11.0, 6.4, 1.8, 1.7 Hz, 1H), 4.42 (dd, J = 4.0, 2.1 Hz, 1H), 4.26 (dt, J = 10.8, 2.2 Hz, 1H), 3.18 (dd, J = 8.6, 2.2 Hz, 1H), 3.04 (dd, J = 3.7, 2.3 Hz, 1H), 2.64 (dd, J = 14.9, 3.0 Hz, 1H), 2.48 (dd, J = 14.4, 6.9 Hz, 1H), 2.43 (ddd, J = 14.3, 9.7, 4.3 Hz, 1H), 1.89 (ddd, J = 15.0, 12.7, 8.7 Hz, 1H), 1.86 (ddd, J = 13.9, 10.5, 2.0 Hz, 1H), 1.74 (ddd, J = 13.8, 11.0, 2.1 Hz, 1H), 1.08 (d, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 201.0, 103.3, 78.9, 77.7, 73.9, 72.1, 66.4, 62.0, 61.5, 53.9, 46.9, 39.0, 37.7, 35.7, 10.2; HRMS (ES^+, TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{20}O_3{}^{35}Cl^{79}Br_2$ 440.9468, found 440.9464. There was insufficient material to record a melting point or rotation to compare with the literature values.

*(1R,3R,5S,6R,7R,9S,10S,12R)-7,9-Dibromo-3-[(S$_a$)-3-bromopropa-1,2-dien-1-yl]-12-chloro-5-methyl-4,13-dioxabicyclo[8.2.1]tridecan-6-ol, Obtusallene X (**8**).* To a sample of 12-epoxyobtusallene IV (**7**) (2.0 mg, 0.0043 mmol) in dichloromethane (200 μL) was added hydrobromic acid in water (0.97 μL, 48%, 0.0086 mmol) and the mixture stirred in the dark for 1 h until TLC (*n*-hexane/EtOAc 2:1) showed completion of the reaction. The reaction was quenched with satd aq $NaHCO_3$ solution (1 mL) and stirred for 5 min. The mixture was partitioned between water (1 mL) and CH_2Cl_2 (3 mL), separated, and extracted further with CH_2Cl_2 (2 × 3 mL). The organic layer was dried over Na_2SO_4 and the solvent removed in vacuo to give a colorless oil (4.1 mg). Column chromatography (*n*-hexane/EtOAc 6:1) gave title compound **8** (2.2 mg, 0.042 mmol, 93%) as a colorless oil: R_f 0.33 (*n*-hexane/EtOAc 2:1); ^1H NMR (500 MHz, $CDCl_3$) δ 6.03 (dd, J = 5.6, 0.9 Hz, 1H), 5.73 (dd, J = 8.9, 5.6 Hz, 1H), 4.62−4.53 (m, 3H), 4.48−4.42 (m, 2H), 4.39 (dt, J = 11.3, 5.0, 4.1 Hz, 1H), 4.18 (qd, J = 6.6, 3.2 Hz, 1H), 3.92 (d, J = 3.4 Hz, 1H), 3.69 (dd, J = 6.5, 3.4 Hz, 1H), 2.87 (dd, J = 15.5, 12.1 Hz, 1H), 2.65 (ddd, J = 15.3, 9.3, 2.4 Hz, 1H), 2.53 (ddd, J = 13.7, 9.6, 7.6 Hz, 1H), 2.37 (ddd, J =

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14.7, 11.3, 2.1 Hz, 1H), 2.25 (ddd, J = 13.7, 5.5, 0.9 Hz, 1H), 1.72 (ddd, J = 14.8, 7.3, 3.9 Hz, 1H), 1.36 (d, J = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 202.2, 100.0, 76.5, 76.4, 74.2, 73.5, 72.6, 70.4, 59.7, 58.1, 48.5, 43.6, 41.3, 35.3, 13.0. HRMS (ES^+, TOF) m/z $(M + H)^+$ calcd for $C_{15}H_{21}O_3{}^{35}Cl^{79}Br_3$ 520.8724, found 520.8725. There was insufficient material to record an optical rotation.

