Institut de Chimie Organique
Université de Fribourg

Generation of Alkoxyl Radicals and their Applications for β-Scission Reactions in Bridged Bicyclic Systems

THESE

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par

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A Tous Ceux Que J'Aime

Résumé

Grâce à leur réactivité particulière et à leurs propriétés caractéristiques, les radicaux alkoxyles constituent un outil puissant de la chimie organique moderne. Parmi leurs transformations typiques, les réactions de β-scission ont retenu notre attention. En effet, la conversion stéréoselective de systèmes bicycliques pontés, permet d'obtenir de nombreux intermédiaires synthétiques utiles. Dans ce travail de thèse, nous décrivons nos efforts à ces fins.

Etudiant dans un premier temps les méthodes directes de génération des radicaux alkoxyles, nous avons traité des dérivés du norbornènol avec du tétraacétate de plomb. Dans ces conditions, le 2-méthylbicyclo[2.2.1]hept-5-èn-2-ol produit le *cis*-5-acétylméthyl-2-cyclopentyl acétate, avec un rendement de 65% et une stéréosélectivité totale. Afin de démontrer le potentiel de cette méthode pour la préparation de synthons cyclopentènes, nous avons synthétisé plusieurs précurseurs d'analogues de carbanucléosides.

Nous avons ensuite développé une nouvelle voie de synthèse des bicycles pontés de taille moyenne, en partant d'un dérivé de la norbornanone très facilement accessible. Le processus implique une séquence de cyclisation radicalaire intramoléculaire/β-fragmentation originale.

La réaction de fragmentation d'époxyde induite par un radical nous a permis de générer des radicaux alkoxyles à partir de radicaux oxiranylcarbinyles dérivés de bicyclo[2.2.n]alk-5-ènes. Leur β-scission/cyclisation suivie d'une réduction par un atome d'hydrogène ou d'un piégeage avec un allylstannane, a donné des cétones bicycliques fonctionnalisées avec des stéréoselectivités élevées.

Nous avons appliqué le réarrangement sulfoxyde-sulfénate à la génération de radicaux alkoxyles. En effet, le traitement du 2-(1-phénylsulfinyléthènyl)bicyclo[2.2.1]hept-5-ène avec Bu_3SnH/AIBN dans le toluène à reflux a fournit le radical 2-vinylbicyclo[2.2.1]hept-5-èn-oxyle qui, après fragmentation, cyclisation et piégeage a conduit à la *cis*-bicyclo[4.3.0]non-7-èn-3-one avec un rendement de 46%.

Enfin, nous avons développé une voie originale, donnant accès à un nouveau précurseur de radicaux alkoxyles. La réaction du dérivé phénylsélénylléthanesulfonate du *trans*-2-

phénylcyclohexanol en présence de tris(triméthylsilyl)silane et d'AIBN additionnés au pousse-seringue en 12 h, a produit le *trans*-2-phénylcyclohexanol avec un rendement de 26%, ce qui constitue un résultat encourageant en faveur d'un mécanisme radicalaire de la réaction.

Summary

Due to their peculiar reactivity, alkoxyl radicals have unique characteristic properties, which make them powerful tools in modern organic chemistry. Among their typical transformations, β-scission reactions have retained our interest because of their potential in converting stereoselectively bridged bicyclic systems into a variety of useful synthetic intermediates. In this work, we describe our efforts directed toward this goal.

We first decided to study a direct method for the generation of alkoxyl radical and treated several norbornenol derivatives with lead tetraacetate. When starting from 2-methylbicyclo[2.2.1]hept-5-en-2-ol, yields up to 65% and total selectivity has been obtained in favor of *cis*-5-acetylmethyl-2-cyclopentyl acetate. To demonstrate the potential of the developed method for the preparation of versatile cyclopentene synthons, synthesis of a variety of carbanucleoside analogue precursors was achieved from the latter.

In a different approach, we developed a new and promising method for the synthesis of medium-sized bridged bicycles with good yields, starting from a readily available norbornenone derivative. The process involves a novel radical intramolecular cyclization/β-fragmentation sequence.

Further work led us to take advantage of the radical-induced epoxide fragmentation reaction to generate alkoxyl radicals from oxiranylcarbinyl radicals of bicyclo[2.2.n]alk-5-ene derivatives. Upon β-scission, cyclization and hydrogen reduction or trapping with an allylstannane, those afforded functionalized bicyclic ketones with moderate to good yields and high stereoselectivities.

We then found an application of the well-known sulfoxide-sulfenate rearrangement for the generation of alkoxyl radicals. Indeed, treatment of 2-(1-phenylsulfinylethenyl) bicyclo[2.2.1]hept-5-ene with Bu_3SnH/AIBN in refluxing toluene gave 2-vinylbicyclo[2.2.1]hept-5-en-oxyl radical which, after fragmentation, cyclization and trapping, afforded the expected *cis*-bicyclo[4.3.0]non-7-en-3-one in about 46% yield.

Finally, in a preliminary study, we prepared the phenylselenylethanesulfonate derivative from *trans*-2-phenylcyclohexanol and tested it as an alkoxyl radical precursor. Its reaction with syringe-pump addition of tris(trimethylsilyl)silane and AIBN over 12 h in

refluxing toluene, resulted in formation of a 26% yield of *trans*-2-phenylcyclohexanol, which constituted an encouraging result in favor of a radical pathway for the reaction.

Table of Contents

Generation and Application of Alkoxyl Radicals in Organic Synthesis

1. Introduction

Over the past 30 years, radical chemistry has known a big surge.[1-5] While it was first considered as the dark part of chemistry, radicals being believed to be too reactive and unstable to be useful for synthetic purposes, it has now become an unavoidable chapter of the synthetic organic chemistry library. However, most of the research has focused on carbon-centered radicals, alkoxyl radicals having attracted interest to a much lesser extend. Early work was reported by Barton,[6] Mihailovic[7] and Surzur,[8] but systematic study has developed only during the past few years.

This review summarizes the actual knowledge on alkoxyl radical chemistry. Most of the methods for the generation of that species and its chemistry will be described.

2. Reactivity

As supported by the bimolecular rate of hydrogen abstraction from tributyltin hydride ($\sim 10^8$ $M^{-1}s^{-1}$, 30°C), measured by Ingold,[9,10] alkoxyl radicals are believed to be electrophilic. Due to their high reactivity, alkoxyl radicals have unique characteristic properties, which make them suitable for ring closure reactions,[11,12] for selective hydrogen abstractions[13-15] and remote functionalizations of non-activated carbon hydrogen bonds[16] as well as for ring expansion of cycloaliphatic compounds by β-scission.[17,18]

Intramolecular hydrogen atom transfer, giving alcohols, has been observed to occur only *via* six-centered transition structures.[19-21] The preference for δ-H-atom abstraction has been attributed to a more favorable entropy of activation, while ε-H-atom abstraction is enthalpically favored.[22] The rate constant of the reaction has been shown to be relatively independent of the nature of the alkoxyl radical.[19,23]

In alkoxyl radical 5-*exo-trig* cyclization, formation of the five-membered tetrahydrofuran derivative, happening with rates on the order of 5.2 x 10^8 s^{-1},[24,25] is favored over the six-membered tetrahydropyran ring. In contrast, 6-*exo-dig* cyclization produces both six- and seven-membered ring compounds.[6,26] A stereochemical model, based on the study of substituted 4-pentenyl-1-alkoxyl radicals, was proposed by Hartung for oxygen radical cyclization.[12,27] Indeed, data derived from competition kinetics point to a chairlike transition state which should be similar to the one found in the 5-hexenyl radical rearrangement. Thus, the major products arise from transition geometries with the substituents aligned in pseudo-equatorial position (Figure 1).[28]

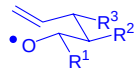
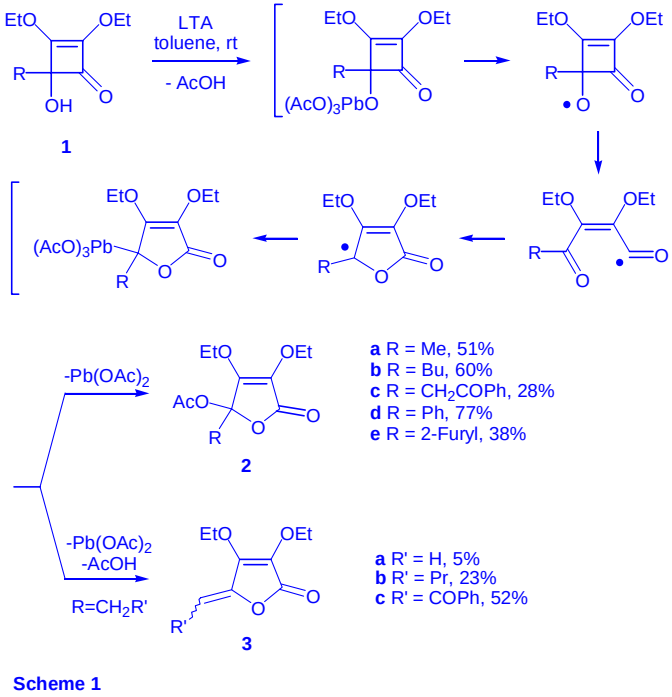


Figure 1

Driving forces in β-scission reactions are of three types: relief of ring strain,[29] cleavage of carbon-heteroatom bonds[30] and formation of the π C-O bond.[31] Its cleavage pattern reflects the interplay of multiple thermodynamic and kinetic factors whose precise nature or impact remains undetermined.[32] The process is helped by increasing substitution on both the alkoxyl carbon atom, and on the resulting C-centered radical,[33] but polar and steric effects may influence it.[34,35] Thus, if β-scission is usually reported to occur more rapidly than the competing processes as H-abstraction or disproportionation, Beckwith has demonstrated its reversibility and, in certain conditions, the possibility for the competing H-abstraction process to take place faster.[36,37]

The use of alkoxyl radical for organic synthesis is largely dependent on the availability of the adequate radical precursor. Indeed, formation of the radical and its evolution in the chemical transformation through a radical chain process relies on a delicate balance: if the starting molecule stability has to be high enough for manipulations, one bond must have a sufficiently low dissociation energy for selective homolysis on an appropriate kinetic time scale.[3]

One of the most attractive methods for the generation of alkoxyl radicals is the straightforward formation of the radical from an alcohol. This approach allows direct access to the wanted species, avoiding tedious synthesis of a precursor. To this purpose, a palette of reagents has been developed. However, this strategy has not provided a universal solution to the problem of alkoxyl radicals generation. Consequently, a number of alternative methods have shown their efficiency in the alkoxyl radical chemistry.



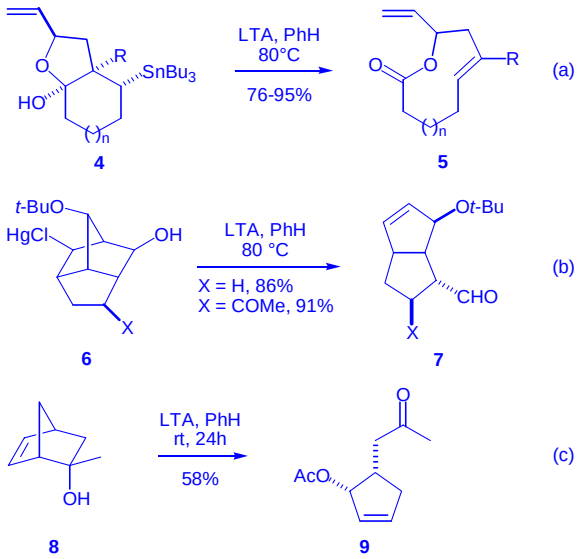
Scheme 1

3. Direct methods of generation

Lead tetraacetate ($Pb(OAc)_4$). Although reactions of lead tetraacetate (LTA) with alcohols are reported since the early sixties,[38,39] their mechanism was admitted to involve an alkoxyl radical only in the seventies when Mihailovic and Surzur studied extensively the

course of the reaction which can follow ionic, radicalar or mixed pathways, depending on the reaction conditions.[7,40-43] Since pioneering work, the method has been applied to organic synthesis. Thus, as reported by Egushi, treatment of 4-hydroxy-2-cyclobutenones **1** with LTA (2 equiv.) in dry toluene at room temperature gave good yields of 5-acetoxy-2(5*H*)-furanones **2** and moderate yields of 5-alkylidene-2(5*H*)-furanones **3** *via* a possible alkoxyl-radical-triggered mechanism (β-scission) and subsequent 5-*endo* ring closure (Scheme 1).[44,45]

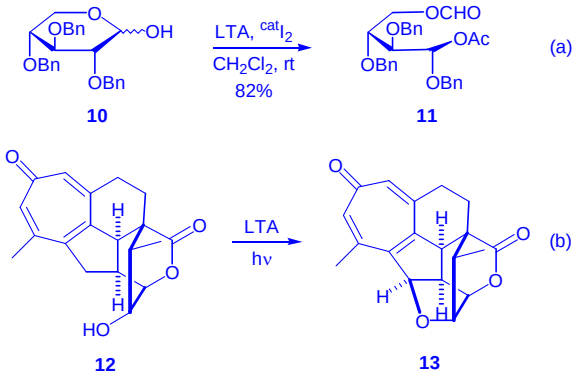
By a similar procedure, Posner[46] has demonstrated that lactols could be converted to lactones *via* an alkoxyl fragmentation/tributylstannyl radical elimination sequence. Continuation of this strategy led Zhao[47] to the preparation of functionalized nine or ten-membered lactones **5** with 76-95% yields, after fragmentation of bicyclic hemiacetals **4** (Scheme 2a).



Scheme 2

Moreover, triquinane precursors were synthesized in 1998 by Lautens and Blackwell.[48] Indeed, upon mixing the norbornane derivative **6** and LTA in benzene at 80°C, compound **7** was obtain in 86-91% yields after a highly regioselective fragmentation and elimination of the mercurial substituent (Scheme 2b). Recently, taking advantage of this methodology, we were able to synthesize carbanucleoside analogues derived from **9**, which was obtained with a nearly complete stereocontrol in 58% yield, by treatment of **8** with LTA (2 equiv.) in anhydrous benzene during 24 h (Scheme 2c).[49]

Several variations have been brought to the classical procedure. As described by Ianaga, erythrose and threose have been prepared from mixed acetal formates as **11** formed in 82% yield by LTA-promoted fragmentation of the C_1-alkoxyl radicals of pyranose derivatives **10** in the presence of iodine catalyst (Scheme 3a).[50]

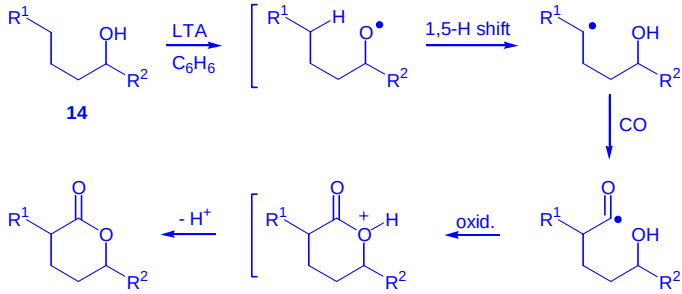


Scheme 3

In 1998, the structure of hainanolidol (**12**) was established thanks to its conversion into the already known harringtononlide (**13**) by transannular oxidation with LTA under irradiation (Scheme 3b).[51,52]

Combination of the LTA-oxidation system with free radical carbonylation offers a direct access to δ-lactones. Indeed, on the one hand, generation of an alkoxyl radical from a linear primary alcohol **14** or secondary alcohol is followed by a 1,5-hydrogen-transfer, which creates a carbon-centered radical δ to oxygen. Trapping of this species with carbon

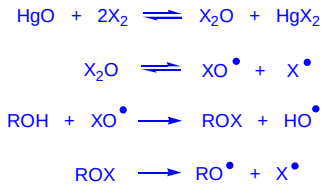
monoxide, oxidation and cyclization of the resulting radical yields the δ-lactone **15** in 38-68% yields (Scheme 4).[53] On the other hand, β-scission of C_1-unsubstituted cyclobutoxy radicals and subsequent carbonylation of the resulting radical affords δ-lactones with ring expansion.[54] However, while tertiary linear alcohols are unreactive, C_1-substituted cyclobutanols afford 5-oxoacid derivatives.



Scheme 4

Lead dioxide (PbO_2). As reported by Miura, PbO_2 was able to promote direct formation of an alkoxyl radical from an alcohol. Thus, exceptionally persistent and oxygen insensitive 2,7-di-*tert*-butylpyren-1-oxyl radical was generated when the hydroxypyrene precursor was treated with PbO_2 and K_2CO_3 in benzene.[55]

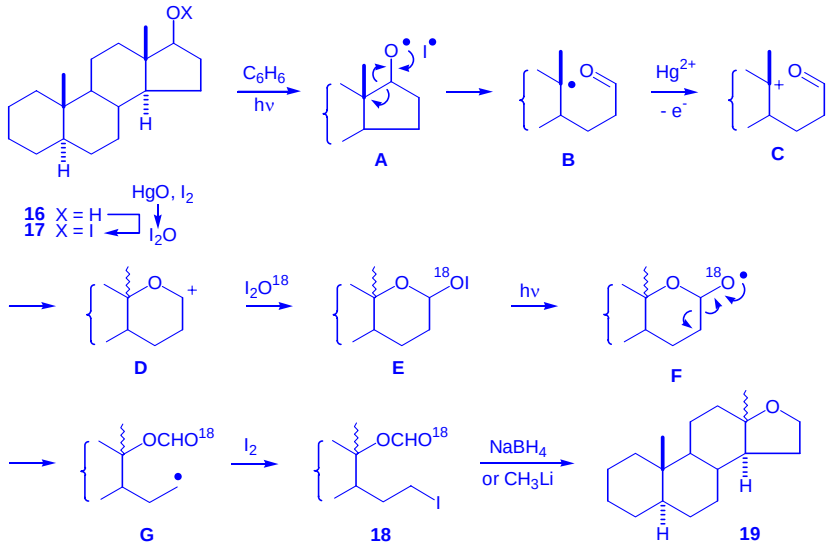
Mercury II oxide/iodine (HgO/I_2). As reported by Galatsis, it is assumed that the HgO/I_2 system first forms mercuric iodide and diiodomonoxide (I_2O). Homolysis of this gives the active species, an hypoiodide radical, which in turn generates alkoxyl radicals (Eq. 1).[56]



Equation 1

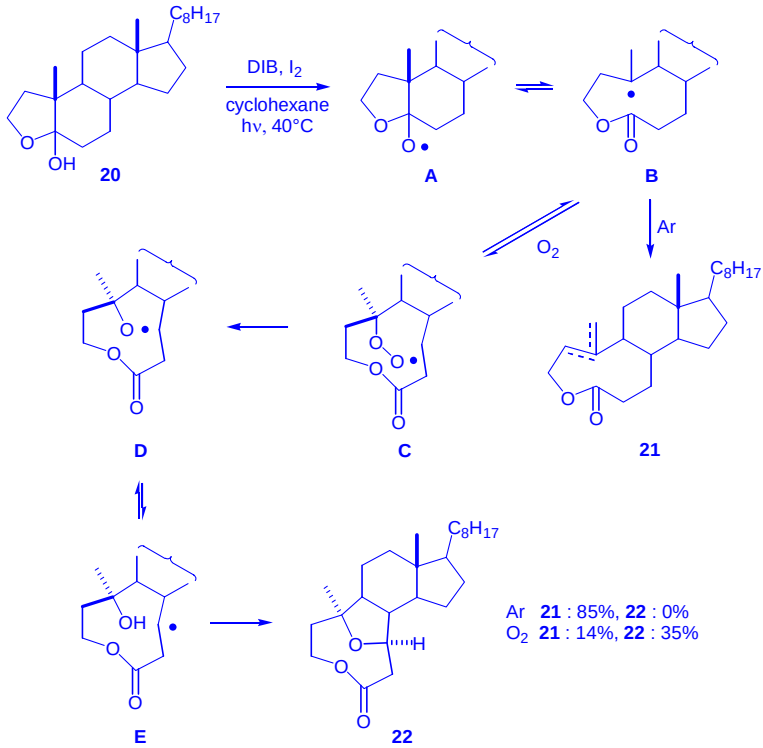
Introduced by Akhtar and Barton,[57] the mercury II oxide/iodine reagent has been used extensively for β-scissions by Suginome,[58-79] who has developed the methodology and its applications to the synthesis of natural products. Thus, a variety of molecules have been prepared by synthesis involving a selective fragmentation of alkoxyl radicals as the key step. In standard procedure, those were generated by photolysis of the corresponding hypoiodites formed *in situ* with HgO/I_2, in benzene, with Pyrex-filtered light. The class of molecules obtained by this method include heterosteroids, [58-61] 18- and 19-norsteroids,[62] steroidal lactones,[63] benzohomotropones,[64] 18-functional steroids,[65] lignans,[66,67] medium-sized lactones,[68] macrolides,[69] phthalides,[70] naphthalide lignanes,[71] monocyclic lactones,[72] macrocyclic lactones,[80,73] macrocyclic ketones,[74,32,75] furanoheterocycles,[76] furanoquinolones,[77] isocoumarins[78] and sesquiterpenes.[79]

Clarified by ^{18}O-labeling, the reaction path for the formation of **18** from cyclic alcohols **16** involves a hypoiodite **17**, formed *in situ* by treatment of the starting material with an excess of HgO/I_2. Irradiation of the hypoiodite **17** gives an alkoxyl radical **A**, which undergoes fragmentation to the stabilized tertiary carbon-centered radical **B**. One-electron oxidation to the corresponding stabilized tertiary carbocation **C**, combination with the formyl oxygen to form a tetrahydropyranyl cation **D** and its subsequent trapping by I_2O^{18} generates a lactol hypoiodite **E**. Photolysis of this results in a secondary alkoxyl radical **F**. Regioselective β-scission and abstraction of an iodine from an I_2 molecule by the carbon-centered radical **G**, furnishes the formate **18**. The latter can be readily converted into oxasteroids **19** by treatment with a complex metal hydride or methyllithium (Scheme 5).[58,59,81]



Scheme 5

Diacetoxyiodobenzene/iodine (DIB/I_2). Among the hypervalent iodine reagents,[82] which have been used for alkoxyl radical generation, diacetoxyiodobenzene (DIB)/iodine system has been the most deeply studied. Having found application for fragmentations, cyclizations as well as for rearrangements, the methodology was recently effectively used in a number of total syntheses.[83-85] Introduced by Suárez, the standard procedure involves treatment of the alcoholic substrate with DIB in the presence of iodine, under irradiation with visible light.[86-89] For example, photolysis of steroidal lactol **20** with stoichiometric amounts of DIB and iodine, under inert atmosphere leads to alkoxyl radical **A**. Its β-fragmentation provides a C-centered radical **B**, which is stabilized by elimination of an hydrogen atom to afford medium-sized lactones **21** in good yield (Scheme 6).[86,90] Meanwhile, in the presence of molecular oxygen, peroxidation of **B** and homolysis of the hydroperoxide bond of radical **C** furnishes an alkoxyl radical **D**, which undergoes hydrogen abstraction to give the tetrahydrofuran derivative **22** in 35% yield (Scheme 6).[91,92]

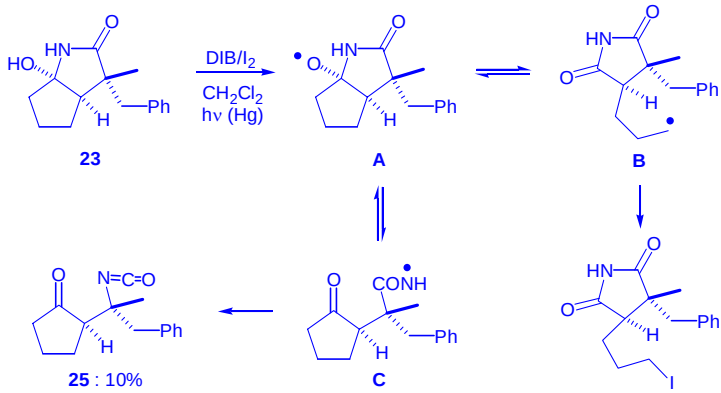


Scheme 6

Similar sequential alkoxyl radical fragmentations can be applied to the preparation of various interesting medium-sized ketones,[93,94] aldehydic biquinanes[95] and lactones.[96-99] Extension of the Suárez methodology to a variety of substrates has opened an access to building blocks for the synthesis of natural products.

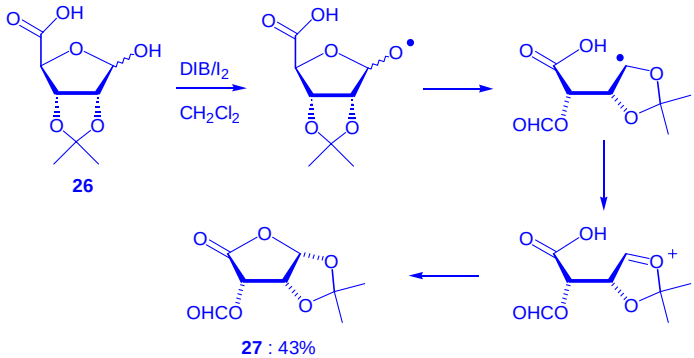
Thus, DIB/I_2-assisted β-fragmentation of bicyclic carbinol amides of the type **23** is a mild and simple method for the preparation of 2-(3-iodopropanyl)-substituted succinimides as **24**. The process occurs through an initial alkoxyl radical **A**, which undergoes two types of β-fragmentation to generate radicals **B** and **C**. While radical trapping of **B** by an iodine radical from the medium delivers a 72% yield of **24**, N-radical **C** suffers an amidyl rearrangement to give the isocyanate **25** in 10% yield. No scission of the C_1-C_5 bond is

observed, the more stable five-membered imide being obtained in all cases as the major product, along with some isocyanide (Scheme 7).[100]



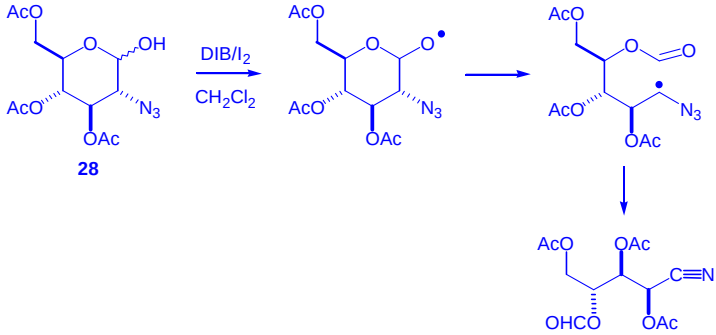
Scheme 7

Fragmentation of anomeric alkoxyl radicals of carbohydrates generated with the DIB/I_2 system provides a convenient entry into chiral building blocks.[101] And, after chiral furanose and pyranose derivatives,[102] aldopyranosuronic and aldofuranosuronic acid lactones as **27**, obtained in 43%, were synthesized by a tandem β-fragmentation-cyclization strategy (Scheme 8).[103]



Scheme 8

Similarly, chiral nitrile **29** was obtained in 88% yield by β-fragmentation of alkoxyl radicals deriving from β-hydroxy azide **28** (Scheme 9).[104]

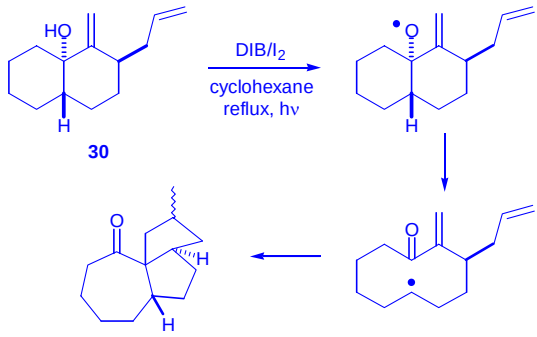


28

Scheme 9

29 : 88%

By way of a cascade radical fragmentation-transannular cyclization sequence, ketone **31** was prepared in 81% yield after treatment of bicylic dienol **30** with DIB/I_2 in degassed cyclohexane under irradiation and reflux (Scheme 10).[105] More recently, transannular cyclization of 6-hydroxyalkyl 5-cyclodecenones were reported by Suárez.[106]

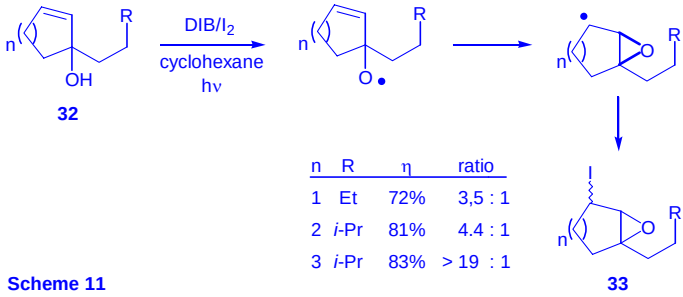


30

31 : 81%

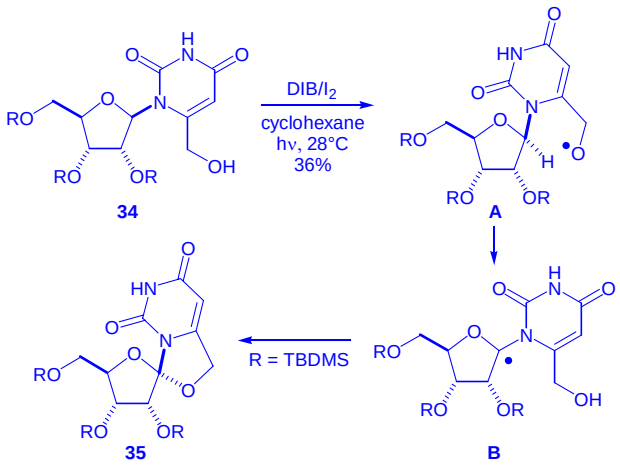
Scheme 10

Tertiary allylic alcohols **32** react with DIB/I_2 in cyclohexane under irradiation to give α-iodo epoxides **33** in 72-83% yields, as a result of alkoxyl radical rearrangement[107,108] (Scheme 11).[108]



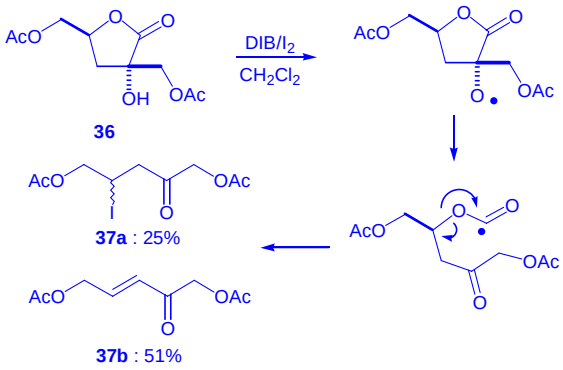
Scheme 11

Recently, Suárez conditions were found to be efficient for the preparation of spironucleosides in moderate yields from nucleoside analogues **34**, *via* 1,5-hydrogen migration of a conveniently situated alkoxyl radical **A** to anomeric position.[109] The mechanism involves subsequent oxidation and stereospecifical cyclization of the resulting anomeric C-1' radical intermediate **B** into orthoamide **35** (Scheme 12).



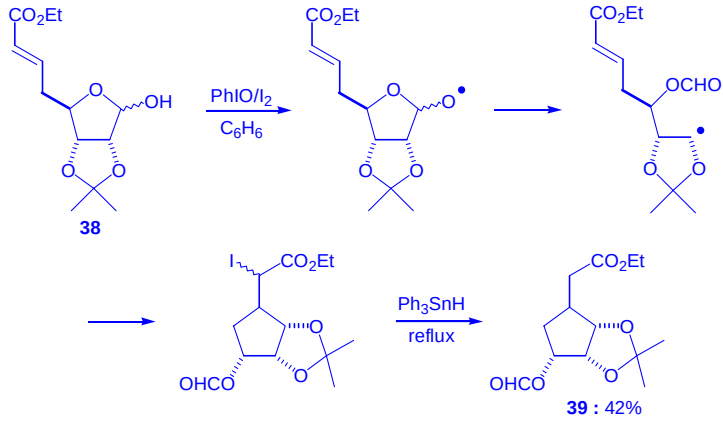
Scheme 12

Procedures that do not require irradiation have also been described. For example, Ianaga developed a fragmentation of pyranose derivatives, which proceed smoothly at room temperature, in toluene, with catalytic iodine.[50] Suárez reported that α-hydroxylactones as **36** undergo decarboxylation when submitted to the DIB/I_2 system in non-photochemical conditions (Scheme 13).[110] However, as outlined by Egushi, with 4-alkynyl-4-hydroxycyclobutenones, the reaction mechanism then switches from radicalar to ionic.[45]



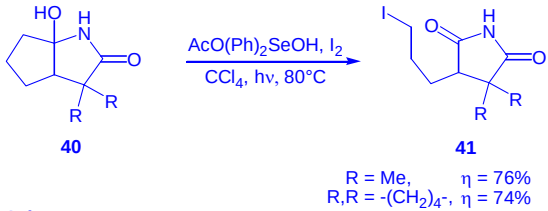
Scheme 13

In contrast to DIB/I_2 system, other hypervalent iodine reagents have only been little explored. However, on the one hand, Iadonisi has reported the use of hemiketal as substrate for a Suárez reaction with $(CF_3COO)_2IPh/I_2$ as reagent, to produce aldehydo tetroses *via* fragmentation of the generated alkoxyl radical.[111] On the other hand, Suárez has investigated tandem β-fragmentation/intramolecular cyclization sequences of alkoxyl radicals generated by treatment of carbohydrates by the system iodosylbenzene/iodine. Thus, while similarly as with DIB/I_2, aldotetroses and aldopentoses, resp. furanose and pyranose forms of hexuloses were synthesized from simple, resp. C2 hydroxymethylated carbohydrate derivatives,[112,113] C-C bond forming was achieved in moderate yields from carbohydrate lactols as **38** containing a suitable unsaturated ester side-chain, to produce cyclopentane derivatives as **39** (Scheme 14).[114]



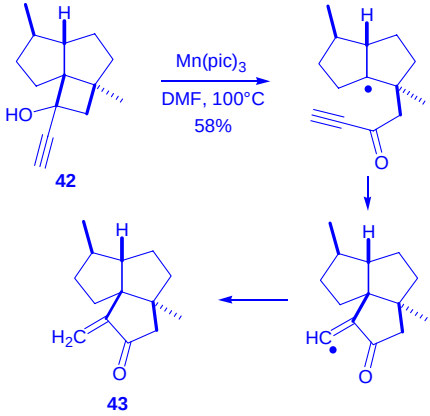
Scheme 14

Diphenylselenium hydroxyacetate/iodine. The diphenylselenium hydroxy acetate/iodine system was introduced by Suárez in 1988 as an efficient reagent to generate alkoxyl radicals.[115] It has proven to be an interesting agent to add to the library of organic synthesis.[83] Moreover, good yields of 3,4-substituted cyclic imides **41** were cleanly obtained by irradiation of a variety of carbinoamides **40** with diphenylselenium hydroxyacetate/iodine (Scheme 15, see also Scheme 7).[116]



Scheme 15

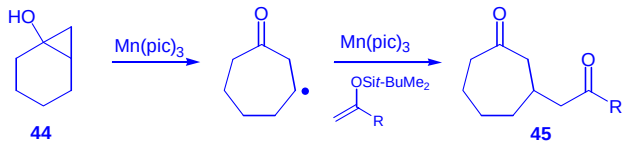
Mn(III)-reagents. Tris(2-pyridinecarboxylato)manganese[117,118] has been reported to promote oxidative fragmentation-cyclization of ethynyl cylclobutanol **42**, providing an efficient route to the methylene-cyclopentanone **43**, a key intermediate for the total syntheses of (-)-silphiperfol-6-ene and (-)-methyl cantabradienate (Scheme 16).[119]



42 **43**

Scheme 16

Further utilization to the generation of β-keto radicals from cyclopropanols as **44** and their addition to olefins allowed preparation of compounds such as 1,5-diketones **45** (Scheme 17).[120] Manganese triacetate ($Mn(OAc)_3$) has been used similarly with vinyl cyclobutanols[121] and 4-hydroxycyclobutenones.[44]



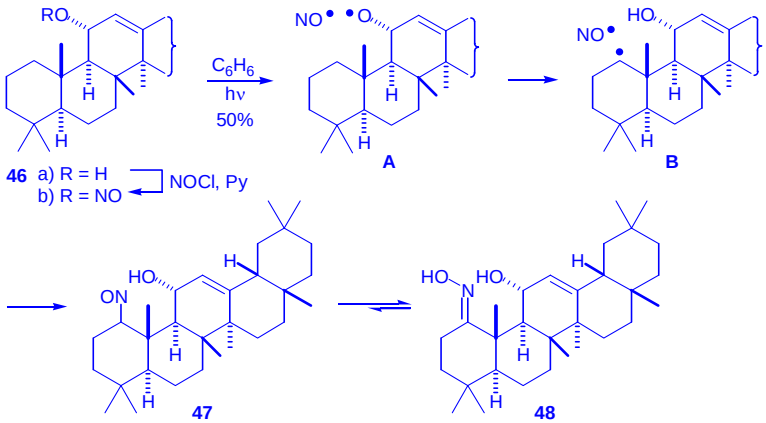
44 **45**

Scheme 17

4. Indirect methods of generation

Nitrite esters. After pioneering work on the behavior of the alkoxyl radicals generated by photolysis of the corresponding nitrite esters, i.e. intra- and intermolecular H-abstraction[122,123] or, as for cycloalkyl nitrites, C-C bond fission, the free radical chemistry of nitrite esters was essentially derived from two reactions. On the one hand, the Barton nitrite ester reaction[124,16] constituted a starting point in the development of free radicals as

useful intermediates in synthetic chemistry but also in allowing the functionalization of remote and inactivated positions within steroids. For example, in total synthesis of β-amyrin, 11-α-hydroxy-β-amyrene **46a** was treated with nitrosyl chloride in pyridine and the resulting crystalline nitrite **46b** photolyzed in benzene solution. After hydrogen atom transfer from the methylene carbon to the intermediate alkoxyl radical **A**, nitrosation of the resulting C-centered **B** radical took place. Tautomerization of the obtained nitroso-alcohol **47** afforded 11-α-hydroxy-1-oximino-β-amyrene **48** in 50% yield (Scheme 18).[6] The fact that only carbon situated in the position δ to the original OH group becomes nitrosated indicate a six-membered transition state for the H-abstraction.

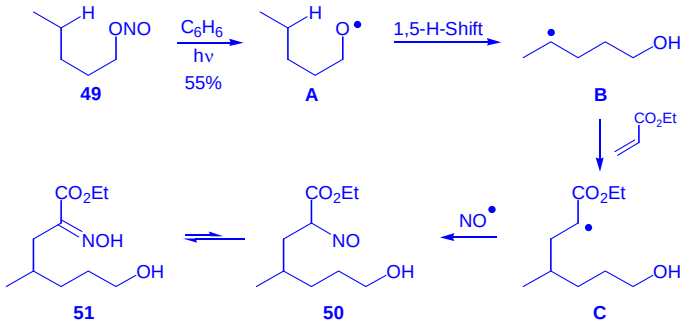


Scheme 18

On the other hand, nitrite esters of γ,δ–unsaturated alcohols were described as valuable precursors of the formation of oxime through photolysis of the corresponding nitrite ester and cyclization of the resulting radical onto alkenes.[125,42,43]

As a combination of those studies, Petrovic and Cekovic[126] managed to functionalize the δ–carbon atom of alkyl nitrites **49** by a Michael type alkylation. Indeed, alkoxyl radical **A**, generated by irradiation of **49**, undergoes 1,5-hydrogen rearrangement to give δ–carbon radical **B**. In the presence of large excess of electron deficient olefins (Michael acceptors),

this is trapped to form a new radical **C**, which is quenched by NO affording acceptable yields of nitroso compound **50** and then oxime **51** (Scheme 19).

