Stereoselective Electrophilic Cyclization of Doubly Activated Imines with Allylsilanes and Simple Alkenes[1)]

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The cyclization of *Z*- and *E*-hexenyliminomalonates **9** and **10** with TMS-OTf stereoselectively affords the *cis*-annulated piperidine lactones **13/14** and **15**, respectively, with complete retention of the double bond geometry. In contrast, the allylsilane **11** leads exclusively to the vinyl piperidine **12**. Cyclization of the imines **19** and **22** gives in high yield prefentially the tetrahydropyridine **20** and the octahydroisoquinoline **23**, respectively.

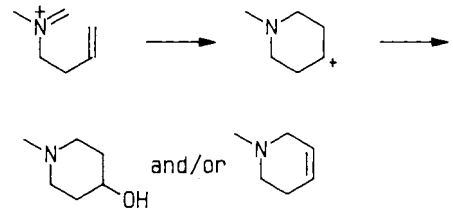
Stereoselektive, elektrophile Cyclisierung doppelt aktivierter Imine mit Allylsilanen und einfachen Olefinen

Die Cyclisierung der *Z*- und *E*-Hexenyliminomalonate **9** und **10** mit TMS-OTf ergibt stereoselektiv die *cis*-anellierten Piperidin-Lactone **13/14** und **15** unter vollständiger Retention der Doppelbindungsgeometrie. Im Gegensatz dazu reagiert das Allylsilan **11** ausschließlich zum Vinylpiperidin **12**. Cyclisierung der Imine **19** und **22** führt bevorzugt mit sehr guten Ausbeuten zum Tetrahydropyridin **20** bzw. Octahydroisochinolin **23**.

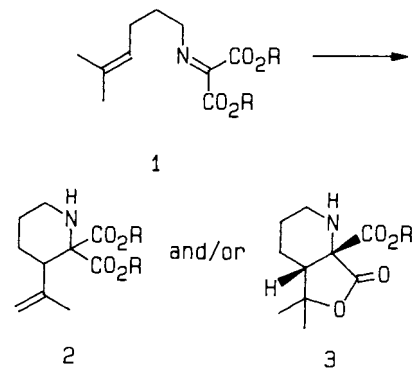
The electrophilic cyclization of olefins constitutes an elegant method for the construction of alicyclic and heterocyclic frameworks. Pioneered by the work of Johnson, a high degree of stereoselectivity can be achieved in these cyclizations[2)]. A crucial role in the design of cationic cyclization reactions is assigned to the functionalities which initiate and terminate the cyclization process[2)]. In the field of iminium ion initiated cyclizations remarkable efforts have been made in recent years a) by the development of *N*-acyl iminium ions as initiators[3)] and b) by the introduction of vinyl-[4)] allyl-[5)] and propargylsilanes[6)] as terminating groups.

The use of simple alkenes, although well-known, has found much less attention, since formation of mixtures is often encountered and the yields are sometimes less satisfactory[7)]. Thus, reaction products are either a result of an intermolecular capture of the intermediately formed cation by the solvent or of an elimination process (Scheme 1).

Scheme 1



However, we have shown in recent papers[8)] that a cyclization of simple alkenes can be performed with excellent yield and selectivity by using doubly activated imines. These reactions are initiated efficiently by Lewis acids or trialkylsilyl triflates. The employed imines were derived from alkyl mesoxalates and glyoxylates and the cyclization leads to derivatives of α-amino acids. For example, reaction of **1** yields, selectively, depending on the reaction conditions, either the diester **2** or the annulated piperidine lactone **3**.



In this paper we describe the cyclization of imines with 1,2-disubstituted alkenes of defined configuration as well as allylsilanes and 1,1-disubstituted alkenes to reveal the stereochemistry and reactivity in this type of reaction. The investigations were performed with the imines **9**–**11**, **19** and **22** which are accessible by condensation of the amines **5**–**7**, **16** and **17** with diethyl mesoxalate.

Results

For the synthesis of **5** the known alcohol **4a**[9)] was transformed by nucleophilic displacement via **4b** into the azide **4c**. Staudinger reaction[10)] to **4d** and stereoselective reduction of the triple bond with Brown's H_2/P2-Ni catalyst[11)] gave the *Z*-amine **5** with a small amount of the *E*-amine **6** (ratio = 13:1; ^{13}C NMR). **6** was obtained from *E*-4-hexenal[12)] by reduction of the corresponding oxime with lithium aluminium hydride. Condensation of **5** and **6** with

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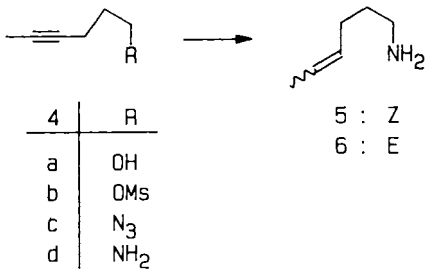
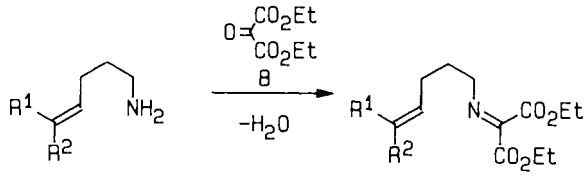
diethyl mesoxalate **8** in benzene with azeotropic removal of water gave the two imines **9** and **10** in 89% and 72% yield; the sample of **9** contained about 10% of **10**.



4	R
a	OH
b	OMs
c	N_3
d	NH_2

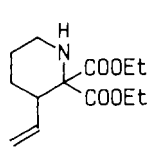
5 : Z
6 : E



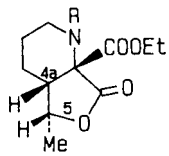
	R^1	R^2	
5	CH_3	H	9
6	H	CH_3	10
7	CH_2SiCH_3	H	11

The cyclization of **9** and **10** was performed using TMS-OTf in dichloromethane at room temperature. As expected, **9** and **10** were less reactive than **1**. Imine **9** afforded stereoselectively after 4 days a 2:3 mixture of the *cis*-annulated secondary and tertiary amino lactones **13** and **14** with a *cis* arrangement of 4a-H and 5-H in a total yield of 80%. **14** is presumably formed by an alkylation of **13** with ethyl triflate which is obtained as a byproduct in the cyclization process. Cyclization of **10** led after 5d to the *cis*-annulated lactone **15** with a *trans* arrangement of 4a-H and 5-H in 56% yield (22% of starting material recovered).

