

23. Approaches to the Synthesis of Cytochalasans. Part 3¹⁾. Synthesis of a Substituted Tetrahydroisoindolinone Moiety Possessing the Same Relative Configuration as Proxiphomin

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Summary

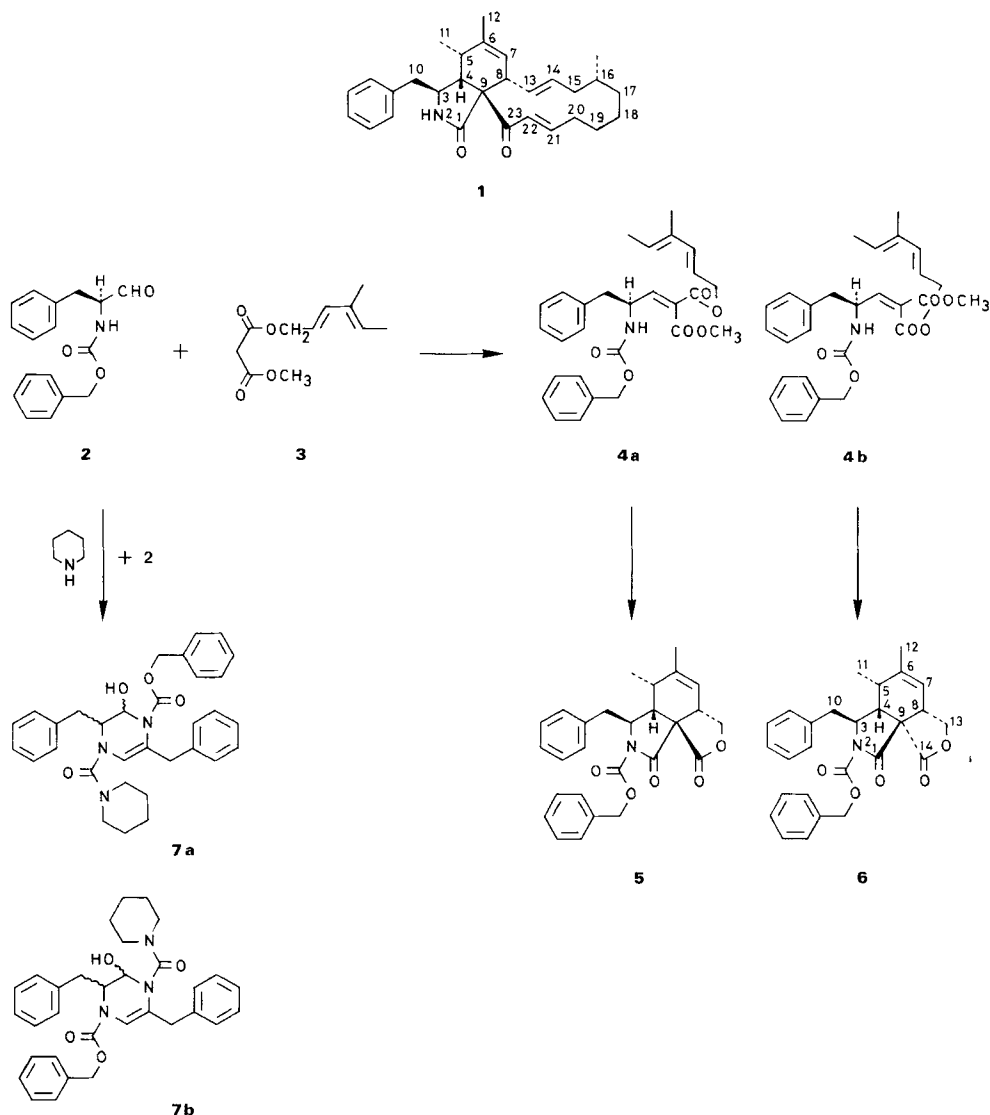
The total synthesis of the tetrahydroisoindolinone moiety corresponding to proxiphomin (**1**) is described, bearing functional groups for the attachment of the macrocyclic ring. *Knoevenagel-Cope* condensation of racemic 2-(benzyloxycarbonylamino)-3-phenylpropanal (**2**) with methyl (4-methyl-2,4-hexadienyl) malonate (**3**) yielded a mixture of the (*E*)- and (*Z*)-olefins **4a** and **4b**, which upon heating underwent intramolecular *Diels-Alder* cyclization (*cf. Scheme 1*). From the resulting products the tetrahydroisoindoline derivative **6** was isolated. X-ray analysis of **6** [5] revealed the same relative configurations at C(3), C(4), C(5) and C(8) as in **1**, but not at C(9). Hydrolysis of **6** with KOH was accompanied by a change in configuration at C(9) yielding the hydroxy acid **14** which was converted into the hydroxy ester **11** (*cf. Scheme 4*). The presence of a *cis*-anellated lactam ring in **11** has been confirmed by X-ray analysis of its *O*-acetyl derivative **16** [5]. Ring closure of the hydroxy acid **14** gave the lactone **17**, corresponding to the natural product **1** as to the configuration. The presence of the *N*-benzyloxycarbonyl group in lactone **6** has been shown to be essential for the above-mentioned 'inversion' at C(9), because no configurational change occurred with the *N*-unprotected lactone **8** when treated under the same conditions. The only product obtained was the hydroxy ester **10** possessing the same configuration at C(9) as **8**. Along with stereochemical considerations, mechanistic aspects of the reactions are discussed.

In a preliminary communication [2] concerning the construction of the tetrahydroisoindolinone moiety of proxiphomin (**1**) (*cf. Scheme 1*) we had described the synthesis of two synthons, **2** and **3**, and their *Knoevenagel-Cope* condensation yielding a mixture of the alkylidenemalonates **4a** and **4b**. Further, it had been shown that this (*E/Z*)-mixture easily undergoes intramolecular *Diels-Alder* reaction to form a doubly anellated cyclohexene derivative to which structure **5** had been assigned.

¹⁾ Part 2: s. [1].

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Scheme 1



On the basis of mechanistic reasons four different transition states had to be considered for the [2+4]-cycloaddition. Compound **5** was expected to be formed from the thermodynamically more stable (*E*)-olefin **4a**. As Scheme 2 shows, addition modes **a** and **b** should be favoured over **c** and **d** with respect to steric interaction of the substituent bearing chirality. For stereoelectronic reasons considerable secondary overlap between the orbital lobe at C(1)³ in the LUMO of the dienophile with that at C(7) in the HOMO of the diene can be expected for the transition states **a** and **c**, and only to a lesser extent for **b** and **d**. Taking both effects into account mode **a** leading to **5** should be preferred.

³) For convenience, the numbering used in this communication corresponds to that proposed for the cytochalasans [3]; compare also footnote 7 in the exper. part.

Evidence for the relative configurations at C(3), C(4), C(5), and C(8)³) of the cycloadduct was obtained from decoupling experiments on the 400-MHz-¹H-NMR. spectrum (*cf.* Fig. 1). The coupling constants observed (*cf.* Table 1) were consistent

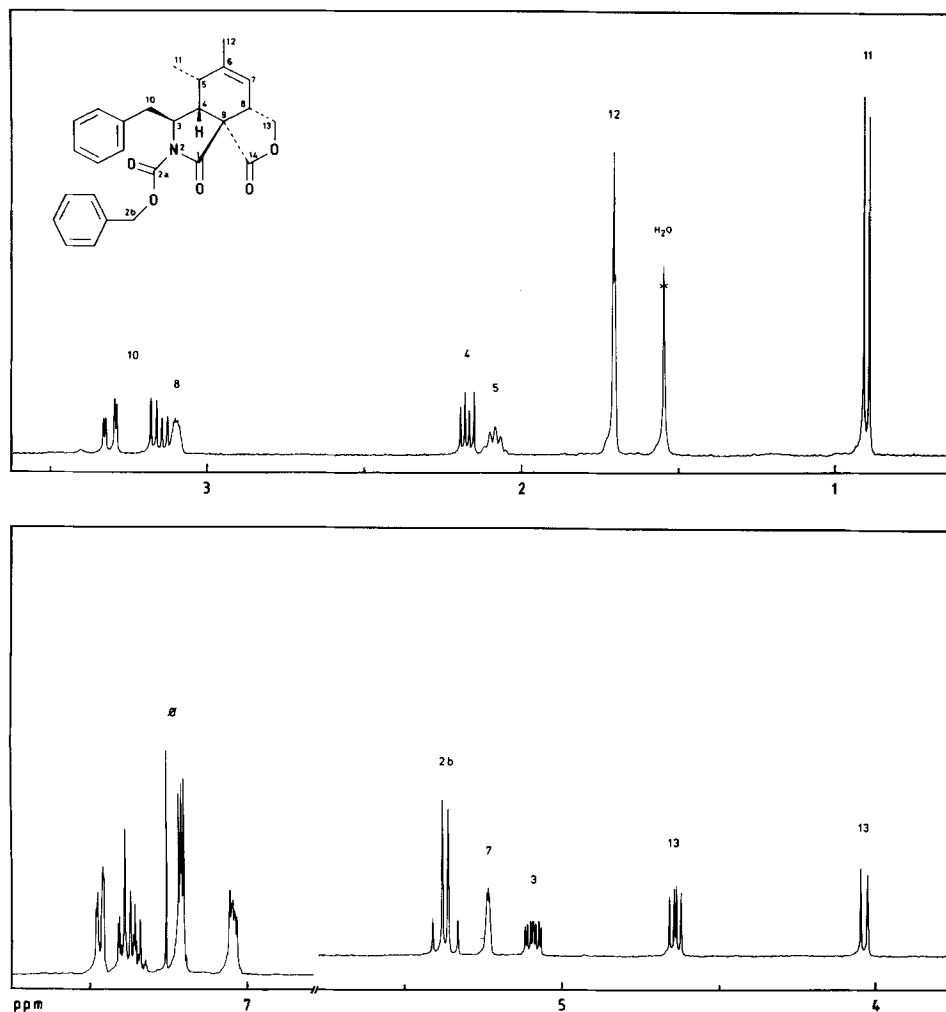
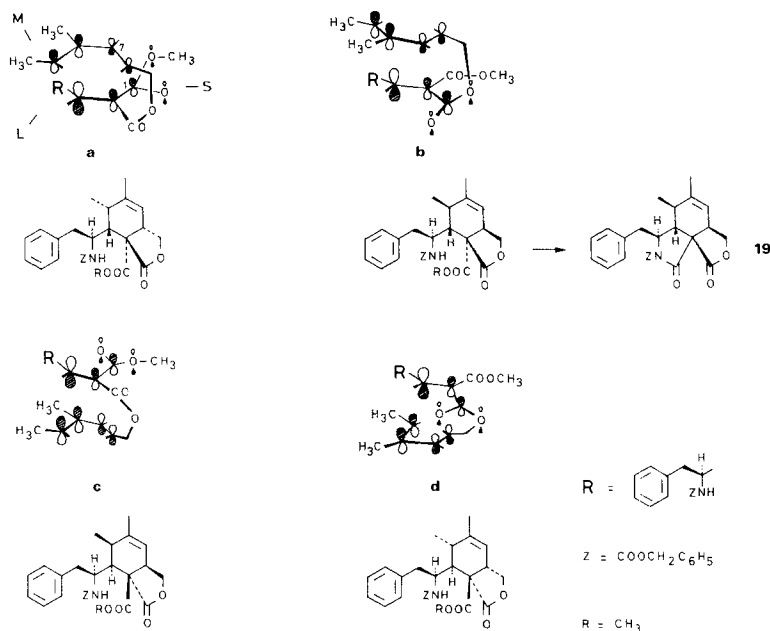