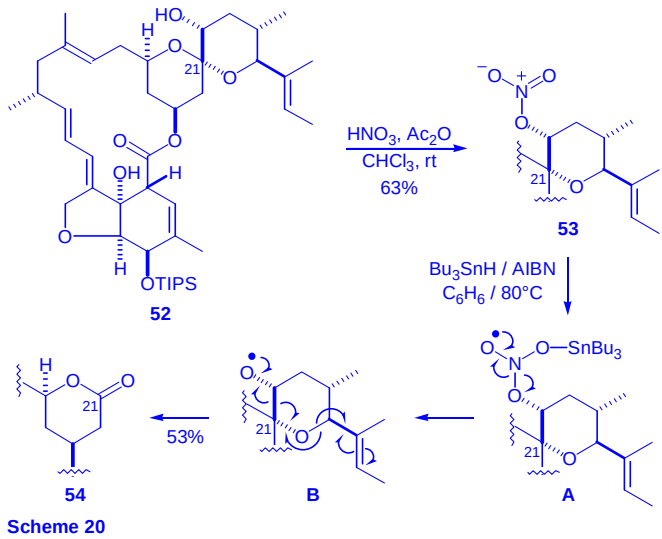


Scheme 19

Besides remote functionalization and β-scission, some examples of ring expansions of alkoxyl radical deriving from nitrite esters have been reported on bicyclic systems.[127,128] Moreover, Grossi[129,130] has recently suggested that also simple alicyclic nitrites can undergo a steroid-type ring expansion process. Due to their availability, nitrite esters have become attractive reagents for expanding the general repertoire of synthetic reactions.[31]

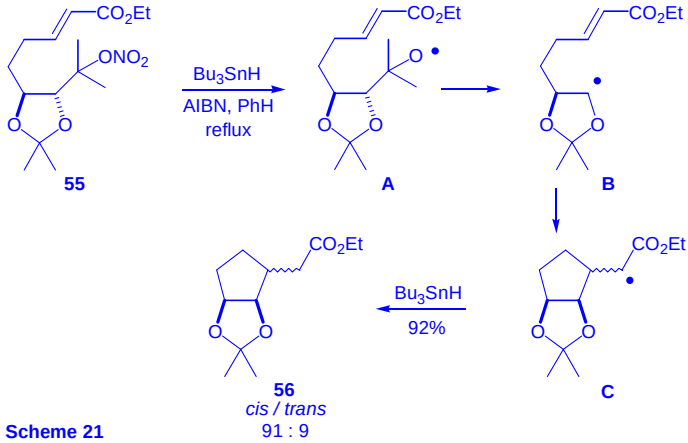
Nitrate esters. In contrast with nitrite esters, nitrate esters do not incorporate nitrogen oxide units into the product of their reaction. Robust and easily formed, they can be removed with tributyltin hydride/AIBN[131,132] or by photochemical means.[133,134] The apparent harsh conditions for their formation, *i.e.* treatment of the alcohol with fuming nitric acid (2 equivalents) and acetic anhydride, are in fact compatible with sensitive functional groups.

Application of this methodology allowed synthesis of complex compounds[135-138] as amino acids,[35] or as lactone-containing macrocycle **54**, an intermediate for the preparation of semi-synthetic milbemycins.[139] Thus, heating of **53** obtained from the corresponding alcohol **52**, in benzene solution with AIBN and tributyltin hydride resulted in the formation of lactone **54** in 53% yields *via* a probable mechanism involving **A**-**B**, as showed in Scheme 20.[139] Nitrate esters have also been used for reactivity studies.[35,140]



Scheme 20

An original utilization of nitrate esters was reported by Murphy.[137,138] Indeed, reaction of alkyl nitrate **55** with tributyltin hydride generated an intermediate alkoxyl radical **A** which, upon fragmentation, afforded the dioxolanyl radical **B**. Cyclization of the latter gave products *cis*-**56** and *trans*-**56** in 84% and 8% yields respectively, after reduction of radical **C** (Scheme 21).[137]



Scheme 21

N-alkoxypyridine-2-thiones. Inspired by Barton's chemistry, *N*-alkoxypyridine-2-thione **A** utilization as alkoxyl radical precursor was introduced by Beckwith and Hay in 1988.[141,142,36] Prepared by treatment of a salt of 2-mercaptopyridine-*N*-oxide with one molar equivalent of a suitable alkyl halide in DMF, they generate alkoxyl radicals after homolysis of the N-O bond when heated under argon in the dark, at 80°C, in dilute solution of benzene containing tributylstannane and AIBN.[142] The utility of these precursors in radical chain reaction is based on the observation that the formation of the strong Sn-S bond and the restoration of pyridine aromaticity should provide sufficient driving force to effect generation of alkoxyl radicals by attack of tributyltin radical on the precursor **A** (Figure 2).[141,143]

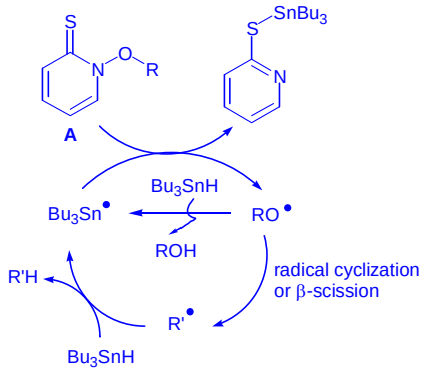


Figure 2

N-alkoxypyridine-2-thiones have shown to be very useful compounds for the generation of alkoxyl radicals in mechanistic studies.[144] Thus, besides Beckwith work, aimed essentially at studying kinetic of H-abstraction *versus* β-scission of alkoxyl radicals,[141,36] Hartung studies gave data on substituted pentenoxy radical cyclization rate and mechanism,[12,27] which constitutes a new entry to the stereoselective synthesis of substituted tetrahydrofurans. As a matter of fact, investigation of the photoreaction of *N*-alkoxypyridine-2-thiones **57** in the presence of reactive hydrogen donors allowed to determine the stereo- and regioselectivities of the radical reactions **A**-**58** and **A**-**59**, the degree of conversion of **57** and the yields of alkoxyl radical products **58**, **59** and **60** (Figure 3).

Drawback associated with the use of *N*-alkoxypyridine-2-thiones are not related to their efficiency in radical reactions, but rather to the mediocre yield of their preparation and to their physical properties. Indeed, generally obtained as thermally labile yellow oils, they often decompose upon storage at temperatures higher 5°C or rearrange into the thermodynamically more stable 2-(alkylsulfanyl)pyridine *N*-oxide.[12,145]

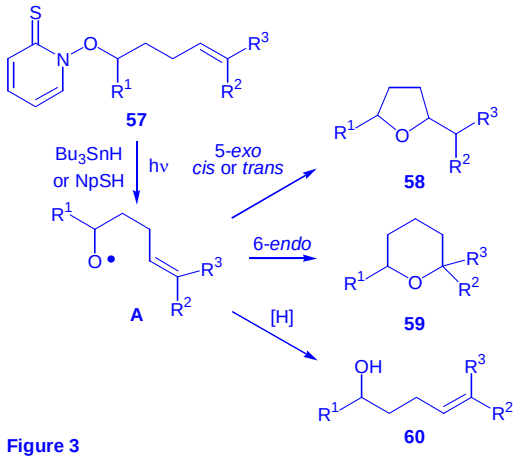


Figure 3

N-Alkoxy-4-(p-chlorophenyl)thiazole-2(3H)-thiones. To overcome the drawbacks of the pyridinethione chemistry, novel sources of alkoxyl radicals that take advantage of their useful properties have been developed. Inspired by Barton's finding[146] that *O*-acyl derivatives of *N*-(hydroxy)-4-phenylthiazole-2(3*H*)-thione (**62**, Z=H) and its methyl derivative are less sensitive to visible light than the respective *N*-(acyloxy)pyridine-2(1*H*)-thiones, Hartung reported recently the preparation of *N*-(alkoxy)-4-arylthiazolethiones **63** in good yields and useful quantities, from *p*-substituted acetophenones **61**, and their efficient use as alkoxyl radicals precursors.[147,148,143] Based on the result of their studies, they selected the *p*-chlorophenyl derivatives (**62**, Z=Cl) for further exploration in alkoxyl radical chemistry (Figure 4).

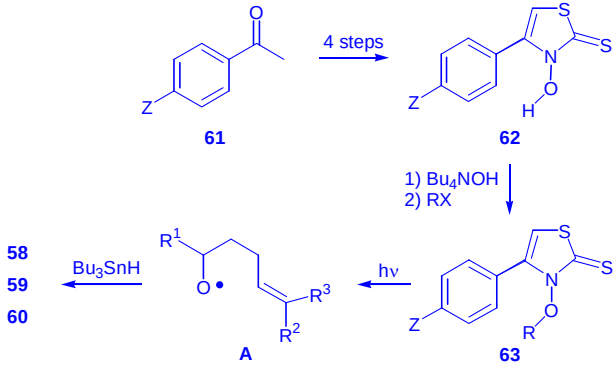


Figure 4

N-Alkoxyphthalimides. On the other hand, Kim reported that *N*-alkoxyphthalimides **65** are promising precursors for the generation of alkoxyl radicals. Very stable and easily accessible, they were readily prepared by treatment of alkyl halides with the sodium salt of *N*-hydroxyphthalimide (**64**, M=Na) in DMF or by treatment of alcohols with *N*-hydroxyphthalimide (**64**, M=H), diethyl azodicarboxylate and triphenylphosphine, following Mitsunobu procedure. The resulting *N*-alkoxyphthalimides **65** were refluxed in benzene with tributyltin hydride/AIBN to afford alkoxyl radical (Figure 5).[149]

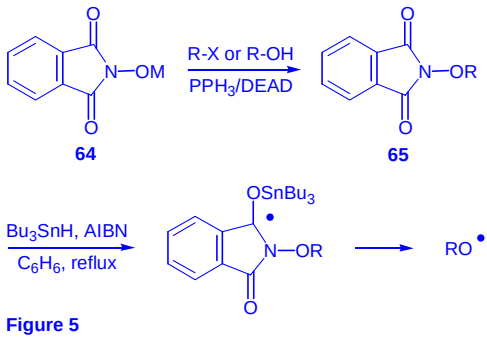
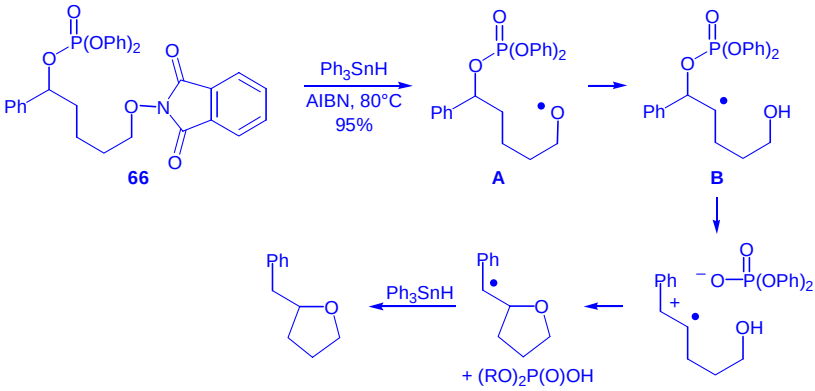


Figure 5

An interesting application of Kim's methodology was published by Crich, Huang and Newcomb. Indeed, tetrahydrofurans, as **67** obtained in 95% yield, were synthesized by the reaction of a series of 5-(*N*-phthalimidoxy)-1-phenyl-1-(diphenylphosphatoxy)pentanes (**66**) with triphenyltin hydride and AIBN. The intermediate alkoxyl radicals **A** undergoes 1,5-hydrogen atom abstraction to give β–(phosphatoxy)alkyl radicals **B**. Conversion into the products **67** presumably proceeds via a stepwise fragmentation of the β-(phosphatoxy)alkyl radical **B** to give a styrene radical cation/phosphate anion pair **C** which cyclizes onto the more stable benzylic radical **D**. (Scheme 22).[150,151]

Very recently, Suárez brought a contribution to the carbohydrate synthetic chemistry making use of *N*-phthalimido glycofuranosides and glycopyranosides as alkoxyl radical precursors.[152]



66 A B C D 67

Scheme 22

Ether derivatives of Se-phenyl benzohydroximate. An other recent precursor to alkoxyl radical introduced by Kim is the phenylselenohydroximate derivative **69**, prepared in high yield by treatment of an alkyl bromide with **68** and cesium carbonate in DMF at 0°C. Alkoxyl radicals were generated efficiently from **69** under the standard radical conditions (Bu_3SnH/AIBN) (Figure 6).[153]

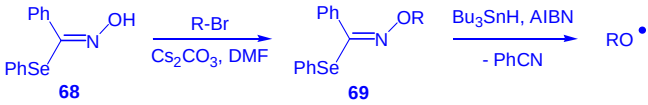


Figure 6

Arylsulfenic acid O-esters. Essentially developed for mechanistic studies,[154,155,24,25] arylsulfenic acid *O*-esters **70** were prepared by treatment of alcohols with sulfenyl chloride in the presence of triethylamine (Figure 7)[156,12] and used under different radical conditions to afford alkoxyl radicals. For example, photolysis of alkylbenzenesulfenates by high pressure mercury lamp, with tributyltin hydride and in the presence of excess of electron deficient olefins allowed formation of a δ-carbon radical, arisen by 1,5-hydrogen migration to alkoxyl radical, which was intercepted by the radicophilic olefin in a Michael-type alkylation.[126] When hexabutylditin was used as a catalytic reagent, irradiation of alkylbenzenesulfenates[157] or primary, secondary and even tertiary 4-nitrobenzenesulfenates[158-160] resulted in a free radical phenylthio transfer from oxygen to the non-activated δ-carbon atom and δ-phenylthio alcohols were obtained. However, by increasing the substitution at the carbinol atom and enhancing the stability of the formed carbon radical, product of β-scission or of cyclization of the alkoxyl radical were obtained.[161,162,158]

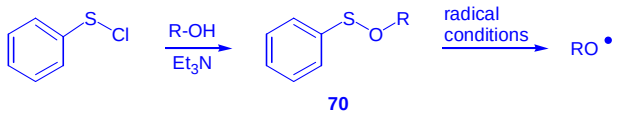
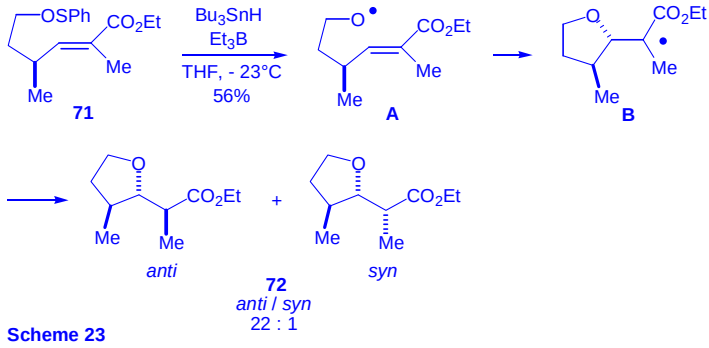


Figure 7

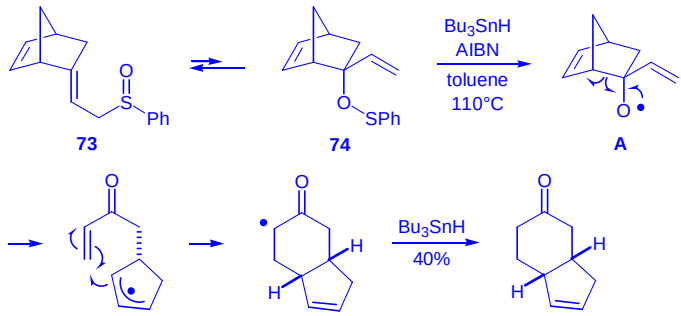
Moreover, while Hartung studied mechanistic aspects of the cyclization of alkoxyl radicals generated photochemically or thermally, by treatment of benzenesulfenic acid *O*-esters in presence of tributyltin hydride,[12] Guindon reported a stereoselective synthesis of 2,3-*trans*-disubstituted tetrahydrofurans **72** by treatment of the alkylbenzenesulfenate precursors **71** with tributyltin hydride and triethylborane. The reaction takes place through

a tandem process which features intramolecular addition of oxygen radical **A** to an α,β-unsaturated ester and hydrogen transfer to the resultant carbon-based radical **B**, creating two new contiguous stereogenic centers with high levels of 1,2-induction in both tandem steps and good yields (Scheme 23).[28]



Scheme 23

In a promising approach, we were recently able to generate alkoxyl radicals of tertiary allylic benzene sulfenates. Indeed, allylic sulfoxides, which are easily obtained from the corresponding alcohols, are known to rearrange thermally to sulfenate esters by a [2,3]sigmatropic process.



Scheme 24

Thus, treatment of sulfoxide **73** with tributyltin hydride and AIBN afforded the alkoxyl radical **A** derived from the rearranged sulfenate **74**, which was transformed into *cis*-bicyclo[4.3.0]non-7-en-3-one (**75**) in about 40% yield *via* the sequence of fragmentation-cyclization-trapping **A**-**C** (Scheme 24).[49]

Product analysis and spin trapping techniques have shown that photolysis of dialkoxyl disulfides ROSSOR, easily and safely prepared with any kind of R group by reacting the appropriate alcohol with ClSSCl,[163,164] generates alkoxyl radicals RO·, along with radicals ROS· and ROS·=O (Eq. 2).[165]

Equation 2

Alkyl peroxyboranes. Research for new stable radical initiators of polymerization systems resulted in the development of alkyl peroxyboranes **77**. Indeed, treatment of adducts of alkyl-9-BBN **76** with oxygen at ambient temperature, furnished peroxyborane **77** that, decomposing homolitically by itself, generated an alkoxyl radical and a borinate radical **78** (Figure 8). In presence of free radical-polymerizable monomers such as methacrylates, vinyl acetate, acrylonitrile, etc., the alkoxyl radical was able to initiate radical polymerization.[166]

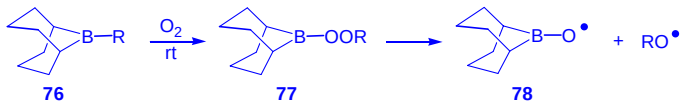
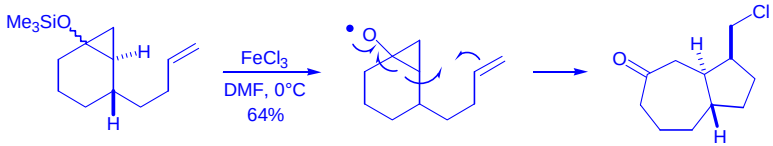


Figure 8

Cyclopropyltrimethylsilyl ethers and iron(III). In 1976, Saegusa reported that treatment of cyclopropyltrimethylsilyl ethers with anhydrous ferric chloride in dimethylformamide gave rise to β-chloroketones.[167-169] Inspired by those results, Booker-Milburn developed and extended the reaction,[170,171] demonstrating the utility of alternative iron salts in the

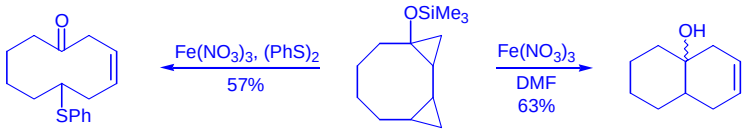
procedure,[172] showing that the carbon-centered radical resulting from the C-C bond cleavage can be cyclized onto pendant unsaturated side-chains[173] and applying the reaction to alternative types of substrates.[174] For example, he found a rapid construction of diastereomerically pure [*n*.3.0]bicyclic chloro ketone **80**, with 64% yield, from [*n*.1.0]cyclopropyl trimethylsilyl ether **79** by a tandem ring expansion-cyclisation procedure.[175] Studies of the reaction mechanism have shown that the cyclopropane ring is an essential part of it: prior ring opening is required to initiate a free radical process which is thought to proceed *via* an intermediate cyclopropyl alkoxyl radical **A** (Scheme 25).[175]



79 **A** **80**

Scheme 25

Further extension of the method was recently provided by Simpkins, who developed a two carbon ring expansion protocol utilizing iron-mediated bond cleavage reactions of *bis*-cyclopropane **81**, affording β,γ-unsaturated ketone **83** acceptable yields, or bicyclic alcohol **82** in 63% yield, depending on the reaction conditions (Scheme 26).[176]

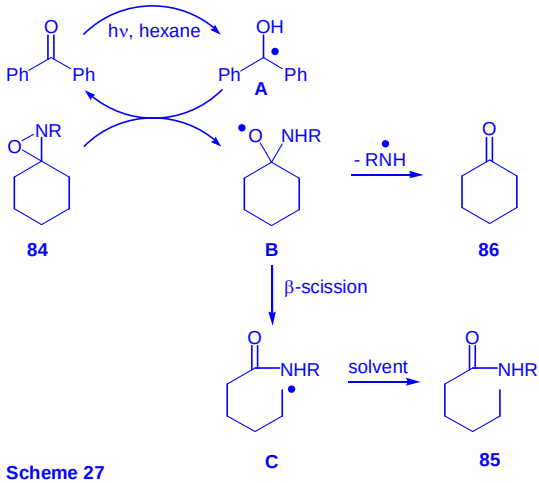


83 **81** **82**

Scheme 26

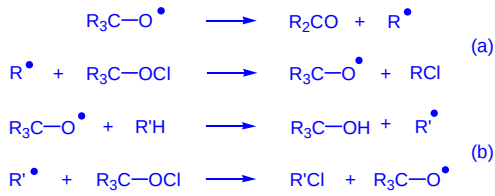
Oxaziridines and ketyl radicals. Studies on the photoinduced rearrangements of oxaziridines[177] have shown that photosensitization of oxaziridines as **84** with the classical triplet sensitizer (benzophenone) resulted in the formation of ring-opened amide **85** and cyclohexanone (**86**). The proposed mechanism involves a ketyl radical **A**, formed by the

photolysis of benzophenone, which transfers a hydrogen atom to the oxaziridine nitrogen. Concomitant cleavage of the N-O bond generated an alkoxyl radical **B** that is further transformed into the products *via* **C** (Scheme 27).[178]



Scheme 27

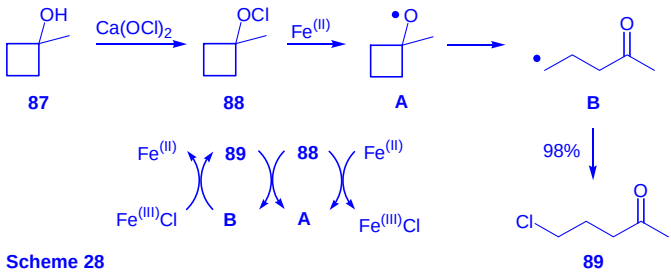
Hypochlorites. Hypochlorites constitute one of the oldest knew precursor of alkoxyl radicals. Their reactions provided a very convenient means of pioneering studies of alkoxyl radical reactions[19] since these are chain carriers both in hypochlorite decomposition involving the sequence shown in Eq. 3a, and in their use as chlorinating agents[33] *via* the chain depicted in Eq. 3b.



Equation 3

Moreover, alkyl hypochlorites containing a side chain of at least four carbons are readily converted to δ–chloro alcohols upon irradiation[179,180] or by ferrous and other one-electron oxidizable metal ion induced decomposition.[181] Extensive studies showed that, while in the reaction of tertiary alkyl hypochlorites, β-fragmentation competes with intramolecular δ-chorination, five- and six-membered tertiary cycloalkyl hypochlorites fragments into ω–chloro ketones.[182,183,181,135,184] For example, preparation of 5-chloropentan-2-one (**89**) was achieved in 98% converted yield by treatment of methylcyclobutanol (**87**) with $Ca(OCl)_2$, followed by decomposition of the hypochlorite **88** thus obtained in the presence of $Fe^{(II)}$ salt.[185] The probable mechanism involves one-electron reduction of the hypochlorite **88** to afford 1-methylbutoxyl radical (**A**), which fragments into 4-oxopent-1-yl radical (**B**). Abstraction of a chlorine atom from the starting hypochlorite **88** or from the $Fe^{(III)}$ salt gives the ketone **89** (Scheme 28).[185]

In 1977, Hargis and Hsu reported a direct partial kinetic resolution of 2-phenylbutane by taking advantage of the difference in the rate of H-abstraction reaction of the two enantiomers with optically active 2-phenyl-2-butoxyl radical.[186]



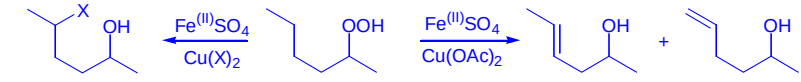
Scheme 28

Dialkyl peroxides and alkyl hydroperoxides decomposition. Although the chemistry of dialkyl peroxides and alkyl hydroperoxides has been extensively investigated, their use as alkoxyl radical precursors for synthetic organic purposes has only been scarcely reported. Homolysis of the O-O bond can be achieved thanks to photoirradiation, thermal means or low valent transition metal-catalysis. Nevertheless, due to its flexibility, the latter method has provided the most effective route to alkoxyl radicals,[187-189] iron$^{(II)}$ systems being

generally used as initiators. Formation of the oxygen-centered radicals is a well-known reaction that occurs *via* electron transfer from the metal ion to the peroxide and cleavage of the O-O bond (Eq. 4).[190]

Equation 4

Hydrogen atom abstraction of 2-hexyloxyl radical generated from the parent 2-hexyl hydroperoxide **90** with iron(II) sulfate and copper(II) salts, has been reported by Cekovic to afford δ-olefinic alcohol **92** in 60% yield along with a 10% of the γ-unsaturated alcohol **91**, or good yields of δ-functionalized alcohol **93** depending on the reaction conditions (Scheme 29).[191,192]



93a X = SCN, 48%
93b X = N_3, 62%
93c X = Cl, 65%

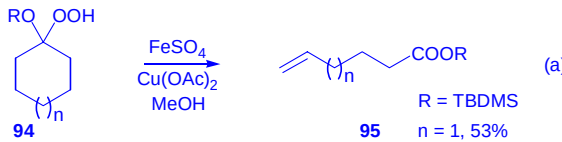
90

91 : 10%

92 : 60%

Scheme 29

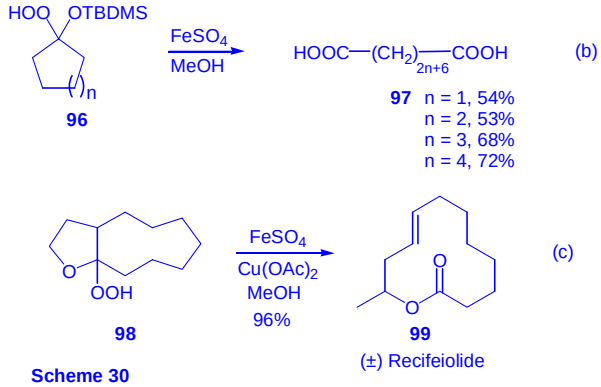
While application of the method for ring opening reaction by alkoxyl radical fragmentation of α-hydroxy and α-alkoxyl hydroperoxides **94**, has provided a route to carboxylic acids **95** (Scheme 30a, R = H)[193-195] and esters **95** (Scheme 30a, R = TBDMS[196] or CH_3[197]), dimer dicarboxylic acids **97** have been prepared from α-silyloxy hydroperoxides **96** (Scheme 30b).[196]



94

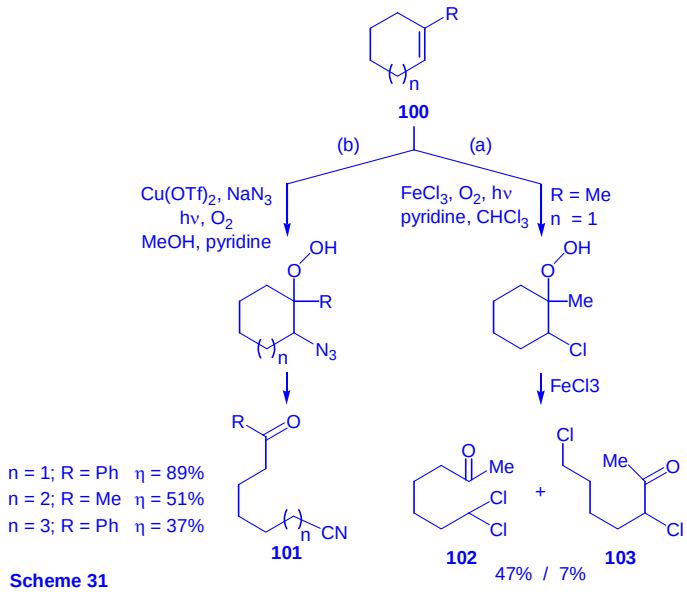
R = TBDMS

95 n = 1, 53%
n = 2, 44%
n = 3, 73%



Scheme 30

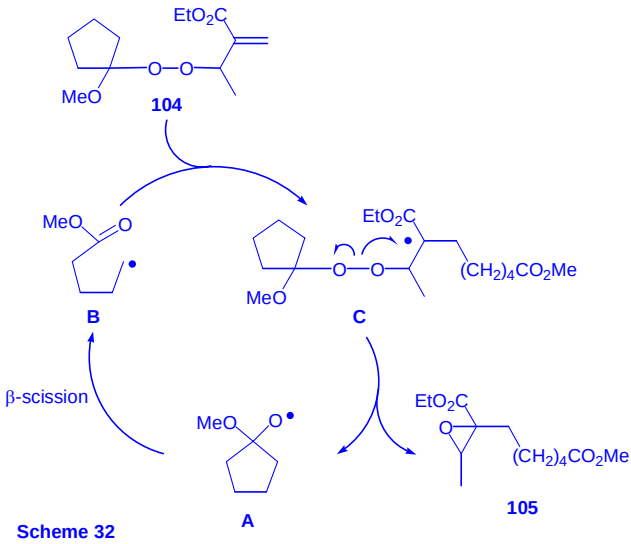
Other examples of fragmentation have led to the synthesis of ring expanded products[198-201,195] as the macrocyclic lactone (±)-recifeiolide **99** (Scheme 30c), synthesized in 96% yield from **98** by Schreiber.[202]



Scheme 31

In a modified one-pot procedure reported by Sato, photolytic cleavage of trisubstituted olefins **100** in presence of metal salts such as $FeCl_3$ gives chlorine-containing ketones. The reaction proceeds *via* β-chloro hydroperoxide, which transforms to chloro ketones **102** and **103** by homolytic O-O and C-C bonds breaking (Scheme 31a).[203-205] Extension of this strategy allowed synthesis of keto nitrile **101** by the pathway depicted in Scheme 31b.[206]

In an example of cyclization reaction, 3-(*p*-methylphenyl)propan-1-oxy radical generated from the corresponding hydroperoxyde with $Fe^{(II)}$ and $Cu^{(II)}$ was described by McCleland to undergo competing 1,5- and 1,6-cyclization.[207]



Scheme 32

Following his studies on homolytically induced decompositions of unsaturated peroxy derivatives,[208-210] Maillard has described a new method for the preparation of oxygenated heterocycles. In particular, he has developed a tricky synthesis of glycidic esters. The strategy consists in a chain process, where generation of alkyl radical **B** by β-fragmentation from 1-alkoxyalkyloxy radical **A** precludes its addition to the double bond of "acrylic" peroxyketal **104** to provide alkyl radicals **C**. The latter promotes induced

decomposition of the peroxyketal moiety to afford glycidic ester **105** in 88% yield, along with alkoxyl radical **A** (Scheme 32).[211]

5. Generation from a C-centered radical

Epoxide fragmentation. Homolysis of the carbon-oxygen bond of an epoxide by an adjacent carbon centered radical **A**, happening with lower rate limit rate of 10^{-8}-10^{-10} M^{-1} s^{-1},[212] constitutes a useful strategy for the generation of alkoxyl radical **B**, which can undergo further rearrangements by cyclization, β-scission or hydrogen transfer. Evidences for the reversibility of the reaction have been reported.[213-215,107,108,56,212,216] Product derived from the C-O bond cleavage normally predominates, those derived from the C-C bond cleavage being formed when the resultant carbon centered radical **C** is stabilized (R^2 = aryl, vinyl or acyl) (Figure 9).[217-220] However, Marples recently reported that, even if no products of C-C bond cleavage are obtained, the C-C bond cleavage in aryl substituted oxiranylcarbinyl radicals is reversible.[220]

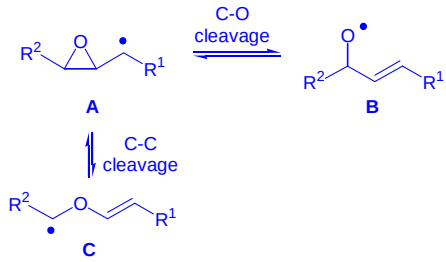
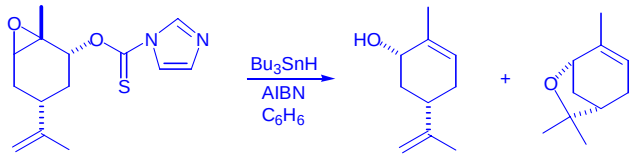


Figure 9

One of the first applications of epoxide ring opening by an oxicarbinyl radical was reported by Barton, who described a tetrahydrofuran ring formation, by the 5-*exo* cyclization of an alkoxyl radical.[221] Thus, generation of the oxiranylcarbinyl radical from thiocarbonylimidazolide **106** was followed by ring opening to the alkoxyl radical, which could either abstract an hydrogen atom to afford **107** in 18% yield, or undergo cyclization

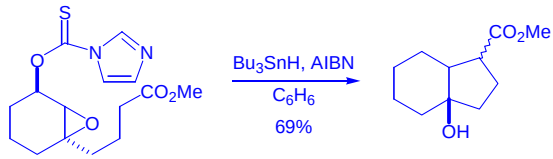
to the remote double bond in the 5-*exo* sense, to afford the tetrahydrofuran ring **108** in 16% yield (Scheme 33).



106 **107** : 18% **108** : 16%

Scheme 33

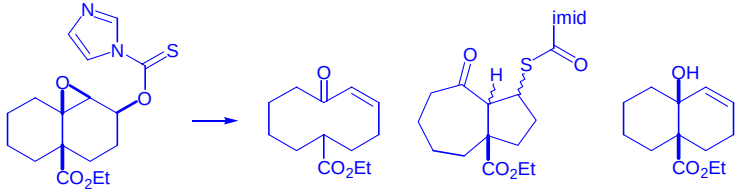
While further developments of the method were brought by Murphy[11] and Walton,[222] Rawal[21] introduced a method that combines fragmentation with intramolecular hydrogen abstraction, affording the bicyclic product **110** in 69% yield (Scheme 34).[21]



109 **110**

Scheme 34

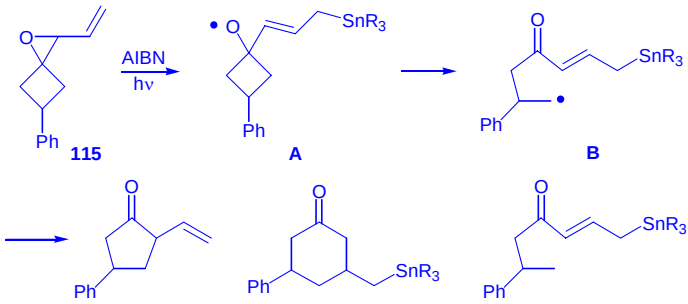
By a similar methodology, following Marples's work,[223,217] Rawal[224] devised a sequence of epoxide fragmentation/β-scission of several bicyclic compounds as **111** providing access to functionalized medium sized ring compounds as **112**. By selecting the reaction conditions, he was able to favor formation of either the medium ring **112**, a hydrazulene **113**, or the simple epoxide fragmentation-reduction product **114** (Scheme 35).[224]



	111	**112**	**113**	**114**
1. Bu_3SnH (1.2 eq.), AIBN		69%	5%	10%
2. Bu_3SnH (5 eq.), AIBN		18%	0%	56%
3. $(Bu_3Sn)_2$, AIBN, hν		0%	59%	0%

Scheme 35

Beside thiocarbonylimidazolide precursors, vinyl epoxides, which are readily prepared by the reaction of cycloalkanones with allyl sulfur ylides derived from allyl sulfonium salt, have proven to be efficient precursors for alkoxyl radicals.



115 **A** **B**

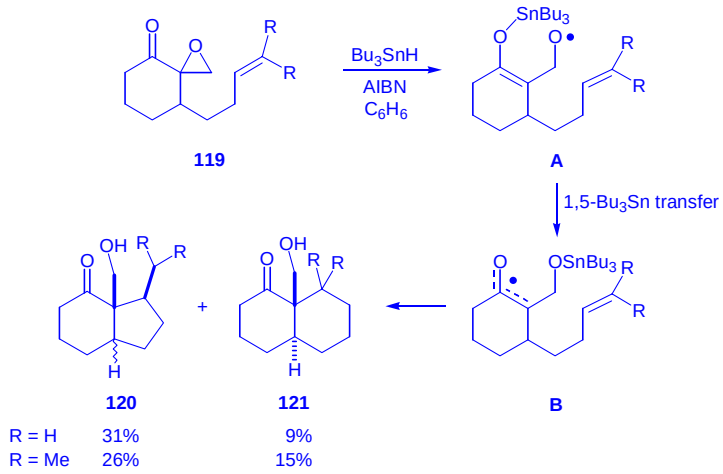
	5-*exo* cyclization **116**	6-*endo* cyclization **117**	H-abstraction **118**
n-Bu_3SnH	56%	18%	4%
Ph_3SnH	85%	10%	0%
PhSSPh	75%	0%	0%

Scheme 36

As reported by Kim,[225] radical ring expansion of vinyl epoxides as **115** were originally initiated by *n*-Bu_3Sn radical addition to the vinyl epoxide, but Ph_3Sn and PhS radicals were found to promote also the reaction. Subsequent epoxide fragmentation yielded alkoxyl radical **A,** that β-fragmented to produce the carbon-centered radical **B**. 5-*Exo*

cyclization, 6-*endo* cyclization or direct reduction of the latter provided good yields of product **116**, along with small quantities of **117** and **118** respectively (Scheme 36).

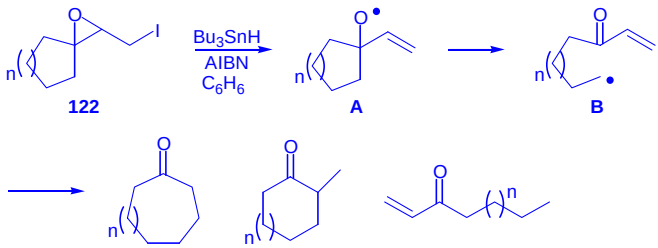
Extension of this strategy to 1,5-hydrogen atom transfer from the generated cyclic alkoxyl radical and subsequent cyclization of the resulting carbon centered radical, afforded bicyclic alcohols.[29] Moreover, by treatment of a non-cyclic ether analogue of a DNA ribose containing a vinyl epoxide, with thiyl radical, modeling of the hydrogen atom abstraction from DNA sugar was accomplished by Murphy.[226] The variety of tested substrates included acetoxyalkenyl epoxides,[227] epoxy silyl enol ethers[228] and epoxy ketones.[229,230]



Scheme 37

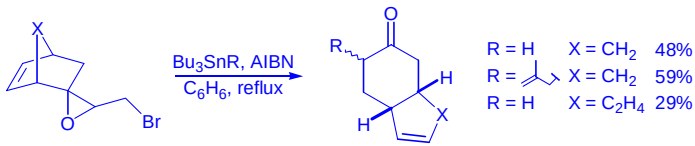
As a variation on the 1,5-hydrogen transfer strategy, Kim introduced an original ring-forming radical reaction of vinyl epoxides,[29] resp. of epoxyketones,[229] based on the 1,5-shift of tributyltin group. Thus, addition of Bu_3Sn radical to the substrates **119**, is followed by epoxide fragmentation onto the alkoxyl radical **A**. Tri-*n*-butyltin transfer to the latter yields an alkyl radical **B** that cycles on the olefin to form the products **120** and **121** in modest yields (Scheme 37).

In 1993, Galatsis reported a ring expansion strategy making use of iodo spiroepoxides, to synthesize medium sized carbocycles.[56] Thus, after homolysis of the epoxide **122**, β-scission of the formed alkoxyl radical **A** yields a primary radical **B**, which, upon *endo* or *exo* cyclization to the olefin, gives moderate yields of two-carbon **123** or one-carbon **124** ring expansion products, along with small quantities of direct reduction compound **125** (Scheme 38).



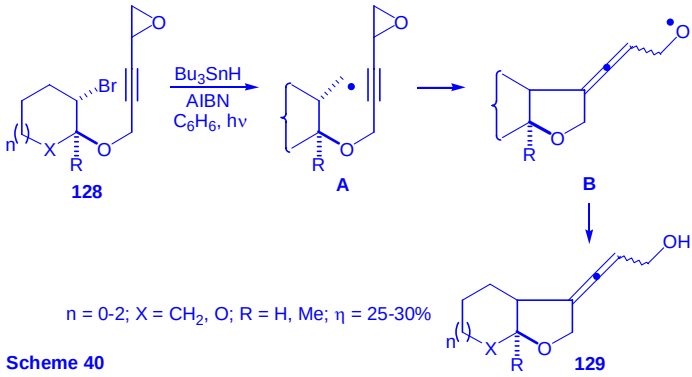
Scheme 38

The methodology was successfully applied by Ziegler on linear bromo epoxides for kinetic studies.[212] Recently, we extended its scope by developing a general method for the stereoselective synthesis of bicyclic compounds **127** in 29-59% yields, starting from bridged bicyclic derivatives **126** (Scheme 39).[49]



Scheme 39

Bromoalkynyloxiranes **128** have shown to be interesting precursors of alkoxyl radicals involved in the synthesis of an original class of compounds, allenylidenetetrahydrofurans **129**.[231] Indeed, when submitted to classical radical reaction conditions, they underwent sequential carbocyclization, epoxide fragmentation and reduction of the resulting alkoxyl radical *via* **A**-**B** to give the products **129** in 25-30% yields (Scheme 40).



