231. Approaches to the Synthesis of Cytochalasans

Part 8[1])

Further Transformations and Optical Resolution of the Tetrahydroisoindolinone Subunit

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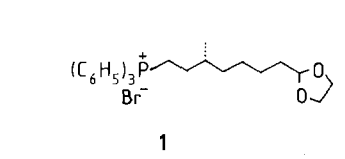
(7.VIII.84)

Summary

The bicyclic aldehyde **7** was prepared from the hydroxy ester **3** for the attachment of the macrocyclic moiety of the cytochalasans. To protect the C(6),C(7)-double bond the intermediates **8**, **9** and **13** were transformed into the epoxides **10**, **11** and **14**, respectively. Treatment of **10** and **11** with $Al(i\text{-}PrO)_3$ gave the allylic alcohol **12**. Protection of the olefinic double bond was also effected by hydroxylation with OsO_4. The triol **17** obtained from **3**, after acetalization to **18**, was oxidized to the aldehyde **20**. Attachment of the ylide of the phosphonium salt **1** to **20** gave **24**, an intermediate of proxiphomin (**2**). Removal of the C(6),C(7)-diol group was achieved *via* the thiocarbonate **23**.

Resolution of racemic hydroxy ester **3** was possible by esterification with (+)-L-*O*-acetylmandelic acid. The diastereoisomeric esters were separated by HPLC.

In [1] of this series, we have described *inter alia* the synthesis of an optically active building block **1** possessing all the requirements of a C_8-segment to the macro-carbocyclic ring of *e.g.* proxiphomin (**2**). According to the strategy designed previously [2], the



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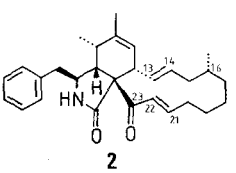

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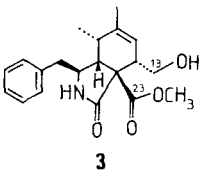

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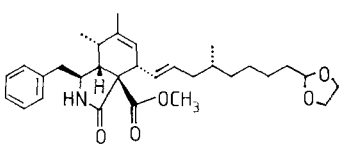

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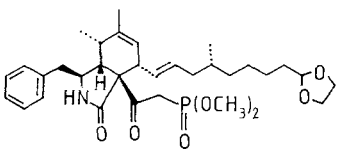

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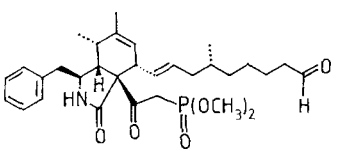

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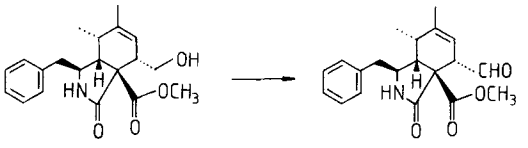
[1]) Part 7: [1].

chain **1** should be linked to the tetrahydroisoindolinone unit **3** [3] at C(13) to yield the olefin **4**. Subsequent introduction of the remaining C-atom C(22) should be performed by alkylating the ester carbonyl group of **4**, *e.g.* by conversion into the phosphonate **5**. After deprotection of the aldehyde group, followed by carbanion formation at C(22) in **6**, ring closure should lead to the target molecule **2**.

To realize this plan, transformation of the alcohol **3** to the aldehyde **7** was required *(Scheme 1)*. However, it was expected and confirmed by the results which are described subsequently that aldehyde **7** is a rather sensitive compound. Another serious difficulty arises when the racemic subunit **7** is linked to the optically active building block **1**, because the desired (*E*)-olefin would be obtained as a pair of diastereoisomers. The separation of such a mixture might be troublesome.

Scheme 1



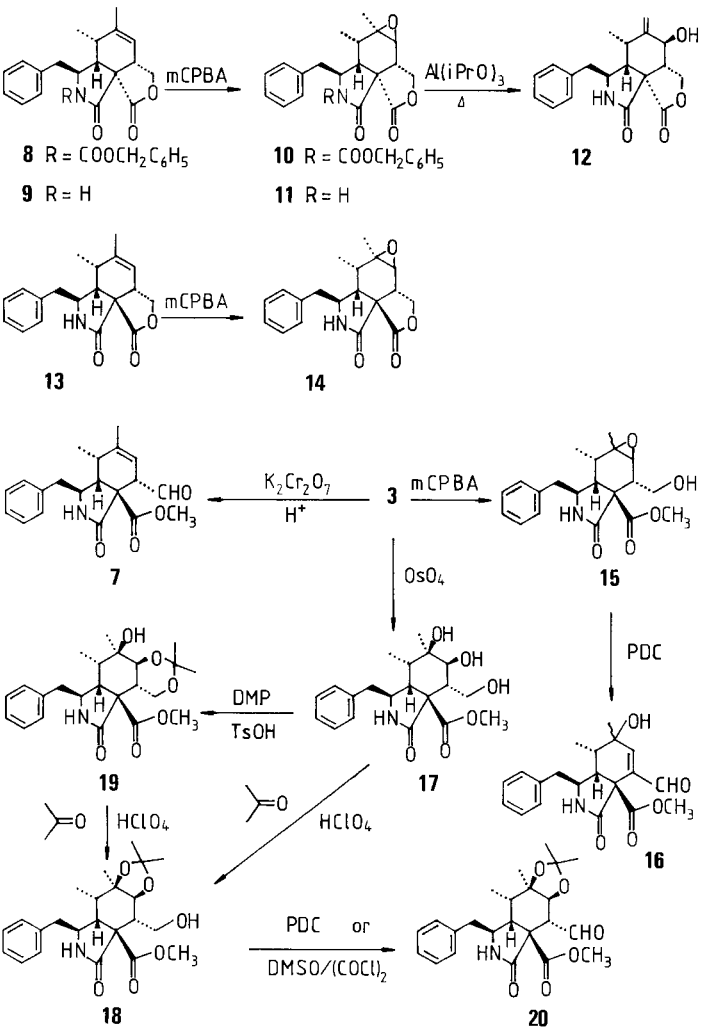
3 **7**

In the first part of this paper, we describe the preparation of aldehyde **7** and the synthesis of modified analogues, as well as successful attempt to connect a suitably protected species with the chain **1**. In the second part, the experiments are reported which allowed the resolution of the racemic subunit **3**.

With *N*-Iodosuccinimide in the presence of butylammonium iodide [4] no oxidation of the alcohol **3** occurred, while pyridinium dichromate (PDC) as well as *Swern*'s method [5] led to complex mixtures. Finally, aldehyde **7** was obtained in moderate yield using $K_2Cr_2O_7$ in acidic solution [6] as an oxidizing agent. Evidently, the C(β),C(γ)-double bond can interfere. To suppress double bond migration and to preserve an O-function at C(7) which is essential for the cytostatic activity of the cytochalasans [7], we have investigated the epoxidation of some of the tetrahydroisoindolinone subunits synthesized earlier [3]. Compound **8** as well as **9** were easily converted to the epoxides **10** and **11**, respectively *(Scheme 2)*. The attack of *m*-chloroperbenzoic acid (MCPBA) occurs from the less hindered front side. On heating with Al(i-PrO)$_3$ [8] at 90° epoxide **10** gave only the *N*-deprotected compound **11**, but increasing the temperature to 140° effected the conversion of **10** as well as **11** to the allylic alcohol **12**. This transformation proves the configuration of the epoxides **10** and **11**. Epoxidation of lactone **13**, possessing the 'natural' configuration, by MCPBA yielded epoxide **14**. Conversion of the subunit **3** by the same reagent gave epoxide **15** as an approximately 1:1 mixture of both epimers. The latter was subjected to mild oxidation by treatment with PDC. The main product obtained proved to be the α,β-unsaturated aldehyde **16**. Obviously, a change in hybridization at C(6) and C(7), in going from sp^2 to sp^3, is necessary to avoid any participation of this moiety in the following reactions.