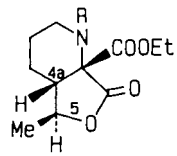
Inspection of the ^{13}C-NMR spectrum of **14** revealed that the sample contained about 10% of **15** which correlates well to the amount of **6** obtained in the hydrogenation of the alkinyl amine **4d**. Performing the reaction in other solvents like tBuOMe and toluene and with other inductors like $FeCl_3/Al_2O_3$ resulted only in the recovery of unchanged starting material. It is noteworthy that not a trace of the diester **12** could be detected under any conditions tested.



12



R	
13	H
14	Et



15

For comparison, the cyclization of the corresponding allylsilane-imine **11**, which was obtained by condensation of the known amine **7**[5b-c] with diethyl mesoxalate to give the required imine **11** in 93% yield, was investigated. Treatment of **11** with 1.1 equiv. of TMS-OTf afforded within 5 h in a smooth reaction exclusively the expected 3-vinylpiperidine **12** in 65% yield using toluene as solvent and 60% yield in tBuOMe. The higher reactivity of **11** compared to **9** and **10** is due to the cation stabilizing β-effect of the Si atom[13]. Catalytic amounts of TMS-OTf are not sufficient to bring the reaction to completion, thus, with 0.1 equiv. of TMS-OTf only an incomplete turnover could be detected after 24 h. The use of $FeCl_3/Al_2O_3$ was less appropriate, since 2.5 equiv. of the Lewis acid were necessary and **12** was obtained in only 40% yield.

Experiments to initiate the cyclization of **11** with an allylsilane and an imine moiety using fluoride resulted only in the formation of a complex mixture[14]. This type of initiation is employed extensively for additions of allylsilanes to carbonyl compounds[15]. Finally we tried to cyclize **12** to give either **13** or **15**. However, a mixture of **12** and 5 equiv. of TMS-OTf did not show any changes even after 7 days at room temperature. Only addition of 10 equiv. of CF_3SO_3H led within 5 h to the formation of **13** and **15** in nearly equal amounts as indicated by TLC.

Cyclization Reactions with 1,1-Disubstituted Olefins

The cyclization reaction is also applicable to 1,1-disubstituted alkenes **19** and **22**, which are accessible by condensation of the known amines **16** and **17**[16] with diethyl mesoxalate **8** in 80% and 86% yield, respectively. Treatment of **19** with $FeCl_3/Al_2O_3$ as well as TMS-OTf in different solvents led to the cyclization products **20** and **21** in a 7.1 – 19.0:1.0 ratio (GC, NMR) and 71 – 96% yield depending on the reaction conditions (Scheme 2). In all reactions the thermodynamically more stable *endo* isomer **20** was the main product.

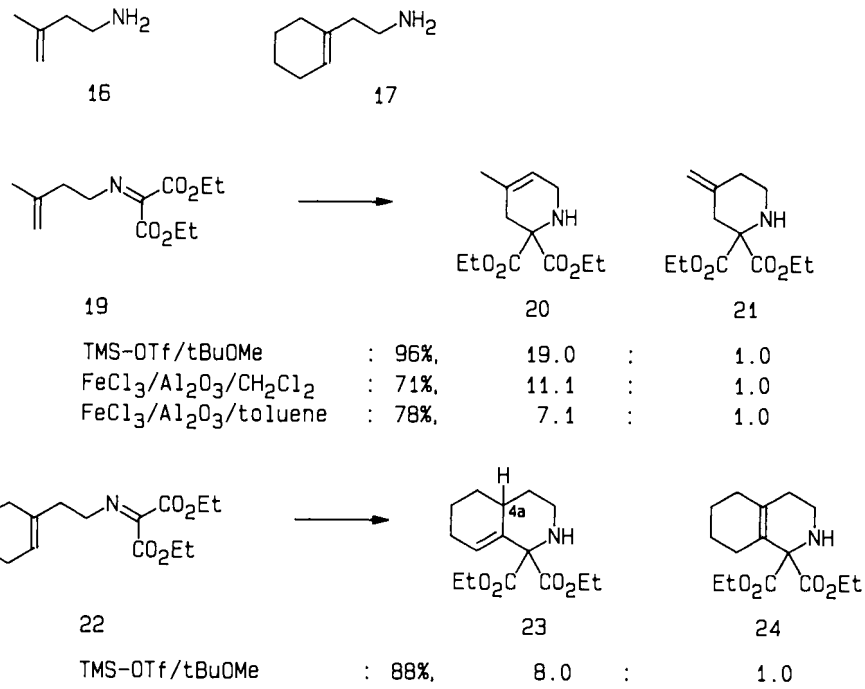
In a similar way, cyclization of the imine **22** using TMS-OTf as inductor afforded the two isomeric octahydroisoquinolines **23** and **24** in a 8:1 ratio and excellent yield. As already observed for similar reactions, the inductor TMS-OTf which was introduced by us for the electrophilic cyclization of alkenes with imines gave again the highest yields and best selectivities.

