145. Analytic and Preparative Resolution of Racemic γ- and δ-Lactones by Chromatography on Cellulose Triacetate. Relationship between Elution Order and Absolute Configuration

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Enantiomers of various chiral five- and six-membered-ring lactones, which are important classes of compounds (flavour and pheromone components, key intermediates in the synthesis of biologically active substances) have been separated chromatographically on the chiral phase cellulose triacetate, crystallographic form I (CTA I). For different series of five-membered-ring lactones, relationships have been found between the elution order of the enantiomers and their absolute configuration. Preparative resolutions of γ-phenyl-γ-butyrolactone (**1**) and of the pheromone component **5b** have been carried out to demonstrate the applicability of the method to g-scale separations.

Introduction. – Lactonic functionality is present in a large variety of natural products and biologically active compounds. Lactone derivatives are very common flavour components [1] and used in the perfume and food industry. They have also been reported to be sex attractant pheromones of different insects [2] and plant-growth regulators [3], and they are useful intermediates in the synthesis of natural products. Most of them are chiral, and the physiological activity often depends on the absolute configuration [4]. Even the optical purity of the substance, like in the case of some pheromones [5], can be determining for the biological activity.

Owing to the importance of this class of compounds, many research groups have been dealing with the asymmetric or enzymatic synthesis of lactone rings [6]. However, the optical purity of products from these syntheses is generally not easy to determine. The chromatographic separation of enantiomers on a chiral stationary phase can not only offer a very simple and rapid method to determine the optical purity of products of asymmetric syntheses, but it can also be an alternative method to prepare optically pure enantiomers of lactonic derivatives. In the course of our investigations, we found that cellulose triacetate (CTA I) [7–9] can be a very efficient chiral support for the separation of enantiomers.

Since the introduction of cellulose triacetate as chiral stationary phase for the chromatographic resolution of enantiomers by *Hesse* and *Hagel* [10], some new applications of this support have been reported [11–15], but only for a limited number of classes of compounds, according to the specific areas of interest of the investigators. Comparatively, much more attention has been delivered to the chiral phases developed by *Pirkle*'s group [16]. We think, however, that CTA I has a much greater versatility than recognized up to now and that the inexpensive and simple preparation as well as its high capacity make it an exceptionally valuable support for large-scale separations. Also, a better understanding of the mechanistic aspects of molecular interactions between CTA I and

enantiomers could lead to a greater utilization of this chiral phase for enantiomeric separations.

Results and Discussion. – We recently showed that the supramolecular structure of cellulose triacetate strongly affects its resolution power, probably due to different mechanisms of interactions [7].

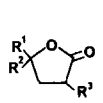
In continuation of these basic investigations on the mechanism of the chiral recognition by CTA I, we decided to investigate a variety of chiral five- and six-membered-ring lactone derivatives. The list includes aryl- and alkyl-, saturated or unsaturated lactones, most of which were subjected to various asymmetric syntheses.

The chromatographic results are summarized in the *Tables 1–4*. The capacity factor k_2' which reflects the strength of the interaction between the chiral stationary phase and

Table 1. *Chromatographic Resolution of Five-Membered-Ring Lactones* **1–18** *on CTA I*[a])

Compound	R^1	R^2	R^3	k_2'[b])	[c])	α[d])	Column[a])
1	C_6H_5	H	H	8.35 (–)	*S*[e])	6.03	*B*
2	*p*-FC_6H_4	H	H	3.33 (–)		2.48	*B*
3a	*o*-$NO_2C_6H_4$	H	H	4.15 (+)		1.47	*A*
3b	*m*-$NO_2C_6H_4$	H	H	3.00 (+)		1.21	*A*
3c	*p*-$NO_2C_6H_4$	H	H	3.25		1.00	*A*
4a	C_6H_5(*cis*)	H	OH	1.39 (–)		1.47	*B*
4b	C_6H_5(*trans*)	H	OH	1.74 (+)		1.27	*B*
5a	CH_3	H	H	0.87 (+)	*R* [17]	1.0	*B*
5b	C_2H_5	H	H	1.07 (+)	*R* [6a] [18]	1.41	*B*
5c	n-C_3H_7	H	H	0.87 (+)	*R* [19] [20]	2.12	*B*
5d	n-C_4H_9	H	H	1.07 (+)		2.37	*B*
5e	n-C_5H_{11}	H	H	0.41 (+)	*R* [6a] [18]	1.64	*B*
5f	n-C_6H_{13}	H	H	0.35 (+)		1.0	*B*
5g	n-C_8H_{17}	H	H	0.08 (+)	*R* [6f]	1.0	*B*
6	$C_2H_5CH{=}CHCH_2$	H	H	0.81 (+)		1.59	*B*
7	n-C_4H_9	CH_3	H	0.40 (–)		1.0	*B*
8	cyclohexyl	H	H	1.51 (+)		2.51	*B*
9	$CH_2CO_2CH_3$	H	H	4.51 (+)	*S* [21]	2.62	*B*
10	$COOC_2H_5$	H	H	1.65 (+)	*S* [6a] [22]	1.0	*B*
11	CH_2OH	H	H	0.63 (+)	*S* [22] [23]	1.0	*B*
12	CH_2OCOCH_3	H	H	1.80 (+)	*S*[f])	1.19	*B*
13	$C_6H_5CH_2OCH_2$	H	H	1.86 (+)	*S* [22]	1.0	*B*
14	$C_6H_5CH_2CH_2$	H	H	1.97 (–)		1.0	*B*
15	H	H	Br	1.61 (–)	*R* [24]	1.0	*B*
16a	H	H	OH	0.71 (–)	*S* [25]	1.0	*B*
16b	H	H	$OCOCH_3$	1.71 (+)	*R*[g])	1.09	*B*
16c	H	H	$OCOC_2H_5$	1.43 (+)	*R*[g])	1.20	*B*
16d	H	H	$OCOC_3H_7$	0.94 (+)		1.0	*B*
17a	H	H	CH_3	0.69	[26]	1.00	*B*
17b	H	H	n-C_4H_9	0.41 (–)	*R* [27]	1.00	*B*
18	H	H	C_6H_5	4.95 (+)		2.81	*A*

[a]) For chromatographic conditions, see *Exper. Part.*
[b]) Capacity factor and sign of the optical rotation (λ = 365 nm) of the best retained enantiomer.
[c]) Absolute configuration for the best retained enantiomer.
[d]) Separation factor $\alpha = k_2'/k_1'$.
[e]) This work.
[f]) Confirmed after acetylation of the optically pure (+)-(*S*)-**11**.
[g]) Confirmed after esterification of the optically pure (–)-(*S*)-**16a** [44].



