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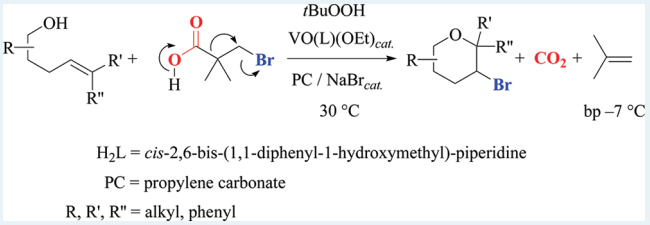
Vanadium(V)-Catalyzed Oxidative Bromination of Acid Labile Alkenols and Alkenes in Alkyl Carbonates

Oliver Brücher and Jens Hartung*

Fachbereich Chemie, Organische Chemie, Technische Universität Kaiserslautern, Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany

Supporting Information

ABSTRACT: Molecular bromine is formed from bromide and *tert*-butyl hydroperoxide under mild and neutral conditions. The oxidation is catalyzed by vanadium(V)-complexes and requires bromide- and proton- aliquots that are slowly released from a 3-bromopropionic acid-bromide buffer in solutions of alkyl carbonates. In such an environment, bromocyclization of acid labile alkenols occurs without hydrolytically cleaving acetal- or ester-protecting groups. 4-Pentenols having methyl- and/or phenyl-groups attached to the terminal carbon atom of the alkenol double bond undergo 6-*endo*-selective ring closures if subjected to oxidative bromination and provide bromotetrahydropyrans in synthetically useful yields. Application of the new procedure affords a hexasubstituted tetrahydropyran-building block en route to synthesis of the marine natural product aplysiapyranoid A.



KEYWORDS: alkyl carbonate, alkyl hydroperoxide, bromocyclization, bromoperoxidase model, oxidation catalysis, vanadium(V) complex

INTRODUCTION

The growing demand for organobromines we use in our society as intermediates,[1−3] materials,[4,5] flame retardants, emulsifiers,[6] agrochemicals, or pharmaceuticals,[7,8] is covered by hydrocarbon functionalization that mechanistically proceed via nucleophilic substitution, free radical chain reaction, or electrophilic-bromination. The largest proportion of technically produced organobromines thereby originates from reactions between molecular bromine[9−11] and carbon nucleophiles.[12,13]

Molecular bromine is not only a low-cost chemoselective oxidant but also a volatile, toxic, and corrosive chemical. Transport, storage, and application of molecular bromine therefore require safety standards that are met by most protocols based on in situ-generation of bromine from bromide and environmentally benign oxidants, such as dioxygen (O_2), which is economically favored,[14] or a peroxide, which is the more chemoselective route.[12]

The rates of bromide oxidation by *tert*-butyl hydroperoxide and hydrogen peroxide are surprisingly slow at neutral pH. To accelerate bromide oxidation by hydrogen peroxide, nature uses vanadate(V)-dependent bromoperoxidases, whereas industry uses synthetic Lewis- or Brønsted-acids.[15,16] The strategy to activate peroxides by Brønsted-acids is limited to oxidative transformations of acid-resistant substrates, which, however, are rare in organic chemistry. Bromoperoxidases catalyze the oxidation of bromide under physiological conditions, but require water as solvent.[9,15,16] Water behaves in many organic transformations as a nucleophile and thus changes selectivity to some extend from dibromination or bromocyclization to vicinal bromohydrin formation. To circumvent this problem, hydrogen peroxide-based oxidations are often conducted in biphasic solvent mixtures, where the organic substrate is brominated in the lipophilic layer and a functional bromoperoxidase mimic is added as catalyst.[17] Other approaches for bromocyclization of alkenols start from *tert*-butyl hydroperoxide as oxidant. This reagent dissolves in lipophilic solvents and allows to oxidize substrates in the absence of water.

To effectively mediate oxygen atom transfer to bromide, the alkyl hydroperoxide has to bind rapidly and selectively to a Lewis acid, such as a vanadium(V) complex (Scheme 1).[18,19] The rate of hydroperoxide binding to vanadium(V) compounds thereby gradually increases as the proton concentration rises. Oxidative bromination therefore is performed in most instances in an acidic environment, to obtain reasonable time-yield factors.[9] In strongly acidic aqueous solutions, many functional groups, such as the acetal or the ester group, hydrolyze whereas others, for example nucleophilic carbon−carbon double bonds, add water.[20]

To overcome acid- and water-mediated side reactions in a project dealing with synthesis of brominated marine natural products[21] from acid labile alkenols, we developed a method for in situ-generation of bromine from buffered hydrogen bromide-equivalents and *tert*-butyl hydroperoxide (Scheme 1). In the course of this study we found that 3-bromopropionic acids liberate proton- and bromide-aliquots, which are oxidized by *tert*-butyl hydroperoxide in a vanadium(V)-catalyzed process. The reaction furnishes molecular bromine under mild and neutral conditions, to conduct bromocyclization of acid labile alkenols in alkyl carbonates or ethyl acetate. This new method was used to

