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Stereoselective syntheses of functionalized cyclic ethers via (Schiff-base)vanadium(V)-catalyzed oxidations*,**

Jens Hartung

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

Abstract: (Schiff-base)vanadium(V) complexes catalyze the oxidation of Br^- (formation of Br_2) and the stereoselective synthesis of functionalized tetrahydrofurans from substituted bishomoallylic alcohols. In both instances, *tert*-butyl hydroperoxide (TBHP) serves as primary oxidant. The oxidation of Br^- was applied as the key step for stereo- and 6-*endo*-selectively constructing the 2,2,3,5,6,6-substituted tetrahydropyran nucleus of the marine natural product aplysiapyranoid A starting from an adequately substituted bishomoallylic alcohol. In the absence of Br^-, 1-alkyl-, 1-vinyl-, and 1-phenyl-5,5-dimethyl-substituted bishomoallylic alcohols are selectively oxygenated to furnish 2,5-*cis*-configured tetrahydrofurans as major products. 2- Or 3-substituted ω,ω-dimethyl-substituted bishomoallylic alcohols afford *trans*-disubstituted tetrahydrofurans under these conditions. Oxidation of substituted 4-penten-1-ols, i.e., substrates with a terminal π-bond, proceeds with a preference for formation of *trans*-disubstituted tetrahydrofurans. According to data from (i) ^{51}V NMR spectroscopy, (ii) mass spectrometry, (iii) a structure-selectivity survey, (iv) competition kinetics, and (v) a stereochemical analysis, the oxygen atom transfer onto a bishomoallylic alcohol occurs in a peroxide- *and* alkenol-loaded (Schiff-base)vanadium(V) complex.

Keywords: Vanadium; oxidation; *tert*-butyl hydroperoxide; tetrahydrofuran; tetrahydropyran; bromide; bromoperoxidase.

INTRODUCTION

In recent years, a remarkable number of tetrahydrofuran- and tetrahydropyran-derived secondary metabolites have been isolated from terrestic and marine organisms (Fig. 1) [1]. A considerable fraction of these compounds exhibits notable cytotoxic and/or antibiotic properties [2,3]. This circumstance has brought about a growing demand of functionalized cyclic ethers, which, however, cannot be covered from natural sources alone [4–6]. The invention of methods for stereoselectively constructing hydroxylated or halogenated heterocycles from alkenols, in particular via transition metal-catalyzed oxidations, has therefore received considerable attention [7–12]. However, none of the procedures reported so far has provided a solution for a longstanding problem: the control of diastereoselectivity *and* regioselectivity in the ring closing *and* the heteroatom functionalization step by means of the applied auxiliary and not by the selected substrate or the oxidant [10,13].

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**Dedicated to Prof. Dr. Bernd Giese on the occasion of his 65th birthday.

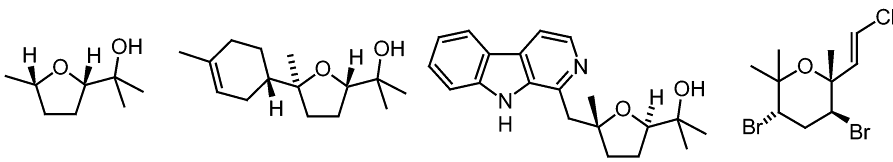
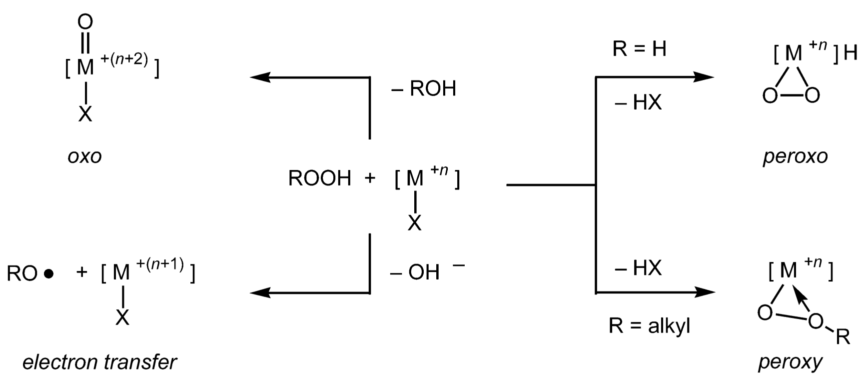


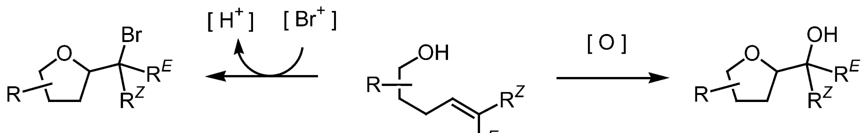
Fig. 1 Selection of biologically active natural products with a tetrahydrofuran or a tetrahydropyran subunit [14–17].

The prerequisite for the formation of functionalized cyclic ethers from alkenols is the availability of an adequately strong oxidant that is able to chemoselectively oxidize the olefinic π-bond (Fig. 1). In view of this consideration, *tert*-butyl hydroperoxide (TBHP) has been selected for conducting (Schiff-base)vanadium(V)-catalyzed oxidations in organic media. It is a comparatively strong oxidant ($E°$ = 1.20 V vs. NHE, CH_3OH/C_6H_6) that was discovered by Milas almost 70 years ago [18,19]. The commercially available 5.5 M solution of TBHP in nonane corresponds to a satisfactory active oxygen atom content of 11 %. *tert*-Butanol is obtained as major co-product from oxygenation reactions and can easily be removed via distillation (bp = 83 °C). TBHP is readily soluble in organic solvents and thermally surprisingly stable under neutral conditions. A major advantage of TBHP compared to H_2O_2 is the fact that it is less sensitive to metal contamination and does not react with most organic compounds in the absence of metal-catalysts [20,21]. Activation of TBHP for an application in selective oxidation reactions is attainable using transition-metal complexes, either via high-valent oxometal compounds or peroxy intermediates (Scheme 1). The third pathway for peroxide activation involves single electron transfer from the transition-metal complex [X–M^{+n}] onto TBHP, which is followed by homolytic cleavage of the O,O bond and free radical-based transformations [10,20].



Scheme 1 Formation of transition metal-based oxidants from peroxides and coordination compounds [X–M^{+n}]. R = H or alkyl; [X–M^{+n}] = coordinatively saturated transition-metal complex; X = monovalent labile ligand; n = oxidation number.

The results of a screening survey [22] indicated that reagents formed by in situ mixing TBHP and a vanadium(V) complex with a dibasic tridentate Schiff-base auxiliary [23–27] constitute powerful but selective oxidants for chemo-, regio-, and stereoselectively converting bishomoallylic alcohols **I** into functionalized tetrahydrofurans **II** (Scheme 2) [22,28]. In the presence of Br^- and one equivalent of H^+ per oxidizable halide ion, the selectivity of this system entirely changes from π-bond oxygenation to Br^- oxidation. In the latter case, the reaction furnishes products of selective bromocyclization, i.e. heterocycles **III** (Scheme 2) [29].