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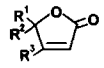

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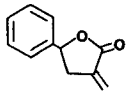

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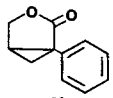

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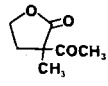

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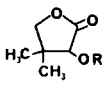
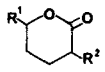


22a R = H
b R = $COCH_3$
c R = $COCH_2CH_3$
d R = $COCH_2CH_2CH_3$



29-36

Table 2. *Chromatographic Resolution of Five-Membered-Ring Lactones* **19–22** *on CTA I*[a])

Compound	k_2'[b])	[c])	α[d])	Column[a])
19	11.97 (+)	*S* [6k]	3.06	*B*
20	3.95 (+)		1.24	*B*
21	2.75 (−)		1.0	*B*
22a	0.73 (+)	*S*	1.0	*B*
22b	1.59 (−)	*R* [24][e])	1.35	*B*
22c	1.56 (−)	*R*[e])	1.87	*B*
22d	1.15 (−)	*R*[e])	1.73	*B*

[a–d]) See *Footnotes a–d* in *Table 1.*

[e]) The absolute configuration has been confirmed by measuring the optical rotation of the optically pure ester obtained by esterification of (−)-(*R*)-pantolactone ((−)-(*R*)-**22a**).

Table 3. *Chromatographic Resolution of Unsaturated Five-Membered-Ring Lactones* **23–28** *on CTA I*[a])

Compound	R^1	R^2	R^3	k_2'[b])	[c])	α[d])	Column[a])
23	C_2H_5	H	H	0.99 (−)	*R* [28]	1.29	*B*
24	CH_2COOCH_3	H	H	9.03 (−)		5.19	*B*
25	CH_2COOCH_3	H	CH_3	8.01 (+)		4.74	*B*
26	C_6H_5	H	H	4.41 (−)	*S* [29]	2.69	*B*
27	C_6H_5	CH_3	H	1.64 (+)	*R* [30]	1.0	*B*
28	$C_6H_5CH_2OCH_2$	H	H	2.52 (−)	*S* [31] [32]	1.19	*B*

[a–d]) See *Footnotes a–d* in *Table 1.*

Table 4. *Chromatographic Resolution of Six-Membered-Ring Lactones* **29–36** *on CTA I*[a])

Compound	R^1	R^2	k_2'[b])	[c])	α[d])	Column[a])
29	H	C_2H_5	0.63	[6e]	1.00	*B*
30	H	C_6H_5	4.76 (−)		3.11	*B*
31	CH_2=$CHCH_2CH_2$	H	1.15 (+)		1.32	*B*
32	n-C_4H_9	H	0.42 (+)		1.0	*B*
33	n-C_5H_{11}	H	0.15 (+)	*R* [40]	1.0	*B*
34	n-C_7H_{15}	H	0.06 (+)		1.0	*B*
35	C_6H_5	H	29.70 (−)		23.32	*C*
36	*p*-ClC_6H_4	H	7.50 (−)		5.81	*B*

[a–d]) See *Footnotes a–d* in *Table 1.*

the best retained enantiomer as well as the separation factor α which is a measure of the chiral discrimination (difference between the interaction energies with each enantiomer) are given for each racemate. A separation factor $\alpha \geqslant 1.3$ can be considered to be sufficient for attempting a preparative large-scale separation[1]).

Five-Membered-Ring Lactones. With five-membered-ring lactones, CTA I generally exhibits a good chiral recognition *(Tables 1–3)*. In some cases, exceptionally large α values indicate a high chiral discrimination associated with a strong interaction with one enantiomer. Among the non-aromatic five-membered-ring lactones, the largest α value has been observed for compound **24**, the (−)-enantiomer of which is very strongly retained (capacity factor $k_2' = 9.03$). This example and to a lesser extent the separation of several other aliphatic lactones (**5c**, **5d**, **5e**, **8**, and **9**) demonstrate that CTA I can also be a useful sorbent for the chromatographic resolution of non-aromatic compounds (see *Fig. 1* and *2*)[2]).

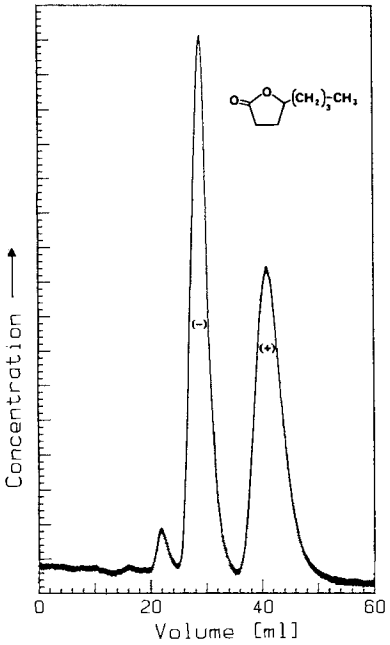


Fig. 1. *Chromatographic resolution of γ-butyl-γ-butyrolactone* (**5d**) *on CTA I* (column *B*)

