Lithium and Potassium Trialkylborohydrides. Reagents for Direct Reduction of α,β-Unsaturated Carbonyl Compounds to Synthetically Versatile Enolate Anions[1]

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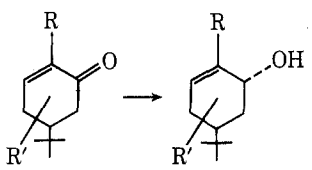
The utility of lithium and potassium tri-*sec*-butylborohydrides (L- and K-Selectrides) and lithium triethylborohydride as reagents for the conjugate reduction and reductive alkylation of unsaturated ketones and esters is surveyed. In general, β-unsubstituted cyclohex-2-en-1-ones undergo exclusive 1,4 reduction to ketone enolates which can be protonated or alkylated in high yield. Efforts to achieve with this method the reduction of α,β-enoates to ester enolates are described, culminating in the first synthetic methodology which generally accomplishes this transformation. Many examples are presented and the dependence on various reaction parameters including solvent, temperature, nature of borohydride, and ester type is explored. The resulting ester enolates exhibit the same reactivity as those prepared by direct metalation of saturated esters, particularly with regard to alkylation. α,β–γ,δ dienoic esters were found to be very resistant to conjugate reduction, and α-acetylenic esters furnish only propargylic alcohols in good yield. A series of competition experiments between various carbonyl-containing substances is also reported which defines some relative rates of reduction.

The quest for chemical reagents which can effect the reduction of ketones to alcohols in a stereoselective fashion has been an active area of research in recent times. Among the many reducing agents which have been devised for this purpose, the bulky trialkylborohydrides such as lithium and potassium tri-*sec*-butylborohydride[2] are the most convenient (commercially available from Aldrich Chemical Co. as L- and K-Selectride) and the most effective. For example, the reductions of alkyl-substituted mono- and bicyclic ketones to the corresponding less stable alcohols having isomeric purity generally above 95% are readily carried out with these reagents.

For one of our research projects at Cornell we required a series of isomerically pure pseudoaxial cycloalk-2-enols **2**. A

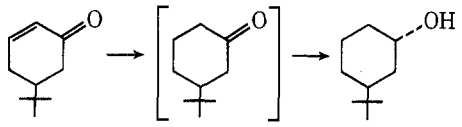


1 **2**

few specific substances of this type are available by highly specialized procedures,[3] but it quickly became evident that no general access to structures such as **2** from some readily available source had been devised. The obvious possibility that such pseudoaxial allylic alcohols might be prepared by stereoselective reduction of the corresponding enones **1** prompted the investigation which is the subject of this article.

The most versatile reagent for the synthesis of allylic alcohols from enones, both cyclic and acyclic, has been diisobutylaluminum hydride.[4] Although yields are high, the resulting mixtures of cycloalkenols contain preponderantly but by no means exclusively the pseudoequatorial isomer. A literature search revealed that no other methodology exists for reducing cyclic enones to allylic alcohols of high isomeric purity. Corey and co-workers, however, have reported very high stereoselectivity in the reduction of an acyclic enone belonging to the prostaglandin family using L-Selectride.[5] In view of this single successful report we decided to subject cycloalkenones such as **1** to trialkylborohydride reduction.

Reduction of Enones. Following the experimental procedure of Brown,[1] 5-*tert*-butylcyclohex-2-enone (**3**) was treated with 3 equiv of K-Selectride at −78 °C in ether or THF and the reaction quenched at low temperature with water. Oxidative workup by addition of 10% NaOH and 30% H_2O_2

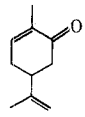
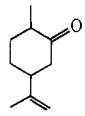
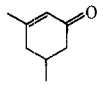
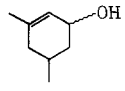
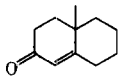
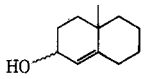
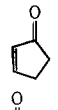
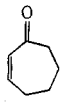
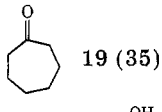
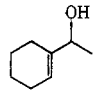
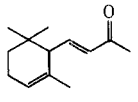
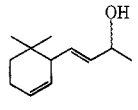
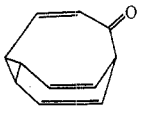


3 **4** **5**

to destroy the borane by-product afforded a 92% yield of the saturated alcohol **5**, presumably arising by sequential 1,4, then 1,2 reduction. When this experiment was repeated using 1 equiv of reducing agent, obtention of a 99% yield of ketone **4** confirmed the proposed mechanistic pathway. This exclusive 1,4 reduction was in contrast with the Corey prostaglandin reduction; to determine its generality a series of representative enones were treated in the same fashion with K-Selectride. Results are summarized in Table I. From Table I it is evident that conjugate reduction is critically dependent on both steric factors about the electrophilic alkene (measured by changes in alkyl substitution) as well as ring size. Although β-unsubstituted cyclohexenones such as **3**, **6**, **8**, and **10**[6] undergo exclusive 1,4 reduction, the presence of a β-methyl substituent as in **12** completely suppresses this mode in favor of 1,2 carbonyl addition. When the enone is in a five-membered ring, a complex product mixture is formed which includes cyclopentanol as a major product. Expanding the ring size to seven (reduction of **18**) also has a deleterious effect in that 1,2 and 1,4 reduction compete to furnish a mixture of cycloheptanone and 2-cycloheptenol. In the reduction of homobullvalenone (**25**) whose enone functionality is contained in two eight-membered rings, no conjugate reduction is observed whatsoever.[7] The exclusive formation of allylic alcohols from acetylcyclohexene (**21**) and α-ionone (**23**) is consistent with previous results[5] and suggests that acyclic enones generally undergo exceptionally rapid 1,2 addition.

