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Asymmetric Synthesis in the Methoxy-mercuration of α, β-Unsaturated Esters[1]

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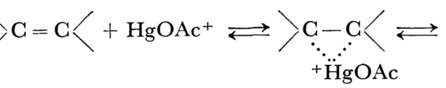
The methoxy-mercuration of (—)-menthyl crotonate, cinnamate, and β-methylcinnamate resulted in partial asymmetric syntheses of the corresponding β-methoxylated derivatives, (—)-*R*-β-methoxybutyric acid, (—)-*S*-β-methoxy-β-phenylpropyl alcohol, and (—)-*S*-β-methoxy-β-phenylbutyl alcohol. The results suggested an ionic mechanism involving a cyclic mercurinium ion as an intermediate, formed by the electrophilic attack of mercuric acetate from the least-hindered side of the double bond in the Cram-Prelog model of the systems, followed by the attack of the methoxy anion from the opposite side. The reaction mechanism leading to the predominant enantiomers was discussed.

The investigation of the methoxy-mercuration of olefins has been reviewed in detail by Chatt,[3] in which a number of interesting questions of stereochemistry and mechanism deduced from stereochemical and kinetic studies of this reaction were raised. Two different mechanisms, one ionic (Eq. (1)) and the other non-ionic (Eq. (2)), have been proposed for the oxy-mercuration of different types of unsaturated compounds. Wright[4] proposed a non-ionic mechanism for the methoxy-mercuration of methyl cinnamate, and later Wright *et al.*,[5] on the basis of an accumulation of extensive studies, established this non-ionic mechanism for the oxy-mercuration of cyclohexene[5a] and 2, 6-dimethylheptene-5-ol-2[5b] and the ionic mechanism for norbornene,[5c] as had been suggested earlier by Lucas *et al.*[6] Mallik and Das[7] have found that, with acrylic esters, the reaction proceeds through an ionic mechanism. More recently, they have obtained kinetic evidence in favor of the ionic mechanism for the methoxy-mercuration of methacrylic, cinnamic esters, and cinnamaldehyde,[8] and in favor of the non-ionic mechanism for acrylonitrile.[9]

$$Hg(OAc)_2 \rightleftharpoons Hg(OAc)^+ + OAc^-$$



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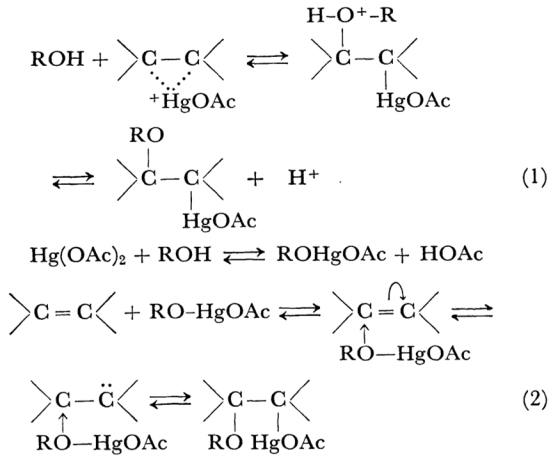
3) J. Chatt, *Chem. Revs.*, **48**, 7 (1951).
4) G. F. Wright, *J. Am. Chem. Soc.*, **57**, 1993 (1935).
5) a) J. Romeyn and G. F. Wright, *ibid.*, **69**, 697 (1947); A. Rodgman and G. F. Wright, *J. Org. Chem.*, **18**, 1617 (1953). b) A. G. Brook, A. Rodgman and G. F. Wright, *ibid.*, **17**, 988 (1952). c) M. J. Abercrombie, A. Rodgman, K. R. Bharucha and G. F. Wright, *Can. J. Chem.*, **37**, 1328 (1959).
6) M. J. Lucas, F. R. Hepner and S. Winstein, *J. Am. Chem. Soc.*, **61**, 3102 (1939).
7) K. L. Mallik and M. N. Das, *ibid.*, **82**, 4269 (1960).
8) A. K. Chaudhuri, K. L. Mallik and M. N. Das, *Tetrahedron*, **19**, 1981 (1963).
9) A. K. Chaudhuri and M. N. Das, *ibid.*, **21**, 457 (1965).