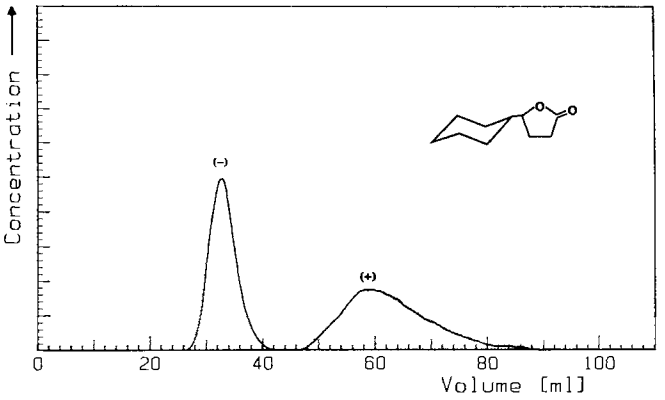


Fig. 2. *Chromatographic resolution of γ-cyclohexyl-γ-butyrolactone* (**8**) *on CTA I* (column *B*)

For the series **5a–g**, the length of the alkyl chain has a determining effect on the stereoselectivity as depicted in *Fig. 3*. The separation factor reaches a maximum for the butyl derivative **5d** whereas practically no separation is observed when the alkyl chain is much shorter (methyl) or longer (hexyl). This result suggests that the solute has to adapt

[1]) The efficiency of the separation is not only affected by the separation factor α, but also by the resolution factor R_S which itself depends on different experimental parameters.

[2]) Only a very limited number of enantiomeric separations of non-aromatic compounds has been reported on CTA I columns until now [13b] [14].

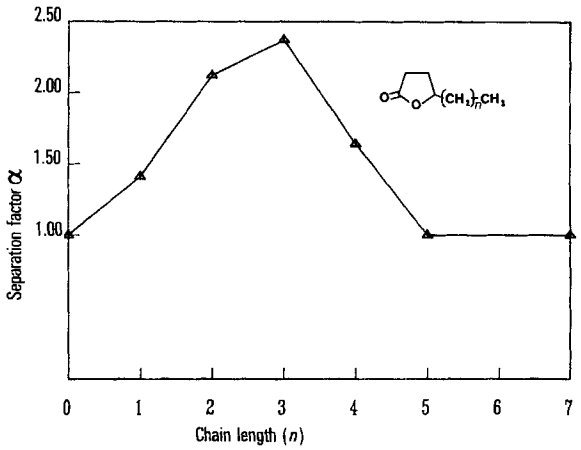


Fig. 3. *Influence of the chain length of γ-alkyl-γ-lactones* **5a–g** *on the separation factor* α

to a well defined spatial arrangement of the polymer chains in the supramolecular structure of CTA I. In the series above, the butyl derivative **5d** appears to fit the best into this arrangement (cavity).

Compounds **5b** and **6**, which are components of the sex attractant pheromone of *Trogoderma* species [33] and of the perfume of *Polianthes tuberosa* [34], respectively, are reasonably well resolved. The presence of a second substituent at the γ position of the lactone affects considerably the separation as illustrated by **7** and **27** which are rapidly eluted with a very poor chiral discrimination.

The presence of an endocyclic (**23–26, 28**) or exocyclic (**19**) double bond at the lactone ring often has a marked favourable influence on both the retention time and the chiral recognition. This might be explained by a more pronounced flatness and a possibly more favourable electronic interaction between CTA I and the double bond of the molecule, both factors seeming very important in the interaction process [35].

As generally observed [9] [13b] [15b] [36], compounds bearing an OH functionality (alcohols, acids, *etc.*) are not resolved under the usual chromatographic conditions ($EtOH/H_2O$ 95:5 as eluent). The strong solvatation of such compounds by the eluent probably disfavours the interaction with the solid phase, as indicated by short retention times. For this reason, lactones **11**, **16a**, and **22a** are not resolved and exhibit very low capacity factors (0.63, 0.71, and 0.73 respectively). However, by using an ester of the given alcohol, it is often possible to considerably improve the optical resolution of the compound [9]. This has been carried out for the chiral synthon **11**, for the hydroxylactone **16a**, and for the chiral auxiliary reagent pantolactone **22a**. The corresponding acetate **12** or propionates **16c** and **22c** give all base-line separations. For **16a** and **22a**, the better separation is obtained with their propionate derivatives **16c** and **22c**, CTA I showing a poorer chiral differentiation for the corresponding acetates and butyrates.

In general, lactones bearing an aryl substituent show a higher capacity factor (*i.e.* stronger interaction with the support) than the analogous alkyl lactones. However, the substituent on the aromatic moiety can have a dramatic influence on both the capacity factor and the chiral discrimination as exemplified by the chromatographic resolution of **1** and **2** *(Fig. 4)* and as observed also for other types of chiral aromatic compounds [9]

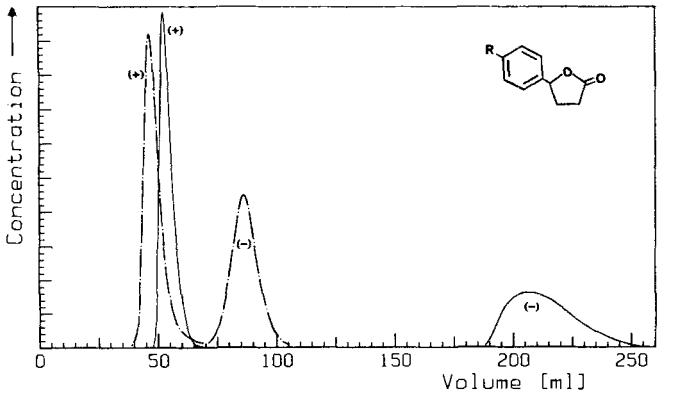


Fig. 4. *Chromatographic resolution of the γ-aryl-γ-butyrolactones* **1**(R = H; ——) *and* **2** (R = F; –·–·–) *on CTA I* (column *B*)

[37]. The chiral differentiation can also be considerably affected by the position of the substituent on the aromatic ring. Indeed, although all three nitrophenyl-butyrolactones **3a–c** are relatively well retained, the separation factor $\alpha = 1.0$ (no separation) for the *p*-nitro derivative increases to 1.21 for the *m*- and to 1.47 for the *o*-nitro derivative. This order is not always respected and cannot be taken as a general rule [37], but it indicates that a variation of the position of the substituent which might induce conformational changes in the molecule (thus modifying the inclusion capability) can play a dominant role in the global interaction.

