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DIASTEREOSELECTIVITY IN THE CYCLIZATION OF 1-[2-(BENZYLOXYMETHYL)-3-BUTENYL]-5-ETHOXY-2-PYRROLIDINONES

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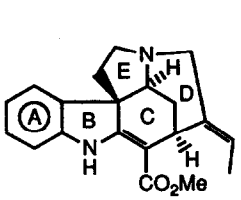
Abstract: 1-[2-(Benzyloxymethyl)-3-butenyl]-5-ethoxy-2-pyrrolidinones **12** cyclize upon formic acid treatment to indolizinones. The effect of some substituents α to the iminium carbon atom on the diastereoselectivity of the cyclization is discussed.

In a study directed towards the total synthesis of Strychnos-alkaloids (for example akuammicine **1**) we hoped to synthesize ring D via the N-acyliminium ion reaction **2** → **3**. The benzyloxymethyl substituent in **3** should provide a handle to introduce an ethylidene substituent like the one found in **1**; the formyloxy substituent would be used to close ring C. Since N-acyliminium ion reactions with a 2-(benzyloxymethyl)-3-butenyl terminator and the influence of substituents α to the iminium carbon atom were largely unknown, we decided to study some model reactions.



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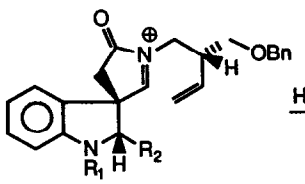
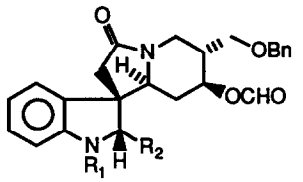


2

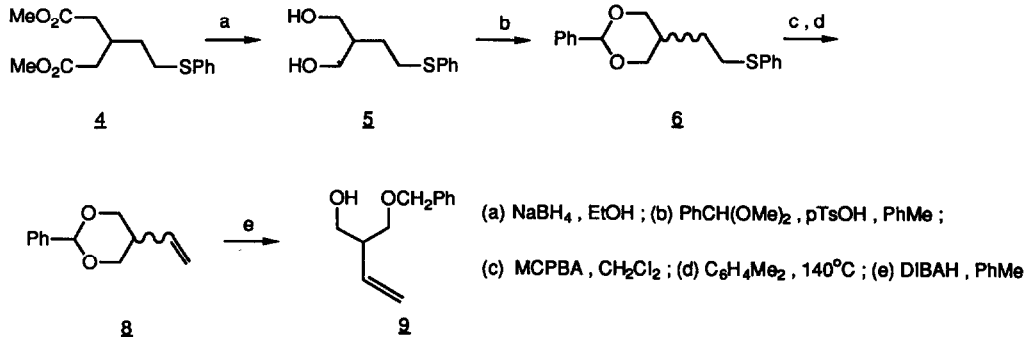
HCOOH



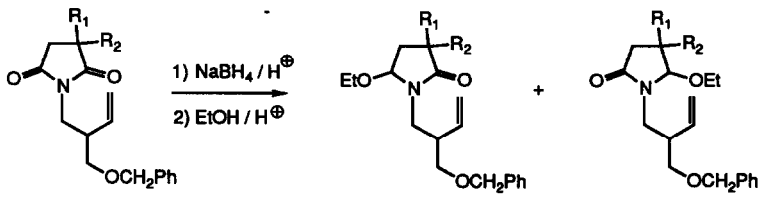
3

RESULTS AND DISCUSSION

The Mitsunobu oxidation-reduction procedure[2] would be a feasible method for the synthesis of the N-substituted succinimides. Therefore the alcohol **9** had to be prepared first. Although **9** was not known at the time, after completion of its synthesis several approaches towards compounds derived from 2-vinyl-1,3-propanediol appeared,[3] including **9**.[3d] All of these were published in connection with the total synthesis of talaromycin B.Our approach started with the alkylation of dimethyl malonate with 1-bromo-2-phenylthioethane[4] to give malonate **4** (53%). The reduction of **4** with an excess of $NaBH_4$ in EtOH at 0^0 to room temperature gave diol **5** in almost quantitative yield. This remarkable reduction is most likely due to and facilitated by the thiophenyl group. Reductions with $LiAlH_4$ and Red-Al® were less satisfactory. After protection of diol **5** as benzylidene acetal **6** (cis/trans ratio 1:2, 96%), the vinyl substituent was elaborated via oxidation to the sulfoxide (98%) and thermolysis in refluxing xylene (65%). Reduction of **8** with diisobutylaluminium hydride in toluene[5] finally afforded alcohol **9** (65%).



Starting imides **10a** and **10b** were obtained by Mitsunobu coupling[2] of alcohol **9** with succinimide (80%) and 3-methylsuccinimide[6] (1:1 mixture of diastereoisomers, 68%). Imides **10c** and **10d** were obtained by condensation of 3-phenylsuccinimide[6] with **9**, and alkylation (K_2CO_3/DMF)[6] with methyl iodide (46%) and benzyl bromide (97%), respectively, of the thus obtained imide. Both were 1:1 mixtures of diastereoisomers. The best yields in the Mitsunobu coupling reactions were obtained upon adding the imide after the azo compound had been added to the alcohol and the triphenyl phosphine.

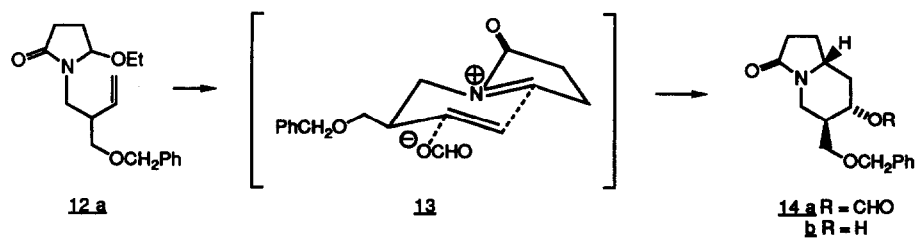


10a $R_1 = R_2 = H$
b $R_1 = Me$; $R_2 = H$
c $R_1 = Ph$; $R_2 = Me$
d $R_1 = Ph$; $R_2 = CH_2Ph$

11a - d

12 a - d

After $NaBH_4$ reduction of the imides and subsequent conversion of the in situ formed mixture of regioisomeric hydroxy lactams into the ethoxy lactams,[7] the regioisomers were separated by column chromatography to furnish the pure compounds **12**. Upon stirring overnight in formic acid at room temperature the ethoxy lactams **12** cyclized to give the corresponding indolizinone derivatives.



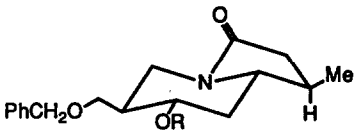
12 a

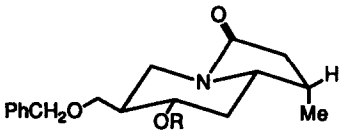
13

14 a R = CHO
b R = H

Ethoxy lactam **12a** gave after work-up, saponification, and purification by column chromatography the alcohol **14b** (70%). The crude reaction mixture nearly completely consisted of one product, according to ^{1}H-NMR

analysis, namely formate **14a**. Its stereochemistry can be explained by assuming a chair-like transition state **13**, the benzyloxymethyl substituent occupying an equatorial position. Similar results had been obtained by Nossin [8] with methyl, 2-phenylethyl, and 1-naphthylmethyl substituents instead of a benzyloxymethyl substituent.

