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AMIDE BOND SURROGATES: A NOVEL ALTERNATE SYNTHESIS OF THE LEU-ASP TRANS CARBON-CARBON DOUBLE BOND ISOSTERE OF CCK_4.

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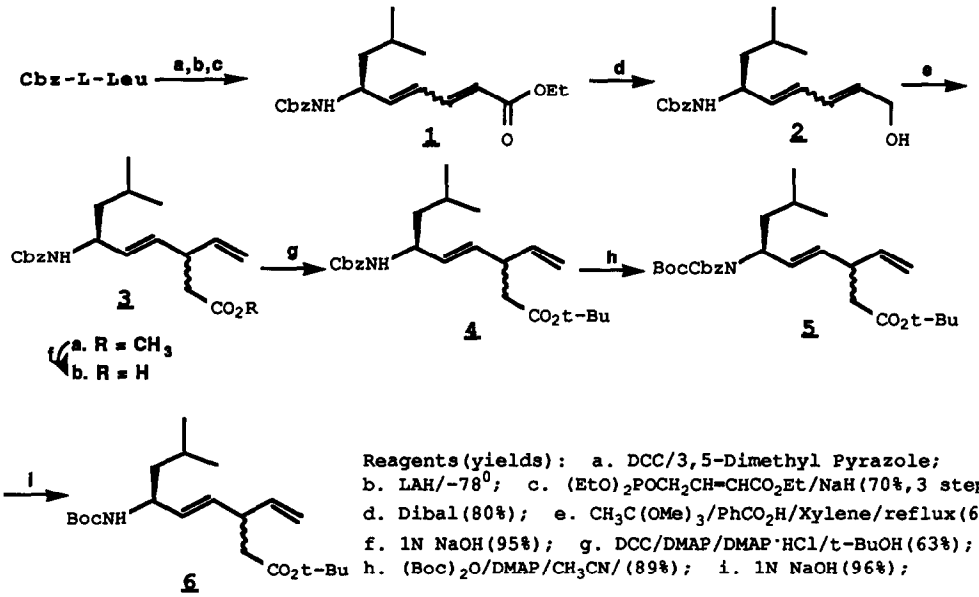
Summary: A novel alternate synthetic route was developed specifically for the Leuψ[E-CH=CH]Asp pseudodipeptide.

Amide bonds play an important role in determining peptide conformations through restricted rotation, i.e., double bond character and potential hydrogen bonding interactions. Therefore, amide bond surrogates capable of retaining all or some functions of the parent amide bond will serve as valuable tools to study the significance of these linkages at specific sites in the peptide. Among the many amide bond surrogates studied, the trans carbon-carbon double bond best mimics the transoid nature of the amide bond in terms of rigidity, bond angle, and bond length.[1] In an effort to gain insight into potential bioactive conformations for CCK_4 **[I]**, the C-terminal tetrapeptide of cholecystokinin (CCK), we replaced the center amide bond (between Met and Asp) with a trans carbon-carbon double bond. Since SAR studies previously showed that leucine is an acceptable replacement for methionine in the parent, the corresponding [Leu^2]CCK_4 **[II]** was utilized for the synthetic study. The synthesis described herein is designed specifically for the Leu-Asp segment of CCK_4. This novel route provides an alternate solution to overcome the problems associated with preparation of pseudodipeptides that bear an aspartic acid side chain at the second residue using our general methodology[2] reported previously.

Trp-Met-Asp-PheNH$_2$ [I]
Trp-Leu-Asp-PheNH$_2$ [II]

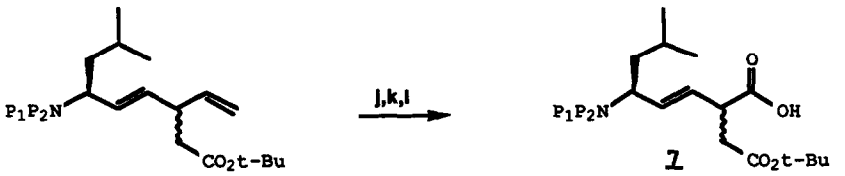
Optically pure Cbz-L-leucinal, derived from its corresponding dimethylpyrrazolide via a LAH reduction,[3] was treated with the anion of triethyl 4-phosphonocrotonate to give the desired diene-ester **1** in 70% yield. The E-configuration[4] of the newly formed γ-δ double was confirmed at a latter stage. Dibal reduction of the diene-ester **1** gave the desired diene-alcohol **2** in 85% yield. The aspartic acid side chain of **3** was introduced through

an ortho-ester Claisen rearrangement. To minimize the undesired ester formation between the catalyst and the starting alcohol **2**, the Claisen rearrangement was conducted using benzoic acid (8 mole %) as catalyst. After refluxing in xylene for 2 hr., the reaction proceeded only to partial completion; extended reaction times did not improve the yield. Purification of the mixture gave the desired diene-ester **3a** in 64% yield along with recovered starting material **2** (29%). Other catalysts (eg. propionic acid) gave less satisfactory results. To avoid the isomerization of the deconjugated double bond of **3a** at the latter stage, the methyl ester was converted to its corresponding t-butyl ester **4** in 63% yield, through acid **3b** via the DCC/DMAP/DMAP·HCl methodology.[5]



