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TWO ENANTIOSELECTIVE SYNTHESES OF A PRECURSOR OF THE BIOLOGICALLY MOST ACTIVE ISOMER OF CGA 80000 (CLOZYLACON)[1]

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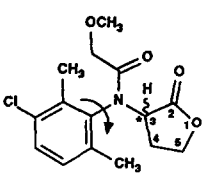
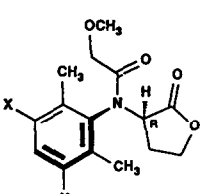
Abstract The unchlorinated precursor 4 of CGA 80000 (1) was synthesized enantioselectively by two conceptionally different routes a) by a "chiral pool" approach starting from L-malic acid and b) by enantioselective hydrogenation of an enamide intermediate, catalyzed by chiral Rh- or Ru-phosphine-complexes

CGA 80000 (1) is the internal Ciba-Geigy code number for a new phenylamide fungicide with the proposed common name **clozylacon** and the systematic name N-(3-chloro-2,6-dimethyl-phenyl)-2-methoxy-N-(tetrahydro-2-oxo-3-furanyl)-acetamide [1] It is especially suited for soil application against oomycetes [2]

Figure 1



1 CGA 80000
(mixture of 4 stereoisomers)



2 X=Cl Y=H
3 X=H Y=Cl
4 X=Y=H

Because of the stereogenic centre (marked with an *), and the atropisomerism due to hindered rotation around the carbon nitrogen bond (marked with an arrow), 1 (CGA 80000) consists of four stereoisomers, which can be separated by chromatography [3] Biological tests have shown that the desired fungicidal activity arises mainly from 2 (CGA 204726), the isomer with the absolute configuration αS,3R

[1] presented in part in a poster at the Seventh International Congress of Pesticide Chemistry; Hamburg, August 5-10, 1990, abstract Nr 01B-10
+ Agricultural Division
# Central Research Laboratories

The synthesis of 1 (CGA 80000), as well as the separation and characterisation of its four stereoisomers and the biological activities of all tested isomers and isomer mixtures, are the subject of another paper [4]

The purpose of our work was to develop a technically feasible and competitive synthesis of 2 (CGA 204726) and to provide the stereochemically pure material needed for further biological testing We focussed on an enantioselective synthesis of the unchlorinated precursor 4 for the following reasons it was known, that 4 can be chlorinated easily, to afford a mixture of 2 and its atropisomer 3, which can be separated by crystallization Furthermore, a method had been established to epimerize the undesired isomer 3 to a mixture of 2 and 3 (see [4]) In need of a competitive process, we aimed to develop an enantioselective route using, to as large an extent as possible, the existing knowledge from the large scale synthesis [4]

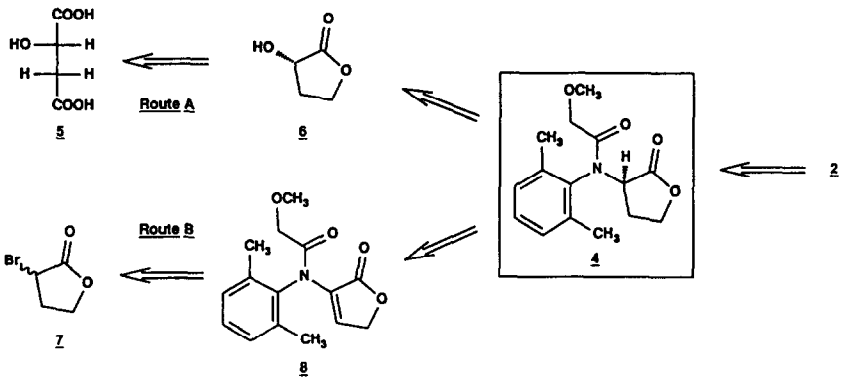
Results and Discussion

We followed two conceptionally different synthetic routes to the target molecule 4 (see fig 2)

A) using L-malic acid (5) from the chiral pool, which provides both the required absolute configuration and the correct number of C-atoms for the butyrolactone ring,