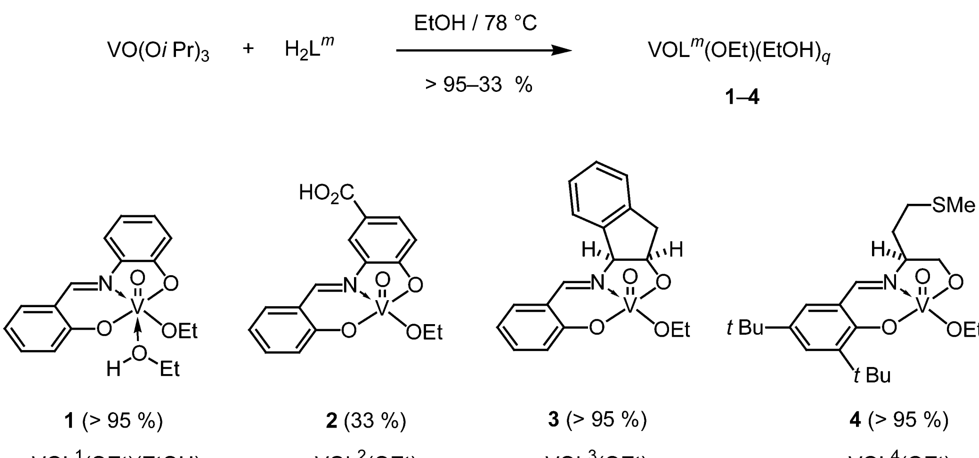


Scheme 2 Reagent-controlled divergence of reaction channels in oxidation catalysis: The stereoselective formation of hydroxymethyl-substituted tetrahydrofurans **II** or bromocyclization products **III**. R^E, R^Z = H, alkyl, phenyl. [O] = TBHP / VOL(OEt); [Br^+] = pyHBr/TBHP/VOL(OEt) (see Scheme 3 for structure formulae of vanadium complexes).

In view of this background, it is the aim of this review to summarize the principles, the mechanisms, and some of the more recent applications of (Schiff-base)vanadium(V)-catalyzed oxidations in the stereoselective synthesis of heteroatom-functionalized cyclic ethers, with a focus on the formation of natural products and structurally closely related derivatives thereof (Fig. 1).

(SCHIFF-BASE)VANADIUM(V) COMPLEXES: PREPARATION, PROPERTIES, AND REACTION WITH TBHP

(Schiff-base)vanadium(V) complexes **1–4** were crystallized as dark red to black products in analytically pure form from reaction mixtures, which were obtained by treatment of equimolar amounts of tris(isopropyl) or triethyl vanadate with a dibasic tridentate Schiff-base H_2L^m (m = 1–4) in anhydrous EtOH (Scheme 3) [28,29]. Compounds **1–4** were selected out of a larger set of similarly prepared reagents, in order to pursue (i) ^{51}V NMR investigations (complexes **1–3**), (ii) ESI-MS studies (**1** and **2**), (iii) mechanistic investigations (**1**), (iv) stereoselective oxygenations (**1** and **3**), and (iv) heteroatom oxidations (**1** and **4**) [10,28,29]. Vanadium(V) complexes **1–4** are readily soluble in DMF, CH_3CN, soluble in $CHCl_3$, EtOH, and sparingly soluble in C_6H_6 or in hydrocarbons.



Scheme 3 Preparation of (Schiff-base)vanadium(V) complexes **1–4** [23,28]. m = 1–4, q = 0,1.

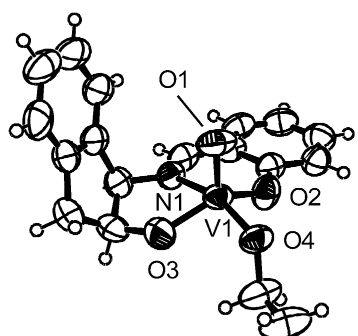
Coordination compounds **1–4** were characterized by ^{51}V NMR [referenced vs. $VOCl_3$ (≡ 0 ppm) as external standard], IR spectroscopy, UV/vis measurements (Table 1), and C,H,N-analysis.

Table 1 Selected spectroscopic data of (Schiff-base)vanadium(V) complexes **1**–**4** [28,29].

Entry	Parameter	**1**	**2**	**3**	**4**
1	^{51}V NMR δ [ppm] ($CDCl_3$)	–529	–538	–542/–545	–562/–573
2	^{51}V NMR δ [ppm] ($CDCl_3$ + TBHP)	–571	–578	–574/–578	– [a]
3	$\nu_{V=O}$ [cm^{-1}]	990	991	997	987
4	λ_{max} [nm] (lg ε)	659 (2.40)		652 (2.39)	652 (2.06)
		361 (3.80)		435 (2.44)	437 (1.91)
		341 (3.78)	359 (4.07)	345 (3.74)	350 (3.69)
		242 (4.16)	269 (4.48)	272 (4.22)	251 (4.25)

[a]Not determined.

The analytical data were supplemented by results from single-crystal X-ray diffraction analysis, e.g., for 1,2-aminoindanol-derived complex **3** (Fig. 2) [28]. Coordination compound **3** crystallizes in space group $P2_12_12_1$ and exhibits (*C*)-configuration at vanadium [30–32]. The central ion is located 0.52 Å above the NO_3 plane in a distorted square pyramidal coordination polyhedron. The V–O distance decreases along the series V1–O2 = 1.855(2) Å, V1–O3 1.815(3) Å, V1–O4 1.777(2) Å, to V1–O1 = 1.586(2) Å. The observed long distance of V1–N1 = 2.106(3) Å has been attributed to the well-known low affinity of neutral imino nitrogens to vanadium(V) [33]. The bond angles toward vanadium decrease in going from O2–V1–O4 [94.0(1)°, phenolato to ethanolato oxygen], via O3–V1–O4 [91.8(1)°, aminoalcoholato to ethanolato oxygen], N1–V1–O2 [82.7(1)°, imine nitrogen to phenolato oxygen] to N1–V1–O3 [77.0(1)°, imine nitrogen to aminoalcoholato oxygen].



(*C*)-**3**

Fig. 2 Geometry of (Schiff-base)vanadium(V) complex (*C*)-**3** in the solid state ($P2_12_12_1$) [28,30].

Complexes VOL^3(OEt) (**3**) and VOL^4(OEt) (**4**), which were prepared from enantiomerically pure chiral ligands (H_2L^m), exhibit in $CDCl_3$ solution two ^{51}V NMR resonances (Table 1). In view of the fact that the central ion in vanadium(V) reagents **1**–**4** constitutes a stereogenic center (for **1** and **3**, see Fig. 3), it is likely that the two ^{51}V NMR signals originate from diastereomers with respect to the absolute configuration at vanadium [10,34–37].

