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Publication Date

DOI

Chlorine-Atom-Controlled Terminal-Epoxide-Initiated Bicyclization Cascade Enables a Synthesis of the Potent Cytotoxins Haterumaimides J and K

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Abstract

Haterumaimide J (hatJ) is reportedly the most cytotoxic member of the lissoclimide family of labdane diterpenoids. The unusual functional group arrangement of hatJ—C18 oxygenation and C2 chlorination—resisted our efforts at synthesis until we adopted an approach based on rarely studied terminal epoxide-based cation-π bicyclizations that is described herein. Using the C2-chlorine atom as a key stereocontrol element and a furan as a nucleophilic terminator, the key structural features of hatJ were rapidly constructed. The 18-step stereoselective synthesis features applications of chiral pool starting materials, and catalyst-, substrate-, and auxiliary-based stereocontrol. Access to hatJ and its acetylated congener hatK permitted their biological evaluation against aggressive human cancer cell lines.

Our laboratory has been investigating the chemistry and biology of the potently cytotoxic labdane diterpenoids in the lissoclimide family.[1–3] Nearly two dozen such natural products were isolated from sea squirts as described by the groups of Malochet-Grivois/Roussakis,[4] Ueda/Uemura,[5] and Schmitz.[6] Among these compounds, many of which were named haterumaimides, several showed potent cytotoxicity against the P388 murine leukemia cell line (Figure 1); dichlorolissoclimide (1) and chlorolissoclimide (2) were also very active against KB cells and non-small-cell lung cancer,[4b,c] and were later shown by Pelletier and co-workers to be inhibitors of eukaryotic translation.[7] With the Alexanian group, we completed semisyntheses of haterumaimide Q (3) and chlorolissoclimide from sclareolide, featuring in the latter case a selective radical C–H chlorination reaction to install the salient C2-halogen atom.[1,8] In a separate report focused more on the biological properties of these

compounds, we disclosed a more general, π-cyclization-based approach, SAR data among several natural and unnatural congeners, and an X-ray cocrystal structure of chlorolissoclimide bound to the eukaryotic 80S ribosome.[2] A serious limitation of our previous efforts became clear: we were never able to access haterumaimides J and K (hatJ and hatK; **4** and **5**, respectively), the two compounds reported to be the most cytotoxic in the family. Notably, these targets bear oxygenation at C18, but C3 is unfunctionalized. This arrangement of structural features motivated the distinct synthesis design described herein, which is based on rarely studied terminal-epoxide-initiated polycyclizations.

In spite of the significant number of *trans*-decalin-type diterpenoid alcohols and acids that are C3-unfunctionalized but are oxygenated at C18 or C19 (terpenoid numbering, see Figure 2a), the previous use of simple terminal epoxides as activators to induce polycyclizations is essentially limited to the single report of Goldsmith and Phillips from a half century ago,[9] with important later work on more functionalized systems by the groups of van Tamelen[10] and Corey.[11] In the seminal study,[8] an epoxide of type 6 (Figure 2b), wherein the terminator was a *m*-methoxyphenyl ring, was shown to generate as the major product a compound of type **8a** (equatorial, C18 oxygenation) in low yield; other mono-cyclized and oxabicyclized products of unconfirmed relative C4–C5 configuration were also observed (the *trans*-C5–C10 ring junction of course remains constant). As a result, we were uncertain about the relative preference for the stereochemical outcome of bicyclizations of type **6**; however, with the required C2-chlorine substituent in place (see **7**), we postulated that a preference for its equatorial disposition in transition structures would lead selectively to the arrangement **9a** needed for a synthesis of hatJ. We hypothesized that the relatively small A-value of a chlorine atom (ca. 0.5 kcal/mol) would still be enough for effective diastereocontrol because of the exacerbation of nonbonded interactions resulting from the two other putative axial groups at C4 and C10 in the transition structure leading to the undesired product **9b**. Moreover, the diastereomer of **7** (chlorine and epoxide arranged *syn*) should permit the selective formation of compounds with C19 oxygenation (not shown, see below).

