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Empirical Chiroptical Analyses of Vicinal Bromochloro Natural Products by van't Hoff's Principle of Optical Superposition: Assignment of the C-16 Configurations of Callophycols A and B

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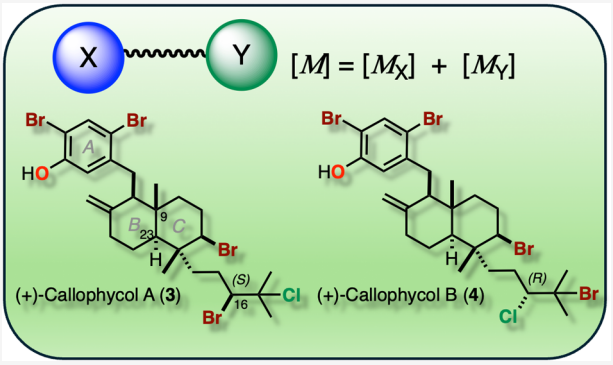
ABSTRACT: A simple empirical method is described that allows the assignment of absolute configurations of natural products containing chiral vicinal bromochloro (VBC) units, including the bromochloro substituted isoprenyl units present in the structures of antiproliferative halomon (**1a**) and its halogen-swapped isomer *iso*-halomon (**1b**) from the red alga, *Portieria hornemannii*, and callophycols A (**3**) and B (**4**) from *Callophycus serratus*. The relative configurations of **3** and **4**, published in 2007, were incomplete: C-16 was left unassigned. It is now shown that the additivity of molar rotations, $[M]_D$ (herein, abbreviated $[M]$)—a consequence of van't Hoff's principle of optical superposition—could be used to deconvolute rotatory contributions, designated as $[M_X]$ and $[M_Y]$ of the two remotely spaced chiral substructures within **3** and **4** using simple arithmetic. Input of proxy values, $[M_{Y_1}]$ and $[M_{Y_2}]$, for the two different VBC units in two equations for $[M_X]$ and application of a "conditional test" returns the same value for $[M_X]$ only when a proxy with the correct configuration is included. It is revealed that **3** and **4** have opposite configurations at the C-16 stereocenter: 16*S* and 16*R*, respectively. Two important implications lie in these findings: **3** and **4** appear to qualify as paired-regioisomers, coupled through a putative dyotropic rearrangement (DR), and the biosyntheses of other *Callophycus* secondary metabolites, now numbering over 50, are tightly controlled by stereoelectronic considerations including neighboring group interactions of the DR. It now appears, counter to earlier suggestions, that the chirality of *Callophycus* secondary metabolites, despite their high chemodiversity, are surprisingly highly conserved. Enantiofacial halogenation additions to the C=C double bonds of precursor alkenes appear to direct the formation of the remaining stereocenters at both the halogenated benzoate-decalin core and the distal VBC of **3** and **4**. A consistent hypothesis is proposed to account for macrolactonizations in other *Callophycus* natural products including bromophycolides A and B. The conditional test of molar rotations was applied in a different context to understand the chiroptical properties and trends observed in the highly iodinated meroditerpenes, iodocallophycols A−E, also from *Callophycus* sp., resulting in the revision of the configuration of callophycol E from (10*R*,14*R*) to (10*S*,14*S*).



Mixed polyhalogenated (interhalogen) natural products are mainly marine-derived; their provenance is mostly from Rhodophycae (red algae), but some are also produced by Porifera (sponges).[1,2] Most of the 8000 or more reported halogenated marine natural products are brominated, and about 700 have both Cl and Br in their structures. Of these compounds, the polyhalogenated monoterpene halomon (**1a**)—containing a vicinal bromochloro isoprenyl group (hereafter referred to as VBC) from *Portieria hornemannii* reported in 1975 by the Moore group in Hawaii[3]—drew renewed interest from the National Cancer Institute in the early 1990s with the discovery of its potent antiproliferative activity against cultured human cancer cells lines[4] and expression of highly differential activities within the standard NCI cultured cancer cell panel (NCI-60).[5] *iso*-Halomon (**1b**), a 1,2-halogen-vicinally swapped isomer of **1a**, also displayed antiproliferative properties, albeit with attenuated potency (mean 60-cell panel, GI_{50} 1.32 μM) or about half active as **1a** (GI_{50} 0.676 μM) measured under the same conditions.[6] Halomon (**1**) was advanced to preclinical trials, but interest in **1a** faded due to compound-limiting supply issues and poor prognoses of "drugability" for cancer treatment of these highly lipophilic natural products.

More recently, it was found that the long-chain VBCs, mollenynes A and B (**2a**,**b**), from the sponge *Spirastrella mollis*, also exhibited substantial cytotoxicity toward cultured HCT-116

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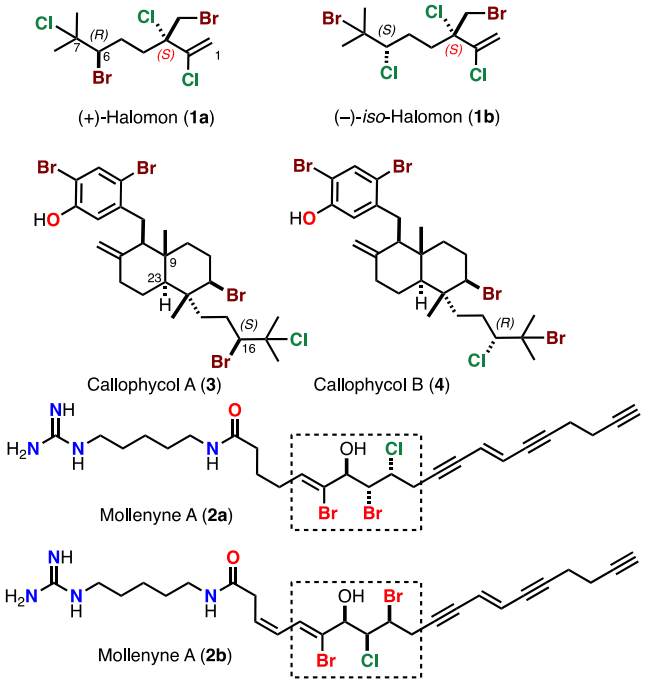
cells (colon tumor cells, IC_{50} 1.3 μM) comparable to etoposide (IC_{50} 0.55 μM; both ~1 μM).[7] Kubanek and co-workers described callophycols A (**3**) and B (**4**) from the Fijian red alga, *Callophycus* sp.:[8] other collections of the same alga that delivered several related brominated meroditerpenoids, including bromophycolides A (**5a**) and B (**5b**).[9] The former exhibited modest cytotoxicity (mean GI_{50} 6.7 μM, NIH-60 panel) and induction of apoptosis in human ovarian cancer cells, A2780 (19.3% at 10 μm **5a**). More recent reports of compounds from *Callophycus* sp. include benzofuran and benzopyran variations of the benzoate core,[10] bromophycolides J-Q,[11] and R-U,[12] including pyran-containing macrolides, iodinated callophycols, and callophycoic acids from Fiji[13] and Tonga.[14]

Syntheses of pentahalogenated terpene **1a** have been accomplished through judicious introduction of halogens to alkene precursors by electrophilic addition. The first total synthesis of (±)-**1a**, by Hirama and co-workers starting from myrcene, is notable for the strategic insertion of three VBC groups by sequential dihalogenations of C=C double bonds using the interhalogen dichlorobromate salt, nBu$_4$N$^+$[BrCl$_2$]$^-$,[15] followed by selective elimination of 1 equiv of HBr to afford the vinyl chloride.[16] The first asymmetric synthesis of natural (+)-**1a** and *ent*-(−)-**1a**, by Burns and co-workers, exploited the enantiomers of a purpose-built chiral Schiff-base catalyst, paired with a Lewis acid Cl−Ti(i-PrO)$_3$ and *N*-bromosuccinimide (NBS) to deliver both targets in high enantiomeric excess (>99.8% ee).[17]