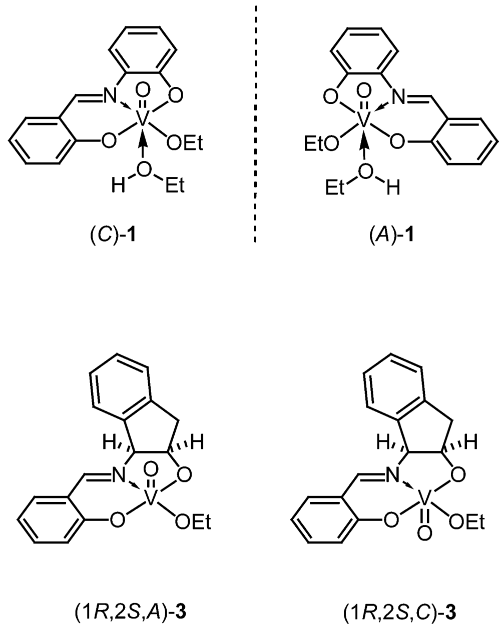
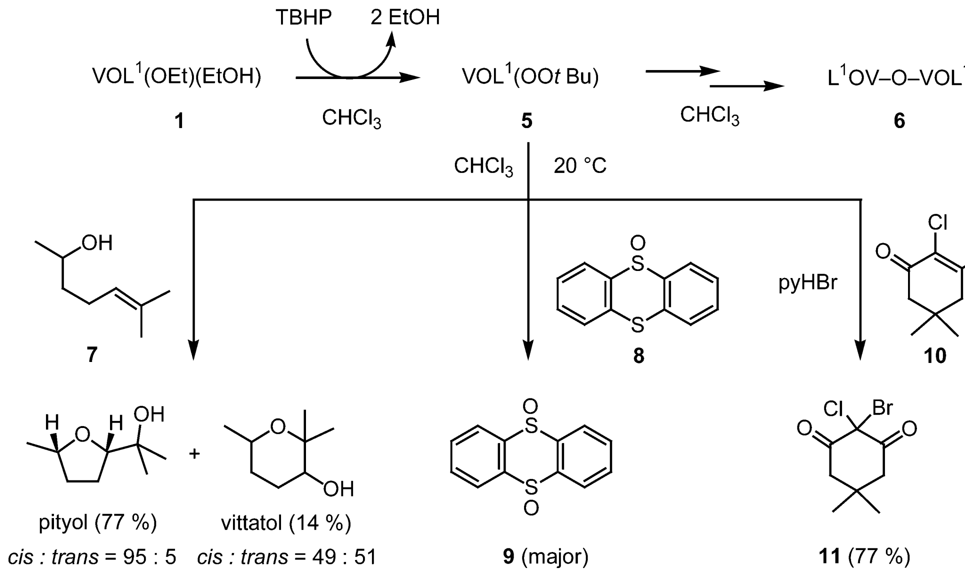


Fig. 3 Visualization of enantiomers (top) and diastereomers (bottom) caused by dissymmetric vanadium(V) central ions in **1** and **3** [10,28,30,31].

Treatment of $VOL^1(OEt)(EtOH)$ (**1**) with a 1.5 molar excess of TBHP in $CDCl_3$ at 61 °C provides a brown solution, which is characterized by a highfield-shifted ^{51}V NMR signal at $\delta = -571$. In combination with additional analytical data from earlier studies [23,38], the resonance at –571 ppm has been assigned to (*tert*-butyl peroxy)vanadium(V) complex **5** (Scheme 4). In a more recent study, the in situ-formation of a *tert*-butyl peroxy complex starting from $VOL^2(OEt)$ (**2**) has been confirmed by results from ESI-MS investigations [29]. In view of this information, a highfield shift of ~40 ppm (^{51}V NMR) upon addition of an excess of TBHP to a solution of a (Schiff-base)vanadium(V) coordination compound in $CDCl_3$ has been interpreted as evidence for the in situ formation of a (*tert*-butyl peroxy)(Schiff-base)vanadium(V) complex in general.

In the absence of a reducing agent, peroxy complex **5** decomposes into the oxo-bridged dimer **6** (Scheme 4), which has been characterized by X-ray diffraction [28]. If treated with 6-methyl-5-hepten-2-ol (**7**), peroxy complex **5** selectively delivers its active oxygen atom to the alkenol substrate, to provide in a stoichiometric reaction 77 % of pityol (*cis*:*trans* = 95:5) and 14 % of vittatol (*cis*:*trans* = 49:51) (Scheme 4). It should be noted that pityol or vittatol are not formed from substrate **7** and TBHP alone. The *cis*-isomers of the latter two ethers have been isolated from insect volatiles of the elm bark beetle *Ptleobius vittatus*. Their significance as pheromones and their application in bark beetle traps are under current investigation [14].

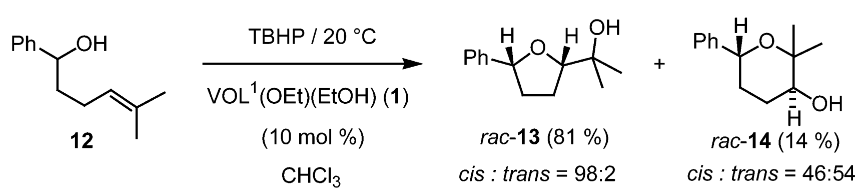
The reaction between (*tert*-butyl peroxy)(Schiff-base)vanadium(V) complex **5** and thianthrene-*S*-oxide (**8**) affords bis-*S*-oxide **9** as major product. On the basis of a quantitative analysis of all thianthrene-*S*-oxide-derived products, an Adam x_{SO} value of 0.2 has been calculated for this reaction (reference data: $x_{SO} = 1.0$ for $NaOH/H_2O_2$; $x_{SO} = 0.0$ for $TBHP/HClO_4$) [29,40,41]. This information classifies peroxy complex **5** as electrophilic oxidant thus being suited to oxidize typical nucleophiles such as Br^-. The latter reaction affords an electrophilic brominating reagent, which has been trapped by chlorodimedone (**10**) to provide 77 % of 2-bromo-2-chlorodimedone (**11**) (Scheme 4) [29,42].



Scheme 4 Reactivity and selectivity of (*tert*-butyl peroxy)(Schiff-base)vanadium(V) complex **5** [29,39].

