°C caused neither hydrolysis nor elimination of these sulfonate esters.

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(40) Elemental analysis. Calcd for $C_{16}H_{26}O_3S$: C, 64.39; H, 8.78; S, 10.74. Found: C, 64.56; H, 9.17; S, 10.59.

(41) Ester was prepared from decanal by condensation with *tert*-butyllithium and esterification of the alcohol with tosyl chloride; NMR and IR were consistent with structure.

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(43) Sample prepared by methylation of lithium cyclohexanementhylate with dimethyl sulfate; $n^{24.5}{}_D$ 1.4333 [lit. $n^{25}{}_D$ 1.4325; J. H. Stocker, *J. Org. Chem.*, **27**, 2288 (1962)].

Reductions of Conjugated Carbonyl Compounds with Copper Hydride—Preparative and Mechanistic Aspects

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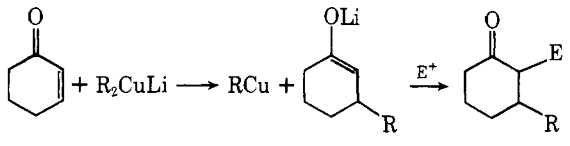
The reaction of lithium trimethoxyaluminum hydride with 0.5 molar equiv of cuprous bromide produces a heterogeneous mixture referred to as the Li complex, while sodium bis(2-methoxyethoxy)aluminum hydride with 1.0 molar equiv of cuprous bromide gives a similar mixture, the Na complex. Both reagents are effective in selective reduction of the olefin unit in conjugated ketones and esters, including two examples of acetylenic esters. The Li complex is more efficient with cyclohexenones, while the Na complex gives better yields in reduction of acyclic enones and enoates, especially in the presence of 2-butanol. Deuterium labeling experiments show that the hydrogen which is transferred to the β position of the conjugated carbonyl compound originates from the hydridocuprate reagent; the 2-butanol appears to serve as a weak acid, inhibiting polymerization. In the absence of 2-butanol, reduction of methyl cinnamate produces dimethyl *meso*-3,4-diphenyladipate as a major product, apparently the result of radical anion intermediates. Aldehyde, ketone, and halide functionality are reduced at rates comparable to the rate of enone reduction, but nitrile and ester units are inert.

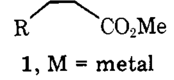
Organocopper reagents have been developed into powerful methods for carbon–carbon bond formation,[1,2] especially utilizing the remarkable preference for delivery of carbon units to the β position of α,β-unsaturated carbonyl compounds.[1] This general method of conjugate addition is selective not only for 1,4 instead of 1,2 addition, but also highly chemiselective: most nonacidic functional groups do not interfere. An added dimension in synthesis is the technique of "enolate trapping", where the product enolate anion from addition to the β position reacts with an electrophile in the α position.[3]



E = electrophilic species

Until recently, addition of hydrogen to the olefin unit in an α,β-unsaturated carbonyl compound was commonly achieved by catalytic hydrogenation[4] and dissolving metal reduction,[5] each method having characteristic technical advantages and conveniences in particular systems, and with shortcomings in chemiselectivity. Recently, hydride transfer reagents involving iron,[6,7] boron,[8] and aluminum[9] have been developed for 1,4 reduction; the boron reagent allows enolate trapping with carbon electrophiles.[8]

In analogy with the alkyl–copper chemistry, hydrido–copper reagents might provide selective conjugate addition of hydride, compatibility with most common functional groups, and would generate an enolate anion which could be trapped with protons (overall reduction of the olefin unit) or with electrophiles at the α position. We were particularly intrigued with the possibility of generation and trapping of α-metalloacrylate anion **1**, perhaps via conjugate addition of a hydrido–copper species to methyl propiolate. A few specific examples of organometal species closely related to **1** have been detected, through dialkyl cuprate addition to propiolate derivatives,[10] through halogen–metal exchange with α-bromo



1, M = metal

Li[H-Cu-R]

2, R = 1-pentynyl

3, R = $OC(CH_3)_3$

4, R = *n*-butyl

acrylates,[11] and through abstraction of the α-hydrogen from acrylates using strong base.[12] Since we began this project,[13] rapid development has occurred in the use of hydrido–copper reagents for organic reductions.

Early applications by Whitesides and coworkers in cleavage of alkyl–copper bonds provided a recipe for preparation of soluble hydrido(tri-*n*-butylphosphine)copper(I) using diisobutylaluminum hydride and cuprous bromide at low temperature.[14] The reaction of lithium trimethoxyaluminum hydride with cuprous iodide provides a heterogeneous mixture which cleaves carbon–halogen bonds efficiently. The required 2:1 stoichiometry of hydride–copper led to the suggestion that the effective reagent was lithium dihydridocopper(I), parallel with lithium dimethylcopper(I).[15] Conjugate addition of hydride to α,β-unsaturated ketones was reported by Boeckman and Michalak, using the "ate" complexes (**2, 3**) prepared by adding an anionic ligand to CuH (from diisobutylaluminum hydride and CuI at −50 °C, filtered).[16] Excellent selectivity for 1,4 addition was reported with a variety of cyclic and acyclic ketones.[16,17] Masamune[18] employed a similar reagent (**4**), prepared in the same way, and observed closely similar results; it is suggested that this homogeneous reagent (**4**) is more reproducible in cleavage of carbon–halogen bonds and enone reduction compared to the heterogeneous reagent[15] obtained under carefully specified conditions from lithium trimethoxyaluminum hydride–cuprous iodide. A simple mixture of lithium aluminum hydride and cuprous iodide in the ratio of 1:4 is successful in conjugate reduction of acyclic α,β-unsaturated ketones, but fails for 2-cyclohexenone derivatives, and no results were reported with unsaturated esters.[19] An intriguing feature of this work is that the results can be interpreted as reactions of H_2AlI or $HAlI_2$; no copper hydride need be invoked.[19]

From the experiments of House and DuBose,[20] and consistent with the stoichiometry generally used to prepare the active reagents, CuH itself does not add to conjugated ketones, but the "ate" complexes such as **2–4** are generally successful. The simplest such species, $LiCuH_2$, has been prepared and largely characterized by Ashby,[21] but no evidence of conjugate addition reactions was presented. Just as for the general reaction of organocuprates with unsaturated carbonyl compounds,[22] both electron transfer and nucleophilic addition mechanisms have been considered for the addition of hydride, but no direct experimental evidence has been presented.

Results

Using the general technique of earlier workers,[14,16] we have developed convenient preparations of copper-based reagents which provide efficient 1,4 reduction of both conjugated ketones and esters. The more generally efficient hydrido–copper species were prepared according to eq 1 and 2. The reagent involving the lithium cation (eq 1, here referred to as Li complex) was obtained as a brown-black suspension in tetrahydrofuran by simply mixing a solution of 2 molar equiv of lithium trimethoxyaluminum hydride with anhydrous cuprous bromide at 0 °C for 0.5 h. An equimolar mixture of sodium bis(2-methoxyethoxy)aluminum dihydride (Vitride,[23a] Red-al[23b]) and cuprous bromide in tetrahydrofuran at 0 °C for 0.5 h gives a similar suspension, here referred to as the Na complex. No attempt was made to purify the reactive species, but filtration at low temperature produced a filtrate which was not an active reducing agent.

$$2LiAlH(OCH_3)_3 + CuBr \xrightarrow[\text{THF}]{0\ °\text{C}} \text{"Li complex"} \qquad (1)$$

$$NaAlH_2(OCH_2CH_2OCH_2)_2 + CuBr \xrightarrow[\text{THF}]{0\ °\text{C}} \text{"Na complex"} \qquad (2)$$

Reaction with Conjugated Ketones. Table I displays the results of reactions of 2-cyclohexenone and derivatives **5** and **6** with the Li complex and the Na complex. Simple aluminum hydride reagents give mainly 1,2 reduction (entry 16), but the hydrido–copper species give predominate 1,4 reduction under a variety of conditions. The Li complex tends to be superior in selectivity and yield; the results in entries 1, 10, and 14 are easily reproducible. Complete conversion requires more than 1 molar equiv of the Li complex and excess reagent seems not to be harmful. Cuprous iodide in place of cuprous bromide (entry 3) gives a much less selective reagent; similar effects are observed with (triphenylphosphine)cuprous iodide in preparation of an Na complex (entry 7). Other solvents such as toluene or ether (entry 8) used in place of tetrahydrofuran (both in complex formation and in reaction with the enone) lead to substantial amounts of 1,2 reduction or recovered enone. Reduction with the Li complex is quite fast, being about 90% complete after 20 min at −78 °C (entry 1). The addition of 2-butanol during the reaction of Na complex with the enone is not very beneficial (entries 9 and 13), in contrast to results below. The more highly substituted enones, 5,5-dimethyl-2-cyclohexenone (**5**) and 3,5,5-trimethylcyclohexenone (**6**), react more slowly than 2-cyclohexenone; at least 3 molar equiv of reducing agent are necessary for complete conversion (compare entries 10, 11, and 14).

