(1*R*,2*S*)-(+)-*cis*-1-Methoxycarbonyl-2-methylcyclobutane

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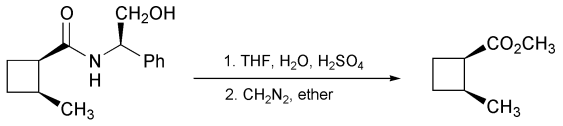
An X-ray crystallographic structure determination for the related (*R*)-(−)-2-phenylglycinol derived amide demonstrates that (+)-*cis*-1-methoxycarbonyl-2-methylcyclobutane is the (1*R*,2*S*) isomer.

In the course of work requiring synthetically useful amounts of chiral 2-methylcyclobutanecarboxylic acid derivatives of securely known absolute stereochemistry we prepared a sample of (+)-*cis*-1-methoxycarbonyl-2-methylcyclobutane, 99% ee by GC on an Astec 10-m octakis(2,6-di-*O*-pentyl-3-trifluoroacetyl) γ-cyclodextrin capillary column. The observed rotation of our sample, $[\alpha]_D$ +58 ($CHCl_3$), seemed hardly consistent with a report[1] that the (+)-enantiomer of this ester of better than 97% ee had a rotation of $[\alpha]_D$ +22.4 ($CHCl_3$). An X-ray crystallographic structure determination[2] for the corresponding amide (**2**) derived from (*R*)-(−)-2-phenylglycinol quickly settled the stereochemical point (Scheme 1, Fig. 1).



2 (1*R*,2*S*)-(+)-**1**

Scheme 1

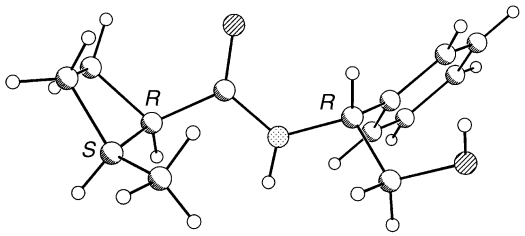
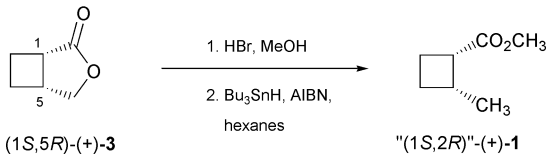


Fig. 1 X-ray crystallographic structure based drawing of *N*-[(*R*)-α-(hydroxymethyl)benzyl]-(1*R*,2*S*)-*cis*-2-methylcyclobutanecarboxamide (**2**).

The relative stereochemistry provided by the X-ray structure and the known absolute stereochemistry of the (*R*)-phenylglycinol unit[3] provide unambiguous evidence for a sure assignment of absolute stereochemistry: (+)-*cis*-1-methoxycarbonyl-2-methylcyclobutane, $[\alpha]_D$ +58 ($CHCl_3$), is (1*R*,2*S*)-(+)-**1**.

The earlier assignment of (1*S*,2*R*) absolute stereochemistry for (+)-**1**[1] must be reversed, and some assignments of absolute stereochemistry for related structures need to be reconsidered. The concerns are of more than academic interest, for structural correlations leading to configurational assignments based on links to (1*R*,2*S*)-(+)-**1** extend to numerous natural products as well as patented analogs of leukotriene, oxetanocin A, prostaglandins, and spermine.[4]

The original stereochemical assignment depended on a structural correlation from the bicyclic lactone (1*S*,5*R*)-(+)-**3** to (+)-**1** (Scheme 2). A sample of (+)-**3**, $[\alpha]_D$ +116.7 ($CHCl_3$), was combined with HBr in CH_3OH to give *cis*-1-methoxycarbonyl-2-(bromomethyl)cyclobutane; reduction of the CH_2Br group to CH_3 with Bu_3SnH gave (+)-**1**, $[\alpha]_D$ +22.4 ($CHCl_3$), in 97% yield.[1] Since the stereochemical correlation of Scheme 2 leads



(1*S*,5*R*)-(+)-**3** "(1*S*,2*R*)"-(+)-**1**

Scheme 2 Reported[1] structural correlation.

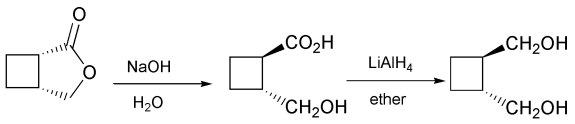
to the wrong assignment of absolute sterechemistry for (+)-**1**, either the stereochemical assignment for (+)-**3** must be reversed, or the synthetic chemistry involved must, somehow, be misformulated.