Structure Elucidation of the Cyclization Products

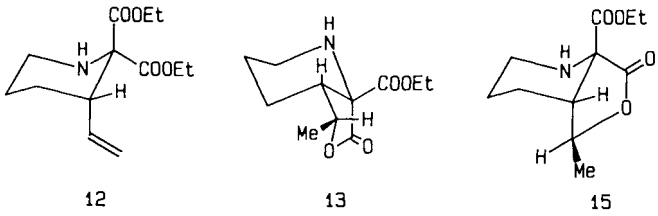
Structural assignment of **12**, **13**, **14**, and **15** is based on ^{1}H- and ^{13}C-NMR data. The signal for 3-H in **12** appears at δ = 3.08 with two small coupling constants (J = 4 Hz) to the vicinal protons at C-4 and a large coupling to (J = 9 Hz) 1′-H, indicating an axial orientation of the vinyl group. The vinylic protons absorb at δ = 5.08 (2′-H_{cis}), 5.14 (2′-H_{trans}) and 6.20 (1′-H). This is in agreement with earlier findings for 3-isopropenyl derivatives[8a,c].

The structure elucidation of **13** – **15** was less simple because of signal overlap. However, 4a-H in **13** causes a triple doublet at δ = 2.67 with a large, a middle and a small coupling constant, indicating an axial orientation of 4a-H ($J_{4a,4ax}$ = 11.5, $J_{4a,4eq}$ = 7, $J_{4a,5}$ = 4.5 Hz). In **15**, 4a-H should have an equatorial orientation, since the signal of 4a-H (δ =

Scheme 2



Scheme 3



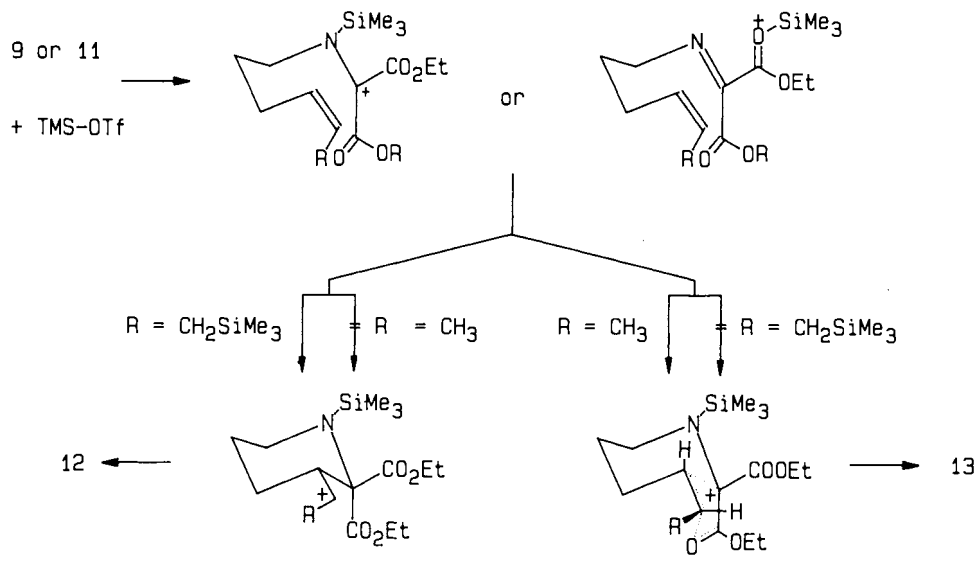
2.62–2.79), though not well-resolved, has a half width of ≈15 Hz which is much smaller than the appropriate peak in the spectrum of **13** (≈22 Hz). As a coupling between 4a-H and 5-H of J = 10 Hz is found, the half width of ≈15 Hz clearly indicates the lack of a diaxial coupling, thus 4a-H must have an equatorial orientation.

The configuration at C-5 in **13** is derived from the coupling constants between 4a-H and 5-H and DNOE experiments. An inspection of Dreiding models shows that the two protons have a synclinical arrangement. This is supported by the 4.5 Hz coupling between these protons and a strong NOE, observed for 4a-H by irradiation at 5-H (δ = 4.77). Such an NOE was not found for **15** which indicates together with the coupling contant of J = 10 Hz an antiperiplanar arrangement of 4a-H and 5-H. ^{13}C-NMR data complement these findings.

In the ^{1}H-NMR spectrum of **20** only one signal for an olefinic proton at δ = 5.40 is found, whereas in the spectrum of **21** (crude mixture) the absorptions for two protons are observed at δ = 4.85.

24 was easily identified as the $\Delta^{4a,8a}$ isomer by the lack of signals for vinylic protons in the ^{1}H-NMR spectrum. The

Scheme 4



$\Delta^{8,8a}$ position of the double bond in **23** was concluded from the following findings: 1) 4-H shows no allylic coupling, which should be present in the spectrum of the $\Delta^{4a,5}$ isomer. 2) The signal shape of 4a-H at δ = 2.64 which appears as a broad triplet is more compatible with **23** (4 contiguous protons) than with its $\Delta^{4a,5}$ isomer (2 contiguous protons).

Mechanistic Considerations

The cyclization of the imines is initiated either by the formation of an iminium salt or through activation of the imine by silylation at a carbonyl oxygen. Independent from this consideration, nucleophilic attack of the alkene should formally lead to a carbocation which could finally afford a new alkene by an elimination step[17]. This type of reaction is found for **11** where the intermediate carbocation is stabilized by a silicon atom in β-position.

However, in the transformation of **9** and **10** a free carbenium ion is not an intermediate, but in a concerted way with chair-type geometries of the transition state, a C–C and a C–O bond formation takes place to give stereoselectively the bicyclic lactone **13** and **15**. Thus the cyclization allows the stereoselective formation of three stereogenic centers with complete retention of the double bond geometry. It is of interest that the stabilizing effect of the adjacent carbonyl groups is completely overruled by a silicon atom. In the cyclization of **19** and **22** a neighbouring group effect of the ester moieties is not possible for geometric reasons. Thus the primarily formed carbocation reacts with elimination of a proton to give preferentially the more stable tetrahydropyridine **20** and the octahydroisoquinoline **23**, respectively.

