gave, after chromatography (pentane), **18** (53 mg, 82%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85–2.20 (m (br), 17); ^{13}C NMR (200 MHz, $CDCl_3$) identical with literature.[75]

The column was further eluted (pentane 50%, ethyl acetate 50%) to give compound **7** (73 mg, 86%).

***trans*-4a-Bromodecahydronaphthalene (19).** Sonication of ester **17** (92 mg, 0.32 mmol) in 9.5 mL of carbon tetrachloride and 0.5 mL of bromotrichloromethane gave, after chromatography (pentane), **19** (58 mg, 84.6%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85–2.20 (m (br), 17); ^{13}C NMR (200 MHz, $CDCl_3$) identical with literature.[73] Anal. Calcd for $C_{10}H_{17}Br$: C, 55.31; H, 7.89. Found: C, 55.50; H, 8.07.

***trans*-4a-Iododecahydronaphthalene (20).** Sonication of ester **17** (95.1 mg, 0.33 mmol) and 1.2 equiv of iodoform (155 mg, 0.39 mmol) in 10 mL of carbon tetrachloride gave, after chromatography (pentane), **20** (72 mg, 83.7%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85–2.15 (m (br), 17); ^{13}C NMR (200 MHz, $CDCl_3$) identical with literature.[75]

***cis*-1-Chloro-8-heptadecene (23).** Sonication of ester **22** (141.2 mg, 0.36 mmol) in 10 mL of carbon tetrachloride gave, after chromatography (pentane), **23** (75 mg, 76.2%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.35 (m, 2, H vinyl), 3.53 (t, 2, J = 7 Hz), 2.02 (m (br), 4), 1.78 (tt, 2, J = 7, 7 Hz), 1.28 (m (br), 20), 0.89 (t, 3, J = 7 Hz). Prepared previously.[67]

***cis*-1-Bromo-8-heptadecene (24).** Sonication of the ester **22** (131.8 mg, 0.34 mmol) in 9.5 mL of carbon tetrachloride and 0.5 mL of bromotrichloromethane (15 equivalents) gave, after chromatography (pentane), **24** (90.3 mg, 84.7%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.33 (m, 2, vinyl H), 3.38 (t, 2, J = 7 Hz), 2.00 (m, 4), 1.83 (tt, 2, J = 7, 7 Hz), 1.25 (m (br), 20 H), 0.86 (t, 3, J = 7 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 130.01, 129.60, 57.75, 33.95, 32.82, 31.91, 29.76, 29.62, 29.53, 29.33, 29.06, 28.79, 28.67, 28.15, 27.22, 27.13, 22.71, 14.13. Prepared previously.[67]

The column was further eluted (pentane 50%, ethyl acetate 50%) to give compound **7** (70 mg, 91%).

(6*R*)-7-Bromo-2,6-dimethyl-2-heptene (27). Sonication of ester **26** (107.6 mg, 0.38 mmol) in 10 mL of bromotrichloromethane gave, after chromatography (pentane 50%, ethyl acetate 50%), **27** (65 mg, 82.6%) as a colorless oil: ^{1}H NMR (200 MHz) δ 5.12 (tm, 1, 5, J = 7 Hz), 3.38 (m, 2, 1), 2.05 (m, 2), 1.71 (s, 3), 1.64 (s, 3), 1.20–1.80 (m (br), 3), 1.05 (d, 3, J = 5 Hz). Identical with reported literature spectrum.[76]

The column was further eluted (pentane 50%, ethyl acetate 50%) to give compound **7** (69 mg, 79%).

Sonication of Ester 4 in Chloroform or Methylene Chloride. Ester **4** (0.3 mmol) was dissolved in 10 mL of chloroform or methylene chloride and sonicated during 1 h under an argon atmosphere. A 20 °C water bath was used to maintain the reaction temperature below 35 °C. The reaction was followed by observing the disappearance of the yellow color characteristic of the ester. After chromatography the only compound isolated was acid **1** quantitatively.

A similar experiment executed in deuterochloroform gave acyl chloride **2** as the only identifiable product in the reaction mixture by taking ^{1}H NMR spectra of aliquots during the reaction.

Acknowledgment. This research was supported by National Science Foundation Grant No. 8618303. We are indebted to Professor K. S. Suslick for helpful discussions.

Registry No. **1**, 57-10-3; **2**, 112-67-4; **3**, 15922-78-8; **4**, 89025-67-2; **6**, 4862-03-7; **7**, 66832-24-4; **8**, 89025-53-6; **9**, 629-72-1; **10**, 35599-78-1; **12**, 123540-79-4; *cis*-**13**, 123540-80-7; *trans*-**13**, 123540-86-3; *cis*-**14**, 123540-81-8; *trans*-**14**, 123540-87-4; *cis*-**15**, 123540-82-9; *trans*-**15**, 123540-88-5; **17**, 123540-83-0; **18**, 5597-82-0; **19**, 7731-69-3; **20**, 82823-27-6; **22**, 119520-40-0; **23**, 123540-84-1; **24**, 81861-58-7; **26**, 123540-85-2; **27**, 106130-55-6; CCl_4, 56-23-5; (Z)-$CH_3(CH_2)_7CH{=}CH(CH_2)_7COCl$, 112-77-6; (R)-$(CH_3)_2C{=}CHCH_2CH_2CH(CH_3)CH_2COCl$, 77732-35-5; $BrCCl_3$, 75-62-7; CHI_3, 75-47-8; $CDCl_3$, 865-49-6; decahydro-(1α,4aα,8aα)-naphthalene-1-carbonyl chloride, 123540-78-3; *trans*-4a-decahydronaphthalenecarbonyl chloride, 3021-76-9.

(75) Schneider, H.-J.; Gschwendtner, W. *J. Org. Chem.* **1982**, *47*, 4216.

(76) Barton, D. H. R.; Crich, D.; Kretzschmar, G. *J. Chem. Soc., Perkin Trans. 1* 1986, 39.

Synthesis of Deuterium-Labeled Sesquiterpene Lactones Isolated from *Inula helenium* L.

Marcel Schaeffer, Jean-Luc Stampf, and Claude Benezra*

Laboratoire de Dermatochimie, Associé au CNRS (UA 31), Université Louis Pasteur, Clinique Dermatologique, CHU, 67091 Strasbourg, France

Received May 15, 1989

Reduction of the vinyl sulfoxides **9** and **10** derived from isoalantolactone (**1**) and alantolactone (**2**) with $NaBD_4$ yielded deuterium-labeled lactones **11** and **12**. Amalgam reduction of sulfides **7** and **8** or sulfoxides **9** and **10** gave labeled products but not the expected deuterated lactones **11** and **12**. Satisfactory deuteration of alantolactone **2** could be achieved by CF_3COOD hydrolysis of (tributylstannyl)alantolactone (**23**) obtained in four steps from alantolactone **2**.

Introduction

Allergic contact dermatitis (ACD) to simple chemicals is a dermatologic problem concerning a number of patients in the world. It is believed that the allergy-producing molecules, also called *haptens*, are low molecular weight (~1000 Da maximum) with electrophilic properties, able to bind to nucleophilic groups of skin proteins.[1] The molecular mechanism of ACD is a clue to the understanding of this biological phenomenon and a better knowledge of the factors regulating ACD might enable one to effect prevention. In this respect, availability of isotope-labeled haptens is an important step for the study of hapten–protein interaction ultimately leading to ACD induction.

We have been involved for a number of years now in the synthesis of model α-methylene-γ-butyrolactones for the purpose of uncovering structure–activity relationships, including the stereospecificity of molecular recognition.[2]

(1) Dupuis, G.; Benezra, C. *Allergic Contact Dermatitis to Simple Chemicals: a molecular approach*; Marcel Dekker Inc.: New York, 1982.

(2) (a) Schlewer, G.; Stampf, J. L.; Benezra, C. *J. Med. Chem.* **1980**, *23*, 1031–1038. (b) Corbet, J. P.; Benezra, C. *J. Org. Chem.* **1981**, *46*, 1141–1147. (c) Barbier, P.; Benezra, C. *J. Med. Chem.* **1982**, *25*, 943–946. (d) Barbier, P.; Benezra, C. *J. Org. Chem.* **1983**, *48*, 1141–1147. (e) Mattes, H.; Hamada, K.; Benezra, C. *J. Med. Chem.* **1987**, *30*, 1948–1951.

