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Synthesis of an 11-Unsubstituted Analogue of (±)-Huperzine A

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Abstract

The synthesis of a new analogue of (±)-huperzine A lacking the ethylidene appendage at position 11 has been accomplished. The key steps of the synthesis were: a) the reduction of the keto function of the known methyl 7,7-ethylenedioxy-3-methyl-9-oxobicyclo[3.3.1]non-3-ene-1-carboxylate into a methylene group by reduction to a mixture of stereoisomeric alcohols followed by alcohol-deoxygenation through a Barton-McCombie procedure and b) the elaboration of the pyridone ring in a late stage of the synthesis by reaction of a pyrrolidine enamine with propiolamide, which gave a mixture of regioisomeric pyridone derivatives.

keywords: Biologically active compounds; Polycyclic heterocyclic compounds; Pyridones; X-Ray crystal structures.

Alzheimer's disease (AD) is the most common cause of dementia in the aged [1]. Most neurotransmitter systems have been implicated in the etiology of AD, the cholinergic neurotransmission being specially affected [2-6]. Accordingly, enhancement of the central cholinergic function, for example by means of reversible acetylcholinesterase (AChE) inhibitors [7,8], is one of the most promising methods for the symptomatic treatment of AD.

Huperzine A (**1**) a lycopodium alkaloid, isolated from the club moss *Huperzia serrata* (Thunb.) Trev. = *Lycopodium serratum* Thunb., a Chinese traditional medicine [9-11], is a potent and selective reversible inhibitor of AChE which appears to be superior to other AChE inhibitors such as tacrine, physostigmine or galanthamine, because of its comparatively longer duration of action and higher therapeutic index [12]. Huperzine A has been considered an important lead compound in the search for better cholinomimetics for the treatment of AD. The low natural abundance of huperzine A induced several groups to develop synthetic routes to this compound [13-19] and to prepare huperzine A analogues with the aim of studying the effects of structural modifications on the biological activity (structure-activity relationships).

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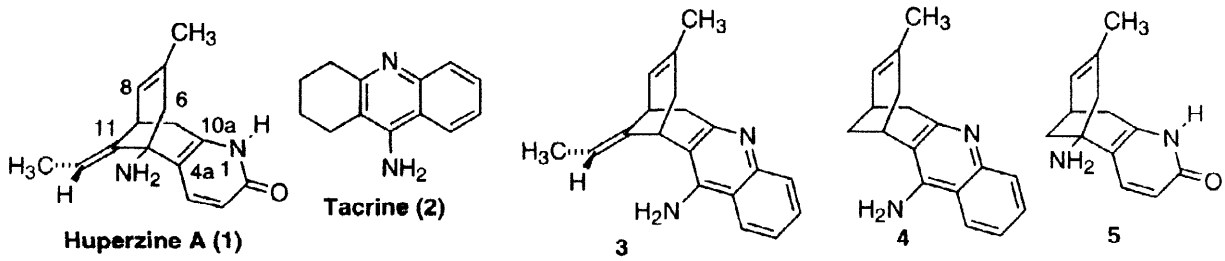


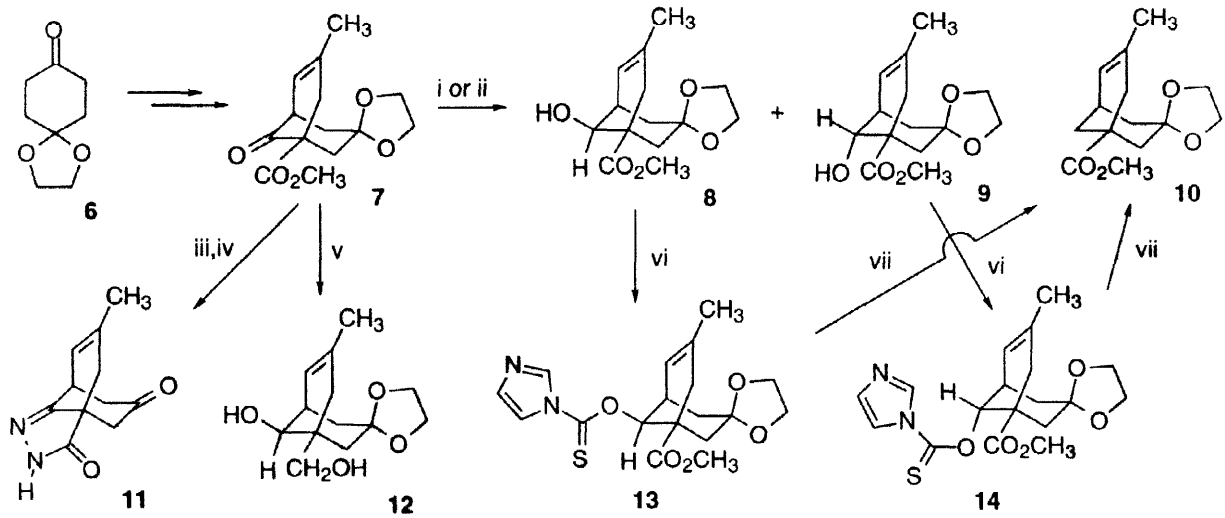
Figure 1. Huperzine A (**1**), tacrine (**2**), and related compounds.

In this sense, numerous huperzine A analogues have been prepared by different modifications of the parent structure. Structural modifications investigated to date include those carried out *at the pyridone ring* (replacement by an unsubstituted benzene ring [20], a monohydroxy and a dihydroxy-substituted benzene ring [21] or different heterocyclic rings [22,23], opening of the pyridone ring and replacement of the amide function with an isosteric carbamate group [24], alkylation of the nitrogen atom [25]), *at the amino group* (alkylation [16], replacement by an aminomethyl group [16]), *at the ethylidene group* (isomerization [26], replacement by a methylene [16], propylidene [16] or by other alkylidene or alkyl groups [17, 27-29]), *at the C-12 methyl group* (replacement by a hydrogen atom [30] or by a phenyl [16], halomethyl [28,29], hydroxymethyl [28] or alkoxycarbonyl [28] group), *at the unsaturated three-carbon bridge* (saturation [31] or isomerization of the endocyclic double bond to an exocyclic position [32], cyclopropanation [33], hydration [25]); *at the C-10 position* (introduction of *axial* and / or *equatorial* alkyl groups [34-36]) as well as those carried out by *extensive simplification of the carbobicyclic moiety* [30,31,37]. It is worth noting that most of these analogues were found not to exhibit useful AChE inhibitory activity. To the best of our knowledge, the sole analogues which can rival the activity of the parent compound are the C-10 *axial* methylated, the 10,10-dimethylated, and the 10-spirocyclopropyl derivatives.

Recently, we published the synthesis and evaluation of a series of compounds, designed by combining the pharmacophores of huperzine A (**1**) (carbobicyclic substructure) and tacrine (THA) (**2**) (4-aminoquinoline substructure) [38]. Among these THA-huperzine A hybrids, compound **3**, the sole compound of the series which incorporated the ethylidene group of huperzine A, turned out to be 2.5-fold less potent than THA as an AChE inhibitor, while compound **4**, lacking the ethylidene substituent, was 2-fold more potent than THA. From the chemical and biological data reported to date it would appear that the ethylidene group is one of the essential features for high AChE inhibitory activity in huperzine A analogues (see above). However, the biological data obtained from our THA-huperzine A hybrids seem to indicate that, in this kind of compound, the presence of this ethylidene group is not necessary for a better AChE inhibitory activity. In order to ascertain the relevance of the ethylidene substituent at position 11 to the biological activity of huperzine A analogues, we embarked upon the synthesis and evaluation of a new analogue of (±)-huperzine A lacking this substituent (**5**).

