Intramolecular Electrophilic Cyclization of Doubly Activated Imines Induced by Lewis Acids and Trialkylsilyl Triflates. An Efficient Route to Substituted Piperidines and Annulated Piperidine Lactones

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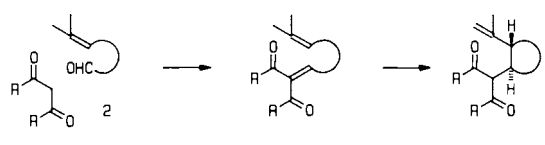
Intramolecular electrophilic cyclization of imines 11a–c with two electron-withdrawing groups at the C=N bond using Lewis and Brønsted acids as well as trialkylsilyl trifluoromethanesulfonates gives the piperidines 12a–c and the annulated piperidine lactones 13a–c and 14. 11b yields mostly 12b with the trialkylsilyl triflates and 13b with Lewis acids such as $FeCl_3$ on Al_2O_3 or $GaCl_3$. The reaction of 11a and 11c always results, using different methods, in the formation of the lactones 13a, 14, and 13c, respectively. Treatment of 13b with aqueous base affords 19, a derivative of a cyclic nonproteinogenic α-amino acid.

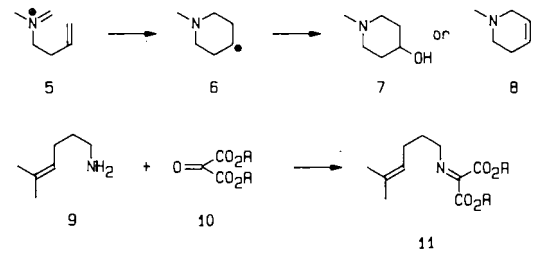
Lewis-Säure- und Trialkylsilyl-trifluormethansulfonat-induzierte intramolekulare elektrophile Cyclisierung doppelt aktivierter Imine. Ein effizienter Weg zu substituierten Piperidinen und anellierten Piperidinlactonen

Die intramolekulare elektrophile Cyclisierung von Iminen **11a–c** mit zwei Elektronenakzeptor-Gruppen an der C=N-Gruppe mit Lewis- und Brønsted-Säuren sowie Trialkylsilyl-trifluormethansulfonaten ergibt die Piperidine **12a–c** und die anellierten Piperidinlactone **13a–c** und **14**. **11b** führt bei Reaktion mit Trialkylsilyltriflaten hauptsächlich zu **12b**, während mit den Lewis-Säuren $FeCl_3$ auf Al_2O_3 und $GaCl_3$ überwiegend das Lacton **13b** erhalten wird. Umsetzung von **11a** und **11c** ergibt unabhängig von den Reaktionsbedingungen nahezu ausschließlich die Lactone **13a** und **14** sowie **13c**. Hydrolyse von **13b** mit wäßriger Base führt unter Decarboxylierung zum Derivat **19** einer cyclischen, nicht proteinogenen α-Aminosäure.

The tandem Knoevenagel ene reaction using 1,3-dicarbonyls **1** or analogous compounds and unsaturated aldehydes **2** is a valuable method for an efficient and selective synthesis of substituted cyclohexane and cyclopentane derivatives **4**[1]. In this transformation an alkylidene-1,3-dicarbonyl system **3** is formed as an intermediate, which acts as a highly reactive enophile. Thus, the high reaction rate in the ene reaction is due to the two electron-withdrawing groups at the enophile moiety in **3**, which causes a decrease in the energy of the LUMO. It is considered to be of great interest to extend this protocol to the synthesis of N-heterocycles using imines with two electron-withdrawing groups.



The electrophilic cyclization of imines and iminium salts **5** is a general principle in the biosynthesis of many nitrogen-containing natural products, as, for example, in the formation of strictosidin, the key intermediate in the biosynthesis of a multitude of alkaloids[2]. This type of reaction has also been widely used in organic synthesis[3]. The necessary imines or iminium salts are usually obtained from an appropriate amine or carbamate and formaldehyde or other reactive aldehydes. The transformations are normally performed in the presence of an aqueous proton acid, and the resulting carbocation **6** can either give an alcohol **7** by addition of water or an alkene **8** by elimination of a proton[4]. However, cyclization reactions with unactivated alkenes are sometimes less suitable; thus, to obtain reasonable results, vinyl-[5] or allylsilanes[6] have to be used as a terminating functionality in the cyclizations. In contrast to simple imines obtained from aliphatic aldehydes, imines with one electron-withdrawing group at the carbon react in an aza-ene-type reaction with C–N- instead of C–C-bond formation[7].



In this paper, we describe the C–C-bond-forming intramolecular cyclization of imines **11** with two electron-withdrawing groups at the carbon atom to give substituted piperidines and annulated piperidine lactones. This new type of reaction allows an easy entry to cyclic nonproteinogenic

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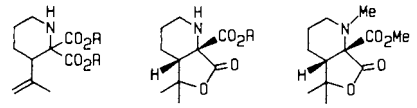
amino acids, gives excellent yields, and is easy to perform. The transformation can be carried out as a sequential reaction, since the required imines **11** are obtainable by a simple condensation of an appropriate amine such as **9** with oxopropanedioate **10**. The amine **9** was synthesized by reduction of the corresponding nitrile using lithium aluminium hydride or Raney nickel according to the method of Egli[8]. The mesoxalates **10** were prepared by ozonolysis of the appropriate benzylidene malonates[9]. Condensation of **9** with the mesoxalates **10** in benzene with azeotropic removal of water resulted in the formation of the imines **11** in excellent yields; however, for the reaction of **2a**, the condensation in dichloromethane in the presence of *p*-toluenesulfonic acid and molecular sieves (4 Å) was even superior. The iminomalonates **11** are stable at room temperature and may be obtained analytically pure after chromatography on silica gel. However, the crude material can usually be used for the following reaction without purification. Several Lewis and Brønsted acids were tested for the intramolecular cyclization of **11**. In addition, we investigated the application of trimethylsilyl trifluoromethanesulfonate (TMS–OTf) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMS–OTf) for the transformation, which have, to our knowledge, not been used for this type of reaction so far. We assume that by applying TMS–OTf or TBDMS–OTf a fast formation of a highly reactive iminium salt by silylation at the nitrogen would occur in situ. However, it is also possible that silylation takes place at one carbonyl group to give a carbenium ion in α-position to the imine and thus activate the imine. To assume a pentacoordinate silicon is less likely, since the silicon in the reagents used does not carry any electron-withdrawing groups[10]. The results obtained with TMS–OTf and TBDMS–OTf were superior to other inductors[11] in most cases.