*(1S,2S,4S,6S,7S,9S,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecane-9-carbonitrile (**29**).* To a solution of *E*-macrocycle **9** (22.5 mg, 0.0672 mmol) in CH_2Cl_2 (400 μL) was added *m*-CPBA (23.2 mg, 75%, 0.101 mmol). The colorless solution was stirred for 2 h until TLC (*n*-hexane/EtOAc 4:1) showed completion of the reaction. The reaction was quenched with 20% Na_2SO_3 (1 mL) and stirred for an additional 5 min. The mixture was extracted with CH_2Cl_2 (3 × 3 mL), the organic layers washed with satd aq $NaHCO_3$ (2 × 3 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo to give a colorless oil (26.2 mg). Column chromatography (*n*-hexane/EtOAc 4:1) gave epoxide **29** (22.8 mg, 0.0439 mmol, 97%) as a colorless oil: R_f 0.15 (*n*-hexane/EtOAc 4:1); IR (neat) 2926, 1673, 1260, 1090, 927 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.51 (dd, J = 5.1, 3.0 Hz, 1H), 4.42 (dt, J = 11.0, 3.2 Hz, 1H), 4.37−4.32 (m, 3H), 3.36 (dt, J = 9.4, 2.1 Hz, 1H), 3.22 (dq, J = 8.4, 6.4 Hz, 1H), 2.84 (ddd, J = 14.6, 4.5, 2.0 Hz, 1H), 2.76−2.67 (m, 2H), 2.50 (ddd, J = 14.8, 11.1, 8.9 Hz, 1H), 2.42 (dd, J = 14.2, 6.4 Hz, 1H), 2.00 (ddd, J = 14.7, 3.4, 0.9 Hz, 1H), 1.67 (ddd, J = 14.7, 9.4, 2.5 Hz, 1H), 1.42 (d, J = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 119.1, 82.7, 81.5, 79.2, 69.6, 62.5, 61.5, 58.5, 55.1, 42.8, 39.9, 37.0, 19.7; MS (CI^+, NH_3) m/z 350, 352, 354 $(M + H)^+$; HRMS (CI^+, NH_3) m/z $[M + H]^+$ calcd for $C_{13}H_{18}NO_3{}^{35}Cl^{79}Br$ 350.0159, found 350.0161.

*(1R,3S,5S,6S,7R,9S,10R,12R)-9-Bromo-12-chloro-6-hydroxy-10-methoxy-5-methyl-4,13-dioxabicyclo[5.5.1]tridecane-3-carbonitrile (**30**).* To a solution of epoxide **29** (5.0 mg, 0.014 mmol) in MeOH (200 μL) was added CSA (0.33 mg, 0.0014 mmol), and the cloudy suspension was stirred for 2 h. A further quantity of CSA was added (0.33 mg, 0.0014 mmol) and stirring continued for 2 h until TLC (*n*-hexane/EtOAc 2:1) showed completion of the reaction. Water (1 mL) was added to the reaction mixture, which was then extracted with CH_2Cl_2 (3 × 3 mL), dried over Na_2SO_4, and filtered, solvent was removed in vacuo, and the product was chromatographed (*n*-hexane/EtOAc 2:1) to give compound **30** (5.0 mg, 0.0439 mmol, 93%) as a colorless oil: R_f 0.08 (*n*-hexane/EtOAc 2:1); $[\alpha]_D$ −0.09 (*c* 0.24, MeOH/$CHCl_3$ 1:1); IR 3357, 2923, 1641, 1082 cm^{-1}; ^1H NMR (400 MHz, CD_3OD: $CDCl_3$ 1:1) δ 4.82 (t, J = 3.8 Hz, 1H), 4.70 (dd, J = 11.9, 2.0 Hz, 1H), 4.21 (dt, J = 5.9, 1.7 Hz, 1H), 4.03 (d, J = 7.1 Hz, 1H), 3.95 (d, J = 11.0 Hz, 1H), 3.71 (t, J = 10.0 Hz, 1H), 3.58 (dq, J = 9.3, 6.3 Hz, 1H), 3.36 (s, 3H), 3.07 (t, J = 9.2 Hz, 1H), 2.92 (ddd, J = 16.2, 7.2, 1.8 Hz, 1H), 2.60 (ddd, J = 15.2, 4.2, 1.3 Hz, 1H), 2.36 (ddd, J = 14.3, 11.9, 10.7 Hz, 1H), 2.19 (ddd, J = 15.2, 10.7, 3.5 Hz, 1H), 2.12 (dd, J = 16.2, 5.6 Hz, 1H), 1.69 (dt, J = 14.5, 1.7 Hz, 1H), 1.35 (d, J = 6.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, CD_3OD: $CDCl_3$ 1:1) δ 118.3, 86.8, 85.4, 84.5, 79.2, 73.4, 71.5, 63.3, 60.4, 55.7, 42.1, 40.3, 38.3, 19.8; HRMS (ES^-, TOF) m/z $[M + HCO_2]^-$ calcd for $C_{15}H_{22}NO_6{}^{35}Cl^{79}Br$ 426.0319, found 426.0319.

