

# Enantiodifferentiation of aryl-substituted heterocycles: a mechanistic study using $\gamma$ -lactones<sup>1</sup>

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## Abstract

As part of a larger study concerning the nature of the chiral recognition processes utilized by chiral stationary phase CSP 1, we have investigated the chromatographic separation of the enantiomers of a series of aryl-substituted heterocycles, focusing on lactones and analogs with systematically varied structures. Virtually all of the heterocycles described herein are readily resolved. The relation between structure and enantioselectivity, as well as the observed elution orders of the enantiomers, proves to be consistent with the mechanistic hypothesis used to design CSP 1. © 1997 Elsevier Science B.V.

**Keywords:** Chiral recognition; Chiral stationary phases, LC;  $\gamma$ -Lactones

## 1. Introduction

Chiral lactones are prevalent in nature and have been frequent targets for synthesis, either as racemates or as single enantiomers. A number have been used as chiral synthons (building blocks for stereoselective syntheses). Because of this interest, several groups have investigated the chromatographic separation of lactone enantiomers. In particular, aryl-substituted  $\gamma$ -lactones have been resolved on a variety of chiral stationary phases (CSPs) [1–7]. Because most of these CSPs have been developed empirically, it is fair to say that the mechanistic details of these lactone resolutions are not well

understood. In contrast, CSP 1<sup>2</sup> was developed according to an a priori mechanistic rationale [8,9] (Fig. 1 shows the structure of the CSPs used in this study).

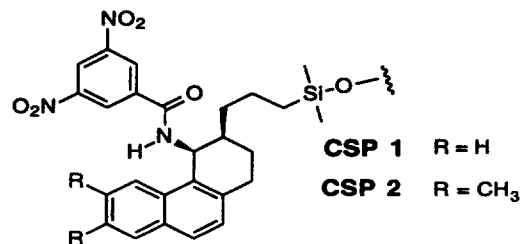


Fig. 1. CSPs used in this study.

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<sup>1</sup> Part of this work was presented at the Fourth International Symposium on Chiral Discrimination, Montreal, PQ, September, 1993.

<sup>2</sup> CSP 1 used in this study was a (3*R*,4*S*) Whelk-O1 column (250 × 4.6 mm), furnished by Regis Technologies, Morton Grove, IL, USA.

The “cleft-like” active site [10] present in CSP 1 is believed to be responsible for the ability of this CSP to separate the enantiomers of a rather broad range of compounds which possess certain structural features. In general, these features include first, and foremost, a  $\pi$ -basic group (usually an aromatic system) in proximity to the stereogenic center. This group participates in a face to face  $\pi$ - $\pi$  interaction with the  $\pi$ -acidic 3,5-dinitrobenzoyl moiety (DNB). Secondly, this CSP requires a hydrogen bond acceptor site in proximity to the stereogenic center to undergo hydrogen bonding by the relatively acidic DNB amide N-H. A final requirement is that the  $\pi$ -basic aryl group used in the face to face  $\pi$ - $\pi$  interaction should be capable of entering the cleft of the CSP in such a way as to present the ring protons along one of its edges to the face of the naphthyl portion of the CSP. The aforementioned considerations are consistent with prior chromatographic studies and with NMR studies employing the selector (or analogs thereof) used in CSP 1 [11–14]. Many aryl-substituted compounds meet these structural requirements and their enantiomers resolve on CSP 1. This study utilizes a series of racemic aryl-substituted  $\gamma$ -lactones and tetrahydrofurans, compounds which appeared a priori to contain the appropriate structural features, to determine whether or not the enantiomers of these heterocycles would resolve in accord with the mechanistic expectations.

## 2. Experimental

### 2.1. General

$^1\text{H}/^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  on either a Varian XL-200 FT-NMR instrument operating at 200 MHz (50 MHz,  $^{13}\text{C}$ ) or a Varian Unity 400 instrument operating at 400 MHz (100 MHz,  $^{13}\text{C}$ ), both in the  $^2\text{H}$  lock mode. Chemical shifts are reported in parts per million (ppm) relative to TMS as the internal standard. GC-MS was performed using a Hewlett-Packard Model 5890 GC equipped with an HP-5 column (30 m $\times$ 0.53 mm capillary) and a Model 5970 MSD quadrupole mass analyzer (Hewlett-Packard, Palo Alto, CA, USA). HPLC analyses were performed using either a Rheodyne injector (Cotati, CA, USA), Rainin Rabbit Model

