The Magnesium−Ene Cyclization Stereochemically Directed by an Allylic Oxyanionic Group and Its Application to a Highly Stereoselective Synthesis of (±)-Matatabiether. Allylmagnesium Compounds by Reductive Magnesiation of Allyl Phenyl Sulfides[1]

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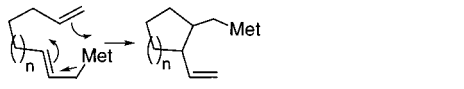
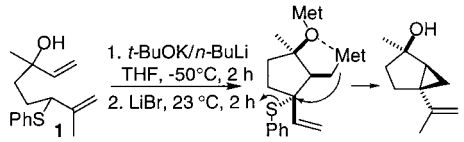
Abstract: The first example of a magnesium−ene cyclization stereochemically directed by an allylic oxyanionic group is demonstrated by a highly stereoselective synthesis of the bicyclic terpene matatabiether **10**. The synthetic method is particularly valuable, not only because of the stereochemical control and the utility of the versatile hydroxyl group introduced into the product, but also because the precursor of the allylmagnesium is an allyl phenyl sulfide, which is more stable and more easily prepared in a connective fashion than the usual allyl halide precursor. Since the presence of lithium ions encourages undesirable proton transfer to the cyclized organometallic and is detrimental to the stereochemical control, the conversion of the allylic thioether to the allylmagnesium utilizes a lithium-free method involving direct reductive magnesiation in the presence of the magnesium−anthracene complex.

During our study of the lithium−ene cyclization (eq 1; Met



(1)



(2)

= Li),[2,3] the important finding was made that an oxyanionic group, allylic to the enophilic alkene, greatly accelerated the carbanionic cyclization and led to a single diastereomeric product in which the organolithium function of the cyclized product was cis to the oxyanionic directing group (eq 2). If these advantages of allylic oxyanionic groups prove to be general in intramolecular carbometalations, the latter would obviously become far more useful because of (1) the facilitating effect of the oxyanionic group, (2) the high stereoselectivity, and (3) the very useful alcohol functionality. Although there have been reports of *intermolecular* carbolithiations and carbomagnesiations that are facilitated by an allylic oxyanionic group, albeit with limited efficiency and generality,[4] this technique apparently has not been applied to *intramolecular* magnesium−ene reactions (eq 1; Met = Mg).[5,6] The likely reason is that the organometallic is usually prepared from an allyl halide that would form a cyclic ether in the presence of the oxyanionic group. In addition, in the case of Mg−ene cyclizations,[5a] the allyl halide is produced from an allylic alcohol, thus presenting a regiochemical problem in differentiation between the two alcohol groups.

We are studying methods for reducing this concept to practice in the case of carbanionic cyclization of allylmagnesiums and nonallylic alkyllithiums.[7] In both cases, phenyl thioethers, which because of the great versatility of divalent sulfur are far easier to assemble than organohalides, are the substrates from which the organometallic is generated. In this paper, we reveal a procedure for performing a highly stereoselective magnesium−ene cyclization in the presence of an allylic oxyanionic group, including a general method for generating Li-free allyl- and benzylmagnesiums from allyl and benzyl phenyl sulfides, and we apply this procedure to the synthesis of a bridged bicyclic terpene.

Results and Discussion

In view of what we have learned about the lithium−ene cyclization,[2,3] in particular the thermodynamic unfavorability

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(1) Taken in part from the M.S. Thesis of Shirong Zhu, University of Pittsburgh, 1996.

(2) Cheng, D.; Zhu, S.; Liu, X.; Norton, S. H.; Cohen, T. *J. Am. Chem. Soc.* **1999**, *121*, 10241−42.

(3) Cheng, D.; Knox, R. K.; Cohen, T. *J. Am. Chem. Soc.* **2000**, *122*, 412−3.

