46. Synthesis of 1,2-Dihydropyridines, 2,3-Dihydro-4(1*H*)-pyridinone, and 1,2,3,4-Tetrahydropyridines *via* *N*-Acyl *N,O*-Hemiacetal Formation[1])

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New procedures are described for the synthesis of α,β-ethylenic and acetylenic aldehydes from 2-butene- and 2-butyne-1,4-diol, respectively (see *Scheme 1*). These are applied to the preparation of a particular δ-acetylamino-α,β-ethylenic aldehyde ((*E*)-**5**) as well as of its acetylenic analogue **15**. On heating in the presence of a silyl enol ether, the former undergoes a complete dehydrative cyclization affording the *N*-acetyl-1,2-dihydropyridine **19**. The addition of HCl to aldehyde (*E*)-**5** results in the production of the 4-chloro-1,2,3,4-tetrahydropyridine **22** which is hydrolyzed to the corresponding alcohol **23** on silica gel. Similarly, the addition of HCl or HBr to the δ-acetylamino-α,β-acetylenic aldehyde **15** leads to the previously unknown 4-halo-1,2-dihydropyridines **26**; these are easily hydrolyzed to the 2,3-dihydro-4(1*H*)-pyridinone **27**. The ring-forming process involves a *N*-acyl *N,O*-hemiacetal as intermediate which is eventually dehydrated.

1. Introduction. – Dihydropyridines play an essential role in biochemistry and find many applications in pharmacology [1] [2]. They are indispensable intermediates in the synthesis of natural products, mainly alkaloids. These aspects as well as the preparation and the chemical or physical properties of dihydropyridines were exhaustively dealt with in several recent reviews [3–5].

Synthetic ways to dihydropyridines can be classified into ring-forming processes and ring transformations. The first general principle is best represented by the versatile *Hantzsch* synthesis. This method conveniently affords 1,4-dihydro- or 3,4-dihydro-, but not 1,2-dihydropyridines. Very recently, the preparation of *N*-acyl-1,2-dihydropyridines by a thermal electrocyclic process was reported by *Fowler* [6]. The second principle may be illustrated by partial reduction of pyridines or pyridinium salts and nucleophilic addition of organometallic reagents to the same species leading to 1,2- or 1,4-dihydropyridines.

The 2,3-dihydro-4(1*H*)-pyridinones have been obtained from acyclic precursors as well as from heterocycles. The first group of methods includes the condensation of *Schiff* bases with 1,3-diketones [7] and its modern equivalent, the cyclocondensation of imines with (silyloxy)dienes derived from 1,3-dicarbonyl compounds [8], as well as some intramolecular condensation reactions [9]. To the second group belong: a) the reduction of 4-alkoxypyridines [10], *N*-acyl- or *N*-alkyl-4(1*H*)-pyridinones [11] [12], and the nucleophilic addition to *N*-acyl-4(1*H*)-pyridinones [13] or 4-alkoxypyridinium salts [14]; b) the oxydation of 4-piperidinols [15] or 4-piperidinones [16], the reaction of 5,6-dihydro-4-pyrones with amines [17], and some special types of rearrangements of other heterocycles.

[1]) Presented at the Swiss Chemical Society meeting in Bern, October 19th, 1982.

[2]) Part of the Ph. D. dissertation of *J.-P. R.*, Université de Lausanne, 1983.

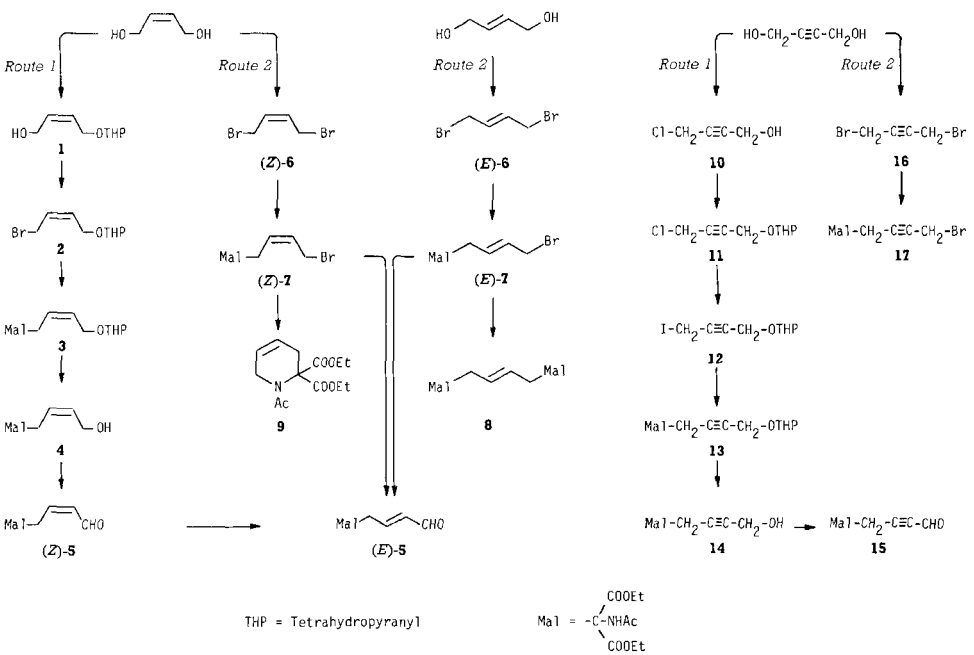
Unlike 4(1*H*)-pyridinones, the 2,3-dihydro-4(1*H*)-pyridinones are not widespread in nature. Examples of such systems are found in the lupine alkaloids [18]; some benzo derivatives (2,3-dihydro-4(1*H*)-quinolones) occur in the metabolites of *Lepidoptera* [19] and of a *Penicillium* strain [20].

We use a new and convenient access to some derivatives of 1,2-dihydro- and 1,2,3,4-tetrahydropyridines based on the ability of γ- and δ-acylamino-aldehydes to form *N*-acyl *N,O*-hemiacetals [21].

This paper describes the preparation of a series of unsaturated aldehydes substituted by the (acetylamino)malonate moiety and their facile dehydrative cyclization to dihydropyridine systems.

2. Results. – 2.1. *Synthesis of α,β-Ethylenic and Acetylenic Aldehydes.* The synthesis of α,β-unsaturated aldehydes is a major concern of organic chemists, and new preparative methods are regularly added to an already large repertoire. We needed a crotonaldehyde substituted at C(4) by a masked glycin-2-yl residue; our synthetic scheme was hence determined by the choice of the (acetylamino)malonate group to this purpose. Nucleophilic monosubstitution of a suitable 1,4-bifunctionalized 2-butene derivative by the (acylamino)malonate *C*-anion would afford the desired carbon framework. The remaining allylic function should allow to generate the aldehyde under neutral conditions avoiding uncontrolled reactions of the amide with the carbonyl group. Two distinct routes were developed according to this principle, both starting from 2-butene-1,4-diol *(Scheme 1)*.