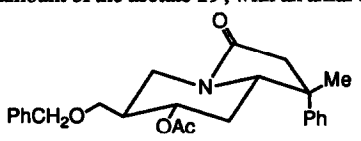




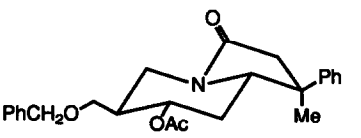
15 R = 3,5 dinitrobenzoyl **16**

Cyclization of the methyl substituted ethoxy lactam **12b** afforded after work-up, aminolysis (NH_3 /MeOH), and derivatization (3,5-dinitrobenzoyl chloride, DMAP, CH_2Cl_2) a 3 : 2 mixture of **15** and **16** in 72% yield. It could not unambiguously be proved that **15** was the major product. Neither the mixture of formates (R=CHO), nor the mixture of alcohols (R=H), acetates (R=$COCH_3$), or 3,5-dinitrobenzoates could be separated by column chromatography or crystallization.

Stirring of the phenyl methyl substituted ethoxy lactam **12c** in formic acid gave after work-up, aminolysis (NH_3/MeOH), acetylation (Ac_2O, DMAP, CH_2Cl_2) and column chromatography two fractions. The main fraction (72%) consisted of a 6 : 4 mixture of the expected products **17** and **18**, respectively. In addition a small amount of the acetate **19**, with an axial benzyloxymethyl substituent, was obtained.



17



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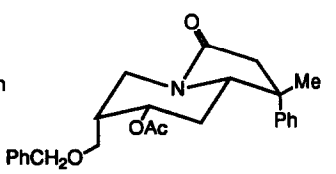
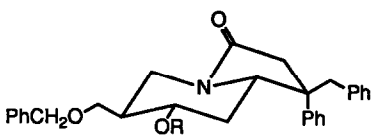
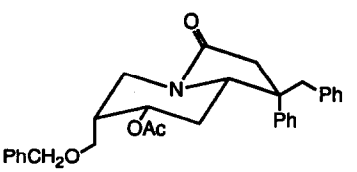


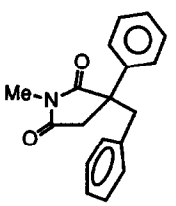
19



20a R = CHO
b R = H



21



22

Cyclization of the phenyl benzyl substituted ethoxy lactam **12d** gave after work-up, aminolysis (NH_3/MeOH), and chromatography two fractions. The main fraction (42%) consisted of alcohol **20b**. The other fraction was acetylated (Ac_2O), DMAP, CH_2Cl_2) to give a 3 : 1 mixture (39%) of two compounds. The major compound was obtained by crystallization and identified as acetate **21**, with an axial benzyloxymethyl substituent. The minor product of this mixture was not identified.

From the cyclizations of **12c** and **12d** a preference follows for addition of the alkene to the N-acyliminium ion at the side of the phenyl ring. Since we can safely assume the phenyl substituent to be larger than the methyl or

benzyl group this is rather surprising. These results can be explained, however, by assuming that in the planar N-acyliminium ion the sterically more demanding phenyl substituent occupies a pseudo-equatorial position, thereby forcing the other substituent into a pseudo-axial position. Evidence for this can be found in the crystal structure of a number of substituted succinimides,[9] where phenyl substituents show exactly this behaviour. Comparison of the conformation of an N-acyliminium ion and a succinimide seems justified since both have two sp^2 carbon atoms.

Still, this does not account for the strong preference of the N-acyliminium ion derived from the phenyl benzyl substituted ethoxy lactam **12d** for cyclization at the phenyl side. Here too, an explanation might be found in a crystal structure. Succinimide **22** was shown[9] to have the benzene ring of the (pseudo-axial oriented) benzyl group folded under the succinimide ring as depicted in the scheme. Thus it may be envisaged that the benzyl side of the pyrrolidinone ring is effectively shielded from approach of the nucleophilic double bond. Therefore, the diastereoisomer for which an equatorial oriented benzyloxymethyl substituent would imply reaction at the benzyl side of the pyrrolidinone ring, is forced to cyclize at the phenyl side, leading to the axial benzyloxymethyl substituent in **21**. Apparently the energy difference between an axial and an equatorial position is not very large, because the benzyloxymethyl substituent has only one 1,3-diaxial interaction in the cyclization products **19** and **21**.

The structure of the cyclization products was proved by ^{1}H-NMR methods, including 2D NMR and 1D multipulse experiments. In case of acyloxy substituents at C-7 in the indolizinones, the position of the C-6 and C-7 substituents was immediately clear from the coupling constants in the absorptions of H_7,[10] found around δ=5 free from other absorptions. Correlation of the stereochemistry around C-8a with the one around C-1 for cyclization products **17**, **18**, **19**, **20a** and **21** was secured by irradiation of the bridge-head proton H_{8a} in NOE-difference experiments.

EXPERIMENTAL

Melting points were measured with a Leitz hot-stage microscope and are uncorrected, as are boiling points. ^{1}H-NMR spectra were recorded on Varian XL-100, Bruker AC-200 or Bruker WM-250 instruments with $CDCl_3$ as solvent. Chemical shifts are given in ppm downfield from tetramethylsilane. IR spectra were taken with Perkin-Elmer 257, 298 and 1310 instruments. Accurate mass measurements were performed on a Varian MAT 711 instrument at 70eV whereby a resolving power of 10,000 (10% valley definition) was used. Chromatography refers to flash chromatography [11] over silica gel (Merck, Kieselgel 80, 230-400 mesh). TLC was performed on silica gel, either on glass plates or plastic sheets (Merck, Kieselgel 60, F_{254}). Spots were located with UV light, iodine vapour or anisaldehyde/H_2SO_4 reagent.[12] THF was distilled from sodium benzophenone ketyl under nitrogen prior to use. With PA, petroleum ether 40-60 is meant; with dipe, diisopropylether.

Methyl 4-phenylthio-2-methoxycarbonyl-butanoate (4). To a solution of sodium methanolate under N_2, prepared from 17.3 g (0.75 mol) of sodium and 300 ml of dry MeOH, was added dimethyl malonate (99.1 g, 0.75 mol) and subsequently 1-bromo-2-phenylthioethane (108.6 g, 0.5 mol). The mixture was stirred overnight at room temperature, refluxed for 5 h and again stirred overnight at room temperature. After work-up (2M HCl, ether) the combined organic layers were washed with sat. $NaHCO_3$ solution and brine, and then dried ($MgSO_4$). Distillation gave diester **4** (bp 125-132°/0.02 mm) as a colourless liquid (71.1 g, 53%). IR ($CHCl_3$): 1730 (CO), 1580, 1480, 1440, 690 (arom) cm^{-1}; ^{1}H-NMR (100 MHz): δ 7.1-7.45 (m, 5H, ArH), 3.75 (s, 6H, 2xOCH_3), 3.67 (t, 1H, *J*=7, MeOOCC*H*), 2.98 (t, 2H, *J*=7, CH_2SPh), 2.22(q,2H, *J*=7, CH_2CH_2SPh).

