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Asymmetric Aza Diels-Alder Reactions of Amino Acid Ester Imines with Brassard's Diene

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Abstract:

Imines **1** obtained from aromatic, aliphatic or functionalized aldehydes and valine *tert*-butyl ester undergo Lewis acid catalyzed hetero Diels-Alder reactions with Brassard's diene **2**. The cycloadducts are formed in good to high yields and with diastereomer ratios of 92:8 - 97:3. For the removal of the chiral auxiliary group a new method was developed whose principle consists in the conversion of the amino acid α–C-atom into an acetalic center employing a Curtius rearrangement as the key step.

Introduction

The carbo Diels-Alder reaction constitutes one of the most powerful methods of preparative organic chemistry. In addition, during the last decades it has been demonstrated that its heteroanalogous variants can be used as efficient tools for the construction of various heterocycles and natural products.[1)] In particular, the cycloadditions of imines with suitable dienes may open up straightforward routes to alkaloids and derivatives thereof.[1,2)] Despite the great potential of this synthetic method only isolated efforts have thus far been made to carry out corresponding transformations asymmetrically using chiral auxiliary groups. Thus, purely thermal cycloadditions with iminium ions formed *in situ* from (*S*)-phenylethylamine[3a)] and from amino acid esters[3b,c,d,4)] were studied, and Lewis acid catalyzed cycloadditions with imines derived from (*S*)-phenylethylamine[5a,b)] or a galactosylamine were carried out.[5c)]

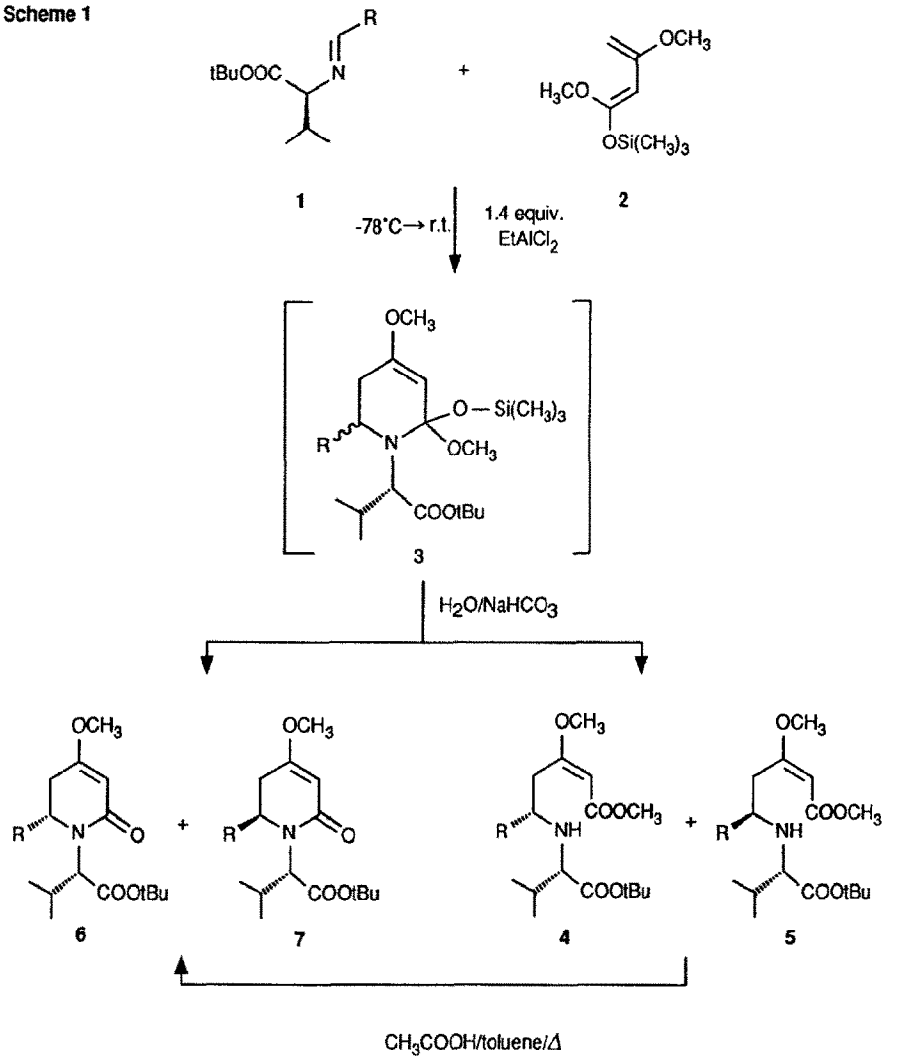
In the course of our studies directed to the use of easily accessible amino acid esters as chiral auxiliaries in asymmetric syntheses[6)] we have now investigated if amino acid ester imines can be advantageously applied as chiral dienophiles in Lewis acid mediated hetero Diels-Alder reactions.[7)] These esters have already proven useful as mediators of chirality in asymmetric carbo Diels-Alder

reactions,[8a-d] thermal aza Diels-Alder processes,[3b-d,4] 1,3-dipolar cycloadditions,[9] Mannich reactions[7] and radical additions to carbonyl groups.[10]

Results and Discussion

Midland et al.[11] have recently demonstrated that the so-called Brassard diene **2** in the presence of Lewis acids forms cycloadducts with imines, however, a removable chiral auxiliary was not introduced. If amino acid ester imines, e.g. **1** are treated with the electron-rich diene **2** in the presence of different Lewis acids, mixtures of the α,β-unsaturated esters **4/5** and the α,β-unsaturated lactams **6/7** are formed (Scheme 1). In contrast to the findings of Midland et al.,[11] the primary cycloadducts **3** with orthoester structure could not be isolated. Whereas $TiCl_4$, $SnCl_4$ and $BF_3{\cdot}Et_2O$ caused a competing decomposition of the diene leading to low yields of the desired products

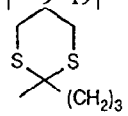
Scheme 1



(Table 1, entries 2, 3, 6, 10), $ZnCl_2$ was not active as a catalyst at all.