It was of interest to ascertain whether variations in the nature of the reducing agent would significantly alter the course of hydride addition. For the most part, substitution of L-Selectride for K-Selectride had little effect on the reduction of β-unsubstituted cyclohexenones such as carvone; saturated ketones were obtained in excellent yield. In one important exception, however, reduction of 3,5-dimethyl-2-cyclohexenone (**12**) with L-Selectride afforded a 1:1 mixture of alcohols **13** and the corresponding dimethylcyclohexanone in 72% yield. The same experiment performed with Super-Hydride (lithium triethylborohydride, −78 °C) produces only alcohols **13** in 90% yield, an experimental outcome which complicates

Table I. Reduction of Enones Using K-Selectride in THF

Expt	Enone	Product (yield)
1	 3	 4 (99)
2	 6	 7 (98)
3	 8	 9 (95)
4	 10	 11 (95)
5	 12	 13 (83)
6	 14	 15 (95)
7	 16	 17 (50)[a]
8	 18	 19 (35) 20 (55)
9	 21	 22 (90)
10	 23	 24 (90)
11	 25	 26 (61)

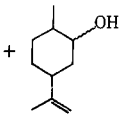
[a] This yield was estimated by VPC.

any rigorous assessment of the importance of steric and electronic factors in trialkylborohydride reactivity.

To determine how changes in solvent might affect the rates of 1,2 and 1,4 addition processes, the action of K-Selectride in pyridine was studied. Jackson and Zurqiyah have reported that 3-methyl-2-cyclohexenone in the presence of sodium borohydride–pyridine is transformed exclusively to the saturated ketone.[9] Our results with this solvent are summarized in Table II. It was convenient to remove under vacuum the bulk of THF from commercially available solutions of L- or K-Selectride, replace it with an equivalent volume of the desired solvent, and repeat this cycle three times. Some THF undoubtedly remains in these preparations so that our data must be interpreted with this limitation in mind.[10] Although reductions are much slower and yields are low, no dramatic reactivity changes with pyridine as solvent are apparent from Table II; K-Selectride still fails to promote saturation of the double bond in **12**.

Two more reaction solvents were investigated. Reduction of **6** and **12** with K-Selectride in toluene revealed essentially no differences in yield or product distribution from reaction in ethereal solvents. Lastly the use of alcohols such as ethanol and 2-propanol was briefly surveyed. K-Selectride demonstrated an unexpectedly long lifetime in such protic media; carvone was reduced at −70 °C in greater than 70% yield to

Table II. Enone Reductions Using K-Selectride in Pyridine

Expt	Enone	Time, min	Temp, °C	Products (yield)
12	**6**	60	−40	**7** (18) +  **27** (8)
13	**6**	60	−40	**7** (8) **27** (18)
		240	r.t.	
14	**12**	60	−40	**13** (25)
15	**12**	60	−40	**13** (42)
		240	r.t.	

mixtures of **7** and **27**. This observation proved crucial in surmounting a problem we encountered later in this work.

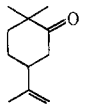
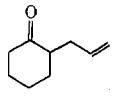
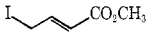
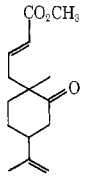
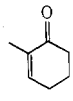
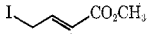
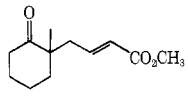
Reductive Alkylation of Enones. In those cases where conjugate enone reduction is successful, we have been able to employ the intermediate enolate in a second, alkylation step by analogy with enol borates, enol borinates, and enolates derived from metal–ammonia reduction.[11] Experiments which demonstrate this capability have been performed using both L- and K-Selectride; they are outlined in Table III. As expected, reductive alkylation of enones using the lithium rather than the potassium reagent leads to higher yields of monoalkylated products. Besides being high-yield processes, Selectride-mediated reductive alkylations, where successful, represent a convenient alternative to dissolving metal reductions in liquid ammonia solution, especially when working on a small scale.

Reduction of Enoates. Although the Selectrides do not represent a general solution to the problem of stereoselectively synthesizing axial allylic alcohols from cyclic enones, we were intrigued with their potential as reducing agents for other conjugated alkenes. Of special concern to us was the 1,4 reduction of α,β-unsaturated esters to saturated ester enolates; at the time no synthetic methodology generally accomplished this transformation.[12] Catalytic hydrogenation of enoates in protic media does afford saturated esters but this technique is only occasionally selective in the presence of other olefinic groups.[13] Alternatively, solutions of alkali metals in amines have been used to reduce the double bond of α,β-unsaturated acids. The success of this technique depends critically on the formation of the corresponding carboxylate salt which protects that group from reduction. Attempted enoate reduction using metal–amine systems is a low-yield process and is usually plagued by overreduction to saturated alcohols.[14] To circumvent these problems, classic schemes for converting α,β-unsaturated esters to saturated, α-alkylated esters employ a standard series of four reactions: hydrolysis of the enoate to enoic acid, dissolving metal reduction to saturated acid, reesterification to furnish saturated ester, and finally alkylation.[15] We hoped that trialkylborohydrides might provide a simpler, one-pot alternative to this awkward four-step operation.

