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Site-Selective Aliphatic C–H Chlorination Using *N*-Chloroamides Enables a Synthesis of Chlorolissoclimide

Ryan K. Quinn,[∥,†] Zef A. Könst,[∥,‡] Sharon E. Michalak,[‡] Yvonne Schmidt,[‡] Anne R. Szklarski,[‡] Alex R. Flores,[†] Sangkil Nam,[§] David A. Horne,[§] Christopher D. Vanderwal,[*,‡] and Erik J. Alexanian[*,†]

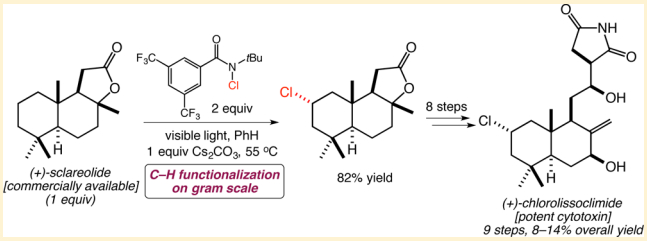
[†]Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, United States

[‡]Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, California 92697-2025, United States

[§]Department of Molecular Medicine, Beckman Research Institute, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, California 91010, United States

Supporting Information

ABSTRACT: Methods for the practical, intermolecular functionalization of aliphatic C–H bonds remain a paramount goal of organic synthesis. Free radical alkane chlorination is an important industrial process for the production of small molecule chloroalkanes from simple hydrocarbons, yet applications to fine chemical synthesis are rare. Herein, we report a site-selective chlorination of aliphatic C–H bonds using readily available *N*-chloroamides and apply this transformation to a synthesis of chlorolissoclimide, a potently cytotoxic labdane diterpenoid. These reactions deliver alkyl chlorides in useful chemical yields with substrate as the limiting reagent. Notably, this approach tolerates substrate unsaturation that normally poses major challenges in chemoselective, aliphatic C–H functionalization. The sterically and electronically dictated site selectivities of the C–H chlorination are among the most selective alkane functionalizations known, providing a unique tool for chemical synthesis. The short synthesis of chlorolissoclimide features a high yielding, gram-scale radical C–H chlorination of sclareolide and a three-step/two-pot process for the introduction of the β-hydroxysuccinimide that is salient to all the lissoclimides and haterumaimides. Preliminary assays indicate that chlorolissoclimide and analogues are moderately active against aggressive melanoma and prostate cancer cell lines.



INTRODUCTION

The free radical chlorination of unactivated alkanes with elemental chlorine is industrially important for the preparation of a number of chlorinated small molecules.[1] The vast majority of these applications involve hydrocarbons with only one type of C–H bond, however. This is a consequence of the promiscuity of the chlorine free radical, which leads to poor site selectivities in free radical alkane chlorinations and a proclivity for undesired polyhalogenations with more complex substrates.[2] This contrasts the controlled, predictable nature of alkane brominations, which are often highly regioselective for the weakest C–H bond present, such as tertiary, allylic, or benzylic positions.[3] Alkyl chlorides are highly useful synthetic building blocks, and >2000 chlorine-containing natural products have been identified to date.[4] New methods for practical, selective aliphatic C–H chlorinations hold significant potential for streamlining the synthesis and derivatization of broad classes of synthetically and medicinally valuable small molecules.[5]

Alternative strategies for intermolecular aliphatic C–H chlorination have been developed that avoid the intermediacy of the chlorine free radical and offer improved site selectivities. For example, prior studies have demonstrated that nitrogen-centered radicals derived from *N*-chloroamines can facilitate site-selective C–H chlorination, but these reactions required the use of a strong acid as solvent and are therefore impractical for complex synthesis.[6] Recent studies have indicated the potential for biomimetic alkane chlorination using manganese porphyrin catalysts,[7] but the intermediacy of reactive high valent metal-oxo species presents challenges in chemoselectivity with functionalized substrates.