The reference compound (+)-**3** had been assigned (1*S*,5*R*) stereochemistry based on a correlation with a chiral sample of *trans*-1,2-di(hydroxymethyl)cyclobutane (Scheme 3).[5] Lactone (+)-**3** ($[\alpha]_D$ +118.7 ($CHCl_3$), 100% ee) was hydrolyzed and epimerized to afford a *trans*-2-(hydroxymethyl)cyclobutanecarboxylic acid as a viscous oil, $[\alpha]_D$ −32.4 ($CHCl_3$), in 52% yield.[5] Reduction gave "(1*R*,2*R*)"-(−)-**5**, $[\alpha]_D$ −4.8 (EtOH), in 97% yield. The literature cited for the "(1*R*,2*R*)" *trans*-diol reported $[\alpha]_D$ −4.3 (EtOH),[6] a seemingly fair match. The reference diol (−)-**5** was thought to be essentially 100% ee, based on criteria related to circular polarization of luminescence;[7] it was derived from (−)-*trans*-cyclobutane-1,2-dicarboxylic acid,[7] a compound of securely known (1*R*,2*R*) absolute stereochemistry.[8]

In the published account of the conversion of (−)-*trans*-cyclobutane-1,2-dicarboxylic acid to the "(1*R*,2*R*)" *trans*-diol,[7] no sign of rotation for the diol was cited[9,10] Reduction of (1*S*,2*S*)-(+)-*trans*-cyclobutane-1,2-dicarboxylic acid ($[\alpha]_D$ +156.4 (H_2O)) with $LiAlH_4$ gives (1*S*,2*S*)-(−)-**5**, $[\alpha]_D$ −67.1 (benzene).[11] In an independent study, the (1*R*,2*R*)-(−)-diacid was reduced to (1*R*,2*R*)-(+)-**5**, $[\alpha]_D$ +64 (benzene).[12]

The chemical correlation steps in Scheme 3 apparently involve a great loss of optical purity. For *trans*-diol "(1*R*,2*R*)"-(−)-**5** $[\alpha]_D$ −4.8 (EtOH) was reported,[5] far from the value more recently determined for the (1*S*,2*S*) isomer, $[\alpha]_D$ −67.1 (benzene).[11] The base-catalyzed reaction in Scheme 3, conducted with conc. aq. NaOH in a stainless steel tube at 130 °C over 8 days,[5] may well have involved more than a simple epimerization at C1 adjacent to the carboxylic acid (carboxylate anion) function.[13]

Given the poor preservation of stereochemical integrity and the faulty reference sample employed, the synthetic steps in Scheme 3 cannot provide a sure designation of configuration for lactone (+)-**3**. Nevertheless we believe that lactone (+)-**3** is indeed the (1*S*,5*R*) isomer, even though the original grounds for the assignment now appear to be indecisive, since it has been converted through a rational synthetic sequence to a sample of enantiomerically pure (+)-grandisol.[14]



(+)-**3** "(1*R*,2*R*)"-(−)-**4** "(1*R*,2*R*)"-(−)-**5**

Scheme 3 Reported[5] correlation of (+)-**3** with *trans*-diol (−)-**5**.

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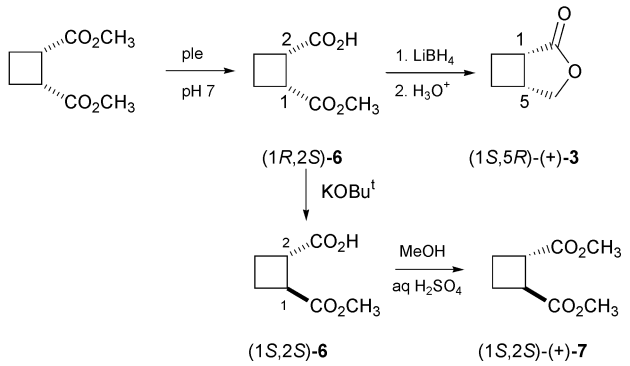
A related stereochemical puzzle is posed by various reports of pig liver esterase (ple) catalyzed hydrolyses of *cis*-1,2-di(methoxycarbonyl)cyclobutane (Scheme 4): the reported $[\alpha]_D$ values of the ester-acid products are −3.6 ($CHCl_3$),[15] −3.0 ($CHCl_3$),[16] +1.6 ($CHCl_3$),[17] +2.7 (EtOH)[18] and +4.4 (EtOH).[19]

Correlations establishing the absolute stereochemistry of ester-acid **6** are outlined in Scheme 4. A levorotatory sample of **6** ($[\alpha]_D$ −3.0 ($CHCl_3$)) was converted as shown to (+)-**3**, $[\alpha]_D$ +106.7 ($CHCl_3$), estimated to be of 97% ee.[16] Thus the assignment is (1*R*,2*S*)-**6**. A dextrorotatory sample of **6** ($[\alpha]_D$ +4.4 (EtOH)) was correlated with (1*S*,2*S*)-(+)-1,2-di(methoxycarbonyl)cyclobutane,[8] (1*S*,2*S*)-(+)-**7** (86% ee by chiral GC; $[\alpha]_D$ +120 (acetone), +119 ($CHCl_3$)), confirming the assignment (1*R*,2*S*)-**6**.[19]