Results and Discussion

We describe herein the synthesis of the new (±)-huperzine A analogue **5** from the known keto ester **7**, which was prepared in 34% overall yield from commercially available



i) Ni_2B, $NaBH_4$, MeOH, r.t., 30 min, 24% yield of **8** and 26% yield of **9**; ii) $LiBHEt_3$, THF, r.t., 30 min, 58% yield of **8** and 29% yield of **9** based on recovered **7**; iii) 80% aq. $NH_2NH_2{\cdot}H_2O$, KOH, diethylene glycol, 140 °C, 17 h; iv) Conc. HCl, r.t., 5 min, 40% overall yield of **11** from **7**; v) $NaBH_4$, MeOH, r.t., 24 h, 31% yield; vi) 1,1'-Thiocarbonyldiimidazole, 1,2-dichloroethane, reflux, 3 h, 71% yield of **13**; vii) Bu_3SnH, AIBN, toluene, reflux, 1.5 h, 42% yield of **10** from **13** and 60% overall yield of **10** from **9** *via* **14**.

Scheme 1. Reduction of keto ester **7** to **10**.

1,4-cyclohexanedione monoethylene ketal **6**, following an improved procedure developed by our group [39]. The main features of the synthetic plan are: 1) the deoxygenation of the keto function of **7** to give **10**, 2) the conversion of the ester function of **10** into a protected amino group, 3) the elaboration of the pyridone ring, and 4) the deprotection of the amino function.

The reduction of keto ester **7** to **10** proved to be a rather difficult task (Scheme 1). For this transformation, only alkaline or neutral conditions could be used, due to the presence of acid-sensitive functionalities, *i.e.* C=C double bond and ketal group. Treatment of **7** under standard Wolff-Kishner reduction conditions [40] did not afford the expected methylenic product, pyrazolinone **11** being formed instead in about 40% yield. The formation of **11** might be easily explained by intramolecular nucleophilic addition of the amino group of an initially formed hydrazone to the ester function, followed by ketal hydrolysis during the acid work-up. Thus, we decided to prepare ester **10** through a two-step sequence which involved initial reduction of the keto group to an alcohol followed by removal of the hydroxy group by a Barton-McCombie [41] deoxygenation reaction. Reduction of keto ester **7** with an excess of $NaBH_4$ in MeOH at room temperature gave diol **12** in 31% yield, as the sole isolated product. The same reaction carried out by using a limited amount of $NaBH_4$ gave a complex mixture of products. Attempted reduction of **7** with an equimolar amount of $NaBH_3CN$ left the starting compound unchanged. Finally, we were able to selectively reduce the keto group of keto ester **7** with nickel boride / $NaBH_4$ [42-44]. Reaction of keto ester **7** with $NiCl_2{\cdot}6H_2O$ and $NaBH_4$, in the molar ratio of 1:1.1:2.5, afforded a mixture of diastereomeric alcohols **8** and **9**, which was separated by column chromatography (24% and 26% yield, respectively). Moreover, reaction of **7** with lithium triethylborohydride (Super-Hydride®) [45] in THF at room temperature for 30 min afforded hydroxy esters **8** and **9** in better overall yield (50% and 25% yield, respectively; 58% and 29%, respectively, based on recovered starting material).

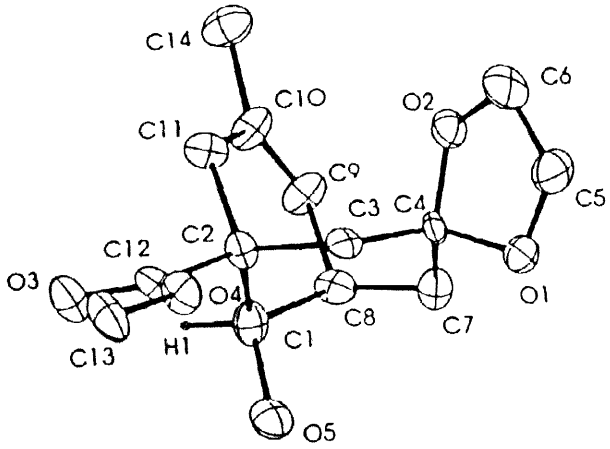
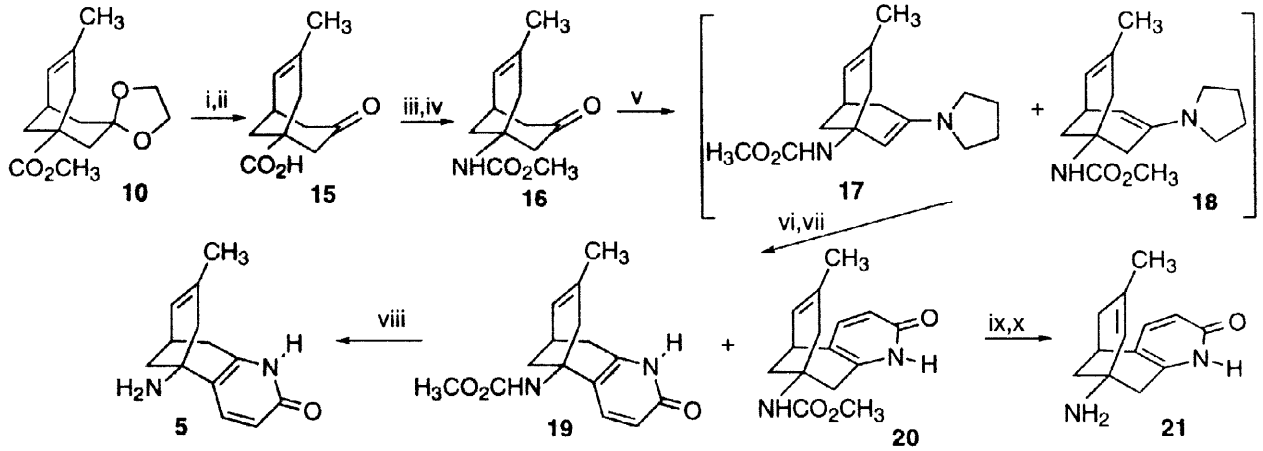


Figure 2. Crystal structure (ORTEP) of hydroxy ester **9**.

The configuration of hydroxy esters **8** and **9** was established through the analysis of their ^{13}C NMR spectra (Table 1). As can be seen from Table 1, the signals of the C6 and C8 carbon atoms of the *syn*-hydroxy ester **9**, in which the hydroxy group is *axial* with respect to the dioxolane-bearing cyclohexane, appear at 6.2 and 5.5 ppm, respectively, shifted upfield compared with the corresponding signals of the *anti*-derivative **8**, due to the γ-gauche effect of the hydroxy group. For the same reason, the signals of the C2 and C4 carbon atoms of hydroxy ester **8** appear at 5.7 and 4.0 ppm, respectively, shifted upfield as compared with the corresponding signals of hydroxy ester **9**. Comparison of the chemical shifts of C2, C4, C6 and C8 of diol **12** with the corresponding values of hydroxy esters **8** and **9**, show very small differences due to the change of the methoxycarbonyl for the hydroxymethyl group (0.1-0.3 ppm), when compared with hydroxy ester **8** and much larger differences (4.1-6.0 ppm) when compared with **9**, in accord with an *anti* arrangement of the secondary hydroxy group of diol **12**. X-ray diffraction analysis of hydroxy ester **9** (Figure 2) allowed us to clearly establish the *syn* arrangement of its hydroxyl group. In Table 3 further crystallographic data of this compound are compiled.

The removal of the hydroxy group of hydroxy esters **8** and **9** was carried out through a Barton-McCombie deoxygenation procedure [41] (Scheme 1). Hydroxy ester **8** was easily converted into the corresponding thiocarbonyl imidazolide **13** in 71% yield, on reaction with 1,1'-thiocarbonyldiimidazole in 1,2-dichloroethane under reflux. However, the conversion of **9** into the imidazolide **14** was not so efficient. Treatment of the more hindered hydroxy ester **9** with 1,1'-thiocarbonyldiimidazole under the same reaction conditions gave imidazolide **14** in only 12% yield, much of the starting compound being recovered unchanged (70%). When the above reaction was carried out in a pressure flask at a higher temperature (120 °C), unreacted **9** was recovered in 50% yield while imidazolide **14** was obtained in somewhat better yield (32%; 64% yield based on recovered **9**). Compound **14** was not stable enough to allow its complete characterization and was used as such in the next step.