Our interest in interhalogen organic VBCs originates from speculations[7] such that halogen-swapped regioisomers may arise from dyotropic rearrangement (DR): the concerted double vicinal *syn*-facial migrations of halogens with simultaneous double inversion (Figure 1). The vicinal halogen DR, driven by orbital-symmetry and highly participatory halogen neighboring group interactions, can be slow even when the necessary stereoelectronic conditions are met: antiperiplanar arrangement of halogen−carbon bonds. Thermally, a spontaneous, rapid interchange of vicinal Br−Br, Br−Cl, or Cl−Cl at room temperature is prohibitive ($\Delta G^{\ddagger}$ > 38 kcal mol^{-1}). For example,

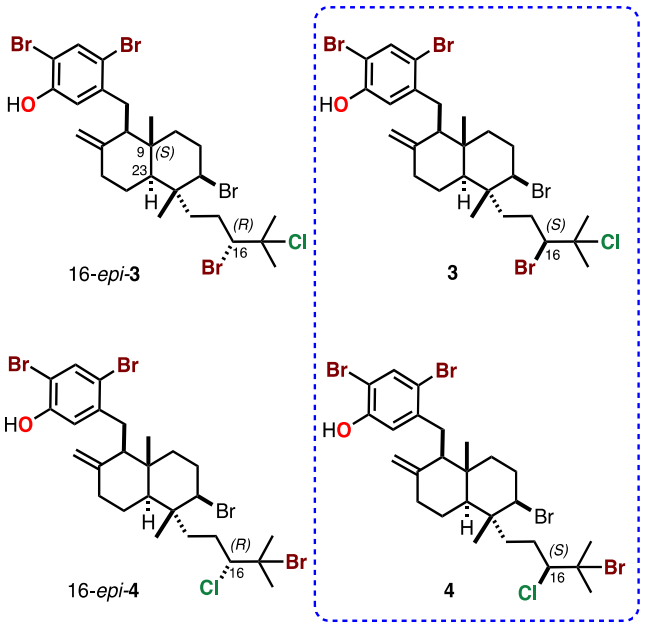


Figure 1. Callophycols A (**3**) and B (**4**) and their epimers, 16-*epi*-**3** and 16-*epi*-**4**. Shown in the blue box are the correctly assigned absolute configurations (this work).

Winstein[18] and Barton[19,20] independently showed that thermal DR of 2β,3α-dibromo- and 2β,3α-dichloro-cholestanes (mp 122−124 and 108−112 °C, respectively) only occurred, at appreciable rates, at temperatures above the melting points.

Reetz's definition of dyotropic rearrangement (DR) is qualified by the adjective "uncatalyzed",[21,22] but a DR in the biosynthesis of natural VCBs at ambient temperatures is predicated upon—and, indeed, necessitates—a reaction promoted by an enzyme: a hypothetical "dyotropase" that has yet to be discovered and characterized.[23] Two conditions must be met to qualify VBC natural products as isomers paired through DR: for asymmetric molecules, at least one stereocenter in the pair must be epimeric with respect to halogen−C bonds, and inversion of asymmetry must proceed with stereofidelity, that is, complete double inversion rather than erosion of enantiomeric (or epimeric) integrity. These conditions were met with **5a** and its halogen-swapped analog, mollenyne B (**5b**): their absolute configurations (AC) were solved by integrative MS, NMR, and CD analyses, coupled with chemical derivatization.[7] Less clear are the structures of the halogen-swapped isomers callophycols A and B (**3** and **4**), where their C-16 ACs, at the time of publication, were undefined. Here, we present a reliable, general methodology for determining the configuration of distal VBC groups in the structures of natural products based on a venerable empirical rule: van't Hoff's principle of optical superposition.[24,25]

RESULTS AND DISCUSSION

The stereoassignment of remote stereoelements in natural products is a formidable problem, one that Faulkner and others had noted earlier in the context of brominated chamigranes containing VBCs.[26,27] Defining the correct C-16 configuration of callophycols A (**3**) and B (**4**) by NMR was impossible; indeed, the ^{1}H and ^{13}C NMR chemical shifts of their bromodecalin cores were almost identical. The optical rotations of **3** and **4** were reported with $[\alpha]_D$ +75 and +110 (MeOH), respectively. Structure elucidation led to **3** and **4**, which differed

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in two respects: regioisomerism within the terminal VCB group but no assignment of the C-16 configurations. Thus, there are four possible isomers (Figure 1): **3** and **4** and their epimers, 16-*epi*-**3** and 16-*epi*-**4**.

van't Hoff's principle of optical superposition predicts that the asymmetry imparted to a molecular structure will be additive of its asymmetric components if they are sufficiently separated: the molar rotation, $[M]_D$ of the entire structure will be the sum of the molar rotations of its asymmetric components. Consider a molecular structure comprising three chiral substructures X, Y, and Z (Figure 2a) separated by methylene chains. When suitably

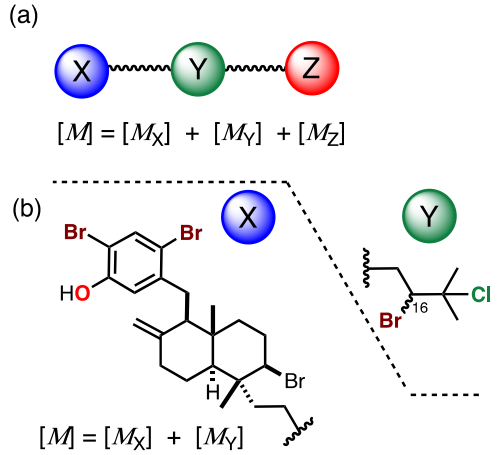

Figure 2. (a) Hypothetical three-component molecule comprising spatially distanced stereosubstructures, X, Y, and Z. (b) Two-component bromophycols **3** and **4** comprising distal "bromodecalin core", X, and "VBC", Y. The molar rotation, $[M]$, of each will be the arithmetic sum of their respective asymmetric contributions, $[M_X] + [M_Y] + [M_Z]$ or $[M_X] + [M_Y]$. See text.

"insulated" by achiral linkers (Kishi defined the minimum linker as a 1,2-disubstituted ethane[28]), stereoelectronic effects from asymmetric components contribute additively, and intramolecular interactions can be neglected.[29] Assuming the latter condition is met, the principle of optical superposition predicts that the molar rotation $[M]_D$ (herein, simplified to $[M]$, but still implying rotation at the "D" line of Na emission) will be the arithmetic sum of 3 components: the contributions of $[M_X]$, $[M_Y]$, and $[M_Z]$ to the local asymmetries. This principle has been successfully applied by Wipf and co-workers to assign the complex stereostructure of bistramide C, an antiproliferative polyketide from the tropical tunicate *Lissoclinum bistratum*[30,31] using an integrated approach: synthesis of proxies for X, Y, and Z (Figure 2a), measurement of their respective $[\alpha]_D$ values, conversion to molar rotations, and generation of permutations of all three plus their enantiomers to arrive at calculated $[M]$ values, one of which best matched the measured value.[32] This successful prediction guided the first total of the bistramide C.[33]