*(1R)-1-[(1S,2S,4S,6S,7S,9S,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecan-9-yl]prop-2-yn-1-ol (**31**).* To a stirred solution of nitrile **29** (21.0 mg, 0.0599 mmol) in THF (300 μL) at −78 °C was added DIBAL-H in THF (105 μL, 0.86 M, 0.0898 mmol), and the colorless solution was warmed to −40 °C. After 30 min, a further aliquot of DIBAL-H in THF (105 μL, 0.86 M, 0.0898 mmol) was added and the mixture stirred for an additional 30 min until TLC (*n*-hexane/EtOAc 1:1) showed completion of the reaction. The reaction was quenched with a 1 M aqueous citric acid solution (1 mL) and stirred for 15 min. The mixture was extracted with CH_2Cl_2 (3 × 3 mL), the organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo to give the desired aldehyde as a white solid (10.5 mg) that was carried through to the next step without further purification. To a stirred solution of the crude aldehyde (10.5 mg) in THF (300 μL) at 0 °C was added ethynylmagnesium bromide in THF (89 μL, 0.5 M, 0.0447 mmol) and the yellow solution stirred for 30 min. A second aliquot of ethynylmagnesium bromide in THF (100 μL, 0.5 M, 0.0500 mmol) was added and the mixture stirred for an additional 1 h. A third aliquot of ethynylmagnesium bromide in THF (100 μL, 0.5 M, 0.0500 mmol) was added and stirred for an additional 30 min until TLC (*n*-hexane/EtOAc 1:1) showed completion of the reaction. The reaction was quenched with satd aq NH_4Cl (1 mL) and stirred for 5 min. The mixture was extracted with CH_2Cl_2 (3 × 3 mL), the organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo to give a yellow oil (12.4 mg). Column chromatography (toluene/MeCN 9:1) gave title compound **31** (7.0 mg, 0.018 mmol, 31%, 3:1 dr) as a colorless oil: R_f 0.09 (toluene/ MeCN 9:1); ^1H NMR (400 MHz, $CDCl_3$) δ 4.51 (dd, J = 5.3, 3.0 Hz, 1H), 4.45−4.35 (m, 3H), 4.32 (td, J = 4.7, 2.2 Hz, 0.77H), 4.19 (ddd, J = 7.1, 4.7, 2.2 Hz, 0.23H), 3.72 (dd, J = 8.3, 4.7 Hz, 0.25H), 3.67 (dd, J = 8.1, 4.8 Hz, 0.75H), 3.43 (dt, J = 9.3, 2.1 Hz, 1H), 3.32 (dq, J = 8.2, 6.4 Hz, 0.25H), 3.24 (dq, J = 8.4, 6.4 Hz, 0.76H), 2.84 (ddd, J = 14.6, 4.8, 2.0 Hz, 1H), 2.77 (dd, J = 8.3, 2.3 Hz, 1H), 2.74 (ddd, J = 13.8, 8.4, 5.1 Hz, 1H), 2.49 (d, J = 2.2 Hz, 0.61H), 2.47 (d, J = 2.2 Hz, 0.20H), 2.41 (dd, J = 14.1, 6.5 Hz, 1H), 2.23 (d, J = 4.7 Hz, 0.67H), 2.05 (ddd, J = 14.6, 11.0, 8.1 Hz, 1H), 1.92 (dd, J = 14.3, 2.7 Hz, 0.75H), 1.77 (dd, J = 14.6, 2.6 Hz, 0.24H), 1.70 (ddd, J = 14.6, 9.3, 2.3 Hz, 1H), 1.42 (d, J = 6.4 Hz, 0.73H), 1.40 (d, J = 6.4 Hz, 2.27H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 84.7, 83.0, 81.4, 79.1, 77.2, 74.6, 65.9, 63.4, 62.4, 58.9, 55.6, 42.8, 39.9, 32.9, 20.5; HRMS (ES^+, TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{21}O_4{}^{79}Br^{35}Cl$ 379.0307, found 379.0306. The alcohol dr was established by integration of the C_3 proton resonances at 3.72 ppm (minor) and 3.67 ppm (major).

