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Short Communication

Synthesis and Stereochemical Characterization of the Optical Isomers of 2-Methoxycarbonyl-1-thiaindane 1-Oxide

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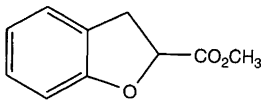
Chiral bicyclic ester substrates such as the dihydrobenzofuran **1** have been intensively studied with respect to enantioselectivity in chymotrypsin-catalysed ester hydrolysis,[1] since conformationally rigid structures of this kind are very useful to probe the steric requirements of the enzyme's active site. In the case of compound **1**, the two substrate enantiomers have been found to exhibit a rate ratio of ca. 90; the *R*-form being the more reactive. Interestingly, the effect was found to reside entirely in the k_{cat}-value,[2] meaning that the binding of the substrate to the active site is not changed with respect to orientation and is not influenced by the configuration at the stereogenic centre.

To extend the experimental studies on the chymotrypsin-catalysed ester hydrolysis we have selected compounds **2** as enzyme substrates. Structure **2** represents four stereoisomers, i.e., two enantiomeric pairs of *trans*- and *cis*-isomers. In this paper their syntheses, chemical properties and stereochemical characterization are described.



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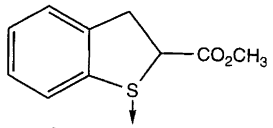

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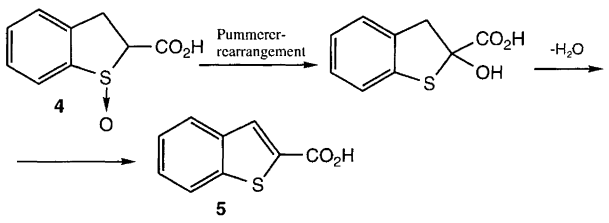
Results and discussion

1-Thiaindane-2-carboxylic acid (**3**) was synthesized and resolved as described by Fredga.[3] An X-ray crystallographic investigation of the brucine salt of the (+)-rotating form of **3** showed this to have an *S*-configuration.[4]

Oxidation of **3** with MCPBA in ether at 0 °C yielded mixtures of *trans*- and *cis*-diastereomers **4**, from which the pure forms could be isolated after repeated recrystallizations at low temperature. Harsher conditions led to the degradation of **4** yielding mainly benzo[b]thiophene-2-carboxylic acid (**5**), clearly the result of a Pummerer-rearrangement followed by elimination of water (Scheme 1).



Scheme 1.

Studies of the product compositions of **4** immediately after the oxidation step and at various stages of recrystallization indicated that *trans*-**4** is the kinetically favoured isomer but also the more labile, yielding the unsaturated product **5** (Scheme 1) more readily than *cis*-**4**. This explains why the minor product *cis*-**4** could be isolated from recrystallization procedures carried out at elevated temperatures, since such conditions will selectively cause Pummerer rearrangement and elimination of *trans*-**4**.

Assignment of the geometric configuration was inferred from NMR-data (Table 1), particularly the chemical shift anisotropy displayed. Differentiation between the A and B protons in the ABX spin system was achieved via NOESY spectra, showing signal enhancement for H_A (H_A defined as located *cis* to H_X). The geminal H_A and H_B are subject to the deshielding anisotropy effect across the ring depending on the orientation of the sulfoxide

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Table 1. ^{1}H NMR characteristics of the ABX spin system of the *trans*- and *cis*-isomers of the sulfoxides. The spectra were recorded in acetone-d_6 (A) and benzene-d_6 (B), respectively.

Compound No.	(Solvent)	Isomer	δ(ppm) H_A	H_B	H_X	J/Hz AB	AX	BX
4	(A)	*cis*	3.55	4.04	4.46	16.7	7.7	9.5
		trans	3.89	3.65	4.30	16.9	7.9	5.1
2	(A)	*cis*	3.56	4.06	4.50	16.6	7.6	9.2
		trans	3.89	3.64	4.29	16.6	8.0	5.3
	(B)	*cis*	2.66	4.05	3.37	16.6	7.8	9.3
		trans	ca. 3.16[a]	ca. 3.16[a]	3.95	16.4	7.3	6.2

[a] Overlap of resonance signals, $|\delta_{H_A} - \delta_{H_B}| = 0.07$ ppm.