Scheme 40

Intramolecular addition of radical to carbonyl groups. Intramolecular addition of radical to carbonyl groups constitutes an indirect but very efficient way of generating alkoxyl radicals which can then undergo further reactions. Application of this strategy for ring expansion processes has been reviewed in detail first by Dowd and Zhang,[232] and very recently by Yet,[233] who have shown its potential for the synthesis of medium and large rings (Figure 10).

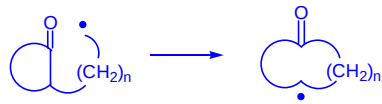
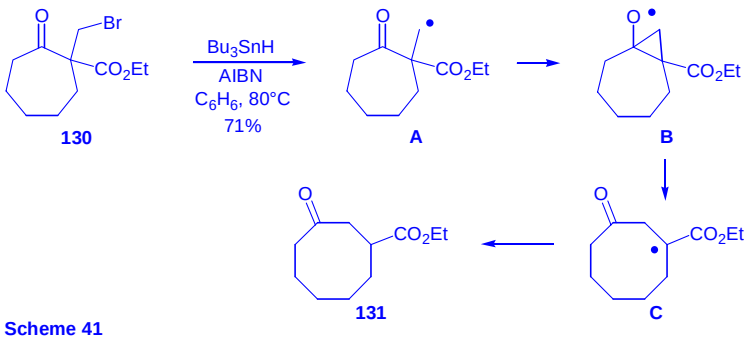


Figure 10

Thus, one carbon ring expansion of cyclic ketones is a straightforward, broadly based procedure with many potential applications. Brominated β-keto esters as **130** have been

developed first,[234,235] but the corresponding iodides and selenides[236] also undergo ring expansion, selenophenyl derivatives being of special value in the reaction of heterocyclic compounds.[237] In addition, organocobalt complexes have been reported as substrates.[238,239] Besides tributyltin hydride and AIBN, organocobaloximes[240,241] and electroreductive conditions,[242] have been used to initiate the reaction. Moreover, tri-*n*-butyltin adducts have been employed in a modification leading to olefinic products[243] and in a reaction of penam conversion into cepham.[30] The mechanism is believed to involve formation of a primary radical **A** which, upon attack on the ketone carbonyl, yields an intermediate cyclopropyloxy radical **B**, that fragments into the ring expanded product **131** in 71% yield from **130,** *via* the radical **C** (Scheme 41). Tandem sequences involving one carbon ring expansion have been reported.[244-246]



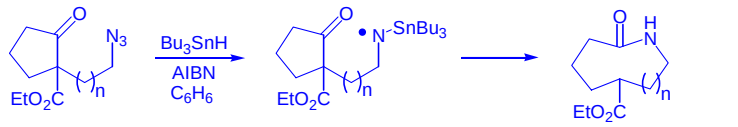
Scheme 41

As a logical consequence, the method found extension in larger increment ring expansions. In contrast with two-carbon ring expansions, that are not feasible because of the low rate of 4-*exo* ring closure, three- and four-carbon ring expansion were successfully developed.[236,235]Their scope includes bromides and iodides as substrates, the latter giving generally better results,[247] but addition of tin hydrides to alkynes and other indirect methods have also been described.[248,249] However, in the benzocyclic ketones series, conjugated ketones afford only non-ring-expansion reduction products.[250] Detailed studies on free radical-based ring expansion of fused cyclobutanones[251-255] and of spiro-cyclobutanones[256,257] have been reported by Dowd and Zhang. The mechanism of

multicarbon ring expansion proceeds like the postulated pathway for one-carbon ring expansion, *i.e.* by radical addition to the carbonyl group, followed by bond cleavage of the intermediate alkoxyl radical leading to the enlarged ring (see Scheme 41).

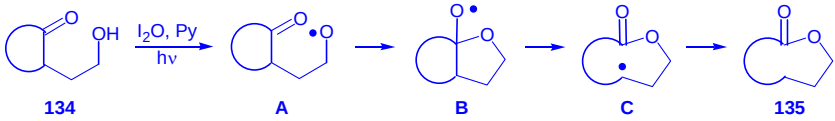
The library of molecules synthesized by the ring expansion *via* an alkoxyl radical strategy includes medium rings[234,236,235,237] that may contain heteroatoms,[250] macrocycles,[258] simple bicycles and polycycles,[245,259,253,248,249,260] benzannelated bicycles,[250] spiro-bicycles,[256,257] bridged bicycles,[246,49] and polycyclic bridged ring systems.[261,254] However, if aldehydes and ketones are good radical acceptors, ester and amide carbonyl groups are usually not reactive enough to undergo cyclization.

Interesting contributions to this methodology, are the synthesis of ring-expanded lactams and lactones. Indeed, on the one hand, Kim[262] reported the use of azido alkehydes and ketones as aminyl radical precursors to produce ring-expanded lactams. His work was extended by Benati[263] to reaction of acyclic, monocyclic, benzocyclic and bicyclic α-azido-β-keto esters. Thus, treatment of the substrates **132** with tributyltin hydride and AIBN afforded a variety of medium sized lactams **133** *via* **A**, as a result of 3-*exo* cyclization of a transient (tributylstannyl)aminyl radical onto the ketone moiety and prompt regiospecific β-scission of the derived alkoxyl radical (Scheme 42).



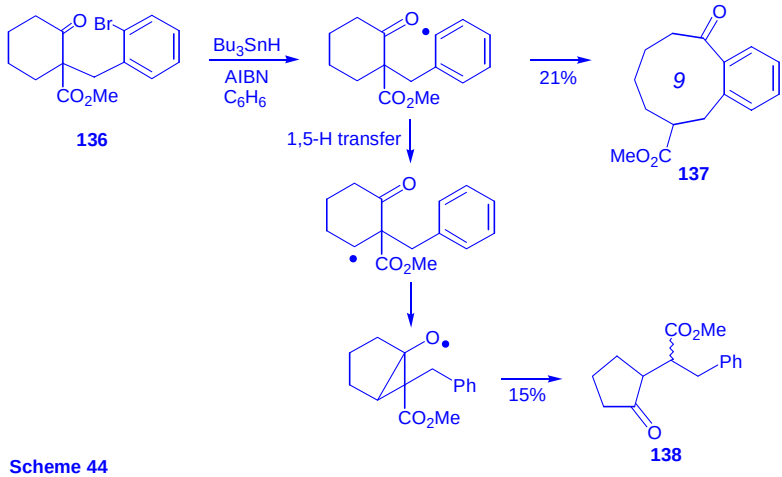
Scheme 42

On the other hand, Suginome[69] took advantage of his procedure (treatment of alcohol **134** with HgO/Iodine) to generate an alkoxyl radical **A** which, upon addition to the carbonyl group of the substrate, gave the alkoxyl radical **B** that fragmented via **C** to afford lactone **135** (Scheme 43).



Scheme 43

Worth to note is that the explorations of free radical expansion led in several cases to the formation of ring contracted by-products as **138**, derived from precursor **136**.[236,264,258] The process is generally initiated by a 1,5-hydrogen abstraction and, like the ring expansion process, occurs *via* an intermediate alkoxyl radical (Scheme 44).[236]



Scheme 44

With simple cyclizations,[265-267] the chemistry of intramolecular addition to carbonyl group provides alternatives to the ring expansion methodology. Nevertheless, only 5-*exo* and 6-*exo* cyclizations have up to day been successful, the problem associated with cyclization onto carbonyl group being their reversibility, fragmentation being much faster than cyclization,[36,37] and the consequent difficulty to trap the closed product.[268] The strategies devised to overcome this drawback divide in two main types: the fast and irreversible

trapping of the intermediate alkoxyl radical and the β-scission of a suitable group, allowing restoration of the carbonyl functionality (Figure 11).

Although radical cyclizations onto carbonyl groups with organostannanes have been demonstrated, due to high affinity of the stannyl radical for carbon-centered radicals, their efficiency remains very low.[269] So, another straightforward method described by Batey, takes advantage of greater selectivity of organosilanes as H-atom donor for trapping of oxygen-centered radicals.[270] 5-*Exo*-trig and 6-*exo*-trig cyclization of halocarbonyl compounds were accomplished using phenylsilylane and tristrimethylsilylsilane, to afford cyclopentanols and cyclohexanols (Figure 11: X = CH_2Br; Z = H; T = H; n = 1 or 2). Along the same line, Fu devised a tributyltin hydride-mediated pinacol coupling of 1,5- and 1,6-dicarbonyl compounds.[271]

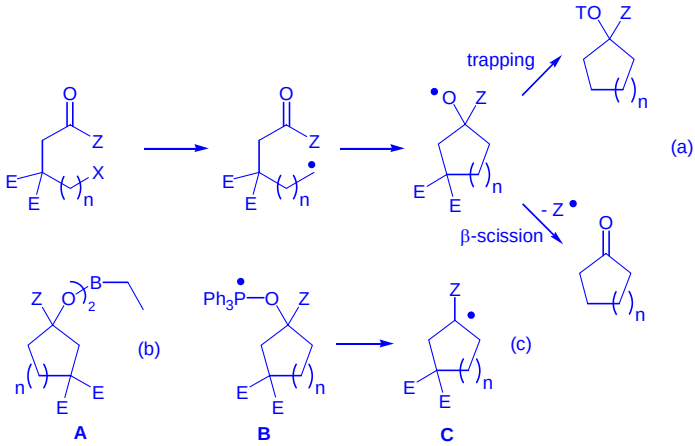
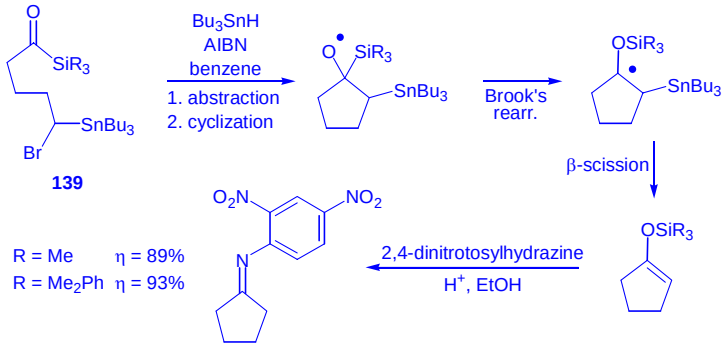


Figure 11

Following Brown's observation[272] of the affinity of alkoxyl radical toward trialkylboron derivatives, triethylborane was investigated as a radical quencher for alkoxyl radicals. Thus, Malacria[273,274] developed an efficient synthesis of cyclopentanols and cyclohexanols by intramolecular 5-*exo* resp. 6-*exo* cyclization of ω-iodoaldehydes or ketones, with triethylborane as a radical initiator and terminator, no tin mediator being necessary. The effective product of the reaction is a dimeric boronic ester **A**, which hydrolyses to the

alcohol upon aqueous treatment (Figure 11: X = CH_2I or $CH(Br)=CH_2$; Z = H or Me; T = BR_3; n = 2). As a Lewis acid triethylborane played an additional role in increasing the reactivity of the carbonyl group toward cyclization.

An alternative approach, based on the previously known deoxygenation of alkoxyl radicals with organophosphorous$^{(III)}$ compounds[275] devised by Kim[276] involves trapping of the alkoxyl radical by triphenylphosphine to give **B**, which, upon elimination of triphenylphosphine oxide, triggers deoxygenation, providing a cycloalkyl radical **C** (Figure 11: X = CH_2I or $CH(Br)=CH_2$; Z = H; T = $\cdot PPh_3$; n = 1 or 2). Products derived from reduction, intermolecular addition to olefins or tandem reaction of the cycloalkyl radical **C**, could be synthesized in good yields.



Scheme 45

A tricky method to trap cyclized alkoxyl radicals was developed by Tsai.[269,277] The idea relies on radical-Brook rearrangement of β-silyloxyl radicals resulting from the cyclization of acylsilane, to afford α-silyloxyl radicals by a quick and most likely irreversible silyl migration (Figure 11, X = CH_2I or CH_2SePh or $CH(Br)=CH_2$; Z = T = SiR_3; n = 1 or 2). The method[278] provides access to cyclopentyl silyl ethers by successful 5-*exo* and somewhat less efficient 6-*exo* cyclization of primary and secondary radicals on acylsilanes. 6-*Exo* cyclizations have shown to be more sensitive to the size of the silyl group and to proceed more slowly. Intramolecular cyclization of vinyl radicals with acylsilane constitutes a new regiospecifical route to cyclic silyl enol ethers.

As an alternative, those, isolated as their dinitrophenylhydrazone derivative **140** in high yields, could be obtained by sequential cyclization, radical Brook's rearrangement and β-scission of α-stannyl radicals generated from acylsilanes **139** (Scheme 45).[279]

Parallely to Tsai's study of acylsilanes, Curran developed the radical chemistry of acylgermanes.[280,281,268,282] In this system, the cyclized α-germyl alkoxyl radical undergoes a β-scission reaction to afford cyclic ketone with concomitant formation of a germyl radical which carries on the chain reaction (Figure 11, X = CH_2I or CH_2Br; Z = GeR_3; n = 1 or 2). 5-*Exo* and 6-*exo* cyclizations showed good to excellent scopes but as for the other systems, parent cyclization in other modes failed. However, 3-*exo* cyclization resulted in a 1,2-acyl shift, which can be conducted alone or in tandem with a subsequent cyclization to the rearranged acyl german.

Reminiscent to the acylgerman system, Kim and Jon[283,284] recently reported the radical cyclization of thioesters and selenoesters (Figure 11, X = CH_2I or CH_2Br; Z = SPh or SePh; n = 1 or 2). Instead of a catalytic cycle, as in the acylgerman system, the thioester and selenoester systems require the use of 1.1 equivalents of hexabutylditin. The β-scission process involved in these reactions serves to drive the carbonyl cyclization to the right-hand side.

6. Conclusion

Known from more than a half century, alkoxyl radicals have received an increasing interest, which has lightened their unique characteristics. The variety of developed methods for their generation and their peculiar reactivity has brought them into the library of intermediates possessing a great synthetic potential. Further study and use of alkoxyl radical will with no doubt be reported.

7. References

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β-Scission of Bicyclo[2.2.1]hept-5-en-2-ols Promoted by LTA : Study and Application to the Synthesis of Carbanucleoside Analogues

1. Introduction

Over the past decades, interest for free-radical chemistry as a synthetic tool has known a remarkable upsurge focused primarily on the use of carbon-centered[1-4] and nitrogen-centered[5,6] radical processes, alkoxyl radicals receiving much less attention. Nevertheless, interest for alkoxyl radical in synthetic organic chemistry has increased,[7] as witnessed by the number of synthetic approaches involving them as intermediates in transformations like ring-closure reactions,[8] hydrogen-atom abstraction[9] and remote functionalization of non-activated carbon-hydrogen bonds.[10] As well, extensive studies of β-scission reactions have allowed development of a powerful methodology for the synthesis of medium sized compounds by ring expansion processes,[11,12] but relatively little attention has been paid to other processes involving β-scission reactions.[13]

Our own interest in this field led us to envisage fragmentation of alkoxyl radicals **I** from bridged bicyclic norbornenol derivatives for stereocontrolled synthesis of polysubstituted cyclopentanes. Indeed, while norbornenols are readily available compounds, in racemic or optically active forms, this approach constituted a promising route toward products of biological interest, cyclopentene ring being the precursor of a variety of biologically active compounds. The ionic variant of this strategy has been successfully developed, but is limited by the harsh condition needed for fragmentation, *i.e.* strongly alkaline,[14,15] acid,[16] or oxidizing media.[17]

In norbornenoxyl β-scission, relief of ring strain and formation of a stabilized carbon-centered allylic radical **II** was expected to drive regioselective opening of the bicyclic skeleton. The fixed structure of the starting molecule would induce total stereocontrol on the ketone containing side-chain and presumably influence the stereochemical outcome of the side-chain resulting from trapping of the allylic C-centered radical **II** (Figure 1). In

this paper, we present our work directed toward efficient generation of alkoxyl radicals from 2-substituted bicyclo[2.2.1]hept-5-en-2-ols and its application to the synthesis of carbanucleoside analogues. As 6'-modified nucleosides have showed significant antiviral activities,[18] we decided to prepare 6'-hydroxyethyl carbocyclic precursors.

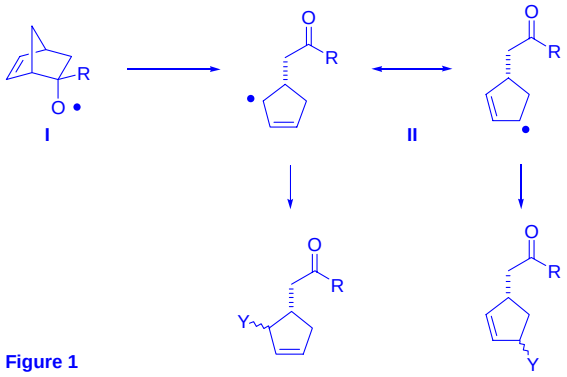


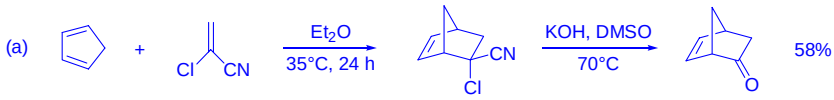
Figure 1

2. Results and Discussion

Synthesis of 2-substituted bicyclo[2.2.1]hept-5-en-2-ols. All the alcohols were synthesized nearly exclusively as their *endo*-epimer, which demonstrate the preferential attack of the reagents on the sterically less encumbered *exo*-face of the substrate,[19] from norbornenone (bicyclo[2.2.1]hept-5-en-2-one, **2**). This was prepared according to a slightly modified literature procedure:[20] Diels-Alder reaction of 2-chloroacrylonitrile and cyclopentadiene in refluxing ether afforded the crude chloronitrile adduct **1**, which was hydrolyzed to the ketone **2** in a hot aqueous solution of KOH in DMSO, with an overall yield of 58% (Scheme 1a).

Norbornenol (**3a**) was obtained in a 59% yield by sodium borohydride reduction of norbornenone **2**. While treatment of **2** with the appropriate Grignard reagent afforded 2-methyl, 2-phenyl and 2-vinylbicyclo[2.2.1]hept-5-en-2-ols (resp. **3b**, **3d**, and **3e**)[15] in resp. 94%, 93% and 69% yields, 2-*t*-butylbicyclo[2.2.1]hept-5-en-2-ol **3c** was prepared in a 83% yield from *t*-butyl lithium addition to **2** (Scheme 1b). Due to competing

reduction of the substrate by hydride transfer from the reagent,[21] *t*-butylmagnesium chloride treatment afforded only traces of **3c**, along with large quantity of norbornenol (**3a**).

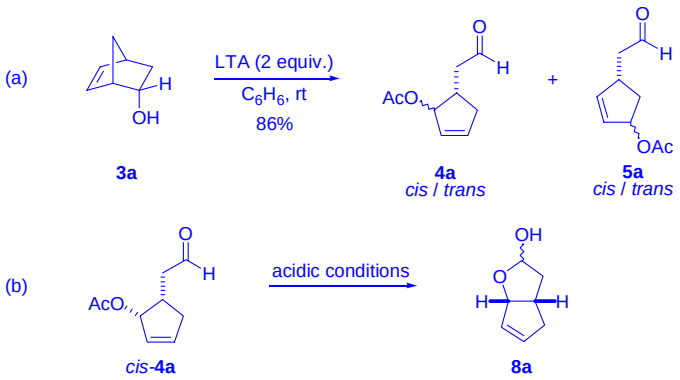


Entry	R	Reagent	Yield
3a	H	$NaBH_4$	59%
3b	Me	MeMgBr	94%
3c	*t*-Bu	*t*-BuLi	83%
3d	Ph	PhMgBr	93%
3e	C_2H_3	C_2H_3MgBr	69%

Scheme 1

Radical reactions. Norbonenol (**3a**) was chosen as adduct for preliminary studies, because its fragmentation was expected to afford an easily identifiable aldehydic cyclopentene (see Figure, R = H). In order to test the feasibility of the fragmentation reaction, various methods for the generation of alkoxyl radicals, were investigated. However, while treatment of benzenesulfenate precursor,[22,23] synthesized in 46% yield from **3a**,[24] in radical conditions resulted in a sluggish reaction mixture. The low 6% yield obtained in synthesis of the *N*-alkoxypyridinethione precursor[25] from secondary alcohol **3a** let no hope for efficient formation of tertiary precursors. Consequently other hindered systems were not investigated. Thus, our attempts to generate the requisite alkoxyl radical concentrated essentially on direct treatment of the alcohol. To this purpose, several potentially effective reagents were tested. Utilization of manganese triacetate,[26] ceric ammonium nitrate,[26] lead dioxide,[27] all reported to promote homolysis of the C-O bond, as well as application of Suarez's conditions (diacetoxyiodobenzene/I_2)[28] and Macdonald's[29] or Suginome's[30] conditions (HgO/I_2), only resulted in recovery or destruction of the starting material. Likewise, *in situ* formation and decomposition of the hypochlorite[31] did not lead to any result.

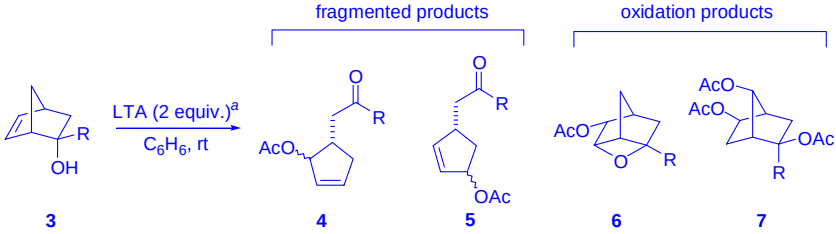
Finally, action of lead tetraacetate (LTA, 2 equiv.)[26] on norbornenol (**3a**) in dry benzene at room temperature during 24 h gave a 86% isolated yield of the wanted aldehydes, as an unstable mixture of the four possible isomers **4a** (*cis* and *trans*) and **5a** (*cis* and *trans*) in a GC ratio of 77:15:7:<1 (Scheme 2a). Along with the mixed isomers, work up and chromatography afforded a small quantity of pure major isomer, which could be characterized as the 1,5-*cis* compounds **4a**, and a new product that was identified as the cyclized hemiacetal **8a** derived from *cis*-**4a** (Scheme 2b).



Scheme 2

To investigate the scope and limitations of the reaction, compounds **3b-e** were submitted to the same reaction conditions, affording complex reaction mixtures whose composition are summarized in Schemes 3 and 5. The low yields partially reflect the instability of products. Indeed, most of them decomposed to tarry mixtures on standing at room temperature on the bench.

The reaction of **3b-e** with LTA gave two classes of compounds: fragmented products and oxidation products. Expected ketones **4** and **5** resulted from β–scission of the alkoxyl radical and oxidation compounds **6-7** arose directly from the substrates. However the harsh reaction conditions, *i.e.* an acidic and oxidizing medium, led to partial transformation of *cis*-**4** into acetalyzed derivatives **8**, **9** and **10** (Scheme 5).



3 **4** **5** **6** **7**

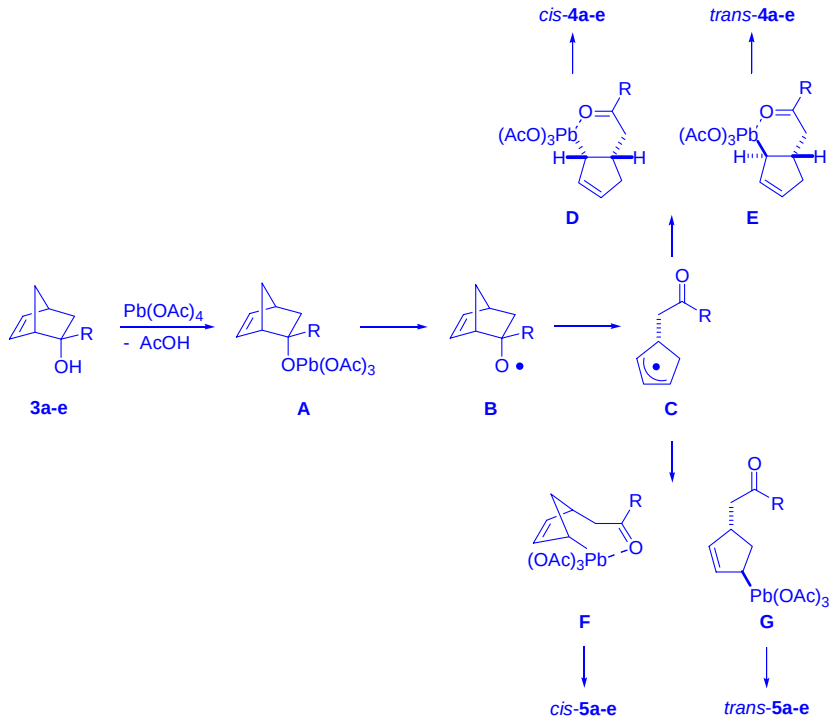
Entry	R	% Yield[c] of **4** (*cis*/*trans*)[b]	% Yield[c] of **5** (*cis*/*trans*)[b]	% Yield[c] of **6**	% Yield[c] of **7**
3b	Me	65%; (99/1)	-[d]	5%	7%
3c	*t*-Bu	27%; (8/1)	-[d]	7%	7%
3d	Ph	53%; (52/1)	10%; (4/1)	-[d]	-[d]
3e		54%; (99/1)	-[d]	-[d]	-[d]

[a]A benzene solution of LTA (2 equiv.) and substrate was reacted during 24 h. [b]The *cis*/*trans* ratio were determined by ^{1}H-NMR integration. [c]Isolated yield. [d]No products were detected.

Scheme 3

Although the mechanism of LTA action on alcohols has been extensively studied, it has been poorly discussed for the case of β–scission of unsaturated alcohols and remains speculative in most of the cases. Very dependent on the reaction conditions, it can follow radical, ionic as well as mixed pathway, affording different compounds.[32-34] Thus, while compounds similar to **6** have already been reported as the result of ethylenic alcohols cyclization with LTA,[33] **7** are best explained by Wagner-Meerwein type rearrangements. Formation of the expected cyclopentenes **4** and **5** shows an interesting selectivity, in all the cases, the 1,5-*cis* compound being the major one. According to Eguchi's report,[26] a possible mechanism for the synthesis of **4** and **5** is depicted in Scheme 4. Its first step involves reversible formation of alkoxyl-lead(IV) acetate **A** which is readily homolytically cleaved to generate alkoxyl radical **B**. β–Scission affords the allylic carbon-centered radical **C** that is trapped, giving lead(IV) intermediates **D**-**G**. These collapse into the products **4** (*cis*/*trans*) and **5** (*cis*/*trans*) *via* reductive elimination of lead(II) acetate. The surprising observed selectivity in favor of the 1,5-*cis* compounds **4** may be explained by chelation between the carbonyl oxygen and the lead(IV), followed by intramolecular acetate transfer from the lead triacetate moiety to the cyclopentenyl

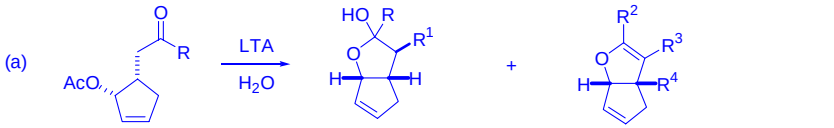
moiety. Thus formation *cis*-six-membered chelated **D** ring is favored over that of the more strained *trans*-six-membered ring **E** and the bridged *cis*-seven-membered ring **F**. For strain reasons, no chelation seems possible in the 1,4-*trans*-case **G** (Scheme 4). Nevertheless, steric as well as stereoelectronic factors which remain unexplained must govern the reaction. Worth to note is that, for the 2-vinylbicyclo[2.2.1]hept-5-en-2-ol **3e**, intermolecular trapping of the allylic radical **C** seems faster than Michael-type intramolecular cyclization onto the α,β-unsaturated ketone intermediate (Scheme 4, R = $CH=CH_2$). No product of tandem β-scission/cyclization has been detected.



Scheme 4

Transformation of *cis*-**4** into **8**, **9** and **10** is attributed to the combination of acidic and oxidizing reaction conditions. It occurs presumably *via* a sequence of acetate

deprotection, acetalyzation and over-oxidation. Compounds *cis*-**4a-d** afforded the bicycles **8** and **9** (Scheme 5a), and the never isolated vinyl ketone **4e**, which was never isolated, gave bicyclic derivatives **10e$_{1\text{-}5}$** with total destruction of the ethylenic moiety (Scheme 5b). Interestingly, diacetylation of the double bond by LTA was predominant and furnished vicinal diacetates **10e$_{1\text{-}3}$**. In the case of reaction products from *t*-butyl precursor **3c**, an observation should be outlined: column chromatography of by-product **8c** transformed it partially into an epoxide (18% yield from **8c**) as the result of intramolecular substitution of the acetate group (R^1) by the alcohol function (Scheme 5a). The stereochemistry of bicycles **8**, **9** and **10** shows undoubtedly that they derive exclusively from *cis*-**4**.



cis-**4** **8** **9**

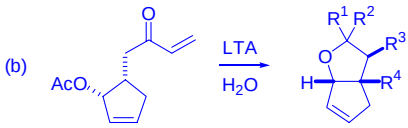
4a : R = H **8a** : R^1 = H; 6%

4b : R = Me **9b** : R^2 = CH_2OAc; R^3 = H; R^4 = OAc; 7%

4c : R = *t*-Bu **8c** : R^1 = OAc; 17%

4d : R = Ph **8d** : R^1 = OAc; 18% **9d$_1$** : R^2 = Ph; R^3 = R^4 = H;10%

9d$_2$: R^2 = Ph; R^3 = OAc; R^4 = H; 20%



cis-**4e** **10e**

10e$_1$: R^1 = $CH(OAc)CH_2OAc$; R^2 = OH; R^3 = R^4 = H; 12%

10e$_2$: R^1 = $CH(OAc)CH_2OAc$; R^2 = R^3 = R^4 = H; 30%

10e$_3$: R^1 = $CH(OAc)CH_2OAc$; R^2 = R^3 = H; R^4 = OAc; 6%

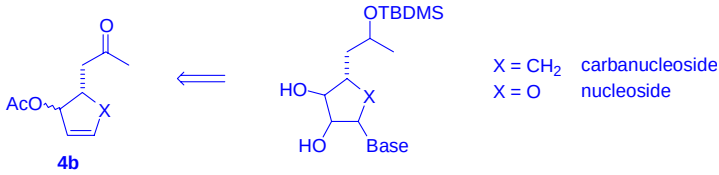
10e$_4$: R^1 = OAc; R^2 = R^3 = R^4 = H; 4%

10e$_5$: R^1 = R^2 = O; R^3 = R^4 = H; 2%

Scheme 5

Combination of the yields of fragmented products **4** and **5** with those of by-products **8**, **9** and **10** shows undoubtedly the efficiency of the alkoxyl radical generation and fragmentation processes from substrates **3**, as well as its selectivity in favor of the 1,5-*cis* compound.

Synthesis of carbanucleoside analogues. Selective synthesis of compounds *cis*-**4** opens a direct route to the preparation of carbanucleosides by simples transformations as Baeyer-Villiger oxidation of the ketonic moiety and appropriate functionalization of the double bond (Figure 2).



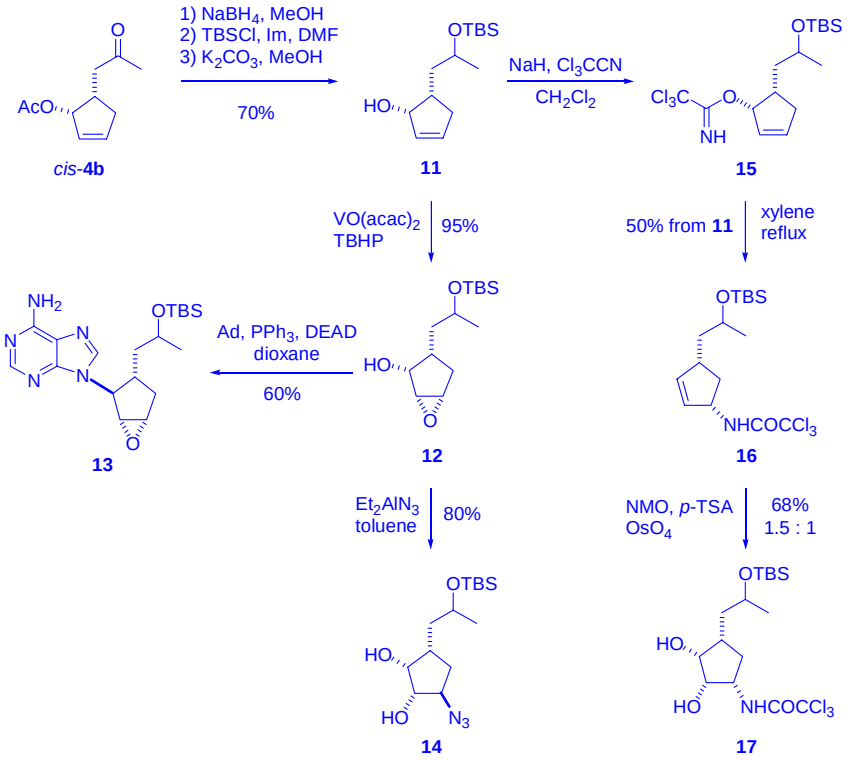
4b

Figure 2

To demonstrate the potential of the developed method for the preparation of versatile cyclopentene synthons, synthesis of a variety of carbanucleoside analogue precursors **13**, **14**, **16** and **17** was achieved from *cis*-5-acetylmethyl-2-cyclopentyl acetate (*cis*-**4b**) (Scheme 6). Selective reduction of ketone *cis*-**4b** with $NaBH_4$ (1.5 equiv.) in cold methanol afforded a 1.2:1 mixture of both epimeric corresponding alcohols, which were silylated with *t*-butyldimethylsilyl chloride. Deprotection of the acetate group with methanolic potassium carbonate, and lobar column separation gave diastereomeric compounds **11** in 70% yield. Configuration of the silyloxy-bearing center was not determined.

Different transformations were achieved on this intermediate **11**. On the one hand, stereoselective epoxidation of the minor isomer **11** with *t*-butyl hydroperoxide and catalytic vanadyl acetyl acetonate ($VO(acac)_2$) following Teranishi's procedure[35] produced *cis*-epoxide **12** as a single isomer, in 95% yield. Then, either Mitsunobu's reaction of **12** with adenine[36] allowed formation of compound **13** in 60% yield, or regio- and stereoselective epoxide opening with triethylaluminium azide generated *in situ* by

addition of triethylaluminium chloride to a sodium azide suspension in toluene[37] furnished a 80% yield of the azido diol **14**. An isomer of **14**, formed in about 1:7 ratio, was detected in NMR spectrum of **14**.



Scheme 6

On the other hand, upon treatment with sodium hydride and trichoroacetonitrile, major isomer of alcohol **11** was converted to its trichloroacetimidate derivative **15**. Due to its instability, the latter was used without purification. When refluxed in xylene for 2 h, it underwent regio- and stereoselective [3,3]-sigmatropic rearrangement[38] onto the trichloroacetamide **16** with 50% yield from **11**. Dihydroxylation with catalytic osmium

tetroxide and N-methyl morpholine oxide (NMO) gave access to diol compounds **17** in a 1.5:1 ration in favor of the all-*cis* isomer, with 68% yield.
Functionalized cyclopentanes **13**, **14**, and **17** as well as cyclopentene **16** can be very easily further derivatized to a big number of potentially biologically active compounds.

3. Conclusion

The β-fragmentation of alkoxyl radicals generated by treatment of norbornenol derivatives with lead tetraacetate, has proven to afford efficiently 5-substituted cyclopentenyl acetate with a surprising high selectivity in favor of the 1,5-*cis* compounds. The reaction pathway was assumed to involve a cyclic transition state were the lead, chelating the ketone oxygen, transferred intramolecularly an acetate group to the allylic carbon radical intermediate.
Despite its limitations due to the strongly oxidizing conditions which led to formation of over-oxidation by-products, the developed methodology demonstrated its high potential in short syntheses of a variety of carbanucleoside precursors, starting from the versatile cyclopentene *cis*-**4b**.

4. Experimental Section

THF was freshly distilled from K under N_2; CH_2Cl_2, DMF and benzene were distilled from CaH_2 under N_2; Et_2O was distilled from Na/benzophenone and toluene from Na under N_2. Solvents for chromatography were distilled. Flash chromatography (FC) and filtration were performed with Baker silica gel (0.063-0.200 mm). TLC were run on Merck silica gel 60 F_{254} analytical plates; detection was carried out with either UV, iodine, spraying with solution of phosphomolybdic acid (25 g), $Ce(NH_4)_2(NO_3)_6{\cdot}4H_2O$ (10 g), concd H_2SO_4 (60 ml) and water (940 ml), or with a solution of $KMnO_4$ (3 g), K_2CO_3 (20 g), water (300 ml) and 5% NaOH (5 ml), with subsequent heating. Mps, not corrected, were determined on a Büchi-Tottoli apparatus. IR spectra were recorded on a Mattson Unicam 5000 spectrophotometer, in cm^{-1}. NMR spectra were recorded on a

Varian Gemini 200 (^{1}H 200 MHz and ^{13}C 50.3 MHz), a Bruker AM 360 (^{1}H 360 MHz) or a Bruker Avance DRX-500 (^{1}H 500 MHz and ^{13}C 125.77 MHz); for ^{1}H δ are given in ppm relative to $CDCl_3$ (7.27 ppm), for ^{1}C δ are given in ppm relative to $CDCl_3$ (77.1 ppm), and coupling constant *J* are given in Hz. ^{1}H NMR splitting pattern abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR multiplicities were determined by the APT and DEPT sequences, abbreviations are: q, CH_3; t, CH_2; d, CH; s, quaternary carbons. Assignments were confirmed by NOE or NOESY, COSY and HETCOR experiments. MS spectra were recorded on a Vacuum Generator Micromass VG 70/70E DS 11-250; EI (70 eV), CI (CH_4 gas); *m/z* (%). Elemental analysis were performed by Ilse Beetz, Microanalytisches Laboratorium, D-96301 Kronach, Germany, and Ciba Geigy Mikrolabor, Marly, Switzerland.

Norbornenone (bicyclo[2.2.1]hept-5-en-2-one) (2). To a solution of 2-chloroacrylonitrile (41.6 g, 0.63 mol) stabilized with hydroquinone (2-3 mg) in dry ether was added freshly distilled cyclopentadiene (55 g, 0.63 mol). The mixture was refluxed for 24 h. Evaporation of the volatiles afforded the crude chloronitrile adduct **1** in 98% yield, as a slightly yellow oil which solidified when cooled.

A hot solution of KOH (79 g, 1.41 mol) in 70 ml H_2O added to a stirred solution of **1** (94.4 g, 0.61 mol) in DMSO. The resulting dark mixture was heated at 70°C for 7 h and let for 15 h at rt, before being poured on iced water (600 ml). Extraction with hexane (6x250 ml), drying ($MgSO_4$) and evaporation of the solvent gave the crude product, which was purified by distillation under reduced pressure to afford **2** as a colorless oil in 58% yield; bp 51°C/10 Torr. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.55 (dd, *J* = 5.5 Hz, 3.0 Hz, 1 H, C*H*=CH), 6.18-6.02 (m, 1 H, CH=C*H*), 3.25-3.12 (m, 1 H, C*H*), 3.07-2.93 (m, 1 H, C*H*), 2.25-1.82 (m, 4 H, CH_2). Compound **2** has already been described in the literature (see ref. 15).