Using a representative unsaturated ester, methyl 2-nonenoate (**34**), as a general prototype for study, an equimolar amount of K-Selectride (1 M in THF) was added to a solution of **34** at −70 °C. Although starting material disappeared very rapidly, the desired methyl nonanoate (**36**) was formed in only low yield. Instead, the major product of this reaction was another, high molecular weight ester which we identified as keto ester **38**. This product arises (Scheme I) from initial 1,4 reduction of **34** followed by attack of the enolate **35** on another molecule of starting material to afford unsaturated keto ester **37**. Rapid reduction of **37** produces **38** whose structural assignment is also supported by its positive $FeCl_3$ test.

The proposed Claisen condensation of **35** with methyl nonenoate finds support in observations by Rathke of similar

Table III. Reductive Alkylation of Enones Using Selectride

Expt	Enone	Reagent	Electrophile	Product (yield)
16	6	K	CH_3I	 **28** (98)
17	6	L	CH_3I	**28** (95)
18	8	K		 **29** (55)  **9** (15) dialkylated ketones **30** (30)
19	8	L		**29** (85) **9** (4) **30** (10)
20	6	L		 **31** (88)
21	 **32**	L		 **33** (60)

Scheme I

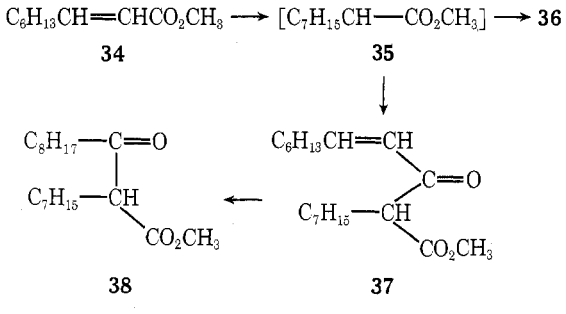


Table IV. Reduction of Methyl 2-Nonenoate Using L-Selectride in THF

Expt	Time, min	Temp, °C	Product (yield)[a]
22	45	−70	**36** (70) **38** (18)
23	20	−70	**36** (71) **38** (21)
24	5	−70	**34** (10) **36** (62) **38** (16)
25	25[b]	−70	**36** (58) **38** (20)
26	20	−90	**34** (79) **36** (9)
27	125	−90 to −70	**34** (63) **36** (36) **38** (4)

[a] Experiments were run on a 2–3-mmol scale; 1 M ester in THF added to 1 M L-Selectride in THF under N_2. [b] Enoate added slowly over 10 min.

dimerization during enoate metalation with lithium dialkylamides at low temperature.[16] Modifying the reaction conditions, including the mode of addition, only slightly altered the proportions of **36** and **38.** Since a reactive potassium ester enolate is a likely intermediate we hoped that substitution of L-Selectride might temper the reactive anion and retard the yield-lowering dimerization. To our satisfaction, addition of **34** to a solution of L-Selectride in THF at −70 °C followed by methanol after 45 min afforded a 4:1 mixture of **36** and **38** in 80% yield. Table IV summarizes our efforts to improve even further the yield of **36** by modifying simple experimental conditions. As can be seen from Table IV, yields of methyl nonanoate could not be improved much above 70%. In an effort to eradicate completely the formation of **38,** we began a systematic investigation of specific reaction parameters.

Table V outlines the results of varying concentration and solvent on the L-Selectride reduction of **34.** We expected substrate concentration clearly to influence the rate of Claisen condensation; a dilution experiment (expt 28) proved that enoate reduction is retarded even more than dimerization and **38** becomes the major product. Our previous experience with toluene as a solvent for conjugate reductions with K-Selectride had revealed its utility as a medium for this transformation. We hoped that in the present work, resulting lithium ester enolates (borates) might be insoluble in toluene at low temperature, thus precluding dimerization. Such was not the case (expt 29) and large amounts of **38** were still produced. When HMPA was employed in 15% v/v ratio with THF, enoate reduction was dramatically retarded. Along with **36** and recovered **34,** dimeric keto ester **38** was also observed in the product mixture. Titration experiments with 4-*tert*-butylcyclohexanone confirmed the stability of L-Selectride in HMPA at low temperature, so that additional deactivation of this reagent through solvation with HMPA must account for the surprising drop in reduction rate.

We have also surveyed the effects of varying ester size on the course of 1,4 reduction since a shift toward bulkier ester groups (ethyl, *tert*-butyl) would be expected to retard carbonyl condensation leading to **38.** In fact changing the ester group to either ethyl or *tert*-butyl failed to suppress the yield-lowering dimerization.

