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Chiral N-Dienyl-L-Pyroglutamic Esters in Asymmetric Hetero-Diels-Alder Reactions with Acylnitroso Dienophiles.

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Abstract: Asymmetric Diels-Alder reaction of the N-dienyl-L-pyroglutamic esters **1a-h** with acyl nitroso dienophiles **4a-h** gave diastereoisomeric adducts **6a-n**, **7a-n** with 12-90 % *de*, depending on solvents and temperature. An interpretation was gived. The "allylic effect" ($\pi_{C=C} - \sigma^*_{N-C}$ MO interactions) was found to be effective to account for the conformations of the adducts.

INTRODUCTION

Hetero-Diels-Alder (HDA) cycloadditions with nitroso dienophiles have been studied extensively in the racemic series¹⁻⁴. Asymmetric HDA reactions have mostly been performed with chiral nitroso dienophiles. Excellent asymmetric inductions were obtained with α -chloronitroso dienophile derivatives of D-mannose⁵, and D-ribose⁶, as well as with N-acylnitroso derivatives of C₂-symmetric chiral pyrrolidines.^{7,8} Chiral dienes were seldom used, since only poor asymmetric inductions could be observed.⁹

We describe herein some results we obtained when asymmetric HDA cycloadditions were performed using type 4 (achiral) acylnitroso dienophiles with type L-2 (chiral) *N*-dienylpyroglutamic esters. As will be shown below, asymmetric inductions reached 84-90% for these reactions. In two preceding communications we described some preliminary results along these lines.^{10,11} Furthermore, some investigations pertaining to HDA cycloadditions of achiral N-dienylpyrrolidone with achiral acylnitroso dienophiles had been shown by us to lead to amino-D,L-erythrose and to amino-D,L-ribose derivatives.¹²

Smith and his coworkers had already prepared diene L-2b, by simple condensation of ethyl Lpyroglutamate L-1b with crotonaldehyde, and showed it to undergo classical homocarbon Diels-Alder reactions with good asymmetric induction.¹³ Furthermore these same authors had prepared a series of L-2 type dienes with various α , β -ethylenic aldehydes.¹³

The highly reactive dienophiles 4a-h we now use, were prepared *in situ* by oxidation of the corresponding hydroxamic acids 3a-h with tetraalkylammonium periodate in the presence of the diene partners¹⁴ (Scheme 1).

RESULTS AND DISCUSSION

Preparation of N-Dienyl-L-pyroglutamic Esters 2a,c-h (Scheme 1)

Simple esters of pyroglutamic acid L-1a and L-1c were prepared according to a procedure Silverman and Levy had used to obtain ester L-1b¹⁵, with one modification : L-pyroglutamic acid L-1g, rather than Lglutamic acid, was reacted with SOCl₂ in the required anhydrous alcohol. t-Butyl ester L-1d was formed via transesterification of L-1g with t-butyl acetate in the presence of perchloric acid.¹⁶ Likewise t-butyl ester (\pm) 1d was obtained from racemic acid (\pm) 1g. Cholesteryl ester L-1e was formed by condensation of acid L-1g with cholesterol, water being removed by azeotropic distillation. We prepared also two amide derivatives: t-butyl amide L-5a was easily obtained by reaction of t-butylamine with the known pentachlorophenol ester L-1f¹⁸ in pyridine. Anilide L-5b, a known product, was prepared according to the literature ¹⁷.



N-Dienyl- γ -lactams L-2a,c,f were obtained by condensation in toluene of the corresponding L-pyroglutamic esters L-1a and L-1c with crotonaldehyde (R²=H), or with pent-2-enal (R²=Me) using a Dean-Stark trap for azeotropic distillation of water.¹³ The t-butyl esters (±) g2d, L-2d,g and L-2h (from hex-2-enal) were prepared in toluene at lower temperature (ca. 100°C) in the presence of molecular sieves to remove water. Yields were in the range 40 - 60%; the N-dienylpyroglutamic esters proved to be air-sensitive and had to be stored at -20°C. 4-Substituted dienes L-2f-h occur as mixtures of (E,E) and (E,Z) isomers in the following ratios : 70:30 for L-2f, 55:45 for L-2g and L-2h. As to amides L-5a,b they did not seem to react under the above described conditions and no N-dienyl derivatives could be isolated.

The optical purity of t-butyl esters L-1d and L-2d was determined, using both NMR and HPLC techniques, by comparison with the corresponding racemates $(\pm)1d$ and $(\pm)2d$:

- by 1H-NMR in CDCl3 using (+)Eu(hfc)3 as a chiral complexing agent (t-butyl esters: c=4.6 10-2 M; Eu(hfc)3:
- c=2.3 10-2 M). $\Delta\delta$ =0.2 ppm for H-C(5) of D-1d and L-1d; $\Delta\delta$ =0.2 ppm for H-C(1) of D-2d and L-2d).
- by HPLC on chiral columns (CHIRALPACK AD and CHIRADEX Merck).

Both methods showed the two products to be optically pure, *i.e.* : ee > 98 %, the minor enantiomer was not detected.

Asymmetric Hetero Diels-Alder Cycloadditions

1-Siloxybutadiene had been shown previously to react with acylnitroso dienophiles in a non-regioselective way, leading thereby to both regioisomeric [4 + 2] cycloadducts.¹⁹ On the other hand achiral N-dienyl- γ -lactams react with complete regioselectivity with the same acylnitroso dienophiles to give the "direct" cycloadducts only, as shown in previous publications.^{11,12} Likewise, acylnitroso dienophiles **4a-h** reacted with chiral N-dienyl- γ -lactam derivatives **L-2a,c-h** - *i.e.* N-dienylpyroglutamic esters - with complete regioselectivity, and led to pairs of diastereomers **6a-n**/7a-n which were formed in various proportions as a function of several parameters. The major diastereomers **6a-n** were formed in the (6S) configuration (with one exception though : **6h**, see Table 1).

Acylnitroso Dienophiles (Scheme 2)

Systematic investigations were made with *in situ* generated acylnitroso dienophiles **4a-h** which were reacted with L-2a as the chiral diene (reference partner), HDA reactions being performed in CH₂Cl₂ at 0°C (*Table 1*).





The R³ substituent appeared to have a pronounced effect upon the ratio of both diastereomeric cycloadducts, albeit no clearcut conclusions could be drawn. The best asymmetric induction was found when R³ = NMe₂ (case a) whereas induction is small (and even reversed) when R³ = NH₂ (h). Moderate inductions were observed when R³ = OR (*i.e.* carbamates : b, c, e) and when R³ = Ph (benzoyl : d). It may be worth mentioning that the diastereomeric ratios could be improved by double asymmetric induction, as shown previously.²⁰

Quantitative measurements of the diastereomeric mixtures were monitored by 13 C-NMR (comparison of the intensities of analogous signals), by ¹H-NMR (integration ratios of analogous signals), and by preparative chromatographic separations - whenever possible - followed by weight determination. These three analytical methods gave very similar results (*Table 1*). As to monitoring through HPLC, it requires calibration of the instrument with each individual diastereomeric adduct, prior to any quantitative determination²¹; these calibrations could not be made with all diastereomeric pairs. As a consequence, and throughout this article, ¹³C -NMR was used for the *d.e.* determinations.

	R ³	Yields	d.e.	13C-NMR	¹ H-NMR	HPLC	Chromatographic Isolation
a	-NMe2	70	84	92/8	-	89/11a)	92/8
b	-OMe	63	52	76/24	76/24	-	c)
с	-OBn	80	46	73/27	70/30	-	67/33
d	-Ph	70	44	72/88	73/27	72/28b)	72/28
e	-OTMSE	76	40	70/30	71/29	66/34a)	70/30
f	-CH3	62	34	67/33	64/36	-	d)
g	-CH2Ph	57	12	56/44	54/46	-	57/43
h	-NH2 ¢)	80	28	36/64	37/63	32.5/67.5	35/65

Table 1. Relative Amounts of Major 6a-h, and Minor 7a-h Cycloadducts, as Monitored by Various Analytical Methods, for HDA Reactions of Dienophiles 4a-h (R³-CON=O) with Diene L-2a in CH₂Cl₂ at 0°C.

a) without calibration. b) after calibration. c) adducts were unstable. d) adducts were not separated. e) in CH₂Cl₂/MeOH 75:25 solution; assignment according to $[\alpha]$ D values of the adducts by comparison with those of cases c, d or g.

Pyroglutamic Ester Moieties, Solvent and Temperature (see Table 2)

In a second series of experiments we kept the dienophile component constant, using benzyloxycarbonylnitroso dienophile 4c, and increased the bulkiness of the ester R¹ group of type L-2 N-butadienylpyroglutamates, step by step (*Scheme 3*). It appeared that the asymmetric induction increased drastically with the size of R¹ : de = 46 % for the 6c/7c pair, 60 % for the 6i/7i pair, 70 % for the 6j/7j pair.

Solvent and temperature also had a pronounced effect on asymmetric induction, a result we had already observed in some preceding experiments²²: methanol proved to be the solvent of choice, rather than methylene chloride, along with a lowering of temperature. The best induction was observed for the 6j/7j pair in methanol at -20°C (de = 76%).



Scheme 3

Best results were obtained when the butadiene moiety is substituted by Me or Et in position C(4). Cycloaddition of dienes L-2f-h with 4c at -20°C in MeOH led to good inductions : de = 90 % for L-6m/L-7m (*i.e.* R¹ = tBu, R²=Me).