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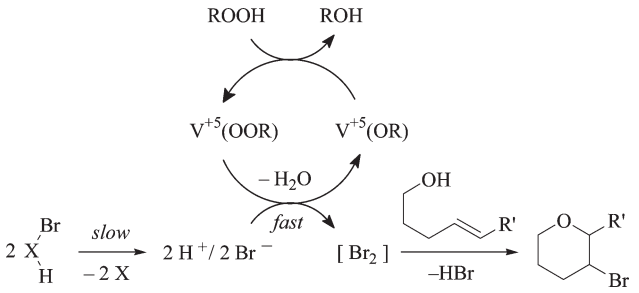
Scheme 1. Concept for Proton- and Bromide- Release from in Situ-Hydrogen Bromide Source (HXBr; section 1), and Mechanistic Proposal for Bromide Oxidation by Hydroperoxides, Catalyzed by a Vanadium Compound, That Is, $V^{+5}(OR)$ (section 2; e.g., R = H; *t*Bu; e.g., R′ = CH_3, Ph)



prepare a hexasubstituted tetrahydropyran-building block required for synthesis of the marine natural product aplysiapyranoid A.

RESULTS AND DISCUSSION

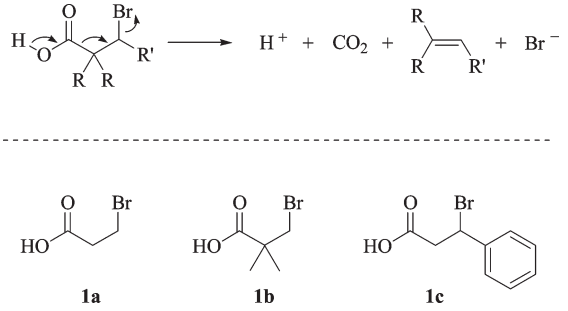
1. Hydrogen Bromide Sources. From a structure−reactivity survey we concluded that 3-bromopropionic acid (**1a**) and substituted derivatives **1b**−**c** (Scheme 2) quantitatively liberate proton- and bromide-aliquots, if treated at 30 °C with catalytic amounts of bromide in solutions of dimethyl carbonate (DMC), propylene carbonate (PC), or ethyl acetate (EtOAc).[22] For reasons of solubility, we used sodium bromide as catalyst for reactions conducted in propylene carbonate, and tetrabutylammonium bromide for transformations performed in dimethyl carbonate or ethyl acetate. The experimental evidence for bromide and proton liberation from **1a**−**c** comes from the mass balance of dibromides and vicinal bromohydrin ethers, formed after adding *tert*-butyl hydroperoxide and a vanadium catalyst (see sections 2−3).

2. Vanadium Compounds. As catalysts to activate peroxides, we used neutral complexes of the general formula O═V(L)-(OEt), having one dibasic tridentate ONO-donor ligand, that is L^{2-}, and one labile ethanolato ligand bound to oxovanadium(V). The auxiliaries H_2L^{1-3} we used to prepare vanadium compounds O═V(L^{1-3})(OEt) from triethyl vanadate (Scheme 3),[23−26] differ in terms of binding affinity toward vanadium(V), thus modifying chemical properties of derived complexes. Piperidine-derived oxovanadium(V) complex VO(L^1)(OEt), for example, is the most reactive catalyst prepared and tested so far in our project on catalytic hydroperoxide-activation, whereas VO(L^2)(OEt) is significantly most stable. The properties of VO(L^3)(OEt) in terms of stability and reactivity are midway between the former two reagents. We also included vanadyl sulfate ($VOSO_4 \cdot 4H_2O$) and oxovanadyl(IV) bis(acetylacetonate) as reagent for peroxide activation into the study, to compare reactivity and selectivity of more readily available vanadium compounds to more specialized catalysts, which we favor for reasons of selectivity (see section 3.1).

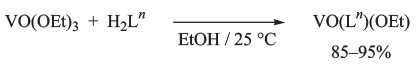
Vanadium complexes VO(L^{1-3})(OEt) are prepared by mixing aliquots of $VO(OEt)_3$ and a chelate ligand H_2L^{1-3} in ethanol at ambient temperature. The complexes separate from solutions of ethanol as pale yellow [VO(L^1)(OEt) and VO(L^3)(OEt)] to brown [VO(L^2)(OEt)] air stable crystalline solids.

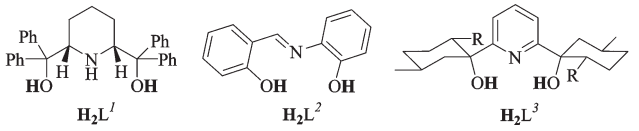
3. Bromofunctionalization of Alkenes. *3.1. Dibromination of Cyclohexenes.* To determine parameters for bromofunctionalization of alkenes in vanadium-catalyzed oxidations, we chose conformationally fixed cycloalkene **2a**,[28−30] and, for testing the

Scheme 2. Structure Formulas of 3-Bromopropionic Acids 1a−c Relevant for the Study



Scheme 3. Synthesis of Vanadium Compounds VO(L^n)(OEt)[a] from Auxiliaries H_2L^n [b]





[a] 85% for n = 1, 95% for n = 2, 87% for n = 3. [b] Acidic protons that are removed in the course of complex formation are printed in bold; VO(L^2)(OEt) crystallizes as EtOH adduct[27] from a solution of ethanol; R = $CH(CH_3)_2$.

significance of acid-mediated hydrolysis of acetal groups in oxidative brominations, protected unsaturated aldehyde **2b** (Tables 1−3). The relative configuration of dibromides formed from the two alkenes allows to model trajectories for π-bond bromination, to identify the underlying mechanism and thus the chemical nature of intermediates involved in brominations. From a systematic variation of reaction conditions, solvents, vanadium compounds, and additives (Tables 1−2), we concluded that the most effective procedure to prepare dibromide **3a** (84%) from the chosen reagents requires treatment of 4-*tert*-butyl cyclohexene (**2a**) with 3-bromo-2,2-dimethylpropionic acid (**1b**), *tert*-butyl hydroperoxide, catalytic amounts of sodium bromide and piperidine-derived vanadium complex VO(L^1)(OEt) in a solution of propylene carbonate containing low concentrations of cyclohexa-1,4-diene (CHD) (Table 1, entry 1).