The action of Super-Hydride on **34** was briefly investigated; this reagent proved to be less reactive than the corresponding tri-*sec*-butylborohydride toward α,β-unsaturated esters. Table VI indicates that exposure of **34** to 1 equiv of Super-Hydride under optimum conditions for L-Selectride reduction (expt 32) affords mostly starting material along with small amounts of **36** and **38.** At higher temperature a fair yield of methyl nonanoate may be realized, but desired product is again contaminated with **38.** At this point all conventional efforts to prevent condensation of ester enolate **35** with **34**

Table V. Effect of Solvent and Concentration on L-Selectride Reduction of 34

Expt	Solvent[a]	Time, min	Temp, °C	Products (yield)		
28	THF[b]	20	−70	34 (14)	36 (39)	38 (44)
29	Toluene[c]	20	−70		36 (56)	38 (30)
30	HMPA–THF 1:4	20	−70	34 (52)	36 (21)	38 (7)
31	HMPA–THF 1:4	60	−70	34 (47)	36 (24)	38 (15)

[a] Equimolar amounts of 34 and L-Selectride were used. Final concentration of each was 0.5 M except in expt 28. [b] Final concentration of ester and Selectride was 0.125 M. [c] Commercial reagent was concentrated (0°C, vacuum), toluene added and distilled (two cycles), and finally fresh toluene added to make 1 M solution.

Table VI. Reduction of Methyl 2-Nonenoate Using Super-Hydride in THF

Expt[a]	Time, min	Temp, °C	Products (yield)		
32	20	−70	34 (77)	36 (8)	38 (2)
33	120	−70	34 (77)	36 (16)	38 (1)
34	10	0		36 (62)	38 (17)
35	5	−70		36 (48)	38 (6)
	20	0			

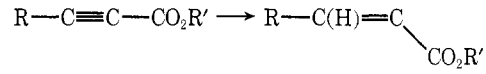
[a] Enoate added to Super-Hydride, each at 1 M concentration.

seemed unpromising. From our earlier work on enone reduction it was clear that Selectride reagents had appreciable lifetimes in alcohol solvents. If conjugate enoate reduction were successful in such a medium, the first formed enolates would rapidly be protonated and avoid Claisen condensation. In fact, slow addition of a mixture of **34** and methanol (2 equiv) to a THF solution of L-Selectride at −70 °C led to a mixture of starting material (78%) and **36** (16%) but no trace of the β-keto ester **38**. When *tert*-butyl alcohol was substituted as the proton source the same experiment afforded pure methyl nonanoate in 92% yield after careful oxidative workup to remove tri-*sec*-butylborane. To determine the synthetic utility of this new enoate reduction we have tested the reaction on a wide variety of structurally diverse α,β-unsaturated esters. Our results are presented below in tabular form (Table VII). In contrast to the results with 2-cyclohexenones, the 1,4 reduction of α,β unsaturated esters seems to be unaffected by alkyl substitution at the β carbon of the conjugated system. Even methyl 3-methylnonenoate (**41**) forms saturated ester **42** in high yield and only a trace of the corresponding allylic alcohol. Reduction is, however, highly sensitive to the extent of π-conjugation, as attempted reduction of methyl sorbate demonstrates. This result suggests that monounsaturated esters might be selectively reduced in the presence of other, more highly conjugated enoates.

It is also apparently for electronic and not steric reasons that methyl cinnamate resists reduction. When the styrene double bond is activated by two electronegative substituents, as in ethyl *p*-nitrocinnamate, it can be reduced with L-Selectride under the usual conditions. Likewise dimethyl succinate can be obtained in acceptable yield from dimethyl fumarate.

Trialkylborohydrides are not very successful in reducing enoates such as **56** and **58** where the conjugated alkene is exo- or endocyclic. Complex mixtures are generally formed in addition to the products reported in experiments 46 and 47. Recovery of starting material in both instances reflects a resistance to reduction which may be due to steric hindrance of the bulky reducing agent by axial hydrogens on the carbocycle. Use of Super-Hydride did not improve this situation and returned mostly (80%) unreacted enoate even after warming to room temperature.[18]

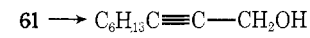
Reduction of α,β-Acetylenic Esters. We have examined the reduction of α,β-acetylenic esters using L-Selectride since intermediates resulting from a single conjugate reduction step would represent versatile acrylate anion synthons such as **63**.[19]



61, R = C_6H_{13}; R′ = CH_3
62, R = H; R′ = C_2H_5

63

A sample of methyl 2-nonynoate (**61**) was prepared by alkylation of the dianion of propiolic acid with 1-bromohexane[20] and subsequent esterification using methyl iodide in HMPA.[21] Reduction of **61** either in the presence of absence of *tert*-butyl alcohol afforded the propargylic alcohol **64** and only traces of



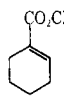
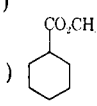
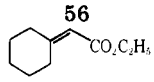
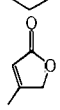
64

methyl nonanoate. This surprising tendency toward nearly exclusive 1,2 reduction was also apparent in the reactions of ethyl propiolate itself. Efforts to reductively alkylate **62** with benzyl bromide in the absence of alcohol furnished good yields of propargyl alcohol and recovered alkylating agent.

