

174. Approaches to the Synthesis of Cytochalasans. Part 5¹⁾. Studies on the Selectivity of the *Diels-Alder* Reaction Leading to the Tetrahydroisoindolinone Sub-Unit

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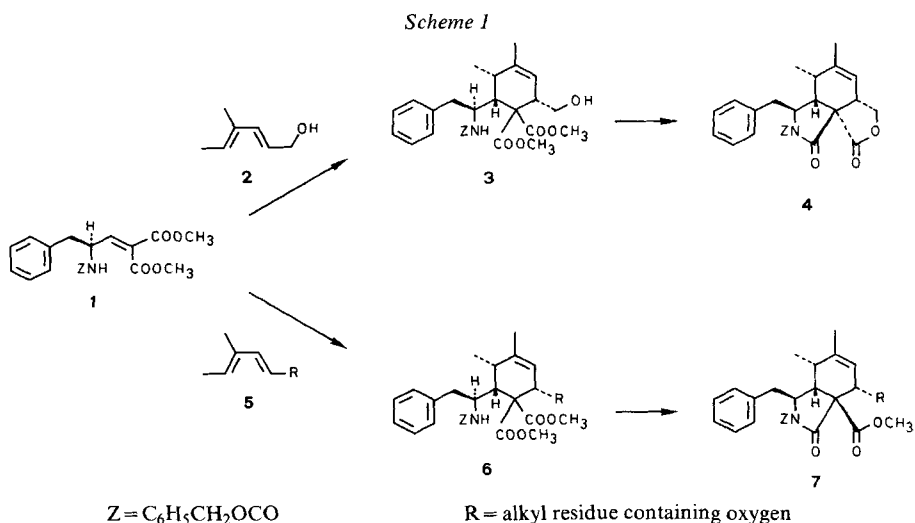
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(1. VI. 83)

Summary

The stereo- and regiochemical course in the [2+4]cycloaddition of the chiral alkylidene malonic ester **1** to selected derivatives of (2*E*, 4*E*)-4-methyl-2,4-hexadien-1-ol (**2**) and (2*E*, 4*E*)-4-methyl-2,4-hexadien-1-al (**12**) has been investigated. The results are discussed on the basis of semiquantitative PMO theory.

The thermally induced [2+4]cycloaddition of the alkylidene malonic ester **1** to (2*E*, 4*E*)-4-methyl-2,4-hexadien-1-ol (**2**) has been shown to be followed immediately by lactone and lactam ring closure of the intermediate **3** to yield compound **4** [1] (cf. Scheme 1). The configuration of C (3), C (4), C (5), and C (8)³⁾ in compound **4**



1) Part 4: [1].

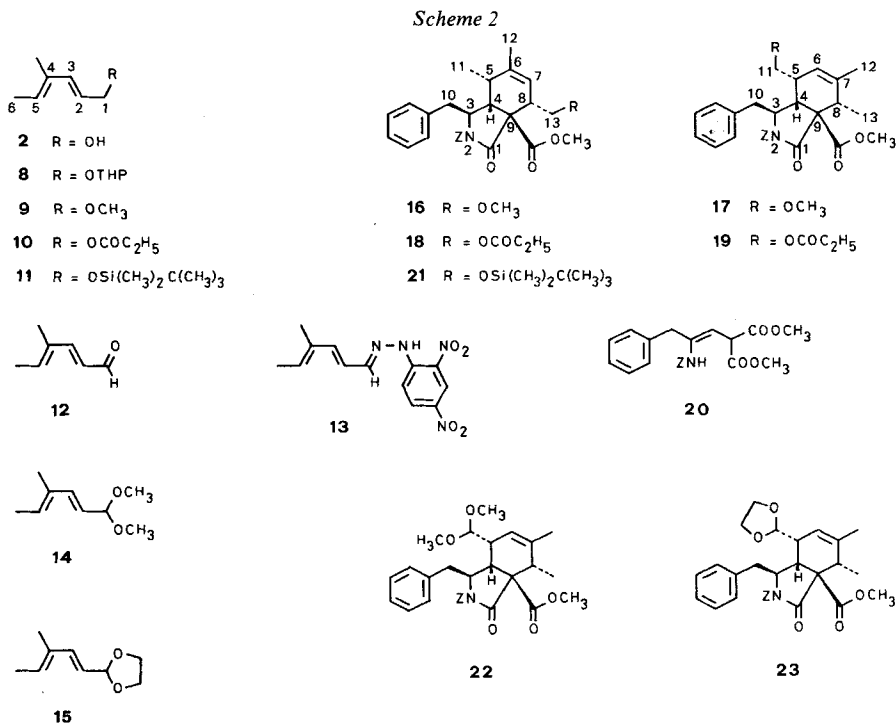
2) Taken from the «Diplomarbeiten», by P. St. 1981 and R. G. 1982.

3) The numbering of the sub-units corresponds to that used for the cytochalasans [2].

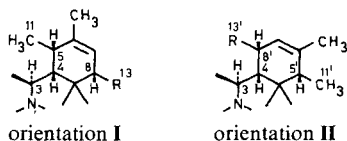
corresponds to that of the tetrahydroisoindolone moiety of cytochalasins, whereas the center C(9) possesses 'unnatural' configuration [3]. The exclusive formation of **4** with aberrant configuration at C(9) has been explained to be a consequence of a thermodynamically governed *cis*-lactone ring closure preceding lactamization.

We now describe the results of experiments devised to prevent lactone ring formation in the expected intermediate **3** by the use of dienes **5** containing blocked O-functions. Cycloaddition of the latter to the olefin **1**, according to the procedure in [1], should preferably form adducts of type **6** which, in a thermodynamically governed reaction may undergo *cis*-lactam ring closure to give compounds of type **7**. Obviously, if the reaction proceeds in this manner, the natural configuration at C(9) in **7** would be obtained directly.

We blocked the O-function in dienes of type **5** either by simple protection of the alcohol group in **2**, or by its oxidation to the corresponding aldehyde. The latter was converted to more stable acetals. Thus, (2*E*, 4*E*)-4-methyl-*O*-tetrahydropyranyl-2,4-hexadien-1-ol (**8**), (2*E*, 4*E*)-*O*-methyl-4-methyl-2,4-hexadien-1-ol (**9**), (2*E*, 4*E*)-4-methyl-*O*-propionyl-2,4-hexadien-1-ol (**10**), and (2*E*, 4*E*)-4-methyl-*O*-(*tert*-butyldimethylsilyl)-2,4-hexadien-1-ol (**11**) were prepared starting from the alcohol **2**. Oxidation of **2** by pyridinium dichromate [4] afforded 4-methyl-2,4-hexadien-1-al (**12**), a sensitive aldehyde which was characterized by its 2,4-dinitrophenylhydrazone **13**. The acetals **14** and **15** were obtained with trimethylorthoformate and 2-methoxy-1,3-dioxolane, respectively, in the presence of anhydrous copper (II) sulfate [5] (*cf.* Scheme 2).



