174. Approaches to the Synthesis of Cytochalasans. Part 5[1]). Studies on the Selectivity of the *Diels-Alder* Reaction Leading to the Tetrahydroisoindolinone Sub-Unit

by **Tibur Schmidlin, Remo Gamboni[2]), Peter Strazewski[2]) and Christoph Tamm***

Institut für Organische Chemie der Universität, St. Johanns-Ring 19, CH-4056 Basel

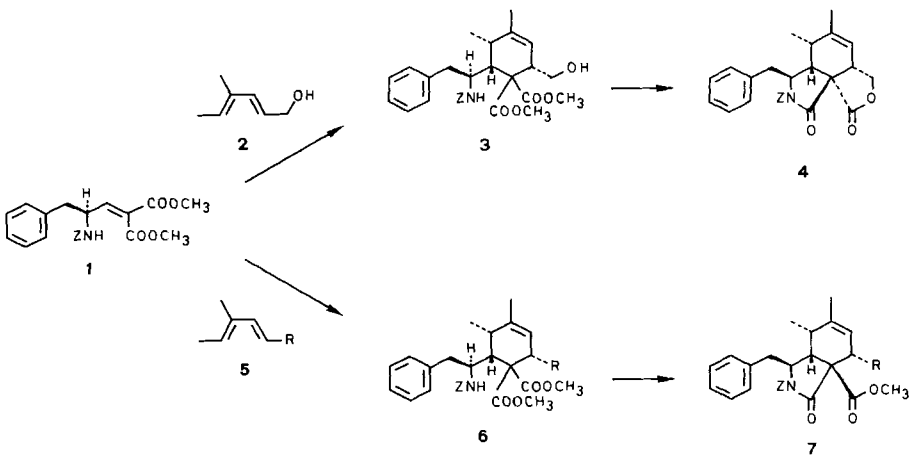
(1.VI.83)

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**

Scheme 1



Z = $C_6H_5CH_2OCO$ R = alkyl residue containing oxygen

[1]) Part 4: [1].

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

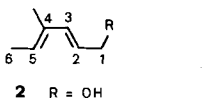
[3]) The numbering of the sub-units corresponds to that used for the cytochalasans [2].

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.

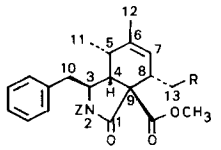
We now describe the results of experiments devised to prevent lactone ring formation in the expected intermediate **3** by the use of dienes **5** containing blocked O-functions. Cycloaddition of the latter to the olefin **1**, according to the procedure in [1], should preferably form adducts of type **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)*.

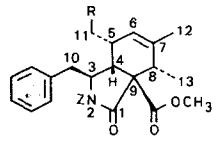
Scheme 2



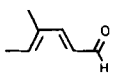
2 R = OH
8 R = OTHP
9 R = OCH_3
10 R = $OCOC_2H_5$
11 R = $OSi(CH_3)_2C(CH_3)_3$



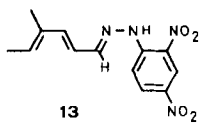
16 R = OCH_3
18 R = $OCOC_2H_5$
21 R = $OSi(CH_3)_2C(CH_3)_3$



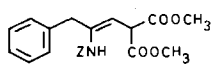
17 R = OCH_3
19 R = $OCOC_2H_5$



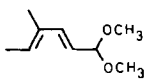
12



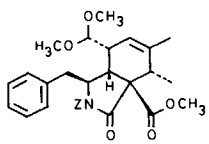
13



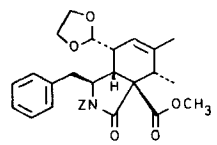
20



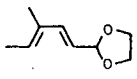
14



22

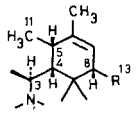


23

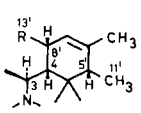


15

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}H-NMR spectroscopy[4]) 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



orientation **I**



orientation **II**

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 H–C(3)[5]) reveals the signal of H–C(4), which is identical in both orientations. A third decoupling experiment performed by irradiation at the position of the signal corresponding to H–C(5) or H–C(5′) allowed the final distinction between the two regioisomers. Whereas in one case decoupling of H–C(4) was observed as expected for orientation **I**, in the other case no change in the signal of 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 H–C(4) and 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

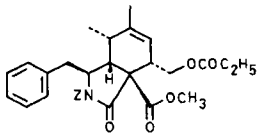
---

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

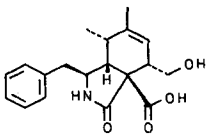
[5]) It is shifted by the presence of the *α*-N-atom to low field.

