Bromonium-Ion Induced Transannular Oxonium Ion Formation-Fragmentation in Model Obtusallene Systems and Structural Reassignment of Obtusallenes V-VII

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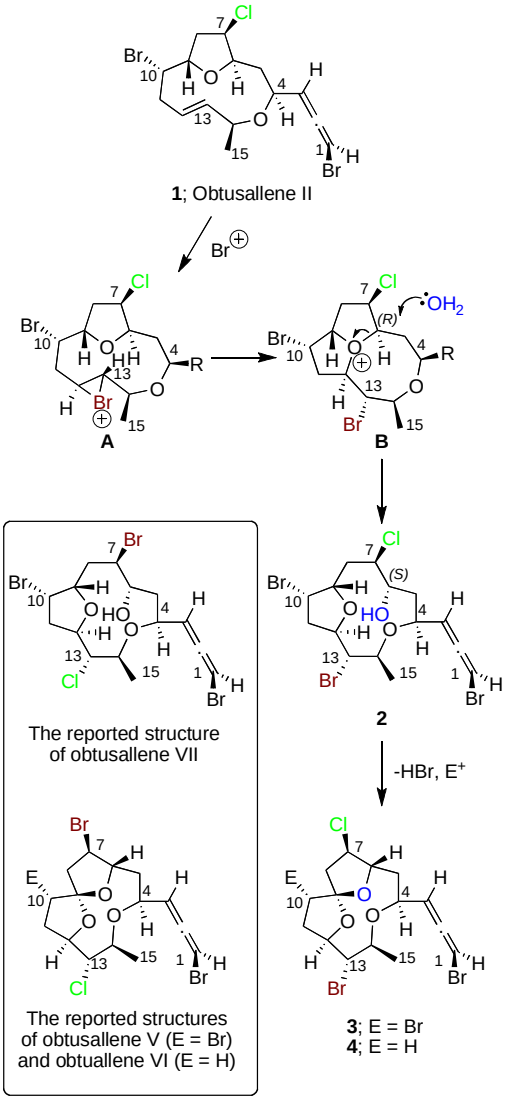
Abstract: Ring-closing metathesis was used to construct the strained 11-membered ring of obtusallenes II (and IV). Bromonium-ion induced transannular oxonium ion formation-fragmentation gave the macrocyclic carbon skeleton of obtusallene VII with a bromine atom at C-13 in line with a previously published hypothesis. An additional brominated [5.5.1]bicyclotridecane adduct that must arise from a bromonium-ion induced transannular oxonium ion formation-fragmentation could also be isolated, suggesting that this adduct represents the core of an as yet undiscovered natural product. An authentic sample of obtusallene V was studied by NMR spectroscopy and the position of the halogens at C-7 and C-13 were reassigned on the basis of a ^{13}C NMR chlorine-induced isotopic shift. This revised structure was subsequently confirmed by X-ray crystallography. These findings allow us to confidently conclude that the structures of obtusallenes VII and VI should also be reassigned.

Introduction

Recently one of us proposed an internally self-consistent hypothesis concerning the biosynthesis of the obtusallene family – complex halogenated C_{15}-acetogenic marine natural products isolated from *Laurencia* species. Multiple electrophilic bromination events are invoked.[1,2,3] The hypothesis correctly predicts the macrocyclic carbon frameworks, and all relative and absolute stereochemistries of obtusallene I,[4,5] obtusallenes II and III,[6] and obtusallene IV[7,8] whose structures have all been unambiguously solved by X-ray crystallography. It also correctly predicts the macrocyclic carbon frameworks, and the absolute and relative stereochemistries of all the stereocentres for obtusallenes V-VII.[9,10] Interestingly, while the reported structures of obtusallenes V-VII - as solved by NMR spectroscopy - show a bromine atom at C-7 and a chlorine atom at C-13, the hypothesis predicts that obtusallenes V-VII should bear a bromine atom at C-13 and a chlorine atom at C-7.[1,11] This prediction arises from invoking an electrophilic bromination of the C12-13 *trans*-double bond in obtusallene II (**1**) to give bromonium ion **A** (Scheme 1), followed by transannular attack of the THF-oxygen at C-12 to generate tricyclic oxonium ion **B**. This intermediate would subsequently undergo nucleophilic attack at C-6 by water with the signature inversion of stereochemistry.[1] Thus, the hypothesis predicts that the actual structure of obtusallene VII is represented by compound **2**. Subsequently, invoking HBr elimination across C9-10 and spiroketalization *via* electrophilic bromination or protonation of the resulting enol ether leads to the conclusion that obtusallene V and obtusallene VI may be represented by structures **3** and **4**, respectively. Therefore there is a need to investigate the viability of this bromonium ion induced transannular oxonium ion formation-fragmentation

experimentally, in order to validate the proposed biosynthetic pathway and as a consequence, confirm or correct the reported structures of obtusallenes V-VII.



Scheme 1. Proposed bromonium ion-driven rearrangement from obtusallene II (R = *R*-bromoallene)

