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DIASTEREOSELECTIVE SYN OR ANTI OPENING OF PROPARGYLIC EPOXIDES. SYNTHESIS OF α-ALLENIC ALCOHOLS

A. Alexakis*, I. Marek, P. Mangeney and J.F. Normant.

Laboratoire de Chimie des Organoéléments, Université P et M Curie, CNRS URA 473
Tour 44-45, 4 Place Jussieu, 75232 Paris Cedex 05, France

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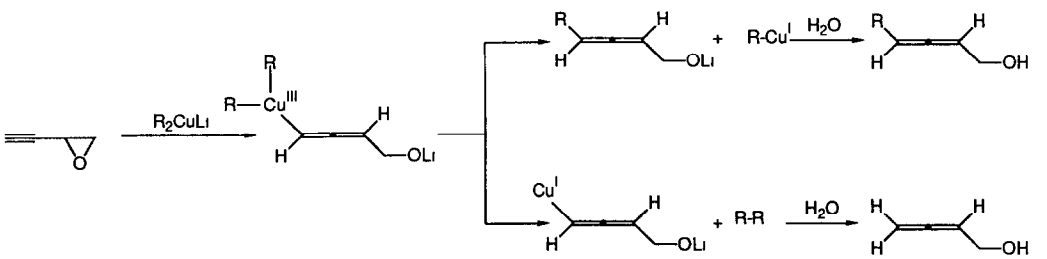
Abstract *Propargylic epoxides easily react with Grignard reagents and catalytic amounts of copper(I) salt to afford α-allenic alcohols The reaction is highly diastereoselective and its stereochemical outcome (syn or anti isomer) can be fully controlled The syn diastereomer, probably arising through an addition-elimination mechanism, is better obtained with RMgCl and copper(I) bromide, whereas the anti diastereomer, is better obtained with RMgBr and a complexed copper(I) salt With RLi and a catalytic amount of copper salt, phenethynyl cyclohexene oxide reacts through reductive lithiation, affording, stereoselectively, an allenyl lithium reagent*

INTRODUCTION

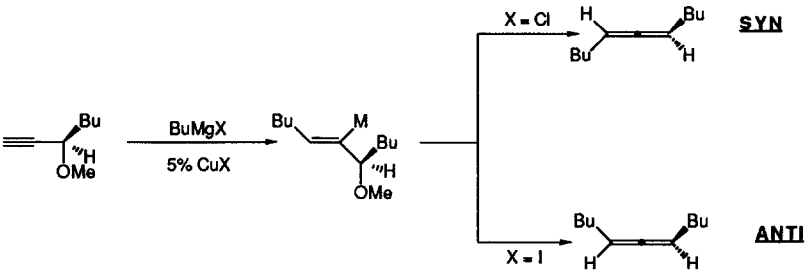
The opening of epoxides by carbon nucleophiles is a common reaction in organic synthesis Among these carbon nucleophiles, organocopper and cuprate reagents are the most widely used [1] In the case of propargylic epoxides the reaction affords α-allenic alcohols [2] It was shown, later on, that the same result could be obtained with Grignard reagents and a catalytic amount of copper(I) salt instead of the stoichiometric organocopper reagent [3] Since then, a great number of α-allenic alcohols were prepared in this way,[4] as intermediates in multi-step syntheses or as target molecules for their biological interest

The stereochemical course of this reaction was also shown to be an *anti* overall process,[5] through a postulated Cu^{III} intermediate, on the basis of analogies with other propargylic substrates having a good leaving group[6] (OAc, OCOR, OSO_2R, OSOR, halogen etc) Support to this mechanism can be found from the fact that Ortiz de Montellano[2] obtained as major by-product an unsubstituted allenol Such reduction by-products are typical of a Cu^{III} intermediate



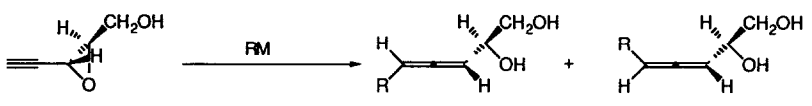
Scheme 1

We have, for our part, disclosed another mechanism for the formation of allenes from propargylic ethers and stoichiometric organocopper reagents a *syn* addition across the triple bond, followed by a β-elimination [7,8] In the cuprocatalyzed Grignard version of this reaction,[9] this β-elimination step is crucial for the stereochemical outcome With **RMgBr** and **RMgI** it is mainly an *anti* β-elimination, whereas with **RMgCl** it is mainly a *syn* β-elimination In the first case the allene results from an overall *anti* S_N2' displacement of the propargylic ether, whereas in the second the allene results from an overall *syn* S_N2' displacement



Scheme 2

This "halogen effect" operates only when an addition-elimination mechanism is involved It is completely inefficient on a reaction proceeding through a Cu^{III} intermediate [9b] If the reaction with propargylic epoxides proceeds through the latter mechanism, leading to α-allenic alcohols, it should be insensitive to a "halogen effect" If, however, one considers that epoxides are a special kind of *ethers*, then, an addition-elimination mechanism could be operative as well Therefore a "halogen effect" could influence the steric course of the reaction In this context, it was not surprising to find a recent report in the litterature concerning a non-stereoselective reaction of propargylic epoxide with a cuprate reagent [10]



	SYN	ANTI
R_2CuMgX	60	40
R_2CuLi, Me_2S	4	96

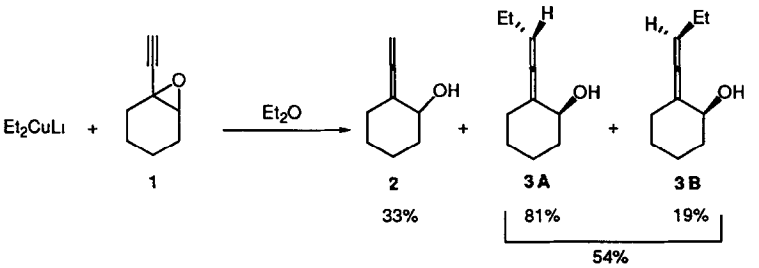
Scheme 3

This result may be understood if the addition-elimination path is the predominant one in this reaction We report herein our full results concerning this study which shows that, indeed, the addition-elimination mechanism predominates in the cuprocatalyzed Grignard reaction, whereas a Cu^{III} intermediate seems more plausible with organolithium derived stoichiometric organocuprate reagents [11]

RESULTS AND DISCUSSION

Optimization studies.

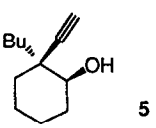
Our first experiments were done with ethynyl cyclohexene oxide **1** as model epoxide Indeed, in an early attempt, we reacted **1** with Et_2CuLi under the conditions described by Ortiz de Montellano[2] and we obtained the same result as him, considering the amount of reduction **2** and alkylation product **3A** + **3B** However, upon examination of the ^{13}C NMR spectrum[12] it was clear that two alkylation products were present (in the ratio 81 19) In view of the known propensity of organocopper reagents to promote preferential anti substitution,[1,13] we ascribed to the major isomer **3A** the *anti* configuration



Scheme 4

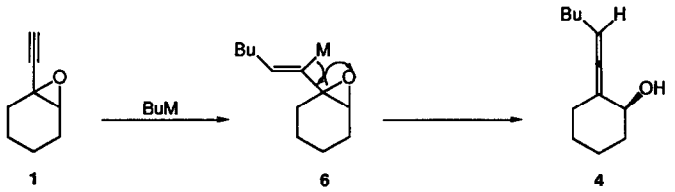
It, thus, appears that ethynyl cyclohexene oxide **1** is an adequate model for our study since the *anti* and *syn* stereoisomers are well distinguished by ^{13}C NMR, or by G C on the acetates We first started with the optimization of the experimental condition leading to the *anti* diastereomer, having in mind that, for propargylic ethers,[9] these best conditions require *a)* a good ligand to copper and *b)* a Grignard reagent RMgX with X = I or Br The results are quoted in table I

It appears that the reaction is not always very clean Several by-products are formed among which some were identified by their characteristic NMR signal, but were not isolated The most important are the reduction allenol **2** and the product of direct opening of the epoxide, **5**, having presumably the following configuration



5

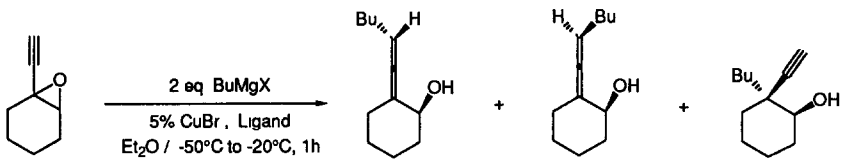
The best stereoisomeric ratio was, as expected, obtained with two equivalents of ligand (per Cu salt) instead of one, and with PBu_3 or $P(NMe_2)_3$ as ligand PBu_3 was preferred because the reaction mixture remained homogeneous throughout the reaction Finally it should be noticed that the directing effect of the ligand overcomes the nature of X in RMgX, since butyl magnesium **chloride** and **iodide** behave as the corresponding **bromides** (as far as the *anti / syn* ratio is concerned) Compared to propargylic ethers, the reaction of propargylic epoxides is much faster, being completed in a few minutes at -50° to -30°C In no instance was it possible to isolate any adduct, such as **6** (scheme 5), which, anyway, would be too unstable , the β-elimination in such a strained molecule should be very fast



Scheme 5

From the above results it is not possible to draw any conclusion concerning a Cu^{III} process or an addition-elimination one Reactions where the *syn* process would predominate would be more indicative of an addition-elimination mechanism It immediately turned out that the *syn* process was indeed a viable pathway We modified, then, the experimental conditions to get synthetically interesting levels of diastereoselection These optimization results are quoted in table II