We have previously reported the development of a set of easily accessed, bench stable *N*-bromoamides for the site-selective, intermolecular bromination of unactivated C–H bonds.[8] These reactions used substrate as the limiting reagent and delivered products using elements of both steric and electronic control. Herein, we have extended our approach to C–H chlorination using household lamp irradiation and *N*-chloroamides that are trivially prepared from amides and NaOCl. Our studies have shown that in contrast to C–H bromination with *N*-bromoamides, background reactions (e.g., Cl• reactivity) were significant in these studies (Figure 1). We have developed a practical protocol that overcomes this unselective background reactivity. We have also demonstrated the unique site and chemoselectivities of our aliphatic C–H

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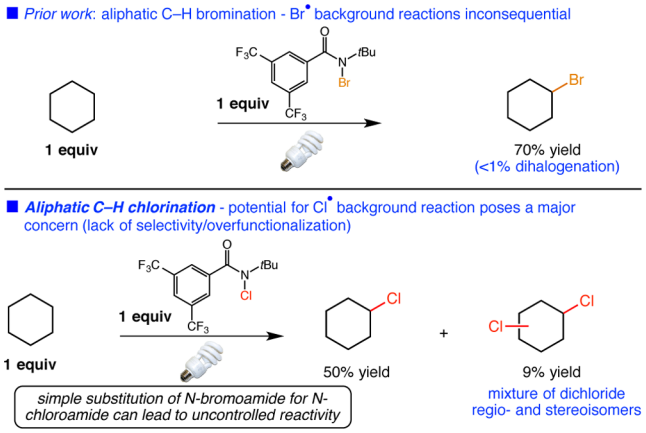


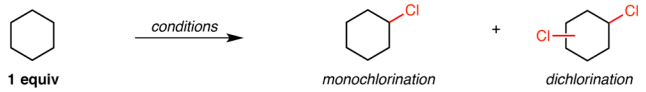
Figure 1. Aliphatic C–H chlorination using *N*-chloroamides introduces the possibility of unselective background reactions, potentially lowering reaction site selectivity and chemoselectivity.

chlorination, including applications to substrates containing more reactive tertiary, allylic, or benzylic C–H bonds. Unsaturated substrates are rare in studies of intermolecular aliphatic C–H functionalization and are a notable aspect of this approach.[9] Finally, we demonstrate the practical utility of our chlorination method in the short synthesis of the potent cytotoxin chlorolissoclimide and analogues, wherein gram-scale, highly selective monochlorination of sclareolide plays a pivotal role.

DEVELOPMENT OF THE ALIPHATIC C–H CHLORINATION

Our studies commenced with the C–H chlorination of 1 equiv of cyclohexane (Table 1). As with aliphatic C–H bromination, methods for intermolecular aliphatic C–H chlorination using substrate as the limiting reagent are extremely rare.[7] A survey of classical C–H chlorinations demonstrated either low reactivity with *N*-chlorosuccinimide (entry 1, 5 equiv substrate) or uncontrolled reactivity with SO_2Cl_2 (entry 2). Chlorination using a biomimetic Mn–porphyrin system provided good conversion; however, a significant amount of dichlorination product was formed (entry 3).[7a] The cyclohexane chlorination using the conditions previously reported for alkane bromination with *N*-chloroamide **1** (irradiation using 23 W compact fluorescent bulbs) also provided moderate conversion and similar mono- versus dichlorination selectivity (entry 4). An alternative approach using radical initiation with benzoyl peroxide (BPO) was also suboptimal (entry 5).

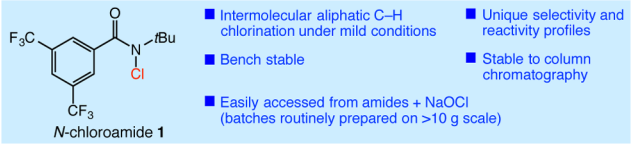
Table 1. Chlorinations of Cyclohexane with Substrate as Limiting Reagent[a]



entry	reagents	% mono chloride	% dichloride	% conversion
1	NCS, AIBN, 60 °C (5 equiv cyclohexane)	71.1	28.9	N/A
2	SO_2Cl_2, BPO, 85 °C	71.1	28.9	85.7
3	Mn(TPP)Cl/NaOCl	89.9	10.1	62.3
4	chloroamide **1**, *hν*, rt	85.1	14.9	58.6
5	chloroamide **1**, BPO, 65 °C	86.0	14.0	46.1
6	chloroamide **1**, *hν*, 1 equiv Cs_2CO_3, rt	90.5	9.5	60.8
7	**chloroamide 1, *hν*, 1 equiv Cs_2CO_3, 55 °C**	**96.9**	**3.1**	**71.6**

[a]Reactions were performed with $[substrate]_0$ = 1.0 M in PhH under an Ar atmosphere with 1 equiv of substrate and *N*-chloroamide, unless otherwise noted. Yields and selectivity determined by GC analysis.

