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Chemodivergent, Tunable, and Selective Iodine(III)-Mediated Bromo-Functionalizations of Polyprenoids

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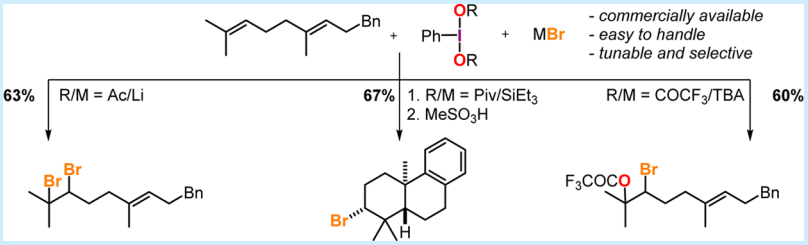
Supporting Information



ABSTRACT: Mild oxidation of bromides by iodine(III) reagents generated active electrophilic bromination species that were reacted with polyprenoids. By simple and minor variations of an I(III)/Br combination, the reactivity could be selectively steered toward dibromination, oxybromination, or bromocyclization, giving access to a wide array of brominated motifs.

Brominated terpenoids of marine origin constitute a particularly wide class of natural products that exhibit a vast array of structural diversity[1] and potential therapeutic applications.[2] A myriad of motifs, arising from diverse biosynthetic pathways,[3] can be found in different families and sometimes in the same molecule. For example, by just considering the brominated moieties of the bromophycolide A[4] macrocycle (**1**, Figure 1), fragments arising from a

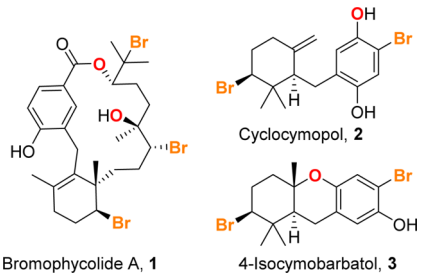


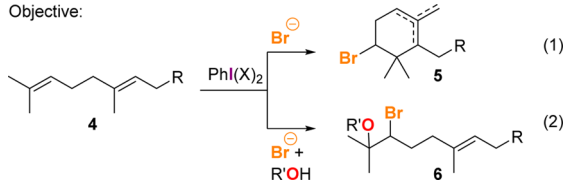
Figure 1. Examples of brominated terpenoids of marine origin.

carbobromination, a hydroxybromination, and an acyloxybromination (with the opposite regiochemistry) of a geranyl−geranyl chain can be delineated. A carbobromination accounts for the formation of cyclocymopol **2**,[5] but in this case the double bond lies outside of the ring. Isocymobarbatol **3**[6] stems from the same linear precursor but through a formal cascade cyclization, resulting in a tricyclic scaffold. This variability could be explained by the intermediacy of one or several halogenating enzymes,[3] but raises complex chemo-, regio-, and stereoselectivity issues, which remain challenging for organic chemists. One way to address this challenge is to design specific reagents for one transformation, as shown by Snyder with the development of a bromocyclization specific BDSB reagent.[7,8]

For our part we thought that it would be highly desirable to design a general strategy that would demand only limited modifications of the *modus operandi* to completely deviate the reactivity in one or another chemical direction. Based on our previous experience[9] with iodine(III)-mediated bromination reactions,[10] we believed that when generating the active bromination species by *in situ* oxidation of a bromide by a hypervalent iodine(III) species,[11] several parameters would be easily tunable so as to govern the selectivity of the reaction. Thus, running the reaction in a nonparticipating solvent in the absence of an external nucleophile should favor bromocyclization[9d] toward bromocyclohexenyl **5** (Scheme 1, eq 1), while adding an alcohol to the reaction mixture would trigger an oxybromination[9a] toward alkyl-bromohydrine **6** (Scheme 1, eq 2).

