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Tetrahedron: *Asymmetry*

Observing the enantiomeric ^1H chemical shift non-equivalence of several α-amino ester signals using tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]samarium(III): a chiral lanthanide shift reagent that causes minimal line broadening

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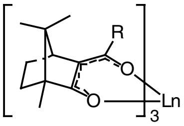
Abstract—The chiral lanthanide shift reagent, tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]samarium(III) [Sm(tfc)$_3$], was shown to resolve the ^1H NMR signals of the enantiomers of α-amino esters without causing serious line broadening. This distinctive feature of Sm(tfc)$_3$ made it possible to examine the enantiomeric chemical shift non-equivalence of several protons in ester substrates, increasing the reliability of the empirical assignment of the absolute configuration as compared to earlier techniques.

1. Introduction

Chiral lanthanide shift reagents (CLSRs)[1–10] have potential in the determination of the absolute configuration of organic compounds without the inconvenience of using chiral derivatizing agents prior to NMR analysis. This potential for the well-known CLSRs, Eu(tfc)$_3$ **1**,[6,7] and Eu(hfc)$_3$ **2**[8], which feature 1,3-diketonate ligands derived from (+)-camphor, has not yet been fully realized, although for a limited number of closely related substrates, the correlation of the absolute configurations with the relative magnitude of lanthanide-induced shifts (LISs) has been examined.[11–14]



Ln = Eu, R = CF_3: Eu(tfc)$_3$ **1**
Ln = Eu, R = C_3F_7: Eu(hfc)$_3$ **2**
Ln = Sm, R = CF_3: Sm(tfc)$_3$ **3**

It is noteworthy that a study has been made by Mosher et al. who examined the enantiomeric signal separation for a series of secondary alcohols in the presence of **2** and found that the correlation between the relative shifts in the NMR signals of substrate enantiomers and their absolute configurations depended on the probe used.[14] This study suggested that it was important to examine a number of protons on the probe in order to find as many as possible with good correlations. Although the mechanism of the enantiomeric signal separation produced by tris-chelate-type CLSRs is poorly understood,[2,7,10] finding several suitable probes for a series of substrates would allow us to increase the reliability of empirically assigning the absolute configuration of a substrate by confirming the consistency of the assignments from all the probes.

A modified Mosher method exemplifies the advantage of using a collection of probes to improve the reliability of the NMR determination of the absolute configuration.[15] In attempts to correlate LISs with absolute configurations, most of the earlier work was conducted in the early 1970s on 60–100 MHz ^1H NMR instruments.[11–14] These low resolutions understandably precluded the clear correlation of most protons that were probed. A later study reported the use of 220 and 300 MHz instruments to determine the absolute configuration of arene oxides through correlations between the LISs caused by Eu(hfc)$_3$.[16] This study, however, was an isolated case with no further studies with other substrates reported to date. The most probable drawback responsible for this lack of progress is due to the inherent line broadening caused by lanthanide shift reagents, which become

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enhanced in stronger magnetic fields and for substrates with a strong coordinating ability.

In our investigation of water soluble CLSRs for the determination of the absolute configurations of underivatized α-amino acids, we found that replacing the europium ion of the optically active Eu(III)-pdta complex (pdta=propylenediaminetetraacetate) with a samarium ion greatly reduced line broadening when using a 400 MHz instrument.[17] Since samarium has the smallest magnetic moment of all of the paramagnetic lanthanides, it was expected to induce small but observable signal shifts that could be compensated by the high resolution of the instrument. These signals should not only experience reduced line broadenings, caused by the exchange of free and complexed states of the substrate, but also experience enhanced paramagnetic relaxations.

On the basis of these results, we examined the use of Sm(tfc)$_3$ **3** in $CDCl_3$ to correlate LISs with the absolute configuration of certain chiral substrates. We selected α-amino acid methyl esters as the substrates in expectation of chelate formation between Sm^{3+} and the amino nitrogen and carbonyl oxygen. In such a chelate, the enantiomeric protons would be on opposite sides of the chelate ring and experience different chemical shifts that are induced by the lanthanide ion. In addition, this chelate formation might prevent any unwanted complexity from 1:2 (reagent:substrate) adducts, because the α-amino acid ester would occupy two coordination sites at a time, thereby preventing further coordination of an additional ester substrate.

