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APPROACH TO THE PERHYDROISOINDOLE SYSTEM IN CYTOCHALASIN B

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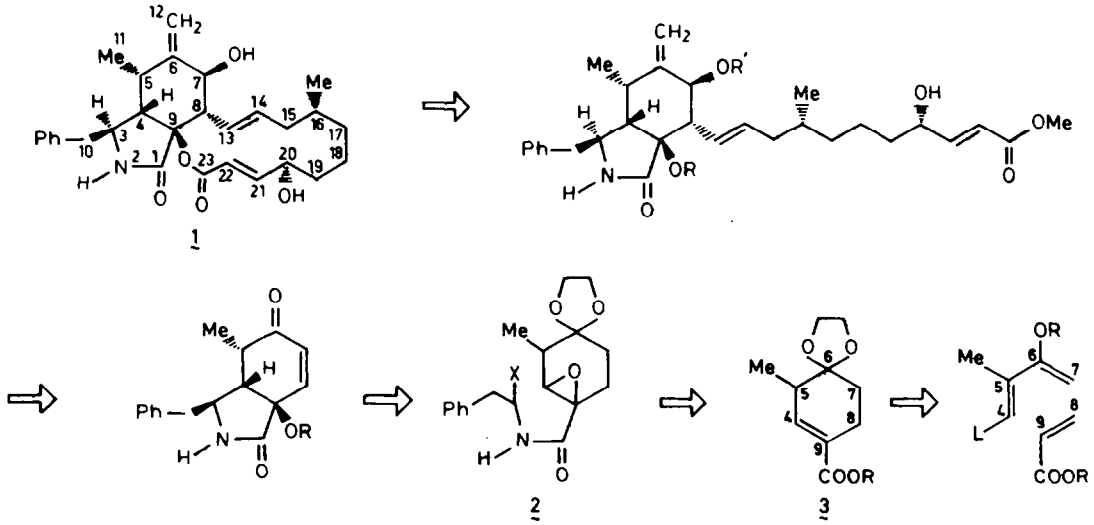
Abstract—The synthesis of the perhydroisoindole systems **17a, b**, **22** and **23** is described using the following sequence of reactions. Diels–Alder cycloaddition of silyloxydienes **4** with methyl acrylate leads, after methanolysis, to cyclohexenonecarboxylates **6**, subsequent acetalization and epoxidation of the α,β-unsaturated esters **7** yields the epoxy esters **8** and **9**. Conversion of these esters into acyl chlorides **11**, *via* the sodium salts **10**, and subsequent treatment with an amine component (phenylalanine methyl ester, diethyl aminomalonate and ethyl 2-amino benzoyl-acetate) produces the epoxy carbonamides **12**, **15** and **18**, respectively. These epoxy amides are subjected to acid-catalyzed hydrolysis to give the cyclohexenonecarbonamides **13**, **16** and **19**, respectively. Subsequent ring-closure of the amides **16** and **19** with base leads to the perhydroisoindole derivatives **17a, b** and **22**, respectively. The formation of **22** proceeds *via* a concomitant benzoyl transfer reaction. The amide **13** failed to ring-close. A by-product of the acid treatment of **18** is **21** which with base undergoes a benzoyl transfer to perhydroisoindole **23**. The structures of the products **9a**, **22** and **23** were ascertained by means of an X-ray analysis.

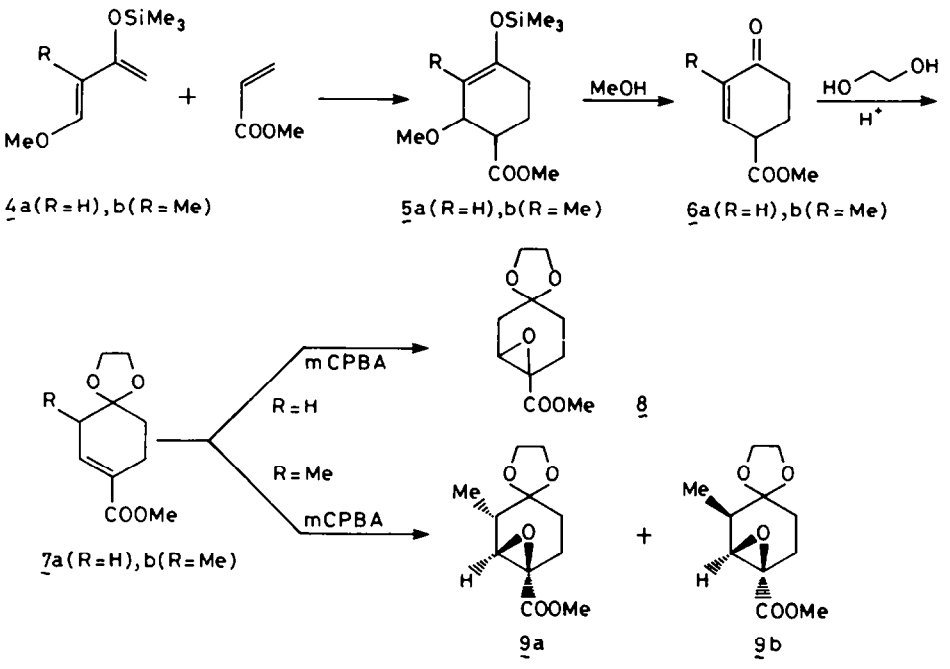
Cytochalasin B **1** (phomin, a 24-oxa-[14]-cytochalasan) is an important member of a class of natural cytostatic substances having remarkable biological properties.[1] The challenge of synthesizing this compound has been taken up by several research groups.[2] The first total synthesis of cytochalasin B, the most abundant member of this group of fungal metabolites, was recently completed by Stork *et al.*[3]

In our synthetic design which is outlined in Scheme 1, we plan to attach the long carbon chain of the macrocyclic lactone part to the perhydroisoindolone unit for instance by a conjugate addition. An essential feature of our plan is that the oxygen atom present at the angular position (C_9) of the isoindolone skeleton and which ultimately becomes part of the macrocyclic lactone, is introduced in an early stage of the synthesis. In the context of our interest in the chemistry of highly functionalized epoxides, we focus on the possibility of incorporating an epoxide function to serve this purpose. As indicated in Scheme 1 we intend to use an expoxy carboxamide **2** for the construction of the isoindolone skeleton. The precursor for such an epoxide, *viz.* cyclohexenecarboxylate **3**, is thought to be accessible by a Diels–Alder reaction. It should be noted that in the present plan the future C_8–C_9 bond† in **1** is introduced through the dienophilic partner in the construction of the six-membered ring. The syntheses of the perhydroisoindolone nucleus reported in the literature also involve a [4 + 2]-cycloaddition, however, in all cases with the C_4–C_9 bond incorporated in the dienophile.