Norbornenol (3a). To a solution of ketone **2** (10.8 g, 0.1 mol) in MeOH (100 ml) under N_2 at –10°C, was added in small portions $NaBH_4$ (4.0 g, 0.1 mol). The mixture was stirred for a further 30 min and allowed to warm up to rt After evaporation of the MeOH,

the crude product was dissolved in AcOEt (100 ml), washed with water (100 ml) and the aqueous phase extracted with AcOEt (2 x 100 ml). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by FC (Hexane/AcOEt 8:2) to yield 6.47 g (59%) of alcohol **3a** as a white solid. IR (KBr) 3580, 3440, 3060, 2970, 1752, 1220, 763. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.45 (dd, J = 5.7 Hz, 3.0 Hz, 1 H, C*H*=CH), 6.04 (dd, J = 5.7 Hz, 3.0 Hz, 1 H, CH=C*H*), 4.48-4.44 (m, 1 H, C*H*-OH), 3.00-2.97 (m, 1 H, C*H*), 2.82-2.80 (m, 1 H, C*H*), 2.11 (ddd, J = 12.1 Hz, 8.3 Hz, 4.0 Hz, 1 H, CH_2), 1.51-1.44 (m, 1 H, CH_2), 1.31-1.26 (m, 1 H, CH_2); 1.12 (s, 1 H, O*H*), 1.81-1.72 (m, 1 H, CH_2). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 140.59 (d), 130.94 (d), 72.63 (d), 48.42 (t), 48.23 (t), 43.03 (d), 37.97 (d). CI-MS 110 (7, M^+), 67 (10), 66 (100), 65 (11). Anal. Calcd for C_7H_8O (110.15): C, 76.33; H, 9.15; Found: C, 76.27; H, 9.22.

2-Methylbicyclo[2.2.1]hept-5-en-2-ol (3b). A solution of **2** (2 g, 18.5 mmol) in Et_2O (8 ml) was added dropwise to a solution of CH_3MgBr (3 M in Et_2O; 7.4 ml, 22.2 mmol) under N_2 at rt. The mixture was let for 30 min after addition, hydrolyzed at 0°C with saturated aqueous NH_4Cl (80 ml), extracted with Et_2O (4 x 80 ml) and dried ($MgSO_4$). Evaporation of the solvent and FC (Hexane/Et_2O 1:1) afforded pure **3b** (2.16 g, 94%) as a pale yellow liquid. IR (film) 3400, 3060, 2870, 1280, 1260, 1070, 838, 770. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.44 (dd, J = 5.7 Hz, 3.0 Hz, 1 H, C*H*=CH), 6.20 (dd, J = 5.7 Hz, 3.0 Hz, 1 H, CH=C*H*), 2.84 (m, 1 H, C*H*), 2.67 (m, 1 H, C*H*), 1.82 (dd, J = 12.3 Hz, 3.7 Hz, 1 H, C*H*H), 1.60-1.43 (m, 2 H, CH_2), 1.51 (s, 3 H, CH_3), 1.16 (dd, J = 12.3 Hz, 3.2 Hz, 1 H, CH*H*). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 140.01 (d), 133.52 (d), 82.61 (s), 53.89 (d), 49.52 (t), 44.97 (t), 43.08 (d), 28.23 (q). CI-MS 124 (7, M^+), 81 (5), 66 (100), 58 (8), 43 (18). Anal. Calcd for $C_8H_{12}O$ (124.74): C, 77.38; H, 9.74; Found: C, 77.25; H, 9.70.

2-*t*-Butylbicyclo[2.2.1]hept-5-en-2-ol (3c). A solution of **2** (1 g, 9.25 mmol) in Et_2O (10 ml) was added dropwise *via* a syringe to a *t*-BuLi solution (1.5 M in hexane; 6.17 ml, 9.25 mmol) at –78°C under N_2. The reaction mixture was let for 15 min at –78°C and for 45 min at rt. After hydrolysis with aqueous saturated Na_2CO_3 (50 ml) at 0°C and extraction with Et_2O (4 x 50 ml), the organic phase was dried ($MgSO_4$) and the solvent

evaporated. FC (Hexane/AcOEt 9:1) of the crude afforded pure **3c** (1.28 g, 83%) as a colorless liquid. IR (film) 3600, 3070, 2970, 1726. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.49 (dd, *J* = 5.7 Hz, 2.9 Hz, 1 H, C*H*=CH), 6.29 (dd, *J* = 5.7 Hz, 3.2 Hz, 1 H, CH=C*H*), 2.91 (m, 1 H, C*H*), 2.85 (m, 1 H, C*H*), 1.99 (dd, *J* = 12.8 Hz, 3.7 Hz, 1 H, C*H*H), 1.64-1.45 (m, 2 H, CH_2), 1.02 (s, 9 H, CH_3), 0.95 (dd, *J* = 12.8 Hz, 3.7 Hz, 1 H, CH*H*). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 141.32 (d), 137.05 (d), 86.00 (s), 50.77 (d), 49.03 (t), 42.91 (t), 40.65 (d), 37.78 (s), 27.51 (q). Anal. Calcd for $C_{11}H_{18}O$ (166.26): C, 79.46; H, 10.92; Found: C, 79.62; H, 11.12.

2-Phenylbicyclo[2.2.1]hept-5-en-2-ol (3d). A solution of **2** (1 g, 9.25 mmol) in Et_2O (4 ml) was added dropwise to a solution of PhMgBr (3 M in Et_2O; 3.7 ml, 11.1 mmol) under N_2 at rt. The mixture was refluxed for 1 h after addition, cooled and hydrolyzed with saturated aqueous NH_4Cl (50 ml), extracted with Et_2O (3 x 50 ml) and dried ($MgSO_4$). Evaporation of the solvent and FC (Hexane/Et_2O 7:3) afforded pure **3d** (1.60 g, 93%) as a pale yellow liquid. IR (film) 3450, 2880, 1500, 1445, 1340, 1270, 1172, 1130, 990, 730, 700, 660. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.59-7.20 (m, 5 arom. H) 6.55 (dd, *J* = 5.7 Hz, 3.0 Hz, 1 H, C*H*=CH), 6.28 (dd, *J* = 5.7 Hz, 3.0 Hz, 1 H, CH=C*H*), 3.19 (m, 1 H, C*H*), 2.95 (m, 1 H, C*H*), 2.48 (dd, *J* = 12.5 Hz, 3.8 Hz, 1 H, C*H*H), 1.88 (s, 1 H, O*H*), 1.60 (m, 2 H, CH_2), 1.50-1.41 (m, 1 H, CH*H*). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 147.02 (s), 141.14 (d), 133.55 (d), 128.16 (d), 126.96 (d), 126.38 (d), 82.12 (s), 53.10 (d), 49.21 (t), 44.69 (t), 43.25 (d). CI-MS 186 (3, M^+), 120 (98), 105 (33), 91 (3), 77 (23), 66 (100). Anal. Calcd for $C_{13}H_{14}O$ (186.25): C, 83.83; H, 7.58; Found: C, 83.99; H, 7.25.

2-Vinylbicyclo[2.2.1]hept-5-en-2-ol (3e). A solution of **2** (1 g, 9.25 mmol) in THF (2 ml) was added dropwise during 45 min, to a solution of vinylmagnesium bromide (1 M in THF; 11.1 ml, 11.1 mmol) under N_2 at 0°C. The mixture was let warm to rt, and cooled to 0°C for hydrolysis with saturated aqueous NH_4Cl (20 ml). The product was extracted with Et_2O (3 x 20 ml), the combined organic layers were washed with 2% aqueous $NaHCO_3$ (10 ml) and water (10 ml), dried ($MgSO_4$) and evaporated. FC

(Hexane/AcOEt 8:2) of the crude afforded pure **3e** (0.865 g, 69%) as a volatile pale yellow liquid. IR (film) 3450, 3070, 1640, 1340, 1280, 1175, 915, 838, 722. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.46-6.44 (m, 1 H, C*H*=CH), 6.23-6.17 (m, 1 H, CH=C*H*), 6.16 (dd, *J* = 17.3 Hz, 10.7 Hz, 1 H, C*H*=CH_2), 5.33 (dd, *J* = 17.3 Hz, 1.4 Hz, 1 H, CH=CHH_{trans}), 5.08 (dd, *J* = 10.7 Hz, 1.4 Hz, 1 H, CH=CHH_{cis}), 2.89 (m, 1 H, C*H*), 2.75 (m, 1 H, C*H*), 2.02 (dd, *J* = 12.5 Hz, 3.8 Hz, 1 H, C*H*H), 1.81 (s, 1 H, O*H*), 1.56-1.53 (m, 2 H, CH_2), 1.20-1.12 (m, 1 H, CH*H*). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 144.18 (d), 140.21 (d), 133.13 (d), 111.64 (t), 80.30 (s), 53.26 (d), 48.54 (t), 43.18 (t), 42.95 (d). CI-MS 136 (5, M^+), 119 (100), 109 (8), 95 (19), 69 (20). Anal. Calcd for $C_9H_{12}O$ (136.19): C, 79.37; H, 8.88; Found: C, 79.62; H, 8.80.

General procedure for reaction of alcohols 3 with LTA. A solution of alcohol (9.1 mmol) and LTA (18.2 mmol) in dry benzene (45 ml) under N_2 was stirred at rt for 24 h. The reaction mixture was poured into water (45 ml) and insoluble material, when present, were filtered off on cellite. The filtrate was extracted with Et_2O (1 x 50 ml and 2 x 25 ml) and dried ($MgSO_4$). Evaporation of the solvents afforded the crude products, which were separated by successive FC.

Reaction of norbornenol (3a). According to general procedure. From **3a** (1.00 g, 9.1 mmol) and LTA (8.05 g, 18.2 mmol). FC (Hexane/AcOEt 8:2, 1% Et_3N) gave unstable aldehyde *cis*-**4a** (0.20 g, 13%), along with both the alkoxyl epimers of hemiacetal **8a** derived from **4a** (69 mg, 6%) and a mixture of aldehydes *trans*-**4a** and *cis*/*trans*-**5a** (298 mg, 21%).

Data of *cis*-5-formylmethylcyclopent-2-enol 1-*O*-acetate (*cis*-4a). Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.80 (t, *J* = 1.4 Hz, 1 H, C*H*O), 6.07-6.03 (m, 1 H, C*H*=CH), 5.78-5.75 (m, 1 H, CH=C*H*), 5.45-5.42 (m, 1 H, C*H*OAc), 2.90-2.83 (m, 2 H, CH*H*CHO, CHH_{trans}), 2.68-2.61 (m, 1 H, C*H*CH_2CHO), 2.56 (ddd, *J* = 16.7 Hz, 9.3 Hz, 1.4 Hz, 1 H, C*H*HCHO), 2.07 (s, 3 H, CH_3), 2.02-1.95 (m, 1 H, CHH_{cis}). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 201.17 (s), 171.16 (s), 136.37 (d), 128.52 (d), 84.86 (d), 48.16 (t), 37.99 (d), 37.75 (t), 21.19 (q). CI-MS 137 (7), 125 (15), 109 (100), 81 (25).

Data of 8a (mixture of diastereomers). Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.92-5.89 (m, 1 H, C*H*=CH, minor), 5.89-5.86 (m, 1 H, CH=C*H*, minor), 5.81-5.78 (m, 1 H, C*H*=CH, major), 5.76-5.73 (m, 1 H, CH=C*H*, major), 5.54 (dd, *J* = 5.2 Hz, 1.6 Hz, 1 H, CH_{exo}OH, minor), 5.50 (d, *J* = 4.4 Hz, 1 H, CH_{endo}OH, major), 5.29 (d, *J* = 7.5 Hz, 1 H, C*H*O-, major), 5.16 (d, *J* = 7.5 Hz, 1 H, C*H*O-, minor), 3.12-3.04 (m, 1 H, C*H*, major), 2.97-2.89 (m, 1 H, C*H*, minor), 2.71-2.64 (m, 1 H, CH=CHCHH_{exo}, minor), 2.63-2.56 (m, 1 H, CH=CHCHH_{exo}, major), 2.48-2.41 (m, 1 H, CH=CHCHH_{endo}, minor) 2.28 (ddd, J = 13.4 Hz, 10.10 Hz, 5.22 Hz, 1 H, CHH_{exo}, minor), 2.21 (dd, *J* = 12.7 Hz, 8.7 Hz, 1 H, CHH_{exo}, major), 2.16 (m, 1 H, CH=CHCHH_{endo}, major), 1.83 (ddd, J = 13.4 Hz, 2.9 Hz, 1.7 Hz, 1 H, CHH_{endo}, minor), 1.54 (ddd, J = 12.7 Hz, 9.2 Hz, 4.4 Hz, 1 H, CHH_{endo}, major). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 134.11 (d, minor), 133.11 (d, major), 132.41 (d, minor), 130.77 (d, major), 100.22 (d, minor), 98.70 (d, major), 90.15 (d, minor), 89.06 (d, major), 41.67 (t, minor), 41.35 (t, major), 40.18 (t, minor), 38.40 (d, minor), 38.21 (t, major), 37.45 (d, major). CI-MS 125 (6, $[M-1]^+$), 109 (100), 107 (3), 81 (7).

Reaction of 2-methylbicyclo[2.2.1]hept-5-en-2-ol (3b). According to general procedure. From **3b** (850 mg, 6.84 mmol) and LTA (6.07 g, 13.69 mmol). FC (CH_2Cl_2/Et_2O 9:1 to 97:3 and Hexane/AcOEt 8:2) gave compounds *cis*-**4b** (810 mg, 65%), **6b** (62 mg, 5%), **7b** (116 mg, 7%), and **9b** (114 mg, 7%).

Data of *cis*-5-acetylmethylcyclopent-2-enol 1-*O*-acetate (*cis*-4b). Colorless liquid. IR (film) 2928, 1728, 1361, 1244, 1020. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.04-6.00 (m, 1 H, C*H*=CH), 5.74-5.71 (m, 1 H, CH=C*H*), 5.40-5.38 (m, 1 H, C*H*OAc), 2.88 (dd, *J* = 16.4 Hz, 3.8 Hz, 1 H, CH*H*COCH_3), 2.86-2.78 (m, 1 H, CHH_{trans}), 2.63-2.54 (m, 1 H, C*H*CH_2COCH_3), 2.52 (dd, *J* = 16.4 Hz, 9.8 Hz, 1 H, C*H*HCOCH_3), 2.15 (s, 3 H, OCOCH_3), 2.04 (s, 3 H, OCOCH_3), 1.94-1.88 (m, 1 H, CHH_{cis}). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 206.48 (s), 170.10 (s), 135.36 (d), 127.45 (d), 83.84 (d), 46.77 (t), 38.10 (d), 36.85 (t), 29.02 (q), 20.15 (q). CI-MS 183 (0.3, $[M+1]^+$), 151 (4), 124 (11), 123 (100), 81 (7). Anal. Calcd for $C_{10}H_{14}O_3$ (182.22): C, 65.91; H, 7.74; Found: C, 65.81; H, 7.82.

Data of 6b. Yellow liquid. IR (film) 2963, 2926, 1746, 1236, 1030. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.96 (s, 1 H, C*H*OAc), 4.37 (dd, *J* = 4.4 Hz, 2.0 Hz, 1 H, C*H*O), 3.28 (dddd, *J* = 4.4 Hz, 1.5 Hz, 1.5 Hz, 1.5 Hz, 1 H, C*H*), 2.81-2.78 (m, 1 H, C*H*), 2.02 (s, 3 H, OCOC*H*$_3$), 1.95 (ddd, *J* = 13.0 Hz, 2.4 Hz, 0.9 Hz, 1 H, C*H*H), 1.77-1.72 (m, 1 H, C*H*H), 1.44 (dd, *J* = 13.0 Hz, 3.8 Hz, 1 H, CH*H*), 1.40-1.36 (m, 1 H, CH*H*), 1.35 (s, 3 H, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 169.95 (s), 80.15 (d), 77.30 (d), 76.98 (s), 48.05 (d), 41.79 (t), 41.72 (d), 33.50 (t), 23.17 (q), 21.09 (q). CI-MS 183 (24, $[M+1]^+$), 153 (7), 123 (33), 93 (10). Anal. Calcd for $C_{10}H_{14}O_3$ (182.22): C, 65.91; H, 7.74; Found: C, 66.20; H, 7.78.

Data of 7b. Yellow liquid. IR (film) 3451, 2972, 1736, 1368, 1246, 1059. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.18-5.16 (m, 1 H, C*H*OAc), 4.59 (ddd, *J* = 7.5 Hz, 3.6 Hz, 1.0 Hz, 1 H, C*H*OAc), 2.55 (d, *J* = 5.2 Hz, 1 H, C*H*), 2.17-2.14 (m, 1 H, C*H*), 2.10-2.01 (m, 1 H, C*H*H), 2.02 (s, 3 H, OCOC*H*$_3$), 2.00 (s, 3 H, OCOC*H*$_3$), 1.84-1.76 (m, 2 H, CH*H*, CH*H*), 1.27 (d, *J* = 14.0 Hz, 1 H, C*H*H), 1.25 (s, 3 H, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 170.88 (s), 170.58 (s), 80.04 (d), 75.73 (d), 73.77 (s), 51.46 (d), 44.14 (d), 41.46 (t), 31.43 (t), 26.35 (q), 21.36 (q), 21.26 (q). CI-MS 239 (5), 225 (26), 184 (10), 183 (100), 179 (10), 165 (23), 123 (88). Anal. Calcd for $C_{12}H_{18}O_5$ (242.27): C, 59.49; H, 7.49; Found: C, 59.45; H, 7.20.

Data of 9b. Colorless liquid. IR (film) 3451, 2940, 1739, 1373, 1248, 1047. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.96-5.93 (m, 1 H, C*H*=CH), 5.74-5.71 (m, 1 H, CH=C*H*), 5.66-5.63 (m, 1 H, C*H*), 5.39 (d, *J* = 1.0 Hz, 1 H, C*H*=C), 4.60 (d, *J* = 0.9 Hz, 2 H, C*H*$_2$OAc), 3.10-3.04 (m, 1 H, CH*H*$_{exo}$), 2.79-2.77 (m, 1 H, CH*H*$_{endo}$), 2.10 (s, 3 H, CH$_3$), 2.04 (s, 3 H, C*H*$_3$), 2.04 (s, 3 H, OCOC*H*$_3$). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 170.27 (s), 170.18 (s), 156.00 (s), 134.92 (d), 127.19 (d), 102.17 (d), 95.65 (s), 95.06 (d), 58.77 (t), 44.90 (t), 21.52 (q), 20.72 (q). CI-MS 238 (12, M^+), 237 (12, $[M-1]^+$), 180 (11), 178 (100), 137 (14), 123 (15), 119 (15). Anal. Calcd for $C_{12}H_{14}O_5$ (238.24): C, 60.50; H, 5.92; Found: C, 60.35; H, 7.91.

Reaction of 2-*t*-butylbicyclo[2.2.1]hept-5-en-2-ol (3c). According to general procedure. From **3c** (1.00 g, 6.01 mmol) and LTA (5.33 g, 12.02 mmol). FC (CH_2Cl_2/Et_2O 9:1 to

10:0 and Hexane/AcOEt 8:2 to 7:3) gave unseparable compounds *cis*- and *trans*-**4c** in a 8:1 ratio (135 mg, 27%), compounds **6c** (94 mg, 7%) and **7c** (120 mg, 7%), along with unstable **8c** (about 202 mg, 17%), which partially decomposed on the column to give an epoxide (33 mg, 3%).

Data of *cis*- and *trans*-4c. Colorless liquid. IR (film) 2970, 1735, 1706, 1367, 1243, 1059, 1017. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.10-6.08 (m, 1 H, C*H*=CH, *trans*), 6.00-5.99 (m, 1 H, C*H*=CH, *cis*), 5.91-5.89 (m, 1 H, CH=C*H*, *trans*), 5.81-5.79 (m, 1 H, CH=C*H*, *cis*), 5.64-5.61 (m, 2 H, C*H*OAc, *cis*, *trans*), 3.13-3.07 (m, 1 H, C*H*, *cis*), 2.87-2.76 (m, 2 H, C*H*, *trans*, CH*H*CO*t*-Bu, *trans*), 2.68-2.52 (m, 5 H, C*H*HCO*t*-Bu, *trans*, CH_2CO*t*-Bu, *cis*, CHH_{trans}, *cis*, CHH_{cis}, *trans*), 2.03 (d, *J* = 8.6 Hz, 1 H, CHH_{trans}, *trans*), 2.03 (s, 3 H, OCOCH_3, *cis*), 1.99 (s, 3 H, OCOCH_3, *trans*), 1.31 (ddd, 1 H, *J* = 14.3 Hz, 4.3 Hz, 4.3 Hz, 1 H, CHH_{cis}, *cis*), 1.16 (s, 9 H, CH_3, *trans*), 1.14 (s, 9 H, CH_3, *cis*). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 214.68 (s, *cis*), 214.56 (s, *trans*), 170.74 (s, *cis*), 170.44 (s, *trans*), 140.46 (d, *cis*), 137.39 (d, *trans*), 129.60 (d, *trans*), 129.46 (d, *cis*), 79.52 (d, *cis*), 79.43 (d, *trans*), 43.94 (s, *trans*), 43.88 (s, *cis*), 43.05 (t, *cis*), 39.31 (d, *cis*), 37.29 (t, *trans*), 36.67 (t, *cis*), 36.28 (t, *trans*), 35.65 (d, *trans*), 26.52 (q, *trans*), 26.24 (q, *cis*), 21.23 (q, *cis*), 21.08 (q, *trans*). CI-MS 223 (0.5, $[M-1]^+$), 165 (100), 85 (12), 57 (10). Anal. Calcd for $C_{13}H_{20}O_3$ (224.30): C, 69.61; H, 8.99; Found: C, 69.07; H, 8.97.

Data of 6c. Yellow liquid. IR (film) 2964, 1740, 1373, 1365, 1240, 1043. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.95 (s, 1 H, C*H*OAc), 4.31 (dd, *J* = 4.6 Hz, 2.1 Hz, 1 H, C*H*O), 3.38 (dddd, *J* = 4.6 Hz, 1.5 Hz, 1.5 Hz, 1.5 Hz, 1 H, C*H*), 2.83-2.81 (m, 1 H, C*H*), 2.02 (s, 3 H, OCOCH_3), 1.80 (ddd, *J* = 12.9 Hz, 2.3 Hz, 1.0 Hz, 1 H, C*H*H), 1.75 (dddd, *J* = 11.5 Hz, 1.9 Hz, 1.9 Hz, 1.9 Hz, 1 H, C*H*), 1.69 (dd, *J* = 12.9 Hz, 4.0 Hz, 1 H, CH*H*), 1.30-1.36 (dddd, *J* = 11.5 Hz, 1.3 Hz, 1.3 Hz, 1.3 Hz, 1 H, CH*H*), 0.89 (s, 9 H, CH_3). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 169.91 (s), 96.45 (s), (d), 79.16 (d), 42.62 (d), 41.06 (d), 36.02 (t), 33.96 (s), 33.75 (q), 24.41 (q), 21.05 (q). CI-MS 225 (6, $[M+1]^+$), 179 (9), 165 (75), 147 (19), 137 (16), 107 (100). Anal. Calcd for $C_{13}H_{20}O_3$ (224.30): C, 69.61; H, 8.99; Found: C, 68.98; H, 9.10.

Data of 7c. Yellow solid. Mp 84-84.5°C. IR (KBr) 3515, 2960, 1726, 1368, 1244. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.33 (s, 1 H, C*H*OAc), 4.67 (dd, *J* = 6.5 Hz, 4.4 Hz, 1 H,

C*H*OAc), 2.61 (d, *J* = 5.2 Hz, 1 H, C*H*), 2.46 (dd, *J* = 14.4 Hz, 7.4 Hz, 1 H, C*H*H), 2.40 (d, *J* = 3.1 Hz, 1 H, C*H*), 2.05 (s, 3 H, OCOCH_3), 2.00 (s, 3 H, OCOCH_3), 1.82 (ddd, *J* = 14.4 Hz, 4.3 Hz, 4.3 Hz, 1 H, CH*H*), 1.72 (d, *J* = 14.2 Hz, 1 H, C*H*H), 1.55 (dd, *J* = 14.2 Hz, 5.2 Hz, 1 H, CH*H*), 1.13 (s, 1 H, O*H*), 1.02 (s, 9 H, CH_3). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 170.81 (s), 170.55 (s), 80.85 (d), 76.87 (s), 75.66 (d), 50.53 (d), 42.24 (d), 37.69 (s), 35.42 (t), 30.43 (t), 26.74 (q), 21.02 (q). CI-MS 225 (28), 207 (16), 165 (100), 147 (17), 107 (29), 85 (16), 57 (22). Anal. Calcd for $C_{15}H_{24}O_5$ (284.35): C, 63.36; H, 8.51; Found: C, 63.69; H, 8.42.

Data of 8c. Yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.90-5.70 (m, 2 H, C*H*=C*H*), 5.30-5.20 (m, 1 H, C*H*O), 5.10 (d, *J* = 8.0 Hz, 1 H, C*H*OAc), 3.00-2.80 (m, 1 H, C*H*), 2.70-2.00 (m, 2 H, CH_2), 2.18 (s, 3 H, OCOCH_3), 0.95 (s, 9 H, CH_3).

Data of epoxide. Yellow solid. Mp 115°C. IR (KBr) 3454, 3057, 2960, 1724. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.83-5.81 (m, 1 H, C*H*=CH), 5.77-5.75 (m, 1 H, CH=C*H*), 5.14-5.11 (m, 1 H, C*H*O), 3.83 (d, *J* = 7.1 Hz, 1 H, C*H*$O_{epox.}$), 2.75 (ddd, *J* = 15.0 Hz, 7.6 Hz, 1.4 Hz, 1 H, C*H*), 2.66-2.56 (m, 1 H, CHH_{endo}), 2.49-2.44 (m, 1 H, CHH_{exo}), 0.99 (s, 9 H, CH_3). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 132.8 (d), 131.80 (d), 106.71 (s), 85.61 (d), 79.71 (d), 47.77 (d), 37.00 (s), 36.54 (t), 24.94 (q). CI-MS 181 (53, $[M+1]^+$), 163 (100), 96 (15), 67 (18). Anal. Calcd for $C_{11}H_{16}O_2$ (180.24): C, 73.30; H, 8.95; Found: C, 73.36; H, 8.61.

Reaction of 2-phenylbicyclo[2.2.1]hept-5-en-2-ol (3d). According to general procedure. From **3d** (1.00 g, 5.37 mmol) and LTA (4.76 g, 10.74 mmol). FC (Hexane/AcOEt 8:2 and Hexane/Et_2O 6:4 to 9:1) gave unseparable *cis*- and *trans*-**4d** in a 52:1 ratio (700 mg, 53%), unseparable *cis*- and *trans*-**5d** in a 4:1 ratio (131 mg, 10%), along with unseparable **8d** OH-epimers in a 2.7:1 ratio (252 mg, 18%), **9d$_1$** (99 mg, 10%), and unstable **9d$_2$** (260 mg, 20%).

Data of *cis*-4d. Pale yellow liquid. IR (film) 3062, 2930, 1731, 1686, 1242. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.00-7.45 (m, 5 H, arom. H), 6.07-6.04 (m, 1 H, C*H*=CH), 5.77 (dddd, *J* = 5.8 Hz, 2.2 Hz, 2.2 Hz, 2.2 Hz, 1 H, CH=C*H*), 5.54-5.52 (m, 1 H, C*H*OAc), 3.44 (dd, *J* = 17.1 Hz, 4.3 Hz, 1 H, C*H*HCOPh), 3.04 (dd, *J* = 17.1 Hz, 10.1 Hz, 1 H,

CH*H*COPh), 2.89 (ddddd, *J* = 17.4 Hz, 8.0 Hz, 2.3 Hz, 2.3 Hz, 2.3 Hz, 1 H, CHH_{trans}), 2.79-2.73 (m, 1 H, C*H*CH_2COPh), 2.05 (s, 3 H, OCOCH_3), 2.03-1.98 (m, 1 H, CHH_{cis}). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 198.96 (s), 171.24 (s), 136.86 (s), 136.70 (d), 133.08 (d), 128.58 (d), 128.48 (d), 128.01 (d), 85.16 (d), 42.90 (t), 39.66 (d), 38.08 (t), 21.24 (q). CI-MS 244 (2, M^+), 201 (14), 199 (43), 185 (100), 169 (45), 155 (11), 105 (99). Anal. Calcd for $C_{15}H_{16}O_3$ (244.29): C, 73.75; H, 6.60; Found: C, 73.45; H, 6.16.

Data of *cis*-5d. Pale yellow liquid. IR (film) 3064, 2971, 1731, 1685, 1243. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04-7.42 (m, 5 H, arom. H), 6.10 (ddd, *J* = 5.6 Hz, 2.2 Hz, 1.1 Hz, 1 H, C*H*=CH), 5.86 (ddd, *J* = 5.6 Hz, 2.1 Hz, 2.1 Hz, 1 H, CH=C*H*), 5.68-5.65 (m, 1 H, C*H*OAc), 3.30-3.23 (m, 1 H, C*H*CH_2COPh), 3.17 (dd, *J* = 17.1 Hz, 6.4 Hz, 1 H, C*H*HCOPh), 3.07 (dd, *J* = 17.1 Hz, 8.0 Hz, 1 H, CH*H*COPh), 2.68 (ddd, *J* = 14.4 Hz, 7.9 Hz, 7.9 Hz, 1 H, CHH_{cis}), 1.60 (s, 3 H, OCOCH_3), 1.49 (ddd, *J* = 14.4 Hz, 4.1, 4.1 Hz, 1 H, CHH_{trans}). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 198.80 (s), 170.81 (s), 140.27 (d), 136.89 (s), 133.15 (d), 129.81 (d), 128.62 (d), 128.03 (d), 79.56 (d), 45.02 (t), 39.73 (d), 36.71 (t), 21.30 (q). CI-MS 243 (0.4, $[M-1]^+$), 185 (100), 189 (33), 121 (7), 105 (50). Anal. Calcd for $C_{15}H_{16}O_3$ (244.29): C, 73.75; H, 6.60; Found: C, 73.86; H, 6.71.

Data of 8d. White solid. Mp 144°C. IR (KBr) 3366, 2917, 1743, 1366, 1235, 1063, 1022, 912. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65-7.25 (m, 5 H, arom. H, minor), 7.55-7.28 (m, 5 H, arom. H, major), 5.99 (dd, *J* = 5.2 Hz, 2.4 Hz, 1 H, C*H*=CH, minor), 5.93 (dd, *J* = 5.2 Hz, 2.2 Hz, 1 H, CH=C*H*, minor), 5.90 (s, 2 H, C*H*=C*H*, major), 5.41 (d, *J* = 6.6 Hz, 1 H, C*H*O, major), 5.38-5.35 (m, 1 H, C*H*O, minor), 5.32-5.29 (m, 1 H, C*H*OAc, major), 5.06 41 (d, *J* = 8.7 Hz, 1 H, C*H*OAc, minor), 3.52-3.47 (m, 1 H, C*H*, major), 3.36-3.31 (m, 1 H, C*H*, minor), 3.04 (s, 1 H, O*H*, major), 2.90 (s, 1 H, O*H*, minor), 2.77-2.71 (m, 1 H, CHH_{endo}, minor), 2.44-2.39 (m, 1 H, CHH_{exo}, major), 2.38-2.31 (m, 1 H, CHH_{exo}, minor), 2.21-2.17 (m, 1 H, CHH_{endo}, major), 2.14 (s, 3 H, COCH_3, minor), 1.38 (s, 3 H, COCH_3, major). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 169.69 (s, major, minor), 139.13 (s, major, minor), 135.83 (d, minor), 134.93 (d, major), 131.49 (d, minor), 129.86 (d, major), 128.26 (d, minor), 127.66 (d, major), 126.88 (d, major), 126.05 (d, minor), 125.42 (d, minor), 108.00 (s, major, minor), 89.18 (d, major), 88.14 (d, minor), 79.74 (d, minor), 78.03 (d, major), 42.39 (d, major), 40.20 (d, minor), 32.45 (t, minor), 31.38 (t,

major), 20.89 (q, minor), 20.29 (q, major). CI-MS 259 (3, $[M-1]^+$), 199 (12), 183 (100), 123 (17), 105 (50), 61 (22). Anal. Calcd for $C_{15}H_{16}O_4$ (260.29): C, 69.22; H, 6.20; Found: C, 69.23; H, 6.25.

Data of 9d$_1$. White solid. Mp 99°C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.20 (m, 5 H, arom. H), 6.04 (ddd, *J* = 5.7 Hz, 2.4 Hz, 2.4 Hz, 1 H, C*H*=CH), 5.95 (dddd, *J* = 5.7 Hz, 2.2 Hz, 2.2 Hz, 2.2 Hz, 1 H, CH=C*H*), 5.48 (ddd, *J* = 7.1 Hz, 2.2 Hz, 2.2 Hz, 1 H, C*H*O), 4.25 (d, *J* = 10.5 Hz, 1 H, C*H*=C), 3.45-3.39 (m, 1 H, C*H*), 2.23 (dddd, *J* = 18.1 Hz, 9.0 Hz, 2.3 Hz, 2.3 Hz, 1 H, CHH_{exo}), 2.03 (dddd, *J* = 18.1 Hz, 4.8 Hz, 4.8 Hz, 2.3 Hz, 1 H, CHH_{endo}). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 176.83 (s), 135.45 (s), 129.08 (d), 128.54 (d), 128.21 (d), 127.33 (d), 87.10 (d), 49.31 (d), 41.34 (d), 34.13 (t). CI-MS 183 (7, $[M-1]^+$), 173 (22), 155 (100), 135 (19), 129 (21), 105 (20), 91 (31). Anal. Calcd for $C_{13}H_{12}O$ (184.24): C, 84.75; H, 6.57; Found: C, 84.36; H, 6.96.

Data of 9d$_2$. White solid. Mp 142°C. IR (KBr) 3416, 3063, 2932, 1723, 1240, 1024, 700. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55-7.20 (m, 5 H, arom. H), 6.08 (dddd, *J* = 5.8 Hz, 2.3 Hz, 2.3 Hz, 1.1 Hz, 1 H, C*H*=CH), 5.81 (dddd, *J* = 5.8 Hz, 4.3 Hz, 4.3 Hz, 2.2 Hz, 1 H, CH=C*H*), 5.65-5.62 (m, 1 H, C*H*O), 4.07 (ddd, *J* = 9.0 Hz, 6.4 Hz, 3.1 Hz, 1 H, C*H*), 2.53-2.50 (m, 2 H, CH_2), 2.23 (s, 3 H, OCOH_3). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 168.86 (s), 138.98 (s), 135.01 (d), 130.17 (s), 129.67 (s), 129.10 (d), 128.40 (d), 128.32 (d), 125.52 (d), 88.26 (d), 43.64 (d), 35.91 (t), 20.08 (q). CI-MS 243 (27, $[M+1]^+$), 242 (19, M^+), 199 (81), 183 (100), 164 (74), 105 (61).

Reaction of 2-vinylbicyclo[2.2.1]hept-5-en-2-ol (3e). According to general procedure. From **3e** (500 mg, 3.67 mmol) and LTA (3.26 g, 7.34 mmol). FC (Hexane/Et_2O 8:2 to 1:1 and CH_2Cl_2/Et_2O 92:8 to 96:4) gave unseparable *cis*- and *trans*-**4e** in a 99:1 ratio (385 mg, 54%) which unfortunately transformed totally into compounds **10e$_1$** (119 mg, 12%) in a 7.7:2.3:1.9:1 ratio, unseparable AcO-epimers of **10e$_2$** in a 1.3:1 ratio (278 mg, 30%), unseparable AcO-epimers of **10e$_3$** (68 mg, 6%), along with unseparable mixture of **10e$_4$** and **10e$_5$** in a 2:1 ratio (34 mg, 6%).

Data of 10e$_1$. Pale yellow liquid. IR (film) 3455, 2959, 2919, 1745, 1372, 1231, 1042. ^{1}H NMR ($CDCl_3$, 500 MHz) 5.93-5.72 (m, 6 H, C*H*=CH, CH=C*H*, others), 5.81 (m, 1 H,

C*H*=CH, major), 5.71-5.69 (m, 1 H, CH=C*H*, major), 5.30-5.15 (m, 6 H, C*H*O, C*H*OAc, others), 5.29-5.27 (m, 1 H, C*H*O, major), 5.18 (dd, *J* = 7.2 Hz, 2.9 Hz, 1 H, C*H*OAc, major), 4.54-4.15 (m, 6 H, CH_2OAc, others), 4.49 (dd, *J* = 12.1 Hz, 2.9 Hz, 1 H, C*H*HOAc, major), 4.15 (dd, *J* = 12.1 Hz, 7.3 Hz, 1 H, CH*H*OAc, major), 3.17-3.09 (m, 1 H, C*H*, major), 3.08-1.43 (m, 15 H, CH_2, C*H*, others), 2.61-2.54 (m, 1 H, CH=CHCHH_{exo}, major), 2.28-2.17 (m, 2 H, CHH_{exo}, CH=CHCHH_{endo}, major), 2.14 (s, 3 H, OCOH_3, others), 2.13 (s, 3 H, OCOH_3, others), 2.12 (s, 3 H, OCOH_3, others), 2.09 (s, 3 H, OCOH_3, major), 2.08 (s, 3 H, OCOH_3, others), 2.05 (s, 3 H, OCOH_3, others), 2.05 (s, 3 H, OCOH_3, major), 2.04 (s, 3 H, OCOH_3, others), 1.63 (dd, *J* = 12.6 Hz, 9.7 Hz, 1 H, CHH_{endo}, major). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 170.78 (s, major), 170.15 (s, major), 132.73 (d, major), 130.76 (d, major), 105.32 (s, major), 90.10 (d, major), 73.03 (d, major), 63.13 (t, major), 41.64 (t, major), 38.14 (d, major), 37.71 (t, major), 20.93 (q, major), 20.82 (q, major). CI-MS 269 (10, $[M-1]^+$), 253 (57), 227 (14), 209 (33), 193 (100), 151 (52), 125 (35), 61 (56). Anal. Calcd for $C_{13}H_{18}O_6$ (270.28): C, 57.77; H, 6.71; Found: C, 58.01; H, 6.75.

Data of 10e$_2$. Pale yellow liquid. IR (Film) 3475, 2927, 1746, 1372, 1241, 1226, 1047. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.96-5.92 (m, 2 H, C*H*=CH, major, minor), 5.70-5.67 (m, 2 H, CH=C*H*, major, minor), 5.59-5.31 (m, 4 H, C*H*O, C*H*OAc, major, minor), 4.82 (d, *J* = 2.5 Hz, 1 H, C=C*H*, major), 4.78 (d, *J* = 2.5 Hz, 1 H, C=C*H*, minor), 4.29-4.24 (m, 2 H, C*H*HOAc, major, minor), 4.18-4.11 (m, 2 H, CH*H*OAc, major, minor), 3.63-3.57 (m, 2 H, C*H*, major, minor), 2.59-2.53 (m, 2 H, CHH_{exo}, major, minor), 2.26-2.20 (m, 2 H, CHH_{endo}, major, minor), 2.05 (s, 3 H, OCOCH_3, major), 2.05 (s, 3 H, OCOCH_3, minor), 1.99 (s, 3 H, OCOCH_3, minor), 1.99 (s, 3 H, OCOCH_3, major). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 170.40 (s, major, minor), 169.80 (s, major), 169.76 (s, minor), 150.53 (s, minor), 150.29 (s, major), 134.79 (d, major), 134.69 (d, minor), 129.11 (d, major), 129.10 (d, minor), 104.04 (d, major), 103.12 (d, minor), 91.56 (d, major), 91.55 (d, minor), 67.17 (s, minor), 67.03 (s, major), 63.36 (t, minor), 63.34 (t, major), 43.72 (d, minor), 43.69 (d, major), 39.30 (t, major), 39.27 (t, minor), 20.86 (q, major), 20.82 (q, minor), 20.62 (q, major, minor). CI-MS 252 (2, M^+), 193 (85), 151 (100), 135 (26), 133

(68), 107 (14), 79 (11). Anal. Calcd for $C_{13}H_{16}O_5$ (252.27): C, 61.90; H, 6.39; Found: C, 61.82; H, 6.52.

