$$\frac{d[\mathbf{10}]}{dt} = \frac{k_{11}[AN]}{k_{13}[O_2]}\left(1 + \frac{k_{-13} + k_{15}[AN]}{k_{14}[M(I)]}\right)(k_4[AN] \times [M(II)] + k_9[\mathbf{4}][M(II)])$$

$$-\frac{d[O_2]}{dt} = (k_4[AN][M(II)] + k_9[4][M(II)])\left(\frac{3}{2} + \frac{3}{2}\left(\frac{k_{15}[AN]}{k_{14}[M(I)]}\right) + \frac{k_{11}[AN]}{2k_{13}[O_2]}\left(1 + \frac{k_{-13} + k_{15}[AN]}{k_{14}[M(I)]}\right)\right)$$

Since [**4**] may be very small

$$k_4[AN]/[\mathbf{4}] \gg k_9$$

The relation between the rate of production of **10** and the rate of production of **9** is represented as

$$\frac{d[\mathbf{10}]}{dt} = F\frac{d[\mathbf{9}]}{dt}$$

where F is a function. Therefore

$$(-d[O_2]/dt)/(d[\mathbf{9}]/dt) = (3 + F)/2$$

$$\frac{-d[AN]/dt}{-d[O_2]/dt} = \frac{1 + F}{3/2 + F/2}$$

If $k_{14}[M(I)] \gg k_{15}[AN]$

$$-d[AN]/dt = (1 + F)k_4[AN][M(II)]$$

Here, F may be decided on the basis of experimental fact. For example, in the experimental result (Figure 1), F is nearly constant in the initial stage of the oxidation at a value of about 1. Therefore, in the early stage of the oxidation

$$-d[AN]/dt \simeq 2k_4[AN][M(II)] \quad (17)$$

$$d[\mathbf{9}]/dt = k_4[AN][M(II)] \quad (18)$$

$$d[\mathbf{10}]/dt \simeq k_4[AN][M(II)] \quad (19)$$

$$(-d[O_2]/dt)/(d[\mathbf{9}]/dt) \simeq 2 \quad (20)$$

$$(-d[AN]/dt)/(-d[O_2]/dt) \simeq 1 \quad (21)$$

Registry No. Anthracene, 120-12-7; copper(II) acetate, 142-71-2; sodium chloride, 7647-14-5.

Preparation of Chiral 1-Deuteriobenzenemethanethiols by Using α',β Elimination of Carbanions Derived from Benzylic Thioethers

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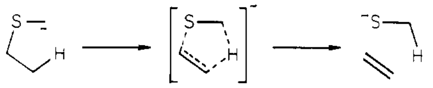
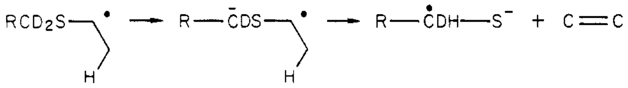
The α',β elimination of the carbanion derived from [α-$^2H_2$]benzyl isolongifolyl thioether and [α-$^2H_2$]benzyl camphyl thioether gives the chiral [α-^2H]benzyl mercaptan, the *S* isomer with 38 ± 6% ee and the *R* isomer with 49 ± 7% ee. The chirality of the [α-^2H]benzyl mercaptan was determined by optical rotation of [α-^2H]benzyl methyl thioether and thiosulfone. The enantiomeric excess was evaluated from ^1H NMR measurement of ethyl (benzylthio)phenylacetate prepared from (−)-mandelic acid. The enantiomeric excess at carbon C-2 of ethyl (benzylthio)phenylacetate was determined with a chiral europium chelate and was about 60%. These results are discussed with reference to the transition state of the α,β elimination and to related processes.

We report here a direct method for the preparation of chiral [α-^2H]benzenemethanethiol. The tedious synthesis of thioaldehydes renders unattractive attempts to achieve their asymmetric reduction by the methods used for the conversion of aldehydes to 1-deuterio primary alcohols.[1-3] The absence of a reaction analogous to the Baeyer–Villiger reaction for a stereospecific sulfur insertion into a C–C bond is also a strong limitation. The high nucleophilic character of thiolates has been widely used in the substitution reaction of activated derivatives of a chiral 1-deuterio primary alcohol to the mercaptan or thioether.[4,5] However, the possibility of chirality on a sulfur atom provides new alternatives. For instance, a neighboring chiral group such as sulfoxide or sulfimine can induce a stereospecific introduction of the label, as was shown with benzyl methyl sulfoxide.[6]

The α',β elimination of carbanions derived from the thioether proceeds in high yields, and its stereochemical course is in agreement with a syn elimination mechanism.



