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(1*R*,2*R*)-(−)-Bis(methoxycarbonyl)spiropentane

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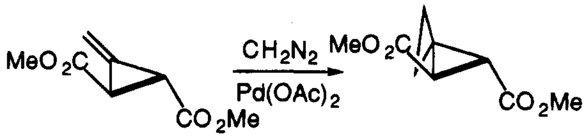
Few chiral derivatives of spiropentane have been prepared. (*S*)-(+)-1-Phenylspiropentane (estimated to be 12% optically pure)[1] and (1*S*,2*S*)-(−)-dimethylspiropentane (estimated to be 84% optically pure)[2] are the exceptions. Optically active samples of methyl- and *n*-hexylspiropentane of unknown absolute configurations and optical purities have also been reported.[3] While much has been learned through studies of the thermal rearrangements of meso and racemic spiropentane systems,[4] still more detailed information which would become accessible through investigations employing chiral spiropentane substrates of high optical purity and defined absolute stereochemistry remains to be uncovered.

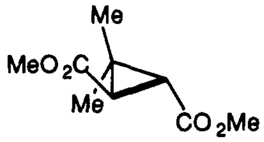
Feist's acid[5] seemed a most suitable precursor to chiral substituted spiropentanes, for the racemic form is commercially available, it may be resolved efficiently,[6–8] and its absolute stereochemistry is secure.[6] Further, in view of its increasing importance in synthetic applications leading toward oxetanocin and related antibacterial and antiviral agents,[9] one may anticipate that both racemic and chiral forms of Feist's acid will soon become still more economically accessible. Methylenation[10] of the exocyclic double bond of the dimethyl ester of one antipode of Feist's acid would give a *trans*-1,2-bis(methoxycarbonyl)spiropentane of known absolute stereochemistry, and the ester groups on the spiropentane framework could be easily converted to other functionalities appropriate to specific objectives.

This simple synthetic and stereochemical objective has now been realized. Feist's acid has been resolved. Correlations of enantiomeric excess (ee) values determined by chiral gas chromatographic analyses using a Lipodex E fused silica capillary column[11] and optical rotations for dimethyl esters derived from various samples of the acid during the resolution gave a linear dependence and an estimated rotation $[\alpha]_{546}$ +157° (CCl_4) for optically pure (*R*,*R*)-(+)-**1** (Figure 1), a rotation slightly higher than values reported in the literature (e.g., $[\alpha]_{546}$ +144.8° (CCl_4)[9a]). A sample of better than 99% ee was treated with diazomethane in ether in the presence of palladium diacetate to give (1*R*,2*R*)-(−)-bis(methoxycarbonyl)spiropentane, $[\alpha]_{546}$ −69° (CCl_4), of better than 99% ee by chiral GC.



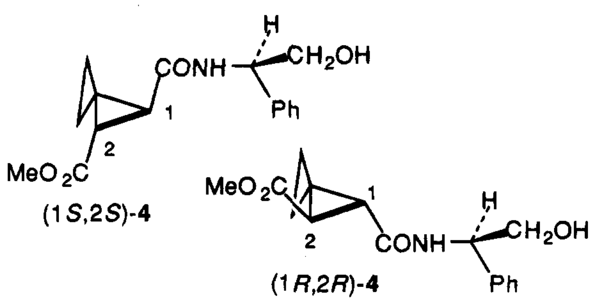
(*R*,*R*)-(+)-**1** (*R*,*R*)-(-)-**2**

Three expectations sensitive to absolute stereochemistry were confirmed through this correlation and experiments based on the racemic spiropentane diester. First, the (1*R*,2*R*)-(−) stereochemistry and sign of rotation combination mirror that seen for *trans*-caronic acid dimethyl ester (1*R*,2*R*)-(−)-**3**.[12] Second, selective hydrolysis of *rac*-**2** with pig liver esterase gives an acid ester product enriched in the (*R*,*R*) enantiomer, while recovered diester is enriched in the (*S*,*S*) form; the same absolute stereochemical preference has been reported for the PLE-catalyzed hydrolysis of *rac*-**3**.[13]



