S_N2' and "S_N2' Like" Ring Openings of Oxa-n-Cyclo Systems

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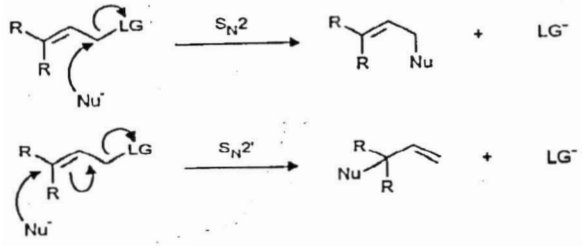
The scope and limitations of reactions involving attack of nucleophiles and reagents at the double bond of oxa-n-cyclo systems, that result in migration of the double bond and opening of the oxa-bridge, are reviewed.

1. Introduction

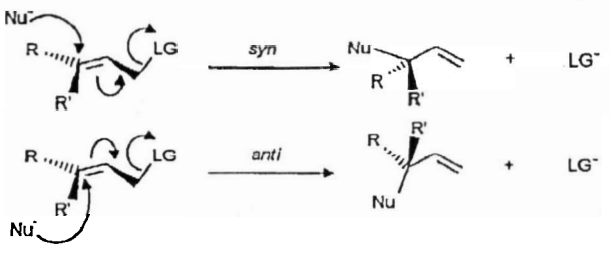
1.1. The S_N2' Reaction

The substitution of a nucleophile for a leaving group is a fundamental transformation in organic chemistry. When the leaving group is allylic, two possible modes of bimolecular nucleophilic substitution may operate (Scheme 1). Nucleophilic attack may occur at the carbon atom bearing the leaving group, in an S_N2 reaction, without a change in the position of the double bond. Alternatively, the nucleophile may react at the alkene carbon atom distal to the leaving group, causing a concomitant shifting of the double bond to displace the leaving group in an S_N2' reaction.[1] Ever since the S_N2' mechanism was first proposed independently by three groups in the late 1930s,[2–4] there has been debate over whether the reaction is truly concerted[5,6] or occurs in a stepwise fashion.[7,8]



Scheme 1

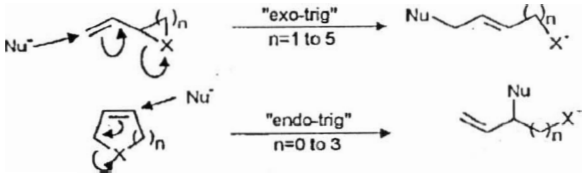
Regardless of the concertedness of the reaction, the S_N2' reaction often shows high selectivity for attack *syn* to the leaving group, although *anti* attack has also been observed (Scheme 2).[9] Stereoelectronic effects have been used to rationalize the preference for *syn* attack.[9]



Scheme 2

1.2. S_N2' Ring-Opening Reactions

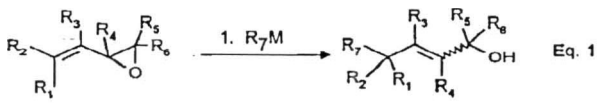
When the leaving group forms part of a cyclic structure, an S_N2' displacement of the leaving group results in the cleavage of the ring. In addition, the leaving group remains tethered to the molecule, providing another functional group and therefore another site at which further transformations can take place. This type of S_N2' ring opening can be considered to be the reverse of an *exo*-trig ring closure, or the reverse of an *endo*-trig ring closure (Scheme 3).



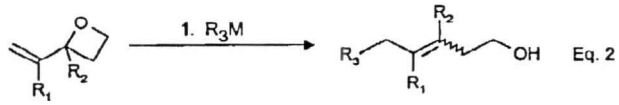
Scheme 3

Since *exo*-trig ring closures are predicted to be favorable for three- to seven-membered rings based on Baldwin's rules,[10] the reverse reaction, the ring opening, should also be favorable. The most well known example of this

type of ring opening, illustrated in Scheme 4, equation 1, is the S_N2' ring opening of vinylic epoxides by organocuprate reagents to produce allylic alcohols. Hundreds of examples of this reaction, employing a variety of vinylic epoxides and organocuprate reagents, have been reported in the literature.[11] Other examples of *exo*-trig ring openings include the S_N2' ring openings of vinylic oxetanes[12] (Scheme 4, eq. 2), and chiral allylic cyclic acetals[13] (Scheme 4, eq. 3).

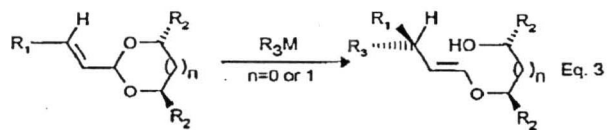


R_7M = organocuprate or organolithium + catalytic Cu(I)



R_1, R_2=H or Me

R_3M=organocuprate, organolithium, or Grignard reagent + catalytic Cu(I)



R_1= Me or Pr, R_2 = Me or Ph

R_3M = phenyl or alkenyl copper, BF_3, and Me_2S or PBu_3; or organolithium

Scheme 4

Conversely, Baldwin's rules predict that *endo*-trig ring closures are disfavored for three- to five-membered rings, so that S_N2' ring openings which are the reverse of *endo*-trig closures should also be disfavored for these sizes of rings. As a result, these types of ring openings have mainly been applied to strained bicyclic systems, where strain forces the molecules to adopt conformations which allow for some overlap between the π orbitals of the double bond and the C–X antibonding orbital, so that Baldwin's rules may be "violated."[14] An interaction between the alkene *p* orbitals and the σ orbitals of the monatomic bridges in norbornene systems has also been proposed,[15] and implies some overlap of the *p* orbitals with the antibonding σ^* orbital as well due to the geometric relationship between the σ and σ^* orbitals. The first example of an *endo*-trig S_N2' ring-opening reaction was reported in 1971 by Caple and co-workers.[16] Although a few more examples were reported in 1974 by the group of Berchtold,[17] for almost two decades the reactivity of oxabicyclic compounds towards nucleophilic ring opening remained largely unexplored. In the past six years, however, a plethora of papers describing S_N2' ring openings on other oxabicyclic ring systems have appeared in the literature. Thus, a review on this subject matter is timely. This paper will review *endo*-trig S_N2' ring openings of oxa-n-cyclic systems, classified according to the type of system in which the ring opening occurs. Some reactions, that result in an opening of the oxa bridge with double bond migration, may not be formally classified as S_N2' ring openings since they may occur in a stepwise rather than a concerted fashion. These "S_N2' like" reactions will

Biographical Sketches

Brian A. Keay, born 1955, received his Ph.D. degree in 1983 from the University of Waterloo (Canada) working with Prof. R. Rodrigo. After an NSERC postdoctoral fellowship with Prof. E. Piers (University of British Columbia, Canada), he joined the faculty at the University of Windsor (Canada) as an assistant professor. In 1989, he moved to the University of Calgary (Canada) where he is now a professor. He is the Canadian Society for Chemistry 1996 recipient of the Merck Frosst Centre for Therapeutic Research Lecture Award. His research interests include the design of asymmetric ligands for use with Lewis acids and palladium catalysts, palladium-catalyzed reactions, intramolecular Diels–Alder reactions, the application of high pressure (2 GPa) to organic reactions, and the synthesis of natural products.

Simon Woo, born 1968, received his B.Sc. in 1990 at the University of Calgary (Canada). He then joined Prof. B.A. Keay's group and completed his Ph.D. degree in 1995 studying S_N2' ring-opening reactions of oxatricyclo systems and its application to the synthesis of the C_{15}–C_{23} segment of venturicidin A. In January 1996, he joined Prof. A.G. Fallis' group at the University of Ottawa (Canada) on a NSERC postdoctoral fellowship.

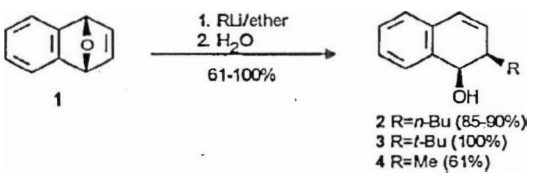
also be included where appropriate. Symmetrical oxa-n-cyclic systems will be considered first, including asymmetric examples, followed by unsymmetrical systems.

2. Ring-Opening Reactions

2.1. Symmetrical Systems

2.1.1. 1,4-Epoxy-1,4-dihydronaphthalene Systems

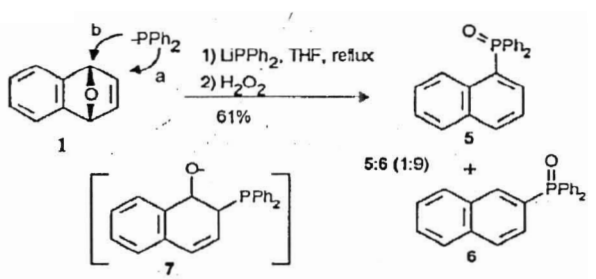
The first example of an *endo*-trig S_N2' ring-opening reaction was reported in 1971 by the group of Caple.[16] Butyllithium and *tert*-butyllithium were observed to add to 1,4-epoxy-1,4-dihydronaphthalene (**1**) from the *exo* face to give the *cis*-alcohols **2** and **3**, respectively (Scheme 5). Several years later, Berchtold and his collaborators[17] reported that alcohol **4** was produced when **1** was treated with methyllithium as part of a larger study of the reactivity of nucleophiles with arene oxides.



Scheme 5

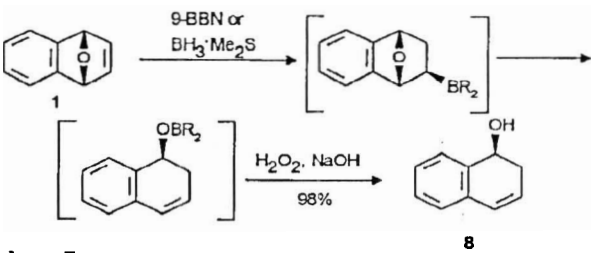
2-*tert*-Butyl-1,2-dihydro-1-naphthol (3):[16]
1,4-Epoxy-1,4-dihydronaphthalene (**1**, 0.250 g, 1.74 mmol) and dry Et_2O (50 mL) were placed in a reaction flask under N_2. *t*-BuLi (3.0 mL, 6.0 mmol) was added and the solution stirred for 1 h at r.t. Water (25 mL) was added to destroy the excess *t*-BuLi and the Et_2O layer was removed and dried. An almost quantitative yield of essentially pure compound **3** was obtained. This material was sublimed twice at 50°C/0.2 Torr to yield crystalline **3**; mp 75–76°C.

Walker and co-workers[18] treated compound **1** with lithium diphenylphosphide to provide after oxidative workup a 1:9 mixture of naphthalenes **5** and **6** in 61% yield (Scheme 6). The formation of **6** was postulated to occur through intermediate **7** by S_N2' attack (path a) at the double bond by the diphenylphosphide anion. Compound **7** presumably dehydrates under the reflux conditions and is oxidized to the λ^5-phosphane oxide when treated with hydrogen peroxide. The formation of **5** was postulated to occur via a direct S_N2 attack (path b) at the bridgehead, followed by a 1,4-dehydration and subsequent oxidation.



Scheme 6

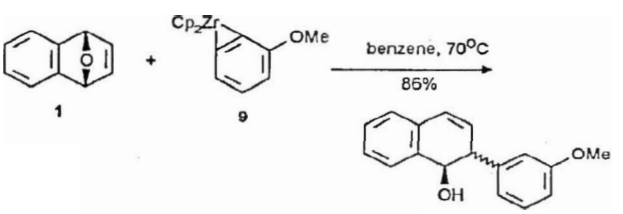
Lewis acidic hydride sources have also been used successfully for reductive ring openings. Brown and Prasad[19] first reported this type of ring opening occurring with compound **1** upon treatment with either borane–dimethyl sulfide complex or 9-BBN (Scheme 7). The reaction was believed to proceed through hydroboration of the double bond followed by *syn* elimination to give **8** after oxidative workup in 98% yield. Bulkier hydroborating agents, such as dicyclohexylborane or disiamylborane, did not produce any ring-opened products. The greater steric demand of the bulkier alkyl groups was believed to interfere with the coordination of the boron atom with the bridging oxygen atom, thereby hindering the elimination step.