Table II presents the results obtained with two acyclic ketones, 2,2,6,6-tetramethylhept-4-en-3-one (**7**) and chalcone (**8**). Conjugate reduction is again the preferred course of reaction; the Na complex is clearly superior, giving no trace of 1,2 reduction under a variety of conditions. The reduction is slow at −78 °C (entry 5), compared to the results with 2-cyclohexenone. Chalcone is a difficult case; the usual reduction conditions give mainly high molecular weight products. Added 2-butanol with the Na complex under carefully defined conditions produces moderate amounts of the 1,4 reduction product. The addition of 2-butanol seems to improve selectivity toward 1,4 reduction with the Li complex, but also destroys much of the reagent, resulting in only partial conversion (entry 2).

Reductions of methyl 2-butenoate (**9**) and methyl 3-methyl-2-butenoate (**10**) were successful with the Na complex (Table III). Reduction of the ester function was not a problem, but high molecular weight material accounted for most of the product from reaction with the Li complex. The presence of excess 2-butanol in the medium during reduction with the Na complex gave consistently higher yields (compare entries 2 and 4). With substrate **10**, good yields were obtained even without added alcohol, but the rate of reduction is slower compared to the rate for **9**; 4 h is required for complete conversion at −20 °C (entries 6–8).

The aryl-substituted acrylates were more difficult to reduce efficiently; methyl cinnamate was studied in detail to define optimum conditions (Table III). The Li complex led to high molecular weight products and only 5–8% of the saturated ester (entry 9). Added 2-butanol had no positive effect (entry 10). However, the Na complex gave moderate yields of the saturated ester under a variety of conditions; the best procedure (entry 13) involves an excess of the copper reagent and 2-butanol in the medium during reduction. From several reactions, a dimer has been isolated and characterized as dimethyl *meso*-3,4-diphenyladipate (**12**), the product of coupling at the β carbons. A preparative run with methyl 3,4,5-trimethoxycinnamate is detailed in the Experimental Section;

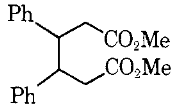


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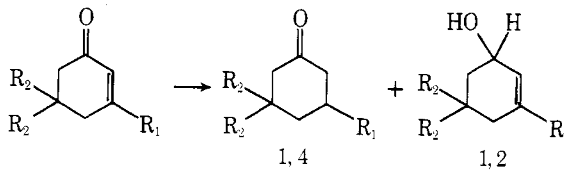
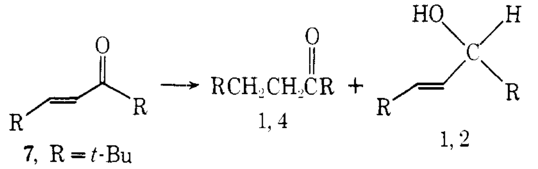
Table I. Reduction of 2-Cyclohexenones



Entry[k]	Hydrido-copper species[a]	Ratio of copper-enone	Reaction conditions[b]	1,4 % yield[b]	1,2 % yield[b]	% conversion[b]
1. $R_1 = R_2 = H$	Li	1.6:1	−78 °C/20 min	64	10	90
2. $R_1 = R_2 = H$	Li	2:1	−20 °C/50 min	84	3	100
3. $R_1 = R_2 = H$	Li[c]	1.6:1	−20 °C/1.5 h	54	22	100
4. $R_1 = R_2 = H$	Na	1.6:1	−20 °C/1 h	60	5	97
5. $R_1 = R_2 = H$	Na	1.2:1	0 °C/ 0.5 h	62	0	100
6. $R_1 = R_2 = H$	Na[d]	2:1	−20 °C/2 h	10	3	55
7. $R_1 = R_2 = H$	Na[e]	1.6:1	−20 °C/1 h	64	18	100
8. $R_1 = R_2 = H$	Na[f]	1.6:1	0 °C/1 h	18	60	100
9. $R_1 = R_2 = H$	Na[g]	3:1	−20 °C/0.5 h	30	0	100
10. $R_1 = R_2 = H$	$LiCuH_2$[h]	2:1	−20 °C/0.5 h	21	64	100
11. $R_2 = CH_3, R_1 = H$	Li	3:1	−20 °C/1 h	98	1	100
12. $R_2 = CH_3, R_1 = H$	Li	2:1	−20 °C/1 h	84	1	85
13. $R_2 = CH_3, R_1 = H$	Na	3.5:1	−20 °C/10 min	17	0	81
14. $R_2 = CH_3, R_1 = H$	Na[i]	4:1	−20 °C/25 min	69	0	80
15. $R_1 = R_2 = CH_3$	Li	4:1	−20 °C/50 min	92	6	100
16. $R_1 = R_2 = CH_3$	Na	4:1	−20 °C/1 hr	61	13	100
17. $R_1 = R_2 = CH_3$	j	2:1	−20 °C/0.5 h	45	49	100
18. $R_1 = R_2 = CH_3$	$LiCuH_2$[h]	2:1	−20 °C/0.5 h	2	48	50

[a] Li refers to the Li complex, eq 1. Na refers to the Na complex, eq 2. [b] The yields were determined by quantitative GLC using an internal standard. [c] Cuprous iodide was used in place of cuprous bromide. [d] The molar ratio of sodium bis(2-methoxyethoxy)aluminum hydride to cuprous bromide was 1:2 instead of the usual 1:1. [e] Triphenylphosphinecuprous iodide was used in place of cuprous bromide. [f] Diethyl ether was used in place of tetrahydrofuran. [g] 8 molar equiv of 2-butanol was added (see procedure C, Experimental Section. [h] Prepared according to the procedure of Ashby (ref 21). [i] 11 molar equiv of 2-butanol was added (see procedure C, Experimental Section). [j] No cuprous halide was involved; lithium trimethoxyaluminum hydride in tetrahydrofuran was the reducing system. [k] Registry no.: $R_1 = R_2 = H$, 930-68-7; $R_2 = CH_3$, $R_1 = H$, 4694-17-1; $R_1 = R_2 = CH_3$, 78-59-1.

Table II. Reduction of Acyclic Ketones



7, R = *t*-Bu
8, R = Ph

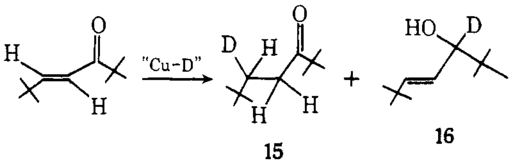
Entry[e] (compd)	Hydrido-copper species[a]	1,4 % yield	1,2 % yield	% conversion
1 (7)	Li	80	20	100
2 (7)	Li[b]	60	0	60
3 (7)	b	0	100	100
4 (7)	Na	98	1	100
5 (7)	Na[c]	32	0	32
6 (7)	Na[d]	98	0	100
7 (8)	Li	16	0	100
8 (8)	Na	32	0	100
9 (8)	Na[d]	54	0	85

[a] The hydride complex was prepared according to procedures A or B (Experimental Section). The conditions for reduction are −20 °C for 1 h in tetrahydrofuran with a 4:1 molar ratio of cuprous–species–enone. [b] No cuprous salt was used. Lithium trimethoxyaluminum hydride–tetrahydrofuran was the reducing system. [c] The reaction temperature was −78 °C instead of −20 °C. [d] 18 molar equiv of 2-butanol was added (procedure C, Experimental Section). [e] Registry no.: 7, 1653-94-7; 8, 94-41-7.

on a 5- or 10-mmol scale, the isolated yield of saturated ester was 85–90%.

Acetylenic esters show a still greater tendency to oligomerize. The simplest case, ethyl propynoate, gave no more than traces of ethyl acrylate and ethyl propionate. Two other cases, methyl 2-butynoate (**13**) and methyl 3-phenylpropynoate (**14**), were successful using the Na complex; partial reduction to a mixture of cis and trans β-substituted acrylates is the major pathway (Table IV). The rate of reduction is similar to that for acrylate esters; the yield decreases as time and temperature of the reduction increase beyond −20 °C for 0.5 h. Added alcohol has little effect on the distribution of products; the proportion of cis product is slightly increased.