We therefore embarked on a synthesis of cyclization precursors related to **7**. The control of relative configuration between the epoxide and the chlorine-bearing stereogenic center was paramount to the effectiveness of this approach. We focused on furan as our choice of nucleophilic terminating group, because oxidative ring opening would afford the requisite functionality to complete the remainder of the synthesis. The utility of this particular approach had previously been established in seminal studies by Tanis and co-workers.[12]

Enantiopure alcohol **10** (Scheme 1) was made from epichlorohydrin, isopropenylmagnesium bromide, and lithiated trimethylsilylacetylene, as previously reported for its enantiomer by Danishefsky and co-workers.[13] Zirconocene-dichloride-catalyzed methylalumination of the alkyne,[14] followed by iododealumination, generated nearly symmetrical diene **11**. Deoxychlorination proved challenging in the face of facile competing elimination processes that generated conjugated dienes. Kartika's conditions were uniquely effective, and provided chloride **12** without minimal loss of enantiopurity.[15]

1,1-Disubstituted alkenes, especially those bearing two unbranched alkyl groups, are notoriously poor substrates for asymmetric oxidation, owing to the very similar enantiotopic

(or diastereotopic in the case of **12**) π-faces presented to the catalysts in question.[16] For the case at hand, we also needed to address the issue of chemoselectivity with respect to the alkenyl iodide,[17] which competed with the nonhalogenated alkene in some preliminary epoxidation experiments. Fortunately, dihydroxylation under Sharpless AD conditions proved to be chemoselective. Figure 3 shows the outcome of representative experiments aimed at the selective generation of anti product **14** using enantiomerically enriched **12**. A ca. 1:2 anti/syn mixture was obtained in the absence of ligand, and the typical AD-mix ligands showed little selectivity. However, application of the less frequently adopted pyrimidine-based ligands (DHQ)$_2$PYR and (DHQD)$_2$PYR[16,18] led to enhanced selectivity, such that *anti*-product 14 could be obtained as the major product of a ca. 6:1 mixture.

The formation of the epoxide **15** from **14** was uncomplicated by the chloride substituent. This building block was joined to furan-containing alkyl iodide **16** in an efficient net reductive B-alkyl Suzuki coupling proceeding through the presumed intermediacy of the methoxy-9-BBN ate complex.[19] After some optimization of Lewis acid and solvent combinations, the key epoxide-initiated, furan-terminated bicyclization of **17** was realized with ethylaluminum dichloride, affording **18** in 45–65% yield and with virtually complete diastereoselectivity (>20:1), which is consistent with the chlorine atom's ability to direct the stereochemical outcome of the reaction (see below).[20,21] The inclusion of 2,6-di-*t*-butylpyridine (DTBP) was critical for reaction reproducibility. Silylation of the neopentylic alcohol and oxidative ring opening of the furan with *in situ*-carboxylate methylation[22] yielded ketoenoate **20**.

Diastereoselective hydrogenation of the alkene, a salt-free Wittig methylenation, and careful partial reduction of the ester provided aldehyde **21**. This electrophile was subjected to our previously developed aldol-based introduction of the hydroxysuccinimide motif,[2,23] which was complicated by the competitive formation of variable and often substantial amounts of the "non-Evans syn" diastereomer in some cases. A simple change of conditions for boron enolate formation (replacement of *n*-Bu$_2$BOTf with Cy$_2$BOTf) alleviated the uncertainty of this previously capricious reaction, leading to a highly diastereoselective imide introduction. Desilylation of the neopentylic silyl ether afforded hatJ (**4**). Acetylation provided hatK (**5**).

Notably, the same epoxide-initiated, furan-terminated bicyclization reaction of the *syn*-diastereomer of the chloroepoxide (**24**,[24] Figure 4) led to the selective formation of diastereomer **25**, with C19 oxygenation (axial hydroxymethyl group). Clearly, the chlorine atom can play a powerful role as a single atom auxiliary[21] for cationic polycyclizations, in this case overturning the intrinsic selectivity for C18 oxygenation observed in the deschloro analogue (not shown).[20] With the easy incorporation and easy reductive removal of the chlorine atom auxiliary, this reaction type could be widely applied to terpenoids bearing C19 oxygenation including, among others, members of the *ent*-kaurene family.[25]

Because our assays of synthetic chlorolissoclimide against the P388 cell line had demonstrated a 15-fold lower cytotoxicity than originally reported by the Malochet-Grivois group (see Figure 1), we wished to see if the reported high potency of hats J and K against P388 could be recapitulated with our synthetic samples and to evaluate their potency against more important human cancer cell lines. These compounds were tested against P388,

HUT78 (cutaneous T-cell lymphoma), A2058 (aggressive melanoma), and DU145 (aggressive prostate cancer) cell lines (Table 1), with our previously reported data for chlorolissoclimide shown for comparison. While we again observed much lower activity against P388 than previously reported, hats J and K are the most potent compounds that we have yet made—natural or unnatural—in the lissoclimide series at ca. 30 nM each. For this reason, we tested them against the human hematological cancer HUT78, and again found nanomolar activities. Consistent with our previous work, **4** and **5** were less active against the solid tumor cell lines A2058 and DU145.

