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ALKENYL COPPER REAGENTS—18[1]

CARBOCUPRATION OF ACETYLENIC ACETALS AND KETALS SYNTHESIS OF MANICONE, GERANIAL AND 2,4 (E,Z)-DIENALS

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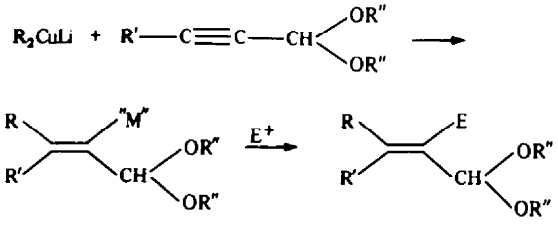
Abstract—Lithium diorganocuprates add across the triple bond of substituted and non-substituted acetylenic acetals and ketals to give dialkenylcuprates, which can be decomposed into alkoxyallenes or may be trapped with a variety of electrophiles, such as alkyl, alkenyl, alkynyl and aryl halides. They may also undergo conjugate addition to α-β unsaturated esters and ketones. The method is used for the synthesis of (±)-manicone, pure geranial and (E,Z)2,4-dienals.

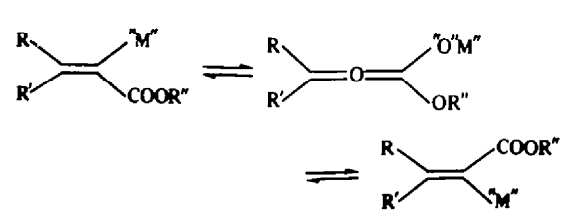
We reported briefly in 1976 on the carbocupration reaction of acetylenic acetals:[2]



Since then, the addition reaction as well as the reactivity of the intermediate alkenyl cuprates have been studied in more details and we describe herein our full results.

The carbocupration reaction of acetylenic esters, first reported by Corey[3] and Sidall[4] has found, since then, a wide synthetic application. The solvent used and the reaction temperature (very low) should be carefully chosen since the intermediate alkenyl cuprate derivative may isomerise via the corresponding allenolate.[5] In many cases it is difficult to avoid the presence of some isomerised product. The reaction of acetylenic ketones and aldehydes[6] is even more sensitive to this isomerisation. The recently reported use of the $RCu\text{-}BR'_3$ reagent[7] seems somewhat more efficient in this respect. On the other hand the carbocupration of acetylenic acids[8,9] and amides[10,11] affords product of much greater stereoisomeric purity.

However, the major drawback of all these reactions lies in the very poor reactivity of the intermediate alkenyl cuprate, which reacts with iodine,[3] methyl iodide,[3,12] allyl bromide[12] or dimethyl disulfide,[12] usually with isomerisation of the double bond. Only acyl halides react cleanly as reported recently by Marino *et al.*[13]



It is therefore desirable to deal with an appropriate alkyne which would be synthetically equivalent to an α-acetylenic ester and would lead, via carbocupration, to an alkenyl cuprate of higher reactivity with no propensity to isomerisation. In 1975, Marino *et al.*[14] reported the use of the following alkenyl cuprate bearing an acetal function as a synthetic equivalent of the ester function, $>C=C(\text{"Cu"})CH(OEt)_2$ instead of $>C=C(\text{"Cu"})CO_2Et$. This cuprate, used also by Grieco *et al.*[15] and by Boeckman *et al.*[16] appears to react as well as normal alkenyl analogues for conjugate addition reaction,[14-16] for the coupling with allylic halides[15,15] and for the opening of α,β-unsaturated epoxides.[17] Based on the same arguments, we thought that acetylenic acetals would be appropriate candidates for the carbocupration reaction as synthetic equivalent of acetylenic esters. Moreover, the resulting alkenyl cuprates would behave as normal alkenyl cuprates as far as reactivity is concerned. This is indeed the case as is shown by the following results.

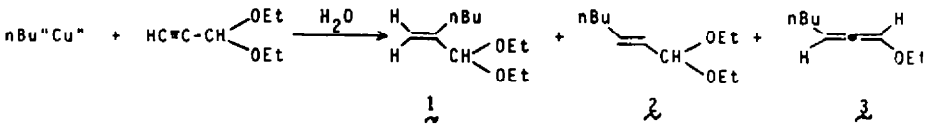
RESULTS AND DISCUSSION

The carbocupration of acetylenic acetals may be performed with various types of organocopper reagents.[18] However, the regioselectivity of the addition is highly dependent on the organometallic precursor of the copper reagent (viz RLi or RMgX). A complete study of the nature of the organocopper reagent (alkyl copper versus alkyl cuprate) and of the solvent used (ether or tetrahydrofuran) has been undertaken.

Addition to non-substituted acetals

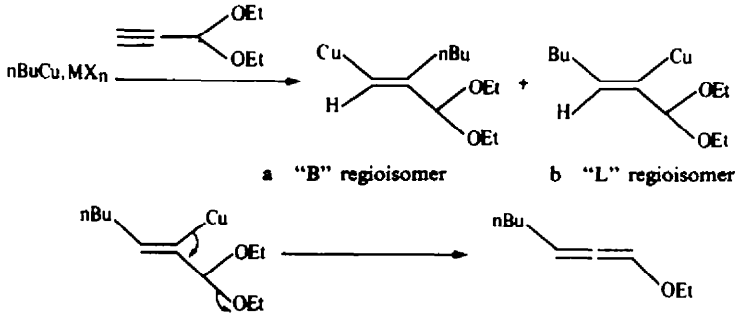
The carbocupration reaction may lead to two regioisomers: (Scheme 1). The linear "L" regioisomer may also decompose by β-elimination to the alkoxy allene. This decomposition occurs rapidly with organocopper or cuprate derivatives prepared from the corresponding Grignard reagent (see Table 1, entries 5–8). Even at temperatures as low as −45° some decomposition to the allene occurs (Table 1, entry 7). On the other hand, organo copper or cuprate reagents prepared from the corresponding organolithium reagent are much more stable towards β-elimination (Table 1, entries 1–4). The decom-

Table 1.



Entry	Copper species	Solvent	Temp.[b] °C	Time[b] h	Proportion 1	2	3	Conversion
1	R_2CuLi [a]	Et_2O	-50°	0.5	2	98	-	99
2	"	THF	-50°→ +20°	4	-	-	-	0
3	RCu,LiX	Et_2O	-45°	1	26	74	-	95
4	"	THF	-30°	4	53	47	-	74
5	R_2CuMgX [a]	Et_2O	-40°	0.5	8	52	40	99 [d]
6	"	THF	-25°	0.5	78	-	22	86 [d]
7	RCu,MgX_2	Et_2O	-45°	1	22	64	14	84
8	"	THF	-20°	4	59	38	3	81

a 2 eq. of acetal are consumed per dialkyl cuprate
b Temperature and reaction time for optimum conversion
c Proportion observed on the crude reaction mixture by GLPC as well as ^1H and ^{13}C NMR
d These results are very similar to those of Vermeer et al[21]



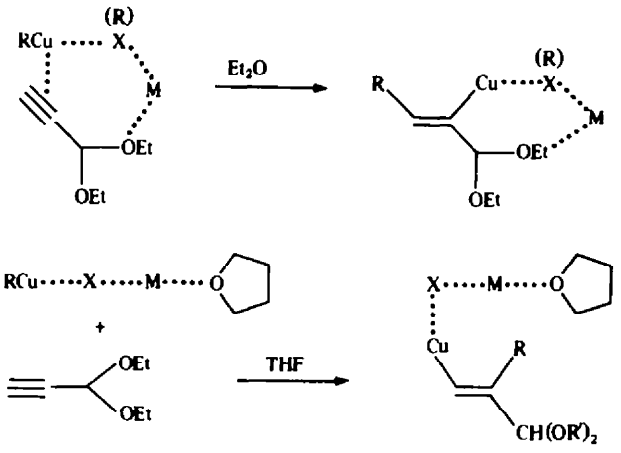
Scheme 1.

position is observed at $-20°$ in ether and at 0° in THF, and its rate is also slower than that observed for the reagents prepared from Grignard precursors.

The branched ("B") regioisomer is the one expected for non-functionalized alkynes.[8,18] The linear ("L") regioisomer may arise from the complexation of the copper atom (or its associated salts) with the oxygens of the acetal.[19,20]

In the more polar solvent tetrahydrofuran, the oxygen atom of the solvent competes efficiently with the oxygen atom of the acetal and the normal "B" regioisomer is favored. Such a variation in the regioselectivity of the carbocupration is not unusual with alkynes bearing a functional group in propargylic[49] position. A complete study of the factors governing this regioselectivity has already been published elsewhere.[19,20] (Scheme 2).

As a general rule *organocopper* reagents, prepared from the corresponding Grignard or organolithium reagent, afford a mixture of both regioisomers with only slight variation according to the solvent used (Table 1, entries 3, 4, 7 and 8). On the other hand,high regiochemical control is obtained with the *organocuprate* species. The "L" regioisomer **2** is obtained almost pure (98%) with *lithium dialkyl cuprates* in Et_2O solvent (Table 1, entry 1) whereas the "B" regioisomer **1** is obtained with *magnesium dialkyl cuprate* in THF solvent (Table 1, entry 6). In



Scheme 2.

this last case the minor "L" regioisomer decomposes to an allene and only the "R" regioisomer remains present as an alkenyl metal species, reactive towards any added further electrophile.

The protonation of the organometallic reagent by the acidic acetylenic hydrogen of propiolaldehyde acetal may compete with the carbocupration reaction in some cases. For example, lithium dibutyl cuprate is basic enough in the more polar solvent tetrahydrofuran to metallate this alkyne (Table 1, entry 2). This metallation is evident from the heavy precipitate of copper acetylide obtained upon hydrolysis, as well as by the formation of 1-iodo 1-alkyne upon iodination. Since the carbocupration reaction does not occur on metallated alkynes, no addition is observed in this case.

Addition to substituted acetals

Substituted acetylenic acetals also react with organocopper or cuprates derivatives. Since they are less reactive than the unsubstituted ones, the reaction temperature is higher and the main problem, in this case, arises from the β-elimination to allene (see Table 2). The regioselectivity of the addition is unambiguous since the electron donating R group favors the same isomer as the complexation effect of the oxygen atoms of the acetal Scheme 3. As shown in Table 2, organocopper or cuprate reagents, prepared from the coresponding Grignard derivative, react with substituted acetylenic acetals to afford only the corresponding allene (entries 13–16). Reagents prepared from the corresponding organolithium derivative also react sluggishly enough to permit partial decomposition to the allene. The only and notable exception are *lithium dialkyl cuprates* in Et_2O solvent, which react at sufficiently low a temperature to afford a stable dialkenyl cuprate (Table 2, entry 9).

