1502-05-2; cyclododecanol, 1724-39-6; 2-methyl-3-heptanol, 18720-62-2; 1-cyclohexylethanol, 1193-81-3; 1-cyclohexyl-1-pentanol, 7338-43-4; 1-phenylethanol, 98-85-1; 2-octanone, 111-13-7; 5-nonanone, 502-56-7; cycloheptanone, 502-42-1; cyclooctanone, 502-49-8; cyclodecanone, 1502-06-3; cyclododecanone, 830-13-7; 2-methyl-3-heptanone, 13019-20-0; 1-cyclohexylethanone, 823-76-7; 1-cyclohexyl-1-pentanone, 5445-35-2; acetophenone, 98-86-2; Raney nickel, 7440-02-0; 1-octene, 111-66-0; ethylbenzene, 100-41-4.

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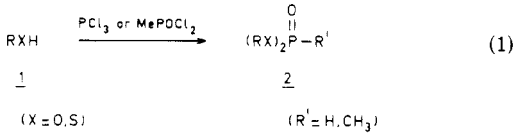
Enantiomeric Excess Determination without Chiral Auxiliary Compounds. A New ^{31}P NMR Method for Amino Acid Esters and Primary Amines

Summary: Amino acid esters and primary amines yield diastereoisomeric methylphosphonic diamides **5** upon reaction with $MePSCl_2$. The enantiomeric excess of amino acid esters and amines is easily determined by measurement of the ratio of diastereoisomers of **5** by ^{31}P NMR spectroscopy.

Sir: We recently developed a facile method for enantiomeric excess (ee) determinations of alcohols[1a] and thiols.[1b] The principle is a coupling reaction of chiral alcohols or thiols **1** with an achiral phosphorus reagent to afford diastereoisomeric phosphonates **2** (eq 1). PCl_3 is



(1)

used for alcohols and $MePOCl_2$ for both alcohols and thiols. The enantiomeric purities of the alcohols or thiols **1** are easily determined by ^{31}P NMR measurement of the ratio of diastereoisomers of **2**.

The increasing use of amino acids,[2] either natural or synthetically obtained, in asymmetric syntheses made the extension of our ^{31}P NMR method for fast and accurate ee determination of these and amines derived therefrom a major goal of our research. Extensive investigations[3] showed, however, that neither phosphorus trichloride nor alkylphosphonic dichloride is a satisfactory reagent for this purpose.

We now report a completely effective method for the ee determination of amino acids and primary amines based on the principles described above. Alkylphosphonothioic dichlorides are well-suited for the coupling reaction of

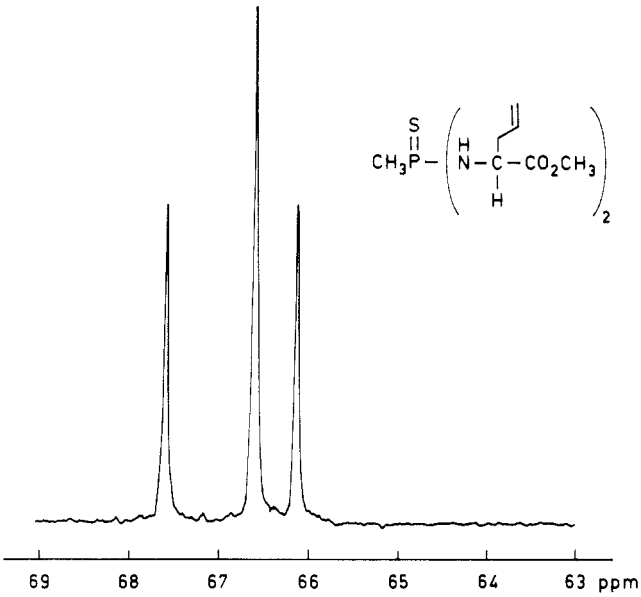
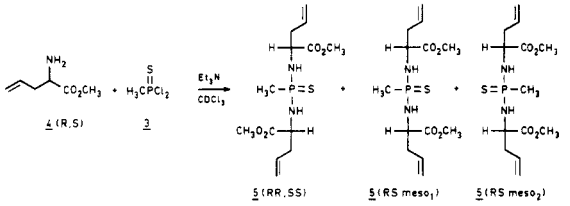


Figure 1. ^{31}P NMR spectrum of **5** obtained from racemic allylglycine and $MePSCl_2$ ($CDCl_3$).

