38. Approaches to the Synthesis of Cytochalasans. Part 4[1][2]. Improved Synthesis of the Tetrahydroisoindoline Subunits Related to the Cytochalasins and Aspochalasins

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Dedicated to Prof. Dr. *Edgar Lederer* on the occasion of his 75th birthday

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Summary

A general scheme for the synthesis of the tetrahydroisoindolinone moiety of naturally occurring cytochalasans and unnatural analogs was developed. The key-step consists of the *inter*molecular [2+4]cycloaddition of 4-methylsorbinol (**7**) to an alkylidene malonic ester derivative such as **6**, **9** or **10**, obtained from the corresponding amino acids. The products obtained, **4a**, **17**, and **18** were converted to the desired lactams **5**, **21**, and **22**.

Cycloaddition of the diene alcohol **7** to the optically active alkylidene malonic ester derivative **9b** (s. Footnote 5) prepared from L-leucine gave compound **17b** with 98% enantiomeric excess. The optical activity was retained during the conversion of **17b** to the lactam **21b**. The latter is a subunit for the synthesis of the aspochalasins.

In a recent paper describing a convenient synthetic approach to the tetrahydroisoindolinone nucleus of proxiphomin (**1**) (*cf. Scheme 1*) [1] we discussed the stereochemical course of an *intra*molecular [2+4]cycloaddition of the alkylidene 4-methylsorbyl esters **2a** and **2b** to the expected anellated cyclohexene intermediates **3a** and **3b**. These should yield the tricyclic species **4a** and **4b**, respectively, by subsequent lactam ring closure. Evidence was presented that the (*Z*)-olefin **2a** leads to a product of structure **4a** with correct relative configurations at C(3), C(4), C(5), and C(8), but with 'unnatural' configuration at C(9)[4]. Also an efficient procedure for the epimerization at C(9) leading to the tetrahydroisoindolinone **5** was described. However, the key intermediate **4a** was obtained only in low yield.

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[1]) Part 3: [1].

[2]) Presented by *T. Sch.* at the *Herbstversammlung der Schweizerischen Chemischen Gesellschaft* on 16th October 1981 in Bern.

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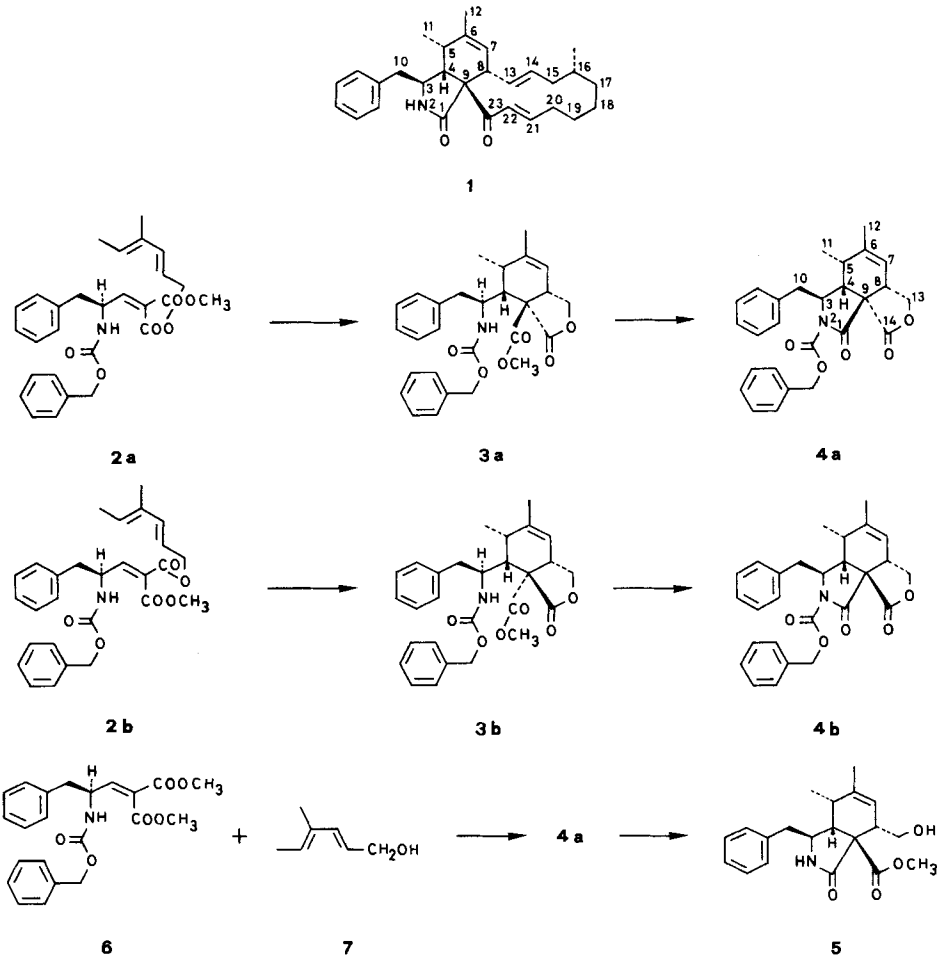
[4]) For convenience, the numbering used in this communication corresponds to that proposed for the cytochalasans [2]; compare also footnotes 3 and 7 in [1].

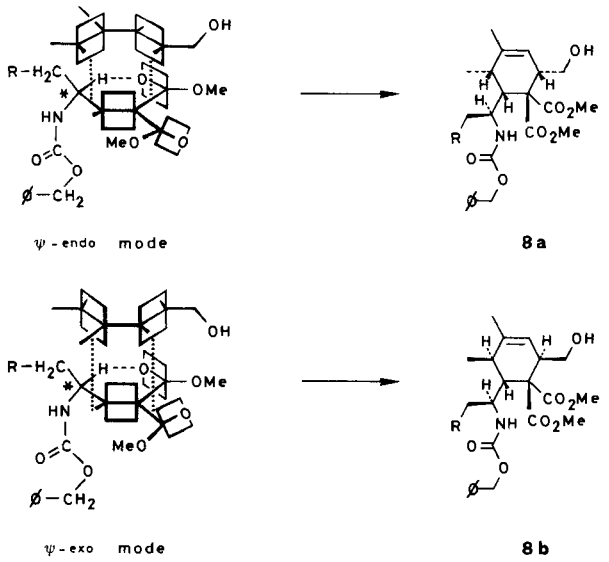
Scheme 1



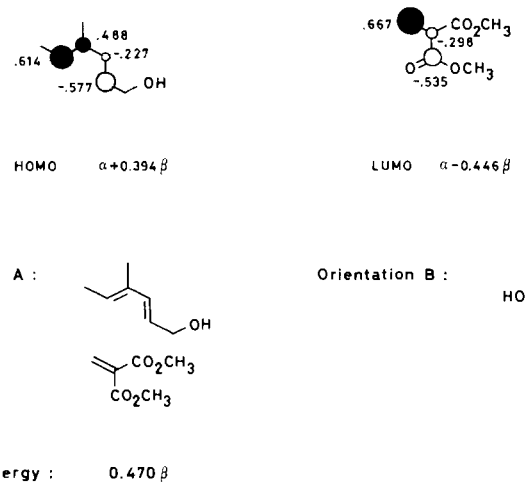
The *intra*molecular reaction takes place only with the (*Z*)-olefin **2a** *via* a transition state which is thermodynamically governed by a *cis*-lactone conformation. Therefore we have investigated the *inter*molecular addition reaction of an olefin, symmetrically functionalized at one end, such as **6** and 4-methyl-2,4-hexadienol (**7**).

As before, an electron-deficient dienophile would have to react with a relatively electron-rich diene, and as will emerge from *Scheme 2*, the same steric interactions should operate in the development of the transition state as has been deduced previously for the *intra*molecular [2 + 4]cycloaddition [1]. Simultaneous formation of an additional ring cannot interfere. Consequently, an unperturbed [2 + 4]cycloaddition may take place to give primarily the cyclohexene derivative **8a**, which can undergo lactamization and/or lactonization. A study of the MO-coefficients of corresponding frontier orbitals at the C-centres involved indicates the correct regioselectivity. Considering the inductive effect of the two methyl groups and the