At this stage, we hypothesized that the promiscuity of the chlorine radical could be adversely affecting our reaction selectivity. This idea is supported by the prior studies of Greene, who demonstrated that the chain carrying species of aliphatic C–H chlorinations with *N*-chloroamides can vary widely depending upon the exact reaction conditions.[10] Specifically, we questioned whether trace acid was reacting with reagent **1** to deliver amide and Cl_2. Adding 1 equiv of Cs_2CO_3 improved the selectivity for monochlorination (90.5%), supporting this hypothesis (entry 6). Increasing the reaction temperature to 55 °C further improved the reaction selectivity to 96.9% monochlorination, potentially owing to greater solubility of the base.



After arriving at our optimized conditions for the C–H chlorination, we next determined the deuterium kinetic isotope effect by the competition reaction between cyclohexane and d_{12}-cyclohexane using reagent **1**. The observed primary kinetic isotope effect was k_H/k_D = 4.9 under these conditions, which is consistent with irreversible hydrogen atom abstraction. For the sake of comparison, the bromination of cyclohexane under these conditions with the *N*-bromo derivative of **1** also resulted in a k_H/k_D = 4.9, consistent with an amidyl radical in both C–H abstractions.

Our studies continued with an investigation of the sterically dictated site selectivities of our C–H chlorination using methylcyclohexane as substrate (Table 2). Prior to conducting reactions with *N*-chloroamide **1**, we surveyed the secondary (desired) versus tertiary (undesired) selectivity using known chlorination methods. Classical methods involving either *N*-chlorosuccinimide or sulfuryl chloride provided modest selectivities ($k_{secondary}/k_{tertiary}$, k_s/k_t, = 0.31 and 0.28, respectively) after correcting for the number of tertiary (one) and secondary (ten) sites available (entries 1 and 2).[11] Chlorination catalyzed by Mn(TPP)Cl provided similar selectivity (k_s/k_t = 0.38, entry 3).[7] As observed in the reactions of cyclohexane in Table 1, chlorination using *N*-chloroamide **1** in the absence of base provides suboptimal selectivities, likely owing to background reactions involving Cl_2 and the chlorine free radical (entries 4 and 5). The addition of 10 mol % amylene, a known Cl_2 scavenger,[12] greatly favors methylene functionalization (97.7%, k_s/k_t = 4.2), albeit at low conversion (entry 6). We found that added base could serve a similar role without decreasing conversion, with a higher yield at 55 °C (entries 7 and 8). The high level of secondary selectivity in this functionalization of a simple cyclic hydrocarbon is higher than any known system for aliphatic C–H chlorination.

We extended our steric selectivity studies to additional hydrocarbon substrates such as norbornane, which under our standard chlorination conditions delivered a 54% yield of 2-*exo*-

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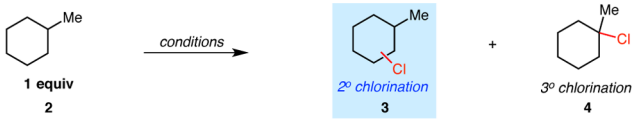
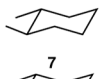
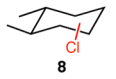
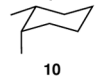
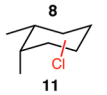
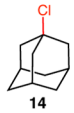
Table 2. Sterically Selective Aliphatic C−H Chlorination of Diverse Hydrocarbons with Bulky *N*-Chloroamide 1[a]



entry	reagents	% 2° Cl	% 3° Cl	$k_{secondary}/k_{tertiary}$
1	NCS, AIBN, 60 °C (neat in **2**)	75.9	24.1	0.31
2	SO_2Cl_2, BPO, 85 °C	73.9	26.1	0.28
3	Mn(TPP)Cl/NaOCl	79.1	20.9	0.38
4	chloroamide **1**, *hv*, rt	74.5	25.5	0.29
5	chloroamide **1**, BPO, 65 °C	75.2	24.8	0.30
6	chloroamide **1**, BPO, 10 mol % amylene, 65 °C	97.7 (<5% yield)	2.3	4.2
7	chloroamide **1**, *hv*, 1 equiv Cs_2CO_3, rt	93.3 (44% yield)	6.7	1.4
8	chloroamide **1**, *hv*, 1 equiv Cs_2CO_3, 55 °C	98.5 (74% yield)	1.5	6.6