The second step in the deoxygenation procedure implied the radical chain reduction of imidazolides **13** and **14** with Bu_3SnH [41]. In terms of initiator requirement, it has been reported that initiators are not usually necessary for substrates such as **13** and **14**, possessing thiocarbonyl imidazolide functionality in secondary alcohols [46]. In practice, reactions of imidazolides **13** and **14** with Bu_3SnH in refluxing toluene furnished ester **10** in only moderate to low yields (13% and



i) 20% aq. NaOH, THF / MeOH 1:1, reflux, 48 h; ii) 5 N HCl, r.t., 5 min, 54% overall yield of **15** from **10**; iii) $(C_6H_5O)_2P(O)N_3$, Et_3N, chlorobenzene, 90 °C, 3.5 h; iv) MeOH, reflux, 17 h, 99% overall yield of **16** from **15**; v) Pyrrolidine, 4 Å molecular sieves, benzene, reflux, 5 h; vi) Propiolamide, reflux, 15 h, 28% overall yield of **19** and 27% overall yield of **20** based on recovered **16**; vii) MPLC separation; viii) *n*-PrSLi, HMPA, 40 °C, 24 h, 81% yield based on recovered **19**; ix) $(CH_3)_3SiI$, $CHCl_3$, reflux, 8 h; x) MeOH, reflux, 14 h, 66% overall yield of **21** from **20**.

Scheme 2. Synthesis of the huperzine A analogues **5** and **21**.

45% yield, respectively). However, these deoxygenation reactions proceeded more efficiently on addition of AIBN (0.1 equiv.) as initiator of the radical chain reduction. In this way, imidazolides **13** and **14** were deoxygenated to ester **10** in 42% and 60% yield, respectively.

Next, we undertook the introduction of a precursor of the bridgehead amino group through a Curtius rearrangement. To this end, ketal ester **10** was first converted into keto acid **15**, by saponification of the hindered ester group with 20% aqueous NaOH in a mixture of THF and MeOH in the ratio of 1:1 under reflux for 48 h [47], followed by hydrolysis of the ketal function during the acid work-up (Scheme 2). Curtius rearrangement of keto acid **15** was carried out by reaction with diphenylphosphoryl azide [48] followed by methanolysis of the resulting isocyanate, keto carbamate **16** being obtained in almost quantitative yield.

Elaboration of the pyridone ring was carried out by using a modification of the procedure described by Kozikowski *et al.* [49]. Keto carbamate **16** was reacted with pyrrolidine in refluxing benzene in the presence of 4 Å molecular sieves and the product thus obtained was heated under reflux with propiolamide, previously prepared from ethyl propiolate and NH_4OH [50]. This reaction provided an approximately 1:1 mixture of the regioisomeric pyridones **19** and **20**, which were partially separated by flash column chromatography, a significant amount of starting **16** (40%) being recovered (55% total yield of pyridones **19** and **20**, based on recovered **16**) (Scheme 2). These pyridones were efficiently separated by medium pressure liquid chromatography (MPLC) through silica gel (40-60 μm) using mixtures of AcOEt / MeOH as eluent. Although the *anti*-enamine **17** must be formed preferentially, as was observed for a related case [24], a significant amount of the *syn*-pyridone **20** was obtained in this reaction. C-alkylation of *anti*-enamine **17** with propiolamide should be slower than C-alkylation of the *syn*-enamine **18** due to the steric effect of the substitutent at the bridgehead position. Isomerization of enamine **17** to **18** under the reaction conditions could explain the formation of the regioisomeric pyridone **20**.

Cleavage of the methyl carbamate of **19** was accomplished without problems by reaction with lithium 1-propanethiolate in hexamethylphosphoramide [48], obtaining the huperzine A analogue **5** in 63% yield (81% yield, based on recovered **19**). However, cleavage of the carbamate group of **20** under the same reaction conditions led to a complex mixture of products not containing the expected amine. Also, attempted hydrolysis of the carbamate group of **20** by reaction with potassium hydroxide in the presence of 18-crown-6 [51] failed. Finally, treatment of **20** with trimethylsilyl iodide (TMSI) followed by reaction with methanol under reflux [47] gave mainly **21**, a product in which not only the carbamate function had been hydrolyzed, but also the C=C double bond had isomerized to a neighbouring position. This isomerization can be easily explained under acid catalysis (some HI formed by hydrolysis of the TMSI) and reflects the greater stability of the *anti*-arrangement for the C=C double bond and the heterocyclic ring in this kind of bicyclo[3.3.1]nonadiene derivative. A similar situation was observed [24] in related cases.

Except for pyrazolone **11** and imidazolide **14**, the new compounds herein described have been fully characterized though their spectroscopic data and elemental analysis or high resolution mass spectrometry (**5** and **21**), and by X-ray diffraction analysis in the case of hydroxy ester **9**.

Assignment of the ^{1}H and ^{13}C NMR spectra was carried out in a standard way with the aid of DEPT, ^{1}H / ^{1}H and ^{1}H / ^{13}C COSY experiments.

The methodology herein described for the synthesis of compound **5** is currently being applied to the synthesis of other huperzine A analogues, whose biological activity will be reported in due course.

Experimental

General. Melting points were determined with a MFB 595010 M Gallenkamp melting point apparatus. 500 MHz ^{1}H NMR spectra were performed on a Varian VXR 500 spectrometer, 75.4 MHz ^{13}C NMR spectra on a Varian Gemini 300, and 200 MHz ^{1}H and 50.3 MHz ^{13}C NMR spectra on a Varian Gemini 200. Except where otherwise stated, ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra at 75.4 MHz, in $CDCl_3$. Chemical shifts (δ) are reported in ppm related to internal tetramethylsilane. Assignments given for the NMR spectra are based on DEPT, $^{1}H/^{1}H$ and $^{1}H/^{13}C$ COSY experiments (HMQC sequence). The ^{13}C and ^{1}H NMR data of compounds **8-10**, **12**, **13**, **15**, and **16** are collected in Tables 1 and 2, respectively, while those of compounds **5**, **11**, and **19-21** are described in the experimental. IR spectra were recorded on a FT/IR Perkin-Elmer spectrometer, model 1600. Routine MS spectra were taken on a Hewlett-Packard 5988A spectrometer, by direct introduction of the sample, using the electron impact technique (70 eV). Significant ions given are those showing the following relative abundances: 5% or more if $m/z > 150$ and 25% or more if $m/z \leq 150$. Silica gel SDS 60 (60-200 μm) was usually utilized for the column chromatography. Medium pressure liquid chromatography (MPLC) separations were carried out on a MPLC equipment which consisted of a pump (Büchi 688) a variable λ detector (Büchi) and a column (45 × 3.5 cm) containing silica gel (40-60 μm) as the stationary phase. Elemental analyses and high resolution mass spectra were carried out, respectively, at the Microanalysis Service and the Mass Spectrometry Laboratory of the *Centro de Investigación y Desarrollo* (C.I.D.), C.S.I.C., Barcelona, Spain.

Methyl 7,7-ethylenedioxy-*anti*-9-hydroxy-3-methylbicyclo[3.3.1]non-3-ene-1-carboxylate (8) and methyl 7,7-ethylenedioxy-*syn*-9-hydroxy-3-methylbicyclo[3.3.1]non-3-ene-1-carboxylate (9).

By reduction with Ni_2B / $NaBH_4$. To a stirred suspension of $NiCl_2 \cdot 6H_2O$ (977 mg, 4.11 mmol) in MeOH (80 mL), $NaBH_4$ (106.2 mg, 2.79 mmol) was added portionwise over a 5-minute-period. The resulting suspension was stirred thoroughly for 2 h and a solution of keto ester **7** (1.00 g, 3.76 mmol) and $NaBH_4$ (250 mg, 6.58 mmol) in MeOH (20 mL) was added dropwise over 5 min. The reation mixture was stirred for 30 min and filtered through Celite®, washing the solid with MeOH (50 mL). The combined filtrate and washings were treated with 25% aqueous NH_4OH (100 mL), diluted with water (100 mL), and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried with anhydrous Na_2SO_4 and concentrated *in vacuo* to give a colorless oily residue (670 mg), which was submitted to column chromatography through silica gel (67 g, hexane / AcOEt, gradient elution). On elution with hexane / AcOEt 1:1, alcohol **9** (190 mg), a mixture of alcohols **9** / **8** (240 mg) in a ratio 7:16 (^{1}H NMR), and alcohol **8** (70 mg) were successively separated (24% total yield of **8** and 26% total yield of **9**). The analytical samples of **8** and **9** were obtained by distillation at 130 °C / 1 Torr and 150 °C / 2 Torr, respectively.

