Representative Metalation and Reduction Reactions of the Superactive Metal Hydrides LiH, NaH, and KH

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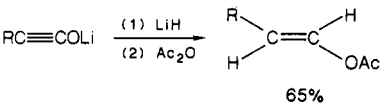
Unusually active alkali metal hydrides, LiH, NaH, and KH, can be prepared easily from hydrogen and superbasic reagents. The synthetic utility of these active hydrides has been explored. Thus, carbonyl and thiocarbonyl compounds, alcohols, dimethyl sulfoxide, and nitriles can be deprotonated. In a number of cases, reduction of the C=O group is an important side reaction with NaH and KH; with LiH, reduction can be the predominant process. Reduction (or addition) also is observed in the reactions of KH with *n*-bromodecane and of LiH with diisopropylcarbodiimide and with lithium phenylethynolate, PhC≡COLi. α,β-Unsaturated aldehydes, C=CCH=O or C≡CCH=O, are converted into the corresponding alcohols by LiH.

Introduction

In contrast to potassium hydride, the reactivity of commercially available lithium hydride and sodium hydride is relatively poor.[1] This reduces the usefulness of these potentially attractive synthetic reagents.[2] Hence, much effort has been spent to activate the commercial hydrides or to prepare reactive forms in other ways. Bank and Prislopski[3] reported an active sodium hydride, prepared by hydrogenation of sodium naphthalenide, which was capable of reducing benzyl chloride to toluene.

Ashby and co-workers[4] obtained active LiH by hydrogenating *tert*-butyllithium under high pressure. The combination of lithium hydride, prepared in this manner, with equimolecular amounts of VCl_3 gave a reagent which reduced aldehydes, ketones, and terminal olefins. Similar experiments have been described by Caubère and Fujisawa, who activated alkali hydrides with metal salts and sodium alcoholates.[5,6] However, a large excess of these activated reagents was needed in order to reduce aldehydes and ketones. Unactivated NaH acted as a reducing reagent only in the cases of difficultly enolizable ketones.[7] The only observed reduction of a C=O group by KH appears to be dimethylformamide.[1d]

Kowalski et al.[8] found that active LiH, formed by elimination from lithiated 1,3- or 1,4-cyclohexadiene, added to alkynolates, RC≡COLi. The intermediates, RCLi=CHOLi, after reaction with a proton source, gave quench products (eq 1).



(1)

Recently we reported the preparation of superactive metal hydrides, LiH, NaH, and KH, by reaction of hydrogen with BuLi·TMEDA or with BuLi, *t*-BuONa(or *t*-BuOK)·TMEDA in hexane,[9] respectively. We have now explored the utility of these hydrides and show them to be very active in deprotonation as well as in reduction.

Reductions. Typical reactions are summarized in Tables I and II. α,β-Unsaturated aldehydes (cf. the reported behavior with LiH/VCl_3)[4] and non- or difficultly enolizable ketones (such as dicyclopropyl ketone) are reduced to alcohols cleanly under very mild conditions. Our active LiH, prepared as described below, also adds to ynolate anions under Kowalski's reaction conditions[8] to produce enol acetates.

Table I. Reduction of Carbonyl Compounds with Active Metal Hydrides

compound	hydride[a]	temp, °C	time, min	% yield[b] of silyltd alcohol
dicyclopropyl ketone	LiH	30	30	96[c]
	KH	RT[e]	15	82[c]
1-cyclooctenaldehyde	LiH	RT	45	96[c]
trans-2-butenal	KH	−40	5	70[d]
trans-cinnamaldehyde	LiH	RT	10	95[c]
2-heptynal	LiH	−20	35	85[c]

[a] The superactive alkali metal hydrides were employed (see Experimental Section). [b] Hexane was used as solvent and trimethylchlorosilane as quench reagent. [c] Isolated compound. [d] Determined by GLC with internal standards. [e] RT = room temperature.

