Synthesis, Characterization and Reactivity of Complex Tricyclic Oxonium Ions, Proposed Intermediates in Natural Product Biosynthesis

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ABSTRACT: Reactive intermediates frequently play significant roles in the biosynthesis of numerous classes of natural products although the direct observation of these biosynthetically relevant species is rare. We present here direct evidence for the existence of complex, thermally unstable, tricyclic oxonium ions that have been postulated as key reactive intermediates in the biosynthesis of numerous halogenated natural products from *Laurencia* species. Evidence for their existence comes from full characterization of these oxonium ions by low temperature NMR spectroscopy supported by DFT calculations, coupled with the direct generation of ten natural products on exposure of the oxonium ions to various nucleophiles.

INTRODUCTION

The biosynthesis of secondary metabolites frequently proceed *via* unstable reactive intermediates.[1] With terpenes, one of the largest classes of natural products, olefin cyclizations *via* carbocations (frequently tertiary carbocations) dominate[2-4] and account for the vast structural diversity exhibited by this class of natural products. Evidence for carbocation intermediates has come from many sources,[5-7] and is supported by the isolation and condensed phase characterization of tertiary (and other) carbocations (carbenium ions),[8-9] along with numerous biomimetic total syntheses of terpenoid natural products designed so as to proceed *via* cationic intermediates.[10] Increasingly, the subtleties of these biosynthetic cyclizations are being probed computationally.[4] In a related manner, the biosynthesis of numerous halogenated acetogenin natural products from *Laurencia* species have been proposed to proceed *via* complex bi- and tricyclic oxonium ions (Figure 1).[11-21] The existence of these trialkyloxonium ions, as with carbocations in terpene biosynthesis, has been implied from the structural and stereochemical diversity of these natural products[22] and initial biosynthetic studies with isolated enzymes[11, 13, 23] as well as from a number of elegant biomimetic syntheses primarily from Kim, Snyder and Braddock that involve ring opening/expansions of *in situ* generated oxonium ions to give a host of structurally diverse *Laurencia* natural products.[15-21, 24-30] However, no direct evidence for the existence of these trialkyloxonium ions has been forthcoming. Herein we report the synthesis and full characterization (both chemically and computationally) of one family of tricyclic trialkyloxonium ions – among the most structurally and stereochemically complex oxonium ions characterized to date.[31] Additionally, the elucidation of the *in vitro* reactivity profile of the tricyclic oxonium ions has resulted in the total synthesis of more than ten complex halogenated natural products. This work provides chemical evidence for the existence of complex, halogenated, tricyclic oxonium ions that have been postulated as key reactive intermediates in the biosynthesis of numerous halogenated natural products.

Oxonium ions in *Laurencia* natural product biosynthesis

Red algae of the genus *Laurencia* and organisms that feed on them produce a vast array of structurally diverse C_{15} halogenated cyclic ether acetogenin natural products[22] which have stimulated synthetic chemists to develop numerous new methods to gain access to these complex secondary metabolites.[22, 32] Since Masamune's ground-breaking synthesis of (±)-laurencin ((±)-**4**, Figure 1) reported in the 1970s,[33-35] the synthesis of over 50 cyclic halogenated acetogenin natural products from *L*. spp. have been reported with many targets being synthesized by multiple independent routes.[36-39] Hand-in-hand with the development of the synthetic methodology has been the development of biosynthetic postulates towards these natural products with many of these biosynthetic postulates being rich in oxonium ion chemistry including bicyclic oxonium ions derived from epoxides,[15-16] oxetanes,[19] tetrahydrofurans[17-18] and oxocenes[21] as well as fused[14, 25] and bridged tricyclic oxonium ions.[11-13, 20, 26] Initial proposals regarding the biosynthesis of C_{15} halogenated acetogenin natural products from *Laurencia* species were put forward by Murai and Fukuzawa[13, 23, 40] which involved bromocyclizations of the linear lauredіols **1** that exist in Nature as mixtures of diastereomers (Figure 1a).[41-42] They postulated that enzymatic bromocyclization of the (3*E*, *R*, *R*)-laurediol (3*E*,*R*,*R*)-**1** gives rise to deacetyllaurencin (3*E*)-**3** *via* bromonium ion **2**,[12, 43] indeed experiments with isolated enzymes yielded deacetyllaurencin (3*E*)-**3** in very low yield (0.015%).[13, 23, 40, 44] More recently, trialkyloxonium ions have been proposed as intermediates in the bromocyclization of linear precursors to give deacetyllaurencins **3**. Braddock proposed that laurepoxides **5**, the potential precursor of the lauredіols **1**, undergoes bromocyclization to give the bicyclic oxonium ions **7** *via* the bromonium ions **6**.[15] Opening of the oxonium ions **7** by water at C-6 gives **3**. Such epoxide bromonium ion cyclizations were first reported by Davies with cyclooctadiene epoxide[45] and expanded by Braddock with biosynthetically relevant model systems.[15-16] Snyder has proposed that deacetyllaurencin (3*E*)-**3** could be biosynthesized from (3*E*, *R*, *R*)-lauredіols (3*E*,*R*,*R*)-**1** by two favorable 5-endo bromocyclizations *via* bromonium ions **8** and **9** to give the bicyclic oxonium ion

