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Note

Enantiomer separation of α-substituted γ-butyrolactones on the chiral polyacrylamide resin ChiraSpher®

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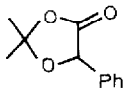
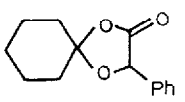
Chiral butyrolactones substituted in the α-position have proved to be valuable synthetic intermediates, *e.g.*, in syntheses of chiral dialcohols[1], but the chiral analysis of these species has not been well studied. The determination of the enantiomer content through optical rotation[2] and proton magnetic resonance in the presence of a chiral solvent[3] or chiral shift reagents[4] have been found to be applicable to only a small number of these lactones.

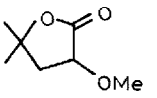
For our studies on the enantioselective protonation of prochiral anions[5] we required a fast and reliable method for the chiral analysis of a series of α-substituted γ-butyrolactones. We have previously successfully demonstrated the high-performance liquid chromatography (HPLC) separation of similar compounds, the 1,3-dioxolanones **1a** and **b** and the O-substituted pantolactones **2a** and **b**[6], on the chiral acrylamide polymer ChiraSpher®[7], and have now extended this application to the above-mentioned α-substituted γ-butyrolactones **3–n** in Table I.



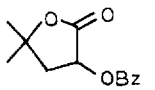
1a



1b



2a



2b

As we wanted to compare the chromatographic properties of the α-alkylated with those of the γ-alkylated γ-butyrolactones, recently investigated by Huffer and Schreier[8], we did not optimize the separation of every lactone, but used a similar eluent to that given in the literature[8].

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EXPERIMENTAL

HPLC equipment

The chromatographic analysis was performed on a Hibar®-ChiraSpher® RT 250-4 column (250 × 4 mm I.D., d_p = 5 μm) or on a Hibar®-triacetylcellulose column (250 × 10 mm I.D., d_p = 10 μm) (both from Merck, Darmstadt, F.R.G.) at ambient temperature. The eluent was delivered with a Knauer 64 HPLC pump. The racemic mixture (30–60 μg) was applied with a Rheodyne 1265 injection valve with a 5-μl loop; the enantiomers were detected with a Soma S-3702 UV–VIS detector at 220 nm.

Light petroleum and *tert.*-butyl methyl ether were distilled prior to use. Dioxane and ethanol were of HPLC grade from Aldrich (Milwaukee, WI, U.S.A.).

Lactones

All α-substituted γ-butyrolactones, except **3a**, which is available from Aldrich, were prepared according to literature procedures. Compounds **3b**, **c** and **e** were synthesized according to Borne *et al.*[9]; the analytical data for **3b** and **c** were identical with those given by Zenk and Wiley[10] and those of **3e** were in accordance with the values given by Jedlinski *et al.*[11]. Compound **3d** was prepared according to Zenk and Wiley[10]. The lactones **3f–l** were prepared according to the procedure of Elad *et al.*[12]. The analytical data for **3f**, **i** and **k** agreed with those found by Rothstein[13]. α-Benzyl-γ-butyrolactone (**3m**) was synthesized according to Jahovac and Jones[4] and gave analytical data in agreement with those found by Flechtner[14]. α-Phenyl-γ-butyrolactone (**3n**) was prepared according to Andresen *et al.*[15] and showed analytical data in agreement with those found by the same group[16].

Prior to injection, all the lactones were purified by medium-pressure LC on silica gel with light petroleum–*tert.*-butyl methyl ether mixtures as eluent.

Assignment of the elution order was made according to Huffer and Schreier[8] by multiple injection of α-methyl-γ-butyrolactone (**3a**), determination of the optical rotation of the enriched fractions and comparison with the values found in the literature[17]. The elution order was found to be *S* before *R*. Transfer of the assignment to the other lactones seems to be valid from information obtained by enantioselective protonation studies[5].

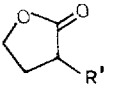
RESULTS AND DISCUSSION

All the racemic mixtures of γ-lactones **3a–n** could be efficiently separated, as can be seen from the data in Table I.