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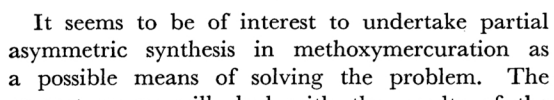
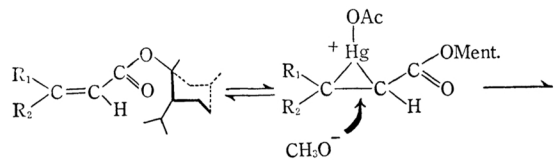
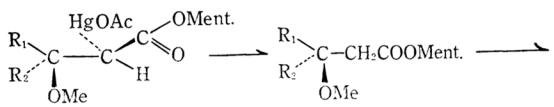


(2)

It seems to be of interest to undertake partial asymmetric synthesis in methoxymercuration as a possible means of solving the problem. The present paper will deal with the results of the methoxy-mercuration of (−)-menthyl crotonate, cinnamate, and β-methylcinnamate, followed by the subsequent removal of the asymmetric moieties initially present, as depicted in Eq. (3), to yield the corresponding β-methoxylated acids or alcohols derived therefrom.



Ia: R_1=H, R_2=CH_3
b: R_1=H, R_2=Ph
c: R_1=CH_3, R_2=Ph



IIa: R_1=H, R_2=CH_3 IIIa: R_1=H, R_2=CH_3
b: R_1=H, R_2=Ph b: R_1=H, R_2=Ph (3)
c: R_1=CH_3, R_2=Ph c: R_1=CH_3, R_2=Ph

IVa: R_1=H, R_2=CH_3, R=H VIa: R_1=H, R_2=Ph
b: R_1=H, R_2=Ph, R=H b: R_1=CH_3, R_2=Ph
c: R_1=H, R_2=Ph, R=CH_3

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Va: R_1=H, R_2=CH_3 VIIa: R_1=H, R_2=Ph
b: R_1=H, R_2=Ph b: R_1=CH_3, R_2=Ph
c: R_1=CH_3, R_2=Ph

Should the reaction proceed through an ionic mechanism, the absolute configuration of the newly-created asymmetric carbon at the β-position should be (R), as would be expected from the Cram-Prelog model,[10] with (−)-menthyl crotonate, and (S) with both (−)-menthyl cinnamate and β-methylcinnamate. Conversely, if the reaction proceeds through a non-ionic mechanism and if the cis-addition prevails, the opposite configurations of β-carbon in the products can be expected.

Consequently, one may be able to determine not only the steric course of the asymmetric synthesis, but also the reaction mechanism by measuring the direction of rotation of the predominant enantiomers, in combination with the absolute configurational correlation.

It has also been well known[1] that the addition of catalysts effectively accelerates methoxy-mercuration, therefore, the catalyzed asymmetric synthesis might provide the means of revealing whether catalysts substantially alter the reaction path or just shift the equilibrium of the first association towards the forward direction.

(−)-Menthyl crotonate (Ia), cinnamate (Ib), and β-methylcinnamate (Ic) were treated with mercuric acetate in anhydrous methanol, in the presence of either acetic acid or boron trifluoride etherate as a catalyst, under standardized conditions.[11] This gave the corresponding β-methoxy-α-acetoxymercurials, IIa, IIb and IIc respectively. It has been known that sulfides,[12a]: thiosulfates,[12b]: and sodium borohydride[12c] easily replace mercury atom of organomercurials with hydrogen atom in alkaline solution. In attempted reductions of IIa, IIb and IIc with sodium borohydride, the aliphatic mercurial, IIa, was alone reduced with success into the corresponding ester, IIIa, but even this was in a poor yield. With the other two, IIb and IIc, a retrogressive elimination reaction predominated over the desired replacement and resulted in the recovery of the starting unsaturated esters, accompanied by the liberation of methanol. In an alternative, where hydrogen sulfide was passed through a pyridine solution of mercuric salts, the mercurial, IIb, was smoothly converted into menthyl β-methoxyhydrocinnamate, IIIb. This was also the case with IIc except the occurrence of an appreciable elimination of methanol. Since the isolation of a pure β-methoxylated product, free from the starting unsaturated ester, was so difficult, the reaction mixture was employed

10) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952); V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).
11) L. T. Sandborn and C. S. Marvel, *J. Am. Chem. Soc.*, **48**, 1409 (1926).
12) a) E. Biilmann, *Ann.*, **388**, 259 (1912); b) G. F. Wright, *J. Am. Chem. Soc.*, **57**, 1997 (1935); c) N. L. Weinberg and G. F. Wright, *Can. J. Chem.*, **43**, 25 (1965).

as such for the following reaction without any further purification. The ester, IIIa, was readily hydrolyzed to afford the desired β-methoxybutyric acid (IVa), in preponderance of the (−)-enantiomer of the well-defined (R)-configuration.[13]

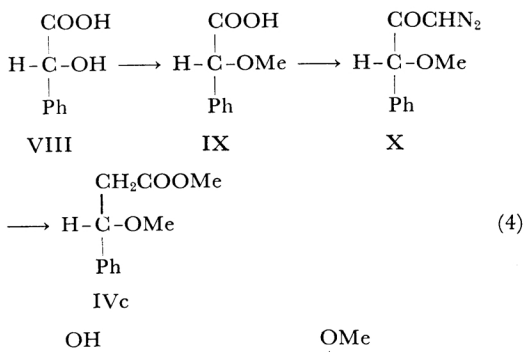
On the other hand, the alkaline hydrolysis of the menthyl esters, IIIb and IIIc gave the original unsaturated acids, Vb and Vc.

Then the two esters, IIIb and IIIc, were reduced with an excess of lithium aluminum hydride into the corresponding alcohols, (−)-β-methoxy-β-phenylpropyl alcohol (VIa) and (−)-β-methoxy-β-phenylbutyl alcohol (VIb) respectively. The alcohol VIa was easily oxidized with potassium permanganate under mild conditions to yield the crude (−)-carboxylic acid, IVb, which was then converted into the pure (−)-methyl ester, IVc.

Furthermore, the methoxy-mercuration of Ic was effectively accelerated by BF_3, while the catalytic effect of acetic acid in this reaction was not so remarkable as that by BF_3, and the reaction mixture still contained a considerable amount of the starting ethylenic compound even after two weeks' reaction at room temperature. It is suspected that the inductive effect of the β-methyl group of Ic inhibits the addition of the methoxide ion which acts as a nucleophile, that steric factors of the β-methyl and phenyl groups play a dominant role in the addition, or that the two factors operate at the same time.

When these experiments using BF_3 as a catalyst were repeated, the optical rotations of the products, IIIa, IVa and IVb, were all found to be levorotatory.

The absolute configuration of the alcohol VIa was established as (S) by chemical correlation with the known (−)-mandelic acid (VIII) (Eq. (4)), while that of (−)-VIb was determined to be (S) by relating it with (+)-(S)-β-oxy-β-phenylbutyric acid XIIb, whose absolute configuration had been established by Mitsui *et al.*[14] (Eq. (5)).



(−)-Mandelic acid (VIII) was converted into methyl ether IX with silver oxide and methyl iodide. (−)-*O*-Methyl mandelic acid IX was converted to diazoketone X in the usual way. The application of Arndt-Eistert reaction[15] to compound IX failed under normal conditions, but a homogeneous Wolff rearrangement[16] afforded a mixture of methyl (−)-β-methoxyhydrocinnamate (IVc) and an unsaturated compound. The desired (−)-methyl ester IVc was isolated in a pure state after ozonolysis to remove the contaminant. The product (−)-IVc, therefore, has the same configuration as (−)-mandelic acid, which was earlier[17] assigned the D-series, *i.e.*, the (R) configuration.

