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Biomimetic chlorine-induced polyene cyclizations harnessing hypervalent chloroiodane–HFIP assemblies†

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While bromo- and iodocyclizations have recently been successfully implemented, the challenging chlorocyclizations have been scantly investigated. We present a selective and generally applicable concept of chlorination-induced polyene cyclization by utilizing HFIP–chloroiodane networks mimicking terpene cyclases. A manifold of different alkenes was converted with excellent selectivities (up to d.r. >95 : 5). The cyclization platform was even extended to several structurally challenging terpenes and terpenoid carbon frameworks.

1 Introduction

The power of terpene cyclases cannot be overemphasized. Starting from simple, achiral, linear C_5 isoprene-derived precursors **1**, nature can generate an entire collection of structurally diverse and highly complex (poly)cyclic carbon frameworks, in a single step.[1] Among the utilized cationic pathways, the head-to-tail (HT) cyclization commences with electrophilic activation of the terminal (head) functional unit (*cf.* Fig. 1a). While the protonation of epoxides and alkenes constitute the most common initiation step, cyclizations triggered by halenium (X^+) addition to the terminal olefin (**1**, Fig. 1a) are likewise possible.[2] The latter has already given rise to over 200 terpene scaffolds,[3] isolated from natural producers. These have mostly been brominated but can also be chlorinated, with hamiltonin C (**9**),[4] haterumaimide L (**10**),[5] and azamerone[6] (**11**, Fig. 1b) among the chlorinated representatives.

Despite significant progress in developing selective and generally applicable bromo- and iodocyclization methods,[2,7–9] chlorocyclizations have barely been touched as they are significantly more challenging. For chlorination-induced cyclizations, the tendency for the closed-ring intermediate **4** to form is generally very low (Fig. 1a). Typically, linear products **5** and **6** result. In addition, the chemical instability of the chlorine addition intermediate **2** constitutes another severe problem. The electronegativity and small radius of the chlorine atom render the linear, carbocationic form **3** preferable over the cyclic haliranium ion **2**.[10] Consequently, the pendant nucleophile attack proceeds *via* an S_N1 mechanism, resulting in low product

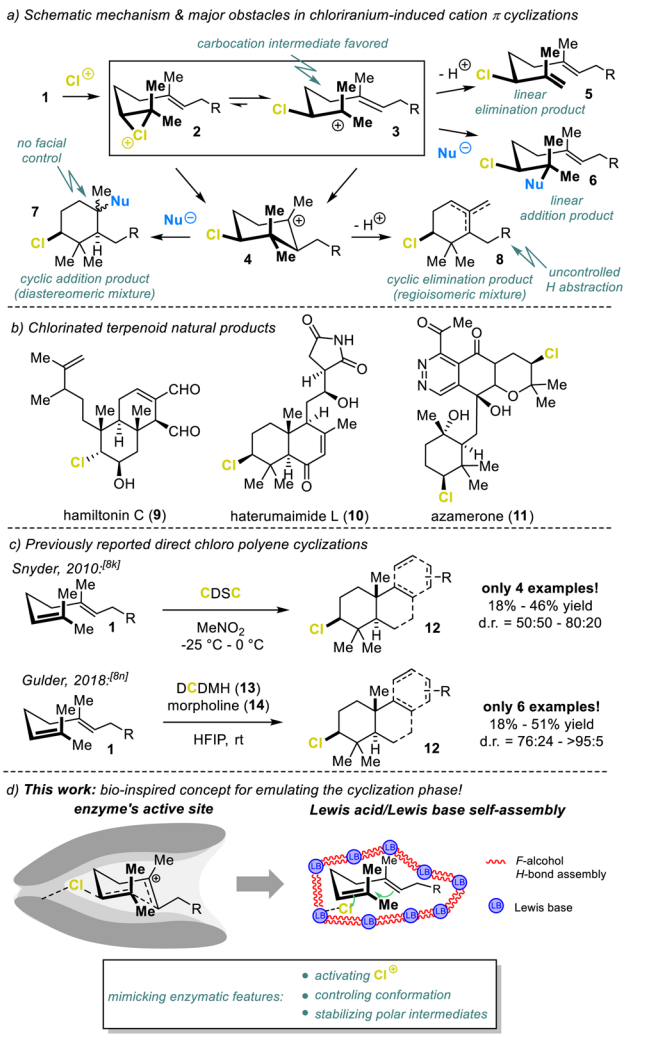

Fig. 1 (a) Mechanistic challenges in chlorination-assisted polyene cyclizations, (b) chlorine-containing terpenes, (c) previous direct chlorocyclizations, and (d) concept of this work.