12 13 14

a : R = Me b : R = Et c : R = iPr

The piperidines **12** and the piperidine lactones **13** and **14** are formed in the reactions. Interestingly, the ratio of products and the yields strongly depend on the alcohol moiety of the ester group, the used inductor, and the solvent (Table 1). The reactions were generally performed by mixing the imine **11** with 1.1 equivalents of a Lewis acid or other inductors in an appropriate solvent at −78 °C. The mixtures were allowed to warm to room temperature and stirred until completion. Synthetically useful results were obtained by using iron(III) halides adsorbed on aluminium oxide[12], gallium trichloride, trifluoroacetic acid, as well as TMS–OTf and TBDMS–OTf. The product ratio did not show a significant dependence on the temperature; however, the yields were lower when the inductor was added at higher temperatures. The use of less than one equivalent resulted in an incomplete turnover. For an exact analysis of the product ratios, the crude reaction mixtures were filtered over silica gel and analyzed by HPLC.

Table 1. Cyclization of the imine **11b**

Inductor (1.1 equiv.)	Solvents	t [h]	Yield (%)[a]	Ratio **12b:13b**
TMS–OTf	*t*BuOMe	18	85	7.2:1.0
TMS–OTf	*t*BuOMe	18	74	4.1:1.0[b]
TMS–OTf	DME	18	55	1.5:1.0
TMS–OTf	anisol	18	73	4.2:1.0
TMS–OTf	Et_2O	18	75	6.5:1.0[c]
TMS–OTf	CH_2Cl_2	18	82	2.2:1.0
TMS–OTf	toluene	18	78	4.0:1.0
TBDMS–OTf	*t*BuOMe	18	98	6.1:1.0
TMSI	CH_2Cl_2	90	48*	–:1.0[d]
$FeCl_3/Al_2O_3$	toluene	40	84	1.0:3.4
$FeCl_3/Al_2O_3$	CH_2Cl_2	18	81	1.0:1.8
$FeCl_3/Al_2O_3$	CH_2Cl_2	18	79*	1.0:1.5[e]
$FeCl_3/Al_2O_3$	CH_2Cl_2	18	65*	1.0:1.5[f]
$FeBr_3/Al_2O_3$	CH_2Cl_2	18	78*	1.0:2.4
$GaCl_3/Al_2O_3$	CH_2Cl_2	18	72*	1.0:5.2
CF_3COOH	CH_2Cl_2	40	50*	1.0:6.1

[a] Yield of combined products after rapid chromatography, determination of the ratios by HPLC [acetonitrile/water (50:50, v/v)]. Ratios determined after preparative separation are indicated by an asterisk. – [b] Addition of 1.1 equiv. of di-*tert*-butylpyridine. – [c] Reaction at room temp. – [d] Formation of several unidentified products. – [e] Addition of **11b** to the inductor at 0 °C. – [f] Addition of **11b** to the inductor under reflux.

The use of metal halides and trifluoroacetic acid in the reaction of **11b** always resulted in the preferred formation of the lactone **13b**. The ratio of **12b:13b** varied from 1.0:1.5 to 1.0:5.2 depending on the inductor and solvent (Table 1). The best ratio for **13b** was obtained using gallium trichloride and trifluoroacetic acid; in the latter case, however, the yields were lower. In contrast to these results, the cyclization with TMS–OTf and TBDMS–OTf, best performed in aliphatic ethers, led to the preferred formation of the diester **12b**. Thus, the reaction of **11b** with TMS–OTf in *tert*-butyl methyl ether gave an 85% yield of a 7.2:1.0 mixture of **12b** and **13b**; by using TBDMS–OTf the yield could be increased to 98% with a ratio of 6.1:1.0. The addition of a base-like di-*tert*-butylpyridine or hexamethyldisilazane had no positive effect on the product ratio.

It should be noted that **12b** is stable in the presence of one equivalent of a Lewis acid or TMS–OTf under the reaction conditions. However, addition of more than one equivalent resulted in the increased formation of lactone **13b**. Thus, the diester **12b** can be transformed into **13b** in the presence of an excess of Lewis acid or TMS–OTf in >85% yield within 48 h at 20 °C.

Since in the formation of the lactone esters **13b** a cleavage of the C–O bond in one ester moiety occurs, we investigated the dependence of the lactone formation on the nature of the alkoxy substituent. Cyclization of the methyl ester **11a** afforded the diester **12a** as well as the two lactones **13a** and **14** (Table 2). The lactones **13a** and **14** were always found as main products, whereby in the formation of **14** a meth-

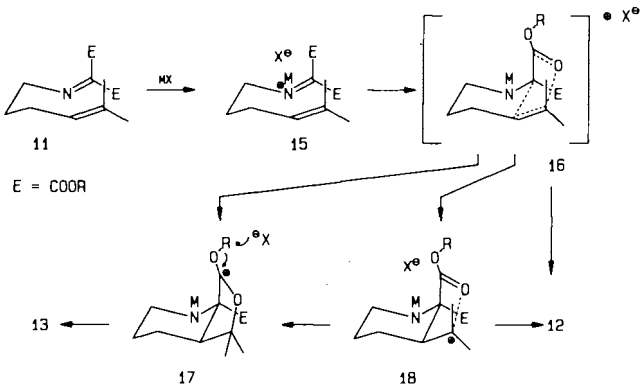
ylation at the nitrogen had occurred. The use of the imine **11c** with an ester moiety obtained from the secondary alcohol 2-propanol led to a preferred formation of the lactone **13c** under all conditions (Table 2).