The large primary isotope effect observed with benzyl cyclooctyl thioether (7.0–9.0) indicates that the α-carbon is close to the proton being transfered from the β-carbon.[7] This prompted the idea that, by using a chiral proton–donating group, the chiral thiol may be prepared in a direct fashion. However, the large primary isotope effect is likely to render impractical a reaction scheme where deuterium is transferred, owing to the increase in the number of side



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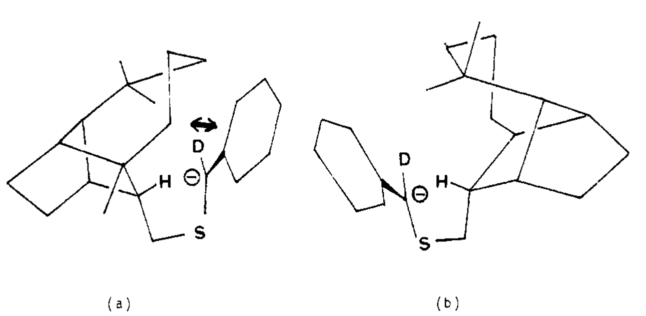
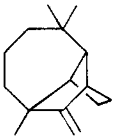


Figure 1. Transition-state configurations for the isolongifolyl derivative.

reactions brought about by rate reduction. Besides, introduction of the deuterium into the inducing skeleton may be difficult. To circumvent this problem, we chose an inducing skeleton where both enantiomers were available. The quite common sesquiterpene (+)-longifolene (1) has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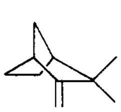
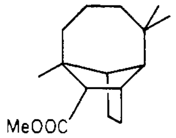

2

a rather asymmetrical skeleton and surprisingly has been little used for chiral induction.[8] Its enantiomer, (−)-longifolene, seems to be rather rare,[9] but the enantiomeric skeleton of (−)-camphene (2) may be derived from *l*-borneol, which is commercially available. From model building, two aspects of the reaction may be postulated. The methyl group (in the camphanyl derivative) or methylene group (in the longifolyl derivative) sterically interferes with the phenyl group and induces a preference for one transition state (Figure 1). In addition, the proton transfer from the carbon will be more difficult for the longifolyl than for the camphanyl skeleton, due to the extra isoprenyl unit.

Isolongifolol (4) was prepared from (+)-longifolene (1) through chromic oxidation, and the acidic fraction was esterified.[10-12] The purification of methyl isolongifolate (3) by crystallization is very convenient. The reduction



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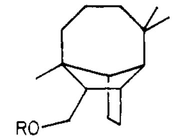
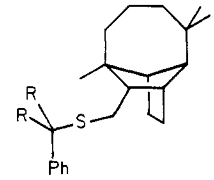


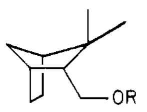
4, R = H
5, R = Tos



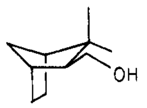
6, R = H
7, R = ^{2}H

of ester 3 gives isolongifolol (4) with a 10% impurity which is probably the epimer at C-7 (7α-H). The latter was removed by crystallization at a further stage: tosylate 5 and thioether 6.

(−)-Camphene (2) prepared from *l*-borneol by solvolysis of the tosylate[13] has an enantiomeric excess of 92% based on the optical rotation. Hydroboration followed by H_2O_2 oxidation of (−)-camphene gave a mixture of the two camphanols 8 and 10, with the desired endoisomer 8 in



8, R = H
9, R = Tos



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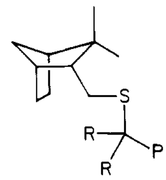
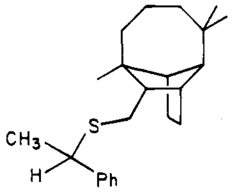


11, R = H
12, R = ^{2}H

excess.[14,15] The stereochemistry of these two isomers 8 and 10 has been described.[15-17] Benzyl *endo*-camphyl thioether (11) was prepared via the crystalline tosylate 9.

The deuterated thioethers 7 and 12 were prepared by the reaction of tosylates 5 and 9 with [α-$^2H_2$]benzenemethanethiol prepared from [α-$^2H_2$]benzyl alcohol.