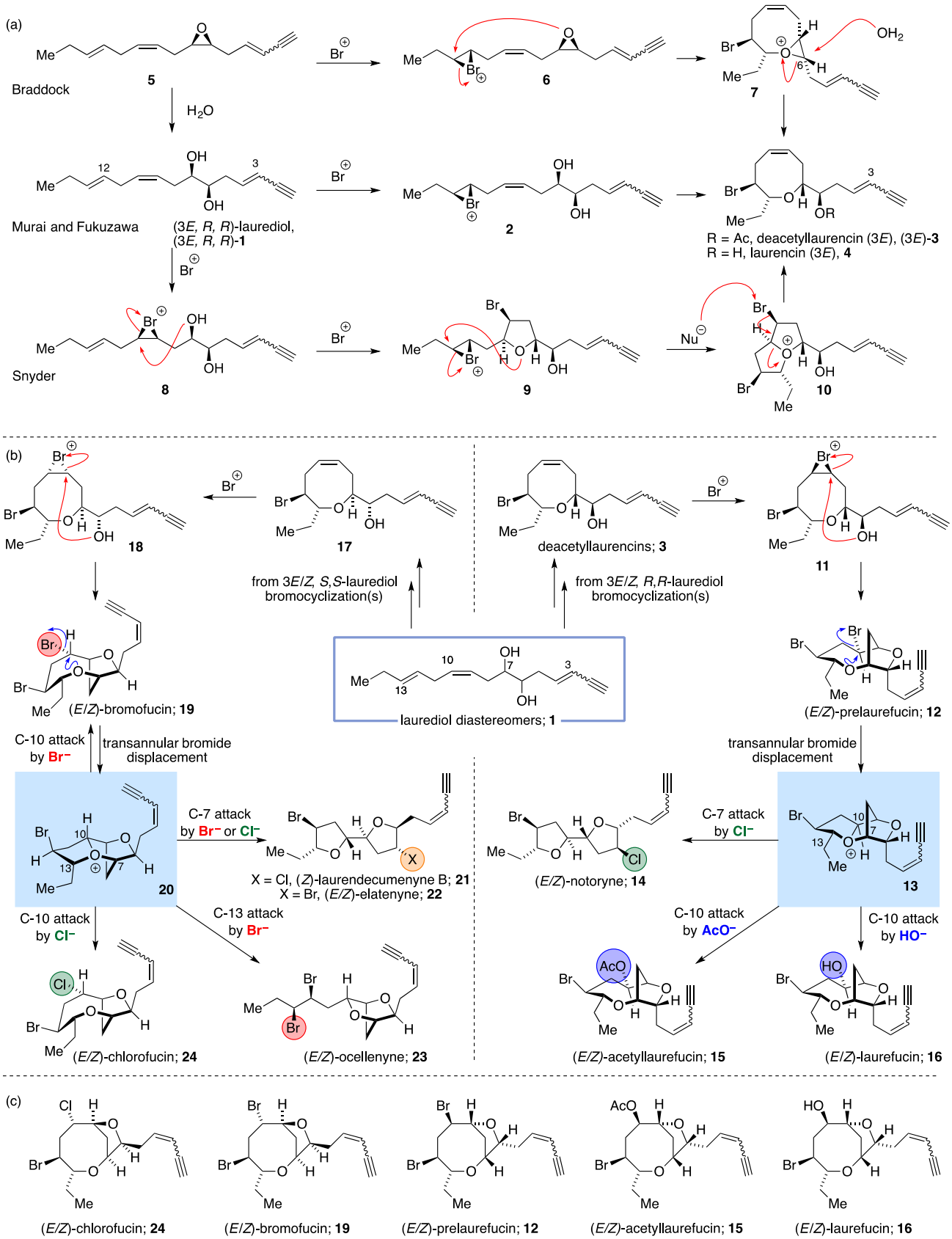


Figure 1. Proposed biosynthesis of some halogenated ethers from *Laurencia* species from laurediols **1**. (a) Proposals regarding the biosynthesis of deacetyllaurencin. (b) Proposed biosynthesis of natural products involving tricyclic oxonium ions. (c) Conventional representations of the lauroxocane natural products the chlorofucins, bromofucins, prelaurefucins, acetyllaurefucins and the laurefucins.

10 which undergoes formal loss of positive bromine to give deacetyllaurencin (3*E*)-**3**.[17-18] Again, this biomimetic ring expansion of an oxonium ion enjoys experimental support.[17-18, 28] In both the Braddock and Snyder proposals the respective oxonium ions can open in other ways to form different ring systems found in other *Laurencia* natural products.

The focus of the current work is the synthesis and characterization of the tricyclic oxonium ions **13** and **20** that are downstream from deacetyllaurencin on the proposed biosynthetic pathway (Figure 1b). Suzuki[12] and Murai and Fukuzawa[11, 13] proposed the intermediacy of the oxonium ions **13** in the biosynthesis of notoryne and the laurefucins. The oxonium ions **13** are proposed to arise by transannular displacement of bromide ion from the prelaurefucins **12** which themselves are derived from bromocyclization of deacetyllaurencins **3** (Figure 1b right).[46] Opening of the oxonium ions **13** with chloride ion at C-7 or with water at C-10 generates the natural products (*E*/*Z*)-notoryne **14**[11-12, 47] and (*E*/*Z*)-laurefucins **16** respectively.[13, 23, 48] A closely related natural product, acetyllaurefucin (*E*)-**15**,[49] may arise from opening of the oxonium ions **13** with acetate at C-10 or by acetylation of (*E*)-laurefucin (*E*)-**16**. Extension of this biosynthetic postulate[20, 26] provides a route to the natural products the bromo-[50] and chlorofucins[51] **19** and **24**, the elatenynes **22**,[52] and laurendecumenyne B **21**[53] suggesting the participation of oxonium ions **20** as the key biosynthetic intermediates (Figure 1b, left). Analogous to the formation of oxonium ions **13**, the oxonium ions **20** are proposed to originate from (3*E*/*Z*, *S*, *S*)-lauradiols (*S*,*S*)-**1**, *via* a series of enzymatic bromocyclizations followed by transannular bromide displacement from the bicyclic bromofucins **19.** Opening of the oxonium ions **20** at C-10 or C-7 with bromide or chloride ions would generate the natural products **19**, **21**, **22** and **24**. Alternatively, opening of **20** with bromide ion at C-13 would give the ocellenyes,[54] the full stereostructures of which have recently been tentatively reassigned based on DFT calculations and biogenetic considerations as **23**.[55]

RESULTS AND DISCUSSION

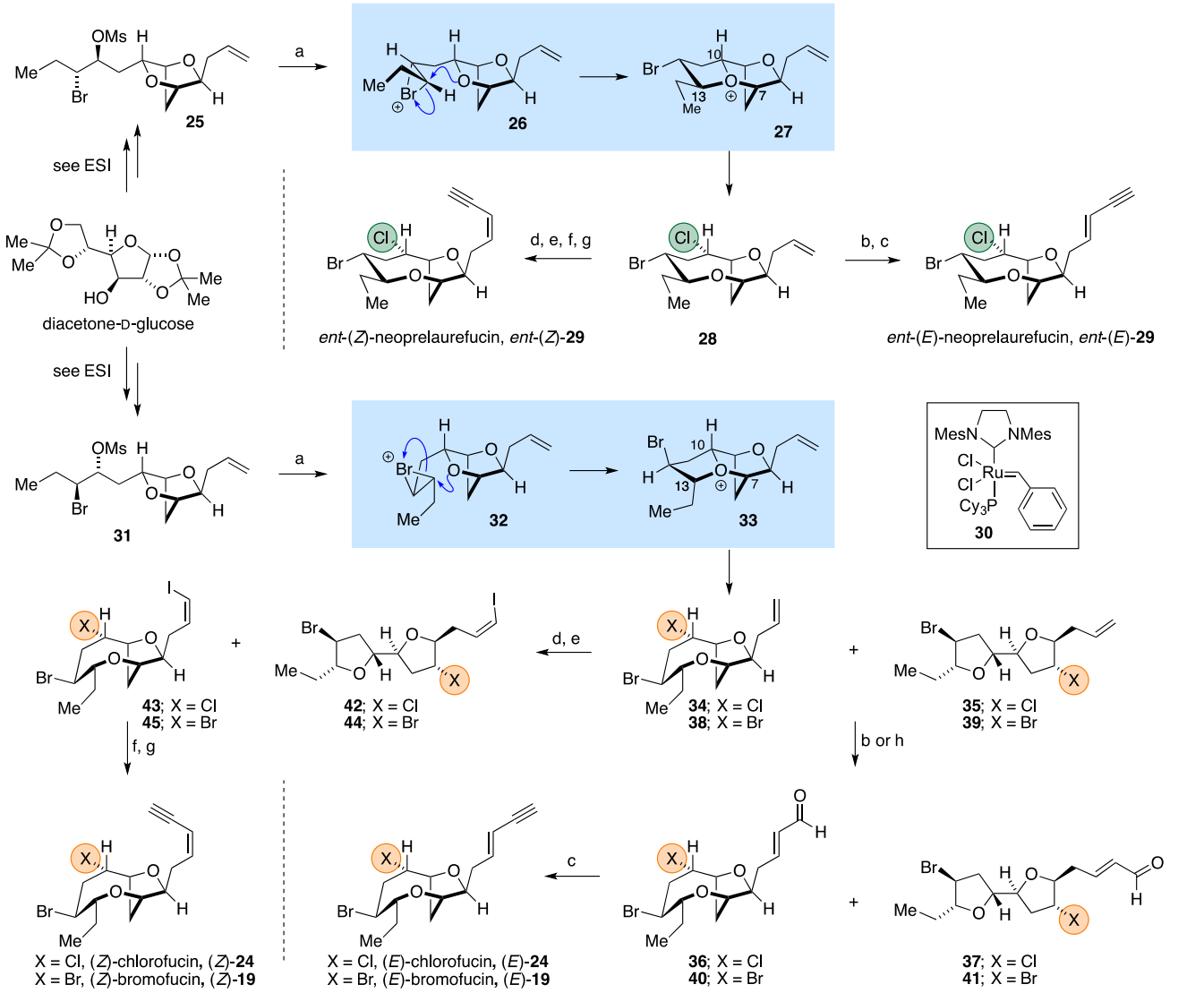
Our strategy for the synthesis of the key oxonium ions **13** and **20** takes its cue from their proposed biosynthesis. This biomimetic approach involves the transannular displacement of halide from bicyclic halo ethers such as **12**, **19** or **24** using a silver(I)-mediated halide abstraction. Here, precipitation of the silver halide would provide the necessary thermodynamic driving force to compensate for the expected endothermic nature of the oxonium ion formation. The choice of the counter anion of the silver(I) salt was also essential to the successful synthesis of our target oxonium ions. Since oxonium ions are known to alkylate heteroatoms,[56] the counter anion must be non-nucleophilic to prevent premature reaction with the target oxonium ions. In the event, successful oxonium ion formation and characterization was achieved using the weakly coordinating Krossing's anion $[Al(pftb)_4]^-$, (pftb = perfluoro-*tert*-butoxy)].[57] The synthesis of the oxonium ions required the total synthesis of their potential precursors, namely the bromo- and chlorofucin natural products **19** and **24**, as well as the prelaurefucins **12** and the corresponding C-10 chlorides the neoprelaurefucins **29** (Scheme 1); the neoprelaurefucins have previously been postulated as natural products based on the proposed biogenesis of the laurefucins.[12, 26]