Scheme 2



Scheme 3



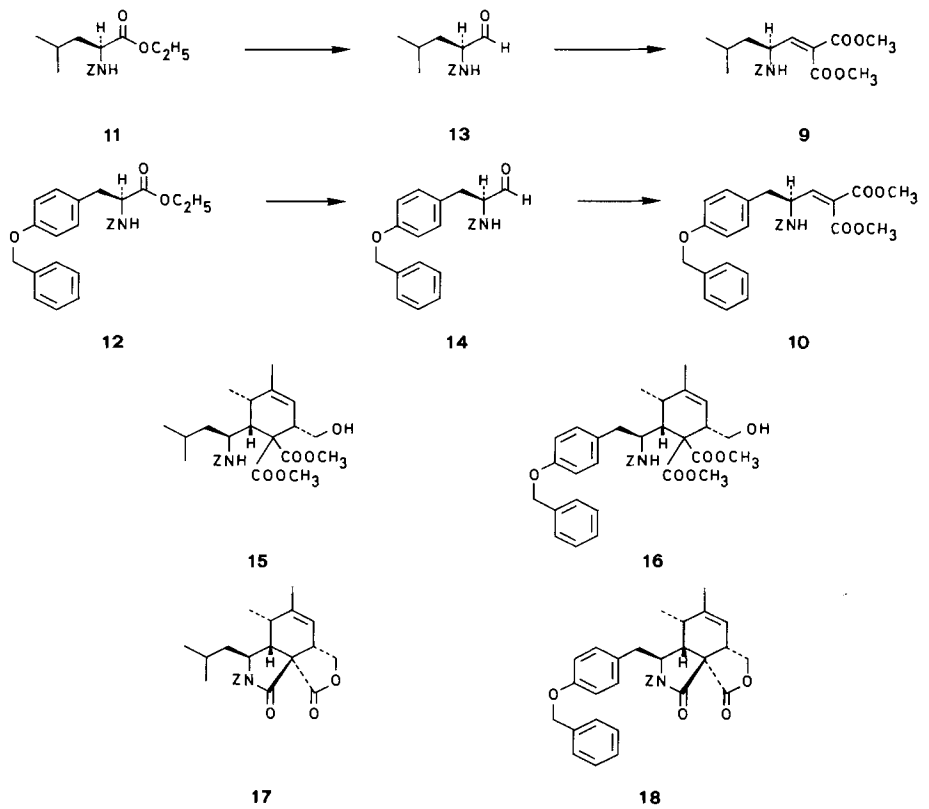
hydroxymethyl group in the diene **7**, and choosing an acrylate system as a rather simplified model for the dienophile **6**, the coefficients were obtained by an ordinary *Hückel* calculation [3] (*cf. Scheme 3*). By application of the *Salem-Klopman* equation [4], the frontier orbital interaction for the two different addition modes is found to favour orientation A.

The results of the corresponding experiments confirmed the anticipated course of the intermolecular [2+4]cycloaddition of the dienophile **6** with **7** as diene. The

alkylidene ester **6** was conveniently prepared from *rac-* or (*S*)-2-benzyloxycarbonylamino-3-phenylpropanal and dimethyl malonate using titanium tetrachloride and pyridine as condensing agents [5]. A yield of 55% of **6** was reached when the reaction was carried out at 0 to 20° for 48 h. Heating of pure **6** with an equimolar amount of diene **7** with xylene as diluent in a sealed tube for 64 h at 145° resulted in the formation of the lactone **4a**. Interestingly, instead of **4b**, the epimer **4a** with 'wrong' configuration at C(9) was again obtained. This fact clearly demonstrates that in the cycloadduct lactone-ring closure preceeds lactam-ring formation.

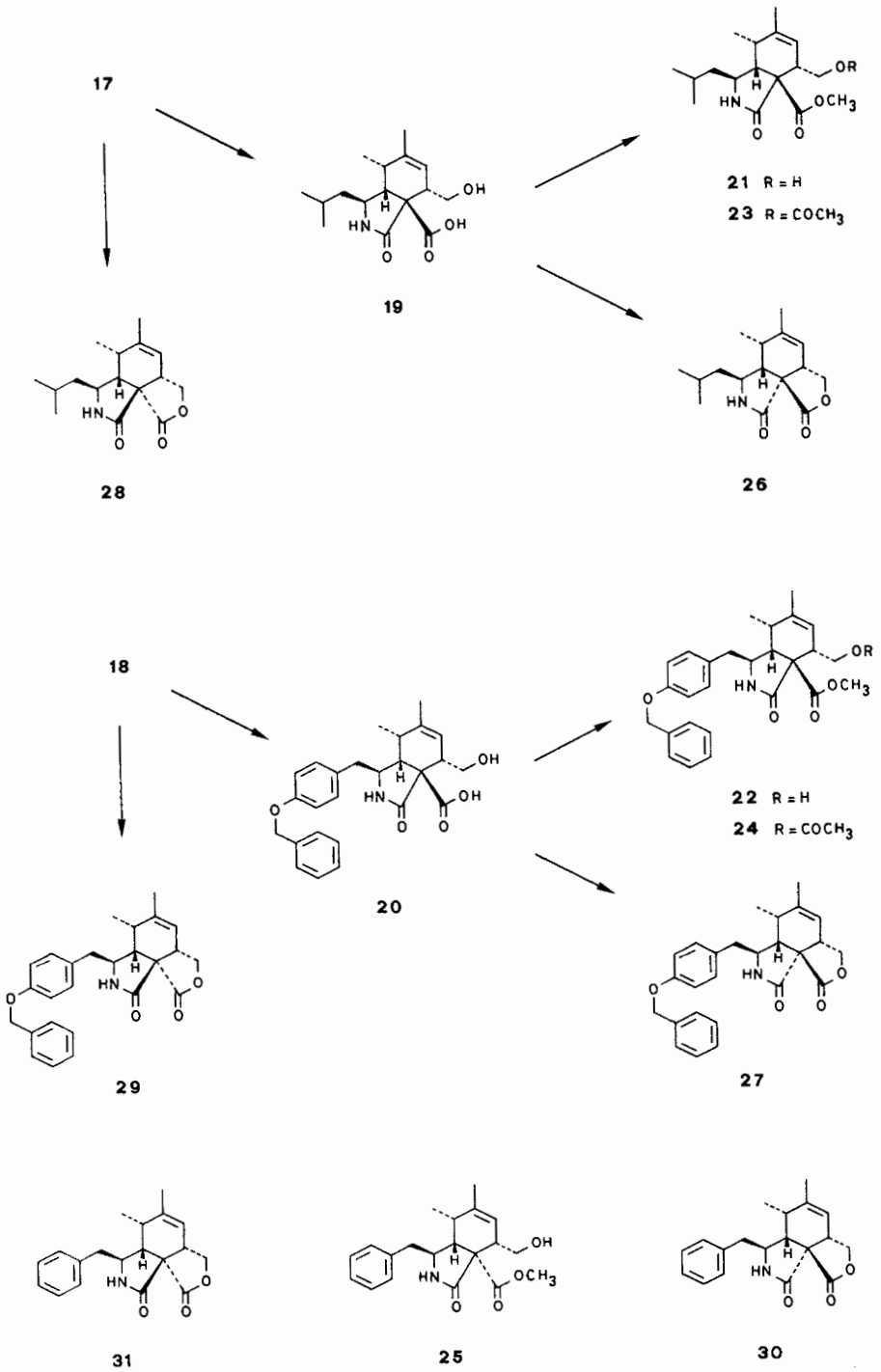
This procedure has improved the accessibility of synthon **4a** significantly. It can also be applied to other amino acids as chiral starting materials [6] for the synthesis of other types of cytochalasans, as demonstrated by the use of tyrosine and leucine. The latter leads to the tetrahydroisoindolinone system of the aspochalasins [7]. The corresponding alkylidene esters **9a** and **10** *(cf. Scheme 4)*[5]) have been synthe-

Scheme 4



[5]) Compounds **9**, **11**, **13**, **17**, **19**, **21**, **23**, **26**, and **28** were prepared in both racemic and optically active form; the former are denoted additionally by letter **a**, the latter by letter **b**. This differentiation is not made in the *Schemes*.

Scheme 5



sized in the same way as the olefin **6**. The different amino acids in either free or protected form, were first converted into their benzyloxycarbonyl ethyl esters **11a** and **12**. The latter were reduced by DIBAH to the corresponding aldehydes **13a** and **14**. Condensation of either aldehyde with dimethyl malonate in the presence of titanium tetrachloride proceeded smoothly to give the required dienophiles **9a** and **10** in 82% and 69% yield, respectively. As in the case of **11b**, the optically active dienophile **9b** was obtained in the same manner, starting from L-leucine.

Heating the dienophiles **9a** and **10** with 4-methyl-2,4-hexadienol (**7**) in xylene resulted in the formation of two nicely crystalline compounds, which were easily separated from the reaction mixtures. The spectral data showed that not only cycloaddition had occurred, but that both products contained, as common structural features, like **4a**, a spirocyclic fused γ-lactone and γ-lactam ring as in formulae **17a** and **18**.

