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Synthesis and X-Ray Crystal Structure of (*S*)-9-Hydroxymethyl-1,5-diazabicyclo[4.3.0]non-5-ene, an Enantiopure DBN-Analogue

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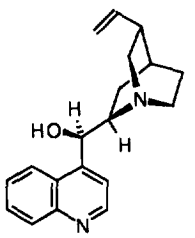
Abstract: Synthetic routes are described to two enantiopure analogues of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) containing a hydroxyl function. Such compounds may be interesting as chiral bifunctional basic catalysts in enantioselective synthesis. Starting from (*S*)-malic acid, silyl protected (*S*)-8-hydroxy-DBN was prepared, but this compound appeared unstable. The title compound prepared from (*S*)-pyroglutamic acid is a stable crystalline solid. Its crystal structure shows a strong intermolecular hydrogen bond.

INTRODUCTION

The development of new methods for the synthesis of chiral non-racemic products from achiral starting materials by using enantioselective catalysis is an intense area of research in contemporary organic synthesis.[1] While chiral (transition) metal complexes are receiving much attention, the study of purely organic catalysts lacking a metal ion has remained a relatively unexplored area of research. Nevertheless, remarkable successes of the latter type of catalysis have been reported. Notable examples are the (*S*)-proline-catalyzed aldol cyclization of the Michael product from methyl vinyl ketone and 2-methylcyclopentane-1,3-dione (94% ee),[2] the quinidine-catalyzed formal [2+2]-cycloaddition of ketene and chloral (98% ee),[3] and the addition of HCN to benzaldehyde catalyzed by a cyclic dipeptide (97% ee).[4]



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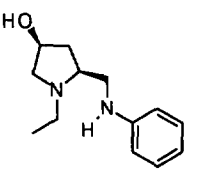

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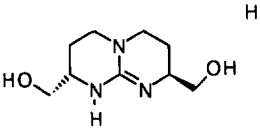

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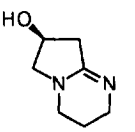

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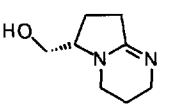

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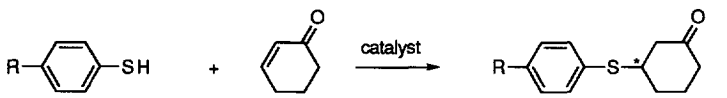
For achieving high enantiomeric excess in a catalytic reaction between two achiral substrates, the process requires an enantiopure catalyst, leading the reaction through a highly structured transition state in order to cause sufficient free energy difference between the pathways to both enantiomers of the product. For some amine base-catalyzed reactions it has been shown that bifunctional catalysis provides a means to achieve

this goal.[1] Thus, in the Michael type addition of thiophenol to 2-cyclohexen-1-one (eq 1), certain enantiopure aminoalcohols serve as highly enantioselective catalysts to yield the adducts in more than 75% ee in certain cases. Examples of successful catalysts are cinchona alkaloids like cinchonidine (**1**)[5] and the 4-hydroxyproline derived aminoalcohol **2**.[6] The bifunctional character of the catalysis pertains to the basic nitrogen to activate the nucleophile, probably as an ion pair, and to the hydroxyl function to activate the electrophile via hydrogen bonding. In this way the reaction partners are both activated and held closely together to allow a successful and enantioselective reaction.[7]



(1)

The applicability of amine catalysts like **1** and **2** is limited due to their low basicity. The scope of organic base catalysis could possibly be extended by incorporating a more basic moiety into the chiral catalyst. Amidine and guanidine functions are more basic than ordinary amines.[8] While enantiopure guanidines have been studied in considerable detail in recent years (especially **3** and derivatives), mainly in connection with their anticipated molecular recognition properties,[9] enantiopure amidines are virtually unknown in this respect.[10] On the other, hand DBN (1,5-diazabicyclo[4.3.0]non-5-ene) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) are achiral amidine bases, which are frequently used in synthesis.[11]