*(1S,2S,4S,6S,7S,9S,11R,12R)-2-Bromo-9-[(R_a)-3-bromopropa-1,2-dien-1-yl]-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]-tetradecane, 12-Epoxyobtusallene II (**32**).* To a stirred solution of alcohol **31** (5.9 mg, 0.016 mmol, 3:1 dr) in CH_2Cl_2 (200 μL) was added a solution of TrisCl and DMAP in CH_2Cl_2 (253 μL, 0.0613 M, 0.0155 mmol of each). The colorless solution was stirred for 17 h until TLC (*n*-hexane/EtOAc 2:1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane/EtOAc 2:1. The solvent was removed in vacuo to give a white solid (6.2 mg). Column chromatography (*n*-hexane/EtOAc 25:1) gave the corresponding trisylate (6.2 mg, 0.0096 mmol, 62%, 3:1 dr) as a white solid: R_f 0.43 (*n*-hexane/EtOAc 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 2H), 5.03 (dd, J = 4.7, 2.2 Hz, 0.75H), 5.01 (dd, J = 5.7, 2.2 Hz, 0.25H), 4.49 (dd, J = 5.1, 2.8 Hz, 1H), 4.40−4.32 (m, 3H), 4.13 (hept, J = 6.7 Hz, 2H), 3.83 (dd, J = 7.9, 4.7 Hz, 0.75H), 3.79 (dd, J = 7.9, 5.9 Hz, 0.25H), 3.39 (dt, J = 9.4, 2.2 Hz, 1H), 3.21 (dq, J = 7.9, 6.3 Hz, 0.75H), 3.16 (dq, J = 7.8, 6.3 Hz, 0.25H), 2.91 (hept, J = 7.4 Hz, 1H), 2.82 (ddd, J = 14.7, 4.7, 2.0 Hz, 1H), 2.76−2.68 (m, 2H), 2.39 (dd, J = 14.1, 6.4 Hz, 1H), 2.32 (d, J = 2.2 Hz, 0.76H), 2.26 (d, J = 2.2 Hz, 0.25H), 2.13−2.03 (m, 1H), 1.87 (dd, J = 14.4, 2.8 Hz, 0.25H), 1.81 (dd, J = 14.5, 2.9 Hz, 0.75H), 1.66 (ddd, J = 14.6, 9.4, 2.3 Hz, 1H), 1.36 (d, J = 6.4 Hz, 0.73H), 1.30−1.23 (m, 21H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.8, 154.0, 150.9, 123.7, 83.0, 82.5, 81.9, 79.1, 77.2, 76.9, 72.2, 63.3, 62.2, 58.8, 55.5, 42.8, 40.0, 34.3, 33.7, 29.7, 24.8, 24.7, 24.6, 23.6, 19.7. LiBr (11.4 mg, 0.131 mmol) and CuBr (18.8 mg, 0.131 mmol) were dissolved in CH_2Cl_2 (1.20 mL). The mixture was stirred at room temperature for 1 h, during which time the salts dissolved and turned bright green. To a stirred solution of the above trisylate (6.2 mg, 0.0096 mmol, 3:1 dr) in CH_2Cl_2 (300 μL) was added the $LiCuBr_2$ solution (265 μL, 0.109 M, 0.0289 mmol). The green solution was heated to 60 °C and stirred for 4 h until TLC (*n*-hexane/EtOAc 2:1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane/EtOAc 2:1. The solvent was removed in vacuo and chromatographed (toluene to toluene/MeCN 50:1) to give title compound **32** (3.6 mg, 0.0096 mmol, 85%, 3:1 dr) as a white solid: R_f 0.52 (*n*-hexane/EtOAc 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (dd, J = 5.7, 2.0 Hz, 0.18H), 6.04 (dd, J = 5.7, 1.7 Hz, 0.54H), 5.43 (t, J = 5.9 Hz, 0.60H), 5.41 (t, J = 5.8 Hz, 0.20H), 4.53 (dd, J = 5.5, 3.1 Hz, 0.24H), 4.50 (dd, J = 5.3, 3.0 Hz, 0.76H), 4.46−4.32 (m, 3H), 4.18 (ddd, J = 7.9, 6.0, 1.7 Hz, 0.75H), 4.13 (td, J = 6.8, 2.1 Hz, 0.25H), 3.43 (dt, J = 9.4, 2.2 Hz, 1H), 3.17−3.07 (m, 1H), 2.83 (ddd, J = 14.5, 4.8, 1.9 Hz, 1H), 2.79−2.71 (m, 2H), 2.42 (ddd, J = 14.1, 6.6, 0.7 Hz, 1H), 2.24−2.15 (m, 1H), 1.75−