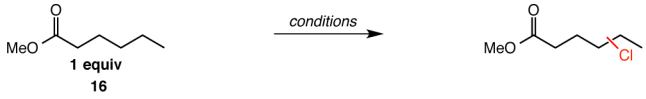
entry	substrate (**1 equiv**)	chlorination products	yield (%)
9	 **5**	 **6**	54 exo:endo >99:1
10[b]	 **7**	 **8** **9**	79 **8:9** >99:1
11[b]	 **10**	 **11** **12**	73 **11:12** 11:1
12	 **13**	 **14** **15**	69 **14:15** 19:1

[a]See Table 1 for conditions. Yields and selectivities were determined by GC analysis. For further details regarding product distributions, see the Supporting Information. [b]Reaction yields determined by ^{1}H NMR spectroscopy of crude reaction mixtures using an internal standard.

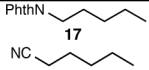
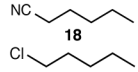
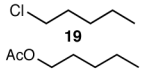
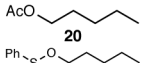
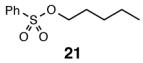
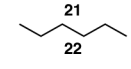
chloronorbornane as a single product (entry 9). As comparison, the C−H chlorination of norbornane with common reagents (e.g., Cl_2 or SO_2Cl_2) leads to mixtures of the *exo* and *endo* isomers.[11] Both *trans*- and *cis*-1,2-dimethyl cyclohexanes—benchmark substrates for sterically selective aliphatic C−H functionalizations[13]—exhibited excellent methylene selectivity (entries 10 and 11). Adamantane C−H chlorination involving the chlorine free radical is documented to be a poorly selective process, with k_t/k_s = 3.5.[14] Reaction of adamantane under our standard reaction conditions furnished the two regioisomers in a 19:1 ratio (k_t/k_s = 57), favoring functionalization of the less hindered tertiary site, and highlighting the unique selectivity profile of the current system.

Next we surveyed the potential to achieve an electronically site-selective C−H chlorination using an array of functionalized linear hydrocarbon substrates (Table 3). Using methyl hexanoate as a test substrate, reactions involving either sulfuryl chloride (entry 1) or Mn(TPP)Cl/NaOCl (entry 2) proceeded with relatively poor selectivity between the most electron-rich γ and δ positions. As observed with methylcyclohexane in Table 2, reactions with *N*-chloroamide **1** under radical initiation (entry 3) also resulted in a poorly selective reaction. Under our optimized conditions in the presence of base, we significantly increase the selectivity for the most electron-rich (δ) site in the molecule. Chlorination at the δ site accounts for 57.6% of all chlorination products (entry 4, 83% combined yield).

Table 3. Studies of the Electronic Site Selectivity of the Aliphatic C−H Chlorination with *N*-Chloroamide 1[a]



entry	reagents	% selectivity of chlorination α β γ δ ω MeO$_2$C—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH$_3$
1	SO_2Cl_2, BPO, 85 °C	— 12.1 37.7 42.0 8.2
2	Mn(TPP)Cl/NaOCl	— 8.2 43.7 44.8 3.3
3	chloroamide **1**, BPO, 65 °C	— 10.8 37.9 42.4 8.9
4	chloroamide **1**, *hv*, 1 equiv Cs_2CO_3, 55 °C	3.6 4.6 19.7 57.6 14.4 (83% combined yield)

	substrate (**1 equiv**)	% selectivity of chlorination α β γ δ ω EWG—CH$_2$—CH$_2$—CH$_2$—CH$_2$—CH$_3$	combined yield (%)
5	 **17**	— — 4.9 81.2 13.9	80
6	 **18**	— — 15.0 65.9 19.1	79
7	 **19**	9.2 5.7 15.3 56.9 12.9	74
8	 **20**	— 9.0 19.8 57.3 13.8	89
9	 **21**	3.5 5.9 16.2 56.2 18.1	86
10	 **22**	23.9 65.5 7.5	70

[a]All reactions were performed with $[substrate]_0$ = 1.0 M in PhH at rt under visible light irradiation with 1 equiv of substrate and 2 equiv of chloroamide. Yields and selectivities determined by GC analysis.