The bicyclic lactone **20**, an intermediate in the synthesis of antidepressive drugs which has previously also been resolved on the *Pirkle* phase CSP-1 [38] ($\alpha = 1.08$), shows a better separation factor on CTA I ($\alpha = 1.24$).

From both key intermediates **13** and **28** used in the synthesis of several naturally occurring antitumor agents derived from lignan lactones [31] [39], only the unsaturated derivative **28** is resolved. This example illustrates again the positive influence of the endocyclic double bond on the separability of five-membered-ring lactone enantiomers.

Six-Membered-Ring Lactones. Only a few six-membered-ring lactones *(Table 4)* have been studied in this work, but the resolution of δ-phenyl-δ-valerolactone (**35**) with its

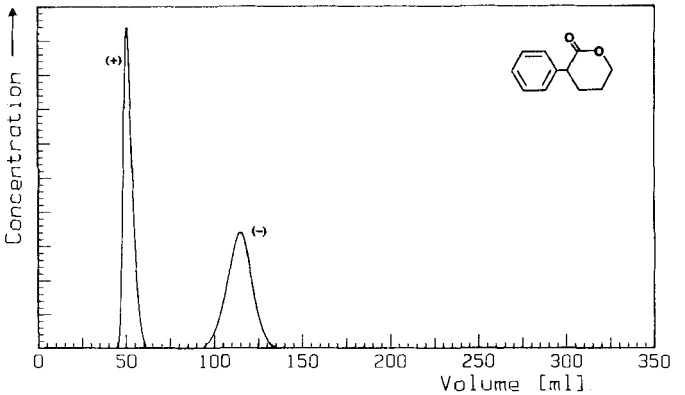


Fig. 5. *Chromatographic resolution of α-phenyl-δ-valerolactone* (**30**) *on CTA I* (column *B*)

exceptionally large α value of 23.3 is remarkable (to our knowledge, the highest value for CTA I until now). This result suggests that the (−)-enantiomer of **35** fits particularly well the chiral environment delimiting the hypothetic CTA I cavity. The corresponding α-phenyl-δ-valerolactone (**30**; *Fig. 5*) is also well resolved, although less efficiently.

In contrast to the corresponding five-membered-ring lactones **5d** and **5e**, the δ-butyl- and δ-pentyl-δ-valerolactones (**32** and **33**, resp.) are not resolved on CTA I under similar chromatographic conditions, whereas the unsaturated analogue **31** is partially separated.

Elution Order and Absolute Configuration. Determination of the absolute configuration of molecules has become a very important task for the chemist working on the synthesis of natural or synthetic chiral substances. The X-ray diffraction analysis provides the most reliable technique for the assignment of the absolute configuration, but it is exclusively applicable on crystalline compounds and requires both time and an expensive equipment. Attempts to correlate the elution order in the chromatography on achiral phases and the absolute configuration have already been reported and successfully applied to several diastereoisomeric series of compounds in liquid [41] and gas [42] chromatography. The use of chiral stationary phases for this purpose has also been reported [16] [43] and, owing to the simplicity of the method, a larger number of applications is to be expected.

Considering the chiral phase CTA I as a molecular assembly containing a multitude of chiral receptors with a more or less defined topology, one can expect that in a homologous series, the affinity of the 'receptor' is always greater for the enantiomers of the same configuration, since the chiral recognition process should be governed by similar types of interactions under defined chromatographic conditions.

The absolute configurations of a number of lactonic derivatives investigated in this work have been reported in the literature and are given in *Tables 1–4* for the best retained enantiomer on the basis of the sign of the optical rotation. For the assignment of the absolute configuration, it has been assumed that there is no change of the sign of the optical rotation between the value determined at $\lambda = 589$ nm ($[\alpha]_D$) and $\lambda = 365$ nm measured during the chromatography. This assumption has been verified for the pure enantiomers of **1**, **5b**, **9**, **11**, **16a,b**, **22a–d**, and **26** which show the same sign of optical rotation at both wavelenghts. Furthermore, for **1**, **5b**, and **9**[3]) which have been preparatively resolved (see below) and for (*S*)-**12**, (*S*)-**16b–c**, (*R*)-**22b–d**, prepared by esterification from (+)-(*S*)-**11** [23], (−)-(*S*)-**16a** [44], and (−)-(*R*)-pantolactone **22a**, respectively, the elution order was determined by chromatographing the pure enantiomers or mixtures with unequal proportions of each enantiomer.

In the series of γ-alkyl-γ-lactones **5a–g**, the best retained enantiomer for the compounds with a known absolute configuration (**5a–c**, **5e**, **5g**), has always the (*R*)-configuration. With respect to the above consideration concerning the relationship between elution order and absolute configuration, the most strongly retained enantiomer of **5d** and **5f** possess very probably also the (*R*)-configuration.

For 4-dodecanolide (**5g**), found in the secretion of the pyrigidial gland of some insects, our result confirms the configuration assigned by *Solladié et al.* [6f] who was in contradiction with the findings of *Pirkle et al.* [6b]. As illustrated in *Fig. 6*, **5g** is not well resolved on

[3]) A detailed description of the chromatographic optical resolution of this compound on a CTA-I column will be reported later in the scope of another investigation. Optical rotation for the pure isolated (−)-(*R*)-**9**: $[\alpha]_D = -46°$ ($c = 0.564$, EtOH) and pure (+)-(*S*)-**9**: $[\alpha]_D = +47.2°$ ($c = 0.544$, EtOH); [21]: $[\alpha]_D = -36.4°$ ($c = 0.5$, EtOH) and $[\alpha]_D = +28.8°$ ($c = 0.4$, EtOH).