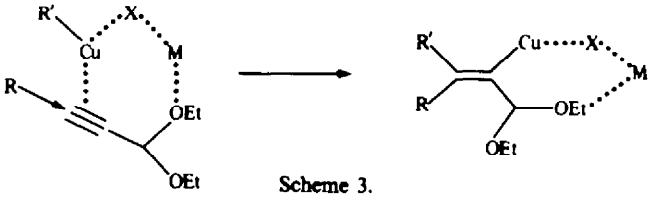
On the other hand, pure alkoxy allenes may be obtained in a more economical manner with only catalytic amounts of copper salt, a reaction complementary to the one described by Vermeer *et al.*[21] for propiolaldehyde diethyl acetal. (Scheme 4).

Despite the complete loss of stereochemical purity of the double bond, these alkoxyallenes are interesting synthetic intermediates, since they are metallated with nBuLi on the carbon bearing the oxygen atom[22] and may react with a variety of electrophiles to afford, after acidic hydrolysis, α-βethylenic ketones:[23,24] (Scheme 5).

In summary, lithium dialkyl cuprates are most suitable reagents for the efficient carbocupration of unsubstituted as well as substituted acetylenic acetals. They afford a stable dialkenyl cuprate species which may be used for a further reaction with various electrophiles. It must be pointed out that *both* alkyl moieties of a dialkyl cuprate add to the triple bond of the alkyne. As shown below the obtained dialkenyl cuprate reagent also transfer *both* alkenyl groups to the electrophile.This complete and economical use of the initial copper salt as well as of the alkyne, compares favorably with the carbocupration of acetylenic esters where an excess of cuprate is usually needed.

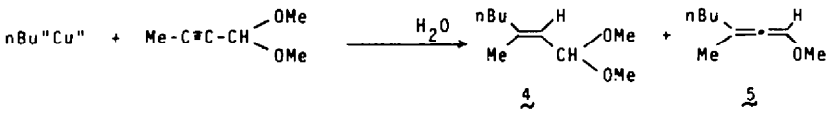
Variation of the cuprates and the acetals

A great variety of lithium diorganocuprates are able to undergo addition to acetylenic acetals (see Tables 3 and 4). The more reactive unsubstituted acetylenic acetals and ketals react with primary (Table 3, entries 17, 18, 25, 27), secondary (Table 3, entry 19) and tertiary (Table 3, entry 20) alkyl cuprates. However in this last case the reaction is non-regioselective and non-stereoselective, since the "R" regioisomer is obtained, as well as both E and Z linear isomers (overall yield 76%). The steric bulk of the tBu group may be responsible for this, which has some precedent in the carbocupration of non-substituted alkynes by tBu_2Cu,MgX.[25] (Scheme 6).



Scheme 3.

Table 2.

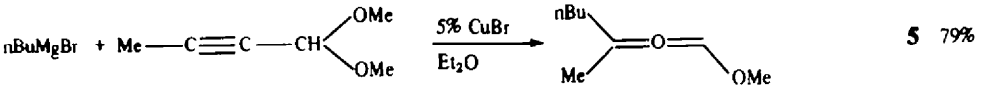


Entry	Copper species	Solvent	Temp.[b] °C	Time[b] h	Proportion[c] 4	5	Conversion
9	R_2CuLi [a]	Et_2O	-35°	0.5	100	0	99
10	"	THF	+20°	15	22	78	82
11	RCu,LiX	Et_2O	+20°	15	73	27	60
12	"	THF	+20°	15	67	33	52
13	R_2CuMgX [a]	Et_2O	+20°	15	0	100	65
14	"	THF	+20°	15	0	100	30
15	RCu,MgX_2	Et_2O	+20°	3	0	100	70
16	"	THF	+20°	3	0	100	30

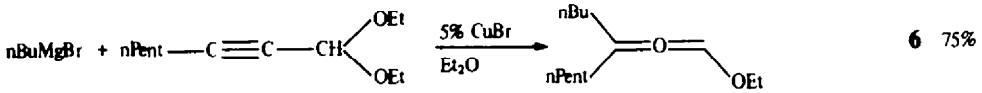
a 2 eq. of acetal are consummed per dialkyl cuprate

b Temperature and reaction time for optimum conversion

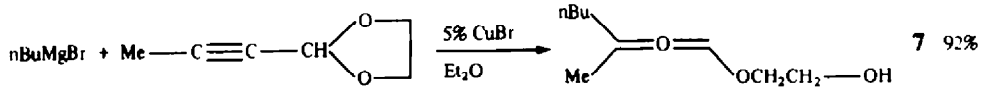
c Proportion observed on the crude reaction mixture by GLPC as well as ^1H and ^{13}C NMR



5 79%

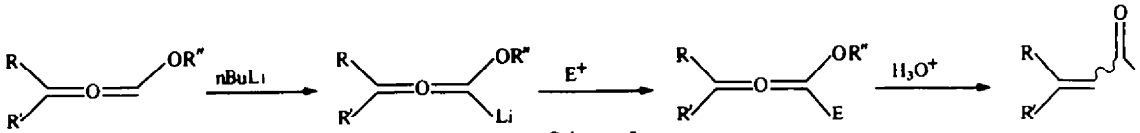


6 75%



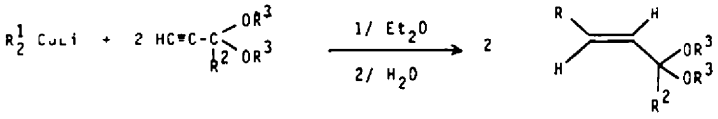
7 92%

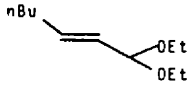
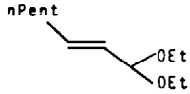
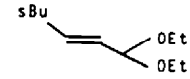
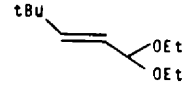
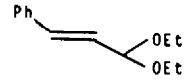
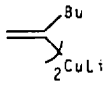
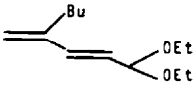
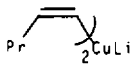
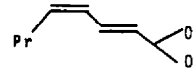
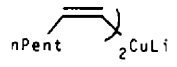
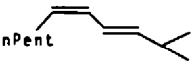
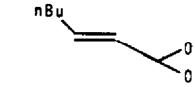
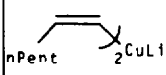
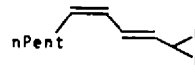
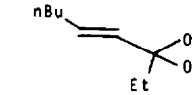
Scheme 4.



Scheme 5.

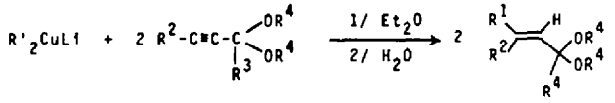
Table 3.

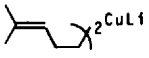
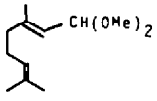
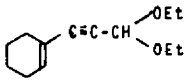
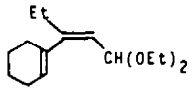


Entry	Cuprate	Acetal	Temperature °C	Time h	Product	N°	Yield[a]
17	nBu_2CuLi	HC≡C-CH(OEt)(OEt)	-50°	0.5		2	94 %
18	$nPent_2CuLi$	"	-50°	0.5		8	91%
19	sBu_2CuLi	"	-50°	0.5		9	89%
20	tBu_2CuLi	"	-50°	0.5		10	76%
21	Ph_2CuLi	"	-15°	1		11	65%
22		"	-30°	1		12	80%
23		"	-30°	1		13	54%
24		"	-30°	1		14	76%
25	nBu_2CuLi	HC≡C-CH(O)(O)	-70°	0.5		15	85%
26		"	-40°	1		16	72%
27	nBu_2CuLi	HC≡C-C(Et)(O)(O)	-60°	0.5		17	71%

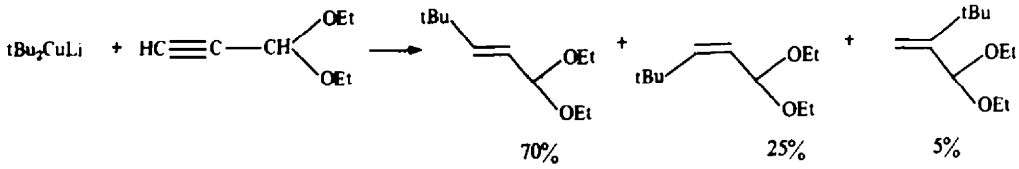
a Yield of isolated product (by distillation)
b This compound is accompanied by its two isomers (see text)
c Only one equivalent of acetal is added

Table 4.



Entry	Cuprate	Acetal	Temp. °C	Time h	Product	N°	Yield [a]
28	Me_2CuLi	nPent-C≡C-CH(OEt)$_2$	-20°	3	-	-	0%
29	nBu_2CuLi	"	-35°	0.5	nBu, nPent, $CH(OEt)_2$	18	85%
30	Et_2CuLi	Me-C≡C-CH(OMe)$_2$	-35°	0.5	Et, Me, $CH(OMe)_2$	19	87%
31	nBu_2CuLi	"	-35°	0.5	nBu, Me, $CH(OMe)_2$	20	91%
32	sBu_2CuLi	"	-35°	0.5	sBu, Me, $CH(OMe)_2$	21	83%
33	tBu_2CuLi	"	-45°	1	tBu, Me, $CH(OMe)_2$	22	43%
34		"	-35°	1		23	92%
35	nBu_2CuLi	Me-C≡C-CH(O,O)	-65°	1	nBu, Me, CH(O,O)	24	81%
36	Et_2CuLi	Ph-C≡C-CH(OEt)$_2$	-35°	0.5	Et, Ph, $CH(OEt)_2$	25	80%
37	"		-30°	0.5		26	90%
38	nBu_2CuLi	Me-C≡C-C(O,O,Me)	-50°	1	nBu, Me, O, O, Me	27	65%
39	Et_2CuLi	Me_3Si-C≡C-C(O,O,Et)	-50° to +20°	5	-	-	0%

a) Yield of isolated product (by distillation)



Scheme 6.

Diphenyl cuprate adds regio and stereoselectively albeit at higher temperature and with moderate yield (Table 3, entry 21). However, only few β-eliminations to alkoxyallenes ($\sim 10\%$) is detected despite the relatively high temperature of the addition. This stabilisation of the alkenylcuprate may be attributed to the adjacent phenyl group. Alkenylcuprates also add regio and stereoselectively (Table 3, entries 22, 23, 24, 26). However, Z-dialkenyl cuprates (obtained by addition of dialkylcuprate to acetylene) are less reactive and a higher yield is obtained using only one eq. of acetal per dialkenyl cuprate (compare entries 23 and 24). The reactivity of methyl cuprates has been checked by performing the iodination of the obtained alkenyl cuprate. In this case the observed regioselectivity is lower than with n-butyl cuprate ("L"/"B": 90/10), but can be improved to 98% using a dioxolan as protective group of the aldehyde (see below). We have also observed that the use of lithium dimethylcuprate did not give reproducible results whereas the use of lithium heterocuprate (viz methylphenylthiocuprate) was much more convenient.