Similarly to the γ-alkylated lactones[8], α-alkylated lactones show increasing separation factors and resolution with increasing chain length but decreasing capacity factors. If the eluent is modified (dioxane instead of *tert.*-butyl methyl ether), γ-butyrolactones with short alkyl chains (**3a–d**) are separated more efficiently. Those with longer alkyl chains (**3e–l**), however, suffer from a decrease in α and resolution. Special cases are α-benzyl- and α-phenyl-γ-butyrolactone, where the α values and the resolutions are very high, as also are the capacity factors. These two lactones are the only ones in the series investigated that can also be separated on a triacetylcellulose stationary phase. Probably the aromatic group favours chiral recognition on the chiral polyacrylamide as well as on the polysaccharide. In contrast to the γ-alkylated butyrolactones, the elution orders of **3m** and **n** are retained on triacetylcellulose.

TABLE I

RETENTION TIMES (t_R), CAPACITY FACTORS (k'), SEPARATION FACTORS (α) AND RESOLUTIONS (R) FOR THE SEPARATION OF α-SUBSTITUTED γ-BUTYROLACTONES ON CHIRASPHER®



Eluent: hexane–*tert.*-butyl methyl ether–ethanol (4000:60:1); flow-rate, 1.2 ml/min.

Compound 3	*R' (min)*	$t_R(S)$ *(min)*	$t_R(R)$	$k'(S)$	$k'(R)$	α	R^a
a	Methyl[b]	19.9	21.5	6.96	7.60	1.09	0.60
b	Ethyl[b]	14.1	15.3	4.64	5.12	1.10	0.81
c	Propyl[b]	11.9	13.4	3.76	4.35	1.16	1.07
d	Butyl[b]	10.3	11.07	3.12	3.70	1.19	1.65
e	Pentyl[c]	9.4	10.7	2.75	3.27	1.19	1.56
f	Hexyl	8.9	10.3	2.56	3.12	1.22	2.11
g	Heptyl	8.3	9.5	2.31	2.81	1.22	1.75
h	Octyl	8.0	9.3	2.19	2.71	1.24	1.52
i	Nonyl	7.6	8.8	2.03	2.51	1.24	2.05
j	Decyl	7.4	8.6	1.95	2.44	1.25	2.31
k	Undecyl	7.2	8.5	1.88	2.40	1.28	2.15
l	Dodecyl[c]	7.0	8.3	1.81	2.32	1.28	2.36
m	Benzyl[d]	33.0	36.5	7.35	8.03	1.09	2.01
n	Phenyl	44.8	59.1	16.92	22.64	1.34	3.20
n	Phenyl[e]	8.4	10.8	4.25	5.12	1.20	2.00

[a] The resolution was calculated from the width at the peak bottom according to Meyer[18].

[b] Hexane–dioxane (96:4) as eluent at a flow-rate of 0.7 ml/min provides better resolutions for **3a–d**, *e.g.*, for **3a** $\alpha = 1.10$, $R = 1.28$.

[c] No separation could be achieved with triacetylcellulose: for unsuccessful separation of **3a** (R = Me) and **3d** (R = Bu) see ref. 19.

[d] Efficient separation could be achieved on triacetylcellulose; eluent 96% ethanol, flow-rate 1.1 ml/min ($\alpha = 1.47$, $R = 1.57$).

[e] The slight tailing disappears with hexane–*tert.*-butyl methyl ether (3:2), flow-rate 1.2 ml/min; the lactone **3n** has previously been separated on triacetylcellulose[19], *S* elutes before *R*; assignment through optically enriched **3n**[20].

In general, the ChiraSpher® phase is much better suited for the separation of lactones than triacetylcellulose because of the wider scope of application and the faster and superior separations. By varying the substitution pattern, ring size and heteroatom(s) in the ring, a better understanding of the chiral interaction between organic substrate and ChiraSpher® may be achieved.

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