(−)-Methyl ether XIII was derived from (+)-(S)-β-oxy-β-phenylbutyric acid (XIIb) by etherification with sodium hydride and methyl iodide in dimethylsulfoxide; it was then reduced with lithium aluminum hydride to yield the (−)-alcohol VIb. On the basis of this chemical conversion, the (−)-alcohol VIb may be assigned the (S) absolute configuration. These results are summarized in Table 1.

Table 1

Product	Absolute configuration	Specific rotation: AcOH	Optical yield	BF_3	Optical yield
IVa[a]	R	−1.39°	12%	−1.8°	15.5%
IVc[b]	S			−2.14°	4.1
VIa[b]	S	−1.3°	2.5	−2.5°	4.9
VI[b,c]	S			−8°	2.3

a) Based on the maximum $[\alpha]_D$ −11.6°: P.A. Levene (Ref. 13).
b) Based on the maximum $[\alpha]_D$ −51.7° for IVc calculated from $[\alpha]_D$ −42.4°, which was derived from (−)-mandelic acid $[\alpha]_D$ −128° of 82% optical purity: T.B. Johnson *et al.* (Ref. 21).
c) As S. Mitsui *et al.* (Ref. 14) recorded the maximum rotation $[\alpha]_D$ −9.88° for XIIb, in the present study optical yield for VIb was calculated on the basis of our maximum value $[\alpha]_D$ −24.2°.

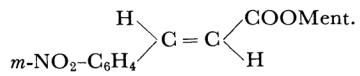
Discussion

On the basis of the asymmetric synthesis and the correlations described above, it appears that the mechanism is trans-addition, as has already been

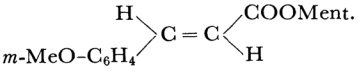
13) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **102**, 297 (1933).
14) S. Mitsui, K. Imano, I. Ohnuma and K. Shimizu, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **85**, 437 (1964).
15) W. E. Bachmann and W. S. Struve, "Organic Reactions," Vol. I, John Wiley & Sons, Inc., New York (1942), p. 38.
16) P. Yates and J. Fugger, *Chem. & Ind.*, **1957**, 1511.; K. Balenović and B. Urbas, *ibid.*, **1959**, 1448. K. Balenović, B. Urbas and A. Deljac, *Croat. Chem. Acta*, **31**, 153 (1959); *Chem. Abstr.*, **54**, 19581 (1960).
17) K. Mislow, *J. Am. Chem. Soc.*, **73**, 3954 (1951)

postulated in the bromine addition; a free radical or non-ionic mechanism seems unlikely. The mechanism may be represented as in Eq. (3); that is, one may suppose, according to Cram's rule of the steric control of asymmetric induction, that the mercuric acetate attacks the double bond preferentially from the least-hindered side, and that the mercurinium cation thus formed, probably a sort of π-complex as depicted, rapidly reacts with the solvent or, more probably, with a methoxide anion generated by the self-ionization of methanol from the opposite side to give the predominant final products. Moreover, it has been proved that the catalyzed reaction proceeds through the same path. Therefore, the catalyst appears merely to function as an electron acceptor.

Apart from the mechanism, it was observed that the resulting mercurials and esters were prone to undergo elimination of methanol to form olefins. The trend of the ease of elimination was in the following order: β-methylcinnamate>cinnamate>crotonante. This trend may be ascribed to both steric and polar effects of the β-methyl and β-phenyl groups. This observation was obtained in a similar reaction of menthyl cinnamates, which were substituted by an electron-attracting nitro group or an electron-releasing methoxy group in the meta-position on the benzene nucleus.