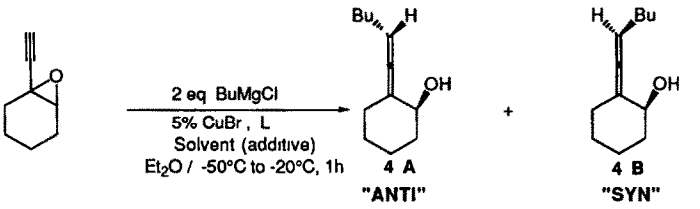
Table I : Optimization of the *anti* process



Entry	RMgX	Ligand	*Anti / Syn*[a]	yield[b] %	By-products
1	BuMgBr	$2P(OEt)_3$	46/54	95%	
2	BuMgBr	$P(NMe_2)_3$	99/1	52%	**5** (30%)
3	BuMgBr	$2P(NMe_2)_3$	100/0	75%	**5** (10%) + **2** (5%)
4	BuMgBr	PBu_3	88/12	50%	**5** (25%) + **2** (10%)
5	BuMgBr	$2PBu_3$	100/0	74%	**5** (18%)
6	BuMgCl	$2PBu_3$	94/6	45%	several
7	BuMgI	$2PBu_3$	90/10	31%	several

a) the *syn/anti* ratio was determined by ^{13}C NMR spectroscopy It is also possible to distinguish the two corresponding acetates on capillary glass GC (OV 101 column, 25 m)
b) Yield of isolated material, by column chromatography on SiO_2

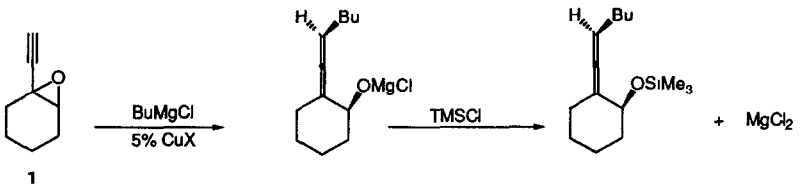
Table II : Optimization of the *syn* process



Entry	CuX	Ligand	Solvent	Additive[a]	*Anti / Syn*[b]	Yield[c] %
1	CuBr	$2P(OEt)_3$	Et_2O	-	41/59	quant
2	CuBr	-	Et_2O	-	35/65	72%
3	CuBr	-	benzene	-	20/80	48%
4	CuBr	-	Et_2O	1eq TMSCl	24/74	82%
5	CuCl	-	Et_2O	1eq TMSCl	29/71	quant
6	CuCN	-	Et_2O	1eq TMSCl	38/62	quant
7	CuSPh	-	Et_2O	1eq TMSCl	37/63	quant
8	CuBr	-	Et_2O/pentane	(1eq TMSCl)	12/88	quant
9	CuBr	-	Et_2O	-	10/90	84%[d]

a) The amount of additive is related to the epoxide
b) Same as a) in table I
c) Yield of isolated allenol **4A** + **4B** When quantitative, the yield was determined by G C with undecane as internal standard
d) The reaction needs to be warmed to 0°C for 2 h

First of all, any ligand has a deleterious effect on the amount of the *syn* adduct **4B** Without ligand, the reaction is as fast and more *syn* selective The solvent plays a role, since a reaction run in benzene (with BuMgCl in benzene) gave a 20/80 *anti /syn* ratio , however the chemical yield is poor As with propargylic ethers,[9] the addition of one equivalent of trimethylsilylchloride (TMSCl) greatly improves the *syn* selectivity It may act by increasing the concentration of $MgCl_2$ salts or by removing the alcoholate from the Grignard aggregate, or both , its exact role cannot presently be ascertained



Scheme 6

A higher *syn* selectivity was unsuccessfully sought by changing the copper salt (entries 5-7) On the other hand we had more success by combining TMSCl and a lower overall basicity of the reaction medium, using a 50/50 mixture of Et_2O and pentane After our study was completed, we observed, first in the case of phenethynyl cyclohexene oxide **9,** and then in all the cases of terminal acetylenic epoxides, that the reaction could be achieved without Cu salt at all ! Moreover it was the best way to obtain a very high *syn* selectivity ! The conclusion of this discovery **was not** that Cu^I salts were completely useless In fact, the reactions without Cu^I salts were very slow (1-2 h at 0°C to room temperature) and impossible with substituted alkynes

The conclusion of these studies were quite puzzling, mechanistically It seems that both a Cu^{III} mechanism and an addition-elimination mechanism are operative as well as a direct S_N' substitution by the Grignard reagent itself Nevertheless the synthetic interest of this stereochemical control motivated our further studies Thus, having established the best conditions of a highly diastereoselective reaction we examined its scope and limitations

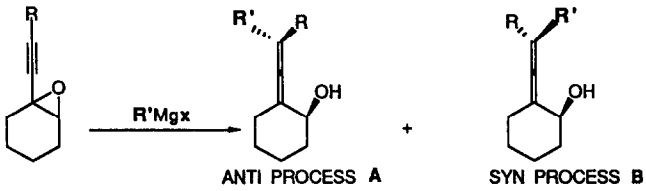
Scope and limitations

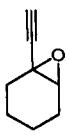
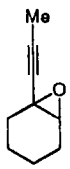
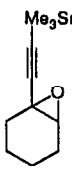
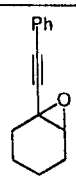
Allenic alcohols are quite interesting synthons in that they contain highly condensed stereochemical information [4] Thus, they may be oxidized on the allenic skeleton to afford, among others, cyclopentenone derivatives,[14] or stereoselectively alkylated [15] We sought, through a series of various epoxide,[5] to generalize our diastereoselective opening Thus, substituted alkynyl cyclohexene oxides **7**, **8** and **9** as well as their non-substituted congener **1** were tested against various Grignard reagents under both our best *anti* and *syn* conditions The results are quoted in table III

The *anti* process is always highly or completely diastereoslective On the other hand, the *syn* process is equally selective, except for phenethynyl cyclohexene oxide **9** where 3 1 to 5 1 mixtures were obtained It should also be noted that in only one instance, **20A** and **20B**, the diastereomers could not be distinguished by either ^{13}C NMR or by G C on the acetates In all the other cases it was possible to get accurate determination of the isomer ratio Thus, both diastereoisomers of an allenic alcohol can thus be obtained at will

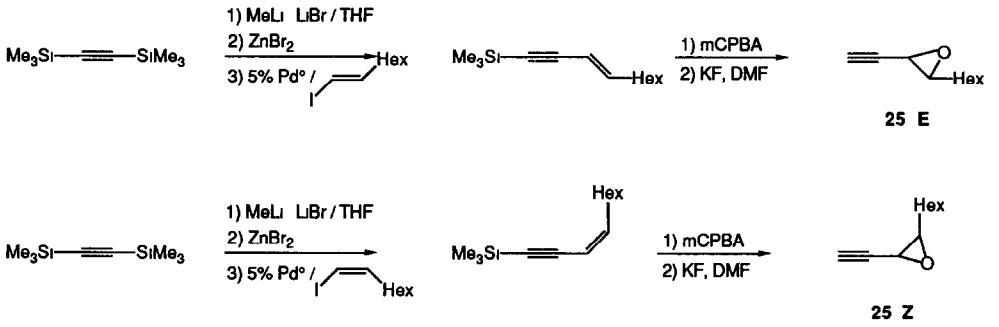
It was of interest to check if this stereochemical control was also operative in the acyclic series To this end, we synthesized the following isomeric epoxides[21] **25E** and **25Z** according to the sequence shown in scheme 7 This high yielding preparation affords both isomers in a very high state of purity (> 99%) [21b]

Table III : Reaction with various epoxides according to an *anti* or *syn* process



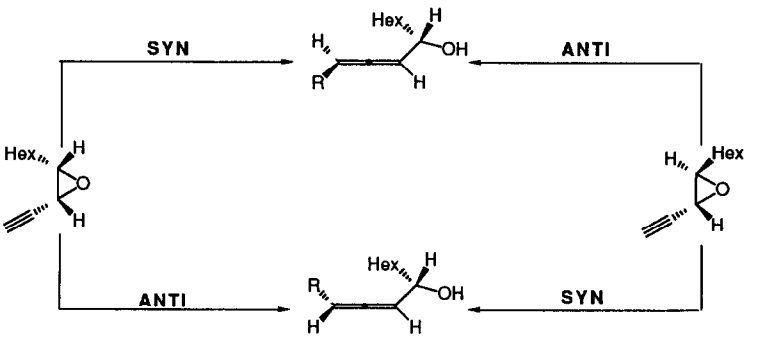
Epoxide	R'	Product	*Anti / Syn*[a] A/B	yield %	Product	*Anti / Syn*[b] A/B	yield %
1 	Me	10A	-	-	10B	*(5/95)*[c]	(91)
	Bu	4A	100/0	74	4B	12/88 *(10/90)*[c]	100 (84)
	IPr	11A	100/0	72	11B	10/90	80
	tBu	12A	96/4	78	12B	6/94 *(15/85)*[c]	100 (78)
	Ph	13A	95/5	60	13B	(4/96)[c]	(90)
7 	Bu	14A	100/0	65	14B	18/82	100
	IPr	15A	100/0	80	15B	16/84	100
	tBu	16A	95/5	98	16B	6/94	100
	Ph	17A	100/0	80			
8 	Me	18A	98/2	83	18B	8/92	61
	IPr	19A	95/5	91	19B	4/96	95
	tBu	20A	d	98	20B	d	92
	Ph	21A	99/1	87			
9 	Bu	22A	100/0	35	22B	50/50 *(20/80)*[c]	85 (53)
	IPr	23A	100/0	50	23B	25/75	84
	tBu	24A	97/3	92	24B	15/85	86

a) *anti* process 2 eq RMgBr + 5% CuBr 2PBu3 + epoxide in Et_2O
b) *syn* process 2 eq RMgCl + 5% CuBr + 1 eq Me_3SiCl + epoxide in Et_2O/pentane
c) modified *syn* process 2 eq RMgCl + 1 eq Me_3SiCl + epoxide in Et_2O
d) the two diastereomers were not distinguished by any analytical method



