BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 2948—2951 (1969)

A Partial Asymmetric Synthesis *via* a Cyclic Oxyphosphorane[1)]

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(Received March 14, 1969)

A partial asymmetric synthesis was achieved in the carbon-carbon condensation which involved the reaction of (−)-menthyl pyruvate with trimethyl phosphite, followed by alkaline hydrolysis of the intermediate cyclic oxyphosphorane to yield (−)-(S:S)-2,3-dimethyltartaric acid. With knowledge of absolute configurations of both the chiral center and the predominant enantiomer of the product, an *ex post facto* interpretation of the steric course was made on the basis of relative steric stability of transition state conformations of the addition step of III to I.

It has been known that a dicarbonyl compound reacts with trialkyl phosphite to give a cyclic oxyphosphorane (1 : 1 adduct), which can further react with another molecule of the same or of other dicarbonyl compound to yield diastereomeric forms of saturated oxyphosphorane (2:1 adduct).[3)]

In the case of methyl pyruvate and trimethyl phosphite,[3c)] the intermediate 1 : 1 adduct was not an isolable 2,2,2-trimethoxy-1,3,2-dioxaphospholene (II) containing new P–O bonds but exclusively an open dipolar species (III) presumably in a rapid equilibrium with a 1 : 1 adduct having a P–C bond (IV), and the quite reactive dipolar intermediate underwent nucleophilic addition to a second molecule of pyruvate with formation of a mixture of stable diastereomeric 1,3,2-dioxaphospholanes (V). Upon alkaline hydrolysis, the resulting cyclic oxyphosphoranes yielded a mixture of *meso* and racemic 2,3-dimethyltartaric acids (VI).

The new carbon-carbon condensation of this type seems to be interesting from the viewpoint of asymmetric synthesis. Should asymmetric synthesis be obtained by this process, two asymmetric carbon atoms would be simultaneously created in the *threo*-form, and furthermore, this might provide the means of preparing optically active hydroxy-acids of biochemical interest and of assigning absolute configurations thereof. Since pyruvic acid has both a suitably activated prochiral carbonyl function (reaction center) and an adequate "handle" (carboxyl group) through which a chiral reagent (asymmetric center) may be properly accommodated, the present system fulfils the requirements for practice of asymmetric synthesis.

As expected, the asymmetric reaction of (−)-menthyl pyruvate with trimethyl phosphite followed by alkaline hydrolysis of the resulting diastereomeric oxyphosphorane mixture gave 2,3-dimethyltartaric acid of a levorotation. The present asymmetric system produced exclusively the *racemic* form of 2,3-dimethyltartaric acid, in contrast to the corresponding non-dissymmetric reaction.[3c)] This may be attributed to the bulkiness effect of carbomenthoxy groups in the intermediate oxyphosphoranes.

The geometry of the two possible optically inactive forms of 2,3-dimethyltartaric acid was determined by the unambiguous stereospecific routes of synthesis: dimethylfumaric acid[4)] was oxidized with hydrogen peroxide in the presence of WO_3 to give the corresponding dihydroxy-acid, mp 178—180°C. As generally accepted,[5)] the WO_3-catalyzed hydroxylation proceeds in a *trans*-fashion, so that the *trans*-addition of hydroxyl groups to *trans*-olefin should lead to *meso*-modification. Thus, the *meso*-configuration can be safely assigned to this form. In a similar way, the hydroxylation of dimethyl dimethylfumarate with permanganate in ethanol at −40°C gave another isomer melting at 186—186.5°C. The *racemic* configuration can be deduced to this form, for the permanganate hydroxylation is a well-established *cis*-addition.[5)] This deduction is in agreement with that from optical resolvability criterion[6)] and from the IR-spectral study of calcium and barium salts of the two optically inactive modifications.[7)]

1) Taken in part from the dissertation submitted by M. M. to Kyoto University.