†For the sake of convenience the number of atoms in the isoindolone system and its precursors is taken as that in cytochalasin B.



Scheme 1.



Scheme 2.

RESULTS AND DISCUSSION

For the implementation of the synthetic plan as outlined above, methoxy substituted silyloxydienes **4a, b** were taken as the diene components in the Diels–Alder reaction with methyl acrylate. The methoxy group serves as leaving group L (Scheme 1). Treatment of the cycloadducts **5a, b** with methanol gave the cyclohexenones **6a, b** which on further reaction with ethylene glycol produced acetals **7a, b** having the double bond in the desired position. The conversion of **5a** into **7a** could also be accomplished by a direct treatment with ethylene glycol. Epoxidation of **7a** with *m*CPBA gave in high yield the epoxy ester **8.** In the case of cyclohexenecarboxylate **7b** a mixture of two diastereomeric epoxy esters (**9a** and **b**) was obtained, which was separated by column chromatography. As the stereochemistry of these compounds is of crucial importance for furthering the plan, the structure of **9a** was unambiguously determined by an X-ray diffraction analysis.[4] A stereoview of the structure is portrayed in Fig. 1. The epoxy esters **8** and **9a** were converted into the corresponding sodium epoxy carboxylates **10a** and **b**, respectively, using the Claisen saponification procedure[5] (Scheme 3). Unexpectedly, the diastereomer **9b** could only be hydrolyzed with difficulty and considerable loss of material.

The sodium salt **10a** was transformed into acid chloride **11a** and subsequently treated with (*S*)-phenylalanine methyl ester to give epoxy carboxamide **12.** Unfortunately, the planned reaction involving a nucleophilic opening of the epoxide ring by the carboxylate carbanion at C_3 did not meet with success despite the several basic conditions tried. (No reaction was observed using t-BuOK/ether/30°, Et_3N/benzene/80°, LDA/THF/70°). As a way out epoxy amide **12** was treated with aqueous acid resulting in a concomitant removal of the acetal function and opening of the epoxide to give cyclohexenone **13.** Attempts to perform an intramolecular Michael addition of the benzoylated **13** led to aromatization producing **14.**

After this set-back it was decided to enhance the acidity of the proton at C_3. Accordingly, the model compound **15a** derived from amino malonic ester was prepared. Treatment with base (Et_3N/t-BuOH/110°) did not give the desired nucleophilic epoxide opening. With acid, however, smooth formation of substituted cyclohexenone **16a** was achieved. This compound gave on subsequent treatment with base indeed the desired ring closure reaction to perhydroisoindolone **17a.** In an analogous sequence of reactions the methyl substituted epoxy acyl chloride **11b** was converted[6] into the bicyclic system **17b.** Product **17b**

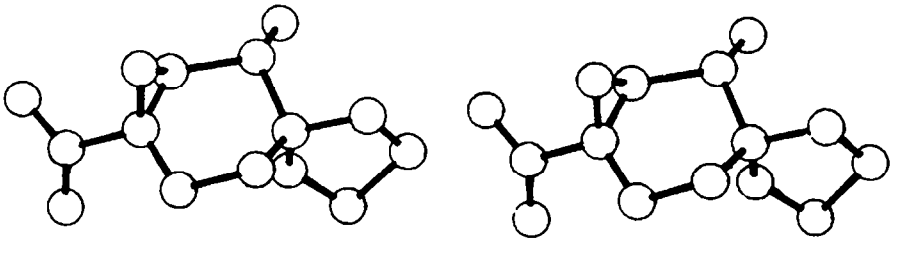
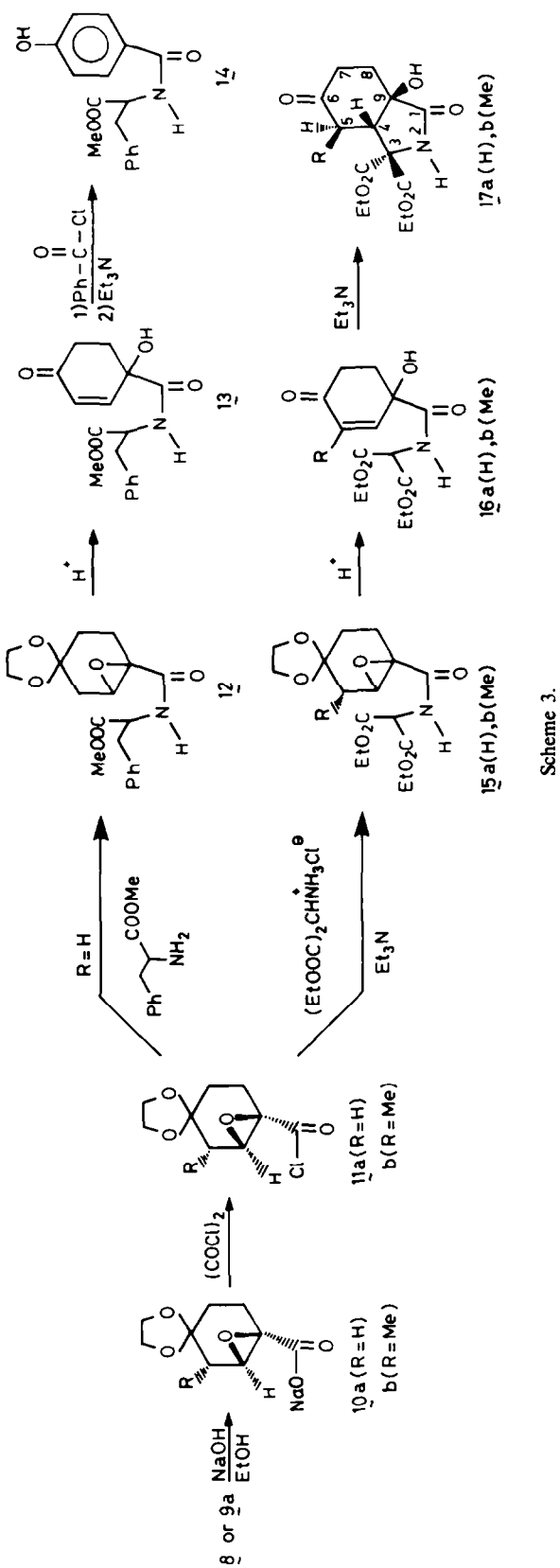