Substituted acetylenic acetals and ketals, on the other hand, are much less reactive (see Table 4). They react only with primary and secondary lithium cuprates. Di-t-butyl cuprate adds conveniently only one t-butyl group (Table 4, entry 33), the second one being added at a temperature ($-30°$) where β-elimination occurs rapidly. In this case the β-elimination to the alkoxy allene occurs at a relatively low temperature, probably for steric reasons. If the reaction medium is left at $-20°$ for 2 h a high yield (78%) of the alkoxyallene is obtained. (Scheme 7).

Variation of the acetylenic acetal is also possible. They may be acetals of aldehydes as well as ketals of ketones (Table 3, entry 27 and Table 4, entries 38, 39). These aldehydes or ketones may be protected as dialkoxy acetals or as cyclic acetals like dioxolans. In the case of dioxolanes, the β-elimination to allene occurs at a lower temperature ($\sim -35°$), but the carbocupration reaction also occurs at a lower temperature, so that the dialkenyl cuprate derivative is easily handled for further reactions with electrophiles. Substituted acetals may bear various substituents at the acetylenic carbon atom, such as alkyl, aryl (Table 4, entry 36) or alkenyl (Table 4, entry 37) groups. However the trimethylsilyl group impedes the addition, either by its bulkiness or by its inductive effect which is opposite to that of alkyl substituents.

Among the various products obtained by simple hydrolysis of the alkenylcuprates it is interesting to note the geranial acetal **23** which, by hydrolysis of the acetal function (see below) affords pure geranial ($> 99\%$) uncontamined by its isomer neral.Dienic acetals such as **12**, **13**, **14**, **16** and **26** are also worth noting. They are usefull synthons for Diels–Alder reaction or for the synthesis of other natural products. For example, the aldehyde derived from **14** or **16** has been used for the synthesis of "Pear Ester" ethyl 2,4-decadienoate[26] and for the synthesis 1,3,5-undecatrienes.[27]

This same aldehyde is also a flavour component of many essential oils; among them, it has been found in groundnuts and carrot root.[28]

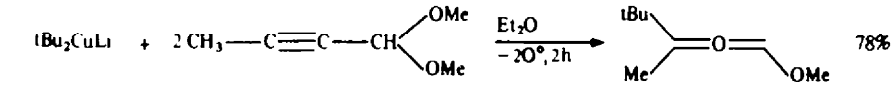
Thus, the carbocupration of acetylenic acetals affords ethylenic acetals (or aldehydes after deprotection) of defined stereochemistry. The stereochemical purity of the double bond is higher than 99% as usually observed for the carbocupration reaction,[18] and there is no possibility of isomerisation of the alkenylcuprate moeity as is observed in the carbocupration of acetylenic esters, ketones or aldehydes.

Reactivity of alkenyl–cuprates

The reactivity of non-functionalised idalkenyl cuprates toward various electrophiles using *both* alkenyl groups, has been previously studied.[18] However, we observed that the functionalised dialkenyl cuprates obtained here, posess a much enhanced reactivity, probably due to the proximity of the oxygen atoms of the acetal function. Marino *et al.*[14,17] as well as Grieco *et al.*[15] and Boeckman *et al.*[16] have already used the following alkenyl cuprate bearing an acetal function. They found this cuprate to react with α-βethylenic ketones in a 1,4 manner, to open epoxides smoothly and to couple with allylic halides (but not with alkyl, alkenyl, aryl and benzyl halides). (Scheme 8).

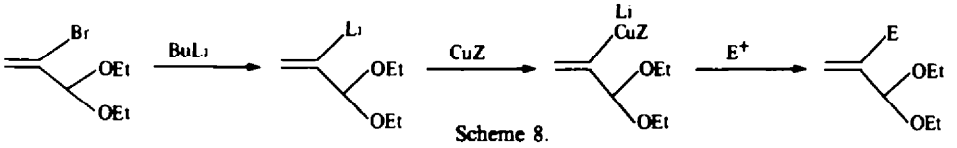
It was expected that our polysubstituted dialkenyl cuprates would behave much in a similar manner, although our goal was to use rationnaly *both* alkenyl moieties. This is indeed the case as shown below.

One of the easiest reactions to perform with dialkenyl cuprates is the iodination reaction. Thus, addition of an equimolecular amount of solid iodine to the solution of the dialkenyl cuprates, affords the corresponding alkenyl iodide in high yield (Table 5). The carbocupration reaction with lithium dimethyl cuprate, followed by addition of iodine afforded a mixture of two regioisomeric alkenyl iodides (Table 5, entries 42 and 43). This result indicates that the smaller methyl group (as compared to the bulkier n-butyl group) is more able to add to the more hindered side of the alkyne. However a high regiochemical control could be obtained again by the use of a dioxolan as protective group of the aldehyde, probably due to the higher coordinating ability of the



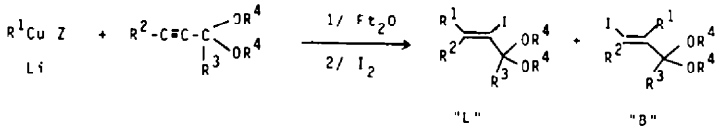
28

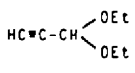
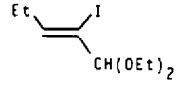
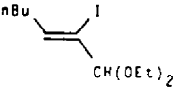
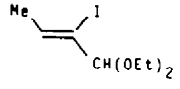
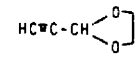
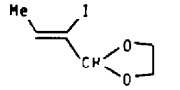
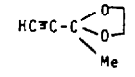
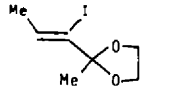
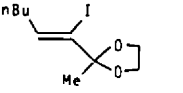
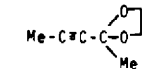
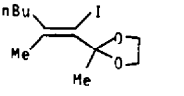
Scheme 7.



Scheme 8.

Table 5.



Entry	Cuprate	Acetal	Carbocupration conditions Temp.	Time	Major product	N°	"L"/"B" [a]	Yield [b]
40	Et_2CuLi		-50°	0.5		29	98/ 2	87%
41	nBu_2CuLi	"	-50°	0.5		30	98/ 2	90%
42	Me_2CuLi	"	-30°	1		31	90/10	67%
43	MeCuSPh Li	"	-30°	1	"	31	90/10	65%
44	"		-40°	1		32	98/ 2	56%
45	"		-30°	1		33	100/ 0	58%
46	nBu_2CuLi	"	-60°	0.5		34	100/ 0	73%
47	"		-50°	1		35	100/ 0	57%

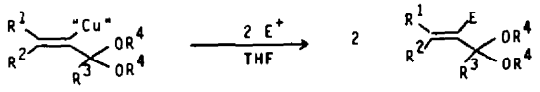
a) This ratio is determined on the crude mixture, by GLPC as well as by ^1H and ^{13}C NMR

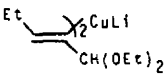
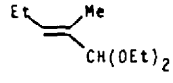
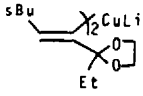
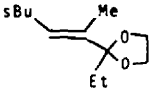
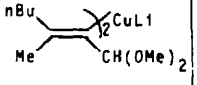
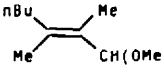
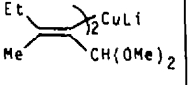
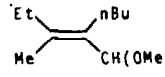
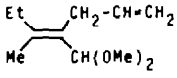
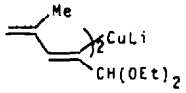
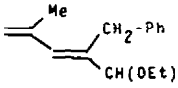
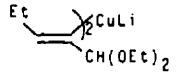
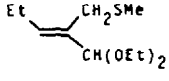
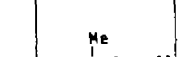
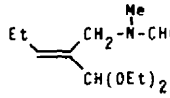
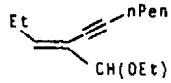
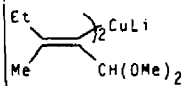
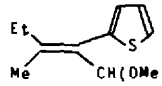
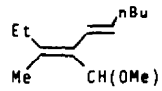
b) Yield of isolated product by distillation

oxygen atoms of the dioxolan ring. This influence of the type of acetal function on the regioselectivity of the addition has previously been observed by us during the carbocupration of alkynes bearing a β-acetal function.[19] It must also be noted that more reproducible results are obtained with the mixed lithium methyl-phenylthio cuprate than with lithium dimethylcuprate. Alkenyl iodides, such as the ones quoted in Table 5 are very interesting synthons, since they lead to the corresponding lithium reagent via metal–halogen exchange with nBuLi.[29] These lithium reagents would react in 1–2 fashion with α-enones, simple ketones, aldehydes or esters, all reactions which cannot be performed with cuprates.

The reaction of our substituted dialkenyl cuprates with other electrophiles are quoted in Tables 6 and 7. Alkylation with methyl iodide is easily performed with a slight excess ($\sim 15\%$) of electrophile, after

Table 6.

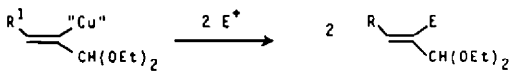


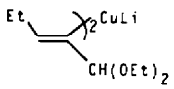
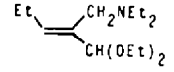
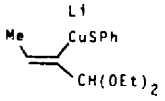
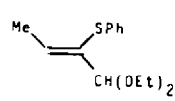
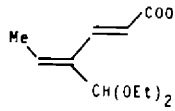
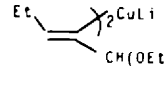
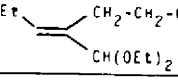
Entry	Alkenyl cuprate	Electrophile	Additive	Reaction Conditions Temp.	Time	Product	N°	Yield [a]
48		MeI	-	-60° to +20°	16h		36	85%
49		"	1 HMPT	"	"		37	81%
50		"	-	"	"		38	87%
51		nBuI	4 HMPT	"	"		39	78%
52	"	CH_2=CH-CH_2Br	-	"	"		40	80%
53		Ph-CH_2-Br	1 HMPT	"	"		41	67%
54		Me-S-CH_2-Cl	-	"	"		42	92%
55	"		-	"	"		43	89%
56	"	nPent-C≡C-I	1 CuBr.LiCl 1.5 TMEDA	-30° to-20°	2h		44	76%
57		 [b]	1 $ZnBr_2$ 3% $Pd(PPh_3)_4$	-50° to + 5°	2h		45	67%
58	"		1 $MgCl_2$ 1 $ZnBr_2$ 3% $Pd(PPh_3)_4$	"	"		46	72%

a) Yield of isolated product (by distillation)

b) Only one equivalent of electrophile is added

Table 7.