Scheme 7

1,2-Dihydro-1-naphthol (8):[19]
In a 25-mL flask equipped with a septum inlet, magnetic stirring bar, and connecting tube leading to a mercury bubbler was placed compound **1** (1.44 g, 10 mmol) and THF (4.2 mL). Tridecane (0.37 g, 2 mmol) was added (internal standard), followed by the dropwise addition of 8.98 M $BH_3 \cdot Me_2S$ (0.37 mL, 3.3 mmol). The reaction was followed by ^{11}B NMR. After 15 min, the reaction mixture was cooled to 0°C and oxidized by adding 3 N NaOH (10 mL) and H_2O_2 (3.8 mL). After stirring at r.t. for 5 h, the aqueous phase was saturated with anhydr. K_2CO_3 and the organic layer was concentrated by removal of the THF. The residue was extracted into Et_2O (20 mL) and the Et_2O was washed with water (2 × 20 mL), dried ($MgSO_4$) and the solvent removed to leave compound **8**; yield: 98% (by GC).

Cuny and Buchwald[20] have shown that compound **1** when treated with the zirconocene-3-methoxybenzene **9**, formed in situ by treating 2-lithio-1-methoxybenzene with $Cp_2Zr(Me)Cl$, provided a 2:1 mixture of *trans*- and *cis*-products **10** in 86% yield (Scheme 8). A variety of cyclic allylic ethers underwent this reaction in yields ranging from 30–86%.

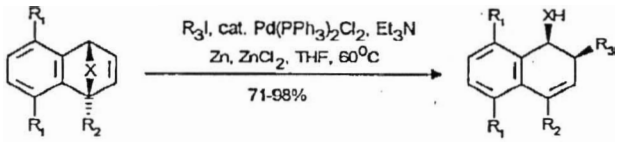


Scheme 8

2-(3-Methoxyphenyl)-1,2-dihydro-1-naphthol (10):[20]
To a solution of 2-bromoanisole (0.393 g, 2.10 mmol) in THF (10 mL) at −78°C was added 1.64 M *n*-BuLi in hexane (1.43 mL, 2.20 mmol). After 30 min, this mixture was added to a cooled so-

lution of $Cp_2Zr(Mc)Cl$ (0.653 g, 2.40 mmol) in THF (20 mL) at −78 °C, and the resulting solution stirred for 15 min before being warmed to r.t. The THF was removed in vacuo, and the residue was redissolved in benzene (10 mL). This mixture was cannula-filtered into a sealable tube, and then compound **1** (2.00 mmol) was added. The reaction mixture was maintained at 70 °C for 18 h. The solution was cooled to r.t., and MeOH (1 mL) was added and the resulting solution stirred for 30 min. The mixture was concentrated, and the residue extracted several times with Et_2O. The Et_2O layers were combined, washed with brine and water, dried ($MgSO_4$) and evaporated. Purification by radial plane chromatography (Chromatotron, 4-mm silica plate, hexane/Et_2O) gave compound **10** as a yellow oil; yield: 86%.

A Heck-type[21] palladium-catalyzed coupling reaction has been used by Duan and Cheng[22,23] to prepare ring-opened products. Compounds **1**, **11**, and **12** formed **13** to **15**, respectively, in yields of 71 to 98% when treated with a palladium catalyst and a variety of aryl and vinyl iodides (Scheme 9). No reaction was observed in the absence of palladium, while the omission of the zinc, zinc chloride, or triethylamine led to diminished yields. The reaction was believed to proceed via insertion of palladium into the C—I bond, carbopalladation of the alkene, palladium-heteroatom β-elimination, and finally protonation to provide the product. Reduction of the palladium(II) by zinc metal was proposed as the final step of the catalytic cycle.



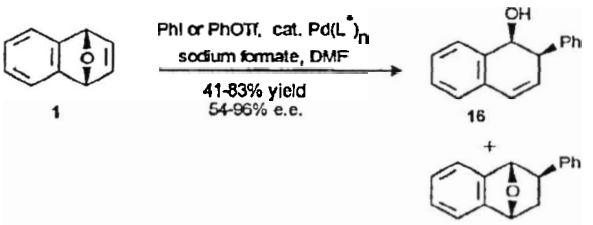
1 R_1=R_2=H, X=O — 13
11 R_1=OMe, R_2=H, X=O — 14
12 R_1=R_2=H, X=NCO_2Me — 15

Scheme 9

2-(4-Tolyl)-1,2-dihydro-1-naphthol (13, R_3 = 4-Tolyl); Typical Procedure:[23]

To a mixture of $Pd(PPh_3)_2Cl_2$ (0.025 mmol), zinc powder (0.327 g, 5.0 mmol), and toluene (10 mL) was added 4-iodotoluene (0.50 mmol), compound **1** (0.50 mmol), and Et_3N (5.00 mmol). The system was heated under N_2 with stirring at 100 °C for 9 h. Upon completion of the reaction, the solution was filtered through Celite. The filtrate was concentrated and separated on a silica gel column (EtOAc/hexane) to give **13**; yield: 85%.

Moinet and Fiaud[24] have recently accomplished an enantioselective palladium-catalyzed ring opening of compound **1** (Scheme 10). When **1** was treated with phenyl iodide or phenyl triflate in the presence of a palladium catalyst and a chiral phosphane ligand [(*R* or *S*)-BINAP, (*S*,*S*)-BDPP, (*S*,*S*)-Chiraphos or (*R*,*R*)-Norphos], a mixture of the ring-opened product **16** and the nonopened product **17** was obtained. The ratio of products showed a dependence on both the phenyl species (iodide or triflate) and the ligand used, with higher steric crowding around the palladium favoring the formation of **16**. Higher e.e.'s were generally observed with phenyl triflate than with phenyl iodide under the same conditions. Of the chiral ligands used, (*R*)-BINAP was the most effective at inducing asymmetry, giving a 15:85 ratio of **16**/**17** in a combined yield of 83% with e.e.'s of 96% [favoring the (+)-enantiomer] and 64%, respectively, when used with phenyl triflate. The inefficiency of the ring-opening reaction was surmounted by the addition of a Lewis acid; however, the e.e.'s were diminished. For example, the addition of zinc chloride to the reaction with phenyl triflate employing (*S*)-BINAP as the chiral ligand formed **16** exclusively in 41% yield and 54% e.e. [favoring the (−)-enantiomer].



1 — 16 + 17

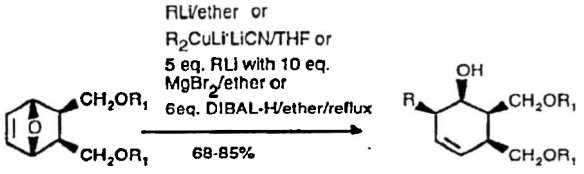
Scheme 10

2.1.2. 7-Oxabicyclo[2.2.1] Systems

The group of Lautens has reported[25] that compound **18** underwent an S_N2' ring-opening reaction with organometallic reagents to produce compounds **19**–**21** (Scheme 11). The compound failed to react with primary (R = Me or *n*-Bu) mixed organocyanocuprates, even in the presence of boron trifluoride–diethyl ether complex, while secondary and tertiary organocuprate reagents were capable of effecting the ring opening. On the other hand, when **18** was treated with butyllithium, compound **19** was produced in good yield, while *tert*-butyllithium gave a complex mixture of products. Attack of the nucleophile occurred *syn* to the bridging oxygen atom in each case, and was proposed to be due to either complexation of the organometallic reagent with the bridging oxygen atom or simply attack of the reagent on the less hindered *exo* face of the bicyclic framework. The replacement of the TBDMS ether with either a benzyl or *p*-methoxybenzyl ether protecting group led to lower yields along with recovered starting material. This problem was attributed to competitive coordination of the organometallic reagent with the ether oxygens when the less sterically hindered protecting groups were used.

Some non-carbon nucleophiles were also found to be capable of causing the ring-opening reactions to occur. Although lithium aluminum hydride was ineffective for delivering a hydride nucleophile to effect the S_N2' ring opening for compound **18**, a reductive ring opening was observed by Lautens and Chiu[26] when **18** was treated with excess magnesium bromide–diethyl ether and an organolithium reagent (*n*-BuLi or *t*-BuLi) containing β-hydrogens to give compound **22** (Scheme 11). The reduction showed a solvent effect as the rate of reaction was faster in diethyl ether than in toluene, while no reduction was observed when THF was used. The reaction was faster when *tert*-butyllithium was used, possibly due

to an increase in the number of β-hydrogens, but the reaction was still generally slow, requiring 48–96 hours to reach completion.



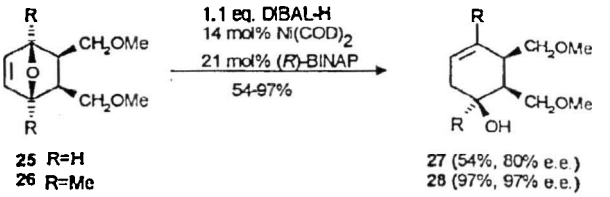
Scheme 11

More recently, Lautens and co-workers[27] have reported that DIBAL-H could be used instead of the above RLi/$MgBr_2$ method for hydride transfer. Compound **23** produced the diprotected triol **24** in 80% yield upon treatment with excess DIBAL-H in refluxing diethyl ether for 16 hours (Scheme 11). However, larger amounts of DIBAL-H or prolonged reaction times resulted in the reduction of the double bond in **24** as well to form the corresponding saturated diprotected triol. These reactions are believed to proceed in an analogous manner to the borane reactions, through hydroalumination of the double bond followed by a *syn* elimination.

all-*cis*-2-Butyl-5,6-bis(*tert*-butyldimethylsilyloxymethyl)cyclohex-3-enol (19);[25] Typical Procedure:
CuCN (2.5 mmol) was dried with a hot-gun under vacuum for 5 min before suspending the solid in THF. The flask was cooled to −78°C and *n*-BuLi (4.9 mmol) was added dropwise over 2–5 min. Upon completion of the addition, the cuprate solution was warmed to 0°C and stirred 1 h. Compound **18** (1 mmol) was dissolved in THF and added dropwise to the cuprate via cannula over 5–10 min followed by warming the reaction to r.t. where it was stirred until TLC indicated the starting material was consumed. NH_4Cl was added and the mixture exposed to air. Filtration of the solids through Celite/silica gel gave a clear solution which was worked up and purified using standard techniques to provide **19**; yield: 73%.

all-*cis*-5,6-Bis(benzyloxymethyl)cyclohex-3-enol (24):[27]
Compound **23** was dissolved in anhydr. hexanes to make a 0.1 M solution and the solution was cooled to 0°C. DIBAL-H (6 equiv) was added dropwise with stirring and the mixture was heated to reflux until TLC indicated the starting material had been consumed. When the reaction was complete, the solution was diluted with Et_2O, cooled to 0°C and quenched with sat. NH_4Cl. The resulting white gel was dissolved by adding 10% H_2SO_4 dropwise. The organic layer was separated and the aqueous layer extracted with EtOAc (3 to 5 times). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (silica gel) provided **24**; yield: 80%.