Following Figure 2b, the asymmetry of the molecular structures of **3** ($[M]$ +139.5) and **4** ($[M]$ +791, See the Supporting Information, S2, for calculations of $[M]$) can be considered as a resultant of only two unequal parts: the brominated benzoate-decalin core (generically defined here as "X") and the distal VBC stereoelement, "Y"; a 16,17-dihaloisoprenyl group (Figure 2b). For example, if the "asymmetric modules" X and Y of callophycols A and B satisfy this condition, an equation can be proposed that predicts that the molar rotations of **3** and **4** would be the arithmetic sum of the molar rotations of those modules. The molar rotations of X and Y in **3** and **4**, $[M_X]$ and $[M_Y]$, are unknown, but $[M_Y]$ can be estimated from specific rotations of suitable models, (+)-**7** and (−)-**8** reported by Burns and co-workers (see the Supporting Information, S2),[34] after their conversion to molar rotations using the relationship $[M] = [\alpha]_D \times MW/100$, where MW is the molecular mass of the compound. Again, from the principle of optical superposition, the Y contribution to rotatory strength, $[M_Y]$, in **3** and **4** can be approximated by the $[M_Y]$ values of **7** and **8** because the contributions of the different distal termini to the molar rotations of the latter two compounds should be negligible. This is supported by observations of nine other VBCs, the structures of which differ only in their termini separated from the vicinal dihalo-terminus by an ethylene group, $-CH_2CH_2-$, and whose molar rotations are of similar magnitude (Supporting Information, S2). Importantly, because **7** and **8** have $[\alpha]_D$s of opposite sign and substantial magnitude, molar rotations for the two regioisomeric subvariants of Y must be defined: $[M_{Y_1}]$ for **7** and $[M_{Y_2}]$ for **8** (Figure 3). Thus, the contribution of the decalin, $[M_X]$, to the overall rotatory strength—the molar rotation, $[M]$—can be calculated from eq 1.

$$[M_X] = [M] - [M_{Y_1}] \quad (1)$$

$$[M_X] = [M] - [M_{Y_2}] \quad (2)$$

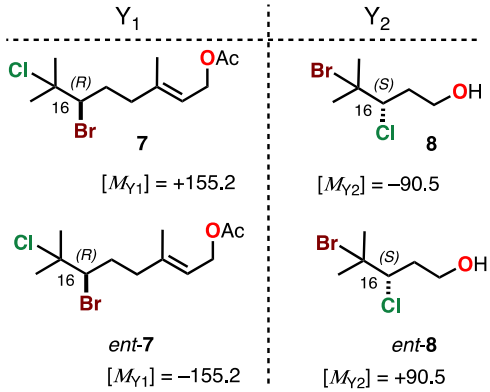

Figure 3. Molar rotations of synthetic analogs **7** and **8** calculated from reported $[\alpha]_D$s (corrected for % ee), Burns et al.[34] See Table 1. $[M] = [\alpha]_D \times MW/100$.

In other words, the hypothetical contribution $[M_X]$ from the invariant decalin is predicted from a simple algebraic derivation: if the correct enantiomorphs of models **7** and **8** (either 16*S* or 16*R*) are selected as proxies for the VBC in **3** and **4**, then the value returned for $[M_X]$ should be the same. This "conditional test" for correctness of fit is best conducted by solving eqs 1 and 2 and semiquantitative evaluation of the minimum differences (similarities) of $[M_X]$ returned for each compound. The values of $[M_{Y_1}]$ and $[M_{Y_2}]$ for the enantiomers, (−)-*ent*-**7** and (+)-*ent*-**8**, are obtained simply by inverting the respective signs of the calculated molar rotations for (+)-**7** and (−)-**8**.

Table 1 shows the outcomes of the conditional tests. Clearly, the best fit for callophycol A (**3**) is obtained by the selection of the VBC, Y_1 from *ent*-(−)-**7**, instead of (+)-**7**. Conversely, Y_2 for the regioisomeric VBC in callophycol B (**4**) is best fitted with (−)-**8** and confers the 16*R* configuration. Consequently, the levorotatory enantiomers of **3** and **4** (*ent*-**3** and *ent*-**4**, Table 1,

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Table 1. Conditional Test for Fitness of the C-16 Configuration in Callophycols A (3) and B (4)[c]

Entry		X, Y_1	X, – Y_1	X, Y_2	X, – Y_2
1[a]	$[M_X]$	384	*694*	881	*700*
2[b]	[*ent*-M_X]	– 384	–694	– 881	–700

[a]Red, italic values are a match to the correct AC of **3** and **4**. [b]Values obtained by inversion of the signs in Entry 1. [c]X, Y_1, and Y_2 refer to asymmetric modules of **3**, **4**, **7**, and **8**. See text.

row 2) can be ruled out because the rotations of these natural products are uniformly positive (see below for a discussion of the absolute configuration of X). The values of $[M_X]$ returned in each test are concordant; therefore, the configurations callophycol of A (**3**) and B (**4**) are 16*S* and 16*R*, respectively.

Several interesting observations and conclusions can be drawn from the foregoing analysis. While simple inspection of only $[\alpha]_D$ or $[M]$ gives no clear indication of the C-16 configurations of **3** and **4**, deconvolution of the molar rotation contributions of each asymmetric module in the natural products does. A simple empirical rule emerges from this analysis: in polyhalogenated terpenoids with terminal VBCs where a natural "insulating" ethylene group separates the optically active modules, determination of the asymmetric center can be made by consideration of their molar rotations only. Conveniently, the conditional test has the advantage that differences in rotations result from experimental conditions, e.g., solvent, are subtracted out, at least to a first degree. Finally, the dominant contributor to the asymmetry and positive rotations of **3** and **4** is clearly the brominated benzoate-decalin module with an estimated $[M_X]$ of +694 or +700. Either positive or negative contributions are made by the VBC depending on the regioisomerism and configuration of the chiral center, C-16.

The conditional test itself can be tested. Application of the conditional test to isomeric halomon (**1a**) and iso-halomon (**1b**, Table 2), the structures of which were determined unambiguously by X-ray crystallography, again returned concordant results only for the correct configuration of Y_1 and Y_2; the best fits for **1** and **2** were seen for Y_1 = (+)-**7** and Y_2 = (−)-**8** which return matched values for $[M_X]$ of −15.2 and −10, respectively. Interestingly, the X component in **1a**,**b** overrides the fixed contribution to $[M]$ of the distal module, Y. In (+)-**1a** and (−)-**1b**, it is the C-6 configuration that dominates the sign of rotation. Note also that both (+)-**1a** and **3** are products of Markovnikov addition to different precursor alkenes, but the chirality of their VBCs is opposite (Figure 4).

Table 2. Conditional Test for the Fitness of Halomon (1a) and *iso*-Halomon (1b)[c]

Entry		X, Y_1[b]	X, – Y_1	X, Y_2[b]	X, – Y_2
1[a]	$[M_X]$	*–15.2*	+279	*–10*	–191
2[b]	[*ent*-M_X]	+15.2	–279	+10	+191

[a]Red, italic values are a match for the correct AC of **1a** and **1b**. [b]Values obtained by inversion of the signs in Entry 1. [c]X, Y_1, and Y_2 refer to asymmetric modules of **1a**, **1b**, **7**, and **8**. See text.

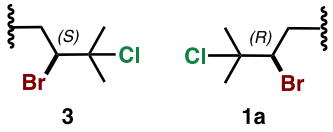

Figure 4. Enantiomorphic VBCs of callophycol A (**3**) and halomon (**1a**).

Some comments on reliability and precision are in order. The accuracy of the conditional test is only as good as the precision with which the optical rotations are measured or reported. The case in counterpoint is seen with the first-reported specific rotation of **1**, an erroneous value of $[\alpha]_D$ +20, correctly signed but with a magnitude almost 7 times the now-accepted value that was revealed by Hirama and Burns through their syntheses (the specific rotation of **1a**, $[\alpha]_D$ +31.14 used in the present calculations is of pure synthetic (+)−**1**, >99.8% ee, mp 50−52 °C,[17] see the Supporting Information).