(*R*,*R*)-(-)-**3**

Third, the two diastereomeric amide esters from *rac*-**2** and (*R*)-(−)-phenylglycinol are well separated by HPLC on silica; hydrolysis of the early eluting diastereomer (1*S*,2*S*)-**4** to the diacid followed by treatment with diazomethane affords (*S*,*S*)-(+)-**2**, while the second eluting amide ester (1*R*,2*R*)-**4** leads to (*R*,*R*)-(−)-**2**. This order of elution is consistent with prior experience with the corresponding amide esters from *trans*-cyclopropane-1,2-dicarboxylates and (*R*)-(−)-phenylglycinol.[14,15]



(1*S*,2*S*)-**4**

(1*R*,2*R*)-**4**

The elution order for the enantiomers of **1** and **2** on the Lipodex E chiral GC column employed was in each

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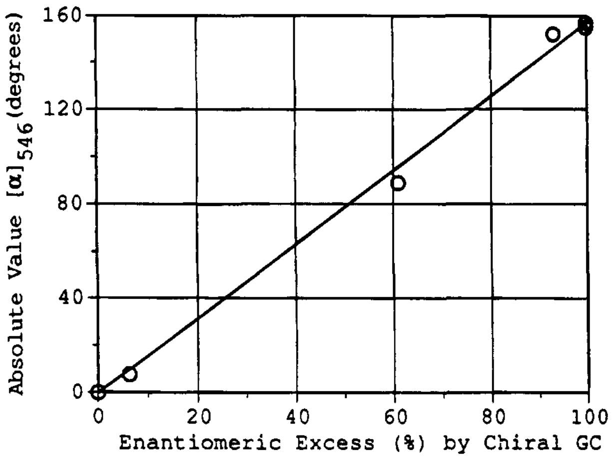

Figure 1. Correlation of enantiomeric excess for the dimethyl ester of Feist's acid determined by chiral GC on a Lipodex E column with the absolute value of specific rotation at 546 nm.

case (1*S*,2*S*) before (1*R*,2*R*), just the *reverse* of simple anticipations based on the elution order shown by the enantiomers of *trans*-1,2-bis(methoxycarbonyl)cyclopropane and *trans*-1,2-bis(methoxycarbonyl)-3-methylcyclopropane ((*S*,*S*) before (*R*,*R*)) and of diester **3** ((*R*,*R*) before (*S*,*S*)).[16] The diastereoselective interactions between these diesters and the modified γ-cyclodextrin GC liquid phase are evidently not restricted to the ester groups. In this case the chiral GC technique proved wonderfully convenient for determining % ee and absolute stereochemistry for samples of **1** or **2** once the correlations between chromatographic behavior and absolute stereochemistry had been rigorously established (Figure 2). Mere analogy based on a naive extrapolation from the chiral GC characteristics of the *trans*-1,2-bis(methoxycarbonyl)cyclopropanes, the *trans*-1,2-bis(methoxycarbonyl)-3-methylcyclopropanes, and the enantiomers of **3** would have led to error.

Experimental Section

Analytical HPLC was carried out with a Rainin system employing Rainen Rabbit HBX pumps, a Gilson 112 UV–vis detector interfaced to a Macintosh computer, and a Macherey-Nagel Nucleosil 50-5 column. Preparative gas chromatographic separations were done using a Varian Aerograph A90-P3, a 4.8-mm i.d. 1-m 10% FFAP on 60/80 Chromosorb W column, and helium as carrier gas. Analytical gas chromatographic (GC) analyses were conducted two-dimensionally on a Hewlett-Packard (HP) 5790 gas chromatograph equipped with one injection port, two flame ionization detectors, HP cross-linked methyl silicone and 5% phenyl methyl silicone 25-m × 2-mm 0.33 μm ultraperformance capillary columns, and a dual channel HP 3396 Series II reporting integrator, with helium as carrier gas. Chiral GC analyses were done isothermally using a 50-m 0.25-mm i.d., 0.4-mm o.d. fused silica Lipodex E column, with octakis(2,6-di-*O*-pentyl-3-*O*-butyryl)-γ-cyclodextrin as the stationary phase (Macherey-Nagel, Düren, Germany). Mass spectra were determined with a HP 5970 mass selective detector interfaced with a HP 5890 gas chromatograph using a HP 25-m × 2-mm 0.33 μm ultraperformance cross-linked methyl silicone column and a HP 59970B workstation. The ^{1}H NMR spectra were obtained in $CDCl_3$ solutions on a General Electric QE-300 spectrometer. Chemical shifts are reported in ppm relative to Me_4Si at 0.0 ppm. Optical rotations were measured on a Perkin-Elmer 241 polarimeter using a 1-mL 100-mm path-length glass microcell. Microanalyses were performed by E + R Microanalytical Laboratories, Inc., Corona, NY.

