Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 3, pp. 633-636, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00051-1

CHROMATOGRAPHIC RESOLUTION OF SEVERAL RACEMIC 9-FLUORENYL DERIVATIVES ON A BONDED CELLULOSE DERIVED CHIRAL STATIONARY PHASE FOR HPLC

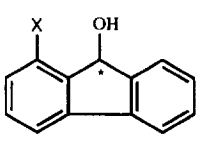
Dolores Velasco[a)]*, Zhanru Yu[a)], Pilar Franco[b)] and Cristina Minguillón[b)]

a) Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona
Martí i Franquès 1-11, E-08028 Barcelona (Spain).
b) Laboratori de Química Farmacèutica, Facultat de Farmàcia, Universitat de Barcelona
Avda. Diagonal s/n, E-08028 Barcelona (Spain).

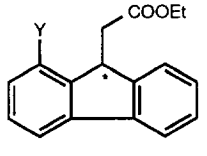
Abstract: The enantiomers of several 9-fluorenyl derivatives have been successfully resolved by HPLC on a chiral stationary phase (CSP) based on a mixed 10-undecenoate/3,5-dimethylphenylcarbamate of cellulose bonded to allylsilica gel. Previous attempts at resolution, such as NMR methods, GC and the use of a multiple interaction type chiral column for HPLC, were unsuccessful. Copyright © 1996 Elsevier Science Ltd

Introduction

In the course of studies concerning the search for new materials, we faced the problem of measuring enantiomeric excesses of some 9-fluorenyl derivatives, obtained by asymmetric reduction of either the corresponding fluorenones (compounds **1** to **9**, Figure 1) or 9-fluorylidene derivatives (compounds **10** to **13**, Figure 1). To our knowledge, there are no published studies on the resolution of 9-fluorenyl derivatives having a stereogenic center at the 9 position. Only the enantiomeric excesses of some ortho-substituted benzhydryl derivatives, through the analysis of their ^{1}H-NMR spectra using chiral shift reagents, have been determined[1]. The difficulty in the induction of asymmetry from the starting symmetric products, as well as in the resolution of the enantiomers of such compounds, can be attributed to the relatively low geometric or electronic difference between the two aromatic substituents bonded to the stereogenic center. This paper deals with several attempts to resolve racemic compounds **1-13** with the aim of using the most suitable method to measure enantiomeric excesses of mixtures of enantiomers of these compounds.



1: X=F **5**: X=Me
2: X=Cl **6**: X=OMe
3: X=Br **7**: X=$CONEt_2$
4: X=I **8**: X=NMe_2
9: X=NH_2



10: Y=Me
11: Y=COOEt
12: Y=OMe
13: Y=$CONEt_2$

Fig. 1. Chemical structures of the 9-fluorenyl derivatives tested.

Results and discussion

Racemic fluorenol derivatives **1-9** were obtained by reduction with lithium aluminiun hydride of the corresponding fluorenone[2], whereas racemic compounds **10-13** were prepared from the corresponding fluorylidene derivatives by catalytic hydrogenation[3].

Mösher esters (3,3,3-trifluoro-2-phenyl-2-methoxy-2(R)-propionates) of **3** and **6** were obtained in standard conditions[4]. The formation of Mösher esters from the corresponding alcohols showed quite different reaction rates for the two enantiomers. Thus, whereas the conversion of one of the enantiomers into the ester derivative was complete after 5 min, the reaction of the other enantiomer needed longer times. To compare the kinetics of the reactions of the two enantiomeric alcohols of **3** and **6** with one homochiral Mosher's reagent, racemic alcohols **3** were allowed to react with racemic Mosher's reagent. The ratio of the diastereomers formed was determined by ^{1}H-NMR. The benzyl protons of the two diastereomers could be clearly distinguished at 7.07 and 7.01 ppm respectively. The ratio of areas showed that the formation of one diastereomer is 4.83 times faster than the other. The same relative rates can be determined by integration of the areas of the methoxy signals at 3.61 and 3.49 ppm respectively. The same experiment carried out with racemic alcohols **6** resulted in a ratio of 5.19. The ^{1}H-NMR signals of benzyl protons were at 6.82 and 6.75 ppm and the methoxy signals were at 3.63 and 3.49 ppm respectively. This should be taken into consideration in further studies about the potentiality of Mosher's reagent for kinetic resolutions. However, the resulting diastereomeric mixtures were studied not only by ^{1}H-NMR but also by ^{19}F-NMR and GC. Nevertheless, the different conversion rates of the two enantiomeric alcohols in their diastereomers prevents the use of this technique in the calculation of enantiomeric excesses for these compounds. The complete diastereomeric separation by GC of the Mösher esters of **3** was only possible using chromatographic conditions[5] that result in long retention times for both diastereomers.