Scheme 7

These two epoxides were expected to give the same diastereomer when reacted under respectively an *anti* and *syn* process The same should be true if we reverse the experimental conditions as summarized in scheme 8

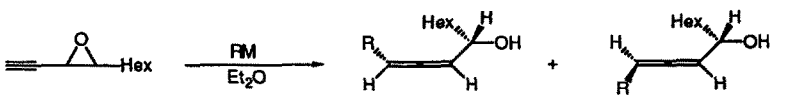


Scheme 8

The results are in complete agreement with our expectations and they are listed in table IV In all cases high selectivities and yields are obtained It should, however, be noted that, with trans epoxide **25E** the selectivities are higher, particularly for the *syn* process The most striking results are those without any copper salt, where, here again, a "halogen effect" appears (compare entries 1 and 2 , and 6 and 7) , moreover, this effect is much stronger with cis epoxide **25Z** than with its trans counterpart These results are quite difficult to rationalize, although the steric requirement of these substrates seem to be of crucial importance

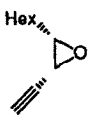
This steric control is, in fact, the dominant factor when working in the steroid series [22] Thus epoxide **28** was treated under our *syn* and *anti* conditions In both cases the *syn* product **29A** was obtained, exclusively in the former case or predominently in the latter one Indeed, an *anti* process implies an attack from the β face, the most sterically hindered one Finally, in a last attempt to obtain the *anti* isomer **29B**, we reacted epoxide **28** with Me_2CuLi , in this case the reduction product **30** was the major one (see scheme 9)

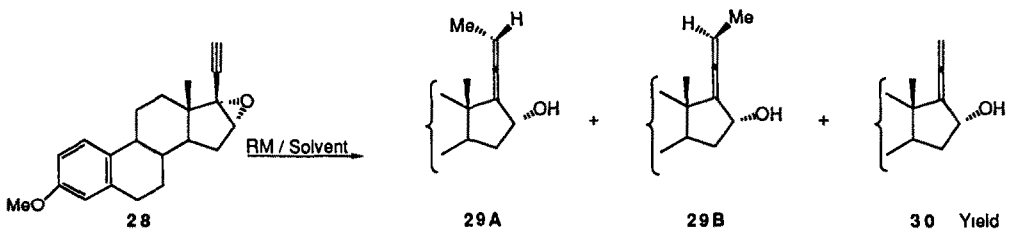
Table IV.: Reactions with aliphatic epoxides.



R Pent — **26A** — **26B**

R tBu — **27A** — **27B**

Epoxide	Entry	Conditions	yield %	Products	*Anti / Syn*
 **25Z**	1	PentMgCl	92%	**26A . 26B**	81/19
	2	PentMgBr	91%	**26A . 26B**	38/62
	3	PentMgBr + 5%CuBr,2PBu3	90%	**26A 26B**	10/90
	4	tBuMgCl	93%	**27A : 27B**	83/17
	5	tBuMgBr + 5%CuBr,2PBu3	84%	**27A 27C**	98/2
 **25E**	6	PentMgCl	94%	**26A 26B**	4/96
	7	PentMgBr	93%	**26A · 26B**	14/86
	8	PentMgBr + 5%CuBr,2PBu3	80%	**26A : 26B**	96/4
	9	tBuMgCl	92%	**27A . 27B**	6/94
	10	tBuMgBr + 5%CuBr,2PBu3	89%	**27A : 27B**	98/2



28 — **29A** — **29B** — **30** Yield

$MeMgCl / Et_2O$	(60	0	40) 42%
$MeMgBr + 5\%\ CuBr\ 2PBu_3 / Et_2O$	(60	12	28) 78%
Me_2CuLi / Et_2O	(15	0	85) 86%

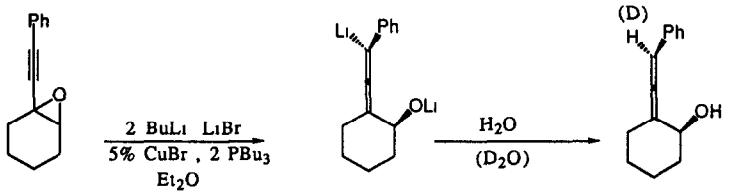
Scheme 9

With the example of this epoxide, we encounter the limits of the stereochemical control by an external factor Here the steric bias of the molecule imposes its rule and the fraction of the reaction which occurs through a

Cu^{III} intermediate prefers to collapse by reductive elimination into the reduction product **30** rather than the *anti* one **29B**

Reductive lithiation

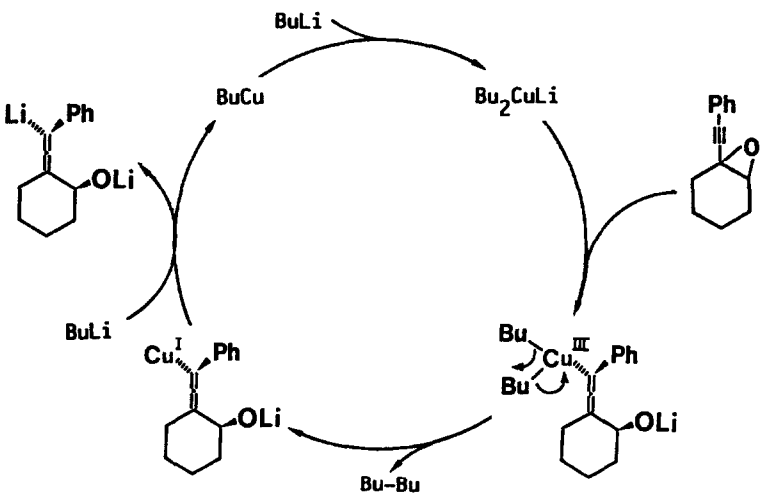
In the course of these studies we were also interested by the behaviour of organolithium reagents towards propargylic epoxides, in the presence of Cu^{I} salts. Although cuprocatalyzed reactions are not usually performed with such reagents,[16] we have already published a notable exception in the case of allylic epoxides. During the present study we observed a very clean reaction of phenethynyl cyclohexene oxide **9** and BuLi, in the presence of 5% CuBr·2PBu$_3$ in Et_2O as well as in THF. After hydrolysis, the already known allenol **13B** was obtained quantitatively, with 90% diastereoselectivity, instead of the expected butylated product **22** (scheme 10).



9 **31** **13B**

Scheme 10

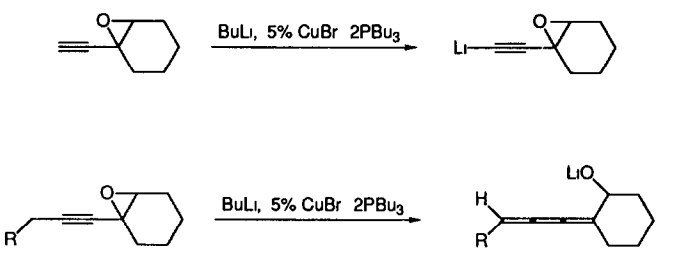
That an intermediate organometallic reagent was involved was shown by deuteration with D_2O, giving 100% deuterated **13B** Such reduction products have already been obtained in a similar reaction by Ortiz de Montellano,[2] and by P Crabbé and A E Greene,[23] but with stoichiometric amounts of Cu^{I} salts (R_2CuLi). Their formation is generally interpreted as typically involving Cu^{III} intermediates[6] (see scheme 1) In our case, where only 5% of Cu^{I} salt is present, **31** has to be an organolithium reagent, whose formation may be tentatively accounted by the following catalytic cycle



Scheme 11

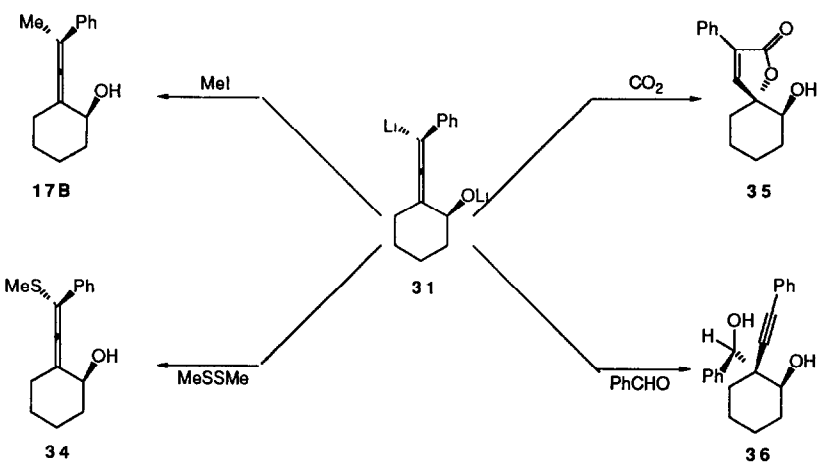
The contrathermodynamic formation of **31Li** from **31Cu** might not be as simplistically formulated and should involve several equilibrated cuprate and higher order cuprate species [17] As for the stereochemical outcome, it involves an *anti* displacement of the epoxide by the cuprate species, in agreement with usual organocopper chemistry What is more unusual is the stereochemical stability of the lithium intermediate **31Li.**

This reductive lithiation cannot be generalized to other propargylic epoxides Indeed monosubstituted alkynes are metallated, whereas disubstituted ones may undergo basic elimination and polymerisation of the resulting cumulene



Scheme 12

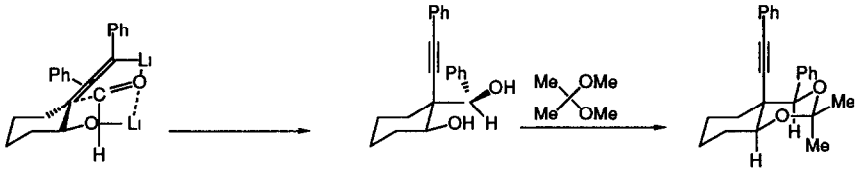
Despite the lack of generalisation of this particular reaction, the lithiated intermediate **31** reacts normally and diastereoselectively with various electrophiles (scheme 13)