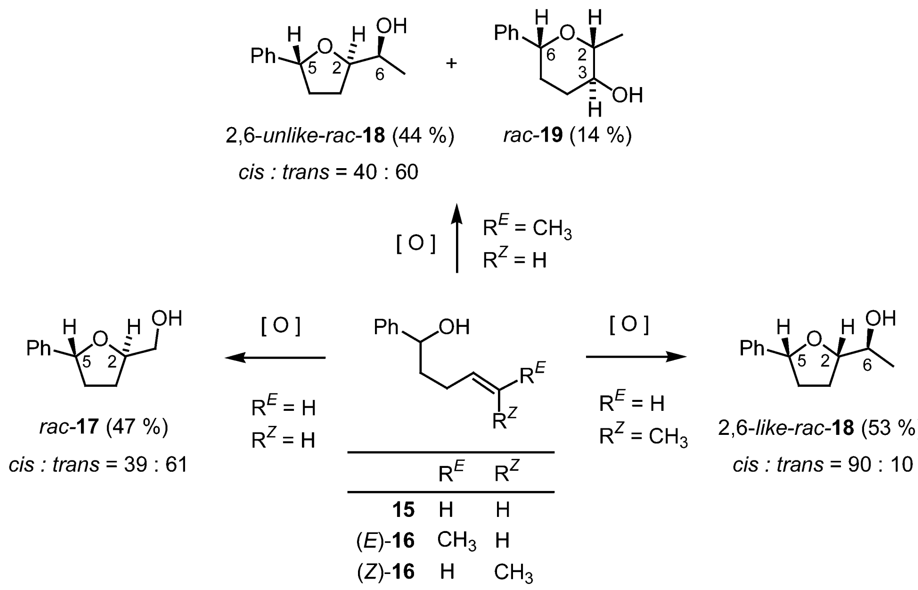
OXYGENATION OF OLEFINIC π-BONDS: THE STEREOSELECTIVE FORMATION OF FUNCTIONALIZED TETRAHYDROFURANS

Suitable conditions for the synthesis of functionalized tetrahydrofurans from substituted bishomoallylic alcohols in catalytic reactions were established by modifying (i) the amount of complex $VOL^m(OEt)(EtOH)_q$ **1**–**4**, (ii) the solvent, (iii) the reaction temperature, and (iv) the primary oxidant. Thus, 1.5 equiv. of TBHP, 10 mol % of catalyst $VOL^1(OEt)(EtOH)$ (**1**), a temperature of 20 °C and $CHCl_3$ as solvent were found to be adequate in order to convert 5-methyl-1-phenyl-4-hexen-1-ol (**12**) into 81 % of 2,5-disubstituted tetrahydrofuran *rac*-**13** (*cis*:*trans* = 98:2) and 14 % of tetrahydropyran *rac*-**14** (*cis*:*trans* = 46:54). In addition, 1–3 % of other oxidation products were formed, isolated, and characterized (not shown in Scheme 5) [28]. Under these conditions, a turnover of 98 % for substrate **12**, a combined yield of 95 % for cyclic ethers *rac*-**13** and *rac*-**14**, and a peroxide efficiency of 65 % is achieved. Other primary oxidants, such as H_2O_2, CHP, UHP, and PhIO were found to be less efficient in this reaction.



Scheme 5 Formation of cyclic ethers *rac*-**13** and *rac*-**14** in a (Schiff-base)vanadium(V)-catalyzed oxidation of 5-methyl-1-phenyl-4-hexen-1-ol (**12**) [38].

In further studies, it was noted that the stereoselectivity for the (Schiff-base)vanadium(V)-catalyzed oxygenation of 1-phenyl-substituted bishomoallylic alcohols is critically dependent on the substitution pattern at the olefinic π-bond (Scheme 6). For example, oxidation of 1-phenyl-4-penten-1-ol (**15**) and (*E*)-1-phenyl-4-hexen-1-ol (*E*)-(**16**) with TBHP in the presence catalyst **1** (10 mol %) affords *trans*-configured 2,5-substituted tetrahydrofurans as major products (*cis*:*trans* = 39:61 for *rac*-**17**, *cis*:*trans* = 40:60 for *rac*-**18** along with 14 % of 2-*trans*,6-*trans*-configured tetrahydropyran *rac*-**19**).

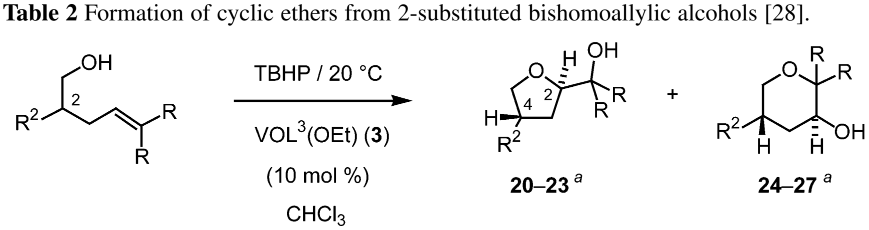


Scheme 6 Diastereoselection caused by the substitution pattern at olefinic π-bonds. [O] = TBHP, $VOL^1(OEt)(EtOH)$ (**1**) (10 mol %), $CHCl_3$, 20 °C [28,43].

The reaction of the (*Z*)-configured alkenol (*Z*)-(**16**) under these conditions proceeds with a marked preference for formation of the *cis*-diastereomer of *rac*-**18** (*cis*:*trans* = 90:10) [28,43]. In view of the side-chain configuration, it is imporatant to note that *unlike*-isomer of *rac*-**18** is formed from (*E*)-**16**, while (*Z*)-**16** furnishes exclusively the corresponding *like*-stereoisomer.

1-Amino-2-indanol-derived complex $VOL^3(OEt)$ (**3**) was the most selective oxidation catalyst (stereoselectivity, regioselectivity, and chemoselectivity) out of a larger set of vanadium(V) compounds and was therefore applied for the conversion of 2- or 3-substituted bishomoallylic alcohols with TBHP into the corresponding functionalized tetrahydrofurans (Tables 2 and 3). All these oxidations proceeded *trans*-selectively. In general, the selectivity and the efficiency for product formation from ω,ω-dimethyl-substituted substrates (entries 3 and 4 in Tables 2 and 3) was superior to reactions starting from substrates with terminal π-bonds (entries 1 and 2 in Tables 2 and 3).

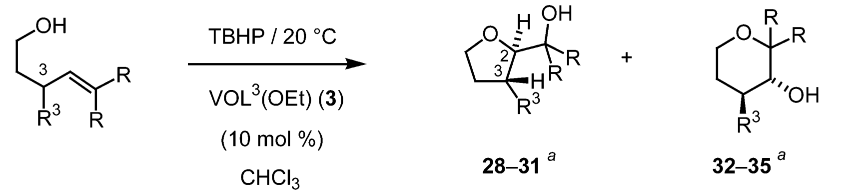
Table 2 Formation of cyclic ethers from 2-substituted bishomoallylic alcohols [28].



Entry	R^2	R	**20–23**	[%] (*cis*:*trans*)	**24–27**	[%] (*cis*:*trans*)
1	$CH(CH_3)_2$	H	**20**	90 (29:71)	**24**	– [b]
2	C_6H_5	H	**21**	43 (36:64)	**25**	– [b]
3	$CH(CH_3)_2$	CH_3	**22**	90 (19:81)	**26**	– [b]
4	C_6H_5	CH_3	**23**	55 (9:91)	**27**	4 (<2:98)

[a]Racemates.
[b]Not detected (^{1}H NMR).