			PhMe	CH	2Cl2	Me	OH
dienes	add	ucts	<u>0°C</u>	0°C	-20°C	<u>0°C</u>	<u>- 20°C</u>
L-2a	6 c	7 c	36	46	-	48	58
L-2c	6i	7 i	-	60	63	64	68
L-2d	6j	7j	-	68	74	72	76
L-2e	6 k	7 k	-	70	-	70a	-
L-2f	61	71	-	42	-	54c	-
L-2g	6 m	7 m	-	76	78b	86	90
L-2h	6 n	7 n	-	76¢	-	84c	84c

Table 2. - Asymmetric Induction (de values, % as determined by ¹³C-NMR) for the Adducts 6c,i-n, 7c,i-n, Obtained by Diels-Alder Reaction of Nitrosodienophile 4c with Dienes L-2a,c-h; as a function of solvent and temperature.

a) MeOH/PhMe 3:1. b) at -15°C. c) as determined by ¹H-NMR only.

Interpretation of the asymmetric Diels-Alder Cycloadditions

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The absolute configurations of two of the major diastereomers - *cis* diacetoxy-derivative 8 of cycloadduct $6c^{10}$, and cycloadduct 6m (see *Figure 1*) - were determined by X-ray diffraction and showed to be (6S) and (3S,6S) respectively. Therefore we shall assume that all major cycloadducts occur in their (6S) configuration, one exception being the 6h/7h pair (R²=NH₂) in which 7h is prevalent over 6h (see *Table 1*).

In all cycloadditions, except the one just cited, a classical HDA reaction is assumed to occur, the dienophile approaching from the less hindered side, *i.e. anti* with respect to the ester moiety of the chiral pyroglutamate auxiliary, as shown in *Scheme 4*. Furthermore the *s*-trans conformation between the amide and the butadiene moieties is postulated in the transition state, so that π -orbital interactions are optimal, as already suggested by Oppolzer in a similar case²³. Consequently the (major) cycloadducts resulting from such a transition state geometry are (6S) configured (*Scheme 4*).



Scheme 4

Accounting in a rational manner for the HDA cycloaddition of 4-substituted diene L-2f, and particularly of 4-substituted dienes L-2g and L-2h, is less obvious ; for two reasons :

- the (E,E)/(E,Z) ratio of these latter dienes is of the order 55:45, whereas the corresponding cycloadducts **6m/7m** and **6n/7n** were formed in a *ca*. 90:10 ratio !

- the minor cycloadducts 71-n occur as *cis* products, *i.e.* they have the (3R, 6R), instead of the expected *trans* configuration.

We could demonstrate experimentally that the major and the minor cycloadducts did not interconvert under the preceding reaction conditions. In particular the minor cycloadduct 7m could be isolated pure and proved to be a stable entity. The reaction of diene L-2g with acylnitroso dienophile 4c was monitored by ¹H-NMR in CDCl₃ at 0°C; this experiment permitted to conclude that the (E,E) isomer disappeared ca. 3 times faster than the (E,Z) isomer. Both cycloadducts 6m and 7m were formed in a ca.90:10 ratio right at the beginning, and this ratio stayed constant throughout the reaction. We had already proposed an explanation for this observation when achiral N-dienyl-pyrrolidone was left to react with 4c¹² and assume the same phenomenon to occur : only the (E,E) isomer reacts and leads to the corresponding *cis* cycloadduct, whereas the (E,Z) diene isomerises to the (E,E) product. This isomerisation is triggered off by iodine which is always formed during the reduction of the periodate anion.

Structure and Conformation of Cycloadducts

¹H- and ¹³C-NMR spectral data of major **6a-n** and minor **7a-n** cycloadducts are collected either in *Table* 3 and *Table 4*, or in the Experimental Part. The ¹³C-NMR spectrum of minor adduct **7n** could not be determined, due to the instability of the compound. Both major and minor adducts, being structurally close diastereomers, have very similar NMR spectra: in ¹³C-NMR the C(3) signals appear in the 40-80 ppm range, the C(6) signals in the 70-80 ppm range, in both series. These chemical shifts clearly point to the same overall regiotopology for both types of cycloadducts (*i.e.* for **6** and for **7**), as anticipated for sp³ C(6) atoms, which are bonded simultaneously to an oxygen and to a nitrogen atom, and for sp³ C(3) atoms which are bonded to a nitrogen (of the N-CO2R³ moiety) atom^{19,24}. As indicated above, the major cycloadducts **6a-n** were shown to occur in their (6S) configuration (and (3S) for disubstituted adducts **61-n**), the minor ones **7a-n** in their (6R) configuration (and (3R) for **71-n**).



Figure 1. ORTEP plot of 6m: 50% probability ellipsoids. Most H-atoms omitted for clarity.

These conformations of the oxazine rings could be deduced directly from the 3J, 4J, and 5J coupling constants (*Table 3*) 19,24,25. The conformations and stereostructures of adducts **61-n** could easily be interpreted : they occur in a type **A** half-chair conformation in which R²-C(3) is *pseudo*axial and the pyroglutamate N-C(6) bond *pseudo*equatorial, *i.e. cis* with respect to R²-C(3) (*Figure 2*), (H-C(3) being *pseudo*equatorial ($J_{3,4} = ca$.

	Heq-C(3)	Hax-C(3)	H-C(4)	H-C(5)	H-C(6)	2H	-C(3')	2H	-C(4')	H-C(5')	RI	R ³
íaa,b	3.85	3.91	6.11	5.62	6.23	2.57	2.32	2.30	2.04	4.44	3.75	NMe2 : 2.97
7ac	3.83	3.77	6.19	5.61	6.22	2.73	2.40	2.20	2.10	4.22	3.67	NMe2 : 2.97
ĝ	4.15	4.08	6.10	5.70	6.22	2.55	2.43	2.37	2.04	4.44	3.74	OMe : 3.80
çca,d	4.20	4.06	6.08	5.70	6.20	2.46	2.21	2.02	1.87	4.36	3.70	CH2 ^e : 5.15, 5.32; Ph : ca.7.38
7ca,b	4.09	4.09	6.12	5.87	5.91	2.63	2.31	2.19	2.05	4.39	3.67	CH2 ^f : 5.21; Ph : ca.7.37
λd	4.70	4.18	6.16	5.70	6.16	2.28	ca.1.85	ca.1.85	ca.1.85	4.26	3.71	2Har : 7.86; 3Har : ca.7.40
p,	4,41	4.19	6.18	5.82	5.93	2.57	2.29	2.08	2.03	4.14	3.57	2Har : 7.74; 3Har : ca.7.42
e,	4.11	4.05	6.06	5.69	6.22	2.55	2.44	2.33	2.02	4.45	3.72	SiMe3 : 0.05; CH2-CH2 : 1.06, 4.27
7e	4.06	4.06	6.12	5.83	5.95	2.67	2.37	2.25	2.08	4.40	3.73	SiMe3 : 0.06; CH2-CH2 : 1.07, 4.27
Ş	4.29	4.03	6.02	5.62	6.11	2.43	2.21	1.84	1.84	4.20	3.65	CH2: 3.69; 2Har: 7.18; 3Har: 7.23
- 6	4.14	3.93	6.11	5.63	6.04	2.74	2.36	2.17	2.05	4.17	3.56	CH2: 3.71; Ph: 7.10-7.30
, ƙ	4.28	3.94	6.16	5.71	6.11	2.48	ca.2.40	ca.2.40	2.06	4.55	3.75	NH2:5.10
μ	4.10	3.88	6.28	5.68	6.15	2.81	2.41	2.26	2.12	4.28	3.71	NH2:5.30
6i	4.20	4.05	6.05	5.69	6.17	2.43	2.16	1.89	1.89	4.26	50	CH2 ^e : 5.10, 5.30; Ph : 7.27-7.40
61	4.23	4.07	6.07	5.74	6.19	2.45	2.18	ca.1.90	ca.1.90	4.20	1.43	CH2 ^e : 5.12, 5.33; Ph : ca.7.36
, <u>7</u>	4.17	4.07	6.10	5.86	5.91	2.59	2.28	ca.2.10	ca.2.10	4.24	1.42	CH2 ^e : 5.19 ,5.22; Ph : ca.7.36
ek .	4.23	4.07	6.07	5.71	6.19	2.47	ч	ų	ч	4.29	ų	CH2 : 5.12, 5.33; Ph : ca.7.36
7k	4.11	4.11	6.11	5.86	5.89	2.63	ų	ч	Ч	4.34	q	CH2 : 5.20; Ph : ca.7.35
61	4.53	1.35 ⁱ	6.00	5.55	6.36	2.60	ca.2.40	ca.2.40	2.05	4.37	3.75	CH2 ^f : 5.19, 5.26; Ph : 7.30-7.44
71	4.52	1.29	60.9	5.58	6.20	2.75	2.42	2.26	2.10	4.27	3.70	CH2 ^f : 5.21, 5.24; Ph : 7.28-7.44
ém	4.55	1.37 ⁱ	5.99	5.61	6.37	2.58	2.37	2.37	1.98	4.23	1.46	CH2 ^e : 5.20, 5.26; Ph : 7.31-7.44
7m	4.52	1.32 ⁱ	60.9	5.55	6.22	2.70	2.39	2.22	2.07	4.08	1.39	CH2 ^e : 5.21, 5.22; Ph : 7.32-7.39
en	4.36	, m	6.01	5.62	6.35	2.58	ca.2.35	ca.2.35	ca.1.96	4.19	1.45	CH2 ^f : 5.18, 5.26; Ph : 7.29-7.44

Table 3. ¹H-NMR Data (CDC13) of Cycloadducts 6a-e, 6g-n, and 7a, 7c-e, 7g, 7h, 7j-m. 250 MHz, 300 K, δ in ppm, J in Hz, int. standard TMS.