4-Phenylthio-2-hydroxymethyl-butanol (5). Diester **4** (69.14 g, 0.258 mol) dissolved in 75 ml of EtOH, was added dropwise in 45 min to a, at 0^0 mechanically stirred, suspension of $NaBH_4$ (48.8 g, 1.26 mol) in 700 ml of EtOH. After addition of the diester the reaction mixture was stirred for another half hour at 0^0 and then slowly warmed to room temperature. Under cooling with a water-bath the mixture was stirred overnight, cooled to 5^0 and, while keeping the temperature below 10^0, 90 ml of 30% HCl was added dropwise (0.5 h). Then 200 ml of water was added, the reaction mixture concentrated in vacuo, and 0.5 l of 1M HCl added. After filtering to remove salts, the filtrate was extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was taken up twice in benzene and concentrated in vacuo to remove residual water. The almost pure product (65.57 g) was taken up in ether after which an equal volume of dipe was added, and left in the freezer for a few days. The crystals were collected on a filter and washed twice with dipe to yield **5** (37.45 g, 68%, white crystals, mp 16-56^0). A recrystallized sample had mp 55-59^0. The mother layer was concentrated and chromatographed on silica (160 g), eluent PA/EtOAc (3:1) to remove by-products and subsequently EtOAc/EtOH (9:1) to elute diol **5** (19.67 g, 36%) as a clear oil. IR ($CHCl_3$): 3400 (OH), 1590, 1480, 1440, 690 (arom) cm^{-1}; ^{1}H-NMR (100 MHz): δ 7.1-7.45 (m, 5H, ArH), 3.81 (dd, 2H, *J*=10.5 and 4, OCH_aH_b), 3.67 (dd, 2H, *J*=10.5 and 6, OCH_aH_b), 3.00 (t, 2H,*J*=7,CH_2SPh), 2.47 (s, 2H, OH, disappeared upon addition of D_2O), 1.70-2.10 (m, 1H, OCH_2CH), 1.66 (q, 2H, *J*=7, CH_2CH_2SPh); accurate mass determination: calcd. for $C_{11}H_{16}O_2S$ m/z 212.0871, found 212.0835.

***cis*- and *trans*-2-Phenyl-5-[2-(phenylthio)ethyl]-1,3-dioxane (6).** A solution of diol **5** (14.97 g, 0.071 mol), pTsOH.H_2O (112 mg), benzaldehyde dimethyl acetal (11.27 g, 0.074 mol) in 50 ml of toluene was heated for 2 h at 100-102^0 using a Dean-Stark trap. After cooling 2 g of K_2CO_3 were added, the mixture stirred for 15 min, and then the solid was filtered off and washed with CH_2Cl_2. The combined filtrates were concentrated in vacuo and the residue column chromatographed on 50 g of silica, eluting with PA/EtOAc (3:1), to yield **6** (20.37 g, 96%) as a colourless solid. The trans/cis ratio wass 2:1. The trans isomer could be obtained pure by crystallization from ether/hexane, followed by recrystallization from dipe/hexane: mp 60-62^0. On TLC (hexane/EtOAc 6:1) the two isomers had a slightly different R_f value (trans isomer 0.27, cis isomer 0.23). IR ($CHCl_3$, mixture of isomers): 1590, 1480, 1440, 695 (arom), 1190, 1145 (C-O-C-O-C) cm^{-1}. Trans isomer: ^{1}H-NMR (100 MHz): δ 7.1-7.6 (m, 10H, ArH), 5.39 (s, 1H, H_2), 4.24 (dd, 2H, *J*=11 and 4, H_{4eq}, H_{6eq}), 3.53 (t, 2H, *J*=11, H_{4ax}, H_{6ax}), 2.90 (t, 2H, *J*=7, CH_2SPh), 2.0-2.50 (m, 1H, H_5), 1.41 (q, 2H, *J*=7.5, CH_2CH_2SPh); accurate mass determination: calcd for $C_{18}H_{20}O_2S$ m/z 300.1184, found 300.1166. Cis isomer: ^{1}H NMR (100 MHz): δ 7.1-7.6 (m, 10H, ArH). 5.48 (s, 1H, H_2), 4.08 (d, 4H, *J*=2, $H_{4eq}H_{4ax}$, H_{6eq}, H_{6ax}), 3.07 (t, 2H, *J*=7, CH_2SPh), 2.19 (q, 2H, *J*=7.5, CH_2CH_2SPh), 1.50-1.80 (m, 1H, H_5).

***cis*- and *trans*-2-Phenyl-5-[2-(phenylsulfinyl)ethyl]-1,3-dioxane (7).** Sulfide **6** (trans/cis 2:1) (14.42 g, 0.048 mol) was taken up in CH_2Cl_2 and the solution cooled in an ice-bath, after which MCPBA (10.87 g, 80%, 0,050 mol,) was added in portions in 45 min, while keeping the temperature under 10^0. After stirring for an additional hour the reaction mixture was washed twice with sat. $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated in vacuo to yield **7**, (14.97 g, 98%) as a white solid (trans/cis 2:1). The isomers could easily be separated by column chromatography (eluent EtOAc). Both isomers (each as a 1:1 mixture of diastereoisomers due to the chiral sulfur atom) solidified on standing. The trans isomer had mp 105-108^0, the cis isomer (after recrystallizaiton from CH_2Cl_2/hexane) mp 91-93^0. Both isomers showed very small molecular ion peaks. Accurate mass determination was therefore done on (M-1). Trans isomer: IR ($CHCl_3$): 1140, 1090 (C-O-C-O-C), 1040 (SO), 695 (arom) cm^{-1}; ^{1}H-NMR (100 MHz): δ 7.20-7.70 (m, 10H, ArH), 5.37 (s, 1H, H_2),

4.00-4.35 (m, 2H, H_{4eq}, H_{6eq}), 1.10-1.80 (m, 2H, CH_2CH_2SOPh); accurate mass determination: calcd. for $C_{18}H_{19}O_3S$ (M-1) m/z 315.1055, found 315.1018. Cis isomer: IR ($CHCl_3$): 1140, 1090 (C-O-C-O-C), 1040 (SO) 695 (arom) cm^{-1}; ^{1} H-NMR (100 MHz): δ 7.20-7.70 (m, 10H, ArH), 5.47 (s, 1H, H_2), 3.90-4.25 (m, 4H, H_{4eq}, H_{4ax}, H_{6eq},H_{6ax}), 2.80-3.10 (m, 2H, CH_2SOPh), 2.00-2.40 (m, 2H, CH_2CH_2SOPh),1.50-175 (m, 1H, H_5); accurate mass determination: calcd. for $C_{18}H_{19}O_3S$ (M-1) m/z 315.1055, found 315.1048.

***cis*- and *trans*-2-Phenyl-5-vinyl-1,3-dioxane (8).** A mixture of sulfoxide **7** (71.0 g, 0.224 mol), $NaHCO_3$ (18.82 g, 0.224 mol) and 225 ml of xylene was refluxed for 22 h using a Dean-Stark trap. After cooling to room temperature the mixture was filtered, the residue washed with CH_2Cl_2, and the combined filtrates concentrated in vacuo and distilled through a 10 cm Vigreux. The vinyl compound distilled (70-56°/0.01 mm) to give a colourless liquid (28.8 g, 65%). IR ($CHCl_3$, mixture of isomers): 1640 (C=C), 1120, 1070 (C-O-C-O-C), 695 (arom) cm^{-1}. Trans isomer: ^{1}H-NMR (100 MHz): δ 7.25-7.65 (m, 5H, ArH), 5.05-5.75 (m, 4H containing 5.44, s, H_2, $CH=CH_2$), 4.25 (dd, 2H, *J*=11.5 and 4, H_{4eq}, H_{6eq}), 3.74 (bt, 2H, *J*=11.5, H_{4ax}, H_{6ax}), 2.65-3.05 (m, 1H, H_5). Cis isomer: ^{1}H-NMR (100 MHz): δ 7.25-7.65 (m, 5H, ArH), 6.40 (ddd, 1H, *J*=18, 7.5 and 10, $CH=CH_2$), 5.56 (s, 1H, H_2), 5.15-5.5 (m, 2H, $CH=CH_2$), 4.18 (d, 4H, *J*=2, H_{4eq}, H_{4ax}, H_{6eq}, H_{6ax}), 2.07-2.34 (m, 1H, H_5); accurate mass determination: calc. for $C_{12}H_{14}O_2$ m/z 190.0994, found 190.0962.