Other synthetically versatile, electron-withdrawing functionality effective at differentiating the methylene sites included protected amines, nitriles, alkyl chlorides, acetates, and sulfonate groups (entries 5−9). The δ selectivity in these studies ranged from 56% to 81%, with the phthalimide group providing the highest level of site selectivity. The general trend in these studies is greater δ selectivity with increased electron withdrawal of the substituent present. The chlorination of *n*-hexane indicates the possibility of a steric component to the C−H chlorination, with 65.5% 2-chlorohexane produced.

We further explored the site selectivity of the C−H chlorination with functionalized acyclic substrates containing more reactive C−H bonds at tertiary, benzylic, and allylic sites. The results in Table 4 clearly indicate that electronic (and possibly steric) factors are capable of deactivating these typically more reactive C−H bonds in favor of more electron-rich methylene sites. This electronically dictated selectivity is substantial with multiple functional groups, and with methyl substitution at both the α and β positions of the chain (entries 1−4). The chlorination of phthalimide-protected norleucine methyl ester displays a major preference for the δ site (77.5% selectivity) owing to the strong polar deactivation of the sites adjacent to the amino acid functionality.

An area of significant interest was the possibility of achieving site-selective aliphatic C−H chlorination in the presence of substrate unsaturation. This chemoselectivity issue remains a roadblock in applying alkane functionalization to many complex substrates, particularly those containing alkenes. This is unsurprising given the propensity for electrophilic heterocycles or metal-oxo complexes—both widely used for alkane functionalization—to react with alkenes. Our preliminary studies in this area are promising (entries 5−7), demonstrating

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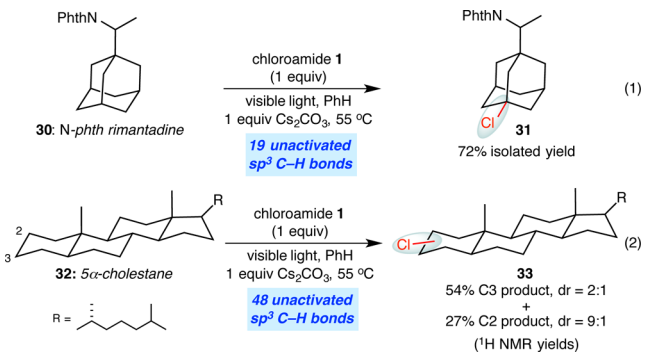
Table 4. Site Selectivity of the Aliphatic C−H Chlorination with *N*-Chloroamide 1 in the Presence of More Reactive C−H Bonds and Substrate Unsaturation[a]

entry	major chlorination product	% selectivity	combined yield (%)[b]	sites of minor chlorination (% selectivity)
	EWG, α, β, γ, δ, ω, Cl, Me			
1	**23**: EWG = PhthN	75.4	88	γ = 8.8; ω = 15.7
2	**24**: EWG = Ph, S, O, O, O	68.3	76	γ = 18.3; ω = 13.6
3	PhthN, Me, Cl **25**	63.6	69	β = 2.4; γ = 7.5; ω = 26.5
4	PhthN, Cl, CO_2Me **26**	77.5	66	ω = 22.5
5	PhthN, Cl **27**	67.9	81	γ = 14.9; ω = 17.1
6	PhthN, Cl **28**	74.0	78	α = 6.5; ω = 18.9
7	MsO, Cl **29**	100	65[c]	

[a]All reactions were performed with $[substrate]_0$ = 1.0 M in PhH at rt under visible light irradiation with 1 equiv of substrate and 2 equiv of chloroamide. Selectivities determined by GC analysis. [b]Yields determined by ^1H NMR spectroscopy of the crude reaction mixture using 2,5-dimethylfuran as an internal standard. [c]Isolated yield with 1 equiv of chloroamide.

successful C−H chlorinations of substrates with both arene and alkene substitution. Of particularly note is the adamantane functionalization in the presence of a simple allyl group (entry 7). We anticipate that this unique aspect of aliphatic C−H functionalization with tuned amidyl radicals will facilitate applications across a broad range of complex substrates.

The ease of preparation of *N*-chloroamides, in addition to the useful levels of site selectivity in the reactions, offers attractive opportunities in the C−H chlorination of complex molecules (eqs 1 and 2). Functionalized adamantanes form the

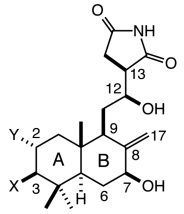


structural core of diverse small molecule drugs, yet there are few mild, site-selective protocols available for the C−H functionalization of these compounds. The chlorination of the *N*-phthalimide derivative of antiviral drug rimantadine (**30**) using *N*-chloroamide **1** provided chlorinated derivative **31** in good isolated yield (66%), with complete site selectivity for the less-hindered tertiary C−H site (eq 1).