Efficient protection of the double bond in **3** was achieved by its transformation into the vicinal diol **17** by OsO_4 addition and subsequent reduction with hydrogensulphide. Diol **17** was also obtained in good yield using the improved catalytic osmylation proce-

Scheme 2

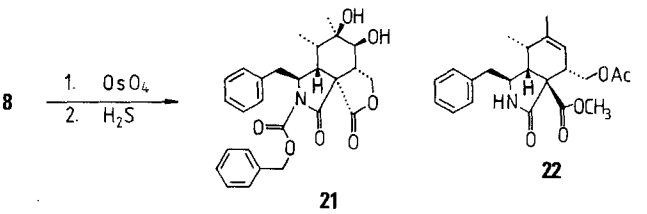


dure by *VanRheenen et al.* [9]. Protection of the vicinal secondary and tertiary OH-group was effected by treatment with acetone containing a trace of $HClO_4$ to yield the cyclic acetal **18** quantitatively. In contrast, treatment of **17** with 2,2-dimethoxypropane (DMP) and TsOH led to compound **19**, containing a six-membered acetal ring. This was deduced from a correlation of the ^{1}H-NMR spectra of **17** and **19**, measured in (D_6)DMSO, which clearly showed that the tertiary OH-group in **19** had not been protected. However, under the influence of $HClO_4$ in acetone compound **19** was converted to **18**. TLC monitoring of the 'direct' reaction of **17** with acetone and acid revealed that compound **19** is also an intermediate. This indicates that the primary OH-group reacts most rapidly, leading to the formation of **19**, which contains a *trans*-anellated six-membered acetal ring. The latter undergoes an intramolecular transetherification to

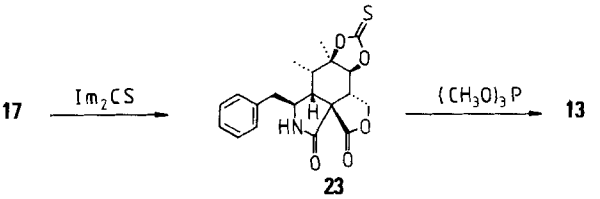
yield the thermodynamically more stable *cis*-anellated five-membered acetal ring, as in compound **18**. Oxidation of the hydroxymethyl group of **18** was performed either with PDC or using *Swern*'s method. In both cases, aldehyde **20** was obtained in good yield. Compounds **17**, **18**, **19**, and **20** are crystalline and therefore easy to purify.

From a detailed analysis of the ^{1}H- and ^{13}C-NMR spectra of the triol **17** and diol **21** it is concluded that the attack of OsO_4 at the double bond in **3** as well as in **8** occurs from the sterically less hindered *Re*-side *(Scheme 3)*. It is noteworthy that the reaction is about 100 times slower in the case of **8** as compared with **3**. In contrast to this observation, epoxidation of **8** yielded **10** having a α-orientated oxirane ring, while compound **3** furnished **15** as a mixture of both epimers. Furthermore, both substrates reacted at comparable rates. The difference in reactivity of the double bond towards OsO_4 encountered in **3** and **8** may not has been associated with a distorted π-bond in **8**. This conclusion was based on the fact that the dihedral angle enclosed by C(5), C(6), C(7) and C(8) in **8** and in the *O*-acetyl derivative **22** of **3**, calculated from the available X-ray data [10], is found to be 1.1° and 1.0°, respectively. The quoted difference has to be ascribed to the H-atom at C(4), which exerts an appreciable steric shielding of the *Re*-side of the double bond in **8**. In compound **3**, an effect of this kind is absent. However, this shielding is only effective when a bulky reagent, *e.g.* OsO_4, is added to the π-bond, but it does not exert any influence in the transfer of a 'small' O-atom from a peracid. The difference observed in the stereochemical outcome of the epoxidation reaction for **8** and **3** may be rationalized from the fact that on the *Si*-side the approach to the double bond is very strongly hindered by the axial α-CH_3-group at C(5) in **8**, but considerably less hindered by the α-oriented lactam ring in **3**, allowing addition of the peracid oxygen from both sides.

Scheme 3



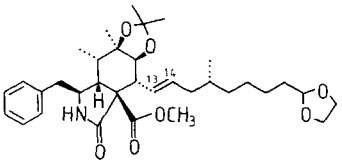
Scheme 4



The removal of the diol-acetonide protecting group was tested using compound **17** as a substrate. The reaction of **17** with 1.5 equiv. of thiocarbonyl-diimidazole (Im_2CS) [11] produced the thiocarbonate **23** by simultaneous lactonization *(Scheme 4)*. To restore the 6,7-double bond compound **23** was heated with $(CH_3O)_3P$ [11]. The resulting product proved to be identical with lactone **13** [3].

Treatment of the aldehyde **20** with the ylide of the phosphonium salt **1** yielded compound **24**, but so far only in low yield. Mass spectroscopy clearly shows M^+ at *m/z* 583. The 360-MHz ^{1}H-NMR[2]) spectrum indicates the (*E*)-configuration of the C(13),C(14) double bond of **24**.

[2]) We wish to thank Mr. *P. Hug* and Dr. *H. Fuhrer, Ciba-Geigy AG*, Basel, for running and interpreting spectra of compounds **20** and **24**.



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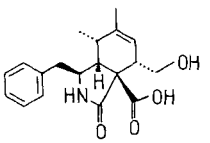
Resolution of the Racemic Intermediate **3**. Efficient resolution is expected to be highly dependent on structural requirements which are difficult to rationalize. Resolution of alcohols can be achieved by converting them into the carboxylic acids and forming diastereomeric salts with an optically active base, *e.g.* an alkaloid [12]. We, therefore, chose acid **25** which is an intermediate in the preparation of the hydroxy ester **3** from the lactone **8** [3] for the resolution. Crystalline **25** contains half a mole of benzene in its lattice as shown by elemental analysis and ^{1}H-NMR spectroscopy. Unfortunately, all attempts to prepare a crystalline strychnine salt failed, perhaps because the two critical chiral centers are too far away from each other and thus create only a very small difference in scalar properties of the two diastereoisomers.



