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Direct enantiomeric resolution of diphosphine and diphosphine oxide ligands by high-performance liquid chromatography

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Abstract

High-performance liquid chromatography was employed for the determination of the optical purity of diphosphine and diphosphine oxide ligands of transition metals used in stereoselective reactions. The separation of the enantiomers was accomplished, without any derivatization, on chiral columns containing, as chiral selectors, urea derivatives [Supelcosil LC-(*R*)-Phenyl Urea and (*R*)-Naphthyl Urea] and cellulose carbamate derivative (Chiralcel OG). The use of these three columns is complementary. The mobile phases were optimised to obtain enantiomeric resolution. The α and R_s values ranged from 1.12 to 1.83 and from 0.62 to 4.97 on Supelcosil LC-(*R*)-Phenyl and (*R*)-Naphthyl Urea based columns, whereas α and R_s values were between 1.11 and 1.38 and 0.24 and 2.00 on a cellulose carbamate based column. Poor α and R_s values were obtained with columns containing tetrahydronaphthyl [(*R*,*R*)-Whelk-01] and cellulose derivatives (Chiralcel OJ) as chiral selectors. The method is capable of determining a minimum limit of 2.5 ng of each enantiomer of compound 1.

Keywords: Enantiomer separation; Diphosphine; Diphosphine oxide

1. Introduction

Over the last few years, optical resolution by high-performance liquid chromatography (HPLC) has become increasingly important for the determination of optical purity of pharmaceutical compounds.

Owing to the development of a wide variety of chiral stationary phases (CSPs), many of which are now commercially available, a large number of substrates of different structures and compositions were made accessible for chiral analysis either at analytical or preparative levels [1–7].

The synthesis and development of a new class of chiral diphosphine and diphosphine oxide ligands for transition metals to use in stereoselective reactions is currently one of the main subjects of investigation [8–10].

In the literature there are only few examples of analyses of atropisomeric diphosphine and diphosphine oxide ligands via chiral HPLC [11–14].

Recently Chemi S.p.A., through its sister company Italfarmaco Sud, patented [15] a new family of bis (diphenyl phosphino) five-membered bis-heteroaryl ligands (Fig. 1), characterised by two interconnected

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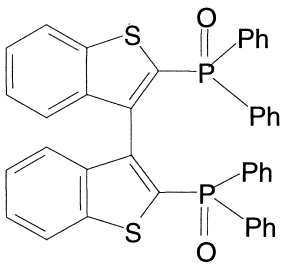

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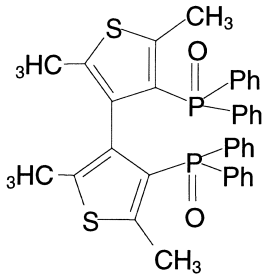

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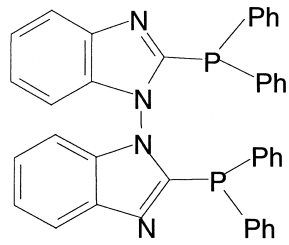

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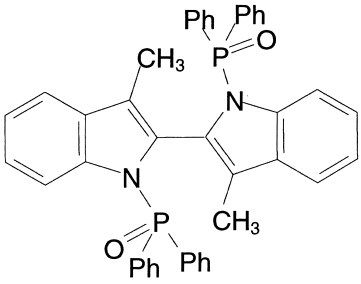

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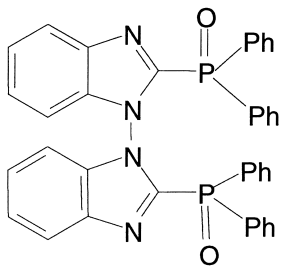

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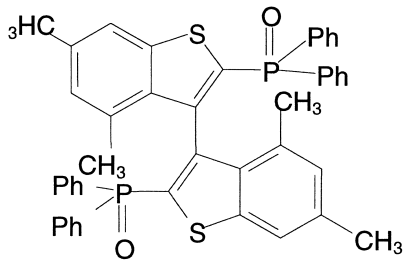

