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Cyclocondensations of Homophthalic Anhydrides with 1-Aza-1,3-dienes

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Abstract : α,β-Unsaturated aldimines (1-aza-1,3-butadienes) **2**, **4** and **7a-d** react with homophthalic anhydrides **1a,b** to give 3,4-dihydro-1(2H)-naphthalenone-4-carboxylic acids **3**, **5**, **8a-d** (R^2 = H) as main products. Homophthalic anhydride **1a** and cinnamaldimine **7d** gave rise to the diastereoisomeric naphthalenones **8d** (R^2 = H), along with the 3,4-dihydro-1(2H)-isoquinolinone-4-carboxylic acids **10** (R^2 = H), and 3,4-dihydro-1(2H)-pyridinone **11** (R^2 = H) as products of 3,4-, 1,2- and 1,4-addition to the 1-aza-1,3-butadiene, respectively. The effect of the reaction conditions on the ratio of adducts, produced by **1a** and **7d**, was studied. The structure and relative configurations of **3**, **5**, **8a-d**, **10** and **11** were determined by NMR spectroscopy. In the case of *cis*-naphthalenone **8c** and dihydropyridinone **11**, the structure was confirmed by X-ray crystal structure analysis.

INTRODUCTION

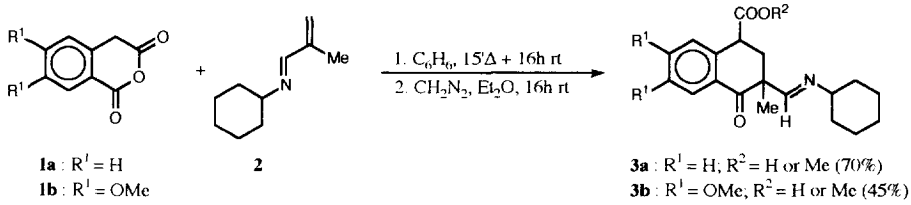
As a continuation of our investigations on the interaction of homophthalic anhydrides **1** with polyfunctional imines,[1,2] we investigated the reactions of homophthalic anhydrides **1** with 1-aza-1,3-butadienes (α,β-unsaturated aldimines; enimines) possessing alkyl or aryl substituents in α- or β-position with respect to the imine carbon. The reason for this interest stems from the high synthetic potential of such cyclocondensation reactions, affording various derivatives of naphthalenones, isoquinolinones and pyridinones. The former compounds would serve as precursors of naphthol derivatives.

RESULTS AND DISCUSSION

The reaction of homophthalic anhydrides **1** with α,β-unsaturated imines in aprotic solvents at room temperature or at reflux proceeds to cyclocondensations. In almost all cases studied, carboxylic acids were obtained as the major reaction products. For the purpose of structural analysis, the acids were transformed into their methyl esters by treatment with diazomethane.

Thus, homophthalic anhydrides **1a,b** react with N-(2-methyl-2-propen-1-ylidene)cyclohexylamine **2**[3] to give 2-(N-cyclohexylformimidoyl)-2-methyl-3,4-dihydro-1(2H)-naphthalenone-4-carboxylic acids **3a,b**

(R^2=H), characterized as their methyl esters **3a,b** (R^2=Me) (Scheme 1).



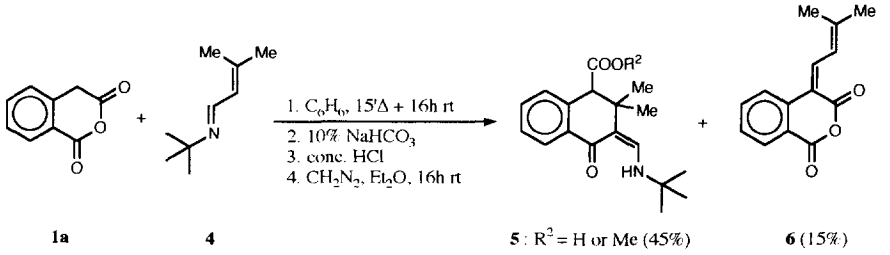
1a : R^1 = H
1b : R^1 = OMe

2

3a : R^1 = H; R^2 = H or Me (70%)
3b : R^1 = OMe; R^2 = H or Me (45%)

Scheme 1

The reaction of homophthalic anhydride (**1a**) with N-(3-methyl-2-butenylidene)-*tert*-butylamine (**4**)[4] yields besides the analogous adduct, i.e. 2-(*tert*-butylaminomethylidene)-3,3-dimethyl-3,4-dihydro-1(2H)-naphthalenone-4-carboxylic acid (**5**) (R^2=H) characterized as its methyl ester **5** (R^2=Me), also the product of a Perkin type condensation **6** (Scheme 2).



1a

4

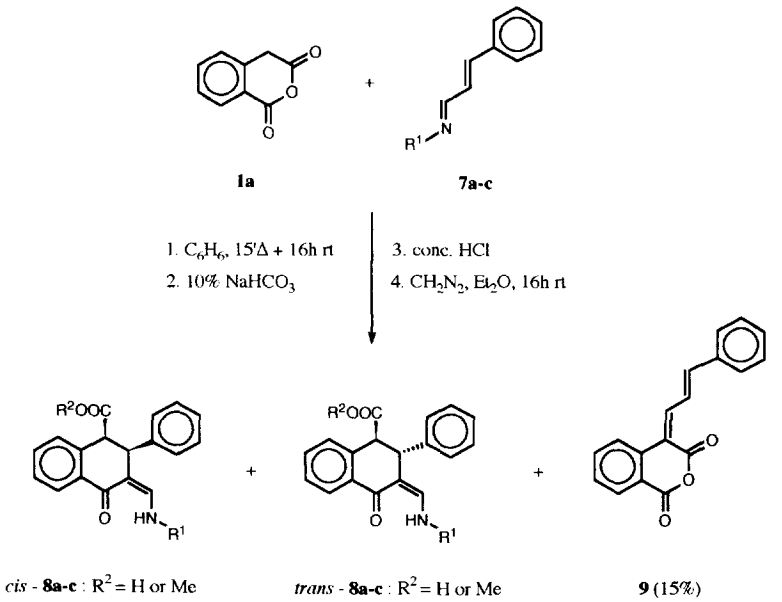
5 : R^2 = H or Me (45%)

6 (15%)

Scheme 2

Analogously, homophthalic anhydride (**1a**) and N-(3-phenyl-2-propen-1-ylidene)alkyl(aryl)amines **7a-c** (cinnamaldimines)[3-5] afford the corresponding diastereoisomeric 2-[alkyl(aryl)aminomethylidene]-3-phenyl-3,4-dihydro-1(2H)-naphthalenone-4-carboxylic acids **8a-c** (R^2=H) characterized as their methyl esters **8a-c** (R^2=Me), together with the known Perkin type condensation product **9**[6] (Scheme 3).