group in the respective isomers.[5] The magnitude of this shift in acetone is similar for both protons: 0.34 and 0.39 for H_A and H_B, respectively. The large difference in J_{BX} between the *trans*- and *cis*-isomers, with $J_{BX} > J_{AX}$ for the *cis*-isomer, should be attributable to the expected change in the dihedral angle, defined by the C2–C3 bond and caused by a difference in puckering of the non-planar five-membered ring and a preferred pseudo-axial orientation of the sulfoxide bond.[6] The large aromatic solvent-induced shifts for the H_A and H_X protons of *cis*-**2** shown in Table 1 are in accordance with the results found from studies of some penicillin-sulfoxides.[7] Benzene coordinates with the electron-deficient sulfur atom of the sulfoxide bond, causing an upfield shift of protons directed towards the benzene ring. In the *cis*-form of **2**, H_A and H_X are both located on the coordination side of the five-membered ring which is further freed from any steric hindrance. Accordingly, the solvent-induced shifts for these protons are as high as 0.90 and 1.13 ppm, respectively, whereas H_B, located on the other side, is virtually not shifted at all.

The *trans*- and *cis*-isomers of **4** showed similar UV spectra but a large difference in their CD spectra. Most apparent is the reversal in sign of the CD-bands above 225 nm for the *cis*-isomer, which is absent for the *trans*-isomer, and also the considerably higher magnitude of [θ] of the latter. This is further reflected in the specific rotations, which are larger in the *trans*-isomers by a factor of 8 at 589 nm. Owing to the lability of the latter, their specific rotations were obtained by extrapolation of the straight line giving [α] as a function of the *trans*/*cis*-composition.

The transformation to the methyl ester derivatives **2** with the use of diazomethane was associated with a substantial change in isomer distribution. This was due to the fact that the esters **2** were even more prone to rearrangement/elimination. The *trans*-form is the more labile, as manifested by a highly increased *cis*/*trans*-ratio in the product when the reaction was run in a protic solvent such as methanol, particularly when the solvent was not immediately evaporated off. Under these conditions epimerization by inversion at C-2 could also take place, as shown by the conversion of (1*S*,2*S*)-**4** to a mixture of (1*S*,2*S*)-**2** and (1*S*,2*R*)-**2**. This was not found, however, when the reaction was run in hexane–dioxane as the solvent, in which case the esterification was quantitative with stereochemical integrity. These esterification reactions were readily studied since the four optical isomers of **2** were partially chromatographically resolved, the enantiomers of the *trans*-form being eluted prior to those of the *cis*-form. The elution orders obtained on chiral LC of the optical isomers of compounds **4** and **2** are given in Table 2.

A preliminary study of the chymotrypsin-catalysed hydrolysis of racemic methyl 1-thiaindane-2-carboxylate by our chiral LC method showed the (−)-(*R*)-form to be hydrolysed faster than its antipode by a factor of *ca.* 10. This is consistent with the experimental results obtained previously[2] from studies of the oxygen analogue **1**, which also could be predicted from theoretical considerations involving computer-aided molecular modelling.[8]

Experimental

Synthesis. The sulfide **3** (0.90 g, 5 mmol) was dissolved in anhydrous diethyl ether (3 ml) and the solution cooled to 0 °C. An ether solution of MCPBA [1.07 g (5.25 mmol) in 4 ml)] was then added with stirring. After a few minutes a white precipitate of **4** appeared and this was filtered

Table 2. Retention data (*k'*-values) of the stereoisomers of compounds **2** and **4**.

Compound No.	Mobile phase system[a]	*k'* (absolute configuration)			
4	A	1.75 (1*S*,2*R*)	1.75 (1*R*,2*S*)	4.06 (1*R*,2*R*)	4.23 (1*S*,2*S*)
2	B	4.32 (1*S*,2*R*)	4.54 (1*R*,2*S*)	5.30 (1*S*,2*S*)	5.87 (1*R*,2*R*)

[a] Mobile phase system A: 2-propanol (2.5%) and formic acid (0.05%) in hexane; mobile phase system B: dioxane (2%) in hexane.

off after ca. 30 min at 0°C. Yield: 0.89 g (91%). The diastereomer composition was found to be 70% *trans*- and 30% *cis*-isomer (by LC and ^{1}H NMR spectroscopy).