primary amines. Thus, methylphosphonothioic dichloride (**3**)[4] in the presence of 2 equiv of triethylamine reacts quantitatively in 10 min at −20 °C with 2 equiv of (*R*,*S*)-allylglycine methyl ester (**4**) to afford diastereoisomeric methylphosphonothioic diamides **5** (eq 2).[5]



(2)

The ^{31}P NMR spectrum of **5** shows three well-separated singlets for the racemate (*RR* + *SS*) and two meso (*RS* meso$_1$, *RS* meso$_2$) diastereoisomers with a meso/*dl* ratio of 49:51 (Figure 1).[6] The ratio of these singlets is directly related to the enantiomeric excess of the amino acid esters.[7] For 96.6% enantiomerically pure **5** (as determined by optical rotation) the two meso peaks could just be observed; an ee of 97% was calculated from the integration. Although $MePSCl_2$ has to be used at −20 °C to avoid byproduct formation whereas commercially avilable $C_6H_5P-SCl_2$ can be used at room temperature, we prefer the former for this ee determination because it gives superior chemical shift differences for the diastereoisomers (see

(1) (a) Feringa, B. L.; Smaardijk, A. A.; Wynberg, H. *J. Am. Chem. Soc.* **1985**, *107*, 4798. (b) Feringa, B. L.; Smaardijk, A. A.; Wynberg, H.; Strijtveen, B.; Kellogg, R. M. *Tetrahedron Lett.* **1986**, *27*, 997.

(2) For example: Martens, J. In *Topics in Current Chemistry*; Boschke, F. L., Ed., Springer Verlag: Berlin, Vol. 125, p 165. Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1984**, *25*, 2545. Vriesema, B. K.; Ten Hoeve, W.; Wynberg, H.; Kellogg, R. M.; Boesten, W. H. J.; Meijer, E. M.; Schoemaker, H. E. *Tetrahedron Lett.* **1986**, *27*, 2045. Vriesema, B. K.; Kellogg, R. M. *Tetrahedron Lett.* **1986**, *27*, 2049. Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783. Seebach, D.; Imwinkelreid, R.; Weber, T. "Enantiomerically Pure Compound Syntheses with C,C Bond Formation *via* Acetals and Enamines" in *Modern Synthetic Methods*, Springer Verlag: Berlin, in press.

(3) Feringa, B. L.; Smaardijk, A. A., unpublished results. For example, $MePOCl_2$ does not give quantitative reaction, byproduct formation is excessive, and ratios for the diastereomers deviate from statistical for primary amines.

(4) Hoffmann, F.; Wadsworth, D.; Weiss, H. *J. Am. Chem. Soc.* **1958**, *80*, 3945.

(5) Only one enantiomer of racemic **5** is shown.

(6) All spectra were recorded in $CDCl_3$ at 80.988 MHz on a Nicolet 200 NT spectrometer; chemical shift values are in hertz with 85% H_3PO_4 (δ 0.0 Hz) as an external standard.

(7) The enantiomeric purity (p) was calculated from the integrated peak area's Q and Q′ of the *d*,*l* isomer and the meso isomers, respectively (with *dl*/meso ratio $K = Q/Q'$) using Horeau's[8] formula, $p^2 = (K - 1)/(K + 1)$.

(8) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055.

(9) Ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* **1985**, *50*, 4508.

(10) Johnson, C. R.; Elliott, R. C.; Penning, T. D. *J. Am. Chem. Soc.* **1984**, *106*, 5019.

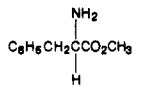
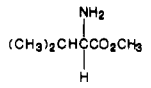
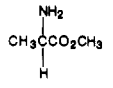
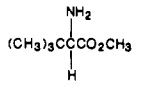
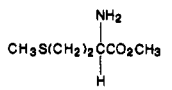
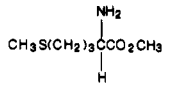
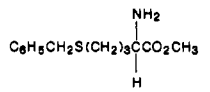
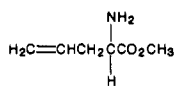
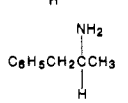
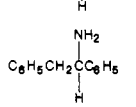
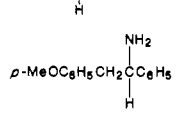
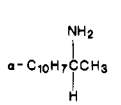
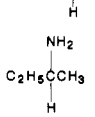
(11) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(12) Frank, H.; Nicholson, G. J.; Bayer, E. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 364. Davankov, V. A. *Adv. Chromatog.* **1980**, *18*, 139. Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 352.

(13) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732. McCreary, M. O.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038. Pirkle, W. H.; Beare, S. D. *Ibid.* **1969**, *91*, 5150.