Table 2. Cyclization of the imines **11a** and **11c**

	Inductor	Solvent	t [h]	Yield (%)[a]	Ratio **12a:13a:14**
11a	TMS–OTf	*t*BuOMe	18	74	1.0: 0.4:1.5
	TMS–OTf	toluene	18	67	1.0:26.2:16.8
	TMS–OTf	CH_2Cl_2	18	95	1.0: 1.5:3.0
	$FeCl_3/Al_2O_3$	toluene	40	95	1.0: 2.1:2.5
	$FeCl_3/Al_2O_3$	CH_2Cl_2	18	67	1.0: 2.0:3.5
					12c:13c
11c	TMS–OTf	*t*BuOMe	18	66	1:10.4
	TMS–OTf	toluene	18	72	1:11.7
	$FeCl_3/Al_2O_3$	CH_2Cl_2	18	76	1: 7.2

[a] Yield of combined products after rapid chromatography; determination of the ratio by HPLC [acetonitrile/water; **11a**:(60:40, v/v), **11c**:(70:30, v/v).

The results, especially the dependence of the ratio **12:13** on the inductor, may be explained by the following considerations. The reaction may be initiated by the formation of a reactive iminium species **15** from **11** either by protonation with a Brønsted acid, complexation with a metal halide, or silylation with TMS–OTf or TBDMS–OTf. **16** can be assumed as a transition structure with a chair-like conformation and a strong interaction of the carbonyl group of one ester moiety with the carbocation-like center. Either in a concerted way or after formation of the cation **18**, deprotonation to give **12** or formation of a C–O bond occurs to give **13** via **17**. In the latter reaction a nucleophile such as a halide or the triflate anion attacks the alkyl group of the ester moiety to give an alkyl halide or an alkyl triflate as a second product. This would also explain the occurrence of *N*-methylation in the reaction of **11a** to give **14**.

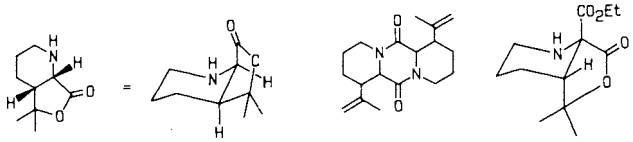


We assume that the ratio of **12:13** mainly depends on the nucleophilicity of the counterion and the accessibility of the alkyl group in the ester moiety as well as its ability to form a cation. Thus, the triflate anion has a low nucleophilic strength with the result that in the reaction of **11b** with TMS–OTf and TBDMS–OTf the diester **12b** is mostly obtained, whereas with bromide or chloride as counterion as in the reaction with $GaCl_3$, $FeCl_3$, and $FeBr_3$ the lactone **13b** is the main product. Using the imine **11c** with the isopropyl ester, the lactone **13c** is always predominantly formed regardless of the employed inductor, since the isopropyl group gives a more stable cation than the ethyl or methyl group. Assuming this mechanism, the preferred formation of the lactones **13a/14** in the reaction of **11a** and the influence of the solvent can also be explained, since the methyl group is better accessible for a nucleophilic attack and the nucleophilic strength would be increased by changing from a more polar solvent such as dichloromethane to a less polar solvent such as toluene.

The ^{1}H-NMR spectra of the diesters **12** show characteristic signals for the vinylic protons and the allylic methyl group at δ = 5.28–5.44, 4.80–4.90, and 1.78–1.79, respectively. 3-H absorbs around δ = 3.1 as a doublet of doublets with J = 4.5 and 2.5 Hz (**12a** and **12b**). These couplings can only be explained by assuming an axial orientation of the isopropenyl group. For the lactones **13** the IR spectra show absorptions at $\tilde{\nu}$ = 1770 and 1740 cm^{-1}. In the ^{1}H-NMR spectra singlets for two methyl groups are observed around δ = 1.5 and 1.6. The 4a-H absorbs at δ = 2.77–2.98 with couplings of J = 6–7 and 2–3 Hz indicating an equatorial orientation of this proton. This clearly proves that the 5,6-system is *cis*-fused, since in a *trans*-annulated piperidine 4a-H must be axial for geometrical reasons. Although little is known about the geometry of fused piperidines, force-field calculations on 8-methyl-1-hydrindanone have shown that the *cis*-isomer is stabilized by 9.6 kJ/mol compared to the *trans* isomer[13]. Our own calculations using the program Model (MM2 and MMX)[14] result in a difference in energy for **13a** and its *trans*-isomer of 13.7 kJ/mol[15]. In agreement with these findings, an equilibration experiment with **13b** in ethanol/sodium ethoxide afforded no change in composition of the starting material.

The products **12** and **13** obtained by cyclization of **11** are cyclic α-aminodicarboxylic acid derivatives, whereby in the lactone **13** the two geminal acyl groups are differentiated. Thus, the removal of an alkoxycarbonyl group in **12** or **13** would give access to cyclic derivatives of nonproteinogenic α-amino acids. The direct dealkoxycarbonylation on **13b** according to the procedure of Krapcho[16] using sodium cyanide, sodium chloride, or lithium chloride in dimethyl formamide and dimethyl sulfoxide at reaction temperatures up to 180°C, resulted only in a 30% yield of the desired *cis*-fused α-aminolactone **19** at the most. However, treatment of **13b** with barium hydroxide in aqueous methanol at 120°C for 12 h gave 69% of **19**. In contrast, base-catalyzed reaction of the diester **12b** resulted only in the formation of the diketopiperazine **20** in low and variable yields. In accordance with the proposed structure of **19**, a new signal for 7a-H at δ = 4.02 was found, which appears as a doublet with J = 7 Hz. It is of interest that **19** shows a different conformation compared to **13b**. Thus, in **19** 4a-H has an

axial orientation, which is clearly demonstrated by its NMR absorption as a doublet of triplets at δ = 2.20 with J = 11.5 and 6 Hz.