From earlier considerations [1], it was assumed that the cycloaddition reaction leading to **15** and **16** took place in the same stereoselective manner as in the formation of the prototype **8a**. Hence, **17a** and **18** should possess the correct configuration at all chiral centres except at C(9). Therefore, the procedure used for the inversion of the configuration at C(9) in **4a** was applied to the tricyclic compounds **17a** and **18**. Again, the cleavage of the hetero rings by alkali was accompanied by a loss of the benzyloxycarbonyl group, yielding the hydroxy acids **19** and **20** (*cf. Scheme 5*). Treatment of the crude acids with diazomethane gave the corresponding esters **21a** and **22** in excellent yield. Mild acetylation of **21a** and **22** afforded the derivatives **23a** and **24**. Characteristic ^{1}H-NMR. shifts were observed for the esters **21a**, **22**, and **5** as compared with the non-rearranged ester **25** which is epimeric to **5** with respect to C(9). The shifts recorded in *Table 1* indicate that **21a**, **22**, and **5** belong to the same configurational series. Further evidence for the configurational rearrangement was obtained after ring closure of the acids **19** and **20**, which led to the new lactones **26a** and **27**. It was necessary to correlate these with the original *Diels-Alder* products **17a** and **18**. For this purpose, the benzyloxycarbonyl group in both **17a** and **18** was removed by treatment with trimethylsilyl iodide in benzene. As expected, the resulting compounds **28a** and **29** differed in each series from the rearranged analogues **26a** and **27**. The conclusion that this difference consists of a formal epimerization at C(9), was strongly supported by comparison of the ^{1}H-NMR. spectra of the two new isomeric pairs with those described earlier [1]. The data summarized in *Table 2* show that the change in configuration at the spiro C(9) in the corresponding *trans*-lactams *cis*-lactones **28a** and **29** and *cis*-lactams *trans*-lactones **26a** and **27**, respectively, is accompanied by a large up-field shift of the proton at C(3). Conversely, a pronounced down-field shift is generally found for the methylene protons at C(13). These observations may be rationalized for these rigid systems in terms of the concept of *Pople* [8] and correlated with the anisotropic behavior of the neighbouring carbonyl groups. *Dreiding* models of the two epimeric structures demonstrate that the H-atom at C(3) is located near the σ-axis of the lactone carbonyl group in the deprotected parent lactones **28a** and **29**; however, these are far away from each other in the rearranged analogues **26a** and **27**. A similar, although less pronounced deshielding effect is expected for the two H-atoms at C(13) in the neighbourhood of the lactam

Table 1. *^{1}H-NMR. data of compounds* **5**, **17**, **18**, *and* **21–25**

[a])	**17**	**21**	**23**	**18**	**22**	**24**	**5**	**25**
H–N(2)	–	6.9 *m*	6.9 br.	–	5.9 br.	5.80 br.	5.93 br	6.05 br.
H–C(3)	4.83 *d*×*d*×*d*	3.14 *d*×*d*×*d*	2.8–3.3 *m*	4.85–5.20 *m*	3.27 *m*	3.10–3.45 *m*	3.31 *d*×*d*×*d*	4.14 *d*×*d*×*d*
H–C(4)	2.24 *d*×*d*	2.15 *d*×*d*	} 2.3–2.6 *m*	} 1.95–2.35 *m*	} 2.3–2.6 *m*	} 2.20–2.80 *m*	} 2.49–2.59 *m*	2.44 *d*×*d*
H–C(5)	2.40 *d*×*qa*	2.50 *m*						2.37 *d*×*qa*
H–C(7)	5.32 br. *s*	5.51 br. *s*	5.53 br. *s*	5.27 *m*	5.56 br. *s*	5.53 br. *s*	5.58 br. *s*	5.24 br. *s*
H–C(8)	3.23 *m*	2.98 *m*	2.8–3.3 *m*	} 2.95–3.35 *m*	} 2.4–3.1 *m*	2.85–3.10 *m*	2.93–3.00 *m*	2.73–2.81 *m*
H–C(10)	1.56 *m*/1.87 *m*	1.27 *d*×*d*×*d*/	1.2–1.7 *m*			2.20–2.80 *m*	2.63 *d*×*d*/	2.60 *d*×*d*/
		1.49 *d*×*d*×*d*					2.95 *d*×*d*	3.04 *d*×*d*
H–C(11)	1.14 *d*	1.15 *d*	1.17 *d*	0.92 *d*	1.22 *d*	1.18 *d*	1.22 *d*	0.90 *d*
H–C(12)	1.80 br. *s*	1.77 br. *s*	1.81 br. *s*	1.72 br. *s*	1.81 br. *s*	1.81 br. *s*	1.80 br. *s*	1.73 br. *s*
H–C(13)	4.09 *d*/4.70 *d*×*d*	3.96 *m*	4.2–4.6 *m*	4.04 *d*/4.65	} 3.5–4.0 *m*	4.42–4.57 *m*	3.77 *d*×*d*×*d*/	3.67 *d*×*d*×*d*/
				d×*d*			3.95 *d*×*d*×*d*	4.09 *d*×*d*×*d*
HO–C(13)	–	3.74 br.	–	–		–	3.69–3.84 *m*	4.86 *d*×*d*
H_3CCOO–C(13)	–	–	2.04 *s*	–	–	2.06 *s*	–	–
H_3COOC–C(9)	–	3.79 *s*	3.80 *s*	–	3.89 *s*	3.79 *s*	3.77 *s*	3.76 *s*
$(H_3C)_2$–C*H*–C(10)	1.75 *m*	1.61 *d*×*d*×*qa*	1.2–1.7 *m*	–	–	–	–	–
$(H_3C)_2$–CH–C(10)	0.86 *d*/0.93 *d*	0.90 *d*/0.93 *d*	0.94 *d*/0.96 *d*	–	–	–	–	–
$C_6H_5CH_2OCO$–N(2)	5.25/5.34 *AB*	–	–	5.37 *s*	–	–	–	–
$C_6H_5CH_2OCO$–N(2)	7.30–7.48 *m*	–	–	7.20–7.65 *m*	–	–	–	–
Arom. H	–	–	–	6.88 *AA'BB'*	6.98 *AA'BB'*	6.99 *AA'BB'*	7.13–7.36 *m*	7.15–7.40 *m*
$C_6H_5CH_2O$	–	–	–	5.20 *s*	5.04 *s*	5.06 *s*	–	–
$C_6H_5CH_2O$	–	–	–	7.20–7.65 *m*	7.20–7.45 *m*	7.20–7.50 *m*	–	–

[a]) The number of H-atoms attached to the C-atoms is not always given in this table.