Fig. 1. 400-MHz-NMR. spectrum of compound 6

Table 1. Comparison of the coupling constant ranges estimated for 5 and 6 from Dreiding models with the observed values

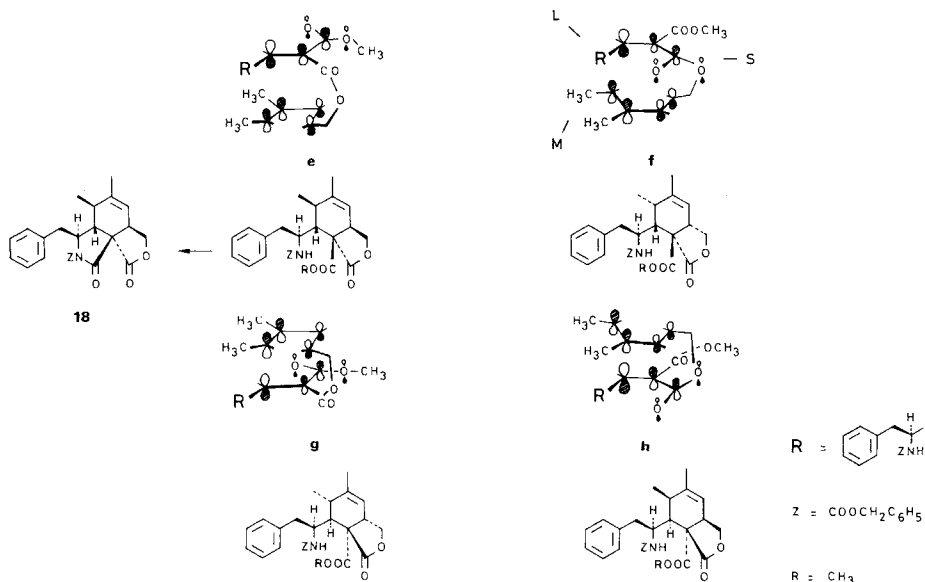
Compound	$\theta_{3,4}$	$J_{3,4}$	$\theta_{4,5}$	$J_{4,5}$
5	120°	2–9 Hz	40°	4–8 Hz
6	175°	9–14 Hz	40°	4–8 Hz
Values found for the cycloadduct		9.2 Hz		5.7 Hz

Scheme 2. Possible transition states in the [2+4]-cycloaddition of the (*E*)-olefin **4a**

with the values calculated from the dihedral angles of the *Dreiding* model of **5** [4]. No direct information, however, was available concerning the configuration of the remaining chiral centre C(9). Therefore, the epimeric structure **6** could not be excluded. Since the values of the coupling constants measured were also compatible with those expected for the epimer **6**, the cycloadduct was subjected to X-ray diffraction analysis [5]. This investigation confirmed the relative configurations at C(3), C(4), C(5), and C(8), but revealed a *cis*-relationship for the attachment of the lactone moiety on the cyclohexene ring and a *trans*-relationship for the attachment of the γ -lactam moiety. Hence, the cycloadduct obtained possesses the structure **6**.

It can be concluded from this result that the [2+4]-cycloadduct **6** must have arisen from the (*Z*)-olefin **4b**. Again four transition states, **e**–**h**, are possible (*cf.* Scheme 3). Thus, assuming that secondary isomerization of the (*E*)- into the (*Z*)-olefin is highly improbable, the *Knoevenagel-Cope* condensation of **2** and **3** must have produced considerable amounts of the thermodynamically less favoured (*Z*)-olefin **4b**, leading *via* transition state **f** to compound **6**. Furthermore, one can conclude that the (*E*)-olefin **4a** present in the mixture either does not react as anticipated, or if it does, the adduct must be insufficiently stable during the formation or isolation.

The total yield of cycloadduct **6** obtained from the (*E/Z*)-mixture **4a/4b** did not exceed 10% based on starting materials **2** and **3** which were used in equimolar amounts (*s. exper. part*). All attempts to improve the yield of **6** failed. However, chromatography of the mother liquor afforded up to 38% of a second compound **7** for which structure **7a** or **7b** was deduced from analytical and spectral data. Taking into account that in the formation of **7** two equivalents of aldehyde **2** are consumed, the possible maximum yield of cycloadduct **6** amounts to 25%, calculated on the basis of the remaining aldehyde **2**.

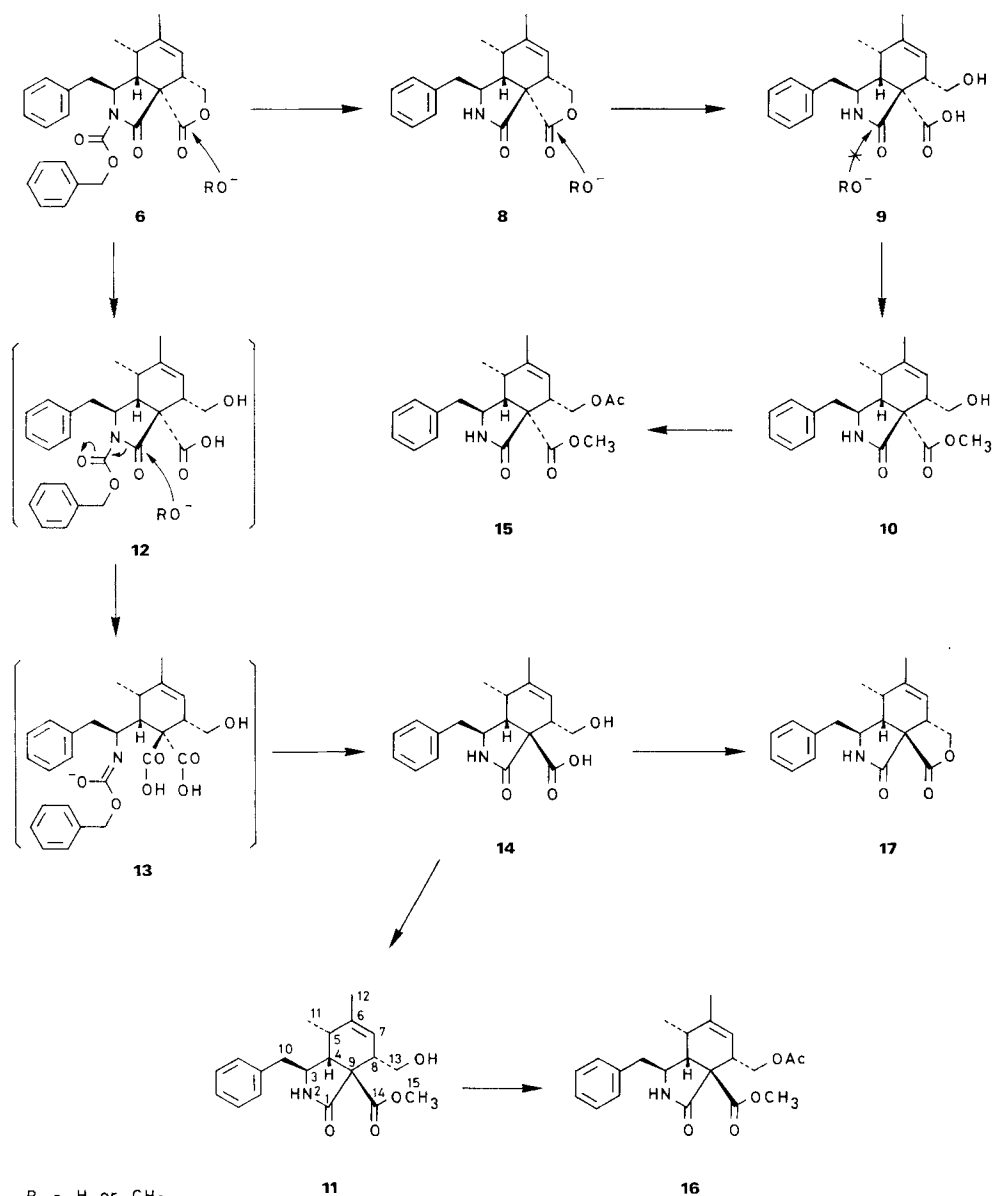
Scheme 3. Possible transition states in the [2+4]-cycloaddition of the (Z)-olefin **4b**

Thus, disregarding the above mentioned competition reaction, the overall yield of **6** would be about 40%, resulting from a sequence of three discrete transformations.