Initial experiments were performed on geranyl acetate **4a** using a combination of (diacetoxyiodo)benzene (DIB) and lithium bromide in acetonitrile, which led to dibromo derivative **7a** in 91% yield (Scheme 2). Running the same reaction in ethanol or

Scheme 1. Chemoselective Iodine(III)-Mediated Bromination of a Geranyl Derivative



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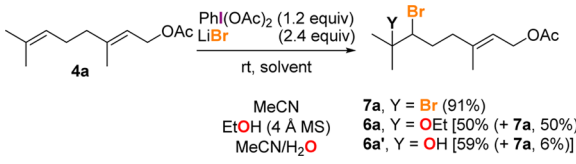
Scheme 2. Solvent Effect in the DIB-Mediated Bromination of Geranyl Acetate

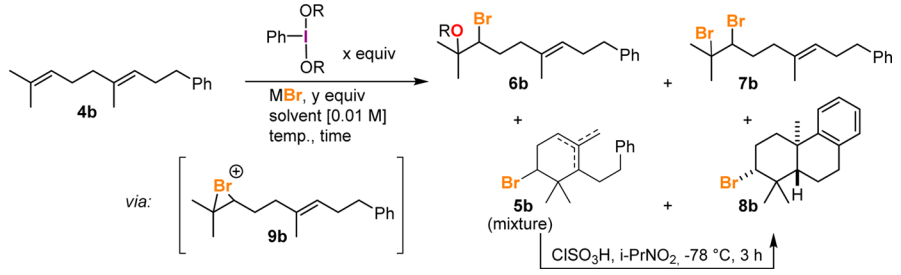


in a water/acetonitrile mixture triggered the oxybromination process yielding ethoxy and hydroxy adducts **6a** and **6a′**, respectively, with satisfying yields. This reactivity switch validated the second half of our premise, but despite extensive screening,[12] geranyl acetate, because of the deactivation of the internal double bond, seemed unsuitable to probe the triggering of the cyclization process.

In order to circumvent this hurdle, we decided to focus our attention on the reactivity of the electron-rich homogeranylbenzene **4b** (Table 1), which has been shown to cyclize more readily toward mono- (**5b**) and/or tricyclic (**8b**) adducts under a variety of conditions.[7,8]

We therefore screened numerous parameters[12] in order to generate the initial bromonium intermediate **9b** and selectively orientate its evolutions toward one of the many possible adducts (**5**−**8**, allylbromide **10b** and cyclopentene **11b**).[12] As with geranyl acetate, the combination of DIB and LiBr in MeCN mainly led to dibromo compound **7b** in 63% yield (Table 1, entry 1).[12] Halving the amount of bromide and adding it slowly as the last reagent in order to prevent dibromination only led to a decrease in yield, without changing the reaction course (Table 1, entry 2). However, using this protocol and replacing the DIB by its trifluoroacetoxy analog (PIFA) diverted the reactivity toward bromocyclization giving **5b** (as a mixture of isomers) and tricycle **8b** in a 39% cumulated yield (Table 1, entry 3). This result could be further improved by using the more soluble TMSBr to give 41% of **5b** and 15% of **8b** (Table 1, entry 4). Treatment of the mixture of brominated cyclohexenes **5b** with chlorosulfonic acid in 2-nitropropane at −78 °C[7,8] to give **8b** led to a cumulated yield of tricyclic adduct of 46%. Increasing the addition time (Table 1, entry 5) or exchanging trimethylsilyl bromide for triethylsilyl bromide (Table 1, entry 6) mostly led to complex mixtures of adducts, including allyl bromide **10b** and cyclopentene **11b**.[12] When alkylammonium bromide salts were used, the acyloxybromination pathway was also observed (Table 1, entries 7 and 8), with **6b** becoming the major product when tetrabutylammonium bromide was employed (Table 1, entry 8). This could be further improved by slightly increasing the concentration and the addition rate, to obtain 60% of **6b** (Table 1, entry 9). Running the reaction in nitromethane with TESBr steered the reactivity back toward cyclization (Table 1, entry 10), and using the bulkier bis(*tert*-butylcarbonyloxy)iodobenzene completely suppressed the oxybromination pathway (Table 1, entry 11). In order to perform the reaction at a lower temperature (− 78 °C), nitroethane was employed instead of nitromethane. This prevented the formation of **10b**, and directly submitting the crude product to $ClSO_3H$ treatment gave **8b** in 54% yield over two steps (Table 1, entry 12). Eventually, performing the same sequence with $MeSO_3H$ in the second step improved the yield up