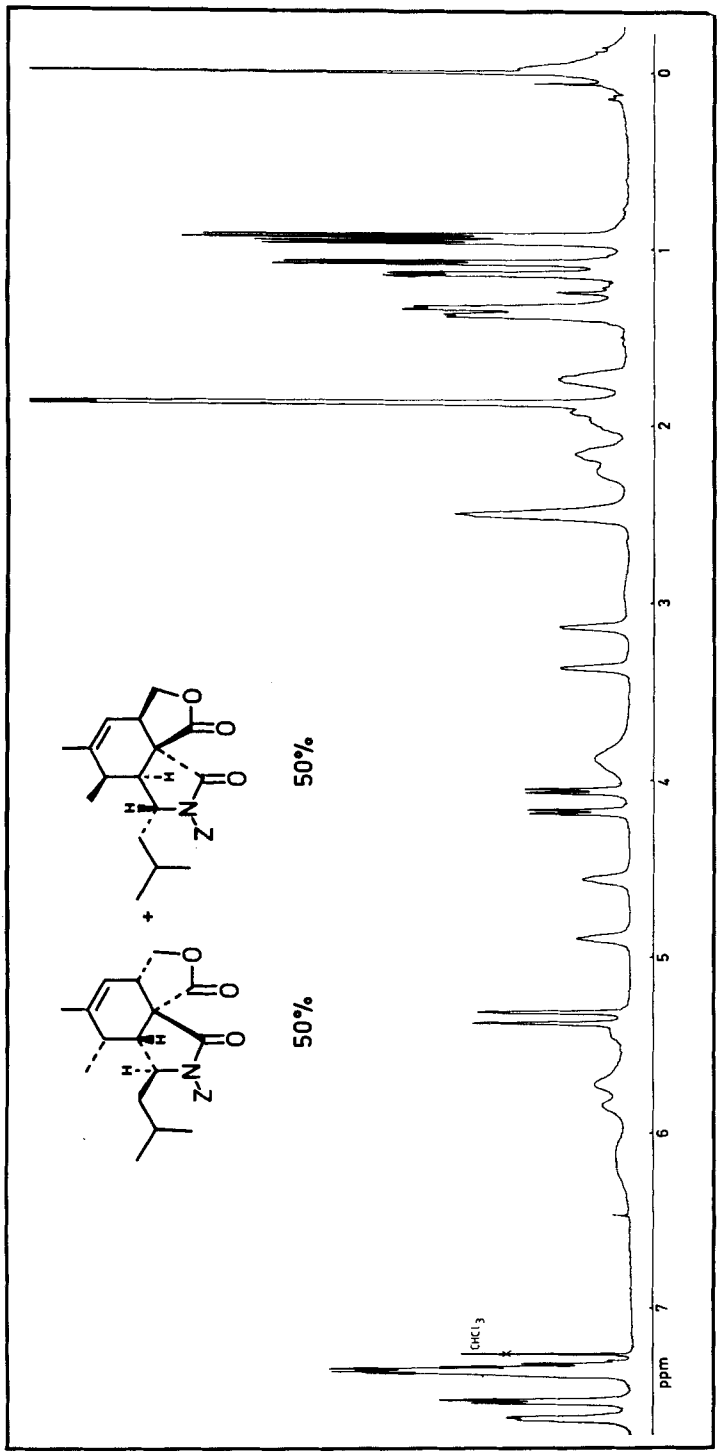


Fig. 1. *^{1}H-NMR. spectrum of* **17a** *in the presence of* $Eu(tfc)_3$

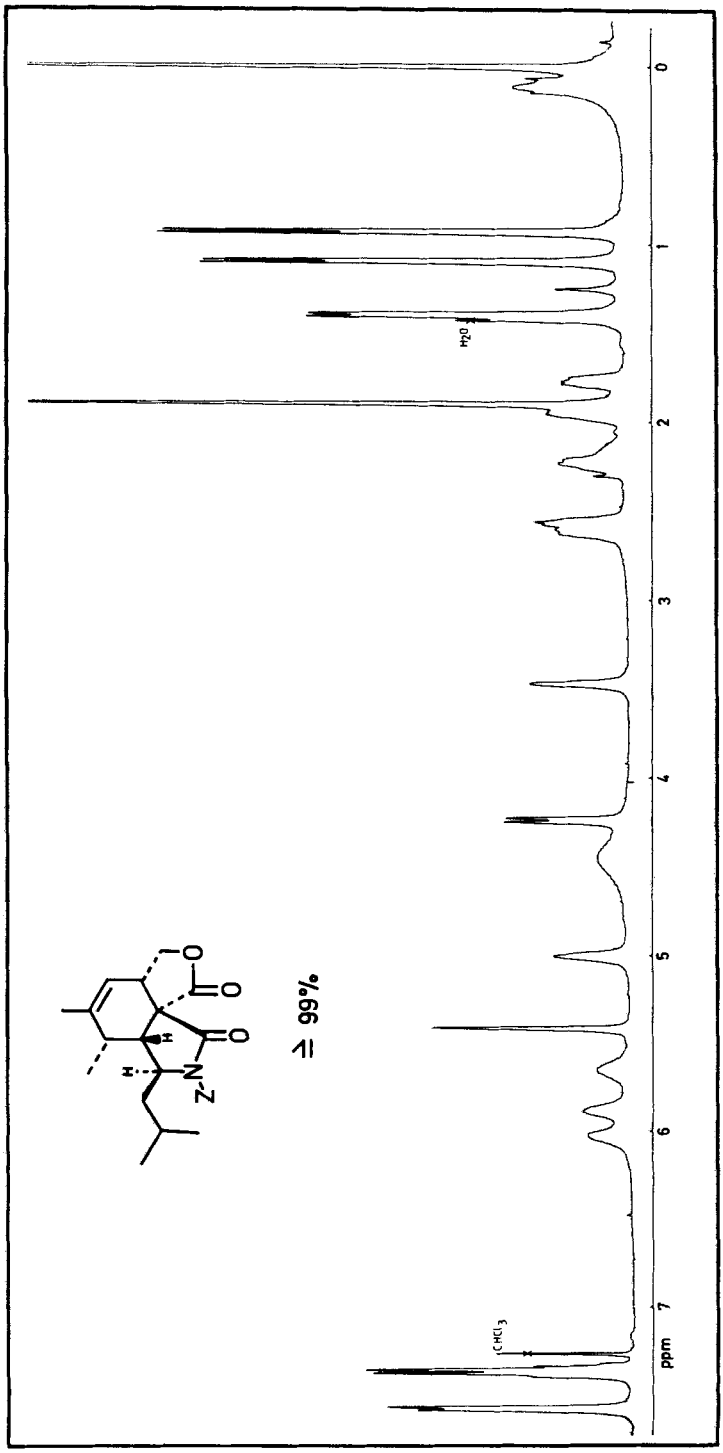


Fig. 2. *^{1}H-NMR. spectrum of* **17b** *in the presence of Eu(tfc)$_3$*

carbonyl O-atom in the rearranged compounds **26a** and **27**. In addition, a further interaction occurs between the lone pair orbital of the lactam N-atom and the bond between C(3) and its H-atom. The effect appears to be stronger in the lactams **28a** and **29** with the 'wrong' configuration than in **26a** and **27**. It is responsible for additional deshielding effect, which would explain the relatively large chemical shift observed for H–C(3).

Additional support for the structural relationship in the above-mentioned isomeric lactam-lactone pairs is derived from a consideration of the increase in lactone ring strain resulting from the configurational change in position 9. In accordance with the known pair **30** and **31**, the stretching frequencies summarized in *Table 3* for the lactone groups in the postulated *trans*-lactones **26a** and **27** are found at higher wave numbers than those of the corresponding *cis*-lactones **28a** and **29**.

Independent proof of the correctness of these conclusions by X-ray analysis is in progress.

Condensation of the dextrorotatory[6]) enantiomer **9b** of the dienophile **9** with 4-methylsorbinol (**7**) under the conditions formerly applied to racemic **9a**, yielded

Table 2. *^{1}H-NMR. data of compounds* **26–31**

[a])	**26**	**28**	**27**	**29**	**30**	**31**
H–N(2)	6.40 br.	6.63 br.	5.79 br.	5.62 br.	5.83 br.	5.67 br.
H–C(3)	3.45 *m*	4.56 *m*	3.10 *m*	4.45 *m*	3.57 *t*	4.68 *d*×*d*×*d*
H–C(4)	2.3–2.7 *m*	2.1–2.5 *m*	2.2–2.5 *m*	2.2–2.5 *m*	2.64 *d*	2.25–2.40 *m*
H–C(5)					2.37 *m*	
H–C(7)	5.86 br. *s*	5.30 br. *s*	5.79 br. *s*	5.32 br. *s*	5.83 br. *s*	5.32 br. *s*
H–C(8)	3.10 *m*	3.15 *m*	2.9–3.3 *m*	3.21 *m*	3.01 *m*	3.20 *m*
H–C(10)	1.2–1.8 *m*	1.22–1.71 *m*	2.5–3.0 *m*	2.49 *d*×*d*/	2.92 *d*×*d*/	2.55 *d*×*d*/
				3.06 *d*×*d*	2.97 *d*×*d*	3.08 *d*×*d*
H–C(11)	1.29 *d*	1.12 *d*	1.02 *d*	1.12 *d*	1.02 *d*	1.13 *d*
H–C(12)	1.83 *s*	1.79 *s*	1.73 br. *s*	1.79 *s*	1.74 *s*	1.79 *s*
H–C(13)	4.45 *t*/	4.13 *d*×*d*/	4.48 *t*/	4.06 *d*/	4.48 *t*/	4.07 *d*/
	5.26 *d*×*d*	4.68 *d*×*d*	5.29 *d*×*d*	4.67 *d*×*d*	5.29 *d*×*d*	4.68 *d*×*d*
$(H_3C)_2$–C*H*–C(10)	1.2–1.8 *m*	1.22–1.71 *m*	–	–	–	–
$(H_3C)_2$–CH–C(10)	0.97 *d*	0.98 *d*	–	–	–	–
Arom. H	–	–	7.03 *AA'BB'*	7.04 *AA'BB'*	7.15–7.40 *m*	7.15–7.40 *m*
$C_6H_5CH_2O$	–	–	5.05 *s*	5.07 *s*	–	–
$C_6H_5CH_2O$	–	–	7.2–7.6 *m*	7.2–7.6 *m*	–	–

[a]) See footnote a) in *Table 1*.

Table 3. *Frequencies of the carbonyl stretching bands in the IR. spectra of compounds* **26b**, **27**, **28a**, *and* **29–31** (values in cm^{-1})

Lactam	**26b** *cis*	**28a** *trans*	**27** *cis*	**29** *trans*	**30** *cis*	**31** *trans*
Lactone	1767	1765	1770	1745	1767	1755
$\tilde{\nu}$ (C=O)						
Lactam	1685	1700	1695	1705	1695	1710

[6]) This enantiomer **9b** is derived from L-(–)-leucine.

Table 4. *^{13}C-NMR. data of compounds* **17**, **18**, **21**, **22**, *and* **26–29** (the signals of the aryl C-atoms are not mentioned)

	17	**28**	**21**	**26**	**18**	**29**	**22**	**27**
C(1)	169.7 *s**	172.8 *s**	175.4*	172.3*	169.4 *s**	172.2 *s**	173.4 *s**	172.2*
C(3)	56.9 *d*	52.0 *d*	52.9	50.8	58.3 *d*	54.9 *d*	56.5 *d*	54.6
C(4)	34.2 *d*	50.2 *d*	48.1	47.3	33.9 *d*	33.7 *d*	34.4 *d*	35.9
C(5)	45.9 *d*	33.7 *d*	34.4	44.6*	39.1 *d*	39.2 *d*	41.7 *d*	43.2
C(6)	143.0 *s*	142.8 *s*	139.8	141.4	142.8 *s*	142.7 *s*	139.6 *s*	141.6
C(7)	121.0 *d*	121.8 *d*	122.8	120.2	120.9 *d*	121.7 *d*	123.3 *d*	119.9
C(8)	39.3 *d*	39.3 *d*	25.6	38.4	42.9 *d*	49.4 *d*	53.5 *d*	43.6
C(9)	54.6 *s*	53.2 *s*	55.3	57.2	53.8 *s*	53.7 *s*	60.3 *s*	59.3
C(10)	42.6 *t*	43.7 *t*	41.3	45.3*	36.4 *t*	39.6 *t*	43.5 *t*	44.5
C(11)	13.7 *qa*	13.5 *qa*	14.3	12.8	13.2 *qa*	13.5 *qa*	14.2 *qa*	13.5
C(12)	22.2 *qa*	22.1 *qa*	20.4	19.4	22.2 *qa*	22.1 *qa*	20.2 *qa*	19.7
C(13)	72.2 *t*	72.0 *t*	62.5	69.4	72.1 *t*	72.0 *t*	62.4 *t*	69.8
C(14)	173.6 *s**	175.2 *s**	173.5*	174.3*	173.5 *s**	175.1 *s**	175.0 *s**	174.5*
H_3CO–C(14)	–	–	52.9	–	–	–	52.7 *qa*	–
$(H_3C)_2$–CH–C(10)	24.8/23.8/	23.7*	23.8/22.9/	24.7/23.0/	–	–	–	–
$(H_3C)_2$–CH–C(10)	22.9	26.1*	21.0	22.1	–	–	–	–
$C_6H_5CH_2CO$–N(2)	151.5 *s*	–	–	–	151.7 *s*	–	–	–
$C_6H_5CH_2CO$–N(2)	68.5 *t*	–	–	–	68.6 *t*	–	–	–
$C_6H_5CH_2O$	–	–	–	–	70.1 *t*	70.2 *t*	70.2 *t*	70.2

*) Assignment may be reversed.

the optically active lactone **17b**. Addition of tris[3-trifluoro-acetyl-d-campherato] europium ($Eu(tfc)_3$) as chiral shift reagent [9] to a solution of racemic **17a** in $CDCl_3$ caused a splitting of signals in the 400-MHz-^{1}H-NMR. spectrum (*cf. Fig. 1*) due to diastereomeric interaction. This observation allowed a rather precise estimation of the optical purity of the product **17b** obtained. In the spectrum of **17b** only one enantiomer was present. With a detection limit of the instrument of 1 percent, this means at least 99% e.e. for **17b**.