Scheme 13

Thus, the alkylation[18] with MeI afforded **17B** in 93% yield and 90% diastereoselectivity The comparison with its isomer **17A** allowed a definite proof of stereochemistry The reaction with a disulfide is known to occur at the allenic center,[18] and, indeed, we obtained the allenic sulfide **34** (diastereomeric purity 90%), whose structure is assumed to be the one shown In the reaction with CO_2 , the resulting allenic acid undergoes cyclization into the lactone[19] **35**, during the acid-base treatment A single isomer was obtained

Finally, on the basis of known studies,[18a,20] the reaction with benzaldehyde was expected to occur from the propargylic site of the organometallic reagent **31Li** We, indeed, obtained a single compound in 88% isolated yield That means that attack at the carbonyl of benzaldehyde also occured diastereoselectively, as shown in the scheme 14



36 **37**

Scheme 14

The stereochemistry of **36** was ascertained by transforming it into the cyclic ketal **37** and two dimensional NMR techniques (NOESY)

CONCLUSION

The fact that it is possible to control the stereochemical course of the above reactions through a "halogen effect" is indicative of an addition-elimination mechanism However, it seems that the "Cu^{III} pathway" is also operative when an *anti* overall process is involved The reduction allenol is usually a good sign that, indeed, such a process occurs The reactions with stoichiometric *lithium* cuprates are particularly sensitive to this mechanism and the described Cu^{I} catalyzed reductive metallation of a propargylic epoxide has to be explained through this way Nevertheless, this stereochemical control of the reaction is of particular synthetic importance, since from the same epoxide it is possible to obtain, at will, either the R*,R* or the R*,S* allenol, These findings are even more interesting when considered in the homochiral series which is accessible through Sharpless epoxidation

EXPERIMENTAL PART

^{1}H and ^{13}C NMR spectra were recorded on a Jeol FX 90 Q or a Brucker AC 200 apparatus ($CDCl_3$, δ ppm from TMS) I R spectra were obtained on a Perkin-Elmer 1420 spectrometer (neat, cm^{-1}) GLPC analyses were performed on a Carlo Erba chromatograph model G1 and 2150 using a 3 m glass column (10% SE 30 on silanized chromosorb G 80/100 mesh or carbowax 20 M) and a 25 m capillary glass column (OV 101) The gas chromatograph was coupled to an integrator Hitachi D2000 Melting points were taken on a Buchi SMP-20 apparatus and are uncorrected Optical rotations were measured with a Perkin-Elmer 141 polarimeter

Starting materials.

1-Ethynylcyclohexene. To a cold (0°C) solution of 1-ethynylcyclohexanol (0 25 mol, 32 g) in pyridine (200 mL) maintained under nitrogen was added, with stirring, phosphorous oxychloride $POCl_3$ over a 30 min period The reaction mixture was allowed to warm to room temperature, stirred for 15 h, and then heated to 70°C for 1 h After cooling, ice (200 g) was added, the layers were separated, and the aqueous layer was extracted with ether The combined ether extracts were washed with 10% hydrochloric acid water, and saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$) and concentrated Distillation affords 21,74 g (82%) of a colorless liquid bp 71-72°C (60 mm) [Litt[24] 60°C (30 mm)] IR 3300, 3030, 2940, 2860, 2840, 2100, 1630, 1440 and 930 ^{1}H NMR 6,2 (m,1H), 2 75 (s,1H), 2 2-1 8 (m,4H), 1 7-1 4 (m,4H) ^{13}C NMR 136 2, 120, 85 6, 74 4, 29 1,25 6,27 3, 21 5

1-Phenethynyl cyclohexanol. To a solution of phenylacetylene (50 mmol, 5 1 g) in THF (100 mL) was added slowly at -40°C, MeLi LiBr (50 mmol, 41 6 mL) Thereafter, the cooling bath was removed and stirring was continued for 1 h at room temperature Then, cyclohexanone (50 mmol, 4 9 g) was added dropwise at -40°C The temperature of the mixture was maintained between -40°C and -20°C during 1 hour, and allowed to warm to room temperature (*ca* 1 h) and water (130 mL) was added The layers were separated, the aqueous phase extracted with ether, and the combined organic phases dried ($MgSO_4$) and concentrated under vacuum to afford the crude product (9,1 g) which is distilled through a Vigreux column to afford 8 8 g of pure material (88% yield) bp 106°C(0 4 mm) [Litt[25] 115°C (3 mm)] IR 3320, 2240, 1580, 1070, 750, 690 ^{1}H NMR 7 6-7 2 (m, 5H), 2 5 (s, 1H), 2 2-1 4 (m, 10H)

1-Phenethynyl cyclohexene. Using the procedure described for the preparation of ethynylcyclohexene from 1-ethynyl cyclohexanol Distillation of the crude product gave a colorless liquid (73% yield) bp 106°C (0 6 mm) [Litt[26] 167°C (16 mm)] IR 2195, 1594, 1488, 1435, 753, 688 ^{1}H NMR 7 4, 7 (m, 5H), 6 2 (m, 1H), 2 4-2 (m, 4H), 1 8-1 4 (m, 4H) ^{13}C NMR 134 8, 131 3, 128 1, 127 6, 123 9, 120 8, 91 3, 86 9, 29 3, 25 8, 22 4, 21 6

1-Propynyl cyclohexene. To a solution of 1-ethynyl-cyclohexene (50 mmol, 5 3 g) in methylene chloride (100 mL) at -40°C, was added dropwise over a 30 min period a solution of MeLi LiBr, (50 mmol, 41 6 mL) The reaction mixture was warmed to room temperature for 1 h, and then, at -40°C, was slowly added iodomethane (55mmol, 3 42 mL) After the addition was completed, the mixture was stirred 12 h at room temperature and hydrolyzed with satured aqueous NH_4Cl solution (100 mL) The layers were separated, the water layer extracted with ether and the organic layers dried (Na_2CO_3) and concentrated under vacuum to afford the crude product (4 7 g) which is distilled to give 4 4 g of pure material (72% yield) , bp 72°C (12 mm) [Litt[27] 68°C (10 mm)] ^{1}H NMR 6 (m, 1H), 2 1-1 9 (m, 4H), 1 8 (s, 3H), 1 7-1 5 (m, 4H) ^{13}C NMR 124 9, 113 3, 79, 73, 21 6, 18 6, 14 5, 13 8, 4 5

1-Trimethylsilyl ethynyl cyclohexene[28]. Using the procedure described above for the preparation of 1-propynyl-cyclohexene, 1-ethynylcyclohexene (50 mmol, 5 3 g) gave 7 g (79% yield) of pure 1-trimethylsilyl ethynyl cyclohexene , bp 110°C (12 mm) ^{1}H NMR 6 (m, 1H), 2 1-1 9 (m, 4H), 1 7-1 5 (m, 4H), 0 1 (s, 9H) ^{13}C NMR 137 1, 122 6, 108 9, 94 1, 30 8, 27 3, 24, 23 2, -0 3

General procedure for the preparation of acetylenic epoxides

1-Ethynyl-7-oxabicyclo [4.1.0] heptane 1[24]. To a solution of ethynylcyclohexene (0 4 mol, 43 5 g) in methylene chloride (100 mL) at 0°C was added over a 30 min period, a solution of m-chloroperbenzoic acid (0 5 mol, 86 2 g) in methylene chloride (150 mL) The reaction mixture was stirred at 0°C for 15 min and at room temperature for 1h30 Sodium sulfite solution (10%) was added until the reaction mixture gave a negative test to starch-iodide paper Aqueous sodium bicarbonate solution was carefully added, the layers separated, and the organic layer washed with saturated aqueous sodium bicarbonate and water, dried (Na_2SO_4), and concentrated under vacuum to give 38 7 g of a yellow liquid which was distilled through a Vigreux column to afford 38 g of pure material (78% yield) , bp 33°C (0 4 mm) [Litt[24] 70°C (15 mm)] IR 3300, 2910, 2870, 2690, 1440 ^{1}H NMR 3 35 (t, 1H, J = 2 4 5 Hz), 2 4 (s, 1H), 2 1-1 7 (m, 4H), 1 5-1 1 (m, 4H) ^{13}C NMR 84 1, 70 2, 59 4, 49 6, 29 9, 29 3, 23,9, 19 2, 18 7

1-Propynyl-7-oxabicyclo [4 1.0] heptane 7[29]. Using the procedure described for the preparation of **1**, a 58% yield was obtained for the compound **7** , bp 36°C (2 mm) [Litt[29] 88°C (20 mm)] ^{1}H NMR 3 25 (t, 1H, J = 2 24 Hz), 2 2-1 8 (m, 4H), 1 8 (s, 3H), 1 6-1 2 (m, 4H) ^{13}C NMR 79 7, 78, 59 6, 50 2, 29 9, 24 1, 19 3, 18 8, 3 22

1-(2-trimethylsilylethynyl)-7-oxabicyclo [4.1.0] heptane 8[31]. Using the procedure described for the preparation of **1**, a 77% yield was obtained for the preparation of **8** , bp 75°C (4,5mm) ^{1}H NMR 3 3 (t, 1H, J = 2 4 Hz), 2 2-1 6 (m, 4H), 1 5-1 1 (m, 4H), 0 1 (s, 9H) ^{13}C NMR 105 9, 86 6, 59 9, 50 1, 29 5, 24 1, 19 3, 18 7, 0 1

1-(2-phenylethynyl)-7-oxabicyclo [4.1.0] heptane 9[30]. Using the procedure described for the preparation of **1**, a 63% yield was obtained for the preparation of **9** , purified by chromatography [SiO_2, cyclohexane/Et_2O 90/10] ^{1}H NMR 7 6-7 2 (m, 5H), 3 45 (m, 1H), 2 4-1 8 (m, 4H), 1 6-1 (m, 4H) ^{13}C NMR 131 7, 128 4, 128 2, 122 2, 89 8, 81 9, 60 1, 50 4, 29 4, 24 2, 19 2, 18 1