0022-3263/86/1951-5484$01.50/0

Table I. ^{31}P NMR Data of Methylphosphonic Diamides from Racemic Amines and $MePSCl_2$[6]

entry	amine	δ(*RS* meso),[e] Hz	δ(*RS* meso),[e] Hz	δ(*RR,SS*), Hz	ratio meso/*dl*
1		5507	5404	5395	49:51
2		5661	5672	5647	50:50
3		5278	5348	5297	51:49
4		5692	5704	5709	*a*, *b*
5		5504	5575	5485	49:51
6		5434	5516	5451	49:51
7		5438	5536	5457	49:51
8		5355	5472	5393	51:49
9		5079	5319	5210	49:51
10		5086	5208	5168	49:51
11		5052	5117	5110	*a*, *d*
12		5161	5409	5315	49.5:50.5
13		5159	5453	5325	50:50
14		5139	5400	5217	50:50
15		4995	5035	5015	49.5:50.5

[a] Incomplete base-line separation.[14] [b] Approximately 50:50. [c] Phenylphosphonothioic dichloride as reagent. [d] Approximately 47:53. [e] The configuration of phosphorus in the meso compounds has not yet been determined.

Table I, entries 9, 10). This observation is in agreement with previous observations with alkylphosphonates[1b] for which the largest chemical shift differences between diastereoisomers were obtained with the smallest alkyl substituents.

Several ee determinations were performed on partially enriched amino acid esters and primary amines with this new method. Some of the data are summarized in Table II together with ee's determined by weight and by rotation. These results show that the enantiomeric purities obtained via the different methods are in good agreement and that no racemization occurs during phosphonic diamide formation. The scope of this ^{31}P NMR method encompasses various types of amino acids esters and primary amines as summarized in Table I. The results show that well-separated signals are observed for the diastereoisomeric methylphosphonothioic diamides, that accurate integration is possible (except for entries 4, 11),[14] and that meso/*dl* ratios are in accord with those expected for racemic compounds. Chemical shift differences are comparable with those obtained using *chiral* phospholidine derivatizing agents, e.g., Δδ 0.175 and 0.628 ppm for α-phenylethylamine and *sec*-butylamine, respectively, using Johnson's reagent.[10] For α-phenylethylamine Δδ 0.24 (^{19}F NMR) and 0.06 ppm (^1H NMR) were found by using Mosher's reagent.[11] With our method, Δδ 1.62, 1.34 ppm for α-phenylethylamine and 0.25, 0.25 ppm for *sec*-butylamine were

(14) Complete base-line separation was obtained when the spectra were recorded at −20 °C.

Table II. Determination of ee's of Optically Active Amines

amine	% ee by weight	% ee by rotation	% ee by ^{31}P NMR
1. *l*-α-phenylethylamine	50	48[a]	50
2. *l*-α-phenylethylamine		95[a]	>98[b]
3. *l*-α-naphthylethylamine	33.3	32	34
4. *d*-α-naphthylethylamine		98	96
5. *d*-β-(*p*-methoxyphenyl)-α-phenylethylamine		*c*	94
6. *l*-valine methyl ester	82	*d*	84
7. *l*-valine methyl ester		100	>98[b]
8. *l*-phenylalanine methyl ester	80	*d*	77.5
9. *l*-homomethionine methyl ester	24	20	25
10. *l*-allylglycine methyl ester		96.6	97

[a] Commercially available, unpurified amine. [b] Other enantiomer could not be detected. [c] $[\alpha]_{578}$ + 64.3° (*c* 1.07, CH_3OH), ee = 95%.[9] [d] Not measured.

observed. Alkylphosphonothioic dichlorides have so far not been satisfactory for the ee determination of chiral secondary amines.

Several methods exist for the ee determination of amino acid derivatives and amines, e.g., chromatographic techniques using chiral phases[12] and NMR methods.[13] The new method presented here compares favorably with the other currently available techniques in view of the large shift differences obtained for the diastereoisomers, the simple experimental procedure (no workup), and the fact that in contrast to all other methods *no chiral auxiliary compound* is necessary.

A typical experimental procedure follows: To a stirred solution of primary amine or amino acid methyl ester (1.0 mmol) and triethylamine (1.0 mmol) and 1 mL of $CDCl_3$ was added at −20 °C 0.5 mmol of $MePSCl_2$ dissolved in 1 mL of $CDCl_3$. After being stirred for 10 min, the solution was transferred into a 10-mm NMR tube and the ^{1}H decoupled ^{31}P NMR spectrum recorded.