The interaction of the anhydride **1a** with N-(3-phenyl-2-propen-1-ylidene)-isopropylamine **7d**[7] proceeds in a more complicated way. Besides the *trans*- and *cis*-carboxylic acids **8d** (R^2=H) characterized as the esters **8d** (R^2=Me) and the Perkin compound **9**, the reaction yields *trans*-3-(2-phenylethenyl)-2-isopropyl-3,4-dihydro-1(2H)-isoquinolinone-4-carboxylic acid (**10**) (R^2=H) and *trans*-3-(2-carboxyphenyl)-4-phenyl-1-isopropyl-3,4-dihydro-1(2H)-pyridinone (**11**) (R^2=H). The latter were characterized as their methyl esters **10** (R^2=Me) and **11** (R^2=Me), respectively (Scheme 4). In cases where a tautomerization is possible (compounds **5**, **8**), enamine structures incorporating an *s-cis*-enone moiety are favoured (**5** and **8**, as compared to **3**). Such enaminones were easily chlorinated by means of N-chlorosuccinimide at room temperature[8] to give the corresponding β-imino-α-chloroketones, as exemplified by the conversion of enaminone *cis*-**8d** into methyl 2-chloro-3-phenyl-2-(N-isopropylformimidoyl)-3,4-dihydro-1(2H)-naphthalenone-4-carboxylate(*cis*-**12**). The

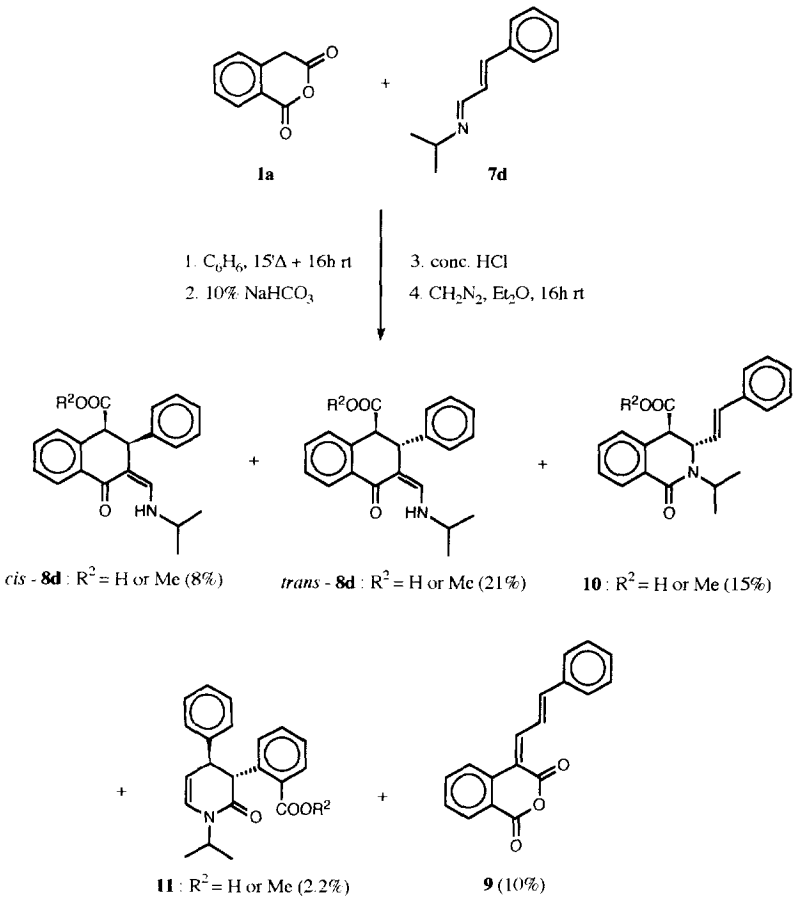


R^1(R^2 = Me)	diastereoisomer	yield %
a = CMe_3	*cis*	20
b = c-C_6H_{11}	*trans*	15
c = C_6H_5	*cis*	49

Scheme 3

chlorination is regio- and stereospecific and occurs at the β-enamine carbon. The α-chloroimine *cis*-**12** was hydrolyzed in aqueous oxalic acid to methyl 2-chloro-2-formyl-3-phenyl-3,4-dihydro-1(2H)-naphthalenone-4-carboxylate (*cis*-**13**). The stereospecifically formed α-chloro-α-tetralone *cis*-12 underwent dehydrochlorination and aromatization by interaction with sodium methoxide in methanol to afford methyl 4-hydroxy-2-phenyl-3-(N-isopropylformimidoyl)-naphthalene-1-carboxylate **14** (Scheme 5).

It is not clear yet whether a phenol-imine **14** or an enaminone **15** is involved. The observation of spin-spin coupling of the amino proton to the adjacent α-proton(s) of the N-alkyl substituent is known as an evidence for the presence of the keto-amine form.[9-11] In the present case (**14**, **15**), there is no extra coupling in the ^{1}H-NMR spectrum (2D-COSY) between the methine hydrogen of the isopropyl group and any other protons than both methyl groups. This absence of coupling is in favour of the naphthol structure **14**. However, the ^{13}C-NMR data point to some extent in the direction of the tautomer **15**. It might be that Zwitterionic forms contribute significantly to the stabilization of the ground state of the molecule. The absence of an observable coupling between $Me_2C\underline{H}$ and NH (if present) is not an absolute evidence for the presence of the naphthol-imine form, because a low energy barrier to the tautomeric interconversion of the proton between nitrogen and oxygen might be responsible for this phenomenon.[9]



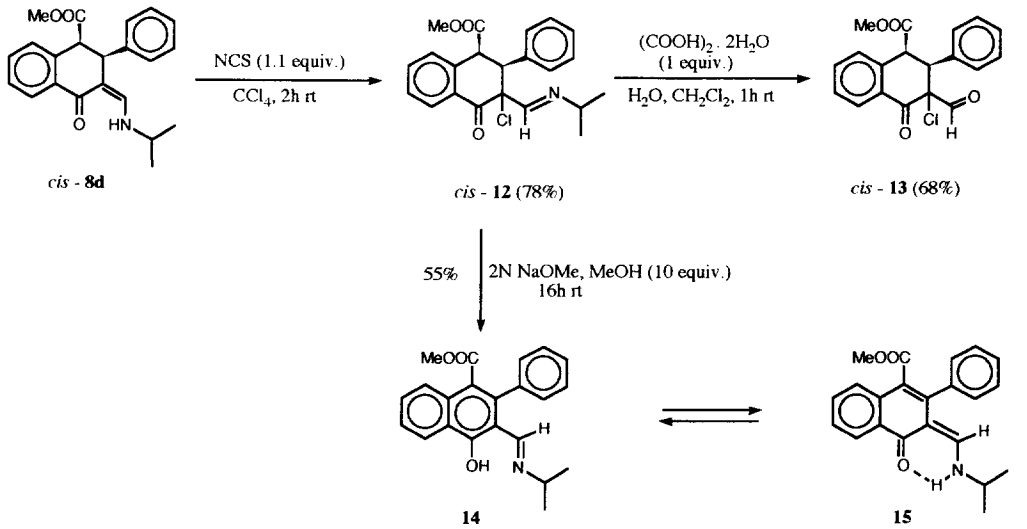
Scheme 4

The reactions leading to compounds **8** are not stereoselective and depending on the properties of **8a-d** and the reaction conditions, pure *cis*- or *trans*-isomers, or mixtures of both stereoisomers were isolated (Schemes 3 and 4). In order to gain more insight into the factors determining the formation of the stereoisomers, a detailed study of the reaction of the anhydride **1a** and the imine **7d** was carried out in five different solvents at room temperature or at reflux as well as in the presence of acidic or basic catalysts. The carboxylic acids **8d**, **10** and **11** (R^2=H) were converted into the corresponding methyl esters **8d**, **10** and **11** (R^2=Me) and estimated quantitatively (Table 1). In spite of the high degree of conversion of the reactants observed (entries 1-9), the yield of the mixture of the isomeric **8d**, **10** and **11** was lowered in the presence of acidic or basic catalyst (entries 9, 10). When using polar solvents and in the presence of acidic catalyst, a slightly lower total yield of diastereomeric acids **8d** within the mixture of isomers **8d**, **10** and **11** at the expense of the products of competitive reactions **10** and **11** (entries 8-9) was observed. Compound **11** is a minor product