Chiral N-dienyl-L-pyroglutamic esters

	J3ax,3eq	J3ax,4	J3eq,4	J3ax,5	J3eq,5	J3ax,6	J3eq.6	J4,5	<i>J</i> 4,6	J5,6
6a	17.8	3.0	4.0	2.3	2.5	2.8	2.6	10.2	61	
7a	17.5	Э.	Şa	(1	2.2a	5.0	ja	10.2	1.9	2.0
6b	17.6	3.0	3.6	2.2	2.2	2.5	1.8	10.3	1.8	9 E
ۍ ور	17.7	2.7	3.9	2.4	2.1	2.4	1.6	10.2	1.8	3.7
7c	17.5	3.	2a	7	2a	2.1	a	10.2	1.8	2.8
6d	18.2	2,7	3.6	2.1	2.1	2.7	1.6	10.3	1.6	3.1
7d	17.9	2.9	3.7	2.1	2.7	2.5	2.0	10.3	1.9	3.0
Se d	17.7	3.0	3.8	2.2	2.1	2.5	1,9	10.2	1.8	3.0
7e	17.5	3.5	3a	2	.2a	2.3	а	10.2	1.8	2.6
58	18.2	2.8	3.6	2.2	2.2	2.6	1.6	10.3	1.6	3.4
7g	18.1	3.0	3.4	2.0	2.6	2.4	2.3	10.3	1.8	2.6
Sh	17.8	2.3	4.3	2.3	2.1	2.7	1.2	10.1	1.6	3.6
7h	17.7	2.4	4.4	2.2	2.0	2.8	1.2	10.1	1.7	3.4
5i	17.7	2.6	3.8	2.1	2.1	2.7	1.5	10.1	1.8	3.2
6j	17.8	2.6	3.9	2.2	2.1	2.6	1.6	10.2	1.7	3.3
2	17.6	2.9	3.6	2.3	2.7	2.3	2.0	10.2	1.8	2.6
51	6.8b	ı	4.6		1.6	ŗ	2.6	10.4	1.9	1.6
12	6.8b	•	4.6	,	1.7	ı	2.6	10.2	2.0	1.5
E	6.7b	ı	4.6	I	1.6	,	2.4	10.4	2.0	1.5
E	6.7b	•	4.6	,	1.7		2.6	10.2	2.0	4
ų	6.8b	•	4.6		1.6	ı	2.5	10.4	2.0	1.7

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Table 3 (continued).

	C(3)	C(4)	C(5)	C(6)	C(2')	C(3')	C(4')	C(5')	R ¹	CO-C(5')	CO-N(2)	R ³
6a a	45.4	121.6	128.5	76.9	175.0	28.5	23.3	56.8	51.7	172.6	160.4	36.9
7a ^b	45.7	122.6	129.5	77.8	175.5	29.2	23.1	56.6	51.8	172.1	160.6	37.6
6b	44.4	122.6	127.6	77.4	175.6	29.1	24.0	57.3	52.3	173.0	155.9	53.2
7b	44.9	122.6	127.5	78.4	175.7	29.0	23.8	57.7	52.2	172.3	156.6	53.1
60°	44.4	122.8	127.7	77.7	175.6	29.2	23.9	57.8	52.4	173.2	155.2	67.7, 128.2, 128.4, 128.6, 135.8
7¢ ^c	45.0	123.0	127.0	79.1	175.6	30.0	23.7	57.9	52.4	172.4	155.8	67.6, 128.1, 128.2, 128.5, 135.8
6d d	41.9	120.9	128.0	77.6	175.0	28.1	23.2	57.5	52.1	172.6	167.7	127.5, 128.9, 130.8, 131.7
7 d d	42.9	122.3	128.1	79.3	175.2	29.2	22.7	57.2	51.8	171.8	169.4	127.4, 128.5, 130.7, 132.3
6e	44.2	122.5	127.5	77.1	175.2	28.9	23.8	57.1	52.0	172.8	155.4	-1.9, 17.3, 64.4
7e	44.7	122.6	127.2	78.1	175.4	29.5	23.5	57.4	51.9	172.0	156.1	-1.9, 17.2, 64.4
6 f	41.5	121.7	127.9	78.0	175.6	28.9	24.0	57.7	52.4	172.7	170.5	19.6
7 f	41.8	121.8	128.4	78.6	176.0	29.3	23.9	57.5	52.3	172.2	170.5	20.1
6g	41.7	121.1	126.3	78.4	175.5	28.7	23.2	57.6	52.0	172.5	171.1	39.0, 127.9, 128.7,
7 g	41.7	121.4	126.1	77.6	175.9	29.0	23.5	57.1	52.0	172.1	171.1	129.2, 133.9 38.2, 127.7, 128.7, 129.2, 134.0
6h	43.1	121.0	128.1	77.0	175.4	28.6	23.3	57.8	51.7	172.4	158.4	
7h	43.9	121.2	128.3	77.2	175.5	28.7	23.6	57.1	51.6	171.7	159.4	
6i	44.4	122.9	127.6	77.6	175.7	29.2	23.9	58.1	69.1e	172.2	155.1	67.7, 128.2, 128.3, 128.5, 135.8
7 i	44.4	123.0	127.0	78.8	175.5	29.7	23.3	57.7	68.7 ^e	171.2	155.3	67.4, ca. 128.4, 135.6
6j	44.5	123.3	127.4	77.8	175.8	29.3	24.0	58.7	82.1 ^f	172.0	155.3	67.8, 128.3, 128.4, 128.6, 135.9
7j	44.6	123.6	126.7	79.5	175.7	30.1	23.4	58.7	82.1 ^t	171.1	155.5	67.8, 128.1, 128.2, 128.5, 135.9
6k	44.5	123.2	127.7	77.7	175.8	29.3	23.8	58.2	g	172.2	155.2	g
7k	44.8	123.4	126.8	79.4	175.8	30.1	23.7	58.1	g	171.5	155.1	g
6l h	49.9	133.2	122.6	77.8	175.7	29.2	23.8	55.6	52.3	173.0	154.6	67.6, 127.9, 128.1, 128.3, 135.6
71h	49.9	133.5	122.7	78.2	175.5	29.4	23.2	56.7	52.2	172.4	154.7	67.4, 127.7, 128.1, 128.3, 135.8
6m ^h	49.8	133.0	123.1	77.8	175.6	29.2	23.9	56.4	81.9f	171.8	154.7	67.5, 127.9, 128.0, 128.3, 135.7
7mh	50.0	133.7	123.4	78.5	175.6	29.8	23.7	58.2	82,2f	171.1	154.8	67.5, 128.0, 128.1, 128.5, 136.1
6n ⁱ	55.0	131.7	123,5	77.2	175.7	29.2	23.8	56.3	81.9f	171.8	155.1	67.6, 127.8, 127.9, 128.3, 135.7

Table 4. ¹³C-NMR Data (CDCl3) of Cycloadducts 6a-n and 7a-m; 62.9 MHz, 300 K, δ in ppm, Internal Standard CDCl3 (77.0 Hz).

a) 318 K . b) 313 K. c) 100 MHz. d) 323 K. e) CH-Me2; 2Me for 6i : 21.5, 21.6; for 7i : 21.3, 21.1. f) CMe3; 3Me for 6j : 27.9; for 7j : 27.8; for 6m and 7m : 27.7; for 6n : 27.6. g) see experimental part. h) Me-C(3) : for 6l : 17.6; for 7l : 16.9; for 6m : 17.7; for 7m : 17.2. i) Et-C(3) : CH2 : 25.9; Me : 10.5.

4.5 Hz) and H-C(6) pseudoaxial ($J_{5,6} = ca. 1.5$ Hz)). The conformation is also determined by the strain between methyl-C(3) and acyl-N(2) groups, the methyl group being strictly in pseudo axial position²⁴. Cycloadducts which are devoid of substituents at C(3) occur as equilibria between type A and type B half-chair conformations, as deduced from the $J_{5,6}$ values (2.5 - 3.5 Hz). As to cycloadducts 6h and 7h, they appear almost entirely in half-chair conformation B ($J_{5,6}=ca.3.5$ Hz and $J_{3eq,4}=ca.4.5$ Hz), *i.e.* the pyroglutamate N-C(6) bond is pseudoaxial.

In our opinion type **B** half-chair conformation as observed for **6h** and **7h** is best accounted for by assuming allylic strain to operate. An allylic effect had been described with 2,3-didehydropyranoses in which an allylic C-O bond appears in its *pseudo*axial orientation. This topology is thought to be favoured by *ca*. 0.9-1.3 kcal. mol⁻¹ because of the π (C=C) - σ^* (C-O) orbital overlapp²⁶. We believe that a similar allylic effect due to π (C=C) - σ^* (C-N) overlap operates here.



Figure 2. Conformation of adducts 6a-n, 7a-n^a

Determination of the structures

Crystal Data of compound **6m** C₂₂H₂₈O₆N₂, M=416.47, monoclinic, a=10.290, b=8.969, c=12.759 Å, β =107.66(2)°, U=1122.08 Å³ (by least squares refinement of diffractometer angles for 25 independent, automatically centered reflections, l=1.54178 Å), space group P21, Z=2, D_c=1.233 g.cm⁻³, F(000)=444. Colourless crystal mounted in a 0.3 mm Lindemann capillary, μ Cu-K α =2.0572 cm⁻¹. Intensity data were collected on a Enraf-Nonius CAD4 diffractometer, ω -20 scan, graphite-monochromated Cu-K α radiation 1.54178 Å; 2813 independent reflections measured [±h,k,l; 2<0<77.5°], 2.559 with F>3 σ (F). Correction for absorbance by ψ -measures was applied. The structure was solved by direct methods. Anisotropic full-matrix least-squares refinement for all non-hydrogen atoms. Hydrogen atoms were calculated and fixed with isotropic thermal U-values of 0.07. Final R=0.037 using unit weights. Programs used (MicrovaxII, cryst. Lab. Chemistry Department. University of Basle) and sources of scattering factors were reported²⁷. Fractional atomic coordinates and Ueq values [Beq= $8\pi^2$ (U11+U22+U33)/3] for structure **6m** are available upon request²⁸.