Our synthesis of haterumaimides J and K showcases the power of underutilized terminal-epoxide-initiated polycyclizations for terpenoid synthesis. Moreover, this work reveals the utility of chlorine (and potentially other halogen) atoms as single-atom auxiliaries to control the stereochemical outcome of such polycyclizations.[26] The chlorine atom's ability to override intrinsic selectivities for C18 oxygenation might be widely applied toward polycyclic terpenoids of the ent-kaurane class. Our synthesis of haterumaimide J was complete in **14** steps from known secondary alcohol **10**, and 18 steps from commercial precursors. Further applications of both terminal epoxides and of halogen atom auxiliaries to complex terpenoid synthesis are ongoing in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

REFERENCES

(1). Quinn RK; Könst ZA; Michalak SE; Schmidt Y; Szklarski AR; Flores AR; Nam S; Horne DA; Vanderwal CD; Alexanian EJ Site-Selective Aliphatic C-H Chlorination Using N-Chloroamides Enables a Synthesis of Chlorolissoclimide. J. Am. Chem. Soc 2016, 138, 696–702. [PubMed: 26694767]

(2). Könst ZA; Szklarski AR; Michalak SE; Pellegrino S; Meyer M; Zanette C; Cencic R; Nam S; Voora V; Horne DA; Pelletier J; Mobley DL; Yusupov M; Yusupova G; Vanderwal CD Synthesis facilitates an understanding of the structural basis for translation inhibition by the lissoclimides. Nat. Chem 2017, 9, 1140–1149. [PubMed: 29064494]

(3). Pellegrino S; Meyer M; Könst ZA; Holm M; Voora VK; Kashinskaya D; Zanette C; Mobley DL; Yusupova G Vanderwal CD; Blanchard SC; Yusupov M Understanding the Role of Intermolecular Interactions between Lissoclimides and the Eukaryotic Ribosome. Nucleic Acids Res. 2019, 47, 3223–3232. [PubMed: 30759226]

(4) (a). Malochet-Grivois C; Cotelle P; Biard JF; Hénichart JP; Debitus C; Roussakis C; Verbist J-F Dichlorolissoclimide, a New Cytotoxic Labdane Derivative from Lissoclinum voeltzkowi Michaelson (Urochordata). Tetrahedron Lett. 1991, 32, 6701–6702.(b)Malochet-Grivois C; Roussakis C; Robillard N; Biard JF; Riou D; Debitus C; Verbist J-F Effects in vitro of Two Marine Substances, Chlorolissoclimide and Dichlorolissoclimide, on a Non-small-cell Bronchopulmonary Carcinoma Line (NSCLC-N6). Anti-Cancer Drug Des. 1992, 7, 493–502. (c)Roussakis C; Charrier J; Riou D; Biard JF; Malochet C; Meflah K; Verbist JF

Chemotherapeutic Inhibition of erb-B2 Oncogene Expression on a Non-small-cell Cancer Line (NSCLC-N6) by Marine Substances. Anti-Cancer Drug Des. 1994, 9, 119–128.

(5) (a). Uemura D; Uddin Md. J.; Kokubo S; Suenaga K; Ueda K Haterumaimides A-E, Five New Dichlorolissoclimide-Type Diterpenoids from an Ascidian Lissoclinum Species. Heterocycles 2001, 54, 1039–1047.(b)Uddin MJ; Kokubo S; Ueda K; Suenaga K; Uemura D Haterumaimides F-I, Four New Cytotoxic Diterpene Alkaloids from an Ascidian Lissoclinum Species. J. Nat. Prod 2001, 64, 1169–1173. [PubMed: 11575950] (c)Uddin MJ; Kokubo S; Ueda K; Suenaga K; Uemura D Haterumaimides J and K, Potent Cytotoxic Diterpene Alkaloids from the Ascidian Lissoclinum Species. Chem. Lett 2002, 31, 1028–1029.(d)Uddin J; Ueda K; Siwu ERO; Kita M; Uemura D Cytotoxic Labdane Alkaloids from an Ascidian Lissoclinum sp.: Isolation, Structure Elucidation, and Structure-activity Relationship. Bioorg. Med. Chem 2006, 14, 6954–6961. [PubMed: 16854586]

(6). Fu X; Palomar AJ; Hong EP; Schmitz FJ; Valeriote FA Cytotoxic Lissoclimide-type Diterpenes from the Molluscs Pleuro-branchus albiguttatus and Pleurobranchus forskalii. J. Nat. Prod 2004, 67, 1415–1418. [PubMed: 15332867]

(7). Robert F; Hao HQ; Donia M; Merrick WC; Hamann MT; Pelletier J Chlorolissoclimides: New Inhibitors of Eukaryotic Protein Synthesis. RNA 2006, 12, 717–725. [PubMed: 16540697]

(8). In light of our previous work that featured the selective C2 chlorination of sclareolide en route to chlorolissoclimide (ref 1), we have attempted direct chlorination of various unhalogenated synthetic intermediates, without success.