It can now be seen that the C-16 configuration in **4** is inverted with respect to **3**; therefore, like (+)-**1a** and (−)-**1b**, the structures of **3** and **4** are suggestive candidates for biosynthetic dyotropic rearrangement. An extension of this premise may be seen in consideration of bromophycolides A (**5a**) and B (**5b**) (Figure 5), an isomeric pair of related brominated meroditerpenes that differ in the mode of macrolide cyclization. One interpretation, postulated by Kubanek and co-workers, is that cyclization to complete **5a** and **5b** occurs by interception of a bromonium ion through two different paths: nucleophilic addition of the carboxyl group at the two differently substituted carbons. It follows that the postulated bromonium ion must be *R*-configured arising from a stereospecific *re*-π-facial attack of an electrophilic Br^+ species upon the C=C double bond of the isoprenyl precursor: the end products, **5a** or **5b**, arise from attack

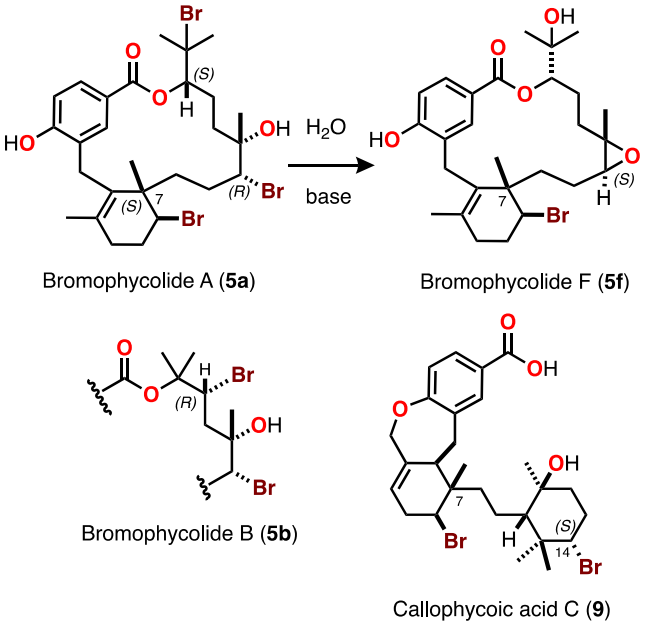

Figure 5. Bromophycolides A, B, F (**5a**,**b**,**f**) and callophycoic acid C (**9**).

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by R-COOH at C-14 or C-15 (bromophycolide numbering), respectively.

We propose a refined scenario for the terminal ring reactions (Figure 6) that is more self-consistent with the configurations.

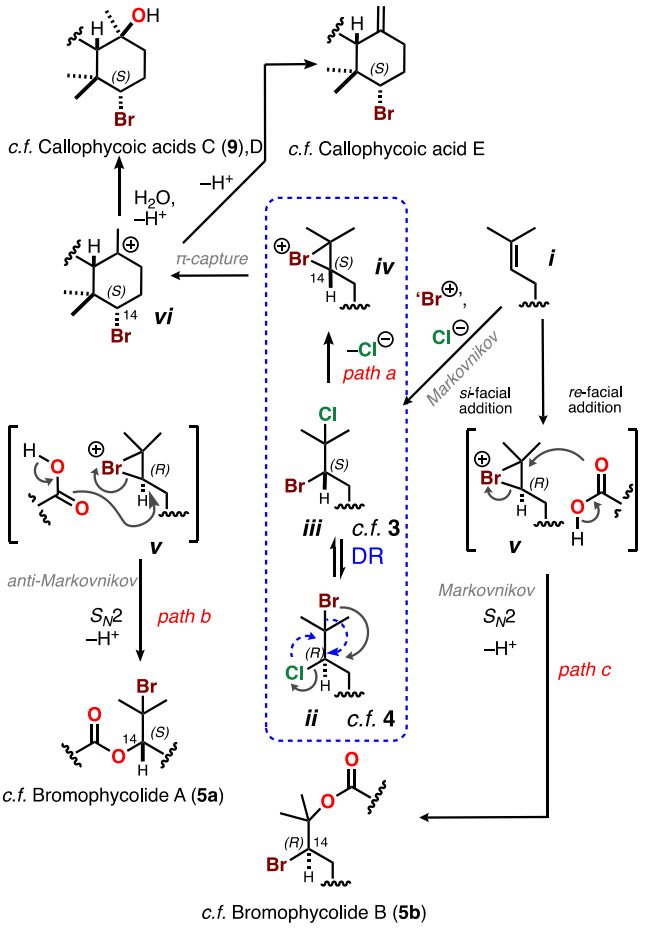

Figure 6. Proposed biosynthesis of the macrolide ring of bromophycolides A and B (**5a**,**b**) and second carbocyclic ring of callophycoic acids C (**9**), D, and E. Dyotropic rearrangement (DR) is shown with dashed arrows.

The favored Markovnikov addition of BrCl to the *si*-face of an alkene precursor, **i**, gives the *R*-configured VBC **ii** (cf. **4**), which undergoes DR to give the isomeric *S*-configured VBC, **iii** (cf. **3**). Ionization of **iii** by loss of Cl^- leads to an *R*-bromonium ion **iv**, common to the two pathways (path a and path b), followed by intramolecular nucleophilic substitution by R-COOH leading to the bromophycolide products **5a** (anti-Markovnikov) and **5b** (Markovnikov), respectively. Subsequent reactions, for example, to form the terminal carbocylic ring in callophycoic acid C (**9**, path c) is initiated by *S*-bromonium ion formation from **ii** by displacement of Cl with inversion of the 14*R* chiral center of **ii**. The foregoing scheme converges on two precursors, and the DR **ii** → **iii**, to rationalize the biosynthesis of **5a**,**b**, along with most of the terminally halogenated *Callophycus* compounds, that obviates the need for stereodivergent brominations by different enzymes. As mentioned earlier, the K_{eq} for the DR of acyclic VBCs is close to unity. From the report of isolation of **3** and **4**, it is interesting to note that both compounds were obtained in almost equal masses (1:0.8),[8] consistent with the estimated equilibrium constant of similar acyclic DRs ($K_{eq} \sim 1.0$), and the notion that [**3**]/[**4**] constitutes a steady-state pool of a bromonium ion proxy.[8]

The proposal has been supported by synthetic studies of VBCs. Burns and co-workers demonstrated facile solvolyses and intramolecular π-cyclization by the capture of incipient bromonium ions derived from various synthetic VBCs by ionization in a high dielectric solvent (hexafluoro-*iso*-propanol, HFIP).[35] Notably, Cl was always displaced and Br retained with preservation of the configuration of the Br-substituted carbons, suggesting VBCs constitute "nonracemizing, enantioenriched bromonium surrogates".[35] Burns' premise, extended into the context of biosynthesis of halogenated meroterpenoids, suggests a corollary: the propensity of a VBC group, itself a product of bromonium-ion-promoted 1,2-addition, to act as a "bromonium proxy": a resting state or "placeholder" for post-halogenation nucleophilic substitutions through regenerative bromonium ion formation by S_N1 ionization but with tight stereochemical control. In this light, the triad of proposed intermediates **ii**–**iv** (Figure 6) comprises a "living bromonium pool" including the DR shunt **ii** → **iii** (cf. **3**), which participates in π-facial attack upon the C=C double bond of the penultimate isoprenyl group.

The biosynthesis of downstream products **5a**,**5b** and other terminally brominated *Callophycus* compounds can only be rationalized, for now, by a separate *R*-configured bromonium ion, **v** derived from **i** by *re*-face selective halogenation, which undergoes Markovnikov or anti-Markovnikov additions ending with S_N2 substitutions by the nucleophilic carboxylic acid to give regioisomers with oppositely configured macrolide rings, (14*S*)-**5a** (proceeding with inversion) and (14*R*)-**5b** (retention).

The structures of *Callophycus* meroditerpenes suggest no promiscuous nucleophilic additions to the incipient bromonium ions, e.g., additions of H_2O to give vicinal bromohydrins,[36] suggesting tightly directed control of both ion-pair formation during the ionization events and DR. Other compounds in the series likely have simpler origins. For example, bromophycolide F[37] (**5f**, Figure 5), lacking two of the three Br atoms of **5a**, arises most likely by adventitious solvolysis (a C-15 *tert*-alcohol) from the latter, and base-promoted epoxide formation from the corresponding 10,11-bromohydrin.