Synthesis of alicyclic α-hydroxyallenes

Stoichiometric procedure. A slurry of CuBr (5 7 mmol, 817 mg) in Et_2O (30 mL) is cooled to -40°C, and, then, a solution of EtLi LiBr (1N in Et_2O, 11 4 mmol, 11 4 mL) was added The temperature was kept at -30°C for 30 min After cooling to -60°C, a solution of 1-ethynyl-7-oxabicyclo [4 1 0] heptane **1** (5 7 mmol 695 mg) in Et_2O (10mL) was added. The mixture was stirred at -40°C for 1h30 and the quantitative formation of the adduct **2** and **3** was checked by G C The hydrolysis was done with a mixture of aqueous NH_3 (1 part) and saturated aqueous NH_4Cl (4 parts) (50 mL) The aqueous phase was extracted twice with ether (2 x 50 mL) and the combined organic phases were washed with the above mixture NH_3/NH_4Cl (3 x 50 mL), then dried over $MgSO_4$ and concentrated in vacuo The residue was distilled to afford 33% of **2** [bp = 50°C, (12mm)] and 54% of **3** [bp = 60°C, (12mm)]

***Anti* catalytic process.** To a solution of propargylic epoxide (3 mmol) in ether (20 mL) was added a solution of CuBr 2PBu3 (1N sol in ether, 0 15 mmol) The mixture was cooled to -50°C and the Grignard reagent RMgBr (2 eq , 6 mmol) was rapidly introduced The temperature is allowed to rise slowly and the reaction was followed by G C The mixture was hydrolyzed, worked up and purified as described for the stoichiometric procedure The residue was chromatographied on SiO_2 (eluent cyclohexane/ether 70/30)

***Syn* catalytic process.** To a solution of propargylic epoxide (3 mmol) in a mixture of solvent [ether (15 mL), pentane (15 mL)] was added 5% of CuBr (20 mg, 0 15 mmol) The temperature was kept to -50°C, then, one equivalent of chlorotrimethylsilane (0 38 mL, 3 mmol) was added and after 5 min, two equivalents (6 mmol) of $RMgCl/Et_2O$ were rapidly introduced The cooling bath was slowly removed and the reaction was followed by G C The mixture was hydrolyzed, worked up and purified as described for the stoichiometric procedure The residue was chromatographied on SiO_2 (eluent cyclohexane/ether 70/30)

Modified *syn* process : (Grignard reagent without copper catalysis). To a solution of 1-ethynyl-7-oxabicyclo [4 1 0] heptane (3 mmol) in ether (50 mL) were added, at -50°C, two equivalents (6 mmol) of $RMgCl/Et_2O$ and, then, the temperature was allowed to rise The mixture is stirred at 20°C for 3 hours, then, hydrolyzed, worked up and purified as usual

Spectroscopic data of the obtained α-hydroxyallenes

(R*,S*)-2-propenylidene-1-cyclohexanol 10B[5]. IR 3420, 2915, 2850, 1955, 1450 ^{1}H NMR 5 4(m, 1H), 4(m, 1H), 2 4-1 1(m, 9H), 1 8(s, 3H) ^{13}C NMR 196 3, 107 1, 89 3, 69, 35 9, 29 8, 26 9, 23 6, 15 2

(S*, S*)-2-propenylidene-1-cyclohexanol 3A. IR 3400, 2915, 1965, 1450, 980 ^{1}H NMR 5 4(m, 1H), 4 (m, 1H), 2 4-1 20(m, 10H), 1 0(t,3H, J= 7 3 Hz) ^{13}C NMR 196 4, 108 7, 96 4, 68 8, 35 7, 29 4, 26 5, 23 6, 21 9, 16 3

(R*, S*)-2 propenylidene-1-cyclohexanol 3B IR 3400, 2915, 1965, 1450, 980 ^{1}H NMR 5 4 (m, 1H), 4 (m, 1H), 2 4-1 2 (m, 10H), 1 0 (t, 3H, J= 7 3 Hz) ^{13}C NMR 195 9, 108 1, 95 7, 68 8, 29, 26 5, 22 8, 21 9, 16 3

(S*, S*)-2 hexenylidene-1-cyclohexanol 4A[5] IR 3400, 2920, 2860, 1960, 1440 ^{1}H NMR 5 4 (m, 1H), 4 (m, 1H), 2 3 (m, 3H), 2 2-1 1 (m, 11H), 0 9 (t, 3H, J = 7 3 Hz) ^{13}C NMR 198, 109 8, 97 0, 71 4, 38 4, 33 8, 32 2, 31 5, 29 5, 25 8, 24 6, 16 3

(R*, S*)-2-hexenylidene-1-cyclohexanol 4B[5] ^{1}H NMR 5 4 (m, 1H), 4 (m, 1H), 2 3 (m, 3H), 2 2-1 1 (m, 11H), 0 9 (t, 3H, J = 7 3 Hz) ^{13}C NMR 197 8, 110 4, 97 5, 71 4, 38 6, 33 7, 32 5, 31 5, 29 5, 26 2, 24 6, 16 3

(S*, S*)-2-(3-methylbutenylidene)-1-cyclohexanol 11A IR 3400, 2930, 2860, 1965, 1435 ^{1}H NMR 5 4 (m, 1H), 4 (m, 1H), 2 35 (m, 2H), 1 (d, 6H, J = 6 75 Hz), 2 1-1 2 (m, 7H) ^{13}C NMR 193 7, 109 0, 103 0, 69 0, 36 1, 30 0, 26 9, 23 6, 28 6, 22 7 Anal calcd for $C_{11}H_{18}O$ (166 265) C 79 46 , H 10 91, Found C 79 47 , H 10 89,

(R*, S*)-2-(3-methylbutenylidene)-1-cyclohexanol 11B IR 3400, 2930, 2860, 1965, 1435 ^{1}H NMR 5 4 (m, 1H), 4 (m, 1H), 2 35 (m, 2H), 1 (d, 6H, J = 6 75 Hz), 2 1-1 2 (m, 7H) ^{13}C NMR 193 0, 109 7, 103 8, 66 8, 36 5, 30 4, 27, 24, 28 2, 22 5

(S*, S*)-2-(3,3-dimethylbutenylidene)-1-cyclohexanol 12A[5] IR 3390, 2940, 2860, 1970, 1460, 1440 ^{1}H NMR 5 35 (m, 1H), 4 (m, 1H), 2 35 (m, 1H), 1 1 (s, 9h), 2 1-1 1 (m, 7H) ^{13}C NMR 192 7, 108 9, 106 3, 66 8, 35 7, 32 1, 30 1, 29 4, 26 8, 22 9

(R*, S*)-2-(3,3-dimethylbutenylidene)-1-cyclohexanol 12B[5] IR 3390, 2940, 2860, 1970, 1460, 144 ^{1}H NMR 5 35 (m, 1H), 4 (m, 1H), 2 35 (m, 1H), 1 1 (s, 9H), 2 1-1 1 (m, 7H) ^{13}C NMR 190 9, 108 4, 106 3, 66 8, 35 7, 32 1, 30 1, 29 4, 26 8, 22 9

S*, S*)-2-(2-phenylethenylidene)-1-cyclohexanol 13A[5] IR 3440, 2920, 2840, 1940, 1595, 1490, 1440 ^{1}H NMR 7 5-7 1 (m, 5H), 6 35 (m, 1H), 4 1 (dd, 1H, J = 4 4 Hz, J = 2 9 Hz), 2 5 (m, 9H) ^{13}C NMR 197 1, 135 2, 128 7, 127 1, 126 8, 111 5, 98, 69 4, 36, 29 6, 26 8, 23 4

(R*, S*)-2-(2-phenylethenylidene)-1-cyclohexanol 13B[5] IR , 3440, 2920, 2840, 1940, 1595, 1490, 1440 ^{1}H NMR 7 5-7 1 (m, 5H), 6.35 (m, 1H), 4 1 (dd, 1H, J = 4 4 Hz, J = 2 9 Hz), 2 5 (m, 9H) ^{13}C NMR 196 4, 135, 128 6, 127, 126 6, 112 3, 98 5, 69 5, 36 8, 30 0, 27 2, 23 9

(S*, S*)-2-(2-methylhexenylidene)-1-cyclohexanol 14A IR 3400, 2920, 2845, 1965, 1445 ^{1}H NMR 3 95 (dd, 1H, J = 4 5 Hz, J = 3 9 Hz), 2 4-1 2 (m, 15H), 1 8 (s, 3H), 0 9 (t, 3H, J = 6 9 Hz) ^{13}C NMR 192 1, 106 6, 103, 69 9, 35 8, 33 9, 29 6, 26 9, 26 6, 23 1, 22, 19 5, 13 5 Anal Calcd for $C_{13}H_{22}O$ (194 319) C 80 35 , H 11 41, , found C 80 358 , H 11 409,

(R*, R*)-2-(2-methylhexenylidene)-1-cyclohexanol 14B IR 3400, 2920, 2845, 1965, 1445 ^{1}H NMR 3 95 (dd, 1H, J = 4 5 Hz, J = 3 9 Hz), 2 4-1 2 (m, 15H), 1 8 (s, 3H), 0 9 (t, 3H, J = 6 9 Hz) ^{13}C NMR 191 9, 107 3, 104 9, 69 3, 36 5, 34 4, 30 3, 30 27 2, 27 1, 23 9, 20 2, 14 1

(S*, S*)-2-(2,3-dimethylbutenylidene)-1-cyclohexanol 15A IR 3400, 2925, 2850, 1940, 1440 ^{1}H NMR 4 (m, 1H), 2 4-1 1 (m, 10H), 1 8 (s, 3H), 1 (d, 6H, J = 6 7 Hz) ^{13}C NMR = 191 1, 110 2, 107 9, 69 1, 36 1, 32 5, 29 9, 27 1, 23 4, 21 7, 18 4 Anal Calcd for $C_{12}H_{20}O$ (180 292). C 79 94 , H 11 18 found C 79 87 , H 11 27