Table 1. Optimization of the Iodine(III)-Mediated Dibromination, Oxybromination, and Bromocyclization of Homogeranylbenzene 4b[a]



entry	R (x equiv)	M (y equiv)	solvent	[M][b]	temp	addition time	**5b**, yield %[c]	**6b**, yield %[c]	**7b**, yield %[c]	**8b**, yield %[c]
1	Ac (1.2)	Li (2.4)	MeCN	0.05	0 °C	5 min[d]	-	-	**63**	-
2	Ac (1.1)	**Li (1.1)**	MeCN	0.02	0 °C	10 min	-	-	46	-
3	**C(O)CF$_3$ (1.2)**	Li (1.1)	MeCN	0.01	0 °C	30 min	17	-	-[e]	22
4	C(O)CF$_3$ (1.2)	**Me$_3$Si (1.1)**	MeCN	0.01	0 °C	20 min	41	-	Traces[f]	15(46)
5	C(O)CF$_3$ (1.2)	**Me$_3$Si (1.1)**	MeCN	0.01	0 °C	**30 min**	16	-	3[f]	19[g]
6	C(O)CF$_3$ (1.2	**Et$_3$Si (1.1)**	MeCN	0.01	0 °C	20 min	33	-	-[f]	15[g]
7	C(O)CF$_3$ (1.2)	**Et$_3$HN (1.1)**	MeCN	0.01	0 °C	10 min	15	6	-[f]	20
8	C(O)CF$_3$ (1.2)	**Bu$_4$N (1.1)**	MeCN	0.01	0 °C	10 min	6	44	-[f]	8
9	C(O)CF$_3$ (1.2)	Bu$_4$N (1.1)	MeCN	**0.04**	0 °C	**5 min**	-	**60**	-	-
10	C(O)CF$_3$ (1.2)	Et$_3$Si (1.1)	**MeNO$_2$**	**0.01**	0 °C	10 min	27	4	-[f]	20
11	**C(O)CMe$_3$ (1.2)**	Et$_3$Si (1.1)	MeNO$_2$	0.01	0 °C	10 min	24	-	-[f]	24
12	C(O)CMe$_3$ (1.2)	Et$_3$Si (1.1)	**EtNO$_2$**	**0.04**	**-78 °C**	10 min	N/A[h]	-	-	(54)
13	C(O)CMe$_3$ (1.2)	Et$_3$Si (1.1)	EtNO$_2$	0.04	-78 °C	10 min	N/A[h]	-	-	(**67**)[i]

[a]A solution of MBr [2C] was slowly added to a solution of **4b** [2C] containing the iodine(III) reagent. [b]Resulting concentration after addition. [c]Isolated yields; for **8b** overall yield after recyclization of **5b** with $ClSO_3H$ is given in parentheses. [d]Direct addition of LiBr and with 4 Å MS. [e]And 7% of **10b**. [f]And traces of **10b**. [g]And 8% of **11b**. [h]The crude reaction mixture (5:2:1 ratio of tetra-, tri-, disubstituted olefins) was recyclized without purification. [i]Recyclization with $MeSO_3H$, dr = 6:1.

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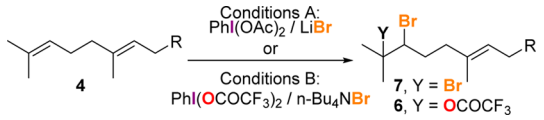
Org. Lett. XXXX, XXX, XXX−XXX

to 67% in a 6:1 diastereomeric ratio (Table 1, entry 13). This thorough optimization helped define three sets of conditions to selectively access dibromo-, oxybromo-, and cyclobromo-derivatives. First, the scope of the former two processes was evaluated.