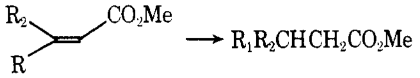
Deuterium Labeling Results. Using lithium trimethoxyaluminum deuteride, the Li complex was prepared with deuterium in place of hydrogen. Reaction of this reagent with 2,2,6,6-tetramethylhept-4-en-3-one for 1.0 h at −20 °C gave deuterium-labeled 2,2,6,6-tetramethylheptan-3-one (**15**) in 87% yield, accompanied by 12% of 2,2,6,6-tetramethylhept-4-en-3-ol (**16**). The ^1H NMR spectrum of **15** showed the characteristic triplet of triplets (J = 7.8, 1.0 Hz) for a $-CHDCH_2-$ arrangement, integrating for 1.13 ± 0.05 hydrogens, consistent with the 5-d_1 isomer (**15**). No significant deuterium was detected at C-4 in **15**. The 1,2-reduction product, **16**, also bears one deuterium, at C-2 (absence of signal at δ 6.28).



15 **16**

In the same way, methyl cinnamate was treated with deuterium-labeled Li complex; the yield of saturated ketone is low, but the methyl 3-phenylpropionate which can be isolated (15% yield) is selectively labeled at C-3; the lone proton at C-3

Table III. Reduction of Acrylate Derivatives



9, $R_1 = H$, $R_2 = CH_3$
10, $R_1 = R_2 = CH_3$
11, $R_1 = H$, $R_2 = Ph$

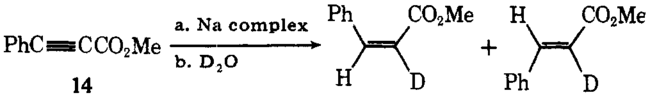
Entry[k] (compd)	Hydrido-copper species[a]	Saturated ester % yield	% conversion
1 (9)	Li	2	100
2 (9)	Na	60	100
3 (9)	Na[b]	62	73
4 (9)	Na[b,c]	84	100
5 (10)	Li	46	90
6 (10)	Na	17	24
7 (10)	Na[d]	60	77
8 (10)	Na[e]	92	100
9 (11)	Li	5	100
10 (11)	Li[f]	2	40
11 (11)	Na	28[g]	100
12 (11)	Na[f]	41	41
13 (11)	Na[f,h]	82	100
14 (11)	Na[h,i]	51	53
15 (11)	Na[h,j]	40	100

[a] The reaction conditions were −20 °C for 1 h, with 2:1 molar ratio of copper–ester unless otherwise noted. [b] 18 molar equiv of 2-butanol was present (procedure C, Experimental Section). [c] The molar ratio of copper reagent–ester was 4:1. [d] The reaction time was 2 h (−20 °C). [e] The reaction time was 4 h (−20 °C). [f] 10 molar equiv of 2-butanol was present (procedure C, Experimental Section). [g] The dimer 12 was isolated in 21% yield. [h] The molar ratio of copper reagent–ester was 8:1. [i] 11 molar equiv of methyl alcohol was added. [j] 11 molar equiv of 2-methyl-2-propanol was added (procedure C, Experimental Section). [k] Registry no.: 9, 18707-60-3; 10, 924-50-5.

appears as the characteristic triplet of triplets for a $-CHDCH_2-$ arrangement after $Eu(fod)_3$[24] is used to separate the chemical shift positions of aliphatic protons. The protons at C-2 appear as a simple doublet ($J = 7$ Hz).

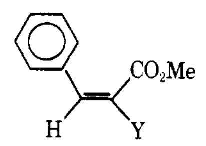
Using the Na complex in the presence of 2-butanol-2-*d*, methyl cinnamate was reduced to methyl 3-phenylpropionate in 81% yield; ^1H NMR analysis with the shift reagent as above indicated no deuterium incorporated in the product. A parallel experiment employing 2-butanol-O-*d* led to 3-phenylpropionate with 0% deuterium at C-3 and 24% deuterium (50% labeling of one H position) at C-2.

Addition of D_2O before the usual aqueous isolation procedure (after the reduction step is complete) generally gives about 50% deuterium in the α position, but no deuterium in the β position. For example, reduction of 2,2,6,6-tetramethylhept-4-en-3-one with the Li complex in THF at −20 °C for 1 h followed by addition of D_2O and then aqueous extraction procedures afforded 2,2,6,6-tetramethylheptan-3-one with 45% deuterium incorporation at C-4. Presumably, the aqueous isolation procedures led to partial exchange of protons for deuterium at C-4. When methyl 3-phenylpropynoate (14) is reduced with the Na complex (40 min/−20 °C) and excess D_2O is then added, the methyl *cis*- and *trans*-cinnamates bear deuterium to the extent of 98.5 ± 2% at C-2 (in 17).



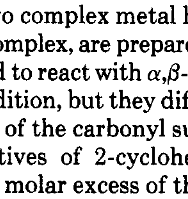
14 17a 17b

Trapping of the Intermediate Enolate with Carbon Electrophiles. As mentioned immediately above, reaction of methyl 3-phenylpropynoate with the Na complex followed by addition of D_2O gives efficient deuteration at C-2 (in 17). However, addition of alkyl halides (methyl iodide, allyl bromide) before aqueous isolation procedure gave no alkylation; only the usual mixture of *cis*- and *trans*-cinnamates was obtained. On the other hand, when the Na complex was allowed to react with methyl 3-phenylpropynoate at −20 °C for 0.5 h, and then benzaldehyde was added (−78 to −20 °C for 6 h), the adduct 18 was isolated as an oil in 47% yield. Treatment with benzoyl chloride afforded crystalline benzoate 19; the *Z* configuration is assigned based on ^1H NMR data (see Experimental Section). The *E* isomer is presumably also present in smaller amounts, but it was not isolated. A parallel reaction, except that the benzaldehyde was added at −78 °C and the reaction mixture was maintained at −78 °C for 19 h, produced no adduct 18; methyl cinnamates (*E*/*Z* mixture) were obtained as the main products.

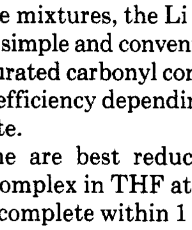


18, Y = PhCH(OH)
19, Y = PhCH(OCOPh)
20, Y = Li (or Cu, Al)

As a test of the 1,2 vs. 1,4 addition selectivity of intermediate 20, reaction with 2-cyclohexenone was studied. The intermediate was generated from the Na complex and methyl 3-phenylpropynoate as before (−20 °C/0.5 h), and allowed to react with a threefold excess of 2-cyclohexenone at −78 to −20 °C. Two major products were obtained, the 1,2 adduct, 21, and methyl cinnamate (cis). Extensive purification by preparative layer chromatography provided a pure sample of 21, but in only 14% yield. No evidence for the presence of a 1,4 adduct (i.e., 22) was obtained. When the reaction mixture with 2-cyclohexenone was maintained at −78 °C (19 h), the major product was methyl cinnamate (cis and trans).



21



22

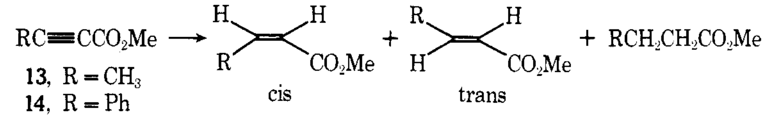
Discussion

The two complex metal hydride mixtures, the Li complex and Na complex, are prepared in a simple and convenient way. Both tend to react with α,β-unsaturated carbonyl compounds by 1,4 addition, but they differ in efficiency depending on the structure of the carbonyl substrate.

Derivatives of 2-cyclohexenone are best reduced by a threefold molar excess of the Li complex in THF at −20 °C. Reduction is slow at −78 °C, but complete within 1 h at −20 °C; β-alkyl substituents tend to slow the rate of reduction without affecting the selectivity for 1,4 over 1,2 addition. The Na complex reacts with 2-cyclohexenone at a similar rate and with high selectivity for 1,4 addition, but significant amounts of high molecular weight products appear (up to 35% from 2-cyclohexenone), perhaps due to condensation reactions of the enolate–metal species, which is presumed to be an important intermediate. Acyclic enones are reduced more efficiently by the Na complex (Table II), as are all of the alkenoate and alkynoate examples (Tables III and IV).