Fig. 1. Stereoview of compound **9a.**



Scheme 3.

was obtained as a single pair of enantiomers with the stereochemistry rac. 4*S*, 5*R*, 9*R*, as was deduced from the ^{1}H-NMR spectrum (Experimental).

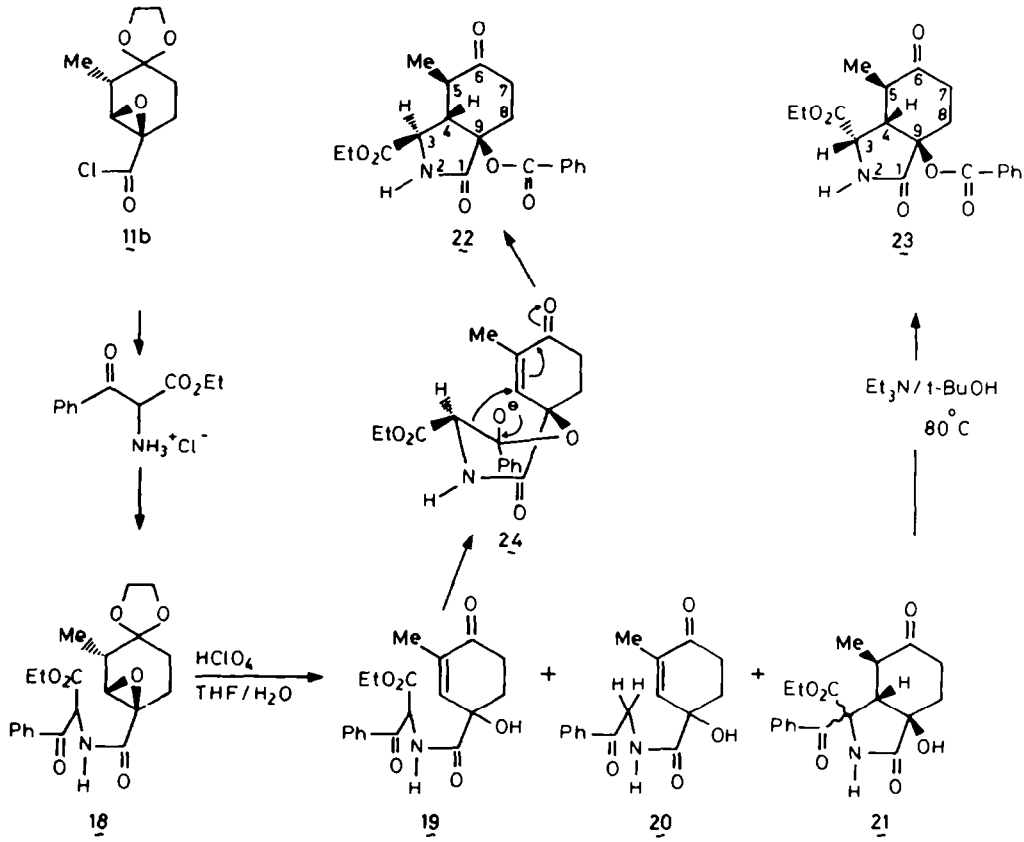
Although the stereochemistry at C_5 is opposite to the one present in naturally occurring cytochalasin 1 and therefore needs further attention, we decided to focus first on the introduction of the phenyl substituent at C_{10}. Therefore, the sequence of events shown in Scheme 3 (**11b**→**17b**) was repeated using ethyl aminobenzoylacetate instead of aminomalonate (Scheme 4).

Epoxy amide **18** again could not be ring-closed by means of base (DBU/t-BuOH/50°). Treatment with perchloric acid in aqueous THF at 65° resulted in a mixture of products containing the compounds **19** (45%), **20** (15%) and **21** (15%). Interestingly, the intramolecular Michael addition of cyclohexenone **19** under influence of base, is accompanied by an unforeseen benzoyl transfer to give **22**. The perhydroisoindolone **21**, obtained under acidic conditions from **18**, gave on further reaction with mild base also a benzoyl transfer (only for its C_3 epimer having the benzoyl group *syn* to the C_9 OH function) to lead to product **23**. The structures of the compounds **22** and **23** were deduced from their spectral characteristics (Experimental) and unambiguously ascertained by means of X-ray diffraction analyses.[7] The stereoviews of these structures are pictured in the Figs. 2 and 3, respectively. The stereochemistry of **22** was established as rac. 3*R*, 4*S*, 5*R*, 9*R* and that of **23** as rac. 3*S*, 4*S*, 5*R*, 9*R*.

