Pergamon

Tetrahedron 55 (1999) 11843–11852

TETRAHEDRON

Preparation of Methylfuro[3,4-*b*][1,4]benzodioxinones as Intermediates for the Synthesis of Substituted Polycyclic Systems. Importance of the Acid Used as Catalyst

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Received 30 March 1999; revised 14 July 1999; accepted 28 July 1999

Abstract

The lactones **10** and **11** were conveniently prepared in excellent yield by reaction of the corresponding γ-hydroxy amides **6**, **7** and **8** in the presence of propionic acid in catalytic amounts. By increasing the ratio of propionic acid used, under the same reaction conditions, the hydroxy amide **6** reacted to give a mixture of ketoamides **13** (*cis* / *trans*).

Keywords: lactonization, benzodioxins, polycyclic heterocyclic compounds

INTRODUCTION

Substituted lactones have considerable potential in organic synthesis [1], act as precursors of a wide variety of compounds with pharmacological activity [2] and are useful synthetic intermediates for the preparation of substituted polycyclic systems with potential antitumour [3] or other activities [4]. Many different methods for synthesising lactones have been developed and most of them are based on the cyclisation of hydroxy acids [5], cyclisation of halo acids [6] or cyclisation of olefinic acids [7]. However, syntheses of lactones by these methods are occasionally difficult.

Direct synthesis of γ-lactones from hydroxy acids which were prepared through directed ortho-metalation on the appropriate acid depends on the nature of the hydroxy groups introduced: tertiary alcohols give lactones, whereas for secondary alcohols this internal cyclisation proved difficult [8] when using classical methods (Scheme 1).

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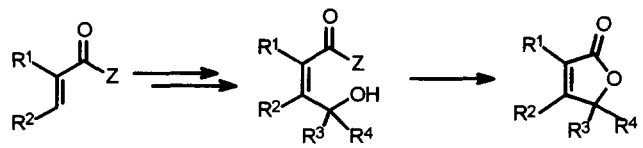
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00670-5

In connection with our work towards the synthesis of benzodioxin structures and in seeking a general and direct route to lactones from γ-hydroxy amides or γ-hydroxy acids we have examined a direct cyclisation using several acid catalysts (Scheme 1). The present report summarises our synthetic endeavours for optimising the lactone formation, which was our main objective. Diverse modifications of the reaction conditions have been proposed with a view to improving the yields and reducing the failures.



Z = OH, NR^3R^4
R^3 = H, alkyl, aryl; R^4 = alkyl, aryl

Scheme 1

First, the formation of lactones from γ-hydroxy acids was studied in acidic media, using camphorsulfonic acid (CSA) or *p*-toluenesulfonic acid (*p*TSA) in catalytic amounts, in toluene. On the other hand, as cyclisation of acyclic hydroxy amides [9] and arylhydroxy amides [10] is little known and constitutes an alternative strategy for the synthesis of lactones, this was studied in detail.