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

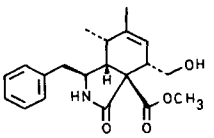
hydrolysis to the acid **25** and re-esterification. The identity of **24** with a sample prepared from **4** established the configuration at C(3), C(4), C(5) and C(8) in the adduct **18**. However, a change of configuration at C(9) during the reaction cannot



18

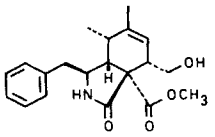


25

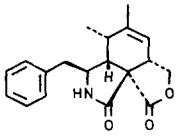


24

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.



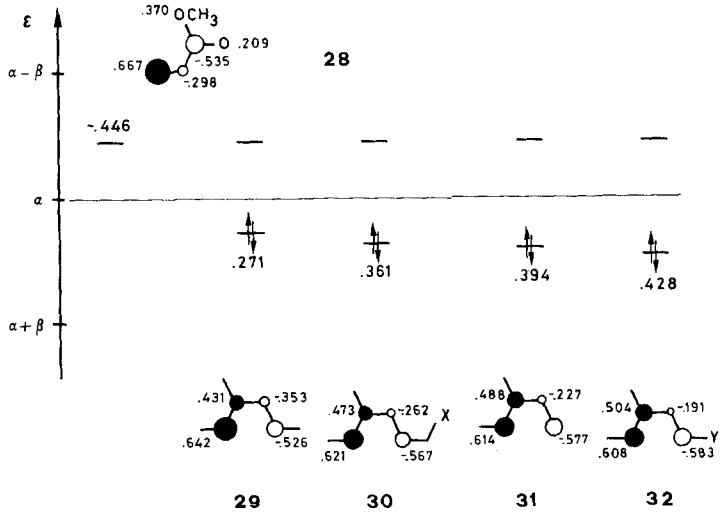
26



27

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 CH_3-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

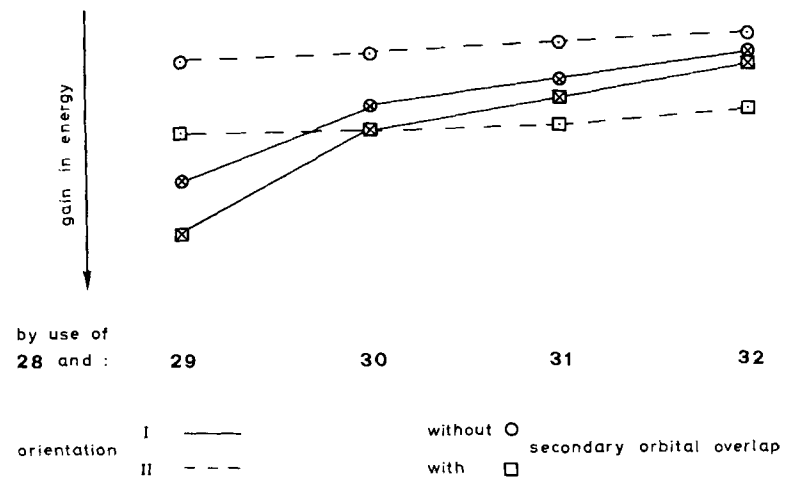
Scheme 3



X and Y = elements with electronegativity greater than carbon

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].