In the course of method development we noted aspects dealing with (*i*) reactivity of bromopropionic acids **1a**−**c**, (*ii*) reactivity of vanadium catalysts, (*iii*) the effect of terminal oxidants, (*iv*) the effect of cyclohexa-1-4-diene on rate and chemoselectivity of alkene functionalization, (*v*) solvent effects, and (*vi*) product selectivity in alkene functionalization that deserve a comment.

(i) The relative rate of bromopropionic acid fragmentation in dimethyl carbonate increases along the series of compounds **1a** (k^{rel} = 1.0) < **1b** (k^{rel} = 1.3) < **1c** (k^{rel} = 1.9) (Scheme 2, Figure 1; all values for 30 °C). The rates of bromopropionic acid fragmentation correlate with the rates dibromide **3a** forms. The proton concentration in such solutions remains approximately constant during turnover of **1**, as probed via hydrolysis of small reaction

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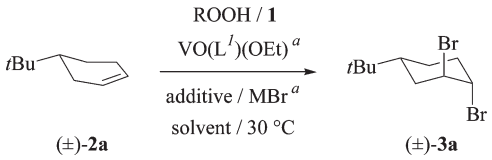
Table 1. Oxidative Bromination of 4-*tert*-Butyl Cyclohexene (2a) in Vanadium-Catalyzed Reactions

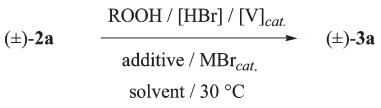


(±)-**2a** (±)-**3a**

entry	1	R[b]	solvent[c]	additive[d]	MBr[e]	3a/%
1	**1b**	*t*Bu	PC	CHD	NBu_4Br	84
2	**1a**	*t*Bu	PC	CHD	NaBr	32
3	**1b**	*t*Bu	DMC	CHD	NBu_4Br	74
4	**1b**	*t*Bu	EtOAc	CHD	NBu_4Br	83
6	**1b**	*t*Bu	PC	none	NaBr	72
7	**1c**	*t*Bu	PC	none	NaBr	79
8	**1b**	H	CH_2Cl_2	none	NBu_4Br	18[f]
9	**1b**	H	PC	none	NBu_4Br	19[g]

[a] 1 mol % of $VO(L^1)(OEt)$. [b] Anhydrous 3 M solution in toluene for R = *t*Bu; 30% (*w*/*w*) aqueous solution for R = H. [c] PC = propylene carbonate, DMC = dimethyl carbonate. [d] CHD = cyclohexa-1,4-diene. [e] 10 mol % of MBr. [f] 42% conversion. [g] 62% conversion; in the absence of $VO(L^1)(OEt)$, 18% of **3a** was obtained

Table 2. Catalyst Variation in Oxidative Bromination of 4-*tert*-Butyl Cyclohexene (2a)



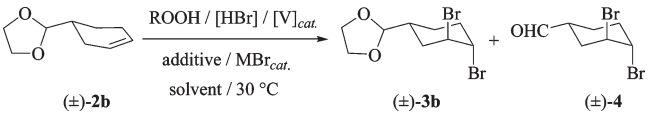
entry	[V][a]	[HBr]	R[b]	solvent[c]	additive[d]	MBr[e]	3a/%
1	$VO(L^1)(OEt)$	**1b**	*t*Bu	PC	CHD	NaBr	82
1	$VO(L^2)(OEt)$	**1b**	*t*Bu	PC	CHD	NaBr	44
2	$VO(L^3)(OEt)$	**1b**	*t*Bu	PC	CHD	NaBr	52
3	$VO(acac)_2$[f]	**1b**	*t*Bu	PC	CHD	NaBr	76
4	$VOSO_4 \cdot 4H_2O$	**1b**	*t*Bu	PC	CHD	NaBr	42
5	none	HBr[g]	H	CH_2Cl_2	none	*h*	84
6	none	HBr[g]	H	DMC	none	*h*	86

[a] 1 mol %. [b] Anhydrous 3 M solution in toluene for R = *t*Bu; 30% (*w*/*w*) aqueous solution for R = H. [c] PC = propylene carbonate. [d] CHD = cyclohexa-1,4-diene. [e] 10 mol %. [f] Hacac = pentane-1,3-dione. [g] 48% (*w*/*w*) aqueous solution. [h] No further bromide added.

volumes in intervals and pH measurement showing values of pH 5−6. In none of the reactions we noticed chemical changes at the acetal group, such as hydrolysis to the free aldehyde, starting from compounds **2b** and **3b**.