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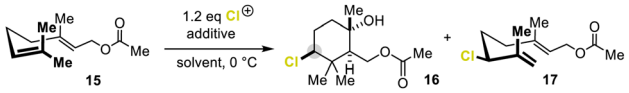
stereoselectivity 7.[11] In addition, β-H abstraction is the predominant cation **3** trapping process, forming the desired products **7** and **8** in small quantities.

To our knowledge, only two direct chloriranium-triggered terpene cyclization methods are known (Fig. 1c).[8k,n,12] In 2010, Snyder *et al.*[8k] employed their newly developed chlorodiethylsulfonium hexachloroantimonate (CDSC, not shown) as the chlorinating agent. Unfortunately, most transformations lacked any diastereoselection. Our group recently published a haliranium-mediated polyene cyclization protocol[8n] using HFIP[13] emulating the intrinsic features of terpene cyclases.[1,14] This method is in principle applicable to chlorine-assisted ring closures but here we were able to target just a small set of electron-rich alkenes **1** (6 examples) albeit with good diastereomeric excess. Nevertheless, these first examples marked milestones in the yet unresolved problem of chloriranium-triggered polyene cyclizations. Encouraged by our preliminary studies, we have advanced our bioinspired concept and provided a generally applicable, direct chlorocyclization to polyenes, thus addressing the general problems associated with such terpene formations (Fig. 1d).

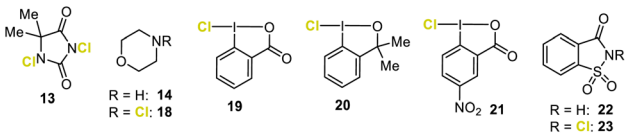
2 Results and discussion

For our investigations here, we chose geranyl acetate (**15**) as the model substrate which constitutes a particular challenge for polyene cyclizations in general but has shown promising results in our brominative ring closures.[8n] Subjecting **15** to the optimized conditions reported earlier by our group[8n] indeed furnished the desired cyclic alcohol **16**, albeit in 9% yield, together with the linear chloropolyene **17** as the main product (52%, Table 1, entry 1). More importantly, however, the formation of **16** occurred with a promising stereoselection (d.r. = 86 : 14), which was similar to that observed for bromocyclization (d.r. = 82 : 18). This result clearly shows that our confined HFIP–Cl^+ network[15] exerts significant stereocontrol, even for chlorine-assisted cation-π cyclizations. Further screening of chloronium reagents, such as *N*-chloro morpholine (**18**), Palau'chlor, chloramine-T, or *N*-chlorosuccinimide, neither enhanced the chemical yield nor the stereoselectivity of **16** (entry 2 and ESI†). Even CDSC introduced by Snyder and co-workers for chlorocyclizations of **15** in nitromethane (entry 12)[8k] led to a messy conversion of **15** in HFIP with no chlorine-containing product detectable (entry 13 and the ESI†). The formation of **16** could only significantly be improved if carboxylic acid-derived, cyclic hypervalent iodanes were employed as electrophilic chlorination reagents (entries 3, 4–11, and the ESI†). Using chloroiodane **19**, the yield of **16** was doubled to 19%, while the d.r. remained high (84 : 16, entry 3). Simultaneously, acyclic product **17** significantly decreased to 41%. The ether analog **20** did not react at all (entry 4). HFIP played a decisive role in terpene cyclization, and no other solvent (entries 5–7) or solvent mixtures with HFIP (*cf.* ESI†) delivered the cyclized products. As a consequence, we tried to further foster electrophilic chlorine transfer by fine-tuning the electronic properties of the chlorobenziodoxolone core structure. Introducing a nitro substituent

