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Use of a Selone Chiral Derivatizing Agent for the Absolute Configurational Assignment of Stereogenic Centers.[1]

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Abstract: Coupling of chiral selone a chiral derivatizing agent to D and L amino acids gives adducts which are characterized by ^{77}Se NMR, UV, and circular dichroism spectroscopy and allows for the determination of the absolute configuration of the parent amino acid

The determination of the absolute configuration of chiral molecules is an important task of both synthetic and natural product chemists[4] Polarimetry, optical rotatory dispersion (ORD), and circular dichroism (CD) are all useful tools for the determination of relative and/or absolute configurations and for conformational studies[5] CD is a particularly valuable technique because the shape of the CD curve can provide information about the orientation of groups about the chromophore[6]

Although, numerous NMR based methods have been used in the determination of enantiomeric excesses (ee) of chiral compounds,[7] few are useful for both ee and configurational assignment Most notable are Trost's use of o-methylmandelate esters and Dale and Mosher's use of α-(trifluoromethyl)-o-methylmandelate esters[8] Their methods enable one to elucidate the configuration of chiral alcohols and amines by using ^{1}H and ^{19}F NMR spectroscopy

Few chiral derivatizing agents (CDA's) have been reported useful for determining ee's of carboxylic acids and, as a result, no model has been proposed to determine the absolute configurations of acids by NMR Our reagents, oxazolidin-2-selones, are useful for determining ee's of chiral carboxylic acids and acid chlorides by ^{77}Se NMR spectroscopy (Figure 1)[9] To extend the applicability of these chiral selones for absolute configurational assignments, we examined a series of D and L N-protected amino acids coupled to the selone Based on our NMR, UV, TLC, and CD results, we conclude that these selone CDA's provide an excellent method for the determination of the absolute configurations for these parent amino acids

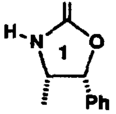
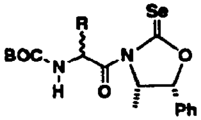


Figure 1

Amino acids featuring the N-*tert*-butoxycarbonyl (N-Boc) protecting group were chosen for these studies because of their availability in optically pure D and L forms and also the variety of substituents available on the α-carbon Coupling of seven optically pure Boc-amino acids and their racemates with 1 was accomplished by dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in methylene chloride at 0°C for 4 to 20 h The bright yellow adducts were then conveniently purified by flash chromatography giving 60-70% yields Although DMAP and DCC have been reported to cause racemization[10] of the activated acid intermediate in O-methylmandelic acid coupling, there was no detectable racemization or epimerization during the coupling of the enantiomerically pure amino acids to the chiral selone as judged by ^{77}Se NMR spectroscopy and thin-layer chromatography (TLC).

An inspection of Table 1 reveals that the ^{77}Se chemical shifts of D-(N-Boc)-amino acid adducts with 1 are always deshielded with respect to the signal of their corresponding L-antipode adducts This is true without exception for all seven amino acid adducts that were evaluated We found that five individual racemate adducts could be separated by TLC and flash liquid chromatography using 30 70 diethylether/hexane (V/V) The diastereomers of the remaining two amino acids, valine and isoleucine, could be partially separated using this system By comparing the R$_f$'s of the diastereomeric mixtures with those of individual diastereomers derivatized from enantiomerically pure amino acids, the diastereomers yielding the deshielded selenium resonances were always the fast eluting stereoisomers Thus, for the amino acids tested, our results indicate, without exception, that the TLC method can also be used as a predictive tool for configurational assignment. Similar TLC trends were also found with Mosher's reagent[8] In addition, we have employed our predictive model to investigate (R) and (S)-2-phenylbutanoyl chloride with 1 Consistent with the model, the R adduct exhibited a deshielded selenium resonance (476.6 ppm) relative to the S adduct (428 8 ppm) and the R adduct eluted faster on TLC[11]

Table 1 Ultraviolet Data and ^{77}Se Chemical Shifts of N-Boc-Protected Amino Acid Adducts of (4S,5R)-4-Methyl-5-Phenyl-Oxazolidin-2-Selone



Name	R	^{77}Se δ ppm (L,D)	π→π*, λmax, (L D)	n→π*,λmax, (L D)
Ala	CH_3-	473 5, 480 6	310, 310	422, 419
Val	$(CH_3)_2CH$-	479 3, 486 2	310, 310	428, 424
Leu	$(CH_3)_2CHCH_2$-	472 2, 475 1	310, 310	424, 415
Ile	$CH_3CH_2(CH_3)CH$-	480 9, 484 1	312, 308	427, 424
Met	$CH_3S(CH_2)_2$-	473 1 486 5	310, 310	422, 419
Phe	$C_6H_5CH_2$-	478 2, 481 7	310, 310	422, 417
Pro	$CH_2CH_2CH_2$-	471 7, 480 6	312, 312	418, 418