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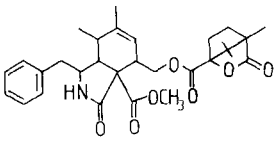

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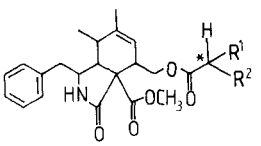

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We also were not able to separate the diastereoisomeric esters **26**, which were prepared from **25** by the reaction with (−)-camphanic-acid chloride according to *Gerlach* [13] by chromatography. Again, the scalar differences might be very small. To make these larger, we decided to prepare an ester of type **27** in which the residues R^1 and R^2 should be as different as possible from each other and relative to hydrogen. This is the case if R^1 = phenyl and R^2 = acetoxy, as for instance in the ester of (+)- or (−)-*O*-acetylmandelic acid. Optically pure (+)-L-*O*-acetylmandelic-acid chloride (**28**) is accessible and its reaction with alcohols is known to proceed without racemization [14][3]). The esterification of racemic **3** with **28** yielded the diastereomeric esters **29** and **30** as a 1:1 mixture as determined from its ^{1}H-NMR spectrum *(Scheme 5)*. Separation of **29** and **30** was achieved by HPLC. Each ester was treated with KOH in MeOH, and the acids of type **25** obtained were re-esterified by CH_2N_2 to give **31** and **32**, respectively. These compounds showed, within experimental error, complementary values of specific optical rotation (measured in two solvents and at several wavelengths). The (+)-L-*O*-acetylmandelic-acid ester which is eluted first led to that alcohol which exhibits a negative $[\alpha]_D$-value in MeOH-solution. On the basis of the comparable, also negative $[\alpha]_D$-value found for the analogous alcohol **33** [16], one might assume that compound **31** possessing 'natural' configuration is obtained from the less polar ester **29**. Nevertheless, this is a tentative correlation which still awaits confirmation.

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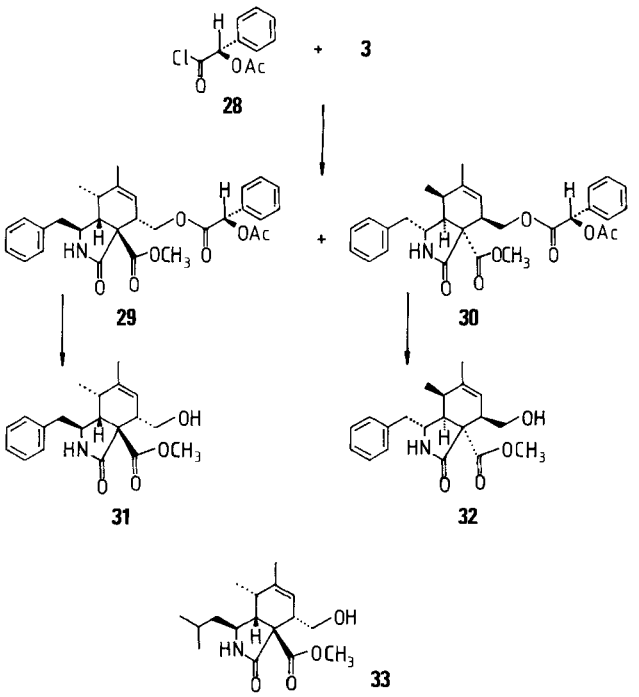
[3]) Direct esterification of alcohols with (−)-D-mandelic acid for the purpose of racemate resolution has been described recently by *Whitesell & Reynolds* [15].

Scheme 5



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

Experimental Part

General. See [1]. Moreover, the *Chromatotron* technique (CT) (discs with a layer of silica gel of 1 mm of thickness) was used for rapid prep. chromatography. For high-pressure liquid chromatography (HPLC) was used either a column *Nucleosil 5 NO_2 (Knauer)* for analytical purposes, or a column *Lichrosorb Si 6010* (length: 50 cm, i.∅: 22.7 mm/*Du Pont*) for prep. separations.

*Methyl (3*RS,*3a*SR,*4*RS,*7*RS,*7a*RS*)-3-Benzyl-7-formyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylate* (**7**). A solution of **3** (31.7 mg, 92 µmol) in 2.0 ml of CH_2Cl_2 was shaken for 15 sec with 2.0 ml 18N H_2SO_4 containing $K_2Cr_2O_7$ (12.5 mg, 42 µmol). The aq. phase was extracted with CH_2Cl_2 (2 × 2.0 ml) and the org. layer was washed by H_2O (5 × 2.0 ml). The combined org. layers were dried and after evaporation of the solvent *i.v.* gave 23.5 mg of crude **7** as a foam. Purification of a 72.3 mg batch by CT (CH_2Cl_2/MeOH 95:5) yielded 40.8 mg (42%) of pure **7** as a colourless oil. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.03 (*d*, *J* = 7, 3H–C(11)); 1.72 (br. *s*, 3H–C(12)); 2.25–2.9 (*m*, H–C(4), H–C(5), H–C(8), H–C(10)); 3.1–3.5 (*m*, H–C(3), H–C(10)); 3.75 (*s*, CH_3OCO); 6.1 (br., H–C(7)); 6.25 (br., NH); 6.9–7.35 (*m*, Ph–C(10)); 9.82 (*s*, H–C(13)).

*(3*RS,*3a*SR,*4*RS,*5*SR,*6*RS,*7*RS,*7a*SR*)-3-Benzyl-2-benzyloxycarbonyl-5,6-epoxy-4,5,7-trimethyl-1-oxoperhydroisoindoline-7a-7α-carbolactone* (**10**). MCPBA (100.0 mg, 0.5 mmol) were aded to **8** (44.7 mg, 0.1 mmol) dissolved in 1.25 ml of CH_2Cl_2 at r.t. This mixture was stirred for 5 h. The excess of MCPBA was removed by 1M NaI, 1M $KHSO_4$, and 1M $Na_2S_2O_3$ (1 × 1.25 ml each) in an extraction procedure using CH_2Cl_2/Et_2O 1:4 (3 × 10 ml) as org. phase. Evaporation *i.v.* left 50 mg of a residue, which crystallized from CH_2Cl_2/Et_2O to yield 37.5 mg (81%) of pure **10**. M.p. 161–162°. IR (KBr): 2970, 1750, 1735, 1715, 1445, 1375, 1290, 1250, 1185, 745, 690. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.86 (*d*, *J* = 7, 3H–C(11)); 1.28 (*s*, 3H–C(12)); 1.9–2.2 (*m*, H–C(5)); 2.58 (*dd*, *J* = 4.5, *J'* = 11, H–C(4)); 2.87 (*s*, H–C(7)); 2.95–3.2 (*m*, H–C(8), H–C(10)); 3.35 (*dd*, J_{AB} = 15, *J*(3,10) = 2,

H–C(10)); 4.26 (*dd*, J_{AB} = 9, *J*(8,13) = 1, H–C(13)); 4.66 (*dd*, J_{AB} = 9, *J*(8,13) = 7, H–C(13)); 4.9–5.2 (*m*, H–C(3)); 5.35 (*s*, PhCH_2OCO–N(2)); 7.0–7.4 (*m*, 2 Ph). MS: 461 (M^+), 417, 370, 326, 91. Anal. calc. for $C_{27}H_{27}NO_6$ (461.51): C 70.27, H 5.90, N 3.04; found: C 70.36, H 5.83, N 2.94.

(3RS,3aSR,4RS,5SR,6RS,7RS,7aSR)-3-Benzyl-5,6-epoxy-4,5,7-trimethyl-1-oxoperhydroisoindoline-7a-7α-carbolactone (**11**). As above (**8**→**10**), 31.4 mg (0.1 mmol) of **9** gave 53.3 mg of crude product, which was recrystallized from acetone/Et_2O to yield 29.0 mg (88%) of pure **11**. M.p. 230–230.5°. IR (KBr): 3350, 3060, 3010, 2970, 1745, 1700, 1475, 1425, 1210, 1190, 1160, 1010, 955, 710, 690. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.10 (*d*, *J* = 7, 3H–C(11)); 1.38 (*s*, 3H–C(12)); 2.3–2.8 (*m*, H–C(4), H–C(5), H–C(10)); 2.9–3.2 (*m*, H–C(8), H–C(10)); 2.95 (*s*, H–C(7)); 4.29 (*dd*, J_{AB} = 9, *J*(8,13) = 1, H–C(13)); 4.45–4.8 (*m*, H–C(3)); 4.17 (*dd*, J_{AB} = 9, *J*(8,13) = 7, H–C(13)); 5.83 (br., NH); 7.1–7.4 (*m*, Ph). Analc. calc. for $C_{19}H_{21}NO_4$ (327.38): C 69.70, H 6.47, N 4.28; found: C 69.82, H 6.50, N 4.47.