HPX pump (Rainin Instrument Company, Woburn, MA, USA), and a linear UVIS 200 variable wavelength detector (Linear Instruments Corporation, Reno, NV, USA) or a Rheodyne injector, Anspec pump (Anspec, Ann Arbor, MI, USA) and a Milton-Roy UV (Riviera Beach, FL, USA) detector system (254, 280 nm). Chromatographic solvents were of HPLC grade and generously donated by EM Science (EM Industries, Gibbstown, NJ, USA). All void volumes were measured using 1,3,5-tri-*tert*-butyl benzene (TTBB). Signs of optical rotation were measured on a Rudolph Autopol III digital polarimeter (Rudolph Research Corporation, Flanders, NJ, USA) operating at 589 nm, equipped with a laboratory-built flow cell. Melting points were taken on a Büchi Apparatus (Rinco Instrument Company, Greenville, IL, USA) and are uncorrected. CSP 1 used in this study was the commercially available (*S,S*)-Whelk-O 1 [note: this column should read (*3R,4S*)]. The column dimensions are 250 $\times$ 4.6 mm. CSP 2 used in this study was prepared by Dr. Myung Ho Hyun<sup>3</sup>. The column dimensions are 250 $\times$ 4.6 mm, and the loading (determined by microanalysis of the packing residue) was 0.15 mmol of selector per gram of silica by carbon content and 0.14 mmol of selector per gram of silica by nitrogen content.

### 2.2. Synthesis of $\alpha$ -aryl- $\gamma$ -butyrolactones (**1a-c**)

The procedure used to produce these analytes (henceforth denoted “Procedure A”) was adapted from Rothstein [15], and is described here for 3-(4-methoxyphenyl)- $\gamma$ -butyrolactone. To a dry 50-ml recovery flask was added freshly distilled diisopropyl amine (2 ml, 14.3 mmol), a stirbar and nitrogen gas inlet. The diisopropyl amine solution was cooled to  $-78^\circ\text{C}$  in a  $\text{CO}_2$ -isopropanol cooling bath and 5 ml dry THF was added. Butyllithium [9.0 ml, (1.4 M in hexanes), 12.6 mmol] was added over 5 min via syringe. The solution became pale yellow and cloudy. 4-Methoxyphenylacetic acid (0.5 g, 3.0 mmol) was dissolved in 5 ml dry THF and added to the LDA solution with stirring over 15 min. The solution was then allowed to warm to  $-15^\circ\text{C}$  (ice-

<sup>3</sup> CSP 2 was prepared by Dr. Myung Ho Hyun for the purpose of probing the effect of increased  $\pi$ -basicity in face-to-edge  $\pi$ - $\pi$  interactions.

methanol cooling bath), and ethylene oxide (170  $\mu$ l, 3.3 mmol, dissolved in 5 ml dry THF) was added over 15 min. The solution was then allowed to warm to room temperature and stirred under nitrogen atmosphere for 5 h. Saturated ammonium chloride solution (10 ml) was added, and the resulting suspension was allowed to stir overnight. The two liquid layers were separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layers were combined, dried over anhydrous  $\text{MgSO}_4$  and evaporated to afford 0.51 g (87.9%) of the crude lactone. An analytical sample was purified by flash chromatography using 20% ethyl acetate in hexanes to afford characterization data.

### 2.3. 3-(4-Methoxyphenyl)- $\gamma$ -butyrolactone (**1a**)

Prepared using "Procedure A" and isolated as a clear viscous oil in 88% yield.  $^1\text{H}$  NMR (200 MHz):  $\delta$  2.31–2.47 (m, 1H); 2.57–2.73 (m, 1H); 3.69–3.81 (m, 4H); 4.23–4.48 (m, 2H); 6.84–6.92 (m, 2H); 7.16–7.23 (m, 2H). GC–MS: 192.10 [ $\text{M}^+$ ] (88%), 147.1 (100), 133.1 (51.5), 91 (55.6).

### 2.4. 3-(4-Methylphenyl)- $\gamma$ -butyrolactone (**1b**)

Prepared using "Procedure A" and isolated as a clear viscous oil in 16.8% yield.  $^1\text{H}$  NMR (200 MHz):  $\delta$  2.33–2.49 (m, 4H); 2.58–2.74 (m, 1H); 3.70–3.80 (dd, 1H); 4.24–4.49 (m, 2H); 7.16–7.20 (m, 4H). GC–MS: 176.10 [ $\text{M}^+$ ] (89%), 132.2 (54), 117.5 (100), 91.1 (49).

### 2.5. 3-(1-Naphthyl)- $\gamma$ -butyrolactone (**1c**)

Prepared using "Procedure A" and isolated as a clear viscous oil in 46.9% yield.  $^1\text{H}$  NMR (200 MHz):  $\delta$  2.30–2.49 (m, 1H); 2.72–2.89 (m, 1H); 4.34–4.52 (m, 3H); 7.34–7.58 (m, 4H); 7.71–7.90 (m, 3H). GC–MS: 212.2 [ $\text{M}^+$ ] (55.4%), 167.2 (44.8), 153.2 (100), 139.2 (8.2).