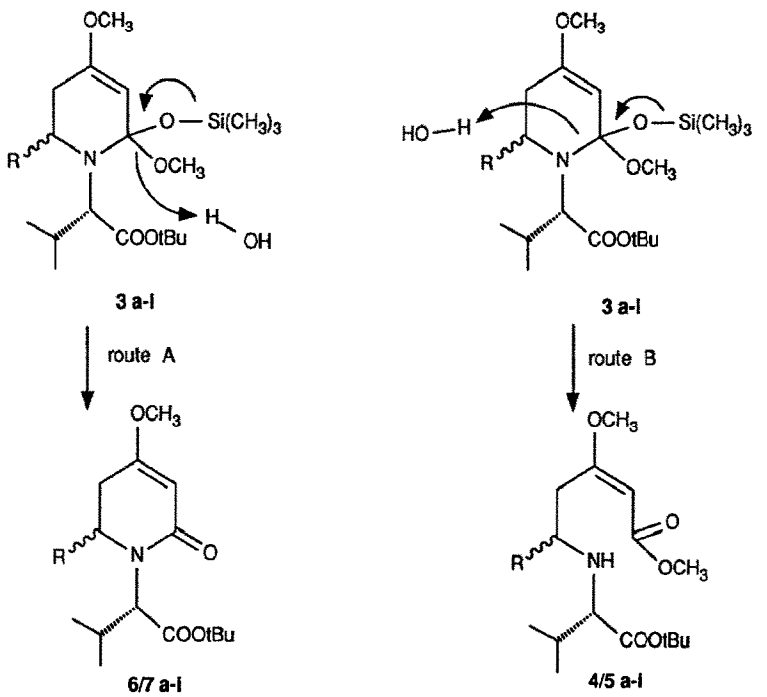
The best results were obtained if the reaction was initiated by the addition of 1.4 equivalents of $EtAlCl_2$ at -78°C, followed by gradually warming to room temperature within 1-1.5h. If less equivalents of the Lewis acid were used, the yield decreased significantly. Among the amino acid derivatives investigated, valine and isoleucine esters gave the highest diastereomeric ratios. Whereas with the methyl- and the benzyl esters the yields were unexpectedly low (30-40% Table 1, entries 4, 5, 6, 11), the use of *tert*-butyl valinate as chiral mediator lead to consistently high yields (Table 1, entries 1, 7, 8, 9, 12, 13, 14). Thus, if the imines **1**, which are easily obtained from *tert*-butyl valinate and the respective aldehyde by stirring over $MgSO_4$ in CH_2Cl_2 or diethylether, are reacted with the diene **2** under the conditions described, the esters **4/5** and the lactams **6/7** are formed in combined yields of 40-84% and with diastereomeric ratios ranging from 92:8 to 97:3 (Table 1). The isomer ratios are easily determined by analytical HPLC of a sample taken from the crude reaction mixture. The results given in Table 1 demonstrate that amino acid ester imines derived from aromatic, aliphatic and functionalized aldehydes can be used advantageously in the hetero Diels-Alder reactions with the diene **2**.

Table 1: Results of the Lewis acid mediated reactions of the amino acid ester imines **1** with the Brassard diene **2**.

Entry	Compound	R	Amino Acid	Ester Group	Lewis Acid	Combined Yield [%]	**4/5:6/7**	Diastereomeric Ratio **4/6:5/7**
1	**a**	Ph	Val	tBu	$EtAlCl_2$	84	<2:98	97.2:2.5
2	**a**	Ph	Val	tBu	$TiCl_4$	30	<2:98	94:6
3	**a**	Ph	Val	tBu	BF_3-Et_2O	28	<2:98	92:8
4	**b**	Ph	Ile	Me	$EtAlCl_2$	40	<2:98	93:7
5	**b**	Ph	Ile	Me	$MeAlCl_2$	34	<2:98	92:8
6	**b**	Ph	Ile	Me	$TiCl_4$	30	<2:98	93:7
7	**c**	3-Cl-Ph	Val	tBu	$EtAlCl_2$	64	<2:98	95:5
8	**d**	4-Cl-Ph	Val	tBu	$EtAlCl_2$	67	<2:98	97:3
9	**e**	nPr	Val	tBu	$EtAlCl_2$	81	82:18	93:7
10	**e**	nPr	Val	tBu	$SnCl_4$	33	78:22	93:7
11	**f**	nPr	Val	Bzl	$EtAlCl_2$	35	80:20	92:8
12	**g**	iPr	Val	Bu	$EtAlCl_2$	60	46:54	96:4
13	**h**	nC_9H_{19}	Val	tBu	$EtAlCl_2$	57	44:56	93:7
14	**i**		Val	tBu	$EtAlCl_2$	40	<2:98	96:4

Depending on the nature of the Schiff base substituent "R", the hydrolysis of the primary adducts **3**, expected to be formed as intermediates,[11] with $NaHCO_3$ leads via elimination of methanol to the lactams **6/7** (Scheme 2, route A) or via ring opening to the methyl esters **4/5** (Scheme 2, route B). Starting from aromatic aldehydes, only the esters **4/5** are formed, while the imines of aliphatic aldehydes give mixtures of **4/5** and **6/7**. The ratio of cyclized to open chain products is lowered if the reaction is quenched with water. The esters can, however, subsequently be converted to the lactams by refluxing in toluene in the presence of acetic acid. Heating in chloroform in the absence of acid, as recommended by Midland et al.,[11] was not successful. Also, all attempts to initiate the desired cyclization by deprotonation of the amino group by means of bases like DBU or BuLi, failed. Obviously the secondary amine in **4/5** is sterically shielded, as is also indicated by the observation that it could not be acylated by acetic acid anhydride or ketene.

Scheme 2

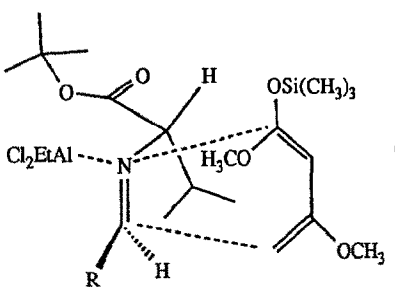


The diastereomers **6** and **7** can easily be separated by flash chromatography. The absolute configuration of the predominating stereoisomer **6** was unambiguously ascertained by an X-ray analysis of **6e** (R= nPr), which revealed that the newly formed stereocenter is *R*-configurated (Figure 1; for details of the X-ray analysis see the Experimental part).

The reactions of the amino acid ester imines **1** with Brassards diene **2** deliver products, whose configuration of the newly formed stereocenter is opposite to the stereochemistry obtained in the

Lewis acid promoted reaction of **1** with Danishefsky's diene.[7] To account for this difference, we assume that the reactions between **1** and **2** proceed as cycloadditions, rather than as a stepwise nucleophilic addition/cyclization sequence, which occurs in the reaction with Danishefskys diene.[7,12] The stereochemical outcome of the asymmetric transformations presented here, can be rationalized if one assumes that the aluminum Lewis acid coordinates to, and thereby activates the imine function. The electron-rich diene **2** then preferably approaches the C=N-double bond in the sense of a Diels-Alder transition state from the *Si*-side (Scheme 3). In this case, the amino acid ester actually adopts an *anti* Felkin-Anh conformation **8**[13]. In the arrangement **8** the unfavorable steric interactions between the bulky substituents on C-1 of the diene and the voluminous amino acid side chain are minimized. This model is also in accord with the finding that the sense of the asymmetric induction is not reversed if the chelating Lewis acid $TiCl_4$ is used instead of $EtAlCl_2$ which usually is only capable of tetra-coordination. In this case the chelate **9** should be found, which is preferably attacked from the *Si* side, too (Scheme 3).

