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94. **Issei Iwai and Kazuo Tomita**: Studies on Acetylenic Compounds. XXX.[*1] Absolute Configuration of 1,4-Diphenyl-2-butyn-1,4-diol.

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Only a few reports[1,2] have been found on the absolute configuration of acetylenic alcohols. In the previous paper,[3] we reported that 1-phenyl-2-propyn-1-ol (I) was resolved into two optically active isomers and their absolute configurations were established by oxidizing *levo-* and *dextro*-rotatory acid 3-nitrophthalates (IIa and IIb) of the acetylenic alcohol (I) with potassium permanganate to acid 3-nitrophthalates of (S)-(+)- and (R)-(−)-mandelic acids,[4] respectively; levorotatory active one of the alcohols (I) was decided to be (R)-(−)-1-phenyl-2-propyn-1-ol, as shown in Chart 1. Furthermore, three isomers of 1,6-diphenyl-2,4-hexadiyn-1,6-diol was synthesized from (R)-(−)- and (S)-(+)-1-phenyl-2-propyn-1-ol (Ia and Ib) by oxidative coupling.

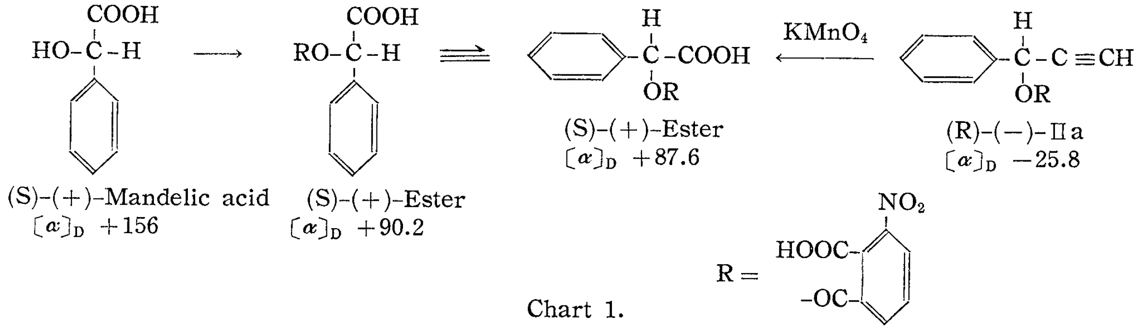

Chart 1.

In this paper, a synthesis of the all probable stereoisomers of 1,4-diphenyl-2-butyn-1,4-diol (III) and the determination of their absolute configurations are described.

Many workers[5~7] isolated the two diastereoisomers of III, namely *alpha*-form (m.p. 142°[5]; 140°[6]; 146°[7]) and *beta*-form (m.p. 103~4°[5]; 102°[6]; 99.5°[7]), from a reaction product of acetylene dimagnesium bromide and benzaldehyde. Lutz, *et al.*[8] suggested that the higher melting isomer (α-form) is to be a *meso*-compound, since this and the corresponding saturated glycol have consistently the higher melting points, comparing with the other isomer (β-form) and its saturated derivative. On the other hand, Zal'kind, *et al.*[9] reported that the optically active glycols $[\alpha]^{14}_{D}$ −33.3° and +30° (in chloroform) could be obtained by the resolution of the higher melting isomer (m.p. 142°). But they did not discuss on the absolute configuration of the enantiomorphs.

When a Grignard derivative of the optically active 1-phenyl-2-propyn-1-ol (Ia) is reacted with benzaldehyde, a *meso*-compound (IIIa) and an optically active diastereoisomer (IIIb) of 1,4-diphenyl-2-butyn-1,4-diol should be obtained, while the other enantiomorphic

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1) E.R.H. Jones, J.D. Loder, M.C. Whiting: Proc. Chem. Soc., **1960**, 180.
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8) R.E. Lutz, J.S. Gillesper Jr.: J. Am. Chem. Soc., **72**, 344 (1950).
9) Yu. S. Zal'kind, A. Efros: C.A., **44**, 3457 (1950); Zhur. Obshchei Khim., **19**, 642 (1949).

isomer (Ib) should give the same *meso*-compound (IIIa) and the other optical isomer (IIIc). Under the consideration, a synthesis of all probable isomers of 1,4-diphenyl-2-butyn-1,4-diol was undertaken.