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Experimental

^{1}H NMR and ^{13}C NMR: Varian XL-200, XL-100, VXR-200 and FT-80A, multiplicities were determined with the APT pulse sequence. – MS: Varian MAT 311A, high resolution: Varian MAT 731. – IR: Perkin-Elmer 297. – UV: Varian Cary 219. – Analytical GC: Varian 3700 with FID and Merck-Hitachi D-2000; Chrompack 0.13 μm CpSil5, 0.32 mm × 25 m fused silica gel. – Elemental analyses were carried out in the analytical laboratory of the university. – All solvents were distilled prior to use. Products were generally isolated by flash chromatography (FC) on SiO_2 (Silica Woelm 32–63, active, Fa. Woelm Pharma, Eschwege). – All chiral compounds were obtained as racemic mixtures.

4-Hexinylamine (**4d**): To a solution of 4-hexinol (**4a**) (13.4 g, 137 mmol) in dichloromethane (300 ml) was added at 0°C with stirring methanesulfonyl chloride (16.4 g, 144 mmol) and triethylamine (16.6 g, 165 mmol) and stirring was continued at 0°C for 1 h. The mixture was washed with water (2 × 100 ml), dried (K_2CO_3), and the solvent was evaporated in vacuo to give the crude mesylate **4b** (21.5 g, 90%) which was used in the following reaction without further purification. – A mixture of the mesylate and finely powdered sodium azide (12.0 g, 185 mmol) in DMSO (250 ml) was stirred overnight and afterwards poured into ice water. After extraction with diethyl ether (4 × 100 ml), the combined organic layers were washed (brine, 50 ml), dried (Na_2SO_4), concentrated in vacuo, and the residue was distilled under reduced pressure (**Caution!**) to give 11.3 g (75%) *4-hexinyl azide* (**4c**); b.p. 68–70°C/10 Torr. – To a solution of **4c** (5.00 g, 41.0 mmol) in THF (50 ml) was added dropwise with stirring and cooling a 5 M solution of triphenylphosphane (8 ml) so that the temperature did not raise above 20°C and stirring was continued for 16 h. After addition of water (5 ml) and stirring for 5 h, the solvent was evaporated and pentane (60 ml) was added. Phosphane oxide was removed by filtration (repeated procedure), the solvent evaporated, and the remaining residue distilled under reduced pressure to give 2.42 g (61%) of the amine **4d**; b.p. 68–69°C/15 Torr. – ^{1}H NMR (60 MHz, $CDCl_3$): δ = 1.10 (s, 2H, NH_2), 1.62 (q, J = 7 Hz, 2H, 2-H), 1.75 (t, J = 4 Hz, 3H, 6-H), 2.00–2.50 (m, 2H, 3-H), 2.80 (t, J = 7 Hz, 2H, 1-H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 3.4 (C-6), 16.2 (C-3), 33.1 (C-2), 41.5 (C-1), 75.6, 78.7 (C-4, C-5).

N-Naphthylthiourea derivative: m.p. 80–82°C (2-propanol).

$C_{17}H_{18}N_2S$ (282.4) Calcd. C 72.30 H 6.42 N 9.92 S 11.33
Found C 72.24 H 6.42 N 9.97 S 11.40

(Z)-4-Hexenylamine (**5**): To a solution of $Ni(OAc)_2 \times 2H_2O$ (572 mg, 2.30 mmol) in ethanol (20 ml) was added in one portion a solution of $NaBH_4$ (86.9 mg, 2.30 mmol) in ethanol (3 ml). After the hydrogen evolution has ceased, ethylenediamine (270 mg, 4.50 mmol) and **4d** (1.76 g, 18 mmol) were added and the solution was kept under hydrogen until the calculated uptake of hydrogen was complete. The catalyst was removed after addition of charcoal by filtration over celite. Distillation (kugelrohr, 100°C/15 Torr) gave 1.22 g (68%) of the amines **5** and **6** in a ratio of 13:1 (^{13}C NMR). – ^{1}H NMR (100 MHz, $CDCl_3$): δ = 1.40 (s, 2H, NH_2), 1.30–1.70 (m, 5H, 2-H, 6-H), 1.80–2.20 (m, 2H, 3-H), 2.72 (t, J = 7 Hz, 2H, 1-H), 5.20–5.50 (m, 2H, 4-H, 5-H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 12.7 (C-6), 24.3 (C-2), 33.4 (C-3), 41.8 (C-1), 124.3 (C-5), 130.1 (C-4).

N-Naphthylthiourea derivative: m.p. 71–74°C (2-propanol).

$C_{17}H_{20}N_2S$ (284.4) Calcd. C 71.79 H 7.09 N 9.85 S 11.27
Found C 71.47 H 7.25 N 9.94 S 11.29

Preparation of Imines. – General Procedure I: Diethyl mesoxalate (**8**) (10.0 mmol) and the amine (10.0 mmol) were dissolved in benzene (100 ml) and heated using a Dean-Stark trap until the reaction was complete. Evaporation of the solvent and filtration of the residue on silica gel (petroleum ether/diethyl ether = 2:1, if not otherwise indicated) gave the imines as light yellow oils.

Diethyl (Z)-(4'-Hexenylimino)malonate (**9**): **8** (879 mg, 5.05 mmol) and amine **5** (500 mg, 5.05 mmol) were condensed as described in procedure I. Eluent: petroleum ether/diethyl ether = 1:1; yield 922 mg (72%); R_f = 0.61 (petroleum ether/diethyl ether = 1:1). – IR (film): $\tilde{\nu}$ = 2990 cm^{-1}, 2940 (CH), 1740 br. (CO), 1660 (CN), 1480, 1240, 1070, 970, 870. – ^{1}H NMR (100 MHz, $CDCl_3$): δ = 1.40 (t, J = 7 Hz, 6H, OCH_2CH_3), 1.62 (d, J = 5.5 Hz, 3H, Me), 1.70–2.30 (m, 4H, 2'-H, 3'-H), 1.62 (t, J = 7 Hz, 2H, 1'-H), 4.40 (q, J = 7 Hz, 4H, OCH_2), 5.24–5.66 (m, 2H, 4'-H, 5'-H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 12.8 (C-6'), 14.1, 14.2 (ester, Me), 24.6 (C-3'), 29.9 (C-2'), 55.2 (C-1'), 61.9, 62.5 (OCH_2), 124.8 (C-5'), 129.4 (C-4'), 153.7 (C-2), 161.2, 162.4 (C-1, C-2). – MS (70 eV): *m/z* (%) = 255 (4) [M^+], 226 (33) [M – Et], 182 (29) [M – CO_2Et], 154 (14) [182 – CO oder C_2H_4], 83 (13) [C_6H_{11}], 55 (100) [C_4H_7], 41 (27) [C_3H_5].