Reductive Alkylation of Enoates. When 1,4 reduction of α,β-unsaturated esters predominates, reaction of the intermediate lithium ester enolates with a variety of electrophiles furnishes good yields of monoalkylated products. In these experiments, of course, *tert*-butyl alcohol is omitted from the reducing medium and care must be taken to avoid enolate protonation prior to alkylation. The problematic Claisen condensation of these enolates with starting enoates has already been described; this side reaction occasionally contaminates the desired product. To sidestep this problem we unsuccessfully attempted the conjugate reduction of **34** in the presence of the alkylating agent. Not surprisingly these reactive electrophiles (inter alia methyl iodide, allyl bromide) were preferentially reduced. However as results in Table VIII substantiate, ester dimerization is often negligible with α- or β-alkyl enoates. In those cases yields of reduced, α-alkylated ester are generally quite good. Our results are comparable to those of Rathke and Lindert,[22] who have generated ester enolates by low-temperature metalation of saturated esters using lithium dialkylamides. Enolates derived by this technique and by our own exhibit identical reactivity in these alkylation experiments.

Competitive Reductions. A series of competition experiments was performed using representative carbonyl compounds with the aim of correlating rates of the various reductive processes described in this article. Table IX presents our results. Some of these experiments are complicated by secondary transformations of the reactive intermediates; still a general pattern does emerge. Conjugate reduction of unsaturated ketones and esters seems to be a slower process than the reduction of saturated ketones. Although cyclohexanone is preferentially reduced in the presence of the enone carvone,

Table VII. Reduction of α,β-Unsaturated Esters Using L-Selectride and *tert*-Butyl Alcohol in THF

Expt[a]	Enoate	Time, min	Temp, °C	Product[c] (yield)
36	**34**	20	−70	**36** (92)
37	$C_6H_{13}CH{=}C(CH_3)CO_2CH_3$	20	−70	$C_7H_{15}CH(CH_3)CO_2CH_3$
		30	0	**40** (90)
38	$C_6H_{13}C(CH_3){=}CHCO_2C_2H_5$	60	−70 to 0	$C_6H_{13}CH(CH_3)CH_2CO_2C_2H_5$
	41	15	0	**42** (70)
39	$CH_3CH{=}C(CH_3)CO_2CH_3$	20	−70	$C_2H_5CH(CH_3)CO_2CH_3$
	43	30	0	**44** (70)
40	$(CH_3)_2C{=}CHCO_2C_2H_5$[b]	15	−70 to 0	$(CH_3)_2CHCH_2CO_2C_2H_5$
	45			**46** (70)
41	$(C_2H_5O)_2CHCH{=}CHCO_2C_2H_5$[17]	20	−70	$(C_2H_5O)_2CH(CH_2)_2CO_2C_2H_5$
	47			**48** (92)
42	Methyl cinnamate	20	−70	**49** (29)
	(**49**)	30	0	$PhCH_2CH_2CO_2CH_3$ (27)
				50
43	Ethyl *p*-nitrocinnamate	20	−70	*p*-$NO_2C_6H_4(CH_2)_2CO_2C_2H_5$
	(**51**)			**52** (62)
44	Methyl sorbate (**53**)	20	−70	**53** (>95)
45	Dimethyl fumarate (**54**)	20	−70	Dimethyl succinate
				55 (40)
46		20	−70	**56** (11) 
	56	30	0	**57** (42)
47	 **58**	60	−70 to 0	**58** (72)
48	 **59**	20	−70	**59** (60)  (10)
				60

[a] Enoate in THF (1 M) containing 1.7–3.6 equiv of *tert*-butyl alcohol (note exceptions) added to 1 M L-Selectride (1 equiv) at −78°C. [b] *tert*-Butyl alcohol was omitted in this experiment; 1.5 equiv of Selectride used. [c] Reported yields represent isolated esters after oxidation of tri-*sec*-butylborane. Products were identified by comparison with authentic samples.

this trend is opposed in the corresponding ester series (expt 61) where 1,4 rather than 1,2 reduction predominates.

Experimental Section

Melting points were determined using a Thomas-Hoover Unimelt instrument and are uncorrected. NMR spectra of deuteriochloroform solutions were recorded on a Varian A-60A spectrometer with tetramethylsilane as an internal standard. Ir spectra were determined on a Perkin-Elmer 137 spectrophotometer. Vapor phase chromatographic analyses were carried out on a Hewlett-Packard HP-5750 gas chromatograph using either column A (6-ft 10% Carbowax 20M on 60–80 acid washed Chromosorb W) or column B (6-ft 10% SE-30 on 60–80 acid washed Chromosorb W) with a helium flow rate of 20–25 ml/min. Products were characterized by coinjection using authentic samples.

Unless otherwise noted, all Selectride reductions were performed under nitrogen in a flame-dried or oven-dried (overnight at 105 °C) 50-ml round-bottom flask equipped with a magnetic stir bar and capped with a rubber septum. All air and moisture sensitive solutions were transferred or dispensed using oven-dried hypodermic syringes. Ethereal solvents (diethyl ether and tetrahydrofuran) were distilled under N_2 from $LiAlH_4$. Trialkylborohydrides were used as obtained from Aldrich Chemical Co.: L-Selectride, 1.0 M in THF; K-Selectride, 0.5 M in THF; Superhydride, 1.0 M in THF. All unsaturated carbonyl compounds used in this study were either commercially available or prepared by routine laboratory procedures.[1]

The phrase "oxidative workup" refers to the following procedure: treatment of an ice-cold reaction mixture with 10% NaOH (7 ml) and 30% H_2O_2 (5 ml) followed by stirring overnight at room temperature. The aqueous layer was then separated and extracted three times with hexane (20 ml). The combined organic layers were washed twice with water (20 ml), twice with $NaHSO_3$ solution (20 ml), once with saturated NaCl solution (10 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure.