Scheme 3



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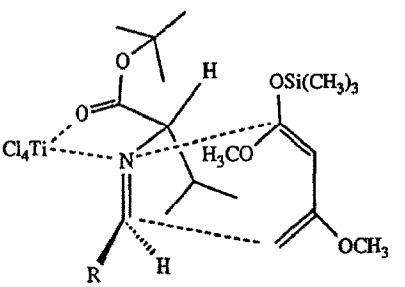

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We stress, that these hypothetical transition state models should be regarded as working hypotheses only. At present, the involvement of a stepwise reaction consisting in the formation of the esters **4/5**, followed by their cyclization to the lactams **6/7** at low temperatures cannot be rigorously ruled out. However, in several control experiments aiming at the verification of this possibility, the esters **4/5** did not cyclize to the lactams on being again exposed to the conditions of the cycloaddition (Lewis acid, -78°C→room temperature, 1.5h).

The high diastereoselectivities which are achieved with the use of amino acid esters are intimately connected to the complexing and coordinating properties of the chiral auxiliary group,[6-10] which are also apparent in **8** and **9**. This is supported by the observation that imines derived from (*S*)-phenylethylamine give inferior diastereomer ratios in the Lewis acid catalyzed reaction with Brassard's diene **2**. For instance, the imine formed from butyraldehyde and (*S*)-phenylethylamine delivers the cycloadducts in a ratio of 90:10, as compared to the diastereoselectivity of 93:7 for the

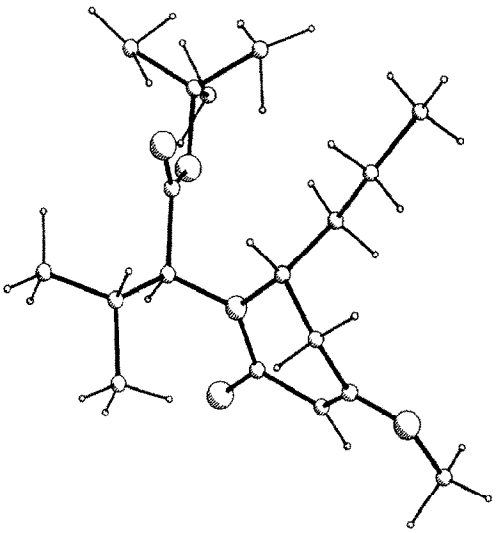


Figure1: Structure of the α,β-unsaturated lactam **6e**, as determined by X-ray analysis (for details see the Experimental part)

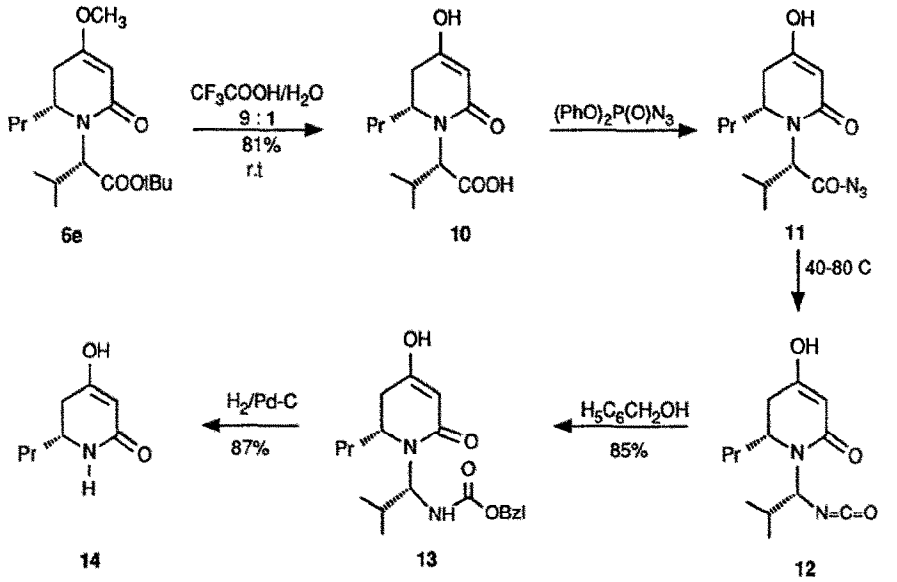
corresponding transformation employing *tert*-butyl valinate. These results are in agreement with the findings for aza Diels-Alder reactions with iminium ions in aqueous solution.[3,4]

To effect the cleavage of the chiral moiety from the α,β-unsaturated amides **6**, the chemically stable bond between the α-carbon of the amino acid and the nitrogen atom has to be broken. This goal has previously been achieved by electrochemical decarboxylation,[14] by the oxidative removal of serine and threonine residues from β-lactams[15] and by N-chlorination of N-alkylamino acid esters followed by elimination of HCl and hydrolysis of the imines generated thereby.[16] However, these procedures either make the use of special equipment necessary or are not general, since they can only be applied to the derivatives of β-hydroxy amino acids[15] or require the presence of a free amino group.[16] In addition, the latter two methods cannot be used for compounds carrying structural elements which are sensitive to oxidation.

To overcome these drawbacks, we developed a new strategy, whose principle consists in the conversion of the amino acid α-C-atom into an easily hydrolyzable acetalic center (e.g. **6d-13**), employing a Curtius rearrangement as the key step (see Scheme 4). The transformation of amino acid α-C-atoms into acetal centers has previously been carried out by using electrochemical methods,[17] oxidations[18] and Curtius-,[19a] Hofmann-[19b] or Lossen[19c] reactions. However, these techniques have not been applied to achieve the above mentioned goal.