5α-Cholestane is a challenging substrate for site-selective C−H functionalization owing to the presence of 48 unactivated C−H bonds with little electronic differentiation considering the absence of heteroatomic functionality. The functionalization of **32** using 1 equiv of reagent **1** favors C3-chlorination (C3:C2 = 2:1) and provides an 81% yield of chlorinated products (eq 2). By comparison, the functionalization facilitated by the bulky, designed catalyst Mn(TMP)Cl (TMP = tetramesitylporphyrin) provides a C3:C2 of 1.5:1 in 55% yield using 3 equiv of NaOCl.[7] We anticipate that the practicality, scalability, and site selectivity of this C−H halogenation are well suited for applications in target-oriented synthesis, as demonstrated by the concise synthesis of the antineoplastic agent chlorolissoclimide described herein.

APPLICATION TO THE SYNTHESIS OF CHLOROLISSOCLIMIDE

In the early 1990s, the groups of Malochet-Grivois and Roussakis described the structures and cytotoxic activities of the succinimide-containing labdane diterpenoids chlorolissoclimide and dichlorolissoclimide (**34** and **35**, respectively, Figure 2).[15,16] Initially, **35** was shown to have potent activity against



34 (X = H, Y = Cl): *chlorolissoclimide*
P388: 4.4 nM
KB: 0.14 mM
NSCLC: 26 nM

35 (X = Y = Cl): *dichlorolissoclimide*
P388: 2.4 nM
KB: 33 nM
NSCLC: 22 nM

36 (X = Y = H): *haterumaimide Q*
P388: 0.14 mM

Figure 2. Chlorolissoclimide, dichlorolissoclimide, and haterumaimide Q with IC_{50} values against cancer cell lines.

both the P388 murine leukemia cell line (IC_{50} = 2.4 nM) and the KB human oral carcinoma cell line (33 nM).[15a] Later, both **34** and **35** were shown to interfere with the cell cycle at the G1 phase of nonsmall-cell bronchopulmonary carcinoma cells (NSCLC-N6), causing antiproliferation.[15b]

Since 2001, the groups of Ueda/Uemura and Schmitz have reported about 20 closely related labdane diterpenoids that they have called the haterumaimides (see **36**, for example).[17] Many of these compounds show equally impressive levels of cytotoxicity. In spite of the obvious potential interest in these compounds from the biological perspective, as well as some particularly interesting biogenetic peculiarities—both the C2-chloride and the succinimide are very unusual—only three groups have reported work toward these compounds. Jung and co-workers studied methods to introduce the two chlorides relevant to **35** onto simplified decalin scaffolds.[18] The González/Betancur-Galvis and Chai groups looked at methods to install the succinimide group onto aldehyde **38** (Scheme 1) derived from readily available (+)-sclareolide (**37**); the former study used an unselective aldol addition of a succinimide enolate,[19] and the latter used Evans aldol chemistry to introduce the heterocycle via a four-step sequence, but could not avoid isomerization of the C8−C17 exocyclic alkene into the endocyclic positions, nor could these isomers be fully