Entry	Alkenyl cuprate	Electrophile	Additives	Reaction conditions Temp.	Time	Product	N°	Yield [a]
59		$PhS-CH_2-NEt_2$	THF	-50° to +20°	16h		47	79%
60		PhS-S-Ph	THF	-	3h		48	56%
61	"	HC≡C-COOEt	-	-60°	0.5		49	82%
62			-	"	"		50	72%

a) Yield of isolated product (by distillation)

addition of tetrahydrofuran (one third of the total volume) to the ethereal reaction mixture, and allowing it to reach room temperature for 2–3 h (Table 6, entries 48 and 50). In the case of the preparation of the acetal of Manicone **37** (Table 6 entry 49) a quantitative alkylation (by GLPC) is achieved only in the presence of one equivalent of hexamethylphosphotriamide (HMPT). In its absence only ~80% of the alkenyl cuprate is alkylated. This method is the most straightforward and stereoselective (E purity >99%) synthesis for this alarm pheromone present in the mandibular glands of *Manica mutica* and *Manica bradleyi*. Previous syntheses[31-36] have been faced with the problem of placing the substituents at the double bond at the right place with a high selectivity. Most of them require a chromatographic purification on the final product. Thus, the carbocupration reaction is the most suitable for preparative purposes.

The alkylation with n-butyl iodide (Table 6, entry 51) requires the additionof more HMPT (viz 4 equiv). Without HMPT or with only one equivalent lower yields (~45% and 75% respectively) of butylated product are obtained. Allylic bromides are known to react smoothly with alkenyl cuprates bearing an acetal function.[14-16] In our case both alkenyl groups react as well with no HMPT needed for (Table 6, entry 52). Benzyl bromide also reacts cleanly (one equiv. of HMPT needed) (Table 6, entry 53). The alkylation reaction may also be performed with highly reactive functionalized alkyl halides. Thus the reaction with phenyl chloromethyl sulfide[37] affords the allylic thioether **42** and with N-formyl, N-methyl chloromethyl amine affords the formamide **43**.[37]

Trimethylchlorosilane does not react at all with our alkenyl cuprates, probably for steric reasons.

Alkylation with 1-halo 1-alkynes is also feasable after transformation of the *alkenyl cuprate* into *alkenyl copper* derivative by addition to the reaction mixture of one equivalent of copper salt.[38] Enynic acetal **44** is thus obtained in high yield (Table 6, entry 56). The coupling of alkenyl cuprates with aryl or alkenyl halide does not occur under a variety of conditions. However, using the previously reported procedure, with Pd° catalysis,[39,40] it is possible to obtain this coupling reaction. Compound **45** is, thus, obtained, in high yield by reaction with 2-iodo-thiophene, under Pd° catalysis. The same procedure, modified for the efficient use of *both* alkenyl groups may also be used as examplified by the coupling with 1-iodo, 1-alkene for the synthesis of dienic acetal **46**.

α,β-Unsaturated epoxides are known to react with alkenyl cuprates bearing the acetal group.[17] On the other hand simple epoxides, such as propylene oxide, also react with our alkenyl cuprates, but only one alkenyl group is transferred. A more rational use of the alkenyl moiety would require the use of an unsymmetrical cuprate.[41] A mixture of at least three compounds was obtained which could not be separated either by distillation or column chromatography (Scheme 9). The reaction with aminothiothers affords allylic amines in high yield (Table 7, entry 59) using our previously reported procedure.[42]

Alkenyl cuprates are also able to cleave dithioethers;[43] thus, the reaction with diphenyl disulfide in THF solvent affords the alkenyl thioether **48** (Table 7, entry 60) in moderate yield.

Conjugate addition of alkenyl cuprates bearing the acetal function has already been performed.[14-16] In our hands, our alkenyl cuprates afforded the diene **49** upon reaction with ethyl propiolate (Table 7, entry 61). On the other hand the reaction with methyl vinyl ketone proceeded with transfer of *both* alkenyl groups. The keto-acetal **50** is thus obtained in high yield (Table 7, entry 62).

From the examples shown above, it is clear that substituted alkenyl cuprates bearing the acetal function, may be used for a great variety of synthetic transformations. This "one pot" procedure allows the obtention of very elaborated synthons, some of which have been synthetised otherwise by lengthy and fastiduous routes.

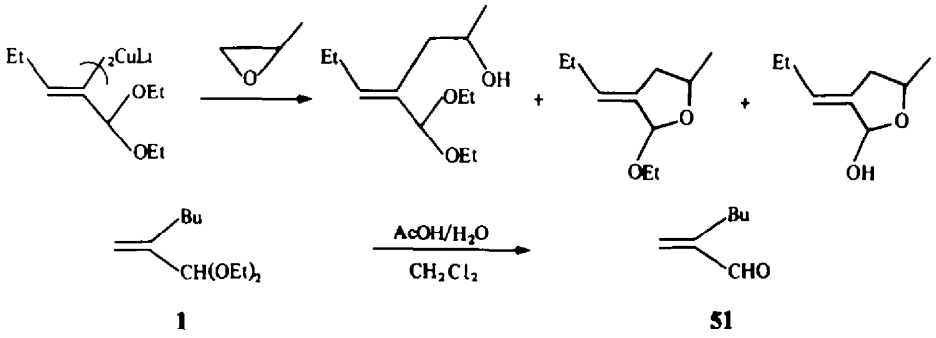
Hydrolysis of acetals and ketals

The obtained acetals are precious precursors of their corresponding aldehydes or ketones. Among the various methods available for the hydrolysis of acetals to aldehydes, we used either the acetic acid/water procedure, or the milder Bestmann procedure.[44] The following aldehydes have been, thus, obtained in quantitative yield. (Scheme 10). These crude aldehydes are homogeneous by GLPC and NMR and may be used directly for further purposes. Aldehydes **53** and **54** are sensitive to isomerisation. Addition of a crystal of iodine in the NMR tube containing the sample shows the appearance of new signals which correspond to the geometrical isomer. Aldehyde **55** is even more sensitive to isomerisation, but is obtained in pure form using a milder hydrolysis.

We have synthetised also pure geranial in the same way. Manicone ketal **37** affords analogously pure manicone **57**. Keto-acetal **50** may also be hydrolyzed to the keto-aldehyde **58**. This in turn is cyclized quantitatively to the enone **59** which retains its stereochemistry. (Scheme 11).

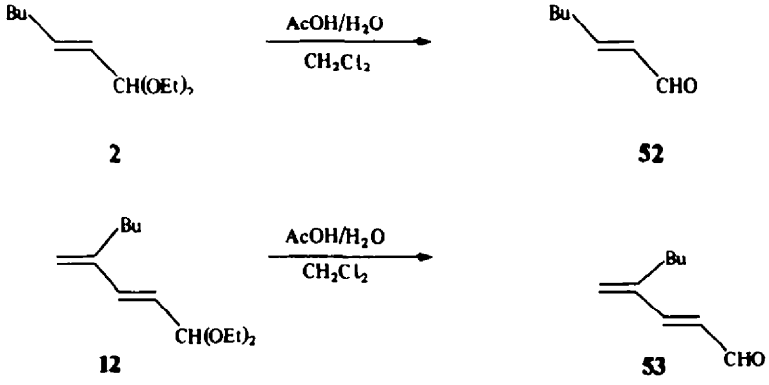
Preparation of acetals and ketals

The carbocupration of acetylenic acetals would not be a useful method if these acetals were not easily available. They are in fact very easily prepared and in high yield. For example propiolaldehyde diethyl acetal is commercially available or may be prepared according to Brandsma[45] in high yield. Higher homologs of aldehyde acetals may be prepared from the corresponding alkyne and ethyl or methyl orthoformiate by either or the two ways (Scheme 12). As for ketals of acetylenic ketones, we have developed a simple methodology to obtain them in high yield, starting from the commerically available bis-trimethylsilylacetylene:



1 **51**

Scheme 9.

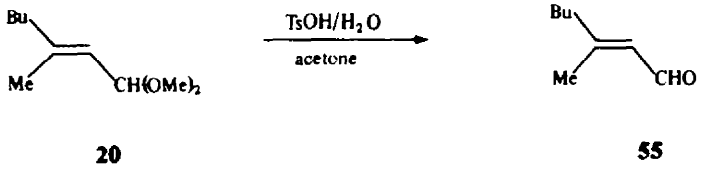


2 **52**

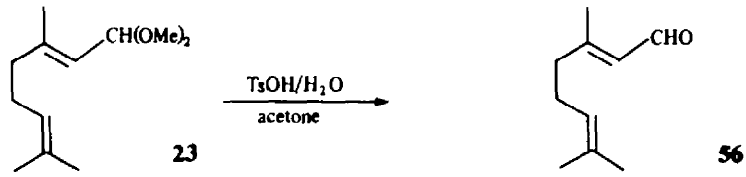
12 **53**

25 **54**

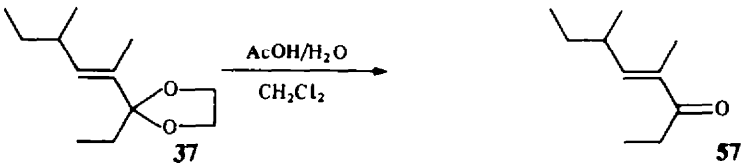
Scheme 10.



20 **55**

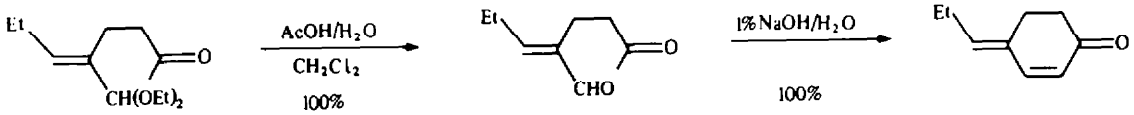


23 **56**



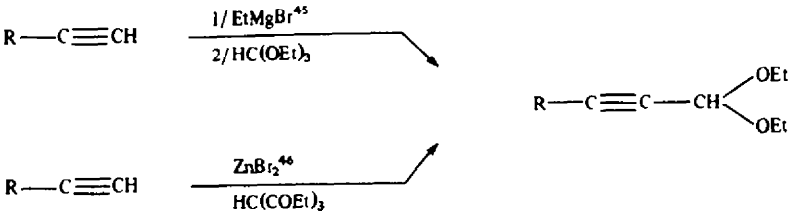
37 **57**

Scheme 10 (*Contd*)



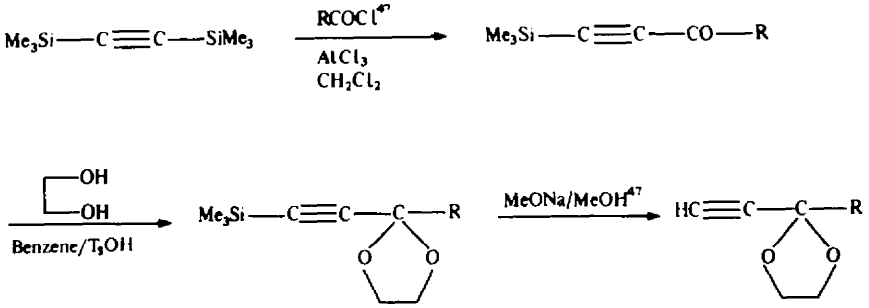
50 **58** **59**

Scheme 11.