Scheme 1



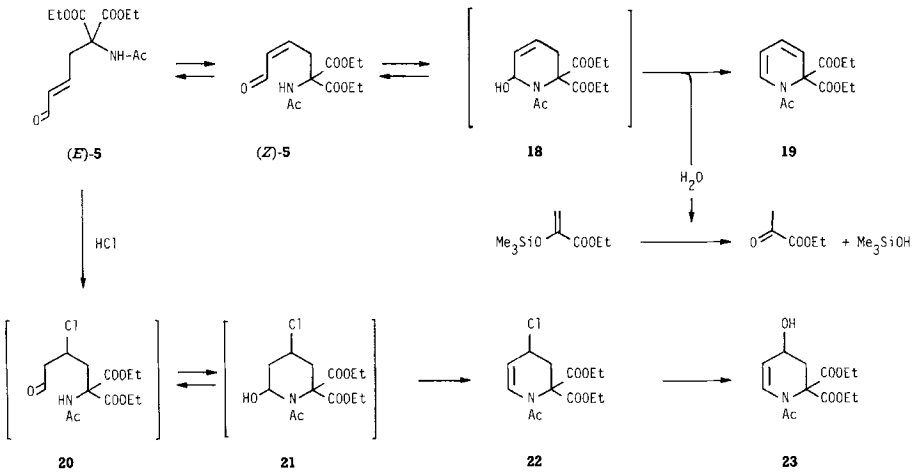
In a first variant *(Route 1)*, (*Z*)-2-butene-1,4-diol is reacted with excess 3,4-dihydro-2*H*-pyran in the presence of a catalytic amount of HCl to give a mixture of mono- and diprotected compounds, from which 4-(tetrahydropyranyloxy)-2-buten-1-ol (**1**) is isolated by distillation (51%). Reaction of **1** with PBr_3 affords 1-bromo-4-(tetrahydropyranyloxy)-2-butene (**2**; 71%) which is condensed with diethyl (acetylamino)sodiomalonate in anhydrous DMF to give the alkylated malonate **3** (90%). Hydrolysis leads to the corresponding alcohol **4**, which is oxidized with MnO_2 in CH_2Cl_2 to the aldehyde **5** (78%), a mixture of the (*E*)- and (*Z*)-isomers. The (*Z*)-form still predominates in the reaction mixture, but slowly isomerizes on standing at room temperature; heating in $CHCl_3$ rapidly completes the isomerization. The (*E*)-aldehyde crystallizes in Et_2O.

An improved synthesis *(Route 2)* involves the nucleophilic substitution of 1,4-dibromo-2-butene (**6**) by the (acylamino)malonate *C*-anion. Phase-transfer catalysis allows to achieve monosubstitution of both (*Z*)- and (*E*)-**6** efficiently. Reacting diethyl (acetylamino)malonate with an excess of (*E*)-**6** in CH_2Cl_2/20% aqueous NaOH solution in the presence of Bu_4NHSO_4 as phase-transfer agent leads to 67% of the allylic bromide (*E*)-**7** and 14% of the disubstituted product **8** which are separated by crystallization. In the case of (*Z*)-**6**, monosubstitution takes places exclusively; however, (*Z*)-**7** (70%) is accompanied by some 1,2,3,6-tetrahydropyridine **9** (15%) resulting from the intramolecular substitution of the allylic bromide by the amidate anion of **7**. Compound **7** crystallizes partially from the mixture, and the rest must be separated by chromatography. Under the same conditions of phase-transfer catalysis, (*Z*)-**7** cyclizes to give **9** in 80% yield. Bis(tetrabutylammonium) dichromate [22] is applied for the conversion of the allylic bromide **7** into the aldehyde **5**. Both (*Z*)- and (*E*)-**7** give the (*E*)-isomer, (*E*)-**5**, which is purified by filtration on silica gel. The moderate yield (66%) of this transformation results from the sensitivity of the product to degradation in the presence of chromium salts.

The α,β-acetylenic aldehyde **15** is prepared analogously from 2-butyne-1,4-diol following *Route 1;* in this case, *Route 2* fails because the desired end products are unstable towards the chromium reagent. Therefore, 2-butyne-1,4-diol is converted into the known chloro-alcohol **10** [23], the OH-group of which is protected by the tetrahydropyranyl group (→**11**). Being a poor alkylating agent, the propargylic chloride **11** is converted into the corresponding iodide **12** using NaI in acetone; this compound has been prepared in a different way by *Eiter et al.* [24]. Substitution of the iodide **12** with diethyl (acetylamino)sodiomalonate in DMF or under phase-transfer conditions gives the alkylated malonate **13** in 90 and 75% yield, respectively. This is hydrolyzed quantitatively (HCl/MeOH 1:100) to the alcohol **14** which, on oxydation with MnO_2, affords the crystalline aldehyde **15** (80%).

2.2. *1,2-Dihydro- and 1,2,3,4-Tetrahydropyridines from the Ethylenic Aldehyde (*E*)-***5***.* Whereas saturated γ-(acylamino)aldehydes exist mainly as *N*-acyl *N,O*-hemiacetals [21], the ethylenic aldehyde (*E*)-**5** does not produce any physical or spectroscopic evidence for the participation of such a cyclic structure at room temperature. However, on heating above its melting point, (*E*)-**5** undergoes a slow dehydrative cyclization forming diethyl 1-acetyl-1,2-dihydropyridine-2,2-dicarboxylate (**19**, *Scheme 2*). The intermediate cyclic *N,O*-hemiacetal **18** must be present in very little amount, since it was not detected in the reaction mixture. It rapidly equilibrates with (*Z*)-**5**, which in turn equilibrates with the prevailing (*E*)-**5**. Thus, the irreversible dehydration of **18** appears to be the rate-determining step in this reaction.

Scheme 2



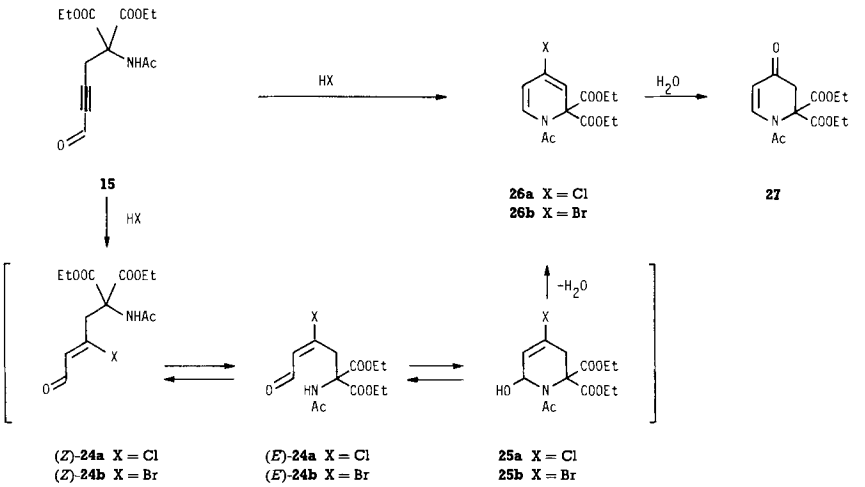
The formation of the dihydropyridine **19** is efficiently promoted by a silyl enol ether: whereas merely heating (*E*)-**5** for 24 h at 110°C yields only 60% **19**, the reaction is complete in 6 h in the presence of excess ethyl 2-(trimethylsilyloxy)acrylate. We prepared this reagent by treatment of ethyl pyruvate with trimethylsilyl trifluoromethanesulfonate following a procedure generally applied to ketones [25]. It is supposed that the silyl enol ether assists the dehydration process by interacting with the OH-group of the intermediate hemiacetal. Traces of acid contained in the silyl enol ether might catalyze both cyclization and dehydration.

2.3. *4-Chloro- and 4-Hydroxy-1,2,3,4-tetrahydropyridines: Addition of HCl to (*E*)-***5***.* Hydrogen halides react rapidly and regioselectively with conjugated carbonyl compounds leading to 1,4-addition products. In the particular case of the aldehyde (*E*)-**5**, the initially formed δ-acetylamino-β-haloaldehyde **20** cyclizes to give the 4-chloro-1,2,3,4-tetrahydropyridine **22** identified in solution by ^{1}H-NMR spectroscopy. The formation of a cyclic *N,O*-hemiacetal **21** is favoured by the entropic factor and the acidic conditions which also catalyze the dehydration *(Scheme 2)*. Besides prevailing **22**, the dihydropyridine **19** and the alcohol **23** are formed as minor products in variable amounts according to the reaction conditions; their proportions increase in particular with time. The chloro-tetrahydropyridine **22** completely hydrolyzes during chromatographic separation on silica gel affording the corresponding alcohol **23** and a small amount of its dehydration product **19**.

2.4. *4-Halo-1,2-dihydropyridines and 2,3 Dihydro-4(1*H*)-pyridinone: Addition of HX to the Acetylenic Aldehyde* **15**. The addition of HCl or HBr to α,β-acetylenic aldehydes or ketones is a mild and selective route to the corresponding α,β-unsaturated-β-halo carbonyl compounds which are useful as ketovinylation reagents [26] or as precursors of 1,3-dicarbonyl compounds.