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1.65 (m, 2H), 1.38 (d, J = 6.3 Hz, 0.75H), 1.37 (d, J = 6.4 Hz, 2.25H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 200.7, 103.1, 82.7, 81.0, 79.9, 79.1, 73.7, 63.5, 62.3, 58.7, 56.0, 42.8, 39.8, 37.1, 20.3; MS (ES^+, TOF) m/z 441, 443, 445, 447 $[M + H]^+$; HRMS (ES^+, TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{20}O_3{}^{35}Cl^{79}Br_2$ 440.9468, found 440.9458. The bromoallene dr was established by integration of the C_1 proton resonances at 6.08 ppm (minor) and 6.04 ppm (major). Approximately 15% of the mixture consisted also of inseparable propargylic bromides in a 3:2 ratio as calculated by comparison of the integral of the C_{15}-methyl protons. The observable peaks are given here: ^1H NMR (400 MHz, $CDCl_3$) δ 5.03 (td, J = 4.5, 2.2 Hz, 0.13H), 3.85−3.77 (m, 0.30H), 3.34−3.20 (m, 0.30H), 2.66 (d, J = 2.4 Hz, 0.06H), 2.65 (d, J = 2.4 Hz, 0.09H), 1.43 (d, J = 6.3 Hz, 0.20H), 1.43 (d, J = 6.4 Hz, 0.30H).

*(1R,2S,3S,5S,7R,8R,10R,11S)-11-Bromo-5-[(R_a)-3-bromopropa-1,2-dien-1-yl]-8-chloro-10-methoxy-3-methyl-4,13-dioxabicyclo-[5.5.1]tridecan-2-ol, Marilzabicycloallene C (**5**).* To a sample of epoxide **32** (2.0 mg, 0.0045 mmol) was added a solution of CSA in MeOH (100 μL, 0.0043 μM, 0.00043 mmol) and the suspension stirred for 1 h. An additional aliquot of CSA in MeOH (100 μL, 0.0043 μM, 0.00043 mmol) was added and stirring resumed for 1 h until TLC (*n*-hexane/EtOAc 2:1) showed completion of the reaction. The reaction was quenched with satd aq $NaHCO_3$ (1 mL) and stirred for 5 min. The mixture was partitioned between water (1 mL) and CH_2Cl_2 (3 mL), separated, and extracted further with CH_2Cl_2 (2 × 3 mL). The organic layer was dried over Na_2SO_4 and the solvent removed in vacuo to give a white solid (2.5 mg). Column chromatography (*n*-hexane/EtOAc 4:1 to 2:1) gave title compound **5** (2.0 mg, 0.042 mmol, 94%, 3:1 dr) as a white solid: R_f 0.19 (*n*-hexane/EtOAc 2:1); ^1H NMR (500 MHz, $CDCl_3$) δ 6.09 (dd, J = 5.7, 2.2 Hz, 0.18H), 6.05 (dd, J = 5.7, 2.1 Hz, 0.54H), 5.47 (t, J = 5.5 Hz, 0.60H), 5.40 (t, J = 5.3 Hz, 0.20H), 4.85 (t, J = 3.9 Hz, 1H), 4.33 (ddt, J = 9.6, 5.0, 2.2 Hz, 1H), 4.18 (dt, J = 5.7, 1.9 Hz, 1H), 4.06 (d, J = 7.2 Hz, 1H), 3.89 (dt, J = 10.9, 1.7 Hz, 1H), 3.74 (t, J = 9.9 Hz, 1H), 3.57 (dq, J = 9.0, 6.1 Hz, 1H), 3.37 (s, 3H), 3.25 (td, J = 9.2, 5.6 Hz, 1H), 2.90 (ddd, J = 16.1, 7.1, 1.9 Hz, 1H), 2.59 (ddd, J = 15.0, 4.1, 1.3 Hz, 1H), 2.27 (ddd, J = 15.6, 10.8, 3.6 Hz, 1H), 2.19 (dd, J = 16.5, 10.6 Hz, 1H), 2.13 (dt, J = 14.5, 10.9 Hz, 1H), 1.52−1.46 (m, 1H), 1.36 (d, J = 6.2 Hz, 0.75H), 1.35 (d, J = 6.2 Hz, 2.25H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 200.9, 103.2, 86.7, 85.1, 84.5, 81.1, 79.0, 74.7, 74.1, 63.9, 61.0, 56.0, 42.2, 40.4, 38.8, 20.5; HRMS (ES^-, TOF) m/z $[M + CHO_2]^-$ calcd for $C_{17}H_{24}O_6{}^{35}Cl^{79}Br_2$ 516.9628, found 516.9639. The bromoallene dr was established by integration of the C_1 proton resonances at 6.09 ppm (minor) and 6.05 ppm (major).