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Table II. Reduction of Other Compounds

compound	hydrde	temp, °C	time, min	quench reagnt	product yield,[a] %	
diisopropyl-carbodiimide	LiH	RT[b]	15	MeI	92	*i*-PrN=CHN(Me)-*i*-Pr
n-bromo-decane	KH	−30	20		95	*n*-decane
PhC≡COLi	LiH	RT	30	Ac_2O	73	enol acetate 1

[a] Isolated compound. [b] RT = room temperature.

Table III. Reaction of Dibromonorcarane (2) with Active Hydrides

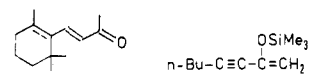
hydrde	reacn conditions: time	reacn conditions: temp	H_2 evolved[a] during the reaction, L	H_2 evolved after the reaction, when H_2O is added, L	yield,[c] % 2	yield,[c] % 3
LiH	1.5 h	reflux	*b*	0.1	23	40
KH	15 min	−90 → 50 °C	1.8	*b*	35	17
KH	15 min	−90 °C	1.0	*b*	42	20
KH	15 min	−30 °C	0.5	1.2	12	10
KH	2 h	50 °C	0.5	0.5	31	40
LiH	2 h	reflux	1.0	0.0	28	40

[a] All reactions were carried out on 0.1-mol scale (at room temperature, 0.1 mol of H_2 has a volume of about 2.3 L). [b] Not measured. [c] Isolated compounds.

Table IV. Metalation of Various Compounds with Active Metal Hydrides

compound	hydrde[a]	temp, °C	time, min	yield, %
cyclododecanone	LiH	35	30	80[b,c]
	NaH	0	15	92[b,c]
3-octyn-2-one	KH	−90	2	65[b,c] (7)[j]
1-phenyl-2-propanone	LiH	RT[i]	15	85[b,c]
1,3-diphenyl-2-propanone	LiH	RT	10	90[c,c]
1,1,3,3-tetraphenyl-2-propanone	LiH	RT	10	90[b,c]
β-ionone (6)[j]	NaH	−40	15	96[b,c]
p-methylacetophenone	LiH	RT	30	70[b,c]
	LiH	40	30	70[b,c]
2,2-diphenylethanal	LiH	30	10	90[b,c]
phenylacetonitrile	LiH	RT	10	78[b,c]
tert-butylacetate	LiH	RT	60	90[c,d]
ethyl phenylacetate	LiH	30	20	70[c,e]
ethyl dithioacetate	LiH	20	10	85[c,f]
dimethyl sulfoxide	LiH	20	5	95[c,g]
3-ethyl-3-pentanol	LiH	RT	1	100[h]
	NaH	RT	1	100[h]
	KH	RT	1	100[h]

[a] The superactive alkali metal hydrides were employed (see Experimental Section). [b] Hexane was used as solvent and trimethylchlorsilane as quench reagent. Yield refers to the silylated products. [c] Isolated product. [d] Condensation product. [e] Condensation product. [f] Quenched with MeI to give CH_2=C(SMe)SEt. [g] Quenched with benzophenone, compound 5. [h] Yield based on hydrogen evolved. [i] RT = room temperature. [j] Structures:



(6) (7)

Diisopropylcarbodiimide also is reduced; after working up with methyl iodide, *i*-PrN=CHN(Me)-*i*-Pr was isolated in 92% yield.

Halides can be reduced with KH. Thus, addition of THF followed by 1-bromodecane to a suspension of KH in hexane (prepared in situ from *t*-BuOK, BuLi, and TMEDA), afforded *n*-decane in 75% isolated yield. However, reaction of these active hydrides with dibromonorcarane (2) was neither very specific nor complete (Table III). The hydrogen formed during the reaction indicated that nucleophilic attack of the hydride ion was not the only reaction and that metalation and/or dehydrohalogenation had occurred.