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EXPERIMENTAL PART

General. Flash chromatography (FC) : silica gel (Merck 60, 230-400 mesh). TLC : Al-roll silica gel (Merck 60, F254). M.p. : Kofler hot bench or Büchi-SMP-20 apparatus, corrected. IR spectra (cm⁻¹) : Perkin-Elmer 157 G and 580 B . ¹H- and ¹³C-NMR spectra: Bruker AC-F250, and AM 400 using double-irradiation techniques ; tetramethylsilane (TMS ; ¹H) and CDCl₃ (δ (CDCl₃)=77.0 ppm rel. to TMS ; ¹³C) as internal references ; δ in ppm and J in Hz. [α]D values were determined with a Schmidt Haensch Polartronic Universal polarimeter. High resolution (HR) MS were measured on a MAT-311 spectrometer at the University of Rennes. Microanalyses were carried out by the "Service Central de Microanalyses" of the CNRS, at 69390 Vernaison, France.

Reagents and solvents. (\pm) and L-pyroglutamic acid, *t*-butyl acetate, cholesterol, pent-2-enal, Eu (hfc)₃, *p*-toluensulfonic acid were purchased from Fluka, 70% perchloric acid and *t*-butylamine from Prolabo, crotonaldehyde from Merck, hex-2-enal from Janssen. Hydroxamic acids **3a-g** were prepared according to lit.^{19,29}, as N-hydroxyurea **3h**³⁰. Acetohydroxamic acid **3f** was purchased from Fluka. Usual solvents were freshly distilled, CH₂Cl₂ was kept over Na₂CO₃.

Pyroglutamic Esters

Methyl (+)-*L*-*pyroglutamate L*-1*a* : prepared according to lit.¹⁵ with some modifications : to a stirred soln. of L-pyroglutamic acid **L**-1*g* (6.88 g, 53 mmol) in MeOH (35 ml) was added SOCl₂ (4.0 ml, 55 mmol) dropwise at 0°C. After 30 mn at 0°C, the soln. was neutralised with 50% KOH in MeOH (40 ml) to pH=5 and evaporated. After dissolution in CH₂Cl₂, KCl precipitated and was removed by filtration; the solvent was evaporated to give **L**-1*a* (5.54 g, 73%) which was purified by distillation as a yellowish resin (5.1 g, 67%). Bp₁=135°C (lit. bp0.06-0.12=107-113°C ³¹, bp0.1=115°C³²). [α]¹⁷D=+9.9 (c=6, MeOH) (lit. [α]²⁶D=+11 (c=6.2, MeOH)³²). IR (neat): 3240, 2950, 1740, 1695, 1440, 1210. ¹H-NMR: identic to lit. data.³² ¹³C-NMR (CDCl₃): 178.4 (C-2), 172.4 (CO₂Me), 55.4 (C-5), 52.3 (OMe), 29.1 (C-3), 24.6 (C-4).

Isopropyl (+)-*L*-*pyroglutamate L*-*Ic* : same procedure as for L-1a with L-1g (4.0 g, 31 mmol), SOCl₂ (3.0 ml, 41 mmol) in anh. iPrOH (30 ml) for 3h at r.t. followed by neutralisation with 25% KOH in iPrOH (35 ml). The crude L-1c was crystallised in iPr₂O as colourless crystals (4.32 g, 82%). Mp=68°C (AcOEt/cyclohexane) (lit.: $60-62^{\circ}C^{33}$). [α]_D=+4.0 (c=5, MeOH). IR (KBr): 3230, 2980, 1730, 1700, 1650, 1450, 1375, 1235, 1195, 1105. ¹H-NMR (CDCl₃): 6.50 (br, NH), 5.08 (sept., *J*=6, CH-Me₂), 4.21 (t, *J*=7, H-5), 2.55-2.15 (m, 2H-3, 2H-4), 1.27 (d, *J*=6, 2Me). Anal. calc. for C₈H₁₃NO₃ (171.20): C 56.12, H 7.65, N 8.18; found: C 55.8, H 7.6, N 8.2.

t-butyl (+)-L-pyroglutamate L-Id : according to lit.¹⁶ with some modifications. To a stirred suspension of L-1g (30 g, 0.23 mol) in AcOtBu (300 ml, 2.6 mol, 11 eq.) was added dropwise 70% aq. HClO4 (15 ml, 0.18 mol) and the solution was left to react overnight at r.t.. Na₂CO₃ (15-20 g, 0.15-0.2 mol) was then added portionwise followed by Et₂O (300 ml). The org. phase was washed with 1M aq. Na₂CO₃ and brine, the aq. phase extracted with AcOEt. The org. phases were dried over MgSO4 and evaporated to give an oil which crystallised in iPr2O or Et2O. L-1d was collected in several crops (32.0 g, 74%) as colourless crystals. Mp=108-9°C (lit.: 91-9°C ^{16,34a}, 106-107°C ^{34b}, 109-110°C ³³, 102-6°C ^{34c}). [α]²⁰D=+7.0 (c=3, MeOH) (lit.: +8.3 (c=3, MeOH)^{34a,c}). ¹H-NMR (CDCl₃): 1.48 (s, 3Me), 2.16-2.48 (m, 2H-3, 2H-4), 4.12 (t, J=8.3, H-5), 5.74 (s, NH). ¹³C-NMR (CDCl₃): 177.9 (C-2), 171.1 (CO₂), 82.2 (CMe₃), 56.2 (C-5), 29.3 (C-3), 27.9 (CMe₃), 24.8 (C-4). Anal. calc. for C9H₁₅NO₃ (185.22): C 58.36, H 8.16, N 7.56; found: C 58.7, H 8.2, N 7.8.

t-Butyl (±)-pyroglutamate (±)-1d : same procedure as for L-1d with (±)-1g (5.0 g, 39 mmol), AcOtBu (50 ml), aq. HClO4 (2.9 ml) to give (±)-1d (4.7 g, 65%). Mp=93°C (lit.: $93^{\circ}C^{35}$).

Cholesteryl (-)-L-pyroglutamate L-le: a soln. of L-1g (1.0 g, 7.75 mmol), cholesterol (3.0 g, 7.77 mmol, leq.) and pTsOH (60 mg) in toluene (10 ml) was refluxed with a Dean-Stark trap overnight. The solvent was evaporated and L-le crystallised in AcOEt as colourless crystals (2.9 g, 75%). Mp=201°C (toluene). $[\alpha]^{20}D=-6$ (c=1, MeOH). IR (KBr): 3240, 2930, 2860, 1735, 1690, 1460, 1380, 1270, 1195. ¹H-NMR (CDCl₃): 6.10 (s, NH), 5.39 (d, J=3, H-6 chol.), 4.68 (m, H-3 chol.), 4.22 (dd, J=4, 6, H-5), 2.56-0.85 (28H chol., 2H-3, 2H-4), 1.02 (s, Me-19 chol.), 0.91 (d, J=7, Me-21 chol.), 0.86 (d, J=7, Me-26, Me-27 chol.), 0.66 (s, Me-18 chol.). Anal. calc. for C_{32H51}NO₃ (497.74): C 77.21, H 10.33, N 2.82; found: C 77.3, H 10.5, N 2.8.

Pentachlorophenyl (+)-*L*-*pyroglutamate L*-*If* : prepared according to lit.¹⁸, 55%. Mp=204-8°C (EtOH) (lit. : 196-199°C (EtOH)¹⁸); [α]¹⁸D=+19 (c=1, DMF), [α]D=+26 (c=1, EtOH) (lit.: [α]²⁶D=+21 (c=2, DMF)¹⁸). ¹H-NMR (CDCl₃): 2.40-2.75 (m, 2H-3, 2H-4), 4.62 (dd, *J*=4, 8, H-5), 6.39 (s, NH).

(+)-N-t-*Butyl-L-pyroglutamide* L-5a : to a solution of L-1f (1.02 g, 2.7 mmol) in pyridine (5 ml) was added *t*butylamine (0.42 ml, 4.0 mmol, 1.5 eq.). After 6h at r.t., the soln. was kept at 0°C and the precipitated salt (2 ArOH, NH2tBu, pyridine) filtered off and washed with pyridine. The soln. was evaporated and the residue crystallised in AcOEt to give L-5a (0.27 g, 68%). FC (AcOEt/EtOH, 10:1) of the mother liquors gave a second crop (11%). L-5a: colourless crystals, Mp=153-4°C (AcOEt). [α]¹⁸D=+26 (c=1, EtOH). IR (KBr): 3370, 3230, 2960, 1665, 1635, 1540, 1435, 1292, 1243, 1220. ¹H-NMR (CDCl3): 1.36 (s, 3Me), 2.10-2.60 (m, 2H-3, 2H-4), 4.04 (dd, *J*=5.6, 8.6, H-5), 5.84, 6.39 (2s, 2NH). Anal. calc. for C9H₁₆N₂O₂ (184.24): C 58.67, H 8.75, N 15.21; found: C 58.6, H 8.7, N 15.2.

(+)-*N*-phenyl-*L*-pyroglutamide *L*-5*b* : prepared according to lit.¹⁷, 51%, Mp=194°C (MeOH) (lit.: Mp=189-191°C¹⁷). ¹H-NMR (CD₃OD): 2.15-2.60 (m, 2H-3, 2H-4), 4.33 (dd, *J*=5, 8.5, H-5), 7.11 (t, *J*=7, Hp arom.), 7.31 (t, *J*=7, 2Hm arom.), 7.57 (d, *J*=7, 2Ho arom.).