B) introducing the chiral information in a catalytic key step by a Rh- or Ru-catalyzed asymmetric hydrogenation of the enamide intermediate 8, an enantioselective modification of the large scale synthesis [4]

Figure 2

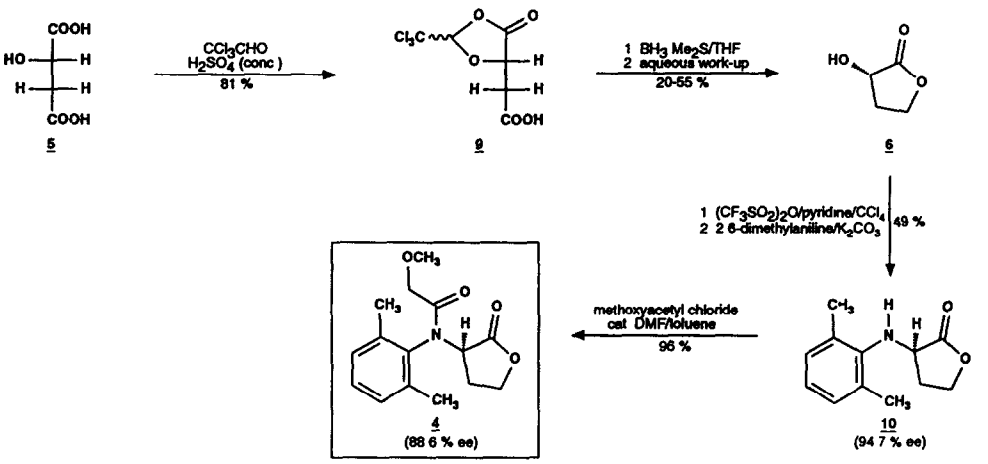


The key intermediate in route A is (3S)-hydroxy-butyrolactone 6, which possesses the opposite absolute configuration of the target molecule 4 A nucleophilic substitution at the activated 3-position, with inversion of the configuration, provides the correct stereochemistry The whole reaction sequence is shown in figure 3

The acid catalyzed reaction of L-malic acid (5) with chloral afforded the dioxolanone 9 in good yield (81 %) as a mixture of two diastereoisomers [5] Reduction of the carboxylic acid group in 9 with borane-dimethylsulfide-complex in THF, followed by aqueous work-up, directly provided the (3S)-hydroxy-butyrolactone 6

Unfortunately, the yield in this step varied considerably and remained unsatisfactory (20-55 %) [1] However, the following steps were straightforward The 3-hydroxy-group in **6** was activated by treatment with triflic acid anhydride under standard conditions Without isolation of the formed triflate intermediate the nucleophilic substitution with 2,6-dimethylaniline was accomplished using potassium carbonate as a base The (3R)-anilino-butyrolactone **10** was thus obtained in moderate yield (49 %) but high optical purity (94 7 % ee, as determined by HPLC on a commercially available Chiralcel-OC-column (Daicel)) Acylation of **10** with methoxyacetyl chloride afforded the target molecule **4** in almost quantitative yield (96 %) In this step, as in some of the others, there was slight racemization, that led to an optical purity of 88 6 % in the final product (as determined by HPLC on a commercially available ChiraSpher-column (Merck)) Crystallization of the racemate from a 1 1-mixture of hexane and ethyl methyl ketone provided optically pure **4** from the mother liquors

Figure 3



This method made it possible to synthesize stereochemically pure material for biological testing However, for the large-scale-production of **4** it was considered both technically unfeasible and too expensive

At that stage promising preliminary results in the enantioselective hydrogenation of enamide **8**, and the great synthetic potential of the homogeneous enantioselective hydrogenation demonstrated in numerous studies [6], prompted us to concentrate our synthetic efforts on route B The whole reaction sequence is shown in figure 4 The first step, taken from the large scale synthesis [4], will not be discussed here