Our previous work with selone CDA adducts indicated the presence of an extended conjugated chromophore that gave rise to intense electronic absorbance bands in a convenient spectral range[12] The UV spectra of all the adducts showed strong $\pi \rightarrow \pi^*$ absorption bands around 310 nm. A much weaker, long wavelength absorption occurred at 420 nm This band can be attributed to a transition similar to the $n \rightarrow \pi^*$ transition observed for ketones. The wavelengths for the L amino acid adducts were longer than those observed for the D amino acid adducts, with proline being the only exception (same maximum for both) A similar trend was found with the R and S 2-phenylbutanoyl adducts of 1 While the underlying reason for this phenomenon is still under investigation, it is possibly due to the differential weak intramolecular interactions between the two diastereomers

The CD spectra of the D and L adducts are shown in Figure 2 Although these spectra have complicated multitransitional bands, one of the bands gave rise to a strong Cotton effect (CE), with opposite signs for the two diastereomers. Each L-amino acid adduct gave a positive CE band at 265-270 nm while each D-amino acid adduct yielded a band of opposite sign Thus, this transition band can also be used as a predictive tool for configurational assignment

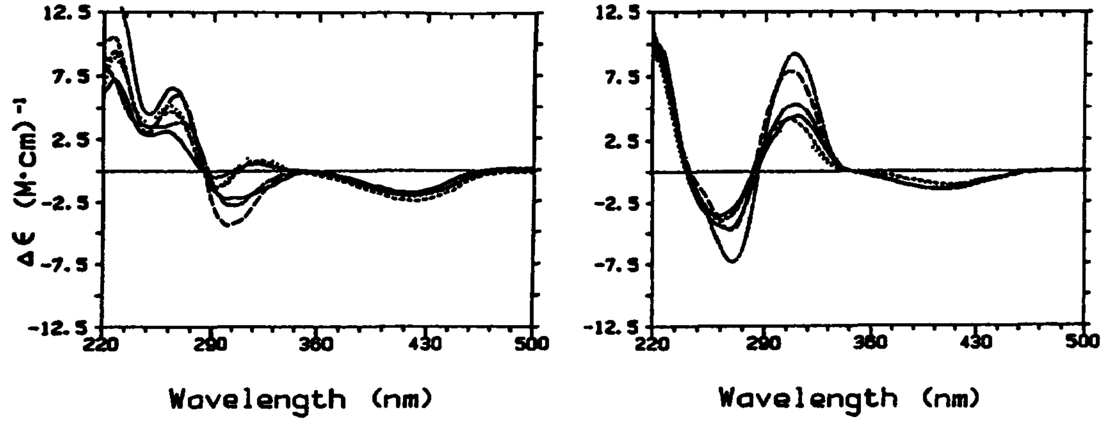


Figure 2 Left panel illustrates the CD spectra of adducts of 1 with the L amino acids Right panel illustrates the CD spectra of the D amino acid adducts.

In conclusion, the absolute configurational assignment of mixtures of amino acids, reported herein, can be deduced by analysis of their adducts with 1 by TLC (R_f), ^{77}Se chemical shift, the UV absorbance, and of course the sign of the CE band at 265-270 nm ($+CE_{265-270}$=L-amino acid, $-CE_{265-270}$=D-amino acid) For example, adducts of the D amino acids consistently migrate more rapidly during TLC, always exhibit the most ^{77}Se deshielded resonance, possesses a blue shifted $n \rightarrow \pi^*$ transition band, and a negative CE band at 265-270 nm

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11 All compounds have been characterized by ^{1}H, ^{13}C, ^{77}Se NMR, and HRMS UV/Vis measurements were performed on a HP-8452A spectrophotometer The standard curves for measuring extinction coefficients were defined by at least 6 experimental points Each value was the average of three readings The digitial resolution of the spectrometer was 2 nm/point The measurements were carried out at room temperature CD spectra were recorded on a JASCO 500 spectropolarimeter Generally, four scans were taken for a spectral range 230-500 nm at 25 ^{o}C An IBM-PC operating with the JASCO software was used to normalize the CD spectra Prior to measurement of the CD spectra, all compounds were purified by flash chromatography to ensure accuracy of the concentration measurements For the CD measurements a 1 00 x 10^{-4} M solutions in hexane was used for amino acid derivatives unless otherwise noted The concentration of all samples was determined by intensities of UV absorbance on the basis of experimentally determined extinction coefficients

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