The addition of the dienes **8**, **9**, **10**, **11**, **14**, and **15** to the alkene **1** gave the following results: [2+4]cycloaddition of **1** to **8** did not yield an adduct of type **7**; but due to the thermolytic loss of the THP-group the lactone **4** was formed. After the [2+4]cycloaddition of **1** and **9** a mixture (1:2) of two regioisomers was isolated. Their distinction is possible by high-field $^1\text{H-NMR}$ spectroscopy⁴⁾ which allowed the examination of two discrete spin-coupling systems involving the H-atoms at positions 3, 4, 5, 11 and 8, 13 in orientation **I** and 3, 4, 8', 13' and 5', 11' in orientation **II**. Proton-proton decoupling by irradiation of the doublet of the CH_3 -group which



is not attached to the double bond permits the identification of the proton at C(5) or C(5'). Irradiation over the range of the typical 8-line-pattern signal of $\text{H-C}(3)$ ⁵⁾ reveals the signal of $\text{H-C}(4)$, which is identical in both orientations. A third decoupling experiment performed by irradiation at the position of the signal corresponding to $\text{H-C}(5)$ or $\text{H-C}(5')$ allowed the final distinction between the two regioisomers. Whereas in one case decoupling of $\text{H-C}(4)$ was observed as expected for orientation **I**, in the other case no change in the signal of $\text{H-C}(4)$ took place thus indicating orientation **II**. Accordingly, the adducts possess structures **16** (minor) and **17** (major). The structures **18**, **19**, **21**, **22**, and **23** of the other adducts were deduced in the same way.

The reaction of **1** and **10** yielded a mixture of the regioisomers **18** and **19** (2:1). When the silylated diene **11** was heated with the alkene **1**, a mixture of about 10 products was obtained. Whereas at a lower temperature and shorter reaction time two products were formed, heating to 80° for 5 h led to a single product in 86% yield. Its spectral data show it to be isomeric to alkene **1** with structure **20**. Finally, the desired cycloaddition was achieved by heating **1** and **11** to 140° for 2 h. From the mixture which contained, besides the starting materials, four new compounds, only a single pure product, **21**, could be isolated in low yield.

From the cycloaddition reaction between **1** and the dimethyl acetal **14** the crystalline compound **22** was obtained in low yield. The ethylene acetal **15** was more stable than **14**. Therefore the reaction with alkene **1** yielded compound **23** in 51% yield as the only product.

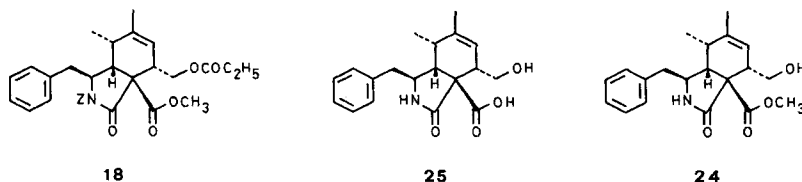
The stereochemistry of the adducts **16**, **17**, **18**, **19**, **21**, **22**, and **23** was derived from the values of $J(4,5)$, which fall in the range 2 to 9 Hz as expected for the ψ -endo-adducts. The *cis*-relationship of $\text{H-C}(4)$ and $\text{H-C}(5)$, and the configuration at C(3) and C(8) in the structures of type **7**, were demonstrated independently by the chemical transformation of the ester **18** to the known lactam **24**⁶⁾ by alkaline

4) We thank Prof. Dr. H. Fritz and Mr P. Hug, Ciba-Geigy AG, Basel for running 360-MHz $^1\text{H-NMR}$ spectra of compounds **16**, **17**, **18**, and **19**.

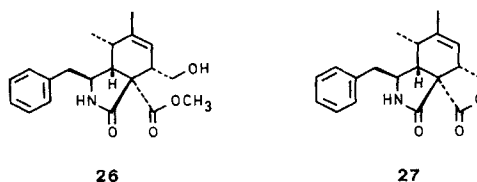
5) It is shifted by the presence of the α -N-atom to low field.

6) Its *O*-acetyl derivative had been subjected to X-ray analysis [6].

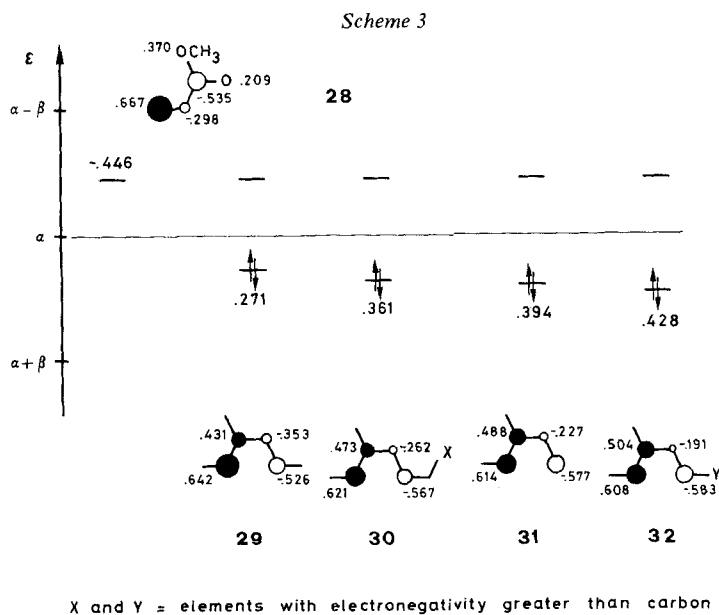
hydrolysis to the acid **25** and re-esterification. The identity of **24** with a sample prepared from **4** established the configuration at C(3), C(4), C(5) and C(8) in the adduct **18**. However, a change of configuration at C(9) during the reaction cannot