2-Benzyloxymethyl-3-buten-1-ol (9). To acetal **8** (19.9 g, 0.105 mol), dissolved in 200 ml of dry toluene, was added dropwise under cooling 175 ml of a 1.5M solution of diisobutylaluminium hydride in toluene, the temperature not exceeding -10°. After warming to room temperature, the mixture was stirred for another 2.5 h, cooled in an ice-bath and then 20% H_2SO_4 was slowly added. The temperature was kept below 10°. The organic layer was separated and the aqueous layer extracted three times with ether. The combined extracts were washed with sat. $NaHCO_3$ solution, dried ($MgSO_4$), and distilled to yield alcohol **9** as a colourless liquid (bp 81-88°/0.03 mm, 14.86 g, 74%). IR ($CHCl_3$): 3500 (OH), 1640 (C=C), 695 (arom) cm^{-1}; ^{1}H NMR (100 MHz): δ 7.35 (s, 5H, ArH), 5.74 (ddd, 1H, *J*=18, 10 and 8, $CH=CH_2$), 5.03-5.30 (m, 2H, $CH=CH_2$), 4.55 (s, 2H, OCH_2Ph),3.45-3.90 (m, 4H, CH_2OH, CH_2OBn), 2.45-2.85 (m, 1H, $CHCH=CH_2$), 2.5 (very bs, 1H, OH, exchangeable in D_2O); accurate mass determination: calcd. for $C_{12}H_{16}O_2$ m/z 192.1150, found 192.1131.

General procedure for the Mitsunobu coupling reaction. To a solution of 2-(benzyloxymethyl)-3-butenol **9** and PPh_3 in dry THF, cooled in an ice-bath, was added dropwise dimethyl azodicarboxylate in dry THF in approximately 5 min. After an additional 5-10 min stirring at 0° the NH-imide, dissolved in dry THF, was added dropwise in a few minutes. The mixture was stirred overnight while warming to room temperature, and concentrated in vacuo. The residue was partitioned between equal volumes of CH_2Cl_2 and 5% KOH solution, the organic layer decanted and the aqeous layer extracted three times with CH_2Cl_2. The combined organic layers were washed three times with 2 M HCl and once with saturated $NaHCO_3$ solution (after each washing the aqueous layer was washed with CH_2Cl_2 and the organic layers combined), dried over Na_2SO_4, filtered and concentrated in vacuo to yield the crude reaction mixture.

General procedure for the synthesis of ethoxy lactams. The $NaBH_4/H^+$ reductions were carried out with a stirred solution of the imide in EtOH at temperatures of 0-5° with an excess of $NaBH_4$. At intervals of 15 min 3-4 drops of 2M HCl in ethanol were added. After the starting material had been consumed (usually 3-4h), the excess of $NaBH_4$ was destroyed in 15-30 min at 0-5° by adding 2 M HCl in EtOH till pH 2. After stirring

for an additional hour at 5° the reaction mixture was poured into diluted $NaHCO_3$ solution. Extraction with CH_2Cl_2 (4 times), drying of the combined organic layers over Na_2SO_4, filtration and concentration in vacuo afforded the crude reaction product. The ethoxy lactams were purified by column chromatography on silica gel.

1-[2-(Benzyloxymethyl)-3-butenyl]-2,5-pyrrolidinedione (10a). Succinimide (0.39 g, 3.93 mmol) and 2-(benzyloxymethyl)-3-butenol (**9**) (0.69 g, 3.56 mmol) were condensed in 20 ml of THF, according to the general procedure, using PPh_3 (0.94 g, 3.58 mmol) and diethyl azodicarboxylate (0.62 g, 3.56 mmol). The crude reaction mixture was column chromatographed (eluent PA/EtOAc 1:1) to yield **10a** as a colourless oil (0.78 g, 80%). IR ($CHCl_3$): 1775, 1700 (CO), 1640 (C=C) cm^{-1}; ^{1}H-NMR (100 MHz): δ 7.34 (s, 5H, ArH), 5,5-5,9(m, 1H, C*H*=CH_2), 4.95-5.2 (m, 2H, CH=C*H*$_2$), 4.49 (s, 2H, OCH_2Ph), 3.64 (bd, 2H, *J*=8, NCH_2), 3.50 (d, 2H, *J*=6, O*CH*$_2$CH), 2.75-3.15 (m, 1H, OCH_2C*H*), 2.55 (s, 4H, $NCOCH_2$); accurate mass determination; calcd. for $C_{16}H_{19}NO_3$ m/z 273.1365, found 273.1344.

1-[2-Benzyloxymethyl)-3-butenyl]-3-methyl-2,5-pyrrolidinedione (10b). 3-Methyl-2,5-pyrrolidinedione (1,36 g, 12.0 mmol) and 2-(benzyloxymethyl)-3-butenol (**9**) (1.92 g, 10.0 mmol) were condensed in 25 ml of dry THF using PPh_3 (3,15 g, 12.0 mmol) and dimethyl azodicarboxylate (1.75 g, 12.0 mmol) following the general procedure. After work-up the residue was column chromatographed (eluent PA/EtOAc 1:1). Imide **10b** was obtained as a colourless oil (1.96 g, 68%, 1:1 mixture of diasereoisomers). IR ($CHCl_3$): 1780, 1700 (CO), 1640 (C=C) cm^{-1}; ^{1}H NMR (250 MHz): δ 7.20-7.40 (m, 5H, ArH), 5.54-5.77 (m, 1H, C*H*=CH_2), 4.97-5.19 (m, 2H, CH=C*H*$_2$), 4.48+4.46 (2xd, 1H, *J*=12, OCH_aH_bPh), 4.42+4.43 (2xd, 1H, *J*=12, OCH_aH_bPh), 3.52-3.73 (m, 2H, NCH_2), 3.38-3.52 (m, 2H, O*CH*$_2$CH), 2.59-2.98 (m, 3H, $NCOCH_aH_b$, OCH_2CH, $NCOCH(CH_3)$), 2.09-2.28 (m, 1H, $NCOCH_aH_b$), 1.20+1.23 (2xd, 3H, *J*=7.3, CH_3); accurate mass determination: calcd. for $C_{17}H_{21}NO_3$ m/z 287.1521, found 287.1514.