The composition of the reagents is not known. Both are heterogeneous mixtures in THF, and the reducing ability

Table IV. Reduction of Propynoate Ester Derivatives

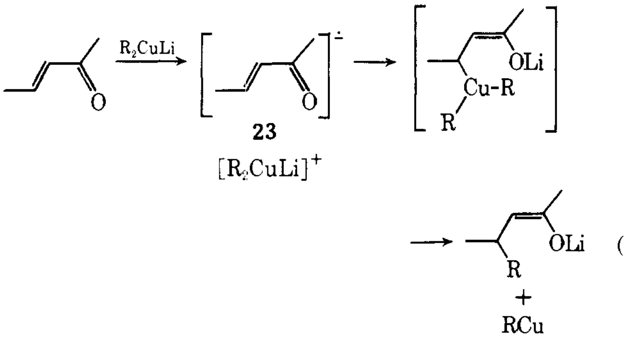


Entry[e] (compd)	Hydrido–copper species[a]	cis % yield	trans % yield	Saturated ester, % yield	% conversion
1 (13)	Li, 3:1, 35 min	9	8	2	100
2 (13)	Na, 6:1, 20 min	25	27	26	100
3 (13)	Na, 3:1, 4 h[b]	2	2	0	4
4 (13)	Na, 3:1, 20 min	21	31	5	73
5 (13)	Na, 3.5:1, 2 h[c]	29	25	18	96
6 (14)	Li, 3:1, 20 min	10	5	0	94
7 (14)	Na, 4:1, 15 min	56	21	6	100
8 (14)	Na, 3:1, 45 min[c]	61	14	4	83
9 (14)	Na, 4:1, 30 min	47	18	11	100
10 (14)	Na, 4:1, 30 min[d]	14	13	19	100
11 (14)	Na, 4:1, 1 h[b]	12	0	0	12

[a] This entry specifies which reducing species was used (Li or Na), the ratio of copper reagent–ester, and the reaction time at −20 °C. [b] The reaction was carried out at −78 °C. [c] 10 molar equiv of 2-butanol was added (procedure C, Experimental Section). [d] The reaction was carried out at 0 °C. [e] Registry no.: 13, 23326-27-4; 14, 4891-38-7.

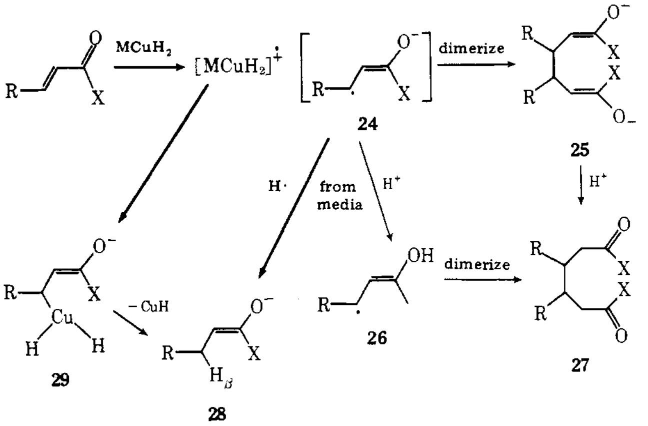
resides in the solid, not in the solution. The effective stoichiometry is hydride units–cuprous bromide = 2:1, and is consistent with the presence of the cuprates, $LiCuH_2$ and $NaCuH_2$. However, we find that the reagent to which Ashby and co-workers[21] assign the composition $LiCuH_2$ does not parallel the Li complex in its pattern of reactivity (Table I, entries 10, 18). Addition to the carbonyl carbon (1,2 addition) is the major pathway of Ashby's $LiCuH_2$ with cyclohexenones. Consistent with earlier hydrido–copper species,[20] the reagent obtained from a 1:1 mole ratio of lithium trimethoxyaluminum hydride–cuprous bromide gives no reaction with enones. The pattern of reactivity for both the Li and Na complexes, especially the efficient reduction of 2-cyclohexenone derivatives, also suggests that simple haloaluminum hydrides are *not* the active ingredients, in contrast to the reagent prepared from lithium aluminum hydride and cuprous iodide.[19]

The isolation of dimethyl *meso*-3,4-diphenyladipate (12) from reaction of the Na complex and methyl cinnamate is particularly significant in considering a mechanism for the reduction. Reaction of dialkyl cuprates with unsaturated carbonyl compounds is thought[22] to proceed via electron transfer to give a transient radical anion (23 in eq 3) followed by a carbon–copper intermediate which can undergo reductive elimination (eq 3). However, the characteristic dimerization of such radical anions[25] has not been observed, even as a minor pathway, in the reaction of dialkyl cuprate with enones.



(3)

A parallel mechanism can be written for reduction with the hydrido–copper species, describing them as $MCuH_2$ for simplicity (eq 4). The radical anion (24) has several established pathways of reaction.[25] The dihydro dimer (27 in eq 4) can arise through dimerization (to give the bisenolate 25) followed by protonation (during isolation or from added alcohol) or through initial protonation (to give 26; proton from the medium) followed by dimerization of the enol radical 26. The reduction product enolate (28) is formed either from coupling of the radical anion (24) with the $MCuH_2$ radical cation (to give transient complex 29) and reductive elimination of CuH or from hydrogen atom abstraction from the medium (to give 28 directly).



Clearly, during the reduction of methyl cinnamate in the absence of 2-butanol, dimerization to form the species 25 is favorable, presumably because the extended conjugation with the phenyl substituent allows a longer lived radical anion (24, R = Ph). Less substituted acrylate and propiolate derivatives also require careful control of reaction conditions in order to minimize oligomerization. Hydrodimerization products (i.e., 27) have not been observed in these cases; condensation polymerization may be the major side reaction. The hydrogen added to the β carbon (i.e., H_β in 28) is clearly derived from the hydrido–cuprate reagent as shown by efficient deuterium (mono) labeling of the β position during reduction of 2,2,6,6-tetramethylhept-4-en-3-one and of methyl cinnamate with the Li complex bearing deuterium. It does not arise from hydrogen atom abstraction from the THF solvent, as shown by carrying out a reduction of methyl cinnamate with the Na complex in THF-d_8.

The addition of alcohols to the medium before reduction tends to minimize oligomerization and completely inhibits hydrodimerization of methyl cinnamate. Among the alcohols tested, 2-butanol offers the best balance between destruction of the hydrido–copper agent and optimum yields of reduction

Table V. Reduction of Other Functional Groups

Entry, compd[a]	Registry no.	Product (% yield)[b]	% conversion
1. $Ph(CH_2)_4CN$	7726-45-6	No reaction	0
2. $PhCH_2CH_2Br$	103-63-9	$PhCH_2CH_3$ (68)	100
3. p-$CH_3OC_6H_4Br$	104-92-7	$CH_3OC_6H_5$ (33)	33
4. $PhCH_2CHO$	122-78-1	$PhCH_2CH_2OH$ (100)	100
5. Cyclohexanone	108-94-1	Cyclohexanol (69)	100

[a] In each case, the compound was added to a fourfold molar excess of the Na complex in THF at −78 °C and allowed to stir at −20 °C/2 h. [b] Product yields and recovery of starting material were determined by quantitative GLC, ^1H NMR spectroscopy, or both.

product. Methyl alcohol reacts too rapidly with the Na complex and 2-methyl-2-propanol is ineffective in avoiding oligomerization. Presumably, the alcohol acts as a proton donor to speed formation of the key carbon–copper intermediate (**29**, eq 4) relative to dimerization, but the detailed role of the alcohol is not clear.[26] Hydrogen atom transfer from position C-2 in 2-butanol is known to be favorable,[27] but the experiment with 2-butanol-*2-d* shows clearly that in the reduction of methyl cinnamate with the Na complex, the added alcohol does *not* deliver deuterium from C-2 to the β position of the product, 2-phenylpropionate. Similarly, 2-butanol-*O-d* does *not* contribute a deuterium to the β position; the α position is found to be partially labeled. This observation contrasts with the results from generation of enone radical anions (using sodium metal) in the presence of 2-methyl-2-propanol-*O-d*, where the β carbon does receive the deuterium.[25]

Vinyl–metal species such as **20** are clearly intermediates in the reduction of acetylenic esters. They are not particularly stable, suffering inversion of configuration and polymerization on standing in solution at 0 °C. No information is available from our studies bearing on the questions of whether the metal is carbon or oxygen bound,[28] or whether the metal is lithium, copper, or aluminum. The intermediate does parallel the related compounds studied by Marino and co-workers, in adding to the carbonyl group of 2-cyclohexenone. By adding the carbonyl trapping agent immediately after reduction at −20 °C, the cis configuration is obtained preferentially.