(4) Reviews: Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1−20. Vara Prasad, J. V. N.; Pillai, C. N. *Organometallics* **1983**, *259*, 1−30. Marek, I.; Normant, J.-F. In *Metal Catalyzed Cross Coupling Reactions;* Diederich, F., Stang, P., Eds.; Wiley VCH: New York, 1998; pp 269−335.

(5) (a) Reviews of metallo−ene reactions: Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38−52. Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, England, 1991; Vol. 5, pp 29−61. (b) The Zn−ene cyclization has only recently come into prominence. For recent references see: Nakamura, E.; Kubota, K. *J. Org. Chem.* **1997**, *62*, 792−3. Lorthiois, E.; Marek, I.; Normant, J.-F. *J. Org. Chem.* **1998**, *63*, 2442−50.

(6) Allylic ethers in alkyllithium cyclizations (Bailey, W. F.; Jiang, X.-L. *J. Org. Chem.* **1994**, *59*, 6528−33) and both allylic ethers and esters in alkylzinc cyclizations (Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J. F. *Tetrahedron* **1994**, *50*, 11665−92. Lorthiois, E.; Marek, I.; Normant, J.-F. *J. Org. Chem.* **1998**, *63*, 2442−2450) give only modest stereoselectivity in five-membered-ring formation.

(7) Review: Bailey, W. F.; Ovaska, T. V. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press: Greenwich, CT.; Vol. 3, 1994; pp 251−73.

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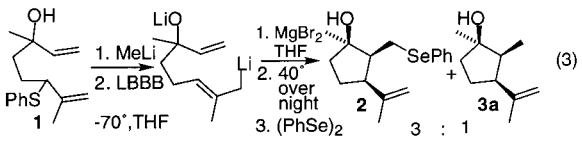
and the tendency of the cyclized organolithium to remove protons from solvent at the temperature required for the cyclization, the magnesium−ene cyclization was deemed to be the more useful of these two types of metallo−ene reactions for demonstrating the value of the allylic oxyanionic group at the enophilic site. Our initial goal in this endeavor was the stereoselective synthesis of the bicyclic terpene matatabiether **10**.[8] Since the all-cis cyclopentanol **2** (eq 3) is a key precursor

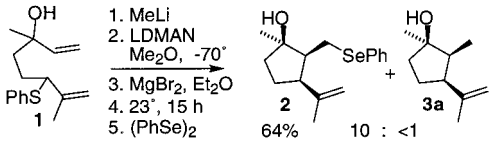


(3)

of **10**, the synthesis of the latter would provide a good demonstration of the directing effect of an allylic oxyanionic group, which would control the cis relationship of the selenium-bearing carbon atom and the hydroxyl group in **2**. The cis relationship between that same carbon atom and isopropenyl group would be a result of the strong preference in the magnesium−ene reaction to yield kinetic product in which the magnesium-bearing carbon atom and the unsaturated group are oriented in a cis fashion.[5a]

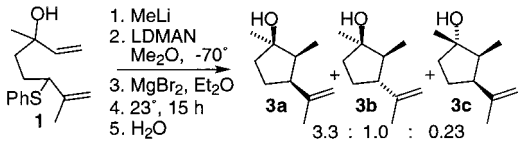
The first method tried to convert an allyl phenyl thioether to an allylmagnesium was reductive lithiation[9] of the thioether in the presence of the radical−anion lithium 4,4′-di-*tert*-butylbiphenylide (LDBB)[10] in THF and conversion of the resulting allyllithium[11] to a Grignard reagent by transmetalation with $MgBr_2$. This procedure was applied to **1**, after deprotonation with methyllithium. When the cold bath surrounding the solution of transmetalated allylmetallic was allowed to warm from −70 °C, the temperature of its generation, to 40 °C, the temperature at which it was maintained overnight, and the cyclization product was treated with the electrophilic trapping agent diphenyl diselenide, the phenylseleninated and protonated cyclization products (**2** and **3a**) were formed in a ratio (NMR) of 3:1 (eq 3). The method of assigning the stereochemistry of these products is outlined below. It was evident that the procedure was being somewhat compromised mainly by proton transfer to the cyclized organometallic either from adventitious moisture or from the THF solvent. Precautions to decrease the formation of **3a** by preventing exposure to moisture, using different electrophiles (such as D_2O) and using excess diphenyl diselenide with prolonged reaction time, failed, suggesting that proton abstraction from THF was the most likely source of **3a**.