1-[2-(Benzyloxymethyl)-3-butenyl]-3-phenyl-2,5-pyrrolidinedione. 3-Phenyl-2,5-pyrrolidinedione (2.10 g, 12.0 mmol) and 2-(benzyloxymethyl)-3-butenol (**9**) (1.92 g, 10.0 mmol) were condensed in 25 ml of dry THF using PPh_3 (3.15 g, 12.0 mmol) and dimethyl azodicarboxylate (1.75 g, 12.0 mmol) according to the general procedure. After work-up the residual oil was taken up in 15 ml of hexane/EtOAc 1:1, upon which the $POPh_3$ partially crystallized, and then filtered and column chromatographed (eluent PA/EtOAc 1:1). The imide was obtained as a colourless oil (3.28 g, 94%, 1:1 mixture of diastereoisomers). IR ($CHCl_3$): 1775, 1700 (CO imide) cm^{-1}; ^{1}H NMR (200 MHz): δ 7.0-7.5 (m, 10H, ArH), 5.56-5.84 (m, 1H, 1C*H*=CH_2), 5.00-5.25 (m, 2H, CH=C*H*$_2$), 4.51 (d, 1H, *J*=11.8, OCH_aH_bPh), 4.47+4.45 (2xd, 1H, *J*=11.8, O*CH*$_a$H$_b$Ph), 3.78-3.95 (m, 1H, PhC*H*CH_aH_b), 3.60-3.78 (m, 2H, O*CH*$_2$CH), 3.40-3.60 (m, 2H, NCH_2), 2.83-3.18 (m, 2H, containing 3.06+3.05, 2xdd, *J*=18.4 and 9.5, $PhCHCH_aH_b$, OCH_2CH), 2.68+2.74 (2xdd, 1H, *J*=18.4 and 5.0, $PhCHCH_aH_b$); accurate mass determination: calc. for $C_{22}H_{23}NO_3$ m/z 349.1678, found 349.1666.

1-[2-Benzyloxymethyl)-3-butenyl]-3-methyl-3-phenyl-2,5-pyrrolidinedione (10c). 1-[2-(Benzyloxymethyl)-3-butenyl]-3-phenyl-2,5-pyrrolidinedione (1.0 g, 2.86 mmol) was taken up in 2 ml of dry DMF. To this solution were added MeI (0.61 g, 4.30 mmol) and 2 g of powdered K_2CO_3 (dried for several hours at 120°).The mixture was stirred for 66 h at room temperature, partitioned between ether and water, and the organic layer was separated. The aqueous layer was extracted three times with ether, the combined organic layers washed with brine, dried (Na_2SO_4), and chromatographed (eluent PA/EtOAc 2:1) to yield, in this order, product **10c** (0.48 g, 46%, colourless oil, 1:1 mixture of diastereoisomers) and starting material (0.42 g, 42%).

IR ($CHCl_3$): 1775, 1700 cm^{-1} (CO); ^1H NMR (200 MHz): δ 7.1-7.5 (m, 10H, ArH), 5.53-5.82 (m, 1H,C*H*=CH_2), 4.90-5.25 (m, 2H, CH=CH_2), 4.33-4.62 (m, 2H, OCH_2Ph), 3.69 (d, 2H, *J*=7.4, NCH_2), 3.48 (d, 2H, *J*=5.9, OCH_2CH), 2.65-3.15 (m, 3H, containing 3.02+3.04, 2xd, *J*=18.2, $NCOCH_aH_b$, 2.73+2.77, 2xd, *J*=18.2, $NCOCH_aH_b$, OCH_2CH), 1.66+1.63 (2xs, 3H, CH_3); accurate mass determination: calcd. for $C_{23}H_{25}NO_3$ m/z 363.1834, found 363.1828.

3-Benzyl-1-[2-(benzyloxymethyl)-3-butenyl]-3-phenyl-2,5-pyrrolidinedione (10d). 1-[2-(Benzyloxymethyl)-3-butenyl]-3-phenyl-2,5-pyrrolidinedione (1.0 g, 2.86 mmol) was alkylated with benzyl bromide (0.73 g, 4.27 mmol) and powdered K_2CO_3 (2 g) in 2 ml of dry DMF according to the procedure described for **10c**. The residue was column chromatographed (eluent PA/EtOAc 2:1) yielding **10d** as a colourless oil (1.22 g, 97%). IR ($CHCl_3$): 1770, 1700 cm^{-1}(CO); ^1H NMR (200 MHz): δ 6.95–7.55 (m, 15H, ArH), 5.46-5.70 (m, 1H, C*H*=CH_2), 4.75-5.02 (m, 2H, CH=CH_2), 4.33-4.55 (m, 2H, OCH_2Ph), 3.20-3.63 (m, 5H), 2.67-3.20 (m, 4H); accurate mass determination: calc. for $C_{29}H_{29}NO_3$ m/z 439.2147, found 439.2131.

1-[2-(Benzyloxymethyl)-3-butenyl]-5-ethoxy-2-pyrrolidinone (12a). Imide **10a** (0.51 g, 1.87 mmol) was reduced with $NaBH_4$ (0.5 g, 13 mmol) in 40 ml of EtOH. Work-up and column chromatography (eluent EtOAc) afforded **12a** as a colourless oil (0.45 g, 79%). IR ($CHCl_3$): 1690 cm^{-1} (CO); ^1H-NMR (100 MHz): δ 7.35 (s, 5H, ArH), 5.55-6.0 (m, 1H, C*H*=CH_2), 4.85-5.3 (m, 3H, CH=CH_2, NCHOEt), 4.54 (s, 2H, OCH_2Ph), 1.7-3.9 (m, 11H), 1.21 (t, 3H, *J*=7, OCH_2CH_3).

1-[2-(Benzyloxymethyl)-3-butenyl]-5-ethoxy-3-methyl-2-pyrrolidinone (11b) and 1-[2-(Benzyloxymethyl)-3-butenyl]-5-ethoxy-4-methyl-2-pyrrolidinone (12b). Imide **10b** (0.49 g, 1.70 mmol) was reduced in 8.5 ml of EtOH with 0.25 g of $NaBH_4$ for 4.5 h. After work-up the mixture of regio isomers **11b** and **12b** was largely resolved by column chromatography (eluent CH_2Cl_2/acetone 15:1 to 9:1) to afford **11b** (148 mg, 27%, colourless oil), a mixture of **11b** and **12b** (89 mg, 16%) and **12b** (236 mg, 44%, colourless oil). **11b**: IR ($CHCl_3$): 1685 cm^{-1} (CO); ^1H NMR (250 MHz): δ 7.29 (s, 5H, ArH), 5.58-5.88 (m, 1H, C*H*=CH_2), 4.93-5.24 (m, 2H, CH=CH_2), 4.72-4.93(m, 1H, NCHOEt), 4.35-4.60 (m, 2H, OCH_2Ph),2.94-3.75 (m, 6H), 2.06-2.94 (m, 3H), 1.40-1.70 (m, 1H), 1.02-1.40 (m, 6H, OCH_2CH_3, $CHCH_3$). **12b**: IR ($CHCl_3$): 1685 cm^{-1} (CO); ^1H NMR (250 MHz): δ 7.30 (s, 5H, ArH), 5.56-5.88 (m, 1H, C*H*=CH_2), 5.0-5.25 (m, 2H, CH=CH_2), 4.35-4.73 (m, 3H, NCHOEt, OCH_2Ph), 3.25-3.80 (m, 5H), 2.95-3.25 (m, 1H), 2.52-2.95 (m, 2H), 2.00-2.40 (m, 1H), 1.78-2.00 (m, 1H), 1.12-1.30 (m, 3H, OCH_2CH_3), 0.91-1.12 (m, 3H, $CHCH_3$).

