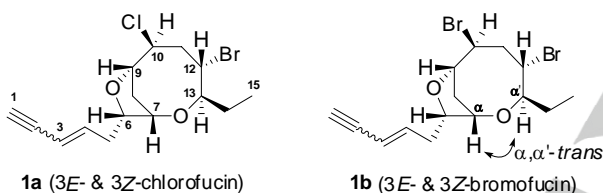


Byungsook Kim<sup>[a]</sup>, Te-ik Sohn<sup>[a]</sup>, Deukjoon Kim<sup>\*[a]</sup>, and Robert S. Paton<sup>\*[b]</sup>*Dedicated to Professor Minoru Suzuki for his vast contribution to the field of natural product chemistry*

**Abstract:** Substrate-controlled asymmetric total syntheses and structure confirmation of (+)-(3*E*)- and (-)-(3*Z*)-chlorofucin [(*E*)-**1a** and (*Z*)-**1a**], and (+)-(3*E*)- and (-)-(3*Z*)-bromofucin [(*E*)-**1b** and (*Z*)-**1b**] were accomplished. Our syntheses feature as key steps haloetherification (either 'conventional' or 'one-pot organoselenium-mediated') of  $\alpha,\alpha'$ -*trans*- $\gamma,\delta$ -unsaturated oxocene alcohol **9** and our (*E*)- and (*Z*)-selective cross-metathesis (CM) protocols. More importantly, a rationale is provided for the strikingly different pathways followed by  $\alpha,\alpha'$ -*trans*- $\gamma,\delta$ -unsaturated oxocene alcohol **9** and its  $\alpha,\alpha'$ -*cis* isomer **9'** in the presence of different electrophiles during the intramolecular electrophilic addition reactions.

## Introduction



**Figure 1.** Structures of Chlorofucins and Bromofucins.

Marine algae have been a prolific source of diverse halogenated secondary metabolites.<sup>[1]</sup> (+)-(3*E*)-Chlorofucin [(*E*)-**1a**], a C<sub>15</sub> acetogenin with a novel  $\alpha,\alpha'$ -*trans*-disubstituted 2,8-dioxabicyclo[5.2.1]decane skeleton, was isolated by Fenical and co-workers from the red alga *Laurencia snyderae* from La Jolla, California in 1980 (Figure 1).<sup>[2]</sup> When (*E*)-**1a** was re-isolated by Bowden and co-workers from *Dasyphila plumariodes* found on Holmes Reef in the Coral Sea in 1993,<sup>[3]</sup> they noted that this red alga is conspicuous by its presence on a reef where herbivores are abundant, and thus it appears to avoid predation. Interestingly, chlorofucin has been shown to reduce grazing by the herbivorous fish *Siganus doliatus* (rabbitfish).<sup>[4]</sup> Soon after, Suzuki and co-workers isolated (*E*)-**1a** from *Laurencia pannosa* in Vietnamese waters in 1996.<sup>[5]</sup> The structure and absolute configuration of (*E*)-chlorofucin were firmly established by X-ray crystallography.<sup>[2]</sup> In

addition, (*E*)-**1a** was fully characterized by NMR spectroscopy by Bowden and co-workers, and complete and unambiguous assignments were provided.<sup>[3]</sup> Meanwhile, (-)-(3*Z*)-chlorofucin [(*Z*)-**1a**] was isolated by Suzuki and co-workers from the red alga *Laurencia pannosa* found in Malaysian waters in 2001.<sup>[6]</sup> The structure and relative configuration of (*Z*)-chlorofucin were established by spectroscopic data. The absolute configuration of the natural product has not been determined, and the isolation chemists noted the possibility that its core bicyclic ring system is enantiomeric with that of (+)-(3*E*)-chlorofucin (*E*)-**1a**, judging from the sign and the value of the optical rotation:  $[\alpha]^{24}_D$  -11.3 (c 0.58, CHCl<sub>3</sub>) for (*Z*)-**1a** [lit.<sup>[2]</sup>  $[\alpha]^{20}_D$  +12.0 (c 1.4, CHCl<sub>3</sub>) for (*E*)-**1a**]. (-)-(3*Z*)-Chlorofucin showed activity against *Chromobacterium violaceum* with an MIC value of 100 mg/disk.

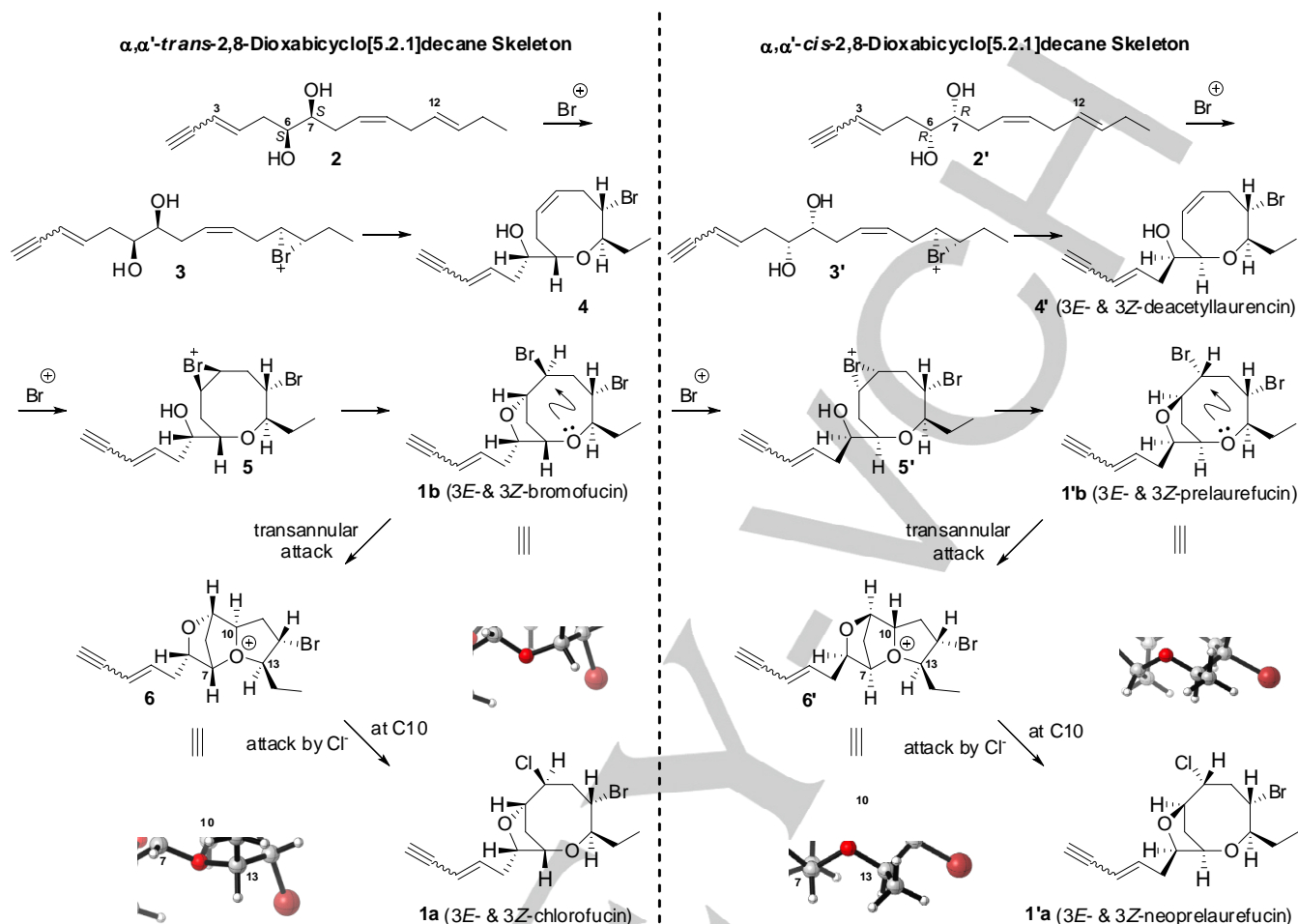
(+)-(3*E*)-Bromofucin [(*E*)-**1b**] was isolated by Coll and Wright from the red alga *Laurencia implicata* in 1989.<sup>[7]</sup> The structure and relative configuration of (*E*)-bromofucin were proposed on the basis of its spectroscopic data, and its remarkable spectral similarity with (*E*)-chlorofucin. The absolute configuration of the natural product was not determined and was assigned by analogy with the absolute configuration of 3(*E*)-chlorofucin. The natural product was re-isolated from *L. pannosa* in 1996 together with (*E*)-chlorofucin by Suzuki and co-workers.<sup>[5]</sup> (-)-(3*Z*)-Bromofucin [(*Z*)-**1b**] was isolated by Davies-Coleman and McPhail from the sea hare *Aplysia parvula* in 2005.<sup>[8]</sup> It has been suggested by the isolation chemists that the source of the (3*Z*)-**1b** was the *Laurencia* algae sequestered by the herbivorous *A. parvula*. The structure and relative configuration of (*Z*)-bromofucin were established by standard spectroscopic methods and its similarity with (*E*)-bromofucin except for the unsaturated side-chain.