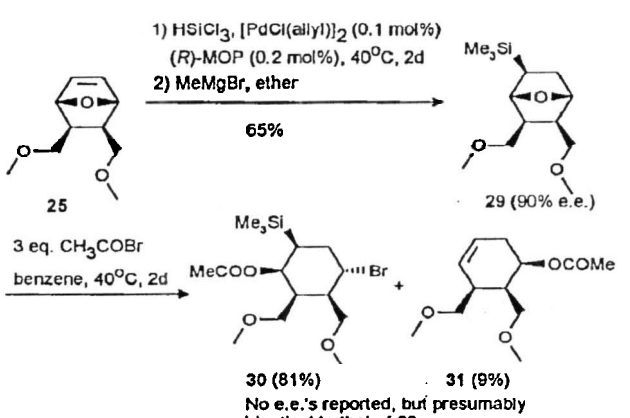
The addition of a nickel compound to the above reaction with DIBAL-H has been found to catalyze the hydroalumination reaction.[28] In the presence of a chiral phosphane ligand, an asymmetric reductive ring opening has been accomplished.[29] Compounds **25** and **26** produced compounds **27** and **28** with e.e.'s of 80% and 97%, respectively, upon treatment with DIBAL-H and catalytic quantities of $Ni(COD)_2$ and (*R*)-BINAP (Scheme 12). The e.e. was dependent on the rate of addition of DIBAL-H and on the (*R*)-BINAP/$Ni(COD)_2$ ratio.



Scheme 12

all-*cis*-5,6-Bis(methoxymethyl)-1,4-dimethylcyclohex-3-enol (28):[29]
$Ni(COD)_2$ (0.033 mmol) was transferred to a dry round-bottomed flask in a glove box. Compound **26** (0.237 mmol) and (*R*)-BINAP (0.049 mmol) were combined in a round-bottomed flask equipped with a stir bar, and N_2 was blown over the mixture. Toluene (1 mL, freshly distilled over sodium metal) was added to the $Ni(COD)_2$ and the solution was transferred to the flask containing compound **26** and (*R*)-BINAP via cannula. The dark burgundy red solution was stirred at r.t. for 30 min under a positive N_2 pressure. 1.0 M in hexanes (DIBAL-H, 0.260 mmol) was added via syringe pump over 1 h. After the addition was complete, TLC indicated complete consumption of starting material and conversion to product. 1.1 M aq Rochelle's salt solution (1.5 mL) was added at 0°C to quench the reaction which was then stirred for 3 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×). The turbid aqueous layer was acidified with 10% H_2SO_4 until the solution cleared, and was then extracted with more EtOAc (2×). The organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (silica gel) provided **28**; yield: 97%; 97% e.e. (GC analysis on a Chiraldex GTA column, Advanced Separation Technologies).

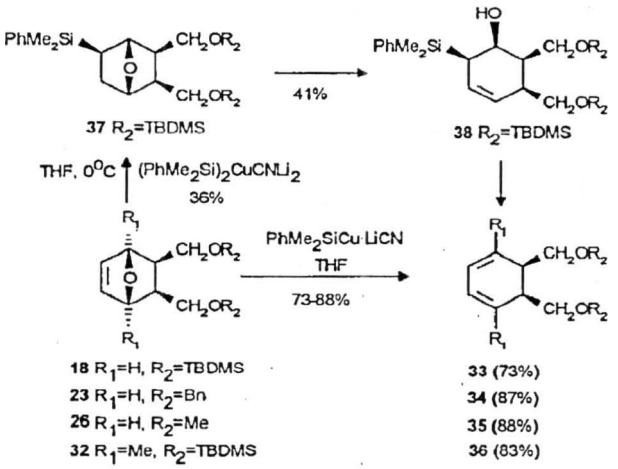
The group of Hayashi[30] has developed a three-step procedure for converting **25** into **31**, albeit in poor yield (Scheme 13). This reaction sequence is the equivalent to a hydride ring opening of **25** with allylic rearrangement. Thus, treatment of **25** with trichlorosilane in the presence of palladium catalyst, followed by methylmagnesium bromide provides **29**, which when treated with acetyl bromide provides **30** and **31** in 81% and 9% yields respectively.



Scheme 13

A silicon-based nucleophile has also been used to create S_N2' ring-opened products by the Lautens group (Scheme

14).[31] Compounds **18**, **23**, **26**, and **32** produced cyclohexadienes **33**–**36** in good to excellent yields upon treatment with a silylcopper reagent. The reaction was proposed to proceed through a silacupration of the strained double bond from the *exo* face followed by a ring-opening reaction to produce an alkoxysilane which then underwent Peterson elimination.[32] The isolation of the two proposed intermediates, **37** (36%) and **38** (41%) (M = R_1 = H, R_2 = TBDMS), by treatment of **18** with $(PhMe_2Si)_2CuCNLi_2$ in THF at 0°C, provided support for this mechanism and illustrated that at least some of the ring-opening reactions of oxabicyclic compounds were not concerted.



Scheme 14

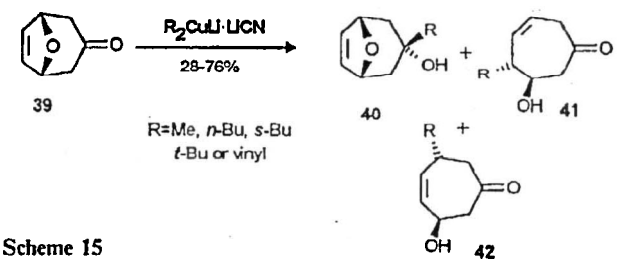
***cis*-5,6-Bis(*tert*-butyldimethylsilyloxymethyl)-1,4-dimethylcyclohexa-1,3-diene (36); Typical Procedure:**[31]

Dimethylphenylsilyllithium was prepared by stirring chlorodimethylphenylsilane (1 mL) and lithium in THF (14 mL) at 0°C for 24 h to make an approximately 0.4 M solution. CuCN was added to a flask and dried overnight in vacuo (0.1 Torr). This flask was cooled in an ice bath, and a solution of dimethylphenylsilyllithium (1:1 ratio of Si–Cu, 2–4 equiv based on oxabicyclic compund) was added. After 30 min at 0°C, compound **32** was added as a solution in THF. After 30 min, the mixture was allowed to warm to r.t. and stirred 4 h. The mixture was quenched with sat. aq NH_4Cl and extracted with Et_2O. Purification by flash chromatography provided diene **36**; yield: 83%.

2.1.3. 8-Oxabicyclo[3.2.1] Systems

Many of the above mentioned ring-opening reactions have also been applied to 8-oxabicyclo[3.2.1] systems. In many cases, the same reaction conditions used with the oxabicyclo[2.2.1] systems have also been successful with the oxabicyclo[3.2.1] systems. However, the presence of an additional carbon atom in the bicyclic framework decreases the strain in the oxabicyclo[3.2.1] compounds so that the ring openings are not as facile. In some cases, a slight modification of either the reagents or the bicyclic system was sufficient to overcome this slightly lower reactivity, while in other cases, the compound followed a different reaction pathway.

Lautens and co-workers[33] have reported that compound **39** underwent an S_N2' ring-opening reaction when treated with a mixed organocyanocuprate (Scheme 15). The chemoselectivity (nucleophilic addition at the carbonyl group versus nucleophilic substitution) and regioselectivity (S_N2 versus S_N2') of the reaction was highly dependent on the reaction temperature, solvent, and nature of the R group on the organometallic reagent. Low temperatures (–78°C) favored attack at the carbonyl group to give **40** exclusively, while warming the reaction mixture to 0°C led to increased amounts of the S_N2' product **41**. More strongly coordinating solvents appeared to enhance S_N2' attack, since the use of diethyl ether or THF as the reaction solvent favored the S_N2' product **41**, but the S_N2 product **42** predominated when the solvent was changed to dimethyl sulfide. With more sterically hindered alkyl groups on the organocuprate reagent, S_N2' compound **41** was the major product; however, as the steric demand of the alkyl group was decreased, increasing amounts of the carbonyl addition product **40** and/or the S_N2 product **42** were observed. For example, while **41** was produced exclusively in 37% yield with R = *t*-Bu, a 1:2:2.5 ratio of **40**/**41**/**42** was obtained in a combined total yield of 76% when R = vinyl. Yields of the desired S_N2' products ranged from 28 to 76%.



Scheme 15

In each case in which the S_N2' ring opening occurred, the alkyl group added in an *anti* fashion. A similar stereoselectivity has been observed in the S_N2' reactions of organocuprates with vinyloxiranes, and this selectivity has been attributed to an overlap of a copper *d* orbital with the π^* orbital of the C–C double bond and the σ^* orbital of the C–O bond simultaneously[11] (Figure 1). A comparable effect may be operating in the ring openings of the oxabicyclic compounds.

The ketone carbonyl was found to be required for the ring-opening reaction of compound **39**. When the ketone carbonyl was converted to a C–C double bond via a Wittig reaction or to a benzylated alcohol via reduction

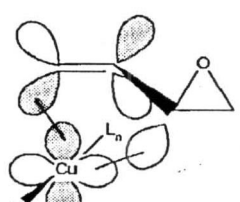
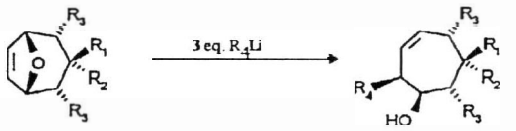


Figure 1. Orbital overlap for S_N2' ring openings of vinyloxiranes

Table 1. S_N2' Ring Openings of Compounds 43–47 with Organolithium Reagents

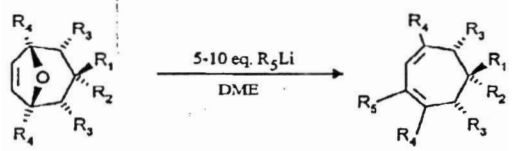


Substrate				R_4	Solvent	Product	Yield (%)
	R^1	R^2	R^3				
43	H	OH	H	*n*-Bu	Et_2O/pentane 1 : 1	48a	82
				t-Bu	Et_2O/pentane 1 : 1	48b	88
44	H	OH	Me	Me	Et_2O/TMEDA 1 : 1	49a	72
				n-Bu	Et_2O/pentane 1 : 1	49b	92
45	H	OTBDMS	Me	*n*-Bu	Et_2O/pentane 1 : 1	50	79
46	Me	OH	Me	*n*-Bu	Et_2O/pentane 1 : 1	51	74
47	*t*-Bu	OH	Me	*t*-Bu	Et_2O/pentane 1 : 1	52	85

followed by protection, the S_N2' ring-opening reaction failed with an assortment of organocuprates under a variety of conditions. No explanation was offered for this phenomenon.