The conjugate base of **1** was next subjected to reductive lithiation by lithium 1-(dimethylamino)naphthalenide (LDMAN)[12] in dimethyl ether, according to the new procedure for preparing and using aromatic radical anions with lithium counterions in non-THF solvents.[13] Transmetalation with $MgBr_2$ in diethyl ether and warming to 23 °C caused cyclization. The product was again captured with diphenyl diselenide and as hoped the ratio of selenide **2** to protonated product **3a** was now considerably greater (>10:1). A 64% yield of the selenide **2** was isolated (eq 4).



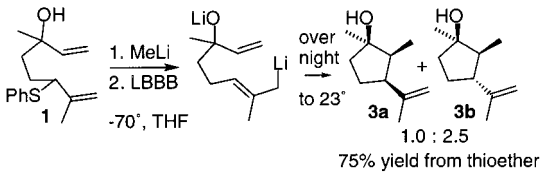
(4)

To assess the stereoselectivity of the ring-closure step, the same reaction was performed but the cyclized organometallic was quenched with water. The secondary methyl groups of three diastereomers were now clearly evident in the NMR spectrum of the crude reaction mixture and it could be determined that significant stereochemical inhomogeneity had occurred (eq 5).



(5)

Since the lithium−ene cyclization in the absence of the alcoholate group occurs with only modest cis-stereoselectivity[2] reminiscent of that observed in eq 5, while the magnesium−ene cyclization usually proceeds with high cis-selectivity,[5a] it was suspected that the relatively low stereoselectivity was due to reversibility of the ring closure because of the presence of lithium ions. The lithium−ene cyclization is reversible even at room temperature,[2] whereas the magnesium−ene cyclization is reversible only at elevated temperatures.[5a] This hypothesis was given more credence when it was shown that reductive lithiation of **1**, without subsequent transmetalation, followed by cyclization produced more of the trans (methyl and isopropenyl) product **3b** than the cis product **3a** (eq 6).[14] It also seemed possible that



(6)

the lithium ions were responsible for the proton transfer to the cyclized organometallic from THF, a known phenomenon in the Li−ene cyclization,[2] since Grignard reagents are known not to be particularly basic.

Therefore, the preparation of the allylmagnesium directly from the allyl thioether was attempted to avoid the presence of lithium ions. In a pioneering paper, Maercker[15] has reported that simple allyl phenyl sulfides could be converted to allylmagnesiums by being heated at reflux in THF with magnesium powder which had been activated by treatment with 1,2-dibromoethane or iodine. While this procedure failed in our hands, probably due to the magnesium powder available to us being less reactive than that used by Maercker (the grade of magnesium was not specified in the paper),[15] reductive magnesiation proceeded smoothly with our similarly activated magnesium powder when anthracene[16] was used. Because allyl phenyl sulfides are so

(8) (a) Sakai, T.; Nakajima, K.; Yoshihara, K.; Sakan, T. *Tetrahedron* **1980**, *36*, 3115−19 and references therein. (b) Kato, N.; Kamitamari, M.; Naganuma, S.; Arita, H. *Heterocycles* **1990**, *30*, 341−45 and references therein.

(9) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152−61.

(10) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *22*, 1924−30.

(11) Cohen, T.; Guo, B.-S. *Tetrahedron* **1986**, *42*, 2803−08. Guo, B. S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc.* **1987**, *109*, 4710−11.

(12) Cohen, T.; Matz, J. R. *Synth. Commun.* **1980**, *10*, 311−17.

(13) Liu, X.; Kulkarni, V.; Cohen, T. *Book of Abstracts*; 219th National Meeting of the American Chemical Society, San Francisco, March 26−30, 2000; ORGN-630.