The benzyl isolongifolyl thioether (6) was converted to the corresponding carbanion at −78 °C by the action of *n*-butyllithium (1.5 equiv to obtain complete metalation)[18] or *sec*-butyllithium in tetrahydrofuran (THF)/tetramethylethylenediamine (TMEDA, 1 equiv). Treatment of the carbanion solution at −78 °C with methyl iodide permitted the isolation of both diastereoisomers of 13 in



13

a high yield. No asymmetric induction was detected, the ratio of the two isomers being close to 1.[19] In the case of the carbanion formed from benzyl isolongifolylthioether (6), elimination was quite slow at 25 °C in hexane (20% elimination after 12 h). In the presence of [2.2.2]cryptand (1 equiv), no elimination was detected at 25 °C after 2 h, and the methylated products 13 were isolated. After a 3-h reflux in THF–TMEDA, the α',β elimination of this carbanion occurred in a yield of 80%.

The carbanion derived from benzyl camphanyl thioether (11) gives a 50% yield of camphene (2) after 3.5 h at 25 °C in THF with TMEDA in addition to 45% of methylated products. In hexane with TMEDA at 25 °C, some *trans*-stilbene was detected in addition to the elimination products. When refluxed in THF/TMEDA, the elimination was quantitative after 2 h.

With the deuterated thioethers 7 and 12, the elimination was conducted under the following conditions: for 7, metalation at −78 °C in THF/TMEDA by butyllithium and reflux for 3 h; for 12, metalation at −20 °C in THF–TMEDA by butyllithium and 6 h at 25 °C.

The deuterated benzenemethanethiol 14 (91% ^{2}H), from benzyl isolongifolyl thioether (7), was converted to [α-^{2}H]benzyl methyl thioether (15). Thioether 15, prepared

$$\underset{14}{PhCHDSH} \rightarrow \underset{15}{PhCHDSCH_3} \rightarrow \underset{16}{PhCHDS(O)_2CH_3}$$

from chiral [α-^{2}H]benzyl alcohol, was described for the (*S*)-(+) isomer [enantiomeric excess 47%; $[\alpha]_D$ +0.75° (*c* 12, EtOH)] and for the (*R*)-(−) isomer, $[\alpha]_D$ −1.12° (*c* 18,

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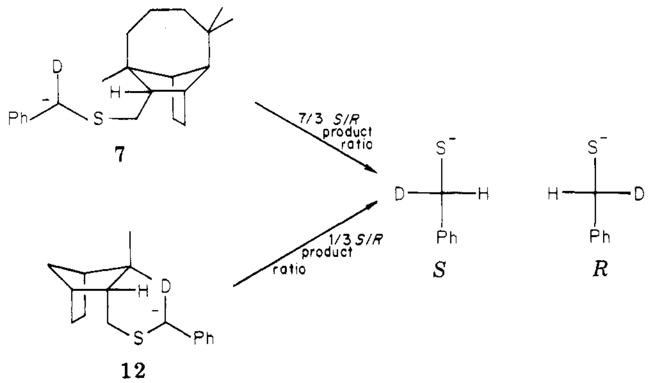
[18] On reaction with methyl iodide, some butylated product was obtained through a metal–halogen exchange.

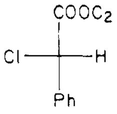
[19] Some induction had been observed. Biellmann, J. F.; Ducep, J. B.; Schirlin, D. *Tetrahedron* **1980**, *36*, 1249.

Scheme I



EtOH).[19] In our sample, the [α-^{2}H]benzenemethanethiol had $[\alpha]_D$ + 0.815° (*c* 13.4, hexane), and [α-^{2}H]benzyl methyl thioether had $[\alpha]_D$ +0.59° (*c* 5.3, EtOH). The chirality of the thioether prepared from [α-$^2H_2$]benzyl isolongifolyl thioether (**7**) was then *S*. This thioether was converted to [α-^{2}H]benzyl methyl sulfone (**16**), $[\alpha]_D$ -0.46° (*c* 3,3, $CHCl_3$). The *S* sulfone had been described as levorotatory $[\alpha]_D$ -0.60° (*c* 6, $CHCl_3$)[20] and -0.9° (*c* 1, $CHCl_3$),[6] and the *R* enantiomer had $[\alpha]_D$ +0.83° (*c* 4, $CHCl_3$).[20] The sign inversion associated with the transformation of the thioether **15** to the sulfone **16** confirms that the rotation was not due to a chiral impurity. The determination of the enantiomeric excess by the optical rotation is uncertain because of the low rotation values.