### 2.6. Synthesis of $\beta$ -aryl- $\gamma$ -butyrolactones (**2a–d**)

The procedure used to synthesize these compounds was adapted from that used by Sato et al. [16] Characterization data ( $^1\text{H}$  NMR and GC–MS)

are consistent with either the literature values [17–22] or with the assigned structures.

### 2.7. Synthesis of $\gamma$ -aryl- $\gamma$ -butyrolactones (**3a–f**)

The synthesis of each of these compounds was carried out by a well established method, using sodium borohydride in dilute aqueous base to reduce a  $\gamma$ -keto acid [23]. Characterization data ( $^1\text{H}$  NMR and GC–MS) obtained were consistent with either the literature values [17,24–28] or with the assigned structures, including the correlation between the sign of rotation and absolute configuration.

### 2.8. Synthesis of $\gamma$ -aryl- $\gamma$ -butyrothionolactones and $\gamma$ -aryl- $\gamma$ -butyrothiolactones (**4a–d**)

All thio- and thiono-lactones were made using modifications of the procedure used by Pirkle and Sowin [29]. This procedure, denoted "Procedure B", is described in detail as follows: 5-(4-bromophenyl)- $\gamma$ -butyrolactone (1.00 g, 4.15 mmol) was placed into a 50-ml round bottom flask along with 25 ml of dry benzene and a magnetic stirring bar. Lawessons reagent (1.50 g, 3.71 mmol) was added and the reaction mixture was brought to reflux for 24 h. The solvent was evaporated and the residue was taken up in a minimum amount of  $\text{CH}_2\text{Cl}_2$ . The solution was then filtered through silica to remove unreacted Lawessons Reagent. The filtrate was carefully chromatographed starting with 30%  $\text{CH}_2\text{Cl}_2$  in hexane and finishing with 100%  $\text{CH}_2\text{Cl}_2$ . The thionolactone was obtained in 37% yield. The position of the sulfur in the lactone ring is easily determined from characteristic chemical shifts of both  $^1\text{H}$  and  $^{13}\text{C}$  nuclei in the NMR spectra of these compounds [30].

### 2.9. 5-(4-Bromophenyl)- $\gamma$ -butyrothionolactone (**4a**)

This compound was prepared using "Procedure B" and was isolated as a white solid in 37% yield. m.p. 68.5–70°C.  $^1\text{H}$  NMR (200 MHz):  $\delta$  2.11–2.31 (m, 1H); 2.61–2.77 (m, 1H); 3.03–3.33 (m, 2H); 5.76–5.83 (m, 1H); 7.19–7.25 (dd, 2H); 7.49–7.55 (dd, 2H).  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  221.40 [C=S], 137.00, 131.97, 127.38, 122.86, 89.77, 44.76, 32.42.

GC–MS: 257.90 [ $M^+$ ] (100%), 255.90 (94.5), 200.90 (32.8), 117.05 (71.1).

#### 2.10. 5-(4-Bromophenyl)- $\gamma$ -butyrolactone (**4b**)

This compound was prepared using “Procedure B” and was isolated as a by-product via semi-preparative HPLC in <1% yield (yellow residue) from the reaction of 5-(4-bromophenyl)- $\gamma$ -butyrolactone with Lawessons reagent using toluene as the solvent.  $^1\text{H}$  NMR (200 MHz):  $\delta$  2.11–2.32 (m, 1H); 2.53–2.80 (m, 3H); 4.90–4.99 (dd, 1H); 7.23–7.34 (dd, 2H); 7.40–7.53 (dd, 2H).  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  207.38 [C=O], 138.48, 132.01, 129.12, 121.98, 53.59, 42.73, 34.97. GC–MS: 257.95 [ $M^+$ ] (100%), 255.95 (89.9), 200.95 (43.5), 177.05 (35.2), 117.05 (62.1).

#### 2.11. 5-Phenyl- $\gamma$ -butyrolactone (**4c**)

This compound was prepared using “Procedure B” and was isolated as white pungent crystals in 11.7% yield following flash chromatography (30%  $\text{CH}_2\text{Cl}_2$  in hexane). m.p. 46–47.5°C.  $^1\text{H}$  NMR (200 MHz):  $\delta$  2.23–2.38 (m, 1H); 2.62–2.78 (m, 1H); 3.05–3.31 (m, 2H); 5.82–5.90 (dd, 1H); 7.31–7.45 (m, 5H).  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  221.88 [C=S], 137.92, 128.85, 128.80, 125.74, 90.75, 44.91, 32.38. GC–MS: 178.05 [ $M^+$ ] (74.4%), 117.05 (100), 91.05 (28.3), 77.05 (18.7).

