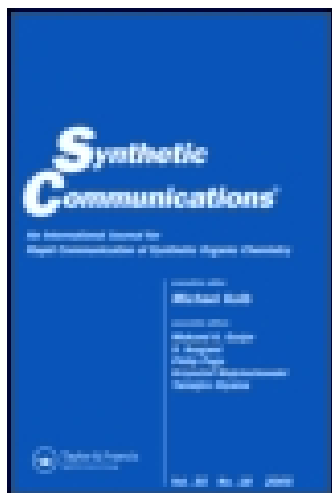


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### Sodium BIS(2- Methoxyethoxy)Aluminium Hydride in Petroleum Ether; A Reagent for the Selective Reduction of Brominated Fatty Esters to Bromo Alcohols

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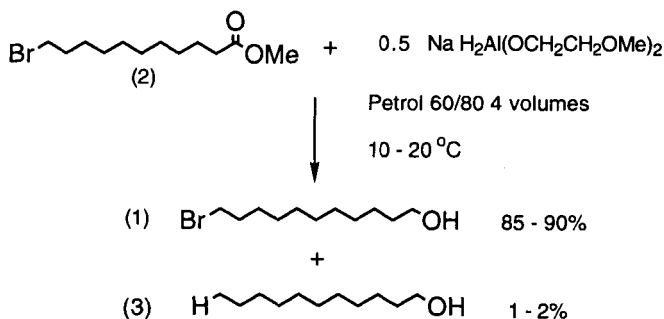
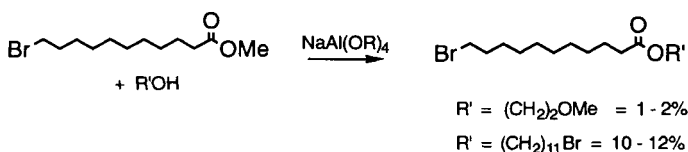
**SODIUM BIS(2-METHOXYETHOXY)ALUMINIUM HYDRIDE IN  
PETROLEUM ETHER; A REAGENT FOR THE SELECTIVE  
REDUCTION OF BROMINATED FATTY ESTERS TO BROMO  
ALCOHOLS**

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**Abstract:** The combination of  $\text{NaH}_2\text{Al}(\text{OCH}_2\text{CH}_2\text{OMe})_2$  / petroleum ether was found to be highly effective for the selective reduction of long chain esters to alcohols in the presence of alkyl bromides.

As a key intermediate in the preparation of a novel pharmaceutical product, 11-bromoundecan-1-ol (1) was required in multi-kilo quantities. It was decided to prepare this material from the readily available 11-bromoundecanoic acid or its methyl ester (2) by the selective reduction of the carbonyl group. This has previously been achieved using  $\text{LiAlH}_4$  in etheral solvents or  $\text{BH}_3$  in THF.<sup>1,2</sup> However, these reactions are volume inefficient since the product is isolated by quenching the reaction into large volumes of aqueous acid. The high cost of oxygenated solvents such as THF and diglyme used with 'in situ' generated  $\text{BH}_3\text{-THF}^3$  can also be prohibitive on a large scale. The pyrophoric nature of  $\text{LiAlH}_4$  is well documented. It was desirable therefore to identify an alternative reducing system that would avoid the problems associated with  $\text{BH}_3$  or  $\text{LiAlH}_4$ . Several alternative reagents have been reported for the reduction of esters in the presence of alkyl bromides, however these were generally too expensive, not available on a commercial scale, very pyrophoric, or possessed the disadvantages described above for  $\text{BH}_3/\text{LiAlH}_4$ .<sup>4</sup> Sodium bis(2-methoxyethoxy) aluminium hydride (Vitride®,

**Scheme 1.****Scheme 2.**

Red-Al<sup>®</sup>) as a 70% solution in toluene does not react rapidly with oxygen and is non-pyrophoric. It has been shown to reduce carboxylic acids and esters,<sup>5</sup> but can also reduce alkyl bromides.<sup>6</sup> It was decided to investigate if Vitride<sup>®</sup> could effect a selective reduction of the carbonyl group in 11-bromoundecanoic acid and the corresponding methyl ester (2).

The initial results with the acid were discouraging. In all solvents examined (toluene, THF, diglyme) contaminant reduction of the primary bromide groups was observed (up to 40%).<sup>7</sup> For the methyl ester (2) a 30% reduction of the bromide groups in diglyme was observed with 70% (1) formed, however a dramatic increase in the degree of selectivity was found in less polar solvents such as t-BuOMe, toluene or, optimally in petroleum ether 60/80. Surprisingly, ester (2) was almost quantitatively reduced to the desired product (1). Analysis by GLC showed only 1-2% undecan-1-ol (3) was produced, a selectivity comparable to BH<sub>3</sub>-THF reduction - Scheme 1.