Spectroscopic and analytical data of alcohol 8: colorless oil. IR (NaCl) ν 3493, 2952, 2916, 1732, 1434, 1356, 1254, 1231, 1151, 1140, 1094, 1054, 998, 979, 950, 826 cm^{-1}. MS, *m/z* (%): 269 (8), 268 ($M^{\cdot+}$, 33), 251 (7), 250 ($M^{\cdot+}$ - H_2O, 29), 237 (5), 236 ($M^{\cdot+}$ - CH_3OH, 26), 218 (6), 210 (5), 209 (M^+ - COOMe, 26), 208 (8), 207 (5), 206 (7), 192 (12), 191 (M^+ - COOMe - H_2O, 70), 188 (8), 179 (6), 178 (5), 175 (18), 174 (45), 167 (23), 166 ($M^{\cdot+}$ - $C_5H_{10}O_2$, 76), 165 (22), 164 (19), 163 (10), 157 (9), 154 (13), 153 (10), 152 (14), 151 (9), 147 (M^+ - COOMe - H_2O - C_2H_4O, 49), 135 (40), 134 (66), 119 (53), 107 (34), 105 (74), 95 (37), 93 (37), 91 (82), 87 (96), 86 (94), 81 (32), 80 (48), 79 (79), 77 (81), 67 (46), 65 (43), 59 (100), 55 (89), 53 (59), 51 (25). Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.52. Found: C, 62.74; H, 7.72.

Spectroscopic and analytical data of alcohol 9: white crystals, m.p. 79-81 °C. IR (KBr) ν 3462, 3044, 2960, 2919, 2890, 1696, 1445, 1427, 1297, 1273, 1240, 1188, 1143, 1113, 1094, 1070, 1005, 987, 956, 938, 832, 802 cm^{-1}. MS, *m/z* (%): 268 ($M^{\cdot+}$, 15), 250 ($M^{\cdot+}$ - H_2O, 10), 209 (M^+ - COOMe, 25), 192 (6), 191 (M^+ - COOMe - H_2O, 32), 188 (10), 175 (9), 174 (15), 166 (5), 165 (M^+ - COOMe - C_2H_4O, 14), 164 (13), 163 (6), 157 (11), 154 (11), 153 (5), 152 (17), 151 (9), 147 (M^+ - COOMe - H_2O - C_2H_4O, 36), 121 (27), 119 (49), 107 (25), 105 (46), 95 (29), 93 (33), 91 (71), 87 (78), 86 (74), 81 (31), 80 (56), 79 (75), 77 (71), 73 (25), 67 (48), 65 (41), 59 (67), 57 (32), 55 (100), 53 (62), 51 (25). Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.52. Found: C, 62.61; H, 7.62.

By reduction with lithium triethylborohydride. A solution of keto ester **7** (3.50 g, 13.2 mmol) in anhydrous THF (220 mL) was treated dropwise with lithium triethylborohydride (1 M solution in THF, 19.8 mL, 19.8 mmol) over 5 min. The reaction mixture was stirred at room temperature for 30 min, treated with saturated aqueous NH_4Cl (250 mL), diluted with water (350 mL), and extracted with CH_2Cl_2 (5 × 150 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated *in vacuo* to give a yellowish oil (4.80 g), which was

Table 1
^{13}C NMR Chemical Shifts[a] of Compounds **8-10, 12, 13, 15**, and **16**.

	8	**9**	**10**	**12**[b,c]	**13**[d]	**15**	**16**
C1	46.9	47.0	42.4	38.5	45.9	44.6	54.1
C2	34.4	40.1	38.7	34.1	35.5	39.3	44.0
C3	134.7	132.9	133.5	136.8	134.1	131.9	131.9
C4	118.5	122.5	123.5	118.4	118.4	124.0	124.4
C5	36.5	35.3	29.6	38.0	32.9	31.0	31.0
C6	38.7	32.5	38.6	38.4	38.1	45.6	45.2
C7	107.5	108.2	108.7	108.2	106.8	209.6	209.2
C8	42.9	37.4	43.4	42.6	43.9	50.0	52.9
C9	70.8	68.9	33.0	73.8	81.7	32.4	35.0
3-CH_3	22.8	22.4	22.9	23.0	22.7	22.9	22.6
OCH_3	52.1	52.1	52.0		52.5		51.7
OCH_2CH_2O	62.8, 64.8	62.9, 64.8	62.8, 64.9	62.8, 64.8	63.1, 65.0		
COO	176.5	177.6	177.8		174.2	182.0	155.1

[a] All these spectra were taken at 75.4 MHz in $CDCl_3$.
[b] **12** has been named as a methanol derivative to keep the same numbering as the rest of compounds of this Table.
[c] Another signal: CH_2OH 70.8.
[d] Other signals: C=S 182.8, C2' 136.4, C4' 130.6, and C5' 117.8.

Table 2
^1H NMR Chemical Shifts[a,b] and Coupling Constants of Compounds **8-10, 12, 13, 15**, and **16**.

	8	**9**	**10**	**12**[c,d]	**13**[e]	**15**[f]	**16**[g]
2-H*exo*	2.09	2.24*	2.34	2.33	2.65	2.59	2.20*
2-H*endo*	2.52	2.29*	2.05	1.75	2.32	2.02	2.28*
4-H	5.27	5.35	5.44	5.25	5.24	5.43	5.38
5-H	2.54	2.46	2.50	2.48	2.98	2.77	2.74
6-H*exo*	1.91	2.16	1.67-1.77	1.84	2.05	2.42	2.43
6-H*endo*	1.81	1.54	1.67-1.77	1.80	1.87	2.33	2.27
8-H*exo*	1.92	2.19	1.84	1.52	2.13	2.69	3.00
8-H*endo*	1.92	1.81	1.97	1.48	2.01	2.46	2.53
9-H*syn*	4.15		1.67-1.77	3.78	5.99	2.19	2.44-2.50
9-H*anti*		4.15	1.85			2.13	2.02
3-CH_3	1.70	1.61	1.63	1.72	1.74	1.62	1.59
OCH_3	3.71	3.70	3.66		3.65		3.62
OCH_2CH_2O	3.73-3.97	3.73-3.98	3.70-3.97	3.69-3.95	3.72-3.98		
9-OH	2.60	3.10		1.90-2.30			
J (Hz)							
2-H*exo*/2-H*endo*	18.5	17.5	18.0	18.5	18.5	17.5	17.0
2-H*exo*/8-H*exo*			1.5		1.0	1.5	
2-H*endo*/9-H*syn*					1.0		
4-H/5-H	6.0	6.5	6.5	6.0	5.5	4.5	4.5
5-H/6-H*exo*	4.5	5.0		4.5	4.5	4.0	4.5
5-H/6-H*endo*	2.0	2.5			3.0	3.0	2.5
5-H/9-H*syn*	3.0				3.5		
5-H/9-H*anti*			3.5			4.0	4.0
6-H*exo*/6-H*endo*	14.0	14.0		14.0	14.0	14.5	14.5
6-H*endo*/8-H*endo*	2.0	2.5	2.0	2.0	3.0	2.0	2.0
6-H*endo*/9-H*anti*			1.5			2.0	2.0
8-H*exo*/8-H*endo*		14.0	13.5	14.0	14.0	15.5	15.5
8-H*endo*/9-H*anti*		1.0	2.0			2.0	2.0
9-H*syn*/9-H*anti*			12.5			13.0	12.5
9-H/9-OH	6.5	2.0		3.0			