The conversion of the cycloadduct **6** into target lacton **17** (*cf.* Scheme 4) which exhibits the same relative configuration as **1** also at C(9) is based again on the general principle of our synthetic concept [2] [6]. It takes advantage of the quasi-symmetrical substitution pattern at the quaternary C-atom C(9). Attempts to open the lactone ring were conducted simultaneously with the original lactone **6** and the corresponding *N*-unprotected lactone **8**. The latter was obtained from **6** in high yield by reaction with iodotrimethylsilane [7] in benzene or on treatment with aluminium isopropylate in boiling xylene. It was found that stereochemical differentiation with respect to the asymmetric centre C(9) in **6** and **8** could be achieved by the attack of hydroxide ion. As expected, alkaline hydrolysis of **8** gave the corresponding hydroxy acid **9** which was converted immediately into its methyl ester **10** by treatment with diazomethane. Interestingly enough, the same sequence of reactions, when applied to the *N*-benzyloxycarbonyl derivative **6**, took a different course resulting in the formation of the epimeric ester **11**. This fact may be understood if one assumes that in both compounds **6** and **8** the first reaction takes place at the lactone carbonyl group to give the corresponding hydroxy acids **12** and **9**, respectively. In the case of **12** a second attack of hydroxide ion at the lactam carbonyl group follows, as the negative charge in **13** is stabilized by resonance. The intermediate **13** is converted into the thermodynamically more stable *cis*-lactam **14** by consecutive cleavage of the *N*-benzyloxycarbonyl group and ring closure between the amino and the α -oriented carboxyl group⁴). In context with the explanation

⁴) A reversed sequence of these two steps, although being less probable, cannot be ruled out.

Scheme 4



given for the different behaviour of **6** and **8** towards alkaline hydrolysis, it is important to note that neither ester **10** nor ester **11** was interconverted when treated again with aqueous methanolic KOH-solution followed by reesterification with diazomethane.

It was inferred from the mass spectra that the esters **10** and **11** which differ little but significantly with respect to their R_f values are indeed stereoisomers. Both compounds show a parent peak at m/z 434 and very similar fragmentation patterns. A close resemblance was also found in the IR. spectra, the absorption in the double bond region being almost identical. More relevant evidence that **10** and **11** differ from each other only relative to the configuration at C(9) was obtained from a comparison of the 400-MHz- ^1H -NMR. spectra⁵⁾ (cf. Fig. 2–5) in which nearly all the coupling constants could be measured. As may be seen from Table 2 all values are in

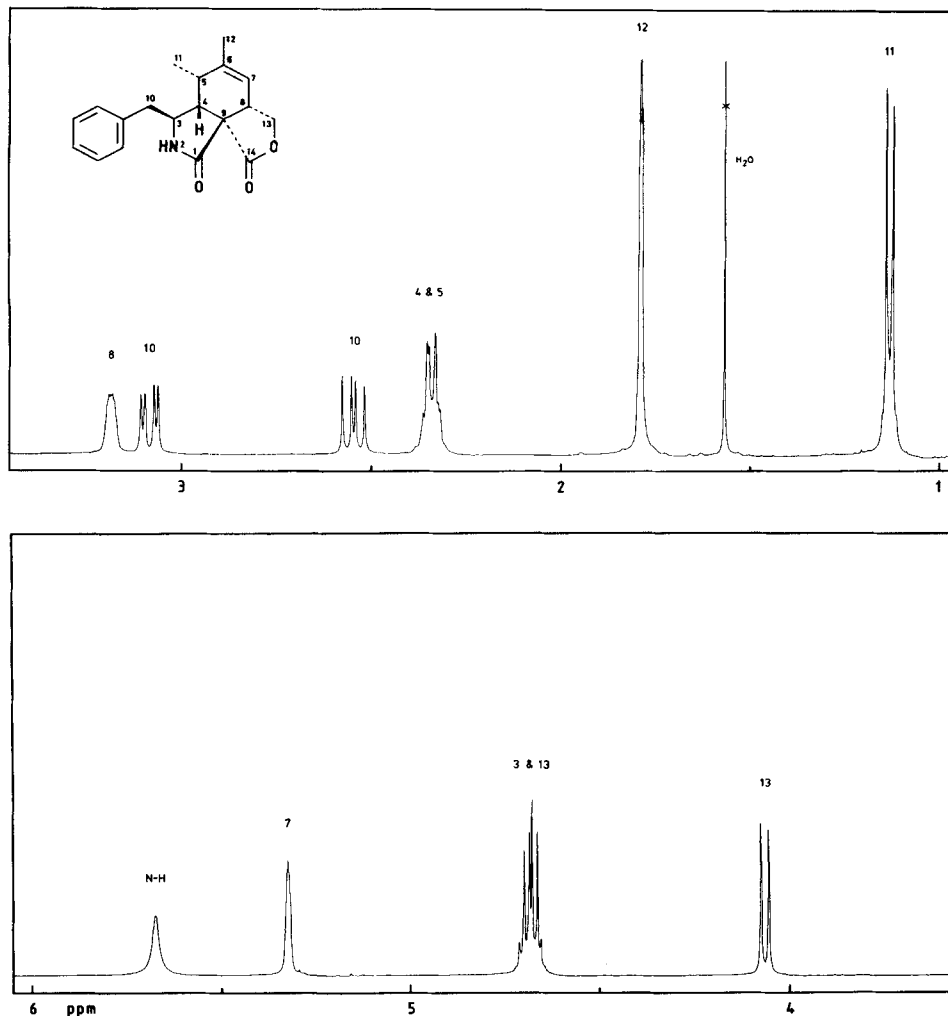
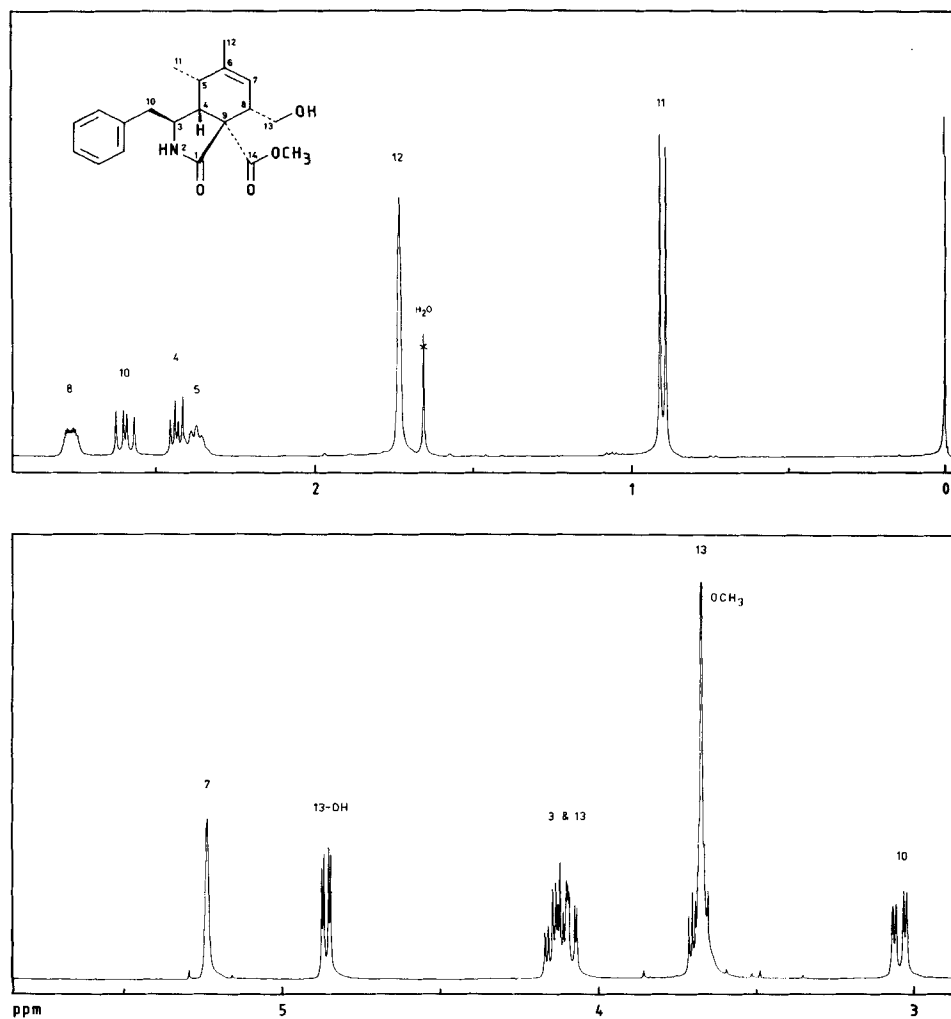


Fig. 2. 400-MHz-NMR. spectrum of compound **8**

⁵⁾ We thank Dr. H.P. Kellerhals and Mr J. Sonderegger, Spectrospin AG, Fällanden, for the measurement of these spectra.