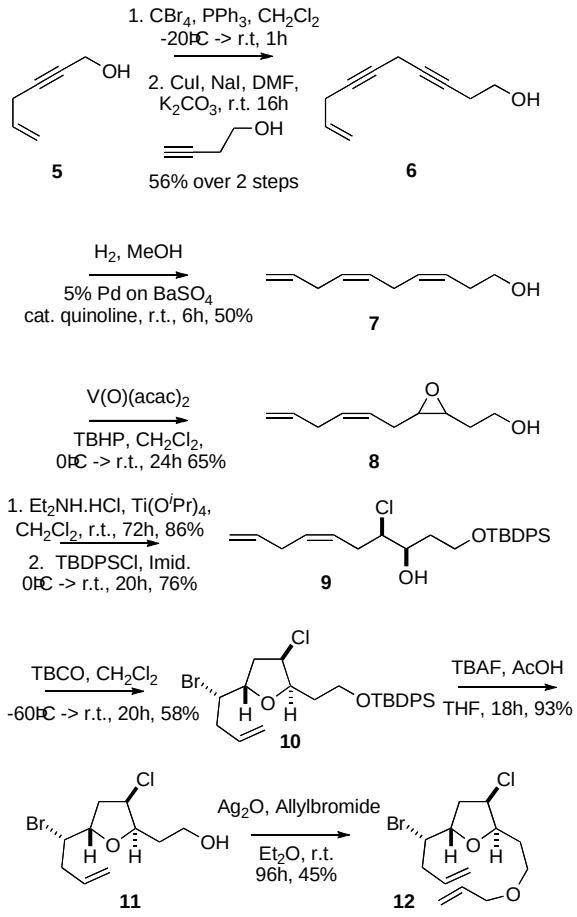
In this paper we show that i) strained macrocycles corresponding to obtusallene II can be prepared by ring-closing metathesis to give the desired *E*-olefin in an eleven-membered

ring; ii) bromonium-ion induced transannular oxonium ion formation-fragmentations occur as predicted to give macrocyclic carbon frameworks corresponding to obtusallene VII with a bromine atom at C-13. The results of these studies strongly support our biosynthetic hypothesis for the obtusallene family. In addition, the isolation of a brominated [5.5.1]bicyclotridecane adduct that must also arise from a bromonium-ion induced transannular oxonium ion formation-fragmentation, suggests that this represents the core of an as yet undiscovered natural product. Furthermore, the observation of a chlorine induced isotopic shift at C-7 in the ^{13}C NMR spectrum of an authentic sample of obtusallene V, and, an X-ray crystallographic determination of its structure allows for the definitive reassignment[11] of obtusallene V as structure **3**, and thence obtusallenes VI and VII as structures **4** and **2**, respectively.

Results and Discussion

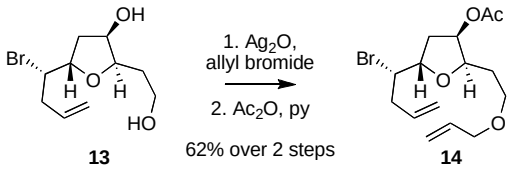
In order to synthesize a macrocyclic model substrate for our studies by ring-closing metathesis, alcohol **5**[12] was activated by conversion to the bromide and immediate coupling[13,14] with but-3-yn-1-ol to give diynene **6** (Scheme 2). *Cis*-selective partial hydrogenation,[14] and directed epoxidation[15] of the resulting *Z*,*Z*-triene alcohol **7** gave epoxide **8**. Regioselective chloride ring-opening[16] and protection of the primary alcohol gave chlorohydrin **9**. Biosynthetically-inspired electrophilic bromoetherification[1,2] gave chlorobromotetrahydrofuran **10** as a single diastereoisomer in excellent yield with all the relative stereochemistry correctly set for the THF core of obtusallene II. Deprotection to

alcohol **11** and allylation[17] gave acyclic diene **12** ready for attempted ring-closing metathesis.



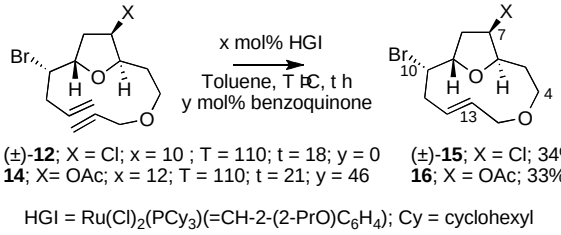
Scheme 2. Preparation of ring-closing metathesis substrate **12**

A second acyclic diene metathesis substrate with an acetate group rather than a chloride at the equivalent C-7 position of obtusallene II position was also prepared. Allylation[17] of enantiopure diol **13**[2] followed by acetylation gave diene **14** ready for ring-closing metathesis (Scheme 3). The acetate group was purposefully introduced to act as a neighboring group participant in the oxonium ion fragmentation (*vide infra*).



Scheme 3. Preparation of ring-closing metathesis substrate **14**

The ring-closing metathesis of dienes **12** and **14** were then explored. Although some spectacular macrocyclic ring-closing metatheses have been performed in recent years[18] the optimum catalyst and conditions tend to be highly substrate dependent.[19] Inspection of the X-ray crystal structure of obtusallene II[6] shows its double bond to be distorted away from planarity, indicative of strain in the macrocycle. In addition, we required only the *E*-olefin, whereas macrocyclic ring-closing metathesis typically provides mixtures of *E* and *Z* olefins. Notwithstanding all these issues we were confident that the desired macrocycles could be constructed in this manner. After much optimization, both substrates **12** and **14** underwent ring-closing metathesis using a Hoveyda modified Grubbs catalyst[20] to provide the macrocyclic *E*-olefins **15** and **16**, respectively (Scheme 4).[21] These macrocyclic alkenes lack only the methyl and bromoallene substituents of obtusallene II (**1**) and should make excellent model systems to explore the proposed bromonium-ion induced transannular oxonium ion formation-fragmentation.[22]



Scheme 4. Ring-closing metatheses to provide macrocycles **15** and **16**.

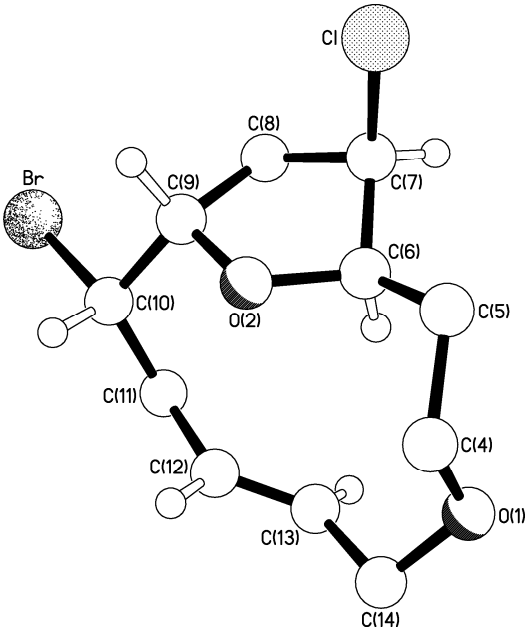


Figure 1. The molecular structure of **15-A**, one of the three crystallographically independent molecules present in the crystals of **15**.