Reagents(yields): a. DCC/3,5-Dimethyl Pyrazole; b. LAH/-78^0; c. $(EtO)_2POCH_2CH{=}CHCO_2Et$/NaH(70%,3 steps); d. Dibal(80%); e. $CH_3C(OMe)_3/PhCO_2H$/Xylene/reflux(64%); f. 1N NaOH(95%); g. DCC/DMAP/DMAP·HCl/t-BuOH(63%); h. $(Boc)_2O$/DMAP/CH_3CN/(89%); i. 1N NaOH(96%);

The degradation of the terminal olefin was carried out on doubly protected diene-ester **5** via a three-step sequence to give the desired acid **7b** in 40% yield. Much lower yields resulted when the degradation was carried out on singly protected analogs **4** and **6** (Table 1). The presence of two protecting groups on the N-terminal nitrogen presumably provided enough steric bulk to effectively shield the internal olefin from attack during the initial OsO_4 mediated hydroxylation. In addition, the Cbz group likely enhanced the stability of Boc group through electronic effects during the subsequent Jones oxidation. Basic hydrolysis of acid **7b** provided the pseudodipeptide **7c** in quantitative yield as a pair of unseparable diastereomers (at the α-center corresponding to Asp).



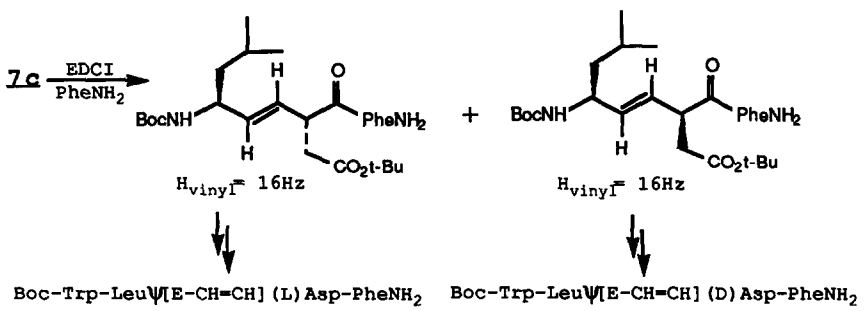
j. OsO_4(cat.)/NMMO/Acetone(aq.)
k. $NaIO_4$/MeOH(aq.). l. Jones reagent.
m. 1N NaOH/40 min/rt.

a. P_1 = Cbz, P_2 = H
b. P_2 = Boc, P_2 = Cbz
c. P_1 = Boc, P_2 = H

Table 1

SM	P1	P2	j	k+l	Overall yield	Product
4	Cbz	H	30%	60%	18%	7a
5	Boc	Cbz	57%	70%	40%	7b
6	Boc	H	25%	30%	8%	7c

Compound 7c was coupled to $PheNH_2$ to afford a pair of diastereomers which were readily separated by flash silica gel chromatography (EtOAc/Hexane/2% AcOH as eluent). The coupling constant between the two vinyl protons in each diasteromer was 16 Hz, thus, establishing the trans stereochemistry at this center. These two pseudotripeptides were then utilized to prepare a pair of CCK_4 analogs. The specific rotations for the resulting pseudotetrapeptides were $[\alpha]_D^{23}$= +4.4 (C=0.25, MeOH) and $[\alpha]_D^{23}$= -49.1 (C=0.11, MeOH).[6] Biological data for each have been reported elsewhere.[7]



Boc-Trp-LeuΨ[E-CH=CH](L)Asp-$PheNH_2$ Boc-Trp-LeuΨ[E-CH=CH](D)Asp-$PheNH_2$

In conclusion, this synthesis was developed specifically for carbon-carbon double bond pseudodipeptides which bear an aspartic side chain at the second residue and represents an alternative route to our previously reported general methodology.[2] These two methodologies are valuable tools that provide general access to trans double bond modified pseudopeptides[8] and allows one to gain information about the role of the amide linkage in peptides which would be difficult to obtain otherwise.

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6. Since there is no sure way to assign the absolute configuration solely by the specific rotations, no attempt was made to correlate the stereochemistry of the α-center corresponding to the Asp residue on the resolved diastereomers.

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