2. Results and discussion

Sm(tfc)$_3$ **3** was prepared according to the method reported by Schurig[18] with a slight modification in the purification step. The shifts of the enantiomeric ^{1}H signals caused by Sm(tfc)$_3$ in the enantiomer mixtures (D/L=1/2) of the methyl esters of 12 common α-amino acids dissolved in $CDCl_3$ were then examined on a 400 MHz instrument. Variations of reagent/substrate ratios of up to 0.2 were surveyed. On addition of **3**, almost all of the signals, except for H_α of L-valine methyl ester (L-Val-OMe), were shifted upfield with slight broadening. In general, the magnitudes of the induced shifts decreased in the order of H_α, $H_\beta \approx H_\gamma$, OMe_{ester}. At a reagent/substrate ratio of 0.2, the largest change in chemical shift (0.304 ppm) was observed for the H_α signals of D-Ala-OMe, while most of the other signals were shifted by less than 0.2 ppm.

For most enantiomers, a clear separation between the signals due to H_α, the side chains protons, and the OMe_{ester} protons occurred and were measurable. The magnitude of signal separation was usually larger for H_α signals over the others, with the largest separation (0.065 ppm) being measured for Ala-OMe. Most signals were separated by less than 0.04 ppm. The separations of the OMe_{ester} signals were generally small when compared with those measured for other signals, while no signal separation was observed for Ser-OMe, His-OMe, Lys-OMe, or Pro-OMe.

A typical ^{1}H NMR spectrum of Phe-OMe (D/L = 1/2) in the presence of **3** is shown in Figure 1. Spectra taken in the presence of the corresponding Eu reagent **1** and in the absence of any reagents are shown for comparison. As shown, the addition of **3** caused a considerably less broadening of line signals as compared to adding **1**; in the presence of **3**, each signal retained its original fine structure. The H_α, two H_βs, and ester methyl (OMe_{ester}) groups were clearly separated.[†] In contrast, **1** broadened all of the signals and separations were only observed for the H_α and OMe_{ester} signals.

The $\Delta\Delta\delta[\Delta\Delta\delta = \Delta\delta_L - \Delta\delta_D = (\delta_L - \delta_0) - (\delta_D - \delta_0)]$ values for the α-amino esters are summarized in Table 1; δ_L and δ_D are the chemical shifts of the L and D isomers in the presence of a shift reagent, respectively and δ_0 is the chemical shift of both isomers in the absence of a shift reagent. Without exception, all of the OMe_{ester} and H_α signals derived from the D-isomers were shifted more than the corresponding signals of the L-isomers, affording positive $\Delta\Delta\delta$ values. In contrast, the signals due to the protons on the side chains afforded negative $\Delta\Delta\delta$ values, with Asp(OMe)-OMe being the only exception. Such a regular pattern observed for a number of probe signals is clearly useful in making a reliable assignment of absolute configuration.

To gain an understanding of the mechanism of the enantiomeric signal resolution induced by **3**, we studied the stoichiometry of adduct formation between the reagent and substrate. First, Job's method[19] was used to examine adduct formation between the reagent and L-Phe-OMe. The maximum in the plot was around a reagent/substrate ratio of 1.5 (60/40), suggesting that both the 1:1 and 2:1 complexes can form (Fig. 2). However, the $\Delta\Delta\delta$ values in Table 1 were obtained at reagent ratios below 0.2, which is considerably lower than these adducts ratios as predicted by Job's plot. Under such conditions, the formation of the 1:1 adduct is therefore inferred to be major to the 2:1 adduct.

To examine this inferred preference for 1:1 adducts, the reciprocal method[20–22] (plot of total concentration of substrate S_0 vs 1/LIS) was used. This method assumes a 1:1 formation of adducts and is usually used to calculate the formation constant K and bound shift value Δ_b (the LIS value of a nucleus in a specific adduct). When the stoichiometry of adduct formation is 1:1, the plot should be a straight line. Accordingly, eight L-Phe-OMe solutions, in which the concentration of **3** was held constant at 0.01 M and the substrate concentration was varied from 0.075 to 0.30 M, were examined. A roughly linear correlation was observed at substrate concentrations above 0.15 M, meaning that the reagent ratio was below 0.07 (Fig. 3). This indicates that 1:1 adducts pref-

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[†] Considerable line broadening was observed for substrates with side chains that could readily coordinate, such as Ser-OMe, His-OMe, and Lys-OMe.