Treatment of the laevorotatory enantiomer **17b** with methanolic potassium hydroxide gave the corresponding hydroxy acid **19b**, which upon esterification with diazomethane yielded the optically pure ester **21b**. Alternatively, lactone ring closure in **19b** by acetic anhydride furnished the *trans*-lactone **26b**, the laevorotatory enantiomer of **26a**. Significantly, once the anellated optically pure cyclohexene system of type **8a** has been formed[7]), the sequence of reactions described earlier may be carried out without any racemization.

The support of this investigation by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung* is gratefully acknowledged.

Experimental Part

General remarks. See [1].

rac-*Dimethyl 2-(2'-benzyloxycarbonylamino-3'-phenylpropylidene)malonate* (**6**). A solution of $TiCl_4$ in CCl_4 (2.78M, 90 ml) was added dropwise to 400 ml of dry THF at 0° under Ar. A solution of 35.1 g

[7]) In contrast to the behavior of **9b**, the analogous condensations with the optically active enantiomers of the alkylidene malonic ester derivatives **6** and **10** under the same conditions proceeded with complete racemization, yielding exclusively **4a** and **18**, respectively.

(0.124 mol) of *rac*-2-(benzyloxycarbonylamino)-3-phenylpropanal [1] and 17.2 g (0.130 mol) of dimethyl malonate in 125 ml of THF was added in one portion to the stirred yellow coloured solution. Over a period of 2 h a mixture of 40 ml (0.451 mol) of pyridine and 85 ml of THF was added at 0°. The mixture was allowed to warm, and stirring was continued at r.t. for 48 h. After this time 420 ml of water/ether 1:2 were added. The aqueous phase was extracted twice with 140 ml of ether, and the combined organic extracts were washed with sat. NaCl-solution (5 × 100 ml) and dried. Evaporation of the solvents *i.v.* left 55.9 g of crude product. which was purified by column chromatography on 1.0 kg of silica gel. Elution with ether (500 ml each fraction) yielded, after recrystallization from ether/diisopropylether, 27.66 g (56.2%) of pure **6** as needles, m.p. 63–64°. – IR. (KBr): 3350, 1730, 1715, 1686, 1632, 1515, 1280, 1255, 1220, 1030, 730, 693. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 7.50–7.05 (*m*, 10 H, 2 C_6H_5); 6.92 (*d*, J = 8, 1 H–C(1′)); 5.04 (*s*, $C_6H_5CH_2O$); 5.00–4.70 (*m*, 2 H, H–N and H–C(2′)); 3.78 and 3.76 (2 *s*, 2 OCH_3); 3.10–2.85 (*m*, 2 H–C(3′)). – ^{13}C-NMR. (22.63 MHz, $CDCl_3$): 165.1, 164.0 (C(1) and C(3)); 155.6 ($C_6H_5CH_2OCO$); 148.5 (C(1′)); 136.4, 136.3, 129.4, 128.6, 128.5, 128.0, and 127.9 (2 × C_6H_5); 127.0 (C(2)); 67.8 ($C_6H_5CH_2OCO$); 52.4, 52.3 (2 × OCH_3); 51,7 (C(2′)); 40.3 (C(3′)).

$C_{22}H_{23}NO_6$ (397.43) Calc. C 66.49 H 5.83 N 3.52% Found C 66.28 H 5.80 N 3.49%

*rac-(3*R*, *3a*S*, *4*R*, *7*R*, *7a*S*)*-3-Benzyl-2-benzyloxycarbonyl-7-hydroxymethyl-4, 5-dimethyl-1-oxo-3a, 4, 7, 7a-tetrahydroisoindoline-7a-carboxylic acid lactone*[8])[9]) (**4a**). The solution of 1.358 g (12.1 mmol) of (*E*,*E*)-4-methyl-2,4-hexadien-1-ol (**7**) [1] and 3.975 g (10.0 mmol) of **6** in 26 ml of xylene was heated to 145° in a sealed tube for 64 h. Evaporation of the solvent *i.v.* left 5.52 g of a yellow oil, which was diluted with 10 ml of ether. Crystallization set in and 3.597 g of crystalline, crude **4a** were obtained. Recrystallization from CH_2Cl_2/ether afforded 2.840 g (63.7%) of **4a** as prisms, m.p. 174–176°. – The spectral data were identical with those reported in [1].

rac-N-*Benzyloxycarbonyl-leucine ethyl ester* (**11a**). To a chilled suspension of 7.0 g (35.7 mmol) of *rac*-leucine ethyl ester hydrochloride in 150 ml of AcOEt, 160 ml of aq. 1M $KHCO_3$ was added rapidly with stirring, then 6.6 ml (46.3 mmol) of benzyl chloroformate was added dropwise within 30 min. The mixture was kept at 0° for 1 h, then acidified to pH ≈ 2 with 35 ml of 2N HCl and extracted with a total of 250 ml of AcOEt. The organic phases were washed with sat. NaCl-solution and dried. Evaporation of the solvent *i.v.* left 12.96 g of crude **11a**, which was purified by flash-chromatography [10]. Elution with CH_2Cl_2/ether 97:3 yielded 9.9 g (94%) of **11a** as a colourless oil. – IR. (film): 3340 (N–H), 1715 (br., C=O, ester and carbamate), 1520. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 7.34 (s, 5 H, C_6H_5); 5.11 (br. *s*, 3 H, H–N and $CH_2C_6H_5$); 4.5–4.2 (*m*, 1 H–C(2)); 4.18 (*qa*, J = 7, OCH_2CH_3); 1.9–1.5 (*m*, 2 H–C(3) and 1 H–C(4)); 1.26 (*t*, J = 7, OCH_2CH_3); 0.94 (*d*, J = 6, 3 H–C(5a), 3 H–C(5b)).

$C_{16}H_{23}NO_4$ (293.36) Calc. C 65.51 H 7.90 N 4.78% Found C 65.67 H 8.03 N 4.79%

(S)-N-*Benzyloxycarbonyl-leucine ethyl ester* (**11b**). Starting from 5.76 g (29.4 mmol) of L-leucine ethyl ester hydrochloride, 7.38 g (90%) of **11b** were obtained in the same manner as **11a**. $[\alpha]_D^{25} = -6.3°$ (c = 1.96, CH_2Cl_2).

rac-*2-Benzyloxycarbonylamino-4-methyl-pentanal* (**13a**). A solution of 9.68 g (33 mmol) of **11a** in 250 ml of dry toluene was cooled to −78° under Ar. A solution of DIBAH in toluene (1.2M, 35 ml) was added within 45 min with stirring, which was continued for 2 h at −78°. After addition of 50 ml 3M ethanol in toluene, followed by 150 ml 1.5N citric acid in water, the mixture was extracted with ether (2 × 200 ml). The organic phases were washed with 1.5N citric acid (2 × 50 ml) and sat. NaCl-solution and dried. Evaporation of the solvents *i.v.* left 11.51 g crude **13a**, which was purified by flash-chromatography. Elution with CH_2Cl_2/ether 97:3 → 94:6 yielded 8.79 g (75%) of **13a** as a colourless oil. – IR. (CCl_4): 3425 (N–H), 1720 (br., C=O, aldehyde, carbamate), 1495. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 9.59 (*s*, 1 H–C(1)); 7.35 (*s*, C_6H_5); 5.12 (*s*, $CH_2C_6H_5$); 5.1–4.7 (*m*, H–N); 4.5–4.2 (*m*, 1 H–C(2)); 1.9–1.2 (*m*, 2 H–C(3), 1 H–C(4)); 0.96 and 0.90 (2 *d*, J = 7, 3 H–C(5a) and 3 H–C(5b)).

2,4-Dinitrophenylhydrazone of **13a**: m.p. 98–99°.

$C_{20}H_{23}N_5O_6$ (429.43) Calc. C 55.94 H 5.40 N 16.31% Found C 55.75 H 5.40 N 16.48%

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[8]) See Footnote 7 in [1].