6
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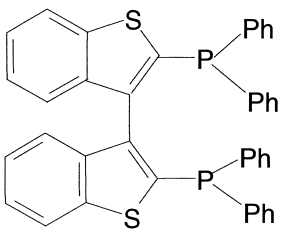

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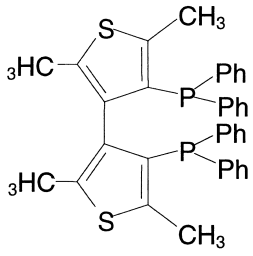

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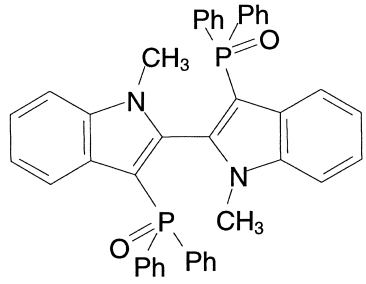

9
(±) 3,3'-bis(diphenylphosphinyl)-N,N'-dimethyl-2,2'-diindole

Fig. 1. Structures of diphosphine and diphosphine oxide ligands.

five-membered heteroaromatic rings, with hindered rotation around the interanular bond. These compounds, synthesised by F. Sannicolò and coworkers, are useful, as ligands, in highly efficient transition metal-catalysed stereoselective reactions; the synthesis of some of these was recently reported [16].

The aim of this study was the chromatographic resolution of enantiomers of atropisomeric diphos-

phine and diphosphine oxide ligands of transition metals commonly developed and used in stereoselective reactions for industrial processes and applications. Of course the enantiomeric purity of the ligand affects the enantiomeric ratio of the final product and therefore a robust and reproducible method to determine the optical purity of these ligands was required.

2. Experimental

2.1. Materials

Stainless-steel Chiralpack AD, AS, Chiralcel OC, OD, OF, OG, OJ, CA-1, OB, OK, (250×4.6 mm I.D.) (Daicel Chemical Industries, Tokyo, Japan); Supelcosil LC-(*R*)-Phenyl Urea and Supelcosil LC-(*R*)-Naphthyl Urea (250×4.6 mm I.D.), (Supelco, Bellefonte, PA, USA); DNB-Phenyl-Glycine (250×4.6 mm I.D.) (J.T. Baker, Phillipsburg, NJ, USA) and (*R,R*)-Whelk-01 (250×4 mm I.D.) (E. Merck, Darmstadt, Germany) columns were used.

HPLC-grade solvents were purchased from Carlo Erba (Milan, Italy). 1,2-Dichloroethane was purchased from E. Merck.

Samples of racemic diphosphine and diphosphine oxide ligands were prepared according to literature methods or kindly supplied by F. Sannicolò (University of Milan, Italy).

2.2. Apparatus

Chromatography was performed using a Perkin-Elmer Series 410 liquid chromatograph (Norwalk, CT, USA), equipped with a Waters Model U6K injector and a Waters Model 991 programmable multi-wavelength diode array detector operated at 240 nm (Waters, Milford, MA, USA); data were collected on a Power Mate 386 Waters Workstation.

2.3. Operating conditions

The following operating conditions were used: with Chiralpak AD, AS and Chiralcel OB, OK, OC, OD, OF, mobile phase, *n*-hexane–2-propanol (90:10, v/v); with Chiralcel CA-1, mobile phase, ethanol (100, v); with Chiralcel OG, mobile phases, *n*-hexane–2-propanol (90:10 and 70:30, v/v), *n*-hexane–ethanol (97.5:2.5 and 80:20, v/v) and *n*-hexane doped with 2-propanol (99.95:0.05, v/v); with Chiralcel OJ, mobile phases, *n*-hexane–2-propanol (90:10, v/v) and *n*-hexane–ethanol (90:10 and 95:5, v/v); with DNB-Phenyl-Glycine, mobile phase, *n*-hexane–2-propanol (90:10, v/v); with Supelcosil LC-(*R*)-Phenyl Urea, mobile phases, *n*-hexane–2-propanol–methylene chloride (80:5:15 and 50:5:45, v/v/v) and *n*-hexane–ethanol (97.5:2.5, v/v); with Supelcosil LC-(*R*)-Naphthyl Urea, mobile phases, *n*-hexane–2-propanol–methylene chloride (80:5:15, v/v/v) and *n*-hexane–methylene chloride (95:5, v/v); with (*R,R*)-Whelk-01, mobile phases, *n*-hexane–ethanol (85:15 and 65:35, v/v), *n*-hexane–ethanol–acetic acid (65:34.5:0.5, v/v/v), *n*-hexane–2-propanol–methylene chloride (70:25:5, v/v/v), *n*-hexane–1,2-dichloroethane–ethanol (25:40:35, v/v/v) and *n*-hexane–methylene chloride–acetonitrile (45:45:10, v/v/v).