The reactivity of the Na complex toward common functional groups will limit its applicability for reduction of conjugated carbonyl units in polyfunctional molecules. As summarized in Table V, saturated ketones and aldehydes, alkyl bromides react with the Na complex approximately as rapidly as a typical conjugated ketone. Nitrile and ester units are inert under these conditions. The yield of alcohol from the saturated ketone is only 69%; the remainder is high molecular weight material. The reduction of organic halides has been observed with other hydrido–copper reagents, but relative rate information was not available.[15,29]

Experimental Section

General. Tetryhydrofuran (THF) and ether were freshly distilled from sodium-benzophenone ketyl under argon immediately before use. All other solvents were ACS reagent grade and were not further purified unless otherwise noted. All reactions involving hydride reagents were carried out under an atmosphere of argon achieved by alternately evacuating and filling the reaction vessel three times with argon. All organic extracts were dried over anhydrous magnesium sulfate. Cyclohex-2-enone, isophorone, 5,5-dimethylcyclohex-2-enone, methyl crotonate, chalcone, *trans*-cinnamic acid, 3-methylbut-2-enoic acid, 3-phenylpropionic acid, and pinacolone were purchased from Aldrich Chemical Co. Methyl 3-methylpropynoate was purchased from Farchan Research Laboratories. 2-Butanol and Vitride were purchased from Eastman Organic Chemicals. Methyl esters of *trans*-cinnamic acid, 3-methylbut-2-enoic acid, and 3-phenylpropionic acid were prepared by dissolving the acid in methyl alcohol, adding 3–4 mL of thionyl chloride, and heating at reflux for 12–18 h. Methyllithium in ether, lithium aluminum hydride (granular and in ether solution), and cuprous bromide were purchased from Alfa Inorganics (Ventron), or prepared according to the procedure of Keller and Wycott.[30a] Cuprous iodide was purchased from ROC/RIC. Colored impurities from the Cu(I) halides were removed from these salts by dissolution in a saturated aqueous solution of the appropriate potassium halide followed by treatment with charcoal, filtration, and dilution with water to reprecipitate the Cu(I) halide.[30b] The purified Cu(I) halide was dried for 24 h under vacuum (0.001 Torr). Lithium aluminum deuteride was purchased from ICN Corp. and was stated to contain 99 atom % deuterium. Following the method of House and co-workers,[25] 2,2,6,6-tetramethylhept-4-en-3-one was prepared.

Lithium Trimethoxyaluminum Deuteride. Exactly parallel with the procedure for preparation of lithium trimethoxyaluminum hydride,[31] lithium aluminum deuteride and methyl alcohol-*O-d* were combined in THF and filtered, and the filtrate used as a solution of lithium trimethoxyaluminum deuteride.

2-Butanol-*2-d*. Lithium aluminum deuteride (1.0 g, 24 mmol) was dissolved in 70 mL of ether and cooled to 0 °C. Methyl ethyl ketone (5.2 g, 72 mmol) was added dropwise over a 45-min period. After the reaction mixture was stirred for 3.5 h at 25 °C, 1.0 mL of water, 1.0 mL of 15% aqueous sodium hydroxide solution, and 3 mL of water were added sequentially. The mixture was filtered, and the filtrate was washed several times with saturated salt solution, dried, and fractionally distilled using *n*-butylbenzene as a "chaser". At bp 95–100 °C, 2-butanol-2-*d* was obtained which showed ^1H NMR ($CDCl_3$) δ 1.42 (m, $-CH_2-$), 0.78–1.2 (m, $-CH_3$), 3.67 (s, $-OH$). No signal due to hydrogen at C-2 was visible (<2%), expected at δ 3.68. The sample was stored over Linde Type 4A molecular sieves.

Preparation of 2-Butanol-*O-d*. All glassware was rinsed with D_2O and dried. Freshly distilled 2-butanol (7 g) was dissolved in 15 mL of dichloromethane and treated four times with batches of D_2O (99.5%) containing a small amount of NaOD. Using *n*-butylbenzene as chaser, fractional distillation produced a fraction of bp 95–100 °C which was 2-butanol with 96 atom % deuterium, as determined by ^1H NMR spectroscopy. The sample was stored over Linde Type 4A molecular sieves.

Procedure A. Preparation and Reactions of the Li Complex. The following procedure is typical of the techniques used to obtain the data involving the Li complex. Lithium trimethoxyaluminum hydride (0.79 M, 5.3 mL, 4.2 mmol) was added dropwise to a suspension of cuprous bromide (315 mg, 2,2 mmol) in 8 mL of THF maintained at 0 to −5 °C. After 30 min, the resulting dark brown suspension was cooled to −78 °C. Cyclohex-2-enone (110 mg, 1.15 mmol) was added rapidly via syringe and after 10 min, the mixture was placed in a bath at −20 °C and stirred for 50 min. Then methyl alcohol (5 mL) was added and the mixture poured into 25 mL of saturated aqueous ammonium chloride solution. Ether was added and the mixture was shaken in a separatory funnel. The blue (copper) layer was separated. The other layer was washed with water, dried, and analyzed by quantitative GLC with an internal standard (*n*-butylbenzene) added at this point. Using a 6 ft × 0.125 in. column packed with 3% Carbowax 20 M on Chromosorb P at 110 °C, quantitative analysis was carried out for unreacted cyclohex-2-enone (retention time: 5.9 min), cyclohexanone (5.0 min), *n*-butylbenzene (5.5 min), cyclohexanol (7.0 min), and 2-cyclohexenol (10.2 min). The identity of the products was assigned based on GLC retention time comparisons with samples of established identity (two columns) and by GCMS, using a Finnegan 3300 instrument. In this example, the yields were: cyclohexanone, 84 ± 2%; 2-cyclohexenol, 3 ± 2%; and cyclohexanol, ≤1%. For a survey of other conditions, see Table I. For reactions under similar conditions with other conjugated carbonyl substrates, see Tables II–IV.

Procedure B. Preparation and Reactions of the Na Complex. A solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene (Vitride[23a] or Red-Al,[23b] 70% solution, 0.56 mL, 2.0 mmol, 4.0 hydride equiv) was added dropwise to a suspension of cuprous bromide in 4 mL of THF at 0 to −5 °C under argon. The resulting brown-black suspension was allowed to stir at 0 °C for 0.5 h, then it was cooled to −78 °C. To this mixture at −78 °C was added via syringe a solution of 2,2,6,6-tetramethylhept-4-en-3-one (84 mg, 0.5 mmol) in 3 mL of THF. After 10 min, the solution was stirred at −20 °C for 1 h, quenched by addition of water (4 mol), and poured into 25 mL of saturated aqueous ammonium chloride solution. Ether was added, the blue (copper) aqueous solution was separated, the ether solution was washed with water and then dried, and finally the ether solution was analyzed by GLC. Ethylbenzene was added as internal standard.

Using a 6 ft × 0.125 in. column packed with 3% Carbowax 20 M on Chromosorb P at 120 °C the following retention times/yields were observed: ethylbenzene, 2.0 min; 2,2,6,6-tetramethylheptan-3-one, 3.75 min, 98 ± 2%; 2,2,6,6-tetramethylhept-4-en-3-one, 4.5 min, <1%; 2,2,6,6-tetramethylhept-4-en-3-ol, 7.0 min, <1%. The identity of the products was assigned based on GLC retention time comparisons with samples of established identity and by GC/MS, using a Finnegan 3300 instrument. For a survey of other conditions, see Table I. For reactions of the Na complex with other conjugated carbonyl substrates, see Tables I–IV.