(R*, S*)-2-(2,3-dimethylbutenylidene)-1-cyclohexanol 15B IR 3400, 2925, 2850, 1940, 1440 ^{1}H NMR 4 (m, 1H), 2 4-1 1 (m, 10H), 1 8 (s, 3H), 1 (d, 6H, J = 6 7 Hz) ^{13}C NMR 190 4, 111 2, 108 5, 68 9, 36 6, 32 3, 30 6, 27 1, 24, 17 8, 21 6

(S*, S*)-2-(2,3,3-trimethylbutenylidene)-1-cyclohexanol 16A[5] IR 3460, 2920, 2850, 1960, 1440 ^{1}H NMR 4 (dd, 1H, J = 3 9 Hz, J = 4 55Hz), 2 3-1 2 (m, 10H), 1 8 (s, 3H), 1 (s, 9H) ^{13}C NMR 191 3, 113 1, 107, 69 2, 36 1, 34 1, 29 9, 27 1, 23 4, 29 3, 15 7

(R*, S*)-2-(2,3,3-trimethylbutenylidene)-1-cyclohexanol 16B[5] IR 3460, 2920, 2850, 1960, 1440 ^{1}H NMR 4 (dd, 1H, J = 3 9 Hz, J = 4 5 Hz), 2 3-1 2 (m, 10H), 1 8 (s, 3H), 1 (s, 9H) ^{13}C NMR 190 5, 114 0, 107 4, 68 6, 36 4, 33 7, 30 6, 26 9, 24, 29 2, 15 2

(S*, S*)-2-(2-phenylpropenylidene)-1-cyclohexanol 17A[5] IR 3410, 2930, 2840, 1950, 1640, 1440 ^{1}H NMR 7 4-7 1 (m, 5H), 4 1 (dd, 1H, J = 3 9 Hz, J = 4 4 Hz), 2 4-1 4 (m, 9H), 2 1 (s, 3H) ^{13}C NMR 195 5, 137 9, 128 4, 126 8, 125 9, 109 8, 104 4, 69 5, 36 3, 29 8, 27 1, 23 6, 18

(R*, S*)-2-(2-phenylpropenylidene)-1-cyclohexanol 17B[5] IR 3410, 2930, 2840, 1950, 1640, 1440 ^{1}H NMR 7 4-7 1 (m, 5H), 4 1 (dd, 1H, J = 3 9 Hz, J = 4 4 Hz), 2 4-1 4 (m, 9H), 2 1 (s, 3H) ^{13}C NMR 195 2, 137 8, 128 2, 126 6, 125 6, 110, 104 2, 69 5, 36 2, 29, 27, 23 8, 18

(R*, S*)-2-(2-trimethylsilylpropenylidene)-1-cyclohexanol 18A IR 3440, 2920, 2850,1945,1445, 1245 ^{1}H NMR 4(dd, 1H, J = 4 5 Hz, J = 3 5 Hz), 2 45-2 25 (m, 2H), 2-1 2 (m, 7H), 1 75 (s, 3H), 0 5 (s,

3H) ^{13}C NMR 197 5, 101 8, 97 3, 68 6, 36 5, 29 9, 27, 24 1, 16 1, 0 5 Anal calcd for $C_{12}H_{22}OSi$ (210 398) C 68 50 , H 10 54 , found C 68 45 , H 10 65

(S*, S*)-2-(2-trimethylsilylpropenylidene)-1-cyclohexanol 18B IR 3440, 2920, 2850, 1945, 1445, 1245 ^{1}H NMR 4(dd, 1H, J = 4 5 Hz, J = 3 5 Hz), 2 45-2 25 (m, 2H), 2-1 2 (m, 7H), 1 75 (s, 3H), 0 5 (s, 3H) ^{13}NMR 198 2, 100 6, 95 5, 69, 35 6, 28 5, 26 9, 22 8, 16, 0 5

(R*, S*)-2-(2-trimethylsilyl-3-methylbutenylidene)-1-cyclohexanol 19A IR 3450, 2960, 2950, 2860, 1935, 1445, 1245 ^{1}H NMR 4 05 (dd, 1H, J = 3 9 Hz, J = 4 45 Hz), 2 4-1 3 (m, 10H), 1 1 (d, 6H, J = 6 79 Hz), 0 2 (s, 3H) ^{13}C NMR 196 6, 109 8, 104 3, 68 5, 36 2, 29 6, 23 7, 29 4, 27, 23 8, 0 5 Anal calcd for $C_{14}H_{26}OSi$ (238 452) C 70 51 , H 10 99 , found C 70 63 , H 10 83

(S*, S*)-2-(2-trimethylsilyl-3-methylbutenylidene)-1-cyclohexanol 19B IR 3450, 2960, 2950, 2860, 1935, 1445, 1245 ^{1}H NMR 4 05 (dd, 1H, J = 3 9 Hz, J = 4 45 Hz), 2 4-1 3 (m, 10H), 1 1 (d, 6H, J = 6 79 Hz), 0 2 (s, 3H) ^{13}C NMR 197 0, 109 5, 104 3, 69, 36 3, 29 3, 23 7, 29 2, 27 3, 23 4, 0 5

(R*, S*) and (S*, S*)-2-(-2-trimethylsilyl-3,3-dimethylbutenylidene)-1-cyclohexanol 20A and 20B IR 3300, 2920, 2850, 1945, 1440, 1245 ^{1}H NMR 4 05 (dd, 1H, J = 4 1 Hz, J = 4 1 Hz), 2 3 (m, 2H), 2 15-1 3 (m, 8H), 1 1 (s, 9H), 0 2 (s, 3H) ^{13}C NMR 197 6, 113 1, 103 3, 69 0, 36 1, 35 2, 31 6, 29 3, 27, 23 5, 1 5 Anal calcd for $C_{15}H_{28}OSi$ (252 479) C 71 35 , H 11 18 , found C 71 42 , H 11 15

(R*, S*)-2-(2-trimethylsilyl 2-phenylethenylidene)-1-cyclohexanol 21A IR 3460, 2930, 2850, 1935, 1440 ^{1}H NMR 7 4-6 9 (m, 5H), 3 9 (dd, 1H, J = 4 1 Hz, J = 4 9 Hz), 3(s, 1H), 2 1-1 (m, 8H), 0 1 (s, 3H) ^{13}C NMR 200 9, 142 9, 138 1, 128 3, 127 6, 126 7, 126 1, 103 8, 92 7, 68 7, 35 9, 29 6, 26 5, 23 6, 0 Anal calcd for $C_{17}H_{24}OSi$ (272 470) C 74 93 , H8 87 , found C 74 59 , H 9 98

(R*, S*)-2-(2 phenylhexenylidene)-1-cyclohexanol 22A[5] IR 3420, 2930, 2840, 1940, 1640, 1440 ^{1}H NMR 7 8-7 2 (m, 5H), 4 1 (dd, 1H, J = 3 9 Hz, J = 4 4 Hz), 2 4-1 1 (m, 15H), 0 9 (t, 3H, J = 6 9 Hz) ^{13}C NMR 195 2, 137 5, 128 1, 126 6, 125 8, 110 7, 108 9, 69 4, 36 4, 30 3, 29 8, 27 3, 26 6, 24 7, 23 3, 14 1

(S*, S*)-2-(2 phenylhexenylidene)-1-cyclohexanol 22B[5] IR 3420, 2930, 2840, 1940, 1640, 1440 ^{1}H NMR = 7 8-7 2 (m, 5H), 4 1 (dd, 1H, J = 3 9 Hz, J = 4 4 Hz), 2 4-1 1 (m, 15H), 0 9 (t, 3H, J = 6 9 Hz) ^{13}C NMR 194 9, 137 6, 128, 126 5, 125 8, 111 1, 109 4, 68 9, 36 3, 30 0, 29 8, 27 3, 26 6, 24 7, 23 3, 14 1 Anal calcd for $C_{18}H_{24}OSi$ (284 481) C 76 00 , H8 50 , found C 75 85 , H 8 66

(R*, S*)-2-(2 phenyl 3methylbutenylidene)-1-cyclohexanol 23A[5] IR 3440, 2930, 2845, 1940, 1650, 1440 ^{1}H NMR 7 4-7 1 (m, 5H), 4 1 (dd, 1H, J = 3 9 Hz, J = 4 1 Hz), 2 4-1 (m, 10H), 1 1 (d, 6H, J = 6 7 Hz) ^{13}C NMR 194 4, 137 3, 131 6, 128 1, 126 4, 116 6, 112 00, 71 9, 36 3, 32, 29 6, 27 3, 22 6, 22 3

(S*, S*)-2-(2 phenyl 3methylbutenylidene)-1-cyclohexanol 23B[5] IR 3440, 2930, 2845, 1940, 1650, 1440 ^{1}H NMR 7 4-7 1 (m, 5H), 4 1 (dd, 1H, J = 3 9 Hz, J = 4 1 Hz), 2 4-1 (m, 10H), 1 1 (d, 6H, J = 6 7 Hz) ^{13}C NMR 193 6, 137, 131 4, 128 3, 126, 117 7, 112 5, 69 2, 36 6, 31 8, 30, 27 3, 22 6, 22 3,

(S*, S*)-2-(2-phenyl-3,3-dimethylbutanylidene)-1-cyclohexanol 24A[5] IR 3400, 2940, 2850, 1935, 1660, 1445 ^{1}H NMR 7 3-7 1 (m, 5H), 4 1 (dd, 1H, J = 4 4 Hz, J = 3 9 Hz), 2 5-1 1 (m, 9H), 1 1 (s, 9H) ^{13}C NMR 194, 138 4, 129 2, 127 6, 126 4, 118 6, 107 4, 69 3, 35 4, 34 8, 29 3, 26 8, 22 7, 30 2