(2) (3)

Metalation. Metalation takes place under mild conditions and rapidly when ketones with very active hydrogen atoms are employed (Table IV). This is also true for cyclododecanone, a compound where the enolate double bond is hyperstable.[10] Although the low reactivity with *tert*-butyl acetate has been described,[1f] in our case even LiH gave condensation product 4 in high yield (90%). Generation of the methylsulfinyl carbanion took place faster than reported;[11] quenching with benzophenone afforded 95% of the expected adduct 5. Hindered tertiary

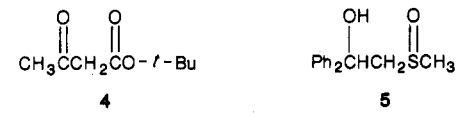


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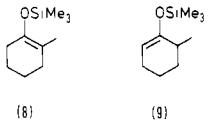
Table V. Competitive Metalation and Reduction of Carbonyl Compounds

compound	hydrde[a]	temp, °C	time, min	tot. yield,[b] %	metaltn[c]	redctn
4-methyl-2-pentanone	KH	RT[d]	5	96	89	11
cyclohexanone	LiH	RT	1	80	40	60
2-methylcyclohexanone	LiH	RT	30	73	58 (8), 17 (9)[e]	25
	NaH	0	12	73	30 (8), 50 (9)[e]	20
	KH	−30	20	95	12 (8), 53 (9)[e]	35
d-(+)-camphor	LiH	35	15	70	50	50
methyl cyclopropyl ketone	LiH	RT	30	82	40	60
phenyl propyl ketone	LiH	RT	10	90	80	20
octanal	LiH	RT	5	96	12	88
cyclohexanaldehyde	LiH	RT	30	95	45	55
	KH	−35	35	88	35	65

[a] Superactive alkali metal hydrides were employed (see Experimental Section). [b] Hexane was used as solvent and trimethylchlorosilane as quench reagent. Yield refers to the total of the silylated products. [c] Percentages determined by GLC and NMR. [d] RT = room temperature. [e] Structures:



(8) (9)

Table VI. Effect of Temperature on the Reaction of *trans*-1-Phenyl-1-buten-3-one with Active Hydrides

hydrde[a]	temp, °C	time, min	yield,[b] %	metaltn[c]	redctn[c]	condnstn[c]
LiH	−20	30	91		71	29
LiH	RT[d]	30	86		90	10
NaH	−40	7	90	91	6	
KH	−20	10	96	75	25	
KH	−60	10	90	92	8	

[a] The superactive alkali metal hydrides were employed (see Experimental Section). [b] The compound was added in ether solution, and the reaction was quenched with trimethylchlorosilane. [c] Determined by GLC and NMR. [d] RT = room temperature.

alcohols have been reported to react vigorously with commercial KH but commercial NaH is nearly inert.[1a] In contrast, 2-ethyl-2-pentanol was metalated instantaneously with all three of the superactive hydrides to give the alcoholate. Hydrogen evolution was complete in less than 1 min.

Metalation and Reduction. All of the carbonyl compounds listed in Table V gave both metalation and reduction products. This contrasts with the results shown in table I and II, where only reduction was observed. Hence, it is difficult to predict the course of each reaction, but the enolate anions of most of the compounds in Table V are not stabilized.

The temperature and metal hydride dependence of the reaction of *trans*-1-phenyl-1-buten-3-one was studied (Table VI). LiH gave predominantly reduction at higher temperatures; reaction with NaH or KH afforded high yields of metalated product.

Comparison of the Active Hydrides. The superactive alkali metal hydrides showed no significant differences in the rate of H_2 evolution as measured by their reaction with dimethyl sulfoxide (Me_2SO) at 0 °C. Conversion to the organometallic derivatives proceeded rapidly (within 1–5 min). In contrast, the commercially available alkali metal hydrides are reported to show enormous differences in the reaction with Me_2SO.[1d] While KH reacted completely, higher temperatures were needed (8 min at 25 °C); NaH gave a conversion less than 20% even at 50 °C, and LiH was inert.