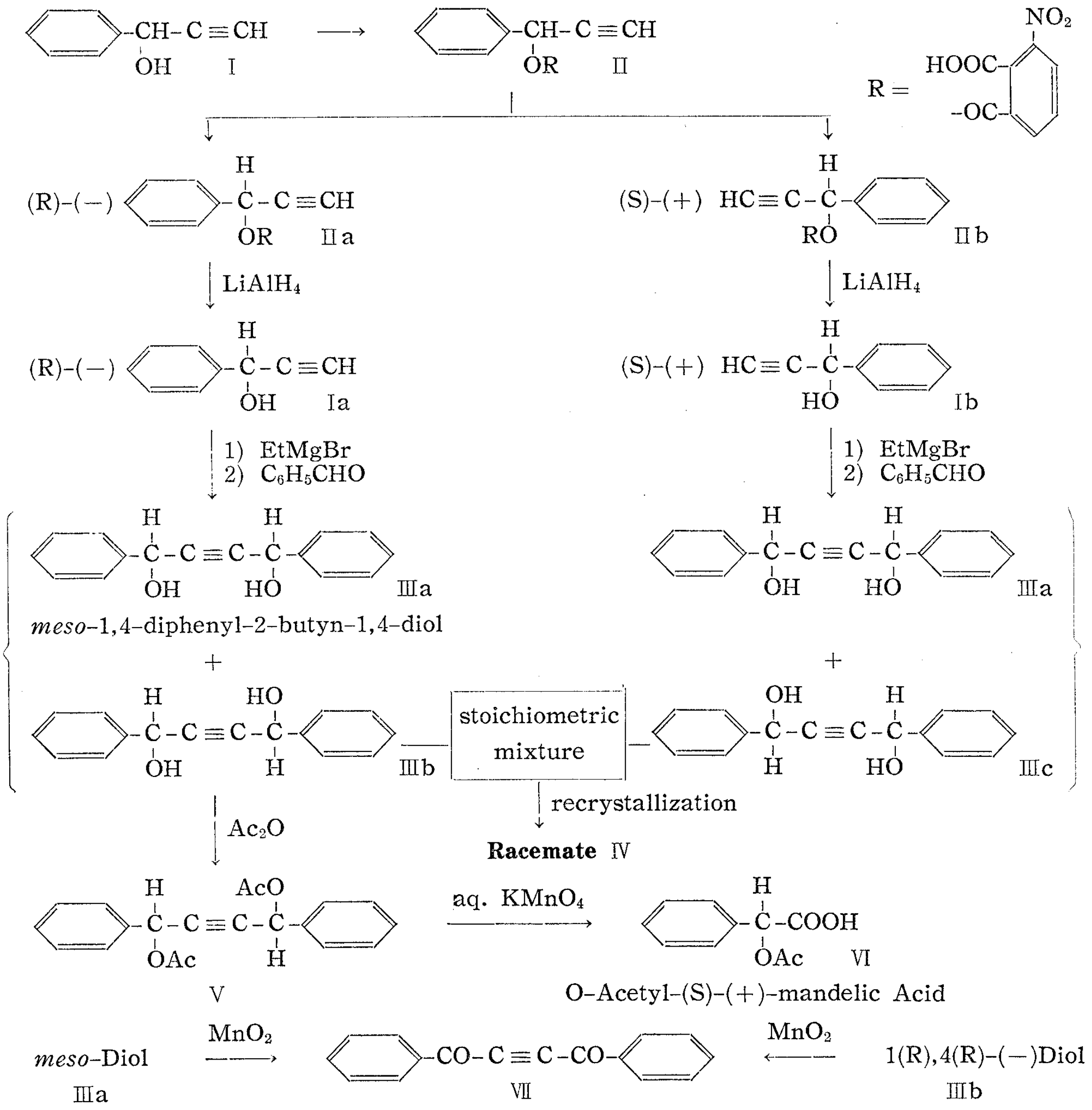

Chart 2.