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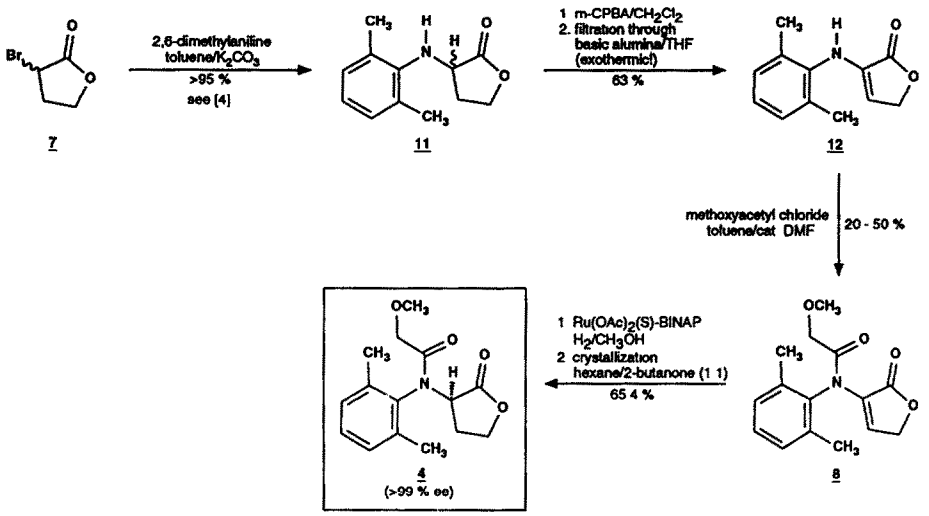
[1] An alternative reaction sequence from **9** to **6** via a two-step catalytic hydrogenation of the corresponding acid chloride gave no improvement of the overall yield and was accompanied by strong racemization in the last step (40 % ee of **6**)

Figure 4

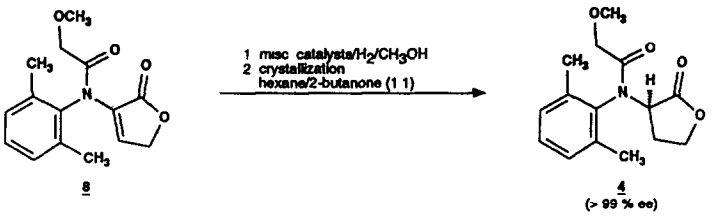


Several methods for the oxidation of the anilino-γ-butyrolactone **11** to the enamine **12** were examined [7] With MnO_2 in refluxing ether the yield remained low (30-40 %) and the transformation only occurred with freshly prepared MnO_2 [8] Slightly higher yields (44 %) and better reproducibility were achieved with ceric ammonium nitrate as the oxidizing agent, but m-CPBA turned out to be the reagent of choice Treatment of **11** with 1 eq of m-CPBA at 0 °C for 1-2 hours led, in good yield (≥80 %), to the N-hydroxylamine of **11**, which, upon treatment with basic alumina, spontaneously eliminated water and tautomerized, to afford the enamine **12** in 60 % overall yield and a very pure, crystalline form The best result was achieved when a THF-solution of the crude N-hydroxylamine of **11** was filtered through a column of basic alumina, which had not been rinsed with solvent beforehand (caution very exothermic!). The fact that other bases like Na_2CO_3 and Na_2HPO_4 gave poor yields of **12** indicates that basic alumina seems to combine both optimal basicity and water-absorption capacity for this reaction

While **11** could be acylated almost quantitatively, the acylation of enamine **12** under the same reaction conditions (methoxyacetyl chloride, toluene, DMF (cat.), reflux) yielded only 20-50 % of enamide **8** Although many other methods and conditions were tested (methoxyacetic acid anhydride, various acylation methods from peptide chemistry), the yields could not be further improved The competition between N- and C-acylation, a very common phenomenon in acylation and alkylation reactions of enamines [9], is probably the main reason for these unsatisfactory yields Indeed, a rather unstable side-product could be isolated and was identified as the product of double acylation of **12** Attempts to circumvent this problem by oxidizing after the acylation step failed None of the tested oxidation methods gave any of the desired product **8**