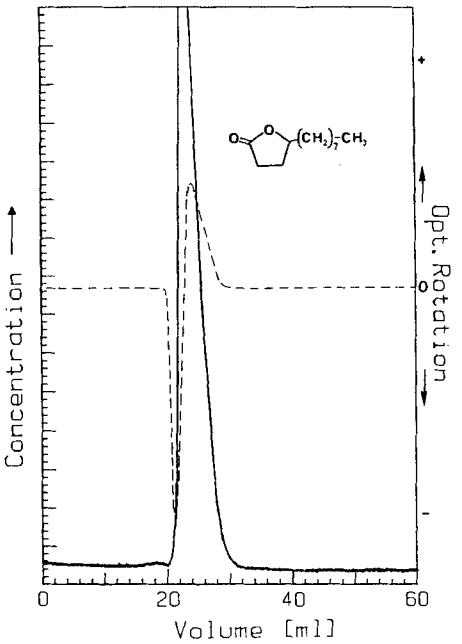


Fig. 6. *Chromatographic resolution of γ-octyl-γ-butyrolactone* (**5g**) *on CTA I* (column *B*). Concentration —, optical rotation – – –.

CTA I, but the polarimetric detection reveals an enrichment in the first and the last eluted fractions which allows to determine the elution order. The application of this concept to **6** and **8** should confer the (*R*)-configuration to the best retained enantiomer in each case.

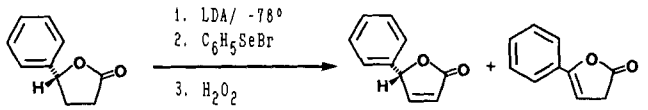
In the series **9**–**13**, the enantiomer with the (*S*)-configuration displays a stronger affinity for the chiral phase CTA I, but this configuration corresponds to the same spatial arrangement around the center of chirality as for the (*R*)-configuration of the alkyl-substituted lactones **5a**–**g** [45].

In the series **15**, **16**, **17b**, and **22**, bearing a substituent at the α position, the (*R*)-configurated enantiomer elutes later[4]) except for the free α-hydroxy-δ-lactones **16a** and **22a** which show an inversion of the elution order ((*S*)-enantiomer) as compared to their corresponding acetate, propionate, or butyrate. This result suggests that the interaction mechanism is different when the molecule has the possibility to form a H-bond which might favour a different approach between the enantiomer and the receptor (chiral phase). It shows that the application of this method for the assignment of the absolute configuration can be ambiguous when some compounds belonging apparently to a same class contain a functional group which by itself interacts strongly with the chiral phase, thus leading to a different interaction mechanism.

Comparing the elution order of the γ-ethyl-γ-butyrolactone **5b** and the derivative **13**, and their respective unsaturated analogues **23** and **28**, the presence of the endocyclic double bond seems to have no influence. To verify the generality of this concept, we

[4]) For **15** and **17b**, the enantiomeric enrichment on CTA I was sufficient to determine the elution order on the basis of the polarimetric detection.

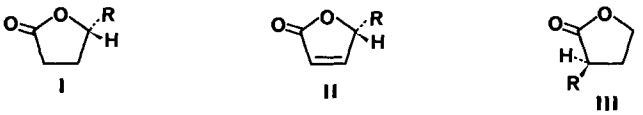
Scheme



(+)-**1** (+)-(*R*)-**26**

synthetized the unsaturated enantiomer (+)-**26** starting from the pure enantiomer (+)-**1**, isolated chromatographically on a preparative scale (see below), using the methodology of *Sharpless et al.* [46] *(Scheme)*[5]). From the known absolute configuration of (+)-(*R*)-**26** [28], it can be deduced that (+)-**1** has the (*R*)-configuration and that in both cases (**1** and **26**) the (*S*)-configurated enantiomer interacts strongly with CTA I. In the same way, it can be predicted that the enantiomer (−)-**24** should have the (*S*)-configuration.

An analysis of the results presented in this last section allows a first interpretation. Based on the established absolute configuration of a large number of chiral five-membered-ring lactones, we found for this class of compounds a relationship between the elution order in the chromatography on cellulose triacetate and the absolute configuration. For γ-butyrolactones, bearing only one substituent other than a H-atom, the most strongly retained enantiomer has the configuration depicted by the structure **I** (or **II** for unsaturated derivatives) when this substituent is at the γ position. The structure **III** represents the configuration of the best retained enantiomer when the substituent is at the



I **II** **III**

α position. This rule is presumably widely applicable, and an extention to five-membered-ring lactones with more than one substituent or to six-membered-ring lactones is currently under investigation.

Conclusion. It has been shown that a large number of racemic γ- and δ-lactones can be resolved on an analytical and preparative scale on the chiral phase CTA I. In addition, it has been found that for some of the investigated series, the chromatographic resolution on a chiral stationary phase in combination with polarimetric detection can be a useful method for the assignment of the absolute configuration without isolation of the enantiomers and even when only a partial resolution is observed. This is particularly valuable for noncrystalline chiral compounds like most of the lactone derivatives studied in this work. A limitation among the considered series is given by the two examples **16a** and **22a** when molecules of the same basic structure but differing by the presence of functional groups that can strongly contribute to interactions with the stationary phase are compared. For multi-functionalized lactones, the interpretation is still not reliable.

Preparative Separations. When necessary, larger amounts of optically pure materials can be prepared by chromatography using larger columns of CTA I. In many cases, this method can considerably simplify the supply of enantiomerically pure compounds whose

[5]) Enantiomer (+)-**26** has been obtained only in a very low yield by using this methodology, but it has been confirmed chromatographically that no detectable racemisation occurred during the different steps.