A comment about the decalin cores of **3**, **4**, and **5a**,**b** is in order. An assumption inherent in the above-described conditional test analysis is that the handedness of the arylmethyldecalin core, X, is invariant. This premise is supported by the X-ray crystal structures of **5a**,**b** and callophycoic acid C (**9**), which reveal that the *trans* ring junction absolute configuration of the bicyclic carbocycle, C-9 and C-23 (or C-7/C-24 in some numbering schemes), is the same in each compound.[38] Similar patterns are revealed in the interesting structures of iodinated *Callophycus* compounds, **10**–**15**, reported by the research groups of Kubanek and Keyzers (Figure 7). Kubanek and co-workers described iodocallophycoic acid A (**10**) and the iodocallophycols A–D (**11**–**15**), obtained from *C. serratus* collections from sites different within the Fijian archipelago, that delivered **3**,**4**, **5a**,**b**, and **9**. The absolute configurations were assigned after extensive comparisons of the calculated ECD spectra (TDDFT) of hypothetical 10*R*,14*R* and 10*S*,14*S* diastereomers of representative compound, **1**, and comparison with the Cotton effects of the natural product.

Surprisingly, the sign of the long-wavelength Cotton effect of **1** (λ = 255 nm, $\Delta\varepsilon$ +5.0) is strongly influenced by the C10–C14 configuration, suggesting either a significant through-space interaction with the phenol chromophore or possibly a

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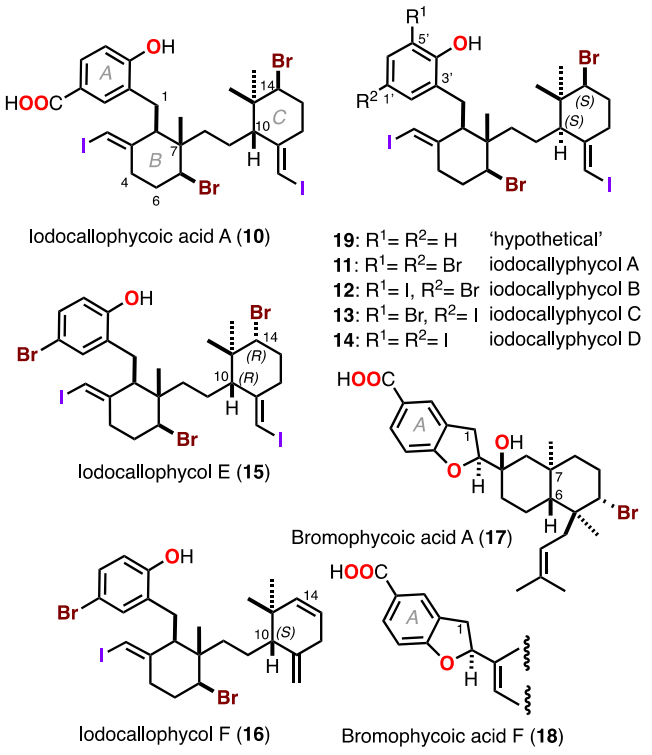

Figure 7. Iodinated *Callophycus* compounds **10**−**16**[13,14] and bromophycoic acids A (**17**)[10] and F (**18**).[13]

substantial contribution from an unexpected chromophore: asymmetric perturbation of the ring C iodovinyl group. It is known that $\sigma-\sigma^*$ UV−vis transitions of halogenated organic molecules become more red-shifted with the replacements H → Cl → −Br → I (reminding us why halogenated solvents are inappropriate for UV−vis and ECD measurements). It is possible that the iodovinyl chromophore is mediated by a 5p−π^* transition (forbidden), the transition energy of which is red-shifted to wavelengths closer to 260 nm. Support for this idea is found in ab initio calculations that show increasing stabilization of HOMO in halogenated ethenes with increasing nonbonding character, *X*(n,p), and halogen mass, *X* (periodic row = 3, 4, 5).[39,40]

The configuration 9β,23α for structures, as drawn (or 7β,24α or 6α,7β in some numbering schemes), is preserved throughout the series of halogenated *Callophycus* compounds (apparently, with the two exceptions, see below), suggesting uniform stereocontrol of the bromonium-initiated π-cyclization to form the carbocycles closest to the benzoate moiety. Exceptions are the benzofuran compounds, e.g., bromophycoic acid F (**17**), which appears to be enantiomorphic inversion of the *trans*-decalin configuration to 6β,7α[41] and **15**.[14]

The configurations of the callophycols and likely the callophycoic acids are likely set by conservative, independent biosynthetic pathways initiated by two bromonium-promoted π-cyclization cascades of opposite enantiofacial specificity. Further analysis may ultimately link the two putative pathways into a unified halonium-promoted cascade, but for now, it appears that two independent halogenation pathways are required to explain the stereochemical relationships within the *Callophycus* meroterpenes.

In order to evaluate the rotatory contributions of different halogenation motifs of ring A in **10**−**16**, the molar rotations of **10**−**17** were calculated (Table 3). In iodocallophycols A−E

Table 3. Calculated Molar Rotations $[M]$ from $[\alpha]_D$ to Estimated $[M_{X_1}]$ (See Text and Equation 3) of Iodocallophycols 11−16 and Related Compounds from *Callophycus*

entry	cmpd	#	MW	$[\alpha]_D$[a] (c, $CHCl_3$)	$[M]$	$[M_{X_1}]$
1	**10**	[b]	820.2	−56.6 (1.08)	−464	−860
2	**11**	A	934.0	−4.3 (0.25)	−40.2	−436
3	**12**	B	981.0	−53.9 (0.2)	−529	−925
4	**13**	C	981.0	−53.2 (0.06)	−529	−925
5	**14**	D	1028.0	−91.3 (0.10)	−939	−1335
6	**15**	E	855.1	−27.1 (0.17)[c]	−232	−628[d]
7	**15**	E	855.1	−27.1 (0.17)[c]	−232	+164[e]
8	**16**	F	648.3	−49.2 (0.12)	−182	
9	**17**	[f]	491.5	+29 (0.23)[c]	+142.5	
10	**18**	[g]	473.5	−696 (0.004)[c]	−3296	

[a]Recorded in $CHCl_3$. [b]Iodocallophycoic acid A. [c]Recorded in MeOH.[14] [d]Assuming (10*S*,14*S*). [e]Assuming (10*R*,14*R*). [f]Bromophycoic acid A.[10] [g]Bromophycoic acid F.[13]

(**11**−**15**), the bromo-iodo-vinylidenecyclohexane (ring C stereocluster), denoted as substructure Y_3 ($[M_{Y_3}]$) or $-Y_3$ ($[-M_{Y_3}]$), was designated the constant, and the rings A and B combination, containing the variably halogenated phenol group, were defined as X_1 (eq 3).

$$[M] = [M_{X_1}] + [M_{Y_3}] \quad (3)$$

The general trend that can be seen from Table 1 is more negative molar rotations (but increasing magnitudes) in moving from **11** to **15**, which follows the rising electron density around the aryl ring accompanying stepwise replacements of Br with I and reaches a minimum of $[M_{X_1}]$ −939 with the 2,4-diodophenol, iodocallophycol D (**15**). Conversely, the molar rotation obtained by the removal of Br from ring A of **11** [entry 6, iodocallophycol E (**15**)] becomes more negative, $[M]$ −232, correlating with the reduced magnitude of $[M_{X_1}]$. Rotatory strength is further diminished in iodocallophycol F (**16**) by lower $[M_{Y_3}]$ associated with eliminations of both halogens, such as HX, from ring C. Collectively, these phenomena are less related to electronic transitions (UV−vis or ECD; the π-donor effects of Br and I are weak) rather but more a consequence of changing refractive index.

We conclude that the contribution of $[M_{X_1}]$ to the overall molar rotation of the iodinated molecules must be significantly levorotatory; the signs of rotation are now uniformly negative compared to **3** and **4**, but not submissive at this time to precise quantitative deconvolution because $[\alpha]_D$ of suitable models, natural or synthetic, that simulate $[M_{Y_3}]$ are not yet available. Despite advances in the development of DFT functionals and basis sets that better deal with the spin−orbit effects of "heavy atoms", adjusted by "parametric corrections",[42] the heavily iodinated **10**−**15** still present formidable challenges for ab initio calculations. Caution must be applied in the interpretation of DFT calculations of NMR or chiroptical parameters. Nevertheless, a semiquantitative interpretation can be offered for the rotatory effects of substructures within iodinated *Callophycus* compounds as follows.