(S*, S*)-2-(2-phenyl-3,3-dimethylbutanylidene)-1-cyclohexanol 24B[5] IR 3400, 2940, 2850, 1935, 1660, 1445 ^{1}H NMR 7 3-7 1 (m, 5H), 4 1 (dd, 1H, J = 4 4 Hz, J = 3 9 Hz), 2 5-1 1 (m, 9H), 1 1 (s, 9H) ^{13}C NMR 192 6, 138 1, 129 2, 128 4, 126 5, 120 6, 108 6, 69, 36 2, 34 6, 30 6, 26 8, 24, 30 1

Spectroscopic data of the byproducts :

(S*, S*)-2(1-butylethynyl)-1-cyclohexanol 5 ^{1}H NMR 3 1 (m, 1H), 2 2 (s, 1H), 2-1 0 (m, 15H), 0 9 (t, 3H, J = 7 3 Hz) ^{13}C NMR 86 5, 75 2, 73 0, 43 9, 38 6, 34 9, 32 3, 26 4, 24 7, 22 3, 14 1

(S*)-2-ethenylidene-1-cyclohexanol 2[2] IR 3400, 2915, 1965, 1450 ^{1}H NMR 4 84 (m2H), 4 05 (m,1H), 2 4 -1 2 (m, 8H) ^{13}C NMR 201 2, 106 8, 78 5, 68 8, 35 7, 29 4, 26 5, 23 6

(E)-1-iodo-1-octene (hydroalumination-iodinolysis of an alkyne)[32] To a solution of 1-octyne (25 mmol, 2 76 g) in hexane (10 mL) was added a solution of diisobutylaluminium hydride (27 5 mmol, 1N in n-hexane 27 5mL) while the temperature was maintained at 25-30°C by means of a water bath The resulting solution was stirred at room temperature for 30 min and was heated at 50° for 2 hours After cooling to 0°C dry tetrahydrofuran (20 mL) is added The resulting solution was cooled to -60°c and treated with a solution of iodine (30mmol, 7 6 g) in dry THF (15 mL) at a rate such that the temperature was maintained below -10°C After 30 min, MeOH (5 mL) was added and the reaction mixture was allowed to warm to 0°C and then, hydrolyzed by a mixture of 5N sulfuric acid (50 mL) and n-pentane (20 mL) The layers were separated and the aqueous phase was extracted with n-pentane The combined organic extract was washed successively with 1N sodium hydroxyde, 10% aqueous sodium sulfite After drying over $MgSO_4$, distillation yielded 3,6 g (65%) of the product bp = 85°C (3 mm) [Litt[32] 85°C (3 mm)] ^{1}H NMR 6 4 (dt, 1H, J = 14 3 Hz, J = 7 1 Hz), 5 9 (dt, 1H, J = 14 3 Hz, J = 1 4 Hz) 2 1 (m, 2H), 1 6-0 9 (m, 11H) ^{13}C NMR 145 6, 74 6, 36, 28 6, 28 3, 25 8, 14

(Z)-1-iodo-1-octene (carbocupration-iodinolysis of an alkyne)[8] The organolithium reagent (1 5N sol ,40 mmol, 26 6 mL) [prepared in Et_2O from bromohexane and lithium chips] was added to a suspension of CuI (20 mmol, 3 8 g) in ether (100 mL) at -35°C The mixture was stirred for 20 min at -35°C (solution), then acetylene (25 mmol, 5 6 l, measured in a water gasometer) was bubbled in the reaction mixture after being dried over a column packed with calcium chloride The temperature was allowed to rise from -50°C to -35°C , The pale green solution was maintained for 30 min at -25°C, then, cooled to -78°C, treated with 10 ml of a solution of iodine (65mmol, 16 5 g in 40 mL dry THF) at such a rate that the temperature is maintained below -50°C After the addition was completed, the mixture was warmed to -10°C and the hydrolysis was done with a mixture of aqueous NH_3/NH_4Cl (1 part / 4 part 50 mL) The aqueous phase was extracted twice with ether (2 x 50 mL) and the combined organic phases were washed with the above mixture NH_3/NH_4Cl (2 x 50 mL) and with aqueous solution of 10% sodium sulfite After drying over $MgSO_4$ distillation yielded 4 7 g of the product (79% yield) bp 85°C (3 mm) [Litt[8] 85°C (3 mm)] ^{1}H NMR 6 2 (m, 2H), 2 3 (m, 2H), 1 8-0 9 (m, 11H) ^{13}C NMR 141 4, 82 2, 34 7, 28 6, 28 3, 25 8, 14 1

Synthesis of (E) and (Z) 1-trimethylsilyl-3-decene-1-yne[21] To a solution of bistrimethylsilylacetylene (20mmol, 3 4 g)in THF (50mL) at -30°C, was added 13 3 mL of MeLi LiBr (1 5 N/l , 20 mmol) and the resulting solution was stirred at room temperature for 3 hours Then $ZnBr_2$ (20 mmol, 4 7 g) was rapidly introduced and after solubilization, a solution of (E) or (Z) 1-iodo-octene (18 mmol, 4 28 g), mixed with Pd $(PPh_3)_4$ (0 9 mmol, 800 mg) in THF (40mL) was added to the resulting mixture The reaction was warmed gradually to room temperature (1h) and, then hydrolyzed at -10°C with 50 mL of aqueous ammonium chloride The salts were filtered off and, the solvents were removed in vacuo and the residue was dissolved in 100 ml pentane to precipitate the residual salts This organic solution was dried over Na_2CO_3, concentrated and the product is distilled

1-trimethylsilyl-(3Z)-decene-1-yne bp 75°C (0 5 mm) 80% yield ^{1}H NMR 5 9 (dt, 1H, J = 10 9 Hz, J = 7 4 Hz), 5 5 (d, 1H, J = 10 9Hz), 2 3 (q, 2H, J = 8 3 Hz), 1 5-1 1 (m, 8H), 0 9 (t, 3H, J = 6 2), 0 3 (s, 9H) ^{13}C NMR 145 8, 109 6, 102 5, 98 6, 96 6, 31 9, 30 5, 29 1, 28 9, 22 8, 14 2, 0 1

1-trimethylsilyl-(3E)-decene-1-yne bp 75°C (0 5 mm) 80% yield ^{1}H NMR 6 (dt, 1H, J = 15 9 Hz, J = 7 1 Hz), 5 3 (dt, 1H, J = 15 9 Hz, J = 1 5 Hz), 1 9 (q, 2H, J = 6 3 Hz) 1 5-1 (m, 8H), 0 9 (t, 3H, J = 6 9 Hz), 0 3 (s, 9H) ^{13}C NMR 145 6, 110, 104 2, 92 2, 33 1, 31 4, 29, 28 5, 22 5, 13 9, 0 1

1-trimethylsilyl-(3,4 cis)-epoxy-1-decyne Using the procedure described for the preparation of 1-ethynyl-7-oxabicyclo [4 1 0] heptane **1**, a 74% yield is obtained for the title compound bp 101°C (40 mm) ^{1}H NMR 3 35 (d, 1H, J = 3 96 Hz), 3 (dt, 1H, J = 3 96 Hz, J = 6 3 Hz), 1 8-1 (m, 10H), 0 9 (t, 3H, J = 6 3 Hz), 0 1 (s, 9H) ^{13}C NMR 100 8, 90 6, 58, 45, 31 8, 29 3, 29 1, 25 8, 22 5, 14, 0

1-trimethylsilyl-(3,4 trans)-epoxy-1-decyne Using the procedure described for the preparation of compound **1**, a 75% yield is obtained for the title compound bp 101°C (40 mm) IR 3300, 2910, 2850, 2670, 1460 ^{1}H NMR 3 (s, 2H), 1 7-1 1 (m, 10H), 0 9 (t, 3H, J = 6.4), 0 1 (s, 9H) ^{13}C NMR 102 3, 88 7, 60 6, 45 3, 31 7, 31 5, 26 5, 25 3, 22 5, 13 9, 0

(3,4 trans)-epoxy-1-decyne 25E To a solution of 1-trimethylsilyl-(3,4 cis)-epoxy-1-decyne (1mmol, 285 mg), in DMF (5 mL), were added two equivalents of potassium fluoride and 5 mL of water The reaction mixture was stirred at room temperature for 3 hours, and the quantitative formation of the desired product was checked by G C The hydrolysis was done with a aqueous solution of NH_4Cl, 25 mL of ether and 25 mL of pentane were added and the organic phases were washed twice with a solution of HCl 1N After concentration under vacuum, the residue was distilled to afford the compound **25E** in 89% yield bp = 89°C (40 mm) ^{1}H NMR 3 (s, 2H), 2 2 (d, 1H, J = 1 5), 1 6-1 1 (m, 10H), 0 9 (t, 3H, J = 6 Hz) ^{13}C NMR 80 8, 71 7, 60, 44 6, 31 7, 31 6, 29 1, 25 7, 22 6, 14

(3,4 cis)-epoxy-1-decyne 25Z Using the procedure described for the preparation of compound **25E**, a 94% yield is obtained for **25 Z** bp = 89°C (40 mm) ^{1}H NMR 3 4 (dd, 1H, J = 1 72 Hz, J = 3 96 Hz), 3 (dt, 1H, J = 3 96 Hz, J = 6 3 Hz) 2 35 (d, 1H, J = 1 72 Hz), 1 9-1 1 (m, 10H), 0 9 (t, 3H, J = 6 0 Hz) ^{13}C NMR 79 1, 73 3, 57 6, 44 5, 31 7, 29 3, 29 1, 25 9, 22 5, 13 9

Synthesis of aliphatic α-hydroxyallenes Using the procedures described for the preparation of α-hydroxyallenes by the *syn* or *anti* process from alicyclic propargylic epoxides, were obtained the compounds