11 *from* **10**. A solution of **10** (13.0 mg, 28 μmol) and Al(i-PrO)$_3$ (5.8 mg, 28 μmol) in 0.5 ml of toluene was warmed to 90° for 12 h. 2.0 ml of 0.5N HCl were added and the mixture was extracted with CH_2Cl_2/Et_2O 1:3 (3 × 10 ml), washed (4 × 2 ml H_2O) and dried. Evaporation *i.v.* yielded 8 mg (87%) of crystalline **11**. M.p. 227 229°. Anal. calc. for $C_{19}H_{21}NO_4$ (327.38): C 69.70, H 6.47, N 4.28; found: C 69.43, H 6.31, N 4.29.

(3RS,3aSR,4RS,6RS,7RS,7aSR)-3-Benzyl-6-hydroxy-4,7-dimethyl-5-methylidene-1-oxoperhydroisoindoline-7a-7α-carbolactone (**12**). A solution of **11** (412 mg, 0.89 mmol) and Al(i-PrO)$_3$ (1.0 g, 4.8 mmol) in 5 ml of xylene was heated to 135° for 45 h. Analogous workup as for **10**→**11** gave 325 mg of crude **12**, which crystallized from CH_2Cl_2/pentane to yield 182 mg (62%) pure **12** and 100 mg of mother liquor containing mainly **12**. M.p. 168–170°. IR (KBr): 3580, 3365, 2930, 2900, 1750, 1705, 1660 (sh), 1200, 1160, 1045, 705. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.20 (*d*, *J* = 7, 3H–C(11)); 2.3–3.3 (*m*, H–C(4), H–C(5), H–C(8), OH, 2H–C(10)); 3.9–4.8 (*m*, H–C(3), H–C(7), 2H–C(13)); 5.00 (br. *s*, H–C(12)); 5.17 (br. *s*, H–C(12)); 5.96 (br. *s*, NH); 7.0–7.4 (*m*, Ph). Anal. calc. for $C_{19}H_{21}NO_4$ (327.38): C 69.70, H 6.47, N 4.28; found: C 69.82, H 6.63, N 4.21.

(3RS,3aSR,4RS,7RS,7aRS)-3-Benzyl-7-hydroxymethyl-4,5,7-trimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-7α-carbolactone (**13**). A solution of **23** (90.0 mg, 0.23 mmol) and freshly distilled trimethylphophite (2.0 ml, 17 mmol) in 4.0 ml of toluene was heated to 110° for 72 h. Evaporation *i.v.* together with toluene (3 × 10 ml) and xylene (2 × 10 ml) gave 60.6 mg of a foam, which was dissolved in CH_2Cl_2/Et_2O 1:1 and filtered through a short column of cotton. The filtrate was concentrated *i.v.* and crystallized from Et_2O to yield 49.0 mg (69%) of pure **13**. M.p. 199–203°. The analytical and spectral data were congruent with those reported in [3].

(3RS,3aSR,4RS,5SR,6RS,7RS,7aRS)-3-Benzyl-5,6-epoxy-4,5,7-trimethyl-1-oxoperhydroisoindoline-7a-7α-carbolactone (**14**). A solution of **13** (31.4 mg, 0.10 mmol) in 1.0 ml of CH_2Cl_2 was treated with MCPBA (100 mg, 0.5 mmol) at r.t. for 21 h. Workup analogous to **8**→**10** gave 82 mg of residue. The latter was digerated with CH_2Cl_2 (2 × 0.5 ml) to yield 50.0 mg of crystalline product, which was free of MCBA. Purification by CC (CH_2Cl_2/acetone gradient) gave 19.5 mg (59%) of **14** as needles. M.p. 135–137°. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.91 (*d*, *J* = 7, 3H–C(11)); 1.22 (*s*, 3H–C(12)); 1.73 (*m*, H–C(5)); 2.4–2.7 (*m*, H–C(4), H–C(10)); 2.9–3.15 (*m*, H–C(8), H–C(10)); 3.24 (*d*, *J*(7,8) = 6, H–C(7)); 3.75 (*m*, H–C(3)); 4.58 (*t*, J_{AB} = 8, *J*(8,13) = 8, H–C(13)); 5.29 (*dd*, J_{AB} = 8, *J*(8,13) = 11, H–C(13)); 7.08 (br. *s*, NH); 7.15–7.4 (*m*, Ph).

Methyl (3RS,3aSR,4RS,5RS,6RS,7RS,7aRS)-3-Benzyl-6-hydroxymethyl-4,5-dimethyl-1-oxoperhydroisoindoline-7a-carboxylate (**15**). To a stirred solution of **3** (1.41 g, 4.1 mmol) in CH_2Cl_2 MCPBA (3.55 g, 18.5 mmol) were added at r.t. After 4 h the solution was poured to a mixture of 450 ml of CH_2Cl_2/Et_2O 1:8, 50 ml 1M NaI, and 50 ml 1M $KHSO_4$ and extracted. I_2 that was formed was reduced by shaking with 50 ml 1M $Na_2S_2O_3$. The org. layers were washed with H_2O until pH = 6. Evaporation *i.v.* left 3.7 g of an oil, which was dissolved in 20 ml of CH_2Cl_2 and treated at 0° by 10 ml of a CH_2N_2-solution in Et_2O. Evaporation *i.v.* gave 1.95 g of crude **15**. Recrystallization from Et_2O yielded 1.004 g (68%) of **15**. M.p. 143–145°. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.03 (*d*, *J* = 7, 3H–C(11)); 1.30 (*s*, 3H–C(12)); 1.90 (*m*, H–C(5)); 2.2–2.7 (*m*, H–C(4), H–C(8), H–C(10)); 2.7–3.0 (*m*, H–C(10)); 2.82 (*s*, 0.5H–C(7)); 3.09 (*d*, *J*(7,8) = 6, 0.5H–C(7)); 3.6–3.8 (*m*, H–C(3)); 3.83 (*s*, CH_3OCO); 3.98 (*d*, *J*(8,13) = 3, 2H–C(13)); 6.36 (br., NH); 7.0–7.4 (*m*, Ph). MS: 327 ($M^+ - 32$ (CH_3OH)), 270, 268, 236, 182, 91. Anal. calc. for $C_{20}H_{25}NO_5$ (359.42): C 66.83, H 7.01, N 3.90; found: C 66.98, H 7.13, N 3.81.