In addition to the above-mentioned results on geranyl acetate **4a** and homogeranylbenzene **4b**, the combination of DIB and LiBr selectively triggered the dibromination of *o*-homogeranylanisole **4c** and geranylbenzene **4d** to give **7a−d** in good to excellent yields (Table 2, entries 1−4). The same protocol could

Table 2. Scope of the Dibromination and the Trifluoroacetoxybromination



entry	4, R	7, yield %[a]	6, yield %[b]
1	**4a**, OAc	91	77
2	**4b**, Bn	63	60
3	**4c**, *o*-MeOBn	52	56
4	**4d**, Ph	55	64
5	**4**, OH	63	57
6	**4f**, NHC(NZ)NHZ	52[c]	25[d]

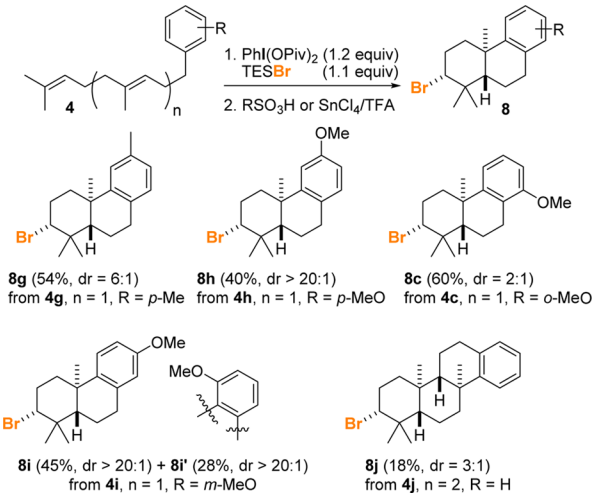
[a]Isolated yields for conditions A: $PhI(OAc)_2$ (1.2 equiv), LiBr (2.4 equiv), 4 Å MS in MeCN, at 0 °C for 5 min. [b]Isolated yields for conditions B: $PhI(OCOCF_3)_2$ (1.2 equiv) n-Bu_4NBr (2.4 equiv) in MeCN, at 0 °C for 5 min. [c]At−78 °C, using TESBr instead of LiBr. [d]At−78 °C, with 13% of **6f** and 31% of **12**.

be applied to geraniol **4e** to give **7e** in 63% yield without any detectable oxidation of the free alcohol (Table 2, entry 5). Finally, the more challenging bis(benzyloxycarbamate)-guanidine **4f** could be selectively dibrominated to yield **7f** by using a reverse addition protocol at −78 °C (Table 2, entry 6). The same substrates were also submitted to the PIFA/n-Bu_4NBr combination to give the α-bromo trifluoroacetyl adducts **6**. Geranyl acetate led to **6a″** and geraniol to **6e** in 77% and 57% yield, respectively (Table 2, entries 1 and 5). In addition to **4b**, the other aryl derivatives **4c** and **4d** reacted equally well to give the oxybrominated adducts in 56% and 64% yield (Table 2, entries 3 and 4). Only guanidine **4f** reacted sluggishly to yield the desired trifluoroacetoxy adduct **6f** in only 25% yield (Table 2, entry 6) along with 13% of **7f** and 31% of cyclic guanidine **12** (see Scheme 5). Finally, it was demonstrated that selective cleavage of the trifluoroacetoxy group of **6b** could be achieved with $NaBH_4$ to give the corresponding bromohydrine in 79% yield.[12]

We then turned our attention toward the third protocol and studied the cyclization of several homogeranyl and geranyl derivatives. First, homogeranylarenes were reacted under the optimized conditions, followed by treatment with sulfonic acid or with tin(IV) chloride, to provide the corresponding tricycles (Scheme 3). *Para*-toluene **4g**, *para*-anisole **4h**, and *ortho*-anisole **4c** derivatives led to the desired bromo-octahydrophenanthrenes **8g**, **8h**, and **8c** with 40% to 60% yields and moderate to good diastereoselectivities.

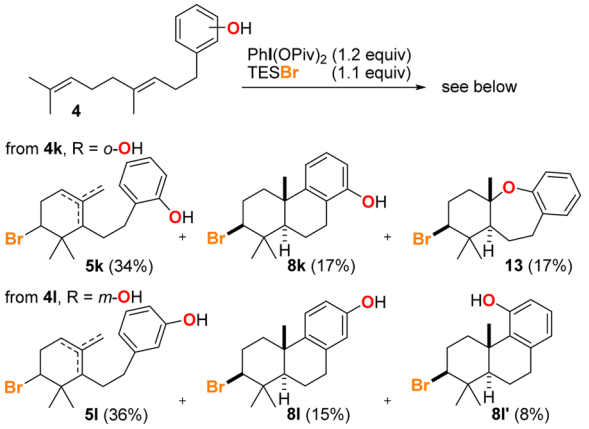
The reaction proceeded even better with *meta*-anisyl substrate **4i**, although the two adducts arising from *para* and *ortho* addition (**8i** + **8i′** = 73% yield) were formed. Finally, homofarnesylbenzene **4j** was reacted to give bromotetracycle **8j** in a low but satisfying yield, considering that one C−Br and three C−C bonds are formed in the sequence.