N-Dienyl-L-Pyroglutamic Esters L-2a-h.

These dienes were prepared according to *method* A or to *method* B but were too oxidable to be isolated analytically pure:

Method A: procedure as described in lit.^{13,36} with some modifications. A solution of L-1 (0.1 mol), pTsOH (30 mg) and the enal (1-2 eq.) in dry toluene (100 ml) was refluxed with a Dean-Stark trap. The reaction was followed by ¹H-NMR, TLC (Et₂O) or according to the amount of trapped water. Ether (50 ml) was added and

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the soln. washed with aq. N NaHCO3 (5 ml), H₂O (3x10 ml) and/or brine; the aq. soln. was again extracted with Et₂O and the combined org. phases were dried over MgSO4 and evaporated to give the crude product, which was purified in most instances by FC (Et₂O).

Method B: a soln. of L-1 (30 mmol), pTsOH (75 mg) and the enal (1-5 eq.) in dry toluene (30 ml) with 4Å molecular sieves (5 g) was heated at 100°C. After 6-8 h., the soln. was filtered off and treated as above.

Methyl (5'S)-N-[1,3-butadienyl]-2'-oxo-pyrrolidine-5'-carboxylate L-2a: method A with L-1a (13,2 g, 92 mmol), pTsOH (30 mg) and crotonaldehyde (7.5 ml, 92 mmol, 1 eq. and 7.5 ml, 1eq. after 4 h) in toluene (100 ml) for 14 h led to the crude product (22,2 g) and gave pure L-2a after distillation (9.59 g, 53 %) or by FC (Et2O, yield 60 %) as a yellowish oil. Bp0,16 = 110°C. IR (film) : 2960, 1745, 1710, 1645, 1430, 1380, 1335, 1290, 1205, 995. ¹H-NMR (CDCl₃): 7.06 (d, H-1), 6.31 (dt, H-3), 5.52 (dd, H-2), 5.13 (dd, Ha-4), 5.00 (dd, Hb-4), 4.44 (dd, J=2.0, 8.8, H-5'), 3.79 (s, OMe), 2.70-2.10 (m, 2H-3', 2H-4') ; $J_{1,2}$ =14.4, $J_{1,3}$ = $J_{1,4a}$ = $J_{1,4b}$ =0.7, $J_{2,3}$ =10.3, $J_{2,4a}$ = $J_{2,4b}$ =0.7, $J_{3,4a}$ =16.9, $J_{3,4b}$ =10.2, $J_{4a,4b}$ =1.5. ¹³C-NMR (CDCl₃) : 172.9 (C-2'), 171.3(CO₂), 134.2 (C-3), 125.4 (C-1), 114.9 (C-4), 112.8 (C-2), 57.9 (C-5), 52.3 (OMe), 29.2 (C-3'), 22.6 (C-4'). HRMS calc. for C10H13NO3: 195.08954; found: 195.0885. MS, m/z (%) : 195, M⁺⁺ (44), 136 (100), 108 (17), 84 (14), 80 (23), 53 (15).

iso-*Propyl* (5'S)-N-[1,3-butadienyl]-2'-oxo-pyrrolidine-5'-carboxylate L-2c: method A with L-1c (0,99 g, 5.8 mmol) pTsOH (3 mg) and crotonaldehyde (0.5 ml, 6.1 mmol, 1 eq. and 0.25 ml, 0.5 eq after 1 h) in toluene (10 ml) for 2.5 h, to give L-2c (0,566 g, 44 %) as yellowish oily crystals. $[\alpha]D^{20}=-146$ (c=3.6, CHCl₃). IR(CHCl₃) = 1734, 1703, 1649, 1430, 1386, 1299, 1148, 1104. ¹H-NMR (CDCl₃): 7.05 (d, H-1), 6.30 (dt, H-3), 5.53 (dd, H-2), 5.10 (d, Ha-4), 5.09 (sept., *CHMe*₂), 4.99 (d, Hb-4), 4.38 (m, H-5'), 2.74-2.30 and 2.14 (2m, 2H-3', 2H-4'), 1.27, 1.24 (2d,2Me); *J*CH,Me₂=6.3, *J*1,2=14.5, *J*1,3=*J*1,4a=*J*1,4b=0.7, *J*2,3=10.5, *J*2,4a=*J*2,4b=0.7, *J*3,4a=16.9, *J*3,4b=10.2, *J*4a,4b=1.5. ¹³C-NMR (CDCl₃): 173.2 (C-2'), 170.8 (CO2), 134.6 (C-3), 125.8 (C-1), 115.2 (C-4), 113.3 (C-2), 69.6 (CHMe₂), 58.7 (C-5'), 29.7 (C-3'), 22.8 (C-4'), 21.7, 21.6 (2Me). Anal. calc. for C₁₂H₁₇NO₃ (223.26): N 6.27; found: N 6.0.

tert-*Butyl* (5'S)-N-[1,3-butadienyl]-2'-oxo-pyrrolidine-5'-carboxylate L-2d: method B with L-1d (10.0 g, 54 mmol), crotonaldehyde (8.8 ml, 0.1 mol, 2 eq. and 13.2 ml, 3 eq. after 2 h), pTsOH (0.2 g), molecular sieves (10 g) in toluene (55 ml) for 8 h to give unreacted L-1d (4.7 g, 47 %) and L-2d (5.2 g, 41 %) as yellowish crystals, mp=72-3°C (iPr2O), $[\alpha]^{24}D=-161$ (c=1, CHCl3). IR (KBr) : 2975, 1728, 1700, 1640, 1420, 1380, 1287, 1145, 1010, 892. ¹H-NMR (CDCl3): 7.05 (d, H-1), 6.32 (dt, H-3), 5.56 (dd, H-2), 5.10 (d, Ha-4), 4.98 (d, Hb-4), 4.28 (dd, J=9.2, 2.2, H-5'), 2.62, 2.49, 2.37, 2.12 (4m, 2H-3', 2H-4'), 1.46 (s, 3Me); $J_{1,2}=14.6, J_{1,3}=0.5, J_{1,4}=J_{1,4}=0.7, J_{2,3}=10.6, J_{2,4}=J_{2,4}b=0.7, J_{3,4}=17.0, J_{3,4}b=10.2, J_{4a,4}b=1.5.$ ¹³C-NMR (CDCl3): 173.0 (C-2'), 170.2 (CO2), 134.4 (C-3), 125.5 (C-1), 114.7 (C-4), 113.0 (C-2), 82.3 (CMe3), 59.0 (C-5'), 29.4 (C-3'), 27.6 (CMe3), 22.4 (C-4'). Anal. calc. for C1₃H1₉NO₃, (237.30) = C 65.8, H 8.07, N 5.90 ; found : C 65.1, H 8.1, N 5.8. HRMS calc. for C1₃H1₉NO₃: 237.13648; found: 237.1355. MS, m/z (%) : 237, M*+ (19), 181 (37), 136 (100), 108 (7), 80 (10).

Racemate (\pm) -2d: prepared according to the same procedure starting from (\pm) -1d.

Cholesteryl (5'S)-N-[1,3-butadienyl]-2'-oxo-pyrrolidine-5'-carboxylate L-2e: method B with L-1e (0.25 g, 0.5 mmol), crotonaldehyde (0.08 ml, 1 mmol, 2 eq.), pTsOH (2 mg) in toluene (2 ml) overnight, to give L-1e (70 mg, 28%) and L-2e as yellow crystals (0.157 g, 57%). Mp=151°C (toluene/iPr2O). [α]²⁰D=-93 (c=1, CHCl3). IR (KBr): 2940, 2860, 1740, 1710, 1648, 1622, 1464, 1379, 1280, 1190. ¹H-NMR (CDCl3): 7.05 (d, H-1); 6.31 (dt, H-3); 5.54 (dd, H-2); 5.37 (s, H-6 chol.); 5.10 (d, Ha-4); 4.99 (d, Hb-4); 4.70 (m, H-3 chol.); 4.38 (d, J=6, H-5'); 2.7-1.0 (m, 18H chol., 2H-3', 2H-4'), 1.02 (s, Me-19 chol.); 0.91 (d, J=7, Me-21 chol.); 0.87 (d, J=7, Me-26, Me-27 chol.); 0.68 (s, Me-18 chol.); J_{1,2}=14.5, J_{2,3}=10.4, J_{3,4a}=16.8, J_{3,4b}=10.2. ¹³C-NMR (CDCl₃): 173.2, 170.7, 139.0, 134.6, 125.8, 123.2, 115.3, 113.3, 75.6, 60.4, 58.7, 56.7, 56.2, 50.0, 42.3, 39.7, 39.5, 37.8, 36.9, 36.6, 36.2, 35.8, 31.9, 31.8, 29.7, 28.2, 28.0, 27.6, 24.3, 23.8, 22.9, 22.8, 22.6, 21.0, 19.3, 18.7, 11.9. Anal. calc. for C₃₆H₅₅NO₃ (549.81): N 2.55 ; found: N 2.76.