[9]) The IUPAC name of this compound would be: rac-*(3*R*, *3a*S*, *4*R*, *7*R*, *7a*S*)*-3-Benzyl-2-benzyloxycarbonyl-4, 5, 7-trimethyl-1-oxo-3a, 4, 7, 7a-tetrahydroisoindoline-7a, 7a-carbolactone.* The IUPAC names of compounds **17**, **18**, **21**, **26**, **27** and **28** would be analogous (Editor).

(S)-*2-Benzyloxycarbonylamino-4-methyl-pentanal* (**13b**). As above (**11a** → **13a**); **13b** was obtained in 73% yield. $[\alpha]_D^{22} = -29.3°$ ($c = 2.36$, CH_3OH).

rac-*Dimethyl 2-(2'-benzyloxycarbonylamino-4'-methylpentylidene)malonate* (**9a**). A solution of $TiCl_4$ in CCl_4 (2.78M, 14.4 ml) was added to 60 ml of dry THF at 0° under Ar. To the stirred orange-coloured solution were added 4.99 g (20 mmol) of **13a** plus 2.52 ml (22 mmol) of dimethyl malonate in one portion. Addition of 6 ml of pyridine in 14 ml of THF proceeded within 1 h. The cooling bath was removed, and stirring continued for 64 h at r.t. The mixture was diluted with 70 ml water/ether 2:5, the organic phase separated, and washed with sat. NaCl-solution. Evaporation of the solvents *i.v.* left 10.0 g of crude **9a**. Purification by flash-chromatography using a CH_2Cl_2/ether gradient yielded 5.95 g (82%) of **9a** as a colourless oil. – IR. (film): 3360 (N–H), 2960, 1725 (br., C=O, ester, carbamate), 1520, 1440, 1260, 1220. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 7.34 (*s*, C_6H_5); 6.83 (*d*, $J = 8$, H–C(1')); 5.08 (*s*, $CH_2C_6H_5$); 4.9–4.5 (*m*, H–N and H–C(2')); 3.78 (*s*, 2 OCH_3); 1.8–1.3 (*m*, 2 H–C(3') and H–C(4')); 0.93 (*d*, $J = 6$, 3 H–C(5'a) and 3 H–C(5'b)). – ^{13}C-NMR. (22.63 MHz, $CDCl_3$): 165.3 and 164.3 (C(1) and C(3)); 155.8 ($C_6H_5CH_2OCO$); 149.4 (C(1')); 136.6, 128.5, and 128.0 (C_6H_5); 127.4 (C(2)); 66.8 ($C_6H_5CH_2OCO$); 52.4 and 52.2 (2 OCH_3); 48.9 (C(2')); 43.3 (C(3')); 24.6 (C(4')); 22.9 and 21.9 (C(5') and C(6')).

(S)-*Dimethyl 2-(2'-benzyloxycarbonylamino-4'-methyl-pentylidene)malonate* (**9b**). As above (**13a** → **9a**), **9b** was obtained in 67% yield. $[\alpha]_D^{22} = +22.7°$ ($c = 1.49$, CH_3OH).

rac-*(3R*,3aS*,4R*,7R*,7aS*)-2-Benzyloxycarbonyl-7-hydroxymethyl-3-isobutyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylic acide lactone*[8][9] (**17a**). The solution of 5.5 g (15.1 mmol) of **9a** and 1.87 g (16.7 mmol) of **7** [1] in 50 ml of xylene was heated to 143° in a sealed tube for 70 h. Evaporation of the solvent *i.v.* left 6.55 g of a brown oil. After 2 days crystallization set in. After careful dilution with methanol and diisopropylether these crystals could be collected. Recrystallization from methanol yielded 1.73 g (28%) of **17a** as needles of m.p. 118–120°. – IR. (KBr): 1760 (C=O, lactone), 1745 (C=O, carbamate), 1735 (C=O, lactam), 1450, 1390, 1290, 1280, 1205, 1160. – ^{1}H-NMR. (400 MHz, $CDCl_3$): see *Table 1.* – ^{13}C-NMR. (22.63 MHz, $CDCl_3$): see *Table 4.* – MS.: 411 (M^+), 368 ($M^+ - 43$ (C_3H_7)), 320 ($M^+ - 91$ (C_7H_7)), 304 ($M^+ - 107$ ($OCH_2C_6H_5$)), 276 ($M^+ - 135$ ($COOCH_2C_6H_5$)), 277, 91.

$C_{24}H_{29}NO_5$ (411.50) Calc. C 70.05 H 7.10 N 3.40% Found C 69.83 H 7.28 N 3.39%

(3R 3aS, 4R, 7R, 7aS)-2-Benzyloxycarbonyl-7-hydroxymethyl-3-isobutyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylic acide lactone[8][9]) (**17b**). As above (**9a** → **17a**); 2.0 g (5.5 mmol) of **9b** and 0.68 g (6.1 mmol) of **7** [1] yielded 555 mg (24,6%) of pure **17b** as needles of m.p. 154–155°. $[\alpha]_D^{22} = -126°$ ($c = 0.76$, CH_3OH). – ^{1}H-NMR. (400 MHz, $CDCl_3$): see *Figure 1.*

rac-N-*Benzyloxycarbonyl*-O-*benzyl-tyrosine ethyl ester* (**12**). A mixture of 22.9 g (56 mmol) of *N*-benzyloxycarbonyl-*O*-benzyl-tyrosine [11], 1 ml conc. H_2SO_4-solution, 20 ml of ethanol and 120 ml of benzene was heated under reflux for 5 h in an apparatus fitted with a *Dean-Stark* trap. The mixture was then cooled to r.t., washed with 2N $NaHCO_3$ and water, and dried. Evaporation of the solvent *i.v.* left a residue, which was recrystallized from ether to yield 18.4 g (76%) of **12**, m.p. 82°. – IR. (KBr): 3360 (N–H), 1716 and 1703 (C=O, ester and carbamate), 1520, 1510, 1282, 1260, 1230, 1010, 850, 750, 690. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 7.5–7.0 (*m*, 2 C_6H_5); 7.0–6.6 (*AA'BB'*, C_6H_4); 5.35–4.9 (br., H–N); 5.0 (*s*, $COOCH_2C_6H_5$); 4.9 (*s*, $OCH_2C_6H_5$); 4.75–4.3 (*m*, 1 H–C(2)); 4.05 (*qa*, $J = 7$, OCH_2CH_3); 3.0 (*d*, $J = 6$, 2 H–C(3)); 1.15 (*t*, $J = 7$, OCH_2CH_3). – MS.: 433 (M^+), 325 ($M^+ - 108$ ($C_6H_5CH_2OH$)); 282 ($M^+ - 151$ ($C_6H_5CH_2OCONH_2$)).

$C_{26}H_{27}NO_5$ (433.50) Calc. C 72.04 H 6.28 N 3.23% Found C 72.20 H 6.27 N 3.17%

rac-*2-Benzyloxycarbonylamino-3-(4'-benzyloxyphenyl)-propanal* (**14**). To a stirred solution of 15.0 g (35 mmol) of **12** in 300 ml of dry toluene at −65° was added dropwise over a period of 1 h 35 ml of 1.2M DIBAH in hexane, under Ar. After stirring for an additional 30 min at −50°, excess reagent was decomposed by careful addition of 10 ml of ethanol in 50 ml of toluene, followed by 50 ml 1.5N citric acid. The mixture was warmed to 0°, the aqueous layer separated and extracted twice with ether. The combined organic phases were washed with sat. NaCl-solution and dried. Evaporation of the solvents *i.v.* left 13.33 g of crude product, which was chromatographed on 200 g of silica gel. Elution with benzene/AcOEt 9:1 yielded 9.85 g (72.2%) of crystalline **14**, m.p. 99–101°. – IR. (KBr): 3360 (N–H), 1730 (C=O, aldehyde), 1680 (C=O, carbamate), 1522, 1510, 1268, 1230, 990, 690. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 9.49 (*s*, 1 H–C(1)); 7.45–7.20 (*m*, 2 C_6H_5); 7.10–6.70 (*AA'BB'*, C_6H_4); 5.65–5.35

(*m*, H–N); 5.04 (*s*, $C_6H_5CH_2OCO$); 4.94 (*s*, $C_6H_5CH_2O$); 4.55–4.20 (*m*, 1 H–C(2)); 2.97 (br. *d*, $J = 6$, 2 H–C(3)).