The Lautens group[34] also found that a variety of 8-oxabicyclo[3.2.1]octenes could be ring opened in an S_N2' fashion with organolithium reagents (Table 1). A number of alcohols **43–47** were observed to undergo the reaction to give the diols **48–52**. Primary and tertiary organolithium reagents were equally effective, although methyllithium required the addition of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) as a cosolvent before any ring-opened products were obtained. Ketones (**44** with $R_1 + R_2 = O$) could also be used; however, nucleophilic addition to the carbonyl group from the *exo* face preceded the ring-opening reaction. This difference in reactivity between nucleophilic addition to the carbonyl and S_N2' ring opening allowed for the introduction of two different groups by successive treatment with two different organolithium reagents. Contrary to the result obtained with the organocuprates, the ring openings occurred with addition of the alkyl group *syn* to the bridging oxygen atom. The ring-opened products could be converted to acyclic chains with several stereocenters via ozonolysis of the double bond followed by a sodium borohydride workup. This strategy was used in the synthesis of the C_{21}–C_{27} segment of the natural product rifamycin S from **49a**.[35]

Table 2. S_N2' Ring Openings with Organolithium Reagents in DME



Substrate					R_3	Product	Yield (%)
	R^1	R^2	R^3	R^4			
43	H	OH	H	H	Me	55a	69
					n-Bu	55b	71
44	H	OH	Me	H	Me	56	84
53	H	OH	H	Me	Me	57a	74
					n-Bu	57b	73
54	H	OH	Me	Me	*n*-Bu	58a	71
					i-Pr	58b	75
					t-Bu	58c	67
45	H	OTBDMS	Me	H	*n*-Bu	–	–
59	OH	H	Me	H	*n*-Bu	–	–

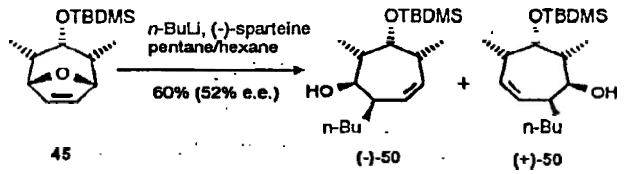
While compounds **43–47** underwent S_N2' ring opening when treated with butyl- and *tert*-butyllithium, albeit with different rates, methyllithium was not capable of causing the ring opening in every case. It was found that oxabicyclo[3.2.1] systems were more reactive towards S_N2' ring opening with organolithium reagents if an alkoxide group was properly situated to interact with the alkene from the *endo* face (e.g. **44** → **49a**).[35] No reaction was observed when **45** was treated with 5 equivalents of MeLi in neat TMEDA. Two possible explanations for the enhanced reactivity resulting from this interaction were proposed. Electron withdrawal from the C–C double bond through coordination of the lithium cation of the lithium alkoxide was argued to make the alkene more susceptible to nucleophilic attack. Alternatively, a weakening of the carbon-bridging oxygen bond due to the donation of electron density from the oxygen anion into the carbon-bridging oxygen antibonding orbital through the alkene π-system could make the ring opening more facile. This phenomenon was referred to as an "*endo* alkoxy effect" and was supported by many other examples.[35]

It was also observed that a change in the reaction solvent altered the products obtained with the ring-opening reactions.[36] When compounds **43**, **44**, **53**, and **54** were treated with organolithium reagents in DME, the cycloheptadienes **55–58** were obtained (Table 2). The reaction exhibited an "*endo* alkoxy effect" since no reaction was observed with the silyl ether **45** or the *exo*-alcohol **59**. The products did not result from the dehydration of the nor-

mal ring-opened diols, such as 49a (Table 1), since none of the cycloheptadienes were observed when the diols were subjected to the reaction conditions. The change in the reaction pathway was not due to the presence of methoxide or methyl vinyl ether from reaction of the organolithium with DME either, since the addition of these compounds to a reaction carried out in diethyl ether produced less than 10% of the diene product. Primary, secondary, or tertiary organolithium reagents could be employed, and the reaction was unaffected by methyl substituents on the oxabicyclo system. The mechanism of this reaction has not been elucidated.

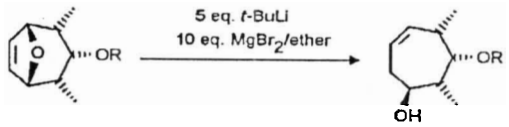
4-Methylcyclohepta-3,5-dienol (55a); Typical Procedure:[36]
To a solution of compound 43 in DME at 0°C was added MeLi (5–10 equiv) dropwise over 5 min (final concentration = 0.05–0.10 M). The reaction mixture was stirred at 0°C for 10 min, warmed to r.t., stirred an additional 4 h, and quenched with 10% H_2SO_4. The crude product was purified by chromatography (silica gel) to provide compound 55a; yield, 69%.

An enantioselective ring opening with carbon nucleophiles has also been examined. Since the alkene carbon atoms of the symmetrical oxabicyclo[3.2.1] systems are related by a plane of symmetry, they are enantiotopic; therefore, attack at one carbon atom from the *exo* face produces the enantiomer of the product obtained from attack at the other carbon atom from the *exo* face. The ability to enhance attack at one carbon atom over the other would then lead to the formation of ring-opened products enriched in one enantiomer. This type of asymmetric induction has been achieved by the group of Lautens with compound **45** through the use of the chiral diamines[37] (Scheme 16). (−)-Sparteine was found to give the highest enantiomeric excesses (e.e.'s). The asymmetric induction was poor if diethyl ether was used as the solvent, but improved with the use of a pentane/hexane mixture. Higher e.e.'s were obtained as the temperature was decreased, possibly due to competing ring opening by the slightly less reactive, noncomplexed butyllithium at reaction temperatures above −40°C. Since no ring opening was observed in the absence of (−)-sparteine at this temperature, it could be employed catalytically to give approximately the same yield and enantioselectivity observed with stoichiometric quantities. The use of less than 15 mole percent of (−)-sparteine, however, led to diminished e.e.'s. Hence, by reacting 5 equivalents of butyllithium and 0.15 equivalents of (−)-sparteine with **45** at −40°C in pentane/hexane, (−)-**50** was produced in 52% e.e. and 60% yield.



Scheme 16

The non-carbon nucleophiles investigated for the oxabicyclo[3.2.1] systems were the same as those examined for the oxabicyclo[2.2.1] systems. The reagent used for the delivery of a hydride for the oxabicyclo[2.2.1] systems was also effective for the reductive ring opening of the oxabicyclo[3.2.1] systems. Thus, the *tert*-butyllithium/magnesium bromide combination delivered a hydride to compound **45** to give **60** in good yield.[26] However, no reaction was observed with the unprotected alcohol **44** (Scheme 17).

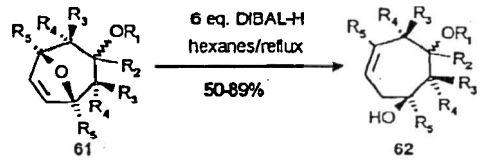


45 R=TBDMS
44 R=H
60 (66%)
No Reaction

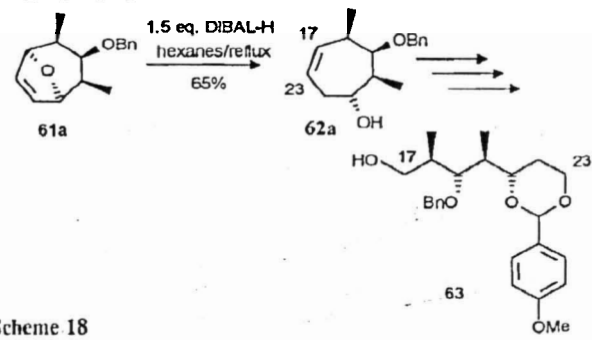
Scheme 17

(1*S,5*S**,6*S**,7*R**)-6-*tert*-Butyldimethylsilyloxy-5,7-dimethylcyclohept-3-enol (60):**[26]
To a 1.3 M $MgBr_2 \cdot Et_2O$ solution (0.6 mL of 0.8 mmol) was added dry Et_2O (1 mL), followed by 1.7 *t*-BuLi (0.23 mL, 0.4 mmol). After stirring for 5 min at r.t., compound **45** (0.08 mmol) was added as a solution in dry Et_2O (1 mL). After 72 h at r.t., the reaction mixture was cooled to 0°C, diluted with Et_2O and quenched with sat. NH_4Cl. Flash chromatography (silica gel) provided compound 60; yield: 66%.

A number of different symmetrical 8-oxabicyclo-[3.2.1.]oct-6-en-3-ols **61** have been reductively ring opened when treated with 6 equivalents of DIBAL-H in refluxing hexanes.[27] Ring-opened products **62** were obtained in yields ranging from 50 to 89% (Scheme 18). Protected (TBDMS and benzyl ethers) and unprotected *exo*- and *endo*-alcohols underwent the reaction, and methyl substituents in a variety of different positions were tolerated. Again, long reaction times or larger amounts of DIBAL-H favored further reduction of the double bond in **62** to give the corresponding saturated diol. This reductive ring opening has been applied to the preparation of the C_{17}–C_{23} fragment of ionomycin (**63**) from compound **61a** via **62a**.[27]



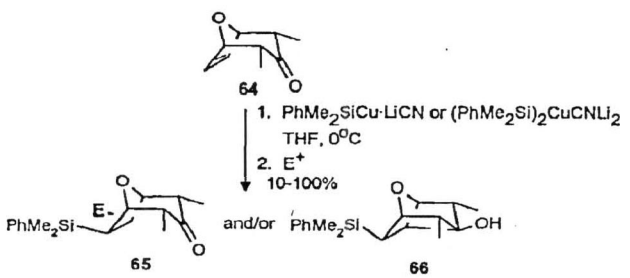
R_1=H, Bn, or TBDMS
R_2, R_3, R_4, R_5= H or Me



Scheme 18

As with the case with oxabicyclo[2.2.1] systems (Scheme 12), the hydroalumination of a variety of symmetrical oxabicyclo[3.2.1] systems was also found to be catalyzed by 5–15 mole percent of $Ni(COD)_2$.[29] The intermediate hydroaluminated species could be "isolated", or directly converted to the ring-opened product by heating the reaction mixture to 70 °C or by treatment with 5 equivalents of DIBAL-Cl. Better yields were generally obtained with the nickel-catalyzed reaction when DIBAL-Cl was used to assist the ring cleavage.

In contrast to the hydride nucleophiles, the silicon-based nucleophiles reacted differently with the oxabicyclo[3.2.1] compounds.[38] For example, although **64** underwent silacupration with either $(PhMe_2Si)Cu \cdot LiCN$ or $(PhMe_2Si)_2CuCNLi_2$, ring opening did not occur. Instead, the resulting anion was trapped with a variety of electrophiles to give **65** (10–100%) or cyclized onto a properly situated carbonyl group to form **66** (59%) upon stirring for a longer length of time in the absence of an electrophile (Scheme 19). Also, contrary to the stereochemistry observed with the addition of organocuprates to the oxabicyclo[3.2.1] systems, the silylcuprates added to the double bond from the *exo* face. The reasons for the differences relative to the reaction with organocuprates are currently not known.



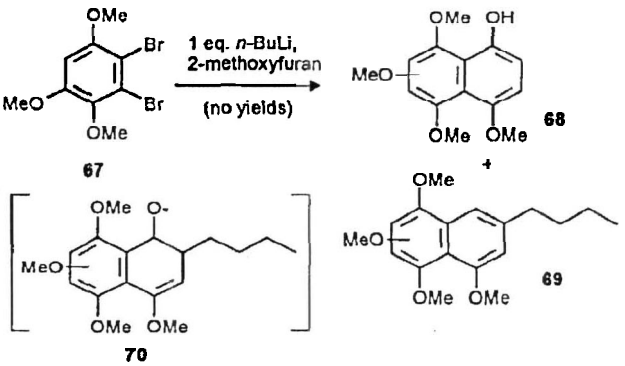
Scheme 19

2.2. Unsymmetrical Systems

In unsymmetrical oxabicyclo systems, the two alkene carbon atoms at which S_N2' attack may occur are no longer related by a plane of symmetry. As a result, attack at one alkene carbon atom produces products that are different from those derived from attack at the other alkene carbon atom; therefore, the regioselectivity of the S_N2' becomes an important factor as well in order to minimize the number of products obtained. The amount of regiocontrol observed seems to vary with different substrates. This section will overview what has been reported to date on S_N2' ring openings of unsymmetrical oxabi-, tri- and tetracyclo systems.