Procedure C. Reductions Using the Na Complex with 2-Butanol Present. Exactly as above, the Na complex was prepared under argon from cuprous bromide (686 mg, 4.8 mmol) and Vitride (1.34 mL, 9.6 equiv of hydride) in 12 mL of THF and cooled to −78 °C. Then 2-butanol (2.0 mL, 1.6 g, 18 mmol) was added all at once, followed within 5 min by a solution of 2,2,6,6-tetramethylhept-4-en-3-one (200 mg, 1.2 mmol) in 4.0 mL of THF. After 10 min at −78 °C, the mixture was stirred at −20 °C for 1.0 h. After the usual isolation procedure, quantitative GLC analysis showed the presence of 2,2,6,6-tetramethylhept-4-en-3-one in 98% yield. Collection of this material by preparative GLC followed by ^{1}H NMR analysis confirmed the identity of the product.

Characterization of Products in Tables I–IV. (a) From Isophorone. Reduction of isophorone according to procedure A gave 3,3,5-trimethylcyclohexanone and 3,5,5-trimethylcyclohex-2-enol which were separated by preparative GLC (5% FFAP at 165 °C). The ketone was identified from comparison of ^{1}H NMR[32] data, mass spectral molecular weight (found, parent at m/e 140; calcd for $C_9H_{16}O$, 140), and by IR (neat): 1710 cm^{-1}. The alcohol was prepared by reduction of isophorone with lithium aluminum hydride[33] and compared with the sample from preparative GLC in ^{1}H NMR and mass spectral properties. The mass spectrum has been published.[34]

(b) From 5,5-Dimethylcyclohex-2-enone. Reduction according to procedure A gave 3,3-dimethylcyclohexanone and 5,5-dimethylcyclohex-2-enol, which were separated by preparative GLC. The ketone was identified by comparison of ^{1}H NMR data,[35] mass spectral data (found, parent at m/e 126; calcd for $C_8H_{14}O$, 126), and IR (neat): 1710 cm^{-1}. The alcohol was prepared by reduction of 5,5-dimethylcyclohex-2-enone with lithium aluminum hydride[36] and compared with the sample from preparative GLC in ^{1}H NMR and mass spectral properties.

(c) From Chalcone. Reduction according to procedure C. The ether extract, after analysis by GLC, was concentrated and the residue was separated into three fractions by preparative layer chromatography (10% ethyl acetate–benzene, silica gel). Fraction 1 (R_f ~0.6) was identified as 1,3-diphenylpropan-1-one by comparison of GLC retention time, ^{1}H NMR data, and melting point (67–69 °C) with corresponding data from a commercial sample (Eastman Organic Chemicals). Fraction 2 (R_f 0.5) was unreacted chalcone, while the slower moving material consisted of a nondistillable mixture which was not further characterized.

(d) From Methyl Crotonate. Reduction according to procedure C produced a single product detectable by GLC which was shown to be methyl butanoate by comparison of GLC retention time and mass spectral properties with corresponding data from a commercial sample (Aldrich Chemical Co.).

(e) From Methyl 3-Methylbut-2-enoate. Reduction according to procedure C produced a single product detectable by GLC which was shown to be methyl 3-methylbutanoate by comparison of GLC retention time and mass spectral properties with corresponding data from a commercial sample (Aldrich Chemical Co.).

(f) From Methyl Cinnamate. Reduction according to procedure B produced an ether solution which was concentrated at reduced pressure. Short-path distillation (up to 50 °C (0.01 Torr)] afforded a colorless liquid distillate which was shown to be a single compound by GLC and TLC, and was identified as methyl 3-phenylpropionate by comparison of ^{1}H NMR and mass spectral data with corresponding data from a commercial sample (Aldrich Chemical Co.). The residue was applied to a preparative layer chromatography plate (silica gel) and eluted with 10% ethyl acetate–benzene. The main component was recovered from the plate, mp 174–175 °C. It was identified as dimethyl *meso*-2,3-diphenyladipate (**12**) by comparison of melting point (lit.[37] 174–175 °C): ^{1}H NMR ($CDCl_3$) δ 6.22 (s, 5 H, ArH), 3.32 (s, 4 H, $-OCH_3$ and $-CHAr$), 2.38 (m, 2 H, $-CH_2CO_2-$); IR (KBr)1710 cm^{-1}; mass spectrum m/e 326 (parent), 296, 253, 252, 220, 163, 121 (base), 104, 91; calcd for $C_{20}H_{22}O_4$, mol wt 326.

(g) From Methyl 3-Methylpropiolate. Reduction according to procedure B produced an ether solution which was analyzed by GLC using a 12 ft × 0.125, in. column packed with 5% Carbowax 20M on Chromosorb P at 70 °C; ethylbenzene was added as internal calibration standard. Peaks observed were attributed to: methyl propionate (25 min, 26%), methyl *cis*-crotonate (4.0 min, 25%), methyl *trans*-crotonate (5.5 min, 27%), ethylbenzene (6.5 min), and methyl 3-methylpropynoate (7.0 min, <1%). The crotonate isomers were identified by comparison of GC retention times and mass spectral data with corresponding data from commercial or independently synthesized material.

(h) From Methyl 3-Phenylpropynoate. Reduction according to procedure B produced an ether solution which was concentrated. Short-path distillation of the residue [50–60 °C (0.01 Torr)] afforded a colorless distillate. Quantitative ^{1}H NMR analysis on the distillate using toluene as internal standard indicated the presence of three major components: methyl *cis*-cinnamate (47% yield, integration of olefinic H doublet centered at δ 5.90),[38] methyl *trans*-cinnamate (18%, integration of olefinic H doublet centered at δ 6.38),[38] and methyl 3-phenylpropionate (11%, integration of $-OCH_3$ at δ 3.75). The components were prepared independently or purchased, and were compared in GLC retention times, mass spectral data, and ^{1}H NMR data with the reaction product mixture.

Reductions with Ashby's $LiCuH_2$. Lithium dihydridocuprate was prepared[21] by adding methyllithium (1.55 M in ether, 3.87 mL, 6.0 mmol) to a suspension of cuprous iodide (571 mg, 3.0 mmol) in 25 ml of ether at −78° under argon. The colorless solution of lithium dimethylcuprate was allowed to stir at −78 °C for ca. 45 min, at which time lithium aluminum hydride (1.44 M in ether, 2.08 mL, 3.0 mmol) was added all at once. The colorless solution changed immediately to yellow and a yellow solid precipitated as the temperature was allowed to rise to 25 °C. The solid was filtered under argon and washed two to three times with 2–3-mL portions of ether. Then to a suspension of the yellow solid in 16 mL of ether stirred at −78 °C under argon was added 154 mg (1.0 mmol) of 2-cyclohexenone via syringe. The color changed to brown immediately. After being stirred at −78 °C for 20 min and at −20 °C for 30 min, the mixture was quenched by cooling to −78 °C and adding 15–20 ml of saturated aqueous ammonium chloride solution. The ether layer was washed with water, dried, and analyzed by GLC as in procedure A above. Present were: cyclohexanone (21%, 5.0 min), cyclohexanol (~3%, 7.5 min), and cyclohex-2-enol (64%, 10.5 min). The products were identified by comparison of retention times with commercial samples. A similar experiment with isophorone gave parallel results; the ratio of 1,4 reduction–1,2 reduction was 1:30.

Reduction of 2,2,6,6-Tetramethylhept-4-en-3-one in the Presence of 2-Butanol-*2-d*. According to procedure C, using 2-butanol-*2-d* in place of 2-butanol, 2,2,6,6-tetramethylheptan-3-one was detected by GLC (98% yield). Following preparative GLC, the deuterium incorporation was assayed by repeated integration of the signals due to the $-CH_2-$ units (δ 2.46 and 1.50) relative to the signals due to the *tert*-butyl units (δ 1.15 and 0.90). No deuterium incorporation into either $-CH_2-$ unit (<5%) was observed.

Reduction of 2,2,6,6-Tetramethylhept-4-en-3-one in the Presence of 2-Butanol-*O-d*. The experiment exactly parallelled that immediately above, except 2-butanol-*O-d* was used in place of 2-butanol-*1-d*. Quantitative GLC analysis indicated the presence of 2,2,6,6-tetramethylheptan-3-one, 99% yield. Isolation by preparative GLC as above gave material with the following properties: ^{1}H NMR ($CDCl_3$) δ 2.46 (m, 1.51 H), 1.50 (m, 2.0 H), 1.15 (s, 8.95 H), 1.00 (s, 9.02 H). These data indicate the incorporation of 24 ± 2 atom % deuterium at the position C-4, corresponding to the signal at δ 2.46.