Oxonium ion precursor synthesis

Our route to these compounds proceeded from the enantiopure bromomesylates **25** and **31** which were readily prepared from diacetone-D-glucose (Scheme 1 and ESI sections 2 and 3, pS4-S24). The bromomesylate **25** would provide the enantiomer of the oxonium ions **13** namely *ent*-**13** and the bromomesylate **31** would give the oxonium ions **20**. The key step in our synthesis of the oxonium ion precursors involved the generation of the diastereomerically pure bromonium ions **26** and **32** from the bromomesylates **25** and **31**. Thus, exposure of the bromomesylate **25** to titanium(IV) chloride,[58] followed by addition of the chloride scavenger $Ag[Al(pftb)_4]\bullet CH_2Cl_2$[57] and then excess tetrabutylammonium chloride delivered the corresponding dioxabicyclo[5.2.1]decane **28** in 68% yield. We propose that this complex transformation proceeds by initial bromonium ion formation, using Braddock's procedure,[58] followed by removal of excess chloride on addition of the silver(I) salt. This allows time for the bromonium ion **26** to evolve into the corresponding oxonium ion **27** *via* 5-endo ring closure.[28] Subsequent addition of excess chloride results in C-10 opening of the oxonium ion **27** to give dioxabicyclo[5.2.1]decane **28**.[59] In a similar manner, exposure of the bromomesylate **31** to titanium(IV) followed by silver(I) and then excess chlorides or bromide gave the known dioxabicyclo[5.2.1]decanes **34** and **38**[26] resulting from C-10 opening of the oxonium ion **33** by halide anion, along with the corresponding known inseparable 2,2'-bifuranyls **35** and **39**[20] arising from competitive C-7 oxonium ion opening. The dioxabicyclo[5.2.1]decanes **28**, **34** and **38** were readily converted into the corresponding oxonium ion precursors, the *ent*-neoprelaurefucins *ent*-(*E*/*Z*)-**29**[59] and the halofucin natural products (*E*/*Z*)-**19**[59] and (*E*/*Z*)-**24**[59] using standard transformations. Thus, *ent*-(*E*)-neoprelaurefucin *ent*-(*E*)-**29** was synthesized from **28** *via* a cross metathesis with crotonaldehyde and catalyst **30** followed by a Colvin-Ohira reaction to install the (*E*)-enyne in 44% yield for the two steps.[24] The (*Z*)-diastereomer, *ent*-(*Z*)-**29** was synthesized from **28** *via* a four step route involving oxidative cleavage of the terminal olefin in **28**, (*Z*)-vinyl iodide formation using a Stork-Zhao reaction,[60] Sonogashira cross-coupling and deprotection. The (*E*)- and (*Z*)- halofucins were prepared from the bromochlorides **34** and **35**, and the dibromides **38** and **39** using closely related procedures. Cross metathesis of an inseparable 7:1 mixture of the bromochlorides **34** and **35** with crotonaldehyde and Grubbs catalyst **30** in dichloromethane at 40 °C gave a 4:1 mixture of separable α,β-unsaturated aldehydes **36** and **37** in 78% overall yield.[20] This change of isomer ratio from 7:1 in the starting materials to 4.2:1 in the products is due to the thermal rearrangement of either **34** or **36** or both (see later) most likely *via* the corresponding tricyclic oxonium ions. Pure **36** has previously been reported by Kim *en route* to (*E*)-chlorofucin (*E*)-**24**[26] and we used Kim's method to convert **36** into (*E*)-chlorofucin (*E*)-**24**.[24, 26] With a mixture of the dibromides **38** and **39**, cross-metathesis using the above conditions resulted in the products **40** and **41** being formed as an inseparable mixture with a small amount of the chlorides **36** and **37**. The formation of the chlorides **36** and **37** most likely occurs by oxonium ion formation from **38** or **40** followed by quenching with the chloride from Grubbs second generation catalyst. Chloride formation could be avoided by conducting the cross metathesis at room temperature in the presence of copper(I) iodide[61] which gave the separable dibromides **40**[26] and **41**[20] in 73% overall yield. Following Kim's precedent, (*E*)-bromofucin (*E*)-**19** was readily prepared from **40** using a Colvin-Ohira homologation.[26] The (*Z*)-halofucins were synthesized from the

bromochlorides **34** and **35**, and the dibromides **38** and **39** using a Stork-Zhao olefination[60] to give mixtures of the inseparable vinyl iodides **42** and **43**, and **44** and **45** followed by Sonogashira cross coupling and deprotection.