Methyl (5'S)-N-[1,3-pentadienyl]-2'-oxo-pyrrolidine-5'-carboxylate L-2f: method A with L-1a (1.7 g, 12 mmol), pTsOH (6 mg), pent-2-enal (1.0 g, 12 mmol, leq.) in toluene (18 ml), to give L-2f (2.0 g, 80%) as yellow crystals (mp=36-39°C and 50-57°C), mixture of (E,E) and (E,Z) isomers (70:30). $[\alpha]^{22}D=-116$ (c=1, CHCl3). IR (CCl4): 2990, 2950, 1740, 1700, 1690, 1650, 1622, 1390, 1280, 1230, 975. ¹H-NMR (CDCl3): (E,E) isomer: 6.93 (d, H-1), 5.98 (m, H-3), 5.60 (m, H-4), 5.48 (m, H-2), 4.42 (m, H-5'), 3.77 (s, OMe), 2.8-2.1 (m, 2H-3', 2H-4'), 1.74 (dd, Me-4); J_{1,2}=14.5, J_{1,4}=J_{2,4}=0.7, J_{2,3}=10.2, J_{3,4}=15.1, J_{3,Me}=1.6, J_{4,Me}=6.7; (E,Z) isomer: 7.02 (d, H-1), 5.98 (m, H-3), 5.74 (m, H-2), 5.45 (m, H-4), 4.48 (m, H-5'), 3.79 (s, OMe), 2.8-2.1 (m, 2H-3', 2H-4'), 1.69 (dd, Me-4); J_{1,2}=14.3, J_{1,4}=0.8, J_{2,3}=10.8, J_{2,4}=1.0, J_{3,4}=10.6, J_{3,Me}=1.7, J_{4,Me}=7.1. HRMS calc. for C1₁H₁₅NO₃ : 209.10519 ; found : 209.1054. MS, m/z (%) : 209, M⁺⁺ (44), 154(2), 150(100), 122(14), 94(15), 84(24), 67(37).

tert-*Butyl* (5'S)-N-[1,3-pentadienyl]-2'-oxo-pyrrolidine-5'-carboxylate L-2g: method B with L-1d (5.0 g, 27 mmol), pent-2-enal (2.35 ml, 24 mmol), pTsOH (75 mg) in toluene (30 ml) with molecular sieves (3.6 g), for 6 h, to give L-1d (2.44 g, 48%) and L-2g (2.47 g, 41%) as a yellow resin, mixture of (E,E) and (E,Z) isomers (55:45). $[\alpha]^{20}D^{=}-136$ (c=1.2, CHCl3). IR (CHCl3): 3007, 2984, 1738, 1698, 1651, 1395, 1370, 1283, 1150. ¹H-NMR (CDCl3): (E,E) isomer: 6.92 (d, H-1), 6.00 (m, H-3), 5.57 (m, H-4), 5.52 (m, H-2), 4.26 (dd, J=9.1, 2.2, H-5'), 2.7-2.0 (2H-3, 2H-4), 1.74 (dd, Me-4), 1.46 (s, 3Me); $J_{1,2}=14.4, J_{1,3}=J_{1,4}=0.6, J_{2,3}=10.4, J_{2,4}=1.0, J_{3,4}=15.0, J_{4,Me}=6.7; (E,Z) isomer: 7.01 (d, H-1), 6.00 (m, H-3), 5.79 (dd, H-2), 5.43 (m, H-4), 4.32 (dd, <math>J=9.1, 2.2, H-5'$), 2.7-2.0 (m, 2H-3, 2H-4), 1.70 (dd, Me-4), 1.46 (s, 3Me); $J_{1,2}=14.1, J_{1,3}=J_{1,4}=0.8, J_{2,3}=10.8, J_{2,4}=0.7, J_{3,4}=10.8, J_{4,Me}=7.1. ¹³C-NMR: (E,E) isomer: 172.8 (C-2'), 170.4 (CO₂), 128.7 (C-3), 127.1 (C-4), 123.0 (C-1), 112.9 (C-2), 82.2 (CMe3), 59.2 (C-5'), 29.6 (C-3'), 27.6 (CMe₃), 22.4 (C-4'), 13.0 (Me-4); (E,Z) isomer: 172.9 (C-2'), 170.4 (CO₂), 126.6 (C-3), 124.7 (C-1), 124.1 (C-4), 108.0 (C-2), 82.3 (CMe₃), 59.2 (C-5'), 29.6 (C-3'), 27.6 (CMe₃), 22.4 (C-4'), 13.0 (Me-4); Forduct too unstable for analysis.$

tert-Butyl (5'S)-N-[1,3-hexadienyl]-2'-oxo-pyrrolidine-5'-carboxylate, L-2h: method B with L-1d (5.0 g, 27 mmol), hex-2-enal (3.2 ml, 27 mmol, 1 eq), pTsOH (83 mg) in toluene (30 ml) with molecular sieves (5 g), for 6 h, to give L-1d (2.92 g, 58 %) and L-2h (1.09, 15 %) as a yellow resin, mixture of (E,E), (E,Z) isomers (55:45). $[\alpha]_D^{20}$ =-146 (c=1.2, CHCl₃). IR (CHCl₃): 2980, 1738, 1702, 1625, 1402, 1370, 1150. ¹H-NMR : (E,E) isomer : 6.93 (d, H-1), 5.91 (m, H-3), 5.60 (m, H-4), 5.52 (m, H-2), 4.25 (m, H-5'), 2.7-2.0 (m, 2H-

3', 2H-4'), 2.10 (q, CH2), 1.45 (s, 3Me), 0.95 (t, Me); $J_{1,2}=14.4$, $J_{1,3}=J_{1,4}=0.6$, $J_{2,3}=10.4$, $J_{2,4}=0.6$, $J_{3,4}=15.2$, $J_{4,CH2}=6.6$, $J_{CH2,Me}=7.4$. (E,Z) isomer : 7.01 (d, H-1), 6.01 (m, H-3), 5.77 (m, H-2), 5.35 (m, H-4), 4.30 (m, H-5'), 2.7-2.0 (m, 2H-3', 2H-4'), 2.10 (q, CH2), 1.45 (s, 3Me), 0.95 (t, Me); $J_{1,2}=14.0$, $J_{1,3}=J_{1,4}=0.7$, $J_{2,3}=10.8$, $J_{2,4}=0.8$, $J_{3,4}=10.5$, $J_{4,CH2}=7.4$, $J_{CH2,Me}=7.4$.

¹³C-NMR : (E,E) isomer : 172.8 (C-2), 170.4 (CO2), 134.3 (C-3), 126.5 (C-4), 123.2 (C-1), 113.0 (C-2),
82.3 (C Me3), 59.2 (C-5'), 29.6 (C-3'), 27.7 (CMe3), 25.5 (CH2), 22.5 (C-4'), 13.4 (Me). (E,Z) isomer :
172.9 (C-2), 170.4 (CO2), 131.9 (C-3), 125.1 (C-4), 124.9 (C-1), 108.2 (C-2), 82.3 (CMe3), 59.3 (C-5'),
29.6 (C-3'), 27.7 (CMe3), 20.8 (CH2), 22.4 (C-4'), 14.0 (Me). Product too unstable for analysis.

Diels-Alder cycloadducts

General procedure. - To a soln. of dienyl lactame L-2 (10 mmol) in CH₂Cl₂ (with *ca* 50 beads of molecular sieves 4Å), in MeOH or in CH₂Cl₂/MeOH (10-20 ml) at 0°C was added ammonium periodate (nPr4NIO4^{14b} in CH₂Cl₂ or Me₃BnNIO4^{14c} in MeOH) (4 mmol) and hydroxamic acid 3 (generally 12 mmol, 1.2 eq.) portionwise over 1 h. 1-2 h after addition, the diene had disappeared and the soln. was diluted with Et₂O or AcOEt (50 ml) washed with aq. N Na₂CO₃ (containing enough Na₂SO₃ to reduce I₂), H₂O (2x10 ml) and brine. The aq. phase was reextracted and the combined org. phases were dried over MgSO₄ and evaporated to give crude adducts **6a-h**, **7a-h**, which were separated by FC (AcOEt in most cases).

For systematic studies of the influence of temperatur, solvent and hydroxamic acid, dienyl lactame L-2 (1 mmol), nPr4IO4 (0.15 g, 0.4 mmol) and hydroxamic acid 3 (1.2 mmol), were dissolved in the appropriate solvent (2 ml) at a given temperature. After work-up the relative amount of diastereoisomers were determined by 13 C-NMR, directly on the crude mixtures.

(6S)-6-[(5'S)-5'(methoxycarbonyl)-2'-oxo-pyrrolidin-1'-yl]-N,N-dimethyl-3,6-dihydro-2H-1,2-oxazine-2carboxamide **6a** and its (6R)-isomer 7a: to a soln. of L-2a (3.0 g, 15.5 mmol) and nPr4NIO4 (1.93 g, 5.1 mmol) in CH₂Cl₂ (10 ml) containing some beads of mol. sieves was added at 0°C dropwise a soln. of **3a** (1.63 g, 15.7 mmol, 1 eq.) in CH₂Cl₂ (10 ml) and MeOH (2 ml) for 1h. After 1 h and 2 h were added nPr4NIO4 (1.78 g, 4.7 mmol and 1.0 g, 2.7 mmol) and **3a** (0.92 g, 8.8 mmol and 0.77 g, 7.4 mmol) at 0°C. After work-up the crude mixture (4.2 g, 91 %) was separated by FC (AcOEt) to give **6a** (2.8 g, 61 %) and **7a** (0.24 g, 5%) **6a** : colourless crystals, mp : 143°C (AcOEt/Et₂O). $[\alpha]_D^{20}$ =-44° (c=5, CHCl₃). IR(KBr) : 3560, 3490, 2960, 2850, 1745, 1705, 1670, 1650, 1405, 1210. ¹H-NMR: *table 3*. ¹³C-NMR: *table 4*. Anal. calc. for C₁₃H₁₉N₃O₅ (297.31) : C 52.51, H 6.44, N 14.13 ; found : C 52.8, H 6.4, N 14.2.