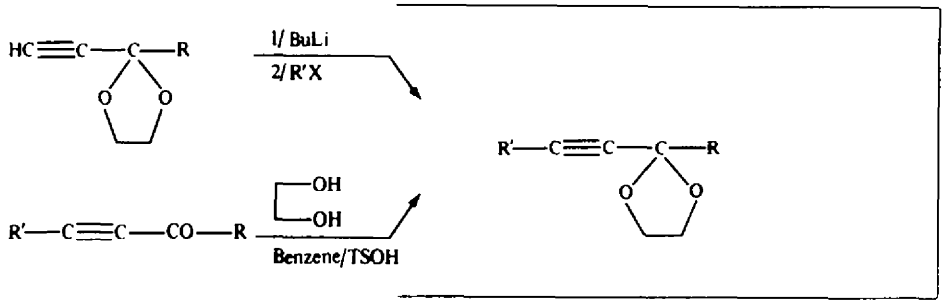


Scheme 12.

and using known methods:



The corresponding substituted alkynes are easily obtained by metallation and alkylation of their unsubstituted precursors, or by direct ketalisation of the acetylenic ketone:



CONCLUSION

The carbocupration of acetylenic acetals is a very competitive methodology as compared to the carbocupration of acetylenic esters, ketones or aldehydes. Although the former substrates are less reactive, they permit the obtention of highly pure products as far as the stereochemistry of the double bond is considered. The obtained alkenyl cuprates are also much more reactive than those obtained by the carbocupration of acetylenic esters. Hence an easy access to very elaborated synthon for further use in multistep synthesis.

This general method may also be used for the synthesis of many natural product such as geranial, (±)-manicone and variously substituted 2,4(E,Z)-dienals.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Jeol MH 100 (CCl_4; δ ppm from TMS), ^{13}C NMR on a Jeol FX 60Q ($CDCl_3$; δ ppm from TMS). IR spectra were obtained on a Perkin-Elmer model 457 spectrometer. GLC analyses were performed on a Carlo Erba gas chromatograph model G 1 and 2150 using a 3 m glass column (10% SE 30 or 10% LAC 860 on silanized Chromosorb G/80/100 mesh) and a 50 m capillary glass column (OV 101). The gas chromatograph was coupled with an LTT 9400 integrator. All reactions are performed under a nitrogen atmosphere in a 250 ml flask equipped with a low-temperature thermometer, a mechanical stirrer and a pressure equalizing addition funnel.

Lithium dialkyl(or dimethyl)cuprates were prepared by addition of an ethereal solution of the corresponding organolithium reagent (50 mmol) to a stirred suspension of CuI (27 mmol; purchased from Prolabo or Merck) in 80 ml diethyl ether at $-40°$. After stirring at $-30°$ ($-10°$ for Me_2CuLi) for 15 min a blue solution of cuprate was obtained (25 mmol of cuprate).

Lithium (Z) alkenyl cuprates were prepared by carbocupration of acetylene as described previously.[18]

All other lithium dialkenyl cuprates as well as lithium diphenyl cuprate are prepared from the lithium reagent (50 mmol) and CuBr·MeSMe complex (27 mmol) as described for dialkyl cuprates.

Lithium methyl phenylthio cuprate was prepared either by addition of 25 mmol of thiophenol to a lithium dimethyl cuprate (25 mmol) in ether at $-30°$, or by addition of 25 mmol of MeLi to a stirred suspensionof PhSCu (25 mmol) in 75 ml diethyl ether, at $-15°$, and stirring at $+10°$ for 1 h. The two procedures afford the same results.

Hydrolysis of alkenyl cuprates

1,1-*Diethoxy* 3(*E*)-*heptene* **2**. To a solution of 25 mmol of the di-n-butyl cuprate in 100 ml ether (prepared from 50 mmol of n-butyl lithium) was added 6.4 g (50 mmol) of diethoxypropyne in 25 ml ether at $-50°$. The stirred solution was kept 30 min at $-45°$, then hydrolyzed by addition of 80 ml of sat NH_4Cl and 20 ml sat NH_3. The salts were filtered off and the organic layer washed once with sat NH_4Cl while the aqueous phase was extracted twice with 50 ml ether. The combined organic phases were dried over K_2CO_3, the solvent was evaporated in vacuo and the residue was distilled through a 10 cm Vigreux column to afford 8.8 g of the title compound (94%). B.p. 90–91°/15 mmHg (lit.[48] 152–156°/600 mmHg; n_D^{20} 1.4247; IR (neat) cm^{-1} 3020, 1685, 1065, 985; ^{1}H NMR (CCl_4, δ) 5.74 (CH=, dt, 1), 5.37 (CH=, dd, 1), 4.78 (CH<O,O>, d,1), 3.46 (CH_2—O, m, 4), 2.04 ($CHCH_2$—C=, 9,2).

1,1-*Diethoxy* 2(*E*)-*octene* **8**. As for **2**, reaction time and temperature quoated in Table 3, entry 18. Yield: 91%. B.p. 100–102°/15 mmHg; n_D^{20} 1.4365; IR (neat) cm^{-1} 3020, 1685, 1065, 985; ^{1}H NMR (CCl_4, δ), 5.72 (CH=, dt, 1), 5.33 (CH=, dd, 1), 4.78 (CH<O,O>, d,1), 3.45 (CH_2—O,m,4); ^{13}C NMR ($CDCl_3$, δ) 135.0, 127.6 (CH=), 102.0 (CH<O,O>), 60.8 (CH_2—O).

1,1-*Diethoxy*, 4 *methyl* 2(*E*)-*hexene* **9**. Same procedure as for **2**. Reaction conditions are quoted in Table 3, entry 19. Yield: 89%. B.p. 40–41°/0.1 mmHg; n_D^{20} 1.4219; IR (neat) cm^{-1} 3015, 1675, 1050, 980; ^{1}H NMR ($CDCl_3$, δ) 5.78 (CH=, dd, 1), 5.47 (CH=, dd, 1), 4.90 (CH<O,O>, d, 1); ^{13}C NMR ($CDCl_3$, δ) 140.2, 126.1 (CH=), 101.9 (CH<O,O>), 60.7 (CH_2—O).

1,1-*Diethoxy* 3-*phenyl* 2(*E*)-*propene* **11**. Reaction conditions are quoted in Table 3, entry 21. Yield: 65% B.p. 88–90°/0.05 mmHg (lit.[49]: 102–105/3 mmHg); n_D^{20} 1.5211 (lit.[49]: n_D^{20} 1.5145); IR (neat) cm^{-1} 3060, 3030, 1680, 1655, 1600, 1580, 1050, 970, 750, 695; ^{1}H NMR (CCl_4, δ) 7.35–7.75 (Ph, m, 5H), 6.84 (CH=, d, 1H), 6.25 (CH=, dd, 1H), 5.15 (CH<O,O>, d, 1H).

1,1-*Diethoxy* 4-*methylene* 2(*E*)-*octene* **12**. Reaction conditions are quoted in Table 3, entry 22. Yield: 80%. B.p. 65–66°/0.05 mmHg; n_D^{20} 1.4563; IR (neat) 3030, 1645, 1620, 1060, 985, 900; ^{1}H NMR (CCl_4, δ) 6.33 (CH=, d, 1H), 5.62 (CH=, dd, 1H), 5.00 (CH_2=, s, 2H), 4.95 (CH<O,O>, d, 1H).

1,1-*Diethoxy* 2,4(*E,Z*) *octadiène* **13**. Reaction conditions are quoted in Table 3, entry 23. Yield: 54%. B.p. 106°/15 mmHg; n_D^{20} 1.4708; IR (neat) cm^{-1} 3005, 1660, 1615, 1130, 1050, 950; ^{1}H NMR (CCl_4, δ) 6.52(CH=, dd, 1H), 5.96 (CH=, dd, 1H), 5.36–5.64 (CH=, m, 2H), 4.90 (CH<O,O>, d, 1H).

1,1-*Diethoxy* 2,4(*E,Z*) *decadiene* **14**. Reaction conditions are quoted in Table 3, entry 24 Yield: 76%. B.p. 81–82°/0.01 mmHg; n_D^{20} 1.4619; IR (neat) cm^{-1} 3005, 1660,

1615, 1130, 1050, 950; ^{1}H NMR (CCl_4, δ) 6.61 (CH=, dd, 1H), 6.00 (CH=, dd, 1H); 5.40–5.70 (CH=, m, 2H), 4.97 (CH(O)O, d, 1H); ^{13}C NMR ($CDCl_3$, δ) 134.3, 129.7, 128.4, 127.5 (CH=), 101.5 (CH(O)O), 61.0 (CH_2—O).

2(*E*) *Heptenal ethylene glycol acetal* **15**. Reaction conditions are quoted in Table 3, entry 25. Yield: 85%. B.p. 100–101°/15 mmHg; n_D^{20} 1.4482; IR (neat) cm^{-1} 3020, 1680, 1140, 1060, 960; ^{1}H NMR (CCl_4, δ) 5.82 (CH=, dt, 1H), 5.38 (CH=, dd, 1H), 5.07 (CH(O)O, d, 1H), 3.80 (CH_2—O, m, 4).

2,4(*E,Z*) *Decadienal ethylene glycol acetal* **16**. Reaction conditions are quoted in Table 3, entry 26. Yield: 72%. B.p. 81–82°/0.01 mmHg; n_D^{20} 1.4862; IR (neat) cm^{-1} 3010, 1660, 1615, 1140, 950; ^{1}H NMR (CCl_4, δ) 6.60 (CH=, dd, 1H), 5.97 (CH=, dd, 1H), 5.36–5.68 (CH=, m, 2H), 5.21 (CH(O)O, d, 1H), 3.80 (CH_2—O, m, 4H).

4(*E*) *Nonen-3, one ethylene glycol ketal* **17**. Reaction conditions are quoted in Table 3, entry 27. Yield: 71%. B.p. 54–55°/0.01 mmHg; n_D^{20} 1.4502; IR (neat) cm^{-1} 3010, 1670, 1050, 970, 920; ^{1}H NMR (CCl_4, δ) 5.64 (CH=, dt, 1H), 5.37 (CH=, d, 1H), 3.86 (CH_2—O, s, 4H), 2.08 (CH_2—C=, q, 2H), 1.62 (CH_2—C(O)O, q, 2H).

1,1-*Diethoxy, 2-methylene hexane* **1**. Reaction conditions are quoted in Table 1, entry 6. Yield: 62%. B.p. 79–80°/15 mmHg; n_D^{20} 1.4281; IR (neat) cm^{-1} 3010, 1645, 910; ^{1}H NMR (CCl_4, δ) 5.05 (CH=, s, 1H), 4.83 (CH=, s, 1H), 4.61 (CH(O)O, s, 1H), 3.46 (CH_2—O, m, 4H); ^{13}C NMR ($CDCl_3$, δ) 146.5 (C=), 112,3 (CH_2=), 103.7 (CH(O)O), 61.4 (CH_2—O).