#### 2.12. 5-(4-Methoxyphenyl)- $\gamma$ -butyrolactone (**4d**)

This compound was prepared using “Procedure B” and was isolated as yellow crystals in 10% yield after flash chromatography. None of the corresponding thionolactone was observed. Characterization data ( $^1\text{H}$  NMR and GC–MS) are consistent with the literature values described for this compound [31].

#### 2.13. Synthesis of 2-aryltetrahydrofurans (**5a–d**)

The procedure used, henceforth denoted “Procedure C”, was adapted from those of Letsinger and Pollart [32] and Pernot and Willemart [33]. Lithium aluminum hydride (0.5 g, 13.2 mmol) was placed in

a 35-ml round bottom flask equipped with a magnetic stirrer. Dry THF (10 ml) was added, and the resulting nitrogen blanketed suspension was cooled in an ice-water bath. 5-Phenyl- $\gamma$ -butyrolactone (1.00 g, 6.2 mmol) was dissolved in dry THF and added over 15 min. The reaction mixture was stirred an additional 30 min at 0°C and the ice bath was removed. The reaction mixture was then stirred for one h after it had warmed to room temperature. The flask containing the reaction mixture was fitted with a reflux condenser and heated on a steam bath for 15 min. The reaction mixture was cooled to room temperature and worked up as per the literature procedure [34], to yield 0.97 g (95.1%) of the crude diol. The crude diol (0.46 g, 2.8 mmol) was placed in a 35-ml round bottom flask with 20 ml of dry benzene. *p*-Toluenesulfonic acid monohydrate (0.28 g, 1.50 mmol) was added and the flask was fitted with a Dean–Stark trap. The solution was heated to reflux for 3 h, the liberated water causing the benzene in the trap to become cloudy. After the reaction mixture had cooled to room temperature, the benzene solution was washed twice with 10 ml of water, 5%  $\text{Na}_2\text{CO}_3$  and brine. The solution was dried over anhydrous  $\text{MgSO}_4$  and evaporated to afford 0.38 g (90%) of a colorless oil.

#### 2.14. 2-Phenyltetrahydrofuran (**5a**)

This compound was prepared using “Procedure C” and was isolated in 78% overall yield from the starting lactone. b.p. 83–84°C (1.9 mm Hg).  $^1\text{H}$  NMR (200 MHz):  $\delta$  1.62–1.82 (m, 1H); 1.86–2.00 (m, 2H); 2.18–2.30 (m, 1H); 3.82–3.93 (m, 1H); 3.99–4.10 (m, 1H); 4.84 (t, 1H); 7.15–7.33 (m, 5H). GC–MS: 148.10 [ $M^+$ ] (65.6%), 147.10 (84.1), 117.10 (17.1), 105.10 (100), 91.10 (25.5).

#### 2.15. 2-(4-Bromophenyl)tetrahydrofuran (**5b**)

This compound was prepared using “Procedure C”, as above.  $^1\text{H}$  NMR showed that a portion of the diol had undergone dehalogenation. Flash chromatography (30%  $\text{CH}_2\text{Cl}_2$  in hexane) afforded the desired 2-(4-bromophenyl)tetrahydrofuran as a colorless oil in 51% yield. b.p. 99–100°C (1.9 mm Hg).  $^1\text{H}$  NMR (200 MHz):  $\delta$  1.66–1.81 (m, 1H); 1.90–2.04 (m, 2H); 2.22–2.37 (m, 1H); 3.85–4.12

(m, 2H); 4.82 (t, 1H); 7.19 (d, 2H); 7.43 (d, 2H).  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  142.46, 131.18, 127.22, 120.65, 79.85, 68.60, 34.56, 25.83. GC–MS: 228.00 [ $\text{M}^+$ ] (12.3%), 226.00 (12.0), 184.90 (49.1), 182.90 (48.5), 147.10 (100), 105.00 (62.1), 91.10 (15.8).

#### 2.16. 2-(4-Methylphenyl)tetrahydrofuran (5c)

This compound was prepared using “Procedure C” and was isolated as a colorless oil in 70% yield. b.p. 107–108°C (2.5 mm Hg).  $^1\text{H}$  NMR (200 MHz):  $\delta$  1.69–1.82 (m, 1H); 1.87–2.01 (m, 2H); 2.16–2.33 (m, 1H); 2.30 (s, 3H); 3.81–3.98 (m, 1H); 4.06 (t, 1H); 4.81 (t, 1H); 7.10 (d, 2H); 7.20 (d, 2H). GC–MS: 162.10 [ $\text{M}^+$ ] (35.9%), 161.1 (31.8), 147.10 (64.7), 119.10 (100), 105.10 (26.5), 91.10 (52.6).