Data of 10e$_3$. Pale yellow liquid. IR (film) 3062, 2930, 1731, 1686, 1242. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.94-5.91 (m, 1 H, C*H*=CH), 5.68 (dddd, *J* = 6.1 Hz, 1.8 Hz, 1.8 Hz, 1.8 Hz, 1 H, CH=C*H*), 5.63-5.60 (m, 2 H, C=C*H*, C*H*OAc), 5.39 (d, *J* = 6.0 Hz, 1 H, C*H*O), 4.32 (dd, *J* = 11.9 Hz, 3.4 Hz, 1 H, C*H*HOAc), 4.21 (dd, *J* = 11.9 Hz, 7.3 Hz, 1 H, CH*H*OAc), 3.06 (dddd, *J* = 18.0 Hz, 1.8 Hz, 1.8 Hz, 1.8 Hz, 1 H, CHH_{endo}), 2.75 (dddd, *J* = 18.0 Hz, 2.5 Hz, 2.5 Hz, 0.9 Hz, 1 H, CHH_{exo}), 2.12 (s, 3 H, OCOCH_3), 2.05 (s, 3 H, OCOCH_3), 2.03 (s, 3 H, OCOCH_3). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 170.37 (s), 170.12 (s), 169.62 (s), 155.99 (s), 134.98 (d), 127.13 (d), 101.80 (d), 95.39 (s), 95.00 (d), 67.15 (d), 63.22 (t), 44.95 (t), 21.47 (q), 20.79 (q), 20.60 (q). CI-MS 311 (3, $[M+1]^+$), 310 (2, M^+), 256 (26), 191 (82), 149 (100), 137 (20), 131 (21), 123 (37), 101 (35), 95 (25). Anal. Calcd for $C_{15}H_{18}O_7$ (310.31): C, 58.06; H, 5.85; Found: C, 57.98; H, 6.02.

Data of 10e$_4$. Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.23 (ddd, *J* = 5.6 Hz, 2.4 Hz, 2.4 Hz, 1 H, C*H*=CH), 5.98-5.96 (m, 1 H, CH=C*H*), 5.64 (d, *J* = 9.5 Hz, 1 H, C=C*H*), 5.40 (ddd, *J* = 6.6Hz, 2.2 Hz, 2.2 Hz, 1 H, C*H*O), 3.41-3.35 (m, 1 H, C*H*), 2.59-2.53 (m, 1 H, CHH_{endo}), 2.45 (dddd, *J* = 18.0 Hz, 9.1 Hz, 2.7 Hz, 1.9 Hz, 1 H, CHH_{exo}), 2.21 (s, 3 H, OCOCH_3). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 169.78 (s), 140.12 (d), 127.98 (d), 86.24 (d), 69.71 (d), 39.12 (d), 31.49 (t), 20.51 (q).

Data of 10e$_5$. Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.10 (dddd, *J* = 5.7 Hz, 2.4 Hz, 2.4 Hz, 0.9 Hz, 1 H, C*H*=CH), 5.89 (dddd, *J* = 5.7 Hz, 4.3 Hz, 2.2 Hz, 2.2 Hz, 1 H, CH=C*H*), 5.54-5.52 (m, 1 H, C*H*O), 3.18-3.11 (m, 1 H, C*H*), 2.84 (dd, *J* = 18.4 Hz, 10.5 Hz, 1 H, CH*H*), 2.80-2.74 (m, 1 H, CH*H*), 2.33 (dd, *J* = 18.4 Hz, 5.8 Hz, 1 H, C*H*H), 2.34-2.29 (m, 1 H, C*H*H). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 172.05 (s), 136.85 (d), 129.05 (d), 89.61 (d), 39.57 (t), 36.04 (t), 35.09 (d).

Alcohol (11). $NaBH_4$ was added by small portions over 45 min. to a solution of *cis*-5-acetylmethylcyclopent-2-enol 1-*O*-acetate (*cis*-**4b**) (2.5 g, 13.72 mmol) in dry MeOH (15 ml) at 0°C, under N_2. The mixture was stirred for a supplementary 5-10 min, until gas emission stopped, and hydrolyzed with water (25 ml). The product was extracted with

AcOEt (4 x 30 ml), dried over $MgSO_4$ and the solvent evaporated to afford the crude alcohols (2.25 g, 89%) as pale yellow liquid containing a 1.2:1 mixture of isomers.

To a solution of this (2.16 g, 11.72 mmol) and imidazole (1.76 g, 25.79 mmol) in dry DMF (10 ml) at rt, was added *t*-butyldimethylsilyl chloride (TBDMSCl). The resulting solution was let at rt for 19 h and poured over Et_2O/H_2O 4:1 (250 ml). The phases were separated and the organic layer washed with H_2O (2 x 50 ml). The combined organic layers were dried ($MgSO_4$). Evaporation of the solvent gave the crude product (3.39 g, 97%) as a pale yellow liquid.

These (3.29 g, 11.0 mmol) were dissolved in MeOH (100 ml). After addition of K_2CO_3 (3.8 g, 27.55 mmol), the solution was stirred at rt for 1 h, before neutralizing with a 1 M solution of HCl. The reaction mixture was concentrated, extracted with AcOEt (1 x 100 ml and 2 x 70 ml) and dried ($MgSO_4$). Evaporation of the solvent afforded the crude alcohols **11**. Lobar chromatography (Hexane/AcOEt 9:1) allowed separation of the *t*-butyldimethylsilyloxyl epimers, giving sequentially minor and major **11** isomers in 81% yield as pale yellow liquids.

11-Minor: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.84-5.78 (m, 2 H, C*H*=C*H*), 5.53-5.50 (m, 1 H, C*H*OH), 4.19-4.11 (m, 1 H, C*H*OTBDMS), 3.58 (br, 1 H, O*H*), 2.57-2.49 (m, 1 H, CH*H*), 2.26-2.16 (m, 1 H, C*H*), 1.96 (ddddd, *J* = 16.2 Hz, 8.6 Hz, 2.1 Hz, 2.1 Hz, 2.1 Hz, 1 H, C*H*H), 1.76 (ddd, *J* = 14.0 Hz, 9.8 Hz, 4.6 Hz, 1 H, CH*H*), 1.66 (ddd, *J* = 14.0 Hz, 4.1 Hz, 4.1 Hz, 1 H, C*H*H), 1.22 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.92 (s, 9 H, C(CH_3)$_3$), 0.11 (s, 3 H, SiCH_3), 0.11 (s, 3 H, SiCH_3). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 133.97 (d), 131.87 (d), 83.10 (d), 68.42 (d), 44.39 (d), 42.08 (t), 38.50 (t), 25.86 (q), 22.40 (q), 18.19 (s), -4.76 (q), -4.98 (q).

11-Major: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.89-5.87 (m, 1 H, C*H*=CH), 5.76 (dddd, *J* = 5.8 Hz, 1.8 Hz, 1.8 Hz, 1.8 Hz, 1 H, CH=C*H*), 4.47-4.45 (m, 1 H, C*H*OH), 3.97-3.88 (m, 1 H, C*H*OTBDMS), 2.62 (ddddd, *J* = 16.5 Hz, 7.9 Hz, 2.1 Hz, 2.1 Hz, 2.1 Hz, 1 H, C*H*H), 2.14-2.04 (m, 1 H, C*H*), 1.95 (ddddd, *J* = 16.5 Hz, 6.1 Hz, 2.1 Hz, 2.1 Hz, 2.1 Hz, 1 H, C*H*H), 1.76 (ddd, *J* = 13.4 Hz, 7.7 Hz, 5.8 Hz, 1 H, CH*H*), 1.43 (ddd, *J* = 13.4 Hz, 8.9 Hz, 4.6 Hz, 1 H, C*H*H), 1.18 (d, *J* = 6.1 Hz, 3 H, CH_3), 0.89 (s, 9 H, C(CH_3)$_3$), 0.07 (s, 3 H, SiCH_3), 0.06 (s, 3 H, SiCH_3). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 133.40 (d), 133.30

(d), 83.76 (d), 67.44 (d), 45.03 (d), 44.29 (t), 37.75 (t), 25.91 (q), 24.27 (q), 18.10 (s), -4.21 (q), -4.63 (q).

Mixed isomers: IR (film) 3368, 3057, 2930, 1472, 1377, 1256, 1053, 837. CI-MS 257 (14, $[M+1]^+$), 139 (41), 159 (5), 119 (7), 107 (100), 79 (7). Anal. Calcd for $C_{14}H_{28}O_2Si$ (256.46): C, 65.57; H, 11.00; Found: C, 65.55; H, 10.85.

Epoxide (12).[35] To a solution of allylic alcohol mino-**11** (200 mg, 780 μmol) and vanadyl acetylacetonate ($VO(acac)_2$) (1 mg, 4 μmol) in dry benzene (3 ml) under N_2 at rt, was added *t*-BuOOH (5.5 M in nonane; 0.17 ml, 936 μmol) dropwise. The resulting solution was stirred at 40°C for 20 h. Then, an additional 0.3 eq. of *t*-BuOOH (5.5 M in nonane; 43 μl, 234 μmol) was dropped into the mixture to complete the reaction which was let for 4 h more at 40°C. Evaporation of the solvent, filtration of the residue on a Florisil column with Et_2O to remove the metal complex and evaporation of the eluent afforded the crude epoxide. FC (Hexane/AcOEt 8:2) gave pure epoxide **12** (201 mg, 95%) as a colorless liquid. IR (film) 3435, 2932, 2251, 1738, 1464, 1256, 1074, 910, 735. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 4.31 (br, 1 H, O*H*), 4.13-4.06 (m, 1 H, C*H*OTBDMS), 3.78 (d, *J* = 7.6 Hz, 1 H, C*H*OH), 3.50 (m, 1 H, C*H*O), 3.37 (d, *J* = 3.0 Hz, 1 H, C*H*O), 2.18 (dd, *J* = 14.0 Hz, 7.4 Hz, 1 H, CH*H*), 1.90-1.80 (m, 1 H, C*H*), 1.56-1.53 (m, 2 H, CH_2), 1.32 (dd, *J* = 14.0 Hz, 10.0 Hz, 1 H, C*H*H), 1.16 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.88 (s, 9 H, C(CH_3)$_3$), 0.08 (s, 3 H, SiCH_3), 0.07 (s, 3 H, SiCH_3). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 78.86 (d), 68.44 (d), 58.24 (d), 53.69 (d), 41.21 (t), 33.76 (d), 33.68 (t), 25.72 (q), 21.89 (q), 18.07 (s), -4.91 (q), -5.15 (q). CI-MS 273 (44, $[M+1]^+$), 257 (24), 215 (25), 197 (26), 141 (100), 123 (49), 81 (24). Anal. Calcd for $C_{14}H_{28}O_3Si$ (272.46): C, 61.72; H, 10.36; Found: C, 61.68; H, 10.18.

Adenine derivative 13.[36] To a suspension of **12** (30 mg, 110 μmol), adenine (30 mg, 220 μmol) and PPh_3 (58 mg, 220 μmol) in dry dioxane (3 ml) under N_2 at rt, was added a solution of DEAD (38 mg, 220 μmol) in dry dioxane (1.5 ml) over a period of 1 h. The resulting mixture was stirred at rt for 24 h and concentrated. FC of the residue (CH_2Cl_2/MeOH 30:1 to 20:1) afforded **13** (26 mg, 60%) as a white solid. Mp 164°C. IR

(KBr) 3430, 3344, 3154, 2930, 1655, 1603, 1254, 1072, 841. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.36 (d, J = 3.7 Hz, 1 H, arom. H), 7.67 (s, 1 H, arom. H), 5.91 (s, 2 H, NH_2), 5.22 (d, J = 6.7 Hz, 1 H, CHAd), 3.82 (d, J = 2.3 Hz, 1 H, CHO), 3.74-3.68 (m, 1 H, CHOTBDMS), 3.62 (d, J = 2.5 Hz, 1 H, CHO), 2.48-2.42 (m, 1 H, CH), 2.39 (dd, J = 13.9 Hz, 7.6 Hz, 1 H, CHH), 1.73 (dd, J = 13.9 Hz, 10.4 Hz, 1 H, CHH), 1.02-0.89 (m, 2 H, CH_2), 0.86 (d, J = 6.0 Hz, 3 H, CH_3), 0.84 (s, 9 H, C(CH_3)$_3$), 0.06 (s, 3 H, SiCH_3), 0.02 (s, 3 H, SiCH_3). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 155.12 (s), 153.22 (d), 149.49 (s), 148.06 (s), 119.00 (s), 66.97 (d), 57.38 (d), 56.90 (d), 56.16 (d), 38.50 (t), 35.53 (d), 32.93 (t), 25.84 (q), 24.04 (q), 17.99 (s), -4.27 (q), -4.61 (q). CI-MS 390 (27, M^+), 332 (15), 279 (60), 201 (14), 136 (23), 119 (100), 105 (13), 57 (12). Anal. Calcd for $C_{19}H_{31}O_2SiN_5$ (389.57): C, 58.58; H, 8.02; Found: C, 58.10; H, 7.74.

Azide 14.[37] Diethylaluminium azide was prepared *in situ* by dropwise addition of Et_2AlCl (1 M in Hexane; 0.16 ml, 155 µmol) to a suspension of NaN_3 (11 mg, 171 µmol) in dry toluene (1 ml) under N_2 at rt. The resulting mixture was stirred at rt for 4 h and cooled to –78°C. A solution of epoxide **12** (30 mg, 78 µmol) in dry toluene (1 ml) was then added dropwise. The reaction mixture was let warm to rt and stirred during 40 h. After dilution with Et_2O (20 ml) and quenching with MeOH (500 µl), $Na_2SO_4{\cdot}10H_2O$ (300 mg) was added, the resulting mixture filtered on cellite and the solvents removed. FC (Hexane/AcOEt 8:2) afforded compound **14** (28 mg, 80%) as a white solid. Mp 80-81°C. IR (KBr) 3383, 2930, 2361, 2342, 2099, 1256, 1086, 837, 775, 669. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.93 (d, J = 1.6 Hz, 1 H, OH), 4.20-4.15 (m, 1 H, CHOTBDMS), 4.01 (m, 1 H, CHOH), 3.82 (dd, J = 7.5 Hz, 2.5 Hz, 1 H, CHN$_3$), 3.66 (ddd, J = 8.1 Hz, 5.4 Hz, 1.5 Hz, 1 H, CHOH), 2.90 (d, J = 1.7 Hz, 1 H, CHOH), 2.34-2.23 (m, 2 H, CH, CHH), 1.71 (ddd, J = 14.4 Hz, 3.0 Hz, 3.0 Hz, 1 H, CHH), 1.59 (dd, J = 14.4 Hz, 4.0 Hz, 1 H, CHH), 1.26-1.23 (m, 1 H, CHH), 1.21 (d, J = 6.3 Hz, 3 H, CH_3), 0.92 (s, 9 H, C(CH_3)$_3$), 0.14 (s, 3 H, SiCH_3), 0.13 (s, 3 H, SiCH_3). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 77.34 (d), 76.94 (d), 68.36 (d), 65.02 (d), 41.84 (t), 37.51 (d), 34.76 (t), 25.76 (q), 21.84 (q), 18.14 (s), -4.87 (q), -5.10 (q). CI-MS 316 (100, $[M+1]^+$), 273 (17), 258 (15), 184

(15), 156 (26), 141 (33), 138 (27), 72 (23). Anal. Calcd for $C_{14}H_{29}O_3SiN_3$ (315.49): C, 53.30; H, 9.27; Found: C, 53.44; H, 9.29.

Trichloroacetimidate 15.[38] To hexane washed 55% NaH (189 mg, 4.32 mmol) under N_2, were added a solution of major alcohol **11** in CH_2Cl_2 (8 ml), and trichloroacetonitrile (446 mg, 2.06 mmol). The reaction was stirred at rt for 4 days, and NaH (0.2 equiv.) and trichloroacetonitrile (0.2 equiv.) added each 24 h. The reaction mixture was then filtered on cellite, the cellite washed with CH_2Cl_2 (10 ml) and the solvent evaporated to afford crude trichloroacetimidate **15** as a yellow liquid. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.25 (s, 1 H, N*H*), 6.08 (dddd, *J* = 5.7 Hz, 2.5 Hz, 2.5 Hz, 0.9 Hz, 1 H, CH=C*H*), 5.90 (dddd, *J* = 5.7 Hz, 2.1 Hz, 1 H, C*H*=CH), 5.5 (m, 1 H, C*H*O), 3.92-3.83 (m, 1 H, C*H*OTBTMS), 2.72 (ddddd, *J* = 17.1 Hz, 7.9 Hz, 2.4 Hz, 2.4 Hz, 2.4 Hz, 1 H, C*H*H), 2.54-2.45 (m, 1 H, C*H*), 2.06-1.99 (m, 1 H, CH*H*), 1.84 (ddd, *J* = 13.4 Hz, 7.3 Hz, 6.1 Hz, 1 H, CH*H*), 1.45 (ddd, *J* = 13.4 Hz, 9.3 Hz, 4.6 Hz, 1 H, C*H*H), 1.17 (d, *J* = 6.10 Hz, 3 H, CH_3), 0.87 (s, 9 H, C(CH_3)$_3$), 0.15 (s, 3 H, SiCH_3), 0.14 (s, 3 H, SiCH_3). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 162.62 (s), 137.14 (d), 128.23 (d), 112.32 (s), 91.02 (d), 66.97 (d), 44.52 (t), 40.20 (d), 37.64 (t), 25.85 (q), 23.99 (q), 18.06 (s), -4.22 (q), -4.84 (q).

Trichloroacetamide 16. A solution of crude **15** (40 mg, 100 μmol) in xylene (4 ml) was heated to reflux under N_2 for 5 h. Evaporation of the solvent under high vacuum for one night afforded the crude **16** which was purified by FC (Hexane/AcOEt 9:1) to afford trichloroacetamide **16** (20 mg, 50% from major **11**) as a slightly yellow solid. Mp 106-107°C. IR (KBr) 3297, 2928, 2857, 1686, 1524, 1258, 824. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.55 (d, *J* = 6.71 Hz, 1 H, N*H*), 6.02 (ddd, *J* = 5.8 Hz, 2.1 Hz, 1.5 Hz, 1 H, CH=C*H*), 5.72 (ddd, *J* = 5.8 Hz, 2.1 Hz, 2.1 Hz, 1 H, C*H*=CH), 4.00-4.93 (m, 1 H, C*H*N), 3.89-3.80 (m, 1 H, C*H*OTBDMS), 3.07-2.98 (m, 1 H, C*H*), 1.99 (ddd, *J* = 13.9 Hz, 7.9 Hz, 5.5 Hz, 1 H, C*H*H), 1.9 (ddd, *J* = 13.9 Hz, 7.4 Hz, 3.7 Hz, 1 H, CH*H*), 1.64 (ddd, *J* = 13.4 Hz, 8.5 Hz, 4.9 Hz, 1 H, C*H*H), 1.26 (ddd, *J* = 13.4 Hz, 9.5 Hz, 3.7 Hz, 1 H, CH*H*), 1.15 (d, *J* = 6.1 Hz, 3 H, CH_3), 0.89 (s, 9 H, C(CH_3)$_3$), 0.06 (s, 3 H, SiCH_3), 0.05 (s, 3 H, SiCH_3). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 161.17 (s), 142.1 (d), 128.31 (d), 92.00 (s), 67.09

(d), 57.38 (d), 45.26 (t), 40.89 (d), 37.76 (t), 25.85 (q), 24.36 (q), 18.05 (s), -4.20 (q), -4.76 (q). CI-MS 125 (32), 107 (100), 74 (94). Anal. Calcd for $C_{16}H_{28}O_2Cl_3SiN$ (400.84): C, 47.94; H, 7.04; Found: C, 47.80; H, 6.96.

Diols 17. To a solution of **16** (20 mg, 50 µmol) in THF/H_2O (95:5, 1 ml) were added sequentially NMO (7 mg, 55 µmol), *p*-toluenesulfonic acid (*p*-TSA) (10 mg, 52 µmol) and a small OsO_4 crystal. The resulting solution was stirred at rt for 18 h and diluted with AcOEt (4 ml). Na_2SO_4 (1.5 g) and *p*-TSA (15 mg) were added before the mixture was filtered on silice and the solvents evaporated. FC (Hexane/AcOEt 7:3) of the crude afforded pure diols **17** as a colorless liquid containing a 1.5:1 ratio of both *cis*-diols, the all-*cis* compound being the major one. IR (KBr) 3389, 2930, 2859, 1703, 1516, 1256, 1072, 824. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (d, *J* = 7.3 Hz, 1 H, N*H*, major), 6.80 (d, *J* = 3.1 Hz, 1 H, N*H*, minor), 4.28-4.23 (m, 1 H, C*H*NH, major), 4.14-4.05 (m, 3 H, C*H*OH, major, C*H*NH, minor, C*H*OH, minor), 4.00 (m, 1 H, C*H*OH, minor), 3.94-3.84 (m, 2 H, C*H*OTBDMS, major, minor), 3.73 (dd, *J* = 8.0 Hz, 4.3 Hz, 1 H, C*H*OH, major), 3.62 (d, *J* = 4.2 Hz, 1 H, O*H*, minor), 3.46 (s, 1 H, O*H*, major), 3.04 (s, 1 H, O*H*, minor), 2.92 (s, 1 H, O*H*, major), 2.27-2.11 (m, 3 H, C*H*H, minor, C*H*H, minor, C*H*, major), 1.94 (ddd, *J* = 14.0 Hz, 9.4 Hz, 4.9 Hz, 1 H, C*H*H, major), 1.84-1.75 (m, 2 H, CH*H*, minor, CH*H*, major), 1.72-1.61 (m, 2 H, CH*H*, minor, CH*H*, major), 1.55-1.48 (m, 2 H, C*H*, minor, CH*H*, major), 1.20 (d, *J* = 6.1 Hz, 3 H, CH_3, major), 1.18 (d, *J* = 6.0 Hz, 3 H, CH_3, minor), 0.90 (s, 9 H, C(CH_3)$_3$, major), 0.90 (s, 9 H, C(CH_3)$_3$, minor), 0.10 (s, 3 H, SiCH_3, minor), 0.10 (s, 3 H, SiCH_3, major), 0.09 (s, 3 H, SiCH_3, major), 0.09 (s, 3 H, SiCH_3, minor). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 163.24 (s, minor), 161.57 (s, major), 93.41 (s, minor), 92.66 (s, major), 80.16 (d, minor), 78.70 (d, major), 73.89 (d, minor), 72.35 (d, major), 68.30 (d, major), 68.14 (d, minor), 58.54 (d, minor), 51.45 (d, major), 43.43 (t, major), 39.72 (t, minor), 39.57 (d, major), 37.06 (d, minor), 35.72 (t, major), 34.70 (t, minor), 25.91 (q, major), 25.90 (q, minor), 24.56 (q. major), 24.53 (q, minor), 18.15 (s, major), 18.08 (s, minor), -4.10 (q, minor), -4,17 (q, major), -4.33 (q, major), -4.54 (q, minor). FAB-MS 435 (18, M^+), 301 (40), 284 (29), 239 (28), 197 (71), 159

(100). Anal. Calcd for $C_{16}H_{30}O_4Cl_3SiN$ (434.86): C, 44.19; H, 6.95; Found: C, 44.36; H, 6.85.

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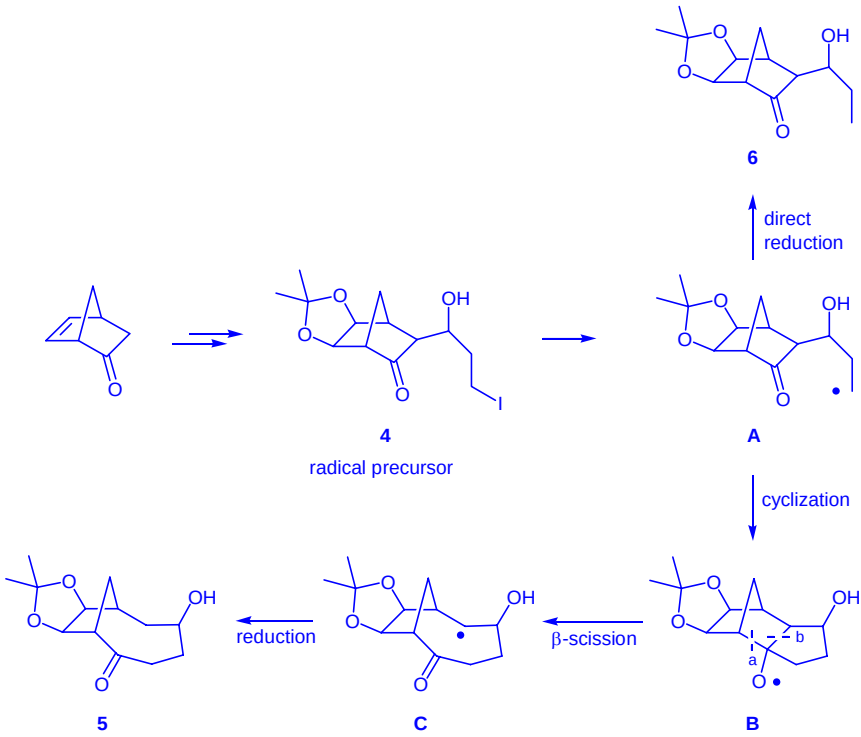
Unusual Radical Cyclization-Fragmentation-Ring Expansion of the Norbornanone Framework : A New Access to Medium-Sized Bridged Bicycles

1. Introduction

Over the past decade, fragmentation of the norbornane framework along the a-bond has been plenty investigated as a powerful method for the stereoselective formation of functionalized cyclopentane synthons.[1-3] However, the idea of taking advantage of the existing skeleton for ring expansion along the b-bond would bring a new method for the formation of medium sized-bridged bicycles. Those represent a useful but often hardly accessible class of compound, as witnessed by the famous example of taxol synthesis.[4,5] Radical cyclization represents a well-known strategy for ring expansion processes.[6,7] It involves addition of a carbon radical to a carbonyl group and leads to the formation of an intermediate alkoxyl radical,[8] which undergoes β-fragmentation. To our knowledge, the only example of scission of the b-bond of a bridged bicycle has been reported by Kim[9,10] and by Benati.[11] It concerns the synthesis of amides and lactams by cyclization of a (tributylstannyl)aminyl radical onto a carbonyl moiety and subsequent fragmentation of the derived alkoxyl radical. Studies on the stereochemical outcome of intramolecular carbon radical cyclization to carbonyl groups of bridged bicyclo[2.2.2]octenones and octanones have been reported by Dowd[12] but led to no ring expanded products.

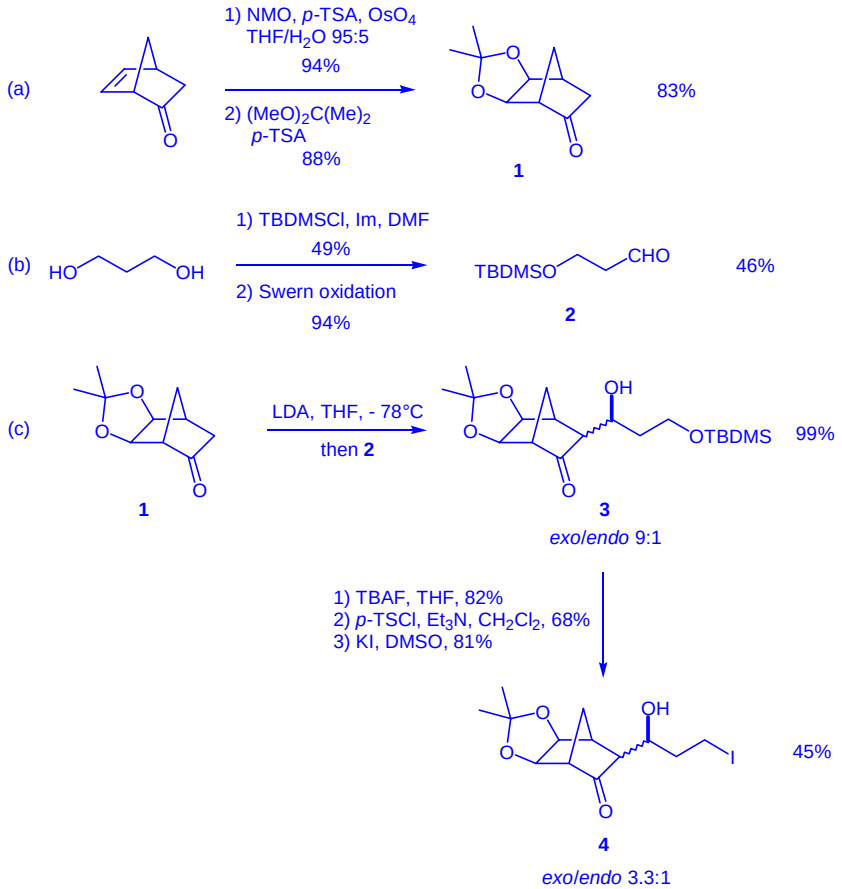
With those ideas in mind, our intent was to explore the intramolecular free radical addition of carbon-centered radical **A** derived from bicyclic ketonic precursor **4** to the carbonyl group, anticipating that this would lead to β-scission of alkoxyl radical **B** along its b-bond, yielding the bicyclic ring-expanded radical **C** (Figure). In this paper, we report the synthesis of radical precursor **4** in 6 steps and 37% overall yield starting from norbornenone, and its radical reactions. As a readily available compound in its racemic[13] and optically active[14,15] forms, norbornenone represented a starting material of choice.



Figure

2. Results and discussion

The radical precursor **4** was synthesized from norbornenone. Thus, one the one hand, dihydroxylation of norbornenone with osmium tetroxide/*N*-methylmorpholine *N*-oxide and *p*-toluenesulfonic acid as additive to avoid retro-aldol reaction of the *cis*-diol onto the *trans*-isomer, gave a 94% yield of 5,6-dihydroxybicyclo[2.2.1]heptan-2-one, which was protected with 2,2-dimethoxypropane, affording 5,6-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-one **1** in 88% yield. On the other hand, 3-*tert*-butyldimethylsilyloxypropan-1-al **2** was prepared in 46% overall yield by mono-silylation of propan-1,3-diol with *tert*-butyldimethylsilyl chloride (TBDMSCl)[16] and Swern oxidation of the resulting *tert*-butyldimethylsilyloxypropanol.[17]

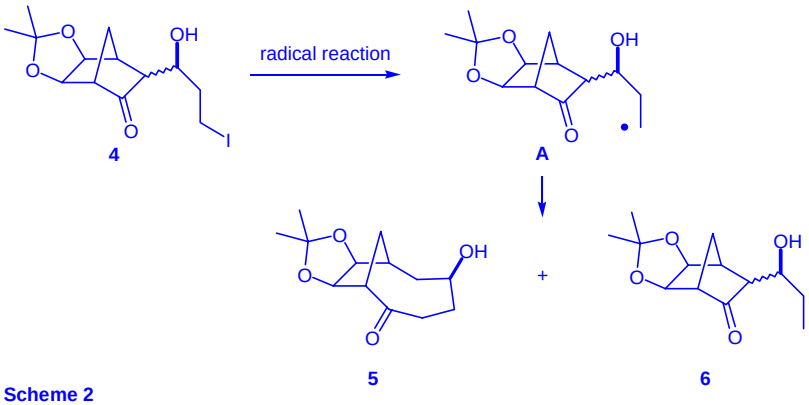


Scheme 1

Aldol coupling of ketone **1** with aldehyde **2** produced adduct **3** as a 9:1 *exo/endo*-mixture of isomers, as determined by NMR-coupling patterns. The configuration of the OH-bearing center was not determined. However, as suggested by the study of aldol reactions of bicyclo[2.2.1]heptan-2-one derivatives,[18] we assumed that only the *threo* adduct had been formed. In the presence of tetrabutylammonium fluoride (TBAF) in a cold THF solution, **3** underwent desilylation in 82% yield. Then, treatment of the diol with 1.06 equiv. of *p*-toluenesulfonyl chloride (*p*-TsCl) in the presence of triethylamine

and catalytic diethylaminopyridine (DMAP) allowed selective tosylation of the primary alcohol in 68% yield. Nevertheless, due to the basic conditions, the side-chain was observed to rearrange partially, obviously *via* a retro-aldol reaction, to furnish a final 3.3:1 *exo/endo*-ratio of tosylates. This side-reaction, leading also to some decomposition, explains the mediocre yield of this step. Finally, displacement of the tosylate with a large excess of solid potassium iodide (KI) in DMSO[19] gave radical precursor **4** in 81% yield (Scheme 1).

In order to test its reactivity, compound **4** was submitted to the different radical conditions with the results summarized in Table (Scheme 2).



Scheme 2

Table. Radical reaction of radical precursor **4** (*exo*/*endo* ratio 3.3:1)

Reductor	Solvent	Temperature	% Yield[c] of **5**	% Yield[c] of **6** (*exo*/*endo* ratio)[d]
Bu_3SnH[a]	C_6H_6	80°C	-	65 (1:1.7)
Bu_3SnH[b]	C_6H_6	80°C	30	56 (1:1.1)
$(TMS)_3SiH$[b]	C_6H_6	80°C	31	54 (1:2.7)
Bu_3SnH[b]	$C_6H_5CH_3$	110°C	40	60 (1:1.9)

[a]One pot addition of reductor and a catalytic amount of AIBN. [b]Syringe pump addition of reductor and a catalytic amount of AIBN over 12 h. [c]Yields of isolated and purified products. [d]NMR determined *exo*/*endo* ratio.

In all the cases, only two products were observed: the expected ring expansion product **5** along with a diastereomeric mixture of direct reduction product **6**. Exclusive scission along the b-bond at the expense of a-bond cleavage is best explained by strain release due to three-carbon ring expansion and formation of a larger [5.2.1] bicycle.

One pot addition of tributyltin hydride in the presence of AIBN in refluxing benzene led only to direct reduction, no product of β-scission being detected then. The 3.3:1 *endo*/*exo* ratio of starting compound **4** was preserved and **6** was obtained in 65% yield. Formation of the expected product **5** needed slow addition of reductor, the process being otherwise no competitive with H-abstraction of Bu_3SnH from the primary C-centered radical. Thus syringe pump addition (12 h) of Bu_3SnH (1.1 equiv.) and AIBN (cat.) to **4** in refluxing benzene gave a 30% yield of **5**, along with a 1.1:1 *endo*/*exo* diastereomeric mixture of **6** in 56% yield. With the aim of enhancing the alkoxyl radical reactivity, other parameters were varied. Utilization of a poor H-donor, tris(trimethylsilyl)silane ($(TMS_3)SiH$),[20] in the same conditions did not improve significantly the fragmentation reaction. However, the *endo*/*exo* ratio of **6** turned to 2.7:1. Finally, augmentation of the temperature by running the reaction in toluene, with Bu_3SnH/AIBN, afforded a 40% of ring expanded **5** and a 60% of reduced **6** in a 1.9:1 *endo*/*exo* ratio. Beside the increase of total yield, the improvement of the β-scission process can be explained by the higher reactivity of intermediate alkoxyl radical **B** at 110°C and its consequent quicker fragmentation.

Nevertheless, the observed variation of the *endo*/*exo* ratio of **5** shows that the *exo* isomer of starting compound **4** is more reactive toward radical cyclization than its *endo* epimer, which reacts maybe not at all. This is best explained by steric reasons. Indeed, less accessible for intramolecular cyclization than the *exo* face, the more crowded *endo* face of **4** reacts very slowly or presumably not. These explanations are consistent with Dowd's observations that, in the bicyclic [2.2.2]octanone series, radical precursors are unreactive toward cyclization.[12] They are supported by the study of simple nucleophilic additions to the carbonyl group of norbornanone derivatives. For instance, reactions of norbonenone with a variety of Grignard reagents afford the product of *exo* attack with a

very high stereocontrol (>10:1) in favor of the *endo* alcohol.[1] Thus, exclusive reaction of the *exo* epimer of **4** should lead to higher yields of ring expanded compound **5**.

3. Conclusion

In summary, we have presented a new and promising approach to the synthesis of medium sized bridged bicycles with good yields, that takes advantage of the existence of readily available norbornenone derivatives and involves a novel radical intramolecular cyclization/β-fragmentation sequence. As a matter of fact, radical precursors can be straightforward synthesized in high yield, optically active compound being also easily available. Moreover, the smooth conditions needed for the radical reaction are compatible with a number of sensitive functional groups and no protection is needed for hydroxyl groups.

4. Experimental Section

THF was freshly distilled from K under N_2; CH_2Cl_2, DMF and benzene were distilled from CaH_2 under N_2; Et_2O was distilled from Na/benzophenone and toluene from Na under N_2. Solvents for chromatography were distilled. Flash chromatography (FC) and filtration were performed with Baker silica gel (0.063-0.200 mm). TLC were run on Merck silica gel 60 F_{254} analytical plates; detection was carried out with either UV, iodine, spraying with solution of phosphomolybdic acid (25 g), $Ce(NH_4)_2(NO_3)_6{\cdot}4H_2O$ (10 g), concd H_2SO_4 (60 ml) and water (940 ml), or with a solution of $KMnO_4$ (3 g), K_2CO_3 (20 g), water (300 ml) and 5% NaOH (5 ml), with subsequent heating. Mps, not corrected, were determined on a Büchi-Tottoli apparatus. IR spectra were recorded on a Mattson Unicam 5000 spectrophotometer, in cm^{-1}. NMR spectra were recorded on a Varian Gemini 200 (^1H 200 MHz and ^{13}C 50.3 MHz), a Bruker AM 360 (^1H 360 MHz) or a Bruker Avance DRX-500 (^1H 500 MHz and ^{13}C 125.77 MHz); for ^1H δ are given in ppm relative to $CDCl_3$ (7.27 ppm), for ^1C δ are given in ppm relative to $CDCl_3$ (77.1 ppm), and coupling constant *J* are given in Hz. ^1H NMR splitting pattern abbreviations

are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR multiplicities were determined by the APT and DEPT sequences, abbreviations are: q, CH_3; t, CH_2; d, CH; s, quaternary carbons. Assignments were confirmed by NOE or NOESY, COSY and HETCOR experiments. MS spectra were recorded on a Vacuum Generator Micromass VG 70/70E DS 11-250; EI (70 eV), CI (CH_4 gas); *m/z* (%). Elemental analysis were performed by Ilse Beetz, Microanalytisches Laboratorium, D-96301 Kronach, Germany, and Ciba Geigy Mikrolabor, Marly, Switzerland.

5,6-(Isopropylidenedioxy)bicyclo[2.2.1]heptan-2-one (1). A solution of norbornenone (6.0 g, 55.5 mmol) in THF/H_2O (95:5, 100 ml) under N_2 at rt was treated sequentially with *N*-methylmorpholine *N*-oxide (8.3 g, 61.0 mmol), *p*-toluenesulfonic acid hydrate (11.1 g, 58.3 mmol) and a solution of osmium tetroxide (282 mg, 1.11 mmol) in THF (5.6 ml). After 46 h, when the reaction was completed, AcOEt (360 ml), Na_2SO_4 (144 g) and *p*-toluenesulfonic acid hydrate (1.45 g) were added to the green mixture. Filtration over silica, elution with AcOEt and evaporation of the solvent afforded a green oil, which was purified by FC (AcOEt) to give 7.04 g (94%) of 5,6-dihydroxybicyclo[2.2.1]heptan-2-one. ^1H NMR ($CDCl_3$, 360 MHz): δ = 4.01-3.95 (*m*, 2 H, C*H*OH), 3.58 (*s*, 1H, O*H*), 2.69-2.65 (*m*, 1 H, C*H*), 2.63 (*s*, 1 H, C*H*), 2.25-2.19 (*m*, 1 H, C*H*HCO), 2.11 (*ddd*, *J* = 18.6 Hz, 5.2 Hz, 0.9 Hz, 1 H, C*H*H), 1.78 (*dd*, *J* = 18.6 Hz, 4.3 Hz, 1 H, CH*H*), 1.73-1.67 (*m*, 1 H, CH*H*CO). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 217.00 (s), 72.88 (d), 68.97 (d), 58.54 (d), 42.50 (d), 41.58 (t), 31.49 (t). IR (film) 3416, 2976, 2922, 1746, 1059. CI-MS: m/z (%) =143 (28, $[M+1]^+$), 125 (72), 107 (36), 83 (100). Anal. Calcd for $C_7H_{10}O_3$ (142.15): C, 59.14; H, 7.09. Found: C, 58.82; H, 7.39.

The diol (7.01 g, 49.3 mmol) was dissolved in 2,2-dimethoxypropane (100 ml, 809 mmol) at rt. After addition of *p*-toluenesulfonic acid hydrate (~10 mg), the mixture was stirred for 1.5 h. Filtration on neutral alox and evaporation afforded the crude **6** which was purified by FC (Hexane/AcOEt 3:7), giving 7.89 g (88%) of a white solid. Mp = 75.5-76°C. ^1H NMR ($CDCl_3$, 360 MHz): δ = 4.34 (*dd*, J = 5.5 Hz, 1.2 Hz, 1 H, C*H*O), 4.28 (*d*, *J* = 5.5 Hz, 1 H, C*H*O), 2.76-2.71 (*m*, 2 H, C*H*), 2.19-2.13 (*m*, 1 H, C*H*H), 2.09 (*ddd*, *J* = 18.3 Hz, 4.9 Hz, 0.9 Hz, 1 H, CH*H*), 1.70-1.64-2.19 (*m*, 1 H, C*H*H), 1.69 (*dd*, *J*

= 18.3 Hz, 4.6 Hz, 1 H, CH*H*), 1.50 (*s*, 3 H, CH_3), 1.32 (*s*, 3 H, CH_3). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 213.68 (s), 111.18 (s), 81.19 (d), 77.17 (d), 55.29 (d), 39.47 (d), 39.29 (t), 31.09 (t), 25.41 (q), 25.26 (q). IR (KBr) 2984, 2936, 1751, 1208, 1057. CI-MS: m/z (%) = 183 (100, $[M+1]^+$), 167 (37), 125 (79), 101 (51). Anal. Calcd for $C_{10}H_{14}O_3$ (142.15): C, 65.92; H, 7.74. Found: C, 65.78; H, 7.61.