The removal of the valine residue from the cycloadduct **6e** is shown in Scheme 4. To this end, the *tert*-butyl ester group and the enol ether structure on the α,β-unsaturated amide **6e** were first removed simultaneously by treatment with aqueous trifluoroacetic acid (TFA : H_2O = 9:1). The carboxylic acid **10** formed in this way in 81% yield, was then converted with diphenylphosphoryl-

Scheme 4



azide into the acid azide **11** which undergoes a Curtius rearrangement already at 40°C. The isocyanate **12** formed thereby is trapped by added benzyl alcohol, delivering the urethane **13** in this one-pot procedure in 85% overall yield. Finally, hydrogenolytic removal of the benzyl group and hydrolysis of the aminal structure furnished the desired amide **14** in an overall yield of 60%. The removal of the amino acid ester by the method described here, is experimentally simple, straightforward and highly practicable. It furthermore turns out to be fairly generally applicable, since it can also be used successfully for the cleavage of the amino acid ester moiety from enaminones, formed in the reaction of the respective imines with Danishefsky's diene.[7]

In conclusion, the amino acid esters prove to be efficient chiral auxiliaries for aza Diels-Alder reactions with Brassard's diene. They make the cycloadducts available in high yields and with high diastereomeric ratios and can be removed by a straightforward method. The amino acid esters, in addition, possess the advantage of being accessible in both enantiomeric forms. In the light of the low costs and the small efforts which, therefore, are associated with the preparation and use of these chiral auxiliaries, their loss during the removal can easily be tolerated.

Acknowledgement: This research was supported by the DEGUSSA AG, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie.

Experimental part

Specific rotations were measured on a Perkin-Elmer polarimeter, 400-MHz-^{1}H- and 100.6-MHz-^{13}C-NMR spectra were recorded on a Bruker AM 400. All shifts refer to tetramethylsilane as internal standard. Diastereomeric ratios were determined by HPLC using a Bischof Spherisorb ODS II column (250*4 mm). $EtAlCl_2$ was applied as 1M solution in hexane (Aldrich Inc. Sure/Seal^{TM} bottle).

General procedure for the synthesis of the α,β-unsaturated esters 4/5 and the α,β-unsaturated lactams 6/7

Preparation of amino acid ester imines:

To a solution of 2 mmol of the amino acid ester in diethyl ether or CH_2CL_2 2 mmol of the respective aldehyde are added and the solution is stirred for 30 minutes. $MgSO_4$ is added until the solution becomes clear, the solid is filtered off and washed twice with the respective solvent. After the removal of the solvent in vacuo, the remaining crude imine is immediately used without further purification in the subsequent reactions with the diene **2**.

Reaction of the amino acid ester imines **1** with Brassards diene **2**:

A solution of 3 mmol of the respective Schiff base in 30 ml of CH_2Cl_2 is cooled to -78°C and 4.2 ml of a 1M solution of ethylaluminumdichloride are injected with a syringe (Preferably a fresh solution of the Lewis acid should be used. If aged solutions are employed, even unopened samples, the reaction mixture turns dark immediately after the injection of the diene and the yields are lowered significantly). After two minutes a solution of 0.85 ml of the diene **2** in 4 ml of CH_2Cl_2 is added and stirring is continued at -78°C for 15 minutes. The cooling bath is then removed and the reaction mixture is allowed to warm to room temperature within 1-1.5h. During this time the colour of the reaction mixture turns deep red. It is poured into a mixture of 50 ml of CH_2Cl_2 and 50 ml of saturated $NaHCO_3$ solution and, after the separation of the organic layer, the aqueous phase is extracted twice with 50 ml of CH_2Cl_2. The combined organic phases are dried with $MgSO_4$, filtered and the solvent is removed in vacuo. The esters **4** and **5** and the lactams **6** and **7** are obtained as pure diastereomers from the remaining residue by flash chromatography on silica gel using petroleum ether/acetone mixtures (5:1 - 10:1 [v/v]) as eluents. For yields and diastereomeric ratios see Table 1.

According to this procedure the following α,β-unsaturated esters **4** were obtained:

N-[(*S*)-1-*tert*-Butyloxycarbonyl-2-methylpropyl]-(5*S*)-5-amino-3-methoxy-5-phenyl-pent-2-enoic acid methyl ester **4a**

$[\alpha]_{25}^{D}$ = -83.2 (c = 1, CH_2Cl_2)

400-MHz-^{1}H-NMR ($CDCl_3$): δ = 7.4 - 7.1 (5H, Ph), 5.04 (s, 1H, 2-H), 3.8 (dd, $J_{5\text{-H},4\text{-Ha}}$ = 4.5 Hz, $J_{5\text{-H},4\text{-Hb}}$ = 9.1 Hz, 1H, 5-H), 3.61 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.1 (dd, $J_{4\text{-Ha},4\text{-Hb}}$ = 13 Hz, 1H, 4-H_a), 2.8 (dd, 1H, 4-H_b), 2.53 (d, J = 6.8 Hz, 1H, α-H Val), 2.3 (s, 1H, NH), 1.73 (m,

1H, β-H Val), 1.4 (s, 9H, $C(CH_3)_3$), 0.89 (d, J = 6.7 Hz, 3H, γ-CH_3 Val), 0.85 (d, J = 6.7 3H, γ-CH_3 Val).

100.6-MHz-^{13}C-NMR ($CDCl_3$): δ = 174.8, 173.3 (C=O), 162.6 (C-3), 143.5 (ipso-C), 128.7, 127.5, 126.8 (Ph), 92.0 (C-2), 80.3 [$\underline{C}(CH_3)$], 65.2 (OCH_3), 60.1 (OCH_3), 55.3 (C-α Val), 50.6 (C-5), 41.1 (C-4), 31.6 (C-β Val), 28.0 [$C(\underline{C}H_3)_3$], 19.2, 18.6 (CH_3 Val).

$C_{22}H_{32}NO_5$ (390.5)	Calc:	C: 67.66	H: 8.26	N: 3.59
	Found:	C: 67.63	H: 8.27	N: 3.36

N-[(1*S*,2*S*)-1-Methoxycarbonyl-2-methylbutyl]-(5*S*)-5-amino-3-methoxy-5-phenyl-pent-2-enoic acid methyl ester **4b**

$[\alpha]_{25}^{D}$ = -61.2 (c = 1.1 CH_2Cl_2)

400-MHz-^{1}H-NMR ($CDCl_3$): δ = 7.4 - 7.1 (m, 5H, Ph), 5.04 (s, 1H, 2-H), 3.8 (dd, $J_{5\text{-H},4\text{-Ha}}$ = 4.5 Hz, $J_{5\text{-H},4\text{-Hb}}$ = 8.7 Hz, 1H, 5-H), 3.61 (s, 6H, OMe), 3.59 (s, 3H, OMe), 3.1 (dd, $J_{4\text{-Ha},4\text{-Hb}}$ = 13 Hz, 1H, 4-H_a), 2.8 (dd, 1H, 4-H_b), 2.53 (d, J = 6.9 Hz, 1H, α-H Ile), 2.2 (s, 1H, NH), 1.53 (m, 2H, γ-CH_2 Ile), 1.1 (s, 1H, β-H Ile), 0.89 (m, 6H, 2 CH_3 Ile).