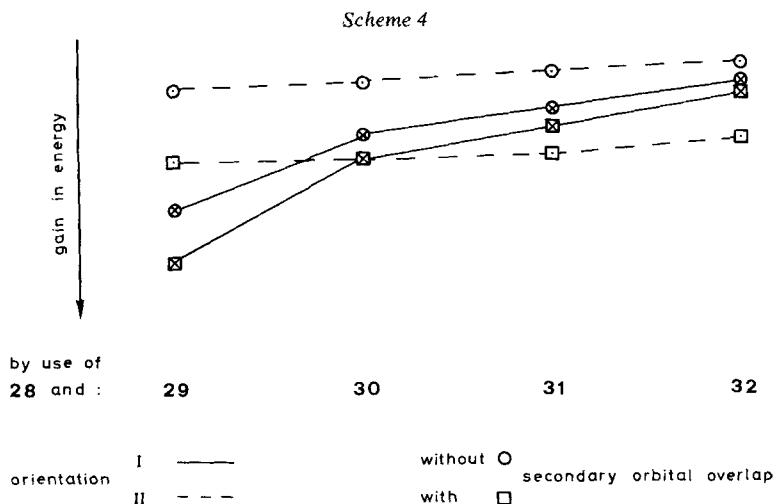
be ruled out *a priori*. Further information on this configuration in **18** was achieved by comparison of the chemical shift of H-C(3) in the C(9)-epimeric pair **24** and **26** with the corresponding shift in **18**. A correction of the values due to the presence of the Z-group is necessary. The correction increment of 0.42 ppm was obtained from the difference in chemical shift of H-C(3) in **4** (5.10 ppm) as compared to the deprotected compound **27** (4.68 ppm). In the *cis*-lactam **24**, H-C(3) is found at 3.31 ppm, whereas in the *trans*-lactam **26** the same proton appears at 4.14 ppm. Formal addition of a Z-group to **24** would give 3.73 ppm for H-C(3) and 4.56 ppm in the case of **26**. The chemical shift of H-C(3) in the compounds **16**, **18**, and **21** is found to range from 3.95 to 4.00 ppm, indicating the presence of a *cis*-lactam in these adducts.



The distribution of the regioisomers obtained depends strongly on the number of O-atoms and the nature of their substitution in the dienes of type **5**. The results can be interpreted on the basis of semi-quantitative PMO theory. Because dipole-dipole and steric interactions turn one of the ester groups of the alkene **1** out of plane, thus diminishing conjugation with the (C=C)-bond, methyl acrylate (**28**) will serve as a simple model of the dienophile **1** (*cf.* Scheme 3). The 1,2-dimethylbutadienes **29-32** were chosen as models for the dienes of type **5**. The two CH₃-groups and the residue R were accounted for by inductive parameters in ordinary *Hückel* calculation [7]. In **29** R is electron-donating, in **30** and **31** this ability is diminished and, finally, in **32** R slightly withdraws electron-density from the π -system. In contrast to **16/17** and **18/19** the adducts **22** and **23** were formed only slowly at 140°. This observation agrees with an increase in the energy gap between the frontier orbitals caused by the energy lowering of the HOMO of the dienes going from **29** or **30** to **31** or **32** which equals a change of diene **9** and **10** to **14** and **15**. To deal with regioisomerism, gain in energy for both addition orientations was calculated by use of the *Salem-Klopman* equation in its simplest form [8]. Secondary orbital overlap was either neglected completely or taken into account, but arbitrarily only as a half-weighted interaction compared with a full orbital overlap which would lead to bond



formation. If secondary orbital overlap does not operate, orientation I will be preferred for all diene models as shown in *Scheme 4*. Assuming secondary orbital overlap to be a small effect [9], it is obvious that dienes like **14** and **15** corresponding to model **31** or **32** favour orientation II. On the basis of this simple model it is, however, not feasible to predict the different ratio of regioisomers observed for ether **9** and ester **10**. A similar difference in regio-chemical behaviour of the latter two dienes, with a pyrrolinone as dienophile, had been observed earlier by *Vedejs & Gadwood* [10].



In the case of diene **11** no cycloaddition occurred at 80°, but a double bond isomerization in the dienophile **1** took place, leading to the enamine **20**. At higher temperatures, however, the adduct **21** was formed. This leads to the assumption that an equilibrium between **1** and **20** should exist. In fact, compound **4** was also obtained from a *Diels-Alder* reaction of the enamine **20** with (2*E*, 4*E*)-4-methyl-2,4-hexadien-1-ol (**2**), confirming the ability of the double bond in **20** to migrate into conjugation to give **1**, which is then removed from the reaction path by the succeeding cycloaddition.

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

Experimental Part

General Remarks. See [6].

rac-(2*E*, 4*E*)-4-Methyl-1-tetrahydropyran-2,4-hexadiene (**8**). 3,4-Dihydro-2*H*-pyran (2.7 ml, 30 mmol) was added to a solution of 1.68 g (15 mmol) of (2*E*, 4*E*)-4-methyl-2,4-hexadien-1-ol (**2**) [6] in 5 ml dry benzene. After addition of two drops of SOCl₂, the mixture warmed and was therefore chilled in a cold water bath. The mixture was then stirred for 2 h at r.t., diluted with 40 ml Et₂O and washed with 7.5 ml 1*M* KHCO₃. The washings were extracted with 10 ml Et₂O. The combined org. phases were dried and evaporation of the solvents *i.v.* gave 2.95 g of a yellow oil. The latter was purified by column chromatography on 200 g of aluminum oxide. Elution with pentane (2 × 300 ml) and pentane/AcOEt (99:1), (98:2), and (96:4) (2 × 100 ml each mixture) afforded 2.23 g (76%) of **8** as a pale yellow liquid. IR (film): 3030 (C–H olefin), 2975, 2860, 1650, 1640 (C=C), 1445, 1355, 1205, 1120, 1030 (C–O–C), 970, 910, 875, 820. ¹H-NMR (60 MHz, CDCl₃): 6.2 (*d*, *J* = 16, 1 H–C(3)); 5.8–5.2 (*m*, 1 H–C(2), 1 H–C(5)); 4.5 (*m*, 1 H (acetal)); 4.3–3.2 (*m*, 2 H–C(1), 2 H (pyran)); 2.5–0.7 (*m*, 3 H–C(6), CH₃–C(4), 6 H (pyran)).