Scheme 1. Synthesis of the oxonium ion precursors, the bromo- and chlorofucins and the *ent*-neoprelaurefucins.[a]



[a]Reagents and Conditions: (a) $TiCl_4$, $AgAl(pftb)_4 \bullet CH_2Cl_2$, CH_2Cl_2 –40 °C, 2 h then –78 °C add Bu_4NCl or Bu_4NBr, **28** 68%; **38**:**39** 3:1 inseparable mixture 50%; **34**:**35** 7:1 inseparable mixture 70%; (b) crotonaldehyde, cat. **30**, CH_2Cl_2, 40 °C, **37** 15%, **36** 63%; (c) Me_3SiCHN_2, *n*BuLi, –78 °C – RT, *ent*-(*E*)-**29** 44% (2 steps); (*E*)-**19** 42%; (*E*)-**24** 43%; (d) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane, water; (e) ICH_2PPh_3I, NaHMDS, HMPA, THF, –78 °C – RT; (f) $Me_3SiC{\equiv}CH$, $Pd(PPh_3)_4$, CuI, Et_3N; (g) K_2CO_3, MeOH, *ent*-(*Z*)-**29** 20% (4 steps); (*Z*)-**19** 17% (4 steps); (*Z*)-**24** 32% (4 steps); (h) crotonaldehyde, cat. **30**, Cu(I)I, Et_2O, RT, **41** 13%, **40** 60%.

Oxonium Ion Synthesis and Characterization

Having secured the synthesis of the oxonium ion precursors, the halofucins **19** and **24** and the enantiomers of the neoprelaurefucins *ent*-**29**, investigation into oxonium ion formation and characterization commenced. Initial experiments demonstrated that a complex tricyclic oxonium ion related to *ent*-**13** was thermally unstable above ca. –40 °C (see Figure 4 below). It was therefore necessary to generate and analyze the oxonium ions at –40 °C or below. Ultimately, we found that exposure of either of the chlorides *ent*-(*E*)-**29** and *ent*-(*Z*)-**29** to $Ag[Al(pftb)_4] \bullet CH_2Cl_2$ in CD_2Cl_2 at –78 °C allowed generation of the oxonium ions, *ent*-**13**•$Al(pftb)_4$, which were characterized by NMR at –78 °C after low temperature filtration of the precipitated silver chloride. The ^1H and ^{13}C NMR spectra of the generated intermediates compared with those of the precursors, along with the ^1H-^{13}C HMBC spectra provided good evidence for the formation of the oxonium ions, illustrated for *ent*-(*E*)-**13**•$Al(pftb)_4$ in Figure 2. Referring to a section of the ^1H-^{13}C HMBC spectrum shown in Figure 2b, the trivalent nature of the oxygen atom within *ent*-(*E*)-**13**•$Al(pftb)_4$ is evident from the correlations of C-7 (blue) to H-10 (green), H-9 (red) and H-13 (purple) as well as from C-10 (green) to H-7 (blue). Additional evidence for the formation of *ent*-**13**•$Al(pftb)_4$ comes from the change in ^1H and ^{13}C chemical shifts in moving from *ent*-(*E*)-**29** to the oxonium ion *ent*-(*E*)-**13**•$Al(pftb)_4$. Figure 2c shows clearly that the resonances for C-7 (blue), C-10 (green), C-13 (purple) carbon atoms move to significantly higher chemical shift on treatment of *ent*-(*E*)-**29** with a silver(I) salt, in keeping with the large ^{13}C NMR chemical shift changes observed on oxonium ion formation in other

tricyclic systems,[62-63] whereas the resonance for C-9 (red) moves to slightly lower chemical shift. In a similar manner, Figure 2d shows the change in chemical shifts of a number of protons on moving from *ent*-(*E*)-**29** to *ent*-(*E*)-**13**•Al(pftb)$_4$. The protons alpha to the trivalent oxygen