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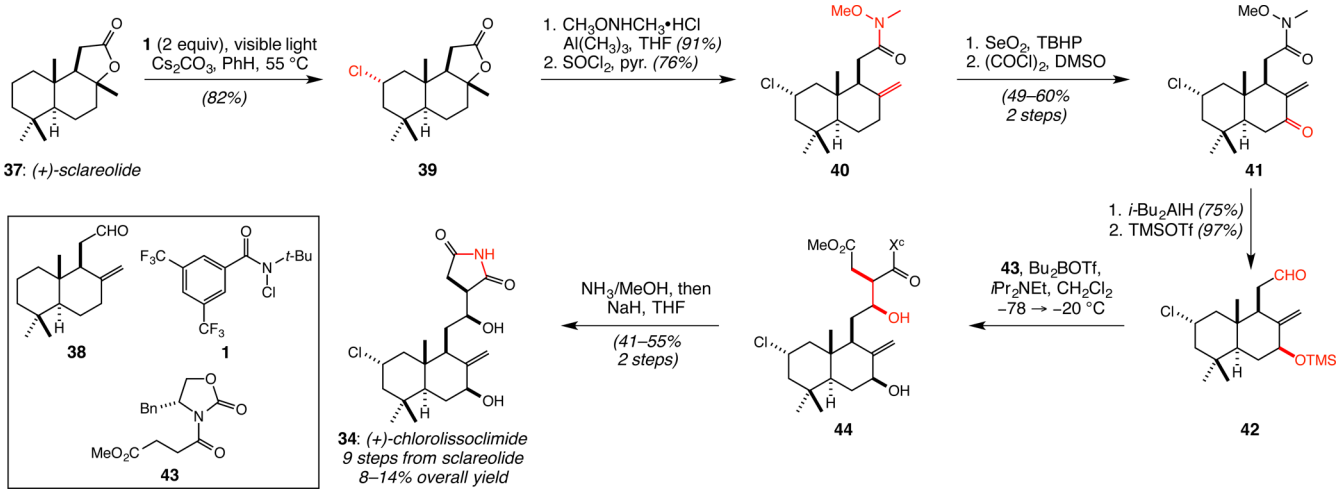
Scheme 1. Synthesis of (+)-Chlorolissoclimide by C−H Functionalization of (+)-Sclareolide



separated from one another.[20] In short, there have been no completed syntheses in this family of structurally and biologically intriguing natural products.

As part of a broader study of this family of diterpenoids, we questioned whether C−H functionalization methods might permit the conversion of sclareolide to chlorolissoclimide (Figure 3). In reverse order, key steps would include the stereocontrolled introduction of the β-hydroxysuccinimide—which had proved challenging in earlier studies[19,20]—stereoselective C7-oxygenation, and regio- and stereoselective C2-chlorination.

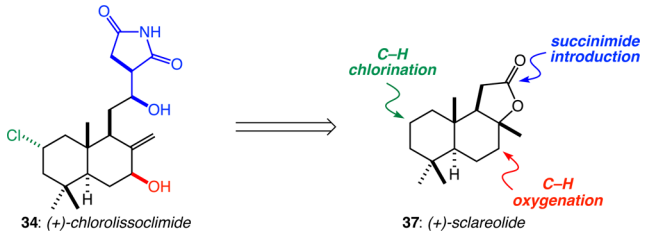


Figure 3. A plan for the conversion of sclareolide to chlorolissoclimide.

Previous reports strongly suggested that the C2 position of sclareolide is the most activated for C−H functionalization under radical conditions.[21] Prompted by the efficient C2-bromination of sclareolide from the Alexanian group,[8] a collaboration was borne to gain efficient access to 2-chlorosclareolide for the purposes of a concise synthesis of chlorolissoclimide. Using reagent **1**, we converted **37** into 2-chlorosclareolide (**39**)[7a,22] with remarkable efficiency, even on gram scale. The selectivity of this reagent is outstanding: only product **39** and traces of residual sclareolide can be observed in the ^{1}H NMR spectra of the crude reaction product. Weinreb aminolysis of the lactone and dehydration of the tertiary carbinol—following a process previously performed on sclareolide[23]—afforded **40** in good yield. C7-oxygenation was performed by selenium dioxide mediated allylic oxidation[19,24] to afford the axial C7 allylic alcohol, which was subjected to Swern oxidation to give enone **41**. Concurrent reduction of the Weinreb amide and the enone was efficient and stereoselective for the introduction of the equatorial C7-hydroxyl group. Silylation of this alcohol afforded **42**, whose aldehyde was subjected to our optimized sequence for introduction of the β-hydroxysuccinimide.

Evans aldol addition of known imide **43**[20,25] to aldehyde **42** was initially low-yielding and inconsistent, which we attributed to nonproductive coordination of the boron Lewis acid to the pendant ester of **43**. This issue was resolved by pretreatment of **43** with dibutylboron triflate for 30 min at −78 °C prior to addition of Hünig's base, resulting in a reliable aldol addition. The labile TMS ether, which is important for reaction efficiency, is cleaved in this step. Direct ammonolysis of the crude imide (**44**) in methanol prevented the undesired lactone formation previously observed by Chai and co-workers;[20] immediate imide formation via the presumed *N*-sodiated amide directly affords the β-hydroxysuccinimide *without alkene migration* and completes the first synthesis of (+)-chlorolissoclimide. This sequence is general and reliable, and this technical advance will prove important in the synthesis of the whole family of lissoclimides/haterumaimides. Notably, chlorolissoclimide is obtained in up to 14% overall yield via the nine-step sequence described in Scheme 1.