The enantioselective hydrogenation of enamides has been investigated extensively, mainly using acetamido cinnamic acid derivatives bearing a secondary nitrogen atom and chiral Rh-phosphine-catalysts The asymmetric hydrogenation of N-substituted enamides has been studied to a much lesser extent [10] To our knowledge N-aryl substituted enamides have never been hydrogenated enantioselectively before Therefore, we tested several Rh- and Ru-catalysts and carried out an extensive parameter screening The most interesting results are summarized in table 1 The optical yields (ee-values) were determined by HPLC on a commercially available ChiraSpher-column (Merck) As mentioned above, optically pure 4 is easily obtained from the chromatographed hydrogenation products by crystallization of the racemate

Table 1



8

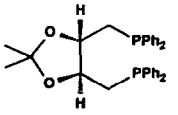
4
(> 99 % ee)

catalyst	% cat.	yield (before cryst.)	ee (before cryst.)	yield
[Rh(NBD)$_2$]BF$_4$/(4S 5S) DIOP	2	> 95 %	30-71 % *	n d
[Rh(NBD)$_2$]BF$_4$/(2S 4S) BDPP	2	> 95 %	75 %	n d
[Ru(OAc)$_2$(S)-BINAP]	2	> 95 %	67 %	n d
[Ru(OAc)$_2$(S)-BINAP]	0 025	> 95 %	66 %	63 %

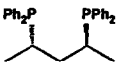
* ee value strongly pressure and temperature dependent

Of all the Rh-diphosphine-catalysts tested [Rh(NBD)$_2$]BF$_4$/(4S,5S)-DIOP [11] and [Rh(NBD)$_2$]BF$_4$/(2S,4S)-BDPP [12] (NBD [2,2,1]-bicycloheptа-1,3-diene) gave the highest optical yields Interestingly, 1,4-diphosphine ligands, which can form a six- or seven-membered metallacycle, lead generally to a higher enantiomeric excess than 1,2-diphosphines

Figure 5



(-)-(4S,5S)-DIOP



(-)-(2S,4S)-BDPP

The best result (75 % ee at 25°C, 35 bar H_2) was achieved with the Rh/(2S,4S)-BDPP catalyst No significant influence of either the temperature or the pressure was observed (range 25-50 °C and 35-98 bar H_2) With the Rh/(4S,5S)-DIOP catalyst maximum optical yields of 71 % were obtained at 20°C and 33 bar H_2 In contrast to the Rh/BDPP catalyst, the enantioselectivity of the Rh/DIOP catalyst proved to be strongly dependent on temperature and pressure (range 20-50°C and 33-100 bar H_2) Increasing temperatures led to poorer enantioselectivities, whereas increasing pressures favoured higher optical yields These findings indicate that both catalysts do not work according to the mechanism described by Halpern [13,14]

With both catalysts substrate/catalyst-ratios greater than 100 1 led to a strong catalyst deactivation and incomplete conversion, even when carefully purified starting material was used No efforts were made to elucidate the cause of this deactivation, however, two possibilities are traces of decomposed starting material or a strong coordination of the product to the catalyst.

Slightly lower optical yields (66 % ee at 50°C, 100 bar) were obtained with the Ru/BINAP catalyst The enantioselectivity was not influenced by temperature and pressure in the range 22-50 °C and 4-100 bar H_2 The fact that no indication of any deactivation, even at a substrate/catalyst-ratio of 4000 1, was found, made it the catalyst of choice for this synthesis, well suited for large-scale-production

We can conclude that the enantioselective key step fulfills our objectives, even though it would be desirable to increase the optical yield by catalyst optimization In order to guarantee technical feasibility of the whole process the synthesis of the enamide intermediate **8** needs further improvement