$C_{13}H_{21}NO_4$ (255.3) Calcd. C 61.16 H 8.29 N 5.49
Found C 61.03 H 8.39 N 5.49

Diethyl (E)-(4'-Hexenylimino)malonate (**10**): **8** (1.74 g, 10.0 mmol) and amine **6** (1.00 g, 10.0 mmol) were condensed as described in procedure I. Eluent: petroleum ether/diethyl ether = 1:1; yield

2.29 g (89%); R_f = 0.60 (petroleum ether/diethyl ether = 1:1). – IR (film): $\tilde{\nu}$ = 2990 cm^{-1}, 2940, 2860 (CH), 1745 br. (CO), 1660 (CN), 1450, 1370, 1320, 1240, 1070, 870. – ^1H NMR (100 MHz, $CDCl_3$): δ = 1.37 (t, J = 7 Hz, 6H, OCH_2CH_3), 1.64 (dd, J = 3.5, 1.3 Hz, 3H, Me), 1.60–2.20 (m, 4H, 2'-H, 3'-H), 3.59 (t, J = 7 Hz, 2H, 1'-H), 4.38 (q, J = 7 Hz, 4H, OCH_2), 5.35–5.53 (m, 2H, 4'-H, 5'-H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 14.1, 14.1 (ester, Me), 17.9 (C-6'), 29.8 (C-3'), 30.2 (C-2'), 55.2 (C-1'), 61.9, 62.5 (OCH_2), 125.8 (C-5'), 130.2 (C-4'), 153.7 (C-2), 161.2, 162.4 (C-1, C-2). – MS (70 eV): m/z (%) = 255 (5) [M^+], 226 (35) [M – Et], 182 (32) [M – CO_2Et], 154 (11) [182 – CO oder C_2H_4], 83 (16) [C_6H_{11}], 55 (100) [C_4H_7], 41 (42) [C_3H_5].

$C_{13}H_{21}NO_4$ (255.3) Calcd. C 61.16 H 8.29 N 5.49
Found C 61.37 H 8.29 N 5.43

Diethyl ⟨[6'-Trimethylsilyl-(Z)-4'-hexenyl]imino⟩malonate (**11**): **8** (413 mg, 2.38 mmol) and amine 7 (407 mg, 2.38 mmol) were condensed as described in procedure I; yield 724 mg (93%); R_f = 0.5. – IR (film): $\tilde{\nu}$ = 2950 cm^{-1}, 1740 br. (CO), 1650 (CN), 860. – ^1H NMR (100 MHz, $CDCl_3$): δ = 0.01 (s, 9H, $SiMe_3$), 1.65 (t, J = 7 Hz, 6H, OCH_2CH_3), 1.20–2.30 (m, 6H, 2'-H, 3'-H, 6'-H), 3.55 (t, J = 7 Hz, 2H, 1'-H), 4.35 (q, J = 7 Hz, 4H, OCH_2), 5.00–5.60 (m, 2H, 4'-H, 5'-H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = –1.9 ($SiMe_3$), 14.0, 14.1 (ester, Me), 18.4 (C-6'), 24.7 (C-2'), 29.9 (C-3'), 55.8 (C-1'), 61.9, 62.5 (OCH_2), 126.0, 126.5 (C-4', C-5'), 153.4 (C-3), 161.1, 162.4 (C-1, C-3). – MS (70 eV): m/z (%) = 327 (3) [M^+], 298 (7) [M – Et], 254 (36) [M – CO_2Et oder $SiMe_3$], 73 (100) [$SiMe_3$].

$C_{16}H_{29}NO_4Si$ (327.5) Calcd. C 58.68 H 8.93 N 4.28
Found C 58.60 H 8.79 N 4.24

Diethyl (3'-Methyl-3'-butenylimino)malonate (**19**): **8** (3.48 g, 20.0 mmol) and amine **16** (1.70 g, 20.0 mmol) were condensed according to procedure I; yield 3.86 g (80%); R_f = 0.38. – IR (film): $\tilde{\nu}$ = 3080 cm^{-1}, 3000 (CH), 1745 br. (CO), 1655 (CN), 1360, 1320, 1250, 1090, 890. – ^1H NMR (100 MHz, $CDCl_3$): δ = 1.37 (t, J = 7 Hz, 6H, OCH_2CH_3), 1.76 (s, 3H, 5'-H), 2.44 (t, J = 8 Hz, 2H, 2'-H), 3.74 (t, J = 8 Hz, 2H, 1'-H), 4.38 (q, J = 7 Hz, 4H, OCH_2), 4.77 (m, 2H, 4'-H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 14.1, 14.2 (ester, Me), 22.6 (C-5'), 38.1 (C-2'), 54.4 (C-1'), 62.0, 62.5 (OCH_2), 111.9 (C-4'), 142.6 (C-3'), 153.9 (C-2), 161.2, 162.2 (C-1, C-3). – MS (70 eV): m/z (%) = 241 (2) [M^+], 195 (24) [M – HOEt], 168 (39) [M – CO_2Et], 69 (85) [C_5H_9], 41 (100) [C_3H_5].

