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New methods for the control of multiple stereocenters

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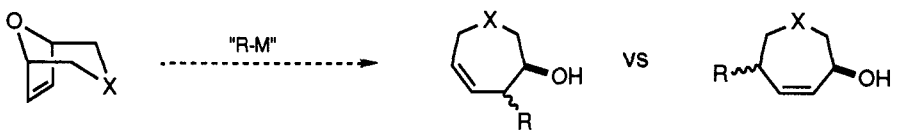
Abstract: Reactions which assemble multiple stereocenters in a highly convergent manner provide new avenues for the synthesis of complex natural products. Oxabicyclic compounds have been shown to be useful precursors to highly functionalized cyclic and acyclic compounds following reaction with a variety of nucleophiles including carbon, silicon and hydride. The regio-, stereo-, and enantioselectivity of the ring opening has been investigated. Syntheses of fragments of the natural products rifamycin and ionomycin illustrate the utility of this approach.

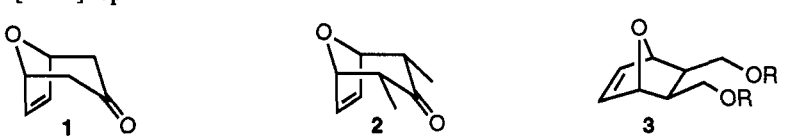
INTRODUCTION

The synthesis of naturally occurring macrocyclic compounds containing arrays of contiguous stereocenters provides a significant challenge to the organic chemist. The structural complexity of the macrolides, polyether antibiotics, and macrolactams have encouraged the development of new methodology as well as the design of novel synthetic strategies (ref. 1-3). One of the most commonly used strategies for their synthesis is based on the diastereoselective addition of a nucleophilic reagent to an electrophilic species such as a carbonyl group (ref. 4,5). New approaches which set multiple stereocenters in a convergent manner would provide a useful alternative to these strategies.

Our initial objective in the development of a convergent approach to these classes of target compounds was to explore the reactivity of an oxabicyclic compound toward a nucleophilic partner. There were several questions which needed to be answered at the outset of the project as illustrated in the equation below. With what types of nucleophiles does ring opening occur in [3.2.1] and [2.2.1] oxabicyclic compounds? Is the product derived from S_N2 or S_N2' attack? What is the stereochemistry of S_N2' opening and can it be controlled (ref. 6)? Can control of the absolute stereochemistry be accomplished in the ring opening if the starting material is *meso*?



Oxabicyclo[3.2.1]octenones **1** and **2** have been available since the 70's when Hoffmann and Noyori described novel routes for their preparation based on a cycloaddition between furan and a polyhalogenated ketone in the presence of a catalyst (ref. 7). Routes which are amenable to the large scale preparation of these materials are now available making these compounds attractive starting materials for our investigation (ref. 8). Diels-Alder cycloaddition between furan and a dienophile followed by reduction and protection of the resulting alcohol yields oxabicyclo[2.2.1]heptenes **3**.

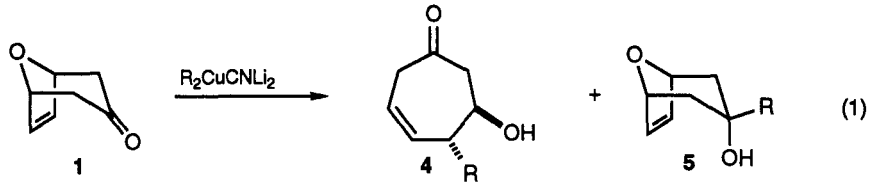


RING OPENING REACTIONS

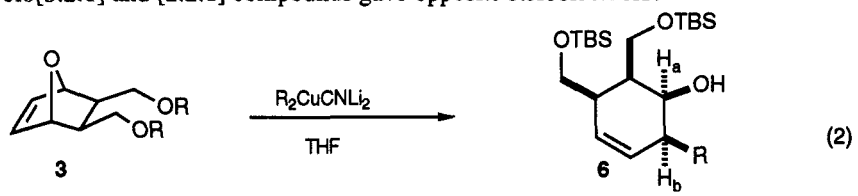
Organocuprate openings

Cuprates are known to be excellent nucleophiles toward a variety of electrophilic species. We have observed that oxabicyclic compounds undergo regio- and stereoselective ring opening when

they are reacted with a higher order cuprate. Higher order cuprates were chosen since they are among the most stable and nucleophilic of the many cuprates currently available (ref. 9). Reaction of **1** at room temperature using MeLi (9 equiv.), CuCN (5 equiv.) in ether (or THF), yielded the desired cycloheptenol **4** (R=Me) (ref. 10). An X-ray crystal structure of cycloheptenol **4** (R=t-Bu), confirmed the proposed stereochemical assignment of [3.2.1] openings (ref. 11). Use of lower temperatures gave **5** as the major product (40-50%). Surprisingly, the presence of the *carbonyl group was essential* to the ring opening. Cuprates derived from secondary and tertiary organolithium compounds were much more effective than primary lithium compounds at inducing the ring opening.