Experimental

All reagents were purchased from Fluka or Aldrich and were used without further purification $[Rh(nbd)_2]BF_4$ and $[Ru(OAc)_2(S\text{-BINAP})]$ were synthesized according to published procedures [15,16] The ligands (4S,5S)-DIOP, (2S,4S)-BDPP and (S)-BINAP were purchased from Strem Chem and Fluka, respectively Solvents were acquired from Fluka or Merck and stored over molecular sieves Methanol for the hydrogenation reactions was dried over sodium methoxide and stored under argon For flash chromatography silicagel 60 (0 040-0 063 mm, Merck) was used, thin layer chromatography was carried-out on silicagel plates 60 F-254 (Merck) HPLC was performed on commercially available chiral columns using HPLC-grade solvents Melting points are uncorrected NMR spectra were recorded on a Bruker AM-300 instrument, chemical shifts are reported in ppm relative to internal TMS-standard (= 0 ppm)

(3S)-Dihydro-3-hydroxy-2(3H)-furanone (**6**) Under argon, 7 5 ml (0 15 mol) of a 2 M solution of borane-dimethylsulfide in THF were slowly added to a solution of 39 5 g (0 15 mol) of **9** [5] in 200 ml THF at -20°C The reaction mixture was allowed to warm up to rt and was stirred overnight It was quenched with 50 ml H_2O and extracted with ether The organic phase was washed with 1 N $NaHCO_3$-solution and brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure Distillation (103-105°C/0 1 Torr) yielded 7 4 g (80 mmol, 55%) of **6** as a colourless oil R_f (hexane/ethyl acetate 1 1) 0 75 ^{1}H-NMR (300 MHz $CDCl_3$) 2 21-2 40 (m, 1H, H-C(4)), 2 57-2 70 (m, 1H, H-C(4)), 3 34 (very br s, 1H, OH), 4 25 (ddd, J=6Hz, 9Hz and 10Hz, 1H, H-C(5)), 4,40-4 59 (m, 2H, H-C(3) and H-C(5)) IR (film) 3380, 1775, 1640, 1485, 1455, 1425, 1380, 1290, 1270, 1222, 1185 MS m/z 103 (M^++1, 14%), 86 (20%), 75 (42%), 57 (100%)

(3R)-[(2,6-Dimethylphenyl)amino]-dihydro-2(3H)-furanone (**10**) Under argon, 4 1 ml (25 mmol) of triflic anhydride were dissolved in 25 ml CCl_4 and cooled to -20°C A solution of 2 50 g (25 mmol) of **6** and 2 0 ml (25 mmol) of pyridine in 5 ml CCl_4 was added dropwise, and the mixture slowly warmed to rt. Then 3 8 g (27 5 mmol) of K_2CO_3 were added to the white suspension Upon addition of a solution of 3 4 ml (27 5 mmol) 2,6-dimethylaniline in 5 ml CCl_4, at 0°C, the colour turned red After stirring overnight at rt, the reaction mixture was taken up in ether and washed with 1 N HCl and brine The organic phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure Chromatography on silicagel (hexane/ethyl acetate 3 1) yielded 2 50 g (12 mmol, 49%, 94 7% ee) of **10** as a brownish oil R_f (hexane/ethyl acetate 2 1) 0 22 HPLC hexane/i-propyl alcohol 90 10, flow=1 5 ml/min, Chiracel-OC (Daicel) 15 7 min (main

enantiomer), 19 7 min (minor enantiomer) ^{1}H-NMR (300 MHz, $CDCl_3$)· 2 13-2 36 (m, 1H, H-C(4)); 2 35 (s, 6H, CH_3), 2 55-2 68 (m, 1H, H-C(4)), 3 53 (very br s, 1H, NH); 3 96 (dd, J=8 5Hz and J=10 5Hz, 1H, H-C(5)), 4 18 (ddd, J=5 5Hz, 10Hz and 10 5Hz, 1H, H-C(5)), 4 37-4 45 (m, 1H, H-C(3)), 6 89 (t, J=7Hz, 1H, H-C(4')), 7 03 (d, J=7Hz, 2H, H-C(3') and H-C(5')) IR (film) 3385, 1775, 1595, 1478, 1378, 1265, 1220, 1170, 1140, 1020. MS m/z. 205 (M^+, 54%), 177 (2%), 161 (5%), 146 (20%), 144 (24%), 132 (100%), 117 (26%)