When plotted as a function of phenol ring halogen substitution (Figure 8), the molar rotations of **11**−**15** show a linear trend: progressive replacements at the 2,4-positions by

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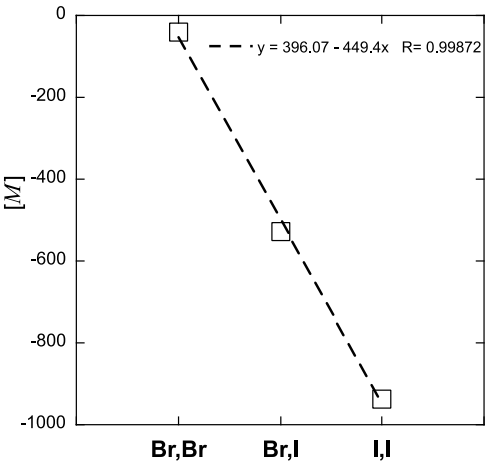

Figure 8. Plot of 2,4-dihalogen substitution of phenol ring in **15**, **12**, and **14** versus molar rotation, [*M*].

halogen atoms of increasing mass make the molar rotation more negative in a linear monotonically decreasing manner. Extrapolation of the line of fit in Figure 8, to the point where $[M_{X_1}] = 0$, we arrive at the ordinate intercept, i.e., a hypothetical achiral substructure X_1 and a reliable estimate of $[M_{Y_3}]$ +396; an appreciably dextrorotatory contribution by the ring C stereocluster in **11**−**15**, opposite to that of $[M_{X_1}]$, is now revealed. Continuing the extrapolation, it is estimated that the hypothetical structure, **18**, where all aryl halogens are replaced by H, has $[M_{X_1}] \sim +50$.

These estimates may be used to test the stereostructure of iodocallophycol E (**15**), which was proposed to have the 10*R*,14*R* configuration in ring C.[14] If **15** were 10*R*,14*R*, opposite of the corresponding stereocenters in **11**−**14**, the ring C contribution to the molar rotation would be the negative of that determined above, $[M_{Y_3}]$ −396. Yet, we find, instead, [*M*] of **15** (Table 3, entry 6 and Figure 8) falls squarely on the line of best fit (linear regression, negative slope, $y = -449.4$, $R = 0.999$). Once again, this can be put to a conditional test of $[M_X]$ values returned from inputted values of [*M*] for **15** and the foregoing estimates of $[M_{Y_3}]$ and $[-M_{Y_3}]$ (Table 4). Entry 1 shows a

Table 4. Conditional Test of Molar Rotation Contributions for the Two Possible Configurations of 15 (10*S*,14*S*) and (10*R*,14*R*)[a]

Entry		Config.	X, Y_1	$X, -Y_1$
1[a]	[*M*x]	(10*S*,14*S*)	−628	+164
2	*ent*-[*M*x]	(10*R*,14*R*)	+628	−164

[a]See eqs 1 and 2 and Tables 1 and 2 for definitions of terms.

levorotatory $[M_{X_1}]$ −628 for (10*S*,14*S*)-**15**. In contrast, the wildly divergent value $[M_{X_1}]$ +164 for (10*R*,14*R*)-**15** is in opposition to the uniformly negative values calculated for **10**−**14** (Table 3), providing a compelling case for reassignment of **15** to the former "normal" configuration.

The outsized contribution of the dihalophenol ring to molar rotations in iodocallophycols can now be fully appreciated by examining the X_1 and Y_3 stereoclusters from a side-by-side perspective (Figure 9). Although the configurations of the pair stereocenters C-2/C-10 and C-6/C-14 of the two iodovinyli-

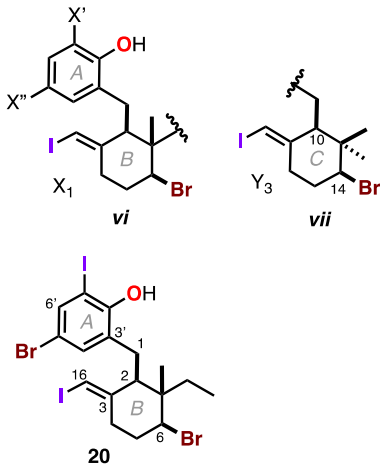

Figure 9. Side-by-side comparison of X_1 and Y_3 stereoclusters, (**vi** and **vii**, respectively) in iodocallophycols A−E. X′ and X″ are variable substituents: halogen or H.

dene-cyclohexane rings embedded in rings B and C are concordant, the heavily halogenated ring A reverses the sign of the molar rotation contribution of X_1. This is not unlike the sign-inverting effects seen in Octant Rule analyses of the ECD n−π* transition in chiral cyclohexanones when significant electron density occupies the "forward" four octants in front of the C═O bond.[43,44] This influence of local asymmetry on the weak chromophore C═C−I can be better appreciated from the geometry of molecular models of energy- and geometry-minimized structures (DFT at the B3LYP/SVP level of theory) of "hypothetical diastereomers" of **10** reported by Kubanek and co-workers (see Figure 2 of the Lavoie et al.[13]), which shows close contacts between the aryl ring B and the *pseudo*-equatorial phenylmethyl substituent bearing ring A.

In order to better understand the stereochemical properties of iodocallophycols, the optimized geometry and energy (E_{rel}) of model compound **20** were calculated (MMFF followed by DFT (ωB97X-D, basis set 6-31G*, nonpolar solvent)). The latter compound models **12** and is simplified over **10** by replacement of the COOH group with Br, and the ethylene-ring C substructure is replaced with $-CH_2CH_3$ (Figure 9). The C-2, C-6, and C-7 substituents in **viii**, the most stable conformer of **12**, have *ax* orientations (Figure 9a): only in **ix** (E_{rel} = 4.33 kJ mol^{-1}), and higher E_{rel} conformers are the balance of 1,3-diaxial steric repulsion and $A_{1,3}$ strain with all-*equ* substituents relieved by a ring flip.[45] Conformer **viii** (Figure 10a) projects the aryl ring and the C═C−I group in almost parallel planes (Figure 10a, θ = +21.9°), but this angle becomes more skew (Figure 10b, θ = −69.5°) in **ix**. Interatomic contacts (e.g., *d*, see Figure 10) of each are similar to those of **10**:[13] the aryl Br is *endo* to the iodovinyl group and *exo* to the HO group.

The calculated structures of **20** support the qualitative observation that varying the electron density above the plane of the iodovinyl group in ring A is responsible for modulating the experimental [*M*] in **10**−**16**, but the Cotton effect (CE) in the experimental ECD spectrum of natural (2*S*,6*S*,7*S*,10*S*,14*S*)-**10** (λ 255 nm, $\Delta\varepsilon$ +5.0) is largely determined by the asymmetry around the iodovinyl group of ring C, as shown by Kubanek and co-workers (inversion of C-10 and C-14 essentially inverts the sign of the CE as shown by TDDFT calculations).[13] Further,

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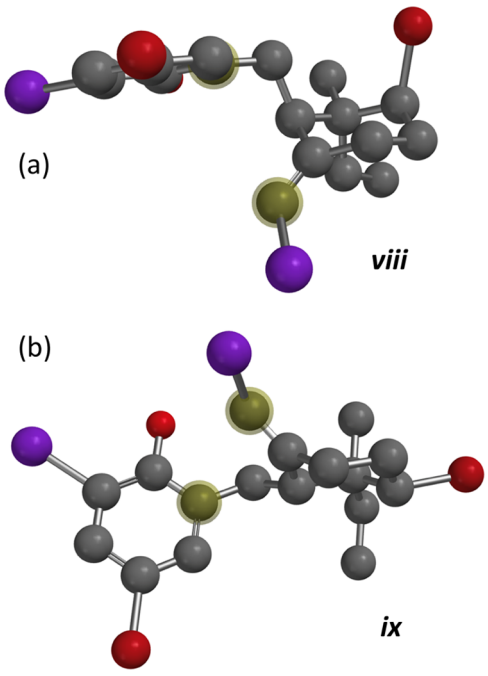

Figure 10. Energy minimized 4′-bromo-2′-iodocallophycol model **20** (replacement of ring C system of **10**−**16** with CH_2CH_3), % Boltzmann populations and distances, *d*, from C-3′ to C-16 (highlighted). (a) Lowest energy conformer, **viii** (E_{rel} 0.00 kcal mol^{-1}, 74.8%, 3.47 Å) and (b) second lowest energy conformer, **ix** (E_{rel} 4.33 kcal mol^{-1}, 13.0%, 3.32 Å).

when the ring A stereocenters were inverted with respect to naturally configured ring C, the CE of the resultant diastereomer (2*S*,6*S*,7*S*,10*S*,14*S*)-**10**, increased in magnitude by ∼4×;[13] another manifestation of optical superposition.