Table 1. Effect of the Reaction Conditions on the Isomeric Ratio in the Reaction of Homophthalic Anhydride (**1a**) and N-(3-Phenyl-2-propen-1-ylidene)isopropylamine (**7d**)[a,b]

Entry	Solvent	Temp. °C (Time)	Yield of the mixture of isomers **8d, 10** and **11** (%)	*cis*-**8d** R^2=Me (%)[c]	*trans*-**8d** R^2=Me (%)[c]	*trans*-*cis* ratio	**10** R^2=Me (%)[c]	**11** R^2=Me (%)[c]	Yield of **9** (%)
1	C_6H_6	rt (8h)	40	32.5	32.5	1.00	31.9	3.0	36
2	C_6H_6	rt (16h)	45	30.5	38.5	1.25	23.0	7.7	37
3	C_6H_6	80(15min)	50	16.0	42.0	2.63	32.0	10.0	10
4	C_6H_6	80(30min)	65	18.7	52.9	2.84	23.5	4.9	15
5	C_6H_6	80 (2h)	77	17.3	54.1	3.13	21.5	7.5	5
6	$C_6H_5CH_3$	110(15min)	60	15.9	44.9	2.89	24.6	14.6	14
7	THF	0 (5min)	90	20.4	35.7	1.75	23.5	20.4	-
8	CH_3CN	82 (15min)	57	21.7	18.9	0.86	54.7	4.7	17
9	CH_2Cl_2:C_6H_6 (1:1) + CF_3COOH (1 equiv.)	rt (16h)	35	12.5	32.5	2.59	35.0	20.0	57
10	CH_2Cl_2, Et_3N (1 equiv.)	0 (15min)	34	21.3	41.5	1.95	35.1	2.1	-

a) Estimated by ^{1}H-NMR integrations.
b) Workup : see the experimental part.
c) Molar part calculated as a % of the total mixture of isomers **8d**, **10** and **11**.



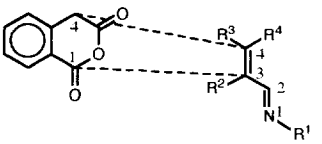
Scheme 5

under all conditions studied. The condensation product **9** is formed predominantly in acidic reaction conditions (entry **9**).

The quantity of the *trans*-isomer is increased at the expense of the *cis*-isomer in the mixture of diastereomeric acids **8d** (R^2=H) in benzene or toluene when using higher temperature or longer reflux periods (entries 1-6). On this basis, it is assumed that the *cis*-isomers of type **8** are products of kinetic, and the *trans*-isomers of thermodynamic control. This is confirmed by the following experiment : the crude mixture of acids obtained from homophthalic anhydride (**1a**) and the imine **7d** in benzene containing *trans*- and *cis*-**8d** in 1:1 ratio (Table 1, entry 1) was refluxed in toluene for 3 hrs and investigated quantitatively by ^{1}H-NMR spectroscopy to show a change of the *trans/cis*-**8d** ratio, namely 2.3:1.

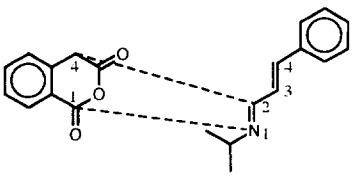
From the foregoing discussion it is seen that the major products of the reaction of homophthalic anhydrides **1** with α,β-unsaturated aldimines (1-aza-1,3-butadienes) **2**, **4** and **7** are the 3,4-adducts of type **3**, **5** and **8** (R^2=H) respectively, all being naphthalene derivatives. The side products are composed of the 1,2-adduct **10** (R^2=H) and the 1,4-adduct **11** (R^2=H), both containing a pyridine ring, along with the condensation product **6**, resp. **9** (Scheme 6).

As it is known,[12] the cycloaddition of homophthalic anhydrides as dienes to different dienophiles requires high temperature or is induced by strong bases and gives rise to linearly condensed phenolic compounds. Recently it was shown however, that 7-methoxyhomophthalic anhydride reacts with such a dienophile as dimethyl acetylenedicarboxylate, to give a Diels-Alder adduct under mild basic conditions and a suggestion was made that the reaction mechanism was alternative to the cycloaddition.[13] Since homophthalic anhydride can be regarded as a benzene analog of 1,3-dicarbonyl compounds, it is worth noting that the latter reacts

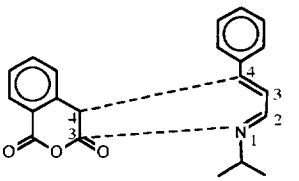


R^1 = alkyl, aryl
R^2 = H, alkyl (methyl)
R^3, R^4 = H, alkyl, aryl

PATH A (3,4-addition)



PATH B (1,2-addition)



PATH C (1,4-addition)

Scheme 6

with 1-aza-1,3-butadienes under mild acid-catalyzed conditions to afford pyridine or cyclohexane derivatives, depending on the structure of the enamine. Their formation is rationalized as a two-step reaction, the first step being a Michael addition.[14,15] In order to interprete the reaction of homophthalic anhydride with Schiff bases leading to carboxyisoquinolinones, a mechanism corroborated by experimental data has been proposed involving iminolysis of the anhydride as initial step.[16]

In spite of the absence of rigorous data, the formation of the compounds **3**, **5** and **8** is interpreted as an attack of the nucleophilic centre of C-4 of the homophthalic anhydrides **1** on the α,β-unsaturated aldimines (1-aza-1,3-butadienes) **2**, **4** and **7** according to a Michael type reaction. The intermediates formed undergo an intramolecular rearrangement involving a nucleophilic attack on the C-1 electrophilic centre of the anhydride moiety followed by ring opening (Path A, Scheme 6). In accordance with the previously raised mechanistic interpretation,[17] the formation of compounds **10** and **11** could be explained by an iminolysis of the anhydride at C-1 (Path B, Scheme 6), resp. C-3 (Path C, Scheme 6), and subsequent transformation of the intermediates obtained. Although insufficient, the experimental data show that the competitive formation of compounds **10** and **11** at the expense of the diastereoisomeric **8d** is favoured by acidic catalysis (Table 1, entry **9**). Therefore, in the cases **10** and **11** a reaction pathway including a carbon-carbon bond formation by linking the position C-4 of the anhydride and position C-2, resp. position C-4 of the enimine, i.e. a Perkin, resp. a Michael type reaction preceding the carbon-nitrogen bond formation, could not be excluded.