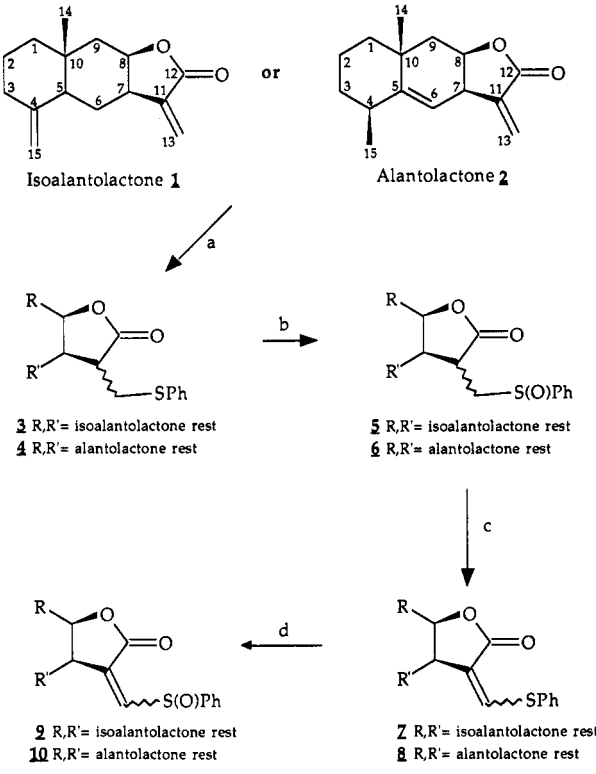
0022-3263/89/1954-6106$01.50/0

Table I. Sodium Borohydride Reduction of Vinyl Sulfoxides 9 (10)

reducing agent	solvent	vinyl sulfoxides	yield, % 1[a] (2)	7 (8)	13 (14)	9 (10)	overall yield, %
$NaBH_4$	$MeOH/H_2O$	10-E,Z (*R*,*S*)	49	17	0	0	66
$NaBH_4$	$MeOD/D_2O$	10-E,Z (*R*,*S*)	35	19	0	25	79
$NaBH_4$	$MeOD/D_2O$	9-Z (*R* or *S*)	69	30	0	0	99
$NaBH_4$	THF/D_2O	9-E (*R*,*S*)	19	21	18	0	58
$NaBH_4$	THF/D_2O	10-E,Z (*R*,*S*)	61	19	0	0	80
$NaBH_4$	THF/D_2O	9-E (*R*,*S*)	17	22	23	0	62

[a] Yields are given for isolated pure products and are calculated from the amount of reacted sulfoxide. 1, 2, α-methylene lactones; 7, 8, vinyl sulfides; 13, 14, methyl lactone; 9, 10, vinyl sulfoxides of isoalantolactone and alantolactone (see Scheme II).

Scheme I



[a] (a) PhS^-Na^+, EtOH; (b) *m*-CPBA, CH_2Cl_2, −15 °C; (c) (1) $(CF_3CO)_2O$, CH_2Cl_2, (2) Et_3N; (d) *m*-CPBA, CH_2Cl_2, −78 °C.

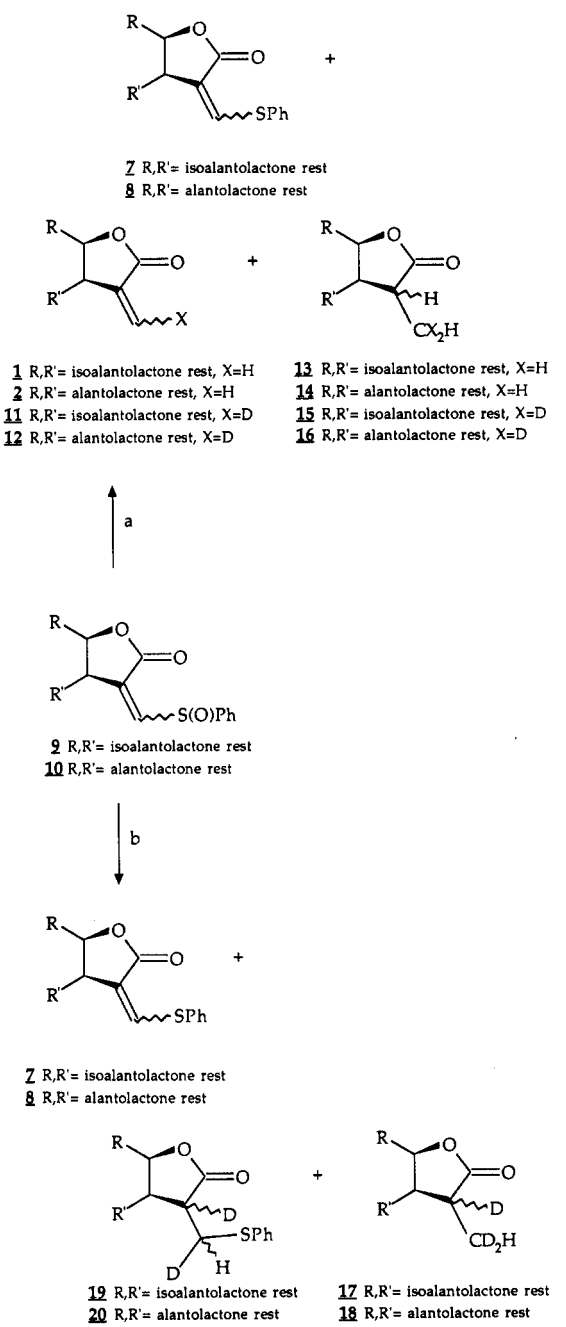
We now describe our efforts to synthesize deuterium-labeled sesquiterpene lactones, isoalantolactone (1) and alantolactone (2), as a model for tritium labeling.

Results and Discussion

Deuterium-Labeled Sesquiterpene Lactones from Vinyl Sulfoxides. (a) Reduction with $NaBD_4$. In previous efforts toward the synthesis of ^{14}C-labeled isoalantolactone 1 (a hapten isolated from a *Compositae* plant, *Inula helenium* L.),[3] we found that vinyl sulfoxides 9 reacted with pyrrolidine to give an enamine.[4] Vinyl sulfoxides 9 (10) were obtained according to Scheme I. The Michael addition of sodium thiophenolate to isoalantolactone (1) and alantolactone (2), respectively, gave 13-thiophenyl-lactones 3 (4) in 95% yields. Oxidation of 3 (4) was done by *m*-CPBA in CH_2Cl_2 to afford the sulfoxides 5 and 6 (*R* or *S* at sulfur), and 5 and 6 (*S* or *R* at sulfur), which were subjected to a modified Pummerer rearrangement[5] to give vinyl sulfides 7-Z (8-Z) and 7-E (8-E) in 80% yield. Oxidation by *m*-CPBA in CH_2Cl_2 afforded the vinyl sulfoxides 9 (10).

By analogy with the addition–elimination reaction described in ref 4, we thought of using sulfoxides 9 (10) to prepare D-labeled lactone in one step, using $NaBD_4$ (Scheme II, path a).

Scheme II



[a] (a) $NaBX_4$, MeOX, X_2O or $NaBX_4$, THF, X_2O (X = H, D); (b) Al–Hg(D), THF or dioxane.

(3) Stampf, J. L.; Benezra, C.; Klecak, G.; Geleick, H.; Schulz, K. H.; Hausen, B. M. *Contact Dermatitis* **1982**, *8*, 16–24.
(4) Corbet, J. P.; Benezra, C. *Can. J. Chem.* **1979**, *57*, 213–217.
(5) Bakuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1985**, 2569–2573.

Table II. Reduction of Vinyl Sulfoxides 9 (10) by Deuterated Complex Hydrides

reducing agent	solvent	vinyl sulfoxides	yield, % 11[a] (12)	7 (8)	15 (16)	9 (10)	overall yield, %
$NaBD_4$	$MeOH/H_2O$	9-E (*R,S*)	28	23	0	28	79
$NaBD_4$	$MeOH/H_2O$	9-Z (*R* or *S*)	27	23	0	40	90
$NaBD_4$	THF/H_2O	9-E (*R,S*)	41	31	7	18	97
$NaBD_4$	THF/H_2O	10-E,Z (*R,S*)	48	29	17	0	94
$NaBD_4$	THF/D_2O	9-E (*R,S*)	22	12	0	28	61
$NaBD_4$	THF/D_2O	10-Z (*R,S*)	35	15	0	31	81
$LiAlD_4$[b]	THF/H_2O	10-E,Z (*R,S*)	23	0	0	37	60

[a] Yields are given for isolated pure products and are calculated from the amount of reacted sulfoxide. 11, 12, deuterated α-methylene lactones; 7, 8, vinyl sulfides; 15, 16, dideuterolactone; 9, 10, vinyl sulfoxides (see Scheme II). [b] Reaction carried out at −78 °C.

Table III. Desulfuration Using Deuterated Aluminum Amalgam

starting material	equiv Al	time, h	solvent	*t*, °C	yield, % 11[b] (12)	7 (8)	17 (18)	19 (20)	overall yield, %
9-E (*R,S*)	32	24	THF	4	0	0	70	15	85
		4		rt[a]	0	0	69	0	69
9-E (*R,S*)	32	48	dioxane	rt[a]			no reaction		
9-E (*R,S*)	2	4	dioxane	rt[a]	29	44	26	0	99
	2	18	dioxane	rt[a]			no reaction		
9-E (*R,S*)	4.5	24	THF	4	0	29	17	29	75
	3	48	THF	4	0	0	51	37	88
8-E,Z (*R,S*)	4	72	THF	4					

[a] Room temperature. [b] Yields are given for pure isolated products. 11, 12, α-methylenelactone; 7, 8, vinyl sulfides; 17, 18, trideuteriolactones; 9, vinyl sulfoxides or isoalantolactone; 19, 20, 13-(phenylthio)dideuteriolactones (see Scheme II).