Different rates were found in the reaction of the active hydrides with excess (4 equiv) pyrrolidine. Thus, at 20 °C KH gave complete metalation in 1 min, but under the same conditions LiH reacted more slowly and incompletely (70%). With NaH, only 40% of hydrogen was evolved, but

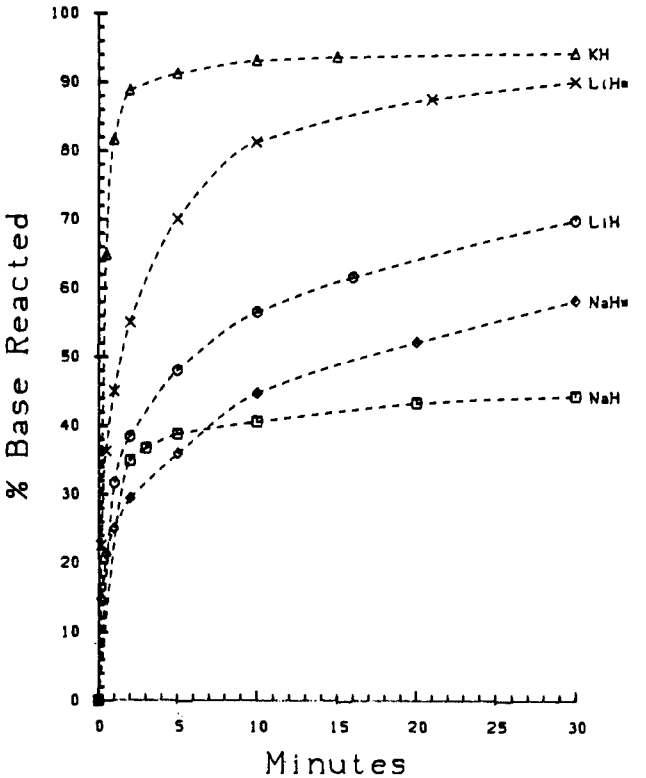


Figure 1. Comparison of the rates of H_2 gas evolution upon reaction of active hydrides with excess pyrrolidine in THF solution at 20 °C. The LiH* and NaH* reactions were carried out in an ultrasound bath and proceed more nearly to completion. When the LiH was prepared in an ultrasound bath, but reacted under normal conditions, the H_2 evolution curve (not shown) was close to that of LiH (rather than to LiH*).

the reaction was essentially over in 1 min. Such incomplete conversions are due to the heterogeneous nature of these processes. After partial conversion, the alkali hydride particle surfaces appear to be covered with metalated products; this prevents further reaction. This assumption is confirmed by ultrasound experiments: the rate and extent of metalation is increased by carrying out the reaction in flasks immersed in an ultrasound bath (Figure 1).[12] The reaction was followed by measuring the hy-

(12) For other examples of the use of ultrasound in organolithium reactions, see: Bonjouk, P.; Sooriyaicumaran, R.; Han, B.-H. *J. Org. Chem.* **1986**, *51*, 2818 and reeferences cited.

drogen evolution at room temperature. As shown in Figure 1 (curves marked with *), the effect of ultrasound on our LiH is quite large. The degree of metalation given by KH is essentially reached after 30 min. The effect of ultrasound on NaH is much less. This may be due to the lower solubility of sodium compounds (generated during the reaction) in organic solvents such as hexane. Ultrasound seems to separate the LiH particles from the soluble lithium compounds so that the reaction can proceed. As shown in Figure 1, it is more important to carry out the reactions in ultrasound than to generate LiH under such conditions.

The influence of the lithium alcoholate present in solution (see preparation of NaH and KH reagents in the Experimental Section) also was investigated. Suspensions of active NaH and KH contained ROLi from the alcoholates, ROM (R = *t*-Bu, *t*-Am; M = Na, K), used in their preparation. ROLi-free NaH and KH suspensions can be obtained if BuNa[13] and BuK[14] are filtered, washed, suspended in hexane–TMEDA, and hydrogenated. However, the reaction with pyrrolidine showed no preparative advantages when the latter reagents were used instead of the ROLi-containing suspension. No appreciably different reactivity (as measured by the rate of hydrogen evolution at 20 °C) was observed when active NaH and KH were prepared either from *t*-AmOH or *t*-BuOM (M = Na, K). However, if pure sodium or potassium derivatives are desired (e.g., for X-ray structural analysis), alcoholate-free NaH or KH may be employed.