1-[2-(Benzyloxymethyl)-3-butenyl]-5-ethoxy-3-methyl-3-phenyl-2-pyrrolidinone (11c) and 1-[2-(Benzyloxymethyl)-3-butenyl]-5-ethoxy-4-methyl-4-phenyl-2-pyrrolidinone (12c). Imide **10c** (436 mg, 1.20 mmol) was reduced in 6 ml of EtOH with 0.22 g of $NaBH_4$ for 2 1/4 h. After work-up the mixture of regio isomers **11c** and **12c** was separated by column chromatography (eluent PA/EtOAc 2:1). Three fractions were obtained. The first two fractions appeared to be the epimers of **11c**, the third was the mixture of epimers of **12c** (all of the fractions were colourless oils). Fraction I (52 mg, 11%), epimer of **11c**: IR ($CHCl_3$): 1690 cm^{-1} (CO); ^1H-NMR (200 MHz): δ 7.1-7.6 (m, 10H, ArH), 5.65-5.98 (m, 1H, C*H*=CH_2), 5.00-5.28 (m, 2H, CH=CH_2), 4.81-5.00 (m, 1H, NCHOEt), 4.39-4.62 (m, 2H, OCH_2Ph), 3.10-3.85 (m, 6H), 2.70-2.96 (m, 1H, OCH_2CH), 2.40-2.61 (m, 1H, $NCH(OEt)CH_aH_b$), 2.11 (dd, 1H, *J*=2.3 and 13.6,

NCH(OEt)CH_aH_b), 1.64 (s, 3H, CH_3), 1.23+1.25 (2xt, approx. 1:1, 3H, *J*=7, OCH_2CH_3). Fraction II (23 mg, 5%), epimer of **11c**: IR ($CHCl_3$): 1690 cm^{-1} (CO); ^{1}H-NMR (200 MHz): δ 7.1-7.6 (m, 10H, ArH), 5.63-5.95 (m, 1H, C*H*=CH_2), 5.00-5.30 (m, 2H, CH=CH_2), 4.86-5.00 (m, 1H, NCHOEt), 4.42-4.61 (m, 2H, OCH_2Ph), 3.12-3.80 (m, 6H), 2.73-3.03 (m, 1H, OCH_2CH), 2.38 (dd, 1H, *J*=13.8 and 2.7, NCH(OEt)CH_aH_b), 2.27 (dd, 1H, *J*=13.8 and 6.1, NCH(OEt)CH_aH_b), 1.51 (s, 3H, CH_3), 1.14 (t, 3H, *J*=7.0, OCH_2CH_3). Fraction III (299 mg, 63%), **12c**: IR ($CHCl_3$): 1690 cm^{-1} (CO); ^{1}H-NMR (200 MHz): δ 7.0-7.6 (m, 10H, ArH), 5.50-5.96 (m, 1H, C*H*=CH_2), 4.25-5.31 (m, 5H), 2.25-3.86 (m, 9H), 1.48+1.49 (2xs, approx. 1.5H, CH_3), 1.36 (s, approx. 1.5H, CH_3), 1.22+1.20 (2xt, approx. 1.5H, *J*=7, OCH_2CH_3), 0.79 (t, approx. 1.5H, *J*=7, OCH_2CH_3).

3-Benzyl-1-[2-benzyloxymethyl)-3-butenyl]-5-ethoxy-3-phenyl-2-pyrrolidinone (11d) and 4-Benzyl-1-[2-(benzyloxymethyl)-3-butenyl]-5-ethoxy-4-phenyl-2-pyrrolidinone (12d). Imide **10d** (0.60 g, 1.36 mmol) was reduced in 7 ml of EtOH with 0.30 g of $NaBH_4$ for 2 3/4 h. After work-up the reaction mixture was column chromatographed (eluent PA/EtOAc 2:1) to yield two fractions. The first fraction consisted of ethoxy lactam **11d** as a 6:4 epimeric, 1:1 diastereoisomeric mixture (43 mg, 7%, colourless oil, R_f=0.46). The second fraction, consisting of ethoxy lactam **12d**, was a 1:1 epimeric, 1:1 diastereoisomeric mixture (303 mg, 47%, colourless oil, R_f=0.27). **11d**: IR ($CHCl_3$): 1680 cm^{-1} (CO); ^{1}H -NMR (200 MHz): δ 6.80-7.65 (m, 15H, ArH), 5.50-5.82 (m, 1H, C*H*=CH_2), 4.75-5.20 (m, 2.4H, CH=CH_2), NCH(OEt)), 4.25-4.60 (m, 2.6H, OCH_2Ph, NCH(OEt)), 2.93-3.24 (m, 8H), 2.60-2.85 (m, 1H, OCH_2CH), 2.10-2.60 (m, 2H), 1.17+1.20 (2xt, 1.2H, *J*=6.9, OCH_2CH_3), 1.03+1.04 (2xt, 1.8H, *J*=7.0, OCH_2CH_3). **12d**: IR ($CHCl_3$): 1680 cm^{-1} (CO); ^{1}H-NMR (200 MHz): δ 6.40-7.50 (m, 15H, ArH), 5.76-6.05 (m, 0.5H, C*H*=CH_2), 5.10-5.63 (m, 2H), 4.20-4.98 (m, 3.5H), 2.35-4.00 (m, 11H), 1.33+1.36 (2xt, 1.5H, *J*=7.0, OCH_2CH_3), 0.81+0.82 (2xt, 1.5H, *J*=6.9, OCH_2CH_3).

***rel*-(6*R*,7*S*,8a*R*)-6-(Benzyloxymethyl)-7-(formyloxy)hexahydro-3(2*H*)-indolizinone (14a).** Ethoxy lactam **12a** (101 mg, 0.33 mmol) was stirred for 18 h at room temperature in 3 ml of HCOOH, concentrated in vacuo and taken up in 10 ml of CH_2Cl_2. The organic layer was washed with sat. $NaHCO_3$ solution, the aqeous layer washed with CH_2Cl_2 and the combined organic layers dried ($MgSO_4$), and concentrated to yield 99 mg of **14a** as an almost pure colourless oil IR ($CHCl_3$): 1725 (CO formate), 1680 (CO lactam) cm^{-1}; ^{1}H-NMR (250 MHz): δ 7.95 (s, 1H, OCHO), 7.15-7.43 (m, 5H, ArH), 5.04 (dt, 1H, *J*=4.2 and 11.0, respectively, H_7), 4.38 (d, 1H, *J*=12, OCH_aH_bPh), 4.44 (d, 1H, *J*=12, OCH_aH_bPh), 4.23 (dd, 1H, *J*=13.6 and 5.0, H_{5eq}), 3.27-3.83 (m, 3H, H_{8a}, OCH_2CH), 2.73 (t, 1H, *J*=13, H_{5ax}), 2.1-2.5 (m, 4H, H_1, H_2), 1.73-1.92 (m, 1H, H_{8eq}), 1.50-1.73 (m, 1H, H_6), 1.25 (q, 1H, *J*=11.7, H_{8ax}); ^{13}C-NMR (62.89 MHz): δ 172.40 (C-3), 159.21 (OCHO), 137.37 (s), 127.57 (d), 126.90 (d), 126.85 (d) (arom C=C), 72.45 (OCH_2Ph), 69.84 (C-7), 66.98 (CH_2OBn), 54.06 (C-8a), 39.90, 39.77, 37.62 (t), 29.41, 23.41 (t),

***rel*-(6*R*,7*S*,8a*R*)-6-(Benzyloxymethyl)hexahydro-7-hydroxy-3(2*H*)-indolizinone (14b).** The crude formate **14a** (214 mg, 0.71 mmol) was stirred for 85 min at 0° in a solution of 59 mg of KOH (85%, 0.89 mmol) in 13 ml of EtOH. The reaction mixture was diluted with 10 ml of water, saturated with NaCl and extracted four times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residual oil (183 mg) was column chromatographed (eluent CH_2Cl_2/acetone 1:1) to yield 135 mg of **14b** as an oil (70% from ethoxy lactam **12a**). Upon treatment with ether **14b** crystallized, mp 109-111°, white needles. IR ($CHCl_3$): 3480 (OH), 1670 (CO) cm^{-1}; ^{1}H-NMR (250 MHz): δ 7.20-7.34 (m, 5H,

ArH), 4.48 (s, 2H, OCH_2Ph), 4.03 (dd, 1H, *J*=13.4 and 4.9, H_{5eq}), 3.35-3.80 (m, 5H, OH, H_7, H_{8a}, OCH_2CH), 2.0-2.5 (m, 5H, H_{5ax}, H_1, H_2), 1.50-1.85 (m, 2H, H_{8eq}, H_6), 1.21 (q, 1H, *J*=11.8, H_{8ax}); after addition of D_2O: 3.35-3.80 (m, 4H, H_7, H_{8a}, OCH_2CH; accurate mass determination: calcd. for $C_{16}H_{21}NO_3$ m/z 275.1521, found 275.1508.