19 20 13b

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Experimental

^{1}H NMR and ^{13}C NMR: Varian XL-200, XL-100, VXR-200 and FT-80 A; 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. – Melting points: Kofler melting point apparatus (corrected values). – HPLC: Knauer HPLC System (Merck-Hitachi Integrator D 2000), nucleosil 7C18 (0.4 × 25 cm) column. – 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). – Acetonitrile for HPLC was purchased from J. T. Baker Chemical Co., water was bidistilled from quartz vessels. The solvents were mixed manually. – All chiral compounds are obtained as racemic mixtures.

5-Methyl-4-hexenylamine (**9**): To a boiling solution of $AlCl_3$ (20.0 g, 150 mmol) and $LiAlH_4$ (5.70 g, 150 mmol) in diethyl ether (300 ml) was added dropwise a solution of 5-methyl-4-hexenenitrile[17] (16.2 g, 150 mmol) in ether (100 ml), and the mixture was refluxed for 12 h. After hydrolysis with an aqueous solution of K/Na tartrate the phases were separated, the aqueous phase containing a white precipitate thoroughly washed with diethyl ether, and the combined organic phases extracted with 6 N H_2SO_4 (6 × 50 ml). After washing with diethyl ether, the acidic solution was alkalized with solid KOH followed by extraction with diethyl ether (3 × 50 ml). Washing of the combined ethereal phases (brine), drying (Na_2SO_4), evaporation, and distillation of the residue over CaH_2 yielded 10.8 g (65%) of the amine. – B.p. 51–53°C/20 Torr. – IR (film): $\tilde{\nu}$ = 3400–3300 cm^{-1} (NH), 2980, 1600, 1450, 1380. – ^{1}H-NMR ($CDCl_3$): δ = 1.10 (s, 2H, NH_2), 1.58 (quint, J = 7 Hz, 2H, 2-H), 1.62 (s, 3H, 6-H), 1.70 (s, 3H, 7-H), 2.03 (q, J = 7 Hz, 2H, 3-H), 2.69 (t, J = 7 Hz, 2H, 1-H), 5.12 (m_c, 1H, 4-H). – ^{13}C-NMR ($CDCl_3$): δ = 17.6 (C-6), 25.6 (C-7), 25.7 (C-3), 34.3 (C-2), 42.1 (C-1), 124.5 (C-4), 131.3 (C-5).

N-Naphtylthiourea derivative: m.p. 60°C (2-propanol).

$C_{18}H_{22}N_2S$ (298.5) Calcd. C 72.44 H 7.43 N 9.38 S 10.74
Found C 72.34 H 7.57 N 9.30 S 10.62

Dimethyl (5'-Methyl-4'-hexenylimino)malonate (**11a**): Dimethyl mesoxalate (1.46 g, 10.0 mmol) was dissolved in dichloromethane (50 ml). After addition of 25 g of molecular sieves (4 Å) and some crystals of *p*-toluenesulphonic acid, a solution of **9** (1.30 g, 10.0 mmol) in dichloromethane (15 ml) was added, and the mixture was stirred for 24 h at room temp. Filtration, evaporation, and chromatography on silica gel [petroleum ether/diethyl ether (2:1)] yielded 2.15 g (89%) of the imine **11a**. – R_f: 0.30 [petroleum ether/diethyl ether (5:1)]. – IR (film): $\tilde{\nu}$ = 2980 cm^{-1}, 1745 br (CO), 1690 (C=C), 1660 (C=N), 1445, 1255, 1090. – ^{1}H-NMR ($CDCl_3$): δ = 1.60 (s, 3H, 6'-H), 1.70 (s, 3H, 7'-H), 1.60–2.20 (m, 4H, 2'-H, 3'-H), 3.78 (t, J = 7 Hz, 2H, 1'-H), 3.90 (s, 6H, OCH_3), 5.09 (m_c, 1H, 4'-H). – ^{13}C-NMR ($CDCl_3$): δ = 17.7 (C-6'), 25.7 (C-7'), 25.7 (C-2'), 30.2 (C-3'), 52.3, 53.2 (OCH_3), 55.4 (C-1'), 123.5 (C-4'), 132.4 (C-5'), 153.2 (C-2), 161.7, 162.6 (C-1, C-3). – MS (70 eV): m/z (%) = 241 (14) [M^+], 226 (10) [M^+ – Me], 209 (3) [M^+ – MeOH], 181 (100) [M^+ – CO_2Me], 122 (50) [181$^+$ – CO_2Me], 99 (84) [$C_7H_{15}^+$], 69 (60) [$C_5H_9^+$], 55 (96) [$C_4H_7^+$].