In the case of the propargylic δ-(acetylamino)aldehyde **15**, the hydrohalide-addition products **24a** and **24b**, respectively, are unstable intermediates. On heating **15** in a HCl-saturated CH_2Cl_2 solution at 55° for several h, a final mixture of the 4-chloro-1,2-dihydropyridine **26a** and the dihydropyridinone **27** is obtained approaching a 1:1 ratio (see *Exper. Part, Run I* and *II*); these are easily separated by chromatography on silica gel.

Scheme 3



Complete hydrolysis of **26a** can be achieved by adding NaI to the solution of **15** and HCl in CH_2Cl_2, thus allowing a clean preparation of **27** (see *Exper. Part, Run IV*). Inversely, formation of dihydropyridinone **27** can be largely prevented by means of molecular sieve; a greater excess of HX is then required since the acid competes with H_2O for the absorption *(Run III)*, and the ratio **26a/27** is then 87:13.

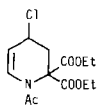
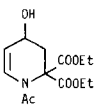
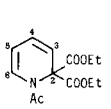
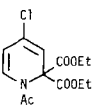
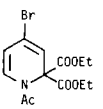
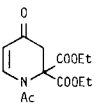
The reaction of HBr with **15** appears to occur more readily under the same conditions; in the final mixture, **27** becomes prevalent. At lower temperature (40°) and in presence of molecular sieve, the reaction can be followed by ^{1}H-NMR. Within the 1st h, besides disappearance of **15**, a mixture of (*Z*)- and (*E*)-**24b** is observed together with a second more important intermediate to which, tentatively, the hemiacetal structure **25b** is assigned. Neither **24b** nor **25b** can be isolated. As final products **26b** and **27** show up; for their isolation and separation, flash chromatography is indispensable in view of the sensitive bromo-dihydropyridine **26b**.

2.5. *Spectroscopic Data.* The ^{1}H-NMR, ^{13}C-NMR, and UV data of the tetrahydropyridines **22** and **23** and of the dihydropyridines **19**, **26**, and **27** are summarized in *Table 1*.

The 4-halo-1,2-dihydropyridines **26a** and **26b** absorb in the UV (CH_2Cl_2) near 310 nm. Compared to the spectrum of the 1,2-dihydropyridine **19**, the halogen atom induces a slight bathochromic shift (see *Table 1*). In the ^{1}H-NMR spectra, all chemical shifts of the ring protons of **26a** and **26b** are close to those of the corresponding protons in compound **19**: H–C(5) has the lowest chemical shift; it couples with H–C(3) (J = 2 Hz) and with H–C(6) (highest chemical shift; J = 8 Hz). The same holds true for the ring C-atoms of **19**, **26a**, and **26b** in the ^{13}C-NMR spectra, with the exception of C(4): surprisingly, Cl and Br exert opposite effects on C(4) relative to the C(4)-unsubstituted **19**, Cl increasing and Br decreasing the chemical shift of C(4) by 5–6 ppm.

3. Discussion. – There are several examples known of the ease of cyclization by intramolecular reaction of amidates carrying γ- and δ-halogen or γ- and δ-tosyloxy-substituents [27]. The general feasability of such substitution reactions is well documented in *Baldwins* rules as 5- and 6-*Exo-Tet* type processes [28]. In the case of our allylic bromide **7**, the reaction proceeds with particular ease to give the tetrahydropyridine **9**; moreover, the phase-transfer conditions provide a clean reaction. The *N*-acetyl-tetrahydropyridine **9**

Table 1. *Spectroscopic Data of* **19**, **22**, **23**, **26**, *and* **27**

	 **22**	 **23**	 **19**	 **26a**	 **26b**	 **27**
^{1}H-NMR ($CDCl_3$)[a]						
H–C(3)	2.79 *dd* (6.8, 5)	2.51 *d* (5.9)	5.62 *d* (9.6)	5.66 *d* (2)	5.85 *d* (2)	3.15 *s*
H–C(4)	4.50 *m*	4.20 *m*	6.03 *dd* (9.6, 5.8)			
H–C(5)	5.07 *dd* (3.2, 8.8)	5.09 *dd* (3.8, 8.2)	5.20 *dd* (5.8, 8)	5.19 *dd* (2/7.8)	5.26 *dd* (2, 8)	5.35 *d* (9)
H–C(6)	6.69 *d* (8.8)	6.67 *d* (8.2)	6.64 *d* (8)	6.69 *d* (7.8)	6.61 *d* (8)	7.54 *d* (9)
CH_3CH_2O	1.29 *t* (7.2)	1.28 *t* (7.2)	1.28 *t* (7.2)	1.29 *t* (6.4)	1.29 *t* (6.8)	1.29 *t* (7)
CH_3CH_2O	4.24 *q* (7.2)	4.23 *q* (7.2)	4.22 *q* (7.2)	4.25 *q* (6.4)	4.24 *q* (6.8)	4.26 *q* (7)
CH_3–CO	2.27 *s*	2.26 *s*	2.29 *s*	2.31 *s*	2.30 *s*	2.40 *s*
^{13}C-NMR ($CDCl_3$)[a]						
C(2)		65.5	69.0	70.2	70.7	69.1
C(3)		37.7	118.8	114.0	117.4	42.5
C(4)		60.0	121.8	128.4	116.1	188.2
C(5)		108.6	102.4	104.2	106.1	106.7
C(6)		126.3	125.8	127.4	127.1	142.5
CH_3 ester		13.9	14.0	13.9	13.9	13.7
CH_2O ester		62.2	62.1	62.5	62.5	62.7
C=O ester		167.1	166.6	165.7	165.5	165.8
CH_3 acteyl		21.7	21.5	21.4	21.4	21.4
C=O acetyl		168.7	169.8	169.5	169.6	169.0
UV (CH_2Cl_2) [nm]		242	307	310	313	284

[a]) Chemical shifts in ppm relative to tetramethylsilane; in parentheses, coupling constants *J* [Hz]. ^{1}H-NMR at 360 MHz, ^{13}C-NMR at 90.5 MHz.

has been prepared simultaneously[1]) by *Leete* and *Müller* [29] in connection with the synthesis of baikiain using the chloride corresponding to **7** for the cyclization.

The transannular nucleophilic additions of our (*N*-acetylamino)aldehydes are as well stereochemically favoured processes designated as *6-Exo-Trig* [28]. Unlike the 5-membered cyclic *N,O*-hemiacetals from saturated γ-(acylamino)aldehydes [21], the 6-membered unsaturated *N,O*-hemiacetals proved not to be isolable. Their concomitant dehydration displaces the equilibrium in favour of synthetically interesting tetra- and dihydropyridines.

Of particular interest appears the 4-chloro-tetrahydropyridine **22**. The high sensitivity of this allylic chloride to hydrolysis reflects the activating stereoelectronic effect of the conjugated amide function. It is well known [30] that allylic halides bearing an electron-releasing group in γ-position are highly susceptible to nucleophilic substitution through S_N1 or S_N1' processes. This reaction is of interest in view of the recent application of an *N*-acyl-1,2,3,4-tetrahydro-4-pyridinol to the synthesis of various monosubstituted tetrahydropyridines involving a *Lewis*-acid-catalyzed nucleophilic substitution of the allylic OH-group [31]. The now easily accessible allylic chlorides similar to **22** would extend the field of potential applications of this methodology.

To our knowledge, 4-halo-1,2-dihydropyridines (like **26a** and **26b**) represent a new type of compounds[3]). They might find interesting applications as dienes in *Diels-Alder* cycloadditions and as vinyl chlorides in transition-metal-catalyzed coupling reactions. Their common product of hydrolysis, the dihydropyridinone **27**, has been obtained before by *Jung et al.* [8a] *via* cycloaddition.

We thank the *Swiss National Science Foundation* for financial support.