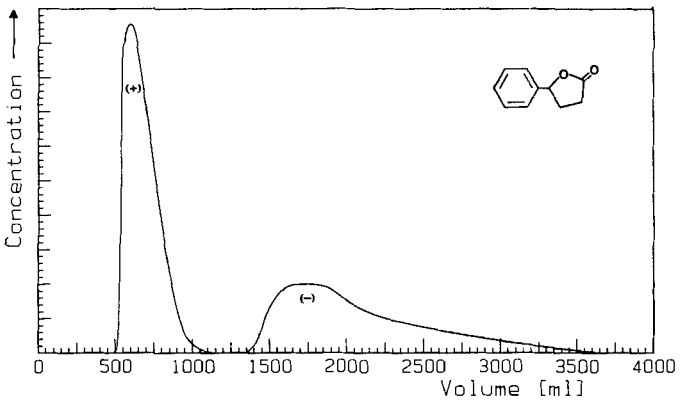


Fig. 7. *Preparative chromatographic resolution of 5 g of γ-phenyl-γ-butyrolactone* (**1**) *on 480 g of CTA I* (column 5 cm × 60 cm)

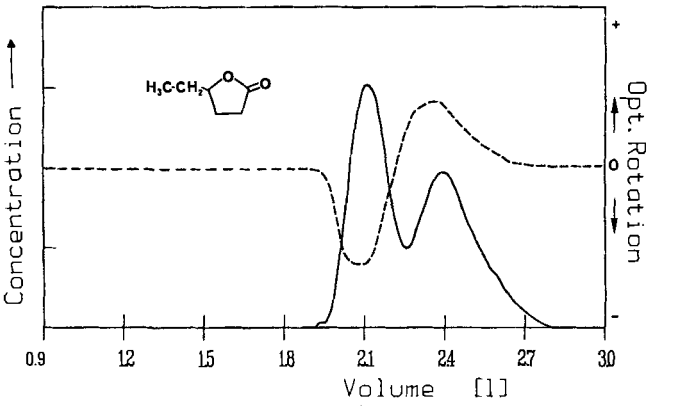


Fig. 8. *Preparative chromatographic resolution of 2.47 g of γ-ethyl-γ-butyrolactone* (**5b**) *on 800 g of CTA I* (column 5 cm × 100 cm). Concentration ——, optical rotation – – –.

Table 5. *Preparative Chromatographic Resolution of γ-Phenyl- and γ-Ethyl-γ-butyrolactone* (**1** and **5b**, resp.) *on CTA I.* For chromatographic conditions, see *Exper. Part.*

Compound[a])	Isolated enantiomer[b])	Optical purity	Optical rotation			
			$[\alpha]_D$	$[\alpha]_{546}$	$[\alpha]_{365}$	*c* (solvent)
1 (5 g)	(−) (2.45 g)	*ca.* 100%	−16.5°	−19.5°	−57.9°	1.0 (EtOH)
	(+) (2.43 g)	*ca.* 100%	+16.3°	+19.6°	+58.4°	0.89 (EtOH)
5b (2.47 g)	(−)-(*S*) (0.81 g)	*ca.* 96%	−51.3°	−60.6°	−155.8°	0.99 (MeOH)[d])
	(+)-(*R*) (0.78 g)	*ca.* 100%	+53.5°	+63.2°	+163.0°	1.01 (MeOH)[d])

[a]) Injected quantity in parentheses.
[b]) Isolated quantity after distillation in parentheses.
[c]) Concentration in %.
[d]) Lit. values: [6a], $[\alpha]_D = +53.2°$ (*c* = 1, MeOH); [6j], $[\alpha]_D = -53.7°$ (*c* = 1, MeOH).

synthetic approach is otherwise very often time-consuming and necessitates more complicated strategies than for the corresponding racemic compounds. To demonstrate the usefulness of the chromatographic separation of enantiomers on a larger scale, we resolved 5 g of γ-phenyl-γ-butyrolactone (**1**) on 480 g of CTA I *(Fig. 7)* and 2.47 g of the pheromone **5b** on 800 g of CTA I *(Fig. 8)*. The pure enantiomers of **1** have been isolated almost quantitatively, and their data are summarized in *Table 5*. The chromatographic resolution of **5b** which gives no baseline separation affords, after fractionation, the pure enantiomers in good yields *(Table 5)*.

We thank Dr. *B. Ernst* and Dr. *H. G. Capraro* for the gift of some of the racemic lactone derivatives. Thanks are due to Miss *G. Baisch* and Mrs. *H. Wuethrich* for excellent technical assistance.

Experimental Part

General. Compounds **1**, **2**, **5a**, **5d–f**, **15**, **17a**, **21**, **22a**, **29**, **33**, and **34** are commercially available. Racemates **3c** [47], **5b** [48], **5c** [47], **5g** [47], **6** [49], **7** [50], **14** [61], **16a** [51], **16b–d** [62], **18** [52], **19** [53], **20** [54], **23** [55], **30** [57], **31** [58], **32** [59], and **35** [60] were prepared according to the procedures given in the respective references. Compounds **3a**, **3b**, **4a**, **4b**, **8**, and **27** were kindly provided by Dr. *B. Ernst* (*Ciba-Geigy AG*, Basel) and compounds **9**, **24**, and **25** by Dr. *H. G. Capraro* (*Ciba-Geigy AG*, Basel). Optical rotations: *Perkin-Elmer 241* polarimeter. NMR-spectra: *Bruker VM-250-MHz* spectrometer; TMS as an internal standard.