Methylenecyclopropane-*trans*-2,3-dicarboxylic acid (Feist's acid) was prepared following the literature[17] or obtained from Aldrich Chemical Co. Fischer esterification with methanol and catalytic H_2SO_4 gave the dimethyl ester *rac*-**2**: bp 55 °C (0.3 mm); lit.[8] bp 69–70 °C (0.5 mm); ^{1}H NMR δ 5.68 (t, 2H), 3.72 (s, 6H), 2.89 (t, 2H); MS *m/e* 170 (M$^+$, 8), 155 (21), 139 (76), 127 (40), 112 (82), 111 (100).

(*R*,*R*)-(+)-1-Methylene-2,3-bis(methoxycarbonyl)cyclopropane ((*R*,*R*)-(+)-1). The resolution of Feist's acid was accomplished using quinine and the procedures reported by Doering and Roth.[6] Small (100 mg) samples of quinine salts obtained during the resolution were converted to optically active samples of Feist's acid with 10% HCl, which were then esterified with diazomethane. The dimethyl esters, after isolation and purification by preparative GC, were analyzed by polarimetry and by chiral GC at 90 °C ((*S*,*S*) enantiomer at 53 min; (*R*,*R*) at 58 min)). The (% ee, $[\alpha]_{546}$) correlation is given in Figure 1 ($r^2 = 0.997$; slope = 1.57); the highest measured rotation was $[\alpha]_{546}$ +157° (c = 0.7, CCl_4). The 6% ee point in Figure 1 was derived from a mother liquor enriched in the (*S*,*S*) diacid; all others were from quinine salts and were enriched in the (*R*,*R*) enantiomer.

***trans*-1,2-Bis(methoxycarbonyl)spiropentane (*rac*-2).** A solution of 5.0 g of *rac*-**1** in 100 mL of ether was stirred and treated with ethereal diazomethane and then with 20 mg of Pd(OAc)$_2$. After 30 min the reaction mixture was filtered and the filtrate was concentrated by distillation. When necessary, the product mixture was re-treated with diazomethane and Pd(OAc)$_2$ to give the spiropentane diester with only traces of unreacted starting material (analytical GC). Kugelrohr distillation at 60 °C (0.3 mm) gave 3.5 g (65%) of *rac*-**2**: ^{1}H δ NMR 3.69 (s, 6H), 2.58 (s, 2H), 1.12 (m, 4H). The analytical sample was secured through preparative GC.

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.85, H, 6.23.

This ester was also prepared through a Simmons–Smith reaction: 5.3 g of *rac*-**1**, 3.2 mL of CH_2I_2, and catalyst prepared from cuprous chloride (0.79 g) and zinc (5.3 g) in ether at reflux for 48 h was subjected to a conventional workup to give 2.8 g (49%) of Kugelrohr-distilled product. Chiral GC analysis at 90 °C showed good separation of the enantiomers, with equal intensity peaks at 78 and 86 min (Figure 2).

(*R*,*R*)-(−)-1,2-Bis(methoxycarbonyl)spiropentane ((*R*,*R*)-(−)-2)). A sample of (*R*,*R*)-(+)-**1**, $[\alpha]_{546}$ +155°, was converted with diazomethane and Pd(OAc)$_2$ to the stereochemically corresponding spiropentane which, after purification by preparative GC, was found to be better the 99% ee (retention time on the Lipodex E column, 87 min; Figure 2) and to have $[\alpha]_{546}$ −69° (c = 0.9, CCl_4).