Experimental Part

General. All starting materials were purchased from *Fluka AG*. Thionyl chloride, 3,4-dihydro-2*H*-pyrane, and ethyl pyruvate were freshly distilled before use; 2-butyne-1,4-diol was recrystallized in $CHCl_3$. (*E*)-1,4-Dibromo-2-butene ((*E*)-**6**) is commercially available; (*Z*)-**6** was obtained from the (*Z*)-diol according to *Valette* [33]. TLC was performed on silica-gel plates *Merck Kieselgel 60 F 254* with CH_2Cl_2/MeOH 19:1. *Kieselgel 60 (Merck)* was used for prep. column chromatography (70–230 mesh) and for flash chromatography (230–400 mesh). UV spectra (λ_{max} (nm), ε): *Unicam SP 1800; Hewlett-Packard 8450 A* diode array spectrophotometer. IR spectra (cm^{-1}): *Beckman IR-20A*. NMR spectra ($CDCl_3$): *Brucker WP 80, WP 60FT*, and *WH 360*. Mass spectra (*m/z*, intensities in % of base peak): *Hewlett-Packard HP 5980 A; Finnigan 1020*.

*(Z)-4-(Tetrahydro-2*H*-pyran-2-yl)oxy-2-buten-1-ol* (**1**) [34]. To a soln. of (*Z*)-2-buten-1,4-diol (8 g, 90.8 mmol) in $CHCl_3$ (10 ml) were added 3,4-dihydro-2*H*-pyran (11.6 ml, 127 mmol) and 3 drops of conc. HCl, and the mixture was stirred at r.t. for 2.5 h. The acid was neutralized with solid $NaHCO_3$, the solv. evaporated, and the residual liquor distilled at 0.1 Torr through a *Vigreux* column. Redistillation of the fraction boiling at 60–80°/0.1 Torr affords 8 g of **1** (51%): R_f 0.42, n_D^{25} = 1.4722. IR (film): 3400*s* (br.), 3030*m*, 2960*s*, 2930*s*, 2875*s*, 2740*w*, 1640*m*, 1467 (sh), 1440*s*, 1387*s*, 1350*s*, 1320*s*, 1260*s*, 1200*s*, 1183*s*, 1156*s*, 1120*s*, 1070–960*s*, 905*s*, 866*s*, 841*m*, 810*s*. ^{1}H-NMR: 1.25–2.0 (*m*, $(CH_2)_3$ of THP); 2.52 (br. *s*, variable, OH); 3.30–4.06 (*m*, CH_2O of THP); 4.11, 4.13 (2*m*, 2H–C(1), 2H–C(4)); 5.61–5.73, 5.75–5.83 (2 *dt*, H–C(2), H–C(3)); 4.58 (*m*, OCHO of THP).

*(Z)-1-Bromo-4-(tetrahydro-2*H*-pyran-2-yl)oxy-2-butene* (**2**). PBr_3 (1.07 g, 3.95 mmol) in anh. Et_2O (10 ml) was added dropwise over 30 min to a soln. of **1** (2 g, 11.6 mmol) in anh. Et_2O (30 ml) at 0°, and the mixture was stirred for 3 h at this temp. It was then poured on 25 g of ice and neutralized with sat. aq. $NaHCO_3$. The org. phase was washed with brine and evaporated. Bulb-to-bulb distillation of the residual oil (0.08 Torr, 45°) gave 1.94 g of **2** (71%) as a colourless oil. IR (film): 3040*m*, 2980*m*, 2880*w*, 1630*w*, 1444*m*, 1384*w*, 1196*s*, 1112*m*, 1050*w*, 1024*w*, 955*m*, 850*m*, 768*s*. ^{1}H-NMR: 1.3–2.0 (*m*, $(CH_2)_3$ of THP); 3.33–4.0 (*m*, CH_2O of THP); 4.01 (*d*, *J* = 7.2, 2H–C(1)); 4.19 (*m*, 2H–C(4)); 4.61 (br. *m*, OCHO of THP); 5.50–6.06 (*m*, H–C(2), H–C(3)). MS (EI): 133/135.

*Diethyl 2-Acetylamino-2-[(Z)-4-(tetrahydro-2*H*-pyran-2-yl)oxy-2-butenyl]malonate* (**3**). A NaH dispersion (0.8 g) in mineral oil (*ca.* 55% NaH) was washed twice with pentane under N_2. Dry DMF (25 ml) was introduced and diethyl (acetylamino)malonate (3.26 g, 15 mmol) was added in small portions with vigorous stirring. The bromide **2** (3.54 g, 15 mmol) was added dropwise over 15 min, and the mixture was heated to 55° for 3 h. The total consumption of **2** was controlled by TLC. After cooling, the mixture, adjusted to pH 5, was extracted 3 times with Et_2O, the org. phase was washed with brine, dried on $MgSO_4$, and evaporated. The crude product was chromatographed on SiO_2 (Et_2O/CH_2Cl_2 7:3) yielding 5.18 g (93%) of **3**, R_f 0.55. IR (film): 3400*m* (br.), 3040*w*, 2990*w*, 2955*m*, 2880 (sh), 1765 (sh), 1755 (sh), 1747*s*, 1690 (sh), 1684*s*, 1670 (sh), 1510 (sh), 1504*m*, 1470*m*, 1445*m*, 1395*w*, 1373*m*, 1307*s*, 1219 (sh), 1204*s*, 1136*w*, 1119*w*, 1060*m*, 1025*s*, 972*w*, 960*w*, 905*w*, 870*w*, 860*w*, 815*w*, 730*m*. ^{1}H-NMR: 1.26 (*t*, *J* = 7, 2 CH_3CH_2O); 1.30–2.0 (*m*, $(CH_2)_3$ of THP); 2.02 (*s*, CH_3CON); 3.10 (*d*, *J* = 7.4, 2H–C(1')); 3.25–4.0 (*m*, CH_2O of THP); 4.05 (*d*, *J* = 6.4, 2H–C(4')); 4.24 (*q*, *J* = 7, 2 CH_3CH_2O); 4.57 (*m*, OCHO of THP); 5.29 (*dt*, *J* = 10.2, 7.4, H–C(2')); 5.75 (*dt*, *J* = 10.2, 6.4, H–C(3')). MS (EI): M^+ absent, 288, 270, 243, 229, 218, 212, 197, 184, 175, 172, 155 (100), 138, 126, 110, 109, 85.

Diethyl 2-Acetylamino-2-((Z)-4-hydroxy-2-butenyl)malonate (**4**). A soln. of 4.45 g (12 mmol) of **3** in 40 ml of 1% HCl/MeOH was left at r.t. until TLC control showed complete hydrolysis (1.5 h). Solid $NaHCO_3$ was added to neutralize the acid, and the solvent was evaporated. The oily residue was extracted with CH_2Cl_2/H_2O, the org. phase dried on Na_2SO_4, filtered, and evaporated. The crude alcohol was purified by chromatography on SiO_2

[3]) *N*-Acetyl-4-chloro-5,6-dihydropyridine was recently obtained by $NaBH_4$ reduction of 4-chloropyridine in presence of AcCl [32].

(Et_2O/CH_2Cl_2 8:2) to give 3.17 g (92%) of pure, oily **4**, R_f 0.35. IR (CH_2Cl_2): 3625*w*, 3420*m*, 3010 (sh), 2980*m*, 2940*m*, 2880*w* (sh), 1735*s*, 1665*s*, 1485*s*, 1437 (sh), 1365*m*, 1290*s*, 1267*s*, 1250*s* (sh), 1200*s*, 1090*m*, 1050*m*, 1008*s*, 945*m*, 920*w*, 895*w*, 850*m*. ^{1}H-NMR: 1.24 (*t*, *J* = 7.2, 2 CH_3CH_2O); 2.0 (*s*, CH_3CON); 2.76 (br. *s*, variable, OH); 3.08 (*d*, *J* = 7.6, 2H–C(1')); 4.07 (*d*, *J* = 6, 2H–C(4')); 4.20 (*q*, *J* = 7.2, 2 CH_3CH_2O); 5.20 (*dt*, *J* = 11, 7.6, H–C(2')); 5.72 (*dt*, *J* = 11, 6, H–C(3')); 6.87 (br. *s*, NH). MS (EI): 287 (0.8), 269 (33.8), 256 (1.3), 242 (7.1), 227 (5.2), 196 (63.5), 182 (9.2), 174 (94.8), 171 (47.5), 154 (100), 150.