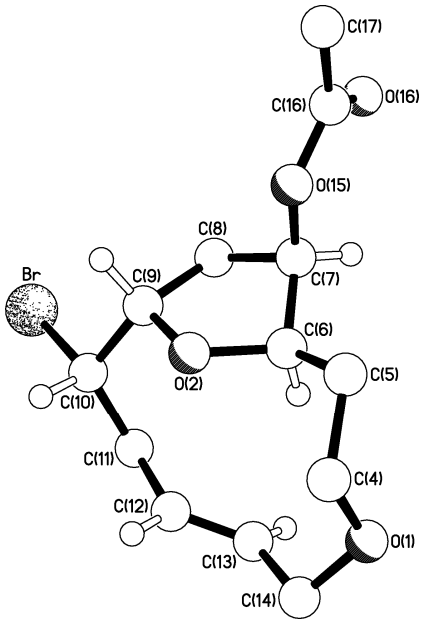


Figure 2. The molecular structure of **16**.

Macrocyclic alkenes **15** and **16** proved to be crystalline and their X-ray crystal structures (Figures 1, 2) were determined confirming the presence of the *E*-double bond in both cases. A distortion of *ca.* 10 degrees of the double bond away from planarity in each case reveals significant strain and underscores further the utility and versatility of the ring-closing metathesis reaction. Macrocycles **15** and **16** have essentially identical conformations (Figure 3), and a comparison with the known X-ray crystal structure of obtusallene II revealed them to be essentially identical outside of a local change in conformation at C14-O-C4-C5 (Figure 4). Of particular note, the transannular separations between the THF oxygen and C-12 are ca. 2.78 Å and 2.780(2) Å in **15**[23] and **16** respectively, distances considerably shorter than the sum of their van der Waal's radii (ca. 3.22 Å), and serves to position the THF oxygen perfectly to trap any bromonium ion formed at C12-13. Interestingly, bromonium ion formation on the exposed *exo* face of the alkene, as seen in the X-ray crystal structures for **1**, **15** and **16**, would lead to a product with the opposite configurations at C-12 and C-13 compared to obtusallene VII. The requisite stereochemistry for obtusallene VII implies bromonium ion formation on the buried *endo* face. This dichotomy can be rationalized by consideration of Guella's careful NMR studies on the obtusallenes. According to these studies, in solution, obtusallenes bearing a *trans*-olefin in the macrocycle are characterized by conformational motion involving 180 degree flipping of the olefinic bond.[7] Clearly, this would expose the other face of the alkene for bromonium ion formation.

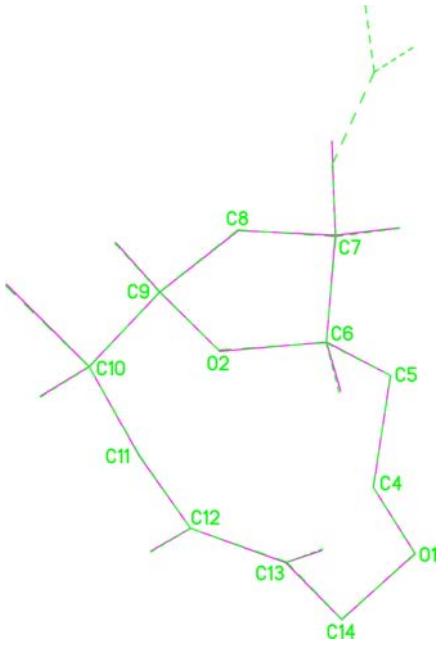


Figure 3. Overlay of molecules **15-A** (magenta) and **16** (green) showing the essentially identical conformations for the 5- and 11-membered ring system.

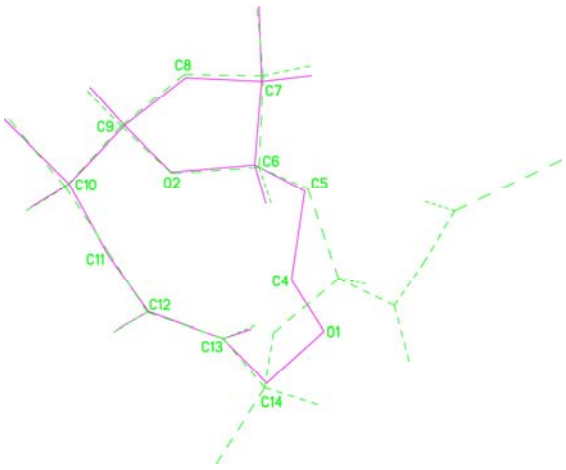
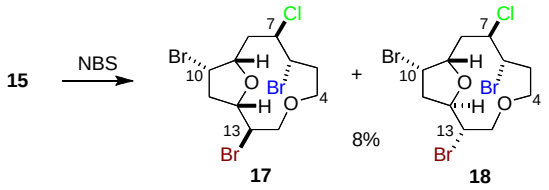


Figure 4. Overlay of molecules **15-A** (magenta) and **1** (green) showing the different conformations for the C14–O1–C4–C5 linkages.