The solvents used as mobile phases were degassed with an ultrasonic bath before use; flow-rate 0.5 ml min^{-1}; column temperature: ambient; volume injected 50 μl; detector wavelength 240 nm. The Supelcosil LC-(*R*)-Naphthyl Urea column was operated at a flow-rate of 1.0 ml min^{-1}.

3. Results and discussion

The results from the chromatography of racemic compounds are presented in Tables 1 and 2.

Among the columns tested, only Supelcosil LC-(*R*)-Phenyl Urea, Supelcosil LC-(*R*)-Naphthyl Urea, (*R,R*)-Whelk-01 and Chiralcel OG columns gave enantiomeric separations of the racemic ligands (Figs. 2 and 3). The columns contained, as chiral selectors, respectively, N (1-Phenyl Ethyl Urea), N (1-Naphthyl Ethyl Urea), 4-(3,5-Dinitrobenzamido)-3-undec-10-en-1-yl-1, 2, 3, 4 - tetrahydrophenanthrene bonded to silica gel and cellulose 4-methyl-phenylcarbamate coated on silica gel.

The mobile phases were optimised to obtain enantiomeric separation.

Supelcosil LC-(*R*)-Phenyl Urea, Supelcosil LC-(*R*)-Naphthyl Urea and (*R,R*)-Whelk-0 1 based CSPs belonged to the so called ''Pirkle phases'' [17–22], prepared by chemically bonding of a chiral selector

Table 1
Chromatographic data for compounds 1–9 on Supelcosil LC-(*R*)-Phenyl Urea, Supelcosil LC-(*R*)-Naphthyl Urea and (*R*,*R*)-Whelk-O1 columns.

Compound	Column	k_1'[a]	α[b]	R_s[c]	Eluent[d]	First eluted isomer
1	(*R*)-Phenyl Urea	2.85	1.16	2.01	F	(−)
2		1.49	1.33	2.01	F	(+)
3		1.24	1.00	0	C	
4		1.58	1.50	4.97	F	
5		2.02	1.25	1.77	F	
6		2.43	1.58	4.18	F	
7		1.08	1.00	0	F	
8		0.49	1.00	0	C	
9		0.72	1.27	1.49	G	(−)
1	(*R*)-Naphthyl Urea	4.50	1.14	1.04	F	(−)
2		4.60	1.55	2.59	F	(+)
3		4.64	1.00	0	N	
4		1.61	1.83	4.96	F	
5		2.60	1.19	0.96	F	
6		2.72	1.78	2.33	F	
7		4.95	1.15	1.09	F	
8		0.64	1.00	0	N	
9		9.34	1.12	0.62	F	(−)
1	(*R*,*R*)-Whelk-O1	9.28	1.12	1.65	H	(+)
2		1.41	1.00	0	I	
3		1.37	1.00	0	Q	
4		2.88	1.07	0.41	L	
5		6.25	1.13	0.99	H	
6		1.12	1.00	0	I	
7		2.84	1.11	1.07	M	
8		0.43	1.00	0	Q	
9		9.23	1.06	0.89	H	(+)