Scheme 4



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-tetrahydropyranyloxy-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 $SOCl_2$, 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 Et_2O and washed with 7.5 ml 1M $KHCO_3$. The washings were extracted with 10 ml Et_2O. 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. ^{1}H-NMR (60 MHz, $CDCl_3$): 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), CH_3–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 Bu_4NHSO_4, 4.49 g (40 mmol) of **2** [6], 29.2 g (206 mmol) of CH_3I and 30 ml 50% KOH was stirred vigorously for 22 h in the dark (*cf.* [11]). Then the mixture was treated with 300 ml Et_2O and 30 ml H_2O and extracted. The org. phase was washed with H_2O (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. ^{1}H-NMR (60 MHz, CCl_4): 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*, CH_3–O–C(1)); 1.7 (*m*, 3 H–C(6), CH_3–C(4)). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 137.7, 134.1 (C(4)), 126.9, 122.5, 73.5 (CH_3O), 57.6 (C(1)), 13.7, 12.0.

$C_8H_{14}O$ (126.20) Calc. C 76.14 H 11.18% Found C 75.14 H 11.37%

(hygroscopic, K.F.-titration showed up to 2% H_2O).

*(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 Et_3N in 20 ml Et_2O. The mixture was stirred for 72 h at r.t., then diluted with 100 ml of Et_2O and extracted with 2N HCl (2 × 50 ml), and H_2O (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. ^{1}H-NMR (60 MHz, CCl_4): 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, H_3CCH_2COO); 1.65 (*m*, 3 H–C(6), CH_3–CC(4)); 1.05 (*t*, *J* = 7, CH_3CH_2COO). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 173.9 (CH_3CH_2COO); 139.4, 134.0 (C(4)); 128.8, 120.1, 65.3 (C(1)); 27.7 (CH_3CH_2COO); 13.8, 12.0, 9.2 (CH_3CH_2COO).

*(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 CH_2Cl_2 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 CH_2Cl_2 [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}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, $(CH_3)_3$C–Si); 0.0 (*s*, 6 H, $(CH_3)_2$Si). ^{13}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.

*(2*E*,4*E*)-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/CH_2Cl_2 → CH_2Cl_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}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}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 (2*m*, *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 ($M^+ - 107$(CH_3CH:$C(CH_3)CH$:$CHCN$)), 182 ($M^+ - 108$), 108 ($M^+ - 182$ (2,4-dinitrophenylamine)), 107 ($M^+ - 183$).

$C_{13}H_{14}N_4O_4$ (290.28) Calc. C 53.79 H 4.86 N 19.30% Found C 53.74 H 4.84 N 19.33%

*(2*E*,4*E*)-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 Na_2SO_4/Na_2CO_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}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)).

$C_9H_{16}O_2$ (156.23) Calc. C 69.19 H 10.32% Found C 68.93 H 10.44%

*2-[(1*E*,3*E*)-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 ½ 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** → **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 (≈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}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*, OCH_2CH_2O); 1.7 (*m*, 3 H–C(6), CH_3–C(4)).

$C_9H_{14}O_2$ (154.21) Calc. C 70.10 H 9.15% Found C 69.88 H 9.43%

rac-*Methyl (3*R**,3a*S**,4*R**,7*R**,7a*R**)-3-benzyl-2-benzyloxy-carbonyl-7-methoxymethyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylate* (**16**) *and* rac-*methyl (3*R**,3a*S**,4*S**,7*R**,7a*S**)-3-benzyl-2-benzyloxycarbonyl-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, CH_2Cl_2/Et_2O (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 Et_2O/hexane, m.p. 110–112°. IR (KBr): 2960, 2920, 1780, 1725, 1695, 1450, 1380, 1270, 1230, 1105, 987. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.54–6.93 (*m*, 2 C_6H_5); 5.46 (br. *s*, 1 H–C(7)); 5.35, 5.31 (*AB*, *J* = 12, $C_6H_5CH_2O$); 3.95 (*m*, 1 H–C(3)); 3.85–3.65 (*m*, 2 H–C(13)); 3.71 (*s*, H_3COCO–C(9)); 3.36 (*s*, CH_3O–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 ($M^+ - 31(CH_3O)$), 432 ($M^+ - 59(CH_3COO)$), 365 ($M^+ - 126$ (retro-*Diels-Alder*-reaction)), 365 ($M^+ - 135(C_6H_5CH_2OCO)$).