Table 2. Comparison of the coupling constant ranges estimated for **8**, **10**, **11** and **17** from Dreiding models with the values actually observed

Compound	$\theta_{3,4}$	$J_{3,4}$	$\theta_{4,5}$	$J_{4,5}$
10	180°	9-14 Hz 10.0 Hz	30°	6-10 Hz 6.0 Hz
11	120°	2-9 Hz 4.2 Hz	35°	5-9 Hz -
8	175°	9-14 Hz 9.5 Hz	40°	4-8 Hz -
17	120°	2-9 Hz 0 Hz	40°	4-8 Hz 7.6 Hz

Fig. 3. 400-MHz-NMR. spectrum of compound **10**

good agreement with those calculated from the individual dihedral angles estimated by appropriate *Dreiding* models.

Specific information concerning the chirality at C(9) of **10** and **11** emerged from a correlation of the spatial arrangements of γ -substituents with the individual chemical shifts observed in the ^{13}C -NMR. spectra (*cf.* Table 3). For instance, a considerable upfield shift is found for the resonance of C(9) in **10** due to an almost *cis*-arrangement of C(9) and C(11) with respect to the C(4),C(5) bond. An analogous effect is absent in **11**.

The presence of a primary hydroxyl group in both esters **10** and **11** was demonstrated by mild acetylation to **15** and **16**, respectively. Although the natural configuration (see **1**) at C(3),C(4),C(5),C(8), and C(9) in the ester **11** had to be

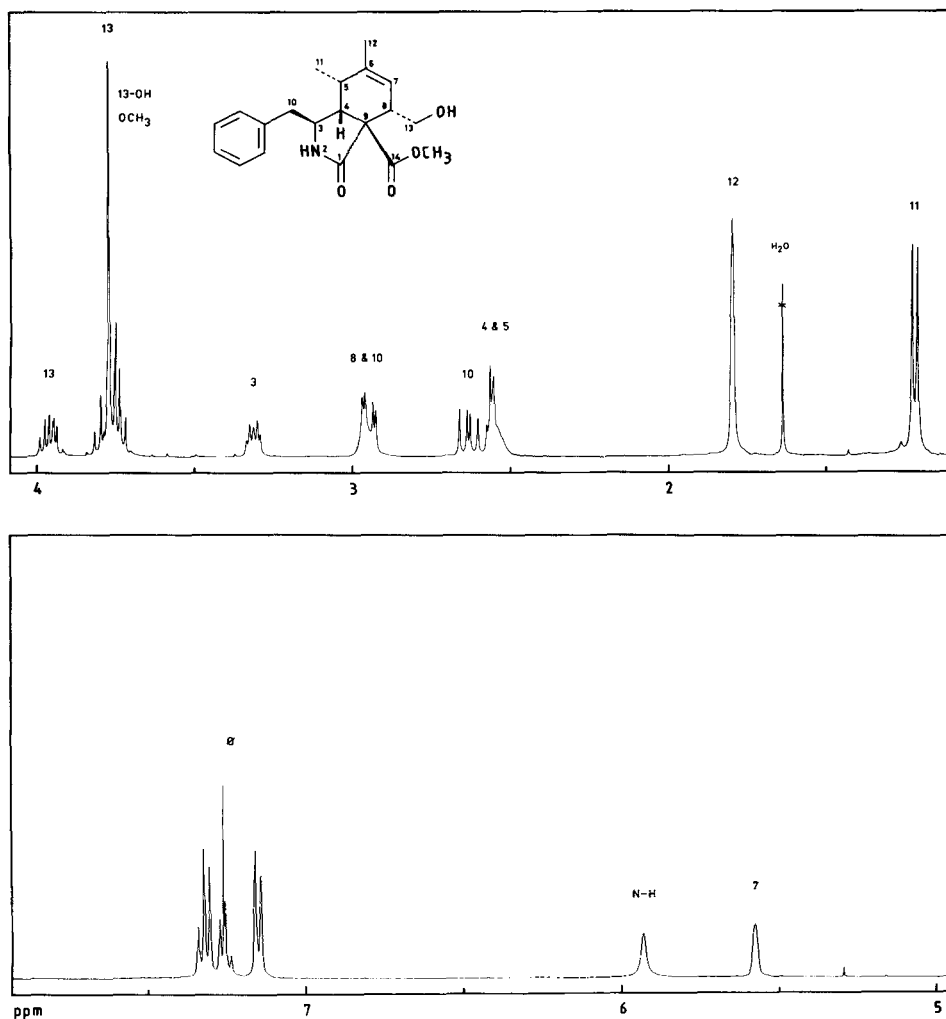


Fig.4. 400-MHz-NMR. spectrum of compound **11**

concluded from the arguments presented above, its crystalline acetyl derivative **16** was analyzed by X-ray diffraction [5]. This additional investigation fully confirmed structure **11**; its relative configuration corresponds to the one of proxiphomin (**1**).

The way to the original goal, the lactone **17**, *i.e.*, the lactone **5** in its *N*-deprotected form, was now free with the achievement of a selective 'inversion' at C(9) of the cycloadduct **6** *via* open chain intermediates such as the hydroxy acid **14**. Treatment of **14** with acetic anhydride/pyridine resulted in the formation of the new lactone **17**, epimeric to the lactone **8** obtained from **6** by removal of the *N*-benzyloxycarbonyl group. The configuration of **17** was proven by smooth reopening of the lactone ring to the hydroxy acid **14** which was identified as its methyl ester **11**. In a more or less rigid system, such as the tetrahydroisoindolinone **17**, a *trans*-fused five-

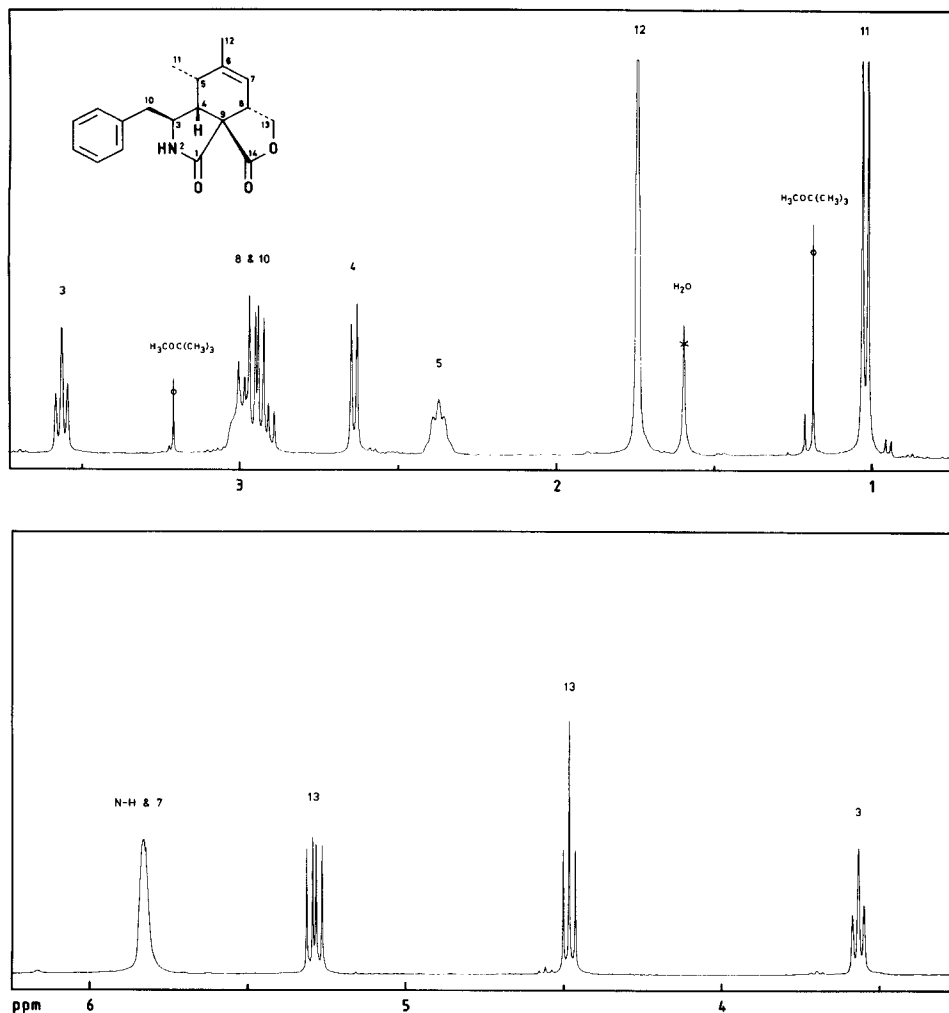


Fig. 5. 400-MHz-NMR. spectrum of compound **17**

Table 3. ^{13}C -NMR. data of the N-protected lactone **6**, the lactones **8** and **17**, and the esters **10** and **11**