The enantiomeric excess of [α-^{2}H]benzenemethanethiol was determined by the ^{1}H NMR of (*R*)-ethyl (benzylthio)phenylacetate (**18**). Thioether **18** was prepared by



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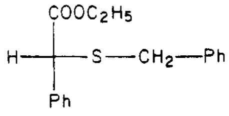
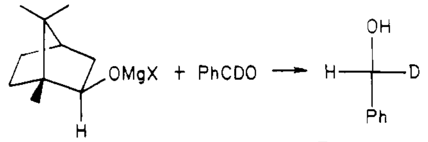


18

nucleophilic substitution on (*S*)-ethyl chlorophenylacetate (**17**) prepared from (*R*)-(-)-mandelic acid.[21] In thioether **18**, the methylenic protons at the benzylic position form a distinct AB system with $\Delta\delta$ = 0.15 ppm. With the [α-^{2}H]benzenemethanethiol arising from α',β elimination of benzyl isolongifolyl thioether, the area ratio gives an apparent enantiomeric excess of 24%.[22] However, in order to determine the enantiomeric excess by this method, the optical purity of the inducing center has to be ascertained. By addition of Eu(hfc)$_3$ to racemic ethyl (benzylthio)phenylacetate, the methylene and methyl groups of the ethyl groups and the proton α to the ester give rise to two groups of signals. For the ester used above, the enantiomeric excess is 63%. This gives the corrected value of 38 ± 6% for the enantiomeric excess of [α-^{2}H]benzenemethanethiol obtained from [α-$^2H_2$]benzyl isolongifolyl thioether (**7**).[23] The $[\alpha]_D$ for optically pure (*S*)-[α-^{2}H]benzyl methyl thioether is close to +1.5° (EtOH) which is in agreement with the value obtained from published data.[20,24] For (*R*)-ethyl ([α-^{2}H]benzylthio)phenylacetate prepared by elimination of [α-$^2H_2$]benzyl camphyl thioether (**12**), the enantiomeric excess was 57% at carbon 2, and from the area ratio, there was an apparent enantiomeric excess at 28% for the deuterated center. Thus, the enantiomeric excess for [α-^{2}H]benzenemethanethiol was 49 ± 7%. From the ^{1}H NMR spectrum of (*R*)-ethyl (benzylthio)phenylacetate it was established that the [α-^{2}H]benzenemethanethiol prepared from [α-$^2H_2$]benzyl isocamphanyl thioether (**12**) was *R* (Scheme I).

The slower α',β elimination in the case of benzyl isolongifolyl thioether (**6**), as compared with benzyl camphyl thioether (**11**), is due to the additional isopropenic unit which shields the proton to be removed.

The enantiomeric excesses obtained with the carbon skeletons used here are close to the highest value obtained with a related reagent in the reduction of 1-deuteriobenzaldehydes such as (-)-isobonylmagnesium alcoholates where an enantiomeric excess of 45% was obtained for



R (45% ee)

(*R*)-[α-^{2}H]benzyl alcohol.[25,26] 3β-Pinanyl-9-borabicyclo[3.3.1]nonane proved to be a very efficient reagent to reduce 1-deuteriobenzaldehyde with an enantiomeric excess of 90%.[3]

This method, which may be extended to the preparation of other 1-deuterio primary mercaptans, may be useful with regard to obtaining a large variety of chiral sulfur derivatives such as thioethers and other functional derivatives at the sulfur such as sulfonic acids and sulfones. The α',β elimination with some group stabilizing the carbanion next to the sulfur should lead to the synthesis of other 1-deuterio primary mercaptans.

Experimental Section

The *n*-butyllithium used here was a commercially available hexane solution which was approximately 2 M in butyllithium. TMEDA is tetramethylethylenediamine. Tetrahydrofuran (THF) was distilled from benzophenone and sodium. Hexamethylphosphoric triamide (HMPT) was distilled under vacuum over calcium hydride. The stationary phase for the gas chromatography (GC) was Triton X-305 (10%) on Chromosorb W-AW 80-100 DMCS or OV-17 (5%) on Chromosorb W-AW 100-120 DMCS, and the mobile phase was nitrogen. The rotatory power was measured with a Perkin-Elmer 241 MC polarimeter. The mass spectra were determined with a Thomson THN 208 spectrometer with direct introduction. The NMR spectra were recorded on a Bruker WH 90 or Cameca (250 MHz) instrument. For high-performance liquid chromatography (HPLC), a Varian Model 5000 was used for analytical or semipreparative purposes and a Jobin-Yvon Chromatospac Prep for preparative separation.