3-*tert*-Butyldimethylsilyloxypropan-1-al (2). A solution of propane 1,3-diol (9.7 g, 127.5 mmol) and imidazole (7.23 g, 106.2 mmol) in DMF (30 ml) was cooled to –25°C and *tert*-butyldimethylsilyl chloride (8.0 g, 53.1 mmol) was added in portions. After 1 h, the mixture was stirred at 0°C for 4 h. Then it was diluted with pentane (150 ml), washed with water (6 x 30 ml) and dried on $MgSO_4$. Evaporation of the solvent afforded the crude 3-*tert*-butyldimethylsilyloxypropan-1-ol which was purified by column chromatography (Hexane/AcOEt 8:2) to afford 5 g (49%) of the alcohol as a colorless liquid. To a solution of oxalyl chloride (2.68 ml, 30.21 mmol) in dry CH_2Cl_2 (100 ml) at –78°C was added DMSO (4.29 ml, 60.41 mmol) in dry CH_2Cl_3 (25 ml). After 15 min, 3-*tert*-butyldimethylsilyloxypropan-1-ol (5 g, 2.63 mmol) in dry CH_2Cl_2 (100 ml) was added. After 1.25 h, Et_3N (10.25 ml, 73.54 mmol) was added. The mixture was let warm to rt during 2 h, quenched with H_2O and extracted with CH_2Cl_2 (3 x 250 ml). The combined organic phases were washed with 1% HCl, water, 5% $NaHCO_3$ and water before drying ($MgSO_4$) and evaporation of the solvent. FC (Hexane/AcOEt 5:1) afforded pure 3-*tert*-butyldimethylsilyloxypropan-1-al (**5**) (4.65 g, 94%) as a colorless liquid. Aldehyde **2** was used quickly after its preparation. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 9.79 (*t*, *J* = 2.0 Hz, 1 H, C_1-*H*), 3.97 (*t*, *J* = 6.0 Hz, 2 H, C_3-H_2), 2.58 (*dt*, *J* = 6.0 Hz, 2.0 Hz, 2 H, C_2-H_2), 0.88 (*s*, 9 H, SiC(CH_3)$_3$), 0.03 (*s*, 6 H, Si(CH_3)$_2$). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 201.59 (s), 57.35 (t), 46.52 (t), 25.74 (q), 18.13 (s), -5.53 (q).

3-(3--*tert*-Butyldimethylsilyloxypropan-1-ol-1-yl)-5,6-(isopropylidenedioxy)bicyclo[2.2.1] heptan-2-one (3). Lithium diisopropylamine was prepared by addition of *n*-butyl lithium (2.71 ml, 5.71 mmol of a 2.1 M solution in hexane), to dry diisopropylamine (0.85 ml, 6.04 mmol) in dry THF (10 ml) at –78°C

under N_2. After 15 min, ketone **1** (1.00 g, 5.49 mmol) dissolved in dry THF (10 ml) was dropped into the LDA solution with a syringe during 30 min. The mixture was kept at –78°C for 30 min before a solution of aldehyde **2** (3.33 g, 17.56 mmol) in dry THF (10 ml) was added. After 15 min, the reaction was quenched at –78°C with acetic acid (1 equiv., 0.37 ml), diluted with aqueous saturated $NaHCO_3$ (20 ml) and let warm to rt. Water (80 ml) and Et_2O (50 ml) were added. The phases were separated. The aqueous phase was further extracted with Et_2O (3 x 100 ml), the combined organic layers were dried over $MgSO_4$ and the solvents were evaporated. FC (Hexane/AcOEt 8:2) of the crude afforded pure aldol adduct **3** (2.01 g, 99%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.33 (*d*, J = 5.1 Hz, 1 H, C*H*O), 4.30 (*d*, *J* = 5.1 Hz, 1 H, C*H*O), 4.01-3.97 (*m*, 1 H, C*H*OH), 3.86-3.76 (*m*, 2 H, CH_2OTBDMS), 2.70 (*s*, 1 H, C*H*), 2.62 (*d*, *J* = 1.5 Hz, 1 H, C*H*), 2.09-2.06 (*m*, 1 H, C*H*H), 1.94-1.91 (*m*, 1 H, CH*H*), 1.83-1.76 (*m*, 1 H, C*H*HCH$_2$OTBDMS), 1.74-1.68 (*m*, 1 H, CH*H*CH$_2$OTBDMS), 1.62 (*dd*, *J* = 7.4 Hz, 3.5 Hz, 1 H, C*H*CHOH), 1.48 (*s*, 3 H, CH_3), 1.32 (*s*, 3 H, CH_3), 0.88 (*s*, 9 H, C(CH_3)$_3$), 0.06 (*s*, 6 H, Si(CH_3)$_2$). ^{13}C NMR ($CDCl_3$, 122.77 MHz): δ = 216.11 (s), 111.27 (s), 81.73 (d), 76.73 (d), 69.96 (d), 60.75 (t), 55.37 (d), 52.92 (d), 42.64 (d), 37.56 (t), 29.11 (t), 25.86 (q), 25.21 (q), 24.11 (q), 18.18 (s), -5.48 (q). IR (film) 3493, 2957, 2858, 1748, 1383, 1059, 837. CI-MS: m/z (%) = 371 (26, M^+), 221 (23), 167 (39), 125 (100), 101 (56), 95 (23), 79 (34). Anal. Calcd for $C_{19}H_{34}O_5Si$ (370.56): C, 61.58; H, 9.25. Found: C, 61.55; H, 9.07.

3-(3-Iodopropan-1-ol-1-yl)-5,6-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-one (4). Tetrabutylammonium fluoride (5.71 ml, 5.71 mmol of a 1 M solution in THF) was dropped to a solution of aldol adduct **3** (1.92 g, 5 19 mmol) in dry THF (50 ml), at 0°C under N_2. After 30 min, the reaction was quenched by addition of water (100 ml). Extraction with water (4 x 100 ml), filtration over $MgSO_4$ and evaporation of the solvents gave the crude desilylated diol. FC (Hexane/AcOEt 1:9) afforded the pure diol (1.09 g, 82%) as a colorless liquid.

Monotosylation was accomplished by treatment of a solution of diol (1.02 g, 3.98 mmol), dimethylaminopyridine (15 mg, 0.119 mmol) and triethylamine (0.67 ml, 4.78

mmol) in CH_2Cl_2 (40 ml) under N_2 at rt. After 18 h, the reaction mixture was poured on water (80 ml). Separation of the phases, extraction with AcOEt (3 x 80 ml), filtration of the combined organic layers over $MgSO_4$, evaporation of the solvent and FC (Hexane/AcOEt) of the crude afforded the pure tosylate (1.22 g, 68%) which was used quickly after preparation.

To a solution of tosylate (1.22 g, 2.97 mmol) in DMSO (50 ml), solid KI (45.4 g, 273.4 mmol) was added. The resulting yellow mixture was stirred at rt during 24 h, before the reaction was quenched with aqueous saturated NaCl (180 ml) and solid $Na_2S_2O_3$ until discoloration of the solution. Extraction with Et_2O (3 x 120 ml), filtration over $MgSO_4$, evaporation of the solvents and FC (Hexane/AcOEt 8:2) of the crude gave a 3.3:1 *exo*/*endo* mixture of pure iodide **4** (882 mg, 81%) as a white solid. Mp = 95.5°C. ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 4.96 (*d*, J = 5.2 Hz, 1 H, C*H*O, minor), 4.36 (*d*, J = 5.2 Hz, 1 H, C*H*O, major), 4.33 (*d*, J = 5.2 Hz, 1 H, C*H*O, major), 4.25 (*d*, *J* = 5.1 Hz, 1 H, C*H*O, minor), 4.17-4.09 (*m*, 1 H, C*H*OH, minor), 3.87-3.80 (*m*, 1 H, C*H*OH, major), 3.46 (*m*, 1 H, OH), 3.36-3.24 (*m*, 4 H, CH_2I, major, minor), 2.85 (*d*, J = 2.8 Hz, 1 H, C*H*, minor), 2.79 (*s*, 1 H, C*H*, minor), 2.76 (*s*, 1 H, C*H*, major), 2.54 (*d*, J = 1.2 Hz, 1 H, C*H*, major), 2.23 (*dd*, *J* = 4.9 Hz, 4.9 Hz, 1 H, C*H*CHOH, minor), 2.19 (*d*, J = 11.0 Hz, 1 H, C*H*H, minor), 2.14-1.91 (*m*, 5 H, C*H*H, major, CH_2, major, minor), 1.85 (*ddd*, *J* = 11.6 Hz, 1.5 Hz, 1.5 Hz, 1 H, *C*H*H*, major), 1.60 (*dd*, *J* = 9.2 Hz, 3.4 Hz, 1 H, C*H*CHOH, major), 1.52 (*ddd*, *J* = 10.7 Hz, 1.4 Hz, 1.4 Hz, 1 H, *C*H*H*, minor), 1.49 (*s*, 6 H, CH_3, major, minor), 1.33 (*s*, 3 H, CH_3, major), 1.32 (*s*, 3 H, CH_3, minor). ^{13}C NMR ($CDCl_3$, 122.77 MHz): δ = 216.57 (s, major), 214.25 (s, minor), 111.45 (s, major), 110.85 (s, minor) 81.49 (d, major, minor), 77.76 (d, minor), 77.64 (t, minor), 77.01 (t, major), 70.42 (d, major), 68.70 (d, minor), 56.87 (d, minor), 55.83 (d, minor), 55.23 (d, major), 52.10 (d, major), 42.23 (d, minor), 42.09 (d, major), 39.29 (t, major), 38.26 (t, minor), 30.57 (t, minor), 29.30 (t, major), 25.22 (q, major, minor), 24.22 (q, major), 24.16 (q, minor). IR (KBr) 3520, 2986, 2903, 1744, 1375, 1209, 1061, 856. CI-MS: m/z (%) = 367 (2, $[M+1]^+$), 349 (10), 119 (10), 94 (44), 81 (55), 73 (73), 61 (100). Anal. Calcd for $C_{13}H_{19}O_4I$ (366.20): C, 42.64; H, 5.23. Found: C, 42.49; H, 5.33.

General procedure (GP). Radical reactions. A degassed solution of radical precursor **4** (1.00 mmol) in solvent (20 ml) was heated to reflux under an inert atmosphere, treated by one pot or dropwise (syringe pump) addition over 12 h with a solution of reductor and 2,2'-azobis(isobutyronitrile) (AIBN; 16 mg, 0.10 mmol) in solvent (20 ml) and kept under reflux for 4 additional h. The solution was cooled to rt, treated with KF (500 mg, 8.61 mmol) for 24 h and the solvent was evaporated. The residue was dissolved in hexane (5 ml) and filtered on FC (hexane 150 ml and then AcOEt 100 ml). The AcOEt-containing fraction was evaporated and purified by FC (Hexane/AcOEt).

According to GP. From **4** (200 mg, 0.546 mmol), Bu_3SnH (0.16 ml, 0.601 mmol) and AIBN (9 mg, 0.055 mmol) added one pot, in benzene (11 ml). FC (Hexane/AcOEt 8:2) gave **6** (85 mg, 65%) as a 1:1.7 *exo*/*endo* mixture of isomers.

According to GP. From **4** (100 mg, 0.273 mmol) in benzene (5.5 ml), and Bu_3SnH (0.09 ml, 0.300 mmol) and AIBN (5 mg, 0.055 mmol) in benzene (5.5 ml) added dropwise. FC (Hexane/AcOEt 7:3) gave **5** (20 mg, 30%) along with **6** (36 mg, 56%) as a 1:1.1 *exo*/*endo* mixture of isomers.

According to GP. From **4** (150 mg, 0.410 mmol) in benzene (8 ml), and $(TMS)_3SiH$ (0.19 ml, 0.614 mmol) and AIBN (7 mg, 0.041 mmol) in benzene (8 ml) added dropwise. FC (Hexane/AcOEt 7:3) gave **5** (30 mg, 31%) along with **6** (53 mg, 54%) as a 1:2.7 *exo*/*endo* mixture of isomers.

According to GP. From **4** (150 mg, 0.410 mmol) in toluene (8 ml), and Bu_3SnH (0.12 ml, 0.451 mmol) and AIBN (7 mg, 0.041 mmol) in toluene (8 ml) added dropwise. FC (Hexane/AcOEt 7:3) gave **5** (39 mg, 40%) along with **6** (59 mg, 60%) as a 1:1.9 *exo*/*endo* mixture of isomers.

5-Hydroxy-8,9-(isopropylidenedioxy)bicyclo[5.2.1]decan-2-one (5). White solid. Mp = 62.5°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.69 (*m*, 1 H, C*H*OH), 4.65 (*ddd*, J = 6.9 Hz, 6.9 Hz, 3.9 Hz, 1 H, C*H*O), 4.25 (*dd*, *J* = 7.4 Hz, 7.4 Hz, 1 H, C*H*O), 3.42 (*dd*, J = 2.2 Hz, 2.2 Hz, 1 H, O*H*), 2.65-2.60 (*m*, 1 H, CHC*H*HCHOH), 2.48 (*ddd*, *J* = 19.0 Hz, 11.7 Hz, 9.1 Hz, 1 H, C*H*HCO), 2.27 (*dd*, *J* = 19.0 Hz, 9.2 Hz, 1 H, CH*H*CO), 2.19-2.15 (*m*, 1

H, C*H*HCH$_2$CO), 2.13-2.05 (*m*, 2 H, CHCH*H*CH, C*H*), 2.04-2.00 (*m*, 1 H, CH*H*CH$_2$CO), 1.96 (*dd*, *J* = 10.7 Hz, 4.2 Hz, 1 H, C*H*CO), 1.87-1.80 (*m*, 1 H, CHCH*H*CH), 1.50 (*s*, 3 H, C*H*$_3$), 1.38-1.30 (*m*, 1 H, CHCH*H*CHOH), 1.32 (*s*, 3 H, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 122.77 MHz): δ = 218.34 (s), 113.23 (s), 85.06 (d), 79.74 (d), 71.94 (d), 58.87 (d), 42.83 (d), 34.91 (t), 30.24 (t), 30.09 (t), 28.54 (t), 27.49 (q), 25.12 (q). IR (KBr) 3451, 2926, 1738, 1379, 1211, 1028, 878. CI-MS: m/z (%) = 241 (74, $[M+1]^+$), 225 (47), 193 (32), 183 (89), 165 (100), 147 (16), 125 (13), 83 (17). Anal. Calcd for $C_{13}H_{20}O_4$ (240.30): C, 64.98; H, 8.39. Found: C, 65.04; H, 8.32.

3-(propan-1-ol-1-yl)-5,6-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-one (6). White solid. Mp = 61°C. ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 4.99 (*d*, J = 5.0 Hz, 1 H, C*H*O, minor), 4.36 (*d*, J = 5.0 Hz, 1 H, C*H*O, major), 4.33 (*ddd*, J = 5.4 Hz, 1.3 Hz, 1.3 Hz, 1 H, C*H*O, major), 4.25 (*ddd*, *J* = 5.3 Hz, 1.4 Hz, 1.4 Hz, 1 H, C*H*O, minor), 3.91 (*dddd*, *J* = 8.3 Hz, 4.9 Hz, 4.9 Hz, 4.9 Hz, 1 H, C*H*OH, minor), 3.70 (*dddd*, *J* = 9.1 Hz, 7.7 Hz, 3.1 Hz, 1.7 Hz, 1 H, C*H*OH, major), 3.33 (*m*, 1 H, OH), 2.89-2.87 (*m*, 1 H, C*H*, minor), 2.78-2.77 (*m*, 1 H, C*H*, minor), 2.74 (*s*, 1 H, C*H*, major), 2.54 (*m*, 1 H, C*H*, major), 2.22 (*dd*, *J* = 5.0 Hz, 5.0 Hz, 1 H, C*H*CHOH, minor), 2.18 (*ddd*, J = 10.9 Hz, 1.1 Hz, 1.1 Hz, 1 H, C*H*H, minor), 2.11-2.08 (*m*, 1 H, C*H*H, major), 1.83-1.80 (*m*, 1 H, *C*H*H*, major), 1.71-1.57 (*m*, 3 H, C*H*CHOH, major, C*H*$_2$CH$_3$, minor), 1.52-1.32 (*m*, 3 H, *C*H*H*, minor, C*H*$_2$CH$_3$, major), 1.49 (*s*, 3 H, C*H*$_3$, major), 1.48 (*s*, 3 H, C*H*$_3$, minor), 1.34 (*s*, 3 H, C*H*$_3$, major), 1.32 (*s*, 3 H, C*H*$_3$, minor), 0.97 (*t*, *J* = 7.4, 3 H, CH$_2$C*H*$_3$, major), 0.92 (*t*, *J* = 7.4, 3 H, CH$_2$C*H*$_3$, minor). ^{13}C NMR ($CDCl_3$, 122.77 MHz): δ = 217.69 (s, major), 215.38 (s, minor), 111.38 (s, major), 110.72 (s, minor) 81.61 (d, major), 78.01 (d, minor), 77.77 (d, minor), 76.47 (d, major), 71.49 (d, major), 70.48 (d, minor), 57.03 (d, minor), 55.69 (d, minor), 55.27 (d, major), 52.21 (d, major), 42.10 (d, major), 41.94 (d, minor), 30.57 (t, minor), 29.26 (t, major), 28.10 (t, minor), 27.97 (t, major), 25.23 (q., minor), 25.21 (t, major), 24.17 (q, minor), 24.13 (q, major), 10.23 (q, minor), 8.87 (q, minor). IR (KBr) 3488, 2986, 2938, 1746, 1377, 1209, 1055, 968, 868. CI-MS: m/z (%) = 241 (36, $[M+1]^+$), 223 (100), 205 (11), 183 (17), 165 (97), 147 (16), 107 (11). Anal. Calcd for $C_{13}H_{20}O_4$ (240.30): C, 64.98; H, 8.39. Found: C, 65.05; H, 8.42.

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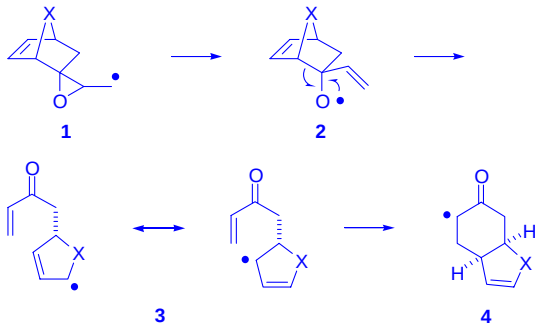
Stereoselective Synthesis of Functionalized Bicyclic Ketones *via* Tandem Radical Induced Epoxyde Fragmentation-β-Scission-Cyclization Sequences

1. Introduction

Due to their peculiar reactivity, alkoxyl radicals have unique characteristic properties, which makes them powerful intermediates in modern organic chemistry.[1] Their typical transformations include ring closure reactions,[2,3] selective hydrogen abstractions,[4-6] remote functionalization of non-activated carbon-hydrogen bonds,[7] as well as ring expansion of cycloaliphatic compounds by β-scission.[8,9] However, such processes depend a great deal on the efficiency of alkoxyl radical generation. For example, radical-induced epoxide fragmentation reaction followed by β-scission of the resulting alkoxyl radical has proven to provide[10] a useful access to functionalized medium sized compounds.[11,12]



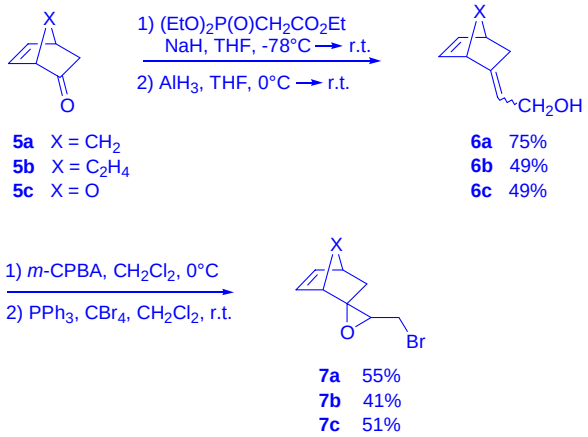
Scheme 1

We recently described radical fragmentation of the norbornene framework as a powerful method for the stereoselective formation of functionalized cyclopentane synthons[13] or for the synthesis of medium size bridged bicycles.[14] As part of our ongoing research in

this area, we devised to take advantage of the epoxide fragmentation methodology to generate alkoxyl radical **2** from oxiranylcarbinyl radical **1**. Upon β-scission and cyclization of the resulting allylic carbon radical **3**, this was expected to afford bicyclic radical **4** (Scheme 1), opening a new entry into the synthesis of functionalized bicyclic ketones which are known to be the precursors of a variety of natural products.[15-18]

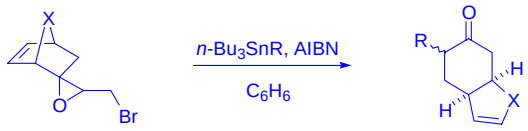
2. Results and discussion

Radical precursors **7a-c** were synthesized by a four steps synthesis from norbornenone (**5a**),[13] 7-oxabicyclo[2.2.1]hept-5-en-2-one (**5b**)[19] and bicyclo[2.2.2]oct-5-en-2-one (**5c**)[20] respectively. Thus, Wittig-Horner-Emmons reaction of the starting ketones **5a-c** was followed by reduction of the formed esters with AlH_3, to afford allylic alcohols **6a-c** in a 49-75% yield.[21] Then, selective epoxidation of the allylic double bond with *m*-chloroperbenzoic acid,[22] and halogenation of the alcohol functionality with carbon tetrabromide and triphenylphosphine[23] gave radical precursors **7a-c** as mixtures of the possible isomers, in a 41-55% yield (Scheme 2).



Scheme 2

To investigate the reactivity of compounds **7a-c** as radical precursors, different radical conditions were tested. Tributyltin hydride, tributyltin deuteride or tributyltin allyl derivatives and 2,2'-azobis(isobutyronitrile) (AIBN) were added to degassed solutions of precursor in benzene. While syringe pump addition was chosen for tributyltin hydride and deuteride, allylic tributylstannanes were added one pot, along with AIBN. All the reaction resulted in exclusive formation of the expected bicycles **8-12** in moderate to good yields. Results of the radical reactions are summarized in Schemes 3 and 5.



7a-c **8** or **9** *cis* / *trans*

Entry	Substrate	X	R	Product	Yield[d] (*cis*/*trans*)
1	**7a**	CH_2	H[b]	**8a**	48%
2	**7a**	CH_2	D[b]	**9a**	48% (1.8:1)
3	**7a**	CH_2	D[a,c]	**9a**	- (2.1:1)
4	**7b**	C_2H_4	H[b]	**8b**	29%
5	**7c**	O	D[b]	**9c**	85%[e] (2.9:1)

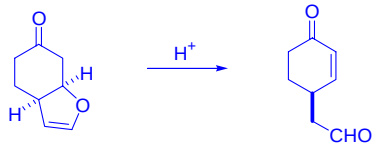
[a]One pot addition of reductor. [b]Syringue pump addition of reductor over 12h. [c]Reaction was conducted at 5°C under irradiation with a Phillips sun lamp.[d]Isolated yields. [e]Mixed with compound **13**.

Scheme 3

The first series of reactions was run on compound **7a** (Scheme 3, Entries 1-3). After a preliminary experiment in thermal conditions, to observe the reaction outcome, deuteration was conducted to measure the *cis*/*trans* selectivity of the final reduction step. While at reflux of benzene, a 1.8:1 *cis*/*trans* ratio was observed, irradiation of the reaction mixture at 5°C led to a small improvement of the selectivity, which reached a 2.1:1 *cis*/*trans* ratio.

Successful experiences with substrates **7b** and **7c** proved the general scope of the reaction. Nevertheless, the mediocre 29% yield of **8b** obtained with **7b** (Scheme 3, Entry

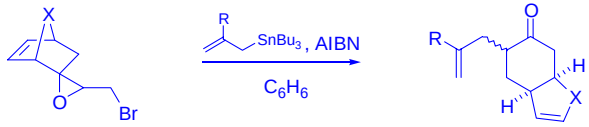
4) and the contrasting high 85% yield of **8c** purchased with **7c** outlined the influence of the radical precursor on the reaction (Scheme 3, Entry 5). These results find an explanation in the β-scission step, where strain release by fragmentation of the intermediate alkoxyl radical **2**, constitutes a driving force of the reaction. Consequently, opening of the larger less strained bicyclo[2.2.2]oct-5-en-bicycle of **7b** promotes the radical process less efficiently than cleavage of smaller and more strained bicyclo[2.2.1]hept-5-en-bicycles of **7a** and **7c**. On the other hand, thanks to its ability at stabilizing carbon radicals in β-position, the oxygen atom of precursor **7c** favors the formation of allylic radical **3** and so, all the radical process. However, enolic compound **9c** (X = O) was found to be unstable; upon work up and column, it partially transformed into **13**, as the result of acid catalyzed hydrolysis and elimination (Scheme 4).



9c **13**

Scheme 4

Changes on the nature of the stannane substituent R have shown only a limited effect on the reaction outcome (Scheme 5). As reaction of **7a** with [2-(methyl)prop-2-enyl]tributylstannane afforded a 1.5:1 *cis*/*trans* ratio of **10a** in 59% yield (Scheme 5, Entry 1), and reaction of **7a** with [2-(trimethylsilyl)prop-2-enyl]tributylstannane gave a 1.5:1 *cis*/*trans* ratio of **12a** in 44% yield (Scheme 5, Entry 3), addition of methyl 2-[(tributylstannyl)methyl]propenoate to **7a** yielded only a 32% of **11a** in a higher 3.6:1 ratio (Scheme 5, Entry 2). In the last case, although the increase of selectivity could be attributed to the presence of an electron-withdrawing group (CO_2Me) on the stannane, it cannot be excluded that a degradation of *trans*-**11a** is responsible for it. Variation in the size of the tributylstannanes, at reflux of benzene, showed no effect on the reaction selectivity and yield of **7a** as well as of **7b**.



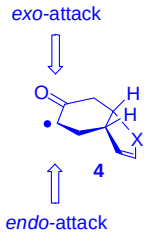
7a-b **10**, **11** or **12** *cis* / *trans*

Entry	Substrate	X	R	Product	Yield[b] (*cis*/*trans*)
1	**7a**	CH_2	Me[a]	**10a**	59% (1.5:1)
2	**7a**	CH_2	CO_2Me[a]	**11a**	32% (3.6:1)
3	**7a**	CH_2	$SiMe_3$[a]	**12a**	44% (1.5:1)
4	**7b**	C_2H_4	Me[a]	**10b**	21% (2.4:1)

[a]One pot addition of reductor. [b]Isolated yields.

Scheme 5

Finally, the total observed selectivity in favor of bicycles **8-12** can be explained by three factors. 1° Formation of the highly stabilized allylic radical upon β-scission **3** excludes fragmentation along the other possible bonds. 2° Due to strain increase, cyclization of **3** into a bridged bicycle is strongly disfavored. 3° Allylic radical **3** cyclized by an attack to the α,β-unsaturated ketone moiety in an "intramolecular radical Michael-type addition"



Scheme 6

In addition, bimolecular rate constants of oxiranylcarbinyl radical **1** opening ($>10^8$ M^{-1} s^{-1}) and that of alkoxyl radical **2** β-scission ($>10^8$ M^{-1} s^{-1}) are higher than rate constants of alkoxyl radical **2** cyclization into epoxide **1** (about 10^3 M^{-1} s^{-1}) and than that of

oxiranylcarbinyl radical **1** trapping (10^{-6} M^{-1} s^{-1}).[24,25] Consequently, direct reduction of **1** was detained and did not happen. Formation of a *cis* junction in the bicycle is well established and attributed to preferential cyclization toward the less strained transition states.[26-28] Global preferential *cis*-trapping of radical **4** is well explained by steric factors: the folded geometry of intermediate radical **4** makes its *endo* face of more hindered but not inaccessible to trapping agents (Scheme 6). Thus, the observed preference for the *exo* attack, giving *cis*-compound, showed to be higher for the more bent [4,4]bicycle of **10b** (Scheme 5, Entry 4) than for was [4,3]bicycle of **10a** (Scheme 5, Entry 1). Geometries of compounds **8-12** were attributed after noe-diff NMR experiments or by comparison with original spectra.

3. Conclusion

Further studies on the application of this new approach to functionalized bicyclic ketones are currently underway and will be reported on in due course.

4. Experimental Section

THF was freshly distilled from K under N_2; CH_2Cl_2 and benzene were distilled from CaH_2 under N_2. Solvents for chromatography were distilled. Flash chromatography (FC) and filtration were performed with Baker silica gel (0.063-0.200 mm). TLC were run on Merck silica gel 60 F_{254} analytical plates; detection was carried out with either UV, iodine, spraying with solution of phosphomolybdic acid (25 g), $Ce(NH_4)_2(NO_3)_6 \cdot 4H_2O$ (10 g), concd H_2SO_4 (60 ml) and water (940 ml), or with a solution of $KMnO_4$ (3 g), K_2CO_3 (20 g), water (300 ml) and 5% NaOH (5 ml), with subsequent heating. Mps, not corrected, were determined on a Büchi-Tottoli apparatus. IR spectra were recorded on a Mattson Unicam 5000 spectrophotometer, in cm^{-1}. NMR spectra were recorded on a Varian Gemini 200 (^1H 200 MHz and ^{13}C 50.3 MHz), a Bruker AM 360 (^1H 360 MHz) or a Bruker Avance DRX-500 (^1H 500 MHz and ^{13}C 125.77 MHz); for ^1H δ are given in ppm relative to $CDCl_3$ (7.27 ppm), for ^1C δ are given in ppm relative to $CDCl_3$ (77.1

ppm), and coupling constant *J* are given in Hz. ^{1}H NMR splitting pattern abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR multiplicities were determined by the APT and DEPT sequences, abbreviations are: q, CH_3; t, CH_2; d, CH; s, quaternary carbons. Assignments were confirmed by NOE or NOESY, COSY and HETCOR experiments. MS spectra were recorded on a Vacuum Generator Micromass VG 70/70E DS 11-250; EI (70 eV), CI (CH_4 gas); *m/z* (%). Elemental analysis were performed by Ilse Beetz, Microanalytisches Laboratorium, D-96301 Kronach, Germany, and Ciba Geigy Mikrolabor, Marly, Switzerland.

General procedure (GP1). Bicyclo[2.2.n]alk-5-en-2-ylidene-acetic acid ethyl ester. A solution of triethyl phosphonoacetate (16.7 ml, 83.2 mmol) in dry THF (40 ml) was added dropwise to a suspension of NaH (8.5 g, 194.2 mmol) in dry THF, (3 ml) at 0°C, under N_2. The mixture was stirred at room temperature for 30 min and cooled to –78°C. Then, ketone (**5**) (27.7 mmol) dissolved in dry THF (10 ml) was added over 10 min. The resulting mixture was let warm gently. After 20 h, it was poured into cold ether/aqueous saturated NH_4Cl (1:1, 200 ml) and the phases were separated. The organic layer was washed with water and the combined aqueous phases were extracted with Et_2O (3 x 100 ml). The combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. Flash chromatography (hexane and then hexane/AcOEt) afforded pure *E*/*Z* mixture of isomers of bicyclo[2.2.n]alk-5-en-2-ylidene-acetic acid ethyl ester.

Bicyclo[2.2.1]hept-5-en-2-ylidene-acetic acid ethyl ester. According to GP1. From **5a** (3.0 g, 27.7 mmol), triethyl phosphonoacetate (16.7 ml, 83.2 mmol) and NaH (8.5 g, 194.2 mmol). FC (Hexane/AcOEt 9:1) gave a 2.8:1 *E*/*Z* mixture of bicyclo[2.2.1]hept-5-en-2-ylidene-acetic acid ethyl ester isomers (4.34 g, 88%) as a colorless oil. IR (film) 2982, 1711, 1184, 1040. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.29 (dd, *J* = 5.5 Hz, 2.9 Hz, 1 H, C*H*=CH, *E*-isom.), 6.25 (dd, *J* = 5.5 Hz, 2.6 Hz, 1 H, C*H*=CH, *Z*-isom.), 6.09 (ddd, *J* = 5.5 Hz, 3.3 Hz, 0.7 Hz, 1 H, CH=C*H*, *Z*-isom.), 6.02 (ddd, *J* = 5.5 Hz, 3.3 Hz, 0.7 Hz, 1 H, CH=C*H*, *E*-isom.), 5.93-5.91 (m, 1 H, C*H*CO_2Et, *E*-isom.), 5.69-5.67 (m, 1 H,

C*H*CO_2Et, *Z*-isom.), 4.55-4.52 (m, 1 H, C*H*, *Z*-isom.), 4.18 (q, *J* = 7.0 Hz, 2 H, $CO_2CH_2CH_3$, *Z*-isom.), 4.14 (q, *J* = 7.0 Hz, 2 H, $CO_2CH_2CH_3$, *E*-isom.), 3.34-3.31 (m, 1 H, C*H*, *E*-isom.), 3.12-3.08 (s, 1 H, C*H*, *E*-isom.), 3.05-2.98 (m, 1 H, C*H*, *Z*-isom.), 2.64-2.57 (m, 1 H, C*H*H, *E*-isom.), 2.41-2.34 (m, 1 H, C*H*H, *Z*-isom.), 2.33 (ddd, *J* = 17.3 Hz, 3.7 Hz, 2.2 Hz, 1 H, CH*H*, *E*-isom.), 1.93 (ddd, *J* = 15.8 Hz, 3.7 Hz, 1.5 Hz, 1 H, CH*H*, *Z*-isom.), 1.78-1.73 (m, 1 H, C*H*H, *Z*-isom.), 1.72-1.67 (m, 1 H, C*H*H, *E*-isom.), 1.60-1.45 (m, 2 H, C*H*H, *E*/*Z*-isom.), 1.30 (t, *J* = 7.0 Hz, 3 H, CH_3, *Z*-isom.), 1.27 (t, *J* = 7.0 Hz, 3 H, CH_3, *E*-isom.). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 166.84 (s, *E*-isom.), 166.21 (s, *Z*-isom.), 166.08 (s, *E*-isom.), 165.33 (s, *Z*-isom.), 139.21 (d, *E*-isom.), 138.57 (d, *Z*-isom.), 133.13 (d, *Z*-isom.), 132.44 (d, *E*-isom.), 111.28 (d, *Z*-isom.), 110.92 (d, *E*-isom.), 59.39 (t, *E*/*Z*-isom.), 52.28 (d, *E*-isom.), 50.69 (t, *E*-isom.), 50.18 (t, *Z*-isom.), 47.72 (d, *Z*-isom.), 41.73 (d, *E*-isom), 40.46 (d, *Z*-isom.), 36.23 (t, *Z*-isom.), 35.76 (t, *E*-isom.), 14.29 (q, *E*/*Z*-isom). CI-MS 179 (100, $[M+1]^+$), 178 (11, M^+), 151 (32), 133 (33), 105 (11). Anal. Calcd for $C_{11}H_{14}O_2$ (178.23): C, 74.13; H, 7.92; Found: C, 74.16; H, 7.94.

Bicyclo[2.2.2]oct-5-en-2-ylidene-acetic acid ethyl ester. According to GP1. From **5b** (5.34 g, 43.7 mmol), triethyl phosphonoacetate (26.2 ml, 131.1 mmol) and NaH (13.4 g, 305.97 mmol). FC (Hexane/AcOEt 95:5) gave a 2.7:1 *E*/*Z* mixture of bicyclo[2.2.2]oct-5-en-2-ylidene-acetic acid ethyl ester isomers (5.7 g, 68%) as a colorless oil. IR (film) 3050, 2947, 2870, 1711, 1645, 1209, 1152, 1042, 702. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.40-6.35 (m, 2 H, C*H*=CH, *E*/*Z*-isom.), 6.20 (dd, *J* = 6.7 Hz, 6.7 Hz, 2 H, CH=C*H*, *E*/*Z*-isom.), 5.68 (dd, *J* = 2.3 Hz, 2.3 Hz, 1 H, C*H*CO_2Et, *E*-isom.), 5.58 (dd, *J* = 1.8 Hz, 1.8 Hz, 1 H, C*H*CO_2Et, *Z*-isom.), 4.76-4.75 (m, 1 H, C*H*, *Z*-isom.), 4.13 (q, *J* = 7.0 Hz, 2 H, $CO_2CH_2CH_3$, *Z*-isom.), 4.12 (q, *J* = 7.0 Hz, 2 H, $CO_2CH_2CH_3$, *E*-isom.), 3.16-3.14 (m, 1 H, C*H*, *E*-isom.), 2.84 (s, 1 H, C*H*, *E*-isom.), 2.73 (s, 1 H, C*H*, *Z*-isom.), 2.66 (ddd, *J* = 19.2 Hz, 2.1 Hz, 2.1 Hz, 1 H, C*H*H, *E*-isom.), 2.47 (dddd, *J* = 19.2 Hz, 2.8 Hz, 2.8 Hz, 2.8 Hz, 1 H, CH*H*, *E*-isom.), 2.29 (ddd, *J* = 17.7 Hz, 1.8 Hz, 1.8 Hz, 1 H, C*H*H, *Z*-isom.), 2.11 (dddd, *J* = 17.7 Hz, 2.8 Hz, 2.8 Hz, 2.8 Hz, 1 H, CH*H*, *Z*-isom.), 1.63-1.24 (m, 14 H, CH_2, CH_3, *E*/*Z*-isom.). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 166.91 (s, *E*/*Z*-isom.),

166.83 (s, *E*/*Z*-isom.), 135.73 (d, *E*-isom.), 135.60 (d, *Z*-isom.), 131.20 (d, *Z*-isom.), 130.54 (d, *E*-isom.), 111.09 (d, *Z*-isom.), 110.73 (d, *E*-isom.), 59.23 (t, *E*/*Z*-isom.), 42.23 (d, *E*-isom.), 37.31 (t, *Z*-isom.), 36.00 (t, *E*-isom.), 34.41 (d, *Z*-isom.), 31.23 (d, *E*-isom), 30.87 (d, *Z*-isom.), 25.44 (t, *E*-isom.), 24.75 (t, *Z*-isom.), 24.61 (t, *Z*-isom.), 24.48 (t, *E*-isom.), 14.28 (q, *E*/*Z*-isom). CI-MS 193 (100, $[M+1]^+$), 165 (21), 147 (40), 119 (11). Anal. Calcd for $C_{12}H_{16}O_2$ (192.26): C, 74.97; H, 8.39; Found: C, 74.92; H, 8.11.