CONCLUSIONS

We have demonstrated a simple chiroptical analysis of terminal vicinal bromochloro compounds exploiting molar rotations and their additivity that follows van't Hoff's principle of optical superposition. A conditional test was devised to unambiguously assign absolute configuration in chiral VBCs, including the stereostructures of callophycols A (**3**) and B (**4**), and used to derive the previously unassigned remote C-16 stereocenter. Regioisomeric **3** and **4** have opposite configurations in their VBC substructures, 16*S* and 16*R*, respectively, suggesting that these natural products are candidates for a biosynthetic dyotropic rearrangement proceeding with high stereofidelity. The conditional test is appealing for its simplicity and its applicability to dozens of known VBCs. It should find use in assignments of new compounds yet to be discovered. Interpretation of the stereostructures of **3** and **4**, the bromophycolides A and B (**5a**,**b**), and callophycoic acids A, B, C (**9**), D, and E suggest a unifying biosynthetic pathway, starting with a 16*S* configured VBC similar to that seen in **3** and **4**, related through dyotropic rearrangement, and bifurcating from an *R*-configured bromonium ion. VBC-mediated bromonium ion formation leads to macrolide rings of **5a**,**5b** with stereoretention and inversion, respectively, and stereoretention within the last carbocyclic ring of callophycoic acids. Monotonic linear trends in molar rotations, $[M]$, were observed in the highly iodinated *Callophycus* natural products, and a compelling case was made, based on $[M]$ deconvolution for reassignment of **15** to the "normal" configuration (10*S*,14*S*).

EXPERIMENTAL SECTION

Molar Rotation Calculations. Molar rotations of compounds were calculated using the literature-reported values of $[\alpha]_D$ from the formula $[M] = ([\alpha]_D \times MW)/100$, where MW is the molecular mass. Where known, $[\alpha]_D$ and derived $[M]$ values of synthetic compounds are corrected for % ee (see the Supporting Information, S-2).

Molecular Model Calculations of 20. The optimized geometry and energy of the 10 lowest energy conformers of **20** were calculated using MMFF, and the resultant conformers were ordered according to the Boltzmann distribution. The conformers were optimized for energy using DFT (ωB97X-D, basis set 6-31G*, nonpolar solvent), and the lowest two DFT-optimized conformers, accounting for ∼90% of the population, are depicted in Figure 10. See the Supporting Information for the *Z*-coordinates (PDB format).

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c00905.

Structures and calculated molar rotations, $[M]$, for **3**, **4**, and nine vicinal bromochloro compounds (VBCs, Figure S1), and *Z*-coordinates for model compound **20** (Table S1) (PDF)

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Notes

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REFERENCES

(1) Gribble, G. W. Naturally Occurring Organohalogen Compounds. In *Progress in the Chemistry of Organic Natural Products*; Kinghorn, D.; Falk, H.; Gibbons, S.; Asakawa, Y.; Liu, J.-K.; Dirsch, V. M., Eds.; Springer, 2023; Vol. *121*.

(2) Gribble, G. W. A Survey of Recently Discovered Naturally Occurring Organohalogen Compounds. *J. Nat. Prod.* **2024**, *87*, 1285−1305.

(3) Burreson, J. B.; Woolard, F. X.; Moore, R. E. *Chem. Lett.* **1975**, *4*, 1111−1114.

(4) Fuller, R. W.; Cardellina, J. H., II; Kato, Y.; Brinen, L. S.; Brinen, L. S.; Clardy, J.; Clardy, J.; Snader, K. M.; Snader, K. M.; Boyd, M. R. A Pentahalogenated Monoterpene from the Red Alga *Portieria hornemannii* Produces a Novel Cytotoxicity Profile against a Diverse