[a] All these spectra were taken at 500 MHz in $CDCl_3$.
[b] The values indicated with * within a column can be interchanged.
[c] Other signals: CH_2OH 3.38 and 3.49, CH_2OH 2.50-3.10.
[d] Another coupling constant: CH_2OH J_{gem} = 11.0 Hz.
[e] Other signals: 2'-H 8.13, 4'-H 6.97, 5'-H 7.46.
[f] Another signal: COOH 9.0-12.0.
[g] Another signal: NH 4.75.

taken up in CH_2Cl_2 (250 mL) and washed with water (125 mL). The organic layer was dried with anhydrous Na_2SO_4 and evaporated at reduced pressure, to give a yellowish oily residue (3.48 g), which was submitted to column chromatography through silica gel (175 g, hexane / AcOEt, gradient elution). On elution with hexane / AcOEt 80:20, starting keto ester **7** (460 mg) was recovered. On elution with hexane / AcOEt 70:30, alcohol **9** (460 mg), a mixture of alcohols **9** / **8** (1.03 g) in a ratio 2:3 (^1H NMR), and alcohol **8** (1.14 g) were successively separated (50% total yield of **8** and 25% total yield of **9**; 58% and 29%, respectively, based on recovered keto ester **7**).

3a,4,6,7-Tetrahydro-9-methyl-3a,7-[1]propeno-2*H*-indazole-3,5-dione (11). A mixture of keto ester **7** (400 mg, 1.50 mmol), KOH pellets (5.19 g, 92.6 mmol), 80% aqueous hydrazine monohydrate (5.30 mL, 85.0 mmol) and diethylene glycol (20 mL) was heated at 120 °C for 2 h, diluted with diethylene glycol (10 mL) and heated at 140 °C for 15 h. The mixture was allowed to cool to room temperature, poured into a water-crushed ice mixture (75 g), made acidic to pH 1 with conc. HCl (4 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried with anhydrous Na_2SO_4 and concentrated *in vacuo* to give a white solid residue (270 mg), which was taken up in dioxane (4 mL) and treated with 2 N HCl for 3.5 h. The organic solvent was evaporated at reduced pressure and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 × 4 mL), dried with anhydrous Na_2SO_4 and concentrated *in vacuo*, affording essentially pure **11** (124 mg, 40% yield) as a white solid. ^1H NMR (200 MHz, DMSO-d_6) δ 1.62 (s, 3 H, 9-CH_3), 2.40-2.50 (complex signal, 4 H) and 2.75 (d, J = 15.5 Hz, 2 H) (methylenic protons), 3.37 (s, NH), 3.39 (br. s, 1 H, 7-H), 5.59 (br. d, J = 5.5 Hz, 1 H, 8-H). ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 22.0 (CH_3, 9-CH_3), 33.9 (CH, C7), 40.7 (CH_2, C10), 46.8 (CH_2, C6), 48.1 (CH_2, C4), 125.1 (CH, C8), 133.2 (C, C9), 164.4 (C, C7a), 179.3 (C, C3), 206.1 (C, C5). The signal corresponding to C3a was not observed.

(7,7-Ethylenedioxy-*anti*-9-hydroxy-3-methylbicyclo[3.3.1]non-3-en-1-yl)methanol (12). A mixture of keto ester **7** (400 mg, 1.50 mmol) and $NaBH_4$ (125 mg, 3.29 mmol) in MeOH (8 mL) was stirred at room temperature for 24 h and quenched with saturated aqueous NH_4Cl (40 mL). The organic solvent was evaporated at reduced pressure and the remaining aqueous phase was diluted with water (80 mL), made alkaline with 25% aqueous NH_4OH (30 mL), and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated *in vacuo* to give a yellow oil (360 mg), which was submitted to column chromatography through silica gel (26 g, hexane / AcOEt, gradient elution). On elution with hexane / AcOEt 40:60, diol **12** (110 mg, 31% yield) was isolated. The analytical sample of **12** was obtained by sublimation at 90 °C / 1 Torr: white crystals, m.p. 102.5-105.5 °C. IR (KBr) ν 3352, 2986, 2939, 2872, 2662, 1465, 1428, 1408, 1375, 1351, 1311, 1289, 1256, 1213, 1149, 1094, 1058, 1031, 998, 974, 947, 895, 878, 823, 786, 739, 666 cm^{-1}. MS, *m/z* (%): 240 ($M^{\cdot+}$, 9), 209 (M^+ - CH_2OH, 14), 191 (M^+ - CH_2OH - H_2O, 12), 178 (8), 161 (10), 160 (48), 153 (7), 152 (12), 149 (6), 148 (6), 147 (25), 121 (36), 120 (55), 119 (37), 109 (35), 107 (29), 105 (46), 95 (31), 93 (42), 91 (82), 87 (93), 86 (42), 81 (36), 80 (52), 79 (69), 77 (70), 73 (25), 69 (30), 67 (49), 65 (42), 59 (67), 57 (44), 55 (100), 53 (69), 51 (28). Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.97; H, 8.39. Found: C, 64.89; H, 8.56.

Methyl 7,7-ethylenedioxy-*anti*-9-[(1-imidazolyl)thiocarbonyloxy]-3-methylbicyclo[3.3.1]non-3-ene-1-carboxylate (13). A solution of alcohol **8** (5.43 g, 20.3 mmol) and 1,1'-thiocarbonyldiimidazole (5.97 g, 33.5 mmol) in 1,2-dichloroethane (90 mL) was heated under reflux for 3 h. The cold mixture was partitioned between CH_2Cl_2 (200 mL) and water (200 mL). The organic layer was dried with anhydrous Na_2SO_4 and evaporated at reduced pressure, to give a brown oil (11.6 g), which was submitted to column chromatography through silica gel (40-60 μm, 325 g, hexane / AcOEt, gradient elution). On elution with hexane / AcOEt 40:60, compound **13** (5.42 g, 71% yield) was isolated. The analytical sample of **13** was obtained by recrystallization from acetonitrile: pale yellow crystals, m.p. 135-136 °C. IR (KBr) ν 3446, 3171, 3122, 2958, 2937, 2883, 1733, 1683, 1654, 1642, 1531, 1515, 1465, 1439, 1388, 1376, 1356, 1324, 1280, 1263, 1245, 1226, 1160, 1141, 1092, 1055, 1025, 1007, 995, 984, 949, 940, 919, 890, 843, 831, 821, 807, 758, 712, 655 cm^{-1}. MS, *m/z* (%): 379 (7), 378 ($M^{\cdot+}$, 30), 345 (13), 311 (M^+ - $C_3H_3N_2$, 19), 251 (M^+ - $C_4H_3N_2OS$, 19), 250 (14), 219 (M^+ - $C_4H_4N_2OS$ - CH_3O, 14), 207 (13), 192 (6), 191 (M^+ - $C_4H_4N_2OS$ - COOMe, 42), 190 (5), 189 (5), 176 (7), 175 (40), 174 (7), 165 (15), 164 (21), 163 (8), 151 (6), 147 (M^+ - $C_4H_4N_2OS$ - COOMe - C_2H_4O, 67), 119 (44), 105 (100), 91 (74), 87 (70), 86 (44), 79 (29), 77 (31), 59 (44). Anal. Calcd. for $C_{18}H_{22}N_2O_5S$: C, 57.13; H, 5.86; N, 7.40; S, 8.47. Found: C, 57.17; H, 5.94; N, 7.55; S, 8.35.

Methyl 7,7-ethylenedioxy-3-methylbicyclo[3.3.1]non-3-ene-1-carboxylate (10).