The formation of perhydroisoindolone **21** from epoxy amide **18** can be envisaged by either an acid-catalyzed intramolecular Michael reaction of enone **19** or by a direct acid-catalyzed, opening of the epoxide ring. The former possibility can be ruled out as independent treatment of enone **19** with acid led to recovery of unchanged material. Therefore, it is suggested that acid-catalyzed epoxide opening by the C_3 enol, followed by acetal hydrolysis at C_6 and thermodynamic equilibration of the C_5 methyl ketone gives product **21**. The stereochemistry at C_3 could not be established, probably both epimers are present, the one with the benzoyl group *syn* to the C_9 OH undergoes the benzoyl transfer reaction to afford **23**.

Product **19** arises from initial hydrolysis of the acetal at C_6 to give a β,γ-epoxy ketone which then opens under the influence of aqueous acid. The remarkable benzoyl transfer of **19** under basic conditions cannot be rationalized by invoking a bicyclic compound of the type **21** with the benzoyl group *anti* to the OH function at C_9. Therefore, it is suggested that the C_9 OH function first reacts with the benzoyl group, as is pictured in intermediate **24**, which is then followed by a benzoyl transfer and a simultaneous enone conjugate addition. It is clear that **19** and **21** are formed from **18** in parallel reactions, the ratio of which is governed by subtle experimental factors.

The results presented in this paper allow the conclusion that the perhydroisoindolone skeleton can indeed be obtained from epoxy amides of the type **2**, although the process of formation deviates from the anticipated one (Scheme 1, 3 and 4). Although the planned introduction of the C_{10} phenyl group was not



Scheme 4.

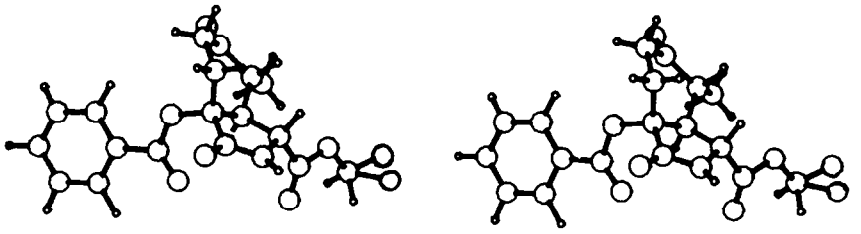


Fig. 2. Stereoview of compound **22**.

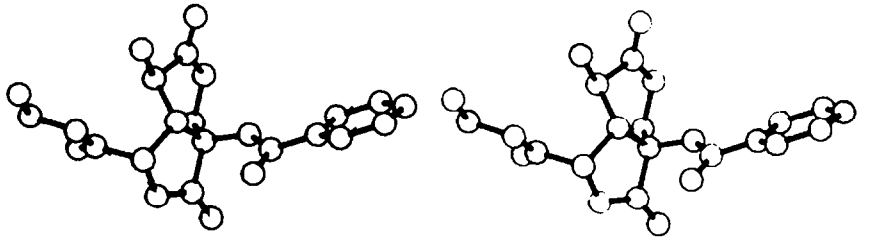


Fig. 3. Stereoview of compound **23**.

successful, the carbethoxy function at C_3 in **22** provides a handle to introduce the C_3 benzyl substituent. The stereochemistry at C_5 is opposite to the desired one for cytochalasin B **1**. However, as this stereochemistry is determined by thermodynamic factors, it may strongly be influenced by a substituent at C_8. Therefore, we will focus our forthcoming efforts on the introduction of a C_8 substituent and study its effect on the stereochemistry at C_5. Results will be reported in due course.

EXPERIMENTAL

All b.ps and m.ps are uncorrected. M.ps were determined on a Reichert m.p. microscope. IR spectra were taken on a Perkin–Elmer 257 grating spectrometer. NMR spectra were recorded on a Varian EM-390 instrument, using TMS as internal standard. In case silyloxy dienes were used or generated the glassware was washed with ammonia and dried at 150°, and the reactions were conducted in a nitrogen atmosphere. The silyloxy dienes **4a and 4b** were prepared according to Danishefsky.[8,9] Elemental analyses were carried out by Mr. J. Diersmann (Micro Analytical Department of the University). Preparative medium pressure column chromatographys were performed on the Chromatospac 100 or Miniprep LC (Jobin–Yvon) with the use of Merck silica gel H Type 60.

Methyl 4,4-*dioxyethylene*-1-*cyclohexene*-1-*carboxylate* **7a**

A mixture of diene **4a** (41 g, 0.238 mol) and methyl acrylate (21.5 g, 0.25 mol) in benzene (100 ml) was heated at reflux for 48 hr. The residue which remained after evaporation of the solvent and excess methyl acrylate was dissolved in benzene (300 ml), then ethylene glycol (31 g, 0.5 mol) and *p*-TosOH (3.3 g) were added and this mixture was refluxed for 16 hr with a Dean–Stark water trap. The soln was poured into a soln of $NaHCO_3$ (10 g) in water (200 ml), the organic phase separated and the aqueous layer extracted with ether (3 × 200 ml). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was distilled, b.p. 88–89°/0.3 mm Hg, yield 15.8 g (33%). ^{1}H-NMR ($CDCl_3$): δ1.74 (dd, 2H), 2.26–2.60 (m, 4H), 3.68 (s, OCH_3), 3.92 (s, 4H), 6.71–6.83 (m, 1H); IR (neat): ν1720 (C=O), 1650 (C=C) cm^{-1}; ^{13}C-NMR ($CDCl_3$): δ167.38 (C=O), 136.60 (–C–H), 129.98 (=C–CO_2CH_3), 107.33 (O–C–O), 64.59 (O–CH_2CH_2–O), 51.66 (OCH_3), 36.24 (1C), 30.78 (1C), 23.67 (1C).