The interaction between the metal hydrides, lithium alcoholate and TMEDA may be very complicated and the nature of active species remains to be investigated. We are continuing to examine the properties of the superactive hydrides in order to extend their applications and to clarify the nature of the reagent.

A further advantage of KH, as prepared by our procedure,[9] has been pointed out by a referee. The commercially available KH, which is prepared by the reaction of hydrogen with metallic potassium, has been reported to give variable results.[1d,15,16] This is due to impurities (mainly potassium or its reaction products) in different lots of the hydride, which lead to side reactions and varying yields. Macdonald et al.[16] have treated the crude KH with iodine to obtain potassium-free hydride and constant results. Our superactive metal hydrides contain no alkali metals, and such problems do not arise.

Experimental Section

General. THF and hexane were distilled under argon from potassium and TMEDA (tetramethylethylenediamine) from CaH_2 under argon. *n*-BuLi was used as a 1.6 M solution in hexane (Aldrich). All other starting materials were used as purchased from commercial sources (Aldrich, Janssen), except for the lithium ynolate, which was synthesized as described by Kowalski.[8] IR spectra were recorded on Beckmann Acculab 3 spectrophotometer, ^1H NMR on Jeol JNM-C-60-HL and Jeol JNM-6X-400 spectrometer, MS on a Varian E-4 mass spectrometer, and GC on Perkin-Elmer F21 gas chromatograph with internal standards. For the preparation of the NaH (or KH) reagents, dry ice/acetone was used as cooling bath.

Preparation of the LiH Reagent. TMEDA (0.06 mol) was added to a solution of 0.055 mol of *n*-BuLi in 70 mL of hexane at room temperature. Hydrogen was then introduced with vigorous agitation, while the suspension was kept between 30 and 35 °C. After about 30 min, no more hydrogen was absorbed, and the substrate to be metalated could be added. It is important that the hydrogenation of *n*-BuLi be complete (unreacted *n*-BuLi will react with the substrates employed). Although not necessary, this can be ensured by filtering the precipitated LiH through a glass frit and then adding hexane (and TMEDA if desired) to give a suspension of the reagent.

Preparation of NaH (or KH) Reagents. To obtain fine suspensions of NaH (or KH), a mixture of 0.055 mol of *t*-BuONa (or *t*-BuOK) and 30 mL of dry hexane was cooled to below −20 °C. Dry TMEDA (0.06 mol) was added, followed by a solution of 0.055 mol of *n*-BuLi in about 40 mL of hexane at −30 °C. After 15 min, hydrogen was led through the BuNa (BuK) suspension with very vigorous stirring at such a rate that practically all gas was absorbed. The reactions are markedly exothermic; cooling is needed to keep the temperature between −20 and −25 °C (KH) or −10 and −15 °C (NaH). After about 40 min no more hydrogen was absorbed, and the suspension of the active metal hydrides was ready for the desired reaction.

In this procedure, *t*-BuOLi also is present. However, NaBu and KBu can be obtained pure by filtration;[13,14] suspension in hexane/TMEDA and hydrogenation gave *t*-BuOLi-free NaH and KH.

Reduction of 2-Heptynal. To a suspension of LiH (0.055 mol) was added 0.050 mol of 2-heptynal at −20 °C in ca. 5 min. A very exothermic reaction took place, and a clear solution formed. After the mixture was stirred for an additional 30 min without cooling, 0.6 mol of trimethylchlorsilane was added at −30 °C. The temperature was allowed to rise to 30 °C, and a suspension formed. After quenching with water and four washings with aqueous saturated solution of ammonium chloride, the organic layer was dried over magnesium sulfate and the solvent removed in vacuo. This gave pure 1-[(trimethylsilyl)oxy]-2-heptyne in 85% yield.