(9). Goldsmith DJ; Phillips CF The Structural and Stereo-chemical Course of in Vitro Epoxy Olefin Cyclization. Diterpenoid Intermediates. J. Am. Chem. Soc 1969, 91, 5862–5870.

(10). Van Tamelen and co-workers used a more complex terminal epoxide with a C3-alkoxy group in their synthesis of (±)-aphidicolin. The isolated yield was low, and the formation of stereoisomers was implied by reference to "repeated tedious HPLC separations": van Tamelen EE; Zawacky SR; Russell RK; Carlson JG Biogenetic-Type Total Synthesis of (±)-Aphidicolin. J. Am. Chem. Soc 1983, 105, 142–143.

(11). Corey and Liu used a terminal epoxide with a potentially chelating alkoxy group at C19 in their synthesis of neotripterifordin, in which the epoxide-derived C18 hydroxy group is ultimately reductively excised: Corey EJ; Liu K Enantioselective Total Synthesis of the Potent anti-HIV Agent Neotripterifordin. Reassignment of Stereochemistry at C(16). J. Am. Chem. Soc 1997, 119, 9929–9930.

(12) (a). Tanis SP; Herrinton PM Furans in Synthesis. 3. Furans as Terminators in Cationic Cyclization. J. Org. Chem 1983, 48, 4572–4580.(b)Tanis SP; Chuang Y-H; Head DB Furans in Synthesis. 8. Formal Total Syntheses of (±)- and (+)-Aphidicolin. J. Org. Chem 1988, 53, 4929–4938.

(13). Dai M; Krauss IJ; Danishefsky SJ Total Synthesis of Spirotenuipesines A and B. J. Org. Chem 2008, 73, 9576–9583. [PubMed: 18973385]

(14). (a)For the specific conditions used, see: Tang W; Prusov EV Total Synthesis of RNA-Polymerase Inhibitor Ripostatin B and 15-Deoxyripostatin A. Angew. Chem., Int. Ed 2012, 51, 3401–3404. For the original reports, see:(b)Van Horn DE; Negishi E.-i. Selective Carbon-carbon Bond Formation via Transition Metal Catalysts. 8. Controlled Carbometalation. Reaction of Acetylenes with Organoalane-zirconocene Dichloride Complexes as a Route to Stereo- and Regio-defined Trisubstituted Olefins. J. Am. Chem. Soc 1978, 100, 2252–2254.(c)Negishi E.-i.; Van Horn DE; Yoshida T Controlled Carbometalation. 20. Carbometalation Reaction of Alkynes with Organoalane-zirconocene Derivatives as a Route to Stereo- and Regiodefined Trisubstituted Alkenes. J. Am. Chem. Soc 1985, 107, 6639–6647.

(15) (a). Villalpando A; Ayala CE; Watson CB; Kartika R Triphosgene-amine base promoted chlorination of unactivated aliphatic alcohols. J. Org. Chem 2013, 78, 3989–3996. [PubMed: 23496045] (b)Villalpando A; Saputra MA; Tugwell TH; Kartika R Triphosgene-pyridine mediated stereoselective chlorination of acyclic aliphatic 1,3-diols. Chem. Commun 2015, 51, 15075–15078.

(16) (a). Kolb HC; van Nieuwenhze MS; Sharpless KB Catalytic Asymmetric Dihydroxylation. Chem. Rev 1994, 94, 2483–2547.(b)Noe MC; Letavic MA; Snow SL Asymmetric Dihydroxylation of Alkenes. Org. React 2005, 66, 109–625.

(17). For an example of Sharpless asymmetric dihydroxylation of an unfunctionalized alkene in the presence of a trisubstituted alkenyl iodide, see ref 14a.

(18). Mohammad S; Dhambri S; Gori D; Vaxelaire C; Sorin G; Ardisson J; Lannou M-I Asymmetric Sharpless Dihydroxylation Reaction of Chiral Bishomoallylic Alcohols: Application to the Synthesis of the C1-C10-C5 Fragment of FR225654. Synlett 2013, 24, 2581–2585.

(19) (a). Marshall JA; Schaaf GM Total Synthesis and Structure Confirmation of Leptofuranin D. J. Org. Chem 2003, 68, 7428–7432. [PubMed: 12968896] (b)Corbu A; Aquino M; Pratap TV; Retailleau P; Arseniyadis S Enantioselective Synthesis of Iridal, the Parent Molecule of the Iridal Triterpenoid Class. Org. Lett 2008, 10, 1787–1790. [PubMed: 18396888] (c)Speck K; Wildermuth R; Magauer T Convergent Assembly of the Tetracyclic Meroterpenoid (−)-Cyclosmenospongine by a Non-Biomimetic Polyene Cyclization. Angew. Chem., Int. Ed 2016, 55, 14131–14135.