Methyl 3-*methyl*-4,4-*dioxyethylene*-1-*cyclohexene*-1-*carboxylate* **7b**

A soln of diene **4b** (17.0 g, 0.091 mol) and methyl acrylate (35 g, 0.4 mol) in benzene (100 ml) was stirred for 3 days at 25° and for 3 days at 60°. The solvent and excess methyl acrylate were evaporated, the residue taken up in MeOH (250 ml) and this mixture was stirred at 25° for 48 hr. Removal of the solvents and distillation of the residue gave 11.4 g (75%) of *methyl*-3-*methyl*-4-*oxy*-2-*cyclohexene*-1-*carboxylate* **6b**, b.p. 87–91°/0.5 torr. ^{1}H-NMR ($CDCl_3$): δ1.83 (t, CH_3), 2.20–2.70 (m, 4H), 3.20–3.60 (m, 1H), 3.73 (s, OCH_3), 6.83 (br.s, 1H). A mixture of this ester (11.4 g, 0.068 mol), ethylene glycol (22 g, 0.35 mol) and *p*-TosOH (1 g) in benzene (200 ml) was heated under reflux (20 hr) using a Dean–Stark water trap. The mixture was poured into Na_2CO_3aq (10%), the benzene layer separated and the water-phase was extracted with ether (3 × 150 ml). Removal of the solvents *in vacuo* gave **7b** (13.6 g, 0.064 mol, 94% Calc on **6b**) which, according to ^{1}H-NMR, was sufficiently pure for further use. ^{1}H-NMR ($CDCl_3$): δ1.06 (d, CH_3), 1.40–2.70 (m, 5H), 3.70 (s, OCH_3), 3.96 (s, 4H), 6.66–6.80 (m, 1H); IR (CCl_4): ν1720 (C=O), 1685 (C=C) cm^{-1}. Because of the thermal lability distillation (b.p. 95–97°/0.4 torr) is accompanied by a considerable loss of material.

Methyl 1,2-*epoxy*-4,4-*dioxyethylene*-*cyclohexane* - 1 - *carboxylate* **8** *and sodium salt* **10a**

A mixture of **7a** (15.8 g, 0.079 mol) and *m*CPBA (24 g, 0.12 mol) in benzene (300 ml) was heated under reflux for 16 hr. After cooling to r.t. the soln was washed with Na_2SO_3aq (0.12 mol in 200 ml of water) and Na_2CO_3aq (0.14 mol in 200 ml of water). Drying over $MgSO_4$ and evaporation of the benzene gave **8** (15.2 g, 0.071 mol, 90%), which according to ^{1}H-NMR was sufficiently pure for further use. ^{1}H-NMR ($CDCl_3$): δ0.45–0.72 (m, 2H), 2.05–2.78 (m, 4H), 3.36–3.48 (m, 1H), 3.71 (s, OCH_3), 3.90 (br.s, 4H); IR (neat): ν1735 (C=O) cm^{-1}.

A "solution" of Na (1.61 g, 0.070 mol) in EtOH (80 ml) was added dropwise to a mixture of **8** (15.2 g, 0.071 mol), water (1.28 g, 0.071 mol) and dry EtOH (350 ml). After stirring for 16 hr at 25°, ether (300 ml) was added to this

mixture. The Na salt **10a** was filtered off, washed with ether and dried (100°, 100 torr). Yield: 12.87 g (0.058 mol, 82%), IR (KBr): ν1610 (C=O) cm^{-1}.

(*rac.*-1R, 2S, 3S) *Methyl* 1,2-*epoxy* - 3 - *methyl* - 4,4-*dioxyethylene* - *cyclohexane* - 1 - *carboxylate* **9a** *and sodium salt* **10b**, (*rac.*-1R, 2S, 3R) *Methyl* 1,2-*epoxy* - 3 - *methyl*-4,4-*dioxyethylene* - *cyclohexane* - 1-*carboxylate* **9b** *and the corresponding sodium salt*

A soln of **7b** (21.2 g, 0.1 mol) and *m*CPBA (40 g, 0.2 mol) in benzene (800 ml) was heated under reflux for 16 hr. After cooling to r.t. the soln was washed with Na_2SO_3aq (400 ml, 12%) and Na_2CO_3aq (500 ml, 10%), dried ($MgSO_4$) and concentrated. The residue, i.e. a mixture of the diastereomeric **9a** and **9b**, was chromatographed (medium pressure column chromatography, silica gel H60, hexane–diethyl ether 4:1) giving five fractions in the following order: 1.6 g of unidentified product, 6.0 g of **9a** (0.026 mol, 26%), 4.2 g of a mixture of **9a** and **9b** (0.018 mol, 18%), 5.3 g of **9b** (0.023 mol, 23%) and 1.0 g of unidentified product. Compound **9a** is a white solid which was crystallized from ether–pentane, m.p. 81–82°. ^{1}H-NMR ($CDCl_3$): δ1.03 (d, J = 7 Hz, CH_3), 1.20–2.70 (m, 5H), 3.10 (s, 1H), 3.73 (s, OCH_3), 3.93 (m, 4H); IR (KBr): ν1740 (C=O) cm^{-1}. (Found: C, 57.83; H, 7.02. Calc for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07%.) Compound **9b** is a light yellow oil. ^{1}H-NMR ($CDCl_3$): δ1.12 (d, J = 8.5 Hz, CH_3), 1.30–2.90 (m, 5H), 3.40 (d, J = 4.5 Hz, 1H), 3.76 (s, OCH_3), 3.90 (m, 4H).

Na (0.46 g, 0.020 mol) dissolved in abs EtOH (20 ml) was slowly added at r.t. to a mixture of **9a** (4.56 g, 0.02 mol) and water (0.36 g, 0.020 mol) in abs EtOH (80 ml). Stirring for 16 hr gave, after filtration, washing with ether and drying (110°, 20 mm Hg) 4.5 g of *sodium salt* **10b** (0.019 mol, 95%).

Na dissolved in abs EtOH (28 ml, 0.1 N) was slowly added at r.t. to a mixture of **9b** (6.9 g, 0.030 mol) and water (0.54 g, 0.030 mol) in abs EtOH (80 ml). This mixture was stirred for 16 hr. The solvent was evaporated, the residue taken up in MeOH (80 ml) and the salt precipitated with ether (800 ml). Filtration and washing with ether gave, after drying (100°, 20 mm Hg), 3.2 g of Na salt corresponding with **9b** (0.0135 mol, 45%). This compound is rather unstable at r.t.