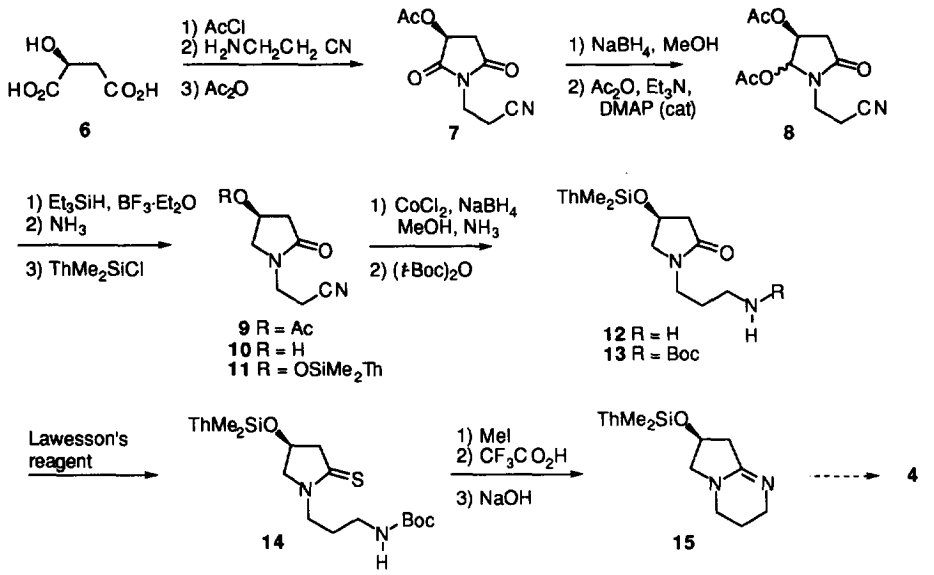
In this paper we wish to report about our studies towards the synthesis of enantiopure analogues of DBN, containing a hydroxyl function. First, hydroxyamidine **4** was prepared from (*S*)-malic acid, but the limited stability of **4** precluded its further study. We then turned to the preparation of enantiomerically pure **5** from (*S*)-pyroglutamic acid. Hydroxyamidine **5** appeared to be a stable crystalline compound and its crystal structure is reported.

RESULTS AND DISCUSSION

For the preparation of enantiopure DBN-analogues, readily available compounds from the chiral pool were selected as starting materials. In connection with earlier studies in our group[12] (*S*)-malic acid (**6**) was first chosen. By applying the known strategy as used for DBN,[11] hydroxyamidine **4** became our first target molecule.

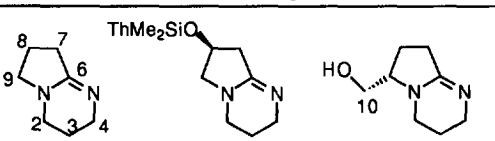
Scheme 1 details the preparation of **4**. In a one-pot process (*S*)-malic acid (**6**) was converted into *N*-(2-cyanoethyl)imide **7** as a crystalline compound (mp 84-86 °C), following the procedure reported for the NH-imide.[13] Regioselective reduction[13] and subsequent acetylation produced the diacetylpyrrolidinone **8** as a 5:1 cis/trans mixture. The extra stereocentre was then removed by Et_3SiH reduction of the *N*-acyliminium ion generated from **8** by using $BF_3{\cdot}Et_2O$. Protective group interconversion occurred uneventfully to give thexyldimethylsilyl ether **11** in 63% overall from **8**.

Extensive experimentation eventually showed that the best method for the reduction of the nitrile function was that reported by Echavarren et al.[14] This method involved treatment with $CoCl_2$ (2 equiv) and a large excess of $NaBH_4$, added portionwise, in methanol as the solvent containing 3% of ammonia in order to prevent the formation of dimers.[15] To isolate the reduction product the amine was protected with the *t*-Boc function to give **13** in 59% yield from **11**.



To close the amidine ring under mild conditions the carbonyl function was activated by treatment, successively, with Lawesson's reagent[16] to thiolactam **14** and neat methyl iodide to give the methylthioiminium salt. The amine was then deprotected with trifluoroacetic acid to the corresponding ammonium salt. When the solution of this salt was made alkaline with NaOH immediate cyclization occurred to amidine **15**. Rapid chromatographic purification over a basic alumina column gave **15** in good yield as a light-coloured oil, which showed correct ^1H and ^{13}C NMR spectral data (see Table 1).

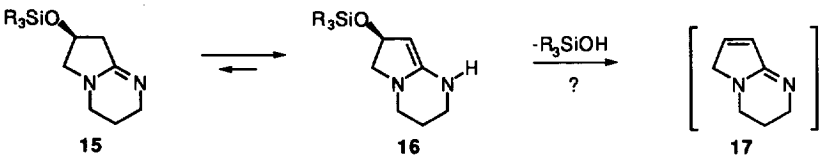
Table 1. ^{13}C NMR chemical shift data (ppm) of DBN, **15**, and **5**.



C2	43.4	42.3	43.3
C3	19.0	18.7	20.6
C4	42.4	40.0	41.2
C6	159.7	162.5	161.0
C7	30.7	38.0	30.1
C8	20.2	65.9	22.3
C9	50.7	61.7	64.0
C10			61.8

Amidine **15** appeared to be unstable. After a few hours of standing at room temperature a black residue resulted, which according to ^1H NMR did not contain much of **15** anymore. This lack of stability of **15** led us to abandon this structural type of hydroxyamidine and its desilylation to **4** was not investigated. We suspect