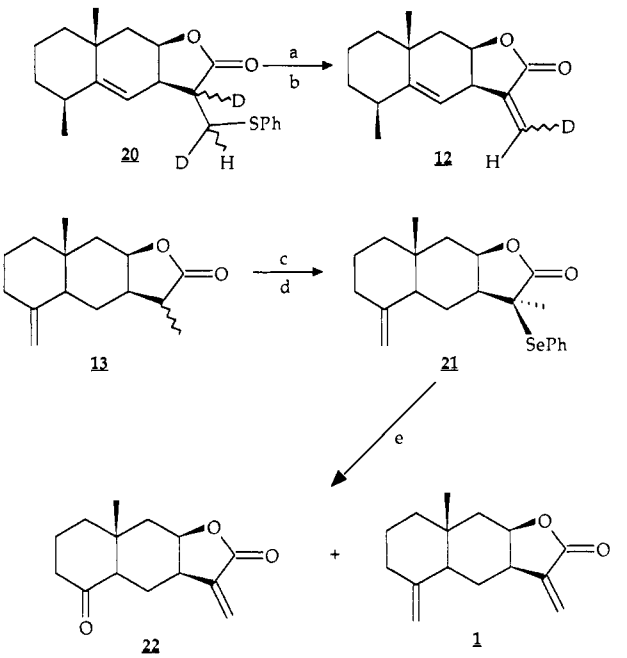
To test the reaction conditions, we first treated the sulfoxides 9 (10) with $NaBH_4$ in $MeOH/H_2O$, $MeOD/D_2O$, and THF/D_2O. A mixture of three compounds was obtained in most cases: the expected lactones 1 (2) along with the sulfides 7 (8) (a result of sulfoxide reduction) and the reduced dihydro lactones 13 (14) (see Table I). Reaction time was 10–15 min; longer reaction times yielded almost exclusively dihydro lactones 13 (14). When sodium borohydride reduction was done in the presence of a deuterated solvent, no deuterated α-methylene-γ-butyrolactones 11 (12) (within the limit of detection of 200-MHz ^1H NMR) were observed.

When sulfoxides 9 (10) were treated with $NaBD_4$ in $MeOH/H_2O$, THF/H_2O, or THF/D_2O, a mixture of three compounds was again obtained: the expected deuterated lactones 11 (12) (1 ^2H at C-13) along with the sulfides 7 (8) and the reduced dideuterio lactones 15 (16) (2 ^2H at C-13) (see Table II). Reaction time was 120–150 min.

(b) Reduction with an Aluminum Amalgam. Reduction of isoalantolactone or alantolactone sulfoxides also could be achieved with an aluminum amalgam.[6,7] When the reaction was carried out according to Corey conditions[7] (32 equiv of aluminum/sulfoxide), sulfoxides 9 (10) reacted smoothly to give dihydro lactones 13 (14) in nearly quantitative yields (94%).

Reduction of isoalantolactone or alantolactone sulfoxides also could be achieved with an aluminum amalgam prepared using deuterated water.[6] Three compounds were again obtained when a small ratio of reagents (equivalents aluminum/sulfoxides 9 (10) = 2–5) was used: the same sulfides 7 (8) as for sodium borodeuteride reduction were obtained, as well as two perdeuterated compounds, hydrogenated trideuterio lactones 17 (18) (1 ^2H at C-11, 2 ^2H at C-13) and dideuterio sulfides 19 (20) (1 ^2H at C-11, 1 ^2H at C-13) (Scheme II, path b). The percentages of the different compounds varied with reaction time and equivalents of amalgam used (see Table III). The α-methylene lactones 11 (12) were formed as an intermediate

Scheme III

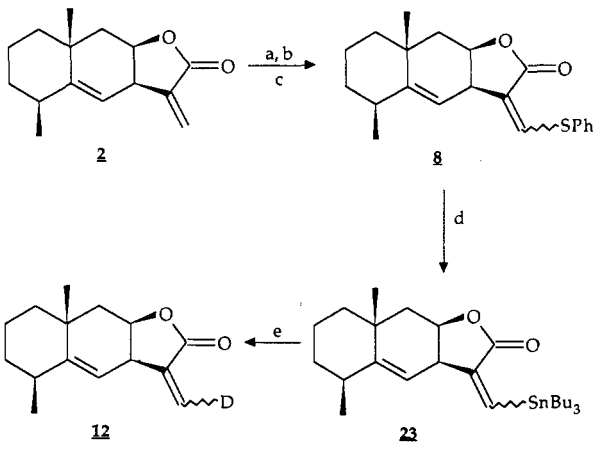


[a] (a) *m*-CPBA, CH_2Cl_2, −15 °C; (b) toluene, reflux; (c) LiICA, THF; (d) PhSeCl; (e) H_2O_2, H_2O, CH_2Cl_2.

product (as shown by TLC) and further reacted. Deuterated isoalantolactone 11 could be isolated in one experiment, but we were unable to determine the conditions where the maximum of the α-methylene lactone in the mixture is present because the reaction was not reproducible. Although the same reaction conditions were used (see the Experimental Section), the reaction did not proceed in some cases. The reaction mixture was then filtered, the solvent was evaporated, and the crude reaction mixture was treated once again with amalgam. Reaction then generally proceeded smoothly. However, it was observed that the average percentage of a product could change tremendously, and therefore some results were not reproducible.

(6) Sawada, S.; Nakayama, T.; Esaki, N.; Tanaka, H.; Soda, K.; Hill, R. K. *J. Org. Chem.* **1986**, *51*, 3384–3386.
(7) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1964**, 1639–1640.

Scheme IV

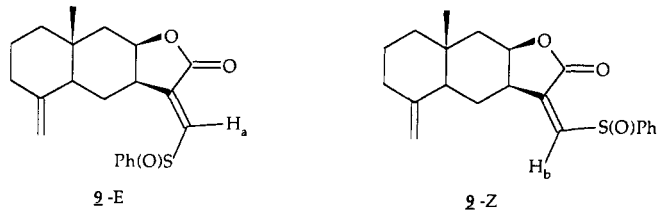


2 8 12 23

[a] (a) PhS^-Na^+, EtOH; (b) *m*-CPBA, CH_2Cl_2, −15 °C; (c) (1) $(CF_3CO)_2O$, CH_2Cl_2, (2) Et_3N; (d) Bu_3SnH, AIBN, toluene, reflux; (e) $(CF_3CO)_2O$, D_2O, toluene, reflux.

Although, at first sight this reaction is of little synthetic interest for the preparation of deuterium (and eventually tritium) labeled compounds, products **20** and **13** could be transformed into the desired labeled α-methylene-γ-butyrolactones by well-known chemistry through: (a) oxidation–elimination of **20**[8] into **12** (Scheme III) [A 1:1 mixture of *E* and *Z* deuterium-labeled alantolactone **12** was obtained in 33% yield by oxidation of the crude reaction mixture (resulting from treatment of vinylsulfides **8** by deuterated amalgam) with *m*-CPBA and subsequent thermal elimination]; (b) introduction of a phenylselenoxide α to the lactone group of **13** and thermal elimination[9-11] (Scheme III). Interesting to note is the finding that, along with the expected isoalantolactone (**1**) (42%), PhSeOH elimination also led to a C-4 norisoalantolactone **22** with a keto group at C-4 (55%) when the reaction was done in CH_2Cl_2, H_2O_2, H_2O. A possible interpretation of this result is that the produced selenic acid PhSeOH could have been transformed through H_2O_2 peroxidation (used to make the phenylselenoxide) into a hydroperoxidic acid PhSeOOH. This in turn, could have oxidized the exomethylidene bond at C-4, resulting in formic acid loss and formation of the C-4 keto group. When the elimination was done in THF and H_2O_2, isoalantolactone **1** was the major product (77%), along with a small amount of the corresponding butenolide.[10]

Deuterium-Labeled Compounds from Tributyltin Derivatives. Tin derivatives **23-Z** and **23-E** (Scheme IV) were obtained from sulfides **8-Z** and **8-E** (see Scheme I) by a radical reaction involving tributyltin hydride in the presence of AIBN.[12] As the C–Sn bond can be easily cleaved by a strong[13] or moderately strong acid,[14,15] we intended to use the latter reaction to introduce a deuterium atom into the α-methylene group of alantolactone (**2**). When the vinyl sulfide **8-Z** derived from alantolactone (**2**) was treated with Bu_3SnH and AIBN in toluene, tributyltin derivative **23-Z** was obtained in 74% yield. When the vinyl sulfide **8-E**, derived from alantolactone (**2**) was treated with Bu_3SnH and AIBN in toluene, tributyltin derivative **23-E** was obtained in very small amounts, tributyltin derivative **23-Z** being the major reaction product. The tributyltin derivatives were reacted with trifluoroacetic anhydride in the presence of D_2O. Deuterium-labeled alantolactone **12** was obtained with a 84% overall yield (Scheme IV). This method can then be used for introducing radioactive isotope using tritiated water.[16] The acid deuterolysis of the tributyltin derivative **23-Z** led to a 6:1 mixture of deuterated alantolactone **12-Z** and **12-E**, the major isomer corresponding to *retention* of configuration at the double bond. Reduction under the same conditions of stereoisomers **23-E** lead again to a 6:1 mixture of **12-E** and **12-Z**, again with predominating retention of configuration at the double bond.