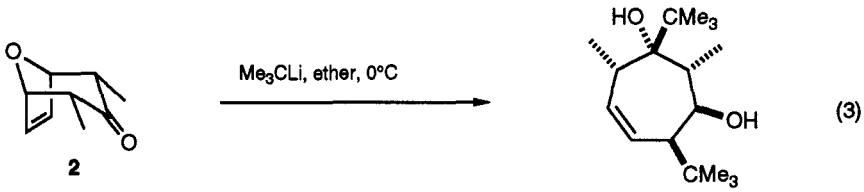


Oxabicyclo[2.2.1] compounds also undergo ring opening. When **3** was reacted with s-$Bu_2CuLiCN_2$ in THF at r.t., **6** (R=s-Bu) was isolated in 78% yield, eq. 2. Apparently the higher ring strain in **3** overcomes the activation required for **1**. The reaction was also successful for R=t-Bu but failed for R=Me and n-Bu (ref. 12). Analysis of the ^1H NMR spectrum of **6** (R=*t*-Bu) clearly showed a very small coupling (2-3 Hz) between H_a and H_b, indicating that the stereochemistry was *cis* not *trans*. It was interesting and somewhat surprising that oxabicyclo[3.2.1] and [2.2.1] compounds gave opposite stereoisomers![25]



Organolithium openings of oxabicyclo[3.2.1] systems

Organolithium reagents were also shown to induce the ring opening, eq. 3 (ref. 13). X-ray crystallography revealed that the first lithium reagent adds from the equatorial direction and the second equiv. adds to the *exo* face of the olefin with concomitant expulsion of the bridging oxygen. It is noteworthy that the stereochemistry of the addition product from an organolithium is *syn* which is complementary to that from an organocuprate opening in the [3.2.1] systems.



The scope of this reaction was investigated on substrates **7-10**. Treatment with 5 equiv. of RLi in ether at 0°C for 1-3 h provided the cycloheptene diols **11-14** (R= n-Bu, s-Bu, i-Pr, t-Bu) in yields ranging from 70-90%. The relative reactivity was t-Bu > s-Bu ≅ i-Pr> n-Bu. In fact,

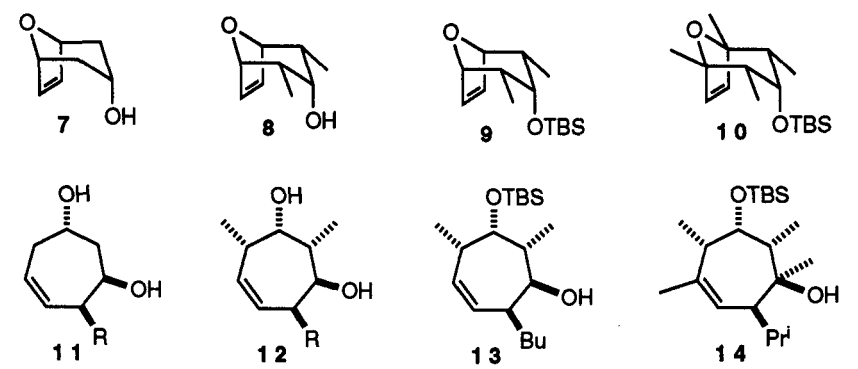
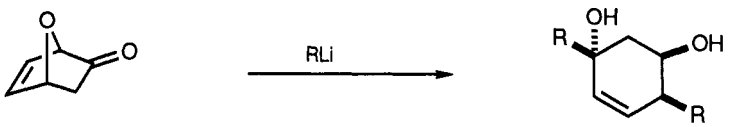


Figure 1

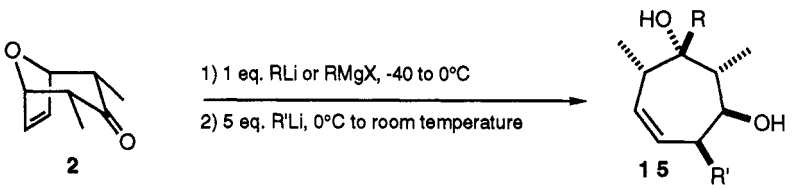
reaction with t-BuLi or i-PrLi can be carried out at -78 °C. Under the standard conditions MeLi was totally unreactive. However, addition of TMEDA to the ethereal solution of MeLi led to ring opening of **9** providing **13** (R=Me) in 65-75% yield.

Arjona and Fernandez de la Pradilla have observed similar reactivity when 7-oxabicyclo[2.2.1]hept-5-en-2-one was treated with organolithium reagents to yield ring-opened products, eq. 4 (ref. 14).



(4)

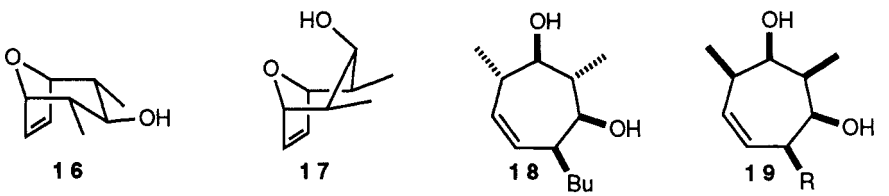
As noted earlier, addition to the carbonyl group was significantly faster than ring opening and thus two different organolithium reagents can be incorporated in the cycloheptenediol, eq. 5.