1,1 *Diethoxy 3-butyl* 2(*Z*)*-octene* **18**. Reaction conditions are quoted in Table 4, entry 29. Yield: 85%. B.p. 91–92/0.2 mmHg; n_D^{20} 1.4427; IR (neat) cm^{-1} 1675, 1060, 1000; ^{1}H NMR (CCl_4, δ) 5.20 (CH=, d, 1H), 5.05 (CH(O)O, d, 1H), 3.44 (CH_2—O, m, 4H).

1,1 *Dimethoxy 3-methyl* 2(*E*)*pentene* **19**. Reaction conditions are quoted in Table 4, entry 30. Yield: 87%. B.p. 63–64°/15 mmHg; n_D^{20} 1.4302; IR (neat) cm^{-1} 3005, 1670, 1060, 970, 910; ^{1}H NMR (CCl_4, δ) 5.26 (CH=, d, 1H), 5.03 (CH(O)O, d, 1H), 3.26 (CH_3—O, s, 6H), 2.04 (CH_2—C=, q, 2H), 1.59 (CH_3—C=, s, 3H); ^{13}C NMR ($CDCl_3$, δ) 143.6 (C=), 120.5 (CH=), 100.6 (CH(O)O), 52.0 (CH_3—O).

1,1 *Dimethoxy 3-methyl* 2(*E*)*-heptene* **20**. Reactions conditions are quoted in Table 4, entry 31. Yield: 91%. B.p. 84–85°/15 mmHg; n_D^{20} 1.4330; IR (neat) cm^{-1} 3005, 1670, 1060, 970, 915; ^{1}H NMR (CCl_4, δ) 5.22 (CH=, d, 1H), 4.18 (CH(O)O, d, 1H), 3.19 (CH_3—O, s, 6H), 2.03 (CH_2—C=, t, 2H), 1.67 (CH_3—C=, s, 3H).

1,1 *Dimethoxy* 3,4 *dimethyl* 2(*E*)*-hexene* **21**. Reaction conditions are quoted in Table 4, entry 32. Yield: 83%. B.p. 76–77°/15 mmHg; n_D^{20} 1.4350; IR (neat) cm^{-1} 1675, 1130, 1050, 965, 910; ^{1}H NMR (CCl_4, δ) 5.24 (CH=, d, 1H), 5.00 (CH(O)O, d, 1H), 3.20 (CH_3—O, s, 6H), 2.00 (CH—C=, m, 1H), 1.63 (CH_3—C=, s, 3H).

1,1 *Dimethoxy* 3,4,4-*trimethyl* 2(*E*) *pentene* **22**. Reaction conditions are quoted in Table 4, entry 33. Yield: 43%. B.p. 69–71°/15 mmHg; n_D^{20} 1.4419; IR (neat) cm^{-1} 1670, 1130, 1050, 960, 910; ^{1}H NMR ($CDCl_3$, δ)5.35 (CH=, d, 1H), 5.12 (CH(O)O, d, 1H), 3.32 (CH_3O—, s, 6H), 1.75 (CH_3—C=, s, 3H); ^{13}C NMR ($CDCl_3$, δ) 150.0 (C=), 119.0 (CH=), 100.9 (CH(O)O), 51.9 (CH_3—O).

1,1 *Dimethoxy* 3,7-*dimethyl* 2(*E*), 6-*octadiene, geranial dimethyl acetal* **23**. Reaction conditions are quoted in Table 4, entry 34. Yield: 92%. B.p. 59°/0.2 mmHg; n_D^{20} 1.4565; IR (neat) cm^{-1} 1680, 1140, 1060, 970, 915; ^{1}H NMR (CCl_4, δ) 5.12 (CH=, m, 4H), 1.67 (CH_3—C=, s, 6H), 1.59 (CH_3—C=, s, 3H).

3, *Methyl* 2(*E*) *heptenal ethylene glycol acetal* **24**. Reaction conditions are quoted in Table 4, entry 35. Yield: 81%. B.p. 55–56°/0.05 mmHg; n_D^{20} 1.4560; IR (neat) cm^{-1} 3010, 1680, 1060, 950; ^{1}H NMR (CCl_4, δ) 5.41 (CH(O)O, d, 1H), 5.20 (CH=, d, 1H), 3.82 (CH_2—O, m, 4H), 2.05 (CH_2—C=, t, 2H), 1.72 (CH_3—C=, s, 3H).

1,1-*Diethoxy* 3-*phenyl*, 2(*E*) *pentene* **25**. Reaction conditions are quoted in Table 4, entry 36. Yield: 80%. B.p. 99–101°/0.05 mmHg; n_D^{20} 1.5004; IR (neat) cm^{-1} 3080, 3060, 3020, 1655, 1600, 1110, 1050, 995, 770, 700; ^{1}H NMR ($CDCl_3$, δ) 7.64 (Ph, m, 5H), 5.94 (CH=, d, 1H), 5.02 (CH(O)O, d, 1H), 3.70 (CH_2—O, m, 4H), 2.52 (CH_2—C=, q, 2H); ^{13}C NMR ($CDCl_3$, δ) 147.4 (C=), 140.2, 128.1, 128.0, 127.1 (Ph), 123.2 (CH=), 99.5 (CH(O)O), 60.8 (CH_2—O).

1,1 *Diethoxy* 3 (1-*Cyclohexenyl*) 2(*Z*)*-pentene* **26**. Reaction conditions are quoted in Table 4, entry 37. Yield: 90% B.p. 80–81°/0.05 mmHg; n_D^{20} 1.4657; IR (neat) cm^{-1} 3010, 1665, 1050, 990, 915; ^{1}H NMR ($CDCl_3$, δ) 5.52 (CH=, t, 1H), 5.30 (CH=, d, 1H), 5.05 (CH(O)O, d, 1H), 3.56 (CH_2—O, m, 4H); ^{13}C NMR ($CDCl_3$, δ) 150.5, 136.5 (C=), 125.6, 121.1 (CH=), 99.6 (CH(O)O), 60.7 (CH_2—O).

4-*Methyl* 3(*E*) *octen* 2-*one ethylene glycol ketal* **27**. Reaction conditions are quoted in Table 4, entry 38. Yield: 65%. B.p. 47°/0.01 mmHg; n_D^{20} 1.4470; IR (neat) cm^{-1} 1670, 1180, 1045, 945, 865, 790; ^{1}H NMR (CCl_4, δ) 5.24 (CH=, s, 1H), 3.82 (CH_2—O, m, 4H), 1.98 (CH_2—C=, t, 2H), 1.78 (CH_3—C=, s, 3H), 1.38 (CH_3—C(O)O, s, 3H).

Iodination of alkenyl cuprates

alkenyl cuprates were prepared as described above, by addition of an alkyl cuprate to an acetylenic acetal. The ethereal reaction mixture was cooled to $-60°$ and finely crushed solid iodine (5% excess) was added at once. The reaction mixture was warmed to $-10°$ in 1 h, then hydrolyzed with a 5/1 mixture of sat NH_4Cl and 17% aqueous ammonia. The salts were filtered off, the aqueous layer extracted twice with ether and the combined organic phases were washed once or twice with an aqueous solution of sodium thiosulfate and dried over K_2CO_3. After evaporation of the solvent on a rotatory evaporator the crude product was distilled through a 10 cm Vigreux column.

1,1 *Diethoxy 2-iodo* 2(*Z*) *pentene* **29**. B.p. 67–68°/0.05 mmHg; n_D^{20} 1.4876; IR (neat) cm^{-1} 1645, 1060, 920, 890, 860; ^{1}H NMR ($CDCl_3$, δ) 6.27 (CH=, t, 1H), 4.66 (CH(O)O, s, 1H), 3.60 (CH_2—O, m, 4H), 2.26 (CH_2—C=, m, 2H); ^{13}C NMR ($CDCl_3$, δ) 139.9 (CH=), 106.1 (=C—I), 103.9 (CH(O)O), 61.6 (CH_2—O).

1,1 *Diethoxy* 2-*iodo* 2(*Z*) *heptene* **30**. B.p. 80°/0.02 mmHg; n_D^{20} 1.4792; IR (neat) cm^{-1} 1645, 1060, 920, 885; ^{1}H NMR (CCl_4, δ) 6.15 (CH=, t, 1H), 4.68 (CH(O)O, s, 1H), 3.51 (CH_2—O, m, 4H), 2.20 (CH_2—C=, q, 2H).

1,1 *Diethoxy 2-iodo* 2(*Z*) *butene* **31**. B.p. 50–52°/0.02 mmHg (partial decomposition); IR (neat) cm^{-1} 1645, 1060, 920, 890; ^{1}H NMR (CCl_4, δ) 6.14 (CH=, q, 1H), 4.60 (CH(O)O, s, 1H), 3.46 (CH_2—O, m, 4H), 1.78 (CH_3—C=, d, 3H).

2-*Iodo* 2(*Z*)*-butenal ethylene glycol acetal* **32**. B.p. 52–53°/0.05 mmHg; n_D^{20} 1.5416; IR (neat) cm^{-1} 1645, 1170,

1050, 950, 815. ^{1}H NMR (CCl_4, δ) 6.16 (CH=, q, 1H), 4.82 (CH(O)(O), s, 1H), 3.96 (CH_2—O, m, 4H), 1.84 (CH_3—C, d, 3H).

3-Iodo 3(Z) penten 2-one ethylene glycol ketal **33**. B.p. 47–49°/0.01 mmHg (partial decomposition); IR (neat) cm^{-1} 1640, 1170, 1040, 950, 875, 830; ^{1}H NMR (CCl_4, δ) 6.14 (CH, q, 1H), 3.84 (CH_2—O, m, 4H), 1.79 (CH_3—C, d, 3H), 1.51 (CH_3—C(O)(O), s, 3H).

3-Iodo 3(Z)-octen 2-one ethylene glycol ketal **34**. B.p. 85–87°/0.01 mmHg (partial decomposition); IR (neat) cm^{-1} 1630, 1170, 1040, 950, 875, 830; ^{1}H NMR (CCl_4, δ), 6.00 (CH=, t, 1H), 3.81 (CH_2—O, m, 4H), 2.18 (CH_2—C=, q, 2H), 1.50 (CH_3—C(O)(O), s, 3H).

3-Iodo 4-methyl 3(Z)-octen 2-one ethylene glycol ketal **35**. B.p. 88–91°/0.01 mmHg (partial decomposition); IR (neat) cm^{-1} 1610, 1165, 1040, 950, 830, 720; ^{1}H NMR (CCl_4, δ) 3.70 (CH_2—O, m, 4H), 2.26 (CH_2—C=, t, 2H), 1.98 (CH_3—C=, s, 3H), 1.48 (CH_3—C(O)(O), s, 3H).