9-E **9**-Z

Figure 1. *E*- and *Z*-vinyl sulfoxides derived from isoalantolactone.

Table IV. Stereochemistry of Sodium Borodeuteride Reduction

reducing agent and solvents	vinyl sulfoxides	D_b/D_a[a]	retention, %	inversion, %
$NaBD_4/MeOH/H_2O$	**9**-E (*R*,*S*)	2	66	34
$NaBD_4/MeOH/H_2O$	**9**-Z* (*R* or *S*)	0.4	71	29
$NaBD_4/THF/H_2O$	**9**-E (*R*,*S*)	3.3	77	23
$NaBD_4/THF/D_2O$	**9**-E (*R*,*S*)	3.3	77	23
$NaBD_4/MeOD/D_2O$	**10**-Z (*R*,*S*)	0.4	71	29

[a] Ratio D_b/D_a determined by 200-MHz ^1H NMR; E is a mixture (*R*,*S*) at sulfur; Z is a mixture (*R*,*S*) at sulfur; Z* is a pure enantiomer at sulfur.

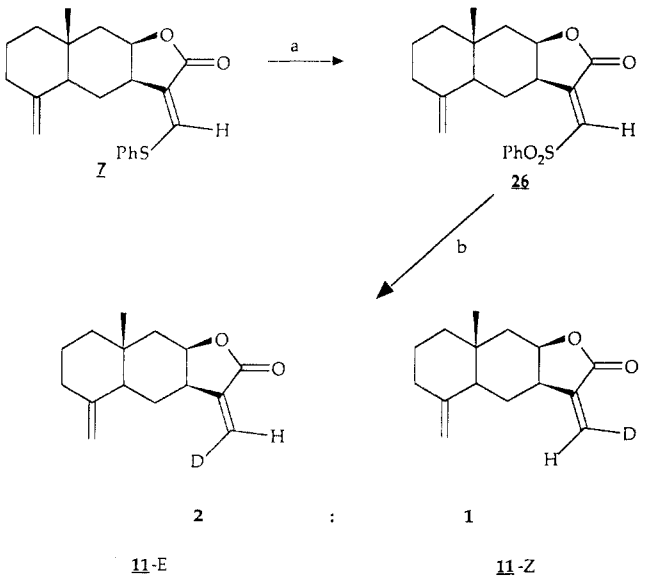
Stereochemistry of Sodium Borohydride Reduction of Vinyl Sulfoxides. *E* and *Z* isomers of isoalantolactone as well as alantolactone sulfoxides **9** (**10**) could be separated by flash chromatography (see Figure 1). Stereoisomers at sulfur (*R* and *S*) could only be separated in the case of the *Z* isomer.

Configurations were determined by NMR; for isoalantolactone the signal for H_{13a} (lying in the deshielding cone of the carbonyl) occurs at lower field (δ = 6.13 ppm) than H_{13b}, anti to the lactone group (δ = 5.59 ppm). Presence of stereoisomers at the sulfoxide center was shown by the splitting of the H_{13} signals.

Sodium borohydride reduction of stereoisomer *E* (*R* + *S* mixture at sulfur) led to a 2:1 mixture of deuterated lactones **11-E** (**12-E**) and **11-Z** (**12-Z**), the major isomer corresponding to *retention* of configuration at the double bond. Reduction under the same conditions of stereoisomers *Z* led again to a 2:1 mixture of **11-Z** (**12-Z**) and **11-E** (**12-E**), once more with predominating retention of configuration at the double bond (see Table IV).

(8) Grieco, P. A.; Miyashita, M. *J. Org. Chem.* **1975**, *40*, 1181–1183.
(9) Greico, P. A.; Miyashita, M. *J. Org. Chem.* **1975**, *39*, 120–122.
(10) Stampf, J. L. D.Sc. Thesis, Université Louis Pasteur, Strasbourg, 1983.
(11) Rathke, M. W., Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318–2320.
(12) Schmidt, R. R.; Betz, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 430–431.
(13) Seyferth, D. *J. Am. Chem. Soc.* **1957**, *79*, 2133–2135.
(14) Cochran, J. C.; Bayer, S. C.; Bilbo, J. T.; Brown, M. S.; Colen, L. B.; Gaspirini, F. J.; Goldsmith, D. W.; Jamin, M. D.; Nealy, K. A.; Resnick, C. T.; Schwartz, G. J.; Short, W. M.; Skarda, K. R.; Spring, J. P.; Strauss, W. L. *Organometallics* **1982**, *7*, 586–590.
(15) Asomaning, W. A.; Eaborn, C.; Walton, D. R. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 137–138.
(16) Seitz, D. E.; Milius, R. A.; El-Wakil, H. *Synth. Commun.* **1981**, *11*, 281–286.

Scheme V



[a] (a) Oxone, THF, H_2O, 72 h at 4 °C; (b) $NaBD_4$, THF, D_2O.

Apparently configuration at sulfur does not influence the stereochemical course of the reaction, in contrast to a recent report in the literature[17] (in our case, however, there are two electron-withdrawing groups at the double bond). Moreover, reduction of the sulfone **26** derived from isoalantolactone (**1**) (Scheme V) by sodium borodeuteride gave the same 2:1 retention to inversion ratio than the reduction of the corresponding sulfoxides **9**.

Discussion of Mechanism. Supposing that the trans addition onto the vinyl sulfoxide **9** occurred with an sp^2 intermediate: four conformer intermediates can be envisaged (Scheme VI). Conformations **25**-S and **25**-R are unfavorable for the trans elimination as the bulky phenylthiono group is syn to the remainder of the molecule. A more favorable arrangement is present in the anti conformation (with respect to the π-system and the C–S bond). If one considers these two favorable conformations, **24**-R and **24**-S, they lead to both *retention* and *inversion*.

The net result of the addition–elimination reaction with $NaBD_4$ is a 2:1 ratio in favor of retention.

Preliminary results from this laboratory concerning borohydride reduction of vinyl sulfoxides[18] could not be reproduced in this work, where all reactions were repeated more than three times, all assays giving the same results.

Conclusion

In conclusion, the desired deuterium-labeled isoalantolactone **11** or alantolactone **12** could be obtained by the reduction of vinyl sulfoxide with labeled sodium borohydride. This method, which presents the advantage of introducing the label in the last step of the synthesis, probably would not work with tritium-labeled sodium borohydride, because a strong isotope effect is expected for tritiation and therefore a substantial tritiation is probably unlikely.

Acid hydrolysis of tributylstannyl lactones **23** proved to be a very clean and stereoselective method for the introduction of a hydrogen isotope in the α-methylene part of sesquiterpene lactones. By this method, the label is introduced in the last step of the synthesis, and originates from a labeled solvent.

Experimental Section

General Methods. Proton NMR spectra of samples were recorded on 60-MHz Perkin-Elmer and 200-MHz Brucker spectrometers in $CDCl_3$. Chemical shifts (δ) are indicated in ppm with respect to TMS as internal standard ($\delta = 0$). Infrared spectra were obtained on a Beckman Acculab spectrometer with $CHCl_3$ solutions. Melting points were determined on a Büchi Tottoli 510 apparatus and are uncorrected. Mass spectra were recorded on a LKB 9000 S spectrometer. Dry solvents were freshly distilled before use. Tetrahydrofuran (THF) was distilled from sodium benzophenone. Dichloromethane was distilled from P_2O_5. Bu_3SnH, $(CF_3CO)_2O$, oxone as well as gold label MeOD and D_2O were purchased from Aldrich; *m*-CPBA was 80% pure and was purchased from Aldrich. All air- and moisture-sensitive reactions were conducted in flame-dried glassware under an atmosphere of dry argon. Flash chromatographic purifications on silica gel columns were used.