(5)

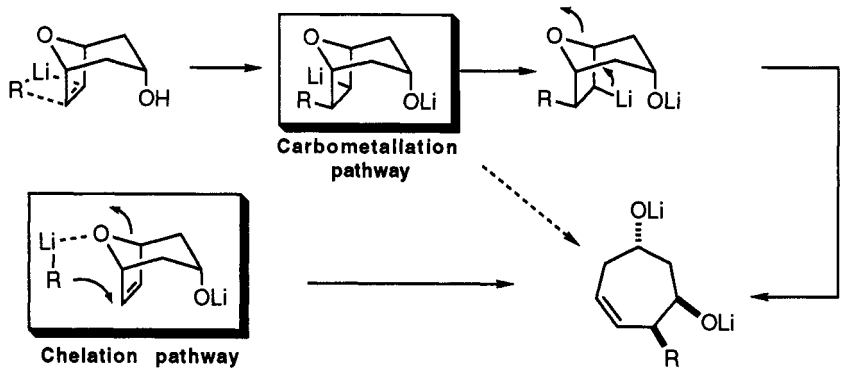
In our studies with substrates **7-10**, the axial hydroxy group (*endo hydroxyl*) at C_3 was found to play a significant role in the rate of the ring opening (ref. 15). When treated with n-BuLi in ether at 0°C, **8** reacted approximately 100x faster than **9**. Methyllithium failed to react with **9** under any of the conditions examined including varying the solvent, temperature, and number of equivalents of reagent! The stereochemistry of the hydroxyl group and the conformation of the six-membered ring also had a significant effect on the reactivity of the substrate. Ring opening reactions initiated with *n*-BuLi in ether were successful and rapid for both **16** and **17**. However, treatment of **17** with 5 eq. MeLi in neat TMEDA at 45°C resulted in no reaction after one hour. At this temperature, **8** was completely consumed within 30 minutes. By increasing the temperature of the reaction to 75°C, ring opening of **17** was successful, yielding **19**. Substrate **16**, on the other hand, withstood treatment with 5 eq. MeLi in neat TMEDA at temperatures up to 100°C without any indications of ring opening.

This result suggests that the ring opening reaction of **8** was not simply the result of forcing conditions, but rather, entailed assistance from the *endo* lithium alkoxide. Although both **8** and **17** undergo ring opening, the nature of the assistance is clearly different. Internal coordination of the lithium alkoxide, formed upon deprotonation of **17**, to the bridging oxygen also assists the ring opening.



Two possible mechanisms can be envisaged for the ring opening process, Scheme 1.

Scheme 1



Nucleophilic attack on the olefin and concomitant expulsion of the bridging oxygen which is coordinated to a lithium would lead directly to the product (Chelation pathway). Alternatively, carbolithiation of the olefin, epimerization and elimination of the β-alkoxy group could occur (Carbometallation pathway). Evidence to support the carbolithiation route is provided by the work of Wittig, Mulvaney, and Caple which demonstrated that strained olefins such as norbornadiene and norbornene undergo addition reactions with strongly basic organolithium reagents (ref. 16). Caple extended these studies to include the addition-dehydration reactions of a benzonorbornadiene with butyllithium to yield 1,4-dihydronaphthalene (ref. 17).

A change in solvent from ether to DME had a dramatic effect on the ring opening. In DME, **7**, **8**, and **20** underwent ring opening followed by elimination of water leading to highly substituted cycloheptadienes **21-23**. The presence of an *endo* hydroxyl group at C-3 was essential for this reaction. After protection of the hydroxyl group as a silyl ether or inversion of the hydroxyl stereochemistry (i.e. **16**) neither the ring opening nor dehydration was observed. Furthermore, treatment of **12** with n-BuLi in DME did not yield **22** but returned starting material (ref. 18).

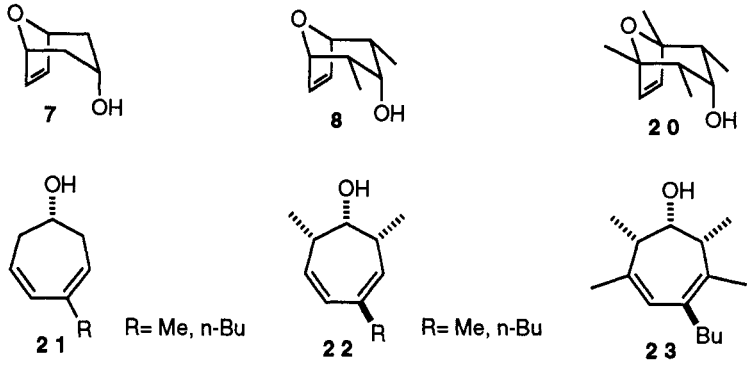
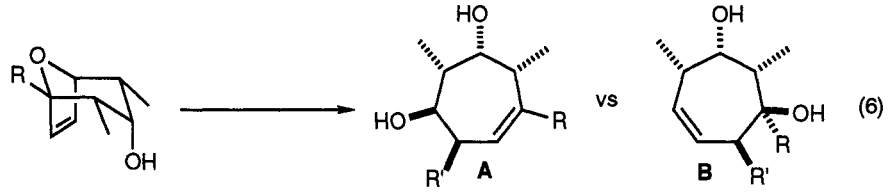


Figure 2

Regioselective ring openings

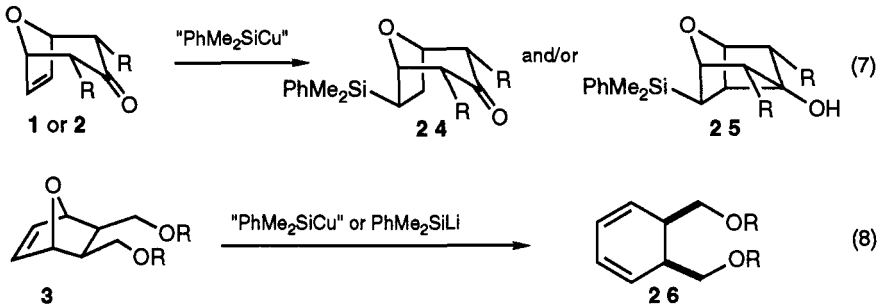
We have also explored the ring opening of unsymmetrical oxabicyclic compounds. Two possible products could arise from this reaction, **A** and/or **B**, depending on the site of attack, eq. 6. Treatment of unsymmetrical oxabicyclo[3.2.1] and [2.2.1] substrates with a variety of



organolithium reagents was investigated. In general, highly regioselective addition was observed for [2.2.1] and [3.2.1] oxabicyclic compounds with Et-, n-Bu-, t-BuLi (ref. 19). Attack occurs predominantly at the carbon distal to the bridgehead substituent providing products of type **A** with >10:1 selectivity. Unfortunately, unsymmetrical substrates fail to react with methyllithium. Alternative sources of Me^- which might be more nucleophilic are currently under investigation.