Reduction of Carvone Using K-Selectride in THF. General Procedure for the Conjugate Reduction of β-Unsubstituted 2-Cyclohexenones. To a dry THF solution (5 ml) of carvone (0.432 g, 2.88 mmol) under N_2 at −78 °C was added 1 equiv of K-Selectride (5.75 ml). After 1 h the low-temperature bath was replaced by an ice bath; oxidative workup afforded 0.422 g (98%) of pure **7** as a colorless liquid, identical with an authentic sample.

In a similar fashion **3** (0.033 g, 0.22 mmol) and K-Selectride (0.44 ml) furnished **4** (0.033 g, 99%), ir (film) 5.85 μ.

Reduction of Carvone Using L-Selectride in THF. A solution of L-Selectride (2.4 ml) was added down the side of a 50-ml round-bottom flask over 5 min to a stirred solution of carvone (0.326 g, 2.4 mmol) in THF (2.4 ml) at −70 °C. After 1 h, the low-temperature bath was replaced with ice–water; oxidative workup afforded 0.327 g (91%) of nearly pure **7**, ir 5.79, 6.02 μ.

Reductive Alkylation of Carvone. Trapping with Methyl Iodide. A solution of **6** (0.350 g, 2.33 mmol) in dry THF (2.3 ml) at −70 °C was treated with L-Selectride (2.3 ml). After 1 h at −70 °C, CH_3I (0.19 ml, 1.3 equiv) was injected by syringe. The cold bath was removed after 5 min and the mixture allowed to warm to room temperature and stir for 1 h. Oxidative workup afforded 0.363 g (95%) of pure **28**: NMR ($CDCl_3$) δ 4.75 (broad s, 2 H), 1.5 (s, 3 H), 1.07 (s, 3 H); ir (film) 5.89, 6.1 μ.

Reductive Alkylation of 2-Cyclohexenones Using L-Selectride and Allyl Bromide. L-Selectride (6.1 ml) was added dropwise to a stirred solution of **8** (0.583 g, 6.1 mmol) in THF (6.1 ml) at −70 °C. After 85 min, allyl bromide (0.8 ml, 1.5 equiv, freshly distilled) was injected and the cold bath removed immediately. After warming to room temperature and stirring for 2.5 h, oxidative workup afforded 0.757 g of product; quantitative VPC analysis (column A, 111 °C) indicated the presence of **9** (4%), **29** (85%), and dialkylated ketone **30** (10%).

Reductive Alkylation of 2-Methyl-2-cyclohexenone Using L-Selectride and Methyl 4-Iodo-*trans*-2-butenoate. To a solution of **32** (0.901 g, 8.18 mmol) in THF (8.2 ml) at −70 °C was added L-Selectride (8.2 ml). After stirring for 20 min at −70 °C, 1.2 ml (1 equiv) of the iodocrotonate was injected and the cold bath removed. Forty-five minutes later the bulk of THF was removed at reduced pressure and replaced with hexane. Oxidative workup, then column chromatography (alumina, Woelm, basic, activity IV) furnished 1.24 g (60%) of **33** as an oil: NMR ($CDCl_3$) δ 5.82 (d, 1 H, J = 14 Hz), 6.6–7.1 (d of t, 1 H), 4.73 (s, 3 H), 1.11 (s, 3 H); ir (film) 5.78–5.82 μ (broad).

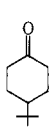
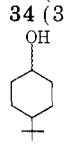
Conjugate Reduction of α,β-Unsaturated Esters. Unless otherwise stated, the reduction of α,β-unsaturated esters using L-Selectride in the presence of *tert*-butyl alcohol was performed by addi-

Table VIII. Reductive Alkylation of α,β-Unsaturated Esters Using L-Selectride in THF

Expt	Enoate[a]	Electrophile	Time, min	Temp, °C	Product (yield)[b]
49	34	CH_3I	20	0	$C_7H_{15}CH(CH_3)CO_2CH_3$ **65** (60)
50	34	$CH_2{=}CHCH_2Br$	20	0	$C_7H_{15}CH(CO_2CH_3)CH_2CH{=}CH_2$ **66** (50)
51	34	C_4H_9I[c]	60	25	$C_7H_{15}CH(C_4H_9)CO_2CH_3$ **67** (63)
52	34	CH_3COCH_3	60	25	$C_7H_{15}CH(CO_2CH_3)C(CH_3)_2OH$ **68** (62)
53	34	$PhCH_2Br$	180	0	$C_7H_{15}CH(CH_2Ph)CO_2CH_3$ **69** (40)
54	39	$CH_2{=}CHCH_2Br$	225	0	$C_7H_{15}C(CH_3)(CO_2CH_3)CH_2CH{=}CH_2$ **70** (75)
55	41	$CH_2{=}CHCH_2Br$	120	0	$C_6H_{13}C(CH_3)(CH_2CH{=}CH_2)CHCO_2C_2H_5$ **71** (60)
56	45	$PhCH_2Br$[c]	150	25	$(CH_3)_2CHCH(CH_2Ph)CO_2C_2H_5$ **72** (50)
57	$CH_2{=}CHCO_2C_2H_5$ **73**	$PhCH_2Br$	150	0	$CH_3CH(CH_2Ph)CO_2C_2H_5$ **74** (18)

[a] Enoate was added to 1.0–1.1 equiv of L-Selectride in THF at −70°C for 20 min. Alkylating agent was subsequently added and reaction completed as described in each case. [b] Yields have not been optimized. All experiments using **34** also afforded 15–20% **38**. [c] In these difficult alkylations the enolate solution was added at room temperature to dry Me_2SO solutions of the alkylating agent (1.5–2.0 equiv).