Variants of the same sequence have led to the synthesis of haterumaimide Q (**36**) and the 7-deoxy analogues of both **34** and **36** (**45** and **46**, respectively, Figure 4).[26] We have evaluated all four compounds for their toxicity to aggressive prostate and melanoma cancer cell lines (DU145 and A2058, respectively). While we have found these compounds to be active at about

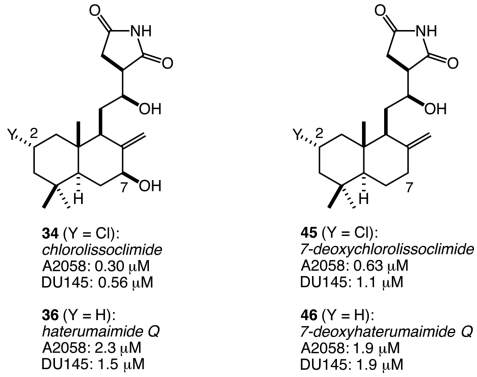


Figure 4. Activities (IC_{50} values) of chlorolissoclimide and analogues against aggressive tumor cell lines (A2058: melanoma; DU145: prostate).

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the micromolar level, they are clearly much less potent toward these more relevant cell lines compared with the P388 murine leukemia cell line, against which all haterumaimides and lissoclimides have previously been tested.[15,17] Clearly a larger panel of cell lines should be evaluated, given the previously reported potency of chlorolissoclimide against nonsmall-cell lung cancer (IC_{50} = 26 nM; see Figure 2). With respect to the two cell lines evaluated in this study, we recognize that this series of compounds affects both the prostate and melanoma cell lines about equally and that the activities vary less than an order of magnitude depending upon the presence or absence of a C2-chloride or a C7-hydroxyl group.

CONCLUSION

In conclusion, we report a practical, site-selective approach to aliphatic C−H chlorination using *N*-chloroamides and visible light. While the chlorination of alkanes is commonly a poorly selective process owing to the promiscuity of the chlorine free radical, these amidyl radical-mediated reactions provide sterically and electronically dictated site selectivities that enable chlorination of complex molecules with diverse C−H bonds. These studies also indicate the potential for chemoselective aliphatic C−H functionalization in the presence of alkenes and arenes. The trivial preparation of *N*-chloroamides, and the use of substrate as the limiting reagent in all cases, bodes well for applications in complex synthesis. In that vein, we also report the first synthesis of natural products in the lissoclimide/haterumaimide family of potent cytotoxins using this chlorination method as the first step. Our semisynthesis of chlorolissoclimide starting with the gram-scale selective chlorination of (+)-sclareolide is short and efficient and includes the first example of a stereocontrolled C−H halogenation for the incorporation of a halogen-bearing stereogenic center of a natural product.[27] The transformation itself is likely relevant to the biosynthesis of the 2-chlorinated lissoclimides and haterumaimides. That this chlorination reaction can support the synthesis of a complex natural product clearly demonstrates its practicality.

Additionally, in the context of the chlorolissoclimide synthesis, we have developed a straightforward and general solution to the β-hydroxysuccinimide motif that is common to all active members of this natural product family. Finally, we have learned that chlorolissoclimide (**34**) and analogues haterumaimide Q (**36**), 7-deoxychlorolissoclimide (**45**), and 7-deoxyhaterumaimide Q (**46**) are cytotoxic to aggressive melanoma and prostate cancer cell lines with IC_{50} values of about 1 μM.

Efforts to further improve the site selectivity of the C−H chlorination and applications to other complex substrates are underway. We are also in the process of expanding our work in the synthesis of haterumaimide natural products to better understand their structure−activity relationship. Each of these studies will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12308.

Experimental procedures and spectral data for all new compounds, and full descriptions of the syntheses of compounds **36**, **45**, and **46** (PDF)

AUTHOR INFORMATION

Corresponding Authors

*cdv@uci.edu

*eja@email.unc.edu

Author Contributions

‖R.K.Q. and Z.A.K. contributed equally.

Notes

The authors declare no competing financial interest.

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