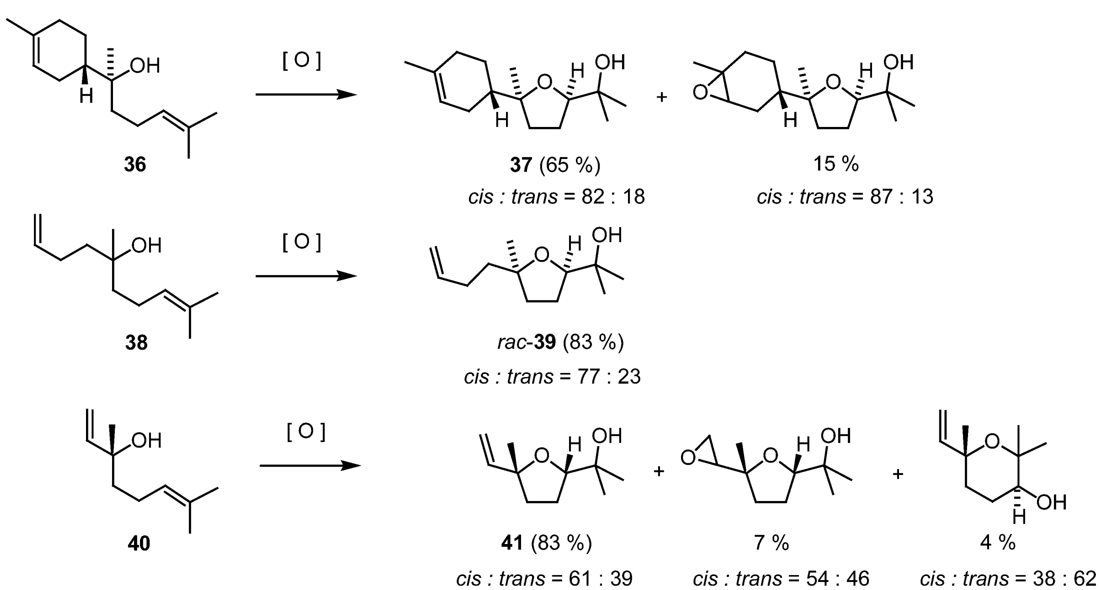
Table 3 Conversion of 3-substituted bishomoallylic alcohols into β-hydroxylated cyclic ethers [28].



Entry	R^3	R	**28–31**	[%] (*cis*:*trans*)	**32–35**	[%] (*cis*:*trans*)
1	$C(CH_3)_3$	H	**28**	61 (<2:98)	**32**	– [b]
2	C_6H_5	H	**29**	43 (40:60)	**33**	– [b]
3	$CH(CH_3)_2$	CH_3	**30**	54 (>2:98)	**34**	16 (<2:98)
4	C_6H_5	CH_3	**31**	76 (>2:98)	**35**	– [b]

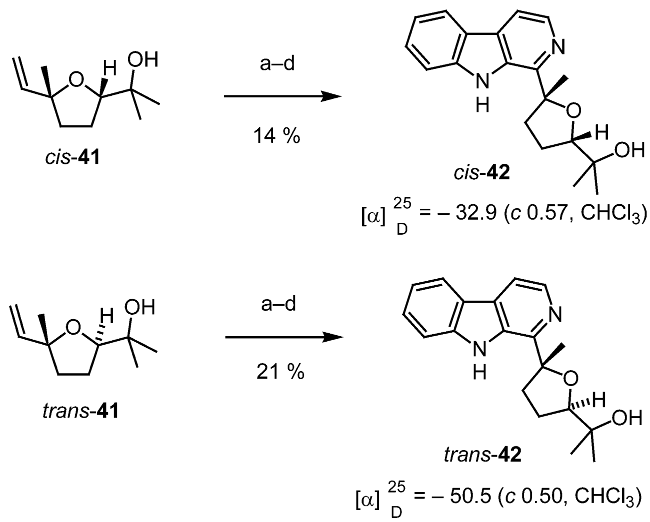
[a]Racemates.
[b]Not detected (^{1}H NMR).

Enantioselective tetrahydrofuran syntheses starting from prochiral bishomoallylic alcohols, TBHP and catalyst VOL^3(OEt) (**3**) have so far not been accomplished [28]. On the other hand, some noteworthy selectivities have been observed in (Schiff-base)vanadium(V)-catalyzed oxidations of dienols, such as (*S*,*S*)-bisabolol (**36**), (*R*)-linalool (**40**), and its twofold higher homologue **38** (Scheme 7). All compounds gave rise to well-defined regioselectivities, as seen in the formation of (–)-*epi*-bisabolol oxide B (**37**) and the twofold higher homologue *rac*-**39** of furanoid linalool oxide **41** [28,43,44].



Scheme 7 Vanadium(V)-catalyzed oxidation of (*S*,*S*)-bisabolol (**36**), tertiary alkenol **38** and (*R*)-linalool (**40**). [O] = TBHP, VOL^3(OEt) (**3**) (10 mol %), $CHCl_3$, 20 °C [28,43,44].

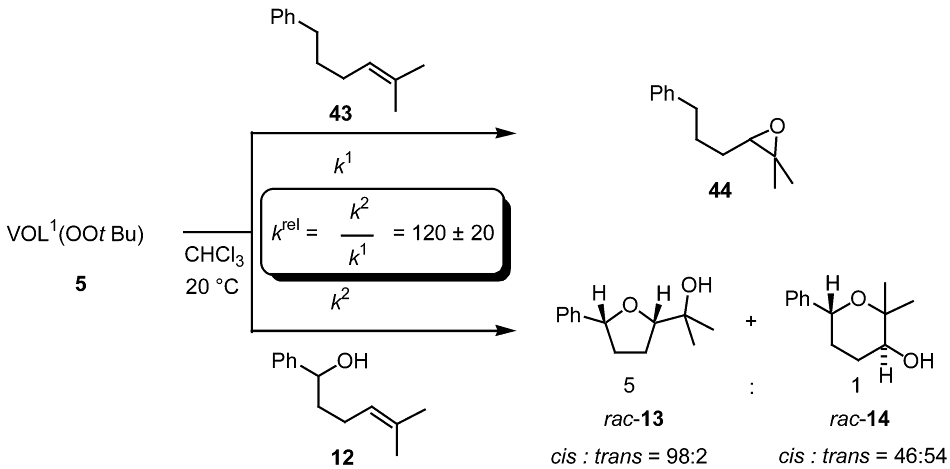
The selective oxygenation of (*R*)-Linalool (**40**) at positions 6,7 is, to my knowledge, the first example for a vanadium(V)-catalyzed oxidation at the bishomoallylic rather than at the allylic π-bond of this substrate [44,45]. The straightforward synthetic access to enantiomerically pure furanoid linalool oxides *cis*-**41** and *trans*-**41** has been opened a new perspective for a short synthesis of hitherto unknown derivatives of the natural product cyclocapitelline (Scheme 8) [16,44]. For example, oxidation of purified isomers *cis*-**41** and *trans*-**41** with $RuCl_3$ and $NaIO_4$ in a two-phase system of $C_2H_4Cl_2/H_2O$ affords the corresponding lactol from *cis*-**41** and a hydroxyaldehyde from *trans*-**41**. Treatment of these products with tryptamine provides Schiff-bases, which were cyclized in the presence of trifluoroacetic acid in a Pictet–Spengler-type reaction. Dehydrogenation of the cyclization products gave rise to β-carbolines *cis*-**42** and *trans*-**42** in satisfactory yields (Scheme 8).