(20). We performed the control experiment with "deschloro-17" under the same conditions shown in Scheme 1; both diastereomeric bicyclization products were formed in a ca. 5:1 ratio favoring the compound with the equatorial hydroxymethyl group (C18 oxygenation, as in 8a in Figure 2b). Please see the Supporting Information for details.

(21). (a)Britton and co-workers have make extensive and creative use of chlorine-bearing stereogenic centers as chiral auxiliaries for aldol-based constructions of natural products. For a review, see: Halperin S; Britton R Chlorine, an Atom Economical Auxiliary for Asymmetric Aldol Reactions. Org. Biomol. Chem 2013, 11, 1702–1705. For selected references, see: [PubMed: 23370443] (b)Kang B; Britton R A General Method for the Synthesis of Nonracemic trans-Epoxides: Concise Syntheses of trans-Epoxide-Containing Insect Sex Pheromones. Org. Lett 2007, 9, 5083–5086. [PubMed: 17975920] (c)Draper J; Britton R A Concise and Stereoselective Synthesis of Hydroxypyrrolidines: Rapid Synthesis of Preussin. Org. Lett 2010, 12, 4034–4037. [PubMed: 20726562] (d)Halperin S; Kang B; Britton R Lithium Aldol Reactions of α-Chloroaldehydes Provide Versatile Building Blocks for Natural Product Synthesis. Synthesis 2011, 2011, 1946–1953.(e)Britton R; Kang B α-Haloaldehydes: Versatile Building Blocks for Natural Product Synthesis. Nat. Prod. Rep 2013, 30, 227–236. [PubMed: 23258610] (f)Dhand V; Draper JA; Moore J; Britton R A Short, Organocatalytic Formal Synthesis of (−)-Swainsonine and Related Alkaloids. Org. Lett 2013, 15, 1914–1917. [PubMed: 23550817] (g)Bergeron-Brlek M; Teoh T; Britton R A Tandem Organocatalytic α-Chlorination-Aldol Reaction that Proceeds with Dynamic Kinetic Resolution: A Powerful Tool for Carbohydrate Synthesis. Org. Lett 2013, 15, 3554–3557. [PubMed: 23819733] (h)Holmes MT; Britton R Total Synthesis and Structural Revision of Laurefurenynes A and B. Chem. - Eur. J 2013, 19, 12649–12652. [PubMed: 23956022] (i)Bergeron-Brlek M; Meanwell M; Britton R Direct Synthesis of Imino-C-Nucleoside Analogues and other Biologically Active Iminosugars. Nat. Commun 2015, 6, 6903. [PubMed: 25903019]

(22). Yoshimura F; Sasaki M; Hattori I; Komatsu K; Sakai M; Tanino K; Miyashita M Synthetic Studies of the Zoanthamine Alkaloids: The Total Syntheses of Norzoanthamine and Zoanthamine. Chem. - Eur. J 2009, 15, 6626–6644. [PubMed: 19479925]

(23). Hajra S; Giri AK; Karmakar A; Khatua S Asymmetric Aldol Reactions under Normal and Inverse Additions Modes of the Reagents. Chem. Commun 2007, 2408–2410.

(24). Syn-chloroepoxide 24 was synthesized in an analogous way to 17, starting from R-epichlorohydrin; see the Supporting Information for details.

(25). For a recent review, see: Riehl PS; DePorre YC; Armaly AM; Groso EJ; Schindler CS New Avenues for the Synthesis of ent-Kaurene Diterpenoids. Tetrahedron 2015, 71, 6629–6650.