$C_{12}H_{19}NO_4$ (241.3) Calcd. C 59.73 H 7.94 N 5.81
Found C 59.65 H 8.05 N 5.82

Diethyl (5'-Methyl-4'-hexenylimino)malonate (**11b**): Diethyl mesoxalate (17.4 g, 100 mmol) and amine **9** (11.3 g, 100 mmol) were dissolved in benzene (200 ml) and heated with a Dean-Stark trap until the reaction was complete. Evaporation of the solvent and chromatography of the residue on silica gel [petroleum ether/diethyl ether (2:1)] gave 25.3 g (94%) of the imine **11b**. – R_f: 0.26. – IR (film): $\tilde{\nu}$ = 2990 cm^{-1}, 2940 (CH), 1745 br (CO), 1655 (CN), 1375, 1245, 1065. – ^{1}H-NMR ($CDCl_3$): δ = 1.35 (t, J = 7 Hz, 6H, OCH_2CH_3), 1.65 (s, 3H, 6'-H), 1.75 (s, 3H, 7'-H), 1.50–2.30 (m, 4H, CH_2), 3.55 (t, J = 5.5 Hz, 2H, 1'-H), 4.35 (q, J = 7 Hz, 2H, OCH_2), 5.05 (m_c, 1H, 4'-H). – ^{13}C-NMR ($CDCl_3$): δ = 14.1, 14.2 (ester-Me), 17.6 (C-6'), 25.7 (C-7'), 25.8 (C-2'), 30.4 (C-3'), 55.1 (C-1'), 61.5, 61.8 (OCH_2), 123.8 (C-4'), 132.2 (C-5'), 153.8 (C-2), 161.3, 162.4 (C-1, C-3). – MS (70 eV): m/z (%) = 269 (22) [M^+], 240 (40) [M^+ – Et], 196 (99) [M^+ – CO_2Et], 168 (9) [196$^+$ – C_2H_4], 41 (100) [$C_3H_5^+$].

$C_{14}H_{23}NO_4$ (269.3) Calcd. C 62.43 H 8.61 N 5.20
Found C 62.53 H 8.68 N 5.15

Diisopropyl (5'-Methyl-4'-hexenylimino)malonate (**11c**): Diisopropyl mesoxalate (4.04 g, 20.0 mmol) and amine **9** (2.26 g, 20.0 mmol) were condensed as described for **12b**; yield 5.14 g (87%) of **12c**. – R_f: 0.59 [petroleum ether/diethyl ether (2:1)]. – IR (film): $\tilde{\nu}$ = 2995 cm^{-1}, 2960 (CH), 1740 br (CO), 1660 (CN), 1380, 1250, 845. – ^{1}H-NMR ($CDCl_3$). δ = 1.32 (d, J = 7 Hz, 12H, CH_3), 1.60 (s, 3H, 6'-H), 1.68 (s, 3H, 7'-H), 1.80 (q, J = 7 Hz, 2H, 2'-H), 2.02 (t, J = 7 Hz, 2H, 3'-H), 3.60 (t, J = 7 Hz, 2H, 1'-H), 5.02 (m_c, 1H, 4'-H), 5.21 (sept, J = 7 Hz, 1H, OCH), 5.27 (sept, J = 7 Hz, 1H, OCH). – ^{13}C-NMR ($CDCl_3$): δ = 17.6 (C-6'), 21.6, 21.7 (C-1'', C-3''), 25.7 (C-7'), 25.9 (C-2'), 30.3 (C-3'), 54.9 (C-1'), 69.8, 70.1 (C-2''), 123.8 (C-4'), 132.1 (C-5'), 154.3 (C-2), 160.6, 161.9 (C-1, C-3). – MS (70 eV): m/z (%) = 297 (1) [M^+], 254 (10) [M^+ – C_3H_7], 210 (25) [M^+ – CO_2iPr], 43 (100) [$C_3H_7^+$], 41 (61) [$C_3H_5^+$].

$C_{16}H_{27}NO_4$ (297.4) Calcd. C 64.62 H 9.15 N 4.71
Found C 64.41 H 9.06 N 4.72

Cyclization Experiments. – General Procedures

1) *Cyclization with Trialkylsilyl Trifluoromethanesulfonates:* To a cooled solution (–78°C) of the imine **11** (1.00 mmol) in 10 ml of an appropriate solvent was added with stirring 1.1 equiv. of TMS–OTf or TBDMS–OTf. Stirring was continued at this temp. for 1 h, and then the mixture was allowed to warm up to room temp. over ca. 12 h. After completion of the cyclization (TLC with solvent as indicated, usually 18 h), the mixture was hydrolyzed by addition of satd. $NaHCO_3$ solution and extracted with diethyl ether (3 × 50 ml) to give the crude products (**12**, **13**, **14**), which were separated by chromatography on silica gel or analyzed by HPLC (solvent as indicated). For this latter purpose, a short filtration over silica gel was carried out first to remove polar impurities.

2) *Cyclization with Lewis Acids on Solid Support:* 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 **11** (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. over ca. 12 h. After completion of cyclization (TLC, solvent as indicated), the mixture was hydrolyzed with a satd. $NaHCO_3$ solution. Further workup was performed as described above.

Reaction of **11b**: 1) 538 mg (2.00 mmol) of **11b** was treated with TMS−OTf in *t*BuOMe as described in general procedure 1 (reaction time 18 h). FC [petroleum ether/diethyl ether (2:1)] gave 396 mg (74%) of **12b** and 54 mg (11%) of **13b**.

2) 269 mg (1.00 mmol) of **11b** was cyclized with 1.1 equiv. of $FeCl_3$ on basic alumina according to the general procedure 2. FC (solvent as above) gave 88 mg (32%) of **12b** and 113 mg (47%) of **13b**.

3) 538 mg (2.00 mmol) of **11b** was dissolved in dichloromethane (20 ml) and cooled to 78°C. With stirring 2.2 equiv. of $GaCl_3$ (1 M solution in hexane) was added. Stirring was continued for ca. 12 h while the mixture was warmed to room temp. Hydrolysis, workup as described above, and FC (solvent as above) gave 63 mg (12%) of **12b** and 291 mg (60%) of **13b**.