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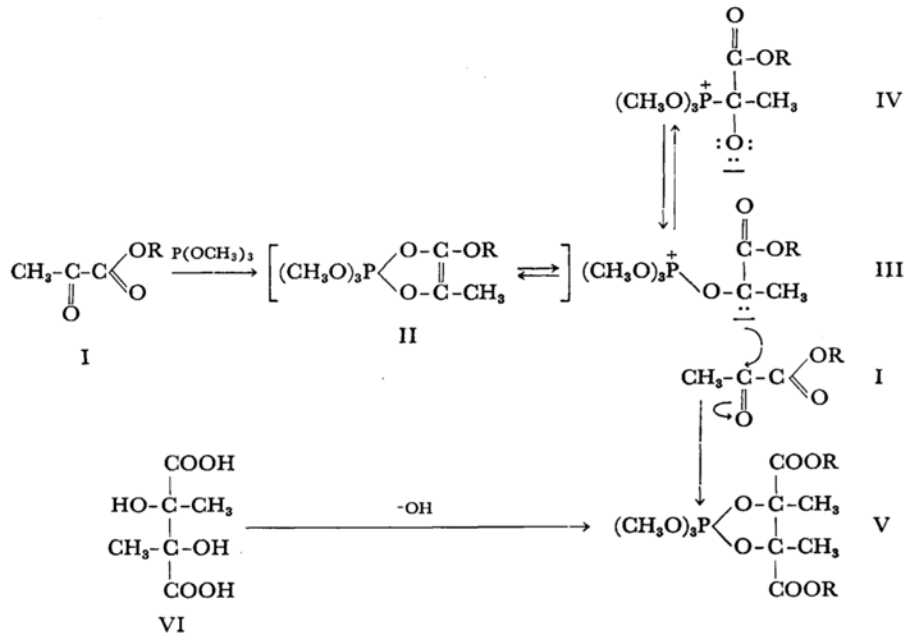
3) F. Ramirez *et al.*, a) *J. Am. Chem. Soc.*, **82**, 2651 (1960); b) *J. Org. Chem.*, **26**, 3041 (1961); c) *Tetrahedron Letters*, **1963**, 323; d) *J. Org. Chem.*, **31**, 3159 (1966); e) *Bull. Soc. Chim. France*, **1966**, 2443.

4) E. Ott, *Ber.*, **61**, 2124 (1928).

5) F. D. Gunstone, in "Advances in Organic Chemistry," Vol. 1, Interscience Publishers, New York (1960), p. 103.

6) Y. Izumi, S. Tatsumi, M. Imaida, Y. Fukuda and S. Akabori, This Bulletin, **39**, 361 (1966).

7) S. Tatsumi, *ibid.*, **39**, 2202 (1966).



R=CH_3- or (−)-menthyl

Scheme 1

The absolute configuration of the chiral form of this acid has not yet been established, without the knowledge of which the steric course of the present asymmetric reaction can not be successfully elucidated. It is hazardous to compare the optical activities of homologous α-hydroxy-acids such as lactic, malic, tartaric and mandelic acids of the well-defined configurations and to extrapolate the correlation as such to the present acid, since the steric environment of the α-carbon atom is substantially changed by replacement of a hydrogen atom with a methyl group. This replacement changes neither configurational series of the conventional DL-system nor notation of configuration based on the RS-system since the sequence of ligands on the chiral α-carbon is not inverted by this process. However, the order of bulkiness of the ligands does alter as one traverses from hydrogen to methyl, the latter being obviously bulkier than hydroxyl. Thus, the characterization of absolute configuration based on both the RS- and DL-systems does not allow unequivocal correlation with sign of the optical activities. Citramalic acid whose absolute configuration has been determined[8] seems to be adequate for configurational correlation with 2,3-dimethyltartaric acid. The stereochemical environments of the α-carbon atom in both acids are closely similar, since the order of priority (sequence rule) parallels that of bulkiness of ligands. The Cotton effect in 200—230 mμ region due to the optically active carboxyl chromophore was observed with both chiral acids. It was found that (+)-(S)-citramalic acid and (−)-2,3-dimethyltartaric acid exhibited a negative Cotton effect in this region, so that the (S:S)-configuration may be tentatively assigned to (−)-2,3-dimethyltartaric acid. The Brewster atomic asymmetry rule[9] also predicts a levorotation for the (S:S)-configuration of this acid.*1

We can now discuss the steric course of the present asymmetric synthesis, having the necessary information on absolute configuration of both the asymmetric center and the final product. The stereochemical-determining step in the present system is the nucleophilic addition of the open dipolar species (III) to a second molecule of (−)-menthyl pyruvate (I) leading to diastereomeric dioxaphospholanes (V). Since it has been shown that, under those conditions (20°C), the condensation is irreversible and there is no detectable equilibration among diastereomers once they are formed[3d], this step must be kinetically controlled. The conformation of the open dipolar III may well be assumed to be coplanar as implicit in the figure, since the lateral overlap of 3d-p-p-p(-p)-p orbitals of $\overset{+}{P}$–O–C–$\overline{\underset{\cdot\cdot}{C}}$(=O)–O concerned may be maximal in this conformation and stabilize the system. The transoidal coplanar topology may reasonably be

8) D. A. Stadler, A. J. Frey and A. Hofmann, *Helv. Chim. Acta*, **46**, 2300 (1963).

9) J. Brewster, *J. Am. Chem. Soc.*, **81**, 5475 (1959).

*1 Other experimental evidence for this assignment will be presented in a future publication.

postulated also for (−)-menthyl pyruvate (I) because this conformation with the minimum dipole-dipole and steric interactions has been invoked by Prelog with some measure of success in his asymmetric reactions involving the nucleophilic addition of Grignard reagent to α-keto esters of chiral alcohols.

