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Absolute Configuration of Some Chiral Cyclopropanes

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Synopsis. The absolute configurations of (1*S* : 2*R*)-(−)-*cis*-, and (1*S* : 2*S*)-(+)-*trans*-1-phenylcyclopropane-1,2-dicarboxylic acids, and (1*S* : 2*R*)-(−)-*cis*-, and (1*S* : 2*S*)-(+)-*trans*-1-phenyl-1,2-bis(acetoxymethyl)cyclopropanes were established by correlation to (*R*)-(−)-2,2-diphenylcyclopropane-1-carboxylic acid.

During the course of studies on asymmetric synthesis, we found that establishment of the absolute configuration of a series of chiral cyclopropanes is necessary.

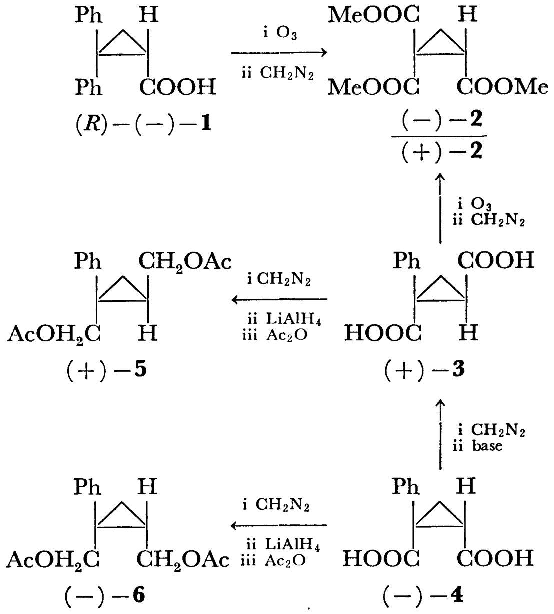
Absolute assignment of configuration is given to *trans*-, (**3**) and *cis*-1-phenylcyclopropane-1,2-dicarboxylic acids (**4**), and *trans*-, (**5**) and *cis*-1-phenyl-1,2-bis(acetoxymethyl) cyclopropanes (**6**) by chemical transformations. These chiral cyclopropanes are correlated to (−)-2,2-diphenylcyclopropane-1-carboxylic acid (**1**) of the known (*R*)-configuration[1] through the key compound, methyl cyclopropane-1,1,2-tricarboxylate[2] (**2**).

(*R*)-(−)-2,2-Diphenylcyclopropane-1-carboxylic acid, −231°, was ozonized to give, after esterification of the ozonolysis product with diazomethane, methyl cyclopropane-1,1,2-tricarboxylate (**2**) having a rotation of −134.8°. The *R*-configuration is thus assigned to (−)-(**2**).

Methyl (+)-*trans*-1-phenylcyclopropane-1,2-dicarboxylate +134.0°, derived from the partially resolved acid (**3**), +85.8°, was converted in the same manner as described above into (+)-(**2**) with a dextrorotation +124.6°. From the conversion, the *S*-configuration can be assigned to the chiral carbon-2 in the parent (+)-(**3**) and consequently, the *S*-configuration of another chiral carbon-1 in (+)-(**3**) reasonably follows from the *trans*-geometry of carboxyl groups.

The optical purity of (+)-(**2**) derived from (+)-(**3**) is 92.4% based on the maximum rotation +134.8°, so that the value 92.8° is given to (+)-(**3**) as its maximum rotation, which is in good agreement with the value 92.9° attained by optical resolution *via* brucine salt. The agreement not only warrants the fact that neither racemization nor fractionation occurred during ozonolysis and the subsequent work-up in the present transformations, but also provides evidence for stereochemical integrity of compounds involved.

The base-catalyzed isomerization of methyl (−)-*cis*-1-phenylcyclopropane-1,2-dicarboxylate obtained by esterification of the corresponding free acid (−)-(**4**), −185.3°, afforded (+)-*trans*-(**3**)-ester with a dextrorotation of +126.1°, which is evidently epimeric at the ring carbon-2. It follows that (−)-(**4**) is assigned to the (1*S* : 2*R*)-configuration and should possess the maximum rotation −212.0°.