#### 2.17. 2-(2-Naphthyl)tetrahydrofuran (5d)

This compound was prepared using “Procedure C” and was isolated as a straw-colored oil in 57% yield.  $^1\text{H}$  NMR (400 MHz):  $\delta$  1.87–1.94 (m, 1H); 2.02–2.09 (m, 2H); 2.28–2.44 (m, 1H); 3.98–4.04 (m, 1H); 4.00–4.21 (m, 1H); 5.08 (t, 1H); 7.43–7.50 (m, 3H); 7.82–7.84 (m, 4H). GC–MS: 198.10 [ $\text{M}^+$ ] (100%), 155.0 (79.6), 127.00 (51.4).

#### 2.18. Synthesis of $\gamma$ -aryl- $\gamma$ -alkyl- $\gamma$ -butyrolactones (6a–f)

The procedure used to prepare these compounds was adapted from Tanaka et al. [35] Characterization data ( $^1\text{H}$  NMR and GC–MS) were consistent with either the literature values [35–40] or with the assigned structures.

### 3. Results and discussion

CSP 1 incorporates a molecular “cleft” into which a  $\pi$ -basic group present in the analyte is intended to “dock,” owing to the occurrence of simultaneous face-to-face and face-to-edge  $\pi$ - $\pi$  interactions. Occurrence of a hydrogen bond to a proximal “basic site” in the analyte provides the third of the three simultaneous interactions which may lead to differential affinity for the enantiomers of the analyte.

Clearly, both analyte enantiomers cannot enjoy these three simultaneous interactions from identical conformations. Even if conformational adjustment were to allow each enantiomer to undergo these three major interactions, the fact that the diastereomeric complexes so formed would require the analytes to assume conformations which are likely to be energetically non-equivalent is potentially capable of causing the diastereomeric complexes to differ in stability. This simple mechanistic picture is quite successful even though it does not consider additional analyte-selector interactions (which may, of course, be present). Basically, the analyte enantiomers heavily populate low energy conformations prior to association with the selector. The enantiomer which can best enjoy the three aforementioned interactions without having to deviate substantially from the heavily populated conformation(s) is expected to be preferentially retained by the CSP. Similar considerations apply to conformational changes which may occur within the selector during the complexation processes.

To illustrate the anticipated enantiodiscrimination process, consider  $\alpha$ -phenyl cyclohexanone in a relatively low energy, hence highly populated, conformation. The phenyl ring would be in the equatorial position with its plane roughly perpendicular to that of the cyclohexanone, as shown in Fig. 2 for the (*S*)-enantiomer. Also shown is a drawing of the essential features of the (3*R*, 4*S*)-CSP 1, showing the cleft-like site with the 3,5-dinitrobenzoyl (DNB) depicted edge-wise with the DNB NH projecting upward toward the viewer.

Imagine the (*S*)-enantiomer of the ketone fitting directly into the cleft atop the naphthyl portion of the

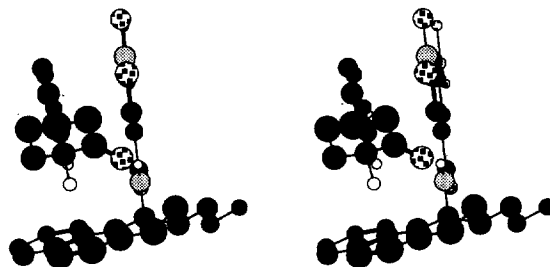


Fig. 2. Stereoview depiction of 2-phenylcyclohexanone complexation with CSP 1. Hydrogen atoms omitted for clarity.

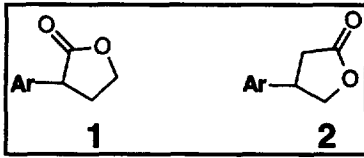
selector. The phenyl presents its face to the di-nitrobenzoyl moiety, with the protons on the lower edge presented to the naphthyl group. The carbonyl oxygen is presented to the relatively acidic amide proton of the CSP. The small (and slightly acidic) methine hydrogen on the ketone would be directed down toward the  $\pi$ -cloud of the naphthyl moiety of the CSP. This potentially gives rise to an additional but weak attractive interaction. Because it is sterically small, the hydrogen does not prevent the ketone from nestling closely into the cleft. Maintaining this same relative arrangement in the cleft, imagine that the carbonyl group of the ketone is shifted to the a position on the other side of the phenyl ring. This converts the analyte to the (*R*)-enantiomer and one can see that there can no longer be a hydrogen bond between the ketone carbonyl and the DNB amide N-H from this conformation. This mental exercise allows one to understand why the (*S*)-enantiomer of the ketone is expected to be more retained by the (3*R*,4*S*)-CSP 1 than the (*R*)-enantiomer<sup>4</sup>.