13-(Phenylthio)alantolactone (4). A solution of alantolactone (**2**)[3,19] (1.941 g, 6.4 mmol) in ethanol (28 mL) was added to a solution of sodium thiophenoxide in anhydrous ethanol [NaSPh was prepared from PhSH (1.9 mL, 17.3 mmol) and sodium, 185 mg, 7.9 mmol]. The mixture was stirred at room temperature for 2 h and quenched with 1 N HCl. After extraction with CH_2Cl_2, drying on $MgSO_4$, and evaporation of the solvents, a white solid was obtained. Chromatography over silica gel [(1) hexane, (2) hexane/ether, 7/3] yielded pure **4** (2.09 g, 6.1 mmol). Yield: 95%. Mp: 120–121 °C. IR (cm^{-1}): 1765, 1640, 1580. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.43–7.23 (5 H, m, Ph), 5.31 (1 H, d, $J_{H\text{-}6,H\text{-}7} = 3.2$, H-6), 4.74–4.68 (1 H, m, H-8), 3.52 (1 H, dd, H-11), 3.25–3.16 (1 H, m, H-7), 3.04–2.79 (2 H, m, CH_2-13), 2.55–2.40 (1 H, m, H-4), 2.24 and 2.20 (1 H, A part of an q AB, $J_{AB} = 13$, $J_{H\text{-}9\alpha,H\text{-}8} = 3$, H-9$\alpha$), 1.24 (3 H, s, Me-10), 1.12 (3 H, d, $J_{H\text{-}15,H\text{-}4} = 7.6$, Me-4). $C_{21}H_{26}O_2S$. MS: *m/e* 342 ($M^{\cdot+}$). Anal. Calcd for $C_{21}H_{26}O_2S$: C, 73.64; H, 7.65. Found: C, 73.51; H, 7.79.

13-(Phenylthio)isoalantolactone (3). Preparation: see **4** (from isoalantolactone (**1**)[3,19] (1.042 g, 4.5 mmol) one obtains **3** (1.470 g, 4.3 mmol), yield 95%). Spectroscopic data (^1H NMR, IR, melting point) as described.[4]

Sulfoxides of Alantolactone 6. To a solution of sulfides **4** (1.247 g, 3.6 mmol) in CH_2Cl_2 (90 mL) was added at −15 °C under argon a solution of *m*-CPBA (772 mg, 4 mmol) in CH_2Cl_2 (90 mL) during 2 h. The reaction mixture was then allowed to raise to −5 °C and was quenched with a 10% aqueous $NaHCO_3$ solution. After extraction with CH_2Cl_2, drying over $MgSO_4$, and removal of the solvents, a colorless oil was obtained. Flash chromatography (hexane/ether, 1:9) yielded pure **6** (a 1:1 mixture of *R* and *S* at sulfur) (1.097 g, 3.1 mmol). Yield: 85%.

Sulfoxide of Alantolactone 6 (*R* or *S* at Sulfur, White Crystals). Mp: 128–129 °C. IR (cm^{-1}): 1760, 1650, 1580, 1160. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.67–7.53 (5 H, m, Ph), 5.35 (1 H, d, $J_{H\text{-}6,H\text{-}7} = 3.1$, H-6), 4.80–4.76 (1 H, m, H-8), 3.45–3.35 (1 H, m, H-11), 3.25–3.09 (3 H, m, H-7 and CH_2-13), 2.60–2.45 (1 H, m, H-4), 2.16 and 2.09 (1 H, A part of an q AB, $J_{AB} = 13$, $J_{H\text{-}9\alpha,H\text{-}8} = 3$, H-9$\alpha$), 1.22 (3 H, s, Me-10), 1.14 (3 H, d, $J_{H\text{-}15,H\text{-}4} = 7.6$, Me-4).

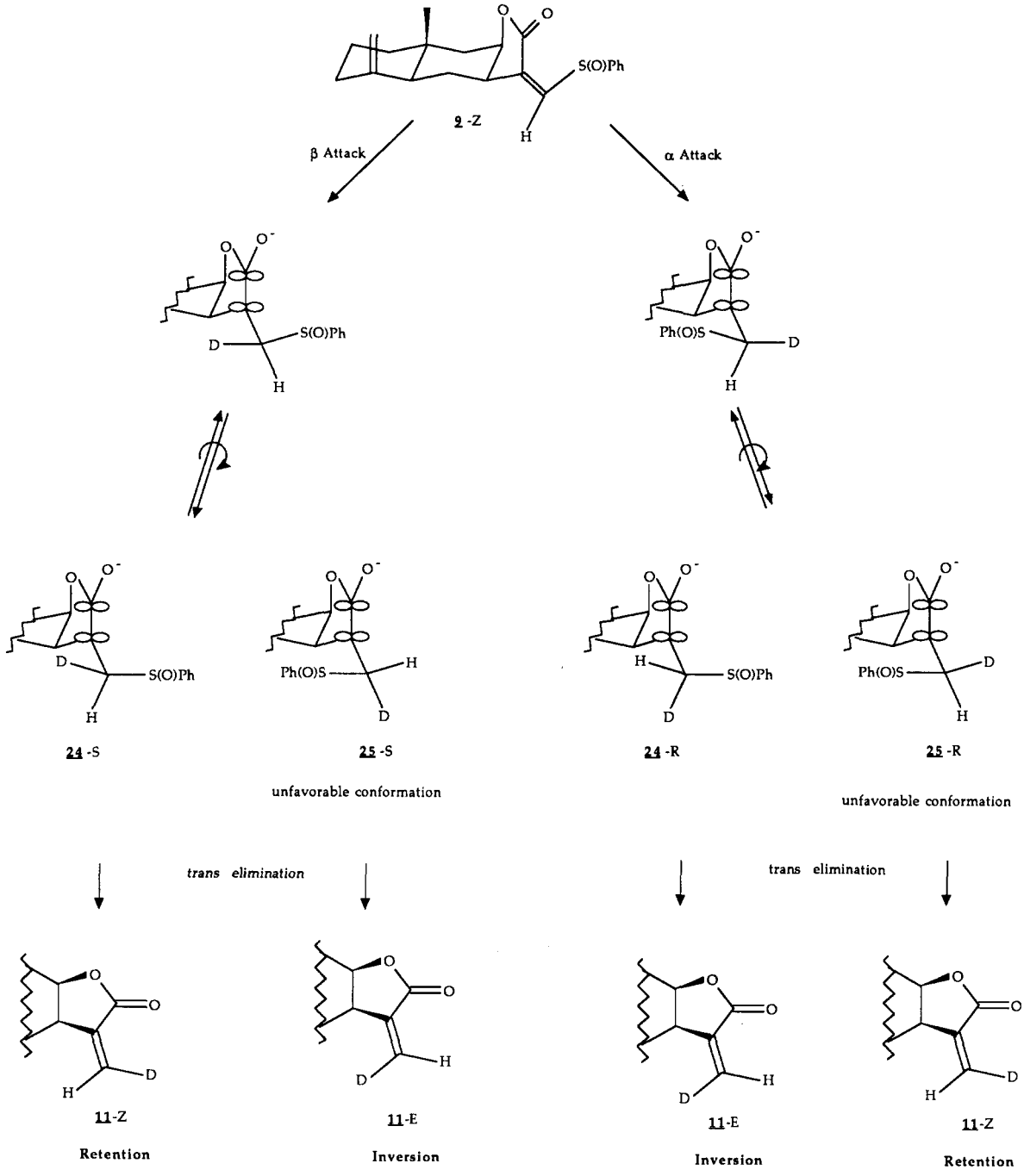
Sulfoxide of Alantolactone 6 (*S* or *R* at Sulfur, Colorless Oil). IR (cm^{-1}): 1760, 1645, 1580, 1160. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.73–7.54 (5 H, m, Ph), 4.99 (1 H, d, $J_{H\text{-}6,H\text{-}7} = 3.0$, H-6), 4.85–4.78 (1 H, m, H-8), 3.50–3.30 (1 H, m, H-11), 3.25–2.95 (3 H, m, H-7 and CH_2-13), 2.55–2.35 (1 H, m, H-4), 2.15 and 2.08 (1 H, A part of an q AB, $J_{AB} = 13$, $J_{H\text{-}9\alpha,H\text{-}8} = 3$, H-9$\alpha$), 1.20 (3 H, s, Me-10), 1.06 (3 H, d, $J_{H\text{-}15,H\text{-}4} = 7.6$, Me-4). Anal. Calcd for $C_{21}H_{26}O_3S$: C, 70.36; H, 7.31. Found: C, 70.29; H, 7.48.

Sulfoxides of Isoalantolactone 5. Preparation: see **6** (from **3** (1.300 g, 3.8 mmol) one obtains **5** (1.226 g, 3.4 mmol), yield 89%). Spectroscopic data (^1H NMR, IR, melting point) as described.[4]

Vinyl Sulfides of Alantolactone 8. To a solution of sulfoxides **6** (*R* or *S* at sulfur) (1.016 g, 2.8 mmol) in freshly distilled CH_2Cl_2 (12 mL) was added at 0 °C under argon trifluoroacetic

(17) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7399–7400.
(18) Stampf, J. L.; Benezra, C. *Tetrahedron Lett.* **1984**, 3917–3920.
(19) Yoshioka, H.; Mabry, T. J.; Timmermann, B. N. *Sesquiterpene Lactones*; University of Tokyo Press: Tokyo, 1973.