The optically active 1-phenyl-2-propyn-1-ols (Ia and Ib) were prepared by the method described in our previous report.3) The grignard derivative of (R)-(−)-carbinol (Ia), prepared from Ia and ethylmagnesium bromide in dried ether, was reacted with benzaldehyde to give a yellow oily product. By fractional crystallization of the product IIIa (m.p. 146°) and IIIb (m.p. 110°) were obtained. The higher melting isomer (IIIa) was to be the *alpha*-form from which Zal'kind *et al.* had resolved two optical isomers. But it showed no rotatory power either in chloroform or in ethanolic solution, so it must be a meso compound. On the other hand, the other isomer (IIIb) clearly showed levorotatory power ($[\alpha]_{D}^{26}$ −34.1°) in ethanolic solution. Oxidation of IIIa with manganese dioxide gave a diketone (VII) which showed no depression on admixture with a diketone prepared by the similar oxidation of the active glycol (IIIb). Moreover, the infrared spectrum of the diketone were coincided with that of 1,4-diphenyl-2-butyn-1,4-dione.10)

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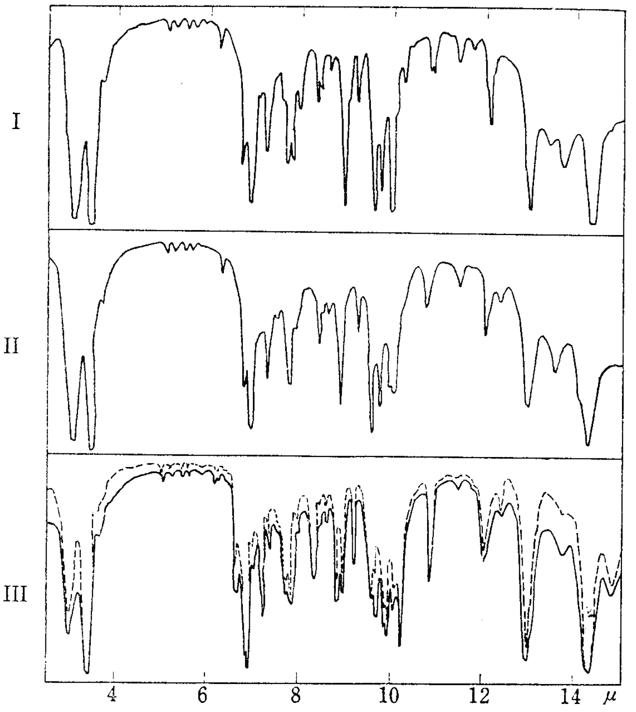
10) L.P. Kuhn, R.E. Lutz, C.R. Bauer: J. Am. Chem. Soc., **72**, 5058 (1950).

From (S)-(+)-carbinol (Ib) and benzaldehyde, the meso compound (IIIa, m.p. 146°) and IIIc (m.p. 110°) were obtained by the same procedure. The glycol (IIIc) showed $[\alpha]^{26}_{\mathrm{D}}$ +34.7° in ethanolic solution, having absolute value almost equal to that of the corresponding levorotatory isomer (IIIb). A mixed melting point of IIIb and IIIc was about 99~105°. From the results of elemental analyses, melting points, specific rotation values and infrared spectra (as shown in Fig. 1), these two isomers (IIIb and IIIc) are confirmed to be enantiomorphs.



meso-1,4-Diphenyl-2-butyn-1,4-diol

rac-1,4-Diphenyl-2-butyn-1,4-diol

1(R),4(R)-(−)-1,4-Diphenyl-2-butyn-1,4-diol (---) and 1(S),4(S)-(+)1,4-Diphenyl-2-butyn-1,4-diol (——)

Fig. 1. Infrared Absorption Spectra (in Nujol)

Crystallizing a stoichiometric mixture of these diols (IIIb and IIIc) from carbon tetrachloride, gave a racemate (IV) which melted at 101~102° and obviously showed mixed melting point depression with another isomers. This racemate was considered to be the *beta*-form isomer.[5~7]