By analogy, one expects that the enantiomers of  $\alpha$ -aryl substituted lactones will resolve on the (3*R*,4*S*)-CSP 1 with preferential retention of the (*S*)-enantiomer. A series of  $\alpha$ -aryl- $\gamma$ -lactones was prepared and chromatographed on CSP 1. The enantioseparations are relatively easy and an in-line polarimetric detector indicates that the (–)-enantiomers are preferentially retained (Table 1).

To determine the influence of what has been termed “spatial complementarity”, several  $\beta$ -aryl- $\gamma$ -lactones were prepared and chromatographed. For these compounds, the increased distance between the  $\pi$ -basic and hydrogen bonding sites was expected to interfere with the chiral recognition process. This is indeed the case. Under the same experimental conditions, the retention factors ( $k'$ ) of the  $\beta$ -aryl- $\gamma$ -lactones are less than half of those observed for the corresponding  $\alpha$ -aryl lactones, and the separation factors ( $\alpha$ ) for the enantiomers are only slightly greater than unity. The polarimetric detector recognized that the leading and trailing edges of the chromatographic bands were enantiomerically enriched, but the ultraviolet detector showed only a slightly broadened peak.

<sup>4</sup> Capacity factor ( $k'$ )=3.41. Separation factor ( $\alpha$ )=1.81. Mobile phase=10% 2-propanol in hexanes.

Table 1  
Separation of the enantiomers of  $\alpha$ - and  $\beta$ -aryl- $\gamma$ -lactones on CSP 1



Analyte	Ar	$k'$ (rotation)	$\alpha$
<b>1a</b>	4-CH <sub>3</sub> O-Ph	15.21 (+)-(R)	1.45
<b>1b</b>	4-CH <sub>3</sub> -Ph	4.29 (+)	1.45
<b>1c</b>	1-Naphthyl	11.24 (+)	1.76
<b>2a</b>	Ph	2.00 (–)-(R)	~1.00 <sup>a</sup>
<b>2b</b>	4-CH <sub>3</sub> -Ph	1.88 (–)-(R)	~1.00 <sup>a</sup>
<b>2c</b>	4-CH <sub>3</sub> O-Ph	3.45 (–)	~1.00 <sup>a</sup>
<b>2d</b>	1-Naphthyl	3.83 (–)	~1.00 <sup>a</sup>

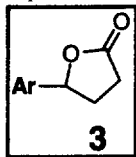
Conditions: 20% 2-propanol in hexanes. Flow-rate 2 ml/min. Column: 250×4.6 mm Whelk-O 1 CSP, Regis Technologies (Morton Grove, IL, USA). Sign of rotation and absolute configuration are shown in parentheses.

<sup>a</sup> Partial enantiomer resolution was evidenced by rotation via polarimeter although only a single broadened peak was observed.

The greatly reduced separation factors could conceivably be explained by suggesting that while one enantiomer utilizes the carbonyl oxygen as a hydrogen bonding site, the other uses the ring oxygen (vide infra) for this purpose. Thus both enantiomers have essentially the same retention and virtually co-elute. However, the reduced retention (relative to the corresponding  $\alpha$ -aryl-substituted  $\gamma$ -lactones) is taken to indicate that greater distance between interaction sites interferes with the simultaneous occurrence of the interactions required for chiral recognition.

By locating the  $\pi$ -basic site in the  $\gamma$ -position for a  $\gamma$ -lactone, one might again imagine that a greater distance between the carbonyl oxygen and the  $\pi$ -basic site would interfere with the chiral recognition process. However, the enantiomers of a series of these analytes are readily separated on CSP 1 and CSP 2 (Table 2). The latter<sup>3</sup> utilizes the same chiral

Table 2  
Separation of the enantiomers of  $\gamma$ -aryl-substituted  $\gamma$ -lactones



Analyte	Ar	CSP 1		CSP 2	
		$k'_1$ (rotation)	$\alpha$	$k'_1$ (rotation)	$\alpha$
<b>3a</b>	4-Br-Ph	3.23 (+)-(R)	1.22	3.11 (R)	1.28
<b>3b</b>	Ph	4.01 (+)-(R)	1.24	2.63 (R)	1.33
<b>3c</b>	4-CH <sub>3</sub> -Ph	2.86 (+)-(R)	1.29	2.82 (R)	1.46
<b>3d</b>	4-CH <sub>3</sub> O-Ph	5.66 (+)-(R)	1.29	5.18 (R)	1.43
<b>3e</b>	2-Naphthyl	7.68 (+)	1.62	5.21 (+)	1.92
<b>3f</b>	1-Naphthyl	6.34 (+)	1.56	4.01 (+)	1.66

Conditions: see Table 1.