[a] The capacity factor of the first eluted enantiomer.
[b] The enantioselectivity factor.
[c] The resolution factor.
[d] Eluents employed were: (C) *n*-hexane–ethanol (97.5:2.5, v/v); (F) *n*-hexane–2-propanol–methylene chloride (80:5:15, v/v/v); (G) *n*-hexane–2-propanol–methylene chloride (50:5:45, v/v/v); (H) *n*-hexane–ethanol (85:15, v/v); (I) *n*-hexane–ethanol–acetic acid (65:34.5:0.5, v/v/v); (L) *n*-hexane–2-propanol–methylene chloride (70:25:5, v/v/v); (M) *n*-hexane–ethanol (65:35, v/v); (N) *n*-hexane–methylene chloride (95:5, v/v); (Q) *n*-hexane–1,2-dichlorethane–ethanol (25:40:35, v/v/v).

to silica gel. The enantiomeric discrimination was influenced by hydrogen bonding, dipole–dipole and π–π interactions, using non-polar solvents as mobile phases. According to Dalgliesh and Pirkle's viewpoints, at least three binding forces were necessary, where one of them had to be stereospecific and can be repulsive or attractive.

Six out of nine compounds were resolved with baseline separation, using the Supelcosil LC-(*R*)-Phenyl Urea column; the best results were obtained for compounds 4 and 6 with resolution values of 4.97 and 4.18, respectively (Fig. 2), whereas no resolution was obtained for compounds 3, 7 and 8 (Table 1).

Good results were also obtained with Supelcosil LC-(*R*)-Naphthyl Urea; in fact seven out of nine compounds were resolved. Nevertheless low α (1.15) and R_s (1.09) values were obtained for compound 7 (Fig. 2), whereas compounds 3 and 8 were not resolved (Table 1).

Poor α and R_s values were obtained with the column containing tetrahydronaphthyl moiety as chiral selector [(*R*,*R*)-Whelk-01]; the α values range from 1.06 to 1.13, whereas the R_s values were

Table 2
Chromatographic data for compounds 1–9 on Chiralcel OG and Chiralcel OJ columns

Compound	Column	k_1'[a]	α[b]	R_s[c]	Eluent[d]	First eluted isomer
1	Chiralcel OG	3.51	1.00	0	A	
2		0.96	1.23	1.52	B	(−)
3		2.52	1.19	2.00	C	
4		1.47	1.38	1.56	A	
5		2.24	1.11	0.24	A	
6		1.34	1.00	0	A	
7		0.73	1.00	0	D	
8		2.43	1.17	0.87	E	
9		4.15	1.00	0	A	
1	Chiralcel OJ	1.40	1.00	0	O	
2		0.56	1.00	0	O	
3		0.96	1.17	0.52	O	
4		2.14	1.20	0.83	P	
5		1.71	1.00	0	O	
6		2.46	1.08	0.43	P	
7		0.81	1.00	0	O	
8		0.12	1.00	0	O	
9		5.08	1.05	0.30	P	

[a] The capacity factor of the first eluted enantiomer.
[b] The enantioselectivity factor.
[c] The resolution factor.
[d] Eluents employed were: (A) *n*-hexane–2-propanol (70:30, v/v); (B) *n*-hexane–ethanol (80:20, v/v); (C) *n*-hexane–ethanol (97.5:2.5, v/v); (D) *n*-hexane–2-propanol (90:10, v/v); (E) *n*-hexane–2-propanol (99.95:0.05, v/v); (O) *n*-hexane–ethanol (90:10, v/v), (P) *n*-hexane–ethanol (95:5, v/v).

between 0.89 and 1.65. Four out of nine compounds were not resolved with this column; surprisingly, compound 7, which was not separated by the (*R*)-Phenyl Urea and Chiralcel OG columns, was resolved with α and R_s values of 1.11 and 1.07, respectively (Table 1).

No chiral resolution was observed with the DNB-Phenyl-Glycine column using a mobile phase consisting of *n*-hexane–2-propanol (90:10, v/v).

CSPs containing cellulose and amylose derivatives are used extensively to solve chiral separation problems [23,24].

Hydrogen bonding, dipole–dipole and π–π interactions were identified as important interactive forces that may be used to form the diastereomeric solute–CSP complex, together with the higher order structure of the chiral polymer bound to the support and the steric fit in the ''chiral cavity'' of the CSP [25–33]. Poor resolution of compounds would be due to poor affinity of compounds toward cellulose or amylose CSPs, or to the difficulty of inclusion of solute in the chiral cavity.