The formation of the condensation products **6** and **9** of homophthalic anhydride and enimines **4**, resp. **7**, can be explained only by assuming of addition-elimination Perkin-type mechanism. The predominant formation of compound **9** in the reaction of the anhydride **1a** and the enimine **7d** under acidic catalysis can

be attributed to the enhanced reactivity of the imino function towards nucleophilic addition by protonation of the nitrogen atom.

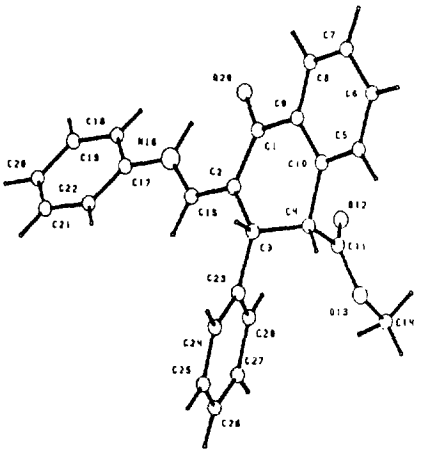
The structure and stereochemistry of compounds **3**, **5**, **6**, **8**, **10** and **11** were determined on the basis of their NMR spectral data. A vicinal coupling constant $J_{3,4}$ of 1.7 Hz was obtained from the ^{1}H-NMR spectrum of the dihydroisoquinolinone ester **10** (R^2=Me), which, according to the literature[2] indicated a *trans*-configuration and di-pseudoaxial conformation for the 3,4-substituents. This configurational assignment was also supported by the results of molecular mechanics calculations using the MM2 force field of Allinger[18]. Thus, for compound **10** the calculated minimum-energy conformation of the *trans*-form is a twist-boat structure with a calculated[19] vicinal coupling constant value $J_{3,4}$ of 1.56 Hz (dihedral angle 67°), which corresponds very well to the experimental value of 1.7 Hz. The energy minima found for the *cis*-form of **10** require a vicinal coupling of *ca.* 4 Hz.

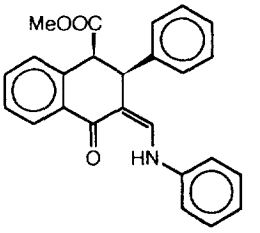
On the other hand, the $J_{3,4}$-values of the substituted 3,4-dihydro-1(2H)-naphthalenone-4-carboxylates **8a-d** (R^2=Me) are in the interval 4.2-5.6 Hz and, if taken alone, not very distinctive for configurational assignments. Attempts to use NOE difference measurements yielded unreliable results, since mutual H-3/H-4 enhancements were observed for both diastereoisomers (e.g., for *cis*- as well as for *trans*-**8d**). The problem was successfully solved on the basis of the X-ray study of **8c** (R^2=Me), which unequivocally proved its *cis*-configuration[20]. An X-ray crystallographic picture of compound *cis*-**8c** (R^2=Me) is given in Figure 1.

The crystal structure data of compound **8c** are the following : triclinic, a=9.684 (2), b=10.786 (2), c=10.881 (2) Å, V=1016.4 (4) Å^3, Z=2, D_x=1.25 g.cm^{-3}, λ (MoKα)=0.71069 Å, μ=0.08 mm^{-1}, T=293 K, R=0.0742 and R_w=0.0742 for 2817 observed reflections with I > 2σ (I). The methoxycarbonyl and phenyl groups have a *cis*-configuration. The unsaturated ring has a sofa conformation with C9, C1, C2, C3 atoms lying in a plane and the C4 and C10 atoms out of this plane by 0.8 (1) and 0.4 (1) Å, respectively. An intramolecular hydrogen bond N16-H16 ... O29 (N...O=2.62 Å, H...O=1.81 Å, < N-H...O=135.0°) has been found in the structure transforming formally the bicyclic system into a tricyclic one. The bond lengths in the chain O29 = C1-C2 = C15-N16 are shortened showing the conjugation in this system. The phenyl ring at N16 is also included in conjugation so far as it forms the angle of 26(7)° with the plane formed by N16 C15 C2 atoms.

Taking this information into account and comparing the $J_{3,4}$-values (see experimental part), one could rather safely assign the *cis*-configuration also to the single isomer of **8a** and to one of the **8d**-isomers possessing somewhat higher $J_{3,4}$-values (5.3-5.6 Hz), and *trans*-configuration to **8b** and the other **8d**-isomer with lower $J_{3,4}$-values (4.0-4.3 Hz). Additional support for these assignments could be obtained from the comparison of the proton and carbon (C<u>O</u> and <u>C</u>H$_3$) chemical shifts of the COOMe group : in all cases the respective signals of the *trans*-isomers are at lower field with respect to those of the *cis*-isomers, although the effects are rather small. The molecular mechanics calculations for compound **8a** (R^2=Me) are also in agreement with the above assignments. Thus, for *trans*-**8a** (R^2=Me), a minimum-energy conformation with diaxial H-3,4 ($J_{3,4}$=12.88 Hz, contrary to the experimental data) was predicted. For *cis*-**8a** (R^2=Me), two most favoured conformations with equatorial Ph group and axial COOMe group and almost equal energy are predicted : a half-chair with $J_{3,4}$=3.75 Hz (54°) and a twist-boat with $J_{3,4}$=6.76 Hz (38°), which agrees well with the experimental value of 5.6 Hz.

The esters **8a-d** as well as **5** possess a conformation with *anti*-orientation of the hydrogens at the C-N bond (J_{CHNH} = 12.0-13.0 Hz), probably caused (or stabilized) by a strong intramolecular NH...O=C hydrogen bond. The latter was demonstrated in the IR as well as in the ^{1}H-NMR spectra : IR-bands at *ca.* 3150 and *ca.* 3420 cm^{-1} for bonded and free NH, resp. in diluted CCl_4-solution, and strongly deshielded NH proton NMR signals. The *s-trans* conformations at the exocyclic double bonds of **6**, **9** and the *trans*-configuration of the double bond in **10** were proven by the high values of the respective vicinal coupling constants (see experimental part).