(26). (a)For important, though only parenthetically related, uses of halogen atoms to control other issues of selectivity, see:Johnson WS; Bartlett WR; Czeskis BA; Gautier A; Lee CH; Lemoine R; Leopold EJ; Luedtke GR; Bancroft KJ The Fluorine Atom as a Cation-Stabilizing Auxiliary in Biomimetic Polyene Cyclizations: Total Synthesis of dl-Dammarenediol. J. Org. Chem 1999, 64, 9587–9595.(b)Roush WR; Brown BB Application of the Steric Directing Group Strategy to the Stereoselective Synthesis of the Octahydronaphthalene Substructure of Kijanolide and Tetronolide. J. Am. Chem. Soc 1993, 115, 2268–2278.
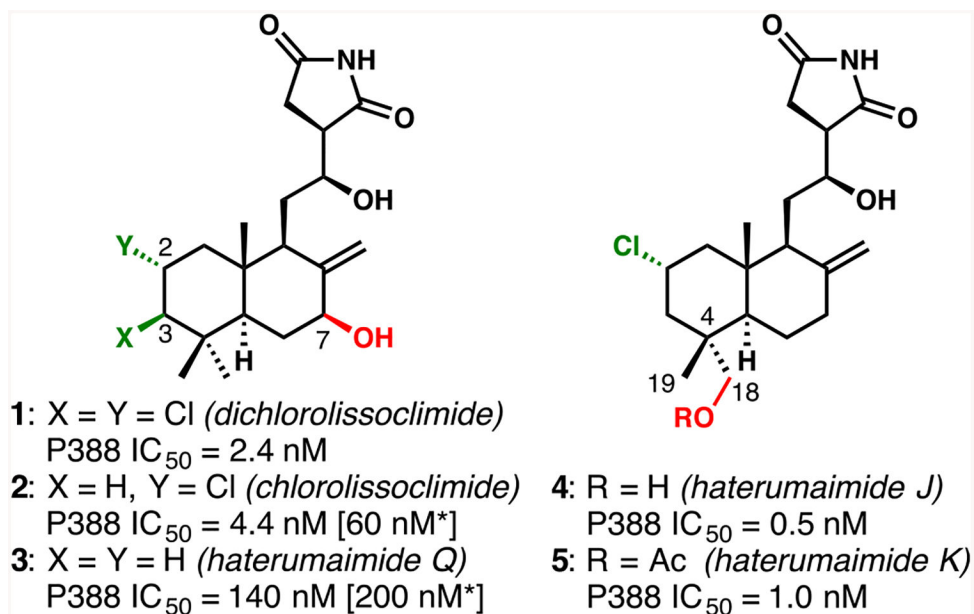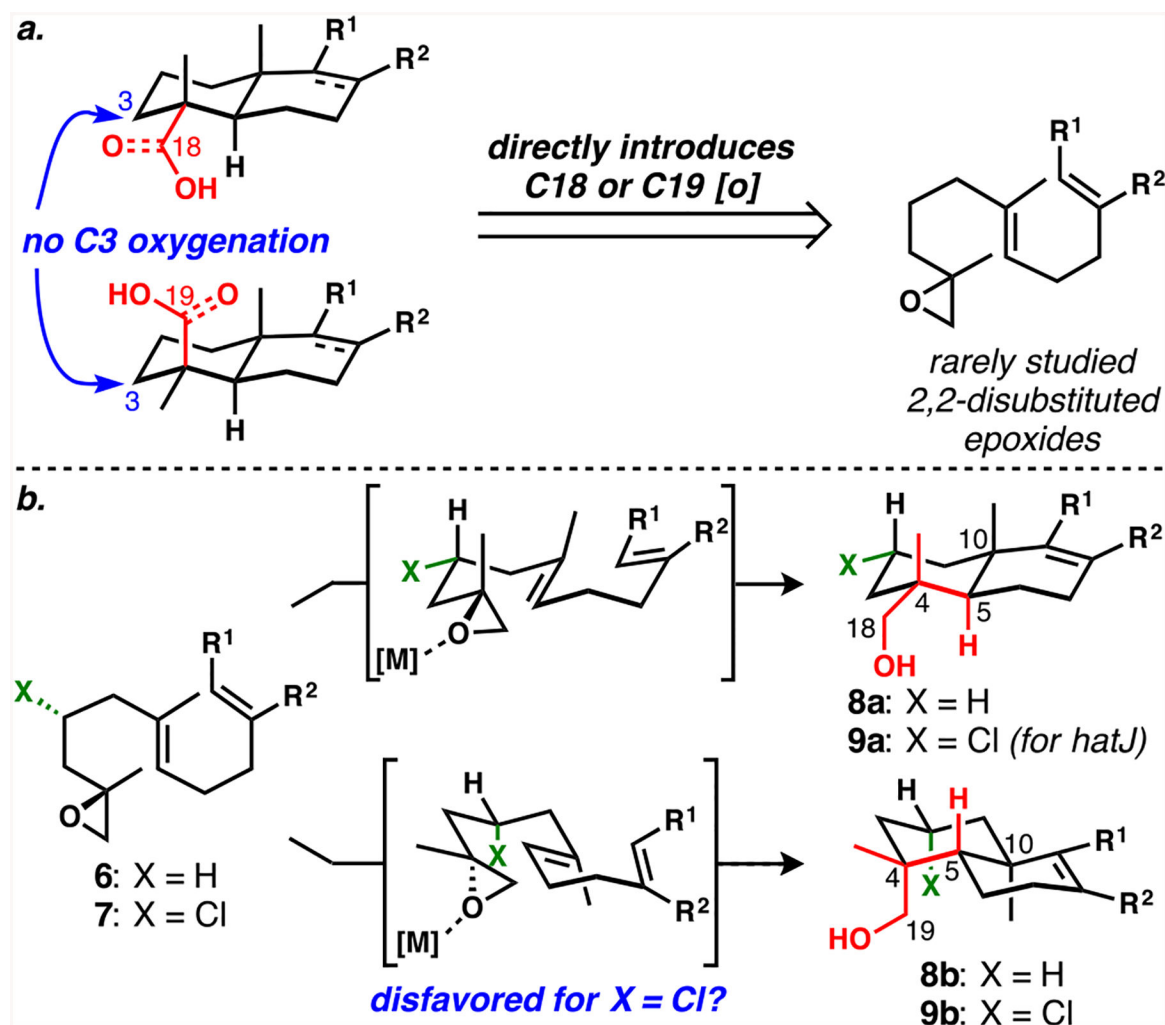
Figure 1.
Representative cytotoxic lissoclimides and haterumaimides. *IC_{50} values in brackets were measured previously by us (refs 1 and 2); all other values are from earlier literature (refs 4 and 5).