100.6-MHz-^{13}C-NMR ($CDCl_3$): δ = 175.8, 173.2 (C=O), 167.6 (C-3), 143.2 (ipso-C), 128.0 127.4 127.0 (Ph), 92.0 (C-2), 63.5 (OCH_3), 60.3 (OCH_3), 55.3 (C-α Ile), 50.9 (C-5), 50.6 (OCH_3), 40.7 (C-4), 38.3 (C-β Ile), 25.0 (C-γ Ile), 15.6, 11.2 (CH_3 Ile).

$C_{20}H_{29}NO_5$ (360.4)	Calc:	C: 66.09	H: 8.04	N: 3.85
	Found:	C: 65.77	H: 7.92	N: 3.70

N-[(*S*)-1-*tert*-Butyloxycarbonyl-2-methylpropyl]-(5*S*)-5-amino-5-(3-chlorophenyl)-3-methoxy-pent-2-enoic acid methyl ester **4c**

$[\alpha]_{25}^{D}$ = -82.2 (c = 1 CH_2Cl_2)

400-MHz-^{1}H-NMR ($CDCl_3$): δ = 7.4 - 7.1 (5H, Ph), 5.04 (s, 1H, 2-H), 3.7 (dd, $J_{5\text{-H},4\text{-Ha}}$ = 4.5 Hz, $J_{5\text{-H},4\text{-Hb}}$ = 9 Hz, 1H, 5-H), 3.6 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.1 (dd, $J_{4\text{-Ha},4\text{-Hb}}$ = 13 Hz, 1H, 4-H_a), 2.8 (dd, 1H, 4-H_b), 2.5 (d, J = 6.7 Hz, 1H, α-H Val), 2.1 (s, 1H, NH), 1.7 (m, 1H, β-H Val), 1.4 (s, 9H, $C(CH_3)_3$, 0.89 (d, J = 6.8 Hz, 3H, CH_3 Val), 0.8 (d, 3H, CH_3 Val).

100.6-MHz-^{13}C-NMR ($CDCl_3$): δ = 174.6, 172.8 (C=O), 167.6 (C-3), 145.9 (ipso-C), 133.9 (ipso-C), 127.3, 126.5 (Ph), 92.2 (C-2), 80.3 [$\underline{C}(CH_3)$], 65.3 (OCH_3), 59.7 (OCH_3), 55.4 (C-α Val), 50.6 (C-5), 40.8 (C-4), 31.6 (C-β Val), 28.3 [$C(\underline{C}H_3)_3$], 19.2, 18.6 (2 CH_3 Val).

$C_{22}H_{32}NO_5Cl$ (424.9)	Calc:	C: 62.05	H: 7.57	N: 3.29
	Found:	C: 61.6	H: 7.34	N: 3.25

N-[(*S*)-1-*tert*-Butyloxycarbonyl-2-methylpropyl]-(5*S*)-5-amino-5-(4-chlorophenyl)-3-methoxy-pent-2-enoic acid methyl ester **4d**

$[\alpha]_{25}^{D}$ = -95.5 (c = 1, CH_2Cl_2)

400-MHz-^{1}H-NMR ($CDCl_3$): δ = 7.43- 7.1 (2dd, 4H, Ph), 5.04 (s, 1H, 2-H), 3.78 (dd, $J_{5\text{-H},4\text{-Ha}}$ = 4.69 Hz, $J_{5\text{-H},4\text{-Hb}}$ =8.9 Hz, 1H, 5-H), 3.62 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.1 (dd, $J_{4\text{-Ha},4\text{-Hb}}$ = 13 Hz, 1H, 4-H_a), 2.8 (dd, 1H, 4-H_b), 2.4 (d, J = 6.8 Hz, 1H, α-H Val), 2.1 (s, 1H, NH), 1.68 (m, 1H, β-H Val), 1.4 (s, 9H, $C(CH_3)_3$), 0.89 (d, J = 6.7 Hz, 3H, CH_3 Val), 0.85 (d, 3H, CH_3 Val).

100.6-MHz-^{13}C-NMR ($CDCl_3$): δ = 174.7, 172.9 (C=O), 167.6 (C-3), 142.1 (ipso-C), 132.3 (ipso-C), 128.2 127.0 (Ph), 92.1 (C-2), 80.5 [$\underline{C}(CH_3)_3$], 65.3 (OCH_3), 59.5 (OCH_3), 55.3 (C-α Val), 50.7 (C-5), 40.9 (C-4), 31.5 (C-β Val), 28.1 [$C(\underline{C}H_3)_3$], 19.2, 18.6 (2 CH_3 Val).

$C_{22}H_{32}NO_5Cl$ (424.9)	Calc:	C: 62.04	H: 7.57	N: 3.29
	Found:	C: 62.07	H: 7.38	N: 3.27

N-[(*S*)-1-*tert*-Butyloxycarbonyl-2-methylpropyl]-(5*R*)-5-amino-3-methoxy-oct-2-enoic acid methyl ester **4e**

$[\alpha]_{25}^{D}$ = -83.2 (c = 1, CH_2Cl_2)

400-MHz-^{1}H-NMR ($CDCl_3$): δ = 5.04 (s, 1H, 2-H), 3.62 (s, 3H, OMe), 3.61 (s, 3H, OMe), 2.93 (dd, $J_{4\text{-Ha},4\text{-Hb}}$ = 12.5 Hz, 1H, 4-H_a), 2.85 (d, J = 6.4 Hz, 1H, α–H Val), 2.63 (m, 1H, 5-H), 2.56 (dd, $J_{4\text{-Hb},5\text{-H}}$ = 8 Hz, 1H, 4-H_b), 1.7 (m, 2H, NH, β–H Val), 1.39 (s, 9H, $C(CH_3)_3$), 1.2 (m, 4H, 6-H, 7-H), 0.89 (d, J = 6.7 Hz, 3H, γ-CH_3 Val), 0.85 (m, 6H, γ-CH_3 Val, 8-H).

100.6-MHz-^{13}C-NMR ($CDCl_3$): δ = 175.1, 174.7 (C=O), 167.8 (C-3), 91.5 (C-2), 80.3 [$\underline{C}(CH_3)_3$], 65.3 (OCH_3), 55.6 (OCH_3), 55.3 (C-α Val), 50.6 (C-5), 37.2 (C-4), 37.1 (C-6), 32 (C-β Val) 28.1 [$C(\underline{C}H_3)_3$], 19.2 (C-7), 18.6, 18.2(CH_3 Val), 14.2 (C-8).