Scheme 8 Formation of derivatives of cyclocapitelline from furanoid linalool oxides *cis*-**41** and *trans*-**41**. Reagents and conditions: (a) $RuCl_3$, $NaIO_4$, $C_2H_4Cl_2$, H_2O; (b) tryptamine, CH_2Cl_2; (c) CF_3CO_2H, CH_2Cl_2; (d) Pd/C, xylenes [44].

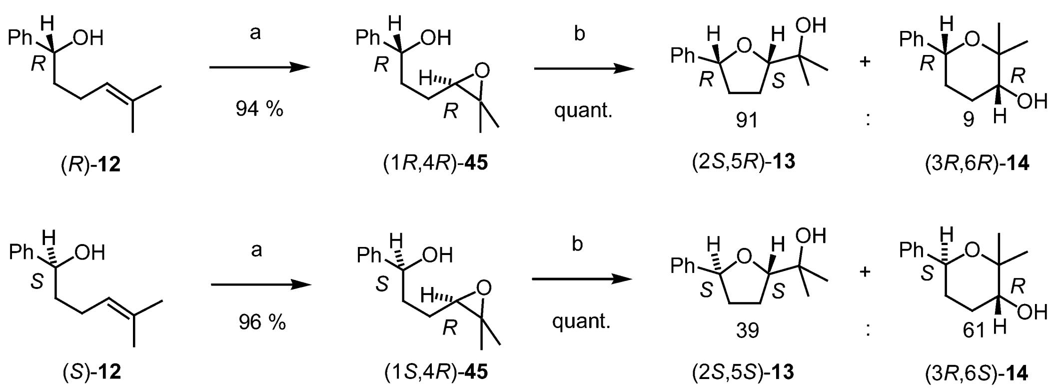
MECHANISTIC INVESTIGATIONS

The oxidation of 1-phenyl-5-methylhexenol **12** with TBHP in the presence of a (Schiff-base)vanadium(V) complex, e.g., *o*-aminophenol-derived catalyst **1**, affords 2-(1-hydroxy-1-methylethyl)-5-phenyltetrahydrofuran *rac*-(**13**) and 2,2-dimethyl-6-phenyltetrahydropyran-3-ol *rac*-(**14**) as major products (Scheme 5). Treatment of 2-methyl-6-phenyl-2-hexene (**43**) under these conditions furnishes 87 % of epoxide **44**. Oxidation of well-defined mixtures of substrates **12** and **43** in a set of competition experiments provides tetrahydrofuran **13** (*cis*/*trans*-isomers), tetrahydropyran **14** (*cis*/*trans*-isomers), *and* epoxide **44** (Scheme 9). A numerical analysis of likewise obtained kinetic data has been performed using a reaction model, which is based on a direct and irreversible oxygen atom transfer from peroxy complex **5** to substrates **12** and **43** under pseudo first-order conditions. The slope of a linear correlation between the ratios of ([**13**]+[**14**])/[**44**] and [**12**]/[**43**] then corresponds to the relative rate constant $k^{rel} = k^2/k^1 = 120 \pm 20$ (20 °C, $CHCl_3$) thus pointing to a rate-enhancing effect of the OH group for the oxygenation of **12** (see below).



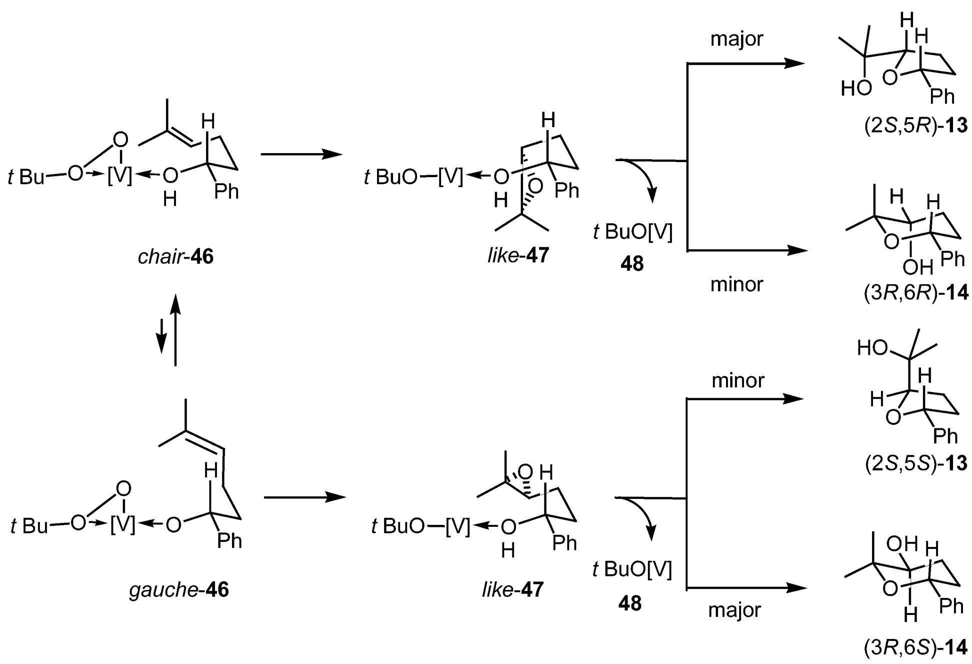
Scheme 9 Competition kinetics: oxygenation of alkenol **12** vs. olefin **43**.

The model for rationalizing the origin of the selectivity in alkenol oxygenation using the combination of TBHP and a (Schiff-base)vanadium(V)-catalyst has been supplemented by a concise stereochemical analysis starting from enantiomerically pure substrates (*R*)-**12** and (*S*)-**12** (both >99 % ee). The two alkenols were epoxidized under Shi-conditions [46] to provide (1*R*,4*R*)-**45** in 94 % yield (76 % de, ^{1}H-NMR, Scheme 10) from alkenol (*R*)-**12** [47] and (1*S*,4*R*)-**45** in 96 % yield (64 % de, ^{1}H NMR) from (*S*)-**12**. Assignment of the (*R*)-configuration at the stereocenter which was constructed in the Shi-epoxidation was based on (i) the general face selection rule for this well-established method [48] and (ii) a correlation of epoxyalcohol configurations with the geometry of rearranged products **13** and **14** (see below). Treatment of epoxyalcohol (1*R*,4*R*)-**45** with 10 mol % of vanadium(V) complex **3** or with 1 equiv of *p*-toluenesulfonic acid (TsOH) quantitatively affords 2,5-*cis*-configured tetrahydrofuran (2*S*,5*R*)-**13** and 3,6-*cis*-configured tetrahydropyran (3*R*,6*R*)-**14** in a ratio of 91:9. The vanadium(V)- or the acid-catalyzed rearrangement of epoxyalcohol (1*S*,4*R*)-**45** yields 2,5-*trans*-disubstituted tetrahydrofuran (2*S*,5*S*)-**13** and 3,6-*trans*-substituted tetrahydropyran (3*R*,6*S*)-**14** in a ratio of 39:61. Since the major component in one sample [e.g., (1*R*,4*R*)-**45**] constituted the enantiomer of the minor in the second probe [e.g., (1*S*,4*S*)-**45**], the by-products from each epoxide isomerization were readily identified.