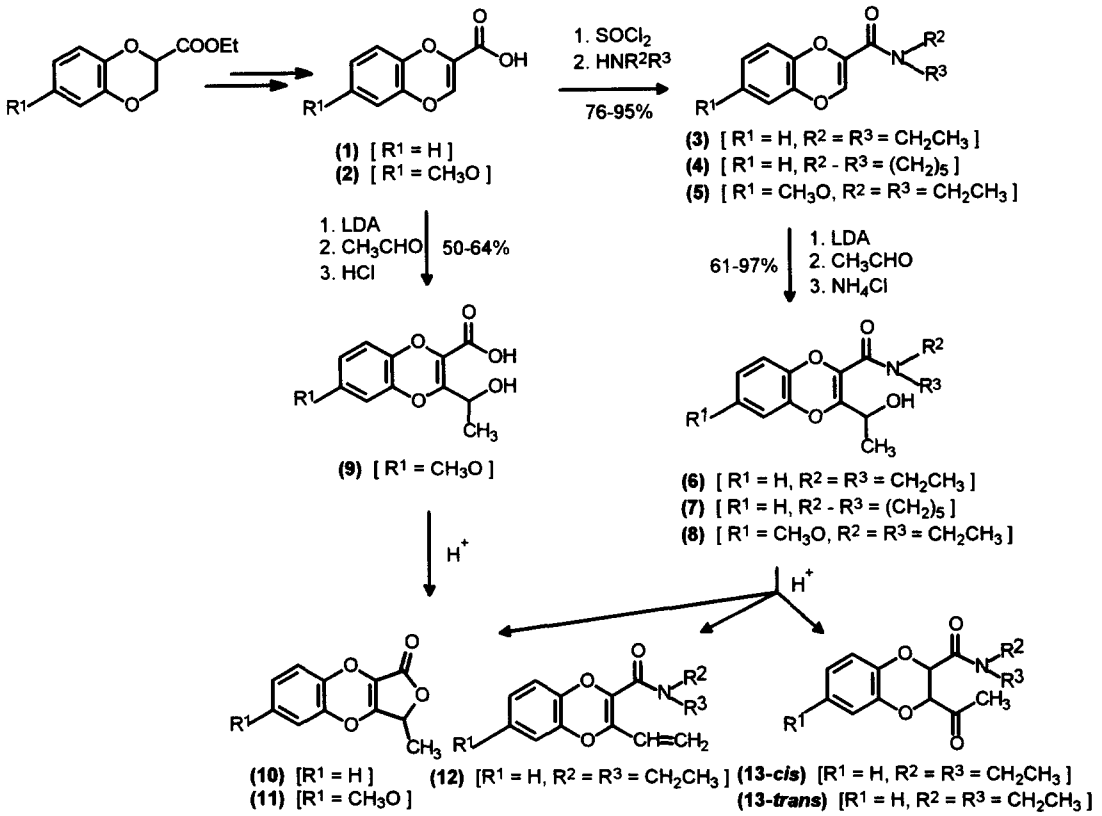
RESULTS AND DISCUSSION

The hydroxy amides **6**, **7** and **8** were synthesised by alkylation of 2-diethylcarbamoyl-1,4-benzodioxin **3**, 2-piperidinocarbonyl-1,4-benzodioxin **4**, or the substituted amide **5**, with LDA and acetaldehyde in THF at -78°C, in 97%, 61% and 82% yield, respectively. The hydroxy acid **9** was similarly prepared from the acid **2** (Scheme 2). The amides **3** and **4** were obtained from the known ethyl 2,3-dihydro-1,4-benzodioxin-2-carboxylate [11] in 3 steps (double bond introduction, ester hydrolysis, amide formation) [12]. The amide **5** was obtained from the same compound in 9 steps (double bond introduction, regioselective Friedel-Crafts acylation on C-6, double bond protection, Baeyer-Villiger oxidation, double bond deprotection, ester hydrolysis, double alkylation, hydrolysis to obtain the acid **2**, amide formation) [13].

As previous related experiences in our laboratory had shown, the transformation of the hydroxy acid **9** to the corresponding lactone **10** took place very slowly, under the studied conditions, due in part to solubility problems of the starting compound in the solvent used.

As for the cyclisation of hydroxy amides, the hydroxy amide **6**, which was obtained in the highest yield, and was most stable, was chosen as the starting compound to study the lactonization reaction. Ring closure of the γ-hydroxy amide **6** to lactone **10** was carried out under different conditions as indicated in Tables 1 and 2.

MS analyses, infrared spectra and NMR confirmed the structures of the products obtained. The reaction period was determined by monitoring the disappearance of the starting hydroxy amide by thin layer chromatography.



Scheme 2

Entry 1 (Table 1) shows that cyclisation was less effective when HCl was used as catalyst, whereas addition of small quantities of CSA and decreasing the amount of HCl increased the yield (entries 2-5); in these conditions, prolonged reaction times did not increase lactone formation considerably (entry 5 *versus* 4). Variations in the proportion of these acids (HCl / CSA) did not significantly modify the yield. In most cases (entries 1-4), a small amount of the olefin **12** (Scheme 2) was also formed. In the case (entry 6) of starting the catalysis with CSA the lactone formation was minor, even after relatively prolonged reaction times. With another inorganic acid, like HBr, the addition of CSA did not improve the yield either (entry 7).

It is evident that addition of carboxylic acids was better than inorganic acids for the ring closure lactones (entries 8-10 and 15-16). Good yields could be obtained when propionic acid was used, and the best results were achieved with the hydroxy amide **6** as starting material and toluene as solvent heated under reflux for 32 hours (entry 9). The catalysis by Lewis acids

(entries 11 and 12) was unfavourable for this cyclisation, and the lactone **10** could not be detected. This trend may reflect increased complexation of BF_3 with the starting compound (entry 12) or may simply be due to decomposition of the heterocyclic system when $ZnCl_2$ was used (entry 11).