Atom	Compound				
	6	8	17	10	11
C(1)	169.3	172.2	172.4	169.2	173.3
C(3)	58.2	54.9	54.5	57.0	56.4
C(4)	33.9	33.8	35.8	33.5	34.4
C(5)	39.0	39.2	43.0	46.6	41.7
C(6)	142.7	142.8	141.6	136.9	139.6
C(7)	120.9	121.8	119.7	122.3	123.3
C(8)	43.1	49.6	44.2	55.7	53.2
C(9)	53.9	53.7	59.4	56.2	60.3
C(10)	37.6	40.6	44.3	39.9	44.1
C(11)	13.1	13.5	13.3	12.2	14.2
C(12)	22.1	22.2	19.6	21.5	20.2
C(13)	72.1	72.1	69.8	64.0	62.4
C(14)	173.5	175.1	174.0	176.2	175.1
C(15)				51.9	52.7
C(1')	135.6	137.0	137.3	136.9	136.9
C(2'/6')	128.6 ^{a)}	128.9 ^{a)}	128.7 ^{a)}	128.9 ^{a)}	128.7 ^{a)}
C(3'/5')	129.8 ^{a)}	129.1 ^{a)}	129.6 ^{a)}	129.0 ^{a)}	129.6 ^{a)}
C(4')	127.0 ^{a)}	127.2	126.7	127.1	126.9
C ₆ H ₅ CH ₂ OCO	151.6				
C ₆ H ₅ CH ₂ OCO	68.6				
C(1'')	135.1				
C(2''/6'')	128.6 ^{a)}				
C(3''/5'')	128.5 ^{a)}				
C(4'')	128.3 ^{a)}				

a) These correlations are only tentative and may be reversed.

membered lactone ring is definitely more strained than the *cis*-fused analogue in **8**. Accordingly, the IR.-stretching band of the lactone carbonyl group in **17** is found at a higher frequency as compared with that of the less strained lactone **8**.

Evidently, the [2+4]-cycloaddition of the (*Z*)-olefin **4b** does not follow the course deduced from generally accepted rules according to which compound **18** should have been formed as a result of kinetic control (*cf.* Scheme 3). It must be considered, however, that in an internal *Diels-Alder* reaction like that described above, simultaneous formation of a five-membered ring is involved. The fact that transition state **f** is preferred over **e** leading to the adduct **6** with an almost unstrained *cis*-fused lactone ring demonstrates, that the reaction is thermodynamically governed. Obviously, secondary orbital overlap stabilizing transition state **e** does not afford the additional energy required for the anellation of a highly strained *trans*-lactone ring as in compound **18**. An analogous consideration should apply to the [2+4]-cycloaddition of the (*E*)-olefin **4a**. Again the adduct **19** is expected to be preferably formed over **5** (*cf.* Scheme 2)⁶⁾.

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⁶⁾ Experimental evidence will be presented in a subsequent paper.

Experimental Part

General remarks. See [1]. Moreover, the 60-MHz- ^1H -NMR. spectra were recorded on a Varian EM 360 spectrometer, and the mass spectra (MS., m/z) were run in the Institute for Physical Chemistry, University of Basel, on an A.E.I. MS-30 instrument by Mr R. Fink.

Synthesis of the aldehyde 2 [8]. - a) *Synthesis of rac-N-benzyloxycarbonyl-phenylalanine ethyl ester.* To a chilled suspension of 6.90 g (30 mmol) of *rac*-phenylalanine ethyl ester hydrochloride in 150 ml of ethyl acetate 120 ml of an aqueous 1M KHCO_3 -solution were added rapidly under stirring. Then 5.80 ml of benzyl chloroformate were added dropwise within 1.5 h, the temp. being kept in the range of 0 to 3° . While still cold, the mixture was acidified to $\text{pH} \approx 3$ with 35 ml of 2N HCl and extracted with a total of 250 ml of ethyl acetate. The organic phases were washed with water (6 times 25 ml), and dried. Evaporation of the solvent i.V. yielded 11.875 g of a viscous oil. The crude product was dissolved in 40 ml of CH_2Cl_2 and purified by column chromatography on 400 g of silica gel. Elution with CH_2Cl_2 and CH_2Cl_2 /ether 99:1, 97.5:2.5 and 95:5 (6 times 200 ml each) afforded 7.545 g of *rac*-N-benzyloxycarbonyl-phenylalanine ethyl ester from fractions 8-16, m.p. $79-80^\circ$. - ^1H -NMR. (60 MHz, CDCl_3): 7.5-7.0 (*m*, 10 H, 2 C_6H_5); 5.5-5.0 (*br.*, HN); 5.1 (*s*, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$); 4.9-4.4 (*m*, 1 H-C(2)); 4.15 (*qa*, $J=7$, $\text{CH}_3\text{CH}_2\text{O}$); 3.1 (*br. d*, 2 H-C(3)); 1.2 (*t*, $J=7$, $\text{CH}_3\text{CH}_2\text{O}$).

b) *Synthesis of rac-2-(benzyloxycarbonylamino)-3-phenylpropanal (2).* A solution of 4.09 g (12.5 mmol) of *rac*-N-benzyloxycarbonyl-phenylalanine ethyl ester in 50 ml of dry benzene was evaporated i.V. to give an oil free of water. The residue was dissolved under Ar in 100 ml of dry toluene, the solution cooled under stirring to -50 to -55° , and 25 ml of a 20% solution of diisobutylaluminium hydride in toluene were added within 30 min. After stirring for an additional 45 min at low temp., 25 ml of 3M ethanol in toluene were added, followed by 50 ml of 1.5N citric acid in water, whereby vigorous shaking was required. During extraction with 200, 100 and 100 ml of ether, 50, 25 and 25 g of ice were used for cooling. The organic phases were washed with 1.5N citric acid (twice 50 ml), sat. NaCl-solution (8 times 25 ml) and dried. Evaporation of the solvents i.V. left 3.92 g of a yellowish oil, which was purified by column chromatography on 250 g of silica gel. Elution with CH_2Cl_2 (3 times 300 ml and 3 times 100 ml) and CH_2Cl_2 /ether 99.5:0.5, 99:1, 97.5:2.5, 95:5 and 90:10 (4 times 100 ml each) afforded 2.530 g of crystalline **2** from fractions 15-23, m.p. $76-78^\circ$. - IR. (CH_2Cl_2): 3425 (N-H), 1735 and 1715 (C=O, ester, aldehyde), 1505, 1495, 1215, 1050. - ^1H -NMR. (60 MHz, CDCl_3): 9.5 (*s*, 1 H-C(1)); 7.5-7.0 (*m*, 10 H, 2 C_6H_5); 5.35 (*br.*, HN); 5.05 (*s*, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$); 4.8-4.2 (*m*, 1 H-C(2)); 3.0 (*br. d*, 2 H-C(3)). - ^{13}C -NMR. (CDCl_3): 199.0 (*s*, C(1)); 156.0 (*s*, $\text{C}_6\text{H}_5\text{CH}_2\text{OCO}$); 136.1, 135.7, 129.3, 128.7, 128.5, 128.1, 128.0, 126.9 (2 C_6H_5); 66.9 (*t*, $\text{C}_6\text{H}_5\text{CH}_2\text{OCO}$); 61.1 ($d \times d$, C(2)); 35.1 (*t*, C(3)).

$\text{C}_{17}\text{H}_{17}\text{NO}_3$ (283.33) Calc. C 72.06 H 6.05 N 4.94% Found C 72.16 H 6.11 N 4.76%

Synthesis of the mixed malonic ester 3. - a) *Synthesis of (E)-2-methyl-2-butenal (tiglic aldehyde).* According to a procedure described in [9] tiglic aldehyde was prepared without difficulty, b.p. $59-60^\circ/102$ Torr ([9]: $61-63^\circ/108$ Torr). - ^1H -NMR. (60 MHz, CDCl_3): 9.35 (*s*, 1 H-C(1)); 6.8-6.3 (*m*, 1 H-C(3)); 2.2-1.85 ($d \times d$, $J=6$, $J'=1$, 3 H-C(4)); 1.75 (*d*, $J=1$, 3 H-C(5)) (*cf.* [10]).

b) *Synthesis of methyl (E,E)-4-methyl-2,4-hexadienoate.* To a stirred suspension prepared from 22.0 g of NaH (55% dispersion in mineral oil) and 400 ml of dry benzene under Ar, 73 ml (0.5 mol) of trimethyl phosphonoacetate were added slowly (2 h, temp. below 30°). After additional stirring for 2 h at RT, a solution of 48.5 ml (0.5 mol) of tiglic aldehyde in 20 ml of dry benzene was added dropwise within 1.5 h, the temp. being kept at $40-50^\circ$. Finally, the mixture was warmed 4 h to 65° , then cooled, diluted with 400 ml of ether and shaken with 200 ml of water. The aqueous phase was extracted further with 560, 400 and 400 ml of ether, the extracts being consecutively washed with water (100 ml) and 2.5M NaCl (3 times 100 ml) and dried. Evaporation of the solvent left 123 g of crude product which was purified by column chromatography on 1.75 kg of silica gel. Elution with CH_2Cl_2 (400 ml each fraction) yielded 37.82 g of colourless methyl (E,E)-4-methyl-2,4-hexadienoate from fractions 12-17, m.p. -15° . - ^1H -NMR. (60 MHz, CDCl_3): 7.3 (*d*, $J=16$, 1 H-C(3)); 6.3-5.7 (*m*, 1 H-C(5)); 5.75 (*d*, $J=16$, 1 H-C(2)); 3.7 (*s*, CH_3O); 2.0-1.7 (*m*, 3 H-C(6) and 3 H-C(7)).

c) *Synthesis of (E,E)-4-methyl-2,4-hexadien-1-ol (4-methylsorbitol).* To 417 ml of 0.81M LiAlH_4 in ether, prepared under Ar, a solution of 37.8 g (270 mmol) of methyl (E,E)-4-methyl-2,4-hexadienoate in 180 ml of dry ether was added at 0 to 4° within 2 h. After stirring for additional 2 h, 120 ml of 1.0N NaOH were added dropwise to the mixture while keeping the temp. below 10° . After filtration and washing with 12 times 50 ml of ether the filtrate was evaporated i.V. to yield 29.3 g of a yellowish liquid.