Diethyl 2-Acetylamino-2-((Z)-4-bromo-2-butenyl)malonate ((Z)-7) and Diethyl 1-Acetyl-1,2,3,6-tetrahydropyridine-2,2-dicarboxylate (**9**). To a vigorously stirred soln. of diethyl (acetylamino)malonate (4 g, 18.4 mmol), Bu_4NHSO_4 (6.25 g, 18.4 mmol) and (*Z*)-1,4-dibromo-2-butene ((*Z*)-**6**; 6.4 g, 30 mmol) in CH_2Cl_2 (60 ml) at r.t. were added 7.5 g of a 20% aq. NaOH soln. After 30 min, the stirring was stopped and the org. phase was separated and evaporated. On shaking the viscous residue in Et_2O (100 ml), Bu_4NBr precipitated and was filtered off. The Et_2O soln. was washed with H_2O, dried on Na_2SO_4, and reduced to 10% of its volume, whereupon crystallization of (*Z*)-**7** occurred; this was recrystallized from Et_2O yielding 2.6 g. From the recombined mother liquors, the excess dibromobutene was distilled off at 0.1 Torr, and a second crop of pure (*Z*)-**7** (1.9 g) as well as 0.74 g (15%) of **9** were separated by chromatography on SiO_2 (Et_2O). Total yield of (*Z*)-**7**: 4.5 g (70%). M.p. 89–90°, R_f 0.49. IR (CH_2Cl_2): 3425*m*, 3070*w*, 3010*w*, 2990*w*, 2948*w*, 2918*w*, 1765 (sh), 1740*s*, 1690 (sh), 1682*s*, 1660*w*, 1630*w*, 1496*s*, 1390*w*, 1370*m*, 1307*m*, 1224 (sh), 1207*s*, 1094*m*, 1065*m*, 1044*m*, 1014*m*, 968*w*, 950*w*, 855*m*. ^{1}H-NMR: 1.26 (*t*, *J* = 7, 2 CH_3CH_2O); 2.04 (*s*, CH_3CON); 3.20 (*d*, *J* = 8.8, 2H–C(1')); 3.94 (*d*, *J* = 8.8, 2H–C(4')); 4.26 (*q*, *J* = 7, 2 CH_3CH_2O); 5.31 (*dt*, *J* = 10, 8.8, H–C(2')); 5.89 (*dt*, *J* = 10, 8.8, H–C(3')); 6.76 (br. *s*, NH). MS (EI): 270 (100), 250/252, 234/236, 228, 211, 203, 196, 183, 174, 165, 155, 149, 141, 137.

9: Oil, R_f 0.46. IR (film): 3050*w*, 2980*m*, 2935*w*, 2903*w*, 2860*w*, 1750 (sh), 1740 (sh), 1730*s*, 1675 (sh), 1670*s*, 1465 (sh), 1440*m*, 1403*s*, 1378*m*, 1368 (sh), 1333*m*, 1295*m* (br.), 1255*s*, 1229*s*, 1204*s*, 1165*m*, 1129*m*, 1098*m*, 1070*s*, 1038*m*, 1015*m*, 950*w*, 920*w*, 890*w*, 865*w*, 760*m*. ^{1}H-NMR: 1.27 (*t*, *J* = 7, 2 CH_3CH_2O); 2.15 (*s*, CH_3CON); 2.85 (*d*, *J* = 3.2, 2H–C(3)); 4.01 (*d*, *J* = 3.2, 2H–C(6)); 4.21 (*q*, *J* = 7, 2 CH_3CH_2O); 5.75 (*m*, H–C(4), H–C(5)). ^{13}C-NMR: 13.85 (2 CH_3CH_2); 22.1 (CH_3CON); 31.9 (C(3)); 45.2 (C(6)); 61.7 (2 CH_3CH_2O); 66.3 (C(2)); 122.4 (C(4), C(5)); 167.5 (2 COO); 171.9 (CH_3CON). MS (EI): 269 (2.1), 254 (0.03), 241 (0.06), 227 (17.9), 226 (26.6), 224 (9.5), 196 (8.2), 181 (1.2), 168 (0.3), 155 (100), 152 (18.4), 135 (2.1), 126 (31), 108 (21.7), 106 (11.1), 80 (50.3).

Cyclization of **7**. To a soln. of **7** (4.6 g, 13.1 mmol) and $(Bu_4NH)_2SO_4$ (3.3 g, 9.7 mmol) in CH_2Cl_2 (35 ml) were added 8 g of 15% NaOH with rapid stirring. After 35 min at r.t., the org. layer is taken in Et_2O and washed with H_2O. An oil is obtained containing **9** besides 10% of an unidentified impurity. Chromatography on SiO_2 (150 g) with Et_2O/pentane 10:1 yielded 2.5 g (80%) of **9**.

Diethyl 2-Acetylamino-2-((E)-4-bromo-2-butenyl)malonate ((E)-7) and Tetraethyl 2,2'-Bis(acetylamino)-2,2'-(2''-butene-1'',4''-diyl)dimalonate (**8**) were prepared as (*Z*)-**7**/**9** above, from diethyl (acetylamino)malonate (4 g, 18.4 mmol), Bu_4NHSO_4 (6.25 g, 18.7 mmol), (*E*)-1,4-dibromo-2-butene ((*E*)-**6**; 7.87 g, 36.8 mmol), CH_2Cl_2 (60 ml), and 20% aq. NaOH (8.5 g; stirring for 1 h). After workup, the dried Et_2O soln. was evaporated. Excess dibromobutene was sublimed from the resulting oil at 0.1 Torr, and **8** (1.1 g) was crystallized from Et_2O (50 ml). The residual material (*ca.* 90% (*E*)-**7**) was separated by chromatography on SiO_2 ($Et_2O/CHCl_3$ 95:5 to 1:9) affording pure (*E*)-**7**, (4.35 g, 67.5%) and **8** (0.15 g, total yield 14%). (*E*)-**7**: M.p. 72.8–73.5°, R_f 0.54. ^{1}H-NMR: 1.25 (*t*, *J* = 7, 2 CH_3CH_2); 2.04 (*s*, CH_3CON); 3.07 (*d*, *J* = 6.4, 2H–C(1')); 3.85 (*d*, *J* = 6.6, 2H–C(4')); 4.22 (*q*, *J* = 7, 2 CH_3CH_2O); 5.49 (*dt*, *J* = 15, 6.4, H–C(2')); 5.77 (*dt*, *J* = 15, 6.6, H–C(3')); 6.73 (br. *s*, NH). ^{13}C-NMR: 13.99 (CH_3CH_2O); 22.95 (CH_3CON); 31.9 (C(1')); 35.25 (C(4')); 62.6 (CH_3CH_2O); 66.0 (C(2)); 128.3 (C(2')); 131.2 (C(3')); 167.1 (COO); 168.8 (CH_3CON).

8: M.p. 120–120.5°, R_f 0.44. MS (CI): 488. MS (EI): 487, 442, 414, 372, 336, 323, 294, 270 (100), 267, 228, 214.

Diethyl 2-Acetylamino-2-(3-formyl-2-propenyl)malonate (**5**). A. *From* **4**. To a thin suspension of active MnO_2 (15.6 g, 180 mmol) in CH_2Cl_2 (300 ml) at r.t. were added 2.87 g (10 mmol) of **4**. Stirring was continued for 6 h, and the suspension was filtered through a plug of *Celite* which was then washed with 300 ml of CH_2Cl_2. Evaporation afforded 2.65 g of crude **5**, which was chromatographed on SiO_2 (Et_2O/CH_2Cl_2 85:15) yielding 2.42 g of a mixture of (*E*)- and (*Z*)-**5** (*ca.* 1:1). Refluxing in $CHCl_3$ for 30 min completed the (*Z*)→(*E*) isomerization; (*E*)-**5** was crystallized from Et_2O/pentane 9:1.