Scheme 10 Diastereoselective conversion of alkenols (*R*)-**12** and (*S*)-**12** into cyclic ethers **13** and **14**. Reagents and conditions: (a) Shi-epoxidation [46]; (b) TsOH (1 equiv) or VOL^3(OEt) (**3**) (10 mol %), $CDCl_3$) [28].

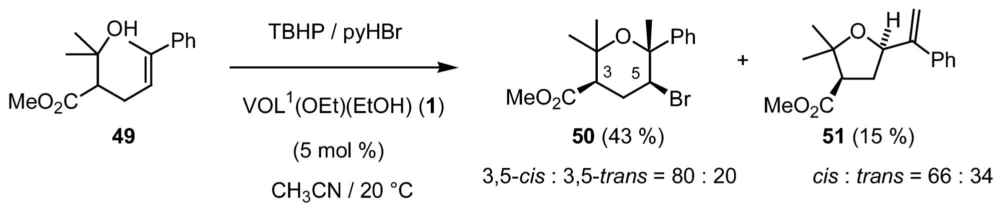
The information from the structure-selectivity survey, competition kinetics, and the stereochemical analysis match with a unified model (Scheme 11). According to this mnemonic device, the observed diastereoselectivities originate from a selective oxygen atom transfer in (*tert*-butyl peroxy)vanadium(V) complex **46**. Evidence for formation of intermediate **46** has been deduced from the result of the competition experiments that point to a rate-enhancing effect of the hydroxyl group in the oxygenation of substrate **12** (Scheme 9). A *syn*-selective oxygen atom transfer in "loaded" peroxy complex **46** onto one of the diastereotopic faces is feasible, if the alkenol chain adopts preferentially a *chair*-like folding (*chair*-**46**) or the geometry of *gauche*-**46**. On the basis of nonbonding interactions, the former should be favored upon an approach of the reacting entities, thus leading to the *like*-configured (epoxyalcohol)vanadium(V) complex *like*-**47**. Rearrangement of *like*-**47** and elimination of vanadium(V) complex **48** provides *cis*-disubstituted tetrahydrofuran *cis*-**13** as major and tetrahydropyran *cis*-**14** as minor product. It should, however, be noted that free epoxyalcohols have so far not been detected in reaction mixtures obtained by mixing a bishomoallylalkohol, TBHP, and a (Schiff-base)vanadium(V) catalyst. Substrate oxygenation in intermediate *gauche*-**46** occurs with an opposite facial selectivity, if compared to the formation of *like*-**47** from *chair*-**46**, thus leading to synthesis of *trans*-substituted heterocycles *trans*-**13** and *trans*-**14**. The reaction starting from *chair*-**46** is in most instances favored. Exception to this guideline are 1-substituted 4-penten-1-ols (e.g., **15**), (*E*)-1-phenyl-4-hexen-1-ol (*E*)-(**16**), and 3-substituted bishomoallylic alcohols, which obviously are oxidized via the pathway that starts from *gauche*-**46** [22,28].



Scheme 11 Stereochemical model for correlating the facial selectivity of π-bond oxygenation in "loaded" peroxy complex **46** with the geometry of likewise formed cyclic ethers **13** and **14**; [V] corresponds to the transition-metal fragment VOL^m, e.g., VOL^1 (see Scheme 3).

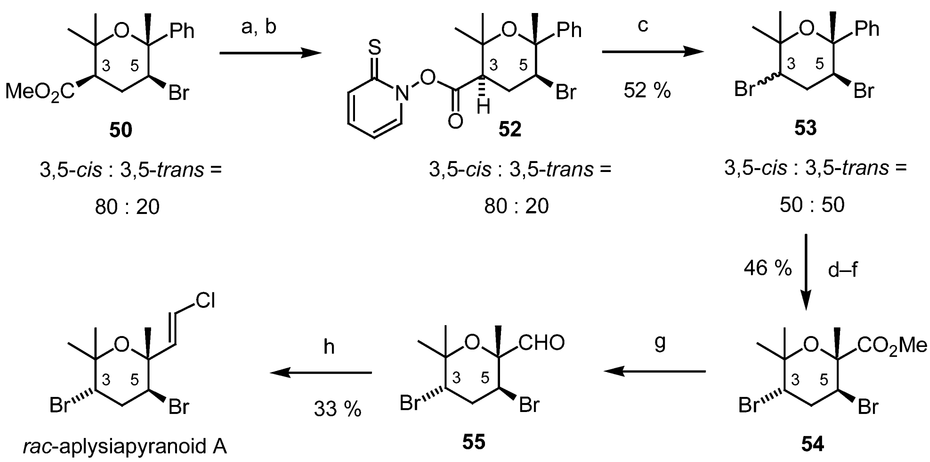
(SCHIFF-BASE)VANADIUM(V)-CATALYZED OXIDATION OF BROMIDE AND ITS APPLICATION IN THE SYNTHESIS OF APLYSIAPYRANOID A

The fact that Br^- is selectively oxidized by TBHP out of a mixture of the halide and a bishomoallylic alcohol has considerably extended the scope of (Schiff-base)vanadium(V)-catalyzed oxidations for selective syntheses of β-heteroatom-functionalized cyclic ethers [29]. According to data from a mechanistic study, Br_2 is formed as electrophilic brominating reagent with a slow but steady rate starting from Br^- and a (*tert*-butyl peroxy)(Schiff-base)vanadium(V) complex. This step is followed by a non-vanadium-dependent process, i.e., bromocyclization of an alkenol substrate [29,49]. The stereo- and regioselectivities in such ring closures therefore resemble those of many relevant examples from the literature [50] because the principles of substrate control [51] and not of transition metal-directed heteroatom transfer apply in the final step of this sequence. Since the primary event, i.e., the in situ generation of Br_2, takes profit from the principles of catalysis and thus does not require an on-site storage and handling of elemental Br_2, it is expected that this procedure opens new perspectives in organic synthesis [52]. This vision has been recently supported by reports on enantioselective syntheses of all naturally occurring muscarine alkaloids [53] and (±)-2-*epi*-magnosalicin—the 2-epimer of the antiallergic natural product (±)-magnosalicin—using this methodology [29,54]. More recently, the (Schiff-base)vanadium(V)-catalyzed oxidation of Br^- has been applied as key step in the synthesis of the heterocyclic core of the marine natural product aplysiapyranoid A using the 1,2-disconnection approach [55,56]. Thus, methyl (*E*)-2-(1-hydroxy-1-methylethyl)-5-phenyl-4-hexenoate (**49**) was treated in the initial step on a 15 g-scale with TBHP, pyridinium hydrobromide (pyHBr), and 5 mol % of catalyst $VOL^1(OEt)(EtOH)$ (**1**) to furnish 43 % of 6-*endo*-bromocyclized product **50** (3,5-*cis*:3,5-*trans* = 80:20) besides 15 % of tetrahydrofuran **51** (*cis*:*trans* = 66:34, Scheme 12). Substituents at C5 and C6 in both diastereomers of **50** exhibit relative *trans*-configuration. Formation of 5-(1-phenyl-1-hydroxy-1-ethyl)-substituted tetrahydrofurans or the corresponding tetrahydropyranols as side products, which might have originated from a competing direct vanadium(V)-catalyzed oxygenation of substrate **49**, was not observed [55]. It is further worth mentioning that attempts to convert alkenol **49** using the state-of-the-art reagent for conducting 6-*endo*-selective bromocyclizations, i.e., 2,4,4,6-tetrabromocyclohexa-2,5-dienone, failed to afford yields of target product **50** that exceeded 20 %.