From compound 13. A solution of Bu_3SnH (1.50 mL, 1.62 g, 5.57 mmol) in anhydrous toluene (100 mL) was treated dropwise over 30 min with a solution of compound **13** (1.00 g, 2.65 mmol) and AIBN (45.2 mg, 0.27 mmol) in anhydrous toluene (100 mL). The reaction mixture was heated under reflux for 1.5 h, cooled to room temperature and concentrated *in vacuo*, to give a yellow oily residue (2.76 g) which was taken up in acetonitrile (250 mL) and washed with hexane (2 × 100 mL). The acetonitrile solution was evaporated at reduced pressure, affording a colorless oil (0.92 g), which was submitted to column chromatography through silica gel (100 g, hexane / AcOEt, gradient elution). On elution with hexane / AcOEt 85:15, slightly impure **10** (320 mg) was isolated. This product was taken up in acetonitrile (100 mL) and washed with hexane (50 mL). Evaporation of the acetonitrile solution at reduced pressure afforded pure **10** (290 mg, 42% yield) as a colorless oil. The analytical sample of **10** was obtained as a colorless oil, by distillation at 80 °C / 0.5 Torr. IR (NaCl) ν 2950, 2919, 1732, 1456, 1432, 1372, 1353, 1290, 1254, 1228, 1162, 1145, 1097, 1056, 1006, 985, 950, 869, 828 cm^{-1}. MS, *m/z* (%): 252 ($M^{\cdot+}$, 21), 237 (5), 221 (5), 220 ($M^{\cdot+}$ - CH_3OH, 26), 194 (6), 193 (M^+ - COOMe, 38), 192 (6), 191 (6), 177 (12), 176 (5), 175 (6), 170 (14), 165 (11), 164 (8), 152 (5), 151 (M^+ - $C_5H_9O_2$, 29), 119 (36), 107 (54), 105 (45), 91 (91), 87 (36), 86 (30), 85 (58), 83 (89), 79 (46), 77 (40), 65 (27), 59 (100), 58 (29), 57 (43), 55 (48). Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 8.00. Found: C, 66.61; H, 8.27.

From alcohol 9. Compound **14** was prepared in a similar manner to that described for compound **13**, starting from a solution of alcohol **9** (2.00 g, 7.46 mmol) and 1,1'-thiocarbonyldiimidazole (2.19 g, 12.3 mmol) in 1,2-dichloroethane (30 mL) but the reaction was carried out by heating at 120 °C in a pressure flask for 3 h. The resulting brown oily residue (4.93 g) was submitted to column chromatography through silica gel (40-60 μm, 120 g, hexane /

AcOEt, gradient elution). On elution with hexane / AcOEt 50:50, starting alcohol **9** (1.00 g) was recovered. On elution with hexane / AcOEt 40:60, compound **14** (900 mg, 32% yield; 64% yield based on recovered **9**) was isolated as a slightly impure material which could not be fully characterized owing to its instability and was used as such in the next step. Compound **10** was prepared from **14** as described from **13**. From a solution of Bu_3SnH (0.30 mL, 324 mg, 1.11 mmol) in anhydrous toluene (20 mL) and a solution of compound **14** (200 mg, 0.53 mmol) and AIBN (9.0 mg, 0.055 mmol) in anhydrous toluene (20 mL), a colorless oil (200 mg) was obtained. This was submitted to column chromatography through silica gel (20 g, hexane / AcOEt, gradient elution). On elution with hexane / AcOEt 90:10, slightly impure **10** (110 mg) was isolated. This product was taken up in acetonitrile (50 mL) and washed with hexane (25 mL). Evaporation of the acetonitrile solution at reduced pressure afforded pure **10** (80 mg, 60% yield) as a colorless oil.

3-Methyl-7-oxobicyclo[3.3.1]non-3-ene-1-carboxylic acid (15). A mixture of ester **10** (1.18 g, 4.68 mmol), 20% aqueous NaOH (95 mL, 0.47 mol), THF (95 mL) and MeOH (95 mL) was heated under reflux for 48 h. The organic solvent was evaporated *in vacuo* and the remaining aqueous phase was diluted with water (50 mL), washed with CH_2Cl_2 (2 × 75 mL), made acidic to pH 1 with 5 N HCl (90 mL), and extracted with CH_2Cl_2 (5 × 75 mL). The combined organic extracts were washed with brine (100 mL), dried with anhydrous Na_2SO_4 and evaporated at reduced pressure, to give a yellow oil (720 mg) which solidified on standing. Recrystallization of this solid from AcOEt (5 mL) afforded pure keto acid **15** (490 mg, 54% yield): white crystals, m.p. 153-155 °C. IR (KBr) ν 3600-2350 (max. at 3423, 3048, 2955, 2928, 2853, 2643, 2501, 2363), 1701, 1449, 1427, 1405, 1303, 1282, 1261, 1219, 1182, 1079, 1061, 1038, 973, 922, 887, 864, 844, 828, 722, 662 cm^{-1}. MS, *m/z* (%): 194 ($M^{\cdot+}$, 18), 176 ($M^{\cdot+}$ - H_2O, 19), 149 (M^+ - COOH, 6), 137 (M^+ - C_3H_5O, 45), 93 (100), 91 (80), 79 (34), 77 (50). Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.98; H, 7.34.

Methyl *N*-{3-methyl-7-oxobicyclo[3.3.1]non-3-en-1-yl}carbamate (16). A solution of keto acid **15** (1.63 g, 8.40 mmol), Et_3N (1.17 mL, 0.85 g, 8.39 mmol) and diphenylphosphoryl azide (1.71 mL, 2.18 g, 7.91 mmol) in anhydrous chlorobenzene (29 mL) was heated at 90 °C for 3.5 h. Anhydrous MeOH (46 mL) was added to the cold solution and the resulting mixture was heated under reflux for 17 h. The solvent was evaporated at reduced pressure to give a brown oil (5.60 g), which was submitted to column chromatography through silica gel (157 g, CH_2Cl_2 / AcOEt, gradient elution). On elution with CH_2Cl_2 / AcOEt 85:15, keto carbamate **16** (1.74 g, 99% yield based on diphenylphosphoryl azide) was isolated as a light yellow oil which solidified on standing. The analytical sample of **16** was obtained by sublimation at 110 °C / 1 Torr: white solid, m.p. 65.5-66.5 °C. IR (KBr) ν 3324, 3054, 3038, 2985, 2961, 2941, 2881, 2841, 1727, 1709, 1674, 1536, 1463, 1436, 1415, 1363, 1342, 1296, 1250, 1222, 1193, 1133, 1112, 1073, 1041, 1032, 927, 816, 779, 716, 602 cm^{-1}. MS, *m/z* (%): 223 ($M^{\cdot+}$, 8), 167 (10), 166 (M^+ - C_3H_5O, 93), 165 (10), 134 (M^+ - C_3H_6O - MeO, 100), 107 (26), 106 (M^+ - C_3H_6O - COOMe, 59), 91 (84), 79 (42), 77 (35), 59 (50), 53 (26). Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.50; H, 7.75; N, 6.30.

5,6,9,10-Tetrahydro-5-(methoxycarbonylamino)-7-methyl-5,9-methano-1*H*-cycloocta[*b*]pyridin-2-one (19) and 5,8,9,10-tetrahydro-9-(methoxycarbonylamino)-7-

methyl-5,9-methano-1*H*-cycloocta[*b*]pyridin-2-one (20). A mixture of keto carbamate **16** (950 mg, 4.26 mmol), pyrrolidine (0.44 mL, 0.38 g, 5.32 mmol), 4 Å molecular sieves (2.5 g) and anhydrous benzene (50 mL) was heated under reflux for 5 h. The mixture was cooled to room temperature and was filtered under argon. The filtrate was treated with propiolamide (0.88 g, 12.8 mmol) and the reaction mixture was heated under reflux for 15 h. The resulting red suspension was allowed to cool to room temperature, diluted with MeOH (200 mL) and filtered. The filtrate was evaporated at reduced pressure to give a red solid residue (2.58 g), which was taken up in AcOEt (600 mL) and extracted with 1 N NaOH (5 × 150 mL). The combined aqueous extracts were neutralized with 0.75 N HCl (ca. 1 L) and extracted successively with CH_2Cl_2 (5 × 100 mL) and AcOEt (5 × 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), dried with anhydrous Na_2SO_4 and evaporated at reduced pressure, to give a yellow solid residue (450 mg), which was submitted to column chromatography through silica gel (40-60 μm, 45 g, hexane / AcOEt / MeOH, gradient elution). On elution with AcOEt / MeOH 95:5, a mixture of pyridones **19** and **20** (240 mg) in a ratio 9:16 (^{1}H NMR) was separated. On elution with AcOEt / MeOH 90:10, a mixture of pyridones **19** and **20** (110 mg) in a ratio 2:1 (^{1}H NMR) and pure **19** (40 mg) were isolated (33% total yield of pyridones; 17% yield of **19** and 16% yield of **20**). Meanwhile, the initial AcOEt solution was dried with anhydrous Na_2SO_4 and evaporated at reduced pressure, to give a residue (1.54 g) which was submitted to column chromatography through silica gel (45 g, CH_2Cl_2 / AcOEt, gradient elution). On elution with CH_2Cl_2 / AcOEt 85:15, starting keto carbamate **16** (380 mg) was recovered (55% total yield of pyridones based on recovered **16**; 28% yield of **19** and 27% yield of **20**).