$C_{19}H_{35}NO_5$ (357.5)	Calc:	C: 63.84	H: 9.87	N: 3.92
	Found:	C: 63.40	H: 9.28	N: 3.38

N-[(*S*)-1-Benzyloxycarbonyl-2-methylpropyl]-(5*R*)-5-amino-3-methoxy-oct-2-enoic acid methyl ester **4f**

$[\alpha]_{25}^{D}$ = -74.7 (c = 1, CH_2Cl_2)

400-MHz-^{1}H-NMR ($CDCl_3$): δ = 7.4 - 7.1 (5H, Ph), 5.2 (s, 2H, $C\underline{H}_2$-Ph), 5.0 (s, 1H, 2-H), 3.7 (dd, $J_{5\text{-H},4\text{-Ha}}$ = 4.6 Hz, $J_{5\text{-H},4\text{-Hb}}$ = 9.1 Hz, 1H, 5-H), 3.61 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.1 (dd, $J_{4\text{-Ha},4\text{-Hb}}$ = 13.4 Hz, 1H, 4-H_a), 2.8 (dd, 1H, 4-H_b), 2.57 (d, J = 6.8 Hz, 1H, α-H Val), 2.3 (s, 1H, NH), 1.73 (m, 1H, β-H Val), 1.35 (m, 4H, 6-H, 7-H), 0.89 (d, J = 6 Hz, 3H, γ-CH_3 Val), 0.85 (m, 6H, γ-CH_3 Val, 8-H).

100.6-MHz-^{13}C-NMR ($CDCl_3$): δ = 174.8, 173.3 (C=O), 162.6 (C-3), 140.4 (ipso-C), 128.7, 127.7, 126.8 (Ph), 92.0 (C-2), 65.2 (OCH_3), 67.1 (CH_2-Ph), 63.6, (OCH_3), 55.3 (C-α Val), 50.6 (C-5), 41.1 (C-4), 36.1 (C-6), 31.6 (C-β Val), 19.5 (C-7) 19.2, 18.6 (CH_3 Val), 14.2 (C-8).

$C_{22}H_{32}NO_5$ (390.5) Calc: C: 67.67 H: 8.20 N: 3.39
Found: C: 67.03 H: 8.27 N: 3.60

N-[(*S*)-1-*tert*-Butyloxycarbonyl-2-methylpropyl]-(5*R*)-5-amino-3-methoxy-6-methyl-hept-2-enoic acid methyl ester **4g**

$[\alpha]_{25}^{D}$ = -53.4 (c = 1 CH_2Cl_2).

400-MHz-^{1}H-NMR ($CDCl_3$): δ = 4.9 (s, 1H, 2-H), 3.58 (s, 6H, OMe), 2.88 (dd, $J_{4\text{-Ha},4\text{-Hb}}$ = 12.5 Hz, $J_{4\text{-Ha},5\text{-H}}$ = 4.3 Hz 1H, 4-H_a), 2.87 (d, J = 6.2 Hz, 1H, α–H Val), 2.55 (m, 2H, 4-H_b, 5-H), 1.4 (m, 2H, NH, β–H Val), 1.36 (s, 9H, $C(CH_3)_3$), 1.13 (m, 1H, 6-H), 0.89 (m, 12H, 4 CH_3).

100.6-MHz-^{13}C-NMR ($CDCl_3$): δ = 175.2, 174.4 (C=O), 167.6 (C-3), 91.5 (C-2), 80.2 [$\underline{C}(CH_3)_3$], 65.1 (OCH_3), 55.2 (OCH_3), 54.1 (C-α Val), 50.6 (C-5), 44.8 (C-6), 37.2 (C-4), 31.9 (C-β Val), 28.1 [$C(\underline{C}H_3)_3$], 24.5 (C-6), 23.2, 22.3 (CH_3), 19.2, 18.6 (CH_3).

$C_{19}H_{34}NO_5$ (356.5) Calc: C: 64.02 H: 9.60 N: 3.92
Found: C: 64.21 H: 9.90 N: 3.96

N-[(*S*)-1-*tert*-Butyloxycarbonyl-2-methylpropyl]-(5*R*)-5-amino-3-methoxy-tetradec-2-enoic acid methyl ester **4h**

$[\alpha]_{25}^{D}$ = -37.2 (c = 1, CH_2Cl_2)

400-MHz-^{1}H-NMR ($CDCl_3$): δ = 5.01 (s, 1H, 2-H), 3.61 (s, 6H, OMe), 2.69 (dd, $J_{4\text{-Ha},4\text{-Hb}}$ = 12.7 Hz, $J_{4\text{-Ha},5\text{-H}}$ = 4.6 Hz 1H, 4-H_a), 2.8 (d, J = 6.2 Hz, 1H, α-H Val), 2.49 (m, 2H, 4-H_b, 5-H), 1.7 (m, 2H, NH, β–H Val), 1.36 (s, 9H, $C(CH_3)_3$), 1.3 (m, 16H, $(CH_2)_8$), 0.9 (m, 9H, 3 CH_3).

100.6-MHz ^{13}C-NMR ($CDCl_3$): δ = 175.2, 174.4 (C=O), 167.6 (C-3), 91.5 (C-2), 80.2 [$\underline{C}(CH_3)_3$], 65.1 (OCH_3), 55.2 (OCH_3), 54.1 (C-α Val), 50.6 (C-5), 44.8 (C-6), 37.2 (C-4), 31.9 (C-β Val), 28.1 [$C(\underline{C}H_3)_3$], 24.5 - 23.2(C-7 - C-14), 22.3 (CH_3), 19.2, 18.6 (CH_3).

$C_{25}H_{47}NO_5$ (441.6) Calc: C: 67.67 H: 10.73 N: 3.17
Found: C: 67.79 H: 10.70 N: 3.16

N-[(*S*)-1-*tert*-Butyoxycarbonyl-2-methylpropyl]-(5*R*)-5-amino-3-methoxy-8-(2-methyl-1,3,dithian-2-yl) oct-2-enoic acid methyl ester **4i**

$[\alpha]_{25}^{D}$ = -23.2 (c = 1, CH_2Cl_2)

400-MHz-^{1}H-NMR ($CDCl_3$): δ = 5.01 (s, 1H, 2-H), 3.6 (s, 6H, 2 OMe), 2.85 (dd, $J_{4\text{-Ha},4\text{-Hb}}$ = 12.3 Hz, $J_{4\text{Ha},5\text{-H}}$ = 4.5 Hz, 1H, 4-H_a), 2.8-2.5 (m, 9H), 2.0 -1.5 (m, 7H), 1.4 (s, 9H, $C(CH_3)_3$), 0.9 (m, 9H, 3 CH_3).