Fragmentation of **1** provides ethene (from **1a**), 2-methylpropene (from **1b**), or styrene (from **1c**), which we expected to form dibromides, similar to **2a**. Our experiments showed that 1,2-dibromoethane was not formed in reactions starting from **1a**, whereas small (<10%) amounts of 1,2-dibromo-2-methylpropane formed from **1b**. The latter dibromide was removed by distillation, as the reaction mixtures were concentrated for isolation and purification of target compound **3a**. In reactions starting from bromocinnamate **1c**, styrene (∼25%) and (1,2-dibromoethyl)-benzene (∼28%) formed as byproduct and thus required separation by chromatography. We therefore chose 3-bromo-2,2-dimethylpropionic acid (**1b**) as standard hydrogen bromide donor for all succeeding experiments.

Table 3. Formation of Dibromide 3b from 3-Dioxolanyl Cyclohexene 2b



(±)-**2b** (±)-**3b** (±)-**4**

entry	[V][a]	[HBr]	R[b]	solvent[c]	additive[d]	MBr[e]	3b/%	4/%
1	$VO(L^1)(OEt)$	**1b**	*t*Bu	EtOAc	CHD	NBu_4Br	80	*f*
2	$VO(L^1)(OEt)$	**1b**	*t*Bu	PC	CHD	NaBr	77	*f*
3	none	HBr[f]	H	PC	none	*g*	20	2

[a] 1 mol %. [b] anhydrous 3 M solution in toluene for R = *t*Bu; 30% (*w*/*w*) aqueous solution for R = H. [c] PC = propylene carbonate. [d] CHD = cyclohexa-1,4-diene. [e] 10 mol %. [f] 48% (*w*/*w*) aqueous solution. [g] No further bromide added.

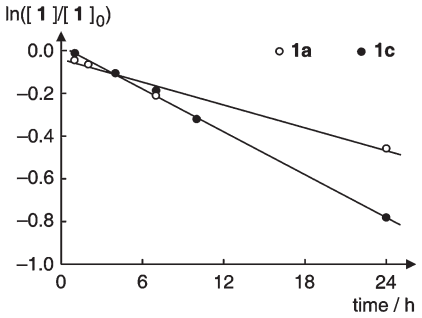


Figure 1. Time dependence of bromopropionic acid-fragmentation in solutions of alkene **2a** (c_0^{2a} = 0.05 M), *tert*-butyl hydroperoxide (c_0 = 0.063 M in toluene) in dimethyl carbonate containing NaOAc (0.02 M), NBu_4Br (0.125 M), and $VO(L^1)(OEt)$ (5×10^{-4} M) (^{1}H NMR, 30 °C, c_0^1 = 0.125 M).

(ii) Reactivity of vanadium catalysts. The reactivity of vanadium compounds to serve as catalyst for bromide oxidation in *tert*-butyl cyclohexene dibromination decreases along the series $VO(L^1)(OEt)$ > $VO(acac)_2$ > $VO(L^3)(OEt)$ > $VO(L^2)(OEt)$ > $VOSO_4 \cdot 4\,H_2O$, from 84% to 42% (Table 2). The amount of 1 mol % of catalyst originates from our own specification, to achieve quantitative conversion of alkene **2a** within 24 h. In the absence of vanadium compounds no dibromination of **2a** occurs (48 h reaction time, GC-analysis). From this information we concluded that bromopropionic acids **1a**−**c** are not able to activate *tert*-butyl hydroperoxide for bromide oxidation.

(iii) The effect of terminal oxidants. *tert*-Butyl hydroperoxide was superior to hydrogen peroxide for synthesis of acetal-protected dibromide **3b** (Table 3). Since structures like these are of interest in our natural product project, we restricted ourselves to the use of *tert*-butyl hydroperoxide for the succeeding experiments.

(iv) The effect of cyclohexa-1-4-diene on rate and chemoselectivity of alkene functionalization. A gradual decrease in product selectivity and turnover rates in combination with appearance of new products, such as ∼9% of 5-*tert*-butylcyclohex-2-en-1-one **5** after 24 h, caused us to test

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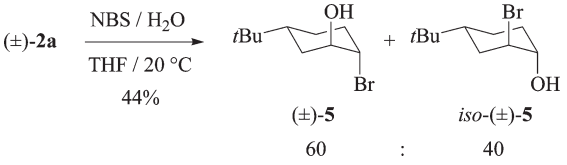
Scheme 4. Preparation of Authentic Bromohydrins 5 and *iso*-5 for Tracing Side Product Formation in Oxidative Brominations of 4-*tert*-Butyl Cyclohexene (2a) (See Also Text)



typical H-atom donors to prevent radical-based side reactions to occur. From a series of H-atom donors, that also included ionol and 2,6-di-(*tert*-butyl)phenol, cyclohexa-1,4-diene was the most effective agent to entirely prevent such side reactions of **2a**.[31] About 2−9% of the cyclohexa-1,4-diene thereby were converted into a derived dibromide, which did not complicate target product isolation and purification.

Addition of cyclohexa-1,4-diene not only improved the yield of dibromide, for example from 72% to 84% for **3a**, but also shortened the reaction time to a third (Table 1, entries 2 and 6). The efficiency of dibromide formation in the vanadium-catalyzed reaction thus compares to yields of alkene dibromination by stoichiometric amounts *N*-bromosuccinimide in combination with tetrabutylammonium bromide (92%) or molecular bromine (96%) in solutions of dichloromethane (Supporting Information).