We describe herein a full account of our substrate-controlled asymmetric total syntheses of (+)-(3*E*)- and (-)-(3*Z*)-chlorofucin [(*E*)-**1a** and (*Z*)-**1a**], and (+)-(3*E*)- and (-)-(3*Z*)-bromofucin [(*E*)-**1b** and (*Z*)-**1b**] from  $\alpha,\alpha'$ -*trans*- $\gamma,\delta$ -unsaturated oxocene alcohol **9** as a common synthetic intermediate by the use of haloetherification (either 'conventional' or 'one-pot organoselenium-mediated') and our (*E*)- and (*Z*)-selective cross-metathesis (CM) protocols.<sup>[9a,b]</sup> Our syntheses of all of these natural products established that the absolute configurations of (+)-(3*E*)- and (-)-(3*Z*)-chlorofucin, and (+)-(3*E*)- and (-)-(3*Z*)-bromofucin are those represented by the structures (*E*)-**1a** and (*Z*)-**1a**, and (*E*)-**1b** and (*Z*)-**1b**, respectively. More importantly, a rationale is provided for the strikingly different pathways followed by  $\alpha,\alpha'$ -*trans*- $\gamma,\delta$ -unsaturated oxocene alcohol **9** and its  $\alpha,\alpha'$ -*cis* isomer **9'** in the presence of different electrophiles during the intramolecular electrophilic addition reactions.

## Results and Discussion

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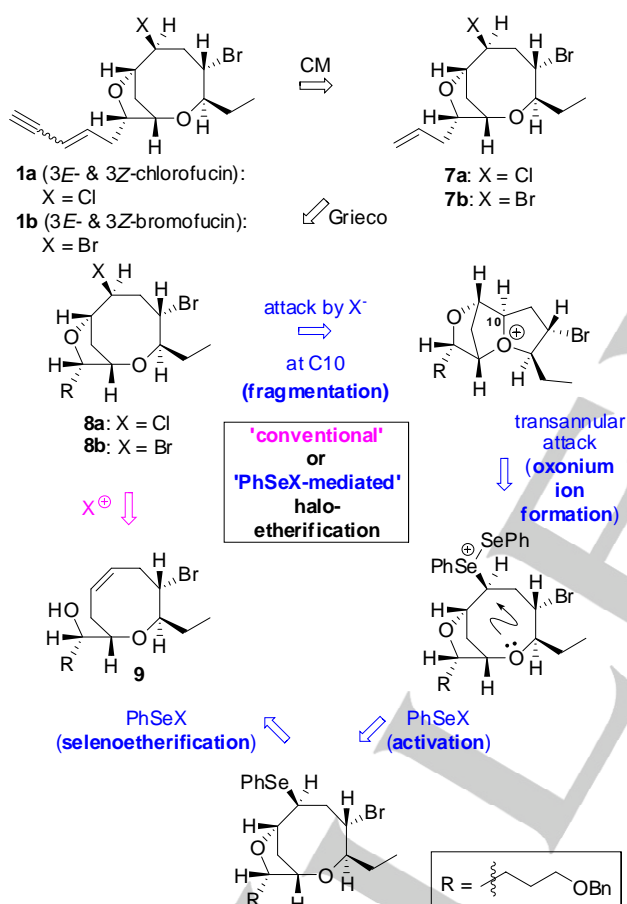
**Scheme 1.** Proposed Biosynthetic Pathway for Marine Natural Products with the 2,8-Dioxabicyclo[5.2.1]decane Skeleton.

The biosynthesis of  $\text{C}_{15}$  halogenated natural products from *Laurencia* species has been widely studied.<sup>[10]</sup> Murai has demonstrated that a number of  $\text{C}_{15}$  halogenated natural products can be derived from laurediols, which are known to exist naturally as unequal mixtures of (3*E/Z*, 12*E/Z*, *RR/SS*) stereoisomers,<sup>[11a]</sup> via bromoperoxidase-mediated bromonium ion-induced cyclizations. It was proposed that prelaurefucin (**1'b**), the  $\alpha,\alpha'$ -*cis* counterpart of bromofucin (**1b**), might be biogenetically derived from (3*E/Z*, 12*E*, *RR*)-laurediol **2'** through the intermediacy of deacetyl-laurencin **4'** as depicted in the right side of Scheme 1.<sup>[11b]</sup> Specifically, the action of bromide and a bromoperoxidase<sup>[12]</sup> would convert (3*E/Z*, 12*E*, *RR*)-laurediol **2'** into the corresponding bromonium ion **3'**, which would undergo cyclization to give deacetyl-laurencin **4'**.<sup>[13]</sup> From **4'**, bromoperoxidase-mediated bromonium ion formation of **5'** followed by bromoetherification would deliver the natural product prelaurefucin (**1'b**). Transannular displacement of bromide would give the tricyclic oxonium ion **6'** which would be opened by chloride at C10 to give neoprelaufucin (**1'a**), the  $\alpha,\alpha'$ -*cis* counterpart of chlorofucin (**1a**). It is of note that neither of the putative biogenetic intermediates