(2*E*, 4*E*)-1-Methoxy-4-methyl-2,4-hexadiene (**9**). A mixture of 611 mg (1.8 mmol) of Bu₄NHSO₄, 4.49 g (40 mmol) of **2** [6], 29.2 g (206 mmol) of CH₃I and 30 ml 50% KOH was stirred vigorously for 22 h in the dark (*cf.* [11]). Then the mixture was treated with 300 ml Et₂O and 30 ml H₂O and extracted. The org. phase was washed with H₂O (4 × 60 ml), dried, and yielded after evaporation of the solvents *i.v.* crude **9**. Purification by distillation gave 3.75 g (74%) of **9** as a colorless liquid, b.p. 66–67°/20 Torr. IR (film): 3030, 2980, 2920, 2820, 1650 (C=C), 1130 (C–O–C), 965. ¹H-NMR (60 MHz, CCl₄): 6.1–5.95 (*d*, *J* = 15, 1 H–C(3)); 5.65–5.2 (*m*, 1 H–C(2), 1 H–C(5)); 3.8 (*d*, *J* = 6, 2 H–C(1)); 3.2 (*s*, CH₃–O–C(1)); 1.7 (*m*, 3 H–C(6), CH₃–C(4)). ¹³C-NMR (22.63 MHz, CDCl₃): 137.7, 134.1 (C(4)), 126.9, 122.5, 73.5 (CH₃O), 57.6 (C(1)), 13.7, 12.0.

C₈H₁₄O (126.20) Calc. C 76.14 H 11.18% Found C 75.14 H 11.37%

(hygroscopic, K.F.-titration showed up to 2% H₂O).

(2*E*, 4*E*)-4-Methyl-2,4-hexadienyl propionate (**10**). Propionic anhydride (6.2 ml, 48 mmol) was added dropwise within 5 min to a chilled solution of 4.49 g (40 mmol) of **2** [6] and 6.7 ml (48 mmol) of Et₃N in 20 ml Et₂O. The mixture was stirred for 72 h at r.t., then diluted with 100 ml of Et₂O and extracted with 2*N* HCl (2 × 50 ml), and H₂O (3 × 50 ml) to yield, after usual workup 8.8 g of crude **10**. Distillation gave 4.9 g (73%) of pure **10** as a pale yellowish oil, b.p. 107–112°/17 Torr. IR (film): 3040, 2980, 2940, 2880, 1730 (C=O), 1650 (C=C), 1460, 1175 (C–O–C), 1080, 965. ¹H-NMR (60 MHz, CCl₄): 6.15 (*d*, *J* = 15, 1 H–C(3)); 5.4 (*m*, 1 H–C(2), 1 H–C(5)); 4.4 (*d*, *J* = 6, 2 H–C(1)); 2.2 (*q*, *J* = 7, H₃CCCH₂COO); 1.65 (*m*, 3 H–C(6), CH₃–CC(4)); 1.05 (*t*, *J* = 7, CH₃CH₂COO). ¹³C-NMR (22.63 MHz, CDCl₃): 173.9 (CH₃CH₂COO); 139.4, 134.0 (C(4)); 128.8, 120.1, 65.3 (C(1)); 27.7 (CH₃CH₂COO); 13.8, 12.0, 9.2 (CH₃CH₂COO).

(2*E*, 4*E*)-1-(*t*-Butyldimethylsilyloxy)-4-methyl-2,4-hexadiene (**11**). A solution of 6.63 g (44 mmol) of *tert*-butyldimethylsilyl chloride in 12 ml dry CH₂Cl₂ was added over a period of 15 min to a chilled mixture of 4.49 g (40 mmol) of **2** [6], 6.7 ml (48 mmol) of triethylamine, and 0.2 g (1.6 mmol) of 4-dimethylaminopyridine in 20 ml dry CH₂Cl₂ [12]. The mixture was stirred at r.t. for 12 h. The precipitate

formed was removed by filtration (30 ml of CCl_4). The filtrate was distilled *i.v.* to yield 7.1 g (78%) of **11** as a colourless liquid, b.p. 124–128°/18 Torr. IR (film): 2930, 2860, 1460, 1380, 1255 (Si–C), 1125, 1070 (Si–O), 965, 840, 780. $^1\text{H-NMR}$ (60 MHz, CCl_4): 6.1 (*d*, $J=16$, 1 H–C(3)); 5.6–5.2 (*m*, 1 H–C(2), 1 H–C(5)); 4.2 (*d*, $J=5$, 2 H–C(1)); 1.65 (*m*, 3 H–C(6), CH_3 –C(4)); 0.85 (*s*, 9 H, $(\text{CH}_3)_3\text{C-Si}$); 0.0 (*s*, 6 H, $(\text{CH}_3)_2\text{Si}$). $^{13}\text{C-NMR}$ (22.63 MHz, CDCl_3): 134.8, 134.0 (C(4)); 126.0, 125.5, 64.1 (C(1)); 26.0, 18.4, 13.6, 12.0.

(2E, 4E)-4-Methyl-2,4-hexadien-1-al (**12**). Pyridinium dichromate [4] (61.5 g, 164 mmol) was added at r.t. to a well-stirred solution of 13.8 g (123 mmol) of **2** [6] in 300 ml of dry CH_2Cl_2 under Ar. After 20 h the reagent was precipitated by addition of 1.2 l of Et_2O and anh. Na_2SO_4 and removed by filtration through a *Celite* layer of 6 cm thickness. The filtrate was evaporated *i.v.* to give 13.9 g of crude **12**. Column chromatography on silica gel using pentane/ $\text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2$ yielded 8.8 g (65%) of pure **12** as a colourless oil. IR (film): 3040, 2925, 2815 (C–H, aldehyde), 1673 (C=O), 1628, 1603 (C=C), 1440, 1384, 1134, 970, 800. $^1\text{H-NMR}$ (60 MHz, CDCl_3): 9.55 (*d*, $J=8$, 1 H–C(1)); 7.15 (*d*, $J=16$, 1 H–C(3)); 6.4–5.8 (*m*, 1 H–C(2), 1 H–C(5)); 1.8 (*m*, 3 H–C(6), CH_3 –C(4)).