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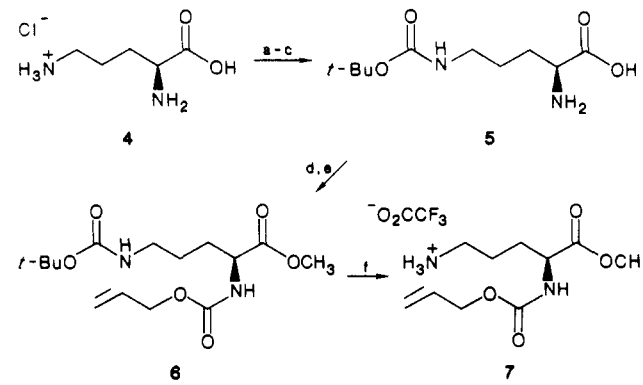
Studies Directed toward the Synthesis of Naturally Occurring Acyltetramic Acids. 2. Preparation of the Macrocyclic Subunit of Ikarugamycin

Summary: The synthesis of a model for the macrocyclic lactam system present in ikarugamycin (1) is described herein. The convergent route is culminated by a novel thermal intramolecular ketene trapping reaction with an amine to afford a 16-membered ring lactam. Treatment of lactams **21** and **22** with potassium *tert*-butoxide gave the model tetramic acids **3** and **23** via a transannular Dieckmann condensation.

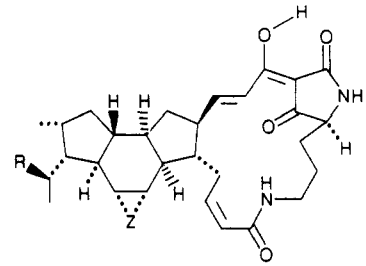
Sir: The antiprotozoal antibiotic ikarugamycin (1), a white crystalline substance isolated from the culture media of *Streptomyces phaeochromogenes*, and the structurally related compound capsimycin (2) are examples of a relatively rare macrocyclic lactam sytem containing a tetramic acid unit as well as a nonterpenoid tricarbocycle.[1]

Scheme I[a]

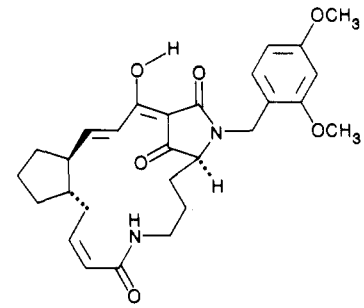


[a] Reagents: (a) $CuCO_3$ (1 equiv), H_2O, Δ, 0.75 h; (b) $((CH_3)_3C-O_2C)_2O$ (excess), $NaHCO_3$, H_2O–dioxane (3:1), 8 °C, 48 h; (c) H_2S; (d) $CH_2{=}CHCH_2OCOCl$ (excess), $NaHCO_3$, H_2O–dioxane (4:1), 0 °C, 16 h; (e) DCC (1.2 equiv), CH_3OH (excess), DMAP (catalytic), CH_2Cl_2, 0 °C, 1.5 h; (f) CF_3CO_2H–CH_2Cl_2 (1:3), 0 °C, 0.5 h.

We have previously reported the synthesis of the carbocyclic portion of 1 via an intramolecular [4 + 2] cycloaddition strategy.[2] The focus of our work has most recently been on the synthetically challenging macrocyclic lactam substructure.



1, Z = —CH=CH—, R = H
2, Z = O, R = OCH_3



3

Retrosynthetically, the macrocyclic unit may be viewed as comprising an L-ornithine subunit and a β-keto ester group bridged by a suitably substituted cyclopentane ring. Our convergent strategy called for the three units to be assembled followed by a macrocyclization (vide infra). The model study described below details the preparation of macrocycles **3** and **23** where the tricyclic system of 1 has been replaced by a single five-membered ring.

Construction of the requisite ornithine derivative **7** and cyclopentane unit **13** is described in Schemes I and II,

(1) (a) Jomon, K.; Kuroda, Y.; Ajisaika, M.; Saki, H. *J. Antibiot.* **1972**, *25*, 271. (b) Ito, S.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1813. (c) Ito, S.; Hirata, Y. *Ibid.* **1977**, *50*, 227. (d) Ito, S.; Hirata, Y. *Tetrahedron Lett.* **1972**, 1181. (e) Ito, S.; Hirata, Y. *Ibid.* **1972**, 1185. (f) Ito, S.; Hirata, Y. *Ibid.* **1972**, 2557.

(2) Boeckman, R. K., Jr.; Napier, J. J.; Thomas, E. W.; Sato, R. I. *J. Org. Chem.* **1983**, *48*, 4152.

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