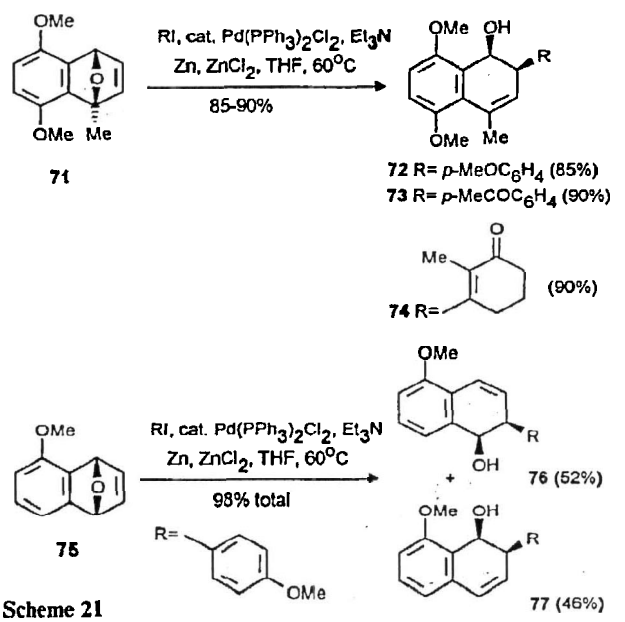
2.2.1. 1,4-Epoxy-1,4-dihydronaphthalene Systems

Giles and co-workers[39] have reported that treatment of **67** with 1.0 equivalent of *n*-BuLi in the presence of 2-methoxyfuran produced a mixture of **68** and **69** (no yields or ratio of products were provided). Compound **69** arose via an S_N2' ring opening of the 1,4-epoxy intermediate, formed by the Diels–Alder reaction between the benzyne derivative of **67** and 2-methoxyfuran, by 1 equivalent of *n*-BuLi to form **70**. Compound **69** is formed by protonation and dehydration of **70** upon workup. Interestingly, treatment of **67** with 0.9 equivalents of *n*-BuLi in the presence of 2-methoxyfuran provided only compound **68** in 73% yield.



Scheme 20

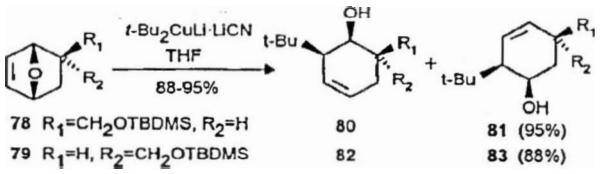
A regio- and stereoselective palladium-catalyzed reductive coupling reaction was performed on compound **71** providing *cis*-1,2-dihydro-1-naphthols **72–74** in 85–90% yield (Scheme 21).[22,23] The 1-naphthol having the opposite regiochemistry was not detected in the crude reaction mixture. It was determined that the methyl group on the bridgehead carbon atom must be controlling the regiochemistry through steric interactions, since compound **75**, having a methoxy group on the aromatic ring, provided a 53:47 mixture of the two possible regiomers **76** and **77** in 52% and 46% yields, respectively.



Scheme 21

2.2.2. 7-Oxabicyclo[2.2.1] Systems

In general, little or no regioselectivity was observed when 7-oxabicyclo[2.2.1] systems were treated with nucleophiles. For example, Lautens and his collaborators[25] reported that the reaction of compound **78** with a mixed organocuprate provided a 60:40 mixture of compounds **80** and **81** in a combined yield of 95% (Scheme 22). Similar results were observed with the stereomer **79**, providing the same ratio of compounds **82** and **83**.



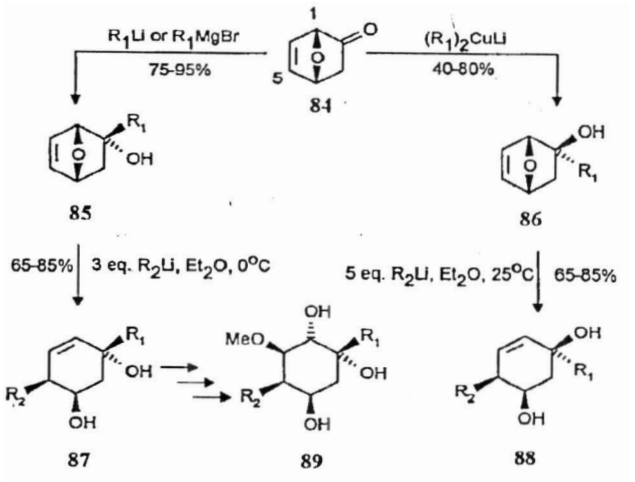
Scheme 22

Certain structural features in the oxabicyclic system, however, were found to affect the regioselectivity dramatically. The group of Arjona, Fernández de la Pradilla, and Plumet[40,41] found that compounds **85** and **86**, formed from **84** by the addition of an organometallic reagent to the ketone carbonyl, underwent highly regioselective ring openings when treated with organolithium reagents to produce **87** and **88**, respectively (Scheme 23). Primary, secondary, tertiary, and alkenyl organolithium reagents were capable of causing the ring-opening reaction, although the reactions with methyllithium, phenyllithium, and vinyllithium required larger excesses (5 to 10 equivalents) of the organolithium reagent and longer reaction times. Oxygen and nitrogen-based nucleophiles have also been examined, but no S_N2' ring-opened products were obtained.[42] The *endo*-alcohols **85** were slightly more reactive than the *exo*-alcohols **86**, possibly due to an "*endo* alkoxy effect", but in each case the attack of the organolithium reagent occurred exclusively from the *exo* face and at C-5 to give products in yields ranging from 65 to 85%. Optically pure (+)-**87**, prepared from optically pure (+)-**85**, has been applied to the enantioselective preparation of deoxycyclitols [(+)-**89**].[43]

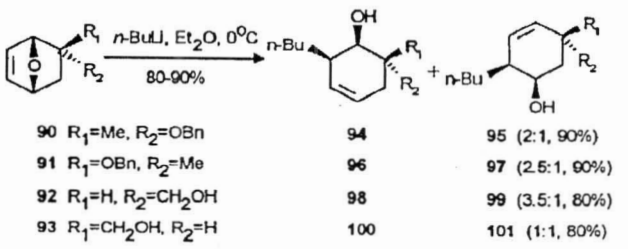
(1*R,3*R**,6*S**)-3,6-Dibutylcyclohex-4-en-1,3-diol (87, $R_1 = R_2 = Bu$); Typical Procedure:**[41]

To a solution of 1.6 M *n*-BuLi in Et_2O (3 equiv) in dry Et_2O (10 mL/mmol of alcohol) at 0°C was added compound **85** (R_1 = *n*-Bu) (1 equiv) in Et_2O (5 mL/mmol of alcohol). The mixture was stirred for 15 min and then quenched with sat. NH_4Cl. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL/mmol of alcohol). The combined organic extracts were washed with brine solution, dried ($MgSO_4$) and removed in vacuo to provide **87** ($R_1 = R_2$ = *n*-Bu) which was purified by column chromatography (silica gel, hexane/EtOAc 1:2, R_f 0.24); yield 85%.

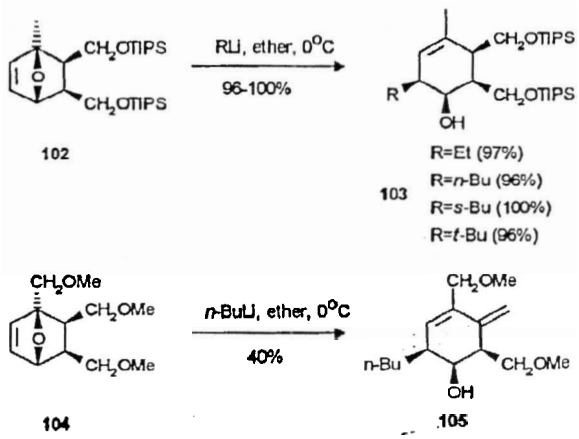
The unprotected hydroxy group at C-2 was found to be essential for the high regioselectivity. Protection of the alcohol as the benzyl ether (**90** and **91**) or the introduction of an additional carbon atom between the ring and the hydroxy group (**92** and **93**) led to an enormous decrease in the regioselectivity. In each of these cases, substantial amounts of both regiomers (**94** to **101**) were observed[40] (Scheme 24). While the reasons for the observed regioselectivity are not known, electrostatic repulsion and changes in the LUMO coefficients caused by interaction with the alkoxide have been suggested as possibilities.



Scheme 23



Scheme 24

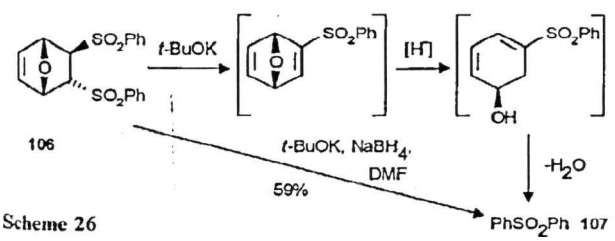


Scheme 25

Substituents at the bridgehead carbon atoms were also capable of enhancing the regioselectivity in the nucleophilic ring openings of unsymmetrical oxabicyclo systems. Lautens and Chiu reported that **102** reacted with primary, secondary, and tertiary organolithium reagents to give **103** in excellent yields,[44] although no reaction was observed with methyllithium[45] (Scheme 25). Compound **104** also underwent a highly regioselective ring opening which was coupled with an elimination reaction to give diene **105**.[46] In each case, attack of the nucleophile occurred exclusively from the *exo* face and at the carbon atom furthest removed from the substituent. The regioselectivity was attributed to reaction at the less sterically hindered site.[46]

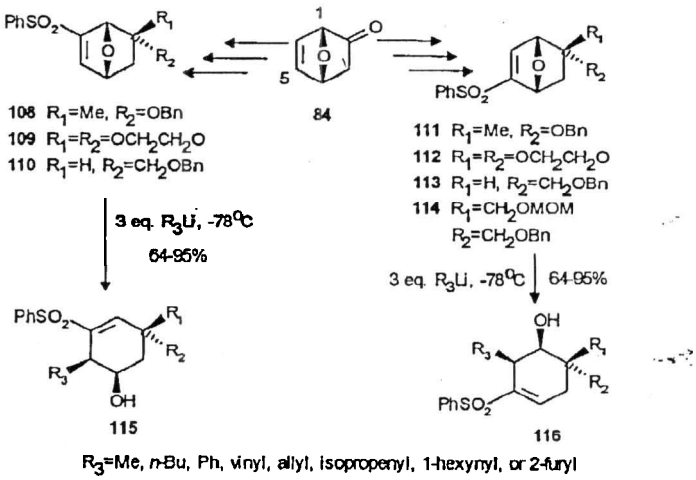
all-*cis*-2-Butyl-4-methyl-5,6-bis(triisopropylsilyloxymethyl)cyclohex-3-enol (103, R = *n*-Bu); Typical Procedure:[44] To a solution of compound **102** (0.280 mmol) in dry Et_2O (1.0 mL) was added 2.5 M *n*-BuLi in hexanes (0.48 mL, 1.2 mmol) at 0°C. The reaction mixture was stirred at 0°C for 3 h, then diluted with Et_2O and quenched with a sat. NH_4Cl. The organic layer was separated and combined with ethereal extracts of the aqueous layer. The Et_2O was dried ($MgSO_4$) and removed in vacuo to leave an oil, which was purified by column chromatography (silica gel, 15% EtOAc/hexanes) to provide compound **103** (R = *n*-Bu); yield: 96%.

Another strategy which has been used to control the regioselectivity of the ring-opening reactions of the unsymmetrical substrates is the placement of an electron-withdrawing group on the double bond. Nucleophilic attack would then proceed in a Michael fashion to give a stabilized carbanion which could subsequently undergo a β-elimination to effect the ring opening. This type of a reaction had been proposed as early as 1985 by Mirsadeghi and Rickborn[47] to explain the formation of diphenyl sulfone (**107**) upon treatment of **106** with potassium *tert*-butoxide and sodium borohydride in DMF (Scheme 26).