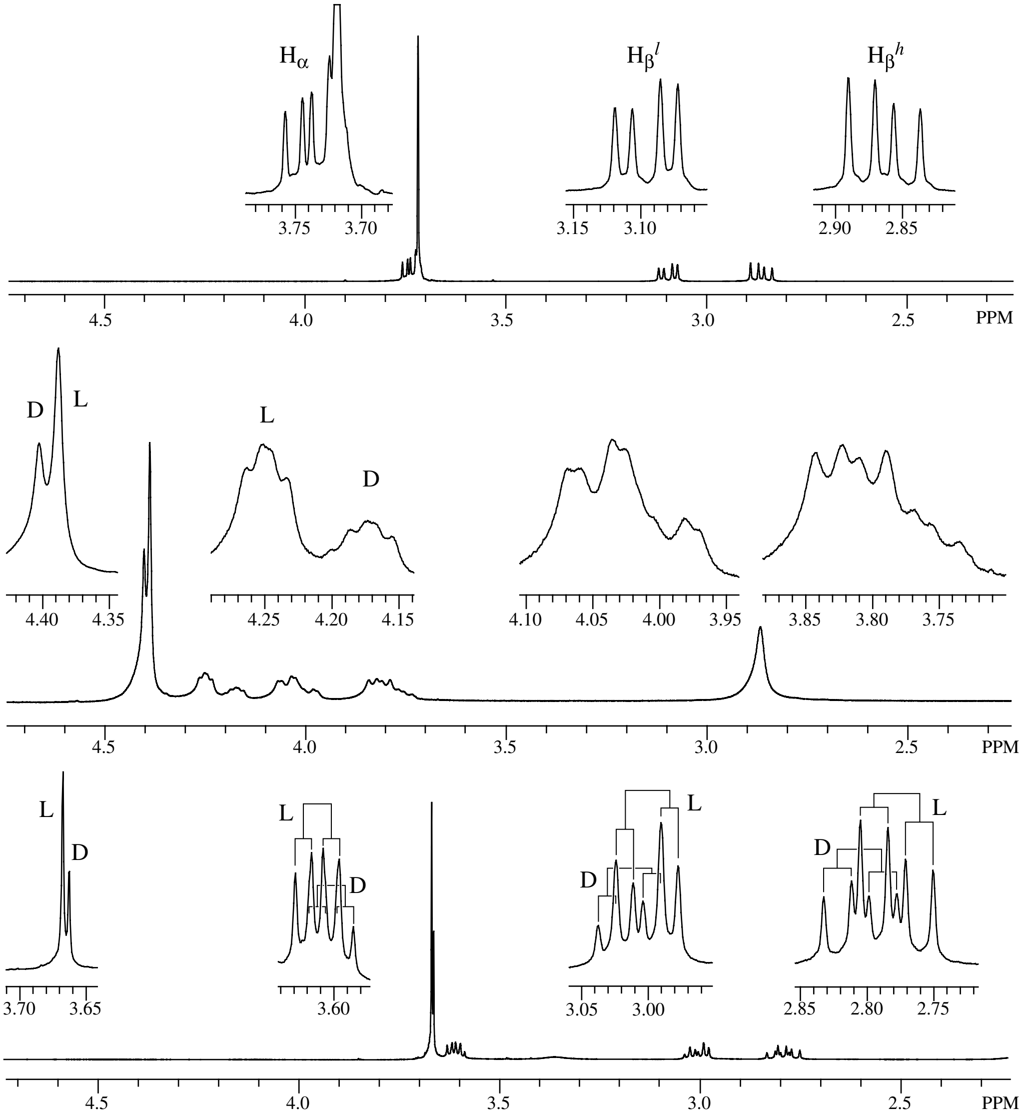

Figure 1. ^{1}H NMR spectra (400 MHz) of 0.1 M Phe-OMe (enantiomer ratio D/L=1/2) in $CDCl_3$ at room temperature: (upper) no shift reagent; (middle) [**1**]/[Phe-OMe]=0.2; (bottom) [**3**]/[Phe-OMe]=0.2.

erentially formed at these concentrations.[‡] At substrate concentrations below 0.15 M, however, the plots deviated from a straight line, implying additional formation of 2:1 complexes. Since this concentration range corresponds to reagent/substrate ratios from 0.1 to 0.2, care must be taken in assigning the absolute configurations in Table 1. It should be noted, however, that the signs of $\Delta\Delta\delta$ for H_α and H_βs observed at a reagent ratio of 0.05 were identical to those observed at the reagent ratio of 0.2 for all substrates, even though the signal separations were very small.