prelaurefucin and neoprelaufucin has been isolated from Nature to date, which is probably due to their lability (especially prelaurefucin). Analogous to the proposed prelaurefucin biosynthetic pathway, bromofucin (**1b**) is most likely biosynthesized from (3*E/Z*, 12*E*, *SS*)-laurediol **2** via sequential bromoperoxidase-mediated bromonium ion-induced cyclizations through the intermediacy of **4**, an  $\alpha,\alpha'$ -*trans* diastereomer of deacetyl-laurencin (**4'**). Displacement of the C10 bromide in bromofucin (**1b**) with transannular participation by the ring oxygen, and subsequent nucleophilic attack by chloride at the C10 position of the resultant oxonium ion **6** with retention of configuration, would lead to chlorofucin (**1a**) as depicted in the left side of the scheme.

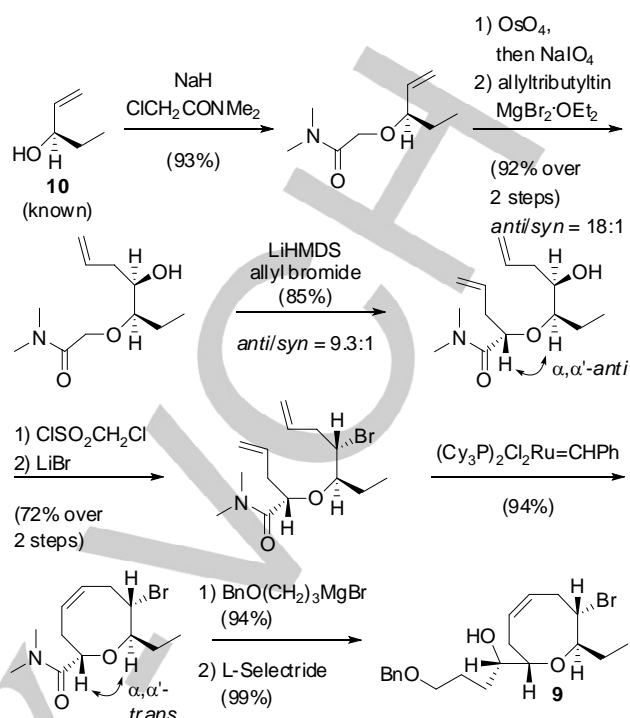
As shown in Scheme 2, we envisioned that the (3*E*- and (3*Z*)-enyne moiety of chlorofucin **1a** and bromofucin **1b** could be elaborated stereoselectively from terminal alkene **7a** and **7b**, respectively, via our (*E*)-selective<sup>[14]</sup> or (*Z*)-selective<sup>[9a,b,15]</sup> cross-metathesis protocol. The terminal alkenes **7a** and **7b** could in turn be prepared from chloro ether **8a** and bromo ether **8b**, respectively by application of the Grieco method.<sup>[16]</sup> Halo ethers

**8a** and **8b** could be synthesized from the common intermediate  $\alpha, \alpha'$ -*trans*- $\gamma, \delta$ -unsaturated oxocene alcohol **9** by haloetherification. In addition, synthesis of the antipode of **9** was recently disclosed in detail in connection with our synthetic work on elatényne (*vide infra*).<sup>[9a]</sup> However, the efficiency of the projected haloetherification caused some concern since the attempted bromoetherification of the corresponding  $\alpha, \alpha'$ -*cis*- $\gamma, \delta$ -unsaturated oxocene alcohol **9'** was unsuccessful due to transannular participation of the oxocene ring oxygen atom (See also Scheme 5).<sup>[14,17]</sup> We anticipated that our organoselenium-mediated haloetherification, which involves a selenoetherification/activation/oxonium ion formation/fragmentation sequence,<sup>[9a,b,14,18]</sup> might serve as an alternative in the event that the conventional haloetherification failed.



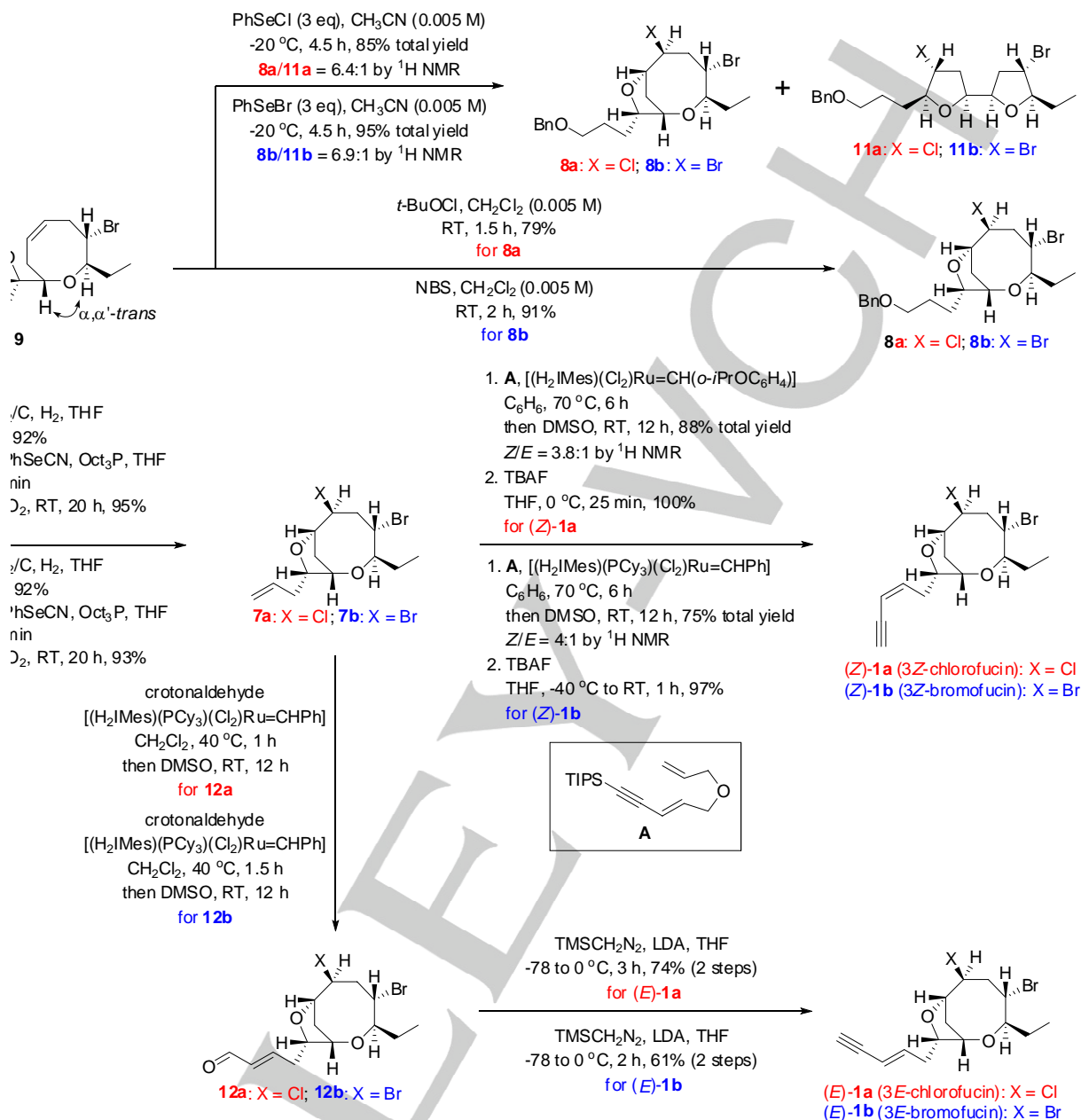
**Scheme 2.** Retrosynthetic Plan for Chlorofucins and Bromofucins.