(14) This is an interesting result since the lithium−ene cyclizations that we have observed in analogous systems but lacking the hydroxyl function (see eq 1) yield more cis than trans product.[2] A possible explanation is that the present ring closure is accelerated by the oxyanionic group and occurs at a lower temperature; we have observed that some cyclization occurs as low as −20 °C. At this low temperature, the quenching of the reaction that occurs by intra- and intermolecular proton transfers[2] may be slow compared to that of the des-hydoxyl analogues, which occur at 25 °C. Such slow quenching may provide time for the equilibration to occur.

(15) Maercker, A.; Jaroschek, H.-J. *J. Organomet. Chem.* **1976**, *116*, 21−37.

Scheme 1

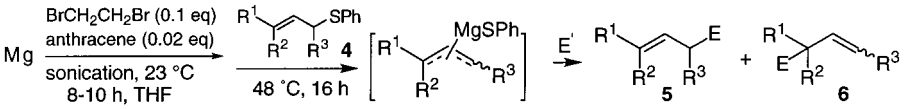


Table 1. Reductive Magnesiation of Allyl and Benzyl Phenyl Sulfides (Scheme 1)

sulfide	R^1	R^2	R^3	E′	product	yield, %
4a	H	H	H	*p*-$CH_3OC_6H_4CHO$	**5a**	92
4b	CH_3	H	CH_3	$Ph_2MeSiCl$	**5b**	53
4c	CH_3	CH_3	H	$Ph_2MeSiCl$	**5c**	59
4d	H	H	$PhCH_2$	$Ph_2MeSiCl$	**6d**	76
4e	H	H	$CH_2{=}CH(CH_2)_3$	H^+	*a*	81
$PhCH_2$				H^+	$PhCH_3$	82[b]
$PhCH_2$				$Ph_2MeSiCl$	$PhCH_2SiPh_2Me$	57

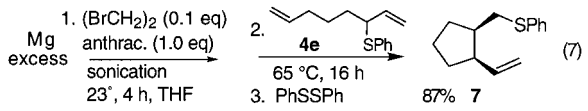
[a] Product not isolated; yield based on GC using an internal standard of chlorobenzene and an authentic sample of 1,7-octadiene. [b] GC yield with an internal standard of chlorobenzene.

stable compared to allyl halides, because they can be prepared by several methods, particularly connective ones, unavailable for the preparation of allyl halides,[11] and because the preparation of allyl Grignard reagents from allyl halides is plagued by Wurtz couplings,[17] we view the preparation of allylmagnesiums from allyl phenyl sulfides as a very important synthetic advance not withstanding the fact that it has never been used for synthetic purposes since Maercker's paper[15] appeared. Perhaps these advantages have not been generally appreciated. Therefore, we now diverge from the main course of this paper to describe our results in this endeavor.

The procedure first used was to mix magnesium powder with about 10 mol % of 1,2-dibromoethane and 2 mol % of anthracene in THF, to sonicate for 8−10 h at ambient temperature, and then to add the allyl phenyl sulfide **4** (or benzyl phenyl sulfide) and heat at 48 °C for 16 h. An electrophile E′ was added to capture the Grignard-type reagent and the yield of product **5** and/or **6** (or the benzyl analogues) was determined (Scheme 1).

The results for allyl phenyl sulfides and for benzyl phenyl sulfide are in Table 1. The optimum time and temperature, 16 h and 48 °C, were determined for allyl phenyl sulfide **4a**. A lower temperature, 23 °C, gave a slightly lower yield (82%) of product and longer reaction times did not improve the yield. As in Maercker's report,[15] no coupled product could be detected; this is understandable on the basis that unlike chloride, thiophenoxide is only a nucleofugal group when it is displaced in an intramolecular nucleophilic substitution to form a three-membered ring.[3,18] Where comparisons are possible, the yields of trapped products in Table 1 are comparable to or far higher than those obtained from the corresponding allyl chloride using 100 mol % of anthracene.[16,19]