Distillation i.V. afforded 24.57 g of pure 4-methylsorbinol, b.p. 93–94°/16 Torr. - $^1\text{H-NMR}$. (60 MHz, CDCl_3): 6.2 (*d*, $J = 16$, 1 H-C(3)); 5.9–5.3 (*m*, 1 H-C(2) and 1 H-C(5)); 4.1 (br. *d*, 2 H-C(1)); 3.05 (*s*, HO); 2.0–1.5 (*m*, 3 H-C(6) and 3 H-C(7)). - $^{13}\text{C-NMR}$. (CDCl_3): 136.2 (*d*, C(3)); 134.1 (*s*, C(4)); 126.8 (*d*, C(2)); 125.3 (*d*, C(5)); 63.4 (*t*, C(1)); 13.7 (*qa*, C(7)); 12.0 (*qa*, C(6)).

$\text{C}_7\text{H}_{12}\text{O}$ (112.17) Calc. C 74.95 H 10.78% Found C 75.06 H 10.96%

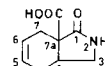
d) *Synthesis of methyl ((E,E)-4'-methyl-2',4'-hexadienyl) malonate (3)*. A solution of 2.73 g (20 mmol) of methyl (chloroformyl)acetate in 18 ml of dry CH_2Cl_2 was added dropwise to a stirred mixture of 2.28 g (20 mmol) of 4-methylsorbinol, 3.2 ml (23 mmol) of triethylamine and 5.0 ml of dry CH_2Cl_2 at 0° under Ar. The mixture was then stirred at RT. for 40 h. For work-up the mixture was diluted with 145 ml of ether, shaken with 2N HCl (25 ml) and ice (25 g) and with sat. NaCl-solution (9 times 25 ml), the aqueous phases being extracted again with ether (twice 75 ml). After drying, evaporation of the solvents i.V. afforded 4.25 g crude **3**. Purification was achieved in batches of 880 mg by column chromatography on 40 g of silica gel. Elution with CH_2Cl_2 /ether 99.5:0.5, 99:1, 97.5:2.5, 95:5 and 90:10 (4 times 20 ml each) yielded 587 mg of pure **3** as a colourless oil from fractions 5–13. - UV. (ethanol): 230.5 (4.06). - IR. (CH_2Cl_2): 1750, 1730 (both C=O), 1645 (C=C), 1330, 1145, 1020, 965. - $^1\text{H-NMR}$. (60 MHz, CDCl_3): 6.3 (*d*, $J = 16$, 1 H-C(3')); 5.85–5.25 (*m*, 1 H-C(2') and 1 H-C(5')); 4.7 (br. *d*, 2 H-C(1')); 3.75 (*s*, CH_3O); 3.35 (*s*, 2 H-C(2)); 2.0–1.6 (*m*, 3 H-C(6') and 3 H-C(7')). - $^{13}\text{C-NMR}$. (CDCl_3): 166.9 (*s*, C(3')); 166.3 (*s*, C(1)); 140.1 (*d*, C(3')); 133.8 (*s*, C(4')); 128.7 (*d*, C(5')); 119.0 (*d*, C(2')); 66.4 (*t*, C(1')); 52.4 (*qa*, CH_3O); 41.4 (*t*, C(2)); 13.8 (*qa*, C(7')); 11.9 (*qa*, C(6')). - MS.: 212 (M^+), 194 ($M^+ - 18$ (H_2O)), 111 ($M^+ - 101$ ($\text{C}_4\text{H}_5\text{O}_3$)), 101 ($M^+ - 111$ ($\text{C}_7\text{H}_{11}\text{O}$)), 95 (111 – 16 (CH_2)), 79 (95 – 16 (CH_2)).

Synthesis of rac-methyl ((E,E)-4'-methyl-2',4'-hexadienyl) (2E/2Z)-2-(2''-benzyloxycarbonylamino-3''-phenylpropylidene)malonate (4a/4b). To a solution of 211.3 mg (1.00 mmol) of **3** and 297.6 mg (1.05 mmol) of **2** in 2.5 ml of dry benzene were added 83 mg (0.40 mmol) of dry piperidinium benzoate and 1.57 g of granulated anhydrous CaSO_4 . This mixture was heated under reflux for 40 h, then diluted with 10 ml of water and extracted with ether (20 ml, twice 15 ml), the organic phases being washed with 2.5M NaCl (3 times 10 ml), and dried. Evaporation of the solvents i.V. afforded 507.9 mg of crude **4a/4b** as a brown oil which was immediately used in the following step.

Synthesis of rac-(3R,3aS*,4R*,7R*,7aS*)-3-benzyl-2-benzyloxycarbonyl-7-hydroxymethyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisindoline-7a-carboxylic acid lactone⁷⁾ 6, and rac-2,5ξ-dibenzyl-1-benzyloxycarbonyl-6ξ-hydroxy-4-piperidinocarbonyl-1,4,5,6-tetrahydropyrazine (7a) or rac-2,5ξ-dibenzyl-4-benzyloxycarbonyl-6ξ-hydroxy-1-piperidinocarbonyl-1,4,5,6-tetrahydropyrazine (7b)*. A solution of 507.9 mg of crude **4a/4b** in 2.5 ml of dry toluene was heated under reflux for 7 days. The mixture was then evaporated i.V. to give 506.0 mg of a brown residue in which a slow crystallization set in. Upon standing for several days 16.4 mg of **6** could be obtained by careful dilution of the residue with small amounts of ether and ether/diisopropyl ether. The mother liquor was subjected to column chromatography on 50 g of silica gel. Elution with CH_2Cl_2 (4 times 20 ml) and CH_2Cl_2 /ether 99:1, 97:3, 95:5, 85:15, and 60:40, ether and ether/acetone 99:1 and 95:5 (4 times 20 ml each) afforded unchanged **3** (fractions 16 and 17), 53.8 mg of **6** (fractions 18–21), and 137.2 mg of very impure **7** (fractions 22–25). Recrystallization from CH_2Cl_2 /ether yielded a further amount of 28.7 mg of pure **6** in colourless prisms of m.p. 174–175°. The crude **7** was further purified by column chromatography on 25 g of silica gel. Elution with CH_2Cl_2 and CH_2Cl_2 /acetone 99.5:0.5, 99:1, 97.5:2.5, and 95:5 afforded, after recrystallization from acetone/petroleum ether, 66.2 mg of pure **7** as plates of m.p. 189–190°.

Compound 6. - UV. (ethanol): 257 (2.85), 205 (4.39) sh. - IR. (KBr): 2970, 1763 (C=O, lactone), 1745 (C=O, carbamate), 1716 (C=O, lactam), 1490, 1445, 1375, 1340, 1270, 1150, 740, 720. - $^1\text{H-NMR}$.

⁷⁾ All cyclic compounds cited in this paper are regarded as derivatives of 1-oxo-3a,4,7,7a-tetrahydroisindoline-7a-carboxylic acid and hence named thereafter for convenience and easy comparison. For **6**, **8** and **17** the names do not correspond to the IUPAC rules (disregarding the specific relative configurations, the IUPAC names are: 3-benzyl-2-benzyloxycarbonyl-4,5-dimethyl-7,7a-(3'-oxo-2'-oxatrimethylene)-3a,4,7,7a-tetrahydroisindolin-1-one (**6**), 3-benzyl-4,5-dimethyl-7,7a-(3'-oxo-2'-oxatrimethylene)-3a,4,7,7a-tetrahydroisindolin-1-one (**8** and **17**)). However, in all NMR. spectra the numbering proposed for cytochalasans [3] is used (cf. Footnote 3 and Schemes 1 and 4).



(400 MHz, CDCl_3 , cf. Fig. 1)⁷): 7.50–7.00 (*m*, 10 H, 2 C_6H_5); 5.39 and 5.35 (*AB*, $J_{\text{gem}} = 12.0$, $\text{C}_6\text{H}_5\text{CH}_2\text{O}$); 5.26–5.22 (*m*, 1 H–C(7)); 5.10 ($d \times d \times d$, $J(3,4) = 9.2$, $J(3,10) = 7.0$, $J'(3,10) = 3.0$, 1 H–C(3)); 4.64 ($d \times d$, $J_{\text{gem}} = 8.4$, $J(8,13) = 6.0$, 1 H–C(13)); 4.04 (*d*, $J_{\text{gem}} = 8.4$, $J'(8,13) = 0$, 1 H–C(13)); 3.31 ($d \times d$, $J_{\text{gem}} = 14.0$, $J'(3,10) = 3.0$, 1 H–C(10)); 3.15 ($d \times d$, $J_{\text{gem}} = 14.0$, $J(3,10) = 7.0$, 1 H–C(10)); 3.12–3.07 (*m*, 1 H–C(8)); 2.17 ($d \times d$, $J(3,4) = 9.2$, $J(4,5) = 5.7$, 1 H–C(4)); 2.13–2.03 (*m*, $J(4,5) = 5.7$, $J(5,11) = 7.0$, 1 H–C(5)); 1.71 (*br. s*, $J(8,12) = 1.8$, 3 H–C(12)); 0.89 (*d*, $J(5,11) = 7.0$, 3 H–C(11)). – ^{13}C -NMR. (CDCl_3 ; cf. Table 3. – MS.: 446 ($M^+ + 1$), 354 ($M^+ - 91$ (C_7H_7)), 338 ($M^+ - 107$ ($\text{C}_7\text{H}_7\text{O}$)), 310 ($M^+ - 135$ ($\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5$)), 91 (C_7H_7).