$C_{12}H_{19}NO_4$ (241.3) Calcd. C 59.73 H 7.94 N 5.81
Found C 59.81 H 7.99 N 5.77

Diethyl [2'-(1''-Cyclohexenyl)ethylimino]malonate (**22**): **8** (3.48 g, 20.0 mmol) and amine **17** (2.50 g, 20.0 mmol) were condensed according to procedure I; yield 4.83 g (86%); R_f = 0.40. – IR (film): $\tilde{\nu}$ = 3000 cm^{-1}, 2940 (CH), 1745 br. (CO), 1660 (CN), 1450, 1320, 1250, 1075, 860. – ^1H NMR (100 MHz, $CDCl_3$): δ = 1.38 (t, J = 7 Hz, 6H, OCH_2CH_3), 1.40–1.70 (m, 4H, 3''-H–6''-H_{ax}), 1.80–2.10 (m, 4H, 3''-H–6''H_{eq}), 2.37 (t, J = 7 Hz, 2H, 2'-H), 3.69 (m, 2H, 1'-H), 4.38 (q, J = 7 Hz, 4H, OCH_2), 5.48 (m, 1H, 2''-H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 14.09, 14.2 (ester, Me), 22.4 (C-5''), 22.9 (C-4''), 25.3 (C-3''), 28.6 (C-6''), 38.4 (C-2'), 54.9 (C-1'), 61.9, 62.5 (OCH_2), 123.1 (C-2''), 134.8 (C-1''), 153.6 (C-2), 161.2, 162.2 (C-1, C-2). – MS (70 eV): m/z (%) = 281 (5) [M^+], 235 (4) [M – EtOH], 208 (100) [M – CO_2Et], 135 (28) [208 – CO_2Et], 109 (12) [C_8H_{13}], 67 (31) [C_5H_7], 41 (28) [C_3H_5].

$C_{15}H_{23}NO_4$ (281.4) Calcd. C 64.04 H 8.24 N 4.98
Found C 63.82 H 8.33 N 4.91

Cyclization Experiments. – General Procedure II

a) Cyclization with Trimethylsilyl Trifluoromethanesulfonate (TMS-OTf): To a cooled solution (–78 °C) of the imine (1.00 mmol) in 10 ml of an appropriate solvent was added with stirring 1.1 equiv. of TMS-OTf. Stirring was continued at this temp. for 1 h and then the mixture was allowed to warm up to room temp. overnight. After completion of the cyclization (TLC, usually 18 h), the mixture was hydrolyzed by addition of sat. $NaHCO_3$ solution and extracted with diethyl ether (3 × 50 ml) to give the crude products which were separated by chromatography (silica gel, petroleum ether/diethyl ether = 2:1), unless otherwise indicated.

b) *Cyclization with Lewis Acids on Solid Support*[18]: To a cooled suspension (–78 °C) of a Lewis acid (1.1 mmol, absorbed on 1.1 g of basic alumina) in 10 ml of an appropriate solvent was added with stirring a solution of an imine (1.0 mmol) in 1 ml of the solvent. Stirring was continued for 1 h and the mixture was allowed to warm up to room temp. overnight. After completion of cyclization (TLC), the mixture was hydrolyzed with sat. $NaHCO_3$ solution. Further workup was performed as described above.

Reaction of **9**: **9** (276 mg, 1.08 mmol) was treated with TMS-OTf in dichloromethane as described in procedure IIa (reaction time 4 d). Workup and chromatography gave 117 mg (48%) of **14** and 78 mg (32%) of **13**.

Ethyl (4aRS,5RS,7aRS)-1-Ethyl-1,2,3,4,4a,5,7,7a-octahydro-5-methyl-7-oxofuro[3,4-b]pyridine-7a-carboxylate (**14**): R_f = 0.50 (petroleum ether/diethyl ether = 1:2). – IR (film): $\tilde{\nu}$ = 2930 cm^{-1}, 2862, 1780 (lactone), 1744, 1722 (ester), 1258, 1233, 1214, 1102. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.04 (t, J = 7 Hz, 3H, NCH_2CH_3), 1.00–1.40 (m, 1H, 3-H_{ax}), 1.30 (d, J = 7 Hz, 3H, 5-CH_3), 1.32 (t, J = 7 Hz, 3H, OCH_2CH_3), 1.42–1.92 (m, 3H, 3-H_{eq}, 4-H), 2.31 (ddd, J = 11.5, 11.5, 3 Hz, 1H, 2-H_{ax}), 2.51 (ddd, J = 12, 5, 4 Hz, 1H, 4a-H), 2.71 (dq, J = 14, 7 Hz, 1H, NCH), 3.06 (dddd, J = 11.5, 4, 4, 1.5 Hz, 1H, 2-H_{eq}), 3.14 (dq, J = 14, 7 Hz, 1H, NCH), 4.37 (q, J = 7 Hz, 2H, OCH_2), 4.52 (dq, J = 4, 7 Hz, 1H, 5-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 14.1 (OEt, NEt), 14.9 (5-Me), 20.9 (C-4), 22.6 (C-3), 43.9 (C-4a), 46.1 (C-2), 47.1 (NCH_2), 62.4 (OCH_2), 75.2 (C-5), 75.7 (C-7a), 170.8 (ester, CO), 172.7 (C-7). – MS (70 eV): m/z (%) = 255 (4) [M^+], 182 (100) [M – CO_2Et], 154 (6) [182 – C_2H_5], 110 (12) [$C_7H_{12}N$], 82 (7) [C_5H_8N], 55 (12) [C_3H_5N].