The relative importance of the formation constant K and the bound shift value Δ_b in the enantiomeric signal separation was determined using the sign of $\Delta\Delta\delta$ for H_α and side chain protons. For all the substrates except Asp(OMe)-OMe, the sign of $\Delta\Delta\delta$ for H_α was opposite to that of the side chain protons. Since the signals due to both H_α and the side chain protons shifted in the same direction, upfield, the opposite signs for $\Delta\Delta\delta$ indicate that the Δ_b values for specific protons clearly differ between the L and D series of isomers, although the K values for adduct formation remain similar. As an exception, the substrate Asp(OMe)-OMe showed positive $\Delta\Delta\delta$ values for both the H_α and side chain signals. Presumably, this outcome was due to the additional coordination of its C_β–CO_2Me group with samarium(III), which could change the coordination geometry or relative importance of Δ_b over K factors in the signal separation of enantiomers.[§]

[‡] The formation constant and bound shift values calculated from the linear part of the plots are as follows: K (M^{-1}) 3.0–4.7; Δ_b (ppm): H_α–1.6, $H_\beta{}^l$ 1.8, $H_\beta{}^h$ −1.1. For comparison, the same plot was examined for D-Phe-OMe, but the shifts in signals due to this isomer were too small to determine K and Δ_b.

[§] A similar deviation from a regular pattern between chemical shift and absolute configuration by a polar group in the side chain of an amino acid has been observed for the enantiomeric signal separation of histidine and 3-aminopropanoic acid by a chiral Sm(III)-pdta complex in D_2O.[17]

Table 1. Resolution of the enantiomeric signals of the α-amino esters in the presence of **3** [**3**]/[amino ester]=0.2

Substrate	$\Delta\Delta\delta$/ppm		
	H_{α}	OMe_{ester}	Side chain
Ala-OMe	0.065	0.017	−0.020 (H_{β})
Val-OMe	0.039	0.023	0.000 (H_{β})[a], −0.025 (H_{γ}^{l}), −0.019 (H_{γ}^{h})
Leu-OMe	0.022	0.007	−0.002 (H_{β}^{l}), −0.01 1 (H_{β}^{h}), −0.009 (H_{γ})[a], −0.001 (H_{δ}^{l}), −0.001 (H_{δ}^{h})
Ser-OMe	—	0.000	−0.001 (H_{β}^{h})[b]
Met-OMe	0.017	0.006[a]	−0.006 (SMe)
His-OMe	—	0.000	−0.045 (H_{β}^{l})[a]
Lys-OMe	0.006	—	
Phe-OMe	0.010[a]	0.005	−0.014 (H_{β}^{l}), −0.028 (H_{β}^{h})
Trp-OMe	0.001	0.010	−0.026 (H_{β}^{l}), −0.063 (H_{β}^{h}) −0.067 (H2′), −0.023 (H4′), −0.002 (H5′), −0.008 (H6′), −0.006 (H7′)
Asp(OMe)-OMe	0.062	0.009	0.000 (H_{β}^{l}), +0.005 (H_{β}^{h}), 0.000 ($C_{\beta}CO_2Me$)
Glu(OMe)-OMe	0.032	0.009	−0.004 (H_{β}^{l}), −0.006 (H_{β}^{h}), −0.010 (H_{γ}^{l}), −0.018 (H_{γ}^{h}), −0.008 ($C_{\gamma}CO_2Me$)
Pro-OMe	0.051	0.000	−0.005 (H_{γ}^{l}), −0.001 (H_{γ}^{h})[a], −0.008 (H_{δ}^{l})[a]

The superscripts l and h denote lower and higher fields, respectively.