Scheme VI. Mechanism Involving an sp^2 Intermediate



anhydride (TFAA) (1 mL, 7.1 mmol). The reaction was allowed to reach room temperature, and stirring was continued during 3 h. Then triethylamine (1 mL, 7.2 mmol) was added at 0 °C under argon. After 2 h of stirring at room temperature, 1 N HCl (5 mL) was added. After extraction with CH_2Cl_2, drying over $MgSO_4$, and evaporation of solvents, a yellow solid was obtained. Flash chromatography (hexane/ether, 8/2) gave a 1:1 mixture of *E*/*Z* sulfides 8 (853 mg, 2.5 mmol). The sulfides 8-E and 8-Z were separated by first doing a recrystallizing in MeOH/hexane (affording 8-Z as white needles). Then, the remaining solvent was evaporated, and the oil was flash chromatographied (hexan/ether, 8/2) to yield pure 8-E (colorless oil) and 8-Z (white needles). Yield: 89%.

8-Z. Mp: 166–167 °C. IR (cm^{-1}): 1740, 1615, 1600, 1180. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.54–7.33 (5 H, m, Ph), 7.05 (1 H, d, $J_{H\text{-}13,H\text{-}7}$ = 1.4, H-13), 5.10 (1 H, d, $J_{H\text{-}6,H\text{-}7}$ = 4.0, H-6), 4.90–4.80 (1 H, m, H-8), 3.59–3.52 (1 H, m, H-7), 2.50–2.35 (1 H, m, H-4), 2.14 and 2.07 (1 H, A part of an q AB, J_{AB} = 13, $J_{H\text{-}9\alpha,H\text{-}8}$ = 3, H-9α), 1.23 (3 H, s, Me-10), 1.12 (3 H, d, $J_{H\text{-}15,H\text{-}4}$ = 7.5, Me-4). $C_{21}H_{24}O_2S$. MS *m*/*e* 340 ($M^{\cdot+}$).

8-E. IR (cm^{-1}): 1740, 1610, 1580, 1180. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.59 (1 H, d, $J_{H\text{-}13,H\text{-}7}$ = 1.9, H-13), 7.50–7.33 (5 H, m, Ph), 5.46 (1 H, d, $J_{H\text{-}6,H\text{-}7}$ = 4.0, H-6), 4.87–4.80 (1 H, m, H-8), 3.75–3.68 (1 H, m, H-7), 2.55–2.40 (1 H, m, H-4), 2.16 and 2.09 (1 H, A part of an q AB, J_{AB} = 13, $J_{H\text{-}9\alpha,H\text{-}8}$ = 3, H-9α), 1.22 (3 H, s, Me-10), 1.12 (3 H, d, $J_{H\text{-}15,H\text{-}4}$ = 7.6, Me-4). Anal. Calcd for $C_{21}H_{24}O_2S$: C, 74.08; H, 7.10. Found: C, 74.11; H, 7.07.

Vinyl Sulfides of Isoalantolactone 7. Preparation: see 8 (from sulfoxides 5 (1.800 g, 5.0 mmol) one obtains 7 (1.430 g, 4.2 mmol), yield 84%). Spectroscopic data (^1H NMR, IR, melting point) as described.[4]

Vinyl Sulfoxides of Isoalantolactone 9. To a stirred solution of vinyl sulfides of isoalantolactone 7 (360 mg, 1.1 mmol) in dry methylene chloride (40 mL) at −14 °C under an argon atmosphere was added dropwise over a 1-h period a solution of *m*-chloroperbenzoic acid (209 mg, 1.2 mmol) in dry methylene chloride (40 mL). After stirring for an additional 30 min at −14 °C, $NaHCO_3$ (20 mL of a 10% solution) was added. The mixture was extracted with methylene chloride and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded an oil. Flash

chromatography (hexane/ether, 6/4) gave the *E*(*R*,*S*)-vinyl sulfoxides **9** (127 mg, 32%, white crystals). Using a more polar eluent (hexane/ether, 1/9) gave the two enantiomers at sulfur for *Z*-vinyl sulfoxides **9** (**9-Z$_1$**, 62 mg, 16% yield, white crystals; **9-Z$_2$**, 91 mg, 23% yield, white crystals). Yield: 71%.

Vinyl Sulfoxide 9-E. IR (cm^{-1}): 1755, 1640, 1580, 1020. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.70–7.55 (5 H, m, Ph), 7.10 ($^1/_2$ H, d, $J_{H\text{-}13,H\text{-}7}$ = 1.4, H-13a), 7.06 ($^1/_2$ H, d, $J_{H\text{-}13,H\text{-}7}$ = 1.4, H-13a), 4.81 (1 H, broad s, H-14a), 4.65–4.55 (1 H, m, H-8), 4.45 (1 H, broad s, H-14b), 0.83, 0.82 (3 H, 2 s, Me-10). Anal. Calcd for $C_{21}H_{24}SO_3$: C, 70.76; H, 6.79. Found: C, 70.93; H, 6.69.

Vinyl Sulfoxide 9-Z$_1$ (*R* or *S* at Sulfur). Mp: 185 °C. IR (cm^{-1}): 1755, 1640, 1575, 1025. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.78–7.46 (5 H, m, Ph), 6.64 (1 H, d, $J_{H\text{-}13,H\text{-}7}$ = 1.1, H-13b), 4.70 (1 H, broad s, H-14a), 4.52–4.45 (1 H, m, H-8), 4.47 (1 H, broad s, H-14b), 2.93 (1 H, m, H-7), 0.83 (3 H, s, Me-10).

Vinyl Sulfoxide 9-Z$_2$ (*S* or *R* at sulfur). Mp: 199–200 °C. IR (cm^{-1}): 1765, 1650, 1575, 1025. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.87–7.50 (5 H, m, Ph), 6.59 (1 H, d, $J_{H\text{-}13,H\text{-}7}$ = 1.1, H-13b), 4.72 (1 H, broad s, H-14a), 4.30–4.25 (1 H, m, H-8), 4.25 (1 H, broad s, H-14b), 3.05–2.95 (1 H, m, H-7), 0.83 (3 H, s, Me-10). Anal. Calcd for $C_{21}H_{24}SO_3$: C, 70.76; H, 6.79. Found: C, 71.22; H, 7.13.

Vinyl Sulfoxides of Alantolactone 10. Preparation: see vinyl sulfoxides of isoalantolactone **9** (from vinylsulfides **8** (511 mg, 1.5 mmol) one obtains **10-E** (*R* or *S* at sulfur) (204 mg, 0.57 mmol), **10-Z$_1$** (*R* or *S* at sulfur) (73 mg, 0.21 mmol), and **10-Z$_2$** (*S* or *R* at sulfur) (119 mg, 0.33 mmol), yield 74%).

Vinyl Sulfoxide 10-E. IR (cm^{-1}): 1755, 1640, 1580, 1025. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.73–7.56 (5 H, m, Ph), 7.10 ($^7/_8$ H, d, $J_{H\text{-}13,H\text{-}7}$ = 2.0, H-13a), 7.09 ($^1/_8$ H, d, $J_{H\text{-}13,H\text{-}7}$ = 2.0, H-13a), 5.51 ($^1/_8$ H, d, $J_{H\text{-}6,H\text{-}7}$ = 2.0, H-6), 5.37 ($^7/_8$ H, d, $J_{H\text{-}6,H\text{-}7}$ = 2.0, H-6), 4.94–4.91 (1 H, m, H-8), 4.54–4.48 ($^7/_8$ H, m, H-7), 4.37–4.30 ($^1/_8$ H, m, H-7), 2.60–2.48 (1 H, m, H-4), 1.21 (3 H, s, Me-10), 1.12 (3 H, d, $J_{H\text{-}15,H\text{-}4}$ = 7.6, Me-4). Anal. Calcd for $C_{21}H_{24}SO_3$: C, 70.76; H, 6.79. Found: C, 70.77; H, 6.73.

Vinyl Sulfoxide 10-Z$_1$ (*R* or *S* at Sulfur). Mp: 155–156 °C. IR (cm^{-1}): 1755, 1640, 1580, 1025. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.79–7.48 (5 H, m, Ph), 6.62 (1 H, d, $J_{H\text{-}13,H\text{-}7}$ = 1.7, H-13b), 5.03–4.99 (1 H, m, H-8), 4.86 (1 H, d, $J_{H\text{-}6,H\text{-}7}$ = 4.0, H-6), 3.70–3.62 (1 H, m, H-7), 2.41–2.30 (1 H, m, H-4), 1.18 (3 H, s, Me-10), 0.95 (3 H, d, $J_{H\text{-}15,H\text{-}4}$ = 7.6, Me-4).