B. *From* **7**. A soln. of (*E*)- or (*Z*)-**7** (1.75 g, 5 mmol) and bis(tetrabutylammonium) dichromate (3.5 g, 5 mmol) in 25 ml of $CHCl_3$ was refluxed until total consumption of **7** (2 h, TLC control). The chromium(IV) salts were precipitated by dilution of the cooled mixture with an equal volume of Et_2O. After filtration and evaporation, the dark residue was immediately chromatographed on a pre-packed SiO_2 column with Et_2O giving 0.94 g (*E*)-**5** (66%) as needles, m.p. 82–82.5°, R_f 0.44. UV (EtOH): 220 (16000). IR (CH_2Cl_2): 3425*m*, 3070*w*, 3000*w* (sh), 2990*m*, 2947*w*, 2915*w*, 2885*w*, 2832*m*, 2753*m*, 1755*s* (sh), 1740*s*, 1695*s*, 1680*s* (sh), 1645*w*, 1630*w* (sh), 1502 (sh), 1493*s*, 1390*m*, 1373*m*, 1304*s*, 1207*s*, 1168*m*, 1134*m*, 1015*m*, 1060*m*, 1040*m*, 1012*w*, 980*m*, 948*w*, 895*w*, 855*m*. ^{1}H-NMR

((*E*)-**5**): 1.27 (*t*, *J* = 7, 2 CH_3CH_2O); 2.05 (*s*, CH_3CON); 3.34 (*d*, *J* = 7, 2H–C(1')); 4.25 (*q*, *J* = 7, 2 CH_3CH_2O); 6.10 (*dd*, *J* = 15.5, 7.8, H–C(3')); 6.65 (*dt*, *J* = 15.5, 7, H–C(2')); 6.83 (br. *s*, NH); 9.48 (*d*, *J* = 7.8, CHO). ^{1}H-NMR ((*Z*)-**5**): only H on C(1'), C(2'), and C(3') and CHO are different; 3.61 (*d*, *J* = 7.6, 2H–C(1')); 9.95 (*d*, *J* = 7.8, CHO); 6.1–6.5 (unresolved, H–C(2'), H–C(3')). ^{13}C-NMR ((*E*)-**5**): 13.95 (CH_3CH_2O); 22.85 (CH_3CON); 36.0 (C(1')); 62.8 (CH_3CH_2O); 65.4 (C(1')); 135.7 (C(3')); 149.8 (C(2')); 166.5 (COO); 169.0 (CH_3CON); 192.5 (CHO). MS (EI): 286 (6.4), 285 (36.8), 267 (2.2), 256 (4.7), 242 (4.6), 240 (12.1), 223 (7.9), 217 (35.6), 212 (19.5), 207 (8.0), 195 (6.0), 180 (8.3), 174 (100), 171 (35.8), 170 (86.6), 153 (59), 152 (44.9), 149 (62.1), 124 (26.5), 106 (29.7), 96 (49.8).

*1-Chloro-4-(tetrahydro-2*H*-pyran-2-yl)oxy-2-butyne* (**11**). To a vigorously stirred soln. of 4-chloro-2-butyn-1-ol [23] (**10**; 5.75 g, 55 mol) in $CHCl_3$ (20 ml) were added at r.t. 10 ml (110 mmol) of 3,4-dihydro-2*H*-pyran (exothermic reaction). Two drops of conc. HCl were added after 20 min. The acid was neutralized with solid $NaHCO_3$ after 1.5 h. Evaporation of the solv. and the excess 3,4-dihydro-2*H*-pyran gave **11** (9.8 g, 95%) as a clear syrup of sufficient purity to be used directly for the subsequent step. Pure **11** was obtained on bulb-to-bulb distillation at 110°/0.1 Torr. R_f 0.53. IR (film): 2950*s*, 2870*m*, 1438*m*, 1388*m*, 1345*m*, 1325*w*, 1264*s*, 1201*m*, 1180*w*, 1137 (sh), 1115*s*, 1050 (sh), 1020*s*, 964*m*, 943*w*, 900*m*, 868*m*, 810*m*, 693*s*. ^{1}H-NMR: 1.34–2.0 (*m*, $(CH_2)_3$ of THP); 3.31–4.0 (*m*, CH_2O of THP); 4.15 (*t*, *J* = 2, 2H–C(1)); 4.24 (*t*, *J* = 2, 2H–C(4)); 4.72 (*m*, OCHO of THP). MS (EI): 188/190, 153, 149, 130/132, 101, 87/89, 85 (100).

*1-Iodo-4-(tetrahydro-2*H*-pyran-2-yl)oxy-2-butyne* (**12**) [24]. Compound **11** (10 g, 53 mmol) were added to 110 ml of a refluxing soln. of 10% NaI in acetone under N_2. Reflux was maintained for 1 h. After cooling to r.t., 150 ml of Et_2O were added; the precipitated NaCl was discarded and the soln. decolorized by filtration through neutral alumina and washing with Et_2O. The solv. was evaporated giving 13.1 g (93%) of **12** as a slightly yellow liquid which could be used without further purification. Although **12** is rapidly destroyed on heating in air, it can be purified by bulb-to-bulb distillation at 90°/0.01 Torr. R_f 0.57. IR (CH_2Cl_2): 3010*w*, 2950*m*, 2880*m*, 2860*m*, 1466*m*, 1452*m*, 1440*m*, 1430*w*, 1390*m*, 1345*m*, 1323*w*, 1265*m*, 1200*m*, 1120*s*, 1077*m*, 1065*m*, 1054*m*, 1025*s*, 970*m*, 941*m*, 930*w*, 970*m*, 900*m*, 867*m*, 856*w*, 813*m*. ^{1}H-NMR: 1.35–1.95 (*m*, $(CH_2)_3$ of THP); 3.35–4.0 (*m*, CH_2O of THP); 3.70 (*t*, *J* = 2, 2H–C(1)); 4.20 (*t*, *J* = 2, 2H–C(4)); 4.66 (*m*, OCHO of THP). MS (EI): 280, 238, 196, 179, 153, 127, 111, 109, 101, 99, 97, 85 (100).

*Diethyl 2-Acetylamino-2-[4-(tetrahydro-2*H*-pyran-2-yl)oxy-2-butynyl]malonate* (**13**). *Method A: NaH/DMF.* Procedure identical with that used for **3**, except for temp. (60°C) and reaction time (2.5 h). Yield (15-mmol scale): 4.98 g, 90%.

Method B: Phase-Transfer Conditions. As for (*Z*)-**7**/**9** above, from diethyl (acetylamino)malonate (3.26 g, 15 mmol), Bu_4NHSO_4 (5.1 g, 15 mmol), **12** (5.04 g, 18 mmol), CH_2Cl_2 (450 ml), and 15% NaOH (10 g; stirring for 1 h). Workup (shaking with 200 ml of Et_2O and filtration), and evaporation of the dried Et_2O soln. afforded an oily residue from which **13** (4.15 g, 75%) and **12** (0.55 g, 13%) were separated by chromatography on silica gel (Et_2O). R_f 0.47. IR (film): 3390*m* (br.), 2990 (sh), 2950*s*, 2880*m*, 1745*s*, 1680*s*, 1500*s*, 1467*m*, 1444*m*, 1425*m*, 1390*m*, 1370*m*, 1302*s*, 1275 (sh), 1220*s*, 1202*s*, 1158*m*, 1130*m*, 1118*m*, 1095*m*, 1078*m*, 1054*m*, 1037*m*, 1022*s*, 970*w*, 945*w*, 900*m*, 867*m*, 814*m*. ^{1}H-NMR: 1.25 (*t*, *J* = 7, CH_3CH_2O); 1.40–1.90 (*m*, $(CH_2)_3$ of THP); 2.04 (*s*, CH_3CON); 3.27 (*t*, *J* = 1.5, 2H–C(1')); 3.34–3.90 (*m*, CH_2O of THP); 4.14 (*t*, *J* = 1.5, 2H–C(4')); 4.21 (*q*, *J* = 7, 2 CH_3CH_2O); 4.71 (*m*, OCHO of THP); 6.92 (br. *s*, NH).