Separation of the diastereomeric sulfoxides was achieved by low-temperature recrystallization. The pure diastereomers of **4** were obtained in low yield after repeated recrystallization from acetone (cooling of the solution to −25°C).

Compound **4** (0.30 g, 1.53 mmol, 70% *trans*-form) was rapidly dissolved in acetone (3 ml) at 30°C and the solution was then immediately cooled to −18°C. After filtration, this procedure was repeated three times yielding 30 mg (ca. 10%) of pure *trans*-**4** as determined by LC. When the dissolution of **4** was carried out at higher temperature (50°C), enrichment of the *cis*-form was obtained after cooling (owing to the faster decomposition of *trans*-**4**). In this way pure *cis*-**4** was obtained in low yield after repeated recrystallizations. Pure *cis*-**4** was also isolated from the product obtained after oxidation of **3** with peracetic acid in acetic acid at 4°C after two recrystallizations from ethyl acetate.

trans-**4**: $[\alpha]_D^{25} = \pm 240°$ (MeCN), *cis*-**4**: $[\alpha]_D^{25} = \pm 30.0°$C (MeCN). The compounds were further characterized by ^{1}H NMR and mass spectroscopy, and k'-values in LC. M.p.s could not be used since, owing to the thermal lability of the compounds, they were found to be close to the m.p. of **5**.

The methyl esters **2** were prepared by addition of an equimolar amount of diazomethane in ether to a solution of **4** (0.50 g, 2.6 mmol, *trans*/*cis*: 70/30) in methanol (5 ml). Evaporation of the solvent gave a product composition of 32% of unsaturated ester and 68% of **2** (*trans*/*cis*: ca. 30/70) as determined by LC.

The same method was used for almost pure (1*S*,2*S*)-**4** [(+)-*trans*-**4**; de > 90%) yielding **2** [(1*S*,2*S*): 67% and (1*S*,2*R*): 33%] with little or no formation of unsaturated ester.

Liquid chromatography. Analytical chiral liquid chromatography for the determination of the enantiomeric or diastereomeric composition was performed by means of equipment consisting of an LDC ConstaMetric mod. 3200 high-pressure pump, a Rheodyne injector with a 20 µl loop, an analytical column, and an ERC-7210 variable wavelength UV detector (Erma Optical Works) coupled to a Hewlett Packard mod. 3395 integrator. For the straight-phase system, a column (4.6 × 200 mm) containing a Kromasil™-based chiral sorbent,[9] obtained from EKA Nobel AB, Bohus, Sweden, was used. A reversed-phase system, incorporating a BSA-based column,[10] was used for determination of the enantiomer composition obtained during the preparative resolution of **3**. Analytical achiral liquid chromatography was performed by means of equipment consisting of an ERC mod. 64 high-pressure pump, a Rheodyne injector with a 20 µl loop, a Nucleosil 5 mm C_8 column (4.6 × 150 mm), and a Perkin-Elmer mod. LC-15 UV detector coupled to a Millipore/Waters model 740 integrator. In some cases, the signs of optical rotation were determined on-line by means of an ACS ChiraMonitor™ mod. 750/25 diode laser-based polarimetric detector.

NMR spectroscopy. One-dimensional spectra were recorded for $CDCl_3$, C_6D_6 and Me_2CO-d_6 solutions with a 400 MHz Varian VXR-400 spectrometer. The chemical shifts were measured from Me_4Si as an internal reference. Assignment of the five-membered ring protons was made via phase-sensitive NOESY spectra using a mixing time T_m (ca. 2 s), equal to the spin–lattice relaxation time T_1 of the AB protons. These 2-D experiments were performed with a Varian Unity 500 MHz instrument.

Techniques used to obtain chiroptical data of the sulfoxides. The optical isomers of **4** used for characterization by CD were obtained by semipreparative chiral LC separation using mobile phase system A (Table 2). Ca. 8 mM solutions of the diastereomeric mixtures of (+)-**4** and (−)-**4**, respectively, were injected (100 µl) onto the column, the separated fractions collected and the mobile phase immediately evaporated off.

CD spectroscopy. Spectra were recorded for solutions in HPLC-grade acetonitrile using a JASCO mod. 720 spectropolarimeter and a quartz cell of 2 or 10 mm pathlength. The cell compartment was flushed with nitrogen during spectrum recording.

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