$\text{C}_{27}\text{H}_{27}\text{NO}_5$ (445.52) Calc. C 72.79 H 6.11 N 3.14% Found C 72.60 H 6.22 N 3.07%

Compound 7. – IR. (CH_2Cl_2): 3430 (O–H), 2950, 1765 (C=O, carbamate). 1700 (C=O, urea), 1605, 1495, 1395, 980. – ^1H -NMR. (90 MHz, CDCl_3): 7.5–7.0 (*m*, 15 H, 3 C_6H_5); 5.18 (*d*, $J = 1$, $\text{C}_6\text{H}_5\text{CH}_2\text{OCO}$); 4.59 (*s*, 1 H–C(3)); 4.54 (*d*, $J = 8$, 1 H–C(6)); 4.25–4.0 (*m*, 1 H–C(5)); 3.4–2.9 (*m*, 2 H, $\text{C}_6\text{H}_5\text{CH}_2\text{C}$ (5)); 2.79 (*d*, $J = 3$, 2 H, $\text{C}_6\text{H}_5\text{CH}_2\text{C}$ (2)); 2.8–2.5 (*m*, 2 H of piperidino); 2.4–2.0 (*m*, 2 H of piperidino); 1.55 (*s*, HO); 1.6–1.25 (*m*, 6 H of piperidino). – MS.: 525 (M^+), 434 ($M^+ - 91$ (C_7H_7)), 397 ($M^+ - 84 - 44$ (C_5H_{10} , and CO_2)), 390 ($M^+ - 135$ ($\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5$)), 91 (C_7H_7).

$\text{C}_{32}\text{H}_{35}\text{N}_3\text{O}_4$ (525.65) Calc. C 73.12 H 6.71 N 7.99% Found C 73.03 H 6.73 N 7.98%

Synthesis of rac-(3R*, 3aS*, 4R*, 7R*, 7aS*)-3-benzyl-7-hydroxymethyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisindoline-7a-carboxylic acid lactone¹) (8). – Method A. To a solution of 1.077 g (2.42 mmol) of 6 in 45 ml of dry benzene were added 5 ml of 0.7M iodotrimethylsilane in benzene under stirring at RT. The solution was stirred for 62 h, then poured on 10 g of ice and 20 ml of water, and extracted with CH_2Cl_2 (3 times 60 ml). The organic phases were washed with 2N NaOH/2N $\text{Na}_2\text{S}_2\text{O}_3$ (10 ml) and water (twice 15 ml), and dried. Evaporation of the solvents i.V. afforded 1.23 g of a yellow oil which was freed from benzyl iodide i.V. at 50° to give 753 mg of crude 8. Recrystallization from CH_2Cl_2 /pentane yielded 728.0 mg of 8 as colourless prisms of m.p. 167–169°.

Method B. A mixture of 233 mg (0.52 mmol) of 6 and 75 mg (0.37 mmol) of aluminium isopropylate in 5 ml of xylene was heated to 120° for 21 h. Then the mixture was cooled to RT., diluted with 50 ml of CH_2Cl_2 , and shaken consecutively with 1N HCl (30 ml) and water (twice 15 ml), the aqueous phases being reextracted twice with 50 ml of CH_2Cl_2 . The combined organic extracts were dried and the solvents distilled off i.V. to give 201.0 mg of crude 8. Recrystallization from acetone/ether yielded 145.1 mg of 8 as colourless needles, m.p. 167–168°. – IR. (KBr): 3240, 1755 (C=O, lactone), 1710 (C=O, lactam), 1150, 1095, 760, 700. – ^1H -NMR. (400 MHz, CDCl_3 , cf. Fig. 2)⁷): 7.40–7.15 (*m*, 5 H, C_6H_5); 5.67 (*br.*, HN); 5.32 (*br. s*, 1 H–C(7)); 4.68 ($d \times d$, $J_{\text{gem}} = 8.3$, $J(8,13) = 5.8$, 1 H–C(13)); 4.68 ($d \times d \times d$, $J(3,4) = 9.5$, $J(3,10) = 9.4$, $J'(3,10) = 4.2$, 1 H–C(3)); 4.07 (*d*, $J_{\text{gem}} = 8.3$, $J'(8,13) = 0$, 1 H–C(13)); 3.22–3.15 (*m*, 1 H–C(8)); 3.08 ($d \times d$, $J_{\text{gem}} = 13.9$, $J'(3,10) = 4.2$, 1 H–C(10)); 2.55 ($d \times d$, $J_{\text{gem}} = 13.9$, $J(3,10) = 9.4$, 1 H–C(10)); 2.40–2.28 (*m*, $J(3,4) = 9.5$, $J(5,11) = 7.0$, 1 H–C(4) and 1 H–C(5)); 1.79 (*br. s*, 3 H–C(12)); 1.13 (*d*, $J(5,11) = 7.0$, 3 H–C(11)). – ^{13}C -NMR. (CDCl_3 ; cf. Table 3. – MS.: 311 (M^+), 220 ($M^+ - 91$ (C_7H_7)), 133 ($\text{C}_{10}\text{H}_{13}$).

$\text{C}_{19}\text{H}_{21}\text{NO}_3$ (311.38) Calc. C 73.29 H 6.80 N 4.50% Found C 73.23 H 7.03 N 4.39%

Synthesis of rac-methyl (3R*, 3aS*, 4R*, 7R*, 7aS*)-3-benzyl-7-hydroxymethyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisindoline-7a-carboxylate (10). To a stirred mixture of 126.0 mg (0.406 mmol) of 8, and 12 ml of methanol/benzene 2:1, 2 ml of 50% aqueous KOH-solution were added. After stirring for 16 h at RT., the mixture was acidified with 2N H_2SO_4 and extracted with CH_2Cl_2 (3 times 30 ml). The extracts were washed with water (twice 10 ml) and dried, affording, after removal of the solvent i.V., 132 mg of crude acid 9. The latter was dissolved in 5 ml of methanol and treated with a diazomethane solution in ether until the yellow colour persisted. Evaporation i.V. left 131 mg of crude 10. Recrystallization from methanol/ CH_2Cl_2 /pentane yielded 105 mg of pure 10 as colourless prisms, m.p. 159–161°. – IR. (KBr): 3380, 3240, 1732 (C=O, ester), 1677 (C=O, lactam), 1210, 1147, 758, 697. – ^1H -NMR. (400 MHz, CDCl_3 , cf. Fig. 3)⁷): 7.40–7.15 (*m*, 5 H, C_6H_5); 6.1–6.0 (*br.*, HN); 5.24 (*br. s*, 1 H–C(7)); 4.86 ($d \times d$, $J(\text{HO}-\text{C}(13), \text{H}-\text{C}(13)) = 8.0$, $J'(\text{HO}-\text{C}(13), \text{H}-\text{C}(13)) = 3.0$, HO–C(13)); 4.14 ($d \times d \times d$, $J(3,4) = 10.0$, $J(3,10) = 9.2$, $J'(3,10) = 4.0$, 1 H–C(3)); 4.09 ($d \times d \times d$, $J_{\text{gem}} = 11.6$, $J(8,13) = 9.0$, $J'(\text{HO}-\text{C}(13), \text{H}-\text{C}(13)) = 3.0$, 1 H–C(13)); 3.76 (*s*, $\text{CH}_3\text{O}-\text{C}(14)$); 3.67 ($d \times d \times d$, $J_{\text{gem}} = 11.6$, $J'(8,13) = 2.0$, $J(\text{HO}-\text{C}(13),$

H-C(13))=8.0, 1 H-C(13)); 3.04 ($d \times d$, J_{gem} =10.0, $J(3,10)$ =4.0, 1 H-C(10)); 2.81-2.73 (m , $J(7,8)$ =2.0, $J(8,13)$ =9.0, $J'(8,13)$ =2.0, 1 H-C(8)); 2.60 ($d \times d$, J_{gem} =10.0, $J'(3,10)$ =9.2, 1 H-C(10)); 2.44 ($d \times d$, $J(3,4)$ =10.0, $J(4,5)$ =6.0, 1 H-C(4)); 2.37 ($d \times qa$, $J(4,5)$ =6.0, $J(5,11)$ =7.5, 1 H-C(5)); 1.73 (br. s, 3 H-C(12)); 0.90 (d , $J(5,11)$ =7.5, 3 H-C(11)). - ^{13}C -NMR. (CDCl_3): cf. Table 3. - MS.: 313 ($M^+ + 1 - 31$ (CH_3O)); 220 ($M^+ - 91 - 32$ (C_7H_7 and CH_3OH)); 133 ($\text{C}_{10}\text{H}_{13}$).