Scheme 3 summarizes our synthesis of the planned haloetherification substrate,  $\alpha, \alpha'$ -*trans*- $\gamma, \delta$ -unsaturated oxocene alcohol **9**, and thus key substrate **9** was prepared from known allylic alcohol **10** in 9 steps in very good overall yield (46%).<sup>[9]</sup>



**Scheme 3.** Summary of Preparation of Haloetherification Substrate **9**. LiHMDS=lithium hexamethyldisilazide.

With  $\alpha, \alpha'$ -*trans*- $\gamma, \delta$ -unsaturated alcohol **9** in hand, we proceeded to explore the haloetherification as summarized in Scheme 4. Fortunately, despite our initial concern regarding the abovementioned efficiency,<sup>[14,17]</sup> we were quite relieved to find that haloetherification of  $\alpha, \alpha'$ -*trans*-oxocene alcohol **9** under typical conditions proceeded without incident, in contrast to the case of  $\alpha, \alpha'$ -*cis*-oxocene alcohol **9'**. In the event,  $\gamma, \delta$ -unsaturated alcohol **9** underwent a smooth chloroetherification upon exposure to *t*-BuOCl in methylene chloride to furnish desired chloroether **8a** with a 2,8-dioxabicyclo[5.2.1]decane skeleton in 79% yield.<sup>[19]</sup> Furthermore, subjection of **9** to our one-pot organoselenium-mediated haloetherification conditions (PhSeCl, CH<sub>3</sub>CN, -20 °C, 4.5 h) afforded a 6.4 : 1 mixture of the desired chlorofucin surrogate **8a** and bis-2,2'-tetrahydrofuran **11a** in 85% total yield. Formation of bis-2,2'-tetrahydrofuran **11a** is in accord with our observation that in the case of  $\alpha, \alpha'$ -*trans*-oxocene alcohol, greater amounts of bis(2,2')-furan are formed by the C7 attack of the  $\alpha, \alpha'$ -*trans*-dioxatricyclic oxonium ion intermediate in a kinetically controlled process relative to the corresponding  $\alpha, \alpha'$ -*cis*-oxocene alcohol.<sup>[9b,14,18a]</sup> It is worthwhile mentioning that proportionately more **11a** was produced at higher reaction temperatures. For instance, the **8a/11a** ratio was 4.2:1 at RT for 20 min, and 5.2:1 at 0 °C for 30 min. Having demonstrated both the 'conventional' and 'organoselenium-mediated' chloroetherification routes, removal of the benzyl protecting group in **8a** followed by conversion of the resultant primary alcohol into terminal olefin **7a** by the Grieco's method<sup>[16]</sup> set the stage for stereoselective introduction of the enyne unit (87% overall yield, 2 steps). Using our previously developed efficient protocol for (*E*)-enyne synthesis<sup>[9a,b,14]</sup> for the synthesis of (+)-(3*E*)-chlorofucin (*E*)-**1a**, cross-metathesis of terminal alkene



**Scheme 4.** Haloetherification and Completion of the Syntheses. THF=tetrahydrofuran, DMSO=dimethyl sulfoxide, TMS=trimethylsilyl, LDA= lithium diisopropylamide, TBAF=tetra-*n*-butylammonium fluoride, NBS=*N*-bromosuccinimide.

**7a** with crotonaldehyde and the Grubbs second generation catalyst,<sup>[20]</sup> followed by an exposure of the resulting *trans*- $\alpha,\beta$ -unsaturated aldehyde **12a** to lithio TMS-diazomethane,<sup>[21]</sup> delivered (+)-(3*E*)-chlorofucin (**E-1a**) in 74% yield for the two steps. On the other hand, (*Z*)-selective cross metathesis<sup>[9a,b,15,22]</sup> of terminal alkene **7a** with enyne **A** in the presence of the Grubbs-Hoveyda second generation catalyst gave rise to TIPS-protected 3(*Z*)-chlorofucin (88% total yield,  $Z/E$  = 3.8:1), which was converted to 3(*Z*)-chlorofucin **1a** in quantitative yield by treatment with TBAF. For the synthesis of the bromofucins, exposure of  $\gamma,\delta$ -unsaturated alcohol **9** to NBS in  $\text{CH}_2\text{Cl}_2$  afforded the desired bromofucin surrogate **8b**.<sup>[9a,b]</sup> Alternatively, exposure of **9** to

$\text{PhSeBr}$ ,  $\text{CH}_3\text{CN}$ ,  $-20\text{ }^\circ\text{C}$ , 4.5 h furnished a 6.9 : 1 mixture of the desired bromofucin surrogate **8b** and bis-2,2'-tetrahydrofuran **11b** in 95% total yield. Similar oxonium ion fragmentation pattern and its temperature dependency to those for  $\text{PhSeCl}$  were observed (see the Supporting Information). The bromo ether **8b** was then elaborated using a pathway parallel to the chlorofucin sequence to produce (+)-(3*E*)- and (-)-(3*Z*)-bromofucinenyn (**E-1b** and **Z-1b**) in comparable overall yields. The spectral and optical rotation data for all four of our synthetic materials were in good agreement with those of the natural products.