[α-$^2H_2$]Benzenemethanethiol. To a solution of methyl benzoate (25 g) in ether (160 mL) under argon was added over 2 h a solution of lithium aluminium deuteride (5.5 g; isotopic purity 99%; Roth, Germany) in ether (80 mL). After being stirred 3 h at 20 °C, the excess reagent was destroyed by addition of aqueous ammonium chloride solution. After acidification, the solution was extracted with ether. After drying over sodium sulfate and sodium carbonate, the ether was removed and the residue distilled

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[22] The values of enantiomeric excess are not corrected for ^{2}H content.

[23] It can be shown that if there is no kinectic resolution during the preparation of the derivatives, the enantiomeric excess (ee) is related to the enantiomeric excess of the inducing center (ee_I; here, the center next to the ester group) and to the apparent enantiomeric excess (ee_{app}) determined by NMR (here the CHD center) by the relation ee_{app}/ee_I.

[24] the optical rotation used to determine the enantiomeric excess of [α-^{2}H]benzyl alcohol used in ref 19 was that published in: Althouse, V. E.;Feigl, D. M.; Sanderson, W. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1966**, *88*, 3595.

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[26] Streitwieser, A., Jr.; Wolfe, J. R., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 903.

under reduced pressure. [α-^{2}H$_2$]Benzyl alcohol [bp 95–96 °C (15 mm Hg)] was obtained in a yield of 84%.

To a solution of this [α-^{2}H$_2$]benzyl alcohol (14.15 g) and pyridine (3 mL) in methylene chloride (70 mL) was added at 15–20 °C dropwise over 40 min a solution of thionyl chloride (18.4 g) in methylene chloride (15 mL). After the mixture was stirred 12 h at 20 °C, water was added, and extraction with pentane (150 mL) was performed. The pentane layer was washed with water, with saturated sodium carbonate solution (twice), and with water. After the mixture was dried with sodium sulfate, the ether was removed and the chloride distilled under reduced pressure [67 °C (15–17 mmHg)]. The yield was 90%.

[α-^{2}H$_2$]Benzyl chloride (3.0 g) was added to a solution of thiourea (1.9 g) in dioxane (50 mL). The mixture was brought slowly to 95 °C, an oily phase separated, and reflux was continued for 3 h. After the mixture cooled, sodium hydroxide solution (1.07 g in 3 mL) was added. After a reflux of 3 h, the solution was acidified with dilute sulfuric acid and extracted with pentane. The pentane layer was washed with water and dried over sodium sulfate. [α-^{2}H$_2$]Benzenemethanethiol was obtained at a yield of 85% (2.7 g). The ^{1}H NMR (90 MHz, CDCl$_3$) showed large peaks at δ 1.69 (1 H) and 7.25 (5 H).

Preparation of [α-^{2}H$_2$]Benzyl Isolongifolyl Thioether (7). Methyl isolongifolate (**3**) was prepared from (+)-longifolene [**1**; [α]$_D$ +44° (c 4.6, benzene)] by oxidation.[11] Ester **3** was reduced with lithium aluminum hydride to the corresponding alcohol **4**. A solution of methyl isolongifolate (**3**, 15.35 g) in anhydrous ether (180 mL) was added over 2 h at 0 °C to a solution of lithium aluminium hydride (1.7 g) in ether (70 mL). After 12 h at 20 °C, an aqueous solution of ammonium chloride was added. The ether layer was decanted and the solid washed with ether. The ethereal solution was washed with water and dried over sodium sulfate. Isolongifolol (**4**, 12.75 g) was recrystallized in hexane: mp 115–115.5 °C; [α]$_D$ –51° (*c* 4, EtOH) [lit.[10] mp 113–114 °C; [α]$_D$ –53° (*c* 4.6, EtOH)]. The tosylate of isolongifolol (**5**) was prepared from isolongifolol (**4**, 8.9 g) in anhydrous pyridine (20 mL) with tosyl chloride (8.4 g). After 12 h at 20 °C, the pyridine was removed under reduced pressure and the tosylate **5** extracted with ether. After the mixture was washed with water and dried with sodium sulfate and the ether removed, the tosylate **5** (12.9 g) was recrystallised from hexane: mp 70–71 °C; [α]$_D$ –22° (*c* 2.5, CHCl$_3$) (lit.[12] mp 69–70 °C).