Table 1 Optimization of the direct chloriranium-induced polyene cyclization of geranyl acetate (**15**)[a]



Entry	Cl^+	Solvent	Additive	Yield **16** (d.r.)[b]	Yield **17**
1	**13**	HFIP	**14**[c]	9% (86 : 14)	52%
2	**18**	HFIP	—	10% (86 : 14)	52%
3	**19**	HFIP	**14**[c]	19% (84 : 16)	41%
4	**20**	HFIP	**14**[c]	<5%	<5%
5	**19**	iPrOH	**14**[c]	—	—
6	**19**	TFE	**14**[c]	<5%	27%
7	**19**	$MeNO_2$	**14**[c]	—	<5%
8	**21**	HFIP	**14**[c]	23% (83 : 17)	19%
9	**19**	HFIP	—	19% (83 : 17)	21%
10	**21**	HFIP	**22**[d]	30% (83 : 17)	14%
11	**23**	HFIP	—	<5%	n.d.
12 (ref. 8k)	**CDSC**	$MeNO_2$	—	18% (69 : 31)	—
13	**CDSC**	HFIP	—	n.d.	n.d.

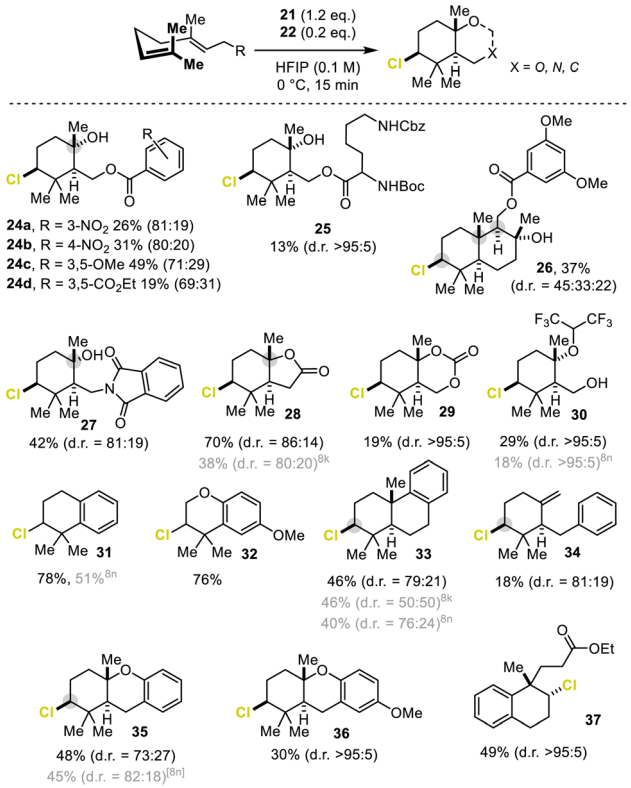


[a] 19.6 mg geranyl acetate **15** (0.10 mmol, 1.0 eq.) was added to a mixture of the Cl reagent (0.12 mmol, 1.2 eq.) and additive in 1.00 mL solvent at 0 °C. [b] determined by ^{1}H-NMR spectroscopy of the crude mixture. [c] 0.14 mmol and 1.4 eq. [d] 20 mol% additive.

at C-5 to increase the electrophilicity at the iodine atom proved superior. The outcome of **16** was enhanced to 23% (entry 8).

Surprisingly, omitting the Lewis basic additive **14** significantly reduced the formation of the unwanted linear allyl chloride **17** to 21% but had no beneficial effect on the cyclization event (entry 9). This result contrasts observations made for the bromo- and iodocyclizations, where morpholine (**14**) was decisive in taming the reactivity and thus following a productive pathway.[8n] Next, additives more acidic than **14** (pK_a < 8) were tested (see the ESI†). The pH optimum for this reaction was achieved by employing saccharin (**22**, pK_a = 1.6, entry 10, and the ESI†). Here, a threefold increase in the yield (30%) of chlorocyclohexane **16** was observed with a d.r. of 83 : 17. The amount of Brønsted acid **22** could even be reduced to catalytic quantities (20 mol%) without any impact on the reaction outcome (entry 10). The *in situ* generation of chlorosaccharin (**23**) and its subsequent reaction with substrate **15** was excluded, as directly adding **23** to the reaction mixture did not give the desired product **16** (entry 11).