A priori, the prime consideration being that all nonbonded repulsive interactions should be minimized in the transition state, the nucleophilic addition of III to I should take place in staggered orientations of substituents of both prochiral carbons and with the carbonyl-oxygen (in I) oriented closer to the phosphorus atom (in II) so as to permit a concerted process in which a new P–O bond concomitantly forms as the new C–C bond does. Under these propositions, four transition state conformations may be possible, if one takes into consideration the diastereotopic faces of both prochiral sp^2-carbanionic carbon in III and carbonyl carbon in I. Of the four, the *re-si* and *si-re* combinations *i.e.* the nucleophilic attack of III with its front side to the rear side of I and the reverse, equally lead to the same and identical transition state conformation, which eventually should afford the *meso*- end product. As can be seen, accumulated *gauche* (*cis*) interactions between substituents, in particular between the two bulkier carbomenthoxy groupings, would make this transition state kinetically unfavorable and this may account for the lack of the *meso*-form in the reaction product. In contrast, the two bulkier carbomenthoxy groups in the *re-re* and *si-si* transition state conformations, which would lead to R:R and S:S enantiomers respectively, are disposed to be *anti* to each other. These transition states are sterically more favored and are thus expected to be energetically more stable than the *meso*-counterpart. Inspection of the scale models reveals that, of these two, the *si-si* transition state conformation is sterically more favored than the *re-re* competitor, since the former is less crowded with respect to the two chiral moieties than the latter. The chemical consequence of this situation is the predominant formation of the (−)-(S : S)-2,3-dimethyltartaric acid in the present asymmetric synthesis. The above-mentioned argument on the steric course combined with its reaction mechanism of the present asymmetric system is in good agreement with what has been found experimentally. This furnishes another example of "double induction"—the discrimination between diastereotopic faces of a chiral compound by another chiral reagent.

Experimental

Asymmetric Synthesis of Dimethyl 2,3-Dimethyltartrate. (−)-Menthyl pyruvate (bp 106—108°C/4 mmHg, n_D^{15} 1.4522, $[\alpha]_D^{25}$ −75.3° (*c* 20.2, methanol);