$C_{29}H_{31}NO_6$ (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 (CH_2Cl_2): 2930, 2860, 1785, 1720, 1375, 1190, 1140, 1110. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.51–6.96 (*m*, 2 C_6H_5); 5.44 (br. *s*, 1 H–C(6)); 5.33, 5.31 (*AB*, *J* = 13, $C_6H_5CH_2O$); 4.04 (*m*, 1 H–C(3)); 3.67 (*s*, H_3COCO–C(9)); 3.15 (*dd*, *J* = 8, *J'* = 6.5, 1 H–C(11)); 3.08 (*s*, CH_3O–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 ($M^+ - 31$ (CH_3O)), 432 ($M^+ - 59$ (CH_3COO)), 414 ($M^+ - 77$ (C_6H_5)), 400 ($M^+ - 91$ (C_7H_7)), 356 ($M^+ - 135$ ($C_6H_5CH_2OCO$)).

rac-*Methyl (3*R*,*3a*S*,*4*R*,*7*R*,*7a*R*)*-3-benzyl-2-benzyloxycarbonyl-4,5-dimethyl-7-propionyloxymethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxylate* (**18**) *and* rac-*methyl (3*R*,*3a*S*,*4*S*,*7*R*,*7a*S*)*-3-benzyl-2-benzyloxycarbonyl-6,7-dimethyl-4-propionyloxymethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-carboxyalate* (**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 CH_2Cl_2/Et_2O (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 Et_2O/pentane, m.p. 107–109°. IR (KBr): 2980, 1785, 1740, 1720 sh, 1380, 1280, 1235, 985, 760, 705. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.53–6.97 (*m*, 2 C_6H_5); 5.43 (br. *s*, 1 H–C(7)); 5.34, 5.32 (*AB*, *J* = 12.5, $C_6H_5CH_2O$); 4.59–4.43 (*m*, 2 H–C(13)); 3.97 (*m*, 1 H–C(3)); 3.72 (*s*, H_3COCO–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, CH_3CH_2COO–C(13)); 1.66 (br. *s*, 3 H–C(12)); 1.11 (*t*, *J* = 7, CH_3CH_2COO–C(13)); 0.63 (*d*, *J* = 7, 3 H–C(11)). MS: 533 (M^+), 502 ($M^+ - 31$ (CH_3O)), 473 ($M^+ - 60$ (CH_3COOH)), 459 ($M^+ - 74$ (CH_3CH_2COOH)), 442 ($M^+ - 91$ (C_7H_7)), 398 ($M^+ - 135$ ($C_6H_5CH_2OCO$)), 91.

$C_{31}H_{35}NO_7$ (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 (CH_2Cl_2): 3040, 2950, 1790, 1730, 1380, 1195, 1150, 1115, 1000, 890. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.52–6.94 (*m*, 2 C_6H_5); 5.43 (br. *s*, 1 H–C(6)); 5.35, 5.29 (*AB*, *J* = 13, $C_6H_5CH_2O$); 4.05 (*m*, 1 H–C(3)); 3.90 (*dd*, *J* = 12, *J'* = 6, 1 H–C(11)); 3.72 (*s*, H_3COCO–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 (2 *q*, *J* = 7, H_3CCH_2COO–C(11)); 1.71 (br. *s*, 3 H–C(12)); 1.39 (*d*, *J* = 7, 3 H–C(13)); 1.07 (*t*, *J* = 7, CH_3CH_2COO–C(11)). MS: 533 (M^+), 489 ($M^+ - 45$ (CH_3CH_2O)), 474 ($M^+ - 60$ (CH_3COOH)), 442 ($M^+ - 91$ (C_7H_7)), 398 ($M^+ - 135$ ($C_6H_5CH_2OCO$)).