After the transformation was established, we turned our attention to the generality of this chlorination-assisted terpene cyclization (Scheme 1). First, different geranyl derivatives were explored. Geranyl ester, imide, and carbamate derivatives were rapidly cyclized (15 min), as was the free acid, to the corresponding cyclohexyl products **24–28** in moderate to excellent yields (13–70%) for chloropolyene cyclizations and with diastereoselectivities of up to >95 : 5. The reaction proved to be



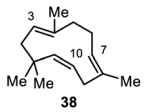
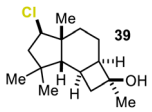
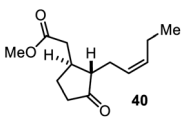
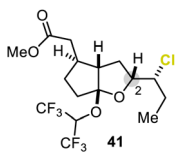
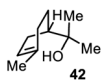
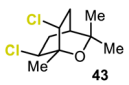
Scheme 1 Substrate scope for direct chloriranium-induced polyene cyclization. The substrate (0.20 mmol, 1.0 eq.) was stirred with 76.8 mg **21** (0.24 mmol, 1.2 eq.) and 7.33 mg **22** (40.0 μmol, 0.2 eq.) in 2.00 mL HFIP at 0 °C for 15 min. The d.r. was determined by ^{1}H-NMR spectroscopy of the crude reaction mixture. The given d.r. refers to the configuration at the carbons highlighted in grey.

tolerant of several functional groups including the acid-sensitive *N*-Boc-protecting group as showcased by the lysine ester **25**. Extended π-systems, such as farnesyl esters (→**26**), were likewise converted in good yields (37%) but suffered from a low diastereoselection. The carbocationic intermediate **4** (*cf.* Fig. 1a), generated during the ring-closure of geraniol, was trapped by the weakly nucleophilic fluoro alcohol. This can be explained by the less stabilizing effect of the alcohol substituent compared to that of the corresponding ester and imide moieties (products **24–27**).[8n] The geraniol-derived intermediate **4** is thus more reactive and already trapped by HFIP during the reaction, while **4** stabilized by a carbonyl adduct reacts with water most likely not before workup. This returned 29% HFIP–ether **30** with perfect diastereoselectivity, which constituted an 11% improvement over our previous method.[8n]

Next, substrates equipped with an aryl terminating nucleophile were subjected to our optimized reaction conditions. All compounds smoothly delivered the corresponding di- or tricyclic products **31–37** with excellent diastereoselectivities (up to >95 : 5) and chemical yields (30–78%), regardless of whether intramolecular O- or C-nucleophiles were applied. For heptadienes, which are one carbon atom shorter than the homogeranyl substrates, only monocyclization to product **34** occurred. This was possibly due to the thermodynamically unfavorable, strained 6–5 ring system (not shown) built by a complete cyclization sequence. In the presence of two competing nucleophiles (aryl *versus* ester moiety) the cationic intermediate **4** was trapped predominantly by the carbon nucleophile affording **37**. It is noteworthy that in general chlorocyclizations of polyenes suffer from low conversion and low diastereoselectivities, thus rendering the chemical yield obtained here good to excellent for this type of transformation.[16]

Encouraged by our results, we extended the cyclization platform to structurally more challenging terpene and terpenoid carbon frameworks (Table 2). Interestingly, the addition of the chlorenium species to the trisubstituted C-3 olefin in α-humulene (**38**) started a selective transannular ring-closing event. This led to the 5-6-4 tricyclic carbon skeleton **39** in 25% yield with perfect diastereoselectivity (entry 1), showing a similar framework as that of protoilludene sesquiterpenes. Methyl jasmonate (**40**) was likewise converted using our method, yielding 51% of the HFIP–acetal **41** (entry 2). The slightly diminished diastereoselectivity may have originated from a partial equilibration of the *Z*-alkene moiety to its *E* conformer, prior to electrophilic addition. This assumption was corroborated by kinetic studies (see the ESI†) revealing a delayed starting point (*ca.* 30 min) for the formation of the minor C-2 epimer of **41** compared to the major isomer **41**. Interestingly, no α-chlorination to the ketone functionality in **40** was detectable, showing the chemoselectivity of the developed methodology. Treating the monoterpene S-α-terpineol (**42**) with 2.4 equivalents of **21** delivered the dichlorinated eucalyptol **43** (40%, d.r. > 95 : 5, entry 3). Product **43** was furnished for the first time directly from **42**, *via* a complex chlorine addition–elimination-chlorination-cyclization cascade. Previous reports on attempted halogenations of **42** resulted in the formation of acyclic chlorohydrin products (not shown) among other side products.[17]