The use of chiral shift reagents was also taken into account. Thus, the ^{1}H-NMR spectra of **3**, **6** and **9** in the presence of Eu(hfc)$_3$[6], in molar ratios from 0.22 to 1.54 respect to the fluorenol derivative, were registered using different solvents ($CDCl_3$, C_6D_6, $(CD_3)_2CO$ and CD_3CN). The partial overlap of signals always prevented the possible use of this approach as a quantitative technique in the measurement of enantiomeric excesses.

To study the HPLC chiral resolution of fluorenyl derivatives, firstly a N-(3,5-dinitrobenzoyl)-(S)-cyclohexylalanine bonded column[8], given its high chemical stability, was tested. Unfortunately, only **5** (a=1.07) and **6** (a=1.08) were partially resolved[9]. Therefore, a bonded cellulose-derived CSP[10,11], with a wider application domain, was used to obtain their resolution. Table 1 shows the chromatographic data using different mobile phases and the best conditions for the resolution of all compounds.

The cellulose-derived chiral selector present in this chromatographic column showed its ability in the chiral recognition of ten of the racemic 9-fluorenyl derivatives tested. Only **1**, **5** and **11** were not separated in the various chromatographic conditions used. The resolution was complete for compounds **6**, **7**, **8** and **13**.

All compounds were quickly eluted with the mobile phases commonly used with commercially available polysaccharide-derived CSPs. The use of a cellulose bonded CSP allowed the search for other kinds of organic modifier in the mobile phase, in order to increase retention times. Thus compounds **2-4**, **10** and **12** were partially resolved using *tert*-butyl methyl ether in the mobile phase. Among them, compounds **2-4** achieved the complete resolution (Rs>1.5) using a longer column (25 cm) with the same CSP. The 25 cm-CSP used also showed its chiral recognition ability in the resolution of compounds **1** and **5**, which presented the

beginning of separation (a=1.06) that was not detectable in the 15 cm length column. Figure 2 shows the resolution of compound 7[12].

Table 1. Chromatographic results on the cellulose-derived column[7].

Compounds	k'1	a	Rs	k'1	a	Rs	k'1	a	Rs	k'1	a	Rs
1	2.27[a]	1.00	-	1.93[a]	1.00	-	27.2[a]	1.00	-	10.6[a]	1.00	-
2	1.68[a]	1.00	-	0.87[a]	1.00	-	14.2[a]	1.11	-	***7.18[a]***	***1.19***	***1.26***
3	1.57[a]	1.00	-	2.02[a]	1.00	-	8.26[a]	1.05	-	***6.43[a]***	***1.20***	***1.25***
4	1.50[a]	1.00	-	1.98[a]	1.00	-	12.8[a]	1.04	-	***6.25[a]***	***1.14***	***0.93***
5	1.80[a]	1.00	-	1.42[a]	1.00	-	19.0[a]	1.00	-	9.43[a]	1.00	-
6	1.11[b]	2.60	5.71	***1.81[b]***	***2.48***	***7.62***	6.91[b]	1.17	1.69	4.38[b]	2.57	6.13
7	1.23[b]	1.77	2.86	***2.30[b]***	***1.71***	***3.83***	13.4[b]	1.03	-	20.2[b]	1.35	1.43
8	0.89[b]	1.81	2.25	***0.90[b]***	***1.94***	***4.40***	>60[b]			>60[b]		
9	3.63[b]	1.07	-	***6.10[b]***	***1.08***	***0.71***	>60[b]			>60[b]		
10	0.36[a]	1.00	-	0.10[b]	1.00	-	4.32[a]	1.00	-	***1.69[c]***	***1.16***	***0.83***
11	0.44[a]	1.00	-	0.12[b]	1.00	-	6.41[a]	1.00	-	1.63[c]	1.00	-
12	1.26[a]	1.00	-	0.54[b]	1.00	-	10.7[a]	1.00	-	***5.17[c]***	***1.24***	***1.32***
13	***3.73[a]***	***1.82***	***5.15***	0.96[b]	1.41	1.42	17.2[a]	1.00	-	13.5[c]	1.64	2.27
Mobile phase*	hept/2-PrOH# a) 98:2 b) 90:10			hept/EtOH/DEA§ a) 97.5:2.5:0.1 b) 95:5:0.1			hept/$CHCl_3$® a) 95:5 b) 70:30			hept/tBuOMe# a) 95:5 b) 70:30 c) 80:20		

* hept: heptane; 2-PrOH: 2-propanol; EtOH: ethanol; DEA: diethylamine; $CHCl_3$: chloroform; tBuOMe: *tert*-butyl methyl ether. UV detection: #, 230nm; §, 280 nm; ®, 254 nm. In ***Italic/Bold*** characters the best chromatographic separations for the compounds studied.