To a solution of sodium methylate in methanol [prepared from sodium (0.5 g) and anhydrous methanol (16 mL)] were added HMPT (8 mL), [α-^{2}H$_2$]benzenemethanethiol (3.5 g), and the isolongifolyl tosylate **5** (7.0 g). After 42 h of reflux, water was added and the extraction performed with ether. The thioether **7** (5.04 g) was recrystallized in methanol: mp 43.5–44 °C; [α]$_D$ –5.7° (*c* 5.8, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 0.78 (s, 3 H), 0.96 (s, 3 H), 1.00 (s, 3 H), 1.10 (m, J = 7.5, 5 Hz, 1 H), 1.15–1.65 (m), 2.19 (m, 1 H), 2.44 (m, J = 7.5, 5 Hz, 2 H), (3.72, s, 2 H, observed in the H$_2$ compound **6**), 7.34 (m, 5 H); ^{13}C NMR in agreement with the structure; MS (at 12 eV for nondeuterated compound) *m/e* (relative intensity) 328 (52, M$^+$) 237 (100), 236 (29), 205 (28), 204 (42). The deuterium content of the thioether prepared as above, determined by mass spectroscopy, was as follows: ^{2}H$_0$, 0%; ^{2}H$_1$, 3%; ^{2}H$_2$, 97%.

Isolongifolyl α-Phenylethyl Thioether (13). A solution of *sec*-butyllithium (0.9 mL, 0.58 M in benzene) was added to a solution of benzyl isolongifolyl thioether (**6**, 156 mg) and TMEDA (0.08 mL) in THF (10 mL) at –78 °C. After 40 min at –78 °C, methyl iodide (1 mL) was added and extraction with hexane performed. The methylated product **13** was obtained as an oil, pure by gas chromatography (OV-17): NMR (250 MHz, CDCl$_3$) δ 0.6990 and 0.7339 3 H), 0.9280 and 0.9447 (3 H), 0.9674 and 0.9750 (3 H), 1.0–2.5 (m), 1.57 (dd, J = 6.8 Hz, $\Delta\delta$ = 0.008, 3 H), 3.92 (1 H, q, J = 6.8 Hz), 7.35 (5 H).

Elimination from [α-^{2}H$_2$]Benzyl Isolongifolyl Thioether (7). The corresponding carbanion was prepared under argon at –78 °C from the thioether **7** (1.64 g) in THF (50 mL) and TMEDA (0.68 mL) by the action of *n*-butyllithium (2 mL of a 2.16 M solution in hexane). After 1 h at –78 °C, the temperature was increased until reflux occurred. After 3 h, the reaction medium was cooled, and a 1 N sodium hydroxide solution (30 mL) and pentane (50 mL) were added. The pentane phase was extracted three times with 1 N sodium hydroxide solution. Longifolene (**1**, 50%) and the initial thioether **7** (48%) were characterized in the pentane phase. The aqueous solutions were acidified at 0 °C with 1 *N* sulfuric acid, and the benzyl mercaptan was extracted with pentane and obtained (290 mg) after removal of the pentane. Minor contaminants were removed by chromatography on silica gel (6 g, elution with pentane). The benzyl mercaptan **14** (135 mg) obtained in this way was used for further work: [α]$_D$ +0.815° (*c* 13.4, hexane); ^{1}H NMR (250 MHz, CDCl$_3$) δ 1.74 (J = 7.6, 0.76 Hz), 3.73 (dt, J = 7.6, 1.9 Hz), 7.3 (m).

[α-^{2}H]Benzyl Methyl Thioether (15). Under argon, the benzyl mercaptan **14** (135 mg) prepared as above and methyl iodide (1 mL) were added to a suspension of sodium hydride (80 mg, 60% in paraffin) in hexane (5 mL). After the mixture was stirred 8 h at 20 °C, the excess hydride was destroyed by the addition of a few drops of sodium carbonate solution. After filtration, the organic layer was washed with 1 N sodium hydroxide and then water and dried over sodium sulfate. After chromatography on silica gel (4 g, elution with pentane), the thioether **15** was distilled under reduced pressure (15 mmHg). The [α-^{2}H]benzyl methyl thioether (**15**, 53 mg) was pure according to gas chromatography (Triton X 305): [α]$_D$ +0.59° (*c* 5.3, EtOH); ^{1}H (CDCl$_3$, 90 MHz) δ 1.99 (s, 3 H), 3.65 (t, J = 1.8 Hz, 1 H), 7,3 (5 H). Mass spectroscopy gave the deuterium content: ^{2}H$_0$, 5.5%; ^{2}H$_1$, 91%; ^{2}H$_2$, 3.5%.