[a] [**3**]/[amino ester] = 0.1.

[b] [**3**]/[amino ester] = 0.05.

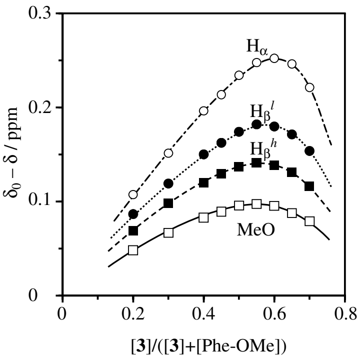

Figure 2. Job's plot of adduct formation for **3** with L-Phe-OMe at a combined solute concentration of 0.10 M.

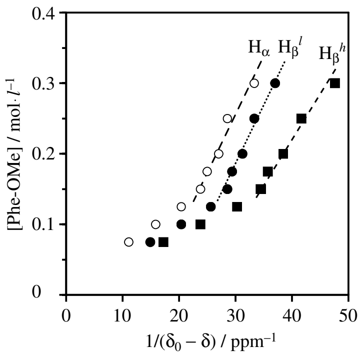

Figure 3. Reciprocal plot of adduct formation for **3** with L-Phe-OMe, keeping the concentration of **3** at 0.10 M.

3. Conclusion

In our study of the enantiomeric chemical shift non-equivalence of α-amino esters induced by **3**, we examined a selection of enantiomeric signals, which overall demonstrated good correlation between the signs of $\Delta\Delta\delta$ and the absolute configuration of the esters. We were able to observe the chemical shift non-equivalence for several signal shifts because **3** causes less line broadening than most other CLSRs. We believe that the consistent assignment of absolute configuration based on the correlations observed for all available probe signals demonstrates the applicability of **3** to determine the configurations of substrates with previously unknown configurations. Since adduct formation between **3** and L-Phe-OMe has not been shown to be defined to a single chemical complex, the use of **3** in determining the absolute configurations of α-amino esters currently needs care in its interpretation. Further work is therefore necessary to develop a reliable method for determining the absolute configuration using a CLSR with an unambiguous mechanism of complexation.

4. Experimental

4.1. General

Eu(tfc)$_3$ was purchased from Aldrich (Milwaukee, WI, USA). Samarium(III) chloride was purchased from Wako Pure Chemical Industries (Osaka, Japan) and used without further purification. NMR spectra were recorded on a JEOL GSX-400 spectrometer (400 MHz) in $CDCl_3$ at room temperature. Chemical shifts are expressed in ppm using TMS as an internal standard. IR spectra were recorded on a Shimadzu FTIR-8100M. Melting points were determined on a Yanaco MP-S3.

4.2. Preparation of Sm(tfc)$_3$ 3

Sm(tfc)$_3$ was synthesized according to the method reported by Schurig,[18] and recrystallized from hexane to yield a pale yellow powder, mp 191–193 °C (hexane); IR (KBr) 2965, 1663 (br), 1298, 1269, 1227, 1202 cm^{-1}.

Anal. Calcd for $C_{36}H_{42}F_9O_6Sm$: C, 48.47; H, 4.75. Found: C, 48.22; H, 4.83.

4.3. Preparation of the methyl esters of amino acids

The methyl esters of amino acids were prepared from their hydrochloric acid salts using a published procedure.[23] Free esters were obtained by treating the resulting salts with 1 M Na_2CO_3 and extracting with ether, or by treating with NH_3 in chloroform.

Alanine methyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, d, J=7.1 Hz), 3.56 (1H, q, J=7.1 Hz), 3.72 (3H, s).

Valine methyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, d, J=6.9 Hz), 0.97 (3H, d, J=6.8 Hz), 2.02 (1H, septd, J=6.9, 5.1 Hz), 3.30 (1H, d, J=4.9 Hz), 3.72 (3H, s).

Leucine methyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, J=5.9 Hz), 0.94 (3H, d, J=6.6 Hz), 1.43 (1H, ddd, J=13.6, 8.8, 6.1 Hz), 1.56 (1H, ddd, J=13.7, 8.3, 5.6 Hz), 1.78 (1H, octd, J=8.1, 6.6 Hz), 3.48 (1H, dd, J=8.5, 5.6 Hz), 3.72 (3H, s).