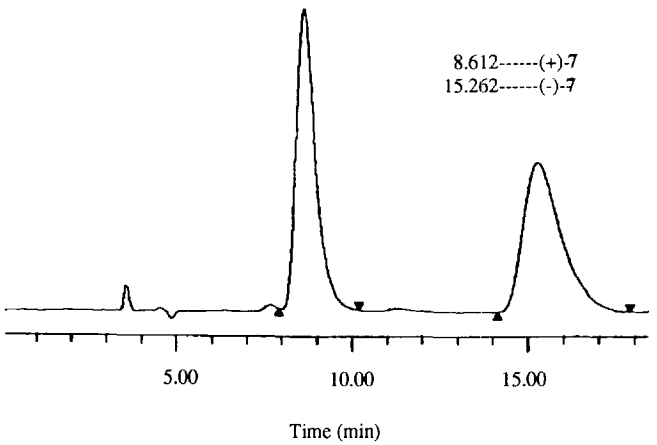


Fig. 2 Chromatographic resolution of **7**: the signal at 8.612 min corresponds to dextrorotatory enantiomer, whereas the signal at 15.262 min corresponds to the levorotatory.

Acknowledgments

Financial support from Comisión Interministerial de Ciencia y Tecnología and from the Generalitat de Catalunya (Project n. QFN94-4612 and QFN94-4605) of Spain is acknowledged.

Pilar Franco gratefully thanks the Comissió Interdepartamental de Recerca i Innovació Tecnològica (Generalitat de Catalunya) for a doctoral fellowship.

References

1. E. Brown, A. Lézé and J. Touet, *Tetrahedron: Asymmetry* **1992**, 3, 841.
2. E. H. Huntress, K. Pfister and K. H. T. Pfister, *J. Am. Chem. Soc.* **1942**, 64, 2845.
3. At atmospheric pressure, in methylene chloride/ethanol (10:2), using 10% palladium over charcoal as a catalyst.
4. D. E. Ward and C. K. Rhee, *Tetrahedron Lett.* **1991**, 32, 7165.
5. Retention time: t_1, 240.9 min; t_2, 244.5 min. Gas chromatographic system: Hewlett Packard 5890; column: SE-54 (25m x 0.20mm ID); mobile phase: He (20 psi); temperature: 200°C (isotherm).
6. Eu(hfc)$_3$: tris(3-heptafluorobutyryl-*d*-camphorato)-europium(III). ^{1}H-NMR spectra obtained in a Varian GEMINI-200 espectrometer (200 MHz).
7. The CSPs were packed into stainless-steel tubes by the slurry method. The chromatographic experiments were performed on an HPLC system consisting of a Shimadzu LC-10AD pump, a Shimadzu SIL-9A autoinjector equipped with a Shimadzu SPD-6AV UV detector and a Chromatopac C-R6A programmer. k'_1 is the capacity factor for the first enantiomer eluted, defined as: $k'_1 = (t_1-t_0)/t_0$, where t_1 and t_0 denote the retention time for this enantiomer and the dead time, respectively. The dead time was determined using tri-*tert*-butylbenzene as non-retained compound. a is the selectivity factor, given by the ratio: k'_2/k'_1, where the subscripts 1 and 2 refer to the first and last eluted enantiomer, respectively. Rs is the resolution, defined as: $Rs = 2(t_2-t_1)/(w_2+w_1)$, where t_2 and t_1 are the retention times of both enantiomers, and w_1 and w_2 their baseline peak widths.
8. L. Oliveros, C. Minguillón and T. González, *J. Chromatogr. A* **1994**, 672, 59.
9. The chromatographic resolutions were performed on a 10 x 0.46 cm ID column. Mobile phase: heptane/chloroform (95:5). Flow rate: 1 ml/min, UV detection l 254 nm.
10. (a) L. Oliveros, C. Minguillón and P. López, French Patent n. 2714671; (b) L. Oliveros, P. López, C. Minguillón and P. Franco, *J. Liq. Chromatogr.* **1995**, 18, 1521; (c) C. Minguillón, P. Franco, L. Oliveros and P. López, *J. Chromatogr. A* **1995**, in press.
11. The chromatographic resolutions were performed on a 15 x 0.46 cm ID column containing a mixed 10-undecenoate/3,5-dimethylphenylcarbamate of cellulose bonded to allylsilica gel. Flow rate: 1 ml/min.
12. The chromatographic resolutions were performed on a 25 x 0.46 cm ID column. containing a mixed 10-undecenoate/3,5-dimethylphenylcarbamate of cellulose bonded to allylsilica gel. Mobile phase: heptane/2-propanol (90:10). Flow rate: 1 ml/min, UV detection l 230 nm. HPLC system consisting of a Waters 600E pump, a Waters 717 auto sampler (Millipore, Milford, MA, USA) equipped with a waters 996 photo-diode array detector and a Perkin-Elmer 241LC polarimetric detector (Perkin-Elmer, Uberlingen, Germany).

(*Received in UK* 9 *January* 1996)