Table IX. Competitive Reduction of Carbonyl Compounds Using Selectride Reagents

Expt	Carbonyl compds[a]	Selectride	Products (yield)
58	Cyclohexanone (**9**)[b] Carvone (**6**)	K	Cyclohexanol (80) **6** (75)
59	Methyl nonenoate (**34**)[b] Carvone (**6**)	K	**36** (1,4 enoate reduction, 24%) **7** (1,4 enone reduction, 53%)
60	Methyl nonenoate (**34**)  **75**	L	**36** (14) **34** (34)  **76** (33) **75** (19)
61	Methyl nonenoate (**34**) Methyl decanoate (**77**)	L	**36** (54) **34** (17) **77** (65) No 1-decanol

[a] Selectride reagent (1 mmol) was added slowly to a mixture (1 mmol each) of the competing substrates and *t*-BuOH (4 mmol) dissolved in THF (2 ml) at −70 °C under N_2. [b] *t*-BuOH was omitted in this experiment.

tion of a solution of the enoate and dry *tert*-butyl alcohol (2–5 equiv) in dry THF (1 ml/equiv) to a stirred solution of L-Selectride (1 equiv) under nitrogen at −70 °C. Oxidative workup in hexane means removal of THF on a rotatory evaporator, addition of 20 ml of hexane, cooling to 0–5 °C in an ice bath, and treatment with a cold solution of 10% NaOH (1 equiv) and 30% H_2O_2 (2–4 ml). After stirring overnight at room temperature, the aqueous layer was separated and extracted three times with ether (5 ml); the combined organic portions were then washed twice with water (10 ml), once with saturated aqueous sodium bisulfite (10 ml), and once with saturated aqueous sodium chloride

(10 ml), dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator.

Reduction of Methyl 2-Nonenoate (34) Using K-Selectride in THF. K-Selectride (1 equiv, 4.0 ml) was added dropwise down the side of a 50-ml round-bottom flask containing a solution of **34** (0.341 g, 2.0 mmol) in dry THF (4.0 ml) under N_2 at −70 °C. After 2 h, this bath was replaced with a −40 °C slurry of dry ice–isopropyl alcohol. Two hours later, oxidative workup in hexane gave 0.567 g of **38**, nearly pure by VPC (column B, 140–235 °C program): NMR ($CDCl_3$) δ 3.68 (s, 3 H); ir (film) 5.74 μ. This substance gave a positive (blue) ferric chloride test in methanol.

Reduction of 34 Using L-Selectride and *tert*-Butyl Alcohol in THF. A solution of **34** (0.506 g, 2.98 mmol) and *tert*-butyl alcohol (2.5 equiv, 0.555 g) in dry THF (3.0 ml) was added over 5 min to L-Selectride (3.0 ml) at −70 °C. After 20 min, the reaction was quenched with methanol (0.2 ml); oxidative workup in hexane afforded 0.490 g (95%) of nearly pure methyl nonanoate. VPC analysis (column B, 140–230 °C program) indicated 97% purity.

Reduction of Methyl 2-Methyl-2-nonenoate (39) to 40. As described above for **34**, a solution of **39** (0.224 g, 1.2 mmol) and *tert*-butyl alcohol (2.5 equiv) in THF (1.2 ml) was treated with L-Selectride (1.2 ml) for 20 min at −70 °C and 30 min at 0 °C. Oxidative workup in hexane yielded 0.201 g (90%) of pure **40**, identical in every respect with an authentic sample.

The above reductions of **34** and **39** are representative directions for the reduction of enoates **41, 43, 47, 53, 54, 56,** and **58.**

Reduction of Ethyl β,β-Dimethylacrylate (45). A solution of **45** (0.343 g, 2.8 mmol) in dry THF (2.7 ml) was added dropwise to 1.5 equiv of L-Selectride (4.0 ml) at −70 °C. After warming slowly (75 min) to 0 °C the reaction was quenched (methanol) and subjected to oxidative workup in hexane. Recovered was 0.340 g of oil, shown by quantitative VPC analysis (internal standard cyclohexanone) to contain 70% of the desired product **46**, identical in every respect with an authentic sample prepared by catalytic hydrogenation.

Reduction of Methyl Cinnamate (49). Methyl cinnamate (0.406 g, 2.47 mmol) and *tert*-butyl alcohol (2.4 equiv) in THF (2.5 ml) were added slowly to L-Selectride (2.5 ml) at −70 °C. The solution was stirred for 20 min at −70 °C and 30 min at 0 °C. The usual oxidative workup in hexane afforded 0.346 g (84%) of a complex product. VPC analysis (column B, 140–250 °C program) revealed 21 components, two of which were identified as **49** (29%) and reduced ester **50** (27%), by coinjection with authentic samples and by comparison of NMR and ir spectral data.