(1R, 2S, 2'S + 1S, 2R, 2'S) - N-1'-(1'-*Methoxycarboxy* - 2'-*phenylethyl*) - 1,2-*epoxy*-4,4-*dioxyethylene* - *cyclohexane*-1-*carbonamide* **12**

Some drops of pyridine were added to a suspension of Na salt **10a** (0.608 g, 2.7 mmol) in dry THF (75 ml). This mixture was cooled to −20° and, while stirring, freshly distilled oxalyl chloride (0.570 g, 4.5 mmol) was gradually added. The mixture was warmed up to r.t. and the solvent and excess of oxalyl chloride were removed *in vacuo* at a temp. < 15°. The residue was dissolved in dry THF (100 ml) and S-phenyl-alanine methyl ester hydrochloride (0.583 g, 2.7 mmol) was added. To this suspension, while stirring and in a N_2 atmosphere, a soln of Et_3N (0.546 g, 5.4 mmol) in ether (100 ml) was gradually added (3 hr) at 25°. The mixture was concentrated *in vacuo*, the residue taken up in ether (150 ml), Et_3N.HCl filtered off and the filtrate was again concentrated. Medium pressure column chromatography (silica gel H60, $CHCl_3$–MeOH 100:1) of the residue gave 0.608 g of **12** (1.6 mmol, 50%). ^{1}H-NMR ($CDCl_3$): δ1.46–2.73 (m, 2H), 1.70–2.23 (m, 3H), 2.45–3.33 (m, 4H), 3.66 and 3.69 (2 × s, OCH_3), 3.91 (s, 4H), 4.63–4.92 (m, 1H), 6.54–6.86 (m, N–H), 6.91–7.33 (m, 5H); IR (CCl_4): ν3410 (NH), 1742 (C=O), 1694 (C=O, amide I). During the chromatographic purification there was some separation of the two diastereomers, this was not elaborated further.

(1S, 1'S + 1R, 1'S)-N-1'-(1'-*Methoxycarbonyl*-2'-*phenylethyl*) - 1-*hydroxy*-4-*oxo*-2-*cyclohexene* - 1 - *carbonamide* **13**

A soln of epoxy amid **12** (4.0 g, 11 mmol) in a mixture of water (200 ml), THF (200 ml) and ClO_4 (17 ml, 70%) was stirred for 25 hr at 60°. After cooling to r.t. the soln was saturated with NaCl, the organic layer separated and the aqueous layer extracted with ether (3 × 150 ml). The combined organic layers were neutralized with $NaHCO_3$ (5%), dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallization of the residue from Et_2O-CH_2Cl_2 gave 2.2 g of **13** (6.9 mmol, 62%, m.p. 82–83°). The two diastereoisomers (1S, 1'S and 1R, 1'S) are easy recognized in the ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$): δ1.90–2.80 (m, 4H), 3.00–3.25 (m, CH_2), 3.73 (s, OCH_3), 4.66–5.00 (m, 1H), 6.06 (d, J = 9 Hz, 1H), 6.47 and 6.60 (both d, J = 9 Hz, together 1H), 7.00–7.36 (m, 6H), the OH-absorption (two separate s) is concentration dependent ($\delta \sim 4.0$); IR (KBr): ν3380 (NH), 3500–3100 (OH), 1750 (C=O), 1685 (C=O–C=C), 1680 (C=O, amide I) cm^{-1}. (Found: C, 63.67; H, 6.07; N, 4.34. Calc for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41%).

N-1'-(1'-*methoxycarbonyl*-2'-*phenylethyl*) - 4-*hydroxybenzamide* **14**

A mixture of **13** (3.17 g, 0.010 mol), benzoyl chloride (3.23 g, 0.020 mol), Et_3N (2 g, 0.020 mol) and 4-(N,N-dimethylamino) - pyridine (2.5 g, 0.020 mol) was stirred at r.t. for 2 hr. Concentration of this mixture *in vacuo* gave after medium pressure column chromatography (200 g silica gel H60, $CHCl_3$–MeOH 25:1) 0.7 g of benzoylated **13** (1.6 mmol, 16%). ^{1}H-NMR ($CDCl_3$): δ2.30–2.80 (m, 4H), 3.06 (d, 2H), 3.66 (s, OCH_3), 4.80–5.20 (m, 1H), 6.06 (d, J = 9 Hz, 1H), 6.56 (d, J = 9 Hz, 1H), 7.00 (m, 5H), 7.30–8.20 (m, 6H). A mixture of this compound (0.7 g, 1.6 mmol) and Et_3N (0.15 g, 1.5 mmol) in t-BuOH (50 ml) was stirred for 2 days at 80°. Concentration *in vacuo* and medium pressure column chromatography (50 g silica gel H60, $CHCl_3$–MeOH 50:1) of the residue gave **14** (440 mg, 1.5 mmol, 93%) as a white solid which was recrystallized from ether–$CHCl_3$, m.p. 132–133°. ^{1}H-NMR ($CDCl_3$): δ3.16 (d, CH_2), 3.73 (s, OCH_3), 4.80–5.20 (m, 1H), 6.50–8.50 (m, 11H); IR (KBr): ν3420 (NH), 3350 (OH), 1730 (C=O), 1640 (C=O, amide I). (Found: C, 68.18; H, 5.65; N, 4.66. Calc for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68%).