(3R)-N-(2,6-Dimethylphenyl)-2-methoxy-N-(tetrahydro-2-oxo-3-furanyl)-acetamide (**4**)

Route A· A mixture of 2 00 g (9 76 mmol) of **10**, 1 5 ml (16 4 mmol) of methoxyacetyl chloride and 3 drops DMF in 30 ml toluene was stirred for 2 h at 100°C The solution was concentrated and chromatographed on silicagel (ether/chloroform 1 1) to afford 2 60 g (9 38 mmol, 96%, 88 6% ee) of **4** as a yellow oil R_f (diethyl ether/dichloromethane 1.1) 0 35 HPLC hexane/i-propyl alcohol 95 5, flow=1ml/min, ChiraSpher (Merck) 46 8 min (minor enantiomer), 51 5 min (main enantiomer) ^{1}H-NMR (300 MHz, $CDCl_3$) 2 27 (s, 3H, CH_3), 2 46-2 64 (m, 1H, H-C(4)), 2 53 (s, 3H, CH_3), 2 86-3 02 (m, 1H, H-C(4)), 3 37 (s, 3H, OCH_3); 3 57/3 66 (2d of AB-system, J=16Hz, 2H, CH_2OCH_3), 3 88 (t, J=10 Hz, 1H, H-C(3)), 4 21-4 31 (m, 1H, H-C(5)), 4 65 (dt, J=3 Hz, and 8Hz, 1H, H-C(5)), 7 10-7 29 (m, 3H, aromatic Hs) IR (film) 1780, 1678, 1471, 1450, 1412, 1385, 1314, 1288, 1225, 1170 MS m/z 277 (M^+, 20%), 247 (8%), 232 (30%), 204 (22%), 146 (20%), 144 (20%), 132 (24%), 45 (100%)

Route B (with Ru/S-BINAP-catalyst) Under argon, a solution of 4 55 g (16 mmol) of **8** in 30 ml of methanol and a solution of 3 5 mg (0 004 mmol) of [Ru(OAc)$_2$S-BINAP] in 10 ml of methanol were successively transferred via a steel capillary into a 50-ml-autoclave The inert gas in the autoclave was replaced by hydrogen in three cycles (20 bar/normal pressure) Finally, the autoclave was pressurized to 95 bar with hydrogen After completion of the reaction (43 hours at 50°C), capillary-GC-analysis showed full conversion of **8** The reaction mixture was concentrated under reduced pressure The oily residue (4 88 g) was chromatographed on silicagel (hexane/ethyl acetate 1 1) to afford 4 7 g (quantitative, 66 % ee) of **4** as a slightly yellow oil This material was dissolved in 20 ml of a refluxing 1 1-mixture of hexane/ethyl methyl ketone After allowing to cool to rt, the resulting suspension was stirred overnight at 0°C. Filtration of the white suspension afforded 1 5 g (5 4 mmol, 33 8 %) of racemic **4** as white crystals melting at 128-131°C From the filtrate 2 9 g (10 5 mmol, 65 4 %, 99 4 % ee) of **4** as a slightly yellow oil were isolated, which could be crystallized from 6 ml of a 1 1-mixture of hexane/toluene (mp 91-93°C, $[\alpha]_D$=86 7° (1 18 % in chloroform)) Analytical data as above