[α-^{2}H]Benzyl Methyl Sulfone (16). To a solution of [α-^{2}H]benzyl methyl thioether (**15**, 70 mg) in acetic acid (2 mL) was added hydrogen peroxide (0.15 mL of a 30% solution). After 24 h at 20 °C, the acetic acid was removed under vacuum and the sulfone **16** recrystallized in ethanol: mp 126–127 °C (lit.[20] mp 127.5–128 °C); [α]$_D$ –0.46° (*c* 3.3, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 250 MHz) δ 2.76 (3 H), 4.24 (1 H), 7.42 (5 H).

(*R*)-Ethyl (Benzylthio)phenylacetate (18). The benzyl mercaptan (0.18 mL) was added to a solution of sodium methylate in methanol (21 mg of sodium/5 mL). A solution of (*S*)-ethyl chlorophenylacetate (**17**, 262 mg), prepared from (*R*)-(–)-mandelic acid[21] in methanol (0.5 mL), was added at –15 °C. After being stirred for 0.5 h at 0 °C, the reaction medium was extracted with hexane. The oily thioether **18** (176 mg) was isolated by chromatography on silica gel: [α]$_D$ –77,4° (*c* 3.2, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$) δ 1.23 (t, J = 7.2, 3 H), 3.69 (AB system, J_{AB} = 13.4 Hz, $\delta_A - \delta_B$ = 0.145 ppm, 2 H), 4.15 (m, J = 7.2 Hz, J_{AB} = 10.5 Hz, $\delta_A - \delta_B$ = 0.046 ppm, 2 H), 4.40 (s, 1 H), 7.25–7.45 (m, 10 H).

In the eliminations from benzyl isolongifolyl (**7**) and benzyl camphyl thioether (**12**), the following procedure was used. The elimination medium was acidified with dilute sulfuric acid and extracted with pentane. The mercaptan was separated by chromatography on silica gel with pentane. The fraction was concentrated under reduced pressure. The benzyl mercaptan was transferred to a solution of sodium methylate in methanol.[27] The benzyl mercaptan should be in excess over sodium methylate in order to obtain a pure product. (*S*)-Ethyl chlorophenylacetate (**17**) in 30% excess was added at –20 °C. After 0.5 h at –15 °C and 0.5 h at 0 °C, extraction with pentane was performed, and ethyl (benzylthio)phenylacetate (**18**) was isolated by chromatography on silica gel. Futher purification may be performed by HPLC on silica gel or by reversed-phase techniques.

Preparation of *endo*-Camphanol (8). From *l*-borneol [Aldrich, [α]$_D$ –35.3° (*c* 5.3, EtOH)] was prepared the bornyl tosylate in the usual manner, and it was solvolyzed to camphene.[13] The camphene **2** obtained had [α]$_D$ –107.7° (*c* 5.4, benzene) [lit.[13] –117.0° (*c* 5, benzene), lit.[3] –108° (*c* 5, benzene)]. A solution of this camphene (13.9 g) in hexane (40 mL) was treated at 0 °C with borane–dimethyl sulfide complex from Aldrich (3.5 mL of a 10 M solution). After 3 h at 20 °C, ethanol (35 mL) was added and then 3 M sodium hydroxide (12.5 mL) and hydrogen peroxide (30% solution, 12.5 mL). After 1 h at 50 °C, water was added and extraction with hexane performed. The mixture of *endo*- and *exo*-camphanols **8** and **10** (4:1) was purified by chromatography on silica gel and resolved partially by preparative HPLC on Lichroprep Si-60 (15–25-mesh) from Merck. A mixture enriched in the exoisomer (endo/exo ratio of 3:2) is eluted first, followed by the endo isomer. For pure endo isomer 8:5.76 g (38%); mp

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[27] Addition of the (*S*)-ethyl chlorophenylacetate to the elimination medium gave the racemic ester.

88-88.5 °C; $[\alpha]_D$ +9.2° (*c* 3.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.83 (s, 3 H), 0.98 (s, 3 H), 1.1-1.7 (m), 1.6 (m, 1 H), 2.25 (m, 1 H), 3.61 (ABX system, J_{AB} = 10 Hz, J_{AX} = 9.1 Hz, J_{BX} = 6.9 Hz, $\delta_A - \delta_B$ = 0.038 ppm).

Tosylate of *endo*-Camphanol (9). A solution of *endo*-camphanol (8, 3.11 g) and tosyl chloride (4.05 g) in pyridine (9 mL) was left for 12 h at 4 °C. After addition of water, the tosylate **9** was extracted with ether and purified by chromatography of Florisil: mp 39-41 °C (Lit.[28] mp 48-48.5 °C); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.81 (s, 3 H), 0.97 (s, 3 H), 2.17 (1 H), 2.42 (s, 3 H), 4.00 (d, J = 7.5 Hz, 2 H), 7.28 (d, J = 7.5 Hz, 2 H), 7.73 (d, J = 7.5 Hz, 2 H).