Attempts to separate, in preliminary trials, the enantiomers of diphosphine and diphosphine oxide ligands, using cellulose and amylose based columns (Chiralpak AD, AS and Chiralcel OD) and *n*-hexane–2-propanol (90:10, v/v) as mobile phase did not succeed; nevertheless we kept on trying with other cellulose based CSPs.

Chromatographic trials, carried out with Chiralcel OB, OC, OF and OK columns using *n*-hexane–2-propanol (90:10, v/v) gave rise to poor separations.

Conversely, diphosphine derivatives, tested on the Chiralcel CA-1 column using ethanol as mobile phase, gave drastically decreased retention times without any resolution.

Disappointing results were obtained when we tried to separate diphosphine and diphosphine oxides ligands enantiomers using a Chiralcel OJ column, containing cellulose 4-methylbenzoate as chiral selector (Table 2). In fact, this column, successfully employed for the separation of N-arylthiazolin-2-(thi)one atropisomers [34], did not succeed in separating our compounds.

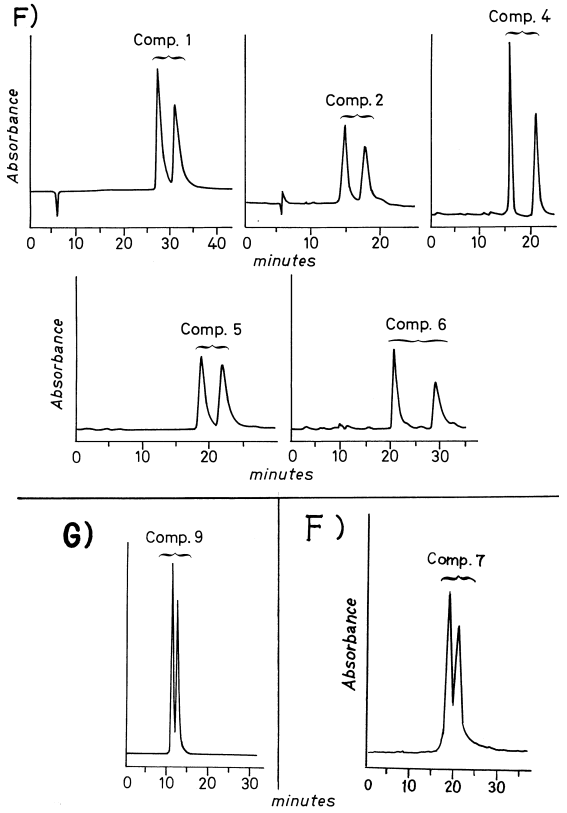

Fig. 2. HPLC of compounds in Fig. 1: compounds 1, 2, 4, 5, 6, eluent F [*n*-hexane–2-propanol–methylene chloride (80:5:15, v/v/v)]; compound 9, eluent G [*n*-hexane–2-propanol–methylene chloride (50:5:45, v/v/v)]. Flow-rate 0.5 ml min^{-1}. Column Supelcosil LC-(*R*)-Phenyl Urea. Wavelength 240 nm. Temperature ambient. Compound 7, eluent F [*n*-hexane–2-propanol–methylene chloride (80:5:15, v/v/v)]. Flow-rate 1.0 ml min^{-1}. Column Supelcosil LC-(*R*)-Naphthyl Urea. Wavelength 240 nm. Temperature ambient.