Scheme 26

The group of Arjona, Fernández de la Pradilla, and Plumet[48,49] have recently expanded upon this idea, and have used the phenylsulfonyl group to direct the addition of carbon nucleophiles in the S_N2' ring-opening reactions. Compounds **108**–**110** and regiomers **111**–**114** were prepared from **84** in 4 to 6 steps (Scheme 27). While Grignard and cuprate reagents did not give the desired products, organolithium reagents reacted in a highly regioselective manner with **108**–**110** to produce only **115**. The regiomers **111**–**114** reacted with the opposite regioselectivity to produce only **116**. This reaction was successful with a number of different organolithium reagents, and even relatively unreactive organolithium reagents such as 1-hexynyllithium produced the ring-opened products at higher reaction temperatures (0°C). However, different organolithium reagents required different solvents for optimum yields. For example, while methyllithium produced the ring-opened products in 87% yield when the reaction was carried out in THF, side reactions were observed with the same solvent when butyllithium was employed. When the solvent was changed to toluene in the reaction with butyllithium, the desired product was obtained in 78% yield. Toluene was also an effective reaction solvent for vinyllithium and phenyllithium, while the other organolithium reagents used required a 1:1 mixture of toluene and diethyl ether. No explanation for the solvent effect was offered. The reaction was also highly stereoselective, and only products resulting from attack of the reagent from the *exo* face were observed. Yields of **115** and **116** ranged from 64 to 95%.



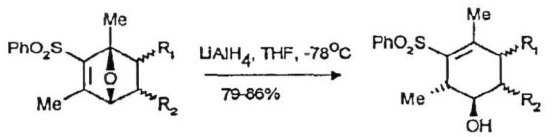
Scheme 27

(1*R,2*R**,5*R**)-5-Benzyloxy-2,5-dimethyl-3-phenylsulfonylcyclohex-3-enol (115, $R_1 = R_3 = Me$, $R_2 = OBn$); Typical Procedure:**[49] To a solution of **108** (473 mg, 1.3 mmol) under argon in THF (13 mL) at −78°C was added 1.6 M MeLi (2.5 mL, 3.9 mmol). After stirring the mixture for 15 min, the reaction was quenched with sat. NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 6.5 mL). The combined organic layers were dried ($MgSO_4$) and removed in vacuo to afford a residue that was purified by column chromatography (silica gel, hexane/EtOAc, 3:1) to provide **115** ($R_1 = R_3 = Me$, $R_2 = OBn$); yield: 87%.

In contrast to the other oxabicyclic compounds discussed, lithium aluminum hydride was effective for the regioselective reductive ring openings of compounds **109** and **111** (Scheme 27).[48,49] The use of 4 equivalents of lithium aluminum hydride in THF at −78°C with **109** and **111** produced **115** and **116**, with $R_3 = H$, in yields of 62% and 65%, respectively. Raising the reaction temperature to 0°C resulted in the reduction of the double bond in the product as well, while the use of less lithium aluminum hydride (1.5 equivalents) at −78°C led to reduction of

the double bond in the starting material without any ring opening.

Bialecki and Vogel[50,51] have also reported reductive ring openings with similar vinyl sulfones bearing additional substitutents. Both **117** and **118** provided the expected ring-opened products **120** and **121** when treated with $LiAlH_4$ at −78°C in THF in 86% and 79% yields respectively (Scheme 28). Compound **119**, on the other hand, did not react at −78°C and provided complex mixtures at higher temperatures.[51] Small quantities of the expected product **122** were isolated from the reaction mixture. The corresponding vinyl sulfides of compounds **117–119** did not react with $LiAlH_4$ at −78°C in THF.



117	R_1= β-OBn, R_2= β-Me	**120** (86%)
118	R_1= α-OBn, R_2= β-Me	**121** (79%)
119	R_1= α-OBn, R_2= α-Me	**122** complex mixtures

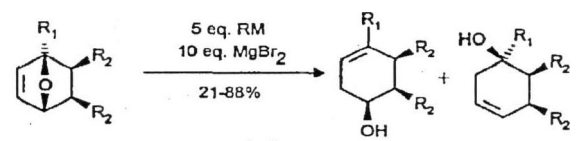
Scheme 28

(1*R,2*S**,5*R**,6*S**)-5-Benzyloxy-2,4,6-trimethyl-3-phenylsulfonylcyclohex-3-enol (121); Typical Procedure:[51]**

To a solution of compound **118** (0.753 g, 1.8 mmol) in THF (20 mL) was added 1 M $LiAlH_4$ in THF (9 mL, 9 mmol) dropwise over 10 min at −78°C under Ar. After stirring for 2 h at −78°C, a mixture of AcOH (3 mL) and MeOH (6 mL) was added. The temperature rose to −50°C, and the cooling bath was removed. At 0°C, brine (20 mL) was added and the layers separated. Extraction with Et_2O (3 × 5 mL), drying the combined extracts, removal of the solvent and flash chromatography (silica gel, $CHCl_3$/acetone, 60:1) gave compound **121**; yield: 79%.

The *tert*-butyllithium/magnesium bromide reagent has also been used to effect the reductive ring opening of unsymmetrical 7-oxabicyclo[2.2.1] substrates. Compounds **104**, **123**, and **124** were ring opened with a hydride nucleophile using this reagent, but the regioselectivity was generally poor (Table 3).[26] Compounds **125** and **126** were obtained in ratios of 1:2.4, 1.2:1, and 3.6:1 for **104**, **123**, and **124**, respectively. Changing the organometallic reagent to butyllithium or isobutylmagnesium chloride altered the ratios of the products obtained, producing more of **126** for **123** and **124**, but more of **125** for **104**. For compounds **125** and **126**, increasing substitution at the β-carbon atom of the organometallic reagent appeared to favor delivery of the hydride to the more sterically hindered alkene carbon atom. No reason for this observation was offered, although **127** (Figure 2) has been proposed as the transition state. The difference in the direction of selectivity of **104** versus **123** or **124** was attributed to complexation of the magnesium to both the bridging oxygen and the bridgehead methoxymethyl group in **104** as the steric hindrance at the α-carbon atom of the organometallic reagent decreased. Combined yields of **125** and **126** ranged from 21 to 88%, while the ratio of products varied from 3.6:1 to 1:1 to 1:4.5.

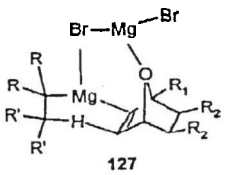
Table 3. Reductive Ring Openings of Oxabicyclo[2.2.1] Systems



104 R_1=R_2=CH_2OMe **125** **126**
123 R_1=Me, R_2=$CH_2OTBDMS$
124 R_1=R_2=$CH_2OTBDMS$

Substrate	Product Ratio of 125/126 Using Conditions*			Yield (%)
	A	B	C	
104	1:2.4	1:1	2.5:1	21–55
123	1.2:1	1:2.4	1:4.5	37–50
124	3.6:1	2:1	1:3.5	42–88

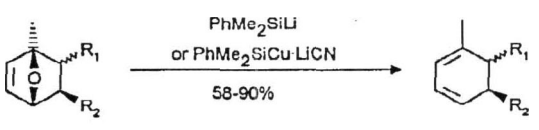
* Conditions: A. 5 eq. *t*-BuLi, 10 eq. $MgBr_2$; B. 5 eq. *n*-BuLi, 10 eq. $MgBr_2$; C. 5 eq. i-BuMgCl, 10 eq. $MgBr_2$



127

Figure 2. Proposed transition state for the hydride transfer from Grignard reagents

The silylcopper reagents have also been used with unsymmetrical bicyclo[2.2.1] compounds; however, in this case, the regioselectivity is not a factor since attack at either alkene carbon atom produces the same product. A number of different unsymmetrical compounds **128** produced cyclohexadienes **129** when treated with either $PhMe_2SiLi$ or $PhMe_2SiCu \cdot LiCN$ in yields ranging from 58 to 90%[31] (Scheme 29). The presence of a free alcohol, benzyl ether or (triisopropylsilyl TIPS) ether, had little effect on the reaction.



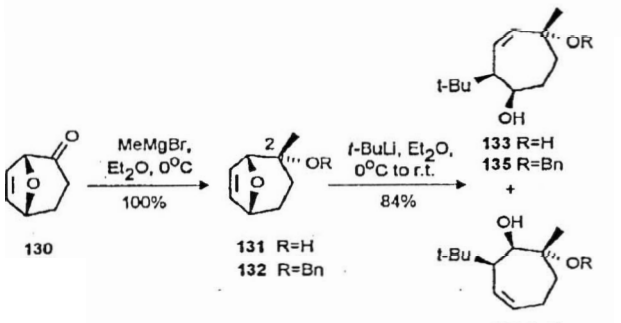
128 **129**
R_1=CH_2OTIPS, CH_2OBn, or CH_2OH
R_2=H, CH_2OTIPS, or CH_2OBn

Scheme 29

2.2.3. 8-Oxabicyclo[3.2.1] Systems

Many of the factors affecting regioselectivity in the unsymmetrical oxabicyclo[2.2.1] systems have the same effect on the oxabicyclo[3.2.1] systems. Again, slight modifications were required in some cases before ring opening was observed in the less strained oxabicyclo[3.2.1] compounds, while a different reactivity was observed in other cases.

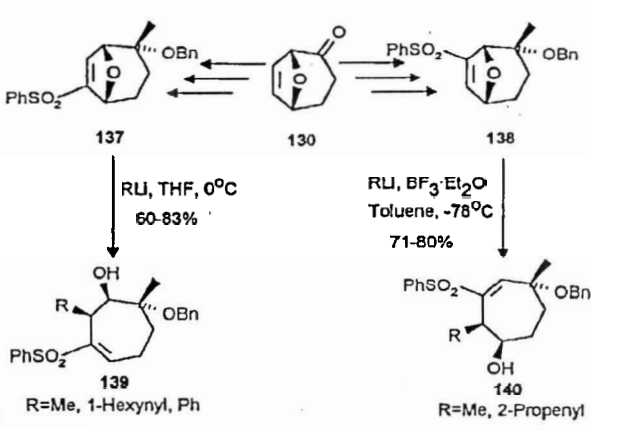
The group of Arjona and Plumet[52] found that **131**, formed from reaction of **130** with a methyl Grignard reagent, underwent a highly stereo- and regioselective ring opening to produce **133** upon treatment with *tert*-butyllithium, isomer **134** was not detected in the reaction mixture (Scheme 30). The scope was somewhat more limited than with the oxabicyclo[2.2.1] systems, however, since no reaction was observed with methyllithium or phenyllithium, and a complex mixture was obtained with butyllithium. The addition of TMEDA as a cosolvent did not lead to any improvements in the reaction. The free alcohol at C-2 was again found to be essential for the regioselectivity, since the benzyl ether **132** produced a 58:42 mixture of **135** and **136** under the same conditions.



Scheme 30

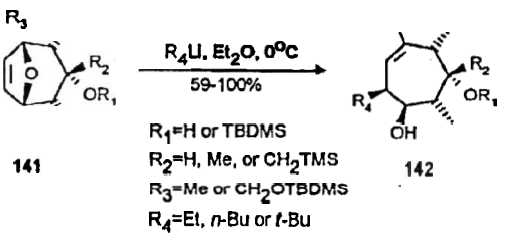
The addition of a phenylsulfonyl group to the double bond was found not only to affect the regioselectivity of the ring opening, but also extended the scope of organolithium reagents which could be employed for the reaction.[49,52] The regiomeric vinyl sulfones **137** and **138** were prepared from **130** in 5 steps (Scheme 31). As in the case of the oxabicyclo[2.2.1]systems, the phenylsulfonyl group was capable of directing the addition of the nucleophile so that the ring-opening reaction was highly regioselective. However, slightly harsher conditions were required before ring opening was observed. When compound **137** was treated with methyllithium at $-78\,^{\circ}C$, which were the conditions used for the oxabicyclo[2.2.1] vinyl sulfones, a methyl group added in a Michael fashion but no ring opening occurred. If the reaction temperature was raised to $0\,^{\circ}C$, however, **139** was formed in 83% yield. Phenyllithium and 1-hexynyllithium reacted in a similar manner to furnish **139** in 60% and 83% yield, respectively. In all three cases, the alkyl group attacked from the *exo* face exclusively to produce the products resulting from *syn* addition.