Zal'kind, *et al.* described that the higher melting isomer (m.p. 142°) could be resolved into two optically active glycols ($[\alpha]^{14}_{\mathrm{D}}$ −33.3° and +30.0° in chloroform, m.p. 141~144°). So the isomer must be a racemic mixture. In our investigation, the compound, melted at 146°, is clearly a meso compound and the racemic compound which is prepared from a stoichiometric mixture of two enantiomorphs (IIIb and IIIc) shows a melting point at 101~102°. Furthermore, we would like to mention some ambiguous points in their report. The cinchonine salts of the enantiomorphs must be the diastereoisomers, so the absolute values of their specific rotation are generally different from each other, but in their report the cinchonine salts of 1,4-diphenyl-2-butyn-1,4-diol mono acid phthalate have almost equal absolute values ($[\alpha]_{\mathrm{D}}$ −16.5° and +15°). Moreover, in their investigation, the hydrolyses of the optically active acid phthalates were carried out in hot dilute sodium bicarbonate solution. Under this condition, the resulting glycols are supposed to be more or less racemized. That is because hydrolysis of optically-active half ester of phthalic acid in dilute basic solution, generally, proceeds as an unimolecular cleavage at the alkyl-oxygen bond of the ester to yield a racemic mixture of the alcohols.[11]

Moreover, our results were confirmed by the following experiment; acetylation of the levorotatory glycol (IIIb) afforded the corresponding levorotatory diacetate (V), which was oxidized with aqueous potassium permanganate solution[12] to give an O-acetyl-(S)-(+)-mandelic acid (VI)[13] as shown in Chart 2.

Consequently we concluded that IIIa is a meso compound and IV is a racemate of 1,4-diphenyl-2-butyn-1,4-diol, and the configurational symbol for the levorotatory glycol (IIIb) and for the dextrorotatory one (IIIc) are the 1(R),4(R)-and the 1(S),4(S)-, respectively, according to a nomenclature sequence rule.[4]

Experimental

(±)-1-Phenyl-2-propyn-1-ol (I) was resolved into (R)-(−)- and (S)-(+)-1-phenyl-2-propyn-1-ol (Ia and Ib) by the method described in a previous paper.[3] Their specific rotatory powers were $[\alpha]_D^{27}$ −24.2° (c=8.73, EtOH) and $[\alpha]_D^{27}$ +23.0 (c=9.24, EtOH), respectively.

***meso*-1,4-Diphenyl-2-butyn-1,4-diol (IIIa) and 1(R),4(R)-(−)-1,4-Diphenyl-2-butyn-1,4-diol (IIIb)**——A solution of Ia (3.0 g.) in Et_2O (5 ml.) was added to a Grignard reagent, prepared from Mg (1.1 g.) and EtBr (5.2 g.) in dehydrated Et_2O (20 ml.) under stirring and ice water cooling. After the addition was completed, the mixture was stirred at room temperature for additional 5 hr. To the above reaction mixture was added dropwise a solution of benzaldehyde (2.4 g.) in dry tetrahydrofuran (20 ml.) under stirring at room temperature. After refluxing for 8 hr., the resulting solid complex was decomposed with aq. 4% H_2SO_4 under ice water cooling. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layer was successively washed with H_2O, saturated $NaHSO_3$ solution and H_2O, and dried over Na_2SO_4. The solvent was evaporated to give a reddish brown oil, which was dissolved in hot benzene and allowed to stand overnight to give white crystals, melting at 135~140°. By three recrystallizations from benzene it afforded 1.6 g. of *meso*-1,4-diphenyl-2-butyn-1,4-diol (IIIa) as white needles, m.p. 146°, $[\alpha]_D^{24}$ 0° (c=0.25, $CHCl_3$). *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.68; H, 5.79.