Table 1. *Lactone formation with acid catalysis, for amounts of 100-200 mg of starting material*

Entry	Solvent	Catalyst	Equivalents	Reaction Time (h)	Yields (%)(*) 10	12	6	13
1	Toluene	HCl c.[a]	6	18	21	14	–	–
2	Toluene	HCl c. / CSA[a]	1 / 0.7	48	54	3	–	–
3	Toluene	HCl c. / CSA[a]	1 / 0.7	48	45	3	20	–
4	Toluene	HCl c. / CSA[a]	0.7 / 0.4	24	54	5	12	–
5	Toluene	HCl c. / CSA[a],[b]	1 / 0.4	100	58	–	19	–
6	Toluene	CSA / HCl c.[a]	0.6 / 1.3	168	33	4	34	–
7	Toluene	HBr / CSA[a]	3 / 0.7	72	23	18	46	–
8	Toluene	CF_3COOH	2	100	75	–	–	–
9	Toluene	CH_3CH_2COOH	0.8	32	93	–	–	–
10	Toluene	CH_3COOH	1	14	64	–	–	–
11	Toluene	$ZnCl_2$ / CSA	1 / 0.4	18	–	14	[c]	–
12	Toluene	$BF_3{\cdot}(CH_3CH_2)_2O$	2	72	–	–	[d]	–
13	Toluene	*p*TSA	0.8	24	4	: 3[e]	–	–
14	THF	*p*TSA	0.7	120	5	: 1	: 7[e]	–
15	DME	CH_3CH_2COOH	0.8	14	68	–	30	–
16	DME	CH_3CH_2COOH	0.8	27	55	–	8	–

(*) All reactions were carried out in the presence of molecular sieves (4 Å), except for entry 11, and the products were purified by column chromatography on silica gel (hexane / ethyl acetate), unless otherwise noted. [a] HCl and/or CSA were added in various portions during the reaction. [b] Refluxing toluene through a funnel containing $CaCl_2$ during the reaction prevented olefin formation. [c] Catechol was obtained by decomposition of the starting material and / or the products formed. [d] Products from complexation with Lewis acid were obtained. [e] Approximated molar ratio by ^{1}H-NMR spectroscopy of crude product mixture.

When *p*TSA in catalytic amounts and toluene or THF as solvent were used, the lactone **10** was obtained in poor yield (entries 13 and 14); in these conditions, the dehydration of **6** to form the olefin took place to a significant extents. Other solvents like dimethoxyethane (DME) with propionic acid as catalyst (entries 15-16) gave moderate results. In this case, longer reaction times (entry 16) not only gave poorer results but also seemed to lead to decomposition of the products.

With the most successful results (entry 9), we proceeded to apply the same conditions to the preparation of lactone **10** from larger amounts of the hydroxy amide. Table 2 outlines our second approach.

Table 2. *Lactone formation with acid catalysis, for amounts of 0.6-3.28 g of starting material*

Entry	Equivalents (CH_3CH_2COOH)	Reaction Time (h)	Yields (%)[*]			
			10	**12**	**6**	**13**[b]
1	0.8	14	75	–	–	12
2	0.8	14	74	–	–	16
3	1	20	41	–	[a]	35
4	0.6	13	72	–	–	14
5	0.2	14	84	–	–	4
6	0.1	26	88	–	–	1

[*] All reactions were carried out in toluene, in the presence of molecular sieves (4 Å), and the products were purified by column chromatography on silica gel (hexane / ethyl acetate). [a] Catechol was obtained by decomposition of the starting material and / or the products formed. [b] The product **13** was obtained as a *cis* / *trans* mixture (1 : 1.7, determined by ^{1}H-NMR), which was difficult to separate from the lactone by column chromatography on silica gel; thus the yield was estimated by ^{1}H-NMR. Further purification of this mixture by column chromatography on silica gel, afforded pure samples of both isomers of **13**, which were used to obtain analytical data.

Thus, when large amounts of the starting hydroxy amide were used and propionic acid was employed, the lactone **10** was obtained in satisfactory yields (entries 1-6), although, interestingly, a secondary product, the ketone **13**, was also formed (Scheme 2). As can be seen in Table 2, the reaction of the hydroxy amide **6** under these reaction conditions and with large amounts of starting compound, affords the ketone amide **13** in a variable proportion. Entry 3 shows a decreased yield in the lactone formation, which may be a consequence of the larger addition of propionic acid. In this case the relative percentage of ketone **13** increased at the expense of the lactone formation. Comparison of entries 1, 3, 4, 5 and 6 suggests that the amount of propionic acid is significant for this reaction and lower amounts increase the lactone formation while decreasing the formation of the secondary product. This ketone **13** was isolated as a *cis* / *trans* mixture and the relative ratio was determined by ^{1}H-NMR.