$C_{24}H_{23}NO_4$ (389.45) Calc. C 74.02 H 5.95 N 3.60% Found C 74.03 H 6.05 N 3.55%

rac-*Dimethyl 2-(2'-benzyloxycarbonylamino-3'-(4''-benzyloxyphenyl)propylidene)malonate* (**10**). A solution of 2.4 ml (22 mmol) of $TiCl_4$ in 3 ml of CCl_4 was added to 50 ml of dry THF at 0°. Then a solution of 4.27 g (11 mmol) of **14** and 1.45 g (11 mmol) of dimethyl malonate in 10 ml THF was added in one portion. Over a period of 30 min a mixture of 3.5 ml (39 mmol) of pyridine and 5 ml of THF was added dropwise to the reaction mixture at 0°. After stirring at r.t. for 48 h, 10 ml of water and 10 ml of ether were added, the layers were separated, and the aqueous phase extracted twice with 10 ml of ether. The organic extracts were dried and yielded after evaporation of the solvents *i.v.* an oily residue. Purification was achieved by column chromatography on 50 g of silica gel using CH_2Cl_2/ether 9:1 as eluent. Recrystallization from ether yielded 3.82 g (69.1%) of **10** as needles, m.p. 94.5–95°. – IR. (KBr): 3340 (N–H), 1732, 1715 (C=O, ester), 1690 (C=O, carbamate), 1608 (C=C), 1530, 1508, 1435, 1263, 1235, 1220, 1110, 1036, 750, 690. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 7.60–7.20 (*m*, 2 C_6H_5); 7.20–6.80 (*AA'BB'*, C_6H_4); 6.90 (*d*, $J = 8$, 1 H–C(1')); 5.02 (*s*, $C_6H_5CH_2OCO$); 5.00–4.70 (*m*, 1 H–C(2') and H–N); 3.76 (*s*, OCH_3); 3.74 (*s*, OCH_3); 3.00–2.80 (*m*, 2 H–C(3')). – ^{13}C-NMR. (22.63 MHz, $CDCl_3$): 165.2 and 164.1 (C(1) and C(3)); 155.5 ($C_6H_5CH_2OCO$); 148.7 (C(1')); 158.0, 137.1, 136.4, 130.4, 128.5, 128.4, 128.2, 128.0, 127.9, and 115.2 (2 C_6H_5 and C_6H_4); 127.4 (C(2)); 70.0 ($C_6H_5CH_2O$); 66.8 ($C_6H_5CH_2OCO$); 52.4 and 52.3 (2 OCH_3); 51.7 (C(2')); 39.4 (C(3')). – MS.: 503 (M^+), 395 ($M^+ - 108$ ($C_6H_5CH_2OH$)), 336 ($M^+ - 108 - 59$ ($C_6H_5CH_2OH + COOCH_3$)), 91.

$C_{29}H_{29}NO_7$ (503.55) Calc. C 69.17 H 5.81 N 2.78% Found C 69.14 H 5.94 N 2.74%

rac-*(3R*, 3aS*, 4R*, 7R*, 7aS*)-3-(p-Benzyloxybenzyl)-2-benzyloxycarbonyl-7-hydroxymethyl-4, 5-dimethyl-1-oxo-3a, 4, 7, 7a-tetrahydroisoindoline-7a-carboxylic acide lactone*[8][9]) (**18**) and rac-*(3R*, 3aS*, 4R*, 7R*, 7aS*)-3-(p-Benzyloxybenzyl)-4, 5-dimethyl-1-oxo-3a, 4, 7, 7a-tetrahydroisoindoline-7a-carboxylic acid lactone*[8][9]) (**29**). A solution of 1.430 g (2.84 mmol) of **10** and 0.318 g (2.84 mmol) of **7** [1] in 10 ml of xylene was heated in a sealed tube for 60 h at 143°. Evaporation of the solvent *i.v.* left a residue which was dissolved in ether. After 2 days 0.430 g of crystalline **18** were obtained. The mother liquor was subjected to column chromatography on 50 g of silica gel. Elution with CH_2Cl_2/ether 9:1 afforded 0.364 g of **18**, 0.192 g of **10** and 0.237 g (20.0%) of **29**. The total yield of **18** was 0.794 g (50.8%).

Compound **18**: m.p. 114.5–115°. – IR. (KBr): 1760 (C=O, lactone), 1740 (C=O, carbamate), 1710 (C=O, lactam), 1505, 1450, 1380, 1300, 1275, 1245, 1200, 1155, 1095, 725, 685. – ^{1}H-NMR. (90 MHz, $CDCl_3$): see *Table 1*. – ^{13}C-NMR. (22.63 MHz, $CDCl_3$): see *Table 4*. – MS.: 551 (M^+), 416 ($M^+ - 135$ ($C_6H_5CH_2OCO$)), 310, 188, 133, 91.

$C_{34}H_{32}NO_6$ (551.64) Calc. C 74.03 H 6.03 N 2.54% Found C 74.07 H 6.05 N 2.51%

Compound **29**: m.p. 204–205°. – IR. (KBr): 3360 (N–H), 1745 (C=O, lactone), 1705 (C=O, lactam), 1510, 1235, 1208, 1160, 1095, 1020, 695. – ^{1}H-NMR. (90 MHz, $CDCl_3$): see *Table 2*. – ^{13}C-NMR. (22.63 MHz, $CDCl_3$): see *Table 4*. – MS.: 417 (M^+), 220 ($M^+ - 197$ ($C_6H_5CH_2OC_6H_4CH_2$)), 133, 91.

$C_{26}H_{27}NO_4$ (417.51) Calc. C 74.80 H 6.52 N 3.36% Found C 75.04 H 6.65 N 3.25%

rac-*Methyl (3R*, 3aS*, 4R*, 7R*, 7aR*)-7-hydroxymethyl-3-isobutyl-4, 5-dimethyl-1-oxo-3a, 4, 7, 7a-tetrahydroisoindoline-7a-carboxylate* (**21a**). To a stirred mixture of 181 mg (0.44 mmol) of **17a** and 14 ml of CH_3OH/benzene 3:2 was added 1.95 ml of 50% aq. KOH-solution. After stirring for 2.5 h at r.t., the mixture was acidified with 11.5 ml of 2N H_2SO_4 and extracted with CH_2Cl_2 (3 × 40 ml). The extracts were washed with water (2 × 7.5 ml) and dried. Removal of the solvents *i.v.* left 124 mg crude acid **19a**. Half was used for the preparation of compound **26a**. The solution of 62 mg of crude acid **19a** in 4.5 ml of CH_3OH was treated at 0° with a CH_2N_2-solution in ether until the yellow colour persisted. Evaporation of the solvents *i.v.* and crystallization from ether/pentane yielded 30 mg (44%) of **21a** as prisms of m.p. 162–164°.

Methyl (3R, 3aS, 4R, 7R, 7aR)-7-hydroxymethyl-3-isobutyl-4, 5-dimethyl-1-oxo-3a, 4, 7, 7a-tetrahydroisoindoline-7a-carboxylate (**21b**). As above (**17a** → **21a**); starting from 101 mg (0.25 mmol) of **17b** 115 mg of crude **21b** was obtained, which was purified by column chromatography on 12 g of silica gel. Elution with CH_2Cl_2/CH_3OH 99:1 (10 × 6 ml), 98:2 (20 × 6 ml), and 96:4 (5 × 6 ml) yielded after recrystallization from ether/diisopropyl ether 57 mg (74%) of **21b** as prisms of m.p. 142–143°. $[\alpha]_D^{25} = -19.5°$ ($c = 1.64$,

CH_3OH). – IR. (KBr): 3450 (O–H), 3200, 3100 (N–H), 2970, 2930, 1740 (C=O, ester), 1700 (C=O, lactam), 1465, 1440, 1235, 1170, 1120, 1060. – ^{1}H-NMR. (400 MHz, $CDCl_3$): see *Table 1.* – ^{13}C-NMR. (90.52 MHz, $CDCl_3$): see *Table 4.* – MS.: 310 ($M^+ + 1$), 292 (310 – 18 (H_2O)), 279 ($M^+ - 30$ (CH_2O)).

$C_{17}H_{27}NO_4$ (309.40) Calc. C 65.99 H 8.80 N 4.53% Found C 66.05 H 8.98 N 4.69%

rac-*Methyl (3R*,3aS*,4R*,7R*,7aR*)-7-acetoxymethyl-3-isobutyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylate* (**23a**). A solution of 16.1 mg (0.052 mmol) of **21a** in 1.5 ml of pyridine/acetic anhydride 2:1 was stirred at r.t. for 17 h. After addition of 6 ml of dry toluene the mixture was freed from the solvents *i.v.* to give a yellow residue of 27 mg, which was dissolved in 1 ml of ether. Crystallization set in, and yielded 18.5 mg of crude **23a**, which was recrystallized from CH_2Cl_2/ether to afford 13.2 mg (72%) of **23a** as plates of m.p. 202–204°. – IR. (CH_2Cl_2): 3420 (N–H), 3045, 2960, 1740 (C=O, ester), 1710 (C=O, lactam), 1235, 1040. – ^{1}H-NMR. (90 MHz, $CDCl_3$): see *Table 1.* – MS.: 352 ($M^+ + 1$), 292 ($M^+ - 59$ ($COOCH_3$)), 278 ($M^+ - 73$ (CH_3COOCH_2)), 232 ($M^+ - 59 - 60$ ($COOCH_3$, H_3CCOOH)), 179.

$C_{19}H_{29}NO_5 + \frac{1}{4}H_2O$ (355.95) Calc. C 64.11 H 8.35 N 3.94% Found C 64.25 H 8.45 N 3.93%

Methyl (3R,3aS,4R,7R,7aR)-7-acetoxymethyl-3-isobutyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylate (**23b**). As above (**21a** → **23a**); starting from 43.3 mg (0.140 mmol) of **21b** 46.2 mg of crude **23b** was obtained, which was purified by column chromatography on 4.5 g of silica gel. Elution with CH_2Cl_2/CH_3OH 99:1 (10 × 2.5 ml), 98:2 (10 × 2.5 ml), and 96:4 (5 × 2.5 ml) afforded after recrystallization from ether/pentane 34.1 mg (69%) of pure **23b** as prisms of m.p. 118–118.5°. $[\alpha]_D^{22} = +26°$ ($c = 0.84$, CH_3OH).

rac-*(3R*,3aS*,4R*,7R*,7aR*)-7-Hydroxymethyl-3-isobutyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylic acide lactone*[8][9]) (**26a**). To a solution of 62 mg of crude acid **19a** (see prep. of **21a**) in 2 ml of CH_2Cl_2/benzene 1:1 was added 2 ml of acetic anhydride at r.t. After stirring the mixture for 65 h, evaporation *i.v.* (twofold addition of 5 ml of toluene) afforded 38 mg of crude product. Recrystallization from CH_2Cl_2/ether yielded 20.8 mg (34%) of pure **26a**, m.p. 178–180°.

