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ALLERGENIC α-METHYLENE-γ-LACTONES. A SIMPLE METHOD FOR THE INTRODUCTION OF DEUTERIUM IN SESQUITERPENIC α-METHYLENE -γ-BUTYROLACTONES.

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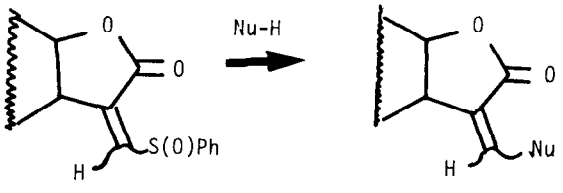
Summary.

Sodium borohydride reduction of sesquiterpene lactone vinylic sulfoxides in a deuterated solvent lead to ^{2}H-labeled natural allergens ; the mechanism of hydride addition is discussed.

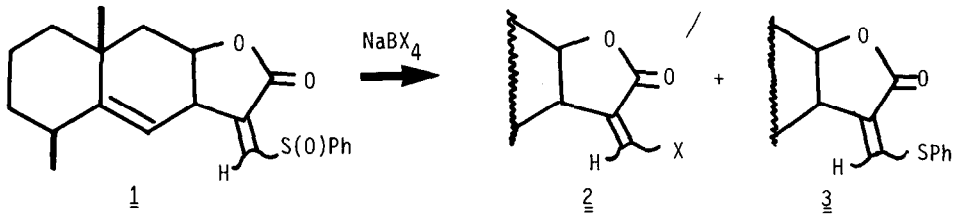
A possible approach to the mechanism of allergic contact dermatitis (ACD)[1,2] is the synthesis of isotope-labeled natural allergens whose fate in the skin can be monitored. For this purpose, we have devised recently two degradation schemes[3,4] of an allergenic sesquiterpene lactone, alantolactone, in order to effect a hemi-synthesis of a ^{14}C-labeled compound. As radioactivity of ^{14}C is very high, histo-pathologists usually prefer ^{3}H which gives clearer histoautoradiograms. We are reporting here a new method for the introduction of a hydrogen isotope in alanto-lactone, the contact sensitizer from *Inula helenium* L. (Elecampane)[5].

During an early investigation on Pummerer rearrangements of sesquiterpene lactone sulfoxides[3], we found that nucleophiles attacked vinylic sulfoxides, in an addition-elimination reaction, eventually leading to the nucleophile-substituted lactone[4] (Scheme I).



SCHEME I

We thought of using this scheme to introduce deuterium (as a model for tritium incorporation), with sodium borodeuteride as the nucleophile (Scheme II).



1 2 3

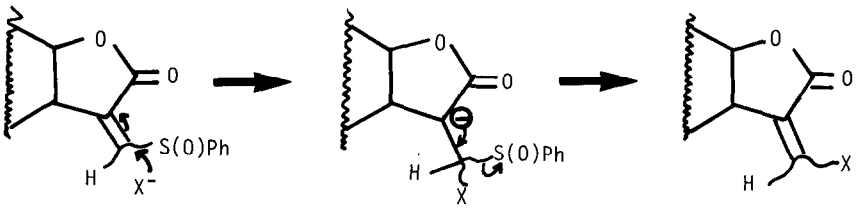
X= H, D, T

SCHEME II

We were encouraged in this direction when we used $NaBH_4$ in a MeOH-H_2O mixture on alantolactone-derived sulfoxide 1 (X=H), prepared as before[3]. Alantolactone 2 (49%, X=H) and sulfide 3 (17%, X=H), a reduction product of the sulfoxide were obtained.

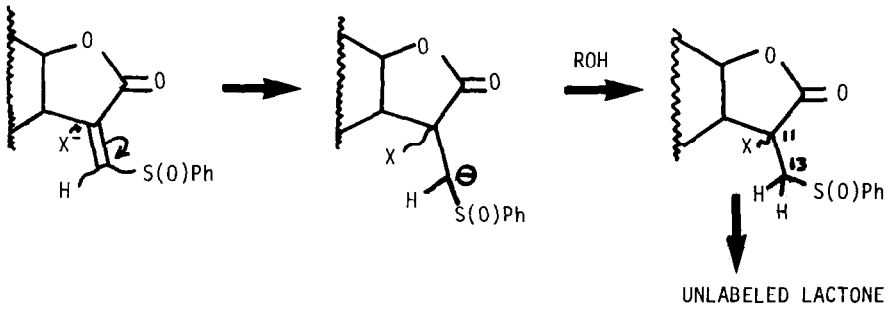
When we used sodium borodeuteride in a MeOH-H_2O mixture, we were surprised to obtain a majority (83:17 ratio) of unlabeled (2, X=H) versus labeled (2, X=D) alantolactone.

According to the expected addition-elimination mechanism, i.e. a Michael addition of X^-, followed by sulfenic acid elimination, we were expecting to get 100% deuterated alantolactone (Scheme III).



SCHEME III

There are, however two possible Michael additions, one based on the γ-lactone electron-withdrawing group (as depicted in Scheme III), another on the phenylsulfoxide electron-withdrawing group (Scheme IV).



SCHEME IV

In the latter case, sulfenic acid is thermally eliminated after a proton is picked up from the solvent and the label (X) is lost. If this scheme is correct, there is no need for an isotope labeled sodium borohydride since the hydrogen introduced in the formed methylene group comes from the solvent. With appropriately chosen solvents, it is therefore possible to label α-methylene-γ-lactones and introduction of a radiolabel only occurs in the last step, a definite advantage when one deals with radioactive material.

We have shown that this was indeed the case by using sodium borohydride and D_2O-MeOD : 55% of deuterium- labeled alantolactone was obtained. The results under different conditions, including the use of sodium borodeuteride,are reported in the Table.

In previously reported reaction of this type with other nucleophiles (e.g. pyrrolidine[4])it is probable that the favored addition on carbon 11 (Scheme IV) was overriden by unfavorable steric effects thus resulting in exclusive addition on carbon 13 (Scheme III).

TABLE. Sodium borohydride and borodeuteride reductions.

Reaction conditions	% Deuterated Alantolactone	% Unlabeled Alantolactone[a,b]	% Vinyl sulfide
$NaBH_4$, CH_3OH, H_2O	0	49	17
$NaBD_4$, CH_3OH, H_2O	0	48	17
$NaBH_4$, $-CH_3OD$, D_2O	55	14	11
$NaBD_4$, CH_3OD-D_2O	65	0	12
$NaBD_4$, D_2O-THF	62	0	17

[a]Isolated yields ; [b]The percentage of labeled vs unlabeled lactone was determined by mass spectrometry (relative intensities of the 232≈$M^{+\cdot}$;unlabeled vs 233≈$M^{+\cdot}$,deuterated, peaks).

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