Table 2 Advanced substrates for direct chloriranium-induced terpene cyclization[a]

Entry	Substrate	Product	Yield[b] (d.r.)
1	 **38**	 **39**	25% (>95 : 5)
2	 **40**	 **41**	51% (73 : 27)
3[c]	 **42**	 **43**	40% (>95 : 5)

[a] Substrate (0.20 mmol, 1.0 eq.) was added to 76.8 mg reagent **21** (0.24 mmol, 1.2 eq.) and 7.33 mg saccharin **22** (40 μmol, 0.2 eq.) in 2.00 mL HFIP at 0 °C. [b] Isolated yield. [c] 2.4 eq. reagent **21** was used. The d.r. was determined by ^{1}H-NMR spectroscopy of the crude reaction mixture. The given d.r. refers to the configuration at the carbon(s) highlighted in grey.

To elucidate the interplay of the Cl-iodanes, saccharine (**22**), and HFIP, NMR experiments were conducted (Fig. 2 and ESI†). To assess the chlorination ability of different chloro λ^3-iodanes,[18] compared to that of other reagents, we determined their halonium affinity (HalA, see the ESI†), a halogenation reactivity and chemoselectivity parameter.[19] A significant influence of the chlorination ability of this reagent type was evident in HFIP. Other commonly used Cl-sources (*e.g.*, **13** and **18**) showed only weak interactions (for details see the ESI†). Thus, the iodanes (*e.g.*, **19** and **21**) were more activated than the other, more common chlorenium sources resulting in a more productive and selective chlorocyclization. ^{1}H-NMR spectra obtained from the titration of iodane **19** (ref. 20) with HFIP showed a significant downfield shift of the hydroxy-proton signal of the fluoro alcohol (Fig. 2a). Simultaneously, the carbonyl group in **19** was shifted downfield by 4 ppm while a small upfield shift of the adjacent C-6 atom was detected in the corresponding ^{13}C-NMR spectra (Fig. 2b). This strongly implies an attractive non-covalent interaction between the F-alcohol and the Lewis basic carbonyl in **19**. This Lewis acid–Lewis base interplay activates **19** for electrophilic chlorine atom transfer and thus, is in line with the observed reactivity. Job's plot analysis (see the ESI†) revealed that this H-bonding interaction already occurs in the 1 : 1 HFIP–**19** complex. As productive chlorocyclizations were only observed in HFIP as solvent, the F-alcohol must have multiple roles in these transformations. Indeed, beyond fine-tuning the chlorination reagent reactivity, the fluorinated alcohol controls the substrate conformation and stabilizes the carbocationic intermediate.[21] Addition of the acid-catalyst saccharine (**22**) to the iodane–HFIP solution shifted the alcohol proton resonance further downfield (3.5 → 3.9 ppm, see the ESI†), while chloro-iodane **19** remained unaffected. Thus, we assume that **22** is integrated in the HFIP–hydrogen-bonding network but without direct interaction with **19**. In no experiment the formation of *N*-chloro saccharine (**23**) was observed, further excluding **23** as the chlorinating agent (*cf.* Table 1 and ESI†).