Medium pressure liquid chromatography (MPLC) separation of a mixture of 19 and 20. The chromatographic separation of pyridones **19** and **20** was carried out by MPLC. The mixture of pyridones (300 mg of a mixture of **19** and **20** in the ratio of 8:7) was introduced in one portion dissolved in MeOH (8 mL). Mixtures of AcOEt / MeOH (gradient elution) were used as eluent, with a flow of 14 mL / min and an initial pressure of 4 bar. On elution with AcOEt / MeOH 95:5, pure pyridone **20** (110 mg) and a mixture of **19** and **20** (60 mg) in a ratio 2:1 were successively isolated. On elution with AcOEt / MeOH 94:6, pure pyridone **19** (110 mg) was isolated. The analytical samples of **19** and **20** were obtained by recrystallization from AcOEt / MeOH 9:2 and AcOEt / MeOH 5:2, respectively.

*Spectroscopic and analytical data of pyridone **19***: white crystals, m.p. 266-269 °C (dec.). IR (KBr) ν 3446, 3245, 3056, 2975, 2928, 2903, 2412, 2367, 1702, 1664, 1613, 1587, 1549, 1458, 1427, 1390, 1358, 1323, 1300, 1281, 1264, 1249, 1197, 1178, 1145, 1136, 1121, 1084, 1053, 1028, 925, 848, 819, 793, 781, 734, 685 cm^{-1}. ^{1}H NMR (CD_3OD) δ 1.59 (s, 3 H, 7-CH_3), 1.71 (ddd, J = 12.0 Hz, J' = 4.0 Hz, J'' = 1.5 Hz, 1 H, 11-H$_{anti}$), 1.96 (br. d, J = 16.5 Hz, 1 H, 6-H$_{endo}$), 2.41 (dm, $J \approx$ 16.5 Hz, 1 H, 6-H$_{exo}$), overlaps in part 2.42 (ddd, J = 17.5 Hz, J' = J'' = 1.5 Hz, 1 H, 10-H$_{endo}$), 2.57 (br. d, $J \approx$ 12.0 Hz, 1 H, 11-H$_{syn}$), 2.76 (m, 1 H, 9-H), 2.90 (dd, J = 17.5 Hz, J' = 5.0 Hz, 1 H, 10-H$_{exo}$), 3.56 (s, 3 H, NHCOOC<u>H</u>$_3$) , 4.87 (s, N<u>H</u>COOCH$_3$ + 1-H + H_2O), 5.51 (dm, J = 4.0 Hz, 1 H, 8-H), 6.35 (d, J = 9.5 Hz, 1 H, 3-H), 7.56 (d, J = 9.5 Hz, 1 H, 4-H). ^{13}C NMR (CD_3OD + D_2O) δ 23.1 (CH_3, 7-CH_3), 31.3 (CH, C9), 34.1 (CH_2, C10), 34.4 (CH_2, C11), 45.1 (CH_2, C6), 52.2 (CH_3, NHCOO<u>C</u>H$_3$), 53.4 (C, C5), 117.9 (CH, C3), 122.4 (C, C4a), 125.7 (CH, C8), 133.4 (C, C7), 141.4 (CH, C4), 144.1 (C, C10a), 157.5 (C, NH<u>C</u>OOCH$_3$),

165.8 (C, C2). MS, *m/z* (%): 274 ($M^{\cdot+}$, 10), 259 (M^+ - CH_3, 16), 232 (7), 215 (7), 206 (10), 205 (7), 200 (15), 199 ($M^{\cdot+}$ - NH_2COOMe, 20), 198 (11), 187 (8), 185 (5), 184 ($M^{\cdot+}$ - NHCOOMe - CH_3, 17), 174 (6), 173 (5), 170 (5), 166 (6), 160 (5), 159 (5), 158 (5), 109 (100). Anal. Calcd. for $C_{15}H_{18}N_2O_3 \cdot 1/3H_2O$: C, 64.27; H, 6.72; N, 9.99. Found: C, 64.25; H, 6.52; N, 10.09.

Spectroscopic and analytical data of pyridone ***20***: white crystals, m.p. 260-262 °C (dec.). IR (KBr) ν 3413, 3267, 3119, 3035, 2969, 2944, 2920, 2896, 2871, 2766, 2422, 2361, 2337, 1713, 1651, 1621, 1557, 1536, 1460, 1405, 1378, 1283, 1233, 1188, 1112, 1092, 1070, 1036, 887, 827, 782, 748, 653 cm^{-1}. ^1H NMR (CD_3OD) δ 1.60 (s, 3 H, 7-CH_3), 1.95 (dd, J = 11.5 Hz, J' = 3.0 Hz, 1 H) and 2.16 (br. d, J = 11.5 Hz, 1 H) (11-H_{syn} and 11-H_{anti}), 2.38 (br. d, J = 17.5 Hz, 1 H, 8-H_{exo}), 2.53 (br. d, J = 17.5 Hz, 1 H, 8-H_{endo}), 3.01 (br. d, J = 19.0 Hz, 1 H, 10-H_{endo}), 3.18 (br. d, J = 19.0 Hz, 1 H, 10-H_{exo}), 3.22 (m, 1 H, 5-H), 3.61 (s, 3 H, NHCOOC$\underline{H}_3$), 4.86 (s, N$\underline{H}$COOCH_3 + 1-H), 5.64 (d, J = 5.0 Hz, 1 H, 6-H), 6.27 (d, J = 9.0 Hz, 1 H, 3-H), 7.35 (d, J = 9.0 Hz, 1 H, 4-H). ^{13}C NMR (CD_3OD + D_2O) δ 22.9 (CH_3, 7-CH_3), 35.2 (CH_2, C11), 35.3 (CH, C5), 41.1 (CH_2, C10), 46.3 (CH_2, C8), 51.4 (CH_3, NHCOO$\underline{C}H_3$), 52.5 (C, C9), 116.7 (CH, C3), 123.2 (C, C4a), 126.6 (CH, C6), 132.4 (C, C7), 143.3 (C, C10a), 143.6 (CH, C4), 158.4 (C, NH$\underline{C}$OOCH$_3$), 165.4 (C, C2). MS, *m/z* (%): 274 ($M^{\cdot+}$, 33), 207 (5), 200 (11), 199 ($M^{\cdot+}$ - NH_2COOMe, 33), 198 (23), 187 (5), 184 ($M^{\cdot+}$ - NHCOOMe - CH_3, 28), 160 (11), 159 (22), 109 (58), 59 (100), 55 (32). Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.62; N, 10.21. Found: C, 65.68; H, 6.69; N, 10.24.