Moreover, less than 1% of ketone **13** was formed when only 0.1 equivalents of propionic acid were used, and the lactone formation increased to 88% yield. In general, the proper time of reaction for lactone formation was between 13-24 hours, and prolonged times caused decomposition of the products formed.

The formation of the corresponding alkene **12** by dehydration of the γ-hydroxy amide **6** proceeds through protonation of the hydroxy group and depends on the acid used. Mineral acids such as HCl or HBr and also organic acids such as CSA favour olefin formation. Formation of the ketone **13** suggests protonation of the amide **6** followed by tautomerization, and this process depends on the concentration of the acid in the reaction media, so that an increase in the acid concentration favours ketone formation.

The established conditions for the cyclisation of the hydroxy amide **6** were applied with success to the transformation of the analogue hydroxy amide **8** to the corresponding lactone **11**, whereas the hydroxy amide **7** (a piperidinyl amide) showed problems due to its instability.

In summary, an efficient one-pot synthesis of γ-lactones by condensation of hydroxy amides in acidic media, principally propionic acid in toluene, has been demonstrated. The method proved to be efficient even for multigram synthesis and the scope of these lactonizations is being investigated.

EXPERIMENTAL

General. Melting points were obtained on an MFB-595010M Gallenkamp apparatus in open capillary tubes and are uncorrected. IR spectra were obtained using a FTIR Perkin-Elmer 1600 Infrared Spectrophotometer. Only noteworthy IR absorptions are listed (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on Varian Gemini-200 (200 and 50.3 MHz respectively) or Varian Gemini-300 (300 and 75.5 MHz) Instrument using $CDCl_3$ as solvent with tetramethylsilane as internal standard or $(CD_3)_2CO$. Other ^1H NMR spectra and heterocorrelation ^1H-^{13}C (HMQC and HMBC) experiments were recorded on Varian VXR-500 (500 MHz). Mass spectra were recorded on a Hewlett-Packard 5988-A. Microanalyses were determined on a Carlo Erba-1106 analyser. All reagents were of commercial quality or were purified before use. Organic solvents were of analytical grade or were purified by standard procedures.

General Procedure for the Preparation of the Hydroxy Acid and the Hydroxy Amides 6-9:

To a stirred commercial solution of 2 M LDA in THF / *n*-hexane (1.70 mL, 3.40 mmol), cooled to -78 °C (CO_2 / acetone in a Dewar bath), under argon atmosphere, a solution of the acid (**2**) or amide (**3-5**) (1.70 mmol) in anhydrous THF (4 mL) was added dropwise. The resulting mixture was stirred for 3-4.5 h at this temperature. A solution of acetaldehyde (0.24 mL, 4.29 mmol) in THF (1.5 mL), previously cooled in an ice bath, was then slowly added. The mixture was stirred at -78 °C for 30 minutes, and then was allowed to warm to r.t. over a minimum time of 1.5 h, while gradually removing the Dewar bath. To the reaction mixture, a saturated solution of NH_4Cl (5 mL) (in the case of amides) or 1 M aq. HCl (10 mL) (in the case of the acid) was added; both phases were separated and the aq. phase was diluted with water (10 mL) and extracted with ether (3 x 10 mL), and further extracted with EtOAc(10 mL) in the case of acid. The combined extracts (including THF separated firstly) were dried (Na_2SO_4), the solvent was evaporated and the residue was purified by column chromatography in the case of amides (silica gel; hexane / EtOAc), or by recrystallisation in the case of acid, to give the corresponding purified hydroxy amides **6-8** or hydroxy acid **9**.

General Procedure for the Preparation of the Lactone 10:

a) For small amounts (Table 1). To a stirred solution of the hydroxy amide **6** (0.36-0.72

mmol) in dry toluene, DME or THF (5-10 mL), in the presence of molecular sieves (4Å), the acid catalyst(s) (equivalents indicated in Table 1) was added, and the reaction mixture was refluxed during the time indicated (TLC). After cooling, the resulting mixture was filtered and washed with CH_2Cl_2, and the solvents were evaporated under reduced pressure. The residue was dissolved in ether (20-30 mL), and washed with 0.5 M aq. $NaHCO_3$ (2 x 10 mL), dried over Na_2SO_4, and the solvent was removed *in vacuo*. The products were purified by column chromatography on silica gel (eluents: hexane-EtOAc in a ratio 85:15 for the olefin **12** and the lactone **10**, and hexane-EtOAc in a ratio 70:30 for the hydroxy amide **6**).

b) For multigram scale (Table 2). To a stirred solution of the hydroxy amide **6** (2.16-11.8 mmol) in dry toluene (40-150 mL), in the presence of molecular sieves (4Å), propionic acid (equivalents indicated in Table 2) was added, and the reaction mixture was refluxed during the time indicated (TLC). After cooling, the resulting mixture was filtered and washed with CH_2Cl_2, and the solvents were evaporated under reduced pressure. The products were purified by column chromatography on silica gel (eluents: hexane-EtOAc 88:12 for the lactone **10** and the ketones **14**).