XIV



XV

The behavior of the *m*-nitro compound, XIV, was the same as cinnamate Ib, the elimination of methanol did not occur during reduction with hydrogen sulfide, but it took place easily on alkaline hydrolysis. On the contrary, the *m*-methoxy compound, XV, easily underwent elimination to give the parent cinnamate instead of having the mercury replaced by hydrogen sulfide. These results indicate that this phenomenon must be mainly due to polar effect. The elimination of methanol was found also in the ester exchange reaction of IIIb with methanol in the presence of sodium ethoxide, and in the direct reduction of mercuric salts, IIb and IIc, with $LiAlH_4$ in ether or THF, although, here, the latter solvent easily dissolved the mercuric salt. Both cases indicate the occurrance of an elimination reaction. On the other hand, we should not neglect the effect of menthyl and methoxy groups, since an inappreciable elimination was observed in methyl cinnamate either during reduction with sodium borohydride and hydrogen sulfide or during hydrolysis with OH^-, and in the case of the menthyl ester, XIIa, during alkaline hydrolysis. It might be considered that, since the bulky menthyl and methoxy groups exert a steric hindrance as significant as that of the β-methyl and phenyl groups, the steric crowding of the molecule was enhanced. Thus, OH^- ion would attack the unshielded acidic α-hydrogen more readily than the shielded carbonyl carbon. Therefore, the less basic substituent, –OMe rather than the OH group was eliminated to yield the unsaturated compound.

Kawana *et al.*[18] have recently reported a partial asymmetric synthesis of α-methoxy-β-phenylbutyric acid (IVb) by the same reaction of (−)-menthyl cinnamate (Ib) *via* its mercuric salt, IIb. They mentioned that IIb was reduced with $NaBH_4$ to give the ester IIIb, which was thus subjected to hydrolysis under mild conditions at room temperature for 80 hr to afford a mixture of optically active acid, IVb and Vb, in a ratio of 30 : 70 (by calculation from the NMR data). They have also found that the specific rotation of the mixture showed a value of −4°, and that the VIa prepared from IIb by reduction with $LiAlH_4$ had a value of −25.8°. In the same hydrolysis of our unsaturated-compound-free sample, IIIb, which was obtained by the reduction with H_2S, it was shown that the hydrolysis was incomplete; the contamination by a considerable amount of the (−)-menthyl ester was clearly indicated by its IR spectrum. Consequently, we were not able to isolate completely all the diastereomers in this way.

Experimental

Methoxy-mercuration of Esters. The mercurial-salts, IIa IIb and IIc, were prepared by a modification of the method of Marvel.[11] A mixture of 0.05 mole of esters and 0.06 mole of mercuric acetate in 200 m*l* of absolute methanol was allowed to stand at room temperature, in the presence of about 5 m*l* of acetic acid or boron trifluoride etherate as a catalyst, until the reaction was over. Then, the methanol was evaporated to dryness under reduced pressure; the residual crude mercurial salts were employed for the following reaction without purification.

Two weeks were required for the completion of the reaction in the presence of acetic acid, while with BF_3 the reaction was complete after 24 hr in Ia and Ib, and 48 hr in Ic.

(−)-β-Methoxybutyric Acid (IVa). 1) A solution of 12 g of IIa in 25 m*l* of 10% aqueous sodium hydroxide was stirred with 1 g of solid $NaBH_4$ for 1 hr at room temperature. Acetic acid was added to the chilled mixture to decompose the excess of $NaBH_4$, and the resulting metallic mercury was filtered off. The filtrate was extracted three times with ether, and the ether extract was washed with water. After drying over anhydrous sodium sulfate, the ether was removed to give 1.2 g of crude (−)-menthyl β-methoxybutyrate (IIIa).

18) M. Kawana and S. Emoto, Abstracts of papers presented at the 19th Annual Meeting of the Chemical Society of Japan in 1966 (Vol. III, 31).