We next applied a modification of this technology to the production of a simple terminally unsaturated allylmagnesium compound, 2,7-octadienylmagnesium thiophenoxide; the corresponding Grignard reagent is known to undergo the magnesium−ene cyclization to produce *cis*-2-(vinylcyclopentyl)-methylmagnesium halide.[20] The modification involved the use of 100 mol % of anthracene as used by Bogdanovic[16] for the preparation of allylmagnesium chlorides from the allyl chlorides. The reductive magnesiation of **4e**,[2] heating the allylmagnesium intermediate to execute its cyclization, and capturing the cyclized organomagnesium with diphenyl disulfide produced the cyclized phenyl thioether **7** in 87% yield as shown in eq 7.[21]



These results in hand, we were now in a position to attempt the reductive magnesiation of **1** in the absence of lithium ions in the hope of maximizing the all cis stereoselectivity and minimizing proton transfer of the cyclized organometallic from solvent. The alcohol was deprotonated with MeMgBr in THF and the conjugate base was subjected to reductive magnesiation in the presence of 0.1 equiv of anthracene at 48 °C for 24 h. About 50% of **1** was converted to the allylmagnesium intermediate which cyclized completely. It was eventually found that higher temperatures and greater amounts of anthracene led to complete reaction of the starting material as well as complete cyclization of the allylmagnesium. To assess the stereoselectivity under these conditions, the cyclized product was trapped by protonation and the three detectable isomers were quantitated

(16) Anthracene has been used for the production of allyl Grignard reagents from the corresponding allyl halides: Bogdanovic, B. *Acc. Chem. Res.* **1988**, *21*, 261−67. Bogdanovic, B.; Janke, N.; Kinzelmann, H.-G. *Chem. Ber.* **1990**, *123*, 1507−15.

(17) Benkeser, R. A. *Synthesis* **1971**, 347−58. Nützel, K. In *Houben-Weyl, Methoden der Organischen Chemie*; Müller E., Ed.; Georg Thieme-Verlag: Stuttgart, 1973; Vol. 13/2a, p 88.

(18) Cohen, T. *Pure Appl. Chem.* **1996**, *68*, 913−18 and citations therein.

(19) We thank Professor Bogdanovic for providing us with chemical yields from the thesis of N. Janke, Bochum University, 1986. Their yields were determined by protonation which, as shown for the benzyl case in Table 1, is expected to give better yields than reaction with other electrophiles. Their yields from allyl chloride itself ranged from 64 to 97%, depending on solvent (compare our yield from **4a**). In preliminary experiments, our yield of silylation product (mixture of three isomers) from crotyl phenyl sulfide was about 60% whereas the yield from crotyl chloride was reported in the thesis to be 28%. Their yields from benzyl chloride ranged from 64 to 71%.

(20) Felkin, H.; Hagaman, E.; Umpleby, J. D.; Wenkert, E. *Tetrahedron Lett.* **1972**, 2285−2288.

(21) The cis stereochemistry is assigned to **7** on the basis of two arguments: (1) The same organomagnesium, with a chloride ligand in place of the thiophenoxide, has been reported to yield the cis cyclization product.[20] (2) The NMR spectrum of **7** is clearly different from that of the isomer prepared by conjugate addition of the cuprate derived from phenylthiomethyllithium to cyclopentene-1-carboxaldehyde in the presence of Me_3SiCl, followed by Wittig olefination; this is thought to be the trans isomer.[1]

(22) Oppolzer, W.; Jacobsen, E. J. *Tetrahedron Lett.* **1986**, *27*, 1141−44.

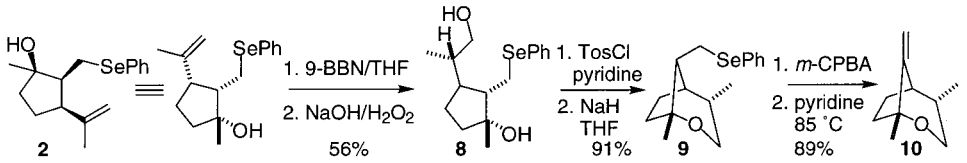
(23) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22−30.