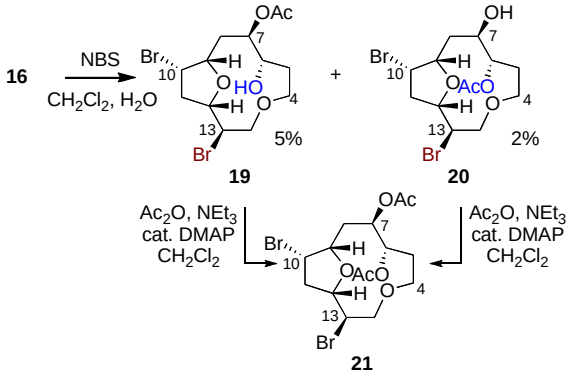


Scheme 5. Products isolated after bromonium-ion induced transannular oxonium ion formation-fragmentation of **15**.

The reaction of macrocycle **15** with NBS was performed in chlorinated solvents saturated with water to encourage progression along the obtusallene VII manifold. After 20 d at rt approximately 50% of the NBS had been consumed and a complex mixture of products had been formed. Extensive column chromatography led to the isolation of a mixture of two components in an approximate 3:2 ratio (8% yield). It was evident by ^{1}H NMR that there was no double bond, and mass spectrometry gave a molecular ion with a characteristic isotopic pattern indicating the presence of three bromine atoms and one chlorine atom. The structures of the two components were solved by X-ray crystallography (See Figure S9, SI) showing that they were the two diastereoisomers **17** and **18** (Scheme 5).[24]

These must have resulted from the predicted bromonium ion induced transannular oxonium ion formation-fragmentation (*c.f.*, Scheme 1) where bromide, rather than water, is functioning as the nucleophile at C-6 with the signature inversion of stereochemistry. In this instance bromide anion presumably arises from the well-known tendency of NBS to produce molecular bromine. It is also evident, by comparison of their stereochemistries at C-12 and C-13 that initial bromonium ion formation occurs on both

faces of the double bond of macrocycle **15.**[25] Most significantly, diastereomer **18** represents the complete macrocyclic carbon framework, with the correct relative stereochemistries of the C-6, C-7, C-9, C-10, C12 and C-13 stereocentres for obtusallene VII, all of which derive from the initial stereocentres of chlorohydrin **9** and two subsequent electrophilic bromination events. Despite the long reaction time, and low isolated yield this result shows that the proposed chemical pathway is perfectly feasible and is therefore completely consistent with our original hypothesis and further supports the reassignment of the structures of obtusallenes V-VII.



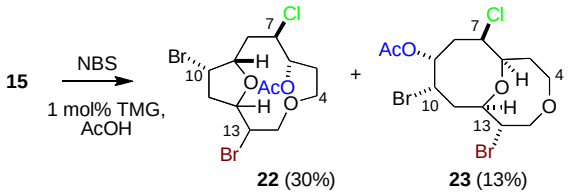
Scheme 6. Products isolated after bromonium-ion induced transannular oxonium ion formation-fragmentation of **16**.

Macrocycle **16** was also treated with NBS to give macrocycles **19** and **20** (Scheme 6). The desired bromonium-ion induced transannular oxonium ion formation-fragmentation (*c.f.*, Scheme 1) has evidently occurred with neighboring group participation of the acetate followed by hydrolysis of the Woodward-type intermediate with adventitious water. The structure of **19** was confirmed by X-ray crystallography (See Figure S10, SI), and the identity of **20** was confirmed by transforming them both into their bis-acetates

which proved to be identical *i.e.* **21**. Although the bromonium ion-induced oxonium ion formation-fragmentation has occurred, the stereochemistry at C-12 and C-13 in **19** and **20** is the opposite to that observed in macrocycle **18** and in obtusallene VII. This illustrates the delicate balance between conformers and reactivity that are clearly in operation here. Again, however, despite the poor yield and long reaction time a bromonium-ion induced transannular oxonium ion formation-fragmentation is clearly a viable chemical pathway.

In an effort to reduce the long reaction times, to increase the yield of these bromonium-ion induced transannular oxonium ion formation-fragmentation reactions, and to introduce an oxygen substituent at C-6 we made two key modifications to our reaction conditions on chloride-containing macrocycle **15**. We elected to catalyse the transfer of electrophilic bromine from NBS by the use of catalytic quantities of tetramethylguanidine.[26] Secondly, we used organic soluble acetic acid as our oxygen-based nucleophile. Much to our delight, the desired bromonium-ion induced transannular oxonium ion formation-fragmentation (*c.f.*, Scheme 1) occurred rapidly (<1 h) with incorporation of acetate at C-6 to give bromoacetate **22** (stereochemistry unassigned at C-12 and C-13) in a much improved yield of 30% (Scheme 7). This is highly significant since the requisite oxygen and halide functionalities have now been installed at C-6 and C-13, respectively, as hypothesized for obtusallene VII. Interestingly, bromoacetate [5.5.1]bicyclotridecane **23** was also isolated in 13% yield from this reaction and characterized by X-ray crystallography (See Figure S11, SI). Evidently, **23** must also have been formed via bromonium-ion induced transannular oxonium ion formation (*c.f.*, Scheme 1), but followed instead by nucleophilic attack of acetate at C-9 as witnessed by the inversion of (relative) stereochemistry at that position. It is interesting to speculate on

the significance of adduct **23**, whereby since the pathway leading to it is apparently competitive with that leading to the obtusallene VII framework **22**, it may represent the core of an as yet undiscovered natural product from *Laurencia* species.



Scheme 7. Bromonium-ion induced transannular oxonium ion formation-fragmentation of **15** using NBS and AcOH catalyzed by TMG.