(v) Solvent effects. Dimethyl carbonate (bp. 90 °C), propylene carbonate (bp. 240 °C), and ethyl acetate (bp. 70 °C) are biodegradable non toxic solvents. The use of such Lewis-basic solvents in oxidations catalyzed by Lewis-acidic vanadium complexes is new and poses an interesting alternative to conventional procedures performed, for example, in chlorinated alkanes or acetonitrile. Since propylene carbonate and alkanes are poorly miscible, products **3a**−**b** were on a routine basis extracted from reaction mixtures by cyclohexane. This workup procedure is attractive particular for larger scale applications, because product separation is feasible by extraction and distillation. Propylene carbonate solutions of VO(L^1)(OEt), which were left from extractions could be charged with further alkene **2a**, bromopropionic acid **1b**, and *tert*-butyl hydroperoxide to provide 69% of dibromide **3a** in a second run.

(vi) Product selectivity in alkene functionalization. To check, whether oxygenation of **2a** or bromohydrin formation from water that forms from *tert*-butyl hydroperoxide and bromide (see Scheme 1) interferes with dibromination of **2a**, we independently prepared 4-*tert*-butyl cyclohexene-1,2-oxide and β-bromohydrins **5** and *iso*-**5** (Scheme 4). None of the two products was detected in the reaction mixtures (GC-MS).

The chemical nature and the configuration of products **3a**−**b** formed in vanadium-catalyzed oxidations point to a bromonium ion pathway, and thus to molecular bromine as key intermediate (Scheme 5). Nucleophilic opening of bromonium ion *anti*-**6** via bromide attack at C4 provides dibromide **3a** having both bromo-substituents attached axially and the *tert*-butyl group equatorially. Formation of the all equatorially substituted stereoisomer of **3a** in this mechanistic picture would occur upon nucleophilic attack of bromide at C3 leading to a boat-like conformer, which is higher

Scheme 5. Stereochemical Model for Synthesis of Trans-Diaxially Substituted Dibromide (±)-3a (for a Description of Ring-Opening of *syn*-6 See Text)

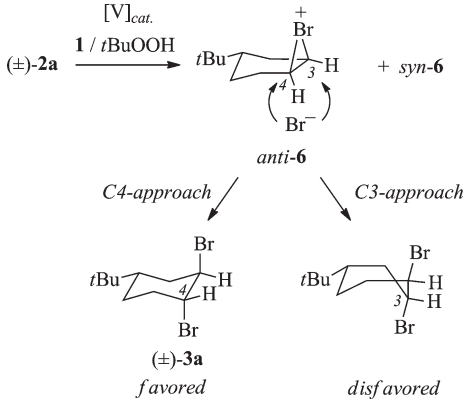
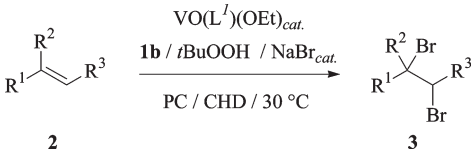


Table 4. Formation of Vicinal Dibromoalkanes via Oxidative Bromination of Terminal and Internal Alkenes[a]



entry	2/3	R^1	R^2	R^3	3/%
1	**c**	C_8H_{17}	H	H	71
2	**d**	$(CH_2)_3Ph$	H	H	63
3	**e**	Ph	H	CH_3	59
4	**f**	C_4H_9	H	C_4H_9	73
5	**g**	CH_3	CH_3	$(CH_2)_2CO_2Et$	69

[a] For reagent abbreviations, concentrations, and equivalents refer to footnotes of Table 1.

in energy and therefore disfavored.[32,33] For the same reason we propose that bromonium ion opening of *syn*-**6** (not shown in Scheme 5) occurs via attack at C3 to afford the trans-diaxially substituted dibromide **3a**, whereas substitution at C4 would furnish the all equatorially substituted product, which we did not observe.

3.2. Dibromination of Terminal, Di-, and Trisubstituted Alkenes. For a survey on reactivity and chemoselectivity in oxidative alkene bromination (Table 4), we selected substrates **2c**−**g** bearing substituents at the carbon−carbon double bond that reflect patterns occurring in natural products. Under conditions referred to as standard (Table 1, entry 1), alkenes **2c**−**g** gave dibromides **3c**−**g** in yields ranging between 59% [(β-methyl styrene **2e**)] and 73% [(*E*)-5-decene **2f**]. The products were in all instances formed diastereomerically pure. Addition of the cyclohexa-1,4-diene improved the yield of dibromides from internal alkenes (**2e**−**g**) by about 8−12%, but not for bromination of substrates having a terminal double bond (**2c**−**d**).