$\text{C}_{20}\text{H}_{25}\text{NO}_4$ (343.42) Calc. C 69.95 H 7.33 N 4.08% Found C 70.10 H 7.45 N 4.04%

Synthesis of rac-methyl (3R,3aS*,4R*,7R*,7aR*)-3-benzyl-7-hydroxymethyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisindoline-7a-carboxylate (11).* As above (**8**→**10**), 192.4 mg (0.432 mmol) of **6**, 12 ml of methanol/benzene 2:1, and 2 ml of 50% aqueous KOH-solution gave 140.5 mg of crude acid **14**, which was esterified as above to afford 170 mg of crude **11**. Recrystallization from methanol/ CH_2Cl_2 and ether/pentane yielded 134 mg of pure **11** as colourless prisms, m.p. 168-170°. - IR. (KBr): 3470, 3240, 1724 ($\text{C}=\text{O}$, ester), 1675 ($\text{C}=\text{O}$, lactam), 1245, 1040, 697. - ^1H -NMR. (400 MHz, CDCl_3 , cf. Fig. 4)⁷: 7.36-7.13 (m , 5 H, C_6H_5); 6.00-5.86 (br., HN); 5.58 (br. s, 1 H-C(7)); 3.95 ($d \times d \times d$, J_{gem} =12.8, $J(8,13)$ =4.8, 1 H-C(13)); 3.84-3.69 (m , HO-C(13)); 3.77 (s , $\text{CH}_3\text{O}-\text{C}(14)$); 3.77 ($d \times d \times d$, J_{gem} =12.8, $J'(8,13)$ =7.1, 1 H-C(13)); 3.31 ($d \times d \times d$, $J(3,4)$ =4.2, $J(3,10)$ =4.0, $J'(3,10)$ =9.6, 1 H-C(3)); 3.00-2.93 (m , $J(8,13)$ =4.8, $J'(8,13)$ =7.1, 1 H-C(8)); 2.95 ($d \times d$, J_{gem} =14.0, $J(3,10)$ =4.0, 1 H-C(10)); 2.63 ($d \times d$, J_{gem} =14.0, $J'(3,10)$ =9.6, 1 H-C(10)); 2.59-2.49 (m , $J(3,4)$ =4.2, $J(5,11)$ =7.0, 1 H-C(4) and 1 H-C(5)); 1.80 (br. s, 3 H-C(12)); 1.22 (d , $J(5,11)$ =7.0, 3 H-C(11)). - ^{13}C -NMR. (CDCl_3): cf. Table 3. - MS.: 313 ($M^+ + 1 - 31$ (CH_3O)); 220 ($M^+ - 91 - 32$ (C_7H_7 and CH_3OH)), 133 ($\text{C}_{10}\text{H}_{13}$).

$\text{C}_{20}\text{H}_{25}\text{NO}_4$ (343.42) Calc. C 69.95 H 7.33 N 4.08% Found C 69.93 H 7.33 N 4.08%

Synthesis of rac-methyl (3R,3aS*,4R*,7R*,7aS*)-7-acetoxymethyl-3-benzyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisindoline-7a-carboxylate (15).* A solution of 47 mg (0.137 mmol) of **10** in 3 ml of pyridine/acetic anhydride 2:1 was kept at 30° for 20 h. Then 10 g of ice and 15 ml of 2N H_2SO_4 were added, and the mixture was stirred for 2 h. The product was extracted with CH_2Cl_2 (3 times 20 ml), the extract washed with water (twice 10 ml), and dried. Evaporation of the solvent afforded 47 mg of crude **15**, which crystallized from acetone/ CH_2Cl_2 /pentane to yield 34.5 mg of pure **15**, m.p. 122-124°. - IR. (KBr): 3200, 1735 ($\text{C}=\text{O}$, ester), 1690 ($\text{C}=\text{O}$, lactam), 1226, 1032, 692. - ^1H -NMR. (90 MHz, CDCl_3)⁷: 7.5-7.1 (m , 5 H, C_6H_5); 6.2-6.0 (br., HN); 5.49 (br. s, 1 H-C(7)); 4.74 ($d \times d$, J_{gem} =9.7, $J=3.5$, 1 H-C(13)); 4.50 (d , J_{gem} =9.7, 1 H-C(13)); 4.3-3.9 (m , 1 H-C(3)); 3.64 (s , $\text{CH}_3\text{O}-\text{C}(14)$); 3.2-2.5 (m , 1 H-C(8) and 2 H-C(10)); 2.5-2.2 (m , 1 H-C(4) and 1 H-C(5)); 2.07 (s , $\text{CH}_3\text{COO}-\text{C}(13)$); 1.74 (br. s, 3 H-C(12)); 0.87 (d , $J(5,11)$ =7.0, 3 H-C(11)).

$\text{C}_{22}\text{H}_{27}\text{NO}_5$ (385.46) Calc. C 68.55 H 7.06 N 3.63% Found C 68.33 H 7.12 N 3.62%

Synthesis of rac-methyl (3R,3aS*,4R*,7R*,7aR*)-7-acetoxymethyl-3-benzyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisindoline-7a-carboxylate (16).* As above (**10**→**15**) with 54 mg (0.157 mmol) of **11**: 57 mg of crude **16**. Recrystallization from acetone/ CH_2Cl_2 /ether yielded 44.5 mg of pure **16** as colourless needles, m.p. 208-209°. - IR. (KBr): 3180, 3070, 1737 ($\text{C}=\text{O}$, ester), 1725 ($\text{C}=\text{O}$, ester), 1692 ($\text{C}=\text{O}$, lactam), 1532, 1243, 700. - ^1H -NMR. (90 MHz, CDCl_3)⁷: 7.45-7.05 (m , 5 H, C_6H_5); 6.05-5.8 (br., HN); 5.6-5.5 (br., 1 H-C(7)); 4.49 (s , 1 H-C(13)); 4.41 (d , $J=2$, 1 H-C(13)); 3.77 (s , $\text{CH}_3\text{O}-\text{C}(14)$); 3.45-3.15 (m , 1 H-C(3)); 3.1-2.3 (m , 2 H-C(10), 1 H-C(8), 1 H-C(5) and 1 H-C(4)); 2.03 (s , $\text{CH}_3\text{COO}-\text{C}(13)$); 1.79 (br. s, 3 H-C(12)); 1.17 (d , $J=7$, 3 H-C(11)). - MS.: 385 (M^+), 312 ($M^+ - 73$ ($\text{CH}_3\text{COOCH}_2$)), 266 ($M^+ - 91 - 28$ (C_7H_7 and CO)), 234 ($M^+ - 91 - 60$ (C_7H_7 and $\text{C}_2\text{H}_4\text{O}_2$)), 179 ($M^+ - 91 - 73 - 42$ (C_7H_7 , $\text{CH}_3\text{COOCH}_2$ and CON)).

$\text{C}_{22}\text{H}_{27}\text{NO}_5$ (385.46) Calc. C 68.55 H 7.06 N 3.63% Found C 68.29 H 7.28 N 3.65%

Synthesis of rac-methyl (3R,3aS*,4R*,7R*,7aR*)-3-benzyl-7-hydroxymethyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisindoline-7a-carboxylic acid lactone⁷ (17).* A mixture of 192 mg (0.431 mmol) of **6**, 12 ml of methanol/benzene 2:1, and 2 ml of 50% aqueous KOH-solution was stirred at RT. for 3 h. The mixture was then acidified with 2N H_2SO_4 , extracted with CH_2Cl_2 (3 times 30 ml), the combined extract washed with water (15 ml), and dried. After evaporation of the solvent i.V. 142 mg of crude acid **14** were obtained. The acid **14** was dissolved in 3 ml of pyridine/acetic anhydride 2:1, and the mixture kept at 45° for 15 h. Then 10 g of ice were added, and after stirring for 30 min, the mixture was shaken with

30 ml of CH_2Cl_2 . The organic phase was extracted with 2N Na_2CO_3 (10 ml), 2N HCl (10 ml), and water (3 times 10 ml). After drying, the solvent was removed and 159 mg of crude **17** were obtained. Crystallization from CH_2Cl_2 /acetone/pentane yielded 94.0 mg of pure **17** as colourless prisms of m.p. 202–203°. – IR. (KBr): 3480, 3190, 3090, 1767 ($\text{C}=\text{O}$, lactone), 1695 ($\text{C}=\text{O}$, lactam), 1188, 1100, 1086, 1000, 728, 697. – ^1H -NMR. (400 MHz, CDCl_3 , cf. Fig. 5)⁷: 7.40–7.15 (m, 5 H, C_6H_5); 5.67 (br., HN); 5.32 (br. s, 1 H–C(7)); 4.68 ($d \times d$, $J_{\text{gem}} = 8.3$, $J(8,13) = 5.8$, 1 H–C(13)); 4.68 ($d \times d \times d$, $J(3,4) = 9.5$, $J(3,10) = 9.4$, $J'(3,10) = 4.2$, 1 H–C(3)); 4.07 (d , $J_{\text{gem}} = 8.3$, 1 H–C(13)); 3.22–3.15 (m, 1 H–C(8)); 3.08 ($d \times d$, $J_{\text{gem}} = 13.9$, $J'(3,10) = 4.2$, 1 H–C(10)); 2.55 ($d \times d$, $J_{\text{gem}} = 13.9$, $J(3,10) = 9.4$, 1 H–C(10)); 2.40–2.28 (m, $J(3,4) = 9.5$, $J(5,11) = 7.0$, 1 H–C(4) and 1 H–C(5)); 1.79 (br. s, 3 H–C(12)); 1.13 (d , $J(5,11) = 7.0$, 3 H–C(11)). – ^{13}C -NMR. (CDCl_3): cf. Table 3. – MS.: 311 (M^+), 236 ($M^+ - 58 - 17$ (COOCH_2 and NH_3)), 220 ($M^+ - 91$ (C_7H_7)).

$\text{C}_{19}\text{H}_{21}\text{NO}_3$ (311.38) Calc. C 73.29 H 6.80 N 4.50% Found C 73.10 H 6.83 N 4.34%

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