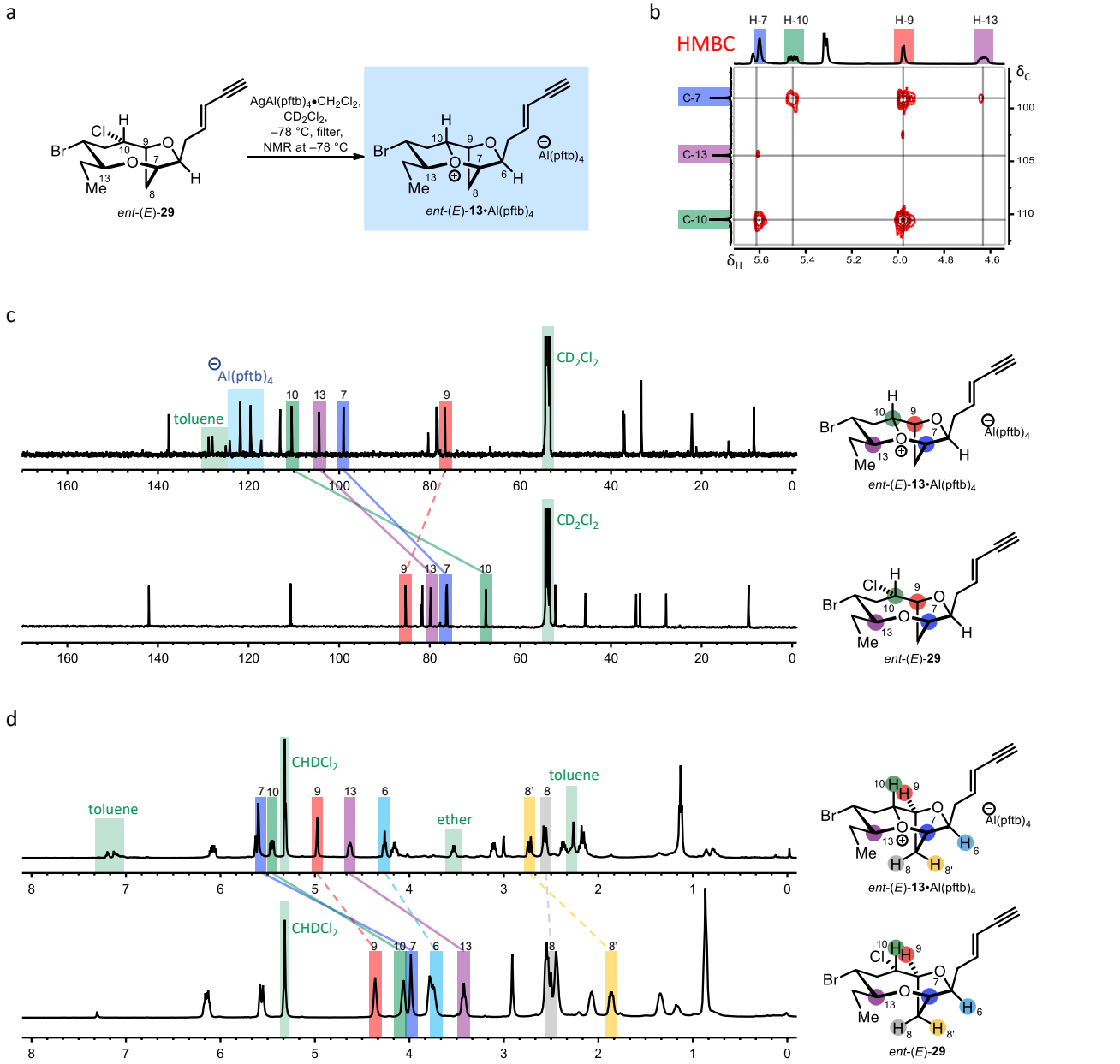


Figure 2. Formation and NMR spectra (CD_2Cl_2, –78 °C) of the oxonium ion *ent*-(*E*)-**13**•Al(pftb)$_4$ along with NMR spectra (CD_2Cl_2, –78 °C) of the starting material *ent*-(*E*)-**29**. The 1-D and 2-D NMR spectra provide evidence for the formation of the oxonium ion *ent*-(*E*)-**13**•Al(pftb)$_4$. In particular, the ^{1}H-^{13}C HMBC spectrum demonstrates the formation of trivalent oxygen. Additionally, on formation of the oxonium ion, the ^{13}C NMR resonances of the carbon atoms directly attached to the trivalent oxygen atom (C-7 blue, C-10 green, and C-13 purple) move to significantly higher chemical shift compared with the starting material whereas non-adjacent carbons (e.g. C-9 red) undergo smaller changes in chemical shift. The protons adjacent to the trivalent oxygen atom (H-7 blue, H-10 green, and H-13 purple) also move to significantly higher chemical shift on oxonium ion formation. The β-protons (H-6 light blue, H-9 red, and H-8' yellow) also move to higher chemical shift indictive of overlap of the occupied σ_{C-H} orbital with the σ^*_{C-O} orbital, whereas the grey β-proton (H-8) does not have the correct geometry for σ_{C-H} orbital overlap with the antibonding σ^*_{C-O} orbital and undergoes a significantly smaller change in chemical shift (see ESI for NBO analysis, Figure S32, pS102-S103). **a**, Formation of the oxonium ion *ent*-(*E*)-**13**•Al(pftb)$_4$ by chloride abstraction from the dioxabicyclo[5.2.1]decane *ent*-(*E*)-**29** at –78 °C. **b**, ^{1}H–^{13}C HMBC (heteronuclear multiple bond correlation) NMR spectrum of *ent*-(*E*)-**13**•Al(pftb)$_4$. **c**, ^{13}C NMR spectrum of *ent*-(*E*)-**13**•Al(pftb)$_4$ (top) and ^{13}C NMR spectrum of *ent*-(*E*)-**29** (bottom) with corresponding carbons joined by filled lines (carbons alpha to trivalent oxygen) and dashed lines (carbon beta to trivalent oxygen). **d**, ^{1}H NMR spectrum of *ent*-(*E*)-**13**•Al(pftb)$_4$ (top) and ^{1}H NMR spectrum of *ent*-(*E*)-**29** (bottom) with corresponding protons joined by filled lines (protons alpha to trivalent oxygen) and dashed lines (protons beta to trivalent oxygen).

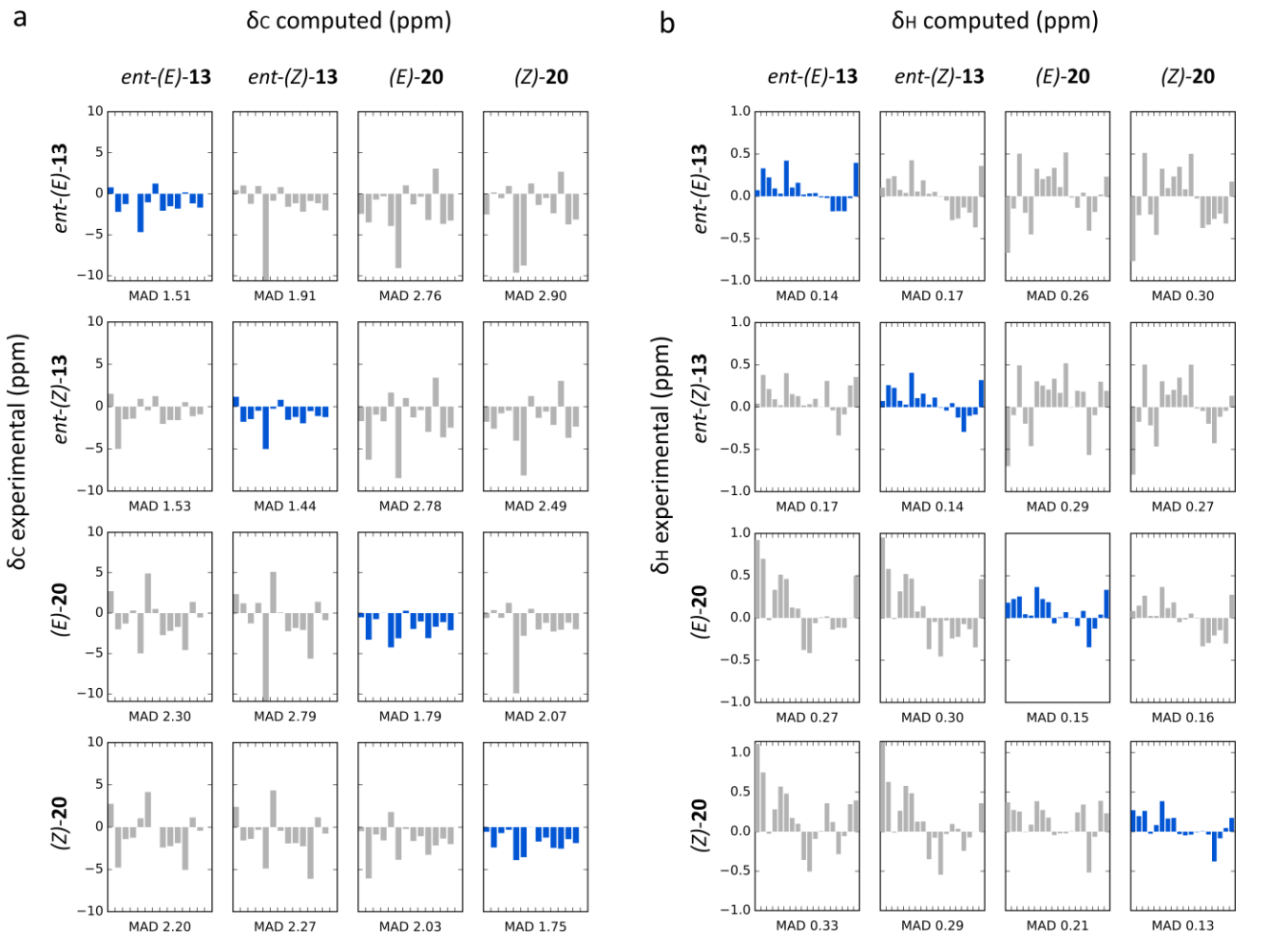


Figure 3. Comparison of experimental and computed ^{13}C and ^{1}H NMR chemical shifts of the oxonium ions *ent*-(*E*/*Z*)-**13** and (*E*/*Z*)-**20**. For each individual histogram, the x-axis corresponds to atom number and the y-axis corresponds to δ_{expt} - δ_{comp}. The computed chemical shifts for each oxonium ion are Boltzmann-weighted averages of the chemical shifts from their contributing conformers at –78 °C. **a**, Comparison of the experimental and computed ^{13}C NMR chemical shifts of the oxonium ions *ent*-(*E*/*Z*)-**13** and (*E*/*Z*)-**20** (C-4 and C-12 were excluded from the analysis – see ESI). **b**, Comparison of the experimental and computed ^{1}H NMR chemical shifts of the oxonium ions *ent*-(*E*/*Z*)-**13** and (*E*/*Z*)-**20**. The entries highlighted in blue correspond to the least deviation between computed and experimental chemical shifts, having the lowest mean absolute deviation (MAD) as well as the lowest individual deviations in ^{13}C and ^{1}H chemical shifts (Table S22-S28, pS89-S95); hence, confirming the structural assignment of the oxonium ions.