(24) Inexplicably the alicyclic protons, except for the ether ones, were omitted from the spectrum reported in ref 8a.

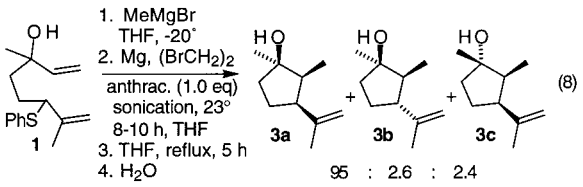
(25) Isoe, S.; Ono, T.; Hyeon, S. B.; Sakan, T. *Tetrahedron Lett.* **1968**, 5319−23. There was no regio- or stereocontrol in this synthesis and the former was extremely poor in the key cyclization step, when repeated by a different group; the cyclization led to a 4:1 mixture containing predominantly the wrong isomer.[8a]

(26) Battioni, J. P.; Capmau, M.-L.; Chodkiewicz, W. *Bull. Soc. Chim. Fr.* **1969**, 976−80. Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521−46.

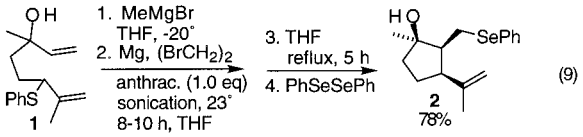
Scheme 2



by NMR spectroscopy. The results indicate that the absence of lithium ions did indeed increase the stereoselectivity; the all cis alcohol **3a** constituted 95% of the cyclization products (eq 8).



To apply this finding to the natural product synthesis, the procedure was repeated and the cyclized organomagnesium was trapped with diphenyl diselenide to produce a 78% yield of the phenyl selenide **2** (eq 9). Only about 3% of protonated product



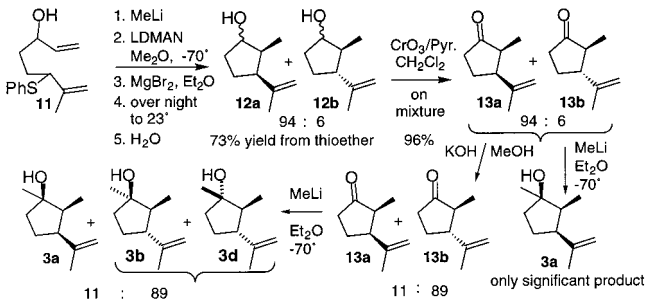
3a was detected. Thus, the use of reductive magnesiation not only led to greater stereoselectivity than reductive lithiation followed by transmetalation but proton transfer from the solvent was all but eliminated as well. Furthermore, this procedure is far easier operationally than reductive lithiation and exchange.

Completion of the synthesis of matatabiether **10** is shown in Scheme 2. Whereas hydroboration of **2** with borane resulted in a 1:1 mixture of diastereomers, the use of 9-BBN followed by oxidative workup gave the desired product in excellent diastereoselectivity; the ratio of product **8** to the other isomer isolated, presumably the diastereomeric product of the hydroboration, was 24.5:1. Oppolzer and Jacobsen observed a similar facial selectivity in a related system.[22] There were other unidentified products in the reaction mixture that were not UV active, suggesting that partial oxidation, by hydrogen peroxide, and elimination of the phenyl selenide had occurred.