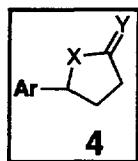
selector as the former save that it has two methyl substituents in the 6,7-positions of the tetrahydrophenanthrene system. These appear to strengthen the face to edge  $\pi$ - $\pi$  interaction, for CSP 2 typically affords greater enantioselectivity than does CSP 1, despite a somewhat lower surface coverage by the chiral selector than is achieved for the commercial CSP 1. Under the same conditions used in Table 1, the retention factors of the  $\gamma$ -aryl- $\gamma$ -lactones are greater than those of the corresponding  $\beta$ -aryl- $\gamma$ -lactones but less than those of the corresponding  $\alpha$ -aryl- $\gamma$ -lactones. The separation factors for the enantiomers of the  $\gamma$ -aryl lactones are similar to those of the corresponding  $\alpha$ -aryl lactones.

This observation raised the question of whether or not the ring oxygen was serving as the hydrogen bonding site rather than the carbonyl oxygen. To address this issue, several sulfur containing lactones were prepared. It is known that sulfur does not function as a hydrogen bond acceptor as well as oxygen. Therefore, one might expect that if the [C=O] moiety of the lactone were being utilized as

the essentially hydrogen bonding site, conversion to the [C=S] group would cause both retention and enantioselectivity to decrease. Conversely, if the ring oxygen is the site of the essential hydrogen bond, replacing it with sulfur would cause enantioselectivity to decrease owing to weakening of this hydrogen bond. The experimental data reported in Table 3 are consistent with the ring oxygen being the site of the essential hydrogen bond during the enantiodifferentiation of the  $\gamma$ -aryl- $\gamma$ -lactones. Interestingly, the separation factors of the two thionolactones are significantly larger than those of the corresponding lactones, presumably owing to the greater electron density at the ring oxygen in the thiono-lactones [41]. The relatively small separation factors observed for the enantiomers of the thio-lactones (the second and fourth entries in the Table 3) indicate that either the sulfur is capable of participating (weakly) in a hydrogen bond or that the more remote carbonyl oxygen is still capable of weak but simultaneous hydrogen bonding.

If the carbonyl oxygen of a  $\gamma$ -aryl- $\gamma$ -lactone is not the primary site for the simultaneous hydrogen bond responsible for chiral recognition, its elimination would be expected to improve the extent of enantiodifferentiation. To whatever extent this oxygen participates in hydrogen bonding leading to retention but not to enantiodifferentiation, the presence of this oxygen is detrimental to the chiral recognition process. To test this hypothesis, a series of racemic  $\alpha$ -aryl tetrahydrofurans were prepared and chromatographed on CSP 1 and CSP 2 using 2% (rather than 20%) 2-propanol in hexanes owing to the greatly reduced retention of these compounds (Table 4). Enantiodifferentiation is indeed more facile than in the case of the analogous lactones. The larger separation factors are felt to result from the absence of the non-specific interactions which accompany the carbonyl group, although the reduction of the 2-propanol concentration in the mobile phase will also tend to increase these values. Note that the enantiomers of 2-( $\beta$ -naphthyl) tetrahydrofuran are strongly retained (even using 20% 2-propanol in hexanes) and show a larger separation factor owing to the greater  $\pi$ -basicity of the naphthyl system. Judging from the signs of rotation, the enantiomers elute in a consistent manner, with the (–)-enantiomers preferentially retained. By analogy with the phenyl analog,

Table 3  
Separation of the enantiomers of thio- and thiono-lactones



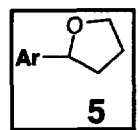
Analyte	X	Y	Ar	CSP 1		CSP 2	
				$k'_1$ (rotation)	$\alpha$	$k'_1$ (rotation)	$\alpha$
4a	O	S	4-Br-Ph	1.57 (+)	1.68	1.19 (+)	2.02
4b	S	O	4-Br-Ph	1.57 (+)	1.04	1.30	1.05
4c	O	S	Ph	1.47 (+)	1.84	1.26	2.33
4d	S	O	4-CH <sub>3</sub> O-Ph	2.43 (+)	1.06	2.03	1.05

Conditions: see Table 1.

these (–)-enantiomers are thought to have the (*S*)-configuration.