Having accomplished the asymmetric total syntheses and structure confirmations of chlorofucins and bromofucins, we

proceeded to address the strikingly different behavior of  $\alpha,\alpha'$ -*trans*- $\gamma,\delta$ -unsaturated oxocene alcohol **9** and its  $\alpha,\alpha'$ -*cis* isomer **9'** towards electrophiles observed during intramolecular electrophilic addition reactions computationally.<sup>23</sup>

All stationary points are optimized using the wB97XD density functional<sup>24</sup> and 6-31G(d) basis set with a conductor-like polarizable continuum model (CPCM) of acetonitrile or dichloromethane as solvent.<sup>25</sup> Single point energies were evaluated with a larger 6-311+G(d,p) basis set. Transition structures are confirmed by the presence of a single imaginary vibrational frequency that corresponds to the reaction coordinate of interest, while minima possess only real vibrational frequencies. Free energies at 298K are quoted in kcal/mol and include an unscaled correction for zero-point vibrational energy and a quasi-harmonic correction for frequencies below 100 cm<sup>-1</sup>.<sup>26</sup> Distances are quoted in Å. Ring conformations of substrates **9** and **9'** were modelled taking the low energy *anti* and *syn* conformations of the parent hexahydrooxonin oxacycle.<sup>27</sup>

Firstly, as summarized in Equations (1) and (1') of Scheme 5,  $\alpha,\alpha'$ -*trans*- $\gamma,\delta$ -unsaturated oxocene alcohol **4** as well as its diastereomer, deacetyllaurencin **4'**, an  $\alpha,\alpha'$ -*cis*- $\gamma,\delta$ -unsaturated oxocene alcohol, undergo bromoperoxidase-catalyzed bromoetherification to give bromofucin **1b** and prelaurefucin **1'b**, respectively, in the proposed biogenetic pathway. In contrast, upon the attempted bromoetherification by exposure to NBS, the  $\alpha$ -bromonium ion derived from deacetyllaurencin surrogate **9'** (an  $\alpha,\alpha'$ -*cis*- $\gamma,\delta$ -unsaturated oxocene alcohol) undergoes transannular attack by the oxocane ring oxygen atom prior to the desired bromoetherification and yields a mixture of **13** and **14** as depicted in Eq. 2'.<sup>[14,17]</sup> Meanwhile,  $\alpha,\alpha'$ -*trans*- $\gamma,\delta$ -unsaturated oxocene alcohol **9** produces bromo ether **8b**, a bromofucin surrogate, in good yield, just as in the biogenetic transformation (Eq. 2).

**Scheme 5.** Electrophilic Additions of  $\alpha,\alpha'$ -*trans*- &  $\alpha,\alpha'$ -*cis*- $\gamma,\delta$ -unsaturated oxocene alcohols **9** and **9'** with NBS and PhSeX

The bromoetherification of  $\alpha,\alpha'$ -*cis* oxocene alcohol **9'** with NBS in dichloromethane was modelled (Scheme 6). This substrate favors the *anti*-conformation **17** over the *syn*-conformation **16** by 1.6 kcal/mol,<sup>[15a]</sup> while the corresponding bromonium ions formed upon treatment with NBS differ in energy by only 0.2 kcal/mol. The

bromonium ions formed on the top face of **17** and bottom face of **16** are predicted to be more stable than their diastereomers formed from bromination of the opposite alkene face by 6.7 and 8.7 kcal/mol. We expect bromination to occur reversibly, although the endergonicity of this step is demonstrably over-estimated. We

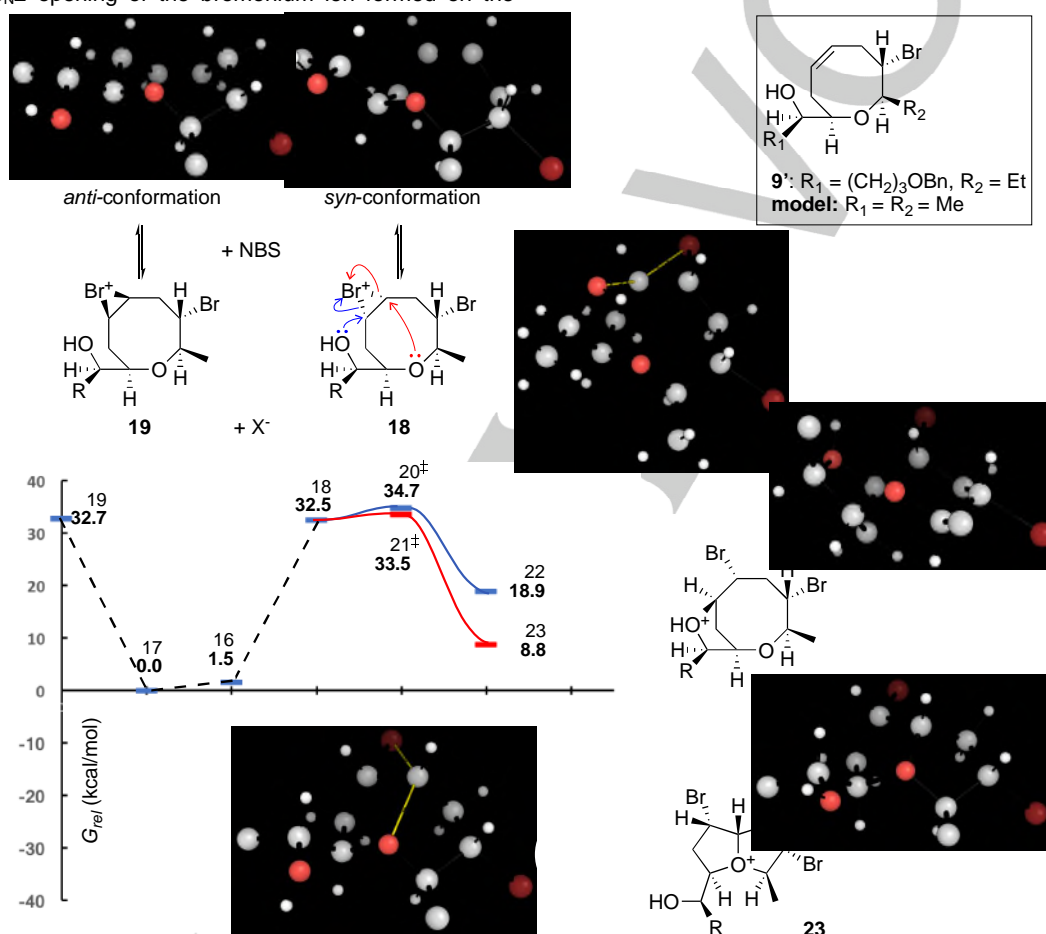


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attribute this to our computational model in which bromonium and succinimide ions are fully solvated and non-interacting.<sup>28</sup> An alternative pathway avoiding a bromonium ion, in which the NBS N-Br bond is cleaved in concert with C-O bond formation was computed, although has a higher barrier by 4.2 kcal/mol. The bromonium formed on the top face as shown (derived from the anti-conformation), however, is unable to undergo S<sub>N</sub>2 opening by either alcohol or ether group in the conformation shown. Flipping the C11-C12-C13 portion of the ring makes attack by the ether possible (not shown), although the free energy barrier for the S<sub>N</sub>2 transition state (TS) is 9.8 kcal/mol. In contrast, the computed barriers for S<sub>N</sub>2 opening of the bromonium ion formed on the

bottom face are extremely small, which is consistent with this being the more reactive of the two conformations.