The crude IIIa was completely saponified by methanolic potassium hydroxide under reflux for 40 hr, a liquid product was obtained upon acidification and extraction. Distillation under reduced pressure gave 0.8 g (14%) of (−)-β-methoxybutyric acid (IVa), bp 116—118°C/20 mmHg, n_D^{20} 1.4180, $[\alpha]_D^{18}$ −0.33° (neat).

2) On passing hydrogen sulfide into a pyridine (100 m*l*) solution of the mercurial IIa (21 g) which had been prepared by the usual method using acetic acid as a catalyst, mercuric sulfide was precipitated at once. The mercuric sulfide was separated on a filter, and the filtrate was poured into ice water containg concentrated hydrochloric acid. After the removal of excessive hydrogen sulfide by passing air, the product was extracted with ether. The ethereal extract was washed with a 1 N alkaline solution and then with water, and dried over anhydrous sodium sulfate. The removal of the solvent left a pale yellow oil, IIIa (12.8 g).

A solution of 12 g of IIIa and 3.2 g of potassium hydroxide in 30 m*l* of methanol was refluxed for 40 hr. After removal of methanol nearly to dryness under reduced pressure, the residual oil was treated with water and then extracted with ether. The alkaline layer was acidified with dilute hydrochloric acid and extracted three times with ether. The ether extract was washed with water and dried over anhydrous sodium sulfate. The ether was evaporated to give a liquid product which, on distillation, yielded 4.4 g (74%) of (−)-β-methoxybutyric acid (IVa), bp 115—117°C/18 mmHg (lit.[13] 115°C/15 mmHg), n_D^{20} 1.4220, $[\alpha]_D^{18}$ −1.39° (neat). The infrared spectrum was identical with that of the previous product (IVa, 1). The NMR spectrum[19] fully substantiated the structure: a singlet signal (τ 2.15, 1H) may be assigned to one proton of the carboxyl group; a strong singlet (τ 6.64, 3H) is due to methyl protons of the methoxy group; a doublet (τ 8.76, 3H) is assigned to methyl protons, and two multiplets centered at τ 7.45 (2H) and τ 6.2 (1H), are due to methylenic protons and the methyne proton of $-CH_2CH-$ respectively.

The reaction catalyzed by BF_3 was carried out on the same scale and in the same way. Yield, 4.8 g. (80%); n_D^{20} 1.4235; $[\alpha]_D^{22}$ −1.8° (neat). A duplicate experiment on a half scale yielded 2.1 g (71%) ($[\alpha]_D^{22}$ −1.1° (neat)).

(−)-β-Methoxy-β-phenylpropyl Alcohol (VIa). A solution of (−)-menthyl β-methoxyhydrocinnamate (7.4 g) (IIIb) in dry ether (30 m*l*), prepared from IIb (23 g) by the same procedure as in the previous experiment (IVa, 2), was stirred, drop by drop, over an hour into a slurry of $LiAlH_4$ (1.2 g) in dry ether (100 m*l*) at room temperature. After the addition of ester had been completed, the mixture was stirred for 2 hr and then heated to reflux for an additional 30 min. The resulting mixture was treated with water to decompose the excess of $LiAlH_4$, and then with dilute hydrochloric acid. The acidified solution was extracted with ether, and the ether extract was washed with water and dried over anhydrous sodium sulfate. The residue (7 g) of the ethereal extract was dissolved in a small amount of *n*-hexane, and the solution was passed through an aluminum oxide column. A separation of the desired alcohol VIa from (−)-menthol was attained by eluting it with chloroform - *n*-hexane (1 : 9).

In the case of acetic acid, the yield was 2.7 g (69%, calculated from IIIb) (n_D^{25} 1.5023, $[\alpha]_D^{23}$ −1.3° (neat)). BF_3, on the same scale, yielded 3.1 g (80%) (n_D^{25} 1.4985, $[\alpha]_D^{22}$ −2.5° (neat)). A duplicate experiment on a 0.055 mole yielded 2.9 g ($[\alpha]_D^{24}$ −2.1° (neat)).