Alkylation of alkenyl cuprates

1,1-*Diethoxy* 2-*methyl* 2(*E*)-*pentene* **36**. The alkenyl cuprate obtained by addition of 25 mmol diethyl cuprate to 50 mmol of diethoxy propyne was cooled to −60°, then 80 ml of THF added, followed by 8.5 g (60 mmol) of methyl iodide. The stirred solution was allowed to reach room temperature overnight, then hydrolyzed with 80 ml sat NH_4Cl sol. The salts were filtered off, and after 1–4 washings with sat NH_4Cl the organic phase was dried over K_2CO_3 and concentrated *in vacuo*. The crude product was distilled through a 10 cm Vigreux column. B.p. 72°/15 mmHg; n_D^{20} 1.4312; IR (neat) cm^{-1} 1645, 1060, 1000, 880, 850; ^{1}H NMR (CCl_4, δ) 5.65 (CH=, t, 1H), 4.59 (CH(O)(O), s, 1H), 3.58 (CH_2O—, m, 4H), 2.3 (CH_2—C=, m, 2H), 1.66 (CH_3—C=, s, 3H).

4,6-*Dimethyl*-4(*E*)-*octen*-3-*one ethylene glycol ketal* **37**. As for **36**, but one equiv HMPT was added before the addition of MeI. B.p. 51°/0.05 mmHg; n_D^{20} 1.4461; IR (neat) cm^{-1} 1670, 1050, 945, 925, 880, 775; ^{1}H NMR ($CDCl_3$, δ) 5.44 (CH=, d, 1H), 3.88 (CH_2—O, m, 4H), 2.28 (CH—C=, m, 1H), 1.76 (CH_2—C(O)(O), q, 2H), 1.61 (CH_3—C, s, 3H); ^{13}C NMR ($CDCl_3$, δ) 133.0 (CH=), 131.7 (C=), 112.0 (C(O)(O)), 64.24, 64.18 (CH_2—O).

1,1-*Dimethoxy* 2,3-*dimethyl* 2(*E*) *heptene* **38**. Same procedure as for **36**. B.p. 89°/15 mm/Hg; n_D^{20} 1.4430; IR (neat) cm^{-1} 3005, 1665, 1110, 1085, 985, 955, 990; ^{1}H NMR (CCl_4, δ) 4.93 (CH(O)(O), s, 1H), 3.18 (CH_3O—, s, 6H), 2.08 (CH_2—C=, t, 2H), 1.74 (CH_3—C=, s, 3H), 1.60 (CH_3—C=,s, 3H).

1,1-*Dimethoxy* 2-*butyl* 3-*methyl* 2(*E*) *pentene* **39**. Same procedure as for **36** but four equiv. of HMPT are added before the addition of BuI. B.p. 54–55°/0.05 mmHg; n_D^{20} 1.4448; IR (neat) cm^{-1} 1660, 1110, 1070, 910, 730; ^{1}H NMR ($CDCl_3$, δ) 5.07 (CH(O)(O), s, 1H), 3.39 (CH_3O—, s, 6H), 2.12 (CH_2—C=, m, 4H), 1.79 (CH_3—C=, s, 3H); ^{13}C NMR ($CDCl_3$, δ) 137.4, 130.5 (C=), 104.7 (CH(O)(O)), 54.4 (CH_3O—).

1,1-*Dimethoxy* 2-*allyl* 3-*methyl* 2(*E*)-*pentene* **40**. Same procedure as for **36**. B.p. 84–85°/15 mmHg; n_D^{20} 1.4540; IR (neat) cm^{-1} 3080, 1670, 1545, 1070, 1000, 950, 910, 800; ^{1}H NMR (CCl_4, δ) 5.74 (CH=, m, 1H), 4.80–5.0 (CH_2=, m, 2H), 4.89 (CH(O)(O), s, 1H), 3.21 (CH_3O—, s, 6H), 2.81 (=C—CH_2—C=, d, 2H), 2.18 (CVH_2—C=, q, 2H), 1.73 (CH_3—C=, s, 3H); ^{13}C NMR ($CDCl_3$, δ) 139.1, 127.6 (C=), 130.3 (CH=), 130.3 (CH=), 113.8 (CH_2=), 104.1 (CH(O)(O)), 54.3 (CH_3O—).

1,1-*Diethoxy* 2-*benzyl* 4-*methyl* 2(*E*),4-*pentadiene* **41**. Same procedure as for **36** with addition of one eq. of HMPT before adding benzyl bromide. B.p. 96–98°/0.01 mmHg; n_D^{20} 1.5059; IR (neat) cm^{-1} 3080, 3060, 3030, 1635, 1605, 1150, 1050, 1000, 725, 700; ^{1}H NMR ($CDCl_3$, δ) 7.27 (Ph, s, 5H), 6.36 (CH=, s, 1H), 5.04 (CH_2=, s, 2H), 4.70 (CH(O)(O), s, 1H), 3.72 CH_2—Ph, s, 2H), 3.48 CH_2—O, m, 4H), 1.92 (CH_3—C=, s, 3H); ^{13}C NMR ($CDCl_3$, δ) 141.2, 140.1, 135.4, 130.7, 120.2, 120.0, 125.7, 115.4 (C= and CH=), 102.3 (CH(O)(O)). 61.4 (CH_2O—).

1,1 *Diethoxy* 2-*methylthiomethyl* 2(*Z*) *pentene* **42**. Same procedure as for **36** with $MeSCH_2Cl$ B.p. 67°/0.01 mmHg; n_D^{20} 1.4701; IR (neat) cm^{-1} 1665, 1050, ^{1}H NMR (CCl_4, δ) 5.84 (CH=, t, 1H), 4.94 CH(O)(O), s, 1H), 3.52 CH_2O—, m, 4H), 3.20 (CH_2—S, s, 2H), 2.08 CH_2—C=, m, 2H), 2.04 MeS—, s, 3H).

1,1-*Diethoxy* 2-(*N-methyl formamidomethyl*) 2(*E*) *pentene* **43**. Same procedure as for 36 with OCH—N—CH_2Cl. B.p. 117°/0.01 mmHg; n_D^{20} 1.4606; IR (neat) cm^{-1} 1675, 1060, ^{1}H NMR (CCl_4, δ) 7.99 (HC=O, s, 1H), 5.82 (CH=, t, 1H), 4.58 (CH(O)(O), s, 1H), 3.94 and 3.84 (CH_2—N, s, and s, 2H), 3.44 (CH_2O—, m, 4H), 2.84 and 2.68 (CH_3—N—, s and s, 3H), 2.18 (CH_2—C=, m, 2H).

1,1-*Diethoxy* 2-(1-*heptynyl*) 2(*E*)-*pentene* **44**. To an ethereal solution of dialkenyl cuprate (prepared as above with 50 ml EtLi, 27 mmol acetylenic acetal) is added, at −60°, a solution of CuBr (27 mmol) and LiCl (55 mol) in 80 ml THF. The mixture turns dark red while the temperature is raised to −30°. Tetramethylethylenediamine (TMEDA, 75 mmol) is then added followed by a slow addition of 1-iodo, 1-heptyne in 20 ml THF. The solution is slowly discoloured and a heavy yellow precipitate appears at −20°. Stirring is continued for 1 h at this temperature, then hydrolysis with 70 ml NH_4Cl sat. sol. and 20 ml 17% aqueous ammonia. The salts are filtered off and the organic phase, to which 100 ml of hexane have been added, is washed twice with NH_4Cl sat. sol., then dried over K_2CO_3 and concentrated *in vacuo*. The residue is distilled through a 10 cm Vigreux column. B.p. 96°/0.05 mmHg; n_D^{20} 1.4606; IR (neat) cm^{-1} 2220, 1675, 1630, 1060, 900, 875; ^{1}H NMR (CCl_4, δ) 6.32 (CH=, t, 1H), 4.98 (CH(O)(O), s, 1H), 3.62 (CH_2—O, m, 4H), 2.22 (CH_2—C= and CH_2—C≡, m, 4H); ^{13}C NMR ($CDCl_3$, δ) 140.4 (CH=), 121.8 (C=), 102.0 (CH(O)(O)), 95.6 and 76.0 (C≡C), 61.4 (CH_2O—).

1,1-*Dimethoxy* 2-(2 *thienyl* 3-*methyl* 2(*Z*) *pentene* **45**. An ethereal solution of dialkenyl cuprate is prepared as described above from 50 mmol EtLi, 27 mmol CuI and 50 mmol acetylenic acetal. To this solution are successively added at −60°, 30 ml THF, then 25 mmol $ZnBr_2$ dissolved in 50 ml THF,then 25 mmol 2-Iodo thiophene admixed with 1 mmol $Pd(PPh_3)_4$ in 30 ml THF. The mixture is warmed slowly to +15° for 1 h, then hydrolyzed with 80 ml NH_4Cl sat. sol. The salts are filtered off and the organic phase is concentrated *in vacuo*. The residue is taken in 150 ml hexane, washed twice with NH_4Cl sat. sol. dried over K_2CO_3 and concentrated *in vacuo*. Distillation through a 10 cm Vigreux column afforded the title compound along with 10% of another product which was identified as the diene obtained by loss of one MeOH moiety. B.p. 85–86°/0.05 mmHg; ^{1}H NMR ($CDCl_3$, δ) 6.84–7.36 (thienyl, m, 3H), 5.19 (CH(O)(O), s, 1H), 3.41 (CH_3O—, s, 6H), 2.08 (CH_2—C=, q, 2H), 1.95 (CH_3—C=, s, 3H); ^{13}C NMR ($CDCl_3$, δ) 127.7, 126.7, 126.0, 124.9, 124.2, 123.6 (C= and CH=), 103.3 CH(O)(O), 54.4 CH_3O—).

3-Methyl 4-dimethoxymethyl 3,5(Z,E) nonadiene **46**. An ethereal solution of dialkenyl cuprate is prepared as described above from 50 mmol EtLi, 27 mmol CuI and 50 mmol acetylenic acetal. To this solution are successively added at $-60°$, 30 ml THF, then 25 mmol $MgCl_2$ (freshly prepared from Mg turnings and 1,2-dichloroethane in 50 ml THF) and finally 50 mmol 1-ido, 1(E)-hexene admixed with 2 mmol $Pd(PPh_3)_4$ in 50 ml THF. The mixture is then warmed slowly to $+15°$ for 1 h and worked up as for **45**. B.p. 75–77°/0.02 mmHg; n_D^{20} 1.4733; IR (neat) cm^{-1} 3020, 1640, 1610, 1075, 965, 730; ^1H NMR ($CDCl_3$, δ) 6.14 (CH=, d, 1H), 5.88 (CH=, dt, 1H), 5.10 CH(O,O), s, 1H), 3.37 (CH_3O—, s, 6H), 1.88 (CH_3—C=, s, 3H); ^{13}C NMR ($CDCl_3$, δ) 139.7, 128.8 (C=), 132.8, 124.5 (CH=), 104.4 (CH(O,O)), 54.5 (CH_3O—).