Chromatographic Resolutions on CTA I. The sorbent CTA I was prepared by heterogeneous acetylation of native or microcrystalline cellulose (*Merck* Nr. *2331* or *2351*) according to the procedure described by *Hesse* and *Hagel* [10]. A particle size of 25–32 μm was ajusted by brief milling and sifting. For anal. separations, a 60 cm (column *A*), 30 cm (column *B*), or 15 cm (column *C*) glass column with i.d. 1.25 cm topped with a column of the same dimension (as a reservoir) was slurry-packed with 32 g (*A*), 17 g (*B*), or 8 g (*C*), resp., of CTA I swollen before in 100, 50, and 30 ml, resp., of EtOH/H_2O 95:5 at *ca.* 75° for 20 min. After decantation of the material in the column, the reservoir was taken away and the stationary phase washed by pumping the eluent (95% EtOH) through the column equipped with an inlet plunger, at a flow rate of 0.7 ml/min until no more absorption was detected in UV at a wavelength of 254 nm. All chromatographies were performed at a flow rate of 0.5 ml/min giving a pressure of 1.0 (*A*), 0.4 (*B*), and 0.3 l (*C*) bar at the column top. *p*-Toluenesulfonic acid served as a chromatographic reference and eluted after 40, 22, and 9.3 ml, resp. The racemates were injected as a soln. of 2–5 mg in 0.3 ml of the eluent (EtOH/H_2O 95:5). The chromatographies were performed using an *Altex 110 A pump*, a *Chromatix* injector with a 0.3-ml loop and a variable-wavelength UV detector *Shimadzu 120-02* in series with a *Perkin-Elmer* (model *241 MC*) polarimeter equipped with a 300-μl flow cell (length 10 cm). For compounds which do not absorb in UV, detection was performed by refractometry (*Shimadzu RI* detector, *RID-2A*). Both signals (UV absorption and optical rotation) were recorded and processes by a *Hewlett-Packard HP-85B* calculator through a *Hewlett-Packard 3421A* data acquisition/control unit. For prep. chromatographic resolutions, the same procedure was applied but using a column of greater dimension (60 or 100 cm × 5 cm i.d.) also equipped with an inlet plunger (currently under development by *Buechi AG*, Flawil, Switzerland) and filled with CTA I (particle size 25–56 μm) as described before. Thus, 5 g of the racemate **1** (column 60 cm × 5 cm containing 480 g of CTA I) and 2.47 g of the racemate **5b** (column 100 cm × 5 cm containing 800 g of CTA I) dissolved in 20 ml of EtOH/H_2O 95:5 were chromatographically resolved on these columns.

Syntheses. Racemates **10** [22], **11** [22], **13** [22], and **28** [31] were synthesized starting from racemic glutamic acid by the same sequence and by the same procedures as those described for the corresponding optically active compound. The racemates exhibited identical spectral data (^{1}H-NMR, IR) as the corresponding optically active derivative.

General Procedure for the Esterification of the Hydroxylactones **11** *and* **22a**. A mixture of 15.4 mmol of the hydroxylactone, 26.8 mmol of anhydride and 26.8 mmol of Et_3N was stirred in presence of a catalytic amount of 4-pyrrolidinopyridine in 20 ml of CH_2Cl_2 for 10 h at r.t. After acidic workup (2N HCl), the org. phase was dried (Na_2SO_4) and the solvent evaporated. The residue was purified by chromatography on silica gel ($CHCl_3$/AcOEt 7:1) or by bulb-to-bulb distillation.

(±)-5-[(Acetoxy)methyl]-4,5-dihydro-2(3H)-furanone (**12**). Yield 92%. B.p. 140–150°/0.1 Torr. IR (film): 2950, 1780, 1745, 1375, 1240. ^{1}H-NMR ($CDCl_3$): 4.68–4.80 (*m*, 1 H); 4.31 (*dd*, 1 H); 4.13 (*dd*, 1 H); 1.96–2.67 (*m*, 4 H); 2.10 (*s*, 1 H).

(+)-(S)-**12**: $[\alpha]_D = +46.8°$, $[\alpha]_{365} = +146.3°$ ($c = 1.586$, EtOH/H_2O 95:5).

(±)-Pantolactone Acetate (= *(±)-3-Acetoxy-4,5-dihydro-4,4-dimethyl-2(3H)-furanone;* **22b**). Yield after chromatography 83%. IR ($CHCl_3$): 2970, 1800, 1750, 1375, 1230, 1100. ^{1}H-NMR ($CDCl_3$): 5.36 (*s*, 1 H); 4.06 (*dd*, 2 H); 3.23 (*s*, 3 H); 1.22 (*s*, 3 H); 1.12 (*s*, 3 H).

(−)-(R)-**22b** *from (−)-(R)-Pantolactone* ((−)-(*R*)-**22a**): $[\alpha]_D = -13.3°$, $[\alpha]_{365} = -56.4°$ ($c = 1.29$, EtOH/H_2O 95:5).

(±)-Pantolactone Propionate (= *(±)-4,5-Dihydro-4,4-dimethyl-3(propionyloxy)-2(3H)-furanone;* **22c**). Yield after chromatography 89%. IR ($CHCl_3$): 2990, 1795, 1755, 1160, 1105. ^{1}H-NMR ($CDCl_3$): 5.36 (*s*, 1 H); 4.05 (*dd*, 2 H); 3.42–3.55 (*m*, 2 H); 1.14–1.28 (*t*, 3 H); 1.22 (*s*, 3 H); 1.12 (*s*, 3 H).

(−)-(R)-**22c** *from (−)-(R)-Pantolactone* ((−)-(*R*)-**22a**): $[\alpha]_D = -9.7°$, $[\alpha]_{365} = -42.1°$ ($c = 1.218$, EtOH/H_2O 95:5).

(±)-Pantolactone Butyrate (= *(±)-3-(Butyryloxy)-4,5-dihydro-4,4-dimethyl-2(3H)-furanone;* **22d**). Yield after chromatography 63%. IR ($CHCl_3$): 2970, 1790, 1750, 1470, 1160, 1105. ^{1}H-NMR ($CDCl_3$): 5.36 (*s*, 1 H); 4.02 (*dd*, 2 H); 2.43 (*dt*, 2 H); 1.70 (*t*, 2 H); 1.18 (*s*, 3 H); 1.09 (*s*, 3 H); 0.96 (*t*, 3 H).

(−)-(R)-**22d** *from (−)-(R)-Pantolactone* ((−)-(*R*)-**22a**): $[\alpha]_D = -10.2°$, $[\alpha]_{365} = -45.4°$ ($c = 1.226$, EtOH/H_2O 95:5).