Fraction 1. — Diethyl 3-Isopropenylpiperidine-2,2-dicarboxylate (**12b**): R_f 0.62. — IR (film): $\tilde{\nu}$ = 3380 cm^{-1} (NH), 3000, 2950, 2880, 1740 br (C=O), 1650 (C=C), 1455, 1260, 1040 (C−O). — ^{1}H-NMR ($CDCl_3$): δ = 1.20 (t, *J* = 7 Hz, 3H, OCH_2CH_3), 1.28 (t, *J* = 7 Hz, 3H, OCH_2CH_3), 1.50−1.20 (m, 4H, 4-H, 5-H), 1.79 (t, *J* = 0.4 Hz, 3H, 3′-H), 2.24 (br s, 1H, NH), 2.53 (ddd, *J* = 11.5, 11.5, 3 Hz, 1H, 6-H_{ax}), 3.00 (m, 1H, 6-H_{eq}), 3.12 (dd, *J* = 4.5, 2.5 Hz, 1H, 3-H), 4.02−4.30 (m, 4H, OCH_2), 4.90 (dq, *J* = 2, 1.1 Hz, 1H, 1′-H), 5.44 (dq, *J* = 2, 1 Hz, 1H, 1′-H). — ^{13}C-NMR (20 MHz, C_6D_6): δ = 13.94, 14.19 (ester-Me), 20.56 (C-4), 25.02 (C-3′), 25.08 (C-5), 41.58 (C-3), 43.32 (C-6), 61.09, 61.39 (OCH_2), 70.89 (C-2), 114.25 (C-1′), 144.70 (C-1′), 169.45, 170.76 (CO). — MS (70 eV): *m/z* (%) = 269 (3) [M^+], 196 (100) [$M^+ - CO_2Et$], 150 (4) [$182^+ - C_2H_6O$], 122 (35) [$C_8H_{12}N^+$], 55 (9) [$C_4H_7^+$], 41 (9) [$C_3H_5^+$].

$C_{14}H_{23}NO_4$ (269.3) Calcd. C 62.43 H 8.61 N 5.20
Found C 62.39 H 8.71 N 5.26

Fraction 2. — Ethyl (4aRS,7aRS)-1,2,3,4,4a,5-Hexahydro-5,5-dimethyl-7-oxofurano[3,4-b]pyridine-7a(7H)-carboxylate (**13b**): R_f 0.44. — IR (film): $\tilde{\nu}$ = 3450 cm^{-1} (NH), 2980, 2950, 1775 (lactone), 1740 (ester), 1450, 1030 (C−O), 920. — ^{1}H-NMR ($CDCl_3$): δ = 1.20−1.34 (m, 4H, 3-H, 4-H), 1.34 (t, *J* = 7 Hz, 3H, OCH_2CH_3), 1.52 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 2.55 (br s, 1H, NH), 2.61 (ddd, *J* = 11.5, 11.5, 2.5 Hz, 1H, 2-H_{ax}), 2.77 (dd, *J* = 6, 3 Hz, 1H, 4a-H), 3.03 (ddd, *J* = 11.5, 3, 2.5 Hz, 1H, 2-H_{eq}), 4.32 (q, *J* = 7 Hz, 2H, OCH_2). — ^{13}C-NMR ($CDCl_3$): δ = 14.12 (ester-Me), 19.44 (C-4), 20.89 (C-3), 25.54 (Me), 28.74 (Me), 42.29 (C-2), 44.61 (C-4a), 62.21 (OCH_2), 67.06 (C-7a), 87.61 (C-5), 170.34 (CO), 172.48 (C-7). — MS (70 eV): *m/z* (%) = 241 (3) [M^+], 168 (100) [$M^+ - CO_2Et$], 110 (67) [$168^+ - CH_3COCH_3$], 82 (64) [$110^+ - CO$].

$C_{12}H_{19}NO_4$ (241.3) Calcd. C 59.73 H 7.94 N 5.81
Found C 59.85 H 7.93 N 5.73

Treatment of **12b** *with Lewis Acids or TMS−OTf:* 1) A solution of a mixture of **12b**/**13b** (269 mg, 1.00 mmol, ratio 5:1) in dichloromethane (25 ml) was treated with 1 equiv. of TMS−OTf for 12 h at 20°C. A change of the ratio of **12b**:**13b** was not observed [HPLC, acetonitrile/water (50:50, v/v)]. Similar experiments were carried out using $FeCl_3/Al_2O_3$ and $GaCl_3$ instead of TMS−OTf.

2) A solution of **12b** (269 mg, 1.00 mmol) in dichloromethane was treated with 5 equiv. of TMS−OTf at 20°C. After 48 h, a complete transformation to **13b** was observed. Workup according to general procedure 1 afforded **13b** in >85% yield.

Treatment of **13b** *with Sodium Ethoxide:* A solution of **13b** (24.1 mg, 0.10 mmol) in anhydrous ethanol (5 ml) and sodium ethoxide (68.0 mg, 0.10 mmol) was heated to reflux for 24 h. Workup afforded unchanged starting material.

Reaction of **11a**: According to general procedure 2, 241 mg (1.00 mmol) of **11a** was cyclized in dichloromethane. FC [petroleum ether/diethyl ether (5:1)] gave 41 mg (17%) of **12a**, 128 mg (53%) of **14**, and 62 mg (27%) of **13a**.