Serine methyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (1H, dd, J=5.9, 4.4 Hz), 3.70 (1H, dd, J=10.8, 5.9 Hz), 3.76 (3H, s), 3.80 (1H, dd, J=10.8, 4.4 Hz).

Methionine methyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (1H, dddd, J=13.9, 8.3, 7.3, 6.6 Hz), 2.05 (1H, dddd, 13.9, 8.1, 7.3, 5.1 Hz), 2.11 (3H, s), 2.63 (2H, m), 3.64 (1H, dd, J=8.1, 4.9 Hz), 3.74 (3H, s).

Histidine methyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 (1H, dd, J=14.9, 8.1 Hz), 3.08 (1H, dd, J=14.9, 4.4 Hz), 3.73 (3H, s), 3.78 (1H, dd, J=8.1, 4.4 Hz), 6.84 (1H, s), 7.55 (1H, s).

Lysine methyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37–1.52 (4H, m), 1.58 (1H, m), 1.74 (1H, m), 2.71 (2H, br t, J=6.6 Hz), 3.45 (1H, dd, J=7.6, 5.3 Hz), 3.72 (3H, s).

Phenylalanine methyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (1H, dd, J=13.7, 8.0 Hz), 3.08 (1H, dd, J=13.5, 5.1 Hz), 3.72 (3H, s), 3.74 (1H, dd, J=8.1, 5.2 Hz), 7.19 (2H, m), 7.24 (1H, tt, J=7.5, 1.5 Hz), 7.31 (2H, m).

Tryptophan methyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06 (1H, ddd, J=14.4, 7.6, 0.5 Hz), 3.28 (1H, ddd, J=14.4, 4.9, 0.7 Hz), 3.71 (3H, s), 3.84 (1H, dd, J=7.8, 4.9 Hz), 7.05 (1H, br d, J=2.2 Hz), 7.12 (1H, ddd, J=8.1, 7.1, 1.0 Hz), 7.19 (1H, ddd, J=8.1, 7.1, 1.2 Hz), 7.35 (1H, dt, J=8.1, 1.0 Hz), 7.62 (1H, br d, 7.8 Hz), 8.17 (1H, br s).

Aspartic acid dimethyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (1H, dd, J=16.6, 7.3 Hz), 2.82 (1H, dd, J=16.4, 4.7 Hz), 3.71 (3H, s), 3.75 (3H, s), 3.85 (1H, dd, J=7.3, 4.7 Hz).

Glutamic acid dimethyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (1H, dddd, J=14.0, 8.3, 7.6, 6.8 Hz), 2.08 (1H, dddd, J=13.9, 7.6, 6.7, 5.4 Hz), 2.47 (2H, t br, J=7.6 Hz), 3.48 (1H, dd, J=8.3, 5.4 Hz), 3.68 (3H, s), 3.73 (3H, s).

Proline methyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (2H, m), 1.85 (1H, ddt, J=14.4, 8.3, 5.4 Hz), 2.13 (1H, m), 2.91 (1H, dt, J=10.0, 0.6 Hz), 3.03 (1H, dt, J=9.8, 6.6 Hz), 3.74 (3H, s), 3.77 (1H, dd, J=8.6, 5.9 Hz).

4.4. ^{1}H NMR measurements

To an NMR tube containing $CDCl_3$ solution (0.6 mL) of an amino acid methyl ester (0.6 mmol, D/L=1/2), the required amount of solid Sm(tfc)$_3$ was added and the mixture shaken to dissolve the reagent. NMR spectra were observed at the addition of 0, 0.05, 0.1, and 0.2 equivalents of the reagent at ambient temperature.

4.5. Evaluation of the stoichiometry of the complex formation between 3 and L-Phe-OMe using reciprocal method

To each of eight separated centrifugal tubes containing 0.200 mL of 0.030 M $CHCl_3$ solution of **3**, a calculated amount of 0.597 M $CHCl_3$ solution of L-Phe-OMe was added. Each solution was evaporated to dryness in vacuo and the residue dissolved in 0.600 mL of $CDCl_3$. NMR measurements were conducted at the concentration of L-Phe-OMe, 0.300, 0.250, 0.200, 0.175, 0.150, 0.125, 0.100, and 0.075 M.

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