Scheme 12 Application of the (Schiff-base)vanadium(V)-catalyzed oxidation of Br^- in the 6-*endo*-selective bromocyclization of styrene-derived alkenol **49** [55].

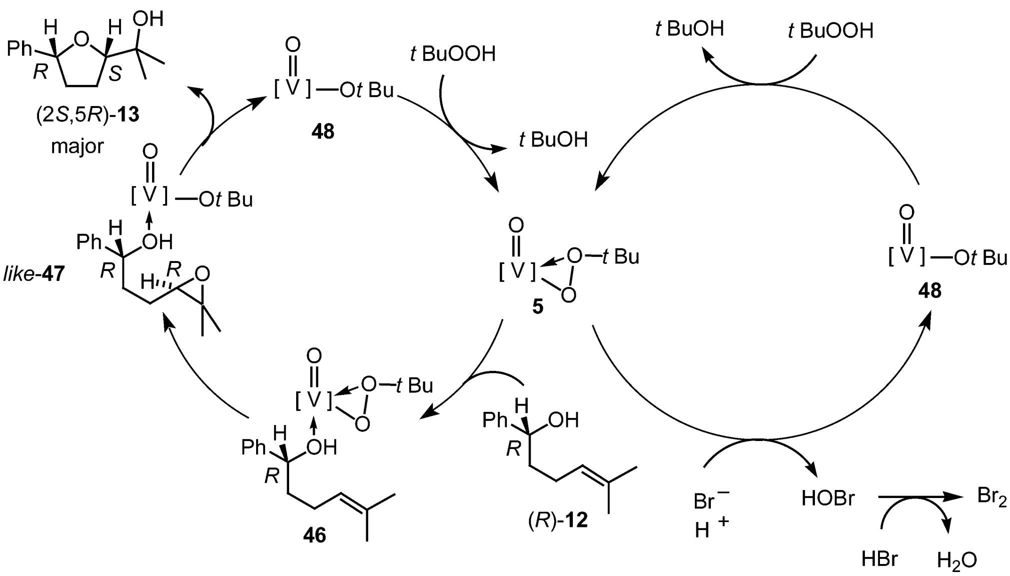
Saponification of methyl ester **50** with LiOH in a solution of aqueous dimethoxyethane provides upon neutralization a carboxylic acid (3,5-*cis*:3,5-*trans* = 80:20, 93 %), which was converted with *N*-(hydroxy)pyridine-2(1*H*)thione and diisopropylcarbodiimide (DIC) into mixed anhydride **52** (Scheme 13). Photolysis of pyridinethione **52** in the presence of $BrCCl_3$ affords dibromide **53** (3,5-*cis*:3,5-*trans* = 50:50, 52 % starting from the carboxylic acid derivative of **50**). For completion of the synthesis, the 3,5-*trans*-diastereoisomer 3,5-*trans*-**53** was purified and subsequently oxidized with the combination of $RuCl_3$ and $NaIO_4$ [57], to afford a crude carboxylic acid that was esterified with MeOH/DIC in CH_2Cl_2 to yield ester **54**. The latter compound was reduced with DIBAH in hexanes/CH_2Cl_2 to afford aldehyde **55**. Treatment of this product with $CrCl_2$ and $CHCl_3$ furnished aplysiapyranoid A as target compound [58].



Scheme 13 Completion of the synthesis of *rac*-aplysiapyranoid A. Reagents and conditions: (a) LiOH, DME, H_2O; (b) *N*-(hydroxy)pyridine-2(1*H*)-thione, DIC, CH_2Cl_2; (c) $BrCCl_3$, hν, C_6H_6, 20 °C; (d) chromatography; (e) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O; (f) CH_3OH, DIC, CH_2Cl_2; (g) DIBAH, hexanes, CH_2Cl_2; (h) $CrCl_2$, $CHCl_3$, THF [55].

SUMMARY AND CONCLUSION

(Schiff-base)vanadium(V) complexes are useful reagents for an activation of TBHP via intermediate formation of peroxy complexes, e.g., **5**. These compounds are electrophilic oxidants that are able to stereoselectively convert alkenols into functionalized cyclic ethers via a peroxy mechanism (Scheme 14). The stereoselectivities in this transformation generally are predictable using a stereochemical model, thus allowing a general application of this method in natural product synthesis. The reactivity of (*tert*-butyl peroxy)(Schiff-base)vanadium(V) complexes is further applicable for the oxidation of bromide (Scheme 14), in order to induce synthetically useful bromocyclizations in a second, non-vanadium-dependent step, as documented in the total synthesis of the marine natural product aplysiapyranoid A.



Scheme 14 Toward a unified mechanism for peroxide activation via in situ formation of (*tert*-butyl peroxy)(Schiff-base)vanadium(V) complex **5** and its application in the stereoselective synthesis of functionalized cyclic ethers via *syn*-selective oxygenation (left) or the generation of Br_2 (right) [28,29].

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32. The stereodescriptors *C* and *A* refer to *c*lockwise and *a*nticlockwise [30,31]. The assignment of the absolute configuration in square pyramidal complexes is performed as follows: (i) The four atoms in the plane of the coordination polyhedron are ranked according to the CIP convention. (ii) The reference projection requires a view on top of the atom that in combination with the central ion defines a C_4 axis. A *C*-configuration is associated with a clockwise arrangement of the four atoms in the plane of the square pyramid in decreasing CIP-hierarchy 1–2–3–4. If the atoms with CIP hierarchy 1 and 2 are bound in opposite and not in vicinal coordination sites, the direction for configuration assignment that proceeds via the atom with the hierarchy 3 is preferred thus leading to the sequence 1–3–2 instead of going from 1 via 4 to 2 and then on to 3. The latter error unfortunately has been made in earlier contributions from my group [10,22,28]. In all instances, the opposite configuration from of what has been reported in these papers is correct in order to agree with the IUPAC convention.
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