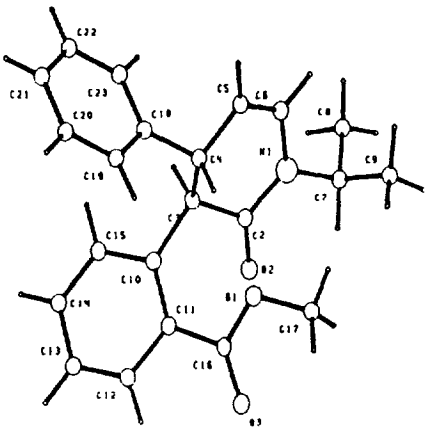


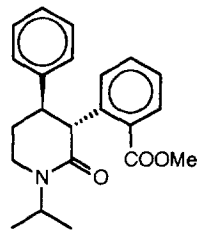
cis-8c (methyl ester)

Fig. 1 : X-ray crystallographic picture of cis-**8c** (methyl ester)

For compound **11**, the $J_{3,4}$-value of 11.5 Hz indicates a *trans*- diequatorial orientation of the respective substituents, whereas the $J_{5,6}$-value (8.2 Hz) is fully compatible with the *cis*-configuration of the endocyclic double bond. These conclusions were proven by the results of the X-ray crystallographic analysis of compound **11**.[20] Figure 2 gives the X-ray crystallographic picture of enamide **11** (methyl ester).

The crystal structure data of compound **11** are the following : triclinic, a=9.378 (1), b=10.189 (1), c=11.577 (2) Å, V=913.3 (2) Å, Z = 2, D_x=1.27 g.cm^{-3}, λ (MoKα)=0.71069 Å, μ=0.08 mm^{-1}, T=293 K, R=0.049 and R_w=0.049 for 2458 observed reflections with I > 2σ (I). The substituents at C3 and C4 have a gauche-orientation with a torsion angle C10-C3-C4-C18=-60.8 (3)°. The heterocycle has a half-chair conformation with the C2 and C3 atoms out of the other four atoms plane by 0.273 (2) and 0.686 (2) Å, respectively. The largest torsion angle in the heterocycle has the value of 43.1° along the C3-C4 bond. The phenyl rings at C3 and C4 have a pseudo-equatorial orientation. The mean plane of the methoxycarbonyl group is turned by 29.1° with respect to the adjacent phenyl ring, which breaks the conjugation of the two π-systems. The C3-C4 bond length [1.549 (4) Å] is somewhat larger than its normal value probably due to the bulky substituents at positions 3 and 4.





11 (methyl ester)

Fig. 2 : X-ray crystallographic picture of enamide **11** (methyl ester)

EXPERIMENTAL

Melting points (mp, uncorrected) : microhot stage Boetius PHMK 0.5. TLC : Silicagel 60 F_{254} on aluminium sheets "Merck", layer thickness 0.2 mm. Solvent systems : ether/hexane 1:1 (1 part) and hexane/ethyl acetate/methanol/ammonia 120:100:15:10, upper layer (1 part) or ethyl acetate/hexane 50:50. Flash chromatography : silica gel type 60 "Merck", particle size 0.040-0.003 mm, ethyl acetate/hexane 10:90, 20:80 as a solvent system and ratio in grams product/silica gel 1:200. Conventional column chromatography : silica gel type 60 "Merck", particle size 0.2-0.063 mm, petroleum ether/ether 20:80 as a solvent system and ratio in grams product/silica gel 1:200. Mass spectra (MS) : m/z (rel. intensity) : Jeol JMS D-300 and Finnigan MAT 112, chemical ionization (CI) or electron impact, 70 eV where stated. IR spectra : C.Zeiss-Jena Specord IR-71 and Perkin-Elmer 1310 IR spectrometer; $CHCl_3$ as solvent if not stated otherwise. ^{1}H-NMR and ^{13}C-NMR spectra : Brüker Spectrospin WM-250 (250 MHz), Varian XL-300 (300 MHz), JEOL EX 270 (270 MHz); $CDCl_3$ as solvent if not stated otherwise. The DEPT sequence and in some cases also 2D H-C correlation spectroscopy was used for the ^{13}C-assignment. The NOE experiments were performed in the difference mode.

X-ray structure determination. The colourless parallelepiped-shaped crystals of **8c** (R^2=Me) (0.25 x 0.2 x 0.15 mm) and **11** (R^2=Me) (0.35 x 0.2 x 0.2 mm) were investigated on a Syntex $P2_1$ diffractometer (MoKα radiation). Cell constants of **8c** (R^2=Me) from 20 reflections with $10 < \theta < 13°$; for θ_{max}=25° (h : 0 to 11, k : -12 to 12, l : -12 to 12) 3584 reflections measured. Cell constants of **11** (R^2=Me) from 20 reflections with $10 < \theta < 12°$; for θ_{max}=25° (h : 0 to 10, k : -12 to 11, l : -13 to 12) 3408 reflections measured.

Reaction of homophthalic anhydride (**1a, b**) with α,β-unsaturated aldimines (1-aza-1,3-butadienes) (**2, 4** and **7a-d**) (general procedure)

To a solution of homophthalic anhydride (**1a,b**, 2 mmol) in dry benzene (4 ml), a solution of the imine (**2**, **4** or **7a-d**, 2 mmol) in dry benzene (4 ml) was added, and the mixture was refluxed for 15 min and left for 16 hours at room temperature. It was then extracted with 3x5 ml of 10% aqueous $NaHCO_3$. The combined alkaline extracts were acidified with conc. HCl and the precipitated acidic product was filtered off, dissolved in 4 ml CH_3OH/CH_2Cl_2 (1:1), treated with excess ethereal solution of diazomethane and left at room temperature for 16 hours. In case of a nonsolid acidic product, the aqueous mixture was extracted three times with chloroform, the combined extracts were dried ($MgSO_4$), the solvent was evaporated in vacuo and the residue was treated with ethereal diazomethane as above. After evaporation of the solvent the residue was purified by conventional column chromatography to give compounds **3a-b** (R^2=Me) and **8a-c** (R^2=Me) or by flash chromatography for compounds **5**, **8d**, **10** and **11** (R^2=Me). The diastereoisomers **8d** (R^2=Me) were separated by two successive flash chromatographies using the same conditions.

The benzene solution from above was dried, the solvent was evaporated and the residue was recrystallized from chloroform to give the neutral **6** and **9**, respectively.

In this way the following compounds were obtained :

3a (R^2=Me) (from **1a** and **2**) Yield 70%, oil. MS : 328(100) [MH^+]. IR : 823, 985 (HC=), 1640 (C=N), 1685 (C=O), 1712 (C=O, ester), 2400-3400 (NH). ^{1}H-NMR : 1.14-1.83 (10H, m, $(CH_2)_5$); 1.75 (3H, s, CH_3C); 2.44 (1H, dd, J=8.0, 16.5) and 2.60 (1H, dd, J=12.5, 16.5, CH_2-3); 3.85 (3H, s, $COOCH_3$); 4.46 (1H, m, N-CH); 4.55 (1H, dd, J=8.0, 12.5, H-4); 5.99 (1H, br s, CH=N); 7.25-7.49 (3H, m, H-5, 6, 7); 7.93 (1H, m, H-8). Calcd. for $C_{20}H_{25}NO_3$ (327.4) : C 73.36, H 7.70; found C 73.70, H 7.98%.