*(1R,3S,5S,6S,7R,9S,10R,12R)-9-Bromo-6,10,12-trichloro-5-methyl-4,13-dioxabicyclo[5.5.1]tridecane-3-carbonitrile (**33**).* To a solution of macrocycle **9** (10.0 mg, 0.0299 mmol) in CH_2Cl_2 (360 μL) were added TMG (0.1 μL, 0.0008 mmol), TMSCl (4.2 μL, 0.033 mmol), and NCS (8.0 mg, 0.060 mmol). The colorless solution was stirred for 3 h until TLC (*n*-hexane/EtOAc 4:1) showed completion of the reaction. The reaction was quenched with 10% Na_2SO_3 (1 mL) and stirred for an additional 5 min. The mixture was extracted with CH_2Cl_2 (3 × 3 mL), dried over Na_2SO_4, and filtered and the solvent removed in vacuo to give a colorless oil (18.0 mg). Column chromatography (*n*-hexane/EtOAc 10:1) gave trichloride **33** (10.6 mg, 0.0261 mmol, 87%) as a colorless oil: R_f 0.22 (*n*-hexane/EtOAc 4:1); IR (neat) 2930, 1677, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.98−4.92 (m, 2H), 4.53 (dd, J = 11.9, 1.9 Hz, 1H), 4.05 (dt, J = 5.5, 1.9 Hz, 1H), 3.98−3.88 (m, 2H), 3.74 (dq, J = 9.6, 6.1 Hz, 1H), 3.51 (t, J = 9.7 Hz, 1H), 3.23 (ddd, J = 16.5, 8.1, 2.1 Hz, 1H), 2.78 (ddd, J = 15.0, 4.7, 1.3 Hz, 1H), 2.63 (ddt, J = 16.4, 5.4, 1.1 Hz, 1H), 2.54 (ddd, J = 14.6, 11.9, 10.9 Hz, 1H), 2.33 (ddd, J = 15.1, 10.4, 3.1 Hz, 1H), 1.69 (dt, J = 14.6, 1.7 Hz, 1H), 1.52 (d, J = 6.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 117.4, 86.7, 85.3, 84.2, 71.9, 62.6, 62.5, 62.1, 59.6, 45.1, 44.1, 37.9, 21.9; HRMS (ES^-, TOF) m/z $[M + HCO_2]^-$ calcd for $C_{14}H_{18}NO_4{}^{35}Cl_3{}^{79}Br$ 447.9485, found 447.9480.

*(1R)-[(1R,3S,5S,6S,7R,9S,10R,12R)-9-Bromo-6,10,12-trichloro-5-methyl-4,13-dioxabicyclo[5.5.1]tridecan-3-yl]prop-2-yn-1-ol (**34**).* To a stirred solution of nitrile **33** (5.0 mg, 0.012 mmol) in THF (200 μL) at −78 °C was added DIBAL-H in THF (22 μL, 0.86 M, 0.019 mmol), and the colorless solution warmed to room temperature and stirred for 30 min until TLC (*n*-hexane/EtOAc 2:1) showed completion of the reaction. The reaction was quenched with a 1 M aqueous citric acid solution (2 mL) and stirred for 10 min. The mixture was extracted with CH_2Cl_2 (3 × 3 mL), the organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo to give the desired crude aldehyde as a cloudy oil (7.5 mg) which was carried through to the next step without further purification. To a stirred solution of the crude aldehyde (7.5 mg) in THF (150 μL) at 0 °C was added ethynylmagnesium bromide in THF (37 μL, 0.5 M, 0.019 mmol) and the yellow solution stirred for 30 min until TLC (*n*-hexane/EtOAc 1:1) showed completion of the reaction. The reaction was quenched with satd aq NH_4Cl (1 mL) and stirred for 5 min. The mixture was extracted with CH_2Cl_2 (3 × 3 mL), the organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo to give a yellow oil (5.2 mg). Column chromatography (*n*-hexane/EtOAc 1:1) gave title compound **34** (4.2 mg, 0.0097 mmol, 79%, 4.5:1 dr) as a colorless oil: R_f 0.52 (*n*-hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.05−4.97 (m, 2H), 4.30 (dd, J = 4.9, 2.2 Hz, 0.82H), 4.17 (dd, J = 5.7, 1.7 Hz, 0.18H), 4.11−4.08 (m, 1H), 4.05−3.93 (m, 2H), 3.85−3.74 (m, 2H), 3.58 (t, J = 9.7 Hz, 1H), 3.28 (ddd, J = 16.4, 8.0, 2.0 Hz, 1H), 2.82 (ddd, J = 15.1, 4.7, 1.3 Hz, 1H), 2.65 (ddt, J = 16.4, 5.4, 1.2 Hz, 1H), 2.53 (d, J = 2.2 Hz, 1H), 2.37 (ddd, J = 15.2, 10.4, 3.2 Hz, 1H), 2.20 (dt, J = 14.5, 11.2 Hz, 1H), 1.76−1.67 (m, 1H), 1.54 (d, J = 6.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 86.8, 86.2, 85.2, 84.0, 75.3, 74.8, 68.2, 63.5, 63.0, 63.0, 60.1, 45.3, 44.3, 38.8, 22.1. The alcohol dr was established by integration of the C_3 proton resonances at 4.30 ppm (major) and 4.17 ppm (minor).