The combined mother liquor was condensed under a reduced pressure on a steam bath to leave a reddish brown syrupy substance, which was dissolved in EtOH and treated with active carbon. The pale yellow residue obtained on evaporation of the EtOH was allowed to stand overnight with small amounts of benzene to yield 2.0 g. of white crystals, which was fractionally crystallized from benzene solution by a stepwise addition of hexane to separate two isomers : 0.3 g. of the *moso*-compound (IIIa) of m.p. 146° and 1.5 g. of a crude levorotatory glycol of m.p. 102~104°, $[\alpha]_D^{26}$ −27.5° (c=4.63, EtOH). The suspension of the latter glycol (1.0 g.) in CCl_4 (ca. 5 ml.) was refluxed on a boiling water bath for a short time, and materials which remained insoluble in hot CCl_4 solution were separated by filtration. The filtrate was cooled to deposit the levorotatory glycol as white needles, which was purified by 5 recrystallizations from CCl_4 to give 0.78 g. of 1(R),4(R)-(−)-1,4-diphenyl-2-butyn-1,4-diol (IIIb), m.p. 110°, $[\alpha]_D^{26}$ −34.1° (c=11.1, EtOH). *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found : C, 80.29; H, 5.71.

1(S),4(S)-(+)-1,4-Diphenyl-2-butyn-1,4-diol(IIIc)——From 1.0 g. of (S)-(+)-1-phenyl-2-propyn-1-ol (Ib) and benzaldehyde (0.8 g.) were obtained 0.37 g. of an inactive glycol (m.p. 146°) and 0.11 g. of 1(S),4(S)-(+)-1,4-diphenyl-2-butyn-1,4-diol (IIIc), m.p. 110°, $[\alpha]_D^{26}$ +34.7° (c=6.05, EtOH), by the same method described above. *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found : C, 80.60; H, 5.79. The inactive glycol proved identical with *meso*-1,4-diphenyl-2-butyn-1,4-diol (IIIa) obtained from (R)-(−)-carbinol (Ia) by a mixed m.p. determination. IR spectra of these three stereoisomers of 1,4-diphenyl-2-butyn-1,4-diol are shown in Fig. 1.

***rac*-1,4-Diphenyl-2-butyn-1,4-diol (IV)**——The mixture of 24.0 mg. of the levorotatory glycol (IIIb) and 24.0 mg. of the dextrorotatory one (IIIc) was dissolved in hot CCl_4, and the solution was cooled to afford 41.3 mg. of *rac*-1,4-diphenyl-2-butyn-1,4-diol (IV) as white needles of m.p. 101~102°. *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found : C, 80.41; H, 5.80. The melting point of the racemic glycol was depressed on admixture with the original active glycols. IR spectrum of the racemic compound is shown in Fig. 1.

1,4-Dipheny-2-butyn-1,4-dione (VII). a) From 1(R),4(R)-(−)-diol (IIIb)——To a suspension of active MnO_2 (1.5 g.) in Me_2CO (15 ml.) was added a solution of 150 mg. of IIIb in Me_2CO (2 ml.) under stirring at room temperature. After 5 hr's stirring the MnO_2 was filtered off, washed with Et_2O, and the solvent

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11) J. Kenyon, S.M. Partridge, H. Phillips : J. Chem. Soc., **1936**, 85 ; M.P. Balfe, M.A. Doughty, J. Kenyon, R. Poplett : *Ibid.*, **1942**, 605.

12) G. Dupont : C.A., **4**, 2934 (1910), Compt. rend., **150**, 1523.

13) A. Mckenzie, H.B.P. Humphries : J. Chem. Soc., **95**, 1106 (1909).

was evaporated under a diminished pressure to leave orange crystals which were recrystallized from benzene-benzine to give 86 mg. of 1,4-diphenyl-2-butyn-1,4-dione (VII) as orange plates of m.p. 110°. *Anal.* Calcd. for $C_{16}H_{10}O_2$: C, 82.04; H, 4.30. Found : C, 81.56; H, 4.39. IR λ_{max}^{Nujol} 6.08 μ (>CO).

b) From *meso*-Diol (IIIa)——The *meso*-diol (160 mg.) was oxidized with active MnO_2 (2.0 g.) by the same method described above to yield 115 mg. of the corresponding diketone (VII), m.p. 110°, which showed no depression of m.p. with the diketone prepared from 1(R),4(R)-(−)-diol (IIIb). *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 82.04; H, 4.30. Found : C, 82.11; H, 4.42. IR λ_{max}^{Nujol} 6.08 μ (>CO).