The lithium aluminum hydride reduction of optically pure (+)-(**3**), followed by acetylation of the reduction mixture gave the corresponding diol acetate, (+)-1-phenyl-*trans*-1,2-bis(acetoxymethyl)cyclopropane (+)-(**5**), +5.4°, while the same treatment of (−)-*cis*-(**4**)-ester −178.8° afforded (−)-1-phenyl-*cis*-1,2-bis(acetoxymethyl)cyclopropane −45.5°, (−)-(**6**). The (1*S* : 2*S*)-configuration of (+)-(**5**) and (1*S* : 2*R*)-configuration of (−)-(**6**) are evident, the maximum rotation of the latter being inferred to be −52.1°.

The Brewster calculation of conformational asymmetry[3] predicts the sign and magnitude of molecular rotation in fair agreement with those observed.

	$[M]^\circ_{\text{calcd}}$	$[M]^\circ_{\text{obsvd}}$
(*R*)−(**2**)	−135	−291
(1*S* : 2*S*)−(**3**)	+135	+191
(1*S* : 2*R*)−(**4**)	−210	−437
(1*S* : 2*S*)−(**5**)	+60	+14
(1*S* : 2*R*)−(**6**)	−90	−137

Experimental

Specific rotations were measured on a Perkin Elmer 241 polarimeter at 25 °C in 1% methanol solution unless otherwise stated.

Ozonolysis. According to the procedure we previously described,[4] (−)-2,2-diphenylcyclopropane-1-carboxylic acid [α]$_D$ −231.1° (chloroform) was ozonized in acetic acid at room temperature and the resulting product was esterified by the standard method with diazomethane to give, after isolation by preparative vpc, methyl cyclopropane-1,1,2-tricarboxylate (−)-(**2**). The IR- and NMR-spectra were identical with those of the authentic specimen.[2] n_D^{30} 1.4477, [α]$_D$ −134.8°.

In the same way, (+)-*trans*-1-phenylcyclopropane-1,2-dicarboxylic acid [α]$_D$ +85.5°, (+)-(**3**), prepared and resolved according to McCoy,[5] gave (+)-(**2**) whose identity was fully substantiated by means of spectroscopy, n_D^{30} 1.4477, [α]$_D$

+124.6°.

Epimerization of methyl (−)-*cis*-1-phenylcyclopropane-1,2-dicarboxylate (50 mg: $[\alpha]_D$ −178.8°; (−)-(**4**)-methyl ester) was effected by treating with methyl phenylacetate (100 mg) and sodium hydride (30 mg) in DMF (1.5 ml) at 40 °C for 1 hr and, after neutralization, the product was subjected to preparative vpc to give pure (+)-(**3**)-methyl ester (28 mg); $[\alpha]_D$ +126.1°.

Resolution of (±)-(**3**), mp 198.5—199 °C,[5] and of (±)-(**4**), mp 152.5—153 °C[5] was performed *via* the brucine salt by fractional crystallizations from methanol eventually to give (+)-(**3**), mp 144 °C, $[\alpha]_D$ +92.9° (methyl ester, n_D^{25} 1.5153, $[\alpha]_D$ +144.3°), and (−)-(**4**), mp 154 °C, $[\alpha]_D$ −185.3°, (methyl ester, n_D^{25} 1.5133, $[\alpha]_D$ −178.8°) respectively.

For the lithium aluminum hydride reductions, the method by Inamasu *et al.*[6] was followed: (+)-(**3**)-methyl ester $[\alpha]_D$ +144.3° gave, after purification by preparative vpc, (+)-1-phenyl-*trans*-1,2-bis(acetoxymethyl)cyclopropane (+)-(**5**), n_D^{25} 1.5004, $[\alpha]_D$ +5.4°, while (−)-(**4**)-methyl ester $[\alpha]_D$ −178.8° yielded the *cis*-counterpart (−)-(**6**), n_D^{25} 1.5018, $[\alpha]_D$ −45.5°. Identification of each was obtained by IR- and NMR- spectroscopies.

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