Short Communication

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

Stig Allenmark† and Malin Andersson

Department of Organic Chemistry, University of Gothenburg S-41296 Gothenburg, Sweden


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.

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$_{A}$ are subject to the deshielding anisotropy effect across the ring depending on the orientation of the sulfoxide.

† To whom correspondence should be addressed.
group in the respective isomers. 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.\(^a\) The large aromatic solvent-induced shifts for the \( H_A \) and \( H_B \) 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 \( H_B \) 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 [\( \alpha \)] 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 [\( \alpha \)] 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 (1S,2S)-4 to a mixture of (1S,2S)-2 and (1S,2R)-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-thiandane-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.\(^3\)

**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.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Mobile phase system*</th>
<th>k′ (absolute configuration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>A</td>
<td>1.75 (1S,2R) 1.75 (1R,2S) 4.06 (1R,2R) 4.23 (1S,2S)</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>4.32 (1S,2R) 4.54 (1R,2S) 5.30 (1S,2S) 5.87 (1R,2R)</td>
</tr>
</tbody>
</table>

* 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 diasteromer composition was found to be 70% trans-
and 30% cis-isomer (by LC and 1H NMR spectroscopy).

Separation of the diastereomeric sulfoxides was achieved by low-temperature recrystallization. The pure
diastereomers of 4 were obtained in low yield after re-
peated recrystallization from acetone (cooking of the so-
lution 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 so-
lution was then immediately cooled to –18°C. After fil-
tration, 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 tem-
perature (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 per-
acetic acid in acetic acid at 4°C after two recrystalliza-
tions from ethyl acetate.

trans-4: [α]D20 = +240° (McCN), cis-4: [α]D20 =
±30.0°(McCN). The compounds were further charac-
terized by 1H NMR and mass spectroscopy, and K+ values in L.C. were not 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
equivolular 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 com-
position 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 (1S,2S)-4
[(+)-trans-4; de >90%] yielding 2 [(1S,2S): 67% and
(1S,2R): 33%] with little or no formation of unsaturated ester.

Liquid chromatography. Analytical chiral liquid chromatog-
raphy 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 var-
iable wavelength UV detector (Erma Optical Works)
coupled to a Hewlett Packard mod. 3395 integrator. For
the straight-phase system, a column (4.6 x 200 mm) con-
taining a Kromasil™-based chiral sorbent,9 obtained
from EKA Nobel AB, Bohus, Sweden, was used. A re-
versed-phase system, incorporating a BSA-based col-
umn,10 was used for determination of the enantiomer
composition obtained during the preparative resolution of
3. Analytical achiral liquid chromatography was per-
fomed 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 C18 column (4.6 x 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 re-
corded for CDCl3, C6D6, and Me6CO-d4 solutions with a
400 MHz Varian VXR-400 spectrometer. The chemical
shifts were measured from Me6Si as an internal reference.

Assignment of the five-membered ring protons was made
via phase-sensitive NOESY spectra using a mixing time
Tm (ca. 2 s), equal to the spin–lattice relaxation time T1
of the AB protons. These 2-D experiments were per-
formed 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 mL solu-
tions 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 spect-
ropolarimeter and a quartz cell of 2 or 10 mm path-
length. The cell compartment was flushed with nitrogen
during spectrum recording.

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