α-Butyl-γ-butyrolactone (**17b**). The procedure was essentially that of *Meyers et al.* [63], starting from 4,5-dihydro-4,4-dimethyl-2-pentyloxazol and ethylene oxide. The dihydrooxazole was prepared by heating a mixture of 8.6 ml (68.8 mmol) of hexanoic acid with 6.6 ml (68.8 mmol) of 2-amino-2-methylpropanol for 2 days at 170°. The mixture was treated with H_2O and extracted with hexane. The org. layer was dried ($MgSO_4$) and evaporated to give an oil which was bulb-to-bulb distilled (35%). B.p. 150°/0.1 Torr. IR (film): 2960, 2870, 1670, 1455, 990. ^{1}H-NMR ($CDCl_3$): 3.90 (*s*, 2 H); 2.23 (*t*, 2 H); 1.58–1.68 (*m*, 2 H); 1.28–1.35 (*m*, 6 H); 1.27 (*s*, 6 H); 0.9 (*t*, 3 H). Under N_2, 7.8 ml of BuLi (1.6M in THF) were added dropwise to a soln. of 2 g (12 mmol) of *4,5-dihydro-4,4-dimethyl-2-pentyloxazole* in 10 ml of THF at −78°. The mixture was stirred for 30 min at −78°, and 1.1 equiv. of ethylene oxyde was added. After 30 min at −78°, the soln. was allowed to reach r.t. (5 h) and quenched with H_2O. The mixture was extracted with Et_2O and the org. layer washed with sat. brine, dried ($MgSO_4$), and evaporated. The residue was heated at reflux in 40 ml of 3N HCl for 1.5 h. After cooling, the soln. was extracted with Et_2O, dried ($MgSO_4$), and evaporated to give crude **17b**. Pure **17b** was obtained by bulb-to-bulb distillation as a colorless oil (0.74 g, 46%). IR (film): 2930, 2860, 1775, 1170, 1030. ^{1}H-NMR ($CDCl_3$): 4.32 (*ddd*, 1 H); 4.6 (*ddd*, 1 H); 2.28–2.56 (*m*, 2 H); 1.80–2.00 (*m*, 1 H); 1.18–1.64 (*m*, 1 H); 0.86 (*t*, 3 H).

(±)-5-Phenyl-2(5H)-furanone (**26**). See [46]. Under N_2, 22 ml of BuLi (1.6M in THF) were added dropwise to a soln. of 3.42 g (34 mmol) of (i-Pr)$_2$NH in 25 ml of dry THF cooled to −78°. The mixture was stirred for 30 min, and 5 g (30.8 mmol) of **1** in 40 ml of dry THF were added dropwise. The soln. was stirred for 3 h at −78°, and 1.3 equiv. of benzeneselenenyl bromide (6.44 g of diphenyl selenide and 3.2 g of Br_2) in 15 ml of THF were added. The yellow soln. was allowed to reach r.t. (5 h). After acidic workup, the crude product was chromatographed on silica gel (hexane/AcOEt 8:2). The isolated crystalline material (1.12 g) was treated overnight with 2 ml of H_2O_2 (30%) in 5 ml of THF. The THF was evaporated and the resultant soln. extracted with CH_2Cl_2. The org. layer was dried (Na_2SO_4) and evaporated. The residue was bulb-to-bulb distilled (100–120°/0.07 Torr) to afford an oil (0.49 g, 10%) which was identified as a mixture of **26** (92%) and 5-phenyl-2(3*H*)-furanone (8%) by comparing the ^{1}H-NMR data with that one of pure **26** [56a] and 5-phenyl-2(3*H*)-furanone [56b].

((+)-(*R*)-**26**) [29]: Under the same conditions as for (±)-**26**, (+)-(*R*)-**26** was prepared starting from 1 g of (+)-**1** (overall yield 12%). The isolated product was also contamined with 7% of the isomeric 5-phenyl-2(3*H*)-furanone, but no detectable amount of the (−)-(*S*)-**26** was observed by chromatography on the CTA 1 column.

δ-(p-Clorophenyl)-δ-valerolactone (**36**). Under N_2, a soln. of 35 g (0.34 mol) of glutarie anhydride in 200 ml of chlorobenzene was added dropwise (1.5 h) to a stirred suspension of 100 g (0.75 mol) of $AlCl_3$ in 150 ml of chlorobenzene cooled with an ice-bath at −15°. The orange soln. was poured onto ice and acidified with conc. HCl soln. giving a white precipitate. The excess of chlorobenzene was evaporated and the resultant suspension treated with a sat. aq. $NaHCO_3$ soln. until no more CO_2 evolution occurred. The insoluble particles were filtered, and the soln. was extracted with Et_2O. The aq. layer was acidified with conc. HCl soln. and the white precipitate filtered, washed with H_2O, and dried at 50°: 10.2 g (13%) of *4-(p-chlorophenyl)-4-formylbutyric acid* were isolated. M.p. 118–120°. IR ($CHCl_3$): 3010, 1710, 1610, 1590, 1195. ^{1}H-NMR ($CDCl_3$): 10.4 (br., 1H); 7.89 (*d*, 2H); 7.43 (*d*, 2H); 3.05 (*t*, 2H); 2.5 (*t*, 2H); 2.07 (*quint.* 2H).

At r.t., 5 g of the above acid were treated for 10 h with a soln. of 1.23 g (22 mmol) KOH in 20 ml H_2O containing 1.4 g (26 mmol) of KBH_4. The soln. was acidified with conc. HCl soln. and the product extracted with Et_2O. The org. layer was dried (Na_2SO_4) and evaporated to afford 4.4 g (95%) of **36** a yellow oil which crystallized upon standing. A sample was bulb-to-bulb distilled for analysis and spectral characterization. M.p. 106–107°. IR

($CHCl_3$): 3005, 2960, 1735, 1490, 1235, 1045. ^{1}H-NMR ($CDCl_3$): 7.35 (*d*, 2H); 7.27 (*d*, 2H); 5.32 (*dd*, 1H); 2.50–2.80 (*m*, 2H); 1.76–2.23 (*m*, 4H).

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