Finally, extensive NMR experiments on an authentic sample of obtusallene V led to an identical interpretation to that of Guella.[9] Thus, ^{13}C NMR analysis showed a resonance with a chemical shift of 57 ppm corresponding to C-7 and the carbon at C-13 showed a resonance at 61 ppm, where one must bear a chlorine atom and one must bear a bromine atom. Using the chlorine-induced isotopic shift method[27,28] at 323K in C_6D_6 the resonance at 57 ppm resolved into two signals in a 3:1 ratio separated by 8 ppb (Figure 5). This definitively locates the chlorine atom at C-7 and the bromine atom at C-13 in obtusallene V directly in line with our hypothesis. This previously liquid sample proved to be crystalline in our hands and the resulting X-ray crystal structure of obtusallene V (Figure 6) confirms these repositionings of the halogens, confirms all other relative and absolute stereochemistries, and confirms the structure of obtusallene V is that of compound **3**. In light of this finding, and also our experimentally-observed bromonium-

ion induced rearrangements of obtusallene II models to give obtusallene VII macrocyclic frameworks with a bromide at C-13 and a signature inversion of stereochemistry at C-6 in accordance with our hypothesis (*c.f.,* Scheme 1), we now also reassign the structure of obtusallene VII as compound **2**. It follows also that obtusallene VI is reassigned as compound **4**.

Figure 5. Chlorine isotope splitting of the ^{13}C resonance of obtusallene V at 57.4 ppm: the data was zero-filled to give a digital resolution of 0.031 Hz per point.

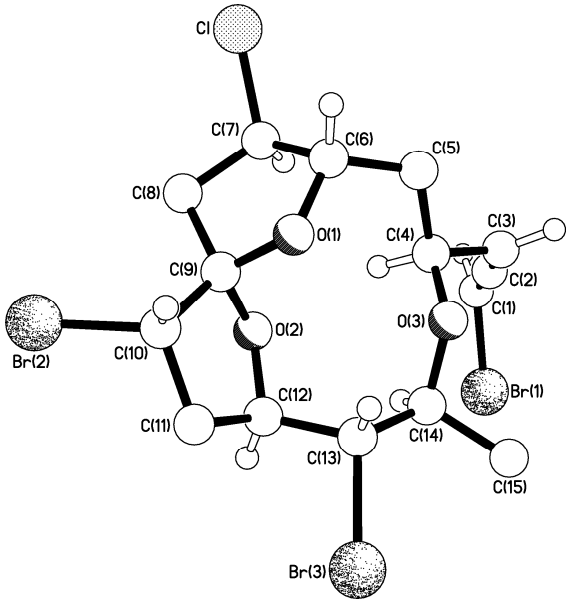


Figure 6. The molecular structure of **3**.

Experimental section

(1*R,6*E*,9*S**,10*S**,12*R**)-9-Bromo-12-chloro-4,13-dioxabicyclo[8.2.1]tridec-6-ene (15).** Tetrahydrofuran **12** (65 mg, 0.20 mmol) was dissolved in toluene (88 mL) and Hoveyda-Grubbs 1st Generation catalyst, $Ru(Cl)_2(PCy_3)(=CH\text{-}2\text{-}(2\text{-}PrO)C_6H_4)$ [Cy = cyclohexyl] (15 mg, 0.02 mmol) was added in one portion. The yellow solution was heated to reflux for 18 h. The solvent was evaporated *in vacuo* and the resulting brown residue was purified by flash column chromatography (3:1 Pet. Ether:EtOAc) to give macrocycle **15** (20 mg, 34%) as a white solid: m.p. 96-98 °C (recrystallized from hexane); IR (neat) 2928, 2871, 1447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (ddd, *J* = 15.2, 10.7, 2.4 Hz, 1H), 5.60-5.52 (m, 1H), 4.76 (ddd, *J* = 9.2, 7.2, 5.6 Hz, 1H), 4.52 (ddd, *J* = 12.5, 5.3, 4.0 Hz, 1H), 4.42 (app. dd, *J* = 4.0, 2.1 Hz, 1H), 4.26 (app. ddd, *J* = 12.3, 4.3, 1.8 Hz, 1H), 4.06-4.01 (m, 2H), 3.44 (dd, *J* = 12.1, 10.6 Hz, 1H), 3.24 (dt, *J* =

12.0, 1.7 Hz, 1H), 2.93-2.86 (m, 1H), 2.57-2.36 (m, 3H), 1.73-1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.6, 125.0, 78.2, 76.6, 73.0, 67.5, 63.0, 50.1, 38.6, 37.5, 32.8; MS (CI^+, NH_3) *m/z* 299, 297 and 295 $(M + H)^+$; HRMS (CI^+, NH_3) *m/z* calcd for $C_{11}H_{17}O_2{}^{35}Cl^{79}Br$ $(M + H)^+$ 295.0100, found 295.0107.

(1*R*,6*E*,9*S*,10*S*,12*R*)-12-Acetoxy-9-bromo-4,13-dioxabicyclo[8.2.1]tridec-6-ene (16). Five identical simultaneous reactions were carried out according to the following protocol. Tetrahydrofuran **14** (0.055 g, 0.16 mmol) was dissolved in anhydrous toluene (10 mL). Aliquots of this solution (2 mL) were added to each of five reaction tubes, and toluene (8 mL) was added to each tube. Benzylidene $Ru(Cl)_2(PCy_3)$(=CH-2-(2-PrO)C_6H_4) [Cy = cyclohexyl] (0.0115 g, 0.02 mmol) was dissolved in anhydrous toluene (10 mL) and 2 mL of this solution added to each of the five sealed tubes. Finally, 1,4-benzoquinone (0.0079 g, 2.3 mmol) was dissolved in toluene (10 mL) and 2 mL of this solution added to each of the five tubes. The five reaction mixtures where then heated at reflux for 21 h. The reaction mixtures were allowed to warm to rt, combined and the solvent evaporated *in vacuo*. The residue was chromatographed (70:30 petroleum ether:Et_2O to 30:70 petroleum ether:Et_2O) to give macrocycle **16** (0.017 g, 33%) as a white solid; m.p. 145-147 °C (recrystallized from hexane); R_f 0.53 (petroleum ether : Et_2O 30 : 70); $[\alpha]_D$ -16.5 (*c* 0.9, $CHCl_3$); IR (neat) 1736 cm^{-1};. ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.73 (ddd, *J* = 15.2, 10.4, 2.4 Hz, 1H), 5.51-5.59 (m, 1H), 5.26-5.27 (br m, 1H,), 4.60-4.65 (m, 1H), 4.46-4.51 (m, 1H), 4.22-4.26 (m, 1H), 3.99 (dt, *J* = 12.0, 3.0 Hz, 1H), 3.93 (app. br d, *J* = 11.6 Hz, 1H), 3.41 (dd, *J* = 12.0, 10.8 Hz, 1H), 3.20 (app. t, *J* = 12.2 Hz, 1H), 2.83-2.89 (m, 1H), 2.47-2.56 (m, 1H), 2.15-2.28 (m, 2H), 2.08 (s, 3H), 1.62-1.70 (m, 1H), 1.35-1.42 (m, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.6, 133.4,