rac-*Methyl (3*R*,*3a*S*,*4*R*,*7*R*,*7a*R*)*-3-benzyl-2-benzyloxycarbonyl-7-(t-butyldimethylsilyloxy)-methyl-4,5-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-7a-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 CH_2Cl_2/Et_2O (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–$(CH_3)_2$), 760, 735, 705. ^{1}H-NMR (90 MHz, $CDCl_3$): 7.55–6.95 (*m*, 2 C_6H_5); 5.55 (br., 1 H–C(7)); 5.32 (br. *s*, $C_6H_5CH_2O$); 4.00 (*d*, *J* = 7, 2 H–C(13)); 4.0–3.9 (*m*, 1 H–C(3)); 3.71 (*s*, H_3COCO–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*, $(CH_3)_3C$–Si); 0.58 (*d*, *J* = 7,

3 H–C(11)); 0.05 (*s*, $(CH_3)_2Si$). MS: 591 (M^+), 576 ($M^+ - 15$ (CH_3)), 460 ($M^+ - 31$ (CH_3O)), 534 ($M^+ - 57$ ($(CH_3)_3C$)), 490, 457, 456 ($M^+ - 135$ ($C_6H_5CH_2OCO$)), 366 (457–91), 290.

$C_{34}H_{45}NO_6Si$ (591.82) Calc. C 68.74 H 7.73 N 2.38% Found C 68.58 H 7.68 N 2.38%

rac-*Methyl (3*R*,3a*S*,4*S*,7*R*,7a*S*)-3-benzyl-2-benzyloxycarbonyl-4-dimethoxymethyl-6,7-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-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 CH_2Cl_2 gave 277 mg of a yellow oil. A second column chromatography of the latter using 30 g of silica gel and CH_2Cl_2, CH_2Cl_2/Et_2O (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 (CH_2Cl_2): 2950, 2830, 1790 (C=O, lactam), 1750 sh (C=O, ester), 1725 (C=O, carbamate), 1605, 1495, 1455, 1375, 1290, 1240, 1127, 1065, 960. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.47–6.93 (*m*, 2 C_6H_5); 5.58 (br. *s*, 1 H–C(6)); 5.31 (*s*, $C_6H_5CH_2O$); 4.29 (*d*, *J* = 8.5, 1 H–C(11)); 4.12 (*m*, 1 H–C(3)); 3.55 (*s*, H_3COCO–C(9)); 3.25, 3.07 (2 *s*, CH_3O–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)). ^{13}C-NMR (90.52 MHz, $CDCl_3$): 172.5 (C(1)); 170.5 (CH_3OCO–C(9)); 151.2 ($C_6H_5CH_2OCO$–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 ($C_6H_5CH_2OCO$–N(2)); 62.5 (C(9)); 58.3 (C(3)); 53.2, 52.7, 52.3 (3 CH_3O); 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 ($M^+ - 60$ (CH_3OCO)), 430 ($M^+ - 91$ (C_7H_7)), 386 ($M^+ - 135$ ($C_6H_5CH_2OCO$)).

$C_{30}H_{35}NO_7$ (521.61) Calc. C 69.08 H 6.76 N 2.69% Found C 69.11 H 6.89 N 2.68%

rac-*Methyl (3*R*,3a*S*,4*S*,7*R*,7a*S*)-3-benzyl-2-benzyloxycarbonyl-4-(1,3-dioxolan-2-yl)-6,7-dimethyl-1-oxo-3a,4,7,7a-tetrahydroisoindoline-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 CH_2Cl_2 (500 ml), CH_2Cl_2/Et_2O (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 (CH_2Cl_2): 2930, 2850, 1770 (C=O, lactam), 1740 (C=O, ester), 1730 (C=O, carbamate), 990, 930. ^{1}H-NMR (90 MHz, $CDCl_3$): 7.6–6.9 (*m*, 2 C_6H_5); 5.8–5.6 (br., 1 H–C(6)); 5.31 (*s*, $C_6H_5CH_2O$); 4.6–4.3 (*m*, 1 H–C(3)); 4.32 (*d*, *J* = 4.5, 1 H–C(11)); 4.1–3.5 (*m*, OCH_2CH_2O); 3.63 (*s*, H_3COCO–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 ($M^+ - 91$ (C_7H_7)), 384 ($M^+ - 135$ ($C_6H_5CH_2OCO$)), 324 (384–60 (CH_3COOH)).