Scheme 3. Bromocyclization of Homogeranyl- and Homofarnesylarenes



In the case of phenolic homogeranyl derivatives, $PhI(OPiv)_2$-mediated bromocyclization gave a good (59% to 68%) overall yield of bromo-cyclized products,[13] the distribution of which varied depending on the initial substitution pattern (Scheme 4).

Scheme 4. Bromocyclization of Homogeranylphenols



Starting from *ortho*-phenol **4k**, in addition to the monocyclic cyclohexenes **5k** and the expected tricycle **8k**, compound **13** embedding a seven-membered ring was also isolated.[14] For *meta*-phenol **4l**, the cyclohexenes **5l** were obtained in 36% yield and the two brominated polycycles arising from *para* and *ortho* addition (**8l** + **8l′** = 23% yield) were also formed.

Finally, the behavior of geranyl compounds was explored (Scheme 5). Geranyl-benzene **4d** led to bromocyclohexenes **5d** in 43% yield as a mixture of *endo*/*exo* adducts. The analogous cyclohexenes **5m** were obtained in slightly higher yield (51%) from *o*-geranylanisole **4m** along with 24% of bromo-hexahydroxanthene **14** arising from a cascade cyclization and concomitant loss of a methyl group.

As could be expected, this isocymobarbatol-like adduct became the major product when *o*-geranylphenol **4n** was subjected to the $PhI(OPiv)_2$/TESBr combination. 3-Bromochromane **15**, resulting from a phenoxybromination of the internal double bond, was also observed as a minor adduct. This change in chemoselectivity might hint at an active participation of the heteroatom in the cyclization process, presumably via

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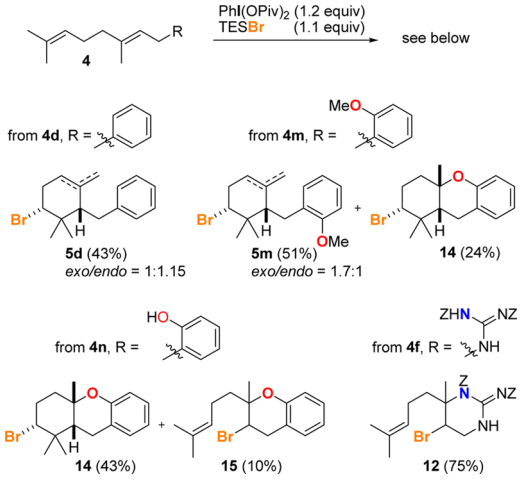
Scheme 5. Bromocyclization of Geranyl Derivatives



initial ligand exchange between the phenol and the ester on the hypervalent iodine center, followed by oxy-halogenation of the proximal double bond. This was further exemplified by the reaction of guanidine **4f** which smoothly led to **12** in 75% yield. Indeed, it is the only substrate that we studied for which the reaction mainly occurred on the internal double bond.

Overall we have shown that by using a combination of a (bisacyloxy)iodobenzene and a bromide source, three different electrophilic brominations of terpenoids with different outcomes could be triggered. Simple adjustments in the nature of the reagents (all commercially available) and the procedure (temperature, rate, and order of addition) could steer the reactivity toward dibromination, oxy-bromination, or bromocyclization, including cascade processes. This strategy grants access to various motifs that can be found in several families of natural products. Studies in this direction as well as the implementation of this methodology for other halides are currently being pursued.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02125.

Comprehensive optimization studies, experimental procedures, analytical data, and copies of NMR spectra for all new compounds (PDF)
Crystallographic data for **5d** (CIF)
Crystallographic data for **8b** (CIF)
Crystallographic data for **13** (CIF)

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Notes

The authors declare no competing financial interest.

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(12) See Supporting Information for details.

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