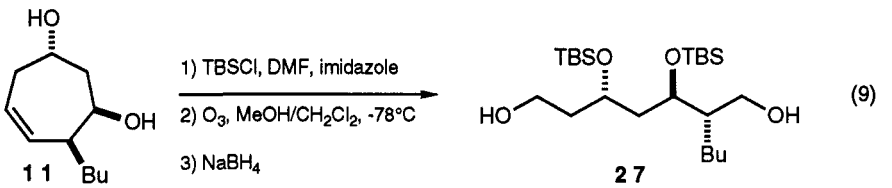
Reactivity of silyl nucleophiles

Non-carbon nucleophiles including silyllithium, silylcopper and silylcuprates were also investigated. Both oxabicyclo[3.2.1] and [2.2.1] compounds were found to undergo the first step in the proposed ring opening reaction when treated with a silylcopper or silylcuprate, namely, the addition of the reagent across the strained olefin. However, from this point the reaction pathways diverged. Whereas **1** and **2** undergo either protonation to give **24**, or cyclization onto the remote carbonyl group to give **25** (depending on the R groups, the silicon reagent, and the time) (ref. 20), **3** undergoes a tandem ring opening-Peterson elimination sequence to give a cyclohexadiene **26**, eq. 7, 8. The latter reaction provides a novel method for the synthesis of substituted cyclohexadienes (ref. 21).

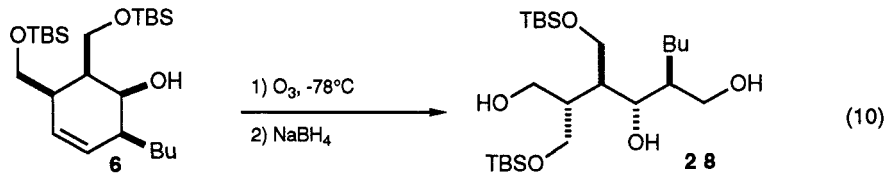


OXIDATIVE CLEAVAGE OF THE CYCLOALKENE

Ring opening and oxidative cleavage of the cycloalkenes resulting from ring opening provides an efficient route to highly functionalized acyclic polypropionate and polyacetate chains (ref. 13). For example, protection of **11** (R=n-Bu) as a bis silyl ether followed by ozonolysis with a reductive work-up ($NaBH_4$) led to heptanediol **27** in 92% yield, eq. 9. The acyclic compounds generated from the ozonolysis contain an *anti* aldol and an *anti* 1,3-diol subunit, stereochemical relationships present in the target molecules, *vide infra*.



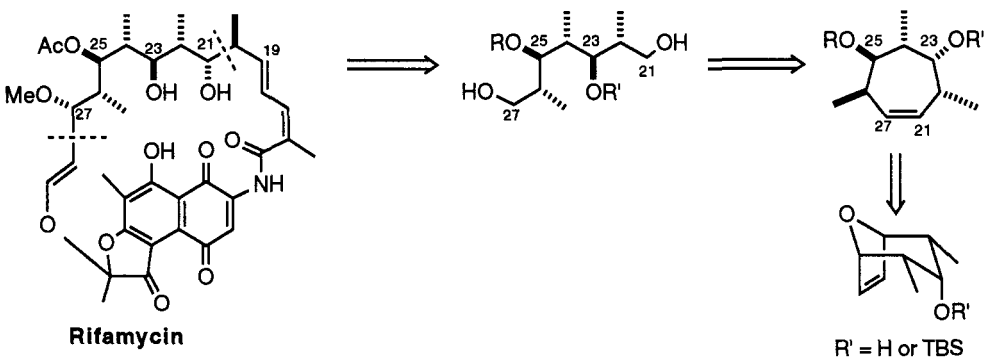
Oxidative cleavage of a tetrasubstituted cyclohexenol was also accomplished under similar conditions to provide **28** in 80% yield, eq. 10 (ref. 22).



SYNTHESIS OF A SUBUNIT OF RIFAMYCIN S

To demonstrate the efficiency of the the ring opening strategy, the synthesis of a subunit of rifamycin was undertaken. Rifamycin is a complex macrolide which has been the subject of considerable synthetic effort culminating in several total syntheses and synthetic approaches to the ansa chain (ref. 23). Our retroanalysis of the C_{21}-C_{27} fragment is shown Scheme 2. In order to differentiate the terminal primary alcohols formed following the ozonolysis- reduction sequence, differentiation of the alcohols at C_{23} and C_{25} in the cycloheptenol was necessary.