atom, H-7 (blue), H-10 (green) and H-13 (purple) in *ent*-(*E*)-**13**•Al(pftb)$_4$ resonate at significantly higher chemical shift compared with the corresponding protons in *ent*-(*E*)-**29**. The resonances for the beta-protons H-6 (light blue), H-9 (red), H-8' (yellow) also move to higher chemical shift, indicative of overlap of the occupied σ_{C-H} orbitals of H-6, H-9 and H-8' with the corresponding σ^*_{C-O} orbitals of the trivalent oxygen. The H-8 (grey) proton does not have the correct geometry to maximize this overlap and hence its chemical shift remains virtually unchanged (see Figure S32, pS102-S103 for NBO analysis).[59] In a similar manner, the oxonium ions (*E*)- and (*Z*)-**20**•Al(pftb)$_4$ could be readily generated from the bromofucins **19** and were characterized as above; equivalent figures to Figure 3 for the oxonium ions *ent*-(*Z*)-**13**•Al(pftb)$_4$ and (*E*)- and (*Z*)-**20**•Al(pftb)$_4$ may be found in the ESI (Figures S10-S12, pS47-S49).

DFT calculated ^{13}C and ^{1}H NMR chemical shifts of the computed structures of each oxonium ion provided further supporting evidence for the formation and structural assignment of the four synthetic oxonium ions *ent*-(*E*/*Z*)-**13**•Al(pftb)$_4$ and (*E*/*Z*)-**20**•Al(pftb)$_4$ (Figure 3). Following a conformational search, Boltzmann-weighted shielding tensors were calculated at the mPW1PW91/6-311+G(2d,p)// B3LYP/6-31+G(d,p) level of theory in dichloromethane, from which ^{13}C and ^{1}H NMR chemical shifts were obtained using the scaling factors reported by Tantillo.[64] For each oxonium ion, the smallest deviation between the experimental chemical shifts and the pool of computed chemical shifts was found only when the configuration of the computed structure matched the configuration of the structure expected from synthesis (diagonals of Figure 3a and 3b). The off-diagonal entries, which correspond to comparison between structures of different configurations, gave larger mean absolute deviations (MADs) as well as larger deviations of individual ^{13}C and/or ^{1}H NMR chemical shifts. Furthermore, the chemical shifts of the carbon and proton atoms adjacent to the trivalent oxygen were in keeping with simpler tricyclic oxonium ions.[62-63]

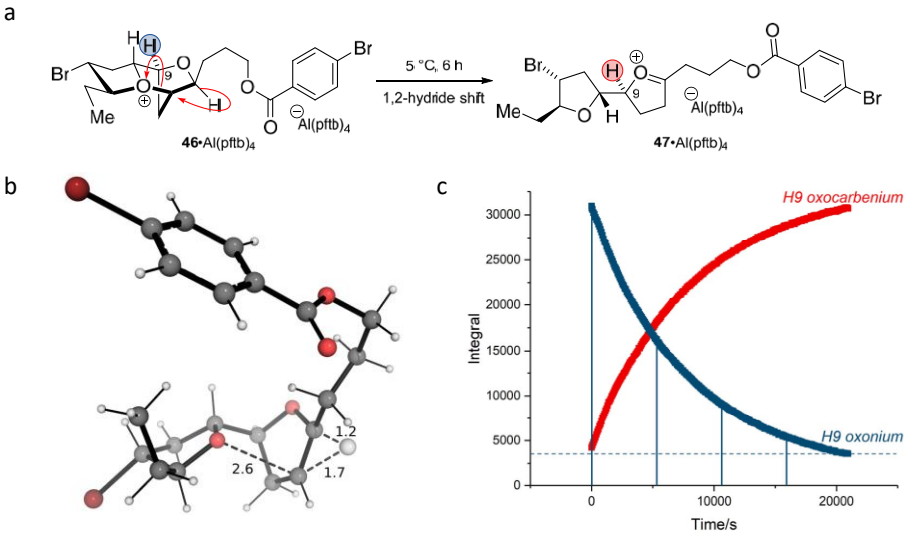


Figure 4. Rearrangement of the oxonium ion **46**•Al(pftb)$_4$ to give the oxocarbenium ion **47**•Al(pftb)$_4$. The stability of the oxonium ion **46**•Al(pftb)$_4$ was quantified by measuring the half-life (*ca*. 5100 s) for conversion into the oxocarbenium ion **47**•Al(pftb)$_4$ at 5 °C by ^{1}H NMR. The calculated transition state for this rearrangement is a highly asynchronous 1,2-hydride shift. **a**, Conversion of **46**•Al(pftb)$_4$ into **47**•Al(pftb)$_4$ with proposed mechanism. **b**, DFT calculated transition structure for the conversion of **46** into **47** – distances in Å. **c**, Plot of the change of the ^{1}H NMR integral for H-9 of **46**•Al(pftb)$_4$ (blue) and H-9 of **47**•Al(pftb)$_4$ (red) versus time, along with half-life intervals on the x-axis.