Conversion of the primary hydroxy group into a tosylate followed by displacement of the latter by the tertiary oxyanionic group generated by treatment with sodium hydride resulted in smooth cyclization to the heterocyclic-bridged structure **9** in 91% yield. Oxidative elimination in **9** turned out to be more difficult than usual,[23] which allowed clean oxidation with *m*-CPBA in CH_2Cl_2 to give the corresponding oxides as a mixture of 1:1 diastereomers. The selenoxide mixture was washed with base and sodium thiosulfate, dried, and heated in pyridine at 85 °C for 15 min yielding 89% of racemic matatabiether **10**, the ^{1}H NMR spectrum of which was in excellent accord with that reported.[8a,24] The only other total synthesis of matatabiether was in connection with its structural proof and no yields or other details were provided.[25]

Finally, we provide the evidence for the stereochemistry of the cyclization products of the lithium−ene and magnesium−ene reactions of the allylmetallics derived from **1**. The stereochemistry of **3a** was assigned on the basis of two lines of evidence: (1) Cyclization of the transmetalated reductive

Scheme 3



lithiation product of the des-methyl analogue **11** of **1** by warming to 23 °C overnight yielded the products **12a** and **12b** in the ratio of 94:6 (Scheme 3). **12a** Consisted of a pair of diastereomers in slightly unequal amounts. On the other hand, **12b** consisted largely of one isomer. Oxidation of the mixture yielded two ketones **13a** and **13b** in the same ratio, 94:6. Thus, the diastereomers of **12a** were due to the two possible orientations of the hydroxyl group. Stereochemical equilibration of the oxidation mixture by means of base essentially reversed the ratio, thus leading to the conclusion that the cis isomer **13a** was the major one from the oxidation. The addition of methyllithium to this ketone mixture from the oxidation gave only one significant product, **3a**. It is a safe assumption that the methyllithium attacks from the side opposite to the substituents on the ring.[26] (2) As indicated in eq 8, **3a** can also be generated by protonation of the magnesium−ene cyclization product of the allylmagnesium derived from **1**. When the intermediate cyclized organomagnesium compound is phenyl seleninated instead of being protonated (eq 9), the resulting compound can be transformed to matatabiether **10** as discussed above; this transformation requires the stereochemistry shown.

The addition of methyllithium to the equilibrated ketone mixture yielded an alcohol mixture containing two major products **3b** and **3d**, comprising 89% of the alcohol product (by NMR integration of the ring methyl peaks) and 11% of **3a**. The ring methyl peaks of **3b** and **3d** overlap but the ratio of **3b** to **3d** is approximately 1:2. Since all of the intramolecular lithium−ene additions to allyl alcohol anions that we have studied[3] give products in which the cyclized organolithium function is cis to the oxyanionic group (as, for example, in eq 2), it is satisfying that this is the arrangement as well in **3b**, generated in eq 6. The small amount of **3c** formed in eq 5 is assigned the structure shown by a process of elimination; no such product was clearly detected upon addition of methyllithium to either ketone mixture, an expected result if the addition to **13a** is highly stereospecific.

In conclusion, a method has been devised by which a magnesium−ene cyclization can be performed on a system bearing an oxyanionic group allylic to the enophilic alkene. It is particularly useful that the precursor of the allylmagnesium intermediate that undergoes the cyclization is an allyl phenyl sulfide that is far simpler to prepare in a connective fashion than the traditional allyl halide precursor. It is of considerable interest that the presence of lithium ions decreases both chemo- and stereoselectivity and as a result the allylmagnesium is best

prepared by reductive magnesiation of the allyl sulfide rather than by the better established reductive lithiation followed by transmetalation. In this connection, a general method of reductive magnesiation of allyl phenyl sulfides has been devised, a key aspect of which is the use of the anthracene−magnesium complex.

The valuable oxyanionic functional group leads to very high stereoselectivity in the ring closure such that the hydroxyl group of the cyclized product is cis to the alkylmagnesium group. There is probably also a rate increase associated with the introduction of this group since cyclization of allylmetallics which were generated by reductive lithiation followed by transmetalation occurred at 23 °C, considerably below the usual temperatures for Mg−ene cyclizations.[5] However, in those cases we cannot be certain that the cyclization is a Mg−ene reaction because of the presence of lithium ions. Unfortunately, the reductive magnesiations require high enough temperatures that the cyclizations occur along with the metalation and we cannot be certain if the hydroxyl group facilitates the ring closure as it does in the case of the lithium−ene cyclization.

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Supporting Information Available: Experimental procedures and compound characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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