Reduction of 2,2,6,6-Tetramethylhept-4-en-3-one with the Li Complex Prepared from Lithium Trimethoxyaluminum Deuteride. According to procedure A, but using lithium trimethoxyaluminum deuteride, 2,2,6,6-tetramethylheptan-3-one was reduced. Preparative GLC afforded the ketone **15** and the alcohol **16**. The ketone **15**: ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 9.1 H), 0.92 (s, 9.0 H), 1.40 (t of t, 1.13 H, $J_{1,2}$ = 7.8, $J_{1,0}$ = 2.3 Hz), 2.45 (d of t, 2.0 H, $J_{2,0}$ = 1.0, $J_{1,2}$ = 7.8 Hz). The alcohol **16**: ^{1}H NMR ($CDCl_3$) δ 3.5–4 (m, 2 H), 1.45 (s, 1 H, OH, exchangeable with D_2O), 1.01 (s, 9.0 H), 0.91 (s, 9.0 H). Less than 0.1 relative H units was observed by integration over the position at δ 3.72, where the methine hydrogen (D in **16**) appears in the ^{1}H NMR spectrum of the unlabeled material.

Reduction of Methyl Cinnamate with the Li Complex Prepared from Lithium Trimethoxyaluminum Deuteride. According to procedure A, except using lithium trimethoxyaluminum deuteride, methyl cinnamate was reduced. The organic product was distilled in a short-path apparatus (50 °C (0.001 Torr)] to afford a colorless distillate (25 mg, 15% yield): ^{1}H NMR ($CDCl_3$) δ 7.25 (s, 5.1 H, ArH), 3.68 (s, 3.0 H, $-OCH_3$), 2.5–2.9 (m, ~3 H, $-CH_2-$, $-CHD-$). Addition of ^{1}H NMR shift reagent, Eu(fod)$_3$,[24] to the ^{1}H NMR sample tube caused the multiplet at ca. δ 2.7 to become a singlet. Additional Eu(fod)$_2$ provided separation of the signals due to the C-1 and C-2 protons in the methyl 3-phenylpropionate product (**31**). With 43 mg of Eu(fod)$_2$ added to the solution, a multiplet (t of t, 1 H, $J_{1,2}$ = 7, $J_{1,0}$ = 3 Hz) assigned to H-1 appeared upfield of a second multiplet (br d, ~2 H, $J_{1,2}$ = 7 Hz).

Reduction of Methyl Cinnamate with the Na Complex in the Presence of 2-Butanol-*2-d*. Reduction of methyl cinnamate (162 mg, 1.0 mmol) exactly according to procedure C except using 2-butanol-2-*d* in place of 2-butanol produced an ether solution which was concentrated by rotary evaporation. The residue was distilled in a short-path apparatus [50 °C (0.001 torr)] to give a colorless distillate, 132 mg, which was identified as methyl 3-phenylpropionate by comparison with a commercial sample.

Reduction of Methyl 3-Phenylpropiolate with the Na Complex with Quenching by Deuterium Oxide. Reduction of methyl 3-phenylpropynoate (147 mg, 0.92 mmol) according to procedure B, except that deuterium oxide (4.0 mL, 99.8 atom % D) was added after reduction was complete, produced an ether solution which was analyzed by quantitative GLC as before. From retention time and mass spectral data comparisons, the following components were determined (5 ft × 0.125 in. 5% Carbowax 20M on Chromosorb P, 170 °C): methyl *cis*-cinnamate (retention time 12 min, 32%), methyl *trans*-cinnamate (18 min, 18%), methyl 3-phenylpropionate (8 min, 18%). The solution was concentrated by rotary evaporation and the residue was distilled in a short-path apparatus [50 °C (0.01 Torr)] to give a colorless distillate (91 mg) which was analyzed by quantitative ^{1}H NMR. The signal from methyl *cis*-cinnamate, which appears in the unlabeled compound at δ 6.88 (d, β-H, $J_{\alpha,\beta}$ = 13 Hz), appeared as a triplet with J = 1 Hz); the signal which appears in the unlabeled compound at δ 5.90 (d, α-H, $J_{\alpha,\beta}$ = 13 Hz) was absent (<0.05 relative proton area) during scanning of the spectrum at high sensitivity (>95 atom % deuterium at α-H in **17a**). The signal from methyl *trans*-cinnamate which appears in the unlabeled compound at δ 6.38 was absent (<0.05 relative proton area, >95 atom % deuterium at α-H). The mass spectra (GC/MS, electron impact) for both the cis and trans methyl cinnamate product showed the base peak at *m/e* 163, with no peak at *m/e* 162 (<5% unlabeled). Calcd for $C_{10}H_9DO_2$: mol wt 163.

Preparative Scale Reduction of Methyl 3,4,5-Trimethoxycinnamate. A solution of sodium bis(2-methoxyethoxy)aluminum hydride (Vitride, 70% solution in benzene, 11.2 mL, 40 mmol, 80 mmol of hydride) was added dropwise to a suspension of cuprous bromide (5.70 g, 40 mmol) in 75 mL of THF maintained at −5 to 0 °C (bath temperature) under argon. After 30 min at 0 °C, the mixture was cooled to −78 °C and 2-butanol (8.0 mL, 90 mmol) was added rapidly. Within 10 min, a solution of methyl 3,4,5-trimethoxycinnamate (1.26 g, 5.0 mmol) in 10 mL of THF was added rapidly. After 15 min at −78 °C, the reaction mixture was stirred at −20 °C for 2 h. Then water (10 mL) was added and the mixture was poured in a saturated aqueous solution of ammonium chloride. The ether layer was washed with water and concentrated by rotary evaporation, and the residue was distilled in a short-path apparatus. The colorless distillate (1.23 g, 96.8% yield) was pure methyl 3-(3,4,5-trimethoxyphenyl)propionate:[39] ^{1}H NMR (CDCl$_3$) δ 6.42 (s, 2 H, ArH), 3.80 (s, 9 H, -OCH$_3$), 2.4–3.1 (m, 4 H, -CH$_2$CH$_2$-); IR (neat) 1740 cm^{-1}; mass spectrum parent at 254.1154, calcd for $C_{13}H_{18}O_5$, 254.1167.

Reduction of Methyl 3-Phenylpropynoate with the Na Complex Followed by Trapping of the Organometal Intermediate. (a) With Benzaldehyde. A solution of sodium bis(2-methoxyethoxy)aluminum hydride (Vitride, 70% solution in benzene, 2.24 mL, 8 mmol, 16 mmol of hydride units) was added dropwise to a suspension of cuprous bromide in 25 mL of THF maintained at −5 to 0 °C. After 30 min at 0 °C, the mixture was cooled to −78 °C and a solution of methyl 3-phenylpropynoate (386 mg, 2.4 mmol) in 5.0 mL of THF was added rapidly. The mixture was stirred at −78 °C for 30 min, then at −20 °C for 30 min, and then it was cooled to −78 °C. Benzaldehyde (848 mg, 8.0 mmol) was added rapidly and the mixture was allowed to stir for 2 h at −78 °C and slowly warmed to −20 °C over 6 h. Then water (5 mL) was added and the mixture was poured into saturated aqueous ammonium chloride solution. Ether was added, the mixture was shaken, and the organic layer was washed with water, dried, and concentrated by rotary evaporation. TLC analysis (ether–hexane–methanol in the ratio 6:14:1 by volume, on silica gel) indicated a major component of R_f 0.24. Preparative layer chromatography (ether–hexane, 3:7; silica gel; develop eight times) afforded 300 mg of an oil; 47% yield based on methyl cinnamate: IR (neat) 3550 (s), 1730 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$–D$_2$O) δ 7.2 (br s, 10 H, ArH), 6.82 (s, 1 H, vinyl H), 5.50 (s, 1 H, -OCHAr), 4.50 (s, 3 H, -OCH$_3$), 3.44 (s, 3 H, -OCH$_3$). The compound (**18**) was characterized by benzoylation (benzoyl chloride–pyridine, 25 °C, 15 h) to give **19**, mp 76–78 °C dec (crystals from isopropyl ether–hexane): IR (CCl$_4$) 1735 (s), 1605 (m), 1590 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8–8.3 (m, 2 H, benzoyl ortho H), 7.3–7.7 (m, 13 H, ArH), 6.95 (d, 1 H, vinyl H, J = 1 Hz), 6.85 (d, 1 H, -OCHAr, J = 1 Hz), 3.55 (s, 3 H, OCH$_3$); mass spectrum, parent at *m/e* 372, fragments at 267, 235, 191.

Anal. Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.39; H, 5.46.