124.9, 78.4, 76.0, 75.7, 73.0, 67.5, 50.6, 37.2, 34.9, 31.1, 21.0; MS (CI^+, NH_3) *m/z* 338 and 336 $(M + NH_4)^+$, 321 and 319 $(M + H)^+$; HRMS (CI^+, NH_3) *m/z* calcd for $C_{13}H_{19}{}^{79}BrO_4$ $(M + H)^+$ 319.0545, found 319.0554. Anal. Found: C, 49.03; H, 6.07. $C_{13}H_{19}BrO_4$ requires C, 48.92, H, 6.00 %.

(1*S,2*R**,7*S**,8*R**,10*S**,11*S**)-8-chloro-4,13-dioxa-2,7,11-tribromobicyclo[8.2.1]tridecane (17) and (1*R**,2*S**,7*S**,8*R**,10*S**,11*S**)-8-chloro-4,13-dioxa-2,7,11-tribromobicyclo[8.2.1]tridecane (18).** Macrocyclic alkene **15** (34 mg, 0.12 mmol) was dissolved in $CDCl_3$ in an NMR tube and NBS (14 mg, 0.12 mmol) added. The mixture was shaken and left covered in foil for a period of 20 d. To the mixture was added CH_2Cl_2 (30 mL) and the solution washed with sodium bisulfite solution (20% w/w) (30 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL x 3), the combined organic layers washed with water (20 mL), brine (20 mL) dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by successive rounds of flash column chromatography (10:1 Pet. Ether:EtOAc) to give the title compounds **17** and **18** as an inseparable mixture in a *ca.* 3:2 ratio (4 mg, 8%) as a white solid. ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.04 (br s, 1H **18**,), 4.92-4.86 (m, 1H **17** + 1H **18**), 4.54-4.44 (m, 1H **17** + 1H **18**), 4.26 (d, *J* = 11.0 Hz, 1H **17**), 4.16-3.86 (m, 4H **17** + 4H **18**), 3.70-3.47 (m, 3H **17** + 3H **18**), 3.10-2.98 (m, 1H **17**), 2.92-2.74 (m, 1H **17** + 1H **18**), 2.60-2.37 (m, 2H **17** + 3H **18**), 2.30-1.93 (m, 2H **17** + 2H **18**); MS (CI^+, NH_3) *m/z* 459, 457, 455, 453 $(M + H)^+$; 476, 474, 472, 470 $(M + NH_4)^+$ HRMS (CI^+, NH_3) *m/z* calcd for $C_{11}H_{17}{}^{79}Br_3{}^{35}ClO_2$ $(M + H)^+$ 452.8467, found 452.8469.

(1*S*,2*R*,7*S*,8*R*,10*S*,11*S*)-8-Acetoxy-2,11-dibromo-4,13-dioxa-7-hydroxybicyclo[8.2.1]tridecane (19) and (1*S*,2*R*,7*S*,8*R*,10*S*,11*S*)-7-Acetoxy-2,11-

dibromo-4,13-dioxa-8-hydroxybicyclo[8.2.1]tridecane (20). Macrocyclic alkene **16** (129 mg, 0.40 mmol) was dissolved in CH_2Cl_2 (13 mL) and NBS (72 mg, 0.40 mmol) added. Periodically, the reaction mixture was worked up as for the conversion of **15** into **18** and **19**. After ^{1}H NMR analysis to monitor conversion, the crude mixture was re-dissolved in CH_2Cl_2 (4 mL, 4 mL) and fresh NBS (72 mg, 144 mg) was added. After the third cycle and a total of *ca.* 100 h reaction time, the mixture was worked up as usual and column chromatography (10:90 petroleum ether:Et_2O and then 30:70 petroleum ether:CH_2Cl_2) gave first isohydroxydibromide **20** (3 mg, 2%) as a colourless oil: $[\alpha]_D^{25}$ -8.7 (*c* 0.16, CH_2Cl_2); IR (KBr) 3550-3100, 1729 cm^{-1}; ^{1}H NMR (500 MHz; CDCl3) δ 4.77 (dd, *J* = 10.3, 4.5 Hz, 1H), 4.60 (ddd, *J* = 11.4, 6.8, 1.1 Hz, 1H), 4.48-4.06 (m, 2H), 3.97 (dd, *J* = 11.9, 6.9 Hz, 1H), 3.83 (dd, *J* = 11.9, 1.8 Hz, 1H), 3.70 (ddd, *J* = 9.8, 3.6, 2.8 Hz, 1H), 3.58 (app. t, *J* = 9.8, 1H) 2.78 (app. quint., *J* = 5.6 Hz, 1H), 2.45-2.34 (m, 2H) 2.24 (ddd, *J* = 13.2, 9.8, 8.2, 1H) 2.09 (s, 3H), 1.84 (dt, J = 14.7, 4.4, 1H), 1.47 (ddd, *J* = 14.5, 11.2, 11.2 Hz, 1H) OH peak not observed; ^{13}C NMR (125 MHz; $CDCl_3$) δ 170.8, 81.7, 79.0, 77.7, 72.2, 71.5, 66.7, 50.1, 45.6, 39.9, 34.5, 29.0, 21.4; MS (CI^+, NH_3) *m/z* 436, 434, 432 $(M + NH_4)^+$, 419, 417, 415 $(M + H)^+$; HRMS (CI^+, NH_3) *m/z* calcd for $C_{13}H_{21}O_5{}^{79}Br_2$ $(M + H)^+$ 414.9756, found 414.9757, and second hydroxydibromide (**19**) (9 mg, 5%) as a white solid: m.p. 128-129˚C; $[\alpha]_D^{25}$ -6.5 (*c* 0.47, CH_2Cl_2); IR (KBr) 3550-3200, 1727 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 5.30 (br s, 1H), 4.61 (m, 2H), 4.43 (br s, 1H) 4.34 (br s, 1H), 4.03-3.87 (m, 3H), 3.73-3.68 (m, 2H), 2.92 (app. quint., *J* = 6.1 Hz, 1H), 2.77 (br d, *J* = 11.2 Hz, 1H), 2.36-2.21 (m, 2H), 2.19-2.09 (m, 1H), 2.10 (s, 3H), 1.61-1.50 (m, 1H), OH peak not observed; ^{13}C NMR (125 MHz; $CDCl_3$) δ 170.5, 83.4, 77.7, 74.6, 74 (broad), 71.1, 66.8, 51.0, 49.0, 42.0, 35.1, 31.9, 21.3;