Dimethyl 3-Isopropenylpiperidine-2,2-dicarboxylate (**12a**): R_f 0.55 [petroleum ether/diethyl ether (2:1)]. — IR (film): $\tilde{\nu}$ = 3380 cm^{-1} (NH), 2980, 1740 (C=O), 1650 (C=C), 1440, 1250 (C−O), 1210, 1190, 840, 670. — ^{1}H-NMR ($CDCl_3$): δ = 1.21−1.82 (m, 4H, 4-H, 5-H), 1.78 (s, 3H, 3′-H), 2.30 (br s, 1H, NH), 2.50 (ddd, *J* = 12, 12, 2.5 Hz, 1H, 6-H_{ax}), 2.95 (ddd, *J* = 12, 4.5, 4.5 Hz, 1H, 6-H_{eq}), 3.10 (dd, *J* = 4.5, 2.5 Hz, 1H, 3-H), 3.65 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.90 (m, 1H, 1′-H), 5.38 (m, 1H, 1′-H). — ^{13}C-NMR ($CDCl_3$): δ = 20.5 (C-4), 24.8 (C-3′), 25.1 (C-5), 41.8 (C-3), 43.3 (C-6), 52.1, 52.3 (OMe), 71.1 (C-2), 114.1 (C-1′), 144.9 (C-2′), 170.0, 171.3 (CO). — MS (70 eV): *m/z* (%) = 241 (3) [M^+], 182 (100) [$M^+ - CO_2Me$], 150 (4) [$182^+ - CH_4O$], 122 (25) [$C_8H_{12}N^+$], 55 (6) [$C_4H_7^+$], 41 (9) [$C_3H_5^+$].

$C_{12}H_{19}NO_4$ (241.3) Calcd. C 59.73 H 7.94 N 5.81
Found C 59.78 H 7.90 N 5.86

Methyl (4aRS,7aRS)-1,2,3,4,4a,5-Hexahydro-1,5,5-trimethyl-7-oxofurano[3,4-b]pyridine-7a(7H)-carboxylate (**14**): R_f 0.38 [petroleum ether/diethyl ether (3:1)]. — M.p. 66°C (diethyl ether/petroleum ether). — IR (KBr): $\tilde{\nu}$ = 2980 cm^{-1}, 2940, 2880, 1770 (lactone), 1735 (ester), 1260, 1030 (C−O). — ^{1}H-NMR ($CDCl_3$): δ = 1.46 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.50−2.00 (m, 3H, 3-H, 4-H), 2.63 (NCH_3), 2.69 (dd, *J* = 6, 4 Hz, 1H, 4a-H), 2.70 (ddd, *J* = 12, 6, 4 Hz, 1H, 2-H_{eq}), 3.12 (ddd, *J* = 12, 12, 3.5 Hz, 1H, 2-H_{ax}), 3.78 (s, 3H, OCH_3). — ^{13}C-NMR ($CDCl_3$): δ = 19.1 (C-4), 21.3 (C-3), 25.9 (Me), 28.8 (Me), 39.2 (C-1), 48.4 (NMe), 49.7 (C-4a), 51.9 (OMe), 70.1 (C-7a), 86.4 (C-5), 169.7 (CO), 170.9 (C-7). — MS (70 eV): *m/z* (%) = 241 (5) [M^+], 182 (100) [$M^+ - CO_2Me$], 124 (14) [$182^+ - CH_3COCH_3$], 96 (50) [$124^+ - CO$].

$C_{12}H_{19}NO_4$ (241.3) Calcd. C 59.73 H 7.95 N 5.86
Found C 59.57 H 7.94 N 5.81

Methyl (4aRS,7aRS)-1,2,3,4,4a,5-Hexahydro-5,5-dimethyl-7-oxofurano[3,4-b]pyridine-7a(7H)-carboxylate (**13a**): R_f 0.26 [petroleum ether/diethyl ether (3:1)]. — M.p. 75°C (diethyl ether/petroleum ether). — IR (KBr): $\tilde{\nu}$ = 3360 cm^{-1} (NH), 1780 (lactone), 1730 (ester), 1250, 1030 (C−O). — ^{1}H-NMR ($CDCl_3$): δ = 1.40−1.90 (m, 4H, 3-H, 4-H), 1.50 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 2.50 (s, 1H, NH), 2.68 (ddd, *J* = 12, 12, 3 Hz, 1H, 2-H_{ax}), 2.98 (dd, *J* = 6, 2.5 Hz, 1H, 4a-H), 3.20 (ddd, *J* = 12, 4, 3 Hz, 1H, 2-H_{eq}), 3.83 (s, 3H, OCH_3). — ^{13}C-NMR (C_6D_6): δ = 19.4 (C-4), 21.1 (C-3), 25.5 (Me), 28.6 (Me), 42.4 (C-1), 44.9 (C-4a), 52.7 (OMe), 67.4 (C-7a), 87.1 (C-5), 171.1 (CO), 172.1 (C-7). — MS (70 eV): *m/z* (%) = 227 (1) [M^+], 168 (100) [$M^+ - CO_2Me$], 110 (28) [$168^+ - CH_3COCH_3$], 82 (36) [$110^+ - CO$].

$C_{11}H_{17}NO_4$ (227.3) Calcd. C 58.14 H 7.54 N 6.16
Found C 58.10 H 7.42 N 6.10

Reaction of **11c**: 595 mg (2.00 mmol) of **11c** was cyclized with TMS−OTf using *t*BuOMe as solvent as described in general procedure 1 (reaction time 18 h). FC [ethyl acetate/petroleum ether (1:3)] gave 28 mg (5%) of **12c** and 288 mg (57%) of **13c**.

Fraction 1. — Diisopropyl 3-Isopropenylpiperidine-2,2-dicarboxylate (**12c**): R_f 0.57. — IR (film): $\tilde{\nu}$ = 3380 cm^{-1} (NH), 3000, 1740 (CO), 1650 (C=C), 1460, 1380, 1250, 1105 (C−O), 915. — ^{1}H-NMR ($CDCl_3$): δ = 1.17 (d, *J* = 6.5 Hz, 3H, CH_3), 1.18 (d, *J* = 6.5 Hz, 3H, CH_3), 1.23 (d, *J* = 6.5 Hz, 3H, CH_3), 1.25 (d, *J* = 6.5 Hz, 3H, CH_3), 1.12−1.84 (m, 4H, 4-H, 5-H), 1.78 (s, 3H, 3′-H), 2.06 (br s,

1H, NH), 2.54 (td, J = 11.5, 3 Hz, 1H, 6-H_{ax}), 3.02 (m_c, 1H, 6-H_{eq}), 3.02–3.16 (m, 1H, 3-H), 4.80 (dq, J = 1, 1 Hz, 1H, 1′-H), 5.04 (quint, J = 6.5 Hz, 1H, OCH), 5.12 (quint, J = 6.5 Hz, 1H, OCH), 5.28 (m_c, 1H, 1′-H). – MS (70 eV): m/z (%) = 297 (1) [M^+], 210 (100) [$M^+ - CO_2iPr$], 168 (96) [$210^+ - C_3H_6$, McL], 150 (8) [$168^+ - H_2O$], 122 (57) [$150^+ - CO$], 43 (43) [$C_3H_7^+$].