(*rac.*-4S,9R)-3,3-*di*(*ethoxycarbonyl*)-9-*hydroxy*-*perhydroisoindol*-1,6-*dione* **17a**

Following the procedure as given for **12** epoxy acyl chloride **11a** [obtained from Na salt **10a** (1.73 g, 7.8 mmol) and oxalyl chloride (2 g, 16 mmol)] was treated with diethyl aminomalonate hydrochloride (1.65 g, 7.8 mmol) and Et_3N (1.60 g, 16 mmol) in THF (100 ml) and afforded N-[*di*(*ethoxycarbonyl*)*methyl*]-1,2-*epoxy*-4,4-*dioxyethylenecyclohexane*-1-*carbonamide* **15a** in quantitative yield as an oil. ^{1}H-NMR ($CDCl_3$): δ1.26 (t, 6H), 1.30–3.00 (m, 6H) 3.26 (broad s, epoxy-H), 1.86 (m, 4H), 4.20 (q, 4H), 5.06 (d, J = 7.5 Hz, 1H, 7.20 (d, J = 7.5 Hz, NH).

The epoxy-amide **15a** (2.20 g, 6.1 mmol) was heated at 60° for 24 hr in a mixture of water (90 ml), THF (90 ml) and $HClO_4$ (3 ml, 70%). After cooling to r.t. the soln was saturated with NaCl, the organic layer separated and the water layer extracted with ether (3 × 150 ml). The combined organic layers were neutralized with $NaHCO_3$aq (5%), dried ($MgSO_4$) and concentrated *in vacuo*, affording 1.30 g (4.1 mmol, 66%) of N-[*di*(*ethoxycarbonyl*)-*methyl*] - 1-*hydroxy*-4-*oxo*-2-*cyclohexene* - 1-*carbonamide* **16a** as an oil. ^{1}H-NMR ($CDCl_3$): δ1.32 (tr, 6H), 1.90–2.85 (m, 4H), 3.90 (s, OH), 4.26 (q, 2 × OCH_2), 5.06 (d, J = 7.5 Hz, 1H), 6.08 (d, J = 10.5 Hz, 1H), 6.75 (d, J = 10.5 Hz, 1H), 7.80 (d, J = 7.5 Hz, NH).

A mixture of **16a** (1.30 g, 4.1 mmol) and Et_3N (0.4 g, 4.0 mmol) in t-BuOH (300 ml) was refluxed for 16 hr. Concentration *in vacuo* and recrystallization of the residue from ether-$CHCl_3$ gave **17a** (1.12 g, 3.5 mmol, 87%), m.p. 138–140°. ^{1}H-NMR ($CDCl_3$): δ1.26 (t, 2 × CH_3), 2.00–3.00 (m, 6H), 3.40 (t, 1H), 4.10–4.50 (m, 2 × OCH_2 and OH), 7.26 (s, NH); IR (KBr): ν3370 (NH), 3260 (OH), 1740 (C=O), 1710–1720 (C=O, lactam and cyclohexanone) cm^{-1}.

(Found: C, 53.63; H, 6.10; N, 4.42. Calc. for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47%).

(rac.-4S,5R,9R)-3,3-Di(ethoxycarbonyl)-9-hydroxy-5-methyl-perhydroisoindol-1,6-dione **17b**

Following the procedure as described for **12**, **11b**, obtained from Na salt **10b** (0.59 g, 2.5 mmol) and oxalyl chloride (0.59 g, 5.0 mmol), was treated with diethyl aminomalonate hydrochloride (0.53 g, 2.5 mmol) and Et_3N (0.50 g, 5.0 mmol) yielding N-[*di(ethoxycarbonyl)-methyl*]-1,2-*epoxy*-3-*methyl*-4,4-*dioxyethylene*-*cyclohexane*-1-*carbonamide* **15b** almost quantitatively as an oil. ^{1}H-NMR ($CDCl_3$): δ1.10 (d, J = 6 Hz, CH_3), 1.30 (t, 6H), 1.35–2.83 (m, 5H), 2.93 (s, epoxy-H), 3.90 (br.s, 4H), 4.23 (2 × q, 4H), 5.03 (d, J = 6.6 Hz, 1H), 7.20 (d, J = 6.6 Hz, NH).

The epoxy-amide **15b** (0.94 g, 2.5 mmol) was heated at 60° for 24 hr in a mixture of water (75 ml), THF (75 ml) and $HClO_4$ (3 ml, 70%). Work-up as described for **16a** gave N[*di(ethoxycarbonyl)methyl*]-1-*hydroxy*-3-*methyl*-4 - *oxo* - 2-*cyclohexene*-1-*carbonamide* **16b** (0.66 g, 2.0 mmol, 85%) as an oil. ^{1}H-NMR ($CDCl_3$): δ1.30 (t, 6H), 1.80 (br.s, CH_3), 1.68–2.75 (m, 4H), 4.23 (q, 4H), 4.90 (br.s, OH), 5.06 (d, J = 6.6 Hz, 1H), 6.52 (s, 1H), 7.93 (d, J = 6.6 Hz, NH).

A mixture of **16b** (0.66 g, 2.0 mmol) and Et_3N (0.20 g, 2.0 mmol) in t-BuOH (150 ml) was refluxed for 16 hr. Concentration *in vacuo* and medium pressure column chromatography (50 g silica gel H60, ether) of the residue gave, after recrystallization of the white solid from benzene, 0.46 g of **17b** (1.4 mmol, 70%), m.p. 128–135°C. ^{1}H-NMR ($CDCl_3$): δ1.24 (d, J = 7.7 Hz, CH_3), 1.30 (2 × t, J = 7 Hz, 6H), 2.13–2.80 (m, 4H), 3.06 (q, J = 7 Hz, C(5)H), 3.55 (d, J = 6.8 Hz, C(4)H), 3.93 (br.s, OH), 4.07–4.41 (m, 4H), 6.82 (br.s, NH); IR (KBr): ν3340 (NH), 3200 (OH), 1740 (–CO–O–), 1715 and 1700 (C=O, lactame and cyclohexanone) cm^{-1}. (Found: C, 55.38; H, 6.45; N, 4.38. Calc for $C_{15}H_{21}NO_7$: C, 55.04; H, 6.47; N, 4.28%.)