2,4-Dinitrophenylhydrazone **13** of **12**: red needles, m.p. 187–188°. $^1\text{H-NMR}$ (90 MHz, CDCl_3): 11.15 (*m*, 1 H–N); 9.12 (*d*, $J=3$, *meta*-H between NO_2 -groups); 8.31 (*dd*, $J=10$, $J'=3$, 1 H–C(1)); 8.0–7.75 (*2m*, *ortho*- and *meta*-H); 6.9–5.7 (*m*, 1 H–C(2), 1 H–C(3), 1 H–C(5)); 2.0–1.75 (*m*, 3 H–C(6), CH_3 –C(4)). MS: 291 ($M^+ + 1$), 290 (M^+), 183 ($M^+ - 107$ ($\text{CH}_3\text{CH}:\text{C}(\text{CH}_3)\text{CH}:\text{CHCN}$)), 182 ($M^+ - 108$), 108 ($M^+ - 182$ (2,4-dinitrophenylamine)), 107 ($M^+ - 183$).

$\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_4$ (290.28) Calc. C 53.79 H 4.86 N 19.30% Found C 53.74 H 4.84 N 19.33%

(2E, 4E)-4-Methyl-2,4-hexadien-1-al dimethyl acetal (**14**). A mixture of 8.86 g (≈ 81 mmol) of crude **12**, 46 ml dry MeOH, 10.9 ml (100 mmol) of trimethyl orthoformate, and 1.59 g (10 mmol) of anh. CuSO_4 was stirred under Ar for 20 h. After addition of 350 ml dry Et_2O containing 2 ml of pyridine and 5 g of $\text{Na}_2\text{SO}_4/\text{Na}_2\text{CO}_3$ (1:1), the mixture was filtered through a column of cotton wool. The filtrate was evaporated *i.v.* to give 9.20 g of a yellow oil, of which 3.40 g were purified by column chromatography on 400 g of aluminum oxide. Elution with pentane (2×300 ml), pentane/AcOEt (998:2), (994:6), and (99:1) (3×100 ml of each mixture) yielded in fractions 2–8 the desired product which was distilled *i.v.* to give 2.91 g (41%) of pure **14** as a colourless liquid, b.p. 48–50°/0.65 Torr. IR (film): 2990, 2940, 2830, 1650, 1640 (C=C), 1490, 1355, 1195, 1140, 1055 (C–O–C), 975, 915. $^1\text{H-NMR}$ (60 MHz, CCl_4): 6.2 (*d*, $J=16$, 1 H–C(3)); 5.9–5.1 (*m*, 1 H–C(2), 1 H–C(5)); 4.75 (*d*, $J=4$, 1 H–C(1)); 3.15 (*m*, 2 CH_3O); 1.7 (*m*, 3 H–C(6), CH_3 –C(4)).

$\text{C}_9\text{H}_{16}\text{O}_2$ (156.23) Calc. C 69.19 H 10.32% Found C 68.93 H 10.44%

2-[(1E, 3E)-3-Methyl-1,3-pentadienyl]-1,3-dioxolane (**15**). A mixture of 13.52 g (≈ 120 mmol) of crude **12**, 19.07 g (183 mmol) of 2-methoxy-1,3-dioxolane, 7.6 g of ethylene glycol, and 6.3 g of anh. CuSO_4 was stirred at r.t. under Ar for 2 $\frac{1}{2}$ days. Then a further 6.3 g of anh. CuSO_4 was added and stirring continued for 3 days. Although the reaction had taken place to an extent of only 10%, workup as above (**12** \rightarrow **14**) was carried out to give 1.06 g of a yellow oil. Purification of the latter by distillation *i.v.* yielded 0.59 g ($\approx 32\%$) of **15** as a colourless liquid, b.p. 64–65°/0.40 Torr. IR (film): 3040, 3020, 2650, 1655, 1635 (C=C), 1400, 1170, 1080, 1035 (C–O–C), 960. $^1\text{H-NMR}$ (60 MHz, CCl_4): 6.25 (*d*, $J=14$, 1 H–C(3)); 5.8–5.2 (*m*, 1 H–C(2), 1 H–C(5)); 5.2–5.0 (*m*, 1 H–C(1)); 4.0–3.6 (*m*, $\text{OCH}_2\text{CH}_2\text{O}$); 1.7 (*m*, 3 H–C(6), CH_3 –C(4)).

$\text{C}_9\text{H}_{14}\text{O}_2$ (154.21) Calc. C 70.10 H 9.15% Found C 69.88 H 9.43%

rac-Methyl (3R*, 3aS*, 4R*, 7R*, 7aR*)-3-benzyl-2-benzyloxy-carbonyl-7-methoxymethyl-4,5-dimethyl-1-oxo-3a, 4, 7, 7a-tetrahydroisoindoline-7a-carboxylate (**16**) and *rac*-methyl (3R*, 3aS*, 4S*, 7R*, 7aS*)-3-benzyl-2-benzyloxy-carbonyl-4-methoxymethyl-6, 7-dimethyl-1-oxo-3a, 4, 7, 7a-tetrahydroisoindoline-7a-carboxylate (**17**). A solution of 994 mg (2.5 mmol) of *rac*-dimethyl 2-[2'-(benzyloxycarbonylamino)-3'-phenylpropylidene] malonate (**1**) [1] and 473 mg (3.75 mmol) of **9** in 20 ml xylene was heated to 140° in a sealed tube for 69 h. Evaporation of the solvent *i.v.* gave 1.4 g of a brown oil. Separation of the products was achieved by column chromatography on 225 g of silica gel. Elution with CH_2Cl_2 , $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ (99:1), (98:2), (96:4), (92:8), (84:16), and (68:32) (4×75 ml of each mixture) yielded 30 mg of **4** (fractions 20–23), 460 mg of **17** (fractions 24–25), 145 mg of **16/17** (fraction 26), and 280 mg of **16** (fractions 27–28). Total yield of **4**, **16**, and **17**: 915 mg (74%).

Compound 16: crystallized from Et₂O/hexane, m.p. 110–112°. IR (KBr): 2960, 2920, 1780, 1725, 1695, 1450, 1380, 1270, 1230, 1105, 987. ¹H-NMR (360 MHz, CDCl₃): 7.54–6.93 (*m*, 2 C₆H₅); 5.46 (br. *s*, 1 H–C(7)); 5.35, 5.31 (*AB*, *J* = 12, C₆H₅CH₂O); 3.95 (*m*, 1 H–C(3)); 3.85–3.65 (*m*, 2 H–C(13)); 3.71 (*s*, H₃COCO–C(9)); 3.36 (*s*, CH₃O–C(13)); 3.10 (*dd*, *J* = 13, *J'* = 4, 1 H–C(10)); 2.84 (*m*, 1 H–C(8)); 2.70 (*dd*, *J* = 13, *J'* = 9, 1 H–C(10)); 2.55 (*dd*, *J* = 6, *J'* = 3, 1 H–C(4)); 2.33 (*m*, 1 H–C(5)); 1.64 (br. *s*, 3 H–C(12)); 0.61 (*d*, *J* = 7, 3 H–C(11)). MS: 491 (*M*⁺), 460 (*M*⁺ – 31(CH₃O)), 432 (*M*⁺ – 59(CH₃COO)), 365 (*M*⁺ – 126 (retro-Diels-Alder-reaction)), 365 (*M*⁺ – 135(C₆H₅CH₂OCO)).