Metalation of β-Ionone (6). To a suspension of NaH, (0.055 mol) was added 0.050 mol of β-ionone in 7 mL of THF at −40 °C. Hydrogen evolved. After 15 min, 0.30 mol of trimethylchlorosilane was added, and the temperature was allowed to rise to 0 °C. Aqueous workup afforded a crude product, which after distillation gave the silyl enol ether in 90% yield, bp 81 °C (0.25 mmHg); $n^{21}{}_D$ 1.4972.

Metalation of 3-Octyn-2-one. To a suspension of KH (0.055 mol) was added 0.050 mol of 3-octyn-2-one at −90 °C; 1.1 L of hydrogen evolved immediately. After the very exothermic reaction, 0.06 mol of trimethylchlorosilane was added, and the temperature was allowed to rise to 0 °C. Aqueous workup afforded a crude product, which contained almost pure silyl enol ether **7** in 90% yield. Distillation gave 65% yield, bp 84 °C (15 mmHg), $n^{21}{}_D$ 1.4463.

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Registry No. **1**, 10521-96-7; **2**, 2415-79-4; *exo*-**3**, 1121-41-1; *endo*-**3**, 1121-40-0; **4**, 1694-31-1; **5**, 2863-39-0; **6**, 79-77-6; **6** (metalation product), 35156-36-6; **7**, 109283-55-8; **8**, 19980-35-9; **9**, 19980-33-7; LiH, 7580-67-8; KH, 7693-26-7; NaH, 7646-69-7; dicyclopropyl ketone, 1121-37-5; dicyclopropyl ketone (reduction product), 109283-51-4; 1-cyclooctenaldehyde, 6038-12-6; 1-cyclooctenaldehyde (reduction product), 109283-52-5; *trans*-2-butenal, 123-73-9; *trans*-2-butenal (reduction product), 86739-16-4; *trans*-cinnamaldehyde, 14371-10-9; *trans*-cinnamaldehyde (reduction product), 109283-53-6; 2-heptynal, 1846-67-9; 2-heptynal (reduction product), 76161-88-1; diisopropylcarbodiimide, 693-13-0; diisopropylcarbodiimide (reduction product), 109283-54-7; *n*-bromodecane, 143-15-7; *n*-bromodecane (reduction product), 124-18-5; 2-phenylethyn-1-ol lithium salt, 57015-19-7; cyclododecanone, 1502-06-3; cyclododecanone (metalation product), 51584-36-2; 3-octyn-2-one, 1119-58-0; 1-phenyl-2-propanone, 103-79-7; 1-phenyl-2-propanone (metalation product), 43108-63-0; 1,3-diphenyl-2-propanone, 102-04-5; 1,3-diphenyl-2-propanone (metalation product), 79990-96-8; 1,1,3,3-tetraphenyl-2-propanone,

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7476-11-1; 1,1,3,3-tetraphenyl-2-propanone (metalation product), 109283-56-9; *p*-methylacetophenone, 122-00-9; *p*-methylacetophenone (metalation product), 54731-27-0; 2,2-diphenylethanal, 947-91-1; 2,2-diphenylethanal (metalation product), 107365-24-2; phenylacetonitrile, 140-29-4; phenylacetonitrile (metalation product), 17983-40-3; *tert*-butyl acetate, 540-88-5; ethyl phenylacetate, 101-97-3; ethyl phenylacetate (metalation product), 31491-20-0; ethyl dithioacetate, 870-73-5; ethyl dithioacetate (metalation product), 109283-57-0; dimethyl sulfoxide, 67-68-5; 3-ethyl-3-pentanol, 597-49-9; 3-ethyl-3-pentanol (metalation product), 6689-17-4; 4-methyl-2-pentanone, 108-10-1; 4-methyl-2-pentanone (metalation product), 2346-32-9; 4-methyl-2-pentanone (reduction product), 109283-58-1; cyclohexanone, 108-94-1; cyclohexanone (metalation product), 6651-36-1; cyclohexanone (reduction product), 13871-89-1; 2-methylcyclohexanone, 583-60-8; 2-methylcyclohexanone (reduction product), 109283-59-2; *d*-(+)-camphor, 464-49-3; *d*-(+)-camphor (metalation product), 70982-26-2; *d*-(+)-camphor (reduction product), 74472-21-2; methyl cyclopropyl ketone, 765-43-5; methyl cyclopropyl ketone (metalation product), 42161-96-6; methyl cyclopropyl ketone (reduction production), 85696-56-6; phenyl propyl ketone, 495-40-9; phenyl propyl ketone (metalation product), 84839-88-3; phenyl propyl ketone (reduction product), 72812-50-1; octanal, 124-13-0; octanal (metalation product), 70109-89-6; octanal (reduction product), 14246-16-3; cyclohexanaldehyde, 2043-61-0; cyclohexanaldehyde (metalation product), 53282-55-6; cyclohexanaldehyde (reduction product), 88773-80-2; *trans*-1-phenyl-1-buten-3-one, 1896-62-4; *trans*-1-phenyl-1-buten-3-one (metalation product), 61140-47-4; *trans*-1-phenyl-1-buten-3-one (reduction product), 76987-16-1; benzophenone, 119-61-9.