Dimethyl (E/Z)-2-(2'-benzyloxycarbonylamino-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 CH_2Cl_2/Et_2O (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. ^{1}H-NMR (90 MHz, $CDCl_3$): 7.4–7.0 (*m*, 2 C_6H_5); 6.82 (br. *s*, H–N); 5.38 (br. *d*, *J* = 8, 1 H–C(1')); 5.00 (*s*, $C_6H_5CH_2O$); 4.33 (*d*, *J* = 8, 1 H–C(2)); 3.75 (br. *s*, 2 H–C(3')); 3.63 (*s*, 2 OCH_3). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 168.4 (C(1), C(2)); 153.5 ($C_6H_5CH_2OCO$); 139.1 (C(2')); 137.8, 136.3, 128.9, 128.5, 128.1, 128.0, 126.6, 111.1 (C(1')); 66.9 ($C_6H_5CH_2OCO$); 52.7 (2 OCH_3); 50.2 (C(2)); 40.5 (C(3')). MS: 397 (M^+), 305 ($M^+ - 1$–91 ($C_6H_5CH_3$)), 262 ($M^+ - 135$ ($C_6H_5CH_2OCO$)), 92, 91.

rac-*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* (**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 H_2SO_4 and extracted with CH_2Cl_2 (3 × 15 ml). The extracts were washed with H_2O (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 Et_2O until the yellow colour persisted. Evaporation *i.v.* gave 82 mg crude **24**. Recrystallization from CH_2Cl_2/diisopropyl ether yielded 43.3 mg (63%) of **24**, m.p. 164–168°. IR, ^{1}H-NMR, and MS data were congruent with those reported [6].

rac-*(3*R*, 3a*S*, 4*R*, 7*R*, 7a*S*)-3-Benzyl-2-benzyloxycarbonyl-4, 5, 7-trimethyl-1-oxo-3a, 4, 7, 7a-tetrahydroisoindoline-7a, 7α-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 Et_2O. Crystallization yielded 207 mg (50%) of **4** as prisms, m.p. 172–173°. IR and ^{1}H-NMR data were identical with those reported [6].

REFERENCES

[1] *T. Schmidlin, P. E. Burckhardt, N. Waespe-Šarčević & Ch. Tamm,* Helv. Chim. Acta *66,* 450 (1983).
[2] *M. Binder, Ch. Tamm, W. B. Turner & H. Minato,* J. Chem. Soc., Perkin Trans. I *1973,* 1146.
[3] *M. Zehnder,* Helv. Chim. Acta *64,* 251 (1981).
[4] *E. J. Corey & G. Schmidt,* Tetrahedron Lett. *1979,* 399.
[5] *B. Glatz, G. Helmchen, H. Muxfeldt, H. Porcher, R. Prewo, J. Senn, J. J. Stezowski, R. J. Stojda & D. R. White,* J. Am. Chem. Soc. *101,* 2171 (1979).
[6] *T. Schmidlin, W. Zürcher & Ch. Tamm,* Helv. Chim. Acta *64,* 235 (1981).
[7] *Cf. E. Heilbronner & H. Bock,* «Das HMO-Modell und seine Anwendung», Verlag Chemie, Weinheim 1968.
[8] *Cf. I. Fleming,* 'Frontier Orbitals and Organic Chemical Reactions', J. Wiley & Sons, Chichester, New York, Brisbane, Toronto, 1978, pp. 27, 37, 132.
[9] *I. Fleming & J. P. Michael* and *L. E. Overman & G. F. Taylor,* Tetrahedron Lett. *1978,* 1313.
[10] *E. Vedejs & R. C. Gadwood,* J. Org. Chem. *43,* 376 (1978).
[11] *H. H. Freedman & R. A. Dubois,* Tetrahedron Lett. *1975,* 3251.
[12] *S. K. Chaudhary & O. Hernandez,* Tetrahedron Lett. *1979,* 99.