Figure 2.
(a) Terminal-epoxide initiated cyclizations are perfectly suited to the synthesis of C18/C19-oxygenated terpenoids that are otherwise devoid of A-ring oxygenation. (b) The two possible diastereomeric reactive conformations of terminal-epoxide-initiated bicyclizations lead to either C18 (equatorial) or C19 (axial) oxygenated decalin diterpenoid substructures.
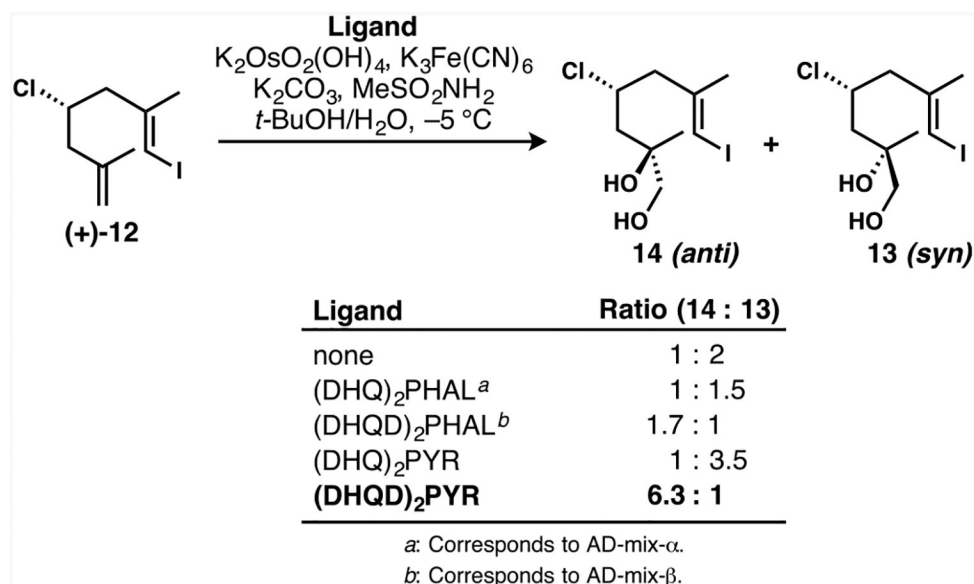
Figure 3.
Catalyst-controlled diastereoselective dihydroxylation of homoallylic chloride **12**. The relative configurations of **13** and **14** were established via X-ray crystallography of **13** (see the Supporting Information).