$C_{13}H_{21}NO_4$ (255.3) Calcd. C 61.16 H 8.29 N 5.49
Found C 61.05 H 8.28 N 5.42

Ethyl (4aRS,5RS,7aRS)-1,2,3,4,4a,5,7,7a-Octahydro-5-methyl-7-oxofuro[3,4-b]pyridine-7a-carboxylate (**13**): R_f = 0.25 (petroleum ether/diethyl ether = 1:2). – IR (film): $\tilde{\nu}$ = 3340 cm^{-1} (NH), 2940, 2860, 1780 (lactone), 1735 (ester), 1450, 1390, 1250, 1205, 1095, 1055, 1025. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.13–1.87 (m, 4H, 3-H, 4-H), 1.28 (d, J = 7 Hz, 3H, 5-CH_3), 1.34 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.30 (s, 1H, NH), 2.58 (ddd, J = 12, 11.5, 3 Hz, 1H, 2-H_{ax}), 2.67 (ddd, J = 11.5, 7, 4.5 Hz, 1H, 4a-H), 2.96 (dddd, J = 12, 3.5, 3.5, 1.5 Hz, 1H, 2-H_{eq}), 4.26 (m_c, 2H, OCH_2), 4.77 (dq, J = 4.5, 6.5 Hz, 1H, 5-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.01 (ester, Me), 14.93 (5-Me), 21.08 (C-4), 22.53 (C-3), 40.33 (C-4a), 42.41 (C-2), 62.67 (OCH_2), 68.90 (C-7a), 76.68 (C-5), 168.54 (ester, CO), 173.57 (C-7). – MS (70 eV): m/z (%) = 227 (2) [M^+], 154 (100) [M – CO_2Et], 110 (41) [$C_7H_{12}N$], 108 (62), 82 (58) [C_5H_8N], 55 (57) [C_3H_5N].

$C_{11}H_{17}NO_4$ (227.3) Calcd. C 58.14 H 7.54 N 6.16
Found C 58.04 H 7.61 N 6.09

Reaction of **10**: **10** (226 mg, 1.06 mmol) was treated with TMS-OTf in dichloromethane as described in procedure IIa (reaction time 5 d). Workup and chromatography (petroleum ether/diethyl ether = 1:1) gave 57 mg (22%) of unreacted imine **10** and 135 mg (56%) of *ethyl (4aRS,5SR,7aRS)-1,2,3,4,4a,5,7,7a-octahydro-5-me-*

thyl-7-oxofuro[3,4-b]pyridine-7a-carboxylate (**15**): R_f = 0.48 (petroleum ether/diethyl ether = 1:2). – IR (film): $\tilde{\nu}$ = 3320 cm^{-1} (NH), 2980, 2940, 2860, 1770 br. (lactone), 1725 br. (ester), 1440, 1300, 1020, 910, 745. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 6.5 Hz, 3H, OCH_2CH_3), 1.47 (d, *J* = 6.5 Hz, 3H, 5-CH_3), 1.44–1.80 (m, 4H, 3-H, 4-H), 2.44 (s, 1H, NH), 2.62–2.79 (m, 2H, 2-H_{ax}, 4a-H), 3.00 (mc, 1H, 2-H_{eq}), 4.33 (mc, 2H, OCH_2), 4.84 (dq, *J* = 10, 6.5 Hz, 1H, 5-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.92 (ester, Me), 18.29 (5-Me), 19.69 (C-4), 20.43 (C-3), 42.33 (C-2), 45.16 (C-4a), 62.31 (OCH_2), 66.71 (C-7a), 77.02 (C-5), 168.41 (ester, CO), 172.52 (C-7). – MS (70 eV): *m/z* (%) = 227 (3) [M^+], 182 (3) [M – OEt], 154 (100) [M – CO_2Et], 110 (23) [$C_7H_{12}N$], 82 (22) [C_5H_8N], 55 (15) [C_3H_5N].

$C_{11}H_{17}NO_4$ (227.3) Calcd. C 58.14 H 7.54 Found C 57.33 H 7.60
Calcd. 227.1158 Found 227.1158 (MS)

Reaction of **11**: 1) **11** (163 mg, 0.50 mmol) was treated with TMS-OTf in toluene (reaction time 3.5 h) as described in procedure IIa. Workup and chromatography gave 83 mg (65%) of **12**.

2) **11** (30.0 mg, 0.092 mmol) was cyclized as described in procedure IIa with TMS-OTf in tBuOMe (reaction time 7 h). Workup and chromatography gave 14.0 mg (60%) of **12**.

3) **11** (33.0 mg, 0.10 mmol) was cyclized according to procedure IIb with 2.5 equiv. of $FeCl_3/Al_2O_3$ in dichloromethane as solvent (reaction time 18 h) to give after workup and chromatography 10.3 mg (40%) of **12**.

Diethyl 3-Vinyl-2,2-piperidinedicarboxylate (**12**): R_f = 0.17. – IR (film): $\tilde{\nu}$ = 3360 cm^{-1} (NH), 3070, 2980, 2940, 2880, 1740 br. (CO), 1640, 1440, 1230, 1040. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7 Hz, 3H, OCH_2CH_3), 1.28 (t, *J* = 7 Hz, 3H, OCH_2CH_3), 1.35–2.02 (m, 4H, 5-H, 6-H), 2.19 (s br., 1H, NH), 2.32 (ddd, *J* = 12, 10.5, 3 Hz, 1H, 6-H_{ax}), 3.00 (dddd, *J* = 12, 4, 4, 1.5 Hz, 1H, 6-H_{eq}), 3.08 (ddd, *J* = 9, 4, 4 Hz, 1H, 3-H), 4.20 (q, *J* = 7 Hz, 2H, OCH_2), 4.27 (q, *J* = 7 Hz, 2H, OCH_2), 5.08 (ddd, *J* = 10.5, 2, 0.5 Hz, 1H, 2′-H_{cis}), 5.14 (ddd, *J* = 17, 2, 1 Hz, 1H, 2′-H_{trans}), 6.20 (ddd, *J* = 17, 10.5, 9 Hz, 1H, 1′-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.09, 14.19 (ester, Me), 21.05 (C-4), 27.59 (C-5), 42.59 (C-3), 42.98 (C-6), 61.56, 61.62 (OCH_2), 70.74 (C-2), 116.68 (C-2′), 137.43 (C-1′), 169.63, 170.48 (CO). – MS (70 eV): *m/z* (%) = 255 (0.5) [M^+], 182 (100) [M – CO_2Et], 154 (7) [182 – C_2H_4, McLafferty], 136 (6) [154 – H_2O], 108 (31) [$C_7H_{10}N$].