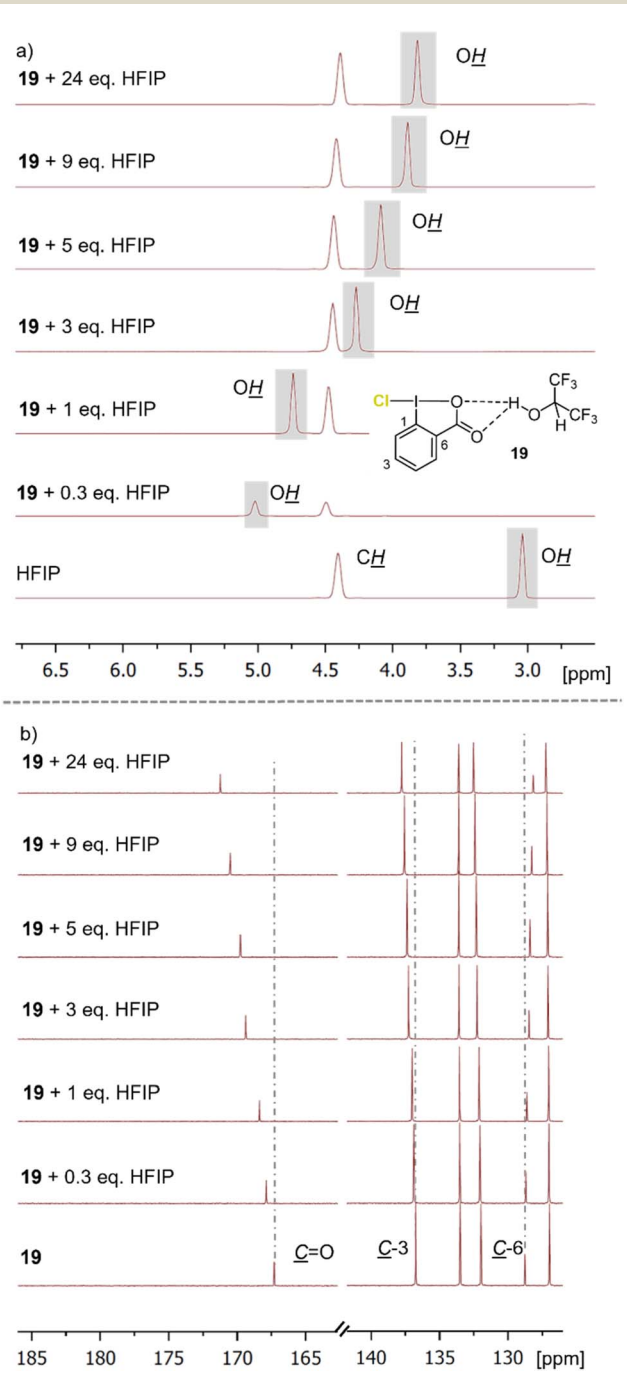


Fig. 2 Overlap of the (a) ^{1}H NMR spectra and (b) the ^{13}C NMR spectra of chloro-iodane **19** and different equivalents of HFIP at 25 °C.

3 Conclusion

In summary, we established a mild and straightforward one-step procedure for the challenging chlorination-assisted cation–π-cyclization of linear polyenes **1**. Both the Lewis basic chlorenium source and the Lewis acid HFIP, played crucial roles and needed to be finely balanced. Only then did the pair form a heterogeneously microstructured environment imitating the protective and activating enzymatic pockets of terpene cyclases.[1,14] The strong H-bonding ability of HFIP[15] was utilized to selectively install iodane **21** in this hydrogen-bond network and, consequently, adjust its reactivity. In addition, cationic intermediates such as **2–4** (*cf.* Fig. 1a) were stabilized inside the H-bonding assembly, and the linear carbon chain of **1** adopted the desired chair-like conformation *via* solvophobic interactions.[15,22] This enabled regio- and diastereoselective transformations (up to d.r. > 95 : 5) for a broad range of substrates. The general applicability of this method was shown with +20 examples. Differently substituted, electron-rich and -poor alkenes were likewise tolerated. The method was even extended to structurally complex substrates. Another step toward the biomimetic cyclization of polyenes has been reached with the presented method. A direct and more selective access to these powerful molecules is now possible.

Data availability

All experimental and characterization data, as well as NMR spectra are available in the ESI.†

Author contributions

J. B. conceived the project, designed and carried out the synthetic and mechanistic work, and analyzed the data. A. B. designed, conducted, and analyzed the mechanistic studies. T. G. conceived the project, provided guidance and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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