Vinyl Sulfoxide 10-Z$_2$ (*S* or *R* at Sulfur). Mp: 134–135 °C. IR (cm^{-1}): 1755, 1640, 1580, 1025. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.79–7.48 (5 H, m, Ph), 6.64 (1 H, d, $J_{H\text{-}13,H\text{-}7}$ = 1.7, H-13b), 5.15 (1 H, d, $J_{H\text{-}6,H\text{-}7}$ = 4.0, H-6), 5.84–4.81 (1 H, m, H-8), 3.58–3.50 (1 H, m, H-7), 2.41–2.30 (1 H, m, H-4), 1.22 (3 H, s, Me-10), 0.95 (3 H, d, $J_{H\text{-}15,H\text{-}4}$ = 7.6, Me-4). Anal. Calcd for $C_{21}H_{24}SO_3$: C, 70.76; H, 6.79. Found: C, 70.57; H, 6.83.

General Procedure for the Sodium Borohydride Reduction of Vinyl Sulfoxides 9 (10). To a stirred solution of vinyl sulfoxides **9** (**10**) in an appropriate solvent (THF or MeOH) was added sodium borohydride (0.55 equiv) in water at room temperature. The reaction was quenched after 15 min with 1 N HCl. The mixture was extracted with methylene chloride and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded an oil. Flash chromatography (hexane/ether, 8/2) afforded the α-methylene lactone **1** (**2**) (see Table I). Sodium borodeuteride reductions were done as above, but reaction time was 150 min (see Table II).

Typical Procedure. To a solution of vinyl sulfoxides *E* of isoalantolactone **9** (88 mg, 0.25 mmol) in THF (1 mL) at room temperature was added $NaBD_4$ (10.5 mg, 0.25 mmol) in D_2O (200 μL). After the mixture was stirred for 2.5 h, the reaction was quenched with 1 N HCl. The mixture was extracted with methylene chloride and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded an oil. Flash chromatography (hexane/ether, 8/2) afforded deuterated isoalantolactone **11** (24 mg, 41%), vinyl sulfides of isoalantolactone **7** (27 mg, 31%), dideuterioisoalantolactone **15** (5 mg, 7%), and unreacted vinyl sulfoxides **9** (16 mg, 18%).

General Procedure for the Amalgam Reduction of Vinyl Sulfoxides 9 (10). An aluminum amalgam was prepared by dipping small pieces of aluminum foil for a few minutes in a 0.5% aqueous solution of mercuric chloride.[6,7] The amalgam was filtered and added to a stirred solution of vinyl sulfoxides **9** (**10**) in THF or dioxane at 4 °C. Progress of the reaction was monitored by TLC. The reaction mixture was filtered, and the residue was washed several times with dichloromethane. The combined filtrate and washings were dried over $MgSO_4$, concentrated under reduced pressure, and flash chromatographed (hexane/ether, 8/2) to yield the pure reaction products (see Table III).

Typical Procedure. To a solution of vinyl sulfoxides *E* of isoalantolactone **9** (70 mg, 0.20 mmol) in THF (1 mL) at room temperature was added deuterated amalgam (prepared from 173 mg of Al, 6.4 mmol[7]). After being stirred for 24 h at 4 °C, the reaction mixture was filtered, and the residue was washed several times with dichloromethane. The combined filtrate and washings were dried over $MgSO_4$ and concentrated under reduced pressure to afford an oil. Flash chromatography (hexane/ether, 8/2) afforded trideuterioisoalantolactone (**17**) (33 mg, 0.14 mmol, 70%) and 13-(phenylthio)dideuteroisoalantolactone (**19**) (10 mg, 0.03 mmol, 15%).

Deuterated Isoalantolactone 11. Reduction of **1** by sodium borodeuteride. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.13–6.12 ($^2/_3$ H, m, H-13a), 5.60–5.58 ($^1/_3$ H, H-13b), 4.78 (1 H, dd, H-15b), 4.55–4.45 (1 H, m, H-8), 4.45 (1 H, dd, H-15a), 3.05–2.85 (1 H, m, H-7), 1.10 (3 H, s, Me-10). $C_{15}H_{19}DO_2$. MS: *m/e* 233 ($M^{\bullet+}$).

Deuterated Alantolactone 12. Reduction of **2** by sodium borodeuteride. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.21–6.19 ($^2/_3$ H, m, H-13a), 5.63–5.61 ($^1/_3$ H, m, H-13b), 5.16 (1 H, d, $J_{H\text{-}6,H\text{-}7}$ = 4.0, H-6), 4.87–4.80 (1 H, m, H-8), 3.62–3.55 (1 H, m, H-7), 2.51–2.38 (1 H, m, H-4), 1.20 (3 H, s, Me-10), 1.10 (3 H, d, $J_{H\text{-}15,H\text{-}4}$ = 7.6, Me-4). $C_{15}H_{19}DO_2$. MS: *m/e* 233 ($M^{\bullet+}$).

Dihydroisoalantolactone 13. Mp: 172–173 °C. IR (cm^{-1}): 1770, 1650. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.77 (1 H, broad s, H-14a),4.48 (1 H, broad s, H-14b), 4.48–4.44 (1 H, m, H-8), 2.77 (1 H, dq, H-11), 1.27 (3 H, d, $J_{H\text{-}13,H\text{-}11}$ = 7.2, Me, 11), 0.80 (3 H, s, Me-10). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.81; H, 9.39. Found: C, 76.78; H, 9.34.

Dihydroalantolactone 14. Mp: 131–132 °C. IR (cm^{-1}): 1770, 1650. ^{1}H NMR ($CDCl_3$8 200 MHz): δ 5.16 (1 H, d, $J_{H\text{-}6,H\text{-}7}$ = 3.2, H-6), 4.77–4.71 (1 H, m, H-8), 3.08–2.99 (1 H, m, H-7), 2.98–2.79 (1 H, m, H-11), 2.55–2.45 (1 H, m, H-4), 2.24 and 2.20 (1 H, A part of an q AB, J_{AB} = 13, $J_{H\text{-}9\alpha,H\text{-}8}$ = 3, H-9α), 1.23 (3 H, s, Me-10), 1.22 (3 H, d, $J_{H\text{-}13,H\text{-}11}$ = 7.1, Me-11), 1.12 (3 H, d, $J_{H\text{-}15,H\text{-}4}$ = 7.6, Me-4). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.81; H, 9.39. Found: C, 76.94; H, 9.29.

Dideuterioisoalantolactone 15. The nondeuterated **15** corresponds to dihydroisoalantolactone **13**. Reduction of **9** by sodium borodeuteride. ^{1}H NMR ($CDCl_3$, 60 MHz): The methyl-13 signal corresponds to 1 H only (two deuterium atoms were introduced).

Dideuterioalantolactone 16. The nondeuterated **16** corresponds to dihydroalantolactone **14**. Reduction of **10** by sodium borodeuteride. ^{1}H NMR ($CDCl_3$, 200 MHz): The methyl-13 signal corresponds to 1 H only (two deuterium atoms were introduced).

Trideuterioisoalantolactone 17. The nondeuterated **17** corresponds to dihydroisoalantolactone **13**. Reduction of **9** by deuterated amalgam. ^{1}H NMR ($CDCl_3$, 60 MHz): The methyl-13 signal corresponds to 1 H only; no H-11 signal at 2.77 ppm (three deuterium atoms were introduced).

Trideuterioalantolactone 18. The nondeuterated **18** corresponds to dihydroalantolactone **14**. Reduction of **10** by deuterated amalgam. ^{1}H NMR ($CDCl_3$, 200 MHz): The methyl-13 signal corresponds to 1 H only; no H-11 signal at 2.98–2.79 ppm (three deuterium atoms were introduced). $C_{15}H_{19}D_3O_2$. MS: *m/e* 237 ($M^{\bullet+}$).

13-(Phenylthio)dideuterioisoalantolactone 19. Spectroscopic data of non deuterated **19**, see ref 4. Reduction of **9** by deuterated amalgam. ^{1}H NMR ($CDCl_3$, 60 MHz): The CH_2-13 signal corresponds to 1 H only; no H-11 signal at 3.5 ppm (two deuterium atoms were introduced).

13-(Phenylthio)dideuterioalantolactone 20. The nondeuterated **20** corresponds to 13-(phenylthio)alantolactone (**4**). Reduction of **10** by deuterated amalgam. ^{1}H NMR ($CDCl_3$, 200 MHz): The CH_2-13 signal corresponds to 1 H only; no H-11 signal at 3.52 ppm (two deuterium atoms were introduced). $C_{21}H_{24}D_2O_2S$. MS: *m/e* 344 ($M^{\bullet+}$).