Spectroscopic data

N,N-Diethyl-3-(1-hydroxyethyl)-1,4-benzodioxin-2-carboxamide (6)[12]: yellow oil.

IR (NaCl), ν (cm^{-1}): 3416, 2980, 1691, 1620, 1494, 1260, 1105.

^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 1.22 (t, J = 7 Hz, 3 H, CH_2-C<u>H</u>$_3$); 1.28 (t, J = 7 Hz, 3 H, CH_2-C<u>H</u>$_3$); 1.40 (d, J = 6.5 Hz, 3 H, CH-C<u>H</u>$_3$); 3.43 (m, 4 H, -CH_2-); 3.72 (d, J = 6.5 Hz, 1 H, OH); 4.43 (q, J = 6.5 Hz, 1 H, O-CH-); 6.6-6.9 (m, 4 H, 5-H, 6-H, 7-H, 8-H).

^{13}C-NMR (50.3 MHz, $CDCl_3$), δ (ppm): 12.3 (CH_3, CH_2-CH_3); 14.1 (CH_3, CH_2-CH_3); 18.5 (CH_3, CH-CH_3); 39.8 (CH_2, CH_2-CH_3); 43.2 (CH_2, CH_2-CH_3); 63.7 (CH, O-CH-); 115.5 (CH, C-5); 116.2 (CH, C-8); 124.2 (CH, C-6, C-7); 129.0 (C, C-2); 141.7 (C, C-8a); 142.2 (C, C-4a); 142.3 (C, C-3); 162.9 (C, CO).

N,N-Pentamethylen-3-(1-hydroxyethyl)-1,4-benzodioxin-2-carboxamide(7): colourless crystals, m.p. 135-136 °C (ether - EtOAc).

IR (KBr), ν (cm^{-1}): 3379, 2936, 1700, 1620, 1492, 1256, 1099.

^{1}H-NMR (500 MHz, $CDCl_3$), δ (ppm): 1.38 (d, J = 6.6 Hz, 3 H, -CH_3); 1.60 (m), 1.66 (m) (6 H, 3'-H_2 4'-H_2, 5'-H_2); 3.36 (bs, 1 H, OH); 3.53 (m, 4 H, 2'-H_2, 6'-H_2); 4.42 (q, J = 6.5 Hz, 1 H, OCH-); 6.66 (m, 1 H, 8-H); 6.75 (m, 1 H, 5-H); 6.84 (m, 2 H, 6-H, 7-H).

^{13}C-NMR (50.3 MHz, $CDCl_3$), δ (ppm): 18.6 (CH_3, -CH_3); 24.4 (CH_2, C-4'); 25.5 (CH_2, C-3'); 26.5 (CH_2, C-5'); 43.3 (CH_2, C-2'); 48.2 (CH_2, C-6'); 63.9 (CH, O-CH-); 115.7 (CH, C-5); 116.3 (CH, C-8); 124.3 (CH, C-6, C-7); 128.7 (C, C-2); 141.8 (C, C-8a); 142.2 (C, C-4a); 142.6 (C, C-3); 162.0 (C, CO).

MS (EI), *m/z* (%): 289 (M^+, 24), 271 (M^+-H_2O, 7), 246 (M^+-C_3H_7, 63), 204 (21), 177 (53), 161 ($C_8H_5O_2CO^+$, 62), 112 ($C_5H_{10}NCO^+$, 22), 86 (100).

Microanalysis: Calc. for $C_{16}H_{19}NO_4$: C 66.42%, H 6.62%, N 4.84%; found: C 66.45%, H 6.93%, N 4.84%.