MS (CI^+, NH_3) *m/z* 436, 434, 432 $(M + NH_4)^+$, 419, 417, 415 $(M + H)^+$; HRMS (CI^+, NH_3) *m/z* calcd for $C_{13}H_{21}O_5{}^{79}Br_2$ $(M + H)^+$ 414.9756, found 414.9764.

Chemical correlation of **19** and **20** by conversion into **(1*S*,2*R*,7*S*,8*R*,10*S*,11*S*)-7,8-Diacetoxy-2,11-dibromo-4,13-dioxabicyclo[8.2.1]tridecane (21)**. To a stirred solution of alcohol **19** (4.7 mg, 0.011 mmol) in dichloromethane (0.4 mL) at 0˚C was added DMAP (1 mg), followed by a solution of acetic anhydride (4.5 μL, 0.047 mmol) and triethylamine (6.6 μL, 0.047 mmol) in dichloromethane (0.1 mL). The mixture was allowed to warm to rt and stirred for 8 h. The mixture was quenched with water and extracted with dichloromethane, and the combined organic phase was dried over magnesium sulfate. The solids were removed by filtration and the solvent evaporated. ^{1}H NMR analysis of the crude reaction mixture showed that the conversion to bis-acetate **21** was quantitative. Meanwhile, to a stirred solution of alcohol **20** (1.6 mg, 0.004 mmol) in dichloromethane (0.2 mL) at 0˚C was added DMAP (1 mg), followed by a solution of acetic anhydride (1.5 μL, 0.017 mmol) and triethylamine (2.5 μL, 0.017 mmol) in dichloromethane (0.03 mL). The mixture was allowed to warm to rt and stirred for 8 h. The mixture was quenched with water, extracted with dichloromethane, and the combined organic phase was dried over magnesium sulfate. The solids were removed by filtration and the solvent evaporated. ^{1}H NMR analysis of the crude reaction mixture showed approximately 60% conversion to the desired bis-acetate and comparison of the ^{1}H NMR spectra of the two samples revealed them to be identical. The samples were then combined, and purified by silica gel column chromatography (1:1 petroleum spirits/diethyl ether) to give bis-acetate **21** (3.8 mg, 55%) as a colourless oil: $[\alpha]_D^{25}$ -47.0 (*c* 0.24, CH_2Cl_2); IR (KBr) 1731 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.31-5.25 (m, 2H),

4.46-4.41 (m, 1H), 4.15 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.05-3.97 (m, 3H), 3.70 (dt, *J* = 12.4, 2.0 Hz, 1H), 3.62-3.50 (m, 3H), 2.95 (app. quint. *J* = 7.2 Hz, 1H), 2.48-2.33 (m, 3H), 2.08 (s, 3H), 2.06 (s, 3H) 1.37-1.31 (m, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.1, 170.2, 82.7, 77.5, 75.8, 75.2 74.8 (broad), 50.6, 43.7, 35.6 (broad), 29.3, 21.2, 21.0; MS (CI^+, NH_3) *m/z* 478, 476, 474 $(M + NH_4)^+$; HRMS (CI^+, NH_3) *m/z* calcd for $C_{15}H_{26}NO_6{}^{79}Br_2$ $(M + H)^+$ 474.0127, found 474.0123.