The infrared spectrum showed the absence of double-bond and ester carboxyl bands, but the presence of a hydroxyl band at 3450 cm.$^{-1}$ NMR spectrum: a singlet at τ 2.7 (5H, due to aromatic protons); a strong singlet at τ 6.85 (3H, due to methyl protons of the methoxy group); a singlet at τ 5.7 (1H, due to the hydroxy group); a multiplet centered at τ 8.0 (2H, due to two protons of $-CH_2-$); a multiplet at τ 6.3 (2H, due to two protons of $-CH_2OH$), and a multiplet at τ 5.65 (1H, due to one proton of $>CH-$).

Methyl (−)-β-Methoxyhydrocinnamate (IVc).[20] To the solution of the above alcohol, ($[\alpha]_D$ −2.1°) (3 g) and potassium hydroxide (0.75 g) in 25 m*l* of water were added, drop by drop, 7 g of potassium permanganate under vigorous stirring at room temperature. The reaction mixture was stirred for 2 hr, during which time a solid separated. This solid was separated on a filter and washed with ether, and the filtrate was acidified with dilute hydrochloric acid and then extracted with ether. After drying over anhydrous sodium sulfate, removal of the solvent left a crude acid IVb (2.3 g, 76%), mp 95—98°C (lit.[12a] 98°C).

The treatment of the acid (2.3 g) with diazomethane in the usual way produced the methyl ester IVc (1.9 g, 73%) bp 80—82°C/0.1 mmHg, n_D^{28} 1.4896, $[\alpha]_D^{25}$ −2.14° (neat). The infrared spectrum was identical with that of an authentic sample prepared from methyl cinnamate *via* β-methoxyhydrocinnamic acid, mp 98—99°C, in the same way. The NMR spectrum: a singlet at τ 2.7 (5H) due to aromatic protons; a singlet at τ 6.4 (3H) due to $-OCH_3$; a singlet at τ 6.85 (3H) due to $-COOCH_3$; a multiplet at τ 7.3 (2H) due to $-CH_2COOMe$, and a multiplet at τ 5.35 (1H) due to the $>CH-$ group.

(−)-β-Methoxy-β-phenylbutyl Alcohol (VIb). Mercuric salt IIc was reduced with H_2S by the procedure described above, yielding an oily product (12 g, bp 140—165°C/1 mmHg) which was found to be a mixture of the desired ester, IIIc, and the parent olefin, Ic. Without separation, the resulting mixture was reduced with $LiAlH_4$ (1.6 g) in dry ether (120 m*l*), as in the previous experiment for VIa. The oily product (7.8 g) was chromatographed on alumina and eluted with chloroform - *n*-hexane (2 : 8). Fifteen fractions were collected. The fractions 1—4 (3.1 g) were a mixture of menthol and olefin (judging by T. L. C.). Fraction 5 (0.8 g) was menthol. Fractions 6—15 (3.7 g) proved to be the desired alcohol, VIb, whose infrared spectrum showed no double-bond absorption band, but it did show a hydroxyl band at 3450 cm^{-1}. The distillation of the last fraction gave 3.6 g. (43%) of pure alcohol VIb, bp 84—85°C/0.1 mmHg, n_D^{25} 1.5146, $[\alpha]_D^{22}$ −5.5° (neat). A duplicate experiment on the 0.033 mole (10 g of Ic) scale yielded 2.7 g (45%) (n_D^{24} 1.5124, $[\alpha]_D^{20}$ −8° (neat)).

NMR spectrum: a singlet at τ 2.7 (5H) due to aromatic protons; a singlet at τ 6.95 (3H) due to

19) The NMR spectra were obtained with a Japan Electron Optics JNM 4H-100 spectrometer, using deuteriochloroform as the solvent and tetramethylsilane as the internal reference.

20) Ger. Pat. 1036250; *Chem. Abstr.*, **54**, 19489 (1960).