*N,N-Diethyl-3-(1-hydroxyethyl)-6-methoxy-1,4-benzodioxin-2-carboxamide (**8**):* yellow oil.
IR (NaCl), ν (cm^{-1}): 3406, 1621, 1617, 1206, 1151.
^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 1.19 (t, *J* = 7.1 Hz, 3 H, CH_2-C<u>H</u>$_3$); 1.28 (t, *J* = 7.1 Hz, 3 H, CH_2-C<u>H</u>$_3$); 1.39 (d, *J* = 6.6 Hz, 3 H, CH-C<u>H</u>$_3$); 3.43 (m, 4 H, -CH_2-); 3.73 (s, 3 H, OCH_3); 4.44 (q, *J* = 6.6 Hz, 1 H, OCH-); 6.37 (m, 2 H, 5-H, 7-H); 6.61 (m, 1 H, 8-H).
^{13}C-NMR (50.3 MHz, $CDCl_3$), δ (ppm): 12.4 (CH_3, CH_2-CH_3); 14.1 (CH_3, CH_2-CH_3); 18.5 (CH_3, CH-CH_3); 39.9 (CH_2, CH_2-CH_3); 43.2 (CH_2, CH_2-CH_3); 55.5 (CH_3, O-CH_3); 63.8 (CH, OCH-); 102.7 (CH, C-5); 108.6 (CH, C-7); 115.7 (CH, C-8); 129.4 (C, C-2); 135.4 (C, C-8a); 141.5 (C, C-4a); 142.6 (C, C-3); 156.2 (C, C-6); 163.1 (C, CO).
MS (EI), *m/z* (%): 307 (M^+, 56), 290 (M^+-OH, 9), 278 (M^+-C_2H_5, 65), 264 (M^+-C_2H_3O, 27), 233 (264-CH_3O, 100), 207 (M^+-$C_4H_{10}NCO$, 74), 191 ($CH_3OC_8H_4O_2CO^+$, 41), 140 (16), 100 ($C_4H_{10}NCO^+$, 13), 72 ($C_4H_{10}N^+$, 33).
Microanalysis: Calc. for $C_{16}H_{21}NO_5$: C 62.53%, H 6.89%, N 4.56%; found: C 62.34%, H 6.98%, N 4.23%.

*3-(1-Hydroxyethyl)-6-methoxy-1,4-benzodioxin-2-carboxylic acid (**9**):* pale yellow solid, m.p. 142-143 °C (acetone - EtOAc).
IR (KBr), ν (cm^{-1}): 3364, 1694, 1642, 1511, 1207, 1153.
^{1}H-NMR (300 MHz, $(CD_3)_2CO$), δ (ppm): 1.39 (d, *J* = 6.6 Hz, 3 H, CH-C<u>H</u>$_3$); 3.78 (s, 1 H, OCH_3); 5.43 (q, *J* = 6.6 Hz, 1 H, OCH-); 6.49 (d, *J* = 2.9 Hz, 1 H, 5-H); 6.54 (dd, J_1 = 8.8 Hz, J_2 = 2.9 Hz, 1 H, 7-H); 6.77 (d, *J* = 8.8 Hz, 1 H, 8-H).
^{13}C-NMR (50.3 MHz, $(CD_3)_2CO$ + CD_3OD), δ (ppm): 19.9 (CH_3, CH-CH_3); 56.0 (CH_3, O-CH_3); 63.3 (CH, O-CH-); 103.1 (CH, C-5); 110.0 (CH, C-7); 116.8 (CH, C-8); 126.3 (C, C-2); 136.8 (C, C-8a); 142.9 (C, C-4a); 150.3 (C, C-3); 157.3 (C, C-6); 163.3 (C, CO).
MS (EI), *m/z* (%): 252 (M^+, 70), 234 (M^+-H_2O, 99), 219 (234-CH_3, 36), 207 (29), 191 ($C_{10}H_7O_4^+$, 100), 163 (191-CO, 30), 140 ($C_7H_8O_3^+$, 51), 83 (37), 55 (61).
Microanalysis: Calc. for $C_{12}H_{12}O_6$: C 57.14%, H 4.80%; found: C 57.57%, H 4.90%.

*3-Methylfuro[3,4-b][1,4]benzodioxin-1(3H)-one (**10**):* colourless crystals, m.p. 125-127 °C (lit.[12]: m.p. 130°C).
IR (KBr), ν (cm^{-1}): 1778, 1772, 1490, 1266, 1110, 1143.
^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 1.58 (d, *J* = 6.6 Hz, 3 H, -CH_3); 4.97 (q, *J* = 6.6 Hz, 1 H, OCH-); 6.89 (m, 2 H, 5-H, 8-H); 7.00 (m, 2 H, 6-H, 7-H).
^{13}C-NMR (50.3 MHz, $CDCl_3$), δ (ppm): 17.3 (CH_3, -CH_3); 71.4 (CH, O-CH-); 117.5 (CH), 117.9 (CH) (C-5, C-8); 122.1 (C, C-9a); 125.3 (CH), 126.5 (CH) (C-6, C-7); 140.5 (C), 141.5 (C) (C-4a, C-8a); 156.1 (C, C-3a); 163.1 (C, CO).
MS (CI, NH_3), *m/z* (%): 222 (M^++18), 205 (M^++1).