7-Oxabicyclo[2.2.1]hept-5-en-2-ylidene-acetic acid ethyl ester. According to GP1. From **5c** (2.0 g, 18.2 mmol), triethyl phosphonoacetate (10.9 ml, 54.5 mmol) and NaH (5.6 g, 127.1 mmol). FC (Hexane/AcOEt 9:1) gave a 1.6:1 *E*/*Z* mixture of 7-oxabicyclo[2.2.1]hept-5-en-2-ylidene-acetic acid ethyl ester isomers (2.30 g, 70%) as a colorless oil. IR (film) 2982, 2940, 1711, 1676, 1371, 1204. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.50 (dd, *J* = 5.7 Hz, 1.7 Hz, 1 H, C*H*=CH, *E*-isom.), 6.44 (s, 2 H, C*H*=C*H*, *Z*-isom.), 6.33 (dd, *J* = 5.7 Hz, 1.3 Hz, 1 H, CH=C*H*, *E*-isom.), 6.12 (s, 1 H, C*H*, *Z*-isom.), 5.97-5.95 (m, 1 H, C*H*CO_2Et, *E*-isom.), 5.78-5.77 (m, 1 H, C*H*CO_2Et, *Z*-isom.), 5.20-5.18 (m, 1 H, C*H*, *E*-isom.), 5.13-5.11 (m, 2 H, C*H*, *E*/*Z*-isom.), 4.22-4.09 (m, 4 H, $CO_2CH_2CH_3$, *E/Z-isom.*), 2.76 (dddd, *J* = 16.5 Hz, 4.0 Hz, 2.2 Hz, 0.7 Hz, 1 H, C*H*H, *E*-isom.), 2.56 (dddd, *J* = 15.1 Hz, 4.0 Hz, 1.8 Hz, 0.7 Hz, 1 H, C*H*H, *Z*-isom.), 2.44 (ddd, *J* = 16.5 Hz, 1.8 Hz, 0.7 Hz, 1 H, CH*H*, *E*-isom.), 2.02 (d, *J* = 15.1 Hz, 1 H, CH*H*, *Z*-isom.), 1.32-1.24 (m, 6 H, CH_3, *E/Z-isom.*). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 166.00 (s, *E*-isom.), 165.31 (s, *Z*-isom.), 157.48 (s, *E*-isom.), 156.76 (s, *Z*-isom.), 137.73 (d, *E*-isom.), 136.55 (d, *Z*-isom.), 132.65 (d, *E*-isom.), 131.86 (d, *Z*-isom.), 111.65 (d, *E*-isom.), 111.49 (d, *Z*-isom.), 81.68 (d, *E*-isom.), 79.66 (d, *Z*-isom.), 78.16 (d, *E*-isom.), 76.99 (d, *Z*-isom.), 59.42 (t, *E/Z-isom.*), 33.71 (t, *E*-isom.), 33.39 (t, *Z*-isom.), 13.81 (q, *E*-isom., *Z*-isom). CI-MS 181 (66, $[M+1]^+$), 151 (14), 135 (100), 107 (48), 79 (25), 68 (12). Anal. Calcd for $C_{10}H_{12}O_3$ (180.20): C, 66.65; H, 6.71; Found: C, 66.74; H, 6.98.

General procedure (GP2). Bicyclo[2.2.n]alk-5-en-2-ylidene-ethanol (6). To a stirred solution of AlH_3 prepared *in situ* by the addition of $LiAlH_4$ (5.5 g, 146.1 mmol) to a solution of $AlCl_3$ (6.5 g, 48.7 mmol) in dry THF (40 ml) at 0°C, under N_2, was added a

solution of ester **6** (24.4 mmol) in dry THF (20 ml) with a syringe, within *ca*. 20 min, at 0°C. The mixture was stirred for further 1 h and quenched with MeOH (10 ml). Water was added and the insoluble residues were filtered off. The aqueous layer was extracted with Et_2O (1 x 200 ml and 2 x 100 ml), the combined organic phases dried over $MgSO_4$ and the solvent evaporated. The resulting crude product was purified by flash chromatography (hexane/AcOEt) to yield pure *E*/*Z*-**6**.

Bicyclo[2.2.1]hept-5-en-2-ylidene-ethanol (6a). According to GP2. From bicyclo[2.2.1]hept-5-en-2-ylidene-acetic acid ethyl ester (4.3 g, 24.4 mmol), $LiAlH_4$ (5.5 g, 146.1 mmol) and $AlCl_3$ (6.5 g, 48.7 mmol). FC (Hexane/AcOEt 7:3) gave pure *E*/*Z*-**6a** (2.82 g, 85%) as a slightly yellow oil. IR (film) 3343, 2978, 1450, 1063. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.16-6.11 (m, 2 H, C*H*=CH, *E*/*Z*-isom.), 6.05 (ddd, *J* = 5.5 Hz, 3.1 Hz, 0.6 Hz, 1 H, CH=C*H*, *E*-isom.), 6.01 (ddd, *J* = 5.5 Hz, 3.1 Hz, 0.6 Hz, 1 H, CH=C*H*, *Z*-isom.), 5.66-5.59 (m, 1 H, C*H*CH_2OH, *E*-isom.), 5.44 (t, *J* = 7.0 Hz, 1 H, C*H*CH_2OH, *Z*-isom.), 4.27-4.15 (m, 2 H, CH_2OH, *Z*-isom.), 4.06 (d, *J* = 7.0 Hz, 2 H, CH_2OH, *E*-isom.), 3.54-3.50 (m, 1 H, C*H*, *Z*-isom.), 3.18-3.15 (m, 1 H, C*H*, *E*-isom.), 3.00 (s, 1 H, C*H*, *E*-isom.), 2.97 (s, 1 H, C*H*, *Z*-isom.), 2.33-2.19 (m, 2 H, C*H*H, *E*/*Z*-isom.), 1.77 (ddd, *J* = 15.0 Hz, 2.1 Hz, 2.1 Hz, 2 H, C*H*H, *E*/*Z*-isom.), 1.66-1.61 (m, 1 H, CH*H*, *Z*-isom.), 1.61-1.56 (m, 1 H, C*H*H, *E*-isom.), 1.39 (d, *J* = 8.2 Hz, 2 H, CH*H*, *E*/*Z*-isom.), 1.35 (s, 2 H, O*H*, *E*/*Z*-isom.). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 145.57 (s, *Z*-isom.), 145.04 (s, *E*-isom.), 136.69 (d, *Z*-isom.), 136.39 (d, *E*-isom.), 133.91 (d, *E*-isom.), 133.38 (d, *Z*-isom.), 118.27 (d, *Z*-isom.), 117.86 (d, *E*-isom.), 60.89 (t, *E*-isom.), 60.10 (t, *Z*-isom.), 50.47 (d, *E*-isom.), 49.79 (t, *E*-isom.), 49.53 (t, *Z*-isom.), 45.17 (d, *Z*-isom.), 41.49 (d, *E*-isom.), 40.87 (d, *Z*-isom.), 33.66 (t, *Z*-isom.), 30.81 (t, *E*-isom.). CI-MS 136 (8, M^+), 119 (10), 118 (17), 91 (12). Anal. Calcd for $C_9H_{12}O$ (136.19): C, 79.37; H, 8.88; Found: C, 79.61; H, 8.66.

Bicyclo[2.2.2]oct-5-en-2-ylidene-ethanol (6b). According to GP2. From bicyclo[2.2.2]oct-5-en-2-ylidene-acetic acid ethyl ester (5.28 g, 27.5 mmol), $LiAlH_4$ (6.25 g, 164.8 mmol) and $AlCl_3$ (7.32 g, 54.9 mmol). FC (Hexane/AcOEt 8:2) gave pure *E*/*Z*-**6b** (2.98 g, 72%) as a colorless oil. IR (film) 3345, 3046, 2942, 1669, 1427, 1003, 698. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.32-6.17 (m, 2 H, C*H*=C*H*, *Z*-isom.), 6.24 (dd, *J* =

4.6 Hz, 3.1 Hz, 2 H, C*H*=C*H*, *E*-isom.), 5.36 (ddt, *J* = 6.7 Hz, 6.7 Hz, 2.4 Hz, 1 H, C*H*CH_2OH, *E*-isom.), 5.32 (ddt, *J* = 7.3 Hz, 7.3 Hz, 1.8 Hz, 1 H, C*H*CH_2OH, *Z*-isom.), 4.13 (d, *J* = 7.3 Hz, 2 H, CH_2OH, *Z*-isom.), 4.02 (dddd, *J* = 6.7 Hz, 1.1 Hz, 1.1 Hz, 1.1 Hz, 1 H, CH_2OH, *E*-isom.), 3.43-3.41 (m, 1 H, C*H*, *Z*-isom.), 2.98-2.95 (m, 1 H, C*H*, *E*-isom.), 2.73-2.68 (s, 1 H, C*H*, *E*-isom.), 2.64 (m, 1 H, C*H*, *Z*-isom.), 2.23-2.12 (m, 2 H, C*H*H, *E*/*Z*-isom.), 2.04-1.96 (m , 2 H, CH*H*, *E*/*Z*-isom.), 1.90 (s, 2 H, O*H*, *E*/*Z*-isom.), 1.64-1.27 (m, 8 H, CH_2, *E*/*Z*-isom.). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 145.29 (s, *Z*-isom.), 144.46 (s, *E*-isom.), 134.99 (d, *Z*-isom.), 134.05 (d, *E*-isom.), 132.70 (d, *E*-isom.), 132.05 (d, *Z*-isom.), 118.29 (d, *E*/*Z*-isom.), 59.66 (t, *E*-isom.), 58.56 (t, *Z*-isom.), 40.91 (d, *E*/*Z*-isom.), 35.67 (t, *Z*-isom.), 33.72 (d, *Z*-isom.), 31.99 (t, *E*-isom.), 31.04 (d, *E*-isom.), 26.13 (t, *E*-isom.), 25.96 (t, *Z*-isom.), 24.99 (t, *E*/*Z*-isom.). CI-MS 150 (27, M^+), 133 (100), 104 (16). Anal. Calcd for $C_{10}H_{14}O$ (150.22): C, 79.96; H, 9.39; Found: C, 79.88; H, 9.21.

7-Oxabicyclo[2.2.1]hept-5-en-2-ylidene-ethanol (6c). According to GP2. From 7-oxabicyclo[2.2.1]hept-5-en-2-ylidene-acetic acid ethyl ester (2.22 g, 12.3 mmol), $LiAlH_4$ (2.80 g, 73.7 mmol) and $AlCl_3$ (3.28 g, 24.6 mmol). FC (Hexane/AcOEt 9:1) gave pure *E*/*Z*-**6c** (1.18 g, 70%) as a slightly yellow oil. IR (film) 3420, 2934, 1721, 1680, 1267, 1011, 737. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.35 (s, 2 H, C*H*=C*H*, *E*-isom.), 6.34 (s, 2 H, C*H*=C*H*, *Z*-isom.), 5.74-5.70 (m, 1 H, C*H*CH_2OH, *E*-isom.), 5.56-5.51 (m, 1 H, C*H*CH_2OH, *Z*-isom.), 5.38 (s, 1 H, C*H*, *Z*-isom.), 5.13 (d, *J* = 4.6 Hz, 1 H, C*H*, *E*-isom.), 5.09 (d, *J* = 4.3 Hz, 1 H, C*H*, *Z*-isom.), 5.01 (s, 1 H, C*H*, *E*-isom.), 4.27-4.03 (m, 4 H, $CO_2CH_2CH_3$, *E*/*Z*-isom.), 2.49-2.39 (m, 2 H, C*H*H, *E*/*Z*-isom.), 1.91.1.87 (m, 2 H, CH*H*, *E*/*Z*-isom.), 1.84 (s, 2 H, O*H*, *E*/*Z*-isom.). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 138.23 (s, *E*-isom.), 138.13 (s, *Z*-isom.), 135.91 (d, *E*-isom.), 135.69 (d, *Z*-isom.), 134.02 (d, *E*-isom.), 133.82 (d, *Z*-isom.), 120.42 (d, *Z*-isom.), 120.19 (d, *E*-isom.), 82.32 (d, *E*-isom.), 78.68 (d, *Z*-isom.), 78.58 (d, *Z*-isom.), 61.41 (t, *E*-isom.), 60.34 (t, *Z*-isom.), 32.38 (t, *Z*-isom.), 30.17 (t, *E*-isom.). CI-MS 137 (7, $[M-1]^+$), 121 (23), 109 (30), 93 (100), 81 (16), 79 (19). Anal. Calcd for $C_8H_{10}O_2$ (138.17): C, 69.55; H, 7.30; Found: C, 69.54; H, 7.15.

General procedure (GP3). Spiro[bicyclo[2.2.n]alk-5-en-2,2'-(3'-bromométhyl)oxirane] (7). *m*-Chloroperbenzoic acid (*m*-CPBA) (3.84 g, 15.57 mmol) was added by portions to a solution of allylic alcohols **6** (15.57 mmol) in CH_2Cl_2 (60 ml) at 0°C. The reaction mixture was let overnight at 0°C and aqueous saturated $Na_2S_2O_4$ (60 ml) was added. The phases were separated and the aqueous layer was further extracted several times with AcOEt. The combined organic layers were dried on $MgSO_4$ and the solvents evaporated to afford the crude epoxy alcohols.

To a solution of crude epoxy alcohols in dry CH_2Cl_2 (110 ml) at 0°C, were added CBr_4 (6.69 g, 20.16 mmol) and triphenylphosphine (5.29 g, 20.16 mmol) by portions. The reaction mixture was let warm gently and stirred until completion of the reaction (3-12 h). Evaporation of the solvent and FC (hexane/AcOEt) of the crude afforded epoxy bromides **7** as mixtures of isomers.

Spiro[bicyclo[2.2.1]hept-5-en-2,2'-(3'-bromométhyl)oxirane] (7a). According to GP3. From **6a** (2.12 g, 15.57 mmol), *m*-CPBA (3.84 g, 15.57 mmol) and then CBr_4 (6.69 g, 20.16 mmol) and PPh_3 (5.29 g, 20.16 mmol). FC (Hexane/AcOEt 98:2) gave a 2.8:2.3:1:1 mixture of pure **7a**-isomers (1.84 g, 55%) as a slightly yellow oil. IR (film) 3059, 2980, 2870, 1726, 1437, 1265, 1120. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.45-6.30 (m, 4 H, C*H*=CH, isom. 1-4), 6.21-6.08 (m, 4 H, CH=C*H*, isom. 1-4), 3.67-3.05 (m, 12 H, C*H*CH_2Br, isom. 1-4), 3.00-2.36 (m, 8 H, C*H*, isom. 1-4), 2.06-1.12 (m, 16 H, CH_2, isom. 1-4). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 140.44 (d), 140.34 (d), 139.48 (d), 138.77 (d), 133.12 (d), 132.93 (d), 132.78 (d), 132.36 (d), 73.34 (s), 72.98 (s), 72.94 (s), 72.63 (s), 60.17 (d), 60.12 (d), 59.30 (d), 58.64 (d), 49.49 (t), 49.10 (t), 48.96 (d), 48.95 (t), 48.84 (t), 47.56 (d), 45.38 (d), 42.88 (d), 42.03 (d), 41.58 (d), 40.92 (d), 40.75 (d), 35.34 (t), 34.81 (t), 31.41 (t), 31.30 (t), 31.06 (t), 30.91 (t), 30.81 (t), 35.43 (t). CI-MS 217 (17, M^+), 215 (18, M^+), 151 (17), 149 (18), 135 (100), 107 (23), 93 (16), 91 (19), 67 (82). Anal. Calcd for $C_9H_{11}BrO$ (215.09): C, 50.26; H, 5.15; Found: C, 50.03; H, 5.38.

Spiro[bicyclo[2.2.2]oct-5-en-2,2'-(3'-bromométhyl)oxirane] (7b). According to GP3. From **6b** (2.89 g, 19.24 mmol), *m*-CPBA (4.74 g, 19.24 mmol) and then CBr_4 (8.29 g, 25.01 mmol) and PPh_3 (4.41 g, 25.01 mmol). FC (Hexane/AcOEt 95:5) gave a 7.9:1 mixture of pure **7b**-isomers (1.80 g, 41%) as a slightly yellow oil. IR (film) 3050, 2947,

2866, 2361, 1445, 1225, 891. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.47-6.39 (m, 2 H, C*H*=CH, major, minor), 6.29-6.24 (m, 2 H, CH=C*H*, major, minor), 3.59 (dd, *J* = 10.1 Hz, 4.9 Hz, 1 H, C*H*HBr, major), 3.54(dd, *J* = 10.4 Hz, 6.1 Hz, 1 H, C*H*HBr, minor), 3.39 (dd, *J* = 10.4 Hz, 7.3 Hz, 1 H, CH*H*Br, minor), 3.29 (dd, *J* = 7.3 Hz, 6.1 Hz, 1 H, C*H*CH_2Br, minor), 3.15 (dd, *J* = 8.9 Hz, 4.9 Hz, 1 H, C*H*CH_2Br, major), 2.99 (dd, *J* = 10.1 Hz, 8.9 Hz, 1 H, CH*H*Br, major), 2.77-2.68 (m, 2 H, C*H*, major, minor), 2.33-2.30 (m, 1 H, C*H*, minor), 2.10-2.07 (m, 1 H, C*H*, major), 1.90-1.22 (m , 12 H, CH_2, major, minor). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 136.08 (d, minor), 135.28 (d, major), 131.09 (d, major), 130.72 (d, minor), 67.98 (s, major, minor), 59.79 (d, major, minor), 38.32 (d, major), 37.19 (t, minor), 33.12 (d, minor), 31.98 (t, major), 30.78 (t, major), 30.38 (d, minor), 30.12 (d, major), 29.25 (t, minor), 24.01 (t, minor), 23.76 (t, major), 22.55 (t, major), 22.37 (t, minor). CI-MS 231 (18, M^+), 229 (19, M^+), 149 (100), 121 (29), 107 (35), 91 (22), 81 (21). *Exact Mass* Calcd for $C_{10}H_{13}BrO$ (229.12): 229.0222514; Found: 229.0220030. 231.0202044; Found: 231.0203280.

Spiro[7-oxabicyclo[2.2.1]hept-5-en-2,2'-(3'-bromométhyl)oxirane] (7c). According to GP3. From **6c** (1.10 g, 7.96 mmol), *m*-CPBA (1.96 g, 7.96 mmol) and then CBr_4 (3.43 g, 10.35 mmol) and PPh_3 (2.71 g, 10.35 mmol). FC (Hexane/AcOEt 7:3) gave a 9.9:2.0:1.7:1 mixture of pure **7c**-isomers (0.88 g, 51%) as a yellow oil. IR (film) 3009, 2947, 2363, 2342, 1736, 1437, 1244, 1020, 905. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.68-6.47 (m, 8 H, C*H*=C*H*), 5.94-4.98 (m, 4 H, C*H*), 4.58-4.45 (m, 4 H, C*H*), 4.09-2.73 (m, 12 H, C*H*CH_2Br), 2.35-1.30 (m, 8 H, CH_2). Major isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.59 (dd, *J* = 5.6 Hz, 1.6 Hz, 1 H, C*H*=CH), 6.42 (dd, *J* = 5.6 Hz, 1.7 Hz, 1 H, CH=C*H*), 5.14 (ddd, *J* = 4.5 Hz, 1.3 Hz, 1.3 Hz, 1 H, C*H*), 4.43 (s, 1 H, C*H*), 3.53 (dd, *J* = 10.3 Hz, 5.5 Hz, 1 H, C*H*HBr), 3.32 (ddd, *J* = 7.7 Hz, 5.5 Hz, 0.5 Hz, 1 H, C*H*CH_2Br), 3.04 (dd, *J* = 10.3 Hz, 7.7 Hz, 1 H, CH*H*Br), 1.90 (dd, *J* = 12.1 Hz, 4.5 Hz, 1 H, C*H*H), 1.69 (d, *J* = 12.1 Hz, 1 H, CH*H*). ^{13}C NMR ($CDCl_3$, 125.77 MHz) 139.78 (d), 132.88 (d), 82.13 (d), 78.15 (d), 71.16 (s), 55.78 (d), 30.59 (t), 29.22 (t). CI-MS 219 (5, M^+), 217 (5, M^+), 173 (23), 171 (23), 137 (100), 109 (69), 95 (84), 81 (29). *Exact Mass* Calcd for $C_8H_9BrO_2$ (217.06): 216.9858654; Found: 216.9861030. 218.9838184; Found: 218.9836200.

General procedure (GP4). Radical reactions. A degassed solution of radical precursor **7a-c** (0.93 mmol) in benzene (20 ml) was heated at reflux under an inert atmosphere, treated by one pot or dropwise (syringe pump) addition with a solution of stannane and 2,2'-azobis(isobutyronitrile) (AIBN; 16 mg, 0.10 mmol) in benzene (20 ml), and kept under reflux for some additional hours. The solution was cooled to rt, treated with KF (500 mg, 8.61 mmol) for 24 h and the solvent was evaporated. The residue was dissolved in hexane (5 ml) and filtered on. FC (hexane 150 ml and then AcOEt 100 ml). The AcOEt-containing fraction was evaporated and purified by FC (Hexane/AcOEt).

Bicyclo[4.3.0]non-7-en-3-one (8a). According to GP4. From **7a** (200 mg, 0.93 mmol), Bu_3SnH (0.31 ml, 1.15 mmol) and AIBN (16 mg, 0.10 mmol) added dropwise during 18 h, and 8 additional hours of reflux. FC (Hexane/AcOEt 7:3) gave **8a** (60 mg, 48%) as a colorless liquid. IR (film) 3416, 2930, 1711, 756. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.77-5.73 (m, 1 H, C(8)-*H*), 5.60-5.56 (m, 1 H, C(7)-*H*), 3.10-3.00 (m, 1 H, C(6)-*H*), 2.83-2.75 (m, 1 H, C(1)-*H*), 2.72-2.64 (m, 1 H, C(9)-H_{exo}), 2.48 (dd, J = 15.4 Hz, 6.1 Hz, 1 H, C(2)-H_{exo}), 2.32 (dd, J = 15.4 Hz, 6.9 Hz, 1 H, C(2)-H_{endo}), 2.25 (dd, J = 5.5 Hz, 1.8 Hz, 1 H, C(4)-H_{endo}), 2.23 (d, J = 5.5 Hz, 1 H, C(4)-H_{exo}), 2.08-1.95 (m, 2 H, C(5)-H_{exo}, C(9)-H_{endo}), 1.76-1.69 (m, 1 H, C(5)-H_{endo}). ^{13}C NMR ($CDCl_3$, 122.77 MHz) 213.91 (s), 133.31 (d), 130.32 (d), 43.57 (t), 42.99 (d), 40.32 (t), 37.07 (t), 33.66 (d), 25.44 (t). CI-MS 137 (19, $[M+1]^+$), 135 (95), 107 (19), 95 (16). *Exact Mass* Calcd for $C_9H_{12}O$ (136.19): 137.0960904; Found: 137.0960060.

4-(^{2}H)Bicyclo[4.3.0]non-7-en-3-one (9a). Thermal reaction. According to GP4. From **7a** (50 mg, 0.23 mmol), Bu_3SnD (0.09 ml, 0.35 mmol) and AIBN (8 mg, 0.05 mmol) added dropwise during 12 h, and 5 additional hours of reflux. FC (Hexane/AcOEt 7:3) gave **9a** (15 mg, 48%) in a 1.8:1 in favor of the all-*cis* compound, as a colorless liquid. ^{1}H- and ^{13}C data correspond to those of the undeuterated compound. ^{2}H-NMR (106.9 MHz, $CHCl_3$) δ 2.25 (s, minor), 2.23 (s, major).

4-(^{2}H)-Bicyclo[4.3.0]non-7-en-3-one (9a). Photochemical reaction. According to GP4. From **7a** (50 mg, 0.23 mmol) in a cool bath at 5°C, Bu_3SnD (0.09 ml, 0.35 mmol) and AIBN (8 mg, 0.05 mmol) added dropwise during 12 h under irradiation with a Philips

sun lamp, and 5 additional hours of reflux. ^{2}H-NMR of the crude attested the formation of **9a** in a 2.1:1 ratio in favor of the all-*cis* isomer.

Bicyclo[4.4.0]dec-7-en-3-one (8b). According to GP4. From **7b** (200 mg, 0.87 mmol), Bu_3SnH (0.25 ml, 0.96 mmol) and AIBN (16 mg, 0.10 mmol) added dropwise during 12 h, and 12 additional hours of reflux. FC (Hexane/AcOEt 9:1) gave **8b** (33 mg, 25% or 29% converted yield) as a colorless liquid, along with starting compound **7b** (26 mg, 13%).

Data of 8b. IR (film) 3408, 3018, 2926, 2868, 1713, 1431. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.77-5.73 (m, 1 H, C(8)-*H*), 5.62 (dddd, *J* = 10.0 Hz, 2.5 Hz, 2.5 Hz, 2.5 Hz, 1 H, C(7)-*H*), 2.54-2.50 (m, 1 H, C(6)-*H*), 2.42-2.23 (m, 5 H, C(1)-*H*, C(2)-H_2, C(4)-H_2), 2.09-2.05 (m, 2 H, C(9)-H_2), 2.00-1.94 (m, 1 H, C(5)-H_{exo}), 1.89-1.82 (m, 1 H, C(5)-H_{endo}), 1.73-1.66 (m, 1 H, C(10)-*H*H), 1.59-1.52 (m, 1 H, C(10)-H*H*). ^{13}C NMR ($CDCl_3$, 122.77 MHz) 212.62 (s), 129.49 (d), 127.68 (d), 44.09 (t), 38.66 (t), 35.97 (d), 34.28 (d), 30.51 (t), 25.58 (t), 22.82 (t). CI-MS 151 (100, $[M+1]^+$), 133 (21), 91 (8). *Exact Mass* Calcd for $C_{10}H_{14}O$ (150.22): 151.1117404; Found: 151.1118910.

4-(^{2}H)-9-Oxabicyclo[4.3.0]non-7-en-3-one (9c). According to GP4. From **7c** (100 mg, 0.46 mmol), Bu_3SnD (0.18 ml, 0.69 mmol) and AIBN (8 mg, 0.05 mmol) added dropwise during 12 h, and 4 additional hours of reflux. FC (Hexane/AcOEt 8:2) gave **9c**, along with decomposition derivative **13** (in total: 45 mg, 85%).

Data of 9c. IR (film) 3441, 2932, 1719, 1618, 1140, 1047. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.03-6.02 (m, 1 H, C(8)-*H*), 4.36 (ddd, *J* = 10.1 Hz, 3.6 Hz, 3.6 Hz, 1 H, C(1)-*H*), 4.31 (dd, *J* = 2.7 Hz, 2.7 Hz, 1 H, C(7)-*H*), 2.60-2.56 (m, 1 H, C(2)-*H*H), 2.54-2.49 (m, 1 H, C(6)-*H*), 2.09-2.04 (m, 1 H, C(4)-H_{exo}), 1.97 (dddd, *J* = 16.7 Hz, 3.7 Hz, 2.0 Hz, 0.7 Hz, 1 H, C(2)-H*H*), 1.95-1.92 (m, 1 H, C(4)-H_{endo}), 1.18 (ddd, *J* = 14.0 Hz, 14.0 Hz, 5.6 Hz, 1 H, C(5)-*H*H), 1.00-0.92 (m, 1 H, C(5)-H*H*). ^{13}C NMR ($CDCl_3$, 122.77 MHz) 207.38 (s), 146.70 (d), 146.68 (d), 102.86 (d), 79.21 (d), 41.61 (t), 36.22 (d), 24.41 (t). ^{2}H-NMR (106.9 MHz, $CHCl_3$) δ 2.10 (s, major), 1.92 (s, minor). CI-MS 140 (100, $[M+1]^+$), 137 (11), 122 (16), 85 (12), 81 (26). *Exact Mass* Calcd for $C_8H_9O_2D$ (139.16): 140.0816314; Found: 140.0818520.

Data of 13. IR (film) 3430, 2936, 2870, 1719, 1678, 1451, 1061. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.03 (t, J = 1.2 Hz, C*H*O), 5.99 (dddd, J = 10.2 Hz, 2.8 Hz, 2.8 Hz, 1.4 Hz, 1 H, C*H*=CHCO), 5.83 (dd, J = 10.2 Hz, 2.5 Hz, 1 H, CH=C*H*CO), 2.26-2.19 (m, 1 H, C*H*CH_2CHO), 2.10-2.06 (m, 1 H, C*H*D), 1.90-1.82 (m, 1 H, CD*H*), 1.51-1.48 (m, 2 H, CH_2CHO), 1.27-0.90 (m, 2 H, CH_2). ^{13}C NMR ($CDCl_3$, 122.77 MHz) 225.95 (s), 198.57 (s), 151.42 (d), 151.40 (d), 32.51 (d), 30.13 (d), 28.68 (t). CI-MS 140 (32, $[M+1]^+$), 125 (94), 97 (100), 93 (13). *Exact Mass* Calcd for $C_8H_9O_2D$ (139.16): 140.0816314; Found: 140.0815760.

4-[2'-(Methyl)prop-2'-enyl]bicyclo[4.3.0]non-7-en-3-one (10a). According to GP4. From **7a** (200 mg, 0.93 mmol), $Bu_3SnCH_2C(CH_3)=CH_2$ (0.48 g, 1.39 mmol) and AIBN (16 mg, 0.10 mmol) added one pot and 18 h of reflux. FC (Hexane/AcOEt 9:1) gave **10a** (104 mg, 59%) in a 1.5:1 ratio in favor of the all-*cis* isomer, as a colorless liquid. IR (film) 3407, 2932, 1711, 1443, 1042, 891. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.78 (dddd, J = 5.8 Hz, 2.3 Hz, 2.3 Hz, 2.3 Hz, 1 H, C(8)-*H*, major), 5.69 (dddd, J = 5.8 Hz, 2.1 Hz, 2.1 Hz, 2.1 Hz, 1 H, C(8)-*H*, minor), 5.64 (dddd, J = 5.8 Hz, 2.0 Hz, 2.0 Hz, 2.0 Hz, 1 H, C(7)-*H*, minor), 5.59 (dddd, J = 5.8 Hz, 2.0 Hz, 2.0 Hz, 2.0 Hz, 1 H, C(7)-*H*, major), 4.79-4.75 (m, 2 H, C=C*H*H, major, minor), 4.68-4.65 (m, 2 H, C=CH*H*, major, minor), 3.12 (m, 1 H, C(6)-*H*, major), 2.95 (m, 1 H, C(6)-*H*, minor), 2.85-2.78 (m, 1 H, C(1)-*H*, major), 2.74-1.67 (m, 18 H), 1.66 (s, 3 H, CH_3, minor), 1.64 (s, 3 H, CH_3, major), 1.28-1.22 (m, 1 H, C(5)-*H*, minor). ^{13}C NMR ($CDCl_3$, 122.77 MHz) 214.80 (s, major), 214.60 (s, minor), 143.12 (s, major), 140.53 (s, minor), 133.71 (d, major), 133.65 (d, minor), 130.75 (d, major), 128.94 (d, minor), 112.17 (t, minor), 112.02 (t, major), 45.68 (d, minor), 43.97 (d, minor), 43.45 (t, minor), 43.33 (t, major), 43.06 (d, major), 42.35 (d, major), 40.63 (t, major), 39.50 (t, minor), 38.29 (t, minor), 37.71 (t, major), 34.80 (d, major), 31.35 (t, minor), 30.83 (t, major), 27.01 (d, minor), 22.00 (q, minor), 21.87 (q, major). CI-MS 191 (100, $[M+1]^+$), 173 (32), 133 (12), 93 (10), 81 (19). *Exact Mass* Calcd for $C_{13}H_{18}O$ (190.29): 191.1430404; Found: 191.1438840.

4-[2'-(Methyl)prop-2'-enoyl]bicyclo[4.3.0]non-7-en-3-one (11a). According to GP4. From **7a** (200 mg, 0.93 mmol), $Bu_3SnCH_2C(CO_2Me)=CH_2$ (0.54 g, 1.39 mmol) and AIBN (16 mg, 0.10 mmol) added one pot and 18 h of reflux. FC (Hexane/AcOEt 9:1) gave **11a** (70 mg, 32%) in a 3.6:1 ratio in favor of the all-*cis* isomer, as a colorless liquid. IR (film) 3418, 2980, 2953, 1723, 1441, 1202. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.22 (dd, *J* = 1.4 Hz, 0.3 Hz, 1 H, C=C*H*H, minor), 6.20 (dd, *J* = 1.2 Hz, 0.5 Hz, 1 H, C=CH*H*, major), 5.78 (dddd, *J* = 5.7 Hz, 2.4 Hz, 2.4 Hz, 2.4 Hz, 1 H, C(8)-*H*, major), 5.69 (dddd, *J* = 5.7 Hz, 2.1 Hz, 2.1 Hz, 2.1 Hz, 1 H, C(8)-*H*, minor), 5.64 (dddd, *J* = 5.7 Hz, 2.1 Hz, 2.1 Hz, 2.1 Hz, 1 H, C(7)-*H*, minor), 5.58 (dddd, *J* = 5.7 Hz, 2.1 Hz, 2.1 Hz, 2.1 Hz, 1 H, C(7)-*H*, major), 5.56 (dd, *J* = 2.4 Hz, 1.3 Hz, 1 H, C=CH*H*, minor), 5.54 (dd, *J* = 2.4 Hz, 1.4 Hz, 1 H, C=CH*H*, major), 3.76 (s, 3 H, CH_3, minor), 3.75 (s, 3 H, CH_3, major), 3.08-3.03 (m, 1 H, C(6)-*H*, major), 2.99-2.90 (m, 1 H, C(6)-*H*, minor), 2.96 (ddd, *J* = 14.2 Hz, 5.0 Hz, 1.3 Hz, 1 H, CH*H*C(CO_2Me)CH_2, minor), 2.90 (ddd, *J* = 14.5 Hz, 5.2 Hz, 0.9 Hz, 1 H, CH*H*C(CO_2Me)CH_2, major), 2.83-2.76 (m, 1 H, C(1)-*H*, major), 2.74-2.67 (m, 1 H, C(1)-*H*, minor), 2.67-1.60 (m, 2 H, C(9)-H_{exo}, major, minor), 2.52-2.34 (m, 4 H, C(4)-*H*, major, minor, C(2)-H_2, minor), 2.47 (dd, *J* = 15.1 Hz, 6.3 Hz, 1 H, C(2)-H_{exo}, major), 2.32 (dd, *J* = 15.1 Hz, 6.2 Hz, 1 H, C(2)-H_{endo}, major), 2.19 (ddd, *J* = 14.5 Hz, 8.6 Hz, 1.0 Hz, 1 H, C*H*HC(CO_2Me)CH_2, major), 2.12 (ddd, *J* = 14.2 Hz, 8.9 Hz, 0.9 Hz, 1 H, C*H*HC(CO_2Me)CH_2, minor), 2.10-2.03 (m, 2 H, C(9)-H_{endo}, C(5)-H_{exo}, minor), 2.00-1.95 (m, 1 H, C(9)-H_{endo}, major), 1.92 (ddd, *J* = 14.0 Hz, 4.7 Hz, 3.2 Hz, 1 H, C(5)-H_{exo}, major), 1.72 (ddd, *J* = 14.0 Hz, 12.0 Hz, 6.0 Hz, 1 H, C(5)-H_{endo}, major), 1.29-1.21 (m, 1 H, C(5)-H_{endo}, minor). ^{13}C NMR ($CDCl_3$, 122.77 MHz) 213.75 (s, major), 213.55 (s, minor), 167.46 (s, major), 167.40 (s, minor), 138.25 (s, major), 138.22 (s, minor), 133.72 (d, minor), 133.70 (d, major), 130.92 (d, major), 129.15 (d, minor), 127.13 (t, minor), 126.71 (t, major), 51.86 (q, minor), 51.83 (q, major), 46.53 (d, minor), 44.26 (d, major), 43.78 (d, minor), 43.41 (t, major), 43.37 (t, minor), 42.62 (d, major), 40.83 (t, minor), 40.66 (t, major), 35.69 (d, major), 35.35 (d, minor), 32.48 (t, minor), 31.88 (t, major), 31.72 (t, major), 31.64 (d, minor). CI-MS 235 (29, $[M+1]^+$), 203 (68), 168 (22), 136 (100). *Exact Mass* Calcd for $C_{14}H_{18}O_3$ (234.29): 235.1328684; Found: 235.1325240.

4-[2'-(Trimethylsilyl)prop-2'-enyl]bicyclo[4.3.0]non-7-en-3-one (12a). According to GP4. From **7a** (200 mg, 0.93 mmol), $Bu_3SnCH_2C(SiMe_3)=CH_2$ (0.52 g, 1.39 mmol) and AIBN (16 mg, 0.10 mmol) added one pot and 18 h of reflux, before new addition of $Bu_3SnCH_2C(SiMe_3)=CH_2$ (1.13 g, 2.79 mmol) with AIBN (16 mg, 0.10 mmol) to complete the reaction, and 12 h of reflux. FC (Hexane/AcOEt 9:1) gave **12a** (102 mg, 44%) in a 1.5:1 ratio in favor of the all-*cis* isomer, as a slightly yellow oil. Lobar chromatography (hexane, 3% Et_2O) of a sample allowed separation of the two isomers for NMR analysis.

Data of *trans*-12a. IR (film) 3395, 2953, 1713, 1412, 1248, 839. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.69 (dddd, J = 5.8 Hz, 2.1 Hz, 2.1 Hz, 2.1 Hz, 1 H, C(8)-*H*), 5.64 (dddd, J = 5.8 Hz, 2.1 Hz, 2.1 Hz, 2.1 Hz, 1 H, C(7)-*H*), 5.52 (ddd, J = 3.3 Hz, 1.9 Hz, 1.1 Hz, 1 H, C=C*H*H), 5.40 (ddd, J = 2.7 Hz, 1.2 Hz, 0.6 Hz, 1 H, C=CH*H*), 2.96-2.89 (m, 1 H, C(6)-*H*), 2.86 (dddd, J = 14.6 Hz, 3.7 Hz, 1.8 Hz, 1.4 Hz, 1 H, C*H*HC=CH_2), 2.74-2.66 (m, 1 H, C(1)-*H*), 2.66-2.61 (m, 1 H, C(9)-H_{endo}), 2.40-2.38 (m, 2 H, C(2)-H_2), 2.37-2.29 (m, 1 H, C(4)-H_{exo}), 2.11 (ddd, J = 13.7 Hz, 6.0 Hz, 4.4 Hz, 1 H, C(5)-H_{exo}), 2.06 (ddd, J = 4.5 Hz, 2.2 Hz, 2.2 Hz, 1 H, C(9)-H_{exo}), 1.88 (dd, J = 14.6 Hz, 10.4 Hz, 1 H, CH*H*C=CH_2), 1.19 (ddd, J = 13.7 Hz, 12.7 Hz, 12.0 Hz, 1 H, C(5)-H_{endo}), 0.10 (s, 9 H, $Si(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 122.77 MHz) 214.57 (s), 149.71 (s), 133.72 (d), 128.98 (d), 125.65 (t), 46.62 (d), 43.98 (d), 43.49 (t), 39.41 (t), 36.48 (t), 34.85 (d), 31.42 (t), -1.40 (q).

Data of *cis*-12a. IR (film) 3395, 2953, 1711, 1441, 1248, 1071 837. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.77 (dddd, J = 5.8 Hz, 2.3 Hz, 2.3 Hz, 2.3 Hz, 1 H, C(8)-*H*), 5.58 (dddd, J = 5.8 Hz, 2.0 Hz, 2.0 Hz, 2.0 Hz, 1 H, C(7)-*H*), 5.50 (ddd, J = 2.8 Hz, 1.8 Hz, 1.1 Hz, 1 H, C=C*H*H), 5.38 (ddd, J = 2.8 Hz, 1.2 Hz, 0.7 Hz, 1 H, C=CH*H*), 3.10-3.04 (m, 1 H, C(6)-*H*), 2.86 (ddd, J = 14.6 Hz, 3.8 Hz, 1.9 Hz, 1.4 Hz, 1 H, C*H*HC=CH_2), 2.82-2.77 (m, 1 H, C(1)-*H*), 2.68-2.61 (m, 1 H, C(9)-H_{exo}), 2.50 (dd, J = 15.2 Hz, 6.3 Hz, 1 H, C(2)-H_{exo}), 2.33 (dd, J = 15.2 Hz, 5.7 Hz, 1 H, C(2)-H_{endo}), 2.31-2.25 (m, 1 H, C(4)-H_{endo}), 2.00-1.94 (m, 1 H, C(9)-H_{endo}), 1.94-1.88 (m, 2 H, C(5)-H_{endo}, CH*H*C=CH_2), 1.64 (ddd, J = 14.0 Hz, 11.6 Hz, 6.0 Hz, 1 H, C(5)-H_{exo}), -0.08 (s, 9 H, $Si(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 122.77 MHz) 214.75 (s), 149.67 (s), 133.85 (d), 130.72 (d), 125.60 (t), 44.00 (d), 43.37 (t), 42.55 (d), 40.65 (t), 36.09 (t), 35.00 (d), 31.03 (t), -1.40 (q).

Data of mixed *cis*/*trans*-12a. CI-MS 249 (42, $[M+1]^+$), 233 (100), 188 (30), 177 (45), 159 (32), 119 (38), 79 (43), 73 (62). Anal. Calcd for $C_{15}H_{24}OSi$ (248.44): C, 72.52; H, 9.74; Found: C, 72.32; H, 9.79.