7a brown oil. IR(film) : 3480, 2960, 1745, 1710, 1670, 1650, 1400. ¹H-NMR: *table 3*. ¹³C-NMR: *table 4*. MS, m/z (%) : 297 M^{•+} (2), 195(12), 136(37), 84(14), 72(100), HRMS, calc. for C₁₃H₁₉N₃O₅ : 297.13246 ; found : 297.1322.

Methyl (6S)-6-[(5'S)-5'-(methoxycarbonyl)-2'-oxo-pyrrolidin-1'-yl]-3,6-dihydro-2H-1,2-oxazine-2-carboxylate **6b** and its (6R)-isomer **7b**: general procedure with L-2a (0.10 g, 0.53 mmol), nPr4NIO4 (0.106 g, 0.28 mmol) and **3b** (63 mg, 0.7 mmol, 1.3 eq) in CH₂Cl₂ (1 ml) for 3 h at 0°C, to give a crude mixture (94 mg, 63 %). The adduct was unstable and quickly separated by TLC (AcOEt/EtOH, 9:1) to give **6b** (33 mg, 22 %) and **7b** (12 mg, 8 %).

6b: colourless resin. IR (film): 3480, 2955, 1747, 1715, 1700, 1650, 1445, 1395, 1210. ¹H-NMR: Table

3.13C-NMR: Table 4.

7b: colourless resin. ¹H-NMR: ca. 6.10 (m, H-4), 6.04 (m, H-6), 5.80 (d, *J*=10, H-5), 4.38 (d, *J*=9, H-5'), ca. 4.10 (m, 2H-3), 3.72, 3.80 (2s, 2OMe), 2.8-2.1 (m, other H). ¹³C-NMR: *Table 4*.

Benzyl (6S)-6-[(5'S)-5'(methoxycarbonyl)-2'-oxo-pyrrolidin-1'-yl]-3,6-dihydro-2H-1,2-oxazine-2-carboxylate 6c and its (6R) isomer 7c: general procedure with L-2a (3.0 g, 15.4 mmol), nPr4NIO4 (2.21 g, 5.9 mmol) in CH₂Cl₂ (15 ml) and hydroxamic acid 3c (4.0 g, 24 mmol, 1.5 eq.) in soln. in CH₂Cl₂ (25 ml). Crude mixture (6.4 g) was separated by FC to give 6c (2.74 g, 50 %) and 7c (1.36 g, 25 %).

6c: yellow resin, [α]D²⁰=-127° (c=0.8, CHCl₃). IR (CCl₄): 2960, 1745, 1715, 1655, 1435, 1395, 1225, 1205, 1175, 905 ¹H-NMR: *Table 3*. ¹³C-NMR : *Table 4*. MS, m/z (%) : 360 (2), 195 (22), 136 (28), 91 (100), 84 (21). HRMS, calc. for C₁₈H₂₀N₂O₆ : 360.1321 ; found : 360.1316.

7c: orange resin, [α]D²⁰=+40 (c=1, CHCl₃). IR (CCl₄): 1740, 1715, 1400, 1210, 910. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*. MS, m/z (%) : 360 (4), 307 (6), 209 (6), 195 (44), 149 (20), 136 (47), 91 (100), 84 (31). HRMS, calc. for C₁₈H₂₀N₂O₆: 360.1321; found: 360.1320.

(6S)-2-benzoyl-6-[(5'S)-5'-(methoxycarbonyl)-2'-oxo-pyrrolidin-1'-yl]-3,6-dihydro-2H-1,2-oxazine 6d and its (6R)-isomer 7d: general procedure with L-2a (0.25 g, 1.26 mmol), nPr4NIO4 (0.29 g, 0.75 mmol) and 3d (0.28 g, 2.0 mmol, 1.6 eq.) in CH₂Cl₂ (2 ml). Crude mixture (0.414 g) was separated by FC (AcOEt/EtOH, 9:1) to give 6d (0.21 g, 51 %, Rf = 0.35) and 7d (83 mg, 19%, Rf : 0.25).

6d: colourless crystals. Mp=126-7°C (AcOEt/Et₂O). [α]_D²⁰=-241 (c=1, CHCl₃). IR (KBr): 3560, 3500, 1750, 1720, 1700, 1615, 1570, 1450, 1400, 1240, 1215, 1185. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*. Anal. calc. for C₁₇H₁₈N₂O₅: C 61.81, H 5.49, N 8.48; found: C 61.7, H 5.5, N 8.6.

7d: colourless crystals. Mp=132°C (AcOEt/Et2O). [α]D²⁰=+28.0 (c=1, CHCl3). IR (KBr): 1740, 1710, 1650, 1405, 1390, 1375, 1250, 1220. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*. Anal. calc. for C17H18N2O5: C 61.81, H 5.48, N 8.48; found: C 62.0, H 5.5, N 8.6.

2-(Trimethylsilyl)ethyl(6S)-6-[(5'S)-5'-(methoxycarbonyl)-2'-oxo-pyrrolidin-1'-yl]-3,6-dihydro-2H-1,2-

oxazine-2-carboxylate **6e** and its (6R)-isomer **7e**: general procedure with L-2a (0.226 g, 1.16 mmol), nPr4NIO4 (0.26 g, 0.68 mmol), **3e** (0.25 g, 1.4 mmol, 1.2 eq.) in CH₂Cl₂ (2 ml). Crude mixture (0.40 g, 95 %). A separation on 0.1 g by TLC (AcOEt/cyclohexane, 9:1) gave **6e** (56 mg, 53 %, Rf = 0.42) and **7e** (24 mg, 23 %, Rf = 0.32).

6e: colourless resin. IR (film): 2980, 1740, 1720, 1710, 1655, 1400, 1250, 1210, 1180, 860, 835. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*. MS, m/z (%): 342 (14), 268 (12), 209 (9), 195 (46), 136 (38), 73 (100). HR MS, calc. for C₁₄H₂₂N₂O₆Si (M⁺- 2CH₂): 342.1247; found: 342.1239.

7e: colourless resin. IR (film): 2950, 1740, 1725, 1700, 1660, 1400, 1330, 1280, 1245, 1205, 1175, 865, 835. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*. MS, m/z (%): 342 (8), 268 (8), 209 (8), 195 (28), 172 (10), 136 (42), 73 (100). HRMS, calc. for C14H22N2O6Si (M*+ 2 CH2): 342.1247; found: 342.1273.

(6S)-2-Acetyl-6-[(5'S)-5'-(methoxycarbonyl)-2'-oxo-pyrrolidin-1'-yl]-3,6-dihydro-2H-1,2-oxazine 6f and its (6R)-isomer 7f: general procedure with L-2a (0.14 g, 0.72 mmol), nPr4IO4 (0.16 g, 0.42 mmol) and 3f (0.195 g, 2.6 mmol, 3.6 eq.) in CH₂Cl₂ (1 ml). The crude 6f + 7f mixture (0.12 g, 62 %) was a yellow resin

and could not be separated. ¹H-NMR of the mixture: 6.25-6.10 (m, H-6, H-4 of **6f+7f**), 5.70 (m, H-5 of **6f+7f**), 4.40-4.05 (m, H-5', 2H-3 of **6f+7f**), 3.76 (s, OMe of **6f**), 3.70 (s, OMe of **7f**), 2.9-2.0 (m, 2H-3', 2H-4' of **6f+7f**), 2.13 (s, Me of **7f**), 2.12 (s, Me of **6f**). ¹³C-NMR of **6f**, **7f**: *Table 4*.

(6S)-6-[(5'S)-5'-(methoxycarbonyl)-2'-oxo-pyrrolidin-1'-yl]-2-phenylacetyl-3,6-dihydro-2H-1,2-oxazine 6g and its (6R)-isomer 7g: general procedure with L-2a (0.23 g, 1.2 mmol), nPr4NIO4 (0.256 g, 0.68 mmol) and 3g (0.38 g, 2.5 mmol, 2.1 eq.) in CH₂Cl₂ (2 ml) for 5 h. The crude mixture (0.4 g, 98%) was separated by FC (AcOEt/cyclohexane, 9:1) to give 6g (0.136 g, 33%, Rf=0.38) and 7g (0.1 g, 24%, Rf=0.25).

6g: colourless resin. IR (film): 2950, 1740, 1715, 1670, 1650, 1430, 1390, 1275, 1205, 1015, 725. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*. MS, m/z (%): 344, M+ (19), 210 (11), 196 (40), 195 (52), 144 (15), 136 (62), 91(100), 84 (22). HRMS, calc. for C18H20N2O5: 344.1372; found: 344.1385.

7g: colourless resin. IR (film): 2975, 1740, 1710, 1670, 1650, 1430, 1395, 1280, 1205, 1175, 1015, 725, 695. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*. MS, m/z (%): 344, M-+ (10), 210 (15), 209 (11), 196 (58), 195 (60), 144 (15), 136 (76), 91 (100), 84 (26), 83 (25). HRMS, calc. for C₁₈H₂₀N₂O₅: 344.1372; found: 344.1385.

(6S)-6-[(5'S)-5'-(Methoxycarbonyl)-2'-oxo-pyrrolidin-1'-yl]-3,6-dihydro-2H-1,2-oxazine-2-carboxamide **6h** and its (6R)-isomer 7h: general procedure with L-2a (0.116 g, 0.59 mmol), nPr4NIO4 (0.105 g, 0.28 mmol) and 3h (0.104 g, 1.37 mmol, 2.3 eq.) in CH₂Cl₂ (0.6 ml) and MeOH (0.2 ml) for 16 h. The adducts were extracted with AcOEt/acetone (1:1). The crude mixture (0.169 g, quant.) was separated by FC (AcOEt/EtOH, 8:2) to give 6h (45 mg, 28 %, Rf=0.35), and 7h (82 mg, 92 %, Rf=0.28).