*6-Methoxy-3-methylfuro[3,4-b][1,4]benzodioxin-1(3H)-one (**11**):* colourless crystals, m.p. 129-130 °C (ether - EtOAc).
IR (KBr), ν (cm^{-1}): 1782, 1729, 1503, 1264, 1198, 1137, 1041.
^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 1.55 (d, *J* = 6.7 Hz, 3 H, CH-C<u>H</u>$_3$); 3.75 (s, 3 H, OCH_3); 4.95 (q, *J* = 6.7 Hz, 1 H, OCH-); 6.45 (d, *J* = 2.8 Hz, 1 H, 5-H); 6.52 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1 H, 7-H); 6.84 (d, *J* = 8.8 Hz, 1 H, 8-H).

^{13}C-NMR (50.3 MHz, $CDCl_3$), δ (ppm): 17.4 (CH_3, CH-CH_3); 55.8 (CH_3, O-CH_3); 71.5 (CH, CH_3-CH-); 104.1 (CH, C-5); 110.4 (CH, C-7); 118.1 (CH, C-8); 122.5 (C, C-9a); 135.2 (C, C-8a); 140.8 (C, C-4a); 155.2 (C, C-3a); 156.8 (C, C-6); 163.4 (C, CO).
MS (EI), *m/z* (%): 234 (M^+, 100), 219 (M^+-CH_3, 8), 191 (M^+-C_2H_3O, 66), 163 (191-CO, 11), 79 (7), 63 (10).
Microanalysis: Calc. for $C_{12}H_{10}O_5$: C 61.54%, H 4.30%; found: C 61.48%, H 4.33%.

*N,N-Diethyl-3-vinyl-1,4-benzodioxin-2-carboxamide (**12**):* pale yellow oil.
IR ($CHCl_3$), ν (cm^{-1}): 1781, 1726, 1630, 1486, 1257, 1217.
^{1}H-NMR (200 MHz, $CDCl_3$), δ (ppm): 1.20 (t, J = 7.1 Hz, 3 H, CH_2-C<u>H</u>$_3$); 1.25 (t, J = 7.1 Hz, 3 H, CH_2-C<u>H</u>$_3$); 3.45 (q, J = 7.1 Hz, 4 H, -CH_2-); 5.21 (dd, J_{cis} = 11.1 Hz, J_{gem} = 1.6 Hz, 1 H, =CH_c); 5.65 (dd, J_{trans} = 17.1 Hz, J_{gem} = 1.6 Hz, 1 H, =CH_t); 6.34 (dd, J_{trans} = 17.1 Hz, J_{cis} = 11.1 Hz, 1 H, -CH=); 6.72-6.92 (m, 4 H, 5-H, 6-H, 7-H, 8-H).
^{13}C-NMR (50.3 MHz, $CDCl_3$), δ (ppm): 12.6 (CH_3, CH_2-CH_3); 14.3 (CH_3, CH_2-CH_3); 39.7 (CH_2, CH_2-CH_3); 43.2 (CH_2, CH_2-CH_3); 114.7 (CH_2, CH=CH_2); 115.9 (CH), 116.3 (CH) (C-5, C-8); 124.1 (CH, CH=CH_2); 124.5 (CH), 124.8 (CH), (C-6, C-7); 131.0 (C, C-2); 135.9 (C, C-3); 141.7 (C), 142.0 (C) (C-4a, C-8a); 162.1 (C, CO).
MS (EI), *m/z* (%): 259 (M^+, 100), 230 (M^+-C_2H_5, 15), 187 (M^+-$C_4H_{10}N$, 15), 160 (187-C_2H_3, 17), 123 (4), 100 ($C_4H_{10}NCO^+$, 15), 72 ($C_4H_{10}N^+$, 19).