C₂₉H₃₁NO₆ (491.58) Calc. C 70.85 H 6.77 N 2.85% Found C 70.72 H 6.82 N 2.91%

Compound 17: colourless oil. IR (CH₂Cl₂): 2930, 2860, 1785, 1720, 1375, 1190, 1140, 1110. ¹H-NMR (360 MHz, CDCl₃): 7.51–6.96 (*m*, 2 C₆H₅); 5.44 (br. *s*, 1 H–C(6)); 5.33, 5.31 (*AB*, *J* = 13, C₆H₅CH₂O); 4.04 (*m*, 1 H–C(3)); 3.67 (*s*, H₃COCO–C(9)); 3.15 (*dd*, *J* = 8, *J'* = 6.5, 1 H–C(11)); 3.08 (*s*, CH₃O–C(11)); 3.01 (*dd*, *J* = 13, *J'* = 3.5, 1 H–C(10)); 2.89 (*dd*, *J* = 8, *J'* = 7.5, 1 H–C(11)); 2.83–2.74 (*m*, 1 H–C(8)); 2.77 (*dd*, *J* = 8.5, *J'* = 6, 1 H–C(4)); 2.71 (*dd*, *J* = 13, *J'* = 8.5, 1 H–C(10)); 2.45–2.32 (*m*, 1 H–C(5)); 1.69 (br. *s*, 3 H–C(12)); 1.14 (*d*, *J* = 7, 3 H–C(13)). MS: 491 (*M*⁺), 460 (*M*⁺ – 31 (CH₃O)), 432 (*M*⁺ – 59 (CH₃COO)), 414 (*M*⁺ – 77 (C₆H₅)), 400 (*M*⁺ – 91 (C₇H₇)), 356 (*M*⁺ – 135 (C₆H₅CH₂OCO)).

rac-Methyl (3*R**, 3*aS**, 4*R**, 7*R**, 7*aR**)-3-benzyl-2-benzoyloxycarbonyl-4,5-dimethyl-7-propionyloxymethyl-1-oxo-3*a*,4,7,7*a*-tetrahydroisoindoline-7*a*-carboxylate (**18**) and *rac*-methyl (3*R**, 3*aS**, 4*S**, 7*R**, 7*aS**)-3-benzyl-2-benzoyloxycarbonyl-6,7-dimethyl-4-propionyloxymethyl-1-oxo-3*a*,4,7,7*a*-tetrahydroisoindoline-7*a*-carboxylate (**19**). A solution of 994 mg (2.5 mmol) of **1** [**1**] and 473 mg (3.75 mmol) of **10** in 20 ml of xylene was heated to 145° in a sealed tube for 68 h. Evaporation of the solvent *i.v.* gave 1.70 g of a brown oil, which was subjected to column chromatography on 170 g of silica gel. Elution with CH₂Cl₂/Et₂O (99:1), (97.5:2.5), (95:5), (90:10), and (80:20) (6 × 60 ml of each mixture) gave 380 mg of **19** (fractions 22–24), 87 mg of **18/19** (fraction 25), and 735 mg of **18** (fractions 26–28). Total yield of **18** and **19**: 1.20 g (90%).

Compound 18: crystallized from Et₂O/pentane, m.p. 107–109°. IR (KBr): 2980, 1785, 1740, 1720 sh, 1380, 1280, 1235, 985, 760, 705. ¹H-NMR (360 MHz, CDCl₃): 7.53–6.97 (*m*, 2 C₆H₅); 5.43 (br. *s*, 1 H–C(7)); 5.34, 5.32 (*AB*, *J* = 12.5, C₆H₅CH₂O); 4.59–4.43 (*m*, 2 H–C(13)); 3.97 (*m*, 1 H–C(3)); 3.72 (*s*, H₃COCO–C(9)); 3.10 (*dd*, *J* = 13, *J'* = 3.5, 1 H–C(10)); 2.90 (*m*, 1 H–C(8)); 2.71 (*dd*, *J* = 13, *J'* = 9, 1 H–C(10)); 2.56 (*dd*, *J* = 6, *J'* = 2, 1 H–C(4)); 2.38–2.25 (*m*, 1 H–C(5)); 2.28 (*q*, *J* = 7, CH₃CH₂COO–C(13)); 1.66 (br. *s*, 3 H–C(12)); 1.11 (*t*, *J* = 7, CH₃CH₂COO–C(13)); 0.63 (*d*, *J* = 7, 3 H–C(11)). MS: 533 (*M*⁺), 502 (*M*⁺ – 31 (CH₃O)), 473 (*M*⁺ – 60 (CH₃COOH)), 459 (*M*⁺ – 74 (CH₃CH₂COOH)), 442 (*M*⁺ – 91 (C₇H₇)), 398 (*M*⁺ – 135 (C₆H₅CH₂OCO)), 91.

C₃₁H₃₅NO₇ (533.62) Calc. C 69.77 H 6.61 N 2.63% Found C 69.54 H 6.86 N 2.62%

Compound 19: further purified by column chromatography as above: pure (TLC), colourless oil. IR (CH₂Cl₂): 3040, 2950, 1790, 1730, 1380, 1195, 1150, 1115, 1000, 890. ¹H-NMR (360 MHz, CDCl₃): 7.52–6.94 (*m*, 2 C₆H₅); 5.43 (br. *s*, 1 H–C(6)); 5.35, 5.29 (*AB*, *J* = 13, C₆H₅CH₂O); 4.05 (*m*, 1 H–C(3)); 3.90 (*dd*, *J* = 12, *J'* = 6, 1 H–C(11)); 3.72 (*s*, H₃COCO–C(9)); 3.56 (*dd*, *J* = 12, *J'* = 7, 1 H–C(11)); 3.05 (*dd*, *J* = 13, *J'* = 3, 1 H–C(10)); 2.86–2.74 (*m*, 1 H–C(8)); 2.75 (*dd*, *J* = 6, *J'* = 2, 1 H–C(4)); 2.66 (*dd*, *J* = 13, *J'* = 9, 1 H–C(10)); 2.49–2.38 (*m*, 1 H–C(5)); 2.15 (*q*, *J* = 7, H₃CCCH₂COO–C(11)); 1.71 (br. *s*, 3 H–C(12)); 1.39 (*d*, *J* = 7, 3 H–C(13)); 1.07 (*t*, *J* = 7, CH₃CH₂COO–C(11)). MS: 533 (*M*⁺), 489 (*M*⁺ – 45 (CH₃CH₂O)), 474 (*M*⁺ – 60 (CH₃COOH)), 442 (*M*⁺ – 91 (C₇H₇)), 398 (*M*⁺ – 135 (C₆H₅CH₂OCO)).