Looking at the S<sub>N</sub>2 opening of bromonium **18**, the computed barriers for attack by ether (1.0 kcal/mol via TS **20**) and by alcohol (2.2 kcal/mol via TS **21**) are extremely small and, which is consistent with these processes occurring readily and irreversibly, with the former process slightly favored kinetically. With a free energy change of -23.7 kcal/mol, formation of the fused-5,5 bicyclic **23** is indicative of irreversible opening. The formation of the 5,5-bicyclic oxonium can be rationalized since it is the kinetic product of bromonium opening, and occurs irreversibly.



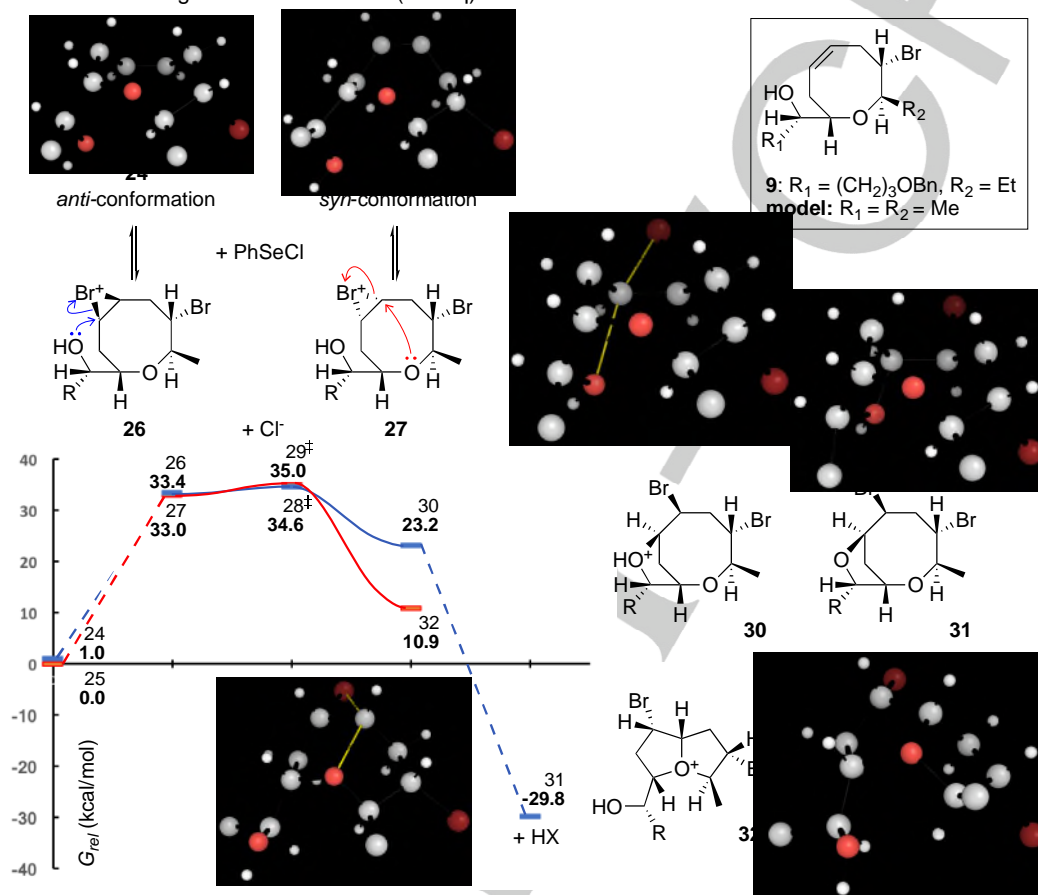
**Scheme 6.** Electrophilic Addition of  $\alpha,\alpha'$ -cis oxocene alcohol **9'** with NBS, with CPCM(DCM)-wB97XD/6-311++G(d,p)//CPCM(MeCN)-wB97XD/6-31G(d) Gibbs energies in kcal/mol.

The  $\alpha,\alpha'$ -trans oxocene alcohol **9** was modelled similarly (Scheme 7). Syn and anti conformers **25** and **24** are separated by only 1.0 kcal/mol, with the syn conformation favored,<sup>[15a]</sup> while the two bromonium ions also lie close in free energy, the top face of the anti-conformer being favored by 0.4 kcal/mol. Unlike **9'**, both bromonium ions **26** and **27** may undergo facile S<sub>N</sub>2 opening in the conformations shown: with Br on the bottom face, the ether is aligned to attack, and with Br on the top face the alcohol is approximately aligned to attack.

Attack by the ether oxygen proceeds with a barrier of 2.0 kcal/mol via TS **29** to give a fused-5,5-bicyclic **32** which is 22.1 kcal/mol downhill. Attack by the alcohol is kinetically favored with a barrier of 1.2 kcal/mol via TS **28** and forms the 5,8-bicyclic **30** 11.2 kcal/mol below the bromonium ion. Formation of the 5,8-bicyclic product is attributed to the lower barrier for its opening by the alcohol oxygen, and by facile deprotonation of the alcoholic proton of **30** that renders this pathway irreversible. With succinimide acting as base, this final process is very favourable (by 53.0 kcal/mol), forming neutral **31**.

Secondly, in contrast to the bromoetherification,  $\alpha,\alpha'$ -*trans*- $\gamma,\delta$ -unsaturated oxocene alcohol **9** as well as  $\alpha,\alpha'$ -*cis*- $\gamma,\delta$ -unsaturated oxocene alcohol **9'** (a deacetyllaurencin surrogate), undergo an efficient phenylselenoetherification as summarized in Equations (3) and (3') of Scheme 5, respectively. We have demonstrated that treatment of  $\alpha,\alpha'$ -*trans*- $\gamma,\delta$ -unsaturated oxocene alcohol **9** with a limiting amount of PhSeCl (1.1 eq) in

CH<sub>3</sub>CN at 0 °C for 10 min produce the corresponding selenoether **15** in 98% yield (see the Supporting Information). The resulting selenoethers undergo further reactions with an excess amount of organoselenium reagent to give rise to a variety of products under different reaction conditions, which have been exploited in natural product synthesis in our laboratories.<sup>[9a,14,18a]</sup>