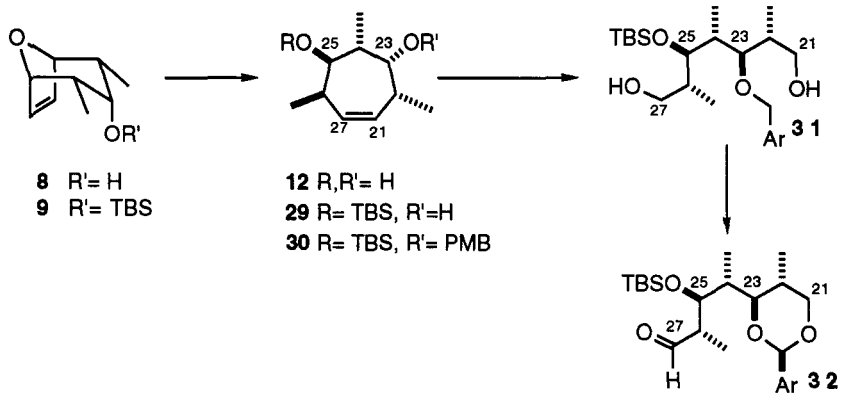
Scheme 2



Since ring opening was impossible on the protected alcohol **9**, it was necessary to selectively

protect one of the secondary alcohols in **12** which was prepared by ring opening of **8**. In the presence of 1.5 equivs. of TBS-Cl, protection of the hydroxyl group at C_{25} was achieved in 78% yield. The alcohol at C_{23} was then protected as a *para*-methoxybenzyl ether using PMB-Br (KH, DMF, 18-c-6) to give **30** (90%). Ozonolysis and reduction with $NaBH_4$ furnished the diol **31** in 75% yield. Treatment of **31** with DDQ in anhydrous CH_2Cl_2 and oxidation of the remaining alcohol under the Swern conditions gave **32** in 97% yield for the two steps. The fragment is stereochemically equivalent to the C_{21}-C_{27} subunit of rifamycin S with each of the four oxygens differentiated (ref. 15).

Scheme 3



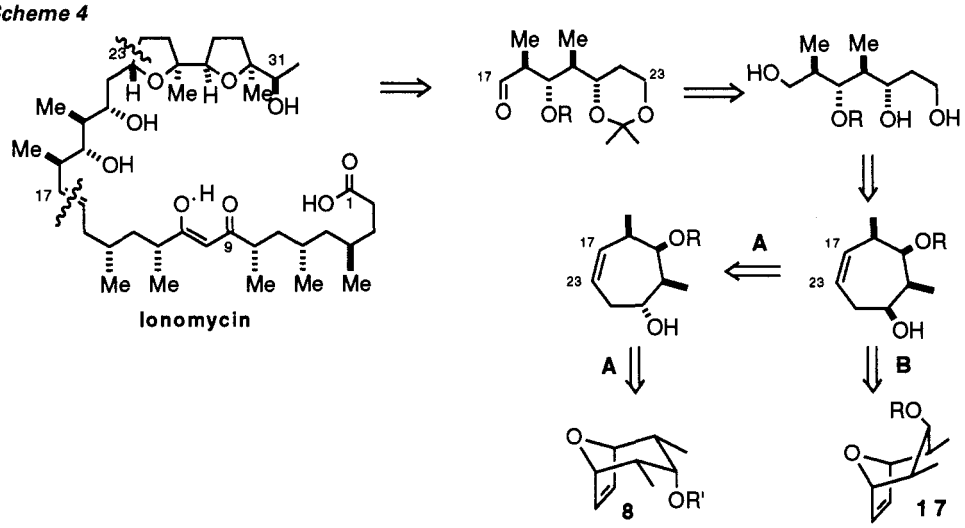
8 R'= H
9 R'= TBS

12 R,R'= H
29 R= TBS, R'=H
30 R= TBS, R'= PMB

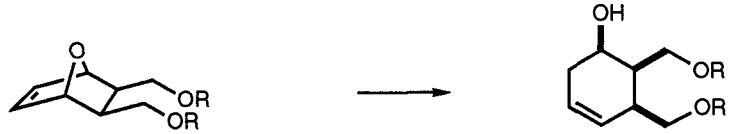
REDUCTIVE RING OPENINGS: SYNTHESIS OF A SUBUNIT OF IONOMYCIN

Retrosynthetic analysis of the ionophore, ionomycin (ref. 24), revealed that a strategy for the subunit comprising C_1-C_{23} could be developed based on ring opening and coupling of three oxabicyclic subunits. Specifically, C_{17}-C_{23} could be readily prepared from ring opening an oxabicyclo[3.2.1] system using a hydride as the nucleophile, Scheme 4, Routes **A**,**B**.

Scheme 4



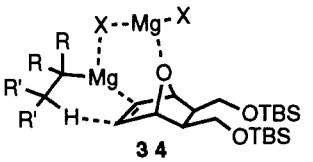
These routes both hinged on discovering a viable source of hydride. Nucleophilic hydride reagents such as $NaBH_4$, $LiAlH_4$, and L-selectride were ineffective, yielding recovered starting material. However, upon addition of excess magnesium bromide to *t*-butylmagnesium bromide, reductive ring opening occurred and led to **33** in 68% yield (ref. 25).



3 **33** (11)

The requirement for excess magnesium bromide suggests that assistance from the magnesium

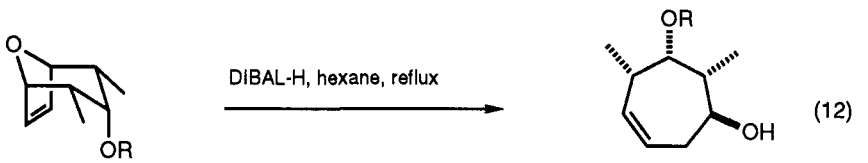
bromide probably occurs through coordination to the bridging oxygen. Complex **34** was proposed to explain the stoichiometry of the reaction.