1,1-Diethoxy 2-(N-diethylaminomethyl) 2(E)-pentene **47**. Same procedure as for **36** with Et_2N—CH_2—SPh. B.p. 73°/0.01 mmHg; N_D^{20} 1.4442; IR (neat) cm^{-1} 1670, 1120, 1060; ^1H NMR ($CDCl_3$, δ) 5.72 (CH=, t, 1H), 4.87 CH(O,O), s, 1H), 3.42 (CH_2—O, m, 4H), 2.88 (=C—CH_2—N, s, 2H), 2.38 (CH_2—N, q, 4H), 2.09 (CH_2—C=, m, 2H); ^{13}C NMR ($CDCl_3$, δ) 133.4 (C=), 131.8 (CH=), 101.2 (CH(O,O)), 61.7 CH_2O—), 49.8 (=C—CH_2—N), 46.6 (CH_2—N).

1,1 Diethoxy 2-phenylthio 2(Z)-butene **48**. To an ethereal solution of phenylthio-alkenyl cuprate, prepared as described above (30 mmol MeLi, 30 mmol PhSCu, 30 mmol acetylenic acetal) are added 50 ml THF and one equivalent of HMPT, then 25 mmol of PhSSPh in 20 ml THF, at $-50°$. The cooling bath is removed and the mixture is stirred 3 h at room temperature, then hydrolyzed with 70 ml NH_4Cl sat. sol. and worked up as for **45**. B.p. 103–105/0.01 mmHg; n_D^{20} 1.5327; IR (neat) cm^{-1} 3060, 3010, 1640, 1585, 1050, 850, 740, 690; ^1H NMR ($CDCl_3$, δ) 7.20–7.50 (Ph, m, 5H), 6.68 (CH=, q, 1H), 4.82 (CH(O,O), s, 1H), 3.52 (CH_2—O, m, 4H), 1.92 (CH_3—C=, d, 3H).

Ethyl 4-diethoxy methyl 2,4(E,E)hexadienoate **49**. An ethereal solution of phenylthio-alkenyl cuprate is prepared as described above (30 mmol MeLi, 30 mmol PhSCu, 30 mmol acetylenic acetal) and cooled to $-70°$ whereupon ethyl propiolate (25 mmol) in 30 ml ether is slowly added. The reaction mixture is stirred 30 min at $-60°$, then hydrolyzed with NH_4Cl sat. sol. The salts are filtered off, the organic layer washed twice with NH_4Cl sat. sol., then dried over K_2CO_3 and concentrated *in vacuo*. The residue is distilled through a 10 cm Vigreux column. B.p. 110–112°/0.05 mmHg; n_D^{20} 1.4859; IR (neat) cm^{-1} 1725, 1650, 1625, 1185, 1060, 990, 880; ^1H NMR (CCl_4, δ) 7.51 (CH=, d, 1H), 6.26 (CH=, q, 1H), 6.19 (CH=, d, 1H), 4.98 (CH(O,O), s, 1H), 4.16 (CH_2—O—C=O, q, 2H) 3.51 (CH_2—O, m, 4H), 1.90 (CH_3—C=, d, 3H).

5-Diethoxy methyl 5(E)-octen -2 one **50**. To an ethereal solution of dialkenyl cuprate (50 mmol EtLi, 27 mmol CuI, 50 mmol acetylenic acetal) are slowly added, at $-70°$, 50 mmol methyl vinyl ketone in 30 ml ether. The reaction mixture is stirred 30 min at $-60°$, then hydrolyzed and worked up as above. B.p. 86–87°/0.06 mmHg; n_D^{20} 1.4485; IR (neat) cm^{-1} 3020, 1715, 1640, 1060, 900, 850; ^1H NMR ($CDCl_3$, δ) 5.86 (CH=, t, 1H), 4.88 (CH(O,O), s, 1H), 3.62 (CH_2O—, m, 4H), 2.14 (CH_3—C=O); ^{13}C NMR ($CDCl_3$, δ) 208.2 (C=O), 134.3 (C=), 131.9 (C=), 105.9 (CH(O,O)), 61.7 (CH_2—O).

Preparation of alkoxyallenes

The ethereal solution of dialkenyl cuprate was allowed to reach room temperature for 3 h, then hydrolyzed with sat NH_4Cl and worker up as above.

1-Methoxy 3,4,4-trimethyl 1,2-pentadiene **28**. B.p. 52°/15 mmHg; n_D^{20} 1.4449; IR (neat) cm^{-1} 3020, 1955, 1670, 1110, 1060, 965, 910; ^1H NMR ($CDCl_3$, δ) 6.92 (CH=, m, 1H), 3.58 (CH_3O—, s, 3H), 1.93 (CH_3—C=, d, 3H), 1.16 (CH_3—, s, 9H); ^{13}C NMR ($CDCl_3$, δ) 187.4 (=C=), 125.0 (C=), 121.3 (CH=), 55.0 (CH_3O—).

The catalytic procedure for preparing these allenes is as follows. To a cooled solution (ice bath) of 40 mmol of acetal and 2 mmol $CuBr \cdot Me_2S$ in 100 ml ether are added slowly 50 mmol of an ethereal solution of the appropriate Grignard reagent. The mixture is stirred 3 h at room temperature, then hydrolyzed with NH_4Cl sat. sol.and worked up as above.

1-Methoxy 3-methyl 1,2-heptadiene **5**. B.p. 65°/15 mmHg; n_D^{20} 1.4498; IR (neat) cm^{-1} 3015, 1965, 1130, 980, 930; ^1H NMR (CCl_4, δ) 6.54 (CH=, m, 1H), 3.28 (CH_3—O, s, 3H), 2.06 (CH_2—C=, t, 2H), 1.81 (CH_3—C=, d, 3H).

1-Ethoxy 3-butyl 1,2-octadiene **6**. B.p. 80–81°/15 mmHg; IR (neat) cm^{-1} 3020, 1960, 1130, 965, 925; ^1H NMR (CCl_4, δ) 6.56 (CH=, m, 1H), 3.51 (CH_2O—, q, 2H), 2.08 (CH_2—C=, m, 4H).

1-(2-Hydroxy ethoxy) 3-methyl 1,2-heptadiene **7**. B.p. 72–73°/0.01 mmHg. During the distillation some of the product cyclised back to the dioxolane. IR (neat) cm^{-1} 3400, 3030, 1960, 1130, 1070, 900, 790; ^1H NMR (CCl_4, *d*) 6.58 (CH=, m, 1H), 3.60 (CH_2O, m, 4H), 2.08 (CH_2—C=, t, 2H), 1.82 (CH_3—C=, d, 3H).

Hydrolysis of acetals and ketals. A mixture of 5 ml AcOH and 5 ml H_2O was added at room temp. to a mixture of 5 mmol acetal and 5 ml CH_2Cl_2. After 5 min 50 ml of pentane and 20 ml H_2O were added, the organic phase is washed once with 20 ml H_2O, once with 10 ml $NaHCO_3$,then dried over Na_2SO_4 and concentrated *in vacuo*. The residue is pure aldehyde which may be distilled.

2-Methylene hexanal **51**. B.p. 46–48°/15 mmHg; n_D^{20} 1.4379; IR (neat) cm^{-1} 1690, 1625, 945; ^1H NMR (CCl_4, δ) 9.44 (CHO, s, 1H), 6.14 and 5.90 (CH_2=, s and s, 2H), 2.18 (CH_2—C=, t, 2H).

2(E) Heptenal **52**. B.p. 62–63°/15 mmHg; n_D^{20} 1.4464; IR (neat) cm^{-1} 1690, 1635, 975; ^1H NMR (CCl_4, δ) 9.39 (CHO, d, 1H), 6.80 (CH=, dt, 1H), 5.98 (CH=, dd, 1H), 2.32 (CH_2—C=, q, 2H).

4-Methylene 2(E) octenal **53**. IR (neat) cm^{-1} 1695, 1635, 1610, 980, 910; ^1H NMR (CCl_4, δ) 9.50 (CHO, d, 1H), 7.10 (CH=, d, 1H), 6.23 (CH=, dd, 1H), 5.47 and 5.40 (CH_2=, s and s, 2H), 2.28 (CH_2—C=, t, 2H).

3-Phenyl 2(Z) pentenal **54**. B.p. 105°/0.2 mmHg; n_D^{20} 1.5503; IR (neat) cm^{-1} 3060, 3030, 1675, 1620, 865, 770, 745, 700; ^1H NMR ($CDCl_3$) 9.58 (CHO, d, 1H), 7.30–7.60 (Ph, m, 5H), 6.18 (CH=, d, 1H), 2.61 (CH_2—C=, q, 2H); ^{13}C NMR ($CDCl_3$, δ) 193.4 (CHO), 167.7, 137.9, 128.8, 128.5, 127.4 (CH= and C=), 32.7 (CH_2), 12.0 (CH_3).

3-Methyl 2(Z)-heptenal **55**. IR (neat) cm^{-1} 1670, 1630, 850; ^1H NMR ($CDCl_3$) 10.0 (CHO, d, 1H), 5.86 (CH=, d, 1H), 2.21 (CH_2—C=, t, 2H), 2.16 (CH_3—C=, s, 3H); ^{13}C NMR $CDCl_3$, δ) 191.2 (CHO), 164.3 (C=), 127.2 (CH=).

3,7-Dimethyl 2(E),6-octadienal (geranial) **56**. This compound was compared on GLPC with an authentic sample. ^1H NMR (CCl_4, δ) 9.90 (CHO, d, 1H), 5.78 (CH=, d, 1H), 5.10 (CH=, t, 1H).

E,6 Dimethyl 4(E) octen,3-one **57** "*manicone*". The hydrolysis of the corresponding ketal **37** was slow and needed 24 h at room temperature. B.p. 49–50°/0.1 mmHg; n_D^{20} 1.4522; IR (neat) cm^{-1} 3030, 1675, 1640, 995, 800; ^1H NMR ($CDCl_3$, δ) 6.42 (CH=, d, 1H), 2.71 (CH_2—CO, q, 2H), 2.50 (CH—C=, m, 1H), 1.84 (CH_3—C=, s, 3H); ^{13}C NMR ($CDCl_3$, δ) 202.5 (C=O), 147.7 (CH=), 135.7 (C=).

5-Formyl 5(E) octen 2-one **58**. The identification of this compound was performed by ^1H NMR since it was further transformed into **59**. ^1H NMR (CCl_4, δ) 9.87 (CHO, s, 1H), 6.87 (CH=, t, 1H), 2.12 (CH_3—CO). Upon treatment with 1% aqueous NaOH, at room temperature for 10 min, this ketoaldehyde afforded 4(E)-propylidenecyclohexenone **59**, IR (neat) cm^{-1} 1675, 1630, 1580, 870, 820; ^1H NMR

($CDCl_3$, δ) 7.38 (CH=, d, 1H), 6.14 (CH=, d, 1H), 6.20 (CH=, m, 1H); ^{13}C NMR ($CDCl_3$, δ) 198.9 (C=O), 149.5, 139.0, 125.4 (CH=), 132.4 (C=).

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