100.6-MHz-^{13}C-NMR ($CDCl_3$): δ = 175.2, 174.4 (C=O), 167.6 (C-3), 91.5 (C-2), 80.4 [$\underline{C}(CH_3)_3$], 70.1 (S-$\underline{C}$-S), 65.1 (OCH_3), 55.5 (OCH_3), 55.3 (C-α Val), 50.7 (C-5), 43.9 (C-6), 43.2 (S-$\underline{C}H_2$), 37.2 (C-4), 32.1 (C-β), 31.3 (CH_2), 28.1 [$\underline{C}(CH_3)_3$], 26.5, 26.4, 25.7, 25.1, 25.0, (CH_2), 19.9, 19.2, 18.6 (CH_3).

$C_{24}H_{42}NO_5S_2$ (488.7)	Calc:	C: 57.83	H: 9.07	N: 2.93
	Found:	C: 57.67	H: 8.89	N: 2.88

According to the above mentioned general procedure the following lactams **6** were obtained:

N-[(*S*)-1-*tert*-Butyloxycarbonyl-2-methylpropyl]-(6*R*)-4-methoxy-6-n-propyl-3,4-didehydro-piperidin-2-one **6e**

$[\alpha]_{25}^{D}$ = -53.6 (c = 1, CH_2Cl_2), m.p. 109°C

400-MHz-^{1}H-NMR ($CDCl_3$): δ = 5.09 (s, 1H, 2-H), 4.75 (d, J = 11 Hz, 1H, α–H Val), 3.6 (s, 3H, OMe), 2.69 (dd, $J_{5\text{-}Ha,5\text{-}Hb}$ = 16.0 Hz, 1H, 5-H_a), 2.2 (m, 2H, 5-H_b, 6-H), 1.7 (m, 1H, β–H Val), 1.44 (s, 9H, $C(CH_3)_3$), 1.2 (m, 4H, 7-H, 8-H), 0.91 (d, J = 6.7 Hz, 3H, γ-CH_3 Val), 0.9 (d, 3H, γ-CH_3 Val), 0.8 (t, J = 6.9 Hz, 3H, 9-H).

100.6-MHz-^{13}C-NMR ($CDCl_3$): δ = 170.5 (C=O), 166.5 (C-4), 94.1 (C-3), 81.3 [$\underline{C}(CH_3)_3$] , 60.7 (C-α Val), 55.4 (OCH_3), 50.6 (C-6), 34.1 (C-5), 31.1 (C-7), 28.8 (C-β Val) 27.1 [$C(\underline{C}H_3)_3$], 19.9, (C-8), 19.1 (CH_3), 18.8 (CH_3) 14.2 (C-9).

$C_{18}H_{31}NO_4$ (329.6)	Calc:	C: 64.02	H: 9.60	N: 3.92
	Found:	C: 63.83	H: 9.71	N: 3.80

N-[(*S*)-1-*tert*-Butyoxycarbonyl-2-methylpropyl]-(6*R*)-4-methoxy-6-n-nonyl-3,4-didehydro-piperidin-2-one **6h**

$[\alpha]_{25}^{D}$ = -40.3 (c = 1, CH_2Cl_2)

400-MHz-^{1}H-NMR ($CDCl_3$): δ = 5.09 (s, 1H, 3-H), 4.75 (d, J = 11 Hz, 1H, α–H Val), 3.6 (s, 3H, OMe), 2.69 (dd, $J_{5\text{-}Ha,5\text{-}Hb}$ = 16.0 Hz, $J_{5\text{-}H,6\text{-}H}$ = 6.2 Hz, 1H, 5-H_a), 2.2 (m, 2H, 5-H_b, 6-H), 1.7 (m, 1H, β–H Val), 1.44 (s, 9H, $C(CH_3)_3$), 1.3 (m, 16H, $(CH_2)_8$), 0.91 (m, 9H, 3 CH_3).

100.6-MHz-^{13}C-NMR ($CDCl_3$): δ = 170.6, 166.5 (C=O), 165.8 (C-4), 94.1 (C-3), 81.3 [$\underline{C}(CH_3)_3$], 60.8 (C-α Val), 55.5 (OCH_3), 50.6 (C-6), 32.1 (C-5), 31.1-30.1(8 CH_2), 28.8 (C-β Val) 27.9 [$C(\underline{C}H_3)_3$], 19.1(CH_3), 18.8 (CH_3) 14.0 (CH_3).

$C_{24}H_{43}NO_4$ (409.7)	Calc:	C: 71.79	H: 8.79	N: 3.49
	Found:	C: 72.00	H: 8.96	N: 3.40

The cycloadducts **6f** and **6g** were not further characterized by high field nmr. The ratios of products **4f,g/6f,g** were obtained after separation by flash chromatography.

Cyclization of the esters 4/5 to the lactams 6/7

To a solution of 2 mmol of the ester **4** in 20 ml toluene are added 0.09 ml (2 mmol) of acetic acid and the reaction mixture is heated to reflux for 3 hours. The solvent is evaporated in vacuo and the remaining residue is purified by flash chromatography using petroleum ether / acetone mixtures as eluents. According to this procedure **6e** was obtained in 73% yield from **4e** and 15% of the starting material was recovered.

General procedure for the removal of the chiral auxiliary from the α,β- unsaturated amides 6

Simultaneous hydrolysis of the *tert*-butyl ester and the enol ether

A solution of 6g (18.5 mmol) of the lactam **6e** in a mixture of 18 ml of trifluoroacetic acid and 2 ml of water was stirred at room temperature for 14 - 16h. The solvent was removed in vacuo and after repeated codistillation of the residue with toluene, the remaining solid was triturated with ether/ petroleum ether. The resulting crystals were collected by filtration and dried in vacuo to give 3.8 g (81%) of the carboxylic acid **10**.