The regiomer **138** did not produce any ring-opened products when treated with methyllithium, even after the reaction temperature was raised to $0\,^{\circ}C$. In the presence of a Lewis acid, however, the ring opening occurred regioselectively at $-78\,^{\circ}C$ to provide the ring-opened product **140** in 80% yield. 2-Propenyllithium reacted similarly to give **140** in 71% yield. A methyllithium–boron trifluoride complex was also effective under the same conditions. Again, the organolithium reagent attacked from the *exo* face exclusively.



Scheme 31

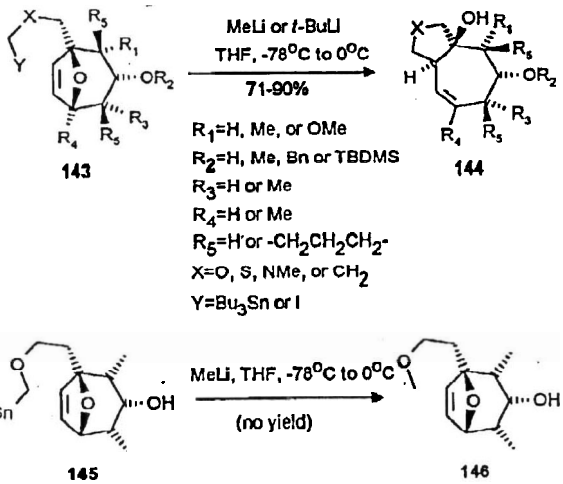
As in the oxabicyclo[2.2.1] systems, the presence of substituents at the bridgehead carbon atoms affected the regioselectivity of the ring-opening reactions of the oxabicyclo[3.2.1] systems.[44] A number of compounds **141** produced only products **142** (Scheme 32), resulting from regioselective attack at the carbon atom furthest removed from the substituent and stereoselective approach from the *exo* face, upon treatment with organolithium reagents. Both primary and tertiary organolithium reagents could be employed, and a free or protected alcohol could be used as the substrate. Yields varied from 59 to 100%,



Scheme 32

Lautens and Kumanovic[53] have also accomplished an intramolecular S_N2' ring opening to produce fused ring products (Scheme 33). A number of different precursors **143** gave the 5,7-*trans*-fused ring systems **144**, formed from an intramolecular attack on the *exo* face of the alkene, in yields varying from 71 to 90% upon treatment with an organolithium reagent. Geometric constraints imposed by the tether dictated the regioselectivity of the reaction. Both tributylstannanes and iodides were effective as anion precursors, although hydroxy groups in **143** required protection when iodides (Y = I) were used. Transmetalation with methyllithium was used to generate the anions from the tributylstannanes, while *tert*-butyllithium was employed for a lithium–halogen exchange with the iodides. A tether consisting solely of carbon atoms or containing or a number of different heteroatoms could be employed with the exception of a carbamate nitrogen ($X = NCO_2Me$). Either additional stabilization of the anion or a bond angle change was believed to be responsible for the production of a complex mixture of

products with no cyclized products in this case. The intramolecular ring-opening reaction was more facile than the corresponding intermolecular reaction since α-heteroatom stabilized organolithium reagents were not capable of inducing ring opening in the intermolecular case. Substituents at various positions on the oxabicyclic system were tolerated, but the reaction was limited to a three atom tether since attempts to extend the methodology to the preparation of 6,7-fused ring systems using **145** produced only **146**.

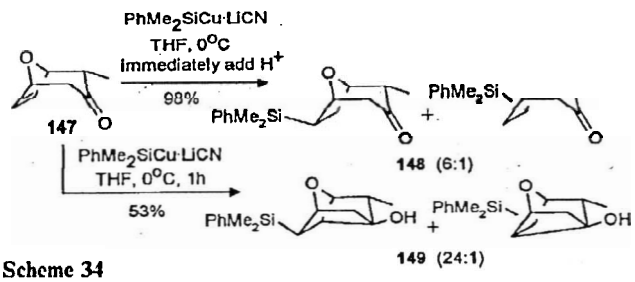


Scheme 33

(1*R,2*R**,3*R**,4*R**,7*S**)-2,4-Dimethyl-9-oxabicyclo[5.3.0]dec-5-ene-1,3-diol (144, $R_1 = R_3 = Me$, $R_2 = R_4 = R_5 = H$, X = O); Typical Procedure:**[53]

To a solution of compound **143** [$R_1 = R_3 = Me$, $R_2 = R_4 = R_5 = H$, X = O, Y = Sn(*n*-Bu)$_3$] (206 mg, 0.42 mmol) in THF (4 mL) at −78°C was added 1.4 M MeLi in Et_2O (1.6 mL, 2.12 mmol) dropwise. The reaction mixture was warmed to 0°C and stirred an additional 3 h. The reaction mixture was quenched with water and the solvent separated and removed in vacuo to provide a residue which was purified by flash chromatography (silica gel, hexanes/EtOAc, 20:1 to 0:100) to provide compound **144** ($R_1 = R_3 = Me$, $R_2 = R_4 = R_5 = H$, X = O); yield: 85%.

The silicon nucleophiles have also been applied to **147** (Scheme 34).[38] As with the symmetrical oxabicyclo[3.2.1] systems, no ring-opened products were observed, but mixtures of regiomers of compounds **148** or **149** could be isolated. Interestingly, the regioselectivity of the reaction giving the cyclized product **149** was higher than that producing **148**, suggesting that the silacupration of the double bond may be reversible.



Scheme 34

An interesting change in the regioselectivity was observed when various unsymmetrical oxabicyclo[3.2.1] systems were treated with DIBAL-H in the absence[27] or presence[29] of a nickel catalyst. Generally, a better selectivity was observed in the presence of $Ni(COD)_2$ and triphenylphosphane, and the regioselectivity was reversed (Table 4). So, while **150–152** reacted with DIBAL-H to produce predominantly **153–155** respectively with good or poor selectivity, the addition of $Ni(COD)_2$ and triphenylphosphane to the reaction led to the formation of **156–158** respectively with higher selectivities. The intermediates **159a** and **159b** were invoked to explain the change in regioselectivity upon the addition of nickel (Figure 3).

The intermediate **159b**, which gives rise to **156–158**, was proposed to be the more stable of the two for steric reasons, since the nickel, with its bulky triphenylphosphane ligands, was further away from the bridgehead group. Deprotonation of the alcohol **151** with methyllithium prior to treatment with DIBAL-H was another method which could be used to change the regioselectivity,[27] producing mainly **157** (Table 4). The *endo*-alkoxide was proposed to affect the hydroalumination reaction through interaction with the alkene double bond, although no rationale was given for the direction of selectivity observed in this case.

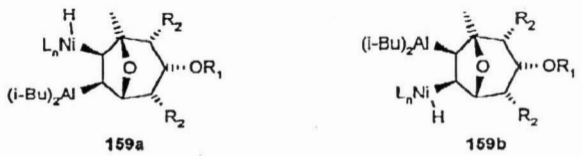
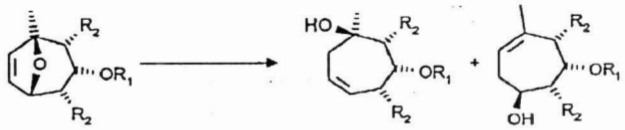


Figure 3. Proposed intermediates in the nickel-catalyzed hydroalumination reaction

Table 4. Reaction of Unsymmetrical Oxabicyclo[3.2.1] Systems with DIBAL-H



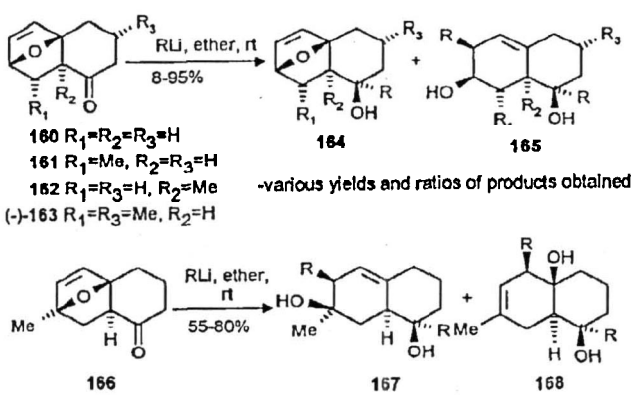
150	R_1=TBDMS, R_2=Me	**153**	**156**
151	R_1=H, R_2=Me	**154**	**157**
152	R_1=R_2=H	**155**	**158**

Substrate	Conditions	Product Ratio	Yield (%)
150	5 eq. DIBAL-H	6.4 : 1.0	72
	0.1 eq. $Ni(COD)_2$, 0.3 eq. Ph_3P, DIBAL-H	1.0 : 9.4	71
151	6 eq. DIBAL-H	1.3 : 1.0	75
	0.1 eq. $Ni(COD)_2$, 0.3 eq. Ph_3P, DIBAL-H	1.0 : 28.5	72
	(1) 1.2 eq. MeLi; (2) 5 eq. DIBAL-H	**1.0 : 9.5**	**85**
152	6 eq. DIBAL-H	1.1 : 1.0	74
	0.1 eq. $Ni(COD)_2$, 0.3 eq. Ph_3P, DIBAL-H	1.0 : 15.5	87

2.2.4. Oxatricyclo Systems

Ring-opening reactions have been accomplished with a number of other ring systems, although in many cases the reactions have not been examined extensively.

Woo and Keay have reported[54,55] that oxatricyclo adducts **160–163**, which do not have a substituent on the bridgehead carbon atom, undergo both a highly regio- and stereoselective S_N2' ring opening and a highly stereoselective attack at the carbonyl carbon atom to provide **164** and/or **165** depending on the amount and type of RLi (R = Me, *n*-Bu, *i*-Pr, *t*-Bu) employed in the reaction in poor to excellent yields (8–95%) (Scheme 35). Attack of the RLi occurred exclusively from the β-face of the double bond and the α-face of the carbonyl carbon atom. Reactions with adduct **166**, which has a methyl group at the bridgehead position, were highly stereoselective (attack of the β-face of the double bond and the α-face of the ketone) but not regioselective. Ratios ranging from 1.7–2.2:1 of **167/168** were obtained when *n*-BuLi, *i*-PrLi and *t*-BuLi were used as the nucleophile.