Methyl (3RS,3aSR,4RS,5RS,7aRS)-3-Benzyl-7-formyl-5-hydroxy-4,5-dimethyl-1-oxo-3a,4,5,7a-tetrahydroisoindoline-7a-carboxylate (**16**). Compound **15** (38.8 mg, 0.11 mmol), PDC (72.2 mg, 0.19 mmol), and 3 drops of Et_3N were diluted with 4.0 ml of CH_2Cl_2 and stirred at r.t. for 20 h. Filtration through a column of cotton using Et_2O (1 × 4 and 2 × 2 ml) removed the reagent. The filtrate was evaporated *i.v.* to give 34.8 mg of a foam. Purification of the latter by CC (CH_2Cl_2/acetone 6:4) yielded 22.8 mg (60%) of crystalline **16**. M.p. 185–187°. ^{1}H-NMR (90 MHz, $CDCl_3$/C_5D_5N): 1.15 (*d*, *J* = 7, 3H–C(11)); 1.36 (*s*, 3H–C(12)); 2.23 (*m*, H–C(5)); 2.6–3.2 (*m*, H–C(4), 2H–C(10)); 3.62 (*s*, CH_3OCO, OH); 3.88 (*m*, H–C(3)); 7.03 (*s*, H–C(7)); 7.18

(*s*, NH); 7.22 (*s*, Ph); 9.75 (*s*, H–C(13)). MS: 358 ($M^+ + 1$), 339 ($M^+ - 18$ (H_2O)), 329 ($M^+ - 28$ (CO)), 266, 248, 220, 189, 188.

Methyl (3RS,3aSR,4RS,5SR,6RS,7RS,7aRS)-3-Benzyl-5,6-dihydroxy-7-hydroxymethyl-4,5-dimethyl-1-oxoperhydroisoindoline-7a-carboxylate (**17**). OsO_4 (104.5 mg, 411 µmol) was added at 0° to a solution of **3** (110.7 mg, 322 µmol) in 3.2 ml of THF. After 1 h at 0° all **3** was converted to the osmate, which was cleaved by saturation of the solution with H_2S-gas. Before doing this operation, it is advisable to add a small amount of H_2O (0.33 ml THF containing 5% of H_2O). The resulting black suspension was filtered through a column of cotton using THF for rinsing (12 × 0.8 ml). The solvent of the filtrate was evaporated *i.v.* to give 115.9 mg (95%) of crystalline **17** as plates (from CH_2Cl_2/Et_2O). M.p. 148–149°. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.06 (*d*, *J* = 7, 3H–C(11)); 1.28 (*s*, 3H–C(12)); 2.17 (*m*, H–C(5)); 2.4–3.2 (*m*, H–C(4), H–C(8), 2H–C(10)); 3.3–4.5 (*m*, H–C(3), H–C(7), 2H–C(13), 3 OH); 3.73 (*s*, CH_3OCO); 6.75 (*s*, NH); 7.1–7.5 (*m*, Ph). MS: 378 ($M^+ + 1$), 328 ($M^+ - 49$ (H_2O,CH_2OH)), 286 ($M^+ - 91$ (C_7H_7)), 254, 233, 200, 91. Anal. calc. for $C_{20}H_{27}NO_6$ (377.44): C 63.64, H 7.21, N 3.71; found: C 63.43, H 7.38, N 3.73.

Catalytic Procedure. To a solution of **3** (1.00 g, 2.91 mmol) and *N*-methylmorpholine-*N*-oxide dihydrate (580 mg, 3.78 mmol) in 35 ml of acetone and 2 ml of H_2O were added 0.6 ml of a solution of OsO_4 in *t*-BuOH (100 mg in 4 ml). After stirring at r.t. for 72 h, 10 ml of 20% $NaHSO_3$-solution were added. Then, the mixture was neutralized with 2N H_2SO_4 and the acetone was evaporated *i.v.* The aq. suspension was saturated with salt and extracted with CH_2Cl_2/Et_2O 1:2 to give 993 mg (90%) of pure **17** as prisms (from CH_2Cl_2/Et_2O). M.p. 210–212°. IR (KBr): 3510, 3430, 3370, 3320, 3065, 3035, 2995, 2970, 2925, 1735, 1705. ^{1}H-NMR (90 MHz, $(CD_3)_2SO$): 0.75 (*d*, *J* = 7, 3H–C(11)); 1.08 (br. *s*, 3H–C(12)); 1.65–1.95 (*m*, H–C(5)); 2.26–2.70 (*m*, H–C(4), H–C(8), 2H–C(10)); 3.24 (*dd*, *J* = 12, *J'* = 7, H–C(7)); 3.42–3.72 (*m*, H–C(3), 2H–C(13)); 3.56 (*s*, CH_3OCO–C(9)); 4.12 (*s*, HO–C(6)); 4.66 (*t*, *J* = 6, HO–C(13)); 4.71 (*d*, *J* = 7, HO–C(7)); 7.11–7.34 (*m*, Ph); 8.34 (br. *s*, NH). MS: 378 ($M^+ + 1$). Anal. found: C 63.56, H 7.47, N 3.65.

Methyl (3RS,3aSR,4RS,5SR,6RS,7RS,7aRS)-3-Benzyl-7-hydroxymethyl-4,5-dimethyl-5,6-(dimethylmethylenedioxy)-1-oxoperhydroisoindoline-7a-carboxylate (**18**). To a stirred suspension of **17** (41.7 mg, 110 µmol) in acetone (2.2 ml) 0.55 ml of 5.0×10^{-3}M $HClO_4$ in acetone were added at r.t. and stirring was continuated for 2 h. Then, the acid was neutralized by addition of 2.75 ml of 2.0×10^{-3}M $NaHCO_3$. The product was isolated by extraction, using CH_2Cl_2/Et_2O 1:3 (3 × 10 ml) and H_2O (4 × 2.5 ml). Evaporation of the solvents *i.v.* left a residue, which was crystallized from $Et_2O/(i\text{-}Pr)_2O$ to yield 44.4 mg (97%) of **18** as prisms. M.p. 145–147°. IR (KBr): 3360, 3260, 2980, 2930, 1735, 1630, 1450, 1230, 1055. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.93 (*d*, *J* = 7, 3H–C(11)); 1.26 (*s*, 3H–C(12)); 1.40 (*s*, 2 $(CH_3)_2C$); 2.24 (*m*, H–C(5)); 2.3–2.9 (*m*, H–C(4), H–C(8), 2H–C(10)); 3.5–4.3 (*m*, H–C(3), H–C(7), 2H–C(13), OH); 6.2 (br. *s*, NH); 7.0–7.5 (*m*, Ph). MS: 417 (M^+), 402, 385, 370, 310, 294 ($M^+ - 91 - 32$ (C_7H_7 & CH_3OH)), 236, 232, 91. Anal. calc. for $C_{23}H_{31}NO_6$ (417.50): C 66.16, H 7.48, N 3.36; found: C 65.91, H 7.77, N 3.27.

18 *from* **19**: In an analogous experiment as above (**17**→**18**), 94 mg of **19** yielded 80 mg (85%) of pure **18**. ^{1}H-NMR (90 MHz, $(CD_3)_2SO$): 0.42 (*d*, *J* = 7, 3H–C(11)); 1.14 (br. *s*, 3H–C(12)); 1.2–1.4 (br. *s*, 2 $(CH_3)_2C$); 1.70–2.06 (*m*, H–C(5)); 2.13–3.00 (*m*, H–C(4), H–C(8), 2H–C(10)); 3.44–4.17 (*m*, H–C(3), H–C(7), 2H–C(13)); 3.72 (*s*, CH_3OCO); 4.78 (*dd*, *J* = 9, *J'* = 3, OH); 7.05–7.46 (*m*, Ph); 8.53–8.66 (br. *s*, NH). MS: 417 (M^+). Anal. found: C 66.24, H 7.61, N 3.35.