3.3. Bromocyclization of 4-Pentenols. The results obtained from dibromination of alkenes allowed us to step toward the main objective of this project dealing with development of a catalytic method for oxidative bromocyclization of acid labile alkenols. To explore technical details of this reaction, we chose

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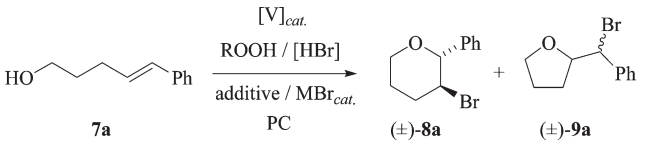
Table 5. Summary of Results from Parameter Variation for Synthesis of Brominated Tetrahydropyran 8a from 5-Phenyl-4-pentenol 7a



entry	[V][a]	[HBr]	R[b]	T/°C	additive[c]	MBr[d]	8a/%	9a/%
1	VO(L[1])(OEt)	**1b**	*t*Bu	30	CHD	NaBr	71	<5
2	VO(L[1])(OEt)	**1b**	H	30	none	NBu_4Br	19[f]	*e*
3	none	HBr[g]	H	20	none	*h*	47	*e*

[a] 1 mol %. [b] Anhydrous 3 M solution in toluene for R = *t*Bu; 30% (*w*/*w*) aqueous solution for R = H. [c] CHD = cyclohexa-1,4-diene. [d] 10 mol %. [e] Not detected. [f] 17% yield in the absence of VOL[1](OEt) under otherwise identical conditions. [g] 48% (*w*/*w*) aqueous solution. [h] No bromide added.

5-phenyl-4-pentenol (**7a**) as substrate. Styrene-type alkenol **7a** bears structural elements relevant for the natural product project. This substrate has a nucleophilic π-bond that is prone to undergo side reactions in the presence of protons and external nucleophiles, such as water. The stereochemical information associated with the π-bond in **7a** furthermore allows to extract mechanistic information of carbon−bromine- and carbon−oxygen-bond formation on the basis of relative configuration of substituents in derived bromocyclization products.

The results from a screening of parameters for bromocyclization showed that phenylpentenol **7a** is most effectively transformed in a solution of propylene carbonate containing bromopropionic acid **1b**, *tert*-butyl hydroperoxide, and 1 mol % of VO(L[1])(OEt). The reaction provides 71% of stereochemically pure 2,3-trans-substituted tetrahydropyran **8a**, besides a minor fraction of bromobenzyltetrahydrofuran **9a** (Table 5, entry 1). Addition of 40 mol % of cyclohexa-1,4-diene improved the yield of product **8a** and shortened the time for quantitative conversion of **7a**. From the yields of **8a** we concluded that *tert*-butyl hydroperoxide is superior to hydrogen peroxide for oxidative bromocyclization of **7a** (Table 5, entry 2). We also checked, whether an aqueous solution of hydrogen peroxide containing hydrogen bromide[34] would provide a simpler alternative for synthesis of tetrahydropyran **8a** compared to the new method, which however was not the case (Table 5, entry 3).

The chemical nature of products formed from oxidative bromination of **7a** is consistent with a two step mechanism proceeding via cyclic bromonium ion formation and opening of this intermediate by backside attack of the hydroxyl oxygen in a S_N2-manner (Scheme 6). Carbon−oxygen bond formation from the proposed intermediate **10** occurs in a late transition state. Since charge effects become important in late transition states, the incoming oxygen nucleophile favors attack of the bromonium ion at the benzylic carbon.[32,33] Stereoelectronic prerequisites associated with the backside attack guide stereospecificity of bromonium ion opening and copies the (*E*)-configuration of substrate **7a** into the 2,3-trans-configuration of product **8a**.

To investigate selectivity in bromocyclization of substrates having terpenol-type π-bonds, we subjected 5-methyl-1-phenyl-4-hexenol **7b** and linalool **7c** to conditions developed in the preceding sections. From these reactions we isolated bromocyclization products **8b**−**c** and **9b**−**c** in combined yields of about

Scheme 6. Mechanistic Model for Synthesis of Cyclic Ethers from 5-Phenyl-4-pentenol (7a) in Oxidative Bromination

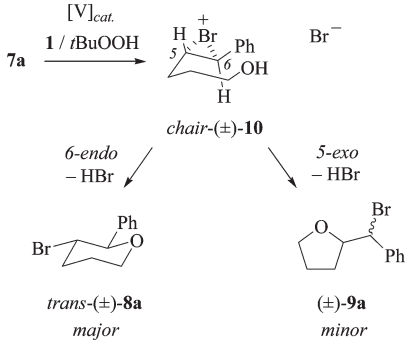
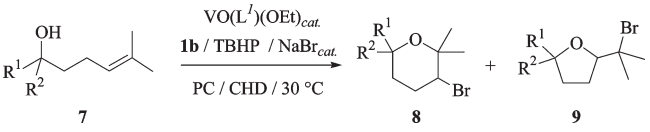
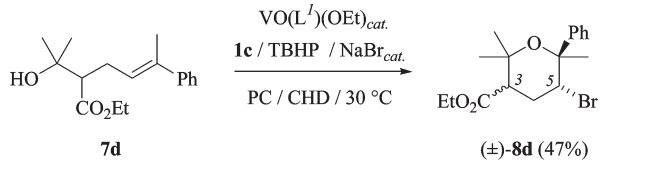


Table 6. Bromocyclization of Alkenols in Vanadium(V)-Catalyzed Oxidations



entry	7−9	R^1	R^2	8/% (*cis*:*trans*)	9/% (*cis*:*trans*)
1	**b**	Ph	H	68 (4:96)	14 (41:59)
2	**c**	CH_3	$CH{=}CH_2$	42 (64:36)	37 (62:38)

Scheme 7. Synthesis of Building Block 8d for the Synthesis of Aplysiapyranoid A[37]



80% (Table 6). We scaled up the process for bromocyclization of linalool **7c** by a factor of 10 and successfully used a simplified work up-procedure via extraction and distillation to obtain pure linalool bromides **8c** and **9c** (Supporting Information). We think that this procedure is quite generally applicable for products having similar polarity to cyclic ethers **8c** and **9c**.