Characterization of a Decomposition Pathway

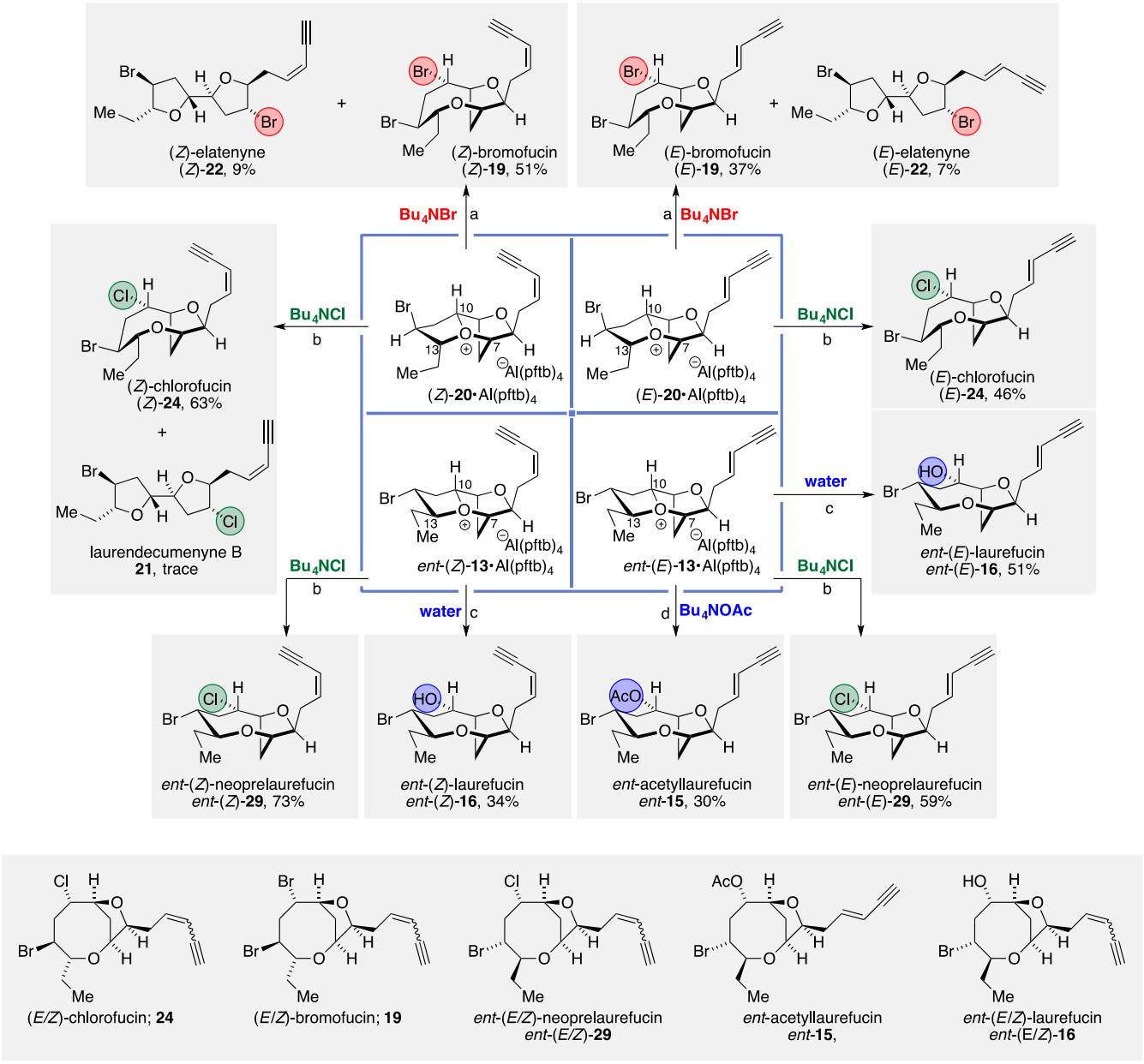
The synthetic oxonium ions *ent*-(*E*)- and *ent*-(*Z*)-**13**•Al(pftb)$_4$ and (*E*)- and (*Z*)-**20**•Al(pftb)$_4$ were thermally unstable and readily decomposed above –40 °C. Indeed, it was not possible to synthesize the oxonium ion (*E*)-**20**•Al(pftb)$_4$ from (*E*)-chlorofucin (*E*)-**24** as the halide abstraction reaction only occurred above –40 °C (for energy profile for oxonium ion formation, see ESI Figures S33-S35, pS104-S108).[29] The thermal instability of a closely related oxonium ion was studied which resulted in the characterization of a clean decomposition pathway (Figure 4). The oxonium ion **46**•Al(pftb)$_4$ was synthesized at –78 °C by halide abstraction from the corresponding chloride precursor using AgAl(pftb)$_4$•CH_2Cl_2 and characterized by NMR spectroscopy at –78 °C (see ESI, pS57); the chloride precursor was readily prepared from the alkene **28** by a hydroboration/oxidation/esterification sequence (see ESI, pS56-S57). At higher temperature (>–40 °C) the oxonium ion **46**•Al(pftb)$_4$ was readily and cleanly transformed into the oxocarbenium ion **47**•Al(pftb)$_4$ which itself was fully characterized (see ESI pS56-S59). Incubation of the oxonium ion **46**•Al(pftb)$_4$ at 5 °C in an NMR spectrometer allowed the rate of this isomerization to be determined. The half-life for the conversion of **46**•Al(pftb)$_4$ into **47**•Al(pftb)$_4$ at 5 °C was *ca.* 5100 s (average of three experiments) corresponding to a Gibbs energy of activation of 21.2 kcal/mol. The conversion of **46** into **47** computationally was shown to be a highly asynchronous 1,2-hydride shift with a calculated Gibbs energy barrier of 20.6 kcal/mol, consistent with experiment.[65-66]

Oxonium Ion Reactivity with Nucleophiles

Having characterized the complex halogenated tricyclic oxonium ions both spectroscopically and computationally we sought to investigate their reactivity with a variety of nucleophiles to garner evidence to support their proposed intermediacy in the biosynthesis of *Laurencia* natural products. Trapping of the various oxonium ions with a range of nucleophiles directly generated ten natural products (Scheme 2). Trapping of the oxonium ions (*E*)- and (*Z*)-**20**•Al(pftb)$_4$ with bromide anion gave rise to the (*E*)- and (*Z*)-bromofucins **19** in 37% and 51% yields respectively,[26] along with small amounts of (*E*)- and (*Z*)-elatenyne **22**.[20] Using chloride in place of bromide anion gave the corresponding (*E*)- and (*Z*)-chlorofucins **24** in 46% and 63% yields respectively along with a trace amount of laurendecumenyne B **21**.[20, 26] In the other diastereomeric series, treatment of the oxonium ions *ent*-(*E*)- and *ent*-(*Z*)-**13**•Al(pftb)$_4$ with water gave the corresponding *ent*-laurefucins *ent*-**16** in 34% and 51% yields respectively.[24, 28] Using acetate anion with *ent*-(*E*)-**13**•Al(pftb)$_4$ gave *ent*-acetyllaurefucin *ent*-**15** in 30% yield. Both *ent*-(*E*)- and *ent*-(*Z*)-**13**•Al(pftb)$_4$ were also treated with chloride anion which gave the *ent*-(*E*)- and *ent*-(*Z*)-neprelaurefucins *ent*-**29** in 59 and 73% yields respectively.[12, 26] What is clear from these quenching experiments is that all four oxonium ions undergo kinetic quenching at C-10 in keeping with results in related systems.[24, 26, 29, 67] Additionally, the oxonium ions (*E*)- and (*Z*)-**20**•Al(pftb)$_4$ undergo a small amount of C-7 quenching analogous to previous work;[26, 29, 67] in keeping with related results, products from quenching of the oxonium ions at C-13 were not observed.[55] The quenching experiments provided the 2,2'-bifuranyl natural products **21** and **22** in low yields. However, it is known that C-10 halogenated dioxabicyclic compounds related to the halofucins can undergo slow rearrangement to the corresponding 2,2-bifuranyls in the presence of activated silica gel.[12, 20, 27, 67, 48b] Hence exposure of the bromofucins **19** to activated silica gel in hexanes or petroleum ether for 36 hours at ambient temperature gave (*E*)- and (*Z*)-elatenyne **22** in 61% and 60% yields respectively (Scheme 3).[20] In a similar manner, heating (*Z*)-chlorofucin (*Z*)-**24** with activated silica gel in chloroform at 80 °C (bath temperature) gave laurendecumenyne B **21** in 73% yield, whilst (*E*)-chlorofucin (*E*)-**24** gave (*E*)-laurendecumenyne B (*E*)-**21** which has yet to be isolated from Nature,[20] in 50% yield on exposure to activated silica gel in hexanes at 80 °C (bath temperature).[29] *ent*-(*E*/*Z*)-Neoprelaurefucins *ent*-**29** as solutions in hexanes when treated with

silica gel at 80 °C (bath temperature) for 12 hours gave *ent*-(*E*)- and *ent*-(*Z*)-notoryne *ent*-**14** quantitatively.[47]

Scheme 2. Natural products from oxonium ions via quenching with nucleophiles.[a,b,c]