Methyl (3RS,3aSR,4RS,5SR,6RS,7RS,7aRS)-3-Benzyl-7-formyl-4,5-dimethyl-5,6-(dimethylmethylenedioxy)-1-oxoperhydroisoindoline-7a-carboxylate (**20**). *Method a.* A suspension of **18** (1.75 g, 4.19 mmol) and PDC (6.48 g, 17.22 mmol) in 33 ml of CH_2Cl_2 was stirred at r.t. for 6 d. After addition of Et_2O (70 ml), the stirring was continued for 20 min. Then, the suspension was filtered by passing through a column of cotton (length: 25 cm, i.∅: 70 mm) using Et_2O (6 × 30 ml) for elution. The filtrate yielded on evaporation of the solvents *i.v.* 1.90 g of a brown oil. Purification of the latter by CC (Et_2O) gave 1.66 g of colourless, oily compound **20**, which was crystallized from Et_2O to yield 1.502 g (86%) of pure **20** as aggregated plates of m.p. 156–159°. IR (KBr): 3300, 2980, 1725, 1705, 1690 (sh), 1380, 1245, 1110. ^{1}H-NMR (360 MHz, $CDCl_3$): 0.89 (*d*, *J* = 7.2, 3H–C(11)); 1.25 (*s*, 3H–C(12)); 1.39, 1.41 (2*s*, 2 $(CH_3)_2C$); 2.07 (*quint.*, *J*(5,11) = 7.2, *J*(4,5) = 6.4, H–C(5)); 2.57 (*dd*, *J*(3,4) = 2.1, *J*(4,5) = 6.4, H–C(4)); 2.74 (*dd*, J_{AB} = 13.0, *J*(9,10) = 6.2, 1H–C(10)); 2.85 (*dd*, J_{AB} = 13.0, *J*(3,10) = 8.6, 1H–C(10)); 3.11 (*d*, *J*(7,8) = 9.8, H–C(8)); 3.67 (*m*, H–C(3)); 3.91 (*s*, CH_3OCO); 4.27 (*d*, *J*(7,8) = 9.8, H–C(7)); 5.98 (br. *s*, NH); 7.10–7.40 (*m*, Ph); 9.98 (*d*, *J*(8,13) = 1.0, H–C(13)). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 11.0 (*q*, C(11)); 23.3 (*q*, C(12)); 27.8, 29.3 (2*q*, $(CH_3)C$ 38.7 (*d*, C(4)); 44.1 (*t*, C(10)); 47.7 (*d*, C(5)); 53.2 (*d*, C(8)); 53.3 (*q*, CH_3OCO); 54.9 (*t*, C(3)); 57.0 (*s*, C(9)); 78.8 (*d*, C(7)); 81.4 (*s*, C(6)); 109.6 (*s*, $(CH_3)_2C$); 127.2, 128.9, 129.5 (3*d*), and 136.8 (*s*) (all from C_6H_5); 172.5, 172.7 (2*s*, C(1), CO–C(9)); 199.8 (*d*, C(13)). MS: 416 ($M^+ + 1$), 400, 387 ($M^+ - 28$ (CO)), 339, 328, 294, 266, 248, 232, 220, 154, 91. Anal. calc. for $C_{23}H_{29}NO_6$ (415.49): C 66.49, H 7.04, N 3.37; found: C 66.23, H. 7.26, N 3.35.

Method b. To a solution of oxalyl chloride (0.44 ml, 5.1 mmol) in 30 ml of CH_2Cl_2 was added at −78° a solution of $(CH_3)_2SO$ (0.85 ml, 12 mmol) in 5 ml of CH_2Cl_2. After 2 min a solution of **18** (1.4 g, 3.35 mmol) in 20 ml of CH_2Cl_2 was added during a period of 10 min. Stirring was continued for 15 min at −78° before the reaction was quenched by addition of Et_3N (10 ml). Then, the mixture was allowed to warm to r.t. The product was obtained by extraction with CH_2Cl_2, the org. phases being washed with chilled 2N H_2SO_4, sat. NH_4Cl, and brine. On evaporation of the solvent *i.v.*, the org. layer yielded a yellowish, crystalline residue. The latter was recrystallized from $CH_2Cl_2/(i\text{-}Pr)_2O$ to give 1.268 g (91%) of pure **20**. M.p. 178–179°. Anal. found: C 66.31, H 7.25, N 3.30.

Methyl (3RS,3aSR,4RS,5SR,6RS,7RS,7aRS)-3-Benzyl-5-hydroxy-4,5-dimethyl-6,7α-(dimethylmethylenedioxy)-1-oxoperhydroisoindoline-7a-carboxylate (**19**). A solution of **17** (40 mg, 106 μmol) and PPTS (4 mg) in 2 ml of 2,2-dimethoxypropane was stirred at r.t. for 2 h. Then, the mixture was taken up in Et_2O. The org. phase was washed with sat. $KHCO_3$ and brine. Evaporation *i.v.* of the org. layer left colourless crystals, which were recrystallized from $(i\text{-}Pr)_2O$ to yield 40 mg (90%) of **19**. M.p. 176–177°. IR (KBr): 3560, 3220, 3110, 3035, 2985, 2940, 1740, 1690. ^{1}H-NMR (90 MHz, $(CD_3)_2SO$): 0.77 (*d*, *J* = 7, 3H–C(11)); 1.08 (br. *s*, 3H–C(12)); 1.20–1.45 (2*s*, $(CH_3)_2C$); 1.60–1.95 (*m*, H–C(5)); 2.28–2.81 (*m*, H–C(4), H–C(8), 2H–C(10)); 3.29–3.73 (*m*, H–C(3), H–C(7), H–C(13)); 3.56 (*s*, CH_3OCO); 3.88 (*s*, OH); 4.40 (br. *t*, *J* = 11, H–C(13)); 7.16–7.42 (*m*, Ph); 8.19 (br., NH). MS: 418 ($M^+ + 1$), 417 (M^+). Anal. calc. for $C_{23}H_{31}NO_6$ (417.51): C 66.16, H 7.48, N 3.36; found: C 65.97, H 7.63, N 3.32.

(3RS,3aSR,4RS,5SR,6RS,7RS,7aSR)-3-Benzyl-2-(benzyloxycarbonyl)-5,6-dihydroxy-4,5,7-trimethyl-1-oxoperhydroisoindoline-7a,7α-carbolactone (**21**). By the same procedure as described for **3**→**17**, 446.4 mg (1.0 mmol) of **8** yielded 472.3 mg (98%) of pure **21**. M.p. 147–148°. IR (KBr): 3550, 3510, 3410, 3060, 3030, 2980, 2890, 1770, 1755, 1685, 1260, 1245, 1215, 1160, 1120, 1035, 740, 690. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.82 (*d*, *J* = 7, 3H–C(11)); 1.27 (*s*, 3H–C(12)); 1.65 (br. *s*, HO–C(7)); 1.88 (br. *s*, HO–C(6)); 1.80–2.05 (*m*, H–C(5)); 2.33 (br. *d*, *J* = 7, H–C(4)); 2.51 (*dd*, J_{AB} = 11, *J'* = 4, H–C(10)); 2.94 (*dd*, J_{AB} = 11, *J'* = 5, H–C(10)); 3.10–3.60 (*m*, H–C(7), H–C(8)); 4.35 (*d*, J_{AB} = 9, H–C(13)); 4.76 (*dd*, J_{AB} = 9, *J'* = 4.5, H–C(13)); 4.90–5.25 (*m*, H–C(3)); 5.35 (*s*, $C_6H_5CH_2OCO$–N(2)); 6.95–7.55 (*m*, 2 C_6H_5). Anal. calc. for $C_{27}H_{29}NO_7$ (479.53): C 67.63, H 6.10, N 2.92; found: (highly hygroscopic compound) C 66.46, H 6.46, N 2.76.