As final step in method development and a first step toward application in synthesis, we chose to prepare the heterocyclic core of the aplysiapyranoids,[35] using the vanadium-catalyzed method. Aplysiapyranoids are functionalized tetrahydropyrans having a total of four substituents attached to carbons 2 and 6, and two additional functional groups at carbons 3 and 5 of the heterocyclic core. The strain imposed by axial positioning of substituents at carbon atoms 2 and 6 generally renders bromocyclization of δ,ε-unsaturated alcohols inefficient for constructing 2,2,6,6-substituted tetrahydropyrans.[36]

We thus subjected tertiary alkenol **7d** to standard conditions using bromocinnamic acid **1c** as hydrogen bromide donor, and isolated 2,2,3,5,6,6,-substituted tetrahydropyran **8d** in 47% yield as only low molecular weight product (Scheme 7). This yield is

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higher than the value of 20% obtained for bromocyclization of the O-methyl derivative of **7d** by 2,4,4,6-tetrabromocyclohexa-2,5-dienone and 43% for an oxidative bromination using pyridinium hydrobromide and *tert*-butyl hydroperoxide in acetonitrile.[37] An UV-active spot located at $R_f = 0$ on tlc-sheets using a 50/50-mixture of diethyl ether and pentane as eluent shows that additional products form from substrate **7d**. These products, unfortunately, could not be characterized with our analytical methods.

CONCLUDING REMARKS

The oxidation of bromide by *tert*-butyl hydroperoxide in solutions of alkyl carbonates is an effective and synthetically useful method to prepare vicinal dibromoalkanes from alkenes and products of bromocyclization from alkenols. The fundamentals of this bromination chemistry derive from nature, where vanadate(V)-dependent bromoperoxidases catalyze the oxidation of bromide from ocean water by hydrogen peroxide at ambient temperature and pH 6.

Over the years, substantial effort was spent to mimic the chemistry of the marine bromoperoxidases for conducting organobromine synthesis under approximately neutral conditions.[38,39] The discovery that the combination of bromide and 3-bromopropionic acids act as buffered, slow release hydrogen bromide progenitor in this sense solves a long-standing problem and has the potential to further develop this field of bioinspired organic synthesis.

We are well aware of the fact that other methods for oxidative bromination exist. A number of attractive procedures are based on aerobic oxidation,[14] while others transform bromide by hydrogen peroxide under strongly acidic conditions into bromoelectrophiles, which are suitable for arene bromination or vicinal dibromination of acid stable alkenes.[13] In strongly acidic media, however, peroxides and alkenes are consumed not only by bromination, but also by unspecific acid-induced background reactions.[40] In the new method for oxidative bromination, no background reactivity exists thus explaining efficiency and selectivity for turning over substrates into products. The task to activate *tert*-butyl hydroperoxide is entirely taken over by vanadium(V)-compounds that structurally range from more specialized catalysts, as in our ongoing projects, to commercially available reagents, such as vanadyl(IV)-bis(acetylacetonate).

The vanadium-catalyzed method for oxidative bromination effectively operates in alkyl carbonates and ethyl acetate, which are nontoxic solvents and therefore pose interesting alternatives to aromatic hydrocarbons, acetonitrile, or chlorinated alkanes, which are customarily used as reaction media for peroxide activation by vanadium compounds. In view of the efficiency of this modification we believe that alkyl carbonate solvents will have the potential to provide a stimulus to the field of oxidation catalysis in a broader sense.

EXPERIMENTAL SECTION

1. General Information. For general laboratory practice and instrumentation see ref 10 and the Supporting Information.

2. Oxidative Bromination of 4-*tert*-Butyl Cyclohexene (2a). To a solution of 4-*tert*-butyl cyclohexene (**2a**) (138 mg, 1.0 mmol) in propylene carbonate (20 mL) was added 3-bromo-2,2-dimethylpropionic acid (**1b**) (452 mg, 2.5 mmol), NaBr (10.3 mg, 0.1 mmol), vanadium catalyst VO(L^1)(OEt) (5.6 mg, 0.01 mmol), and *tert*-butyl hydroperoxide (TBHP) (3.5 M in toluene, 455 μL, 1.6 mmol). 1,4-Cyclohexa-1,4-diene (32.1 mg, 0.4 mmol) dissolved in propylene carbonate (3 mL) was added via syringe pump (0.003 mL/min). The reaction mixture was stirred at 30 °C in a water bath for 24 h. The yellowish solution was extracted with cyclohexane (4 × 15 mL), combined organic extracts were washed with H_2O (1 × 20 mL) and sat. aqueous NaCl (1 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to leave a residue, which was purified by column chromatography (SiO_2, CH_2Cl_2). Quant. conversion (NMR). Yield: 244 mg (82%) *rel*-(1*R*,3*S*,4*S*)-3,4-dibromo-1-*tert*-butyl cyclohexane (**3a**) from 139 mg (1 mmol) of **2a**, colorless oil, R_f 0.77. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 0.89 (s, 9 H, CH_3), 1.55−1.70 (m, 3 H, 1-H, 6-H), 1.97 (t, J 14.4 Hz, 2 H, 2-H, 5-H), 2.17 (ddd, J 14.6, 11.9, 3.1 Hz, 1 H, 2-H), 2.44 (ddt, J_d 15.3, 12.1, J_t 3.6 Hz,1 H, 5-H), 4.67 (br s, 1 H, 4-H), 4.77 (br s, 1 H, 3-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 21.2 (C6), 27.3 (CH_3), 28.9 (C5), 29.4 (C2), 32.1 (C_q), 41.2 (C1), 53.8 (C4), 54.9 (C3) ppm. Anal. Calc. for $C_{10}H_{18}Br_2$: C, 40.30; H, 6.09; Found: C, 40.54; H, 6.05.