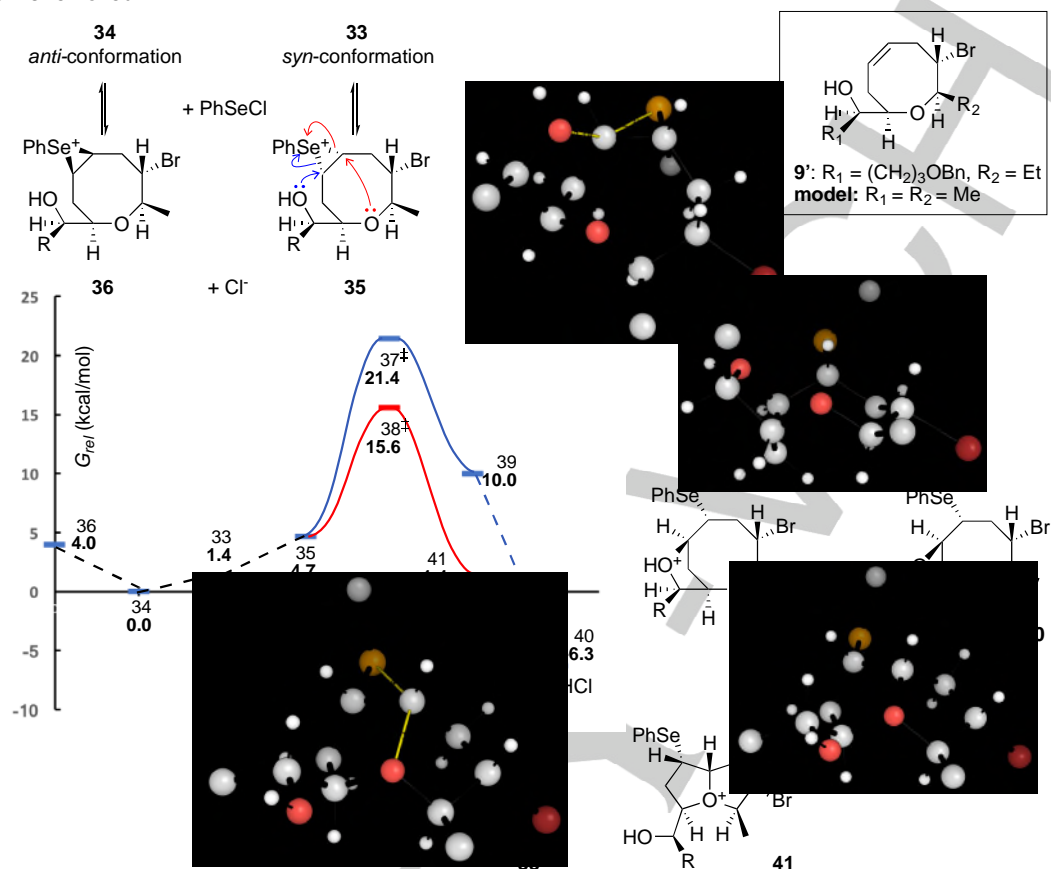
**Scheme 7.** Electrophilic Addition of  $\alpha,\alpha'$ -*trans* oxocene alcohol **9** with NBS, with CPCM(DCM)-wB97XD/6-311++G(d,p)//CPCM(MeCN)-wB97XD/6-31G(d) Gibbs energies in kcal/mol

Phenylselenoetherification of *cis* oxocene alcohol **9'** by PhSeCl in acetonitrile was modelled (Scheme 8). Seleniranium ions are favored on the top face by 2.9 kcal/mol, however, as was found for bromonium ions **18** and **19** only the opening of seleniranium **35**, with the phenylselenenyl group on the bottom face, is possible without having to undergo an unfavorable conformational flip, as shown in Scheme 8. As for bromonium ion formation, we expect seleniranium ion formation to occur reversibly.

The reactive seleniranium intermediates are less reactive than the corresponding bromonium ions. Computed barriers (relative to common intermediate **35**) for the S<sub>N</sub>2 opening of

seleniranium **35** are much higher than the corresponding bromoniums at 10.9 kcal/mol for ether attack via TS **38** and 16.7 kcal/mol via TS **37** for alcohol attack. Also in contrast with the behavior of the bromonium ions, the bicyclic products thus formed lie close to the seleniranium in free energy, so that either ring closing is reversible – it is alcohol deprotonation that will render the formation of the 5,8-bicyclic ether irreversible. With chloride this is favorable to form neutral **40**, although with a smaller driving force than computed with succinimide. The formation of 5,8-bisether product is therefore attributable to the fact that either nucleophilic openings are possible, however, they occur

reversibly, and the major product is only trapped out when the alcoholic proton is removed.



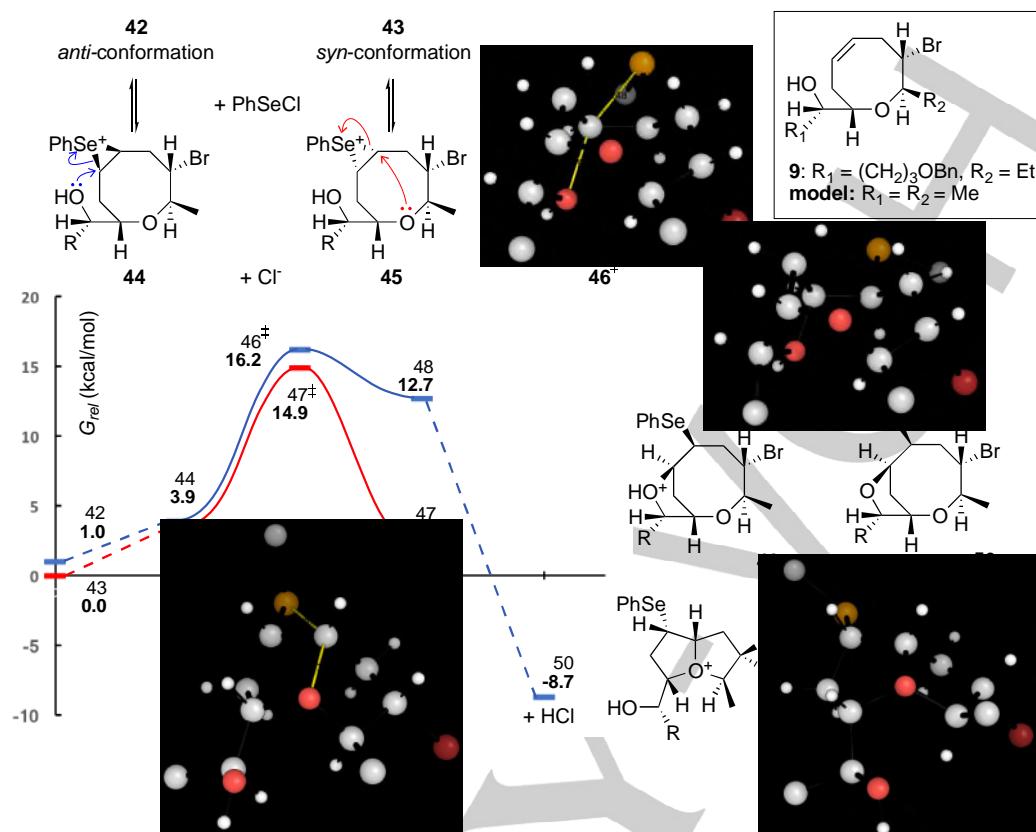
**Scheme 8.** Electrophilic Addition of  $\alpha,\alpha'$ -cis oxocene alcohol **9'** with PhSeCl, with CPCM(MeCN)-wB97XD/6-311++G(d,p)//CPCM(MeCN)-wB97XD/6-31G(d) Gibbs energies in kcal/mol.