(b) With 2-Cyclohexenone. Reduction of methyl 3-phenylpropynoate with the Na complex was carried exactly as in (a) above. In place of benzaldehyde, 2-cyclohexenone (769 mg, 8.0 mmol) was added rapidly to the reduction product mixture at −78 °C. After 2 h at −78 °C, the bath temperature was allowed to rise slowly to −20 °C over 6 h. Then, after 30 min at −20 °C, water (5 ml) was added, and the mixture was poured into saturated aqueous ammonium chloride solution. Ether was added, the mixture was shaken, and the ether layer was washed with water, dried, and concentrated by rotary evaporation. Analytical TLC indicated a major component of R_f 0.24 (ether–hexane–methanol in the ratio 6:14:1 by volume; silica gel). Purification by preparative layer chromatography (multiple elution with benzene–hexane–methanol in the ratio 6:6:1; silica gel; repeating on three plates) afforded material which showed a single spot on analytical TLC. The product (87 mg, 14% yield based on methyl 3-phenylpropynoate) showed: IR (mull) 3560 (w), 3000 (s), 1750 (m), 1460 (m), 748 (w), 690 (w); ^{1}H NMR (CDCl$_3$) δ 7.12 (br s, 5 H, ArH), 6.59 (s, 1 H, vinyl H), 5.4–6.0 (br AB q, 2 H, vinyl H), 3.50 (s, 3 H, -OCH$_3$), 2.5 (br s, 1 H, -OH), 1.5–2.2 (br m, 6 H, -CH$_2$-); mass spectrum (electron impact) *m/e* 258 (34%), 240 (76%), -H$_2$O), 226 (73%), 199 (100%). Recrystallization from hexane afforded colorless needles, mp 77.5–78 °C.

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.38; H, 7.02. Found: C, 74.32; H, 7.12.

Registry No.—**12**, 61883-07-6; **15**, 62862-24-2; **16**, 62862-25-3; (*E*)-**18**, 62862-26-4; (*Z*)-**18**, 62862-27-5; (*E*)-**19**, 62862-28-6; (*Z*)-**19**, 62862-29-7; **21**, 62862-30-0; **31**, 62862-31-1; methyl ethyl ketone, 78-93-3; 2-butanol-2-*d*, 19403-02-2; 2-butanol, 78-92-2; lithium trimethoxyaluminum hydride, 12076-93-6; cuprous bromide, 7787-70-4; sodium bis(2-methoxyethoxy)aluminum hydride, 22722-98-1; 3,3,5-trimethylcyclohexanone, 873-94-9; 3,3-dimethylcyclohexanone, 2979-19-3; lithium dihydridocopper, 53201-99-3; lithium trimethoxyaluminum deuteride, 62905-96-8; methyl *cis*-cinnamate, 19713-73-6; methyl *trans*-cinnamate, 1754-62-7; methyl 3,4,5-trimethoxycinnamate 7560-49-8; methyl 3-(3,4,5-trimethoxyphenyl)propionate, 53560-25-1; cuprous iodide, 7681-65-4; triphenylphosphinecuprous iodide, 47107-74-4.

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Notes

Molecular Geometry Studies. The Crystal and Molecular Structure of a 7-Spirocyclopentylbicyclo[2.2.1]heptene Anhydride[1]

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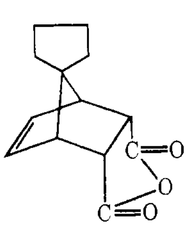
The conformation of the rigid bicyclo[2.2.1]heptane nucleus in various bifunctional derivatives (anhydrides, diacids, diesters) is essential to our study relating the molecular geometry in the solid state to the molecular geometry as determined in solution via NMR-LIS measurements.[3-5] Compound 1, which represents only the second bicyclo[2.2.1]heptane system containing a 7-spiro hydrocarbon substituent that has been reported, is one of the model compounds used in conformational equilibria determinations in the *cis*-1,2,3,6-tetrahydrophthalic anhydride series.[5]

In addition, compound 1 has been included in a series of kinetic studies on the mechanism of the endo–exo transformation.[3] Because compound 1 was the only endo compound in the series which did not thermally rearrange to the corresponding exo isomer, a knowledge of its molecular geometry in the solid state would indicate if steric requirements were too stringent to allow the reverse Diels–Alder reaction to proceed.



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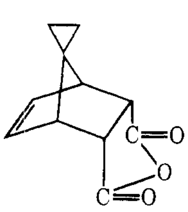

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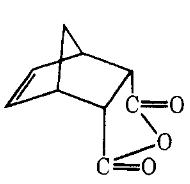

3

In anhydrides 2 and 3 of the series, long carbon–carbon bonds (C_1–C_2, C_3–C_4) peculiar to some Diels–Alder adducts[6] occurred; hence we desired to further investigate this molecular asymmetry in compound 1.

Experimental Section

[3′aβ,4′α,7′α,7′aβ]-3′a,4′,7′,7′a-Tetrahydrospiro[cyclopentane-1,-8′-[4,7]methanoisobenzofuran]-1′,3′-dione (1) was synthesized as previously described.[7] Colorless crystals with well-defined faces were obtained by recrystallization from solution in benzene by vapor diffusion of 60–110 °C petroleum ether into the benzene solution. Preliminary Weissenberg and precession photographs of a small crystal (ca. 0.21 × 0.24 × 0.24 mm) indicated an orthorhombic space group with systematic absences of $0kl$, $l \neq 2n$, and $h0l$, $h \neq 2n$. The choice of space group $Pca2_1$ with $Z = 4$ was confirmed by the eventual solution of the structure. Unit cell dimensions of $a = 12.3397$ (10), $b = 8.3315$ (5), and $c = 10.5058$ (11) Å were provided by least-squares refinement of 14 independent 2θ values obtained by automatic centering routines on a G.E. XRD-490 diffractometer with a scintillation counter detector using Ni filtered Cu Kα radiation. Intensity data were collected out to 120° 2θ using θ–2θ step scans with a 2° 2θ scan range for each reflection; backgrounds were counted at both extremes of each scan. Of the 854 reflections measured, 780 were considered observed by the criteria $I > 3\sigma(I)$ and were used for structure refinement. Lorentz and polarization factors were applied,[8] and the data were corrected for absorption by the method of Tompa[9] ($\rho_c = 1.342$ g cm^{-3}, μ(Cu Kα) = 7.848 cm^{-1}, transmission factor range 0.903–0.938). Weights were calculated by the method of Stout and Jensen,[10] $w(F) = [(k/4LpI)(\sigma^2(I) + (0.03I)^2)]^{-1}$. Scattering factors for nonhydrogen atoms were taken from Cromer and Mann;[11] the scattering factor curve for hydrogen was that of Stewart, Davidson, and Simpson.[12] No correction was made for extinction.

The structure was solved by direct methods using the program MULTAN.[8] Using phases chosen by the program for 80 reflections, an E map revealed the positions of 15 of the 16 nonhydrogen atoms in the asymmetric unit. These positions were refined isotropically by full-matrix least squares minimizing $\Sigma w \Delta F^2$, and a subsequent Fourier map revealed the remaining nonhydrogen atom. The structure was refined isotropically to an R factor of 10.7% ($R = \Sigma||F_o| - F_c||/\Sigma F_o$); further refinement, treating the vibration of all atoms anisotropically, reduced the R to 8.0%. A difference Fourier was calculated which revealed the positions of all hydrogen atoms. Hydrogen atoms were assigned the refined isotropic temperature factors of the atoms to which they were attached, and subsequent refinement of all positional parameters and anisotropic thermal parameters for nonhydrogen atoms reduced the R factor to 4.6%. The R for all data, including unobserved reflections, was 5.2%; the weighted R_w was 6.7% ($R_w = [\Sigma w \Delta F^2]^{1/2}/[\Sigma w F_o{}^2]^{1/2}$). The largest shift divided by the standard deviation was 0.3 for the last refinement cycle, and a final difference Fourier showed no areas higher than ±0.3 e Å^{-3}. A normal probability plot[13] was calculated which was essentially linear with a slope of 1.42 and an intercept of 0.06.

Results and Discussion

Figure 1 shows an ORTEP drawing of compound 1 with atom designations. Bond distances and bond angles for all atoms are given in Tables I and II, respectively. Characteristic bond lengths and bond angles are observed. Two important features of the data should be noted.

The long carbon–carbon bonds (C_1–C_2, C_3–C_4) typical of