34

Attempted reduction of [3.2.1] and substituted [2.2.1] oxabicyclic compounds revealed that significant limitations accompanied these reaction conditions. The reactions were sluggish, required a large excess of the reducing agent, and failed for several substrates. Other sources of hydride were investigated.

Since nucleophilic hydrides were unreactive, a Lewis acidic source of hydride was examined. DIBAL-H was also very sluggish when used in ether, THF or hexane at 0°C to room temperature. However, treatment of **9** with DIBAL-H in refluxing hexane provided **35a** in 52% yield, eq. 12. Reduction of **8**, which failed under the previously described conditions was even more efficient yielding **35b** in 83% yield (ref. 26). These results are in accord with Katzenellenbogen's observations that vinyl epoxides undergo conjugate reduction with DIBAL-H at 60-65°C in hexane (ref. 27).



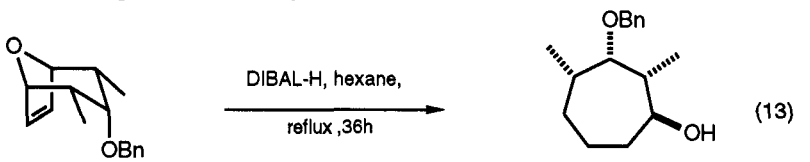
(12)

8 R = H
9 R = TBS

35a
b

In contrast to reactions with $RMgX/MgX_2$, substitution at the bridgehead had relatively little effect on the efficiency or rate of the DIBAL-H reduction. Many substrates undergo successful ring opening under these conditions. The yields are typically 10-25% higher, the reaction typically occurs much faster and substituents are tolerated at C_1 through C_5.

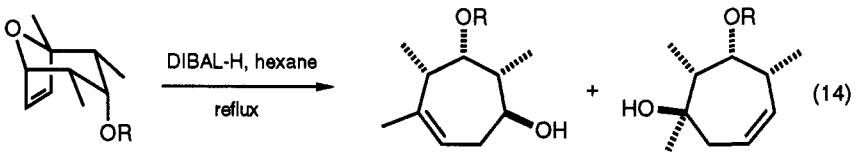
Reductive ring opening and further reduction of the double bond was also achieved by allowing the reaction to continue for an additional 24 h. For example, treatment of **36** with 5 equivs. of DIBAL-H for 36h provided a 75% yield of **37.**



(13)

36 **37**

A remarkable change in the regioselectivity was noted in the reductions of **38** and **39**. Reaction of **38** with DIBAL-H gave predominantly **41**, whereas reaction of the **39** with DIBAL-H was non-selective, eq. 14. However, pre-treatment of **39** with MeLi prior to addition of the DIBAL-H resulted in a dramatic improvement in the selectivity favoring formation of **40**. The result



(14)

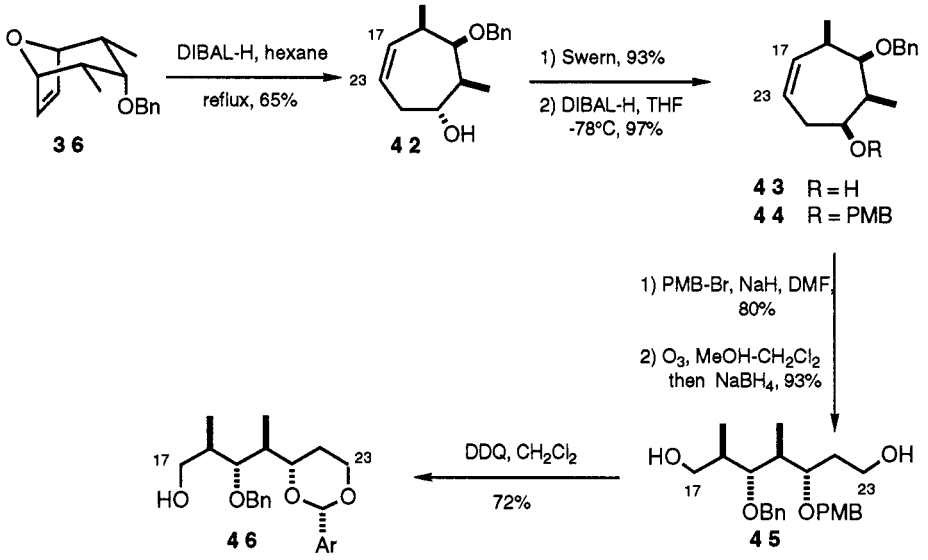
40 **41**

38	R = TBS		1	:	6.4
39	R = H	no MeLi	1	:	1.3
39	R = H	1.2 eq. MeLi	9.5	:	1

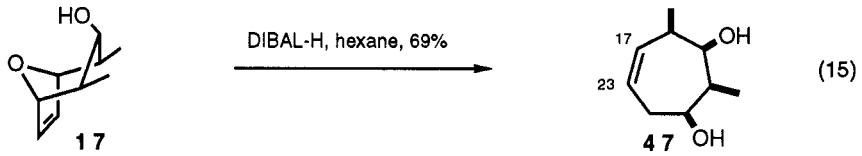
appears to be another manifestation of the *endo* alkoxide effect which not only results in activation of the olefin toward attack but also differentially activates the two reactive sites. Access to either regioisomer can be achieved by changing the substituent on the remote oxygen.