Phenylselenoetherification of *trans* oxocene alcohol **9** was modelled similarly (Scheme 9). As for the bromonium ions derived from **9**, the seleniranium ions **44** and **45** lie close in energy, with the top face favored by 0.9 kcal/mol. Either of these may undergo opening by nucleophilic attack, **45** by the ether oxygen and **44** the alcohol oxygen.

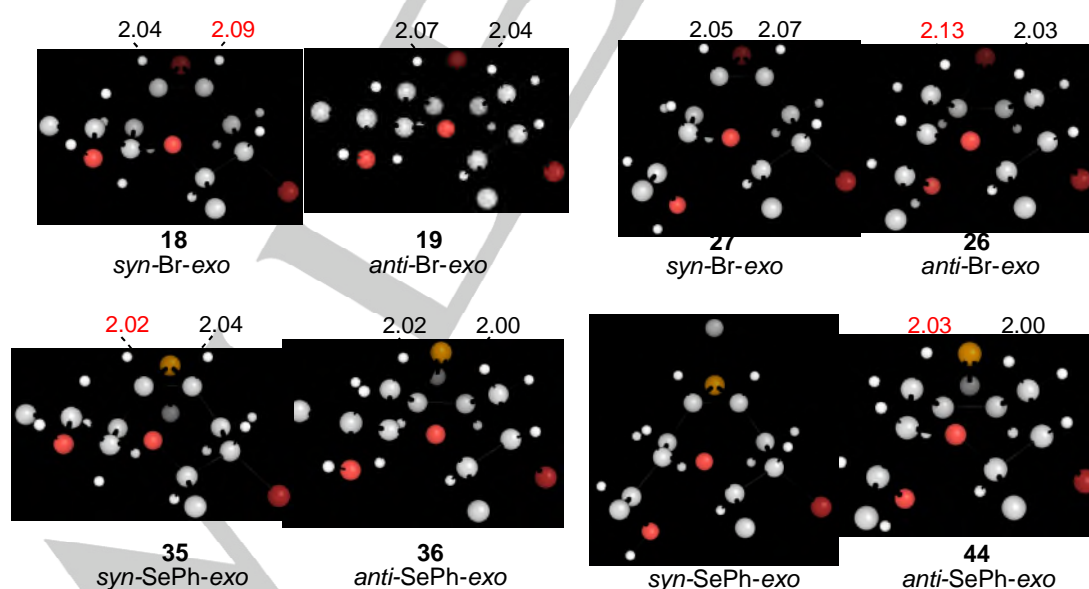
Barriers for S<sub>N</sub>2 attack are again higher than for the bromonium ions and the products both lie uphill in terms of free energy, so a reversible reaction is anticipated. Hence the 5,8-bicyclic will be the major product since both pathways occur reversibly, but once the alcoholic proton is removed from the 5,8-bisether the reverse reaction is inhibited.

The contrast in reactivity between bromoetherification and selenoetherification can be further understood in terms of the optimized structures of the cationic reactive intermediates (Scheme 10). The greater electrophilicity of the bromonium ions is typified by longer C-Br distances in these intermediates vs. the corresponding C-Se distances. Bromonium ions undergo ring-opening more readily and irreversibly. The kinetically favoured site of attack occurs at the carbon atom with the longer C-Br bond, i.e. with greater carbocationic character.





**Scheme 9.** Electrophilic Addition of  $\alpha,\alpha'$ -trans oxocene alcohol **9** with PhSeCl with CPCM(MeCN)-wB97XD/6-311++G(d,p)//CPCM(MeCN)-wB97XD/6-31G(d) Gibbs energies in kcal/mol.



**Scheme 10.** CPCM-wB97XD/6-31G(d) structures of bromonium and phenylseleniranium intermediates. The predominant site of attack is shown in red.

## Conclusions

We have accomplished an highly stereoselective and efficient substrate-controlled asymmetric total syntheses of (+)-(3*E*)- and

(-)-(3*Z*)-chlorofucin (*E*)-**1a** and (*Z*)-**1a**, and (+)-(3*E*)- and (-)-(3*Z*)-bromofucinenyn (*E*)-**1b** and (*Z*)-**1b** from a common synthetic intermediate **9**, an  $\alpha,\alpha'$ -*trans*- $\gamma,\delta$ -unsaturated oxocene alcohol, employing haloetherification (either 'conventional' or 'one-pot organoselenium-mediated') and our (*E*)- and (*Z*)-selective cross-metathesis protocols. Our syntheses of all of these natural products established that the absolute configurations of (+)-3(*E*)- and (-)-3(*Z*)-chlorofucin, and (+)-3(*E*)- and (-)-3(*Z*)-bromofucin are represented by the structures (*E*)-**1a** and (*Z*)-**1a**, (*E*)-**1b** and (*Z*)-**1b**, respectively. More importantly, rationales for the observed contrasting behaviors of  $\alpha,\alpha'$ -*trans*- $\gamma,\delta$ -unsaturated oxocene alcohol **9** and its  $\alpha,\alpha'$ -*cis* isomer **9'** towards different electrophiles during intramolecular electrophilic addition reactions were

provided. Computational analysis shows that bromoetherification is controlled by irreversible ring-opening at the most electrophilic position. Selenoetherification produces less reactive intermediates, which can open reversibly, followed by selectivity-determining deprotonation.

## Experimental Section

**Supporting Information.** Experimental procedures; spectroscopic and analytical data for all new compounds including copies of NMR spectra; computational details.

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**Keywords:** natural product synthesis • halofucins • haloetherification • computational chemistry • oxonium ion formation-fragmentation

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*Byungsook Kim, Te-ik Sohn, Deukjoon Kim\*, and Robert S. Paton\**

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**Asymmetric Total Syntheses and  
Structure Confirmation of  
Chlorofucins and Bromofucins.**

Substrate-controlled asymmetric total syntheses and structure confirmation of chlorofucins and bromofucins have been achieved by the use of haloetherification, either 'conventional' or 'one-pot organoselenium-mediated'. More importantly, a rationale is provided for the strikingly different pathways followed by  $\alpha,\alpha'$ -*trans*- $\gamma,\delta$ -unsaturated oxocene alcohol **9** and its  $\alpha,\alpha'$ -*cis* isomer in the presence of different electrophiles during the intramolecular electrophilic addition reactions.

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