(R*, R*)-8,9-pentadien-7-ol 26A ^{13}C NMR 202 5, 95 9, 93 6, 70 1, 32 1, 31 5, 29 8, 29 5, 29 1, 28 9, 28 2, 25 6, 22 8, 14 1 Anal Calcd for $C_{14}H_{28}O$ (224 389) C 79 93 , H 12 45 Found C 79 85 , H 12 57

(S*, R*)-8,9-pentadien-7-ol 26B ^{13}C NMR 202 7, 95 8, 93 3, 70 6, 32 1, 31 5, 29 8, 29 5, 29, 28 9, 28 2, 25 6, 22 8 14 1 3

(R*, R*)-2-dimethyl-3,4-dodecadien-6-ol 27A ^{13}C NMR 199 7, 105 7, 97 6, 70 0, 37 6, 31 9, 31 8, 29 3, 25 5, 22 7, 30 2, 14 0 Anal Calcd for $C_{14}H_{26}O$ (210 362) C 79 93 , H 12 45 Found C 81 05 , H 12 38

(S*, R*)-2-dimethyl-3,4-dodecadien-6-ol 27B ^{13}C NMR 200 2, 105, 97 5, 70 8, 37 7, 31 9, 31 8, 29 3, 25 5, 22 7, 30 2, 14

Synthesis of 3-methoxy-17-ethynyl-1,3,5(10),16-oestratetraene[22b] Using the procedure described for the preparation of 1-ethynylcyclohexene, was obtained the title compound in 73% yield m p = 148-150°C (acetone methanol) $[\alpha]_D^{25}$ = + 68,6° (c=1 5, CH_2Cl_2) IR = 3300, 2105, 817 ^{1}H NMR 7 2 (d, 1H, J = 8,5 Hz), 6 8-6 6 (m, 2H), 6 1 (t, 1H, J = 2 7 Hz), 3 7 (s, 3H), 3 1 (s, 1H), 2 9-1 4 (m, 13H), 0 9 (s, 3H) ^{13}C NMR 157 3, 139, 138, 132 6, 126 3, 114, 111 7, 87 6, 80, 78, 55 2, 53, 44 4, 43 9, 38 8, 36 4, 29 8, 27 6, 27 5, 26 6, 16 3

Synthesis of 3-methoxy-16α,17α-epoxy-17β-ethynyl-1,3,5(10)-oestratriene 28[22b]. Using the proce-dure described for the preparation of 1-ethynyl-7-oxabicyclo [4 1 0] heptane **1**, was obtained in 63% yieldthe title compound **28** m p 195°C (acetone) $[\alpha]_D^{25}$ = + 103° (c=1 5, CH_2Cl_2) IR 3300, 877, 848 ^{1}H NMR 7 2 (d, 1H, J = 8 5 Hz), 6 8-6 6 (m, 2H), 3 7 (s, 3H), 3 6 (s, 1H), 2 7 (m, 2H), 2 4 (s, 1H), 2 4- 1 1 (m, 11H), 0 93 (s, 3H) ^{13}C NMR 157 3, 137 6, 132 3, 126, 113 8, 111 4, 78 9, 73 3, 61 6, 60 4, 55 1, 44 0, 43 6, 43 5, 37 1, 31, 29 6, 27 6, 26, 15 8

3-methoxy-16α ol-1,3,5(10),17,(20),20-pregnapentaene 30. m p 101°C $[\alpha]_D^{25}$ = + 41 2 (c=1, CH_2Cl_2) IR = 3450, 1965, 1686, 841 ^{1}H NMR 7 2 (d, 1H, J = 8 5 Hz), 6 8-6 6 (m, 2H), 5 1 (dq, 2H, J = 3 Hz, J = 13 2 Hz), 4 7 (m, 1H), 3 7 (s, 3H), 3 1 (m, 13 H), 0 9 (s, 3H) ^{13}C NMR 201 2, 157 8, 138 1, 132 8, 126 4, 118 9, 114 1, 118 8, 92 5, 72 7, 55 4, 51 9, 44 3, 38 6, 36 5, 35 5, 30, 29 9, 27 9, 26 7, 19 3

21α-methyl-16α-ol-3methoxy-1,3,5(10),17,(20),20-pregnapentaene 29A. m p 127°C $[\alpha]_D^{25}$ = +84° (c=1 3, CH_2Cl_2) IR 3450, 1965, 1368, 768 ^{1}H NMR 7 2 (d, 1H, J = 8 5 Hz), 6 8-6 6 (m, 2H), 5 4 (dq, 1H, J = 2 9 Hz, J = 7 2 Hz), 1 8 (dd, 1H, J = 2 9 Hz, J = 5 6 Hz), 3 8 (s, 3H), 2 9-1 3 (m, 13H), 1 7

(d, 3H, J = 7 2 Hz), 0 86 (s, 3H) ^{13}C NMR 196 8, 157 4, 137 9, 132 8, 126 2, 120, 113 7, 111 4, 92, 72 8, 55 3, 51 9, 44 3, 38 6, 36 5, 35 5, 30, 29 9, 27 9, 26 7, 19 3

21β-methyl-16α-ol-3methoxy-1,3,5,(10),17(20),20-pregnapentaene 29B. m p 69°C $[\alpha]_D^{25}$ = -15 5° (c=1 1, CH_2Cl_2) IR = 3450, 1969, 1370, 767 ^1H NMR 7 2 (d, 1H, J = 8 5 Hz), 6 8-6 6 (m, 2H), 5 5 (dq, 1H, J = 2 9 Hz, J = 7 2 Hz), 4 8 (dd, 1H, J = 2 9 Hz, J = 5 6 Hz), 3 8 (s, 3H), 2 9-1 3 (m, 13 H), 1 7 (d, 3H, J = 7 2 Hz), 0 83 (s, 3H)

Synthesis of (R*, S*)-2-(2-phenylethenylidene)-1-cyclohexanol 13B by reductive lithiation. To a solution of phenethynylcyclohexene oxide **9** (2 mmol, 400 mg) in ether (30 mL) or THF (30 mL), was added, at room temperature, a solution of 5% CuBr , $2PBu_3$ (0,1N in Et_2O , 0,1 mmol, 1 mL) Then, at -50°C, was added rapidly BuLi LiBr (1 5N sol in Et_2O, 2 66 mL, 4 mmol) and the reaction mixture was warmed to room temperature The hydrolysis was done with a saturated aqueous NH_4Cl solution (100 mL) The layers were separated, the water layer extracted twice with ether and the combined organic phases were washed with water, dried on Na_2CO_3 and concentrated under vacuum to afford α-hydroxyallene **13B** For the spectroscopic data, see before

Reaction of (R*,S*)-2-lithioethenylidene-1-cyclohexanolate 31 with various electrophiles. To a solution of phenethynylcyclohexene oxide **9** (2 mmol, 400 mg) in ether (30 mL) was added, at room temperature, a solution of 5% CuBr $2PBu_3$ (sol 0 1 N/l , 0 1 mmol, 1 mL) Then, at -50°C, was rapidly introduced BuLi LiBr (4 mmol, 2 66 mL) and the reaction mixture was kept at -50°C for 1 hour Then, the appropriate electrophiles (2 mmol) were added at a rate such that the temperature was maintained below -50°C and the quantitative formation of the adduct was checked by G C The hydrolysis was done with a mixture of aqueous NH_3 (1 part) and saturated aqueous NH_4Cl (4 parts) (50 mL) The aqueous phase was extracted twice with ether (2 x 50 mL) and the combined organic phases were washed with the above mixture NH_3/NH_4Cl (3 x 50 mL), then dried over $MgSO_4$ and concentrated in vacuo

Spectroscopic data of the adduct

(R*,S*)2-(2-thiomethylpropenylidene)-1-cyclohexanol 34A ^1H NMR 7 1-7 5 (m,5H), 4 1 (dd, 1H, J=4 4 Hz, J=2 9 Hz), 2 9(s, 3H), 2 5-1 4(m, 9H) ^{13}C NMR 191 4, 135 8, 128 3, 127 7, 126 5, 117, 103, 65 8, 32, 29 4, 27 3, 22 7, 16 1 Anal Calcd for $C_{15}H_{18}SO$ (246 369) C 73 12 , H = 7 36 , Found C 73 28 , H 7 49

(S*,S*)-(2-thiomethylpropenylidene)-1-cyclohexanol 34B ^1H NMR 7 1-7 5(m, 5H), 4 1 (dd, 1H, J=4 4 Hz, J=2 9 Hz), 2 9(s, 3H), 2 5-1 4(m ,9H) ^{13}C NMR 191 1, 135 8, 128 3, 127 7, 126 5, 117 3, 103, 65 2, 32, 29 4, 27 3, 22 7, 16 1

Spectroscopic data of the spirolactone cyclohexanol 35 ^1H NMR 7 9-7 3(m, 5H), 7 75(s, 1H), 3 8 (dd, 1H, J=4 Hz, J=4 Hz), 3 1-2 65 (s, 1H), 2 1-1 3 (m,8H) ^{13}C NMR 171, 148 9, 132 5, 129 2, 128 5, 127 1, 88 5, 72 6, 33 1, 31 3, 22 7, 22 1

2-(2R*-phenethynyl 2R*-benzylalcool) 1S*-cyclohexanol 36 ^1H NMR 7 5-7(m, 10H), 5 4(s, 1H) , 4 6(s, 1H), 4 2(s,1H), 3 5(m, 1H), 1 9-0 9(m, 8H) ^{13}C NMR 140, 131 7, 128 2, 128 1, 127 5, 123 6, 88 3, 87 6, 82 5, 77 9, 49 1, 33 3, 32 2, 24 3, 21 7

Spectroscopic data of the ketal 37 ^1H NMR 7 65-7 05(m, 10H), 4 6(s, 1H), 3 7(m, 1H), 2 1(m, 14H) ^{13}C NMR 137 5, 131 6, 128 2, 128 1, 128, 127 5, 127 4, 124, 99 7, 89 5, 87, 80, 75 9, 45 4, 31 8, 30 4, 28 8, 24 6, 21 9, 19 7

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