4-[2'-(Methyl)prop-2'-enyl]bicyclo[4.4.0]dec-7-en-3-one (10b). According to GP4. From **7b** (100 mg, 0.44 mmol), $Bu_3SnCH_2C(CH_3)=CH_2$ (0.23 g, 0.66 mmol) and AIBN (8 mg, 0.05 mmol) added one pot and 24 h of reflux. FC (Hexane/AcOEt 95:5) gave **10b** (19 mg, 21%) in a 2.4:1 ratio in favor of the all-*cis* isomer, as a colorless oil. IR (film) 3407, 2932, 1711, 1443, 1042, 891. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.82 (dddd, J = 10.1 Hz, 3.3 Hz, 3.3 Hz, 3.3 Hz, 1 H, C(8)-*H*, major), 5.72-5.68 (m, 1 H, C(8)-*H*, minor), 5.67-5.63 (m, 1 H, C(7)-*H*, minor), 5.57-5.54 (m, 1 H, C(7)-*H*, major), 4.77 (s, 2 H, C=C*H*H, major, minor), 4.66 (m, 2 H, C=CH*H*, major, minor), 2.71 (ddd, J = 13.6 Hz, 6.8 Hz, 1.0 Hz, 1 H, C(2)-*H*H, minor), 2.58-2.50 (m, 7 H, C(2)-*H*, major, C(4)-*H*, C(6)-*H*, C*H*HC=CH_2, major, minor), 2.35-2.30 (m, 2 H, C(1)-*H*, major, minor), 2.26 (dd, J = 13.5 Hz, 2.5 Hz, 1 H, C(2)-H*H*, minor), 2.19 (dd, J = 12.9 Hz, 4.8 Hz, 1 H, C(2)-H*H*, major), 2.10-2.05 (m, 5 H, C(5)-*H*H, minor, C(9)-H_2, major, minor), 2.03 (dd, J = 5.0 Hz, 3.5 Hz, 1 H, C(5)-*H*H, major), 1.89 (ddd, J = 15.8 Hz, 10.0 Hz, 0.8 Hz, 1 H, CH*H*CCH_2, major), 1.88-1.72 (m, 3 H, CH*H*CCH_2, minor, C(10)-*H*H, major, minor), 1.70 (m, 3 H, CH_3, minor), 1.68 (m, 3 H, CH_3, major), 1.59-1.48 (m, 3 H, C(5)-H*H*, major, C(10)-H*H*, major, minor), 1.29-1.26 (m, 1 H, C(5)-H*H*, minor). ^{13}C NMR ($CDCl_3$, 122.77 MHz) 213.31 (s, major), 212.52 (s, minor), 143.28 (s, major), 143.20 (s, minor), 129.93 (d, minor), 129.42 (d, major), 128.14 (d, major), 126.66 (d, minor), 111.85 (t, minor), 111.66 (t, major), 47.32 (t, minor), 46.82 (d, minor), 42.97 (d, major), 42.10 (t, major), 37.43 (t, major), 37.10 (d, minor), 36.98 (t, minor), 36.81 (t, major), 36.74 (d, major), 36.31 (t, minor), 35.56 (d, minor), 33.91 (d, major), 26.42 (t, major), 25.63 (t, minor), 24.16 (t, minor), 22.39 (q, minor), 22.34 (q, major), 20.74 (t, major). CI-MS 205 (100, $[M+1]^+$), 190 (90), 162 (14), 89 (16), 75 (36), 73 (70). *Exact Mass* Calcd for $C_{14}H_{20}O$ (204.31): 205.1586904; Found: 205.158490.

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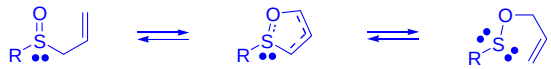
The Evans-Mislow Rearrangement : A New Approach for the Generation of Alkoxyl Radicals

1. Introduction

Studied in the sixties by Mislow,[1-4] the thermal racemization of allyl sulfoxides **1** and the thermal rearrangement of allyl sulfenates **2**, were shown to be both manifestations of the same process: the concerted, reversible, and intramolecular interconversion of **1** and **2** in a [2,3]sigmatropic rearrangement, by the way of a five-membered transition state (Scheme 1). The sulfoxide-sulfenate equilibrium concentration was proven to be dependent upon electronic as well as size effect, no sulfenate ester being generally observable in NMR spectra.[4] The first application of this process allowed transformation of simple allylic alcohols into rearranged allylic sulfoxides *via* their sulfenate ester, in high yields.[3,4] Further work by Evans[5,6] gave access to the reverse transformation, *i.e.* that of sulfoxide into rearranged allylic alcohol, which was accomplished by heating the allylic sulfoxide in the presence of a suitable thiophile. Other studies and synthetic applications of the rearrangement attested its general feature and usefulness.[7-13] However, to our knowledge, no paper has so far reported the use of the sulfoxide-sulfenate rearrangement in radical chemistry.

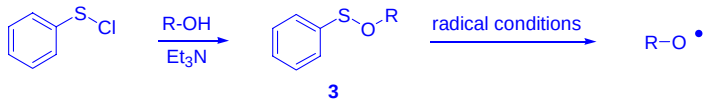


1 **2**

Scheme 1

Benzenesulfenate derivatives **3**, which are normally prepared by treatment of the parent alcohol with benzenesulfenyl chloride in the presence of triethylamine, are known to be good precursors of alkoxyl radicals, under a variety of radical conditions (Scheme 2).

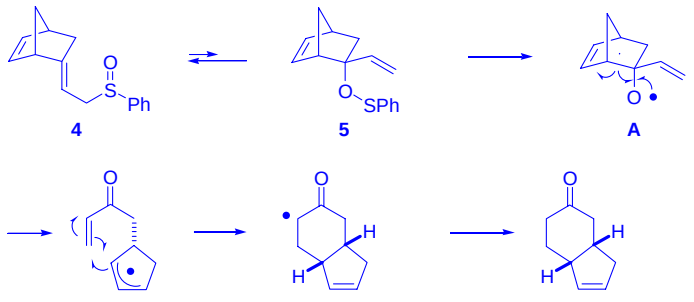
First developed essentially for mechanistic studies,[14-17] they have soon integrated the synthetic radical chemistry.[18,19]



3

Scheme 2

In our work aimed at the development of new methods for the generation of alkoxyl radical from norbonenol derivatives, we devised to take advantage of the allylic sulfoxide **4** – sulfenate **5** rearrangement to generate 2-vinylbicyclo[2.2.1]hept-5-en-2-oxyl radical (**A**). This was expected to undergo β-fragmentation onto an allylic carbon-centered radical **B** which, after Michael-type radical addition on the α,β-unsaturated ketone moiety and trapping, should afford bicyclo[4.3.0]non-7-en-3-one (**6**) *via* **C** (Scheme 3). The interest of this approach relies on the fact that, as reported earlier,[20,21] direct synthesis of the sulfenate **5** from the parent allylic alcohol fails, as it is the case for most of the tertiary alcohols. Thus, synthesis of its sulfoxide **4** provides an indirect access to radical precursor **5**. We describe here our first results in this direction.



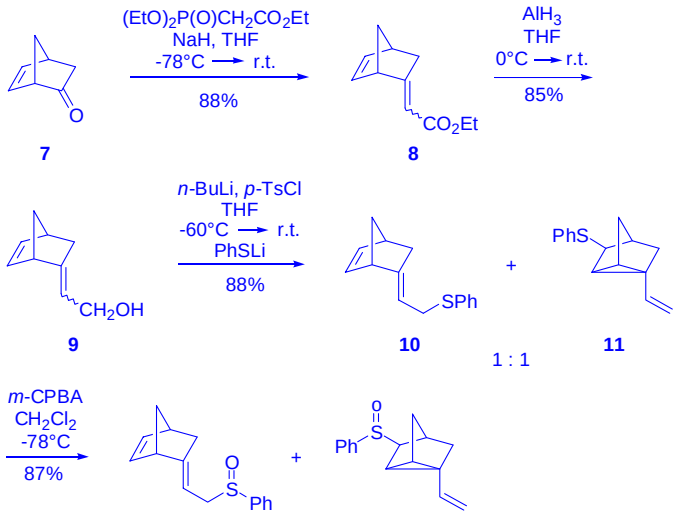
4 **5** **A**

B **C** **6**

Scheme 3

2. Results and discussion

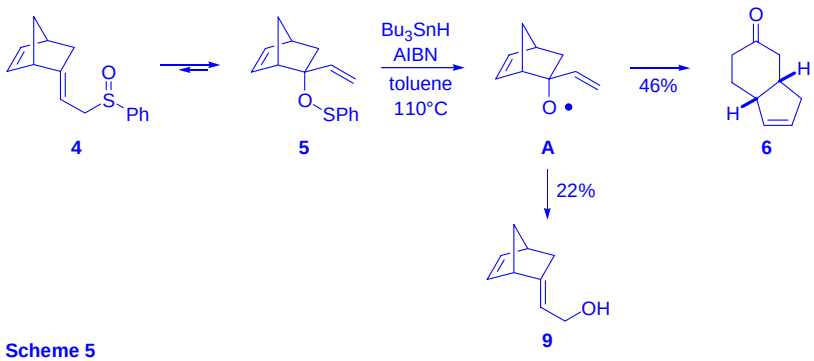
Sulfoxide **4** was obtained from norbornenone (**7**)[22] *via* a four steps synthesis described in scheme 3. Indeed, Wittig-Horner-Hemmons reaction of norbornenone (**7**) with triethyl phosphonoacetate using sodium hydride as a base in dry THF, followed by reduction of the resulting ester **8** with AlH_3 prepared *in situ* by the addition of $LiAlH_4$ to a solution of $AlCl_3$ in THF at 0°C furnished allyl alcohol **9** in 75% yield.[23] In a one pot sequence, this was tosylated by treatment with *n*-butyl lithium and *p*-toluenesulfonyl chloride, and the formed tosylate displaced by freshly prepared lithium thiophenoxide,[24] affording an about 1:1 unseparable mixture of sulfurs *E*/*Z*-**10** and tricycle **11** in 88% yield. The latter presumably arose from attack of lithium thiophenoxide on the 5,6-double bond of intermediate tosylate, cyclization onto the allylic olefin and elimination of the tosylate moiety. Upon standing on the bench, the crude reaction mixture was fully transformed into compound **11**: only traces of sulfur **10** could be detected in NMR spectra after ten days.



Scheme 4

This transformation allowed isolation of a pure sample **11**, which was thus identified and characterized. Oxidation of **10** and **11** mixture with *m*-chloroperbenzoic acid[21] gave a mixture of wanted sulfoxide **4**, as four diastereoisomers along with by-product sulfoxide **12** as two diastereoisomers, in 87% yield (Scheme 4).

Radical reactions were performed on the mixed **4** and **12**. Initiation by 2,2'-azobis(isobutyronitrile) (AIBN) in refluxing solvent and syringe-pump addition of tributyltin hydride over 12 h to a 0.02 M solution of substrates were chosen as standard conditions. However, reaction at reflux of benzene resulted only in recovery of starting material. Consequently, the reaction was next tested in refluxing toluene, furnishing an about 46% yield of *cis*-bicyclo[4.3.0]non-7-en-3-one (**6**) along with a 22% yield of allyl alcohol **9** (Scheme 5). Formation of the latter remains unexplained. Due to its probable decomposition during the radical reaction, no trace of products deriving from sulfoxide **12** was detected.



Scheme 5

3. Conclusion

In summary, we have shown the efficiency of the sulfoxide-sulfenate rearrangement as alkoxyl radical precursor provider.

4. Experimental Section

THF was freshly distilled from K under N_2; CH_2Cl_2, and benzene were distilled from CaH_2 under N_2, and toluene from Na under N_2. Solvents for chromatography were distilled. Flash chromatography (FC) and filtration were performed with Baker silica gel (0.063-0.200 mm). TLC were run on Merck silica gel 60 F_{254} analytical plates; detection was carried out with either UV, iodine, spraying with solution of phosphomolybdic acid (25 g), $Ce(NH_4)_2(NO_3)_6{\cdot}4H_2O$ (10 g), concd H_2SO_4 (60 ml) and water (940 ml), or with a solution of $KMnO_4$ (3 g), K_2CO_3 (20 g), water (300 ml) and 5% NaOH (5 ml), with subsequent heating. Mps, not corrected, were determined on a Büchi-Tottoli apparatus. IR spectra were recorded on a Mattson Unicam 5000 spectrophotometer, in cm^{-1}. NMR spectra were recorded on a Varian Gemini 200 (^1H 200 MHz and ^{13}C 50.3 MHz), a Bruker AM 360 (^1H 360 MHz) or a Bruker Avance DRX-500 (^1H 500 MHz and ^{13}C 125.77 MHz); for ^1H δ are given in ppm relative to $CDCl_3$ (7.27 ppm), for ^1C δ are given in ppm relative to $CDCl_3$ (77.1 ppm), and coupling constant *J* are given in Hz. ^1H NMR splitting pattern abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR multiplicities were determined by the APT and DEPT sequences, abbreviations are: q, CH_3; t, CH_2; d, CH; s, quaternary carbons. Assignments were confirmed by NOE or NOESY, COSY and HETCOR experiments. MS spectra were recorded on a Vacuum Generator Micromass VG 70/70E DS 11-250; EI (70 eV), CI (CH_4 gas); *m/z* (%). Elemental analysis were performed by Ilse Beetz, Microanalytisches Laboratorium, D-96301 Kronach, Germany, and Ciba Geigy Mikrolabor, Marly, Switzerland.

Bicyclo[2.2.1]hept-5-en-2-ylidene-acetic acid ethyl ester (8). A solution of triethyl phosphonoacetate (16.7 ml, 83.2 mmol) in dry THF (40 ml) was added dropwise to a suspension of NaH (8.5 g, 194.2 mmol) in dry THF, (3 ml) at 0°C, under N_2. The mixture was stirred at room temperature for 30 min and cooled to –78°C. Then, norbornenone (**7**) (3 g, 27.7 mmol) dissolved in dry THF (10 ml) was added over 10 min. The resulting mixture was let warm gently. After 20 h, it was poured into cold

ether/aqueous saturated NH_4Cl (1:1, 200 ml) and the phases were separated. The organic layer was washed with water and the combined aqueous phases were extracted with Et_2O (3 x 100 ml). The combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. Flash chromatography (hexane and then hexane/AcOEt 9:1) afforded pure 2.8:1 *E*/*Z* mixture of isomers **8** (4.34 g, 88%) as a colorless oil. IR (film) 2982, 1711, 1184, 1040. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.29 (dd, *J* = 5.5 Hz, 2.9 Hz, 1 H, C*H*=CH, *E*-isom.), 6.25 (dd, *J* = 5.5 Hz, 2.6 Hz, 1 H, C*H*=CH, *Z*-isom.), 6.09 (ddd, *J* = 5.5 Hz, 3.3 Hz, 0.7 Hz, 1 H, CH=C*H*, *Z*-isom.), 6.02 (ddd, *J* = 5.5 Hz, 3.3 Hz, 0.7 Hz, 1 H, CH=C*H*, *E*-isom.), 5.93-5.91 (m, 1 H, C*H*CO_2Et, *E*-isom.), 5.69-5.67 (m, 1 H, C*H*CO_2Et, *Z*-isom.), 4.55-4.52 (m, 1 H, C*H*, *Z*-isom.), 4.18 (q, *J* = 7.0 Hz, 2 H, $CO_2CH_2CH_3$, *Z*-isom.), 4.14 (q, *J* = 7.0 Hz, 2 H, $CO_2CH_2CH_3$, *E*-isom.), 3.34-3.31 (m, 1 H, C*H*, *E*-isom.), 3.12-3.08 (s, 1 H, C*H*, *E*-isom.), 3.05-2.98 (m, 1 H, C*H*, *Z*-isom.), 2.64-2.57 (m, 1 H, C*H*H, *E*-isom.), 2.41-2.34 (m, 1 H, C*H*H, *Z*-isom.), 2.33 (ddd, *J* = 17.3 Hz, 3.7 Hz, 2.2 Hz, 1 H, CH*H*, *E*-isom.), 1.93 (ddd, *J* = 15.8 Hz, 3.7 Hz, 1.5 Hz, 1 H, CH*H*, *Z*-isom.), 1.78-1.73 (m, 1 H, C*H*H, *Z*-isom.), 1.72-1.67 (m, 1 H, C*H*H, *E*-isom.), 1.60-1.45 (m, 2 H, C*H*H, *Z*-isom., *E*-isom.), 1.30 (t, *J* = 7.0 Hz, 3 H, CH_3, *Z*-isom.), 1.27 (t, *J* = 7.0 Hz, 3 H, CH_3, *E*-isom.). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 166.84 (s, *E*-isom.), 166.21 (s, *Z*-isom.), 166.08 (s, *E*-isom.), 165.33 (s, *Z*-isom.), 139.21 (d, *E*-isom.), 138.57 (d, *Z*-isom.), 133.13 (d, *Z*-isom.), 132.44 (d, *E*-isom.), 111.28 (d, *Z*-isom.), 110.92 (d, *E*-isom.), 59.39 (t, *E*/*Z*-isom.), 52.28 (d, *E*-isom.), 50.69 (t, *E*-isom.), 50.18 (t, *Z*-isom.), 47.72 (d, *Z*-isom.), 41.73 (d, *E*-isom), 40.46 (d, *Z*-isom.), 36.23 (t, *Z*-isom.), 35.76 (t, *E*-isom.), 14.29 (q, *E*/*Z*-isom). CI-MS 179 (100, $[M+1]^+$), 178 (11, M^+), 151 (32), 133 (33), 105 (11). Anal. Calcd for $C_{11}H_{14}O_2$ (178.23): C, 74.13; H, 7.92; Found: C, 74.16; H, 7.94.

Bicyclo[2.2.1]hept-5-en-2-ylidene-ethanol (9). To a stirred solution of AlH_3 prepared *in situ* by the addition of $LiAlH_4$ (5.5 g, 146.1 mmol) to a solution of $AlCl_3$ (6.5 g, 48.7 mmol) in dry THF (40 ml) at 0°C, under N_2, was added a solution of ester **8** (4.3.g, 24.4 mmol) in dry THF (20 ml) with a syringe, within *ca*. 20 min, at 0°C. The mixture was stirred for further 1 h and quenched with MeOH (10 ml). Water was added and the

insoluble residues were filtered off. The aqueous layer was extracted with Et_2O (1 x 200 ml and 2 x 100 ml), the combined organic phases dried over $MgSO_4$ and the solvent evaporated. The resulting crude product was purified by flash chromatography (hexane/AcOEt 7:3) to yield pure E/Z-9 (2.82 g, 85%) as a slightly yellow oil. IR (film) 3343, 2978, 1450, 1063. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.16-6.11 (m, 2 H, C*H*=CH, *E*/*Z*-isom.), 6.05 (ddd, *J* = 5.5 Hz, 3.1 Hz, 0.6 Hz, 1 H, CH=C*H*, *E*-isom.), 6.01 (ddd, *J* = 5.5 Hz, 3.1 Hz, 0.6 Hz, 1 H, CH=C*H*, *Z*-isom.), 5.66-5.59 (m, 1 H, C*H*CH_2OH, *E*-isom.), 5.44 (t, *J* = 7.0 Hz, 1 H, C*H*CH_2OH, *Z*-isom.), 4.27-4.15 (m, 2 H, C*H*$_2$OH, *Z*-isom.), 4.06 (d, *J* = 7.0 Hz, 2 H, C*H*$_2$OH, *E*-isom.), 3.54-3.50 (m, 1 H, C*H*, *Z*-isom.), 3.18-3.15 (m, 1 H, C*H*, *E*-isom.), 3.00 (s, 1 H, C*H*, *E*-isom.), 2.97 (s, 1 H, C*H*, *Z*-isom.), 2.33-2.19 (m, 2 H, C*H*H, *E*/*Z*-isom.), 1.77 (ddd, *J* = 15.0 Hz, 2.1 Hz, 2.1 Hz, 2 H, C*H*H, *E*/*Z*-isom.), 1.66-1.61 (m, 1 H, CH*H*, *Z*-isom.), 1.61-1.56 (m, 1 H, C*H*H, *E*-isom.), 1.39 (d, *J* = 8.2 Hz, 2 H, CH*H*, *E*/*Z*-isom.), 1.35 (s, 2 H, O*H*, *E*/*Z*-isom.). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 145.57 (s, *Z*-isom.), 145.04 (s, *E*-isom.), 136.69 (d, *Z*-isom.), 136.39 (d, *E*-isom.), 133.91 (d, *E*-isom.), 133.38 (d, *Z*-isom.), 118.27 (d, *Z*-isom.), 117.86 (d, *E*-isom.), 60.89 (t, *E*-isom.), 60.10 (t, *Z*-isom.), 50.47 (d, *E*-isom.), 49.79 (t, *E*-isom.), 49.53 (t, *Z*-isom.), 45.17 (d, *Z*-isom.), 41.49 (d, *E*-isom.), 40.87 (d, *Z*-isom.), 33.66 (t, *Z*-isom.), 30.81 (t, *E*-isom.). CI-MS 136 (8, M^+), 119 (10), 118 (17), 91 (12). Anal. Calcd for $C_9H_{12}O$ (136.19): C, 79.37; H, 8.88; Found: C, 79.61; H, 8.66.

2-(1-Phenylthioethenyl)bicyclo[2.2.1]hept-5-ene (10). To a solution of alcohol **9** (2.32 g, 17.0 mmol) and some crystals of 2,2'-bipyridine in dry THF (40 ml) at –60°C, was added a *n*-BuLi solution (2.5 M in hexane) until the indicator changed color. The solution was stirred for some minutes, tosyl chloride (3.57 g, 18.7 mmol) in dry THF (15 ml) was added, the cooling bath was removed, ant the solution was allowed to warm to room temperature during 2.5 h. Meanwhile, a solution of lithium thiophenoxide was prepared in a separate flask by adding a solution of *n*-BuLi (2.5 M in hexane) to a solution of thiophenol (2.61 g, 25.6 mmol) and some crystals of 2,2'-bipyridine in THF (10 ml) at –60°C until the indicator turned red. The lithium thiophenoxide solution was then added at room temperature to the tosylate solution. The reaction mixture was stirred

for 2.5 h and poured into water. The aqueous layer was extracted with Et_2O (1 x 100 ml and 2 x 50 ml). The combined organic phases were washed with 1 M aqueous NaOH, dried over $MgSO_4$ and the solvent evaporated. The resulting crude product was purified by flash chromatography (hexane) to yield a nearly 1 : 1 mixture of pure *E*/*Z*-**10** and **11** (3.42 g, 88%) as a slightly yellow oil.

Data of compound*E*/*Z*-10. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.38-7.13 (m, 10 H, C*H*$_{arom}$, *E*/*Z*-isom.), 6.08-6.05 (m, 2 H, C*H*=CH, *E*/*Z*-isom.), 5.98 (dd, *J* = 5.4 Hz, 3.3 Hz, 1 H, CH=C*H*, *E*-isom.), 5.84 (dd, *J* = 5.4 Hz, 3.3 Hz, 1 H, CH=C*H*, *Z*-isom.), 5.52-5.47 (m, 1 H, C*H*CH_2SPh, *E*-isom.), 5.30-5.26 (m, 1 H, C*H*CH_2SPh, *Z*-isom.), 3.69-3.58 (m, 2 H, C*H*$_2$SPh, *Z*-isom.), 3.44 (d, *J* = 7.3 Hz, 2 H, C*H*$_2$SPh, *E*-isom.), 3.34 (m, 1 H, C*H*, *Z*-isom.), 3.12 (d, *J* = 1.5 Hz, 1 H, C*H*, *E*-isom.), 2.92 (s, 1 H, C*H*, *E*-isom.), 2.89 (s, 1 H, C*H*, *Z*-isom.), 2.25-1.21 (m, 8 H, C*H*$_2$, *E*/*Z*-isom.). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 145.95 (s, *E*-isom.), 145.69 (s, *Z*-isom.), 136.69 (d, *E*-isom.), 136.51 (s, *Z*-isom.), 136.48 (s, *E*-isom.), 136.32 (d, *Z*-isom.), 133.86 (d, *E*-isom.), 133.26 (d, *Z*-isom.), 130.19 (d, *E*/*Z*-isom.), 128.48 (d, *E*/*Z*-isom.), 125.91 (d, *E*/*Z*-isom.), 114.02 (d, *E*/*Z*-isom.), 50.50 (d, *E*-isom.), 49.89 (t, *E*-isom.), 49.45 (t, *Z*-isom.), 45.28 (d, *Z*-isom.), 41.48 (d, *E*-isom), 41.04 (d, *Z*-isom.), 34.21 (t, *E*-isom.), 33.73 (t, *Z*-isom.), 31.33 (t, *E*/*Z*-isom.).

Data of isolated compound 11. Colorless liquid. IR (film) 3061, 2994, 2940, 2866, 1632, 1479, 839, 737. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.13 (m, 5 H, C*H*$_{arom}$), 5.78 (ddd, *J* = 17.3 Hz, 10.6 Hz, 0.5 Hz, 1 H, C*H*=CH_2), 5.00 (dd, *J* = 17.3 Hz, 1.7 Hz, 1 H, CH=CH*H*$_{trans}$), 4.94 (dd, *J* = 10.6 Hz, 1.7 Hz, 1 H, CH=CH*H*$_{cis}$), 3.35 (dd, *J* = 1.4 Hz, 1.4 Hz, 1 H, C*H*SPh), 2.12 (m, 1 H, C*H*), 2.02-1.99 (m, 1 H, C*H*$_2$), 1.54-1.43 (m, 5 H, C*H*, C*H*$_2$). ^{13}C NMR ($CDCl_3$, 50.3 MHz) 138.03 (d), 136.52 (s), 130.12 (d), 128.79 (d), 126.04 (d), 111.15 (t), 53.17 (d), 36.04 (d), 34.49 (t), 31.15 (t), 24.96 (d), 20.58 (d). CI-MS 229 (81, $[M+1]^+$), 195 (42), 167 (90), 139 (72), 119 (100), 111 (36), 91 (20), 57 (12). Anal. Calcd for $C_{15}H_{16}S$ (228.35): C, 78.90; H, 7.06; Found: C, 78.95; H, 7.20.

2-(1-Phenylsulfinylethenyl)bicyclo[2.2.1]hept-5-ene (4). The 1:1 mixture of sulfides **10** and **11** (700 mg, 3.07 mmol) and *m*-chloroperbenzoic acid (756 mg, 3.07 mmol, 70%) in CH_2Cl_2 (10 ml) were stirred at –78°C for 5 h. Water (20 ml) and CH_2Cl_2 (20 ml) were

added and the phases were separated. The organic layer was washed with aqueous saturated $Na_2S_2O_4$ (15 ml), aqueous saturated $NaHCO_3$ (15 ml), and dried over $MgSO_4$. Evaporation of the solvent gave the crude sulfoxides which were purified by FC (hexane/AcOEt 6:4) to afford unseparable mixture of four diastereoisomeric sulfoxides **4** and two diastereoisomeric sulfoxides **12** (652 mg, 87%), as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.7-7.42 (m, 30 H, C*H*$_{arom}$), 6.08 (dd, *J* = 5.5 Hz, 2.8 Hz, 1 H, C*H*=CH, **4**), 6.05 (dd, *J* = 5.5 Hz, 3.1 Hz, 1 H, CH=C*H*, **4**), 6.04-6.00 (m, 2 H, C*H*=CH, **4**), 5.96-5.93 (m, 2 H, CH=C*H*, **4**), 5.81-5.78 (m, 1 H, C*H*=CH, **4**), 5.78 (dd, *J* = 17.4 Hz, 10.7 Hz, 1 H, CH=C*H*$_2$, **12**), 5.69 (dd, *J* = 5.7 Hz, 3.2 Hz, 1 H, CH=C*H*, **4**), 5.62 (dd, *J* = 17.1 Hz, 10.4 Hz, 1 H, CH=C*H*$_2$, **12**), 5.38-5.27 (m, 2 H, C*H*=CH$_2$SOPh, **4**), 5.10-4.97 (m, 2 H, C*H*=CH$_2$SOPh, **4**), 4.97 (ddd, *J* = 17.4 Hz, 6.1 Hz, 1.5 Hz, 1 H, CH=CH*H*$_{trans}$, **12**), 4.98 (dd, *J* = 17.4 Hz, 1.5 Hz, 1 H, CH=CH*H*$_{trans}$, **12**), 4.96 (dd, *J* = 17.1 Hz, 1.5 Hz, 1 H, CH=CH*H*$_{trans}$, **12**), 4.94 (dd, *J* = 10.7 Hz, 1.5 Hz, 1 H, CH=CH*H*$_{cis}$, **12**), 4.90 (dd, *J* = 10.4 Hz, 1.5 Hz, 1 H, CH=CH*H*$_{cis}$, **12**), 3.80-0.80 (m, 40 H, C*H*, C*H*$_2$, **4**, **12**).

***cis*-Bicyclo[4.3.0]non-7-en-3-one (6).** A degassed solution of radical precursor **4** and by-product **12** (200mg, 0.818 mmol) in toluene (16 ml) was heated to reflux under an inert atmosphere, and treated dropwise (syringe pump) addition over 24 h with a solution of Bu_3SnH (0.65 ml, 2.46 mmol) and 2,2'-azobis(isobutyronitrile) (AIBN; 16 mg, 0.10 mmol) in toluene (2 ml). The solution was then cooled to rt, treated with KF (500 mg, 8.61 mmol) for 12 h and the solvent was evaporated. The residue was dissolved in hexane (5 ml) and filtered on FC (hexane 150 ml and then AcOEt 100 ml). The AcOEt-containing fraction was evaporated and purified by FC (Hexane/AcOEt 8:2) to afford bicycle **6** (26 mg, about 46% from **4**) along with allyl alcohol **9** (12 mg, about 22% from **4**).

Data of compound 6. IR (film) 3416, 2930, 1711, 756. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.77-5.73 (m, 1 H, C(8)-*H*), 5.60-5.56 (m, 1 H, C(7)-*H*), 3.10-3.00 (m, 1 H, C(6)-*H*), 2.83-2.75 (m, 1 H, C(1)-*H*), 2.72-2.64 (m, 1 H, C(9)-*H*$_{exo}$), 2.48 (dd, *J* = 15.4 Hz, 6.1 Hz, 1 H, C(2)-*H*$_{exo}$), 2.32 (dd, *J* = 15.4 Hz, 6.9 Hz, 1 H, C(2)-*H*$_{endo}$), 2.25 (dd, *J* = 5.5 Hz, 1.8 Hz, 1 H, C(4)-*H*$_{endo}$), 2.23 (d, *J* = 5.5 Hz, 1 H, C(4)-*H*$_{exo}$), 2.08-1.95 (m, 2 H, C(5)-*H*$_{exo}$,

C(9)-H_{endo}), 1.76-1.69 (m, 1 H, C(5)-H_{endo}). ^{13}C NMR ($CDCl_3$, 122.77 MHz) 213.91 (s), 133.31 (d), 130.32 (d), 43.57 (t), 42.99 (d), 40.32 (t), 37.07 (t), 33.66 (d), 25.44 (t). CI-MS 137 (19, $[M+1]^+$), 135 (95), 107 (19), 95 (16). *Exact Mass* Calcd for $C_9H_{12}O$ (136.19): 137.0960904; Found: 137.0960060.

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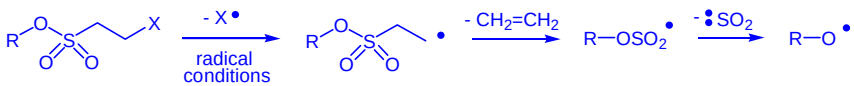
2-(Phenylselenyl)ethylsulfonate : A New Precursor of Alkoxyl Radicals

1. Introduction

As a quite young field of chemistry, radical chemistry has remarkably developed over the past decades. From carbon-centered radical processes[1-4] to nitrogen-[5] and oxygen-centered[6-8] reactions, it has quickly become an unavoidable tool of synthetic organic chemistry. However, the utility of this methodology remains limited to the availability of the suitable radical precursor for the generation of the wanted radical species.

As part of our ongoing research of new alkoxyl radical precursors, we came to the idea of decomposing vinyl sulfonate derivatives to induce formation of alkoxyl radicals. Although the S-O bond of benzenesulfenate derivatives is known to undergo homolytical cleavage under a variety of conditions,[9-12] to our knowledge, nobody has reported so far the use of sulfonates as alkoxyl radical precursors. Thus, we devised that, when treated in adequate radical conditions, radical precursor of type **1**, obtained from the corresponding alcohol, should form carbon-centered radical **2**, which, upon sequential elimination of ethylene and sulfur dioxide, would generate alkoxyl radical **3** (Scheme 1). If simply reduced, this would give back the starting alcohol.



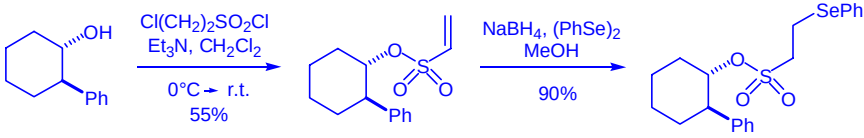
1 **2** **3**

Scheme 1

2. Results and discussion

In order to test the viability of our approach, we synthesized radical precursor **6** from *trans*-2-phenylcyclohexanol (**4**) in two steps and 50% non-optimized yield (Scheme 2). Treatment of alcohol **4** with 2-chloroethanesulfonyl chloride and triethylamine in

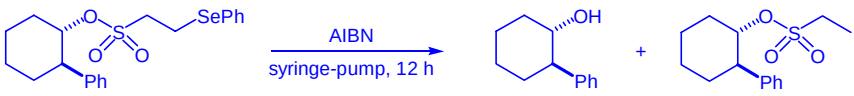
dichloromethane following King's procedure[13] afforded phenylcyclohexyl ethenesulfonate (**5**) in 55% yield. Then, attempts to brominate the olefin with refluxing bromohydric acid, as well as hydroboration and bromination of the double bond with bromine[14] failed. Consequently, we decided to prepare selenylated derivative **6** by adding **5** to a solution of diphenyldiselenium and sodium borohydride in methanol. Phenylselenylethansulfonate **6** was thus obtained in 90% yield (Scheme 2).



4 **5** **6**

Scheme 2

Radical reactions of **6** were initiated by 2,2'-azobis(isobutyronitrile) (AIBN). Syringe-pump addition of tributyltin hydride and catalytic AIBN over 12 h to a 0.1 M solution of radical precursor **6** in refluxing benzene was tested first. However, these conditions resulted in formation of direct reduction product **7** in 30% yield and in partial recovery (5% yield) of starting material **6**. Only traces of the expected alcohol **4**, which could be the consequence of hydrolysis of **6** as well as of its radical reaction, were detected in NMR spectrum of the crude. Consequently, the reaction was next tested in refluxing toluene, with syringe-pump addition of a poorer hydrogen donor, tris(trimethylsilyl)silane[15] and AIBN over 12 h, affording then a 26% yield of **4** and radical precursor **6** in 27% yield (Scheme 3).



6 **4** **7**

Bu_3SnH	(1.1 equiv.)	refluxing benzene	traces	30%
$(TMS)_3SiH$	(1.5 equiv.)	refluxing toluene	26%	-

Scheme 3

This experiment constituted an encouraging result in favor of a radical pathway for the reaction.

3. Conclusion

In summary, alkyl phenylselenylethanesulfonates, which are easily obtained from the parent alcohol, offer a potential as alkoxyl radical precursors.

4. Experimental Section

***trans*-2-Phenylcyclohexyl ethenesulfonate (5).** To a solution of alcohol **4** (500 mg, 2.84 mmol) in CH_2Cl_2 (5 ml) under N_2, was added 2-chloroethanesulfonyl chloride. The mixture was cooled in an ice bath before dropwise addition of ice-cold triethylamine (1.19 ml, 8.52 mmol). The resulting suspension was stirred for 1 h and let warm to r.t. overnight. The reaction was worked up by washing with cold 10% aqueous Na_2CO_3 (3 x 5 ml), and water (5 ml). Drying of the organic layer with $MgSO_4$, and evaporation of the solvent afforded the crude **5**. FC (hexane/AcOEt 8:2) purification gave **5** (418 mg, 55%) as a white solid. Mp 102.5°C. ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 7.32-7.17 (*m*, 5 H, C*H*$_{arom.}$), 5.96 (*d*, *J* = 16.5 Hz, 1 H, CH*H*$_{trans}$=CH), 5.49 (*d*, *J* = 10.0 Hz, 1 H, CH*H*$_{cis}$=CH), 5.24 (*dd*, *J* = 16.5 Hz, 10.0 Hz, 1 H, CH_2=C*H*), 4.40 (*ddd*, *J* = 10.7 Hz, 10.7 Hz, 4.7 Hz, 1 H, C*H*OSO$_2$CH=CH$_2$), 2.69 (*ddd*, *J* = 14.4 Hz, 10.7 Hz, 3.8 Hz, 1 H, C*H*Ph), 2.50-2.42 (*m*, 1 H, CH*H*), 2.08-2.35 (*m*, 7 H, CH_2). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 142.07 (t), 132.49 (d), 128.42 (d), 128.29 (d), 127.61 (s), 127.06 (d), 86.87 (d), 49.83 (d), 34.24 (t), 32.83 (t), 25.31 (t), 24.85 (t).

***trans*-2'-Phenylcyclohexyl-2-(phenylselenyl)ethylsulfonate (6).** Sodium borohydride (34 mg, 0.900 mmol) was added to a solution of diphenyldiselenide (117 mg, 0.375 mmol) in methanol (2 ml) at 0°C. Vinylsulfonate **5** (200 mg, 0.751 mmol) was then added and the reaction mixture was stirred for 5.5 h at r.t. The solution was concentrated *in vacuo*. The residue was dissolved in ether, washed with aqueous saturated $NaHCO_3$

and brine, dried with $MgSO_4$, and the solvent evaporated. FC (hexane, 3% Et_2O) of the crude afforded **6** (286 mg, 90%) as a yellow solid. . ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 7.38-7.20 (*m*, 5 H, C*H*$_{arom.}$), 4.60 (*ddd*, *J* = 11.0 Hz, 11.0 Hz, 4.5 Hz, 1 H, C*H*OSO$_2$(CH$_2$)$_2$SePh), 2.73-1.30 (*m*, 9 H, C*H*, C*H*$_2$). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 142.32 (s), 132.98 (d), 129.25 (d), 128.66 (d), 127.95 (s), 127.63 (d), 127.32 (d), 86.62 (d), 51.53 (t), 49.96 (d), 34.46 (t), 33.49 (t), 25.23 (t), 24.71 (t), 17.92 (t).

General procedure (GP). Radical reactions. A degassed solution of radical precursor **6** (0.314 mmol) in solvent was heated to reflux under an inert atmosphere, treated by dropwise (syringe pump) addition over 12 h with a solution of reductor and 2,2'-azobis(isobutyronitrile) (AIBN; 8 mg, 0.05 mmol) in solvent and kept under reflux for 6 additional hours. The solution was cooled to r.t., treated with KF (167 mg, 2.87 mmol) for 24 h and the solvent was evaporated. The residue was dissolved in hexane (2 ml) and filtered on FC (hexane 50 ml and then AcOEt 30 ml). The AcOEt-containing fraction was evaporated and purified by FC (Hexane/AcOEt 95:5 to 9:1).

***trans*-2-Phenylcyclohexyl ethanesulfonate (7).** According to GP. From **6** (133 mg, 0.314 mmol) in benzene (3 ml), and Bu_3SnH (0.092 ml, 0.346 mmol) and AIBN (8 mg, 0.05 mmol) in benzene (3 ml) added dropwise. FC gave some remaining starting material **6** (6 mg, 5%), along with direct reduction compound **7** (25 mg, 30%) as a white solid. ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 7.34-7.22 (*m*, 5 H, C*H*$_{arom.}$), 4.62 (*ddd*, 1 H, C*H*OSO$_2$CHCH$_2$), 2.74 (*ddd*, 1 H, C*H*Ph), 2.45-2.38 (*m*, 1 H, CH*H*), 2.41 (*dq*, 1 H, C*H*HCH$_3$), 2.22 (*dq*, 1 H, CH*H*CH$_3$), 1.98-1.31 (*m*, 7 H, C*H*$_2$), 0.82 (*t*, 3 H, C*H*$_3$).

***trans*-2-Phenylcyclohexanol (4).** According to GP. From **6** (97 mg, 0.230 mmol) in benzene (4.6 ml), and $(TMS)_3SiH$ (0.11 ml, 0.344 mmol) and AIBN (6 mg, 0.04 mmol) in benzene (4.6 ml) added dropwise. FC gave some remaining starting material **6** (25 mg, 27%), along with alcohol **4** (9 mg, 26%) as a white solid. ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 7.38-7.20 (*m*, 5 H, C*H*$_{arom.}$), 3.71-3.60 (*m*, 1 H, C*H*OH), 2.48-2.37 (*m*, 1 H, C*H*Ph),

2.17-1.27 (*m*, 9 H, C*H*$_2$, O*H*). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 143.71 (d), 128.77 (d), 128.12 (s), 126.83 (d), 74.29 (d), 53.18 (d), 34.43 (t), 33.41 (t), 26.06 (t) 25.11 (t).

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