rac-Methyl (3*R**, 3*aS**, 4*R**, 7*R**, 7*aR**)-3-benzyl-2-benzoyloxycarbonyl-7-(*t*-butyldimethylsilyloxy)-methyl-4,5-dimethyl-1-oxo-3*a*,4,7,7*a*-tetrahydroisoindoline-7*a*-carboxylate (**21**). A solution of 994 mg (2.5 mmol) of **1** [**1**] and 849 mg (3.75 mmol) of **11** in 20 ml xylene was heated in a sealed tube to 140° for 2 h. The solvent was evaporated *i.v.* and the residue of 1.8 g subjected to column chromatography on 150 g of silica gel. Elution with CH₂Cl₂/Et₂O (99:1), (98:2), (96:4), (92:8), and (84:16) (6 × 50 ml of each mixture) gave 140 mg of **21** (fractions 18–20) and 467 mg of by-products containing some **21** (fractions 21–27). Crystallization from diisopropyl ether yielded 130 mg (9%) of pure **21**, m.p. 121–124°. IR (KBr): 2940, 2860, 1755 sh, 1740 sh, 1727, 1450, 1380, 1295, 1235, 1190, 1000 and 860 (Si–O–C), 845 and 780 (Si–(CH₃)₂), 760, 735, 705. ¹H-NMR (90 MHz, CDCl₃): 7.55–6.95 (*m*, 2 C₆H₅); 5.55 (br., 1 H–C(7)); 5.32 (br. *s*, C₆H₅CH₂O); 4.00 (*d*, *J* = 7, 2 H–C(13)); 4.0–3.9 (*m*, 1 H–C(3)); 3.71 (*s*, H₃COCO–C(9)); 3.15 (*dd*, *J* = 13, *J'* = 4, 1 H–C(10)); 2.9–2.6 (*m*, 1 H–C(8), 1 H–C(10)); 2.53 (br. *d*, *J* = 6, 1 H–C(4)); 2.45–2.2 (*m*, 1 H–C(5)); 1.63 (br. *s*, 3 H–C(12)); 0.87 (*s*, (CH₃)₃C–Si); 0.58 (*d*, *J* = 7,

3 H-C(11)); 0.05 (s, (CH₃)₂Si). MS: 591 (M⁺), 576 (M⁺ – 15 (CH₃)), 460 (M⁺ – 31 (CH₃O)), 534 (M⁺ – 57 ((CH₃)₃C)), 490, 457, 456 (M⁺ – 135 (C₆H₅CH₂OCO)), 366 (457–91), 290.

C₃₄H₄₅NO₆Si (591.82) Calc. C 68.74 H 7.73 N 2.38% Found C 68.58 H 7.68 N 2.38%

rac-Methyl (3R*, 3aS*, 4S*, 7R*, 7aS*)-3-benzyl-2-benzoyloxycarbonyl-4-dimethoxymethyl-6, 7-dimethyl-1-oxo-3a, 4, 7, 7a-tetrahydroisindoline-7a-carboxylate (**22**). A solution of 994 mg (2.5 mmol) of **1** [1] and 487 mg (3.1 mmol) of **14** in 20 ml xylene was heated in a sealed tube at 143° for 8 days. Evaporation of the solvent *i.v.* gave 1.66 g of a brown oil, which was subjected to column chromatography on 300 g of aluminum oxide. Elution with CH₂Cl₂ gave 277 mg of a yellow oil. A second column chromatography of the latter using 30 g of silica gel and CH₂Cl₂, CH₂Cl₂/Et₂O (99:1), (97:3), and (95:5) (4 × 7.5 ml each mixture), yielded 63 mg (5%) of crystalline **22**, m.p. 115–116°. IR (CH₂Cl₂): 2950, 2830, 1790 (C=O, lactam), 1750 sh (C=O, ester), 1725 (C=O, carbamate), 1605, 1495, 1455, 1375, 1290, 1240, 1127, 1065, 960. ¹H-NMR (360 MHz, CDCl₃): 7.47–6.93 (*m*, 2 C₆H₅); 5.58 (*br. s*, 1 H-C(6)); 5.31 (*s*, C₆H₅CH₂O); 4.29 (*d*, *J* = 8.5, 1 H-C(11)); 4.12 (*m*, 1 H-C(3)); 3.55 (*s*, H₃COCO-C(9)); 3.25, 3.07 (2 *s*, CH₃O-C(11)); 2.90 (*dd*, *J* = 13.5, *J'* = 6.5, 1 H-C(10)); 2.842 (*dd*, *J* = 6, *J'* = 3, 1 H-C(4)); 2.836 (*dd*, *J* = 13.5, *J'* = 4, 1 H-C(10)); 2.80–2.70 (*m*, 1 H-C(8)); 2.50 (*br.*, 1 H-C(5)); 1.70 (*br. s*, 3 H-C(12)); 1.34 (*d*, *J* = 7, 3 H-C(13)). ¹³C-NMR (90.52 MHz, CDCl₃): 172.5 (C(1)); 170.5 (CH₃OCO-C(9)); 151.2 (C₆H₅CH₂OCO-N(2)); 141.0, 136.0, 135.3 (C(7)); 130.4, 128.8, 128.6, 128.3, 126.8, 122.0 (C(6)); 102.6 (C(11)); 68.4 (C₆H₅CH₂OCO-N(2)); 62.5 (C(9)); 58.3 (C(3)); 53.2, 52.7, 52.3 (3 CH₃O); 42.2 (C(5)); 39.6, 39.5, 39.3 (C(4), C(8), C(10)); 19.7 (C(11)); 11.9 (C(12)). MS: 521 (M⁺), 461 (M⁺ – 60 (CH₃OCO)), 430 (M⁺ – 91 (C₇H₇)), 386 (M⁺ – 135 (C₆H₅CH₂OCO)).