$C_{16}H_{23}NO_3$ (277.36) Calc. C 69.28 H 8.36 N 5.05% (hygroscopic)
Found C 68.65 H 8.42 N 4.98%

(3R,3aS,4R,7R,7aR)-7-Hydroxymethyl-3-isobutyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylic acide lactone[8][9]) (**26b**). As above (**17a** → **21a**); starting from 160.0 mg (0.389 mmol) of **17b** 149 mg of crude acid **19b** was obtained. This was treated with 3 ml of pyridine/acetic anhydride 2:1 at 45° for 17 h. Evaporation of the solvents *i.v.* (twofold addition of toluene) left 126 mg of a reddish oil, which was subjected to column chromatography on 12 g of silica gel. Elution with CH_2Cl_2/acetone 99:1 (5 × 6 ml), 97.5:2.5 (5 × 6 ml), 95:5 (10 × 6 ml), and 90:10 (10 × 6 ml) yielded 42.7 mg (40%) of pure **26b** as a colourless foam, $[\alpha]_D^{22} = +67°$ ($c = 0.75$, CH_3OH). – IR. (KBr): 2960, 1767 (C=O, lactone), 1685 (C=O, lactam), 1460, 1380, 1190, 1090. – ^{1}H-NMR. (90 MHz, $CDCl_3$): see *Table 2.* – ^{13}C-NMR. (22.63 MHz, $CDCl_3$): see *Table 4.* – MS.: 277 (M^+), 220 ($M^+ - 57$ (C_4H_9)), 166, 165, 139, 133.

rac-*(3R*,3aS*,4R*,7R*,7aS*)-7-Hydroxymethyl-3-isobutyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylic acide lactone*[8][9]) (**28a**). After treating 207 mg (0.503 mmol) of **17a** with a solution of 226 mg (1.51 mmol) of NaI in 5 ml of CH_3CN, and 0.13 ml (1.03 mmol) of chlorotrimethylsilane at r.t. for 1 h, the mixture was cooled, 3 ml of sat. HCl-solution in CH_3OH was added at 0°, and stirring was continued for 15 min. The volatile components were removed *i.v.* and the residue was made alkaline by addition of $NaOCH_3$. After addition of water, the product was obtained by extraction with ether (4 × 20 ml). The combined extracts were washed with water (3 × 20 ml), 10% $Na_2S_2O_3$-solution (20 ml), sat. NaCl-solution (20 ml), and dried. Evaporation of the solvents *i.v.* left crude **28a**, which was recrystallized from CH_3OH/diisopropyl ether, yielding 134 mg (96%) of pure **28a**, m.p. 107–110°. – IR. (KBr): 3200 (N–H), 2960, 1765 (C=O, lactone), 1700 (C=O, lactam), 1460, 1370, 1210, 1155, 1095, 975, 870, 680. – ^{1}H-NMR. (90 MHz, $CDCl_3$): see *Table 2.* – ^{13}C-NMR. (22.63 MHz, $CDCl_3$): see *Table 4.* – MS.: 277 (M^+), 276 ($M^+ - 1$ (H)), 249 ($M^+ - 28$ (CO)), 234 ($M^+ - 43$ (C_3H_7)), 220 ($M^+ - 57$ (C_4H_9)).

$C_{16}H_{23}NO_3$ (277.36) Calc. C 69.28 H 8.36 N 5.05% Found C 68.96 H 8.25 N 5.00%

(3R,3aS,4R,7R,7aS)-7-Hydroxymethyl-3-isobutyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylic acide lactone[8][9]) (**28b**). A solution of iodotrimethylsilane in benzene (0.6M, 0.75 ml) was

added to a solution of 107.5 mg (0.261 mmol) of **17b** in 4.25 ml of benzene at r.t. After stirring the mixture for 24 h, 1 g of ice, 2 ml of water, and 5 ml of ether were added. Extraction with CH_2Cl_2 (3×6 ml) and washing of the combined organic phases with 1.5 ml of 2N $Na_2S_2O_3$ and water (4×2 ml) afforded after removal of the solvents *i.v.* 115 mg of crude **28b**. Recrystallization from ether/diisopropyl ether yielded 63.2 mg (87%) of pure **28b**, m.p. 212–213°, $[\alpha]_D^{23} = -382°$ ($c = 0.74$, CH_3OH).

$C_{16}H_{23}NO_3$ (277.36) Calc. C 69.28 H 8.36 N 5.05% Found C 68.96 H 8.55 N 5.09%

rac-*Methyl (3*R*,*3a*S*,*4*R*,*7*R*,*7a*R*)*-3-(*p*-*benzyloxybenzyl)-7-hydroxymethyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylate* (**22**). A solution of 41.5 mg (0.075 mmol) of **18** in 3 ml of CH_3OH/benzene 2:1 was treated with 0.4 ml of 50% aq. KOH-solution at r.t. for 6 h. The mixture was cooled, acidified with 2.4 ml of 2N H_2SO_4, and extracted with CH_2Cl_2 (3×6 ml). The organic phases were washed twice with 2 ml of water, and dried. Evaporation of the solvents *i.v.* afforded 51 mg of crude product, which was dissolved in 2 ml of CH_3OH and treated with CH_2N_2 to yield, after recrystallization from ether/pentane, 25.2 mg (74%) of **22**, m.p. 146–146.5°. – IR. (KBr): 3470, 3250, 3035, 2965, 1732 (C=O, ester), 1712 (C=O, lactam), 1610, 1585, 1512, 1455, 1242, 1060, 1030, 1005, 840. – ^{1}H-NMR. (90 MHz, $CDCl_3$): see *Table 1.* – ^{13}C-NMR. (22.63 MHz, $CDCl_3$): see *Table 4.* – MS.: 449 (M^+), 431 ($M^+ - 18$ (H_2O)), 372, 361, 252 ($M^+ - 197$ ($C_6H_5CH_2OC_6H_4CH_2$)), 219, 198.

$C_{27}H_{31}NO_5$ (449.55) Calc. C 72.14 H 6.95 N 3.12% Found C 71.85 H 7.23 N 3.09%

rac-*Methyl (3*R*, *3a*S*, *4*R*, *7*R*, *7a*R*)*-3-(*p*-*benzyloxybenzyl)-7-acetoxymethyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylate* (**24**). The solution of 25.2 mg (0.056 mmol) of **22** in 1 ml of pyridine was treated with 0.5 ml of acetic anhydride at r.t. for 23 h. After addition of 5 ml of toluene to the mixture and evaporation *i.v.*, 21.7 mg of an orange oil was obtained. Purification by column chromatography on 4 g of silica gel with CH_2Cl_2/acetone 98:2, 95:5, 90:10, and 80:20 (5×2 ml) afforded 17.9 mg (67%) of **24** as a colourless foam. – IR. (CH_2Cl_2): 3420 (N–H), 3040, 2970, 1740 (C=O, ester), 1708 (C=O, lactam), 1612, 1585, 1512, 1430, 1230, 830. – ^{1}H-NMR. (90 MHz, $CDCl_3$): see *Table 1.* – MS.: 491 (M^+), 431 ($M^+ - 60$ (CH_3COOH)), 418 ($M^+ - 73$ (CH_3COOCH_2)), 372, 294 ($M^+ - 197$ ($C_6H_5CH_2OC_6H_4CH_2$)), 266, 252, 234.

rac-*(3*R*, *3a*S*, *4*R*, *7*R*, *7a*R*)*-3-(*p*-*Benzyloxybenzyl)-7-hydroxymethyl-4, 5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylic acide lactone*[8])[9]) (**27**). As above (**18** → **22**); starting from 170 mg (0.308 mmol) of **18** 155 mg of crude acid **20** was obtained. Treatment of this with 5 ml of pyridine/acetic anhydride 2:1 at 55° for 15 h yielded, after addition of 10 g of ice and extraction with CH_2Cl_2, 110 mg of crude **27**. Crystallization from CH_2Cl_2/pentane gave 83.0 mg (65%) of pure **27** as colourless prisms, m.p. 165–166°. – IR. (KBr): 3210, 1770 (C=O, lactone), 1695 (C=O, lactam), 1515, 1235, 1190, 1005. – ^{1}H-NMR. (90 MHz, $CDCl_3$): see *Table 2.* – ^{13}C-NMR. (22.63 MHz, $CDCl_3$): see *Table 4.* – MS.: 417 (M^+), 220 ($M^+ - 197$ ($C_6H_5CH_2OC_6H_4CH_2$), 198.

$C_{26}H_{27}NO_4$ (417.51) Calc. C 74.80 H 6.52 N 3.36% Found C 74.76 H 6.63 N 3.25%

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