*(1R,2S,3S,5S,7R,8R,10R,11S)-11-Bromo-5-[(R_a)-3-bromopropa-1,2-dien-1-yl]-2,8,10-trichloro-3-methyl-4,13-dioxabicyclo[5.5.1]-tridecane, Marilzabicycloallene D (**6**).* To a stirred solution of alcohol **34** (2.5 mg, 0.0061 mmol, 4.5:1 dr) in CH_2Cl_2 (100 μL) was added a solution of TrisCl and DMAP in CH_2Cl_2 (100 μL, 0.061 M, 0.0061 mmol of each). The colorless solution was stirred for 17 h until TLC (*n*-hexane/EtOAc 2:1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane/EtOAc 2:1. The solvent was removed in vacuo to give a white solid (6.2 mg). Column chromatography (*n*-hexane/EtOAc 25:1) gave the corresponding trisylate (3.0 mg, 0.0043 mmol, 70%, 4.5:1 dr) as a white solid: R_f 0.43 (*n*-hexane/EtOAc 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 2H), 5.04 (dd, J = 6.2, 2.3 Hz, 0.18H), 5.02−4.96 (m, 2.72H), 4.14 (hept, J = 6.5 Hz, 2H), 4.06 (dt, J = 5.3, 1.9 Hz, 1H), 4.03−4.00 (m, 1H), 3.99−3.96 (m, 1H), 3.93 (dt, J = 11.1, 1.6 Hz, 1H), 3.78 (q, J = 6.1 Hz, 0.18H), 3.75 (q, J = 6.1 Hz, 0.82H), 3.54 (t, J = 9.7 Hz, 0.20H), 3.52 (t, J = 9.7 Hz, 0.80H), 3.26 (ddd, J = 16.3, 8.3, 2.1 Hz, 1H), 2.94 (hept, J = 6.8 Hz, 1H), 2.80 (ddd, J = 15.1, 4.8, 1.5 Hz, 1H), 2.64 (ddt, J = 16.2, 5.3, 1.0 Hz, 1H), 2.35 (ddd, J = 15.1, 10.4, 2.9 Hz, 1H), 2.33 (d, J = 2.2 Hz, 0.79H), 2.30 (d, J = 2.2 Hz, 0.18H), 2.17 (dt, J = 14.3, 11.1 Hz, 1H), 1.70−1.61 (m, 1H), 1.50 (d, J = 6.1 Hz, 0.54H), 1.45 (d, J = 6.1 Hz, 2.55H), 1.33−1.26 (m, 18H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.0, 150.9, 123.7, 110.0, 85.9, 85.3, 84.4, 83.8, 77.2, 76.3, 71.6, 63.3, 63.0, 62.9, 60.7, 45.5, 40.2, 34.6, 34.3, 33.2, 24.8, 24.7, 23.6, 21.5. LiBr (25 mg, 0.29 mmol) and CuBr (42 mg, 0.29 mmol) were dissolved in CH_2Cl_2 (1.0 mL). The mixture was stirred at room temperature for 1 h, during which time the salts dissolved and turned bright green. To a stirred solution of the above trisylate (3.0 mg, 0.0043 mmol, 4.5:1) in CH_2Cl_2 (100 μL) was added the $LiCuBr_2$ solution (80 μL, 0.29 M, 0.023 mmol). The green solution was stirred for 1 h at room temperature then heated to 60 °C for 2 h until TLC (*n*-hexane/EtOAc 2:1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane/EtOAc 2:1. The solvent was removed in vacuo to give title compound **6** (2.0 mg, 0.0040 mmol, 93%, 4.5:1 dr) as a white solid: R_f 0.63 (*n*-hexane/EtOAc 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.10 (dd, J = 5.7, 2.2 Hz, 0.11H), 6.07 (dd, J = 5.7, 2.1 Hz, 0.52H), 5.43 (t, J = 5.5 Hz, 0.61H), 5.38 (t, J = 5.3 Hz, 0.15H), 5.01 (d, J = 7.7 Hz, 1H), 4.96 (dd, J = 4.3, 3.0 Hz, 1H), 4.35 (ddt, J = 11.2, 5.5, 2.1 Hz, 1H), 4.06 (dt, J = 5.2, 1.9 Hz, 1H), 3.97 (dd, J = 10.3, 9.8, 1.2 Hz, 1H), 3.93 (dt, J = 11.0, 1.9 Hz, 1H), 3.75 (dq, J = 9.8, 6.1 Hz, 1H), 3.51 (t, J = 9.7 Hz, 1H), 3.25 (ddd, J = 16.4, 7.9, 2.0 Hz, 1H), 2.79 (ddd, J = 15.2,