***rel*-(1*R*,6*R*,7*S*,8a*S*)-and *rel*-(1*R*,6*S*,7*R*,8a*R*)-6-(Benzyloxymethyl)-7-(3,5-dinitrobenzoyloxy)hexahydro-1-methyl-3(2*H*)-indolizinone (15 and 16).** A solution of etohoxy lactam **12b** (191 mg, 0.60 mmol) in 4 ml of HCOOH was stirred for 24 h at room temperature and worked-up as described for **14a**. The residue was taken up in 5 ml of 50% sat. NH_3/MeOH and stirred for 35 min at 0°, concentrated in vacuo, taken up in 5 ml of benzene and again concentrated in vacuo. To the residue was added 4-DMAP (107 mg, 0.88 mmol), 3,5-dinitrobenzoylchloride (202 mg, 0.88 mmol) and 2 ml of CH_2Cl_2.After stirring for 30 min at room temperature the reaction mixture was left in the refrigerator for 18 h and stirred at room temperature for an additional 5 h. Then a few drops of water were aded and after stirring for 75 min, the mixture was diluted with CH_2Cl_2, worked-up (washed twice with 2M HCl, sat. $NaHCO_3$ solution, dried over Na_2SO_4) and column chromatographed (eluent CH_2Cl_2/acetone 6:1) to yield a mixture of 3,5-dinitrobenzoates **15** and **16** as a yellow solid (209 mg, 72%). After two recrystallizations (dipe/EtOH) a 55:45 mixture of **15** and **16** (or vice versa) was obtained, mp 142-144° (yellow needles). IR($CHCl_3$): 3100 (arom. CH), 1730 (CO ester), 1680 (CO lactam), 1545, 1340 (NO_2)cm^{-1}; ^{1}H-NMR (250 MHz): δ 8.72-9.25 (m, 3H, ArH), 6.80-7.20 (m, 5H, ArH), 5.36 (dt, 0.45H, *J*=4 and 11, respectively, H_7), 5.30 (dt, 0.55H, *J*=4 and 11, respectively, H_7), 4.11-4.40 (m, 3H, containing 4.38, d, 1H, OCH_aH_bPh and 4.27, d, 1H, OCH_aH_bPh, H_{5eq}), 3.33-3.80 (m, 2.45H, OCH_2CH, H_{8a}), 3.09-3.27 (m, 0.55H, H_{8a}), 2.25-2.85 (m, 3H, containing 2.78+2.74, 2xt, 1H, H_{5ax}), 1.73-2.25 (m, 3H), 1.49 (q, 0.45H, *J*=12, H_{8ax}), 1.42 (q, 0.55H, *J*=12, H_{8ax}), 1.15 (d, 1.65H, *J*=6.3, CH_3), 1.04 (d, 1.35H, *J*=6.6, CH_3); accurate mass determination (mixture of **15** and **16**): calcd. for $C_{24}H_{25}N_3O_8$ m/z 483.1642, found 483.1639.

***rel*-(1*R*,6*R*,7*S*,8a*S*)-, rel-(1R,6S, 7*R*,8a*R*)-, and *rel*-(1*R*,6*S*,7*S*,8a*S*)-7-Acetoxy-6-(benzyloxymethyl)hexahydro-1-methyl-1-phenyl-3(2*H*)-indolizinone (17, 18, 19).** Ethoxylactam **12c** (224 mg, 0.57 mmol) was dissolved in 5 ml of HCOOH and stirred for 26 h at room temperature, concentrated in vacuo, taken up in toluene and concentrated in vacuo again. The residue was stirred for 1 h at 0° in 5 ml of 50% sat. NH_3/MeOH and column chromatographed (eluent EtOAc) to effect a partial separation of the alcohols corresponding to **17**, **18**, and **19**. Both fractions were acetylated by stirring them overnight in 1 ml of $CH_2Cl_2$with 4-DMAP (1.5 eq) and Ac_2O (2 eq.). After quenching with MeOH, the reaction mixtures were worked-up by diluting with CH_2Cl_2, washing with 2M HCl and sat. $NaHCO_3$ solution and drying (Na_2SO_4). The acetylated first fraction was chromatographed (eluent EtOAc), using a UV-detector for monitoring, to yield a 6:4 mixture of compounds **17** and **18** (166 mg, 72%, colourless oil, R_f=0.45/EtOAc). The fraction with R_f =0.39/EtOAc was pooled with the acetylated second fraction of the alcohols and rechromatographed (eluent EtOAc), using an UV-detector, to yield **19** (20 mg, 8%, R_f=0.39/EtOAc) as a colourless oil that solidified on standing, mp 128-136°. **17/18:** IR ($CHCl_3$): 1730 (CO ester), 1680 (CO lactam) cm^{-1}; ^{1}H-NMR (250 MHz): δ 7.05-7.50 (m, 10H, ArH), 4.92 (dt, 1H, *J*=4.0 and 11.0, respectively, H_7), 4.48+4.47 (2xd, 1H, *J*=12.1, OCH_aH_b of **18** and **17**, respectively), 4.24-4.42 (m, 2H, containing 4.37+4.35, 2xd, *J*=12.1, $OCH_aH_b$of **18** and **17**, respectively, H_{5eq}), 3.69 (dd, 0.4H, *J*=12.2 and 3.2, H_{8a} of **18**), 3.52 (dd, 0.6H, *J*=12.2 and 3.0, H_{8a} of **17**), 3.42 (d, 0.8H, *J*=4.3, OCH_2CH of **18**), 3.36 (d, 1.2H, *J*=4.1, OCH_2CH of **17**), 2.96 (d, 0.6H, *J*=16.7, $NCOCH_aH_b$ of **17**), 2.68-2.92 (m, 1.4H, containing 2.87, d, *J*=16.7, $NCOCH_aH_b$ of **18**, H_{5ax}),