(3RS,3aSR,4RS,5SR,6RS,7RS,7aRS)-3-Benzyl-4,5,7-trimethyl-1-oxo-5,6-(thiocarbonyldioxy)perhydroisoindoline-7a,7α-carbolactone (**23**). A mixture of **17** (377.5 mg, 1.00 mmol), 1,1'-thiocarbonyl-diimidazole (273.9 mg, 1.54 mmol), and toluene (6 ml) was refluxed for 4.5 h. The product was obtained by extraction with CH_2Cl_2/Et_2O 1:3 (3 × 20 ml). The org. layers were washed (3 × 5 ml H_2O) and yielded on evaporation of the solvents *i.v.* 416 mg of a foam. Purification by CT (CH_2Cl_2/MeOH 95:5) gave 265 mg (68%) of **23**, which crystallized from $CHCl_3$ and dioxane/Et_2O. M.p. 254° (dec.). IR (KBr): 3400, 3180, 3100, 2980, 1775, 1605, 1310, 1240, 1020, 1000, 945. ^{1}H-NMR (90 MHz, C_5D_5N): 0.90 (*d*, *J* = 7, 3H–C(11)); 1.50 (*s*, 3H–C(12)); 2.60 (*quint.*, H–C(5)); 2.96 (*d*, *J* = 7, H–C(4)); 3.10–3.35 (*m*, 2H–C(10)); 3.35–3.85 (*m*, H–C(8)); 3.90–4.15 (*m*, H–C(3)); 4.60 (*t*, J_{AB} = 7.5, H–C(13)); 5.27 (*d*, *J* = 12, H–C(7)); 5.48 (*dd*, J_{AB} = 7.5, *J'* = 11, H–C(13)); 7.18–7.45 (*m*, Ph).

Methyl (3RS,3aSR,4RS,5SR,6RS,7RS,7aRS,5''RS,7''E)-3-Benzyl-4,5 dimethyl-7-[4-methyl-8-(1,3-dioxolan-2-yl)-1-octenyl]-1-oxo-5,6-(dimethylmethylenedioxy)perhydroisoindoline-7a-carboxylate (**24**). To a solution of **1** (248.6 mg, 0.47 mmol) in THF (7.5 ml), BuLi (4.0 ml, 0.15M) was added at −10°. The colour of the solution turned immediately to red. Then, a solution of **20** (175 mg, 0.42 mmol) in 3 ml of THF was added at −10° dropwise. The mixture was diluted with 1 ml of H_2O and 5 ml of Et_2O, concentrated *i.v.* to *ca.* 3 ml, and extracted with CH_2Cl_2/Et_2O 1:2 (3 × 20 ml). The org. layers were washed with H_2O (4 × 5 ml) and gave after evaporation of the solvents *i.v.* 250 mg of a yellow oil. Purification of the latter by CC (acetone) yielded 58.4 mg (24%) of **24** as a pale yellow oil. ^{1}H-NMR (360 MHz, $CDCl_3$): 0.82, 0.84 (2*d*, *J* = 7, CH_3–C(16)); 0.91 (*d*, *J* = 7, 3H–C(11)); 1.22 (*s*, 3H–C(12)); 1.38 (br. *s*, $(CH_3)_2C$); 1.2–1.6 (*m*, 7H); 1.61–1.71 (*m*, 2H–C(20)); 1.79–1.96 (*m*, H–C(15)); 2.01–2.17 (*m*, H–C(15)); 2.25 (*t*, *J* = 6, H–C(5)); 2.51–2.59 (*m*, H–C(4)); 2.66 ("*d*", 2H–C(10)); 2.92 (*td*, *J*(8,13) = 10, *J*(7,8) = 2, H–C(8)); 3.57 ("*t*", H–C(3)); 3.78 (*s*, CH_3OCO); 3.80–4.00 (*m*, 2 CH_2 of dioxolane; H–C(7)); 4.84 (*dt*, *J* = 4, *J'* = 1, H–C(21)); 5.54 (*m*, H–C(14)); 5.99 (*dd*, *J*(13,14) = 16, *J*(8,13) = 10, H–C(13)); 7.10–7.50 (*m*, Ph). MS: 583 (M^+), 568, 525 ($M^+ - 58$ ($(CH_3)_2CO$), 492 ($M^+ - 91$ (C_7H_7)), 386, 91.

(3RS,3aSR,4RS,7RS,7aRS)-3-Benzyl-7-hydroxymethyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylic Acid (**25**). A mixture of **8** (890 mg, 2.0 mmol), MeOH (38 ml), benzene (18 ml), and 50% KOH (8 ml) was kept stirring at r.t. for 3 h. After it had been chilled, 2N H_2SO_4 (60 ml) were added and the product was extracted with CH_2Cl_2 (3 × 100 ml). The org. layers were washed with H_2O (2 × 25 ml) and yielded on evaporation *i.v.* 1.01 g of a yellow oil, which was crystallized from benzene/Et_2O 1:2 to yield 378.5 mg (58%) of **25** as

plates of m.p. 84–87.5°. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.24 (*d*, *J* = 7, 3H–C(11)); 1.81 (br. *s*, 3H–C(12)); 2.4–3.1 (*m*, H–C(4), H–C(5), H–C(8), 2H–C(10)); 3.15–3.45 (*m*, H–C(3)); 3.8–4.2 (*m*, 2H–C(13)); 4.65–5.2 (br., OH, COOH); 5.53 (br. *s*, H–C(7)); 6.41 (br. *s*, NH); 7.0–7.45 (*m*, Ph, C_6H_6). Anal. calc. for $C_{19}H_{23}NO_4$ C_6H_6 (407.50): C 73.69, H 7.17, N 3.44; found: C 73.84, H 7.19, N 3.14. The crystals were dried (12 h, 50°, 10^{-2} Torr) and analyzed again: Anal. calc. for $C_{19}H_{23}NO_4 \cdot \frac{1}{2}\ C_6H_6$ (368.45): C 71.72, H 7.11, N 3.80; found: C 71.52, H 7.29, N 3.85.

*Methyl (3*RS,*3a*SR,*4*RS,*7*RS,*7a*RS*)-3-Benzyl-7-[(1*S*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyloxymethyl]-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylate* (**26**). A solution of **3** (686.8 mg, 2.0 mmol) in CH_2Cl_2 (8 ml) was treated at 0° consecutively with Et_3N (0.56 ml, 4.0 mmol) and (–)-camphanoyl chloride (487.5 mg, 2.25 mmol) dissolved in 2 ml of CH_2Cl_2. After 3 h of stirring at r.t., the mixture was diluted with CH_2Cl_2 (30 ml) and H_2O (7.5 ml), and washed with 2N HCl (2 × 1.5 ml), 1M $KHCO_3$ (1 × 5 ml), and brine (2 × 5 ml). Evaporation of the solvents *i.v.* left a foam, which was dissolved in Et_2O. On evaporation, 1.041 g (99%) of crystalline **26** were obtained. A small amount was recrystallized from CH_2Cl_2/Et_2O: m.p. 202–233° (dec.). ^{1}H-NMR (90 MHz, $CDCl_3$): 0.95, 1.04, 1.10 (3*s*, 3 CH_3 of camphan); 1.19 (*d*, *J* = 7, 3H–C(11)); 1.4 (*t*, *J* = 7, 1H); 1.78 (br. *s*, 3H–C(12)); 1.8–3.5 (*m*, 9H); 3.81 (*s*, CH_3OCO–C(9)); 4.4–4.8 (*m*, 2H–C(13)); 5.50 (br. *s*. H–C(7)); 5.70 (*s*, NH); 7.1–7.4 (*m*, Ph).