Scheme 4 Correlations[16,19] of (1*R*,2*S*)-**6** with lactone (+)-**3** and diester (+)-**7**

We believe that all enantioselective ple-catalysed hydrolyses of *cis*-1,2-di(methoxycarbonyl)cyclobutane favor formation of (1*R*,2*S*)-(−)-**6**, and that its specific rotation is small. During hydrolyses and isolation procedures a base-catalysed epimerization might occur to a small extent, converting *cis* product (1*R*,2*S*)-(−)-**6** to *trans* ester-acid (1*S*,2*S*)-(+)-**6** having a much larger specific rotation.[8] A minor amount of (1*S*,2*S*)-(+)-**6** in a product mixture might well escape detection and yet have a major impact on the observed specific rotation.

Accordingly, samples of **6** having $[\alpha]_D$ −3.0 ($CHCl_3$)[16] and $[\alpha]_D$ +4.4 (EtOH)[19] are not enantiomeric:[19] both samples are more likely to be largely (1*R*,2*S*)-(−)-**6**, containing different, small, easily overlooked amounts of (1*S*,2*S*)-(+)-**6**. Similarly, samples of **6** with reported $[\alpha]_D$ values of +1.6 ($CHCl_3$)[17] and −1.8 ($CHCl_3$)[20] are not enantiomeric, and the stereochemical assignment "(1*S*,2*R*)"-(−)-**6** suggested by Lukas[20] must be reversed. The "(1*S*,2*R*)"-(−)-**6** sample was obtained from (1*R*,2*S*)-(+)-1-(methoxycarbonyl)cyclobut-3-ene-2-carboxylic acid[21] through a catalytic hydrogenation and correlated with an enantiomer of **3** that could only be formed from (1*R*,2*S*)-**6**.[20]

The present work establishes that (+)-**1** is the (1*R*,2*S*) isomer. We believe that (+)-**3** is (1*S*,5*R*), and that all ple hydrolyses of *cis*-1,2-di(methoxycarbonyl)cyclobutane give predominantly (1*R*,2*S*)-(−)-**6**, in spite of reports of variable and sometimes positive $[\alpha]_D$ values, for under the reaction conditions small amounts of (1*S*,2*S*)-(+)-**6** may be formed.

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Notes and references

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2 *Crystal data* for **2**: $C_{14}H_{19}NO_2$, M_r = 233.30 g mol^{-1}, crystals (mp 138–139 °C) from hexanes–ethyl acetate, colorless plates of dimensions 0.80 × 0.50 × 0.28 mm^3. Mo-Kα (0.71073 Å), 95 K. Tetragonal, space group $P4_12_12$, a = 9.4318(2), c = 27.989(1) Å, V = 2489.87(10) Å^3, Z = 8. ρ calc. 1.245 g cm^{-3}, μ Mo = 0.083 mm^{-1}, 3070 independent reflections ($2.28 < \theta > 28.29$), R_1 (all data) = 0.0347, wR_2 (all data) = 0.0770. CCDC 182/1807. See http://www.rsc.org/suppdata/cc/b0/b006639g/ for crystallographic files in .cif format.

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13 'Based on the new configurational assignment of (+)-**1**, Professors Jones and Toone speculate that in the vigorous conditions required in their correlation, the C-1 center epimerized to some degree, either during the acid-catalyzed ring opening of cyclobutane lactone (+)-**3**, or from hydrogen atom migration to give a tertiary radical in the subsequent tin hydride mediated reduction step (reactions ii and iii of Scheme 1 of ref. 1), giving compound **1** with an invalid sign of rotation. They also note that the active site model interpretation of the ple-catalyzed hydrolysis of (±)-**1** must be revised, with the cyclobutyl ring occupying the H_L site. They suggest that this interesting, and unexpected, situation is dictated by the fact that the previously anticipated preferred binding of **1** depicted in Fig. 2 of ref. 1 is less favorable than having BOTH the hydrophobic groups binding in hydrophobic sites. This extra benefit is achievable with the cyclobutyl group of the (1*R*,2*S*)-**1** substrate located in the H_L site and the methyl group in the H_S site, which is then in accord with a (1*S*,2*R*) configuration for the recovered ester **1**, as required by the present study. They feel that this preferred binding mode is a special case elicited by the particular substitution pattern of **1**, and do not expect this intriguing facet of ple specificity to apply to substrates with larger hydrophobic group differences.' (J. B. Jones, private communication).

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