Reduction of Ethyl *p*-Nitrocinnamate (51). A solution of **51** (0.388 g, 1.76 mmol) and *tert*-butyl alcohol (3.6 equiv) in THF (5 ml) was added slowly to L-Selectride (1.8 ml, 1 equiv) in THF at −70 °C. A bright green color developed immediately. After 20 min methanol (0.2 ml) was added and a deep red-orange color appeared. Oxidative workup in hexane afforded 0.299 g (76%) of red oil. Quantitative VPC analysis indicated 62% of the desired hydrocinnamate **52.** Further proof of structure was obtained by saponification of the crude product mixture (0.171 g) and isolation of *p*-nitrohydrocinnamic acid (0.070 g), mp 166–167 °C (lit. 168 °C[23]).

Reductive Alkylation of Methyl 2-Nonenoate (34) with Methyl Iodide. A solution of **34** (0.416 g, 2.45 mmol) in dry THF (2.4 ml) was added dropwide to L-Selectride (2.4 ml) at −70 °C. After 20 min, methyl iodide (0.18 ml, 1.2 equiv) was injected and the cold bath removed. Oxidative workup in hexane after 3 h at room temperature afforded 0.407 g (89%) of pale yellow oil. Quantitative VPC analysis (column B, 140–230 °C program) indicated a 60% yield of **65** and 24% of **38.**

Reductive Alkylation of 34 with Allyl Bromide. Following the procedure for preparing **65** above, allyl bromide (0.33 ml, 1.5 equiv), **34** (0.433 g, 2.54 mmol), and L-Selectride (2.6 ml) afforded a 50% yield of 4-carbomethoxyundecene (**66**): NMR ($CDCl_3$) δ 4.8–5.2 (m, 3 H), 3.68 (s, 3 H); ir (film) 5.75, 6.10 μ.

Reductive Alkylation of 34 with Acetone. A solution of **34** (0.533 g, 3.14 mmol) in THF (3.1 ml) was added to L-Selectride (3.1 ml) at −70 °C; after 1 h acetone (0.3 ml) was injected. Oxidative workup in hexane afforded 62% of **68:** ir (film) 2.90, 5.76 μ. This material was identical with an authentic sample. Keto ester **38** was also present (17%).

Reductive Alkylation of 34 with *n*-Butyl Iodide in Me_2SO. Methyl 2-nonenoate (0.577 g, 3.4 mmol) in THF (3.4 ml) was added slowly to L-Selectride (3.4 ml) at −70 °C in a 50-ml pear-shaped flask. After 20 min at −70 °C the reaction mixture was transferred by syringe to a solution of *n*-BuI (2 equiv) in Me_2SO (6.8 ml, distilled from CaH_2) at room temperature. The mixture was quenched after 3 h (methanol) and poured into H_2O. The aqueous layer was extracted (5 × 15 ml) with hexane and the combined organic layers washed (5 × 15 ml) with H_2O, once with brine (25 ml) and concentrated at reduced pressure. Oxidative workup in hexane furnished 63% of butylated nonanoate **67** and 11% of keto ester **38.**

Reductive Alkylation of Ethyl β,β-Dimethylacrylate with Benzyl Bromide in Me_2SO. Following the preceding description, **45** (0.326 g, 2.54 mmol) was treated with L-Selectride (3.8 ml, 1.5 equiv) at −70 °C, then the enolate anion injected into a solution of benzyl bromide (0.4 ml, 1.6 equiv) in Me_2SO (6.3 ml) at room temperature. Addition of methanol, extraction, concentration and the usual oxidative workup in hexane afforded a 50% yield of **72** after column chromatography on silica gel using $CHCl_3$–hexane: NMR ($CDCl_3$) δ 7.20 (s, 5 H), 3.98 (q, 2 H, J = 7 Hz), 1.3–3.0 (complex m, 4 H), 1.01 (t, 3 H, J = 7 Hz), 1.01 (d, 6 H, J = 8.0 Hz).

Reduction of Methyl 2-Nonynoate (61) with L-Selectride. To L-Selectride (1.4 ml, 1 equiv) at −70 °C under N_2 was added a solution of **61** (0.234 g, 1.38 mmol) in THF (1.4 ml). After 40 min at −70 °C, oxidative workup in hexane yielded 0.221 g (>90%) of nearly pure **64:** NMR ($CDCl_3$) δ 4.25 (t, 2 H, J = 2 Hz); ir (film) 2.85, 4.4 μ. VPC analysis indicated a trace of methyl nonanoate (**36**).

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Registry No.—**6,** 99-49-0; **28,** 54497-33-5; **32,** 1121-18-2; **33,** 58784-46-6; **34,** 111-79-5; **38,** 56898-41-0; **39,** 56898-36-3; **45,** 638-10-8; **49,** 103-26-4; **51,** 953-26-4; **61,** 111-80-8; **64,** 5921-73-3; **66,** 56898-38-5; **72,** 56898-40-9; L-Selectride, 38721-52-7; K-Selectride, 54575-49-4; Superhydride, 58856-06-7.

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