The original view that hydrogen bonding at the carbonyl oxygen of  $\alpha$ -aryl- $\gamma$ -lactones is essential to chiral recognition by CSP 1 is consistent with the

Table 4  
Enantiomeric separation of 2-aryl-tetrahydrofuran derivatives



Analyte	Ar	CSP 1		CSP 2	
		$k'_1$ (rotation)	$\alpha$	$k'_1$ (rotation)	$\alpha$
5a	Ph	1.00 (+)-(R) <sup>a</sup>	1.47	0.75 (+)-(R)	1.84
5b	4-Br-Ph	1.00 (+)	1.43	0.88 (+)	1.49
5c	4-CH <sub>3</sub> -Ph	1.17 (+)	1.68	0.97 (+)	2.03
5d	2-Naphthyl	2.80	3.11	2.87	2.94

Conditions: as in Table 1, except 2.0% 2-propanol in hexanes was used as the mobile phase.

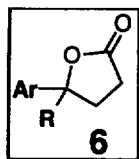
<sup>a</sup> Ref. [42].

body of experimental data. In the case of  $\beta$ -aryl- $\gamma$ -lactones, the carbonyl oxygen appears to be too remote for effective hydrogen bonding to occur simultaneously with the  $\pi$ - $\pi$  interactions. In the case of  $\gamma$ -aryl- $\gamma$ -lactones, it appears that while, at times, the carbonyl oxygen may undergo hydrogen bonding by CSP 1, this interaction contributes primarily to achiral retention and that hydrogen bonding to the ring oxygen is essential to chiral recognition. Enantiomers of other oxygenated heterocycles (e.g., styrene oxide, stilbene oxide) can be resolved on CSP 1, observations which lend support to this view.

All of the analytes discussed thus far have a methine hydrogen on the stereogenic center and the preceding mechanistic argument has suggested that, for the preferentially retained enantiomer, this hydrogen, being small, is directed into the  $\pi$ -cloud of the naphthyl portion of CSP 1 during complexation. Is this an essential requirement for chiral recognition? One might expect that substitution of a larger group for this methine hydrogen would tend to impede the entry of the analyte into the cleft of CSP 1. Moreover, this substituent would tend to alter the conformational disposition of the aryl substituent with unpredictable consequences, in terms of chiral recognition.



Table 5  
Separation of the enantiomers of  $\gamma$ -alkyl- $\gamma$ -aryl lactones on CSP 1



Analyte	R	Ar	$k'_1$ (rotation)	$\alpha$
6a	CH <sub>3</sub>	4-Br-Ph	2.43 (+)-(R)	1.09
6b	CH <sub>2</sub> CH <sub>3</sub>	4-Br-Ph	1.57 (+)	1.14
6c	CH <sub>3</sub>	Ph	1.79 (+)-(R)	1.16
6d	CH <sub>3</sub>	4-CH <sub>3</sub> -Ph	1.54 (+)	1.18
6e	CH <sub>3</sub>	4-CH <sub>3</sub> O-Ph	2.73 (+)	1.14
6f	CH <sub>3</sub>	1-Naphthyl	2.61 (+)	1.46

Conditions: see Table 1.

Table 5 illustrates the chromatographic properties of several  $\gamma$ -alkyl- $\gamma$ -aryl substituted lactones on CSP 1. The enantiomers of these lactones are separable on CSP 1 and elute in the same order [the (*S*)-enantiomers are preferentially retained] but with reduced retention and separation factors.

#### 4. Conclusion

$\gamma$ -Lactones bearing  $\alpha$ - or  $\gamma$ -aryl substituents conform to the general structural requirements required for chiral recognition by CSP 1. From chromatography of different aryl-substituted  $\gamma$ -lactones, one can say that the  $\pi$ -basicity of the analytes aryl substituent influences enantioselectivity, presumably by influencing the strength of the  $\pi$ - $\pi$  interactions. Based on the results of structural modification of  $\gamma$ -aryl- $\gamma$ -lactones, hydrogen bonding of CSP 1 to the ring oxygen appears to be important because of the necessity for simultaneous interactions if chiral recognition is to occur.

It should be made clear that the mechanistic

conclusions reached from the data presented herein are first approximations and that other, more subtle interactions doubtless occur. However, the models presented should be helpful in determining when CSP 1 is likely to resolve the enantiomers of interest and, in favorable cases such as those examined herein, to anticipate the order in which the enantiomers will elute.

The enantiomers of a variety of other aryl-substituted heterocycles can be resolved on CSP 1. Mechanistic accounts of these separations will be described in later publications.

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