3b (R^2=Me) (from **1b** and **2**) Yield 45%, oil. MS : 388(100) [MH^+]. IR : 1600 (C=C, arom.), 1640 (C=N), 1680 (C=O), 1710 (C=O, ester). ^{1}H-NMR : 0.85-1.80 (10H, m, $(CH_2)_5$); 1.26 (3H, s, CH_3-C); 2.45 (1H, dd, J=8.1, 16.4) and 2.55 (1H, dd, J=12.0, 16.3, CH_2-3); 3.88, 3.90 and 3.91 (each 3H, s, $2CH_3O$ and $COOCH_3$); 4.49 (1H, m, N-CH); 4.63 (1H, m, H-4); 5.99 (1H, s, CH=N); 6.73 (1H, s, H-5); 7.51 (1H, s, H-8). Calcd. for $C_{22}H_{29}NO_3$ (387.5) : C 74.33, H 8.22; found C 74.51, H 8.36%.

5 (R^2=Me) and **6** (from **1a** and **4**)

5 (R^2=Me) Yield 45%, oil. MS (70 eV) : 315(10) [M^+], 314(45) [M^+-1], 300(21) [M^+-CH_3], 299(100) [M^+-1-CH_3], 255(16) [M^+-$COOCH_3$]. IR : 1605 (C=C, arom.), 1640 (C=C-C=O), 1730 (C=O, ester), 3100-3600 (NH) (or 3140, 3400 in $1x10^{-3}$ M CCl_4 solution). ^{1}H-NMR : 1.14 and 1.32 (each 3H, s, $C(CH_3)_2$); 1.34 (9H, s, $C(CH_3)_3$); 3.58 (3H, s, $COOCH_3$); 3.59 (1H, s, H-4); 7.08 (1H, d, J=12.9, =CHN); 10.92 (1H, d, J=12.5, NH, H-bonded). ^{13}C-NMR : 25.8 and 32.1 ($C(\underline{C}H_3)_2$); 30.2 ($C(\underline{C}H_3)_3$); 36.9 ($\underline{C}(CH_3)_3$); 51.6 (CH_3O); 52.1 (C-3); 57.8 (C-4); 107.7 (C-2); 126.7, 127.9, 128.0 and 131.2 (C-5, 6, 7, 8); 134.8 and 136.8 (C-4a and C-8a); 146.3 (=CHN); 172.3 (COO); 184.5 (C-1). $C_{19}H_{25}NO_3$ (315.4).

6 Yield 15%, oil. MS (70 eV) : 228(46) [M^+], 229(9) [M^++1], 230(2) [M^++2]. IR (nujol) : 780 (HC=), 1600 (C=C, arom.), 1720, 1760 (CO-O-CO). ^{1}H-NMR : 2.11 (6H, d, J=1.5, $2CH_3$); 7.4-7.8 (3H,

m, H-5, 6, 7); 7.56 (1H, dm, J=12.0, H-10); 7.93 (1H, d, J=12.0, H-9); 8.20 (1H, m, H-8). $C_{14}H_{12}O_3$ (228.2).

Cis-**8a** (R^2=Me) and **9** (from **1a** and **7a**).

Cis-**8a** (R^2=Me) Yield 20%, mp. 140-143°C (ethyl acetate). MS : 364(100) [MH^+]. IR : 1600 (C=C, arom.), 1640 (C=C-C=O), 1730 (C=O, ester), 3100-3600 (NH) (3150, 3430 in $1x10^{-3}$ M CCl_4 solution). ^{1}H-NMR : 1.24 (9H, s, $C(CH_3)_3$); 3.53 (3H, s, $COOCH_3$); 4.15 (1H, d, J=5.6) and 4.36 (1H, d, J=5.6, H-3 and H-4); 6.87 (1H, d, J=13.1, =CHN); 7.14-7.42 (8H, m, arom. H); 8.12 (1H, m, H-8); 10.93 (1H, d, J=13.0, NH, H-bonded). ^{13}C-NMR : 30.1 ($C(\underline{C}H_3)_3$); 47.5 and 52.0 (C-3 and C-4); 51.6 (CH_3O); 52.2 ($\underline{C}(CH_3)_3$); 101.7 (C-2); 126.3, 126.6, 127.3, 127.6, 128.0, 128.4, 128.7, 131.3, 135.4, 135.9 and 141.3 (arom. C and CH); 149.8 (=CHN); 171.9 (COO); 184.5 (C-1). Calcd. for $C_{23}H_{25}NO_3$ (363.4) : C 76.01, H 6.93; found C 76.16, H 6.81%.

9 Yield 15%, mp. 222-224°C (reported mp. 220-221°C[6]). MS : 277(100) [MH^+]; IR (nujol) : 740, 780 (HC=), 1580, 1600 (C=C, arom.), 1720, 1760 (CO-O-CO). ^{1}H-NMR : 7.28 (1H, d, J=15.4, H-11); 7.40-7.85 (8H, m, arom. H); 7.78 (1H, d, J=11.2, H-9); 8.25 (1H, m, H-8); 8.48 (1H, dd, J=11.4, 15.4, H-10). Calcd. for $C_{18}H_{12}O_3$ (276.3) : C 78.25, H 4.38; found C 78.46, H 4.70%.

Trans-**8b** (R^2=Me) and **9** (from **1a** and **7b**).

Trans-**8b** (R^2=Me) Yield 15%, oil. MS (70 eV) : 391(8) [M^++2], 390(50) [M^++1], 389(100) [M^+], 330(62) [M^+-$COOCH_3$]. IR : 1600 (C=C, arom.), 1640 (C=O), 1730 (C=O, ester), 3000-3600 (NH) (or 3170, 3420 in $1x10^{-3}$ M CCl_4 solution). ^{1}H-NMR : 0.8-2.0 (10H, m, $(CH_2)_5$); 3.03 (1H, br. s, NCH); 3.61 (3H, s, $COOCH_3$); 4.03 (1H, d, J=4.2) and 4.37 (1H, d, J=4.2, H-3 and H-4); 6.81 (1H, d, J=12.8, =CHN); 7.0-7.4 (8H, m, arom. H); 8.06 (1H, m, H-8); 10.72 (1H, m, NH, H-bonded). $C_{25}H_{27}NO_3$ (389.5).

9 Yield 17%, mp. 222-224°C.

Cis-**8c** (R^2=Me) and **9** (from **1a** and **7c**).

Cis-**8c** (R^2=Me) Yield 49%, mp. 142-144°C (ethyl acetate). MS : 384(100) [MH^+]. IR : 740 (HC=), 1600 (C=C, arom.), 1650 (C=C-C=O), 1740 (C=O, ester), 2800-3600 (NH) (or 3050, 3150 in $1x10^{-3}$ M CCl_4 solution). ^{1}H-NMR : 3.56 (3H, s, $COOCH_3$); 4.09 and 4.49 (each 1H, each d, each J=5.2, H-3 and H-4); 6.9-7.5 (14H, m, arom. H); 8.15 (1H, m, H-8); 12.29 (1H, d, J=12.0, NH, H-bonded). ^{13}C-NMR : 47.7 and 52.1 (C-3 and C-4); 51.8 (CH_3O); 105.9 (C-2); 116.1, 123.2, 127.2, 127.7, 127.8, 128.4, 128.9, 129.6 and 132.1 (arom. CH); 134.8, 137.1, 140.3 and 140.5 (arom. C); 143.5 (=CHN); 171.8 (COO); 187.0 (C-1). Calcd. for $C_{25}H_{21}NO_3$ (383.4) : C 78.31, H 5.51; found C 78.52, H 5.34%.