[α-$^2H_2$]Benzyl Camphyl Thioether (12). A solution of sodium [α-$^2H_2$]benzenemethanethiolate (14,5 mmol) and *endo*-camphanol tosylate (**9**, 4.1 g) in methanol (13 mL) and HMPT (4.8 mL) was refluxed for 20 h. After extraction with hexane, the thioether **12** was purified by chromatography on silica gel (150 g) and by HPLC (Lichroprep Si-60). The thioether **12** was obtained as an oil: (2.53 g; $[\alpha]_D$ -16.6° (*c* 4.7, $CHCl_3$; for unlabeled product); ^1H NMR δ 0.80 (s, 3 H), 0.95 (s, 3 H), 1.24 (4 H), 1.56 (3 H), 1.74 (1 H), 2.25 (1 H), 2.40 (ABX, J_{AB} = 12 Hz, J_{AX} = 9.6 Hz, J_{BX} = 5.9 Hz, $\delta_A - \delta_B$ = 0.05 ppm), 3.70 (s, 2 H, for the unlabeled compound **11**), 7.3 (5 H). The deuterium content determined by mass spectroscopy was as follows: $^2H_1$, 2.6%; $^2H_2$, 97.4%. The mass spectrum on the deuterated compound was as follows: *m/e* (relative intensity) 262 (80, M^+), 169 (100), 137 (38), 136 (25). Anal. ($C_{17}H_{24}S_{24}$) C, H.

Elimination on [α-$^2H_2$]Benzyl Camphyl Thioether (12). A solution of [α-$^2H_2$]benzyl camphyl thioether (**12**) (460 mg) and TMEDA (0.3 mL) in THF (50 mL) was treated at -20 °C with butyllithium (1 equiv) solution. After 0.5 h, the temperature was raised to 20 °C. After 6 h, cyclodecane (204 mg) was added as an internal standard, water was added, and extraction with pentane was performed, the aqueous phase being acidified. After the mixture was dried over sodium sulfate, the pentane was removed under reduced pressure. The benzyl mercaptan (150 mg) was separated by chromatography on silica gel and transformed into (*R*)-ethyl (benzylthio)phenylacetate (**18**) as described above. The yield of camphene (83%) was determined by GC with cyclodecane as a standard.

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Theoretical Study of Borohydride Addition to Formaldehyde. A One-Step, Nonsynchronous Transition State

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Concerted and stepwise pathways for the reduction of CH_2O by BH_4^- have been investigated with ab initio calculations by using 3-21G and 6-31G* basis sets. The transition structure for the one-step process is *not* the traditional [2 + 2] four-center structure involving BH bond breaking simultaneous with CH and BO bond making. Instead, it is best described as a BH_3 transfer from the already formed CH bond to the oxygen. This transition state lies 30 kcal/mol above the reactants but 5 kcal/mol below the intermediates in the two-step path, BH_3 + CH_3O^-. When a single water molecule is hydrogen bonded to the formaldehyde oxygen, the calculated activation energy is only 9 kcal/mol. An OH substituent on boron and the presence of a counterion also reduce the barrier substantially.

The reduction of ketones by metal hydrides is one of the most extensively used reactions in synthetic organic chemistry. Nonetheless, in spite of numerous studies spanning 3 decades and involving dozens of research groups, the mechanistic problems implicated in these reactions are not entirely resolved. Evidently, a fuller understanding of the reaction mechanism and its transition state is desirable not only for the satisfaction of intellectual curiosity but also from a synthetic viewpoint as it would allow more accurate prediction of regio- and stereoselectivities in reductions of carbonyl functions belonging to a variety of chemical and biochemical systems. The nature of the transition state in metal hydride reductions has been a subject of speculation and controversy for more than a quarter of a century. In 1953, Barton[1] pointed out that the reduction of ketones in alicyclic series "in general affords the equatorial epimer if it is hindered or very hindered". At the same time, Cram and Greene[2] suggested that the approach of an attacking group would occur from the least hindered side of the carbonyl function. The variable stereochemical results led Dauben, Fonken, and Noyce[3] to formulation of the two fundamental concepts:

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† Fellow of the Alfred P. Sloan Foundation, 1981-1983.

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