N-[(*S*)-1-Carboxy-2-methylpropyl]-(6*R*)-4-hydroxy-6-n-propyl-3,4-didehydropiperidin-2-one **10**

m.p. 132°C

400-MHz-^{1}H-NMR (DMSO-d_6): δ = 13.0 (s, 1H, COOH), 4.7 (s, 1H, 3-H), 3.9 (m, 3H, α-H Val, 6-H, OH), 2.69 (dd, $J_{5\text{-Ha},5\text{-Hb}}$ = 4.5 Hz, $J_{5\text{-Ha},\ 6\text{-H}}$ = 8 Hz, 5-H), 2.5 (dd, $J_{5\text{-Hb},6\text{-H}}$ =12.7 Hz, 1H, 5-H_b), 1.7 (m, 1H, β–H Val), 1.44 (m, 4H, 7-H, 8-H), 0.91 (m, 9H, 9-H, 2 CH_3 Val).

100.6-MHz-^{13}C-NMR (DMSO-d_6): δ = 175.5, 172.3 (C=O), 171.6 (C-4), 94.3 (C-3), 61.5 (C-α Val), 50.4 (C-6), 39.1 (C-5), 35.4 (C-7), 30.9 (C-β), 19.9 (C-8), 19.1 (CH_3), 18.8 (CH_3), 13.2 (C-9).

$C_{14}H_{23}NO_4$ (269.3)	Calc:	C: 61.16	H: 8.03	N: 5.49
	Found:	C: 61.14	H: 8.03	N: 5.90

General procedure for the Curtius rearrangement

To a suspension of 1.8 g (7 mmol) of the acid **10** in 30 ml toluene is added 1 ml (7 mmol) of triethylamine. To the resulting clear solution 1.52 ml (1.1 equiv.) of diphenylphosphorylazide and 1.6 ml of benzyl alcohol (2 equiv.) are added. The solution turns deep red and after a period of 5-10 min the evolution of gas is observed. The reaction mixture is stirred at 30 - 40°C until the evolution of nitrogen ceases (30 - 45 min). The solution is stirred for about 1h at ambient temperature, slowly heated to 80°C and kept over night at this temperature. For workup the reaction mixture is poured onto a mixture of water and CH_2Cl_2, the organic layer is separated and the aqueous phase is then extracted twice with a 1:1 mixture of saturated $NaHCO_3$ solution and CH_2Cl_2. The combined organic phases are dried with $MgSO_4$ and the solvent is removed in vacuo. The resulting crude urethane **13**, (2.1 g, 85%) is immediately subjected to hydrogenation.

Removal of the acetal moiety from **13** :(6*R*)-4-Hydroxy-6-n-propyl-3,4-dihydropiperidin-2-one

To a solution of 2.1 g of the urethane **13** in 100 ml of methanol 250 mg of 5% palladium on charcoal are added. The reaction mixture is stirred under atmospheric pressure of hydrogen for 5h. After filtration the solvent is evaporated and the remaining residue is purified by flash chromatography petroleum ether/ acetone 1:1 (v/v) as the eluent, to give 810 mg (81%) of the lactam **14**.

(6*R*)-4-Hydroxy-6-n-propyl-3,4-didehydropiperidin-2-one **14**

$[\alpha]_{25}^{D}$ = -25.4 (c = 1, CH_2Cl_2), m.p. 112°C

400-MHz-^{1}H-NMR ($CDCl_3$): δ = 6.46 (s, 1H, NH), 4.9 (s, 1H, 2-H), 3.52 (dddd, J_1= 12.0 Hz, J_2 = 6.7 Hz, J_3 = 7.6 Hz, J_4 = 14.6 Hz, 1H, 6-H), 2.5 (s, 1H, OH), 2.3 (dd, J_1 = 16.3 Hz, J_2 = 6.7 Hz, 1H, 5-H_a), 2.1 (dd, J_1 = 12 Hz, 1H, 5-H_b), 1.44 (m, 4H, 7-H, 8-H), 0.8 (t, J = 7.2 Hz, 3H, 9-H).

100.6-MHz-^{13}C-NMR ($CDCl_3$): δ = 169.5 (C=O), 160.4 (C-4), 94.1 (C-3), 50.4 (C-6), 36.9 (C-5), 33.2 (C-7), 18.3 (C-8), 13.6 (C-9).

$C_8H_{13}NO_2$ (155.2)	Calc:	C: 61.91	H: 8.44	N: 9.03
	Found:	C: 61.72	H: 8.66	N: 9.40

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20) The crystal structure of **6e** (orthorhombic, space group $P2_12_12_1$; a = 9.993 (2), b = 11.339 (1), c = 17.272 (7) Å, V = 1957 (1) Å^3 ; M_r ($C_{18}H_{31}NO_4$) = 325.4; Z = 4: D_{calcd} = 1.105, D_{exptl} = 1.096 (g/cm^3) has been refined to R = 0.0706 (7866 reflections measured: Mo-K_a radiation, θ_{max} = 32.5°, 3933 Friedel pairs, internal R = 0.0291; 1425 Friedel pairs used with $I > 2\sigma$ (I), 212 parameters, Friedel pairs/parameters = 6.7; R_w = 0.0959, weighting scheme $w^{-1} = (\sigma^2 (F) + 0.001140 \cdot F^2)$. The (*R*) center at the 6-position of the lactame ring has been determined by comparison of the (*S*) center of the valine ester; without this information, it was not possible to determine the absolute configuration in spite of a careful and long (12 days) measurement of the Friedel pairs. The tert butoxy group of the valine ester exhibits a rotational disorder and is split in two positions (55/45 %) on both sides of the ideal 180°-staggered position (-169.5 (5) and +155.9 (8)°).
The bond length and angles of the valine group (C=O 1.198 (6), C-OtBu 1.310(5) Å; torsion (O=C)-(OtBu) -1.1 (5)°) and of the unsaturated lactame ring (N-(C=O) 1.376 (5), N-(CHnPr) 1.487 (5), N-(C_{valine}) 1.446 (5), C=O 1.247 (6), C=C 1.349 (6), C-(OMe) 1.358 (6) Å; torsions around the ring beginning with N-(C=O) + 5.0 (5), +16.9 (6) -1.0 (6), -34 (5), +51.7 (4), -39.8 (4); torsions of the substituents (O=C)-(N-C_{valine}) +7.3 (5), (C=C)-(OMe) +2.8 (6), (C-CH_2)-(CH-C_{nPr}) -72.4°) span the normal limits and deserve no special comment. he six-membered ring exhibits half-chair conformation: the methylene group in position 5 forms the top, and the other five atoms of the ring are not far from planarity. This approximate planarity extends to the three substituents C_{valine}, $O_{C=O}$, $O_{O\text{-}Me}$. The n-propyl group stands axial, and the hydrogen atom stands equatorial.
Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Informationen mbH, W-7514 Eggenstein-Leopoldshafen 2 (FRG), on quoting the depository number CSD-54896 and the names of the authors.