$C_{13}H_{21}NO_4$ (255.3) Calcd. C 61.16 H 8.29 N 5.49
Found C 61.01 H 8.03 N 5.47

Cyclization Experiment with **12**: **12** (13.0 mg, 0.051 mmol) was dissolved in dichloromethane (3 ml) and TMS-OTf (50 µl, 0.25 mmol) was added at ambient temp. After a period of 5 d no reaction could be detected by TLC. Addition of CF_3SO_3H (45 µl, 5.00 mmol) led in 5 h to a complete conversion of **12** to a mixture of **13** and **15**. TLC indicated a ratio of about 1.5:1 of the isomers.

Cyclization of **19**: 1) **19** (487 mg, 2.02 mmol) was cyclized in tBuOMe with TMS-OTf as described in procedure IIa (reaction time 18 h). Workup and filtration over silica gel (petroleum ether/diethyl ether = 1:1) gave 467 mg (96%) of **20** and **21** in a 19.0:1.0 ratio (GC). **20** was obtained in a pure form after chromatography (silica gel, petroleum ether/diethyl ether = 1:1).

2) **19** (241 mg, 1.00 mmol) was cyclized according to procedure IIb with $FeCl_3/Al_2O_3$ in dichloromethane (reaction time 18 h) to give after workup and filtration over silica gel 171 mg (71%) of a mixture of **20**/**21** = 11.1:1.0 (GC).

Diethyl 1,2,3,6-Tetrahydro-4-methyl-2,2-pyridinedicarboxylate (**20**): R_f = 0.17. – IR (film): $\tilde{\nu}$ = 3360 cm^{-1} (NH), 2990, 1745 (CO), 1690 sh (C=C), 1450, 1260, 1185, 1060. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7 Hz, 6H, OCH_2CH_3), 1.74 (m, 3H, 1′-H), 2.44 (s, 1H, NH), 2.58 (m, 2H, 3-H), 3.44 (m, 2H, 6-H), 4.25 (q, *J* = 7 Hz, 4H, OCH_2), 5.40 (m, 1H, 5-H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 14.1 (ester, Me), 23.1 (C-1′), 34.5 (C-3), 42.2 (C-6), 61.6 (OCH_2), 65.9 (C-2), 118.7 (C-5), 130.2 (C-4), 170.0 (CO). – MS (70 eV): *m/z* (%) = 241 (5) [M^+], 168 (100) [M – CO_2Et], 140 (15) [168 – C_2H_4, McLafferty], 122 (7) [140 – H_2O], 94 (43) [122 – CO].

$C_{12}H_{19}NO_4$ (241.3) Calcd. C 59.73 H 7.94 N 5.81
Found C 59.87 H 7.86 N 5.84

Cyclization of **22**; **22** (288 mg, 1.00 mmol) was cyclized according to procedure IIa with TMS-OTf in tBuOMe (reaction time 18 h) to give **23** and **24** in a 8.0:1.0 ratio after aqueous workup (GC). Chromatography (silica gel, petroleum ether/tBuOMe = 1:1) afforded 194 mg (69%) of **23** and 32 mg (12%) of **24**.

Diethyl 1,2,3,4,4a,6,7,8-Octahydro-2,2-isoquinolinedicarboxylate (**23**): R_f = 0.31 (petroleum ether/diethyl ether = 1:2). – IR (film): $\tilde{\nu}$ = 3350 cm^{-1} (NH), 2940, 1735 (CO), 1450, 710. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.32–1.20 (m, 6H, OCH_2CH_3), 1.30–2.20 (m, 7H, CH_2, CH), 2.30 (s, 1H, NH), 2.64 (m, 1H, 4a-H), 2.84 (ddd, *J* = 11.5, 11.5, 4 Hz, 1H, 3-H_{ax}), 3.00 (ddd, *J* = 11.5, 6, 2.5 Hz, 1H, 3-H_{eq}), 4.24 (m, 4H, OCH_2), 5.62 (q, br., *J* = 2.5 Hz, 1H, 8-H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 14.15 (ester, Me), 22.11 (C-6), 24.91 (C-7, C-4), 34.29 (C-5), 41.38 (C-4a), 42.69 (C-3), 60.74, 61.45 (OCH_2), 70.77 (C-1), 123.74 (C-8), 133.35 (C-8a), 169.87, 170.07 (CO). – MS (70 eV): *m/z* (%) = 281 (21) [M^+], 208 (100) [M – CO_2Et], 180 (4) [208 – C_2H_4, McLafferty], 162 (3) [180 – H_2O], 135 (23) [208 – CO_2Et], 134 (19) [162 – CO].

$C_{15}H_{23}NO_4$ (281.4) Calcd. C 64.04 H 8.24 N 4.98
Found C 64.05 H 8.00 N 5.01

Diethyl 1,2,3,4,5,6,7,8-Octahydro-2,2-isoquinolinedicarboxylate (**24**): R_f = 0.24 (petroleum ether/diethyl ether = 1:2). – IR (film): $\tilde{\nu}$ = 3340 cm^{-1} (NH), 2940, 1730 (CO), 1700 sh (C=C), 1450. – ^1H-NMR (200 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7 Hz, 6H, OCH_2CH_3), 1.64 (m, 4H, 8-H–5-H_{ax}), 2.00 (m, 4H, 8-H–5-H_{eq}), 2.04 (t, *J* = 6 Hz, 2H, 4-H), 2.56 (s, 1H, NH), 2.92 (t, *J* = 6 Hz, 2H, 3-H), 4.28 (q, *J* = 7 Hz, 4H, OCH_2). – MS (70 eV): *m/z* (%) = 281 (21) [M^+], 208 (100) [M – CO_2Et], 180 (13) [208 – C_2H_4, McLafferty], 162 (14) [180 – H_2O], 134 (32) [162 – CO], 107 (18) [134 – HCN].

$C_{15}H_{23}NO_4$ (281.4) Calcd. 281.1627 Found 281.1627 (MS)

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