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4.5, 1.3 Hz, 1H), 2.62 (ddt, J = 16.3, 5.6, 1.1 Hz, 1H), 2.35 (ddd, J = 15.2, 10.4, 3.3 Hz, 1H), 2.18 (dt, J = 14.5, 11.1 Hz, 1H), 1.52−1.48 (m, 1H), 1.47 (d, J = 6.2 Hz, 0.57H), 1.46 (d, J = 6.1 Hz, 2.51H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 200.9, 102.7, 86.1, 85.0, 84.3, 81.1, 74.3, 63.4, 63.0, 62.9, 60.1, 45.2, 44.1, 38.3, 22.4; HRMS (ES^+, TOF) m/z $[M - Cl]^+$ calcd for $C_{15}H_{19}O_2{}^{35}Cl_2{}^{79}Br_2$ 458.9129, found 458.9131. The bromoallene dr was established by integration of the C_1 proton resonances at 6.10 ppm (minor) and 6.07 ppm (major). 10% of the mixture consisted also of inseparable propargylic bromides in a 1:1 ratio as calculated by integration of their terminal alkyne protons. The observable peaks are given here: ^1H NMR (400 MHz, $CDCl_3$) δ 2.70 (d, J = 2.5 Hz, 0.05H), 2.68 (d, J = 2.4 Hz, 0.05H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02008.

X-ray crystal structures for nitrile epimers **9** and **10** including overlays with previously determined X-ray crystal structures of obtusallene II (**1**) and obtusallene IV (**2**); ^1H NMR $\Delta\delta$, ^{13}C NMR $\Delta\delta$, ^1H NMR ΔJ root-mean-square analyses, and ^1H NMR multiplicity truth tables of synthetic versus natural **5**−**8**; chiral HPLC chromatograms of epoxides **18** and (±)-**18**; ^1H and ^{13}C NMR spectra for all new compounds, known compounds prepared using modified procedures (**13**, **20**−**21**), and the natural products **5**−**8** (PDF)

X-ray crystal structures for nitrile epimers **9** and **10** (CIF) NMR spectra as FID and transformed spectra accessed via ref 35 using the Mpublish system introduced by MESTRELAB RESEARCH, S.L.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: c.braddock@imperial.ac.uk.

Notes

The authors declare no competing financial interest.

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(25) Model substrates were obtained by the acetalization of heptenal with (±)-but-3-yn-2-ol and subsequent cyanation. The resulting residual alkyne could be subsequently manipulated to give an alkene, alkane, or epoxide functional group.
(26) The ^{1}H and ^{13}C NMR data for this compound matched exactly the data in the literature (see the Supporting Information).
(27) Obtusallene X (**8**) was reported (ref 15) as a compound that showed signals in its ^{1}H NMR in $CDCl_3$ at 298 K that were attributed to two interconverting conformers. Synthetic obtusallene X (**8**) reported here did not display this behavior and showed only one set of resonances (see the Supporting Information).
(28) Model deoxygenations were successfully effected using activated Zn dust (6.6 equiv) in conjunction with $CpTiCl_2$ (2.2 equiv) in THF at rt on the epimeric epoxides obtained from epoxidation of (1*Z*,5*S**,6*S**)-5-bromo-6-chlorocyclooct-1-ene, returning this same alkene. These epoxides have been reported previously from an alternative route (ref 38).
(29) The isolation of (12*S*,13*S*)-epoxyobtusallene IV was reported during the preparation of this manuscript: Gutiérrez-Cepeda, A.; Fernández, J. J.; Norte, M.; López-Rodríguez, M.; Brito, I.; Muller, C. D.; Souto, M. L. *J. Nat. Prod.* **2016**, *79*, 1184−1188.
(30) Attempts to deoxygenate epoxide **32** to obtusallene II also failed. In an alternative strategy to access obtusallene II, the olefin of nitrile **9** could be dihydroxylated to give an *S*,*S*-diol. A successful Corey−Winter deoxygenation could then be demonstrated. However, a successful Corey−Winter deoxygenation could not be effected post nitrile reduction.
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