6h: colourless crystals. Mp=147°C (AcOEt). [α]D²⁰=-107 (c=1, CHCl₃). IR (KBr): 3430, 3310, 1750, 1725, 1678, 1655, 1430, 1398, 1210, 1025. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*. Anal. calc. for C₁₁H₁₅N₃O₅: C 49.07, H 5.62, N 15.61; found: C 49.0, H 5.6, N 15.6.

7h: colourless crystals. Mp=140°C (AcOEt). [α]D²⁰=+22 (c=1, CHCl₃). IR (KBr): 3500, 3330, 1750, 1700, 1665, 1575, 1405, 1230, 1210, 1200, 1180, 1025. ¹H-NMR:*Table 3*. ¹³C-NMR: *Table 4*. Anal. calc. for C₁₁H₁₅N₃O₅: C 49.07, H 5.62, N 15.61; found: C 49.1, H 5.6, N 15.6.

Benzyl (6S)-6-[(5'S)-5'-(isopropyloxycarbonyl)-2'-oxo-pyrrolidin-1'-yl]-3,6-dihydro-2H-1,2-oxazine-2carboxylate **6i** and its (6R)-isomer 7i: general procedure with L-2c (0.15 g, 0.67 mmol), nPr4NIO4 (0.085 g, 0.22 mmol) and 3c (0.112 g, 0.67 mmol, 1 eq.) in CH₂Cl₂ (1.4 ml) for 1.5 h. The crude mixture (0.245 g, 95%) was separated by FC (AcOEt) to give **6i** and **7i**.

6i: colourless resin. [α]_D²⁰=-103 (c=0.7, CHCl₃). IR (CHCl₃): 1734, 1705, 1181, 1145, 1105. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*.

7i: obtained impur and only caracterised by NMR. ¹H-NMR: some data : 6.09 (m, H-4) ; 5.91 (s, H-6) ; 5.83 (dq, J=10.2, 2.2, H-5) ; 4.08 (m, 2H-3). ¹³C-NMR: *Table 4*.

Benzyl (6S)-6-[(5'S)-5'-(tert-butyloxycarbonyl)-2'-oxo-pyrrolidin-1'-yl]-3,6-dihydro-2H-1,2-oxazine-2carboxylate **6j** and its (6R)-isomer **7j**: general procedure with L-2d (3.78 g, 15.8 mmol), BnMe₃NIO₄ (2.17 g, 6.3 mmol) and **3c** (3.17 g, 19 mmol, 1.2 eq.) in CH₂Cl₂ (11 ml) and MeOH (11 ml). The crude mixture (7.13 g, quant.) was separated by FC (AcOEt/Et₂O, 2:8) to give **6j** (5.17 g, 81%, Rf(Et₂O)=0.34) and **7j** (0.78 g, 12%, Rf(Et₂O)=0.16).

6j: colourless resin. [α]D²⁰=-118 (c=2.8, CHCl3). IR (CHCl3): 2980, 1720, 1700, 1400, 1370, 1150, 1100, 1025. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*. MS, m/z (%): 402, M·+ (2), 285 (2), 181 (31), 136 (16), 91 (100), 84 (50), 57 (44). HRMS, calc. for C₂₁H₂₆N₂O₆: 402.17907; found: 402.1809.

7j: colourless resin. $[\alpha]_D^{20}$ =+4 (c=0.8, CHCl₃). IR (CHCl₃): 2980, 1730, 1710, 1410, 1370, 1150. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*. MS, m/z (%): 402, M+ (2), 237 (3), 220 (4), 195 (3), 181 (22), 136 (14), 91 (100), 84 (48), 57 (37). HRMS, calc. for C₂₁H₂₆N₂O₆: 402.17907; found: 402.1809.

Benzyl (6S)-6-[(5'S)-5'-(cholesteryloxycarbonyl)-2'-oxo-pyrrolidin-1'-yl]-3,6-dihydro-2H-1,2-oxazine-2carboxylate 6k and its (6R)-isomer 7k: general procedure with L-2e (80 mg, 0.15 mmol), nPr4NIO4 (22 mg, 0.06 mmol) and 3c (30 mg, 0.18 mmol) in CH₂Cl₂ (1 ml). The crude mixture was separated by FC (AcOEt) to give 6k (60 mg, 58%) and 7k (10 mg, 10%).

6k: colourless resin. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*; cholesteryl and benzyl moieties: 139.0, 135.9, 128.6, 128.4, 128.3, 123.1, 75.3, 67.8, 56.7, 56.2, 50.0, 42.3, 39.7, 39.5, 37.8, 36.8, 36.6, 36.2, 35.8, 31.9, 31.8, 28.2, 28.0, 27.7, 24.3, 24.1, 22.8, 22.6, 21.0, 19.3, 18.7, 11.8. MS, m/z (%): (no molecular ion), 400 (3), 386 (cholesterol) (4), 384 (5), 382 (6), 368 (17), 366 (11), 174 (10), 161 (14), 145 (21), 135 (29), 107 (49), 95 (27), 91 (100), 79 (52).

7k: colourless resin, only caracterized by NMR. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*; cholesteryl and benzyl moieties: 139.3, 135.9, 128.5, 128.2, 128.0, 123.0, 75.3, 67.8, 56.7, 56.2, 50.0, 42.3, 39.7, 39.5, 37.7, 36.9, 36.6, 36.2, 35.8, 31.9, 31.9, 28.2, 28.0, 27.7, 24.3, 23.8, 22.8, 22.6, 21.0, 19.3, 18.7, 11.9.

Benzyl (35,65)-6c-[(5'S)-5'-(methoxycarbonyl)-2'-oxo-pyrrolidin-1'-yl]-3r-methyl-3,6-dihydro-2H-1,2oxazine-2-carboxylate **61** and its (3R,6R)-isomer **71**: general procedure with **L-2a** (5.02 g, 24 mmol), BnMe₃NIO₄ (3.30 g, 9.6 mmol) and **3c** (4.81 g, 29 mmol) in MeOH (32 ml). The crude mixture was separated by FC (AcOEt/cyclohexane, 8:2) to give **61** (4.3 g, 48%, Rf=0.71) and **71** (1.08 g, 12%, Rf=0.60). **61**: yellow resin. [α]D²⁹=-23 (c=2.3, CHCl₃). IR (film): 2980, 2960, 1740, 1720, 1710, 1405, 1282, 1205, 750. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*. MS, m/z (%): 374, M·+ (3), 239 (1), 223 (27), 209 (88), 150 (60), 91 (100), 84 (10), 67 (10). HRMS, calc. for C19H₂₂N₂O₆: 374.14777; found: 374.1478. **71**: yellow resin. [α]D²⁹=-62 (c=0.45, CHCl₃). IR (film): 2950, 1740, 1725, 1710, 1403, 1282, 1205, 750. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*. MS, m/z (%): 374, M·+ (5), 239 (3), 223 (19), 209 (100), 150 (59), 91 (100), 84 (13). HRMS, calc. for C19H₂₂N₂O₆: 374.14777; found: 374.1478.

Benzyl (3S,6S)-6c-[(5'S)-5'-(tert-butyloxycarbonyl)-2'-oxo-pyrrolidin-1'-yl]-3r-methyl-3,6-dihydro-2H-1,2oxazine-2-carboxylate **6m** and its (3R,6R)-isomer **7m**: general procedure with L-2g (2.15 g, 8.55 mmol), nPr4NIO4 (1.29 g, 3.4 mmol) and 3c (1.71 g, 10.3 mmol, 1.2 eq.) in CH₂Cl₂ (15 ml) and MeOH (5 ml). The crude mixture (3.9 g, quant.) was separated by FC (AcOEt) to give **6m** (2.32 g, 65%). **7m** is unstable and difficult to isolate.

6m: yellowish crystals. Mp=107°C (iPr₂O). [α]_D18=-15 (c=0.8, CHCl₃). IR (KBr): 2975, 2925, 1730, 1700, 1655, 1400, 1280, 1218, 1150, 1065, 1020, 734, 690. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*. Anal. calc. for C₂₂H₂₈N₂O₆ (416.16): C 63.44, H 6.78, N 6.73; found: C 63.6, H 6.9, N 6.7.

7m: yellow resin, only caracterized by NMR. ¹H-NMR: Table 3. ¹³C-NMR: Table 4.

Benzyl (3S,6S)-6c-[(5'S)-5'-(tert-butyloxycarbonyl)-2'-oxo-pyrrolidin-1'-yl]-3r-ethyl-3,6-dihydro-2H-1,2oxazine-2-carboxylate **6n** and its (3R,6R)-isomer **7n**: general procedure with L-2h (0.94 g, 3.5 mmol), nPr4NIO4 (0.59 g, 1.6 mmol) and **3c** (0.72 g, 4.3 mmol, 1.2 eq.) in CH₂Cl₂ (10 ml). The crude mixture (1.63 g, quant.) was separated by FC (Et₂O) to give **6n** (0.69 g, 45%). Isomer **7n** was too unstable and could not be isolated.

6n: colourless resin. [α]D¹⁸=-28 (c=1.3, CHCl₃). IR (CHCl₃): 2965, 1732, 1710, 1409, 1370, 1152, 1088. ¹H-NMR: *Table 3*. ¹³C-NMR: *Table 4*. MS, m/z (%): 430, M·+ (2), 313 (3), 279 (11), 265 (14), 223 (7), 209 (55), 164 (12), 91 (100), 84 (15). HRMS, calc. for C₂₃H₃₀N₂O₆: 430.21037; found: 430.2114.

7n: unstable, non isolated product. Caracterized by some signals in ¹H-NMR (CDCl₃): 6.21 (s, H-6); 6.12 (dm, J=10, H-4).

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