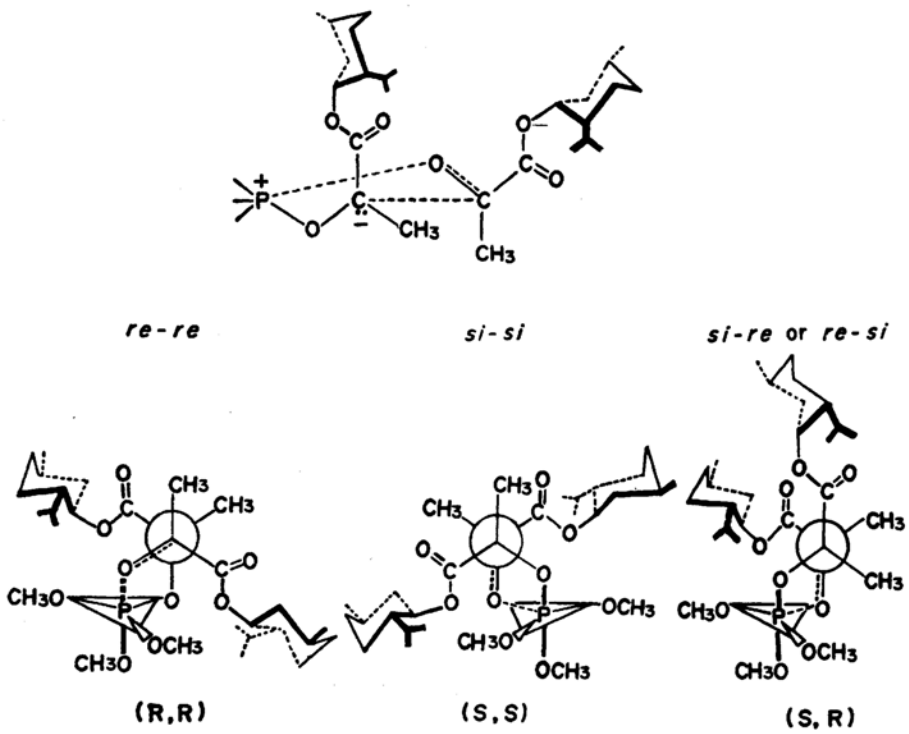


Fig. 1

22.6 g, 0.1 mol) was slowly added to trimethyl phosphite (12.4 g, 0.1 mol) with stirring and external cooling. The mixture was kept at 0°C for 1 hr and at 20°C for 8 hr. The excess of phosphite was removed *in vacuo*, the residue (26.3 g) was poured into water (11 m*l*) and the strongly acidic solution was treated with one equivalent of 2 N NaOH solution. The solution was refluxed for 7 hr and was neutralized with 2 N NaOH and extracted with ether. After removal of ether, the residue (13.8 g) was saponified with an excess of KOH in aqueous methanol for 40 hr. Methanol was evaporated and the liberated menthol was thoroughly extracted with ether. The resulting solution was acidified with dil. sulfuric acid and evaporated to dryness. Ethereal solution of diazomethane was added to the residue and the organic layer was distilled under reduced pressure to give dimethyl 2,3-dimethyltartrate, bp 80—85°C/0.09 mmHg, n_D^{15} 1.4510. The IR-spectrum was identical in every respect with that of the authentic dimethyl (+)-2,3-dimethyltartrate. Yield 2.2 g (35.1%). $[\alpha]_D^{15}$ −1.39° (*c* 9.46, methanol), optical yield 7.06% based on the maximum rotation 19.7° (*vide infra*).

***meso*-2,3-Dimethyltartaric Acid.** Tungstic oxide (150 mg) was dissolved in 30% hydrogen peroxide (10 m*l*) and water (15 m*l*) and to this solution was added dimethylfumaric acid[4] (4.8 g). The mixture was stirred at 70°C for 5 hr and then dried up to give a crystalline product (0.7 g), which was recrystallized from nitromethane to yield *meso*-2,3-dimethyltartaric acid, mp 179—180°C.[6,7] Yield 0.2 g (3.4%).

***racemic* 2,3-Dimethyltartaric Acid.** To a chilled (−40°C) solution of dimethyl dimethylfumarate (5.5 g) in ethanol (180 m*l*) was added a solution of potassium permanganate (5 g) and magnesium sulfate heptahydrate (4.5 g) in water (150 m*l*) during 6 hr. The mixture was set aside at room temperature for 12 hr and then filtered. The combined filtrate and washings were concentrated under reduced pressure to about 30 m*l*-volume and was thoroughly extracted with chloroform. The extract was distilled to give dimethyl 2,3-dimethyltartrate boiling at 91—93°C/0.2 mmHg (3.1 g). The dimethyl ester was saponified with KOH (1.3 g) in boiling methanol and the solvent was removed, acidified with 2 N HCl and extracted with ethyl acetate. Removal of ethyl acetate yielded a crystalline product (2.1 g), which was recrystallized from nitromethane to give *racemic* 2,3-dimethyltartaric acid, mp 185—186°C. Found: C, 40.60; H, 5.64%. Calcd for $C_6H_{10}O_6$: C, 40.45; H, 5.66%. Yield 1.2 g (18.2%).

Resolution of *racemic* 2,3-Dimethyltartaric Acid. The racemic acid (7 g) and (−)-ephedrine (6.5 g) were dissolved in hot ethyl acetate (300 m*l*) and the solution was allowed to stand overnight at room temperature, when the ephedrine salt (10.5 g) crystallized out. After triangular fractional recrystallization from acetone, the salt was decomposed with ammonia to afford, after acidification and usual work-up, the optically active acid of the constant rotation (0.7 g). Mp 161—162°C, $[\alpha]_D^{25}$ 13.6° (*c* 0.99, water).

The active acid was converted by the standard method with diazomethane into the dimethyl ester. bp 81—83°C/0.1 mmHg, n_D^{25} 1.4485, $[\alpha]_D^{25}$ 19.7° (*c* 2.65, methanol).

Synthesis and Resolution of Citramalic Acid. According to the method in literature,[11] (±)-citramalic acid, mp 116—117°C, was prepared and resolved through the brucine salt to afford optically pure (+)-acid, mp 112°C, $[\alpha]_D^{25}$ 23.6° (*c* 3.0, water).

Optical rotatory dispersion curves were measured on a Yanagimoto Model ORD-185A recording spectropolarimeter using a 0.5 cm cell at 20°C in 0.1 N HCl solution.

(+)-Dimethyltartaric acid $[\phi]_{589}$ +24.2° (*c* 1.53): ORD (*c* 0.055)$[\phi]_{350}$ +120°, $[\phi]_{229}$ +3170° (1st extremum), $[\phi]_{218}$ 0°, $[\phi]_{208}$ −4530°! (shoulder). (*a*) +77!.

(+)-Citramalic acid $[\phi]_{589}$ +35.8° (*c* 2.31): ORD (*c* 0.196) $[\phi]_{350}$ +94°, $[\phi]_{240}$ 0°, $[\phi]_{228}$ −197° (1st extremum), $[\phi]_{222}$ 0°, $[\phi]_{212}$ +1290°! (shoulder). (*a*) −14!.

Partial support of this study by grant D86547 from the Ministry of Education is gratefully acknowledged (Y. I.). The authors are indebted also to the referee for his valuable suggestions.

10) *Biochem. Prepns.*, **9**, 25 (1962).