A direct and efficient synthesis of the ionomycin subunit C_{17}-C_{23} was accomplished based on the retroanalyses presented in Scheme 4, routes **A** and **B** (ref. 26). Reductive ring opening of the benzyl protected oxabicyclic compound **36** with 1 eq. of DIBAL-H gave **42** and 24% unreacted **36**. Attempts to convert the remaining starting material to product using longer reaction times or an excess of the reducing agent led to significant amounts of the overreduced product **37**. Inversion of the hydroxyl groups stereochemistry was accomplished by a two step procedure. Oxidation ($(COCl)_2$, Et_3N, DMSO) gave a β,γ-unsaturated enone which upon treatment with with DIBAL-H, -78°C provided alcohol **43** in 91% overall yield and with >15:1 stereoselectivity. Under these conditions, no conjugation of the olefin with the intermediate ketone was observed. Protection of the alcohol as its *para*-methoxybenzyl ether **44** occurred in 80% yield, followed by ozonolysis and *in situ* reduction with sodium borohydride provided **45** in 93% yield. Finally, DDQ oxidation under anhydrous conditions gave to the acetal **46** in which the termini are differentiated. In six steps from **36**, and eight steps from **2**, the C_{17}-C_{23} subunit was prepared (ref. 26). The overall yield is 31%.

Scheme 5



Route **B**, outlined in Scheme 4, was also briefly investigated. Reduction of **17** with DIBAL-H occurred in 69% yield to give diol **47** which is stereochemically equivalent to compound **43**.



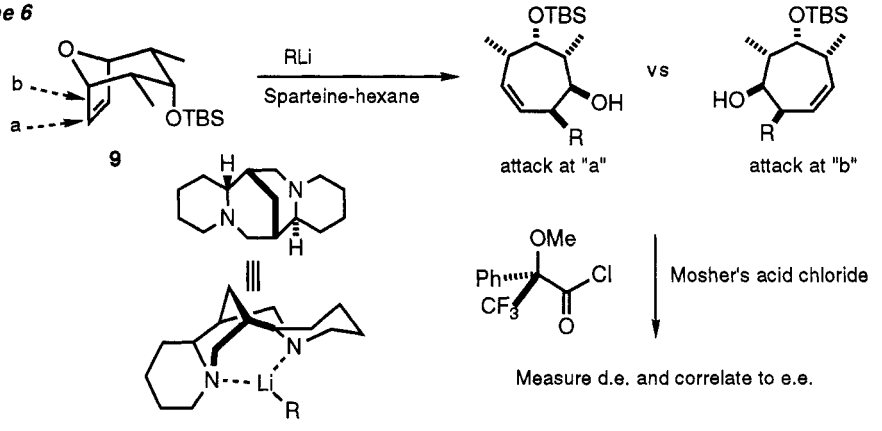
(15)

ENANTIOSELECTIVE RING OPENINGS

The reactivity of oxabicyclic compounds toward various nucleophiles has been demonstrated to be highly regio- and stereoselective, rapidly generating cyclic and acyclic compounds with multiple contiguous stereocenters. Up to this point, the one shortcoming associated with this methodology is the racemic nature of the products. Inspection of the starting materials reveals two possible approaches to the preparation of enantiomerically pure product. One approach would be to start with a enantiomerically pure unsymmetrical oxabicyclic compound requiring a resolution of racemic material or the development of methodology for an enantioselective cycloaddition to form the oxabicyclic ring. This strategy would be ineffective for the symmetrical substrates which are *meso*. However, ring opening at the two enantiotopic positions "a" vs. "b" leads to enantiomeric products.

We considered the use of a chiral "TMEDA equivalent" to promote an enatioselective opening since TMEDA had previously been shown to enhance the rate of ring opening reactions thereby permitting the use of lower temperatures. Our initial investigations have focused on sparteine as the "TMEDA" equivalent based on the precedent of Hoppe and Beak (ref. 28). Following ring opening, esterification of the alcohol with Mosher's acid chloride provides a simple method to measure the enantioselectivity of the ring opening reaction, Scheme 6 (ref. 29).

Scheme 6



We find that treatment of **9** with n-BuLi in pentane with varying amounts of sparteine leads to an enantioselective ring opening. The ee's of the products are affected by the reaction temperature and to a lesser extent by the ratio of sparteine to organolithium. The ee improves from 26% to 52% when the reaction temperature is lowered from room temperature to -78°C. The most promising result obtained thus far is that *catalytic amounts of sparteine* induce ee's of 40-50% when the reaction is carried out at low temperatures. Under these conditions, minimal non-sparteine catalyzed (and therefore non-enantioselective) ring opening occurs (ref. 30).

CONCLUSIONS

The ring opening strategy as outlined in this work represents an alternative to the existing approaches which have been used to construct stereochemically complex natural products. The advantages of using oxabicyclic compounds include; the convergent nature by which the stereocenters are created from readily available starting materials and the a variety of stereochemical arrays which are available depending on the choice of nucleophile and substrate. Furthermore, polypropionate and polyacetate arrays are prepared with equal facility.

Efforts to improve the enantioselectivity beyond the levels we have achieved thus far form the focus of our current studies.