(7*S,8*R**,10*S**,11*S**)-7-Acetoxy-8-chloro-2,11-dibromo-4,13-dioxabicyclo[8.2.1]tridecane (22) and (1*R**,2*S**,7*R**,8*R**,10*R**,11*S**)-10-Acetoxy-2,11-dibromo-8-chloro-4,13-dioxabicyclo[5.5.1]tridecane (23).** Macrocyclic alkene **15** (8.0 mg, 27.1 μmol) was dissolved in CD_2Cl_2. Tetramethylguanidine in CH_2Cl_2 (0.032 M, 10 μL, 0.32 μmol), AcOH in CH_2Cl_2 (2.62 M, 10 μL, 26.2 μmol) and NBS (4.8 mg, 27.1 μmol) were added sequentially at ambient temperature. The mixture was stirred for 1 h and complete conversion of starting material was observed *via* TLC and ^{1}H NMR analyses. To the mixture was added CH_2Cl_2 (30 mL) and the solution washed with sodium bisulfite solution (20% w/w) (30 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL x 3), the combined organic layers washed with water (20 mL), brine (20 mL) dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash column chromatography (5:1 Pet. Ether:EtOAc) to give first bromoacetate **22** (3.5 mg, 30 %) as a colorless oil: R_f = 0.61 (3:1 P.E:EtOAc); IR (KBr) 1731 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.34 (br d, *J* = 7.3 Hz, 1H), 4.49 (br s, 2H), 4.22 (d, *J* = 11.0 Hz, 1H), 4.12 (br s, 1H), 3.95 (br s, 2H), 3.67 (br t, *J* = 12.3 Hz, 1H), 3.53-3.49 (m, 2H), 3.04-2.98 (m, 1H), 2.64-2.55 (m, 2H), 2.37 (br d, *J* = 14.5 Hz, 1H), 2.16-2.13 (m, 1H), 2.07 (s, 3H), 1.45-1.42 (m, 1H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 171.1, 82.8, 77.2, 76.1, 76.0, 68.4, 64.5

(broad), 50.5, 49.7, 44.2, 40.6 (broad), 31.7, 21.2; MS (CI^+, NH_3) *m/z* 450, 452, 454, 456 $(M + NH_4)^+$; HRMS (CI^+, NH_3) *m/z* calcd for $C_{13}H_{23}NO_4{}^{79}Br_2{}^{35}Cl$ $(M + NH_4)^+$ 449.9682, found 449.9690; and second bromoacetate **23** (1.5 mg, 13 %) as white solid: m.p. 134-136˚C (recrystallized from hexane); R_f = 0.42 (3:1 P.E:EtOAc); IR (KBr) 1733 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 5.66 (d, *J* = 8.1 Hz, 1H), 4.62 (br s, 1H), 4.25 (dd, *J* = 12.6, 3.4 Hz, 1H), 4.14-4.09 (m, 2H), 4.04 (ddd, *J* = 12.5, 5.9, 1.8 Hz, 1H), 3.92-3.88 (m, 2H); 3.83 (dd, *J* = 12.6, 5.3 Hz, 1H), 3.77 (td, *J* =11.9, 4.6 Hz, 1H), 3.04 (ddd, *J* = 16.1, 8.1, 2.1, 1H), 2.64 (ddd, *J* = 15.0, 4.4, 1.3 Hz, 1H) 2.42 (ddd, *J* = 14.9, 10.9, 3.2 Hz, 1H), 2.34-2.27 (m, 1H), 2.15 (br dd, *J*= 16.1, 4.3 Hz, 1H), 2.08 (s, 3H), 1.53-1.45 (m, 1H); MS (CI^+, NH_3) *m/z* 450, 452, 454, 456 $(M + NH_4)^+$; HRMS (CI^+, NH_3) *m/z* calcd for $C_{13}H_{23}NO_4{}^{79}Br_2{}^{35}Cl$ $(M + NH_4)^+$ 449.9682, found 449.9681.

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Supporting Information Available: General experimental, experimental procedures and data for **6-12**, **14**, copies of ^1H spectra for **6-12, 14-23** and ^{13}C NMR spectra for **6-12, 14-16,** and **19-22**, details of the chlorine isotope experiment on obtusallene V and X-ray crystallographic data for **3**, **15-19, 23**. This material is available free of charge via the Internet at http://pubs.acs.org.

Footnotes and References:

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‡ Pfizer Global Research and Development

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21. No *Z*-alkenes were observed from these reactions. In scheme 4 the mass balance is tentatively assigned to homo-dimerization products. With *N*-heterocyclic bearing ruthenium benzylidene catalysts (not shown), the desired products were observed in minor quantities (5-10%) in the ^{1}H NMR spectra of the crude mixtures, but extensive decomposition of the substrate had occurred.

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23. The structure of **15** contains three independent molecules with nearly identical conformations (see the supporting information). The THF oxygen$\cdots C_{12}$ distances are 2.761(4), 2.800(4) and 2.770(3) Å in molecules **15**-A, **15**-B and **15**-C respectively.

24. Diastereoisomers **17** and **18** were found to have co-crystallized in the same crystal in a *ca.* 69:31 ratio. Hence the structure is referred to as **17**/**18**. See the supporting information for more details.

25. Guella demonstrated that obtusallene II displayed temperature dependent NMR spectra, existing as a mixture of equilibrating conformers, including a slow 180˚ flipping process of its *trans*-olefin through the macrocyclic ring, giving rise to broad NMR resonances at room temperature (see reference 7). In contrast, macrocycle **15** (and, indeed **16**) shows sharp resonances in its ^{1}H NMR and ^{13}C NMR spectra (See SI). Taken together with the experimental result that both

faces of the olefin in **15** evidently undergo bromination may indicate that this macrocycle enjoys comparable conformation motion at the fast exchange limit at room temperature. Alternatively, room temperature may represent the slow-exchange limit for the aforementioned molecular motion, where the major solution conformation is expected to resemble that of the solid state (*c.f.* Figure 1), and a minor, unobserved, conformer undergoes competitive reaction by the Curtin-Hammett principle.

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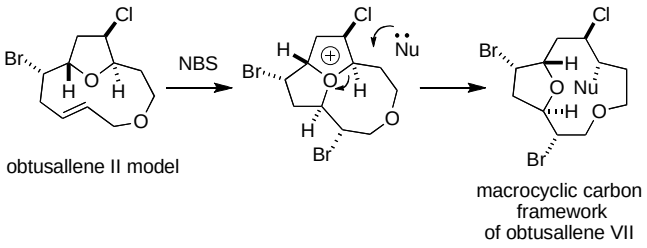
TOC Graphic



obtusallene II model

macrocyclic carbon framework of obtusallene VII