11-(Phenylselenyl)-11-methylisoalantolactone (21). To a solution of lithium isopropylcyclohexylamine LiICA [prepared from isopropylcyclohexylamine (150 μL, 0.95 mmol) and BuLi (590 μL, 1.6 M in hexane, 0.95 mmol) in THF (1 mL)] was added

at −78 °C a solution of dihydroisoalantolactone **13** in THF (2 mL). After 1 h of stirring, the reaction mixture was added dropwise under argon to a solution of PhSeCl in THF (2 mL) at −78 °C. The mixture was stirred for 30 min at −78 °C and was then allowed to reach −20 °C. The reaction was quenched by 1 N HCl, extracted with CH_2Cl_2 and dried over $MgSO_4$. Removal of the solvent gave a yellow oil. Chromatography on silica gel [(1) hexane, (2) hexane/ether, 8/2] gave pure **21** (white crystals, 204 mg, 0.52 mmol). Yield: 61%. Mp: 118–119 °C. IR (cm^{-1}): 1765, 1650. ^1H NMR ($CDCl_3$, 60 MHz): δ 7.8–7.1 (5 H, m, Ph), 5.05–4.85 (1 H, m, H-8), 4.74 (1 H, broad s, H-14b), 4.42 (1 H, s, H-14a), 1.55 (3 H, s, Me-11), 0.80 (3 H, s, Me-10). Anal. Calcd for $C_{21}H_{26}O_2Se$: C, 64.72; H, 6.93. Found: C, 64.82; H, 6.80.

Norisoalantolactone 22. To a solution of **21** (122 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added H_2O (500 μL) under argon as well as H_2O_2 (600 μL, 30% aqueous solution, 1.8 mmol). After 30 min of stirring at room temperature, all **21** had reacted (TLC). After usual workup (extraction by CH_2Cl_2, drying on $MgSO_4$, evaporation of solvents) a colorless oil was obtained. Flash chromatography [(1) hexane/ether, 8/2] gave pure isoalantolactone **1** (30 mg, 0.13 mmol); (2) then pure ether was used, and pure norisoalantolactone **22** (40 mg, 0.17 mmol) was obtained. Formation of **22** could be avoided by effecting the reaction in the same conditions in THF, H_2O_2.[10] Yield: 55%. Mp: 153–155 °C. IR (cm^{-1}): 1760, 1720, 1250. ^1H NMR ($CDCl_3$, 60 MHz): δ 6.11 (1 H, broad s, H-13a), 5.58 (1 H, s, H-13b), 4.52–4.45 (1 H, m, H-8), 3.1–2.8 (1 H, m, H-7), 0.89 (3 H, s, Me-10). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.69; H, 7.68. Found: C, 71.71; H, 7.78.

(Tributylstannyl)alantolactone 23. To a solution of *Z*-vinyl sulfides of alantolactone **8** (100 mg, 0.3 mmol) in degassed dry toluene (5 mL) was added a catalytic amount (6 mg, 0.04 mmol) of AIBN, followed by the addition of Bu_3SnH (80 μL, 0.3 mmol). The solution was refluxed during 4 h. After evaporation and flash chromatography [(1) hexane, (2) hexane/ether, 5/5] the pure *Z*-(tributylstannyl)alantolactone **23** (colorless oil) was obtained.

(Tributylstannyl)alantolactone 23-Z. IR (cm^{-1}): 1755, 1640, 1025. ^1H NMR ($CDCl_3$, 100 MHz): δ 6.92 (1 H, d, $J_{H\text{-}13,H\text{-}7}$ = 1.7, H-13b), 5.06 (1 H, d, $J_{H\text{-}6,H\text{-}7}$ = 3.9, H-6), 4.84–4.80 (1 H, m, H-8), 3.56–3.51 (1 H, m, H-7), 2.46–2.38 (1 H, m, H-4), 2.12 and 2.05 (1 H, A part of an q AB, J_{AB} = 13, $J_{H\text{-}9\alpha,H\text{-}8}$ = 3, H-9α), 0.87 (9 H, t, *J* = 7.1, 3 Me). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 11.2, 13.8, 16.9, 22.7, 27.3, 28.6, 29.2, 32.8, 37.5, 37.6, 41.7, 42.2, 42.3, 43.1, 76.1, 120.1, 146.8, 148.1, 171.5. Anal. Calcd for $C_{27}H_{46}O_2Sn$: C, 62.20; H, 8.89. Found: C, 62.04; H, 9.02.

(Tributylstannyl)alantolactone 23-E. IR (cm^{-1}): 1755, 1640, 1020. ^1H NMR ($CDCl_3$, 50 MHz): δ 7.37 (1 H, d, $J_{H\text{-}13,H\text{-}7}$ = 1.6, H-13a), 5.06 (1 H, d, $J_{H\text{-}6,H\text{-}7}$ = 3.9, H-6), 4.79–4.76 (1 H, m, H-8), 3.45–3.41 (1 H, m, H-7), 2.46–2.38 (1 H, m, H-4), 2.16 and 2.08 (1 H, A part of an q AB, J_{AB} = 13, $J_{H\text{-}9\alpha,H\text{-}8}$ = 3, H-9α), 0.90 (9 H, t, *J* = 7.1, 3-Me). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.3, 13.7, 16.8, 22.5, 27.3, 28.7, 29.1, 29.2, 32.9, 38.1, 41.2, 41.9, 42.7, 75.7, 118.8, 141.9, 147.0, 149.1, 169.0. Anal. Calcd for $C_{27}H_{46}O_2Sn$: C, 62.20; H, 8.89. Found: C, 62.10; H, 8.70.

Acid Cleavage of (Tributylstannyl)alantolactone. To a solution of (tributylstannyl)alantolactone **23-Z** (325 mg, 0.6 mmol) in toluene (10 mL) at 0 °C under argon was added $(CF_3CO)_2O$ (1 mL, 7.1 mmol) followed by slow addition of D_2O (300 μL, 17 mmol). The solution was refluxed for 1 h, and then the mixture was cooled to room temperature and quenched by a 10% aqueous $NaHCO_3$ solution. Extraction by CH_2Cl_2, drying over $MgSO_4$, and evaporation of solvents yielded a colorless oil. Flash chromatography hexane/ether, 8/2, gave pure labeled alantolactone **12** (117 mg, 0.5 mmol); 200-MHz ^1H NMR showed a 6:1 *retention* to *inversion* ratio. Yield: 84%.

Vinyl Sulfone of Isoalantolactone 26. To a solution of vinyl sulfide of isoalantolactone **7-E** (260 mg, 0.76 mmol) in THF (15 mL) was added to 0 °C under argon a solution of oxone[20] (1.23 g, 2.0 mmol) in H_2O (15 mL). The reaction mixture was allowed to reach room temperature and was stirred for 3 days. Longer reaction times gave a number of side products. Evaporation of excess THF, followed by CH_2Cl_2 extraction, drying over $MgSO_4$, and removal of solvents gave a colorless oil. Flash chromatography (hexane/ether, 6/4) gave pure **26** as white crystals (119 mg, 0.31 mmol) and vinyl sulfoxides **9-E** (70 mg, 0.2 mmol). Yield: 42%. Mp: 138–139 °C. IR (cm^{-1}): 1760, 1650, 1580, 1260, 1160. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.97–7.57 (5 H, m, Ph), 7.08 (1 H, d, $J_{H\text{-}13,H\text{-}7}$ = 1.4, H-13), 4.81 (1 H, broad s, H-14a), 4.65–4.55 (1 H, m, H-8), 4.44 (1 H, broad s, H-14b), 4.05–3.95 (1 H, m, H-7), 0.81 (3 H, s, Me-10). Anal. Calcd for $C_{21}H_{24}O_4S$: C, 67.72; H, 6.49. Found: C, 6.92; H, 6.62.

Registry No. **1**, 470-17-7; **2**, 546-43-0; **3**, 69993-35-7; **4**, 123489-73-6; (*R*)-**5**, 69993-36-8; (*S*)-**5**, 69993-26-6; (*R*)-**6**, 123489-74-7; (*S*)-**6**, 123489-84-9; **7**-*E*, 69993-39-1; **7**-*Z*, 69993-40-4; **8**-*E*, 123538-94-3; **8**-*Z*, 123538-98-7; (*R*)-**9**-*E*, 123538-95-4; (*S*)-**9**-*E*, 123748-57-2; (*R*)-**9**-*Z*, 123538-99-8; (*S*)-**9**-*Z*, 123539-02-6; (*R*)-**10**-*E*, 123538-96-5; (*S*)-**10**-*E*, 123539-01-5; (*R*)-**10**-*Z*, 123539-00-4; (*S*)-**10**-*Z*, 123539-03-7; **11**-*E*, 123489-75-8; **11**-*Z*, 123489-87-2; **12**-*E*, 123538-97-6; **12**-*Z*, 123539-04-8; **13**, 1856-58-2; **14**, 40285-97-0; **15**, 123489-76-9; **16**, 123489-77-0; **17**, 123489-78-1; **18**, 123489-79-2; **19**, 123489-80-5; **20**, 123489-81-6; **21**, 123489-82-7; **22**, 74513-15-8; **23**-*E*, 123489-85-0; **23**-*Z*, 123489-83-8; **26**, 123489-86-1.

(20) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, 1287–1290.