Diethyl 2-Acetylamino-2-(4-hydroxy-2-butynyl)malonate (**14**). Prepared from **13** following the same procedure as for **3**→**4**. Yield (6-mmol scale): 90% after chromatographic purification (silica gel, Et_2O(CH_2Cl_2 85:15). Oil, R_f 0.31. IR (film): 3400*s* (br.), 2995*w*, 2945*w*, 2240*w*, 1765 (sh), 1755 (sh), 1748*s*, 1682 (sh), 1669*m*, 1660 (sh), 1515*m*, 1374*m*, 1310*s*, 1225 (sh), 1210*s*, 1140*m*, 1058*m*, 1017*m*, 955*w*, 900*w*, 860*w*. ^{1}H-NMR: 1.26 (*t*, *J* = 7, 2 CH_3CH_2O); 2.05 (*s*, CH_3CON); 2.69 (br. *s*, variable, OH); 3.27 (*t*, *J* = 2, 2H–C(1')); 4.17 (*t*, *J* = 2, 2H–C(4')); 4.24 (*q*, *J* = 7, 2 CH_3CH_2O); 7.05 (br. *s*, NH). MS (EI): 285, 267, 243, 240, 212, 194, 174, 170 (100), 166, 152, 146, 140, 135, 124, 118, 96, 84, 78.

Diethyl 2-Acetylamino-2-(3-formyl-2-propynyl)malonate (**15**). Prepared from **14** following the same procedure as for **4**→**5**, 80% yield after chromatographic purification on silica gel (Et_2O/CH_2Cl_2 9:1). Crystallized from Et_2O, m.p. 52–53°, R_f 0.41. UV (CH_2Cl_2): 237. IR (CH_2Cl_2): 3420*m*, 2990*w*, 2945*w*, 2910*w*, 2870*w*, 2210*m*, 1770 (sh), 1755 (sh), 1745*s*, 1690 (sh), 1675*s* (br.), 1490*s*, 1372*m*, 1305*s*, 1222 (sh), 1207*s*, 1140*m*, 1054*m*, 1012*m*, 947*w*, 856*m*, 831*m*. ^{1}H-NMR: 1.26 (*t*, *J* = 7, 2 CH_3CH_2O); 2.06 (*s*, CH_3CON); 3.52 (*s*, 2H–C(1')); 4.25 (*q*, *J* = 7, 2 CH_3CH_2O); 7.00 (br. *s*, NH); 9.06 (*s*, CHO). MS (EI): 283, 254, 235, 233, 223, 219, 210, 203, 194, 187, 174, 168, 149, 140, 84 (100).

Ethyl 2-(Trimethylsilyloxy)acrylate. To a stirred soln. of ethyl pyruvate (5 ml) in anh. Et_2O (50 ml) at 0° were successively added Et_3N (6.85 ml) and, dropwise over 75 min, trimethylsilyl trifluoromethanesulfonate (9 ml). The mixture was allowed to warm to r.t. and the stirring stopped (biphasic system). The upper Et_2O phase was evaporated under reduced pressure and anh. conditions. Bulb-to-bulb distillation of the residue (35°/0.1 Torr)

afforded 7 g (83%) of ethyl 2-(trimethylsilyloxy)acrylate. UV (CH_2Cl_2): 236. IR (film): 3030*w*, 2980*w*, 2960*m*, 2900*w*, 1727*s*, 1624*s*, 1445*m* (br.), 1372*m*, 1323*s*, 1256*s*, 1184*s*, 1165 (sh), 1100*w*, 1045*m*, 1023*m*, 855*s*, 800*w*, 760*w*, 700*w*. ^{1}H-NMR: 0.23 (*s*, $(CH_3)_3Si$); 1.29 (*t*, *J* = 7.2, CH_3CH_2O); 4.17 (*q*, *J* = 7.2, CH_3CH_2O); 4.81 (*s*, H–C(3) *trans* to COOEt); 5.42 (*s*, H–C(3) *cis* to COOEt). ^{13}C-NMR: 0.1 (CH_3Si); 14.1 (CH_3CH_2O); 61.0 (CH_3CH_2O); 103.6 (C(3)); 147.0 (C(2)); 164.0 (COO). MS (EI): 188 (0.5), 173 (48.6), 145 (85.7), 117 (9), 115 (9.3), 103 (37.6), 75 (100), 73 (51.5).

Diethyl 1-Acetyl-1,2-dihydropyridine-2,2-dicarboxylate (**19**). A. *Reaction without Solvent.* A mixture of (*E*)-**5** (150 mg, 0.53 mmol) and ethyl 2-(trimethylsilyloxy)acrylate (200 mg, 1.06 mmol) was heated at 110° for 17 h in a sealed tube under N_2. The ^{1}H-NMR of the crude mixture indicated the presence of **19**, ethyl pyruvate, trimethylsilanol, and a rest of (*E*)-**5**. The ratio (*E*)-**19**/**5** was 95:5, estimated from the integrations at 6.64 and 9.48 ppm, resp. Ethyl pyruvate was distilled off under reduced pressure, and pure **19** was obtained by chromatography on silica gel (Et_2O/pentane 9:1, then Et_2O).

B. *In Toluene.* A soln. of (*E*)-**5** (256 mg, 0.9 mmol) and ethyl 2-(trimethylsilyloxy)acrylate (0.34 g, 1.79 mmol) in dry toluene (4.3 ml) was heated at 115° for 6 h in a sealed tube. The ^{1}H-NMR of the mixture indicated the total conversion of (*E*)-**5** into **19**. Excess silyl enol ether was hydrolyzed with H_2O, toluene and ethyl pyruvate were evaporated, and **19** was purified as above. Isolated yield: 197 mg (82%) of colourless oil, R_f 0.58. UV (CH_2Cl_2): 307. UV (EtOH): 306 (3800). IR (CH_2Cl_2): 3072*w*, 3017 (sh), 3010 (sh), 3000*m*, 2950*w*, 2918*w*, 2880*w*, 1754*s*, 1740 (sh), 1734 (sh), 1690*s*, 1657 (sh), 1655*m*, 1588*s*, 1477*w*, 1467*w*, 1445*w*, 1380*m*, 1330*m*, 1287*s*, 1230*s*, 1164*w*, 1120*m*, 1095*w*, 1060 (sh), 1048*m*, 950*m*, 863*m*, 846*w*, 820*w*, 624*m*. ^{1}H- and ^{13}C-NMR: see *Table 1*. MS (EI): 268, 243, 229, 226, 195, 175, 153 (100), 115, 107, 77. MS (CI): 269, 227 (100), 203, 195, 153.

*Addition of HCl to (E)-***5**: *Diethyl 1-Acetyl-4-hydroxy-1,2,3,4-tetrahydropyridine-2,2-dicarboxylate* (**23**). (*E*)-**5** (100 mg, 0.35 mmol) was placed in a 10-ml screw-capped tube with a *Teflon*-faced rubber liner. Ar was flushed in the tube, and then 3 ml of dry CH_2Cl_2 sat. with gaseous HCl (*ca.* 0.3M) were added. The soln. was heated at 55° for 5 h and then evaporated. The ^{1}H-NMR of the residual oil showed a highly predominant compound (90%) to which structure **22** was assigned (*Table 1*). On attempted chromatographic purification (silica gel), **22** was not recovered; elution with Et_2O afforded **23** (70%) and **19** (*ca.* 5%). **23**: Oil, R_f 0.26. UV (CH_2Cl_2): 242. UV (96% EtOH): 232 (10800). IR (film): 3450*m* (br.), 3010 (sh), 2980*m*, 2940*w*, 2900*w*, 1740*s*, 1682*m*, 1652 (sh), 1640*s*, 1443*m*, 1377*s*, 1333*s*, 1305*m*, 1275*s*, 1240*s*, 1158*m*, 1130*w*, 1094*s*, 1063*m*, 1034*m*, 960*w*, 920*m*, 870*m*, 737*s*. ^{1}H- and ^{13}C-NMR: see *Table 1*. MS (EI): 286 $(M + 1)^+$, 271, 244, 243, 198, 174, 171 (100), 153, 117, 107.