9 Yield 14%, mp. 222-224°C.

Cis- and *trans*-**8d** (R^2=Me), **9**, **10** (R^2=Me) and **11** (R^2=Me) (from **1a** and **7d**).

Cis-**8d** (R^2=Me) Yield 12%, oil. MS (70 eV) : 349(100) [M^+], 290(83) [M^+-$COOCH_3$]. IR : 1600 (C=C, arom.), 1630, 1680 (C=C-C=O), 1720 (C=O, ester), 2600-3600 (NH) (or 3160, 3420, 3540 in $1x10^{-3}$ M CCl_4 solution). ^{1}H-NMR : 1.20 (3H, d, J=6.4) and 1.23 (3H, d, J=6.4, $CH(C\underline{H}_3)_2$; 3.37 (1H, septet, J=6.4, $C\underline{H}(CH_3)_2$); 3.54 (3H, s, $COOCH_3$); 4.14 (1H, d, J=5.3) and 4.31 (1H, d, J=5.6, H-3 and H-4); 6.75 (1H, d, J=12.7, s after D_2O-exchange, =CHN); 6.9-7.5 (8H, m, arom. H); 8.10 (1H, m, H-8); 10.60 (1H, br., disappears after D_2O-exchange, NH, H-bonded). ^{13}C-NMR : 23.7 and 23.9 ($CH(\underline{C}H_3)_2$); 47.3 and 50.3, C-3 and C-4); 51.6 (CH_3O); 51.9 ($\underline{C}H(CH_3)_2$); 101.7 (C-2); 126.6, 127.3, 127.6, 128.0, 128.5, 128.7, 131.3, 135.3, 135.9 and 141.3 (arom. C and CH); 152.0 (=CHN); 171.9 ($\underline{C}OO$); 184.7 (C-1). $C_{22}H_{23}NO_3$ (349.4).

Trans-**8d** (R^2=Me) Yield 21%, oil. MS (70 eV) : 349(44) [M^+], 290(37) [M^+-$COOCH_3$]. IR : 1600 (C=C, arom.), 1630, 1680 (C=C-C=O), 1720 (C=O, ester), 2600-3600 (NH). ^{1}H-NMR : 1.22 (3H, d, J=5.0) and 1.24 (3H, d, J=4.9, $CH(C\underline{H}_3)_2$); 3.48 (1H, septet, J=4.9, $C\underline{H}(CH_3)_2$); 3.59 (3H, s, $COOCH_3$); 4.04 (1H, d, J=4.3) and 4.38 (1H, d, J=4.0, H-3 and H-4); 6.79 (1H, d, J=12.5, =CHN); 7.02-7.39 (8H, m, arom. H); 8.05 (1H, m, H-8); 10.62 (1H, br, NH, H-bonded). ^{13}C-NMR : 23.75 and 23.8 ($CH(\underline{C}H_3)_2$); 46.0 and 50.4 (C-3 and C-4); 52.2 (CH_3O); 53.1 ($\underline{C}H(CH_3)_2$); 100.8 (C-2); 126.0, 126.5, 127.8, 128.0, 128.05, 128.4, 128.6, 129.0, 131.4, 135.1, 135.2 and 143.9 (arom. C and CH); 143.9 (=CHN); 172.9 ($\underline{C}OO$); 184.3 (C-1). Calcd. for $C_{23}H_{23}NO_3$ (349.4) : C 75.62, H 6.63; found C 75.95, H 6.91%.

9 Yield 10%, mp. 222-224°C.

10 (R^2=Me) Yield 15%, mp. 120-123° (ethyl acetate). MS : 350(100) [MH^+]. IR (nujol) : 970 (C=C, trans), 1595, 1620 (C=C, arom.), 1650 (C=O, lactam), 1740 (C=O, ester). ^{1}H-NMR : 1.22 (3H, d, J=6.9) and 1.25 (3H, d, J=6.9, $CH(C\underline{H}_3)_2$); 3.64 (3H, s, $COOCH_3$); 3.81 (1H, d, J=1.7, H-4); 4.86 (1H, dt, J=1.7, 7.0, H-3); 4.95 (1H, septet, J=6.9, $C\underline{H}(CH_3)_2$); 6.02 (1H, dd, J=7.2, 15.9, H-9); 6.51 (1H, br.d, J=15.9, H-10); 7.17-7.45 (8H, m, arom. H); 8.13 (1H, m, H-8). ^{13}C-NMR : 20.4, 20.6 ($CH(\underline{C}H_3)_2$); 46.0, 50.5 and 55.7 ($\underline{C}H(CH_3)_2$, C-4 and C-3); 52.7 ($\underline{C}H_3O$); 126.4, 126.4, 128.0, 128.3, 128.4, 128.6, 128.8, 128.9, 131.8 and 132.2 (arom. and olefinic CH); 130.0, 132.3, 135.9 (arom. C); 162.9 (C-1); 170.9 ($\underline{C}OO$). Calcd. for $C_{22}H_{23}NO_3$ (349.4) : C 75.62, H 6.63; found C 75.48, H 6.78%.

11 (R^2=Me) Yield 2.2%, mp. 130-133°C (ethyl acetate or ether). MS (70 eV) : 350(8) [M^++1], 349(25) [M^+]. IR : 1440 (C=C, cis), 1600 (C=C, arom.), 1640 (C=O, lactam), 1735 (C=O, ester). ^{1}H-NMR : 1.25 (3H, d, J=6.8) and 1.29 (3H, d, J=6.8, $CH(C\underline{H}_3)_2$); 3.79 (3H, s, $COOCH_3$); 4.07 (1H, dt, J=11.5, 2.6, H-4); 4.49 (1H, br.d, J=11.5, H-3), 4.93 (1H, septet, J=6.8, $C\underline{H}(CH_3)_2$); 5.27 (1H, dd, J=8.2, 2.8, H-5); 6.36 (1H, dd, J=8.2, 2.5, H-6); 6.80-7.30 (8H, m, arom. H); 7.87 (1H, m, H-11). ^{13}C-NMR : 20.4 and 21.0 ($CH(\underline{C}H_3)_2$); 43.9, 46.9 and 54.6 $\underline{C}H(CH_3)_2$, C-5 and C-6); 52.0 (CH_3O); 110.3 (C-4); 124.1, 126.7, 126.8, 128.1 (2C), 128.2 (2C), 129.7, 130.9 and 131.6 (C-3, arom. CH); 131.5, 140.4 and 143.2 (arom. C); 167.9 and 168.2 (C-1 and $\underline{C}OO$). Calcd. for $C_{22}H_{23}NO_3$ (349.4) : C 75.62, H 6.63; found C 75.86, H 6.61%.