Panel of Human Tumor Cell Lines. *J. Med. Chem.* **1992**, *35*, 3007−3011.
(5) Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Boyd, M. Feasibility of a high-flux anticancer drug screen utilizing a diverse panel of human tumor cell lines in culture. *J. Natl. Cancer Inst.* **1991**, *83*, 757−766.
(6) Fuller, R. W.; Cardellina, J. H., III; Jurek, J.; Scheuer, P. J.; Alvarado-Lindner, B.; McGuire, M.; Gray, G. N.; Rios Steiner, J.; Clardy, J.; Menez, E.; Shoemaker, R. H.; Newman, D. J.; Snader, K. M.; Boyd, M. R. Isolation and Structure/Activity Features of Halomon-Related Antitumor Monoterpenes from the Red Alga *Portieria hornemannii*. *J. Med. Chem.* **1994**, *37*, 4407−4411.
(7) Morinaka, B. I.; Molinski, T. F.; Mollenyne, A. a Long-Chain Chlorodibromohydrin Amide from the Sponge *Spirastrella mollis*. *Org. Lett.* **2011**, *13*, 6338−6341.
(8) Lane, A. L.; Stout, E. P.; Hay, M. E.; Prusak, A. C.; Hardcastle, K. I.; Fairchild, C. R.; Franzblau, S. G.; Roch, K. L.; Prudhomme, J.; Aalbersberg, W.; Kubanek, J. Callophycoic Acids and Callophycols from the Fijian Red Alga *Callophycus serratus*. *J. Org. Chem.* **2007**, *72*, 7343−7351.
(9) Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Hardcastle, K. I.; Fairchild, C. R.; Aalbersberg, W.; Raventos-Suarez, C.; Hay, M. E. Antineoplastic Diterpene−Benzoate Macrolides from the Fijian Red Alga *Callophycus serratus*. *Org. Lett.* **2005**, *7*, 5261−5264.
(10) Teasdale, M. E.; Shearer, T. L.; Engel, S.; Alexander, T. S.; Fairchild, C. R.; Prudhomme, J.; Torres, M.; Le Roch, K.; Aalbersberg, W.; Hay, M. E.; Kubanek, J. Bromophycoic Acids: Bioactive Natural Products from a Fijian Red Alga *Callophycus* sp. *J. Org. Chem.* **2012**, *77*, 8000−8006.
(11) Lane, A. L.; Stout, E. P.; Lin, A.-S.; Prudhomme, J.; Roch, K. L.; Fairchild, C. R.; Franzblau, S. G.; Hay, M. E.; Aalbersberg, W.; Kubanek, J. Antimalarial Bromophycolides J-Q from the Fijian Red Alga *Callophycus serratus*. *J. Org. Chem.* **2009**, *74*, 2736−2742.
(12) Lin, A. S.; Stout, E. P.; Prudhomme, J.; Le Roch, K.; Fairchild, C. R.; Franzblau, S. G.; Aalbersberg, W.; Hay, M. E.; Kubanek, J. Bioactive Bromophycolides R-U from the Fijian Red Alga *Callophycus serratus*. *J. Nat. Prod.* **2010**, *73*, 275−278.
(13) Lavoie, S.; Brumley, D.; Alexander, T. S.; Jasmin, C.; Carranza, F. A.; Nelson, K.; Quave, C. L.; Kubanek, J. Iodinated Meroditerpenes from a Red Alga *Callophycus* sp. *J. Org. Chem.* **2017**, *82*, 4160−4169.
(14) Woolner, V. H.; Gordon, R. M. A.; Miller, J. H.; Lein, M.; Northcote, P. T.; Keyzers, R. A. Halogenated meroditerpenoids from a South Pacific collection of the red alga *Callophycus serratus*. *J. Nat. Prod.* **2018**, *81*, 2446−2454.
(15) Negoro, T.; Ikeda, Y. Bromochlorination of Alkenes with Dichlorobromate (−1) Ion. I. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2111−2115.
(16) Sotokawa, T.; Noda, T.; Pi, S.; Hirama, M. A Three-Step Synthesis of Halomon. *Angew. Chem., Int. Ed.* **2000**, *39*, 3430−3432.
(17) Bucher, C.; Deans, R. M.; Burns, N. Z. Highly Selective Synthesis of Halomon, Plocamenone, and Isoplocamenone. *J. Am. Chem. Soc.* **2015**, *137*, 12784−12787.
(18) Grob, C. A.; Winstein, S. Mechanismus der Mutarotation von 5,6-Dibromcholestan. *Helv. Chim. Acta* **1952**, *35*, 782−802.
(19) Barton, D. H. R.; Head, A. J. 196. Long-range effects in alicyclic systems. Part 1. The rates of rearrangement of some steroidal dibromides. *J. Chem. Soc.* **1956**, 932−937.
(20) Alt, G. H.; Barton, D. H. R. Some conformational aspects of neighbouring-group participation. *J. Chem. Soc.* **1954**, 4284−4294.
(21) Reetz, M. T. Dyotropic Rearrangements, a New Class of Orbital-Symmetry Controlled Reactions. Type I. *Angew. Chem., Int. Ed.* **1972**, *11*, 129−130.
(22) Reetz, M. T. Dyotropic Rearrangements, a New Class of Orbital-Symmetry Controlled Reactions. Type II. *Angew. Chem., Int. Ed.* **1972**, *11*, 130−131.
(23) To be fair, as we had previously conjectured,[7] the property in question is 'dyotropase activity': it need not necessarily be conferred by a separate and dedicated enzyme. DR may result within same active site of the haloperoxidase that carries out the elemental steps of vicinal dihalogenation of alkenes, such as seen in the biosynthesis of VBC compounds. It is worth remembering that the forgoing is speculation: to date, nothing is known of the poly halogenating enzymes that deliver **1a**,**b** and other highly halogenated monoterpenes and lipids.
(24) van't Hoff, J. H. *Die Lagerung der Atome im Raume*; Vieweg: Braunschweig, 1908; Chapter 8, pp 95−97.
(25) Hill, H. A. A Test of van't Hoff's Principle of Optical Superposition. PhD Thesis, Department of Chemistry, Massachusetts Institute of Technology, 1942.
(26) Wolinsky, L. E.; Faulkner, D. J. A Biomimetic Approach to the Synthesis of *Laurencia* Metabolites. Synthesis of 10-Bromo-α-chamigrene. *J. Org. Chem.* **1976**, *41*, 597−600.
(27) Faulkner, D. J. Biomimetic Syntheses of Marine Natural Products. *Pure Appl. Chem.* **1976**, *48*, 25−28.
(28) Higashibayashi, S.; Czechtizky, W.; Kobayashi, Y.; Kishi, Y. Universal NMR Database for contiguous polyols. *J. Am. Chem. Soc.* **2003**, *125*, 14379−14393.
(29) One may debate whether the ethylene group in X-CH_2CH_2-Y is sufficiently 'insulating' of distal asymmetries and truly renders the intramolecular interactions of X and Y outside the 'first sphere' and their contributions negligible to global optical rotation. Naturally, it is expected that asymmetric groups with high rotatory strength may interact beyond the first sphere. At a first approximation, with halocarbons lacking strong chromophores, these approximations seem to be upheld; a contention supported by the self-consistency of results in this report.
(30) Foster, M. P.; Concepción, G. P.; Caraan, G. B.; Ireland, C. M. Bistratamides C and D. Two New Oxazole-Containing Cyclic Hexapeptidee Isolated from a Philippine *Lissoclinum bistratum* Ascidian. *J. Org. Chem.* **1992**, *57*, 6671−6675.
(31) Biard, J.-F.; Roussakis, C.; Kornprobst, J.-M.; Gouiffes-Barbin, D.; Verbist, J.-F.; Cotelle, P.; Foster, M. P.; Ireland, C. M.; Debitus, C. Bistramides A, B, C, D, and K: A New Class of Bioactive Cyclic Polyethers from *Lissoclinum bistratum*. *J. Nat. Prod.* **1994**, *57*, 1336−1345.
(32) Wipf, P.; Uto, Y.; Yoshimura, S. Total synthesis of a stereoisomer of bistramide C and assignment and configuration of the natural product. *Chem. - Eur. J.* **2002**, *8*, 1670−1681.
(33) Wipf, P.; Hopkins, T. D. Total synthesis and structure validation of (+)-bistramide C. *Chem. Commun.* **2005**, 3421−3423.
(34) Seidl, F. J.; Burns, N. Z. Selective bromochlorination of a homoallylic alcohol for the total synthesis of (−)-anverene. *Beilstein J. Org. Chem.* **2016**, *12*, 1361−1365.
(35) Burckle, A. J.; Gál, B.; Seidl, F. J.; Vasilev, V. H.; Burns, N. Z. Enantiospecific Solvolytic Functionalization of Bromochlorides. *J. Am. Chem. Soc.* **2017**, *139*, 13562−13569.
(36) Technically, callophycoic acid C (**9**) (and its congeners D-E) can be viewed as a nonvicinal bromohydrin: the formal product of 1,4-addition of HO-Br across a diene π-system.
(37) Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Fairchild, C. R.; Aalbersberg, W.; Hay, M. E. Bromophycolides C-I from the Fijian Red Alga *Callophycus serratus*. *J. Nat. Prod.* **2006**, *69*, 731−735.
(38) Exceptions are the ring-contracted cyclopentene-containing *Callophycus* compounds (e.g., debromophycolide A[9]) where the C-7 configurations were not assigned.
(39) Zou, P.; Strecker, K. E.; Ramirez-Serrano, J.; Jusinski, L. E.; Taatjesa, C. A.; Osborn, D. D. Ultraviolet photodissociation of vinyl iodide: understanding the halogen dependence of photodissociation mechanisms in vinyl halides. *Phys. Chem. Chem. Phys.* **2008**, *10*, 713−728.
(40) A weak (forbidden) UV−vis transition was observed in the gas phase of I-CH=CH_2.[40]
(41) It is also noteworthy that iodocallophycol E (**15**) was reported with inverted stereochemistry, this time in ring C. The diepimeric 10*R*,14*R* configuration assigned by Keyzers and co-workers,[14] is the reverse of the 'normal' 10*S*,14*S* ring C configuration found in other *Callophycus* compounds.

https://doi.org/10.1021/acs.joc.4c00905
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(42) Kutateladze, A. G.; Reddy, D. S. High-Throughput in Silico Structure Validation and Revision of Halogenated Natural Products Is Enabled by Parametric Corrections to DFT-Computed ^{13}C NMR Chemical Shifts and Spin−Spin Coupling Constants. *J. Org. Chem.* **2017**, *82*, 3368−3381.
(43) C Djerassi, C. *Optical Rotatory Dispersion*; McGraw-Hill: New York, 1960; Chapter 13.
(44) Lightner, D. A.; van Toan, V. The Octant Rule XX. Synthesis and Circular Dichroism of (1*S*,5*S*)-Dimethyladamantan-2-one − Predicted to Have Zero Cotton Effect. *Tetrahedron* **1987**, *43*, 4905−4916.
(45) Conversely, the DFT-minimized model of **10** (Kubanek and co-workers)[13] shows only all *eq* substituents, suggestive of an as-yet unexplained influence of the COOH group.

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