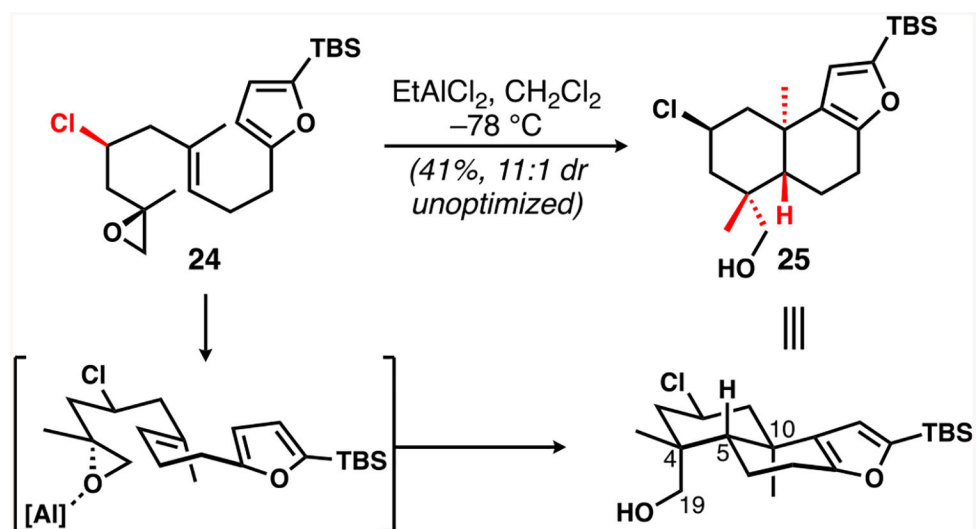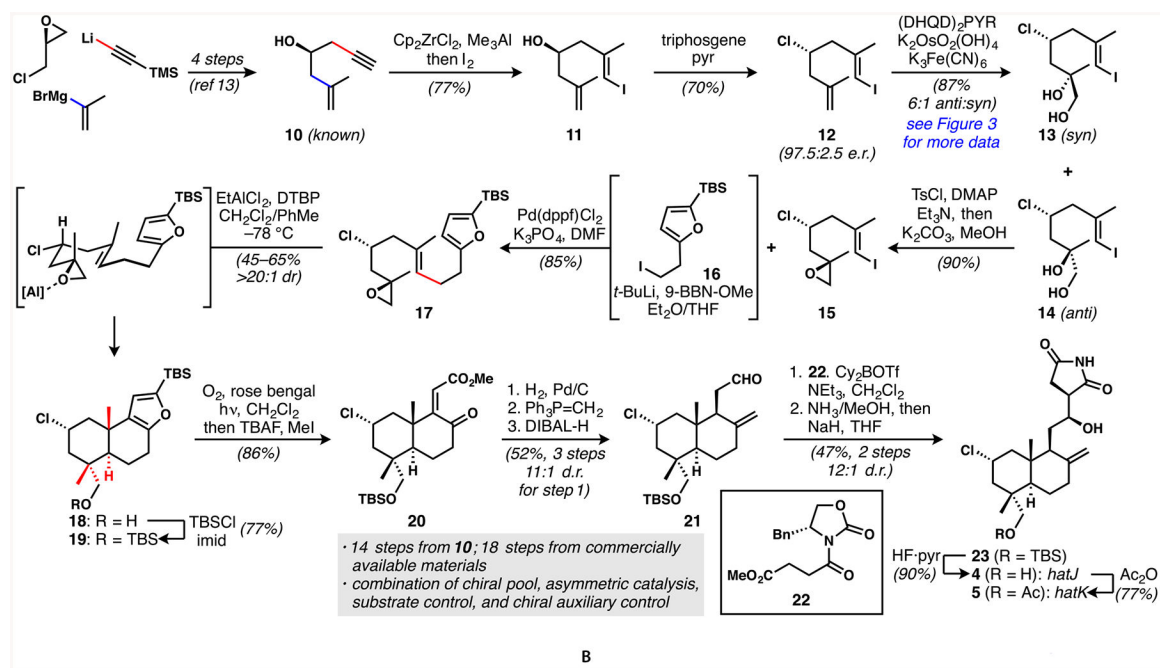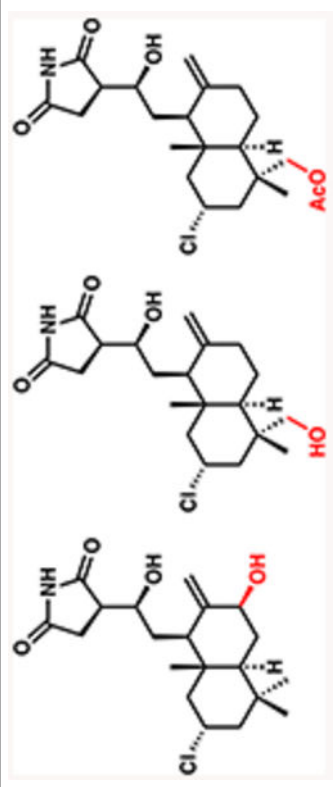
Figure 4.
Syn-chloroepoxide **24** leads selectively to diastereomer **25** with the axial A-ring hydroxymethyl group.

Scheme 1.
Stereocontrolled Synthesis of Haterumaimides J and K

Table 1.

Cytotoxicity of Haterumaimides J and K

	2: chlorolissoclimide	4: haterumaimide J	5: haterumaimide K
	60 nM[a] (lit = 4 nM[b])	26 nM (lit = 0.5 nM[c])	33 nM (lit = 1.0 nM[c])
P388			
HUT78	ND	0.16 μM	0.20 μM
A2058	0.25 μMa	1.4 μM	1.1 μM
DU145	0.49 μMa	0.57 μM	0.53 μM

[a]Ref 2.

[b]Ref 4a.

[c]Refs 5c and 5d.