Determination of the ratio of isomers in the reaction of homophthalic anhydride (**1a**) and N-(3-phenyl-2-propen-1-ylidene) isopropylamine (**7d**)

To a solution of homophthalic anhydride (**1a**) (1 mmol) in dry solvent (2 ml), a solution of the imine **7d** (1 mmol) in the same solvent (2 ml) was added under nitrogen atmosphere and the reaction was performed as indicated in Table 1. The reaction mixture was worked-up as described in the previous procedure, treated with ethereal diazomethane and the crude product was analyzed by ^{1}H-NMR spectroscopy. The effect of the reaction conditions on the ratio of the isomers (*cis*-**8d**, *trans*-**8d**, **10**, **11**; R^2=Me) was estimated by ^{1}H-NMR integration of the following signals : $COOCH_3$ (3H, s) - 3.54 for *cis*-**8d**, 3.59 for *trans*-**8d**, 3.66 for **10**, 3.78 for **11**; H-3, H-4 - 4.04 (1H, d, J=4.3) and 4.38 (1H, d, J=4.0) for *trans*-**8d**, 4.14 (1H, d, J=5.3) and 4.31 (1H, d, J=5.6) for *cis*-**8d**; H-3 - 4.86 (1H, dt, J=1.7, 7.0); C<u>H</u>$(CH_3)_2$ - 4.95 (1H, septet, J=6.9) and H-9 - 6.02 (1H, dd, J=7.2, 15.9) each for **10**; H-5 - 5.27 (1H, dd, J=8.2, 2.8) for **11**.

The organic solution left after treatment with aq. Na_2CO_3 was dried, the solvent was evaporated and the residue was recrystallized from chloroform to give **9**.

When THF was used as solvent, the reaction mixture was treated directly with ethereal diazomethane because of the lack of the product **9**.

The accuracy of the isomer ratios determined in this study was limited by the ^{1}H-NMR integration.

Chlorination of methyl (3SR,4SR) 2-[phenylaminomethylidene]-3-phenyl-3,4-dihydro-1(2H)-naphthalenone-4-carboxylate (*cis*-**8d**, R^2=Me) with N-chlorosuccinimide

To a 10% (w/v) solution of *cis*-**8d** (R^2=Me) (1 mmol) in dry CCl_4, N-chlorosuccinimide (1.1 mmol) was added and the mixture was stirred at room temperature for 2 hours. The reaction mixture was then cooled, filtered and the solvent evaporated in vacuo to give methyl [2SR(2RS), 3SR,4SR] 2-chloro-3-phenyl-2-(N-isopropylformimidoyl)-3,4-dihydro-1(2H)-naphthalenone-4-carboxylate (*cis*-**12**) as a crude oil in 78% yield (purity 96%). This labile compound was used directly as such in the following experiment. MS (70 eV) : 384 (<1) [M^+], 348.5(10) [M^+-Cl], 345 (<1), 280(16), 192(18), 176(100). IR (NaCl) : 760, 790 (HC= and C-Cl), 1600 (C=C), arom.), 1685 (C=N), 1695 (C=O), 1725 (C=O, ester). ^{1}H-NMR : 0.99 (3H, d, J=6.4) and 1.25 (3H, d, J=6.4, $CH(C\underline{H}_3)_2$); 3.25 (1H, septet, J=6.4, C<u>H</u>$(CH_3)_2$); 3.45 (3H, s, $COOCH_3$); 4.60 (1H, d, J=5.9, H-4); 5.10 (1H, d, J=5.9, H-3); 6.8-7.7 (9H, m, arom. H and CH=N); 8.20 (1H, m, H-8). $C_{22}H_{21}NO_3Cl$ (383.9).

Synthesis of methyl [2SR(2RS), 3SR,4SR] 2-chloro-2-formyl-3-phenyl-3,4-dihydro-1(2H)-naphthalenone-4-carboxylate (*cis*-**13**)

A 10% (w/v) solution of α-chloroimine *cis*-**12** (1 mmol) in CH_2Cl_2 was mixed with an equal volume of H_2O, oxalic acid (1 mmol) was added and the mixture was then refluxed under stirring for 1 hour, extracted (CH_2Cl_2) and dried overnight ($MgSO_4$). After removing the solvent in vacuo the crude α-chloroaldehyde *cis*-**13** was obtained as oil in 68% yield (purity 96%). MS (70 eV) : 316(10) [M^++1-CO], 314(30) [M^+-CO], 307(7) [M^+-Cl], 176(100), 149(71), 138(51). IR (NaCl) : 1600 (C=C, arom.), 1690 (C=O, ketone), 1730 (C=O, aldehyde), 1740 (C=O, ester). ^{1}H-NMR : 3.48 (3H, s, $COOCH_3$); 4.31 (1H, d, J=5.9, H-4); 4.91 (1H, d, J=5.6, H-3); 7.0-7.7 (8H, m, arom. H); 8.21 (1H, d, H-8); 9.61 (1H, s, C<u>H</u>O). $C_{19}H_{15}O_4Cl$ (342.8).

Synthesis of methyl 4-hydroxy-2-phenyl-3-(N-iso-propylformimido)-naphthalenone-1-carboxylate (**14**)

To α-chloroimine *cis*-**12** (2 mmol), 2N NaOMe in MeOH (10 equiv.) was added and the mixture was stirred for 16 hours at room temperature. The reaction mixture was then diluted with H_2O and extracted (CH_2Cl_2), dried ($MgSO_4$) and purified by flash chromatography, ethyl acetate/hexane 70:30 as solvent system and product/silica gel 1:100. After removing the solvents, **14** was obtained as yellow crystals in yield 55%, mp. 125-128° (ether). MS (70 eV) : 347(40) [M^+], 247(100) [M^+-C_8H_5], 245(56) [M^+-C_2H_4N]. IR : 1300 (C-O, phenol), 1360 (OH), 1605 (C=C, arom.), 1635 (C=N, imine), 1720 (C=O, ketone), 1730 (C=O, ester), 3440 (OH, NH, H-bond, br). ^{1}H-NMR : 1.30 (3H, d, J=6.6) and 1.32 (3H, d, J=6.6, $CH(C\underline{H}_3)_2$); 3.45 (3H, s, $COOCH_3$); 3.55 (1H, septet, J=6.6, $C\underline{H}(CH_3)_2$); 7.3-7.7 (7H, m, arom. H); 7.72 (1H, dt, J=7.6, 0.7, H-5); 8.51 (1H, dt, J=8.9, 0.7, H-8); 13.8 (1H, br, OH, H-bonded). ^{13}C-NMR : 23.4 and 29.7 ($CH(\underline{C}H_3)_2$); 51.5 (CH_3O); 52.5 ($\underline{C}H(CH_3)_2$); 107.2 (C-2); 117.8 (C-4); 125.0, 125.5, 125.7, 127.8, 127.9, 128.1, 128.3, 129.7, 129.9, 131.3, 134.0, 137.8 and 140.6 (CH and C-arom.); 158.9 (CH=N); 169.7 and 179.3 (C-1 and $\underline{C}OO$). Calcd. for $C_{22}H_{21}NO_3$ (347.4) : C 76.06, H 6.09; found C 75.94, H 6.18%.

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20. Full data of the X-ray crystallographic analysis of compounds *cis*-**8c** and **11** will be reported separately.

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