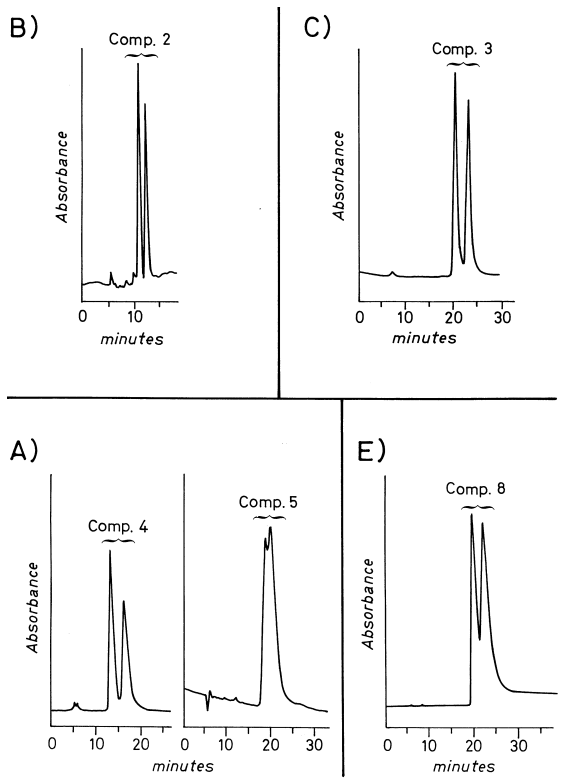

Fig. 3. HPLC of compounds in Fig. 1: compound 2, eluent B [*n*-hexane–ethanol (80:20, v/v)]; compound 3, eluent C [*n*-hexane–ethanol (97.5:2.5, v/v)]; compounds 4, 5, eluent A [*n*-hexane–2-propanol (70:30, v/v)]; compound 8, eluent E [*n*-hexane–2-propanol (99.95:0.05, v/v)]. Flow-rate 0.5 ml min^{-1}. Column Chiralcel OG. Wavelength 240 nm. Temperature ambient.

The Chiralcel OG column, containing as chiral selector cellulose 4-methylphenylcarbammate, gave the best results, with content of *n*-propanol in the mobile phase ranging from 0% to 30% (Fig. 3). Five out of nine compounds were separated, three of which with resolution values larger than 1.0 (Table 2).

The elution order was established only for compounds 1, 2 and 9; the (−), (+) and (−) enantiomers being respectively the less retained on Supelcosil LC-(*R*)-Phenyl Urea column, whereas the (−) enantiomer of compound 2 was the less retained on Chiralcel OG column. An inversion of the elution order was observed with the (*R,R*)-Whelk-01 column, the (+) enantiomers of compounds 1 and 9 being the less retained.

To demonstrate the configurational stability of the atropisomeric diphosphine and diphposphine oxides enantiomers, the more retained enantiomer of compound 1 was heated at 70°C for 3 h in isooctane. The mixture, cooled and analysed using a Supelcosil Phenyl Urea column and the same conditions as described, did not show any racemization.

Diphosphine and diphosphine oxide ligands containing benzothiophene (compounds 1, 6 and 7) or N-methyl-benzopyrrole moieties (compound 9) were not resolved on the Chiralcel OG column.

Enantiomeric separation was not attained, on the Phenyl-Urea based column, for diphosphine ligands (compounds 3, 7 and 8); the oxygen atom of the

diphosphine oxide ligands is likely involved in a hydrogen bonding during the chiral discrimination.

Nevertheless this behaviour was not observed with Naphthyl-Urea based column; in fact compound 7 was resolved with poor α and R_s values.

The steric hindrance of the sulphur groups, in comparison with the nitrogen groups, could be responsible for the different behaviour of compounds 3 and 7 on the Chiralcel OG column; in fact a baseline separation was obtained for compound 3, whereas no resolution was observed for compound 7.

When the phosphor atom is bound to the nitrogen of the benzopyrrole moiety (compound 4), the highest enantioselectivity factors were obtained either on the Chiralcel OG or the Supelcosil columns.

The detection limits obtained with this chromatographic system, using the Supelcosil LC-(*R*)-Phenyl Urea column, were approximately 2.5 ng for each isomer of compound 1 (signal-to-noise ratio greater than three).

4. Conclusions

The HPLC method described is designed for monitoring the chiral purity of diphosphine and diphosphine oxide ligands of transition metals used in stereoselective reactions with Supelcosil LC-(*R*)-Phenyl Urea, Supelcosil LC-(*R*)-Naphthyl Urea and Chiralcel OG columns; the use of these three columns is complementary.

The method appears to be easy to use and reproducible, the main advantage is that no derivatization is necessary to separate the enantiomers and therefore the drawbacks due to racemization, or different rates of reaction of the single enantiomer, with the derivatizing agent, are avoided.

Acknowledgements

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