For optimum results it was found that the reagents should be free from alcohols (MeOH in the case of esters; fresh Vitride<sup>®</sup> to avoid methoxy ethanol contamination). Any alcohols present at the start of the reaction led to the formation

**Table: Reductions of Bromo Esters with  $\text{NaH}_2\text{Al}(\text{OCH}_2\text{CH}_2\text{OMe})_2$** 

Ester	Solvent	Product (5)	Isolated Yield (%)
$\text{Br}(\text{CH}_2)_{10}\text{CO}_2\text{Me}$	A	$\text{Br}(\text{CH}_2)_{11}\text{OH}$	87
$\text{Br}(\text{CH}_2)_4\text{CO}_2\text{Me}$	A	$\text{Br}(\text{CH}_2)_5\text{OH}$	90
$\text{Br}(\text{CH}_2)_3\text{CO}_2\text{Me}$	A	$\text{Br}(\text{CH}_2)_4\text{OH}$	60 +16% desbromo products
$\text{CH}_3(\text{CH}_2)_{11}\text{CBrHCO}_2\text{Et}$	A	$\text{CH}_3(\text{CH}_2)_{11}\text{CBrHCH}_2\text{OH}$	50
$\text{CH}_3\text{CH}_2\text{CBrHCO}_2\text{Me}$	A	Complex Mixture	
p- $\text{BrC}_6\text{H}_4\text{CO}_2\text{Me}$	B	p- $\text{BrC}_6\text{H}_4\text{CH}_2\text{OH}$	~100
$\text{C}_6\text{H}_5\text{CHBrCO}_2\text{Me}$	B	$\text{C}_6\text{H}_5\text{CH}_2\text{CO}_2\text{Me}$	80
p- or o- $\text{BrCH}_2\text{C}_6\text{H}_4\text{CO}_2\text{Me}$	B	p- or o- $\text{CH}_3\text{C}_6\text{H}_4\text{CO}_2\text{Me}$	85-90

A) Petroleum ether 60/80

B) t-BuOMe

of ester by-products (3) and (4). This was traced to the presence of  $\text{NaAl}(\text{OR})_4$  species acting as highly active transesterification catalysts - Scheme 2.

The origin of the high selectivity of the reduction in petroleum ether probably lies in the structure of the aluminium hydride complex in non-polar solvents. Vitride does not dissolve in petroleum ether, but if it is added to solutions of long chain esters in petroleum ether, clear homogeneous solutions are formed. It is likely that the initial stage of the reaction is complexation of one or more ester carbonyl to the aluminium, solubilising the complex as a type of inverse micelle. This would place the alkyl bromide groups far away from any active hydride. Further evidence for this hypothesis comes from the observation that selectivity is reduced as the chain length decreases (see Table).

The reactivity of other bromo esters towards Vitride® in petroleum ether 60/80 or t-butylmethyl ether was briefly examined. The results are presented in the table below. For esters with four or more methylene units between the carbonyl and bromine excellent selectivity was observed. For three or less methylene units

the reduction was less selective. Benzyl bromides were reduced in preference to esters.

In conclusion, the use of Vitride® in petroleum ether 60/80 provides an economical, convenient and highly selective reducing system for certain alkyl esters in the presence of primary bromides, and offers many advantages for large scale preparation when compared to  $\text{LiAlH}_4$  or borane reagents.

## Experimental

Reduction of methyl-11-bromoundecanoate (2):

Methyl-11-bromoundecanoate (206 g, 0.73 mol) was dissolved in petroleum ether 60/80 fraction (825 ml) and the resulting solution cooled to 10°C.  $\text{NaH}_2\text{Al}(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$  (226 ml)<sup>8</sup> of a 70% solution in toluene was added dropwise keeping the temperature between 10-20°C by cooling and adjusting the rate of addition. The  $\text{NaH}_2\text{Al}(\text{OCH}_2\text{CHOC}_2\text{H}_5)_2$  was washed in with toluene (20 ml) and the reaction stirred at room temperature for 10 min. The reaction was quenched by cautiously adding to 5% NaOH solution (250 ml). The resulting mixture was heated to reflux to 10 min, then cooled to 50°C and the layers allowed to separate. The aqueous (lower) layer was removed and the organic layer washed with water (250 ml) at 50°C. After removal of the water the organic layer was dried by Dean & Stark distillation, then filtered hot through Celite. The petrol solution of the product was allowed to cool slowly to 20°C, then cooled to 5°C and stirred for 1 h. The product was filtered off, washed with cold petrol 60/80 (200 ml) and dried in vacuo at ambient temperature. Yield 150 g (87% yield 11-bromo-undecanol based on a 93% purity for the ester starting material).

Other bromo esters were reduced likewise, and after quenching with dilute HCl or NaOH were isolated using standard techniques (crystallisation, column chromatography). The identity of product was confirmed by <sup>1</sup>H NMR (270 MHz), IR and mass spectroscopy.

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- 7) The acid chloride (acid + oxalyl chloride) could be reduced with high selectivity in toluene.
- 8) 2.05 mol equivalents hydride per ester, the use of excess hydride results in rapid reduction of CH<sub>2</sub>Br groups.

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