Route B (with Rh/(2S,4S)-BDPP-catalyst) Under argon, a solution of 15 mg (0 04 mmol) of [Rh(nbd)$_2$]BF$_4$ in 15 ml methanol was treated with 19 4 mg (0 44 mmol) of (2S,4S)-BDPP and stirred for 30 min A separate solution of the enamide **8** (0 55 g, 2 mmol) in 5 ml methanol was prepared The enamide- and the catalyst-solution were successively transferred via a steel capillary into a 50-ml-autoclave under an inert atmosphere The inert gas in the autoclave was then replaced by hydrogen in three cycles (20 bar/normal pressure) Finally, the autoclave was pressurized to 35 bar with hydrogen After completion of the reaction (21 hours at rt), capillary-GC-analysis showed full conversion of **8** The reaction mixture was concentrated under reduced pressure Chromatography of the oily residue (605 mg) on silicagel (hexane/ethyl acetate 1 1) afforded 550 mg (1 92 mmol, quantitative, 75 % ee) of **4** as a slightly yellow oil After crystallization of racemic material from 4 ml of a 1 1-mixture of hexane/ethyl methyl ketone and filtration, 406 mg (1 46 mmol, 73 2 %, 96 9 % ee) of **4** were isolated from the mother liquor Analytical data as above

3-[(2,6-Dimethylphenyl)amino]-2(5H)-furanone (**12**) At 0°C, 2 03 g (10 0 mmol) of m-chlorperoxybenzoic acid (85 %) were added to a solution of 2 05 g (10 mmol) of **11** in 30 ml THF The reaction mixture was stirred at 0°C for 1 h and then filtered through a column filled with 70 g of basic alumina (ICN act I, not rinsed with eluent beforehand) using THF as eluent (caution very exothermic, collecting vessel was ice-cooled) The first 150 ml of filtrate contained 1 28 g (6 3 mmol, 63 %) of **12** as white crystals melting at 85-86° after recrystallization from hexane R_f (diethyl ether/dichloromethane/hexane 1 1 1) 0 68 ^{1}H-NMR (300 MHz, $CDCl_3$) 2 24 (s, 6H, CH_3), 4 78 (d, J=2 5Hz, 2H, H_2-C(5)), 5 35 (t, J=2 5H, 1H, H-C(4)), 5 49 (br s, 1H, exchanges with D_2O, H-N), 7 10 (s, 3H, aromatic Hs) IR (CH_2Cl_2) 3385, 1755, 1663, 1475, 1355, 1212, 1115, 1044 MS m/z 203 (M^+, 100%), 159 (32%), 158 (82%), 157 (24%), 145 (25%), 144 (51%), 143 (33%), 132 (45%), 131 (24%), 105 (38%), 79 (26%), 77 (32%) Anal calc for $C_{12}H_{13}NO_2$ (203 24) C 70 92, H 6 45, N 6 9, O 15 75, found C 71 0, H 6 5, N 7 0, O 16 1

N-(2,5-Dihydro-2-oxo-3-furanyl)-N-(2,6-dimethylphenyl)-2-methoxy-acetamide (**8**) A solution of 10 2 g (50 2 mmol) of **12** and 40 ml (0 439 mol) of methoxyacetyl chloride in 40 ml toluene was refluxed under reduced pressure (100-150 Torr) for 48 hours The reaction mixture was concentrated under reduced pressure, and the residue chromatographed on silicagel initially using a 2 1-mixture and then a 1 2-mixture of hexane/ethyl acetate as eluent The crude product, 3 8 g of a red oil, was crystallized twice from 90 ml of a

2 1-mixture of hexane/ethyl acetate to afford 3 2 g (11 6 mmol, 23 2 %) of **8** as white crystals melting at 106-107°C. R_f (diethyl ether/dichloromethane 1 1) 0 42 ^{1}H-NMR (300 MHz, $CDCl_3$). 2.24 (s, 6H, CH_3); 3 38 (s, 3H, OCH_3), 3 5-3 9 (very br s, 2H, CH_2OCH_3), 4 89 (d, J=2 5Hz, 2H, H_2-C(5)), 7 08-7.31 (m, 3H, aromatic Hs), 7.63-7 9 (very br s, 1H, H-C(4)) IR (CH_2Cl_2) 1772, 1702, 1330, 1232, 1200, 1180, 1130, 1103, 1088, 1054 MS m/z: 275 (M^+, 28%), 230 (25%), 158 (45%), 45 (100%) Anal. calc for $C_{15}H_{17}NO_4$ (275 31). C 65 44, H 6 23, N 5 09, O 23.25, found C 65 4, H 6 0, N 5 3, O 23 3

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