*(2*S*)-2-Acetoxy-2-phenylacetyl Chloride* (**28**). According to the procedure described in [14], we obtained starting from 2.00 g of (L)-mandelic acid 2.308 g (83%) of **28** as a colourless liquid of b.p. 80–81° (0.1 Torr). $[\alpha]_D^{27} = +186 \pm 1°$ (*c* = 3.20, $CHCl_3$). ^{1}H-NMR (90 MHz, CCl_4): 2.12 (*s*, CH_3CO); 6.00 (*s*, H–C(2)); 7.25–7.55 (br. *s*, Ph). Anal. calc. for $C_{10}H_9ClO_3$ (212.63): C 56.48, H 4.26, Cl 16.67; found: C 56.38, H 4.32, Cl 16.64.

*Methyl (3*S,*3a*R,*4*S,*7*S,*7a*S,*2'*S*)-3-Benzyl-7-[(acetoxy)(phenyl)acetoxymethyl]-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylate* (**29**) *and Methyl (3*R,*3a*S,*4*R,*7*R,*7a*R,*2'*S*)-3-Benzyl-7-[(acetoxy)(phenyl)acetoxymethyl]-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylate* (**30**). To a solution of **3** (1.373 g, 4.00 mmol) in CH_2Cl_2 (6 ml) was added **28** (0.990 g, 4.65 mmol). The mixture was kept at r.t. for 3 h. The solvent was evaporated *i.v.* and the residue diluted with Et_2O (10 ml) and MeOH (0.5 ml). After 5 min the solution was evaporated together with Et_2O to give 2.386 g of a colourless foam. Purification of the latter by CC (Et_2O) yielded 1.683 g (81%) of **29** and **30** as an amorphous powder. ^{1}H-NMR (90 MHz, CCl_4): 1.05 (2*d*, 3H–C(11)); 1.70 (br. *s*, 3H–C(12)); 2.15 (*s*, CH_3CO); 2.2–3.5 (*m*, 6H); 3.56 (*s*, CH_3OCO–C(9)); 4.2–4.6 (*m*, 2H–C(13)); 5.17 and 5.36 (2 br. *s*, H–C(7)); 5.77 and 5.81 (2*s*, H–C(2')); 6.95–7.55 (*m*, 2 Ph); 7.95 (br. *s*, NH).

Separation of **29** and **30** was achieved by analytical HPLC (CH_2Cl_2) and by prep. HPLC (CH_2Cl_2/i-PrOH/H_2O 995:5:1).

First eluted compound: $[\alpha]_D^{22} = +10°$ (*c* = 1.1, CCl_4). ^{1}H-NMR (90 MHz, CCl_4): 1.05 (*d*, *J* = 7, 3H–C(11)); 1.70 (br. *s*, 3H–C(12)); 2.16 (*s*, CH_3CO); 2.20–3.00 (*m*, H–C(4), H–C(5), H–C(8), 2H–C(10)); 3.15–3.45 (*m*, H–C(3)); 3.58 (*s*, CH_3OCO–C(9)); 4.15–4.65 (*m*, 2H–C(13)); 5.35 (br. *s*, H–C(7)); 5.76 (*s*, H–C(2')); 7.0–7.5 (*m*, 2 Ph); 7.85 (br. *s*, NH).

Second eluted compound: $[\alpha]_D^{22} = +63°$ (*c* = 1.4, CCl_4). ^{1}H-NMR (90 MHz, CCl_4): 1.00 (*d*, *J* = 7, 3H–C(11)); 1.68 (br. *s*, 3H–C(12)); 2.15 (*s*, CH_3CO); 2.20–3.05 (*m*, H–C(4), H–C(5), H–C(8), 2H–C(10)); 3.10–3.45 (*m*, H–C(3)); 3.53 (*s*, CH_3OCO–C(9)); 4.34 (br. *d*, *J* = 6.5, 2H–C(13)); 5.14 (br. *s*, H–C(7)); 5.80 (*s*, H–C(2')); 6.95–7.50 (*m*, 2 Ph); 7.79 (br. *s*, NH).

*Methyl (3*S,*3a*R,*4*S,*7*S,*7a*S*)-3-Benzyl-7-hydroxymethyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylate* (**31**). First eluted compound **29** (89 mg, 0.17 mmol) was dissolved in MeOH/benzene 2:1 (5.2 ml) and treated with 50% KOH (0.7 ml) at r.t. for 2.5 h. After adition of 4N H_2SO_4 (2.5 ml) at 0°, the acid was extracted with CH_2Cl_2 (4 × 10 ml). Evaporation of the solvents *i.v.* left 76 mg of a residue, which was dissolved in MeOH (3 ml) and treated with CH_2N_2 at 0°. After 5 min, the solvents were evaporated *i.v.* to give 75 mg of crude product, which yielded from Et_2O/(i-Pr)$_2O$ 10 mg of **3** and 49 mg (83%) of **31** as an oil. After CC (CH_2Cl_2/MeOH 98:2) of the latter, 38.6 mg of crystalline **31** were obtained from benzene/hexane, m.p. 157–160°. $[\alpha]_D^{23} = -51 \pm 1°$ (*c* = 2.5, MeOH), $[\alpha]_{365}^{23} = -170 \pm 1°$ (*c* = 2.5, MeOH), and $[\alpha]_D^{23} = +25 \pm 1°$ (*c* = 2.02, CH_2Cl_2). ^{1}H-NMR data matched those reported for the racemic compound (3). Anal. calc. for $C_{20}H_{25}NO_4$ (343.42): C 69.95, H 7.33, N 4.08; found: C 69.82, H 7.44, N 4.06.

*Methyl (3*R,*3a*S,*4*R,*7*R,*7a*R*)-3-Benzyl-7-hydroxymethyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylate* (**32**). Analogous to **29**→**31**, starting from second eluted compound **30** (86 mg, 0.17 mmol) 16 mg of **3** and 44 mg (77%) of **32**, which after CC (CH_2Cl_2/MeOH 98:2) crystallized from benzene/hexane, were obtained. M.p. 158–160°. $[\alpha]_D^{23} = +52 \pm 1°$ (*c* = 2.31, MeOH), $[\alpha]_{365}^{23} = +172 \pm 1°$ (*c* = 2.31, MeOH), and $[\alpha]_D^{22} = -28 \pm 1°$ (*c* = 1.99, CH_2Cl_2). ^{1}H-NMR data are congruent with those of **31**. Anal. calc. for $C_{20}H_{25}NO_4$ (343.42): C 69.95, H 7.33, N 4.08; found: C 70.20, H 7.55, N 4.05.

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