N-[*Benzoyl(ethoxycarbonyl)methyl*]-1,2-*epoxy*-3-*methyl*-4,4-*dioxyethylene*-*cyclohexane*-1-*carbonamide* **18** (mixture of diastereoisomers: rac. 1R,2S,3S,1'S and rac. 1R,2S,3S,1'R)

This product was prepared, following the procedure as described for **12**, from Na salt **10b** (1.18 g, 5.0 mmol), oxalyl chloride (1.0 g, 8.0 mmol), ethyl-2-amino-benzoyl-acetate hydrochloride (1.22 g, 5.0 mmol), and Et_3N (1.0 g, 10 mmol). Medium pressure column chromatography (200 g silica gel H60, ether) gave 2.0 g (4.9 mmol, 98%) of **18**. ^{1}H-NMR ($CDCl_3$): δ1.00 (d, CH_3), 1.13 (t, $CH_2\underline{CH_3}$), 1.20–2.80 (m, 5H), 2.86 and 3.03 (both s, epoxy-H), 3.90 (br.s, 4H), 4.13 (2 × q, OCH_2), 6.11 (d, 1H), 7.31–7.76 (m, 4H), 7.81–8.22 (m, 2H); IR (NaCl): ν3400 (NH), 1755 (C=O), 1685 (C=O, amideI) cm^{-1}. The two signals of the epoxymethine protons clearly show the presence of two diastereomers. This oily product was sufficiently pure for further use.

Reaction of epoxy amide **18** with $H_2O/HClO_4$. *Synthesis of (rac.-3S,4S,5R,9R) -9-benzoyloxy - 3-ethoxycarbonyl-5-methyl - perhydroisoindol-1,6-dione* **23**

A soln of epoxy-amide **18** (2.00 g, 4.9 mmol) in a mixture of water (150 ml), THF (150 ml) and $HClO_4$ (5 ml, 70%)) was heated at 65° for 16 hr. After cooling to r.t. the soln was saturated with NaCl, the layers were separated and the aqueous layer extracted with ether (3 × 150 ml). The combined organic layers were neutralized with $NaHCO_3$aq (5%)), dried over $MgSO_4$ and concentrated *in vacuo*. Medium pressure column chromatography (200 g silica gel H60, diisopropyl ether–MeOH 10:1) of the residue gave four fractions: 0.12 g of unidentified product, 0.80 g of oil **19** (2.2 mmol, 45%), 0.66 g of a mixture of **20** and **21** (~2.0 mmol, ~40%), 0.09 g of unidentified product.

Characteristics of N-[*benzoyl(ethoxycarbonyl)methyl*] - 1-*hydroxy*-3-*methyl* - 4 - *oxo*-2-*cyclohexene*-1-*carbonamide* **19**: ^{1}H-NMR ($CDCl_3$): δ1.13 (t, CH_3), 1.73 (s, CH_3), 1.90–2.80 (m, 4H), 4.10 (q, 2H), 4.75 (br.s, OH), 6.13 (d, J = 7 Hz, CH-N), 6.46 and 6.55 (both a br.s, together 1H, =C–H), 7.21–7.73 (m, 3H), 7.83–8.13 (m, 2H), 8.18 (d, J = 7 Hz, NH); IR (CCl_4): ν3410 (OH, NH), 1750 (C=O), 1680–1690 (C=O, amideI and cyclohexanone) cm^{-1}.

Characterization of the mixture of **20** and **21**; The CH_2–N protons of **20** give an absorption at δ4.72. The presence of **21** was deducted from the signal δ3.42 (d, J = 5 Hz) due to the C_4-methine proton.

A mixture of **20** and **21** (0.66 g, ~2.0 mmol) (which could not be separated) and Et_3N (0.6 g, 6 mmol) in t-BuOH (100 ml) was heated under reflux for 20 hr. Concentration *in vacuo* and crystallization of the residue from EtOH gave 0.19 g of **23** (0.5 mmol, 10%), m.p. 182–197°. ^{1}H-NMR ($CDCl_3$): δ1.15 (d, J = 6.5 Hz, CH_3), 1.31 (t, $CH_2\underline{CH_3}$), 2.23–2.86 (m, 5H), 3.26 (d × d, J(4)(3) = 9.4 Hz, J(4)(5) = 8.8 Hz, C(4)H), 4.25 (q, OCH_2), 4.68 (d, J(3)(4) = 9.8 Hz, C(3)H), 6.58 (br.s, NH), 7.35–7.59 (m, 3H), 7.91–8.01 (m, 2H); IR (KBr): ν3300 (NH), 1745 (–CO–O–), 1700–1730 (C=O) cm^{-1}. (Found: C, 63.51; H, 5.86; N, 3.82; Calc. for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90%).

(rac. - 3R,4S,5R,9R) - 9 - Benzoyloxy - 3 - ethoxycarbonyl-5 - methyl - perhydroisoindol - 1,6 - dione **22**

A mixture of **19** (0.72 g, 2.0 mmol) and DBU (0.1 g, 0.7 mmol) in t-BuOH (300 ml) was stirred at 35° for 24 hr. The soln was concentrated *in vacuo* and the remaining white solid was washed with ether (200 ml). Crystallization from EtOH gave 0.5 g of **22** (1.64 mmol, 82%), m.p. 202–225°. ^{1}H-NMR ($CDCl_3$): δ1.24 (d, J = 6.4 Hz, CH_3), 1.33 (t, $CH_2\underline{CH_3}$), 2.10–2.87 (m, 5H), 2.95 (d × d, J(4)(3) = 3.2 Hz, J(4)(5) = 11.4 Hz, C(4)H), 3.98 (d, J(3)(4) = 3.2 Hz, C(3)H), 4.31 (q, OCH_2), 6.46 (br.s, NH), 7.33–7.58 (m, 3H), 7.90–8.01 (m, 2H); IR (KBr): ν3250 (NH), 1750 (–CO-O-), 1710–1730 (several C=O) cm^{-1}. (Found: C, 63.41; H, 5.88; N, 3.72. Calc for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90%.)

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