*cis-3-Acetyl-N,N-diethyl-2,3-dihydro-1,4-benzodioxin-2-carboxamide (cis-**13**):* pale yellow solid-oil, m.p. 41-43 °C.
IR (NaCl), ν (cm^{-1}): 2975, 1716, 1649, 1597, 1492, 1262, 1108.
^{1}H-NMR (500 MHz, $CDCl_3$), δ (ppm): 0.97 (t, J = 7 Hz, 3 H, CH_2-C<u>H</u>$_3$); 1.21 (t, J = 7 Hz, 3 H, CH_2-C<u>H</u>$_3$); 2.54 (s, 3 H, CO-CH_3); 3.16 (sext, J = 7 Hz, 1 H), 3.28 (sext, J = 7 Hz, 1 H) (-CH_2-); 3.41 (sext, J = 7 Hz, 1 H), 3.62 (sext, J = 7 Hz, 1 H) (-CH_2-); 4.45 (d, J = 3 Hz, 1 H, 3-H); 5.48 (d, J = 3 Hz, 1 H, 2-H); 6.87 (m, 3 H, 6-H, 7-H, 8-H); 7.00 (m, 1 H, 5-H).
^{13}C-NMR (50.3 MHz, $CDCl_3$), δ (ppm): 12.3 (CH_3, CH_2-CH_3); 14.1 (CH_3, CH_2-CH_3); 26.3 (CH_3, CO-CH_3); 40.0 (CH_2, CH_2-CH_3); 41.9 (CH_2, CH_2-CH_3); 74.0 (CH, C-2); 77.3 (CH, C-3); 117.0 (CH, C-8); 117.7 (CH, C-5); 121.7 (CH, C-6); 122.3 (CH, C-7); 140.7 (C, C-8a); 141.8 (C, C-4a); 165.2 (C, N-CO); 205.5 (C, CH_3-CO).
MS (EI), *m/z* (%): 277 (M^+, 30), 235 (M^+-$COCH_2$, 34), 207 (235-C_2H_4, 7), 177 (207-C_2H_6, 5), 163 (177-N, 16), 100 ($C_4H_{10}NCO^+$, 100), 72 ($C_4H_{10}N^+$, 91).
Microanalysis: Calc. for $C_{15}H_{19}NO_4$: C 64.97%, H 6.91%, N 5.05%; found: C 64.78%, H 6.92%, N 4.88%.

*trans-3-Acetyl-N,N-diethyl-2,3-dihydro-1,4-benzodioxin-2-carboxamide (trans-**13**):* pale yellow oil.
IR (NaCl), ν (cm^{-1}): 2974, 1726, 1650, 1597, 1490, 1250, 1107.
^{1}H-NMR (500 MHz, $CDCl_3$), δ (ppm): 1.12 (t, J = 7 Hz, 3 H, CH_2-C<u>H</u>$_3$); 1.26 (t, J = 7 Hz, 3 H, CH_2-C<u>H</u>$_3$); 2.37 (s, 3 H, CO-CH_3); 3.34 (sext, J = 7 Hz, 1 H), 3.40 (sext, J = 7 Hz, 1 H) (-CH_2-); 3.48 (q, J = 7 Hz, 2 H, -CH_2-); 4.92 (d, J = 6 Hz, 1 H, 3-H); 4.97 (d, J = 6 Hz, 1 H, 2-H); 6.88 (m, 3 H, 6-H, 7-H, 8-H); 6.97 (m, 1 H, 5-H).

^{13}C-NMR (50.3 MHz, $CDCl_3$), δ (ppm): 12.5 (CH_3, CH_2-CH_3); 14.3 (CH_3, CH_2-CH_3); 27.9 (CH_3, CO-CH_3); 40.4 (CH_2, CH_2-CH_3); 42.0 (CH_2, CH_2-CH_3); 70.7 (CH, C-2); 77.0 (CH, C-3); 117.1 (CH, C-8); 117.2 (CH, C-5); 121.9 (CH, C-6); 122.2 (CH, C-7); 142.09 (C, C-8a), 142.14 (C, C-4a); 165.7 (C, N-CO); 204.5 (C, CH_3-CO).
MS (EI), *m/z* (%): 277 (M^+, 1), 234 (M^+-$COCH_3$, 82), 205 (234-C_2H_5, 1), 177 (205-C_2H_4, 15), 161 (177-NH_2, 30), 100 ($C_4H_{10}NCO^+$, 95), 72 ($C_4H_{10}N^+$, 82).
Microanalysis: Calc. for $C_{15}H_{19}NO_4$: C 64.97%, H 6.91%, N 5.05%; found: C 64.78%, H 6.92%, N 4.88%.

ACKNOWLEDGEMENTS

The financial support from the CIRIT, Generalitat de Catalunya (QFN95-4704) and a fellowship to C.B. from the *Fundació Universitària Agustí Pedro i Pons* are gratefully acknowledged.

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