Acetylation of Levorotatory Diol (IIIb)——A solution of 330 mg. of crude IIIb (m.p. 102~104°, $[\alpha]_D^{26}$ −27.5° in EtOH), 150 mg. of Ac_2O and 1 ml. of pyridine was gently refluxed for 3.5 hr. Excess Ac_2O and pyridine was distilled off under reduced pressure on a boiling water bath, and the residue was distilled *in vacuo* to give 440 mg. of levorotatory diacetate V as a viscous colorless oil, b.p$_{4\times10^{-4}}$ 155~165°(bath temp.), $[\alpha]_D^{26}$ −32.1 (c=9.83, EtOH). *Anal.* Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.05; H, 5.71. IR $\lambda_{max}^{liq.}$ μ : 5.71, 7.26, 8.15 (−OAc).

Acetyl (S)-(+)-Mandelic Acid (VI)——To a suspension of 400 mg. of the diacetate V in a mixture of H_2O (10 ml.) and Me_2CO (5 ml.) was added, dropwise during 2 hr., a solution of $KMnO_4$ (450 mg.) in H_2O (15 ml.) under efficient stirring and ice-salt cooling. The reaction temperature was maintained at 2~5° during the addition. After additional 3 hr's stirring under ice-salt cooling, the precipitated MnO_2 was filtered off and washed with H_2O and Et_2O and the filtrate was extracted with Et_2O. The combined Et_2O extracts were then extracted three times with aq. 5% $NaHCO_3$ solution. From the ethereal solution was obtained an yellow crystalline material, which was recrystallized from CCl_4 to give 40 mg. of pale yellow plates of m.p. 143~144°, but it was not further studied. The aq. $NaHCO_3$ extracts were acidified with HCl and extracted with Et_2O. The dried ethereal solution was concentrated under a diminished pressure to leave 220 mg. of a viscous colorless oil, which crystallized from H_2O on standing to colorless needles of acetyl (S)-(+)-mendelic acid (VI) as a mono hydrate, m.p. 60~63°, $[\alpha]_D^{26}$ +122°(c=4.09, EtOH). *Anal.* Calcd. for $C_{10}H_{10}O_4 \cdot H_2O$: C, 56.60 ; H, 5.70. Found : C, 56.67; H, 5.50. IR λ_{max}^{Nujol} μ : 5.70, 7.26, 8.17 (-OAc), 5.87 (-COOH).

From the published datum on the O-acetyl-(R)-(−)-mandelic acid; $[\alpha]_D^{15}$ −157.7°(c=2.22, EtOH)13) we may conclude that the optical purity of the levorotatory glycol employed as a starting material for the O-acetyl-(S)-(+)-mandelic acid was about 84%. The calculated rotatory power of the pure 1R,4R(−)-diphenyl-2-butyn-1,4-diol (IIIb) should be about −33° from the above result, which is well agreed with the rotatory power of the 1(R),4(R)-(−)-1,4-diphenyl-2-butyn-1,4-diol ($[\alpha]_D^{26}$ −34.1°) obtained in the present experiment.

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Summary

1(R),4(R)-(−)-1,4-Diphenyl-2-butyn-1,4-diol (IIIb) was obtained accompanying with the *meso*-diol (IIIa) by Grignard reaction of (R)-(−)-1-phenyl-2-propyn-1-ol and benzaldehyde. Each of diasteroisomers was oxidized with manganese dioxide to the same 1,4-diphenyl-2-butyn-1,4-dione. The levorotatory glycol (IIIb) was derived to the corresponding diacetate V, which was oxidized with aqueous potassium permanganate into O-acetyl-(S)-(+)-mandelic acid (VI) and the absolute configuration of IIIb was further confirmed as (R)-system. 1(S), 4(S)-(+)-1,4-Diphenyl-2-butyn-1,4-diol (IIIc) was similarly obtained from(S)-(+)-1-phenyl-2-propyn-1-ol and benzaldehyde. A stoichiometric mixture of the enantiomorphs (IIIb and IIIc) gave the racemic compound IV melted at 101~102°.

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