C₃₀H₃₅NO₇ (521.61) Calc. C 69.08 H 6.76 N 2.69% Found C 69.11 H 6.89 N 2.68%

rac-Methyl (3R*, 3aS*, 4S*, 7R*, 7aS*)-3-benzyl-2-benzoyloxycarbonyl-4-(1,3-dioxolan-2-yl)-6, 7-dimethyl-1-oxo-3a, 4, 7, 7a-tetrahydroisindoline-7a-carboxylate (**23**). A solution of 994 mg (2.5 mmol) of **1** [1] and 584 mg (3.8 mmol) of **15** in 20 ml of xylene was heated in a sealed tube to 145° for 110 h. Evaporation of the solvent *i.v.* gave 1.39 g of an oil, which was subjected to column chromatography on 300 g of silica gel. Elution with CH₂Cl₂ (500 ml), CH₂Cl₂/Et₂O (99:1), (97:3), and (95:5) (4 × 50 ml, 4 × 50 ml and 50 × 50 ml) gave 833 mg of crude **23**. A second similar column chromatography yielded 657 mg (51%) of pure **23** as a colourless oil. IR (CH₂Cl₂): 2930, 2850, 1770 (C=O, lactam), 1740 (C=O, ester), 1730 (C=O, carbamate), 990, 930. ¹H-NMR (90 MHz, CDCl₃): 7.6–6.9 (*m*, 2 C₆H₅); 5.8–5.6 (*br.*, 1 H-C(6)); 5.31 (*s*, C₆H₅CH₂O); 4.6–4.3 (*m*, 1 H-C(3)); 4.32 (*d*, *J* = 4.5, 1 H-C(11)); 4.1–3.5 (*m*, OCH₂CH₂O); 3.63 (*s*, H₃COCO-C(9)); 3.08 (*dd*, *J* = 13, *J'* = 4, 1 H-C(10)); 2.76 (*dd*, *J* = 13, *J'* = 8, 1 H-C(10)); 2.95–2.65 (*m*, 1 H-C(4), 1 H-C(8)); 2.6–2.25 (*m*, 1 H-C(5)); 1.73 (*br. s*, 3 H-C(12)); 1.35 (*d*, *J* = 7, 3 H-C(13)). MS: 519 (M⁺), 428 (M⁺ – 91 (C₇H₇)), 384 (M⁺ – 135 (C₆H₅CH₂OCO)), 324 (384–60 (CH₃COOH)).

Dimethyl (E/Z)-2-(2'-benzoyloxycarbonylamino-3'-phenyl-1'-propenyl)malonate (**20**). A solution of 994 mg (2.5 mmol) of **1** [1] in 20 ml xylene was heated in a sealed tube to 80–85° for 5 h. Evaporation of the solvent *i.v.* gave 1.0 g crude product, which was purified by column chromatography on 100 g of silica gel. Elution with CH₂Cl₂/Et₂O (99:1), (98:2), (96:4), and (92:8) (6 × 50 ml of each mixture) afforded 850 mg (86%) of **20** (fractions 15–18) as a pale yellowish oil. IR (film): 3340, 3030, 2955, 1735, 1665, 1490, 1430, 1235, 1070, 1030, 745, 700. ¹H-NMR (90 MHz, CDCl₃): 7.4–7.0 (*m*, 2 C₆H₅); 6.82 (*br. s*, H-N); 5.38 (*br. d*, *J* = 8, 1 H-C(1')); 5.00 (*s*, C₆H₅CH₂O); 4.33 (*d*, *J* = 8, 1 H-C(2)); 3.75 (*br. s*, 2 H-C(3')); 3.63 (*s*, 2 OCH₃). ¹³C-NMR (22.63 MHz, CDCl₃): 168.4 (C(1), C(2)); 153.5 (C₆H₅CH₂OCO); 139.1 (C(2')); 137.8, 136.3, 128.9, 128.5, 128.1, 128.0, 126.6, 111.1 (C(1')); 66.9 (C₆H₅CH₂OCO); 52.7 (2 OCH₃); 50.2 (C(2)); 40.5 (C(3')). MS: 397 (M⁺), 305 (M⁺ – 1-91 (C₆H₅CH₃)), 262 (M⁺ – 135 (C₆H₅CH₂OCO)), 92, 91.

rac-Methyl (3R*, 3aS*, 4R*, 7R*, 7aR*)-3-benzyl-7-hydroxymethyl-4, 5-dimethyl-1-oxo-3a, 4, 7, 7a-tetrahydroisindoline-7a-carboxylate (**24**). To a stirred mixture of 107 mg (0.2 mmol) of **18**, and 6 ml of MeOH/benzene 2:1, 1 ml of 50% aq. KOH was added. After stirring for 2 ½ h at r.t., the mixture was chilled and acidified with 6 ml of 2N H₂SO₄ and extracted with CH₂Cl₂ (3 × 15 ml). The extracts were washed with H₂O (2 × 3 ml) and dried, yielding after removal of the solvent *i.v.*, 84 mg of crude acid **25**. The latter was dissolved in 5 ml of MeOH and treated with diazomethane in Et₂O until the yellow colour persisted. Evaporation *i.v.* gave 82 mg crude **24**. Recrystallization from CH₂Cl₂/diisopropyl ether yielded 43.3 mg (63%) of **24**, m.p. 164–168°. IR, ¹H-NMR, and MS data were congruent with those reported [6].

rac-(3R*, 3aS*, 4R*, 7R*, 7aS*)-3-Benzyl-2-benzoyloxycarbonyl-4, 5, 7-trimethyl-1-oxo-3a, 4, 7, 7a-tetrahydroisoindoline-7a, 7a-carbolactone (**4**) from **2** and **20**. A solution of 373 mg (0.94 mmol) of **20** and 124 mg (1.10 mmol) of **2** [6] in 4 ml xylene was heated in a sealed tube to 143° for 63 h. Evaporation of the solvent *i.v.* gave 474 mg of a yellow oil, which was diluted with 1 ml of Et₂O. Crystallization yielded 207 mg (50%) of **4** as prisms, m.p. 172–173°. IR and ¹H-NMR data were identical with those reported [6].

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