3. 2-[*rel*-(1′*R*,3′*S*,4′*S*)-3′,4′-Dibromocyclohexyl]-1,3-dioxolane (3b). 2-(Cyclohex-3′-enyl)-1,3-dioxolane (**2b**) (155 mg, 1.0 mmol) was converted as described in section 2 for **2a**. Conversion: 96% (NMR). Yield: 251 mg (80%) colorless oil, R_f 0.58. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.66−1.77 (m, 2 H, 6′-H), 1.95−2.05 (m, 2 H, 2′-H, 5′-H), 2.19 (tq, J_t 11.7, J_q 4.0 Hz, 1 H, -1′-H), 2.28−2.36 (m, 1 H, 2′-H), 2.46 (dddd, J 15.2, 12.2, 4.6, 3.3 Hz, 1 H, 5′-H), 3.82−3.98 (m, 4 H, 3-H, 4-H), 4.61−4.67 (m, 1 H, 4′-H), 4.67−4.74 (m, 2 H, 2-H, 3′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 21.0 (C6′), 27.8 (C2′), 29.1 (C5′), 35.7 (C1′), 52.9 (C3′), 53.1 (C4′), 65.0, 65.0 (C4, C5), 106.3 (C2) ppm. Anal. Calcd. for $C_9H_{14}Br_2O_2$ (314.01): C, 34.42; H, 4.49; Found: C, 34.69; H 4.45.

4. Bromocyclization of (*E*)-5-phenylpent-4-en-1-ol (7a). To a solution of (*E*)-5-phenylpent-4-en-1-ol (**7a**) (162 mg, 1.0 mmol) in propylene carbonate (20 mL) was added 3-bromo-2,2-dimethylpropionic acid (**1b**) (226 mg, 1.25 mmol), NaBr (10.3 mg, 0.1 mmol), vanadium catalyst VO(L^1)(OEt) (5.6 mg, 0.01 mmol), and TBHP (3.5 M in toluene, 455 μL, 1.6 mmol). 1,4-Cyclohexa-1,4-diene (32.1 mg, 0.4 mmol) dissolved in propylene carbonate (3 mL) was added via syringe pump (0.003 mL/min). The reaction mixture was stirred at 30 °C in a water bath for 24 h. The yellowish solution was extracted with cyclohexane (4 × 15 mL), combined organic extracts were washed with H_2O (1 × 20 mL) and sat. aqueous NaCl (1 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to leave a residue, which was purified by column chromatography (SiO_2, CH_2Cl_2). Quant. conversion (NMR). Yield: 173 mg (71%) of a >95/5-mixture of tetrahydropyran **8a** and tetrahydrofuran **9a**, colorless oil. R_f 0.63. Anal. Calc. for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43; Found: C, 54.73; H, 5.30. *rel*-(2*R*,3*S*)-3-Bromo-2-phenyltetrahydropyran (**8a**). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.76 (d, J 13.7 Hz, 1 H, 4-H), 1.88−2.03 (m, 1 H, 4-H), 2.13 (qd, J_q 12.6, J_d 4.1 Hz, 1 H, 3-H), 2.60 (dd, J 9.0, 3.9 Hz, 1 H, 3-H), 3.65 (td, J_t 11.9, J_d 2.0 Hz, 1 H, 5-H), 4.06 (td, J_t 11.0, J_d 4.3 Hz, 1 H, 2-H), 4.14 (dd, J 11.3, 4.7 Hz, 1 H, 5-H), 4.32 (d, J 9.8 Hz, 1 H, 1-H), 7.29−7.43 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 28.3 (C4), 36.2 (C3), 52.3 (C2), 68.7 (C5), 85.5 (C1), 127.5, 128.2, 128.5, 139.5 ppm. 2-(1-Bromo-1-phenylmethyl)-tetrahydrofuran (**9a**). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.90−1.98 (m, 2 H, CH_2), 2.23−2.35 (m, 2 H, CH_2), 3.78−3.98 (m, 2 H, CH_2), 4.43−4.53 (m, 1 H, 2-H), 4.89 (d, J 7.8 Hz, 1 H, CHBr), 7.30−7.48 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C):

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δ = 26.0 (CH_2), 31.0 (CH_2), 57.3 or 60.4, 69.3, 85.5 (C2), 128.2, 128.4, 128.6, 139.6 ppm.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectral and analytical data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +49-631-205-2431. Fax: +49-631-205-3921. E-mail: hartung@chemie.uni-kl.de.

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■ DEDICATION

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