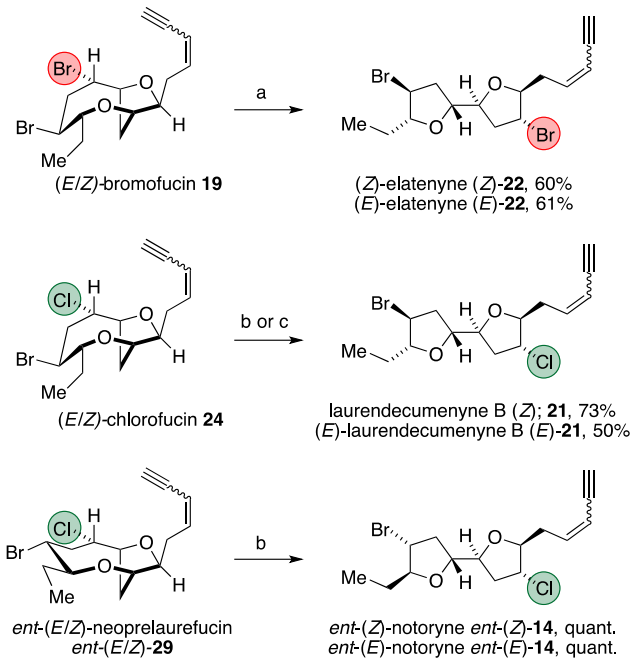
[a]Reagents and Conditions: (a) Bu_4NBr, –78 °C - RT, (*Z*)-**19** 51%, (*Z*)-**22** 9%; (*E*)-**19** 37%, (*E*)-**22** 7%; (b) Bu_4NCl, –78 °C - RT, (*Z*)-**24** 63%, **21** trace; (*E*)-**24** 46%; *ent*-(*Z*)-**29** 73%; *ent*-(*E*)-**29** 59%; (c) water, $NaHCO_3$, –78 °C – RT, *ent*-(*Z*)-**16** 34%, *ent*-(*E*)-**16** 51%; (d) Bu_4NOAc, –78 °C - RT, *ent*-**15** 30%. [b]The conventional representations of the lauroxocane natural products the chlorofucins and bromofucins, and the enantiomers of the neoprelaurefucins, the laurefucins and acetyllaurefucin are given at the bottom of the Scheme. [c]The neoprelaurefucins **29** have previously been predicted to be natural products.[12, 26]

The course of the rearrangement of *ent*-**29** into *ent*-(*Z*)-**14** at 80 °C (bath temperature) in $CDCl_3$ in the absence of silica gel was readily followed by ^1H NMR (see ESI Figure S59, pS206) which indicated clean and quantitative conversion after 12 days.

DFT calculations of transition structures (TSs) helped to explain the observed regioselectivity in the nucleophilic opening of oxonium ions *ent*-(*E*)-**13** and (*E*)-**20**.[25] For *ent*-(*E*)-**13**, the energy barrier for opening at C-10 with chloride is lower than for the corresponding openings at C-7 and C-13 (Figure 5b, also see ESI Figures S36-S48, pS109-S130 for analyses with different oxonium ions and nucleophiles).[68] The O–C-10 bond is longest in the ground state (Figure 5a), indicative of greater carbocationic character at C-10. Accordingly, attack at this position involves the least structural reorganization in the TS: this can also be quantified through distortion-interaction/activation strain analysis along the reaction coordinate (Figure 5c).[69] Attack at C-7 and C-10 involves very similar interaction energy profiles, while the distortion energy term at C-10 is smaller leading up to the TS, giving rise to a smaller barrier for this position. Consistent with the absence of C-13 opening in our

experimental studies, the barrier for attack at this position is much greater than at C-7 and C-10. This principally results from a much larger distortion energy term required to open at this position, also resulting in a later TS with respect to the breaking C–O bond.

Scheme 3. Natural products from natural products.[a,b]



[a]Reagents and Conditions: (a) activated silica gel, hexanes or petroleum ether, RT, (*E*)-**22** 61%; (b) activated silica gel, hexanes or petroleum ether, 80 °C (bath temperature), (*Z*)-**22**, 60%; (*E*)-**21** 50%; *ent*-(*Z*)-**14** quant., *ent*-(*E*)-**14** quant.; (c) activated silica gel, $CHCl_3$, 80 °C (bath temperature), **21** 73%; [b](*E*)-laurendecumenyne is likely to be natural product that is yet to be isolated.

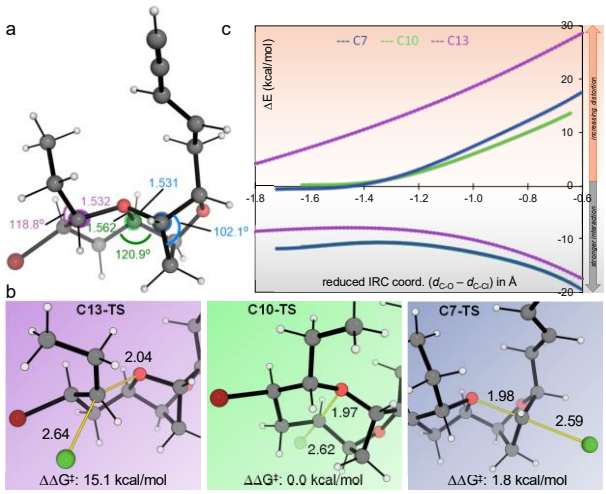


Figure 5. DFT analysis of oxonium ion opening with chloride as nucleophile: **a**, The lowest energy conformer of *ent*-(*E*)-**13** and relevant bond lengths and angles; O–C-10 is the longest bond. **b**, TSs for opening at C-13, C-10 and C-7. **c**, Distortion-interaction/activation-strain analysis along the opening reaction coordinate. The oxonium ion undergoes least distortion when opening at C-10. Distances in Å.

Consistent with synthetic studies (Scheme 3), the preferential site of nucleophilic attack by chloride is computed to be C-10, followed by C-7 for both *ent*-(*E*)-**13** and (*E*)-**20**. With water as the nucleophile, the selectivity between C-10 and C-7 for (*E*)-**20** is calculated to be much more finely balanced with $\Delta E^{\ddagger}$ slightly favoring C-10 opening while $\Delta G^{\ddagger}$ slightly favors C-7 opening (Figures S36-S48, pS109-S130).[29] Regardless, the energetic preference for attack at C-10 over C-7 is relatively modest and could be overcome by the intervention of enzymatic control. The reorganization required for attack at C-13 is substantial for *ent*-(*E*)-**13**, although we found this pathway to be more competitive for (*E*)-**20**: from this oxonium ion, enzymatic promotion of the C-13 pathway is more plausible.[55, 70]

CONCLUSION

We have synthesized and characterized four complex halogenated tricyclic oxonium ions (*E*)- and (*Z*)-**20** and *ent*-(*E*)- and *ent*-(*Z*)-**13**, proposed as key reactive intermediates in the biosynthesis of numerous halogenated acetogenin natural products from *L.* spp. using low temperature NMR experiments and DFT calculations. Furthermore, we have shown that, on exposure to a range of nucleophiles, these oxonium ions directly generate 10 natural products. The above work provides chemical evidence to support the proposed intermediacy of such intermediates biosynthetically and sets-the-scene for future biosynthetic studies on C-15 halogenated acetogenin natural products.

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org. Experimental procedures, characterization data, NMR spectra of reported compounds, computational details (PDF), and xyz coordinates of computed structures (zip file).

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