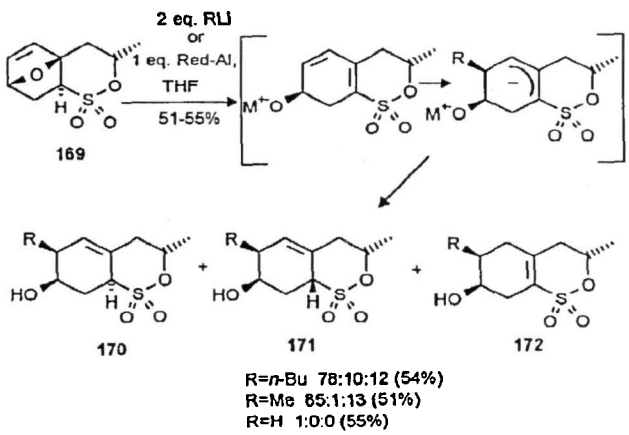


Scheme 35

The ring opening and carbonyl addition with nucleophiles of oxatricyclo adducts is synthetically useful. Optically pure (−)-**163**, prepared from an intramolecular Diels–Alder reaction of a furan diene,[56] when treated with MeLi provided only (+)-**165** (R = R_1 = R_3 = Me, R_2 = H) in 74% yield (Scheme 35).[55] Compound (+)-**165** contains 6 asymmetric centers, 5 of which are contiguous, of known absolute stereochemistry as well as an olefin and a 2° and 3° alcohol for further functional group manipulation. Compounds like (+)-**165** are currently being used by Woo and Keay in the synthesis of venturicidin A.[57]

(1*S*,2*R*,8*R*,9*R*)-2,8-Di-*tert*-butylbicyclo[4.4.0]dec-6-ene-2,9-diol (165, R_1 = R_2 = R_3 = H, R = *t*-Bu); Typical Procedure.[54]
To a solution of *t*-BuLi (0.96 mmol) in dry Et_2O (4 mL) under Ar at −78°C was added a solution of compound **160** (0.32 mmol) in dry Et_2O (6 mL). The mixture was warmed to 0°C. When TLC indicated the starting material was consumed, the mixture was quenched with a sat. NH_4Cl. The Et_2O was separated, dried ($MgSO_4$) and removed in vacuo to provide a residue that was purified by flash chromatography (silica gel), which provided compound **165** as a white solid; yield: 90%.

Metz and co-workers reported that treatment of compound **169** with butyllithium or methyllithium gave a mixture of **170–172** (Scheme 36) which could be equilibrated to **170** exclusively with catalytic quantities of potassium *tert*-butoxide.[58] This reaction was proposed to proceed through an elimination reaction, cleaving the bridging oxygen ring, followed by an alkoxide directed 1,6-addition of a second equivalent of organolithium reagent. The intermediate carbanion could also be trapped with iodomethane to introduce a second alkyl group. The production of a mixture of **170–172** upon treatment of **169** with 1 equivalent of LDA followed by 1 equivalent of methyllithium provided support for the elimination–addition mechanism. In addition, Red-Al was an effective reagent for the reductive ring opening of **169**, producing **170** exclusively in 55% yield.[59] This reaction was also believed to proceed via the elimination–addition mechanism, with one equivalent of the hydride from Red-Al causing the initial elimination.



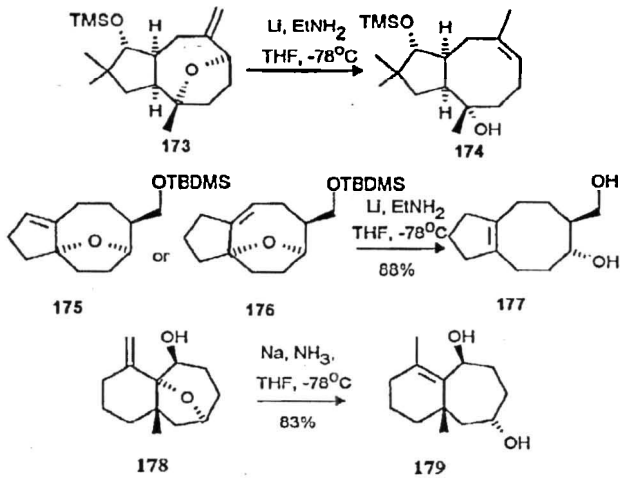
Scheme 36

9-Hydroxy-4,8-dimethyl-2-thia-3-oxabicyclo[4.4.0]dec-6- or -1(6)-ene-2,2-dione 170–172, R = Me; Typical Procedure:[58]
MeLi (3.33 mmol) was added dropwise at −78°C to a solution of compound **169** (1.39 mmol) in THF (10 mL). After stirring 15 min at −78°C and then 1 h at 0°C, the reaction mixture was quenched at −78°C with sat. NH_4Cl. The mixture was warmed to r.t., adjusted to pH 7 with 2 N HCl and extracted with EtOAc (3 ×). The combined organic layers were dried ($MgSO_4$) and removed in vacuo to provide a residue that was purified by flash chromatography (silica gel, EtOAc petroleum ether, 3:2). A mixture of **170/171/172** (R = Me (78:10:12) was obtained; yield: 54%.

(1*S,4*S**,8*S**,9*R**)-9-Hydroxy-4,8-dimethyl-2-thia-3-oxabicyclo-[4.4.0]dec-6-ene-2,2-dione (170, R = Me), by Isomerization of 170–172 (R = Me); Typical Procedure:**[58]
The mixture of compounds **170–172** (R = Me) (2.15 mmol) obtained above was dissolved in toluene (40 mL) and *t*-BuOK (0.36 mmol) was added. After the reaction mixture was stirred for 24 h at r.t., Et_2O and water were added. The aqueous layer was extracted with EtOAc (3 ×), and the combined organic layers were washed with brine and dried ($MgSO_4$). After removal of the solvent in vacuo, flash chromatography (silica gel, EtOAc/petroleum ether 3:2) provided pure **170** (R = Me); yield: 77%.

Reductive ring openings have been accomplished with other reagents and other ring systems as well. As part of

a study on the biomimetic conversion of humulene to pentalenolactone by the group of Matsumoto,[60] **173** was converted to **174** with lithium metal in ethylamine (Scheme 37). Harmata and co-workers[61] have reported a similar conversion of **175** or **176** to **177** under similar conditions, while Williams' group[62] reported a reductive ring opening of **178** to give **179** upon treatment with sodium metal in liquid ammonia.

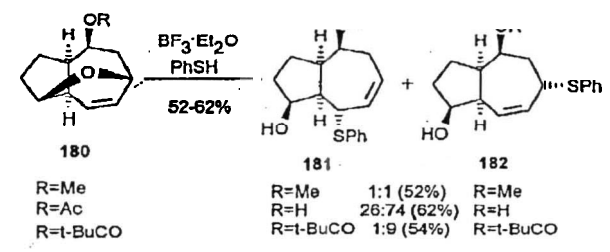


Scheme 37

(2*S,5*S**,7*S**)-7,11-Dimethylbicyclo[5.4.0]undec-1(11)-ene-2,5-diol (179):**[62]

Ammonia (6.7 mL), passed over BaO, was condensed into a dry three-necked flask, cooled to −78 °C and charged with dry THF (1.35 mL). Freshly cut pieces of sodium (0.065 g, 2.81 mol) were added. After the mixture was stirred for 20 min, a solution of **178** (167 mg, 0.803 mmol) in THF (3 mL) was added dropwise to the deep blue mixture. The reaction mixture was quenched with MeOH (1.5 mL) after 20 min. The cold bath was removed and the ammonia allowed to evaporate. The remaining material was partitioned with Et_2O and water (30 mL each). The organic phase was washed with brine, and the combined aqueous layers extracted with Et_2O (10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 4:1) to provide **179**; yield: 78%.

Although the use of nucleophiles other than organometallic reagents or hydride reagents is much rarer, Rigby and co-workers[63,64] have used thiophenol in an S_N2' ring-opening reaction as part of a study of the sythesis of C-8 oxygenated guaianolides and ophiobolane sesterterpenes



Scheme 38

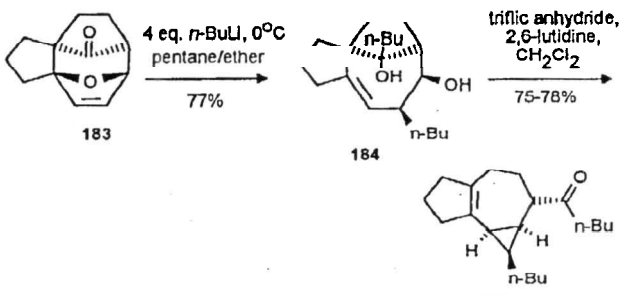
(Scheme 38). Excess boron trifluoride–diethyl ether complex was required before any reaction was observed with **180**, but the reaction was not selective since both the S_N2' product **181** and the S_N2 product **182** were formed. A change in the protecting group of the alcohol oxygen altered the ratio of **181**/**182**, although this effect was not extensively studied and no explanation was offered. Oxygen nucleophiles were reported to be unsuccessful under the same conditions.

6-Phenylthiobicyclo[5.3.0]dec-4-ene-2,8-diol (181, R = H) and 4-Phenylthiobicyclo[5.3.0]dec-5-ene-2,8-diol (182, R = H); Typical Procedure:[63]

Compound **180** (R = Ac) (13.8 g, 66.35 mmol) was dissolved in freshly distilled thiophenol (100 mL), and freshly distilled $BF_3 \cdot Et_2O$ (24.5 mL, 199 mmol) was added. The reaction mixture was stirred at r.t. for 8 h and then poured into Et_2O (1 L). The excess $BF_3 \cdot Et_2O$ was quenched by the careful addition of $NaHCO_3$. The organic layer was separated and washed with several portions of sat. $NaHCO_3$ followed by 5% NaOH (2 × 500 mL) and, finally, with brine. The Et_2O layer was dried and removed in vacuo and the residue purified by flash chromatography (silica gel, Et_2O/hexanes 3:7) to provide a mixture of **181** (R = H) and **182** (R = H) (26:74 ratio); combined yield: 62%.

2.2.5. Oxatetracyclo Systems

The tetracyclic compound **183** has been treated with butyllithium by Harmata and Elahmad[65] to form **184** via an S_N2' ring opening (Scheme 39). The reaction was highly stereo- and regioselective. The regioselectivity is due to the five-membered ring acting as a substituent on one of the bridgehead carbon atoms of the oxabicyclic system. Compound **184** was converted to fused 5,7,3-ring system **185** via a vinylogous Grob fragmentation.



Scheme 39

3. Conclusions

The majority of S_N2' ring openings of symmetrical oxabicyclo systems are highly stereoselective with the nucleophile approaching the double bond from the *exo* face; only cuprates in certain [3.2.1] systems approach the double bond from the *endo* face. The minimum reactivity of an organolithium reagent appears to lie somewhere between that of butyllithium and methyllithium, since the former reagent and more reactive secondary and tertiary organolithium reagents were able to cause the ring opening, while methyllithium required activation by DME and/or TMEDA before any ring opening was observed. Less reactive reagents require pre-activation

of either the oxygen bridge or double bond. Oxabicyclo[2.2.1] systems are more reactive than oxabicyclo[3.2.1] systems due to more ring strain in the former.

The S_N2' ring openings of unsymmetrical oxabi-, tri- and tetracyclo systems are highly stereo- and regioselective. Nucleophiles preferentially attacked the double bond from the *exo* face (stereoselective) and attacked the carbon atom of the double bond which was less sterically hindered (regioselective). Higher regioselectivity was observed when one of the bridgehead carbon atoms was substituted with an alkyl group (a hydrogen atom is attached to the other bridgehead atom) when compared to unsymmetrical systems in which the substituents were further removed from the bridgehead and double bond carbon atoms. The reactivity of the nucleophiles was similar to that observed with the symmetrical systems. In the case of the 11-oxatricyclo[6.2.1.$0^{1,6}$]undec-9-en-5-ones,[54,55] not only was the S_N2' ring opening of the oxygen bridge stereo- and regioselective, but attack at the carbonyl carbon atom was highly stereoselective from the α-face.

Future studies will probably center on (a) the development of alternative asymmetric methods for the desymmetrization of symmetrical oxabicyclo adducts as well as improvements in the existing procedures; (b) further applications of intramolecular openings to unsymmetrical systems due to the enhanced regioselectivity; and (c) applications of the S_N2' ring opening to the synthesis of complex natural products.

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