$-OCH_3$; a singlet at τ 6.2 (1H) due to $-OH$; a triplet at τ 6.4 (2H) due to $-CH_2OH$; a triplet at τ 8.0 (2H) due to $-CH_2-$, and a singlet at τ 8.425 (3H) due to $-CH_3$.

Absolute Configuration of Methyl (−)-β-Methoxyhydrocinnamate (IVc) (Eq. (4)). The resolution of racemic mandelic acid (VIII)[21] was carried out by using (−)-ephedrine.[22] Compound IX was prepared from (−)-mandelic acid (5.0 g, $[\alpha]_D^{24}$ −128° in 2% EtOH) with silver oxide (15.5 g) and methyl iodide (25 m*l*); yield, 3.6 g; mp 63—64°C, $[\alpha]_D^{18}$ −70° (EtOH). *O*-Methylmandelic acid IX was converted into diazoketone X in the usual way. A solution of the diazoketone X (3.4 g), cuprous iodide (2 g) in acetonitrile (5 m*l*), and dry methanol (30 m*l*) was heated to reflux with stirring for 5 hr. After removal of the catalyst and solvent, the residual oil was treated with water and extracted with ether. The ether was evaporated to give a pale yellow oil, which was purified by distillation to give 0.8 g of a liquid, bp 89—105°C/3 mmHg, whose infrared spectrum showed a C=C absorption band at 1635 cm^{-1}. On the ozonolysis of this material in a solution of carbon tetrachloride under cooling with a freezing mixture, the desired (−)-ester was obtained. Yield, 360 mg, bp 112—113°C/1 mmHg, n_D^{25} 1.4882, $[\alpha]_D^{21}$ −42.4° (neat). The infrared spectrum was identical with that of the product prepared from mercuric salt. Therefore, the ester, IVc, and the alcohol, VIa, have the same (S)-configuration as (−)-mandelic acid (VIII).

21) H. F. Manske and T. B. Johnson, *J. Am. Chem. Soc.*, **51**, 1906 (1929).
22) N. Nagai and S. Kanao, *Ann.*, **470**, 157 (1929).

Absolute Configuration of (−)-β-Methoxy-β-phenylbutyl Alcohol (VIb). In order to determine the configuration relationship between (−)-alcohol VIb and (+)-S-β-hydroxy-β-phenylbutyric acid (XIIb),[14] (+)-butyric acid was converted into VIb. A solution of methylsulfinyl carbanions prepared from 0.08 mole of powdery sodium hydride (purity, 50%) and 60 m*l* of anhydrous dimethyl sulfoxide (DMSO) by the method of Corey.[23] The pale yellow solution was cooled at 20°C, and a solution of 7.2 g of XIIb ($[\alpha]_D^{15}$ +10.2°, *c* 8.50 in alcohol) in 40 m*l* of DMSO was added, drop by drop, with stirring. After stirring for 40 min, 20.5 g of methyl iodide were added over a 5-min period with stirring and cooling in an ice bath, the stirring was then continued for 2 hr at room temperature. The reaction mixture was poured into 100 m*l* of water and extracted with ether. The ethereal solution was washed with water, dried, and evaporated. The oily residue was distilled at bp 105—106°C/5 mmHg, giving 3.7 g (44%) of the ester, XIII ($[\alpha]_D^{18}$ −11.4° (neat)). The ester, XIII (2 g) was reduced with $LiAlH_4$ (0.7 g) in ether (50 m*l*) by the usual procedure to give 1.1 g (65%) of (−)-alcohol VIb, bp 96—97°C/2 mmHg, n_D^{20} 1.5178, $[\alpha]_D^{18}$ −24.2° (*c* 1.422, $CHCl_3$). The infrared spectrum was identical with that of the product, IVb, derived in methoxy-mercuration.

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23) M. Chaykovsky and E. J. Corey, *J. Org. Chem.*, **28**, 254 (1963).