2.48 (d, 0.4H, *J*=16.7, NCOCH_aH_b of **18**), 2.44 (dd, 0.6H, *J*=16.7 and 1, NCOCH_aH_b of **17**), 2.12-2.26 (m, 0.4H, H_{8eq} of **18**),1.30-2.00 (m, 8H, containing 1.75, m, H_{8eq} of **17**, 1.96+1.82, 2xs, $OCOCH_3$ of **18** and **17**, respectively, 1.50+1.38, 2xs, CCH_3 of **17** and **18**, respectively, H_{8ax} of **18**, H_6), 0.64 (q, 0.6H, *J*=12, H_{8ax} of **17**); accurate mass determination: calcd. for $C_{25}H_{29}NO_4$ m/z 407.2097, found 407.2099. **19:** IR ($CHCl_3$): 1740 (CO ester), 1680 (CO lactam) cm^{-1}; ^{1}H-NMR (250 MHz): δ 7.00-7.50(m, 10H, ArH), 4.98 (dt, 1H, *J*=12.0 and 4.7, respectively, H_7), 4.37-4.56 (m, 3H, containing 4.45, s, OCH_2Ph, H_{5eq}), 3.48 (dd, 1H, *J*=12.1 and 3.5, H_{8a}), 3.40 (dd, 1H, *J*=9.1 and 3, OCH_aH_bCH), 3.19 (t, 1H, *J*=9.1, OCH_aH_bCH), 2.77-2.94 (m, 2H, containing 2.88, d, *J*=16.7, $NCOCH_aH_b$, H_{5ax}), 2.43 (dd, 1H, *J*=16.7 and 1.3, $NCOCH_aH_b$), 2.16-2.31 (m, 1H, H_6), 1.90 (s, 3H, $OCOCH_3$), 1.53 (s, 3H, CH_3), 1.34-1.50 (m, 1H, H_{8eq}), 0.74 (q, 1H, *J*=12.2, H_{8ax}), accurate mass determination: calcd. for $C_{25}H_{29}NO_4$ m/z 407.2097, found 407.2095.

***rel*-(1*R*,6*R*,7*S*,8a*S*)-1-Benzyl-6-(benzyloxymethyl)-7-(formyloxy)hexahydro-1-phenyl-3(2*H*)-indolizinone (20a), *rel*-(1*R*,6*R*,7*S*,8a*S*)-1-benzyl-6-(benzyloxymethyl)hexahydro-7-hydroxy-1-phenyl-3(2*H*)-indolizinone (20b), and *rel*-(1*R*,6*S*,7*S*,8a*S*)-7-Acetoxy-1-benzyl-6-(benzyloxymethyl)hexahydro-1-phenyl-3(2*H*)indolizinone (21).** Ethoxy lactam **12d** (264 mg, 0.56 mmol) was dissolved in 5 ml of HCOOH and stirred for 18 h at rt. After work-up and aminolysis as described for the cyclization of ethoxy lactam **12c**, the residue was column chromatographed (eluent EtOAc). After rechromatography of a small overlapping fraction (eluent EtOAc), two fractions were obtained. The first fraction (104 mg, 42%) was identified as alcohol **20b** by comparison with a sample obtained from aminolysis of formate **20a**. Formate **20a** had been obtained pure in an earlier experiment by crystallization and recrystallization (dipe/EtOH) of the crude reaction mixture (white needles, mp 185-188°). The second fraction (104 mg) was acetylated by dissolving it in 1 ml of CH_2Cl_2, adding 4-DMAP (46 mg, 1.5 eq) and Ac_2O (about 2 eq) and stirring for 2 h at room temperature. After standing in the refrigerator overnight the reaction mixture was worked-up as described earlier. The residue (107 mg), an approximately 3:1 mixture of compounds, was crystallized from dipe/EtOH to obtain the major product, acetate **21** as white needles (mp 160-162°). Formate **20a**: IR ($CHCl_3$): 1725 (CO-ester), 1680 (CO lactam) cm^{-1}; ^{1}H-NMR (250 MHz): δ 7.85 (s, 1H, OCHO), 6.86-7.40 (m, 13H, ArH), 6.54 (dd, 2H, *J*=8 and 2, ArH), 5.19 (dt, 1H, *J*=4.3 and 11.0, respectively, H_7), 4.47 (d, 1H, *J*=17, OCH_aH_bPh), 4.40 (d, 1H, *J*=17, OCH_aH_bPh), 4.35 (dd, 1H, *J*=13.5 and 5.2, H_{5eq}), 3.78 (dd, 1H, *J*=12.2 and 2.9, H_{8a}), 3.44 (dd, 1H, *J*=9.5 and 4.3, OCH_aH_bCH), 3.40 (dd, 1H, *J*=9.5 and 3.0, OCH_aH_bCH), 3.11 (d, 1H, *J*=13.2, $PhCH_aH_bC$), 3.02 (d, 1H, *J*=13.2, $PhCH_aH_bC$), 2.93 (t, 1H, *J*=13, H_{5ax}), 2.69 (d, 1H, *J*=16.8, $NCOCH_aH_b$), 2.61 (d, 1H, *J*=16.8, $NCOCH_aH_b$), 1.98 (ddd, 1H, *J*=12, 4 and 3, H_{8eq}), 1.65-1.85 (m, 1H, H_6), 0.83 (q, 1H, *J*=12, H_{8a}). Alcohol **20b**: ^{1}H-NMR (200 MHz): δ 6.85-7.45 (m, 13H, ArH), 6.57 (dd, 2H, *J*= 8 and 2, ArH), 4.53 (s, 2H, OCH_2Ph), 4.18 (dd, 1H, *J*=13.3 and 5.0, H_{5eq}), 3.30-3.92 (m, 5H, containing 3.38, bs, 1H, OH, disappeared on addition of D_2O, OCH_2CH, H_{8a}, H_7), 3.13 (d, 1H, *J*=13.2, $PhCH_aH_bC$), 3.03 (d, 1H, *J*=13.2, $PhCH_aH_bC$), 2.72 (d, 1H, *J*=16.7, $NCOCH_aH_b$), 2.60 (d, 1H, *J*=16.7, $NCOCH_aH_b$), 2.52 (t, 1H, *J*=13, H_{5ax}), 1.50-2.00 (m, 2H, containing 1.90, m, H_{8eq}, H_6), 0.78 (q, 1H, *J*=12, H_{8ax}); accurate mass determination: calcd. for $C_{29}H_{31}NO_3$ m/z 441.2304, found 441.2300. Acetate **21**: IR($CHCl_3$): 1735 (CO ester), 1685 (CO lactam) cm^{-1}; ^{1}H-NMR (200 MHz): δ 6.78-7.50 (m, 13H, ArH), 6.60 (dd, 2H, *J*=8 and 2, ArH), 5.10 (dt, 1H, *J*=11.8 and 4.8, respectively, H_7), 4.55 (dd, 1H, *J*=13 and 1.4, H_{5eq}), 4.48 (d, 1H, *J*=11.2, OCH_aH_bPh), 4.42 (d, 1H, *J*=11.2, OCH_aH_b), 3.76 (dd, 1H, *J*=12.1 and 3.2, H_{8a}), 3.54 (dd, 1H, *J*=9.1 and 3.3, OCH_aH_bCH), 3.26 (t, 1H, *J*=9, OCH_aH_bCH), 3.17 (d, 1H, *J*=13.3, $PhCH_aH_bC$), 3.05 (d, 1H, *J*=13.3, $PhCH_aH_bC$), 2.93 (dd, 1H, *J*=13 and 4, H_{5ax}), 2.62 (d, 1H, *J*=17, $NCOCH_aH_b$), 2.56 (d, 1H, *J*=17, $NCOCH_aH_b$), 2.18-2.36 (m, 1H, H_6), 1.94 (s, 3H, $OCOCH_3$), 1.67

(dt, 1H, J=12 and 4, respectively, H_{8eq}), 1.02 (q, 1H, J=12, H_{8ax}); accurate mass determination: calcd. for $C_{31}H_{33}NO_4$ m/z 483.2410, found 483.2408.

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