$C_{16}H_{27}NO_4$ Calcd. 297.1940 Found 297.1940 (MS)

Fraction 2. – Isopropyl (4aRS,7aRS)-1,2,3,4,4a,5-Hexahydro-5,5-dimethyl-7-oxofurano[3,4-b]pyridine-7a(7H)-carboxylate (**13c**): R_f: 0.39. – M.p. 51–52°C (petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3350 cm^{-1} (NH), 3000, 1775 (lactone), 1740 (ester), 1380, 1250, 1110, 1020 (C–O). – ^{1}H-NMR ($CDCl_3$): δ = 1.28 (d, J = 6 Hz, 3H, CH_3), 1.30 (d, J = 6 Hz, 3H, CH_3), 1.36–1.90 (m, 4H, 3-H, 4-H), 1.50 (s, 3H, Me), 1.63 (s, 3H, CH_3), 2.50 (s, 1H, NH), 2.65 (ddd, J = 11.5, 11.5, 3 Hz, 1H, 2-H_{ax}), 2.82 (dd, J = 6.5, 2.5 Hz, 1H, 4a-H), 2.98 (ddd, J = 11.5, 3, 3 Hz, 1H, 2-H_{eq}), 5.12 (sept, J = 6 Hz, 1H, iPr). – ^{13}C-NMR ($CDCl_3$): δ = 19.5 (C-4), 20.9 (C-3), 21.5, 21.7 (ester-Me), 25.5 (Me), 28.8 (Me), 42.3 (C-2), 44.6 (C-4a), 67.0 (C-7a), 70.1 (OCH), 87.5 (C-5), 169.8 (CO), 172.5 (C-7). – MS (70 eV): m/z (%) = 255 (1) [M^+], 168 (100) [$M^+ - CO_2iPr$], 110 (63) [$168^+ - CH_3COCH_3$], 82 (44) [$110^+ - CO$], 41 (22) [C_3H_5].

$C_{13}H_{21}NO_4$ (255.3) Calcd. C 61.16 H 8.29 N 5.49
Found C 61.18 H 8.29 N 5.58

Preparation of the Amino Lactone (4aRS,7aSR)-1,2,3,4,4a,5-Hexahydro-5,5-dimethylfurano[3,4-b]pyridin-7(7aH)-one (**19**): **13b** (93.5 mg, 0.388 mmol) was dissolved in 50% (v/v) aqueous methanol (4 ml) and heated with $Ba(OH)_2 \times 5\ H_2O$ (50.0 mg, 0.194 mmol) to 120°C for 12 h. The solution was extracted with chloroform (5 × 20 ml) and the organic phases were washed (brine) and evaporated. The residue was purified by chromatography on silica gel starting with diethyl ether/petroleum ether (1:1), then diethyl ether, and finally MeOH as eluents to give 45.2 mg (69%) of **19**. – R_f: 0.33 [ethyl acetate/methanol (5:1)]. – IR (film): $\tilde{\nu}$ = 3338 cm^{-1}, 2976, 2938, 2860, 1766, 1646, 1316, 1272, 1150, 1120, 1072. – ^{1}H-NMR ($CDCl_3$): δ = 1.12–1.98 (m, 4H, 3-H, 4-H), 1.37 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.84 (s, 1H, NH), 2.20 (ddd, J = 11.5, 6, 6 Hz, 1H, 4a-H), 2.53 (ddd, J = 12, 12, 2.5 Hz, 1H, 6-H_{ax}), 2.87 (dddd, J = 12, 3, 3, 2 Hz, 1H, 6-H_{eq}), 4.02 (d, J = 7 Hz, 1H, 7a-H). – ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 23.07 (Me), 23.66 (C-3, C-4), 26.44 (Me), 41.86 (C-4a), 42.46 (C-2), 56.52 (C-7a), 83.41 (C-5), 176.43 (C-7). – MS (70 eV): m/z (%) = 169 (7) [M^+], 125 (19) [$M^+ - CO_2$], 110 (100) [$C_7H_{12}N^+$], 82 (42) [$C_5H_8N^+$].

$C_9H_{15}NO_2$ (169.22) Calcd. C 63.88 H 8.93
Found C 63.54 H 9.07

CAS Registry Numbers

9: 115610-15-6 / **9** -N-naphthylthiourea derivative: 119071-80-6 / **10a**: 3298-40-6 / **10b**: 609-09-6 / **10c**: 73972-39-1 / **11a**: 119671-71-5 / **11b**: 119071-72-6 / **11c**: 119071-73-7 / **12a**: 119108-86-0 / **12b**: 119071-75-9 / **12c**: 119071-77-1 / **13a**: 119108-87-1 / **13b**: 119071-76-0 / **13c**: 119071-78-2 / **14**: 119071-74-8 / **19**: 119071-79-3 / TMS-OTf: 27607-77-8 / TBDMS-OTf: 69739-34-0 / TMSI: 16029-98-4 / $FeCl_3$: 7705-08-0 / CF_3COOH: 76-05-1 / $GaCl_3$: 13450-90-3 / $FeBr_3$: 10031-26-2 / 5-methyl-4-hexenenitrile: 23089-87-4

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