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REFERENCES AND NOTES

1. *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Westley, J.W., Ed.; Marcel Dekker: New York, 1982; Vol. 1-2.
2. Rinehart, K.L., Jr.; Shield, L.S. In *Progress in the Chemistry of Organic Natural Products*; Hertz, W.; Grisebach, H.; Kirby, G.M., Eds.; Springer-Verlag: New York, 1976; Vol. 33, p 231.
3. Paterson, I.; Mansuri, M.M. *Tetrahedron*, **1985**, *41*, 3569 and references therein.
4. For reviews, see: a) Heathcock, C.H. *Comprehensive Organic Synthesis*; Trost, B.M. Ed.; Pergamon Press: Oxford, 1991; Vol. 2. pg. 133, 181. b) Kim, B.M.; Williams, S.F.; Masamune, S. *Comprehensive Organic Synthesis*; Trost, B.M. Ed.; Pergamon Press: Oxford, 1991; Vol. 2. pg.239. c) Fleming, I. *Comprehensive Organic Synthesis*; Trost, B.M. Ed.; Pergamon Press: Oxford, 1991; Vol. 2. pg.563

5. For reviews on allylmetal reactivity with carbonyl groups, see: a) Hoffmann, R.W. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 555. b) Yamamoto, Y. *Accts. Chem. Res.* **1987**, *20*, 243. c) Roush, W.R. *Comprehensive Organic Synthesis*; Trost, B.M. Ed.; Pergamon Press: Oxford, 1991; Vol. 2. pg.1.
6. a) Stork, G.; Kreft, A.F. *J. Am Chem. Soc.* **1977**, *99*, 3850, 3851. b) Stork, G.; White, W.N. *J. Am. Chem. Soc.* **1956**, *78*, 4604, 4609. c) Marshall, J.A. *Chem. Rev.* **1989**, *89*, 1503. d) Goering, H.L.; Kantner, S.S.; Tseng, C.C. *J. Org. Chem.* **1983**, *48*, 715. e) Staroscik, J.; Rickborn, B. *J. Am. Chem. Soc.* **1971**, *93*, 3046. f) Anderson, R.J. *J. Am. Chem. Soc.* **1970**, *92*, 4978. g) Herr, R.W.; Johnson, C.R. *ibid* **1970**, *92*, 4979.
7. a) Noyori, R.; *Accts. Chem. Res.* **1979**, *12*, 61. b) Hoffman, H.M.R. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 1. c) Mann, J. *Tetrahedron*, **1986**, *42*, 4611.
8. a) Sato, T.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2745. b) Ashcroft, M.R.; Hoffmann, H.M.R. *Organic Synthesis Collective vol. VI* **1988**, 512, 17. c) Cowling, A.P.; Mann, J.; Usmani, A.A. *J. Chem. Soc. Perkin Trans.1* **1981**, 2116. d) Murray, D.H.; Albizati, K.F. *Tetrahedron Lett.* **1990**, *29*, 4109.
9. Lipshutz, B.H. *Synthesis*, **1987**, 325.
10. Lautens, M.; DiFelice, C; Huboux, A.*Tetrahedron Letters* **1989**, *30*, 6817.
11. Abd-El-Aziz, A.S.; Lautens, M.; Lough, A.J. *Acta. Cryst.* **1991**, *C47*, 1047.
12. Lautens, M.; Smith, A.C.; Abd-El-Aziz, A.S.; Huboux, A.H. *Tetrahedron Letters*, **1990**, *31*, 3523.
13. Lautens, M.; Abd-El-Aziz, A.S.; Lough, A. *J. Org. Chem.* **1990**, *55*, 5305.
14. Arjona, O.; Fernandez de la Pradilla, R.; Garcia, E.; Martin-Domenech, A.; Plumet, J. *Tetrahedron Lett.* **1989**, *30*, 6437.
15. Lautens, M.; Belter, R.K. *Tetrahedron Lett.* **1992**, *33*, 2617.
16. a) Wittig, G.; Otten, J. *Tetrahedron Lett.*, **1963**, 601. b) Mulvaney, J.E.; Gardlund, Z.G. *J. Org. Chem.* **1965**, *30*, 917.
17. Caple, R.; Chen, G. M.S., Nelson, J.D. *J. Org. Chem.* **1971**, *36*, 2874.
18. Gajda, C.J. unpublished results.
19. Chiu, P. unpublished results.
20. Lautens, M.; Belter, R.K.; Lough, A.J. *J. Org. Chem.* **1992**, *57*, 422.
21. Lautens, M.; Ma, S.; Belter, R.K.; Chiu, P.; Leschziner, A. *J. Org. Chem.* **1992**, *57*, 0000.
22. Abd-El-Aziz, A.S. unpublished results.
23. a) Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M.R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962. b) Kishi, Y. *Pure & Appl. Chem.* **1981**, *53*, 1163. c) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. For other work in this area, see: a) Hanessian, S.; Pougny, J.-R,; Boessenkool, I. K. *J. Am. Chem. Soc.* **1982**, *104*, 6164. b) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348. c) Rao, A. V. Rama; Yadav, J. S.; Vidyasagar, V. *J. Chem. Soc., Chem. Commun.* **1985**, 55.
24. For previous work in this area see: a) Hanessian, S.; Cooke, N.G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276. b) Evans, D.A.; Dow, R.L.; Shih, T.L.; Takacs, J.M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290 and references therein.
25. Lautens, M.; Chiu, P, *Tetrahedron Lett.* **1991**, *32*, 4827.
26. Lautens, M.; Chiu, P.; Colucci, J.T. submitted for publication.
27. Lenox, R.S.; Katzenellenbogen, J.A. *J. Am. Chem. Soc.* **1973**, *95*, 957.
28. a) Kerrick, S.T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. b) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1422 and references therein.
29. a) Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543. b) Dale, J.E.; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
30. Gajda, C.J. unpublished observations.