Synthesis of the Oudemansins, Naturally Occurring β-Methoxyacrylates from Basidomycetes

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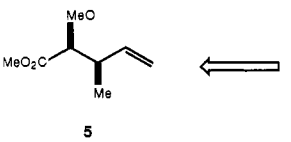
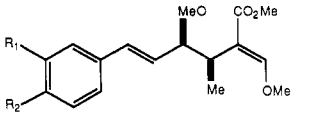
Short, stereocontrolled syntheses of the antifungal metabolites oudemansins A (**1**) and B (**2**) from a common precursor (**5**) are described. Stereospecific olefination of **5** via the β-keto phosphine oxides **12** and **21** affords dienes (*E*)-**7** and (*E*)-**22**, which are transformed to the corresponding styryl esters **14** and **23**. Introduction of the β-methoxyacrylate group by acylation of **14** and **23** with *N*-formylimidazole affords the title compounds exclusively.

Studies of basidomycetes have resulted in the identification of novel metabolites with a broad spectrum of biological activities.[1] Recently, Steglich and co-workers reported the isolation and characterization of four structurally related antibiotics, oudemansins A (**1**)[2] and B (**2**)[3] from mycelial cultures of *Oudemansiella mucida* and strobilurins A (**3**) and B (**4**) from cultures of *Strobilurus tenacellus*.[4] These compounds exhibit antifungal and antibiotic activity and inhibit eukaryotic respiration by blocking cytochrome b–c_1 electron transfer, an activity attributed to the presence of the characteristic β-methoxyacrylate group.[5] This novel biological activity has fostered interest in the oudemansins as synthetic targets, and several routes to oudemansin A have been recorded.[6]

An analysis of the structures of oudemansins A and B suggests that the requisite (*E*)-styryl- and β-methoxyacrylate groups of each could be derived by selective transformation of the terminal functionality of a common synthetic intermediate, ester **5**. This approach has the advantage of allowing a straightforward preparative route to analogues differing at either the styryl or acrylate unit and would facilitate an evaluation of the role of these groups in the biological activity of the parent compounds.

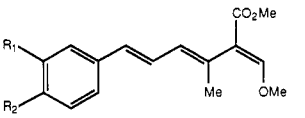


5



1; R_1=R_2=H, oudemansin A

2; R_1=OCH_3, R_2=Cl, oudemansin B



3; R_1=R_2=H, strobilurin A

4; R_1=OCH_3, R_2=Cl, strobilurin B

Our synthetic plan called for initial introduction of the styryl subunit followed by elaboration of the sensitive acrylate system. Herein we detail our studies on the synthesis of the oudemansins, which have resulted in expedient, stereocontrolled routes to **1** and the previously unprepared **2**.[7]

Results and Discussion

Early attempts at introduction of the (*E*)-styryl group of the oudemansins were frustrated by our inability to control the olefin geometry using standard olefination

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