Enantioselective Partial Hydrolysis of *rac*-2. Partial hydrolysis of *rac*-**2** using pig liver esterase (Sigma) in 0.1 M KH_2PO_4 buffer at pH 6.93 was conducted using a pH-stat as detailed for *trans*-1,2-bis(methoxycarbonyl)cyclopropane.[14] The acid ester product was isolated and esterified with diazomethane; the dimethyl ester was found by chiral GC to be of 11% ee, favoring

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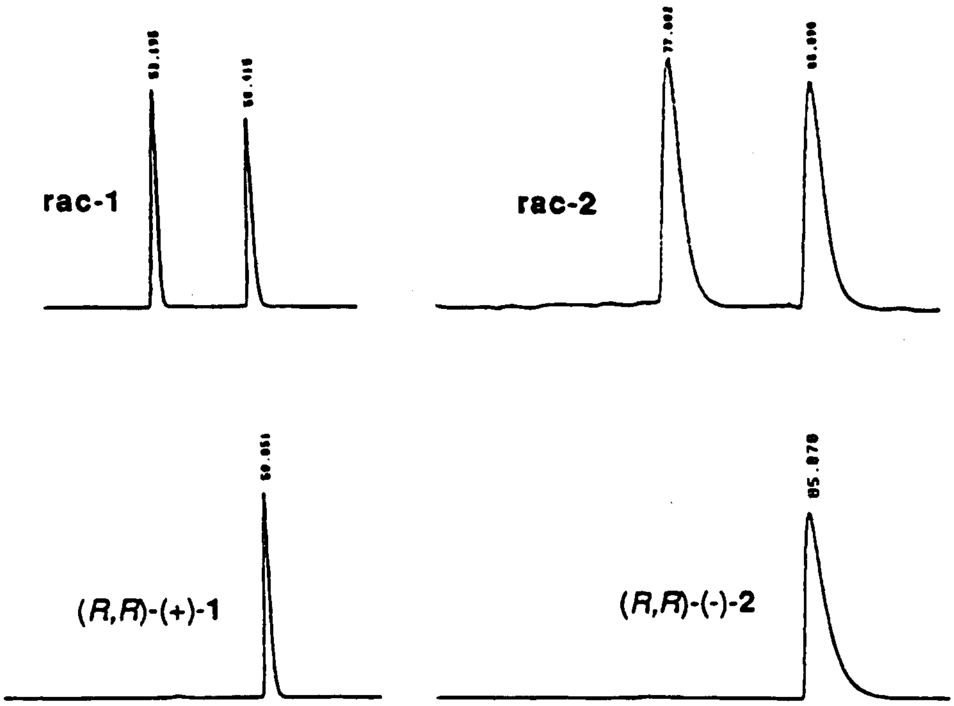

Figure 2. Chiral GC separations of the enantiomers of **1** and **2**, with racemic samples above and (*R,R*) enantiomers below.

the (*R,R*) enantiomer. A sample of diester recovered from the partial hydrolysis was found by chiral GC to be 10% ee, favoring the (*S,S*) enantiomer.

Resolution of *rac*-2 through Amide Esters from (*R*)-(−)-Phenylglycinol. Following procedures detailed elsewhere,[14] the acid ester prepared from *rac*-**2** through selective hydrolysis, as described immediately above, was converted to the corresponding (*R*)-(−)-phenylglycinol-derived amide esters. The diastereomers were separated by HPLC with 65:35 ethyl acetate:isooctane as the mobile phase. A sample of each was collected, hydrolyzed,[18] and esterified with diazomethane. Chiral GC analyses demonstrated that the early eluting amide ester gave rise to (*S,S*)-(+)-**2** (retention time 78 min), while the later eluting diastereomer provided through hydrolysis and esterification (*R,R*)-(−)-**2** (retention time 86 min).

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