5-Amino-5,6,9,10-tetrahydro-7-methyl-5,9-methano-1*H*-cycloocta[*b*]pyridin-2-one (5). A mixture of pyridone **19** (90 mg, 0.33 mmol), anhydrous HMPA (0.6 mL), and lithium 1-propanethiolate (*ca.* 0.5 M solution in anhydrous HMPA [52], 4.40 mL, *ca.* 2.20 mmol) was heated at 40 °C for 24 h. The cold (room temperature) mixture was poured into ice (30 g) and concentrated *in vacuo*. The resulting brown residue (1.09 g) was submitted to column chromatography through silica gel (40-60 μm, 140 g, $CHCl_3$ / MeOH, gradient elution). On elution with $CHCl_3$ / MeOH 90:10, starting **19** (20 mg) was recovered. On elution with $CHCl_3$ / MeOH 60:40, pure amine **5** (45 mg, 63% yield; 81% yield based on recovered **19**) was isolated. The analytical sample of **5** was obtained by recrystallization from AcOEt / MeOH 7:2: white crystals, m.p. 259-260 °C (dec.). IR (KBr) ν 3442, 3392, 3307, 3261, 3173, 3076, 3031, 2951, 2939, 2887, 2818, 2722, 2647, 1644, 1606, 1554, 1461, 1426, 1413, 1295, 1263, 1191, 1177, 1125, 1114, 1070, 1036, 1017, 1000, 987, 968, 953, 888, 876, 850, 686 cm^{-1}. ^1H NMR (CD_3OD) δ 1.58 (s, 3 H, 7-CH_3), 1.78 (dm, J = 12.0 Hz, 1 H, 11-H_{syn}), 1.84 (ddd, J = 12.0 Hz, J' = 4.5 Hz, J'' = 1.5 Hz, 1 H, 11-H_{anti}), 1.96 (br. d, J = 17.0 Hz, 1 H, 6-H_{endo}), 2.27 (dm, J = 17.0 Hz, 1 H, 6-H_{exo}), 2.44 (dm, J = 17.0 Hz, 1 H, 10-H_{endo}), 2.75 (m, 1 H, 9-H), 2.87 (dd, J = 17.0 Hz, J' = 5.5 Hz, 1 H, 10-H_{exo}), 4.88 (s, NH_2 + 1-H), 5.47 (dm, J = 4.5 Hz, 1 H, 8-H), 6.38 (d, J = 9.0 Hz, 1 H, 3-H), 7.84 (d, J = 9.0 Hz, 1 H, 4-H). ^{13}C NMR (CD_3OD) δ 23.1 (CH_3, 7-CH_3), 31.5 (CH, C9), 34.6 (CH_2, C10), 39.1 (CH_2, C11), 47.3 (CH_2, C6), 50.3 (C, C5), 117.9 (CH, C3), 124.1 (C, C4a), 125.2 (CH, C8), 134.8 (C, C7), 141.8 (CH, C4), 143.9 (C, C10a), 165.7 (C, C2). Exact mass calcd. for $C_{13}H_{16}N_2O$ 216.1263, obsd. 216.1258.

9-Amino-5,6,9,10-tetrahydro-7-methyl-5,9-methano-1*H*-cycloocta[*b*]pyridin-2-one (21). To a suspension of carbamate **20** (96.0 mg, 0.35 mmol) in $CHCl_3$ (13 mL), trimethylsilyl iodide (0.50 mL, 0.70 g, 3.51 mL) was added dropwise and the mixture was heated under reflux for 8 h.

MeOH (13 mL) was then added and the reaction mixture was heated under reflux for 14 h. Evaporation of the solvents at reduced pressure gave a brown residue (270 mg) which was submitted to column chromatography through ammonia-saturated silica gel (22 g, $CHCl_3$ / MeOH, gradient elution). On elution with $CHCl_3$ / MeOH 96:4, amine **21** was obtained slightly contaminated with the non-isomerized amine (80 mg). This product was again submitted to column chromatography under the same conditions. On elution with $CHCl_3$ / MeOH 96:4, pure **21** (50 mg, 66% yield) was isolated. The analytical sample of **21** was obtained by recrystallization from AcOEt / MeOH 4:1: white crystals, m.p. > 300 °C (dec.). IR (KBr) ν 3430, 2926, 1652, 1609, 1558, 1446, 1420, 1375, 1159, 1117, 835 cm^{-1}. ^1H NMR (CD_3OD) δ 1.63 (s, 3 H, 7-CH_3), 1.86-1.91 (complex signal, 2 H, 6-H_{endo} and 11-H_{anti}), 1.97 (dm, J = 12.0 Hz, 1 H, 11-H_{syn}), 2.47 (ddm, J = 18.0 Hz, J' = 3.5 Hz, 1 H, 6-H_{exo}), 2.69 (d, J = 17.0 Hz, 1 H, 10-H_{endo}), 2.80 (d, J = 17.0 Hz, 1 H, 10-H_{exo}), 3.17 (m, 1 H, 5-H), 4.85 (s, NH_2 + 1-H), 5.35 (br. s, 1 H, 8-H), 6.38 (d, J = 9.0 Hz, 1 H, 3-H), 7.45 (d, J = 9.0 Hz, 1 H, 4-H). ^{13}C NMR (CD_3OD) δ 23.2 (CH_3, 7-CH_3), 33.7 (CH, C5), 36.5 (CH_2, C11), 38.3 (CH_2, C6), 40.4 (CH_2, C10), 51.2 (C, C9), 118.5 (CH, C3), 120.1 (C, C4a), 126.3 (CH, C8), 137.0 (C, C7), 142.1 (C, C10a), 144.8 (CH, C4), 165.7 (C, C2). Exact mass calcd. for $C_{13}H_{16}N_2O$ 216.1263, obsd. 216.1259.

X-ray Crystal-Structure Determination of 9 [53]. A prismatic crystal was selected and mounted on a Enraf-Nonius CAD4 four-circle diffractometer. Unit-cell parameters were determined by automatic centering of 25 reflections ($12 < \theta < 21°$) and refined by the least-squares method. Intensities were collected with graphite-monochromatized Mo-$K\alpha$ radiation, using $\omega/2\theta$ scan technique. 1720 reflections were measured in the range $2.23 \leq \theta \leq 29.96$, 1647 of which were non-equivalent by symmetry [Rint (on I) = 0.070]. 976 reflections were assumed

Table 3

Experimental data of the X-ray crystal structure determination of **9**.

Molecular formula	$C_{14}H_{20}O_5$	F(000)	572
Molecular mass	268.32	d (calcd) [Mg m^{-3}]	1.324
Temperature	293(2)K	Size of crystal [mm]	0.1 × 0.1 × 0.2
Crystal system	Monoclinic	Measured reflections	1720
Space grup	$P2_1/n$	Independent reflections	1647
Cell parameters	[a]	Observed reflections	976
a [Å]	11.57(3)	μ(Mo-$K\alpha$) [mm^{-1}][b]	0.100
b [Å]	8.747(12)	R	0.076
c [Å]	13.32(2)	Rw	0.180
α [°]	90	$\Delta\rho_{max}$[c] (eÅ^{-3})	0.228
β [°]	95.6(2)	$\Delta\rho_{min}$[d] (eÅ^{-3})	-0.209
γ [°]	90	Refined parameters	176
V [Å^3]	1341(4)	Max. shift / e.s.d.	0.001
Z	4		

[a] Determined by automatic centering of 25 reflections ($12 \leq \theta \leq 21°$).

[b] μ(Mo-$K\alpha$), Linear absorption coefficient. Radiation Mo-$K\alpha$ (λ = 0.71069Å).

[c] Maximum and [d] minimum peaks in final difference synthesis.

as observed by applying the condition $I > 2\sigma(I)$. Three reflections were measured every two hours as orientation and intensity control; significant intensity decay was not observed. Lorentz polarization but no absorption corrections were made. The structure was solved by Direct methods, using the SHELXS computer program [54] and refined by the full-matrix least-squares method with the SHELX-93 computer program [55] using 1597 reflections (very negative intensities were not assumed). The function minimized was $\Sigma w (|F_o|^2 - |F_c|^2)^2$, where $w = [\sigma^2(I) + (0.0814P)^2]^{-1}$, and $P = (|F_o|^2 + 2|F_c|^2) / 3$. f, f' and f'' were taken from International Tables of X-ray Crystallography [56]. All H atoms were computed and refined with an overall isotropic temperature factor using a riding model. Goodness of fit on $F^2 = 1.128$ for all observed reflections. Mean shift / e.s.d. = 0.001.

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