Addition of HCl to **15**: *Diethyl 1-Acetyl-4-chloro-1,2-dihydropyridine-2,2-dicarboxylate* (**26a**) *and Diethyl 1-Acetyl-4-oxo-1,2,3,4-tetrahydropyridine-2,2-dicarboxylate* (**27**). Four different experiments (*I–IV*) were run in parallel. In each case, 8 ml of a soln. of anh. HCl in CH_2Cl_2 (0.18M) were added to 0.3 g of **15** in a 12-ml screw-capped tube with a *Teflon*-faced rubber liner, and the soln. was warmed at 55° under the following conditions: *I*: heating for 6 h; *II*: heating for 9 h; *III*: heating for 9 h with 1.5 g of 4-Å molecular sieve; *IV*: heating for 6 h with 1 equiv. of NaI. After cooling and evaporation of the solv., the mixtures were studied by ^{1}H-NMR and UV. In every case, **15** had disappeared and **26a** and **27**, had formed in the following proportions (calc. from the integrations at 6.69 and 7.54 ppm, resp.): 56:44 (*I*); 51:49 (*II*); 87:13 (*III*); 5:95 (*IV*). They were separated by chromatography on silica gel (Et_2O). Total yield: 82–85%. No **26a** was isolated in *Exper IV*. Compound **27** was crystallized from Et_2O/pentane. **26a**: Oil, R_f 0.50. UV (CH_2Cl_2): 310 (3300). IR (CH_2Cl_2): 3075*w*, 2990*m*, 2945*m*, 2910*w*, 2880*w*, 1757*s*, 1740 (sh), 1695*s*, 1651*s*, 1594*m*, 1376*s*, 1320*m*, 1300*s*, 1222*s*, 1167*m*, 1080*s*, 1050*s*, 952*m*, 906*w*, 869*w*, 858*w*, 830*w*. ^{1}H- and ^{13}C-NMR: see *Table 1*. MS (EI): 301/303, 268, 228/231, 186/188 (100), 158/160, 140/142, 112/114. MS (CI): 302/304, 260/262 (100). Anal. calc. for $C_{13}H_{16}ClNO_5$ (300.73): C 51.75, H 5.35, Cl 11.75, N 4.64, O 26.51; found: C 51.66, H 5.48, Cl 11.49, N 4.62, O 26.75.

27: M.p. 88.5°, R_f 0.47. UV (CH_2Cl_2): 284. UV (EtOH): 284 (17600). IR (CH_2Cl_2): 3060*w*, 2990*m*, 2945*w*, 2915*w*, 2880*w*, 1757*s*, 1740*s*, 1715*s*, 1690 (sh), 1680*s*, 1608*s*, 1440*w*, 1377*s*, 1330*w*, 1310 (sh), 1285*s*, 1230*s*, 1195*s*, 1121*w*, 1094*w*, 1066*s*, 1033*s*, 1010*m*, 954*m*, 908*m*. ^{1}H- and ^{13}C-NMR: see *Table 1*. MS (EI): 283, 241, 168 (100), 122. MS (CI): 284 (100), 242, 168. Anal. calc. for $C_{13}H_{17}NO_5$ (267.28): C 55.12, H 6.05, N 4.94, O 33.89; found: C 55.26, H 6.06, N 4.94, O 33.84.

Addition of HBr to **15**: *Diethyl 1-Acetyl-4-bromo-1,2-dihydropyridine-2,2-dicarboxylate* (**26b**) *and* **27**. Gaseous HBr generated by the reaction of Br_2 with tetralin was bubbled into dry CH_2Cl_2 and its concentration determined by titration with NaOH (indicator: phenolphthaleine), after addition a known volume of H_2O to an aliquot. Freshly prepared, Br_2-free solns. must be used. Then, 18 ml of 0.3M HBr/CH_2Cl_2 were added to 0.71 g of **15** and 2.7 g of 3-Å molecular sieve in a 30-ml screw-capped flask with a *Teflon*-faced rubber liner. After heating at 40° for 3 h, 20 ml of Et_2O were added, the molecular sieve was filtered off and the solv. evaporated. The 2 main constituents of the residual oil, **26b** and **27**, were separated by flash chromatography on silica gel (Et_2O/hexane 9:1). Compound **26b** eluted first (365 mg, 42%), followed by **27** (177 mg, 25%) and 20 mg of an unknown *N*-deacetylated

compound. **26b:** Oil, R_f 0.64. UV (CH_2Cl_2): 313 (4150). IR (film): 3100*w*, 2980*m*, 2940*w*, 2905*w*, 1746*s*, 1690*s*, 1630*s*, 1583*s*, 1465*m*, 1443*m*, 1377*s*, 1324*m*, 1299*s*, 1273*s*, 1224*s*, 1168*m*, 1095*w* (sh), 1070 (sh), 1050*s*, 953*m*, 867*m*, 837*w*, 763*m*. ^{1}H- and ^{13}C-NMR: see *Table 1*. MS (EI): 345/347 (1), 272/274 (4.9), 265 (2.3), 250/252 (2.1), 230/232 (100), 217/219 (2.3), 202/204 (18.9), 184/186 (35.2), 171/173 (2), 157/159 (15.9), 156/158 (23.7), 151 (3.8), 123 (1.1) 105 (2.2). MS (CI): 346/348, 304/306 (100), 230/232. Anal. calc. for $C_{13}H_{16}BrNO_5$ (346.17): C 45.11, H 4.66, Br 23.08, N 4.05, O 23.11; found: C 45.17, H 4.81, Br 23.02, N 4.09, O 22.91.

^{1}H-NMR Study of the Addition of HBr to **15**. The addition of HBr to **15** (0.58 g) was repeated in the presence of molecular sieve (2.2 g) in 3 consecutive heating periods of 30, 30, and 60 min (40° for the 1st and 2nd period, 55°C for the 3rd one). At first, 15 ml of HBr soln. were added, then 5 ml before the 2nd, and 7 ml before the 3rd period. Samples were taken after each period and analyzed by NMR for the products cited in *Table 2*. In addition to the products **26b** and **27**, the following intermediate species were detected: (*Z*)-**24b** [^{1}H-NMR: 9.61 (*d*, *J* = 7.4, CHO); 3.66 (*s*, 2H–C(1'))], (*E*)-**24b** [^{1}H-NMR: 9.80 (*d*, *J* = 6.6, CHO; 3.78 (*s*, 2H–C(1'))], and a compound supposed to be **25b** [^{1}H-NMR: 3.58 (*s*)].The intermediate species **25b** was unstable on silica gel and thus could not be recovered by chromatography.

Table 2. *^{1}H-NMR Study of the Addition of HBr to* **15**[a])

t (h)	**15**	(*Z*)-**24b**	(*E*)-**24b**	**25b**	**26b**	**27**
0.5	25	8	23	32[b])	11	1
1	7	8	22	33[b])	27	3
2	0	0	0	9.5[b])	54	36.5

[a]) Composition of the reaction mixture in % as a function of time as calculated from the integrations of the ^{1}H-NMR absorptions at 9.06 (**15**), 9.61 ((*Z*)-**24b**), 9.80 ((*E*)-**24b**), 3.58 (**25b**), 2.29 or 5.85 (**26b**), and 2.40 or 3.15 ppm (**27**).

[b]) Assumption: the signal at 3.58 ppm is due to a CH_2 group.

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