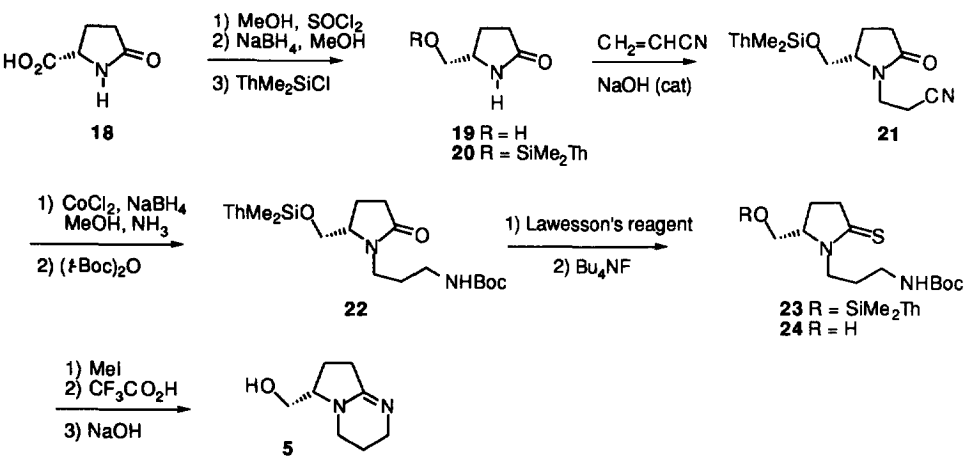
that the ready tautomerization of **15** to **16** could be the reason for the spontaneous decomposition of **15**, as **16** might undergo facile elimination to **17** and further decomposition via pyrrole intermediates. The relevance of the amidine tautomer was recently indicated by Pfau et al.[17]



15 **16** **17**

We then turned our attention to the use of readily available (*S*)-pyroglutamic acid (**18**) as starting material. The problems inherent to the structure of **4** should not apply to **5**, eventually arising from a similar route starting from **18** (see Scheme 2).

(*S*)-Pyroglutamic acid was converted in three steps to silyl protected 5-(hydroxymethyl)pyrrolidinone (**20**) via well-known chemistry.[18] Michael addition to acrylonitrile furnished **21** in high yield.[19] Reduction of the nitrile function as described before, protection, and thiolactam formation produced **23**, which at this stage was desilylated by using fluoride to alcohol **24** as a crystalline solid (mp 104-105 °C). The cyclization of **24** proceeded as described before to give amidine **5** as a crystalline compound, mp 103-108 °C, $[\alpha]^{20}_D$ -64 (*c* 1.45, MeOH). The ^{13}C NMR data of **5** compared well with those of **15** and DBN itself (see Table 1).



18

19 R = H
20 R = $SiMe_2Th$

21

22

23 R = $SiMe_2Th$
24 R = H

5

Amidine **5** was a stable compound, which gave crystals suitable for an X-ray crystal structure determination. The individual molecules appeared to be connected via a strong hydrogen bond between the hydroxyl function and the imine nitrogen with an NO distance of 2.73(3) Å and an NHO angle of 158(3)°. The crystal structure including the relative orientation of two molecules and their hydrogen bond is shown in Figures 1. To the best of our knowledge this crystal structure is the first published on a hydrogen bonded DBN analogue.[20,21]

Some preliminary experiments were carried out to probe the catalytic properties of amidine **5**. The addition of thiophenol to 2-cyclohexen-1-one (eq 1, R = H)[5] proceeded well in the presence of 4 mol % of

(*S*)-**5** (reaction complete within 1 h in THF as the solvent), but the product showed virtually no optical activity. Results on some other Michael reactions indicated that **5** is less effective as a basic catalyst than DBN itself. This may be associated with the fact that the inductive effect of the hydroxyl function as an electron-withdrawing group reduces the basicity of the amidine, while at the same time the hydroxyl group is not well oriented to activate the Michael acceptor.

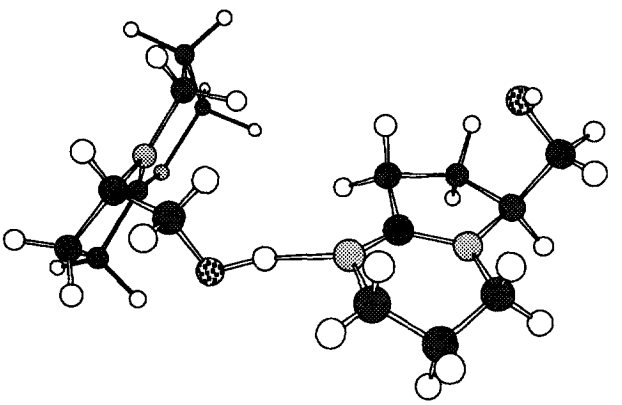


Figure 1. Chem3D™ representation of the crystal structure of two hydrogen bonded molecules of **5**.

In summary, the synthesis of enantiopure (*S*)-9-hydroxymethyl-DBN (**5**) from (*S*)-pyroglutamic acid was achieved and its structure proven by an X-ray crystal structure determination. Further structural fine-tuning including the adjustment of the relative orientation of amidine and hydroxyl functional groups in this catalyst type is required to allow good enantioselectivity in base catalyzed processes.

EXPERIMENTAL

General information: All reactions were carried out under an inert atmosphere of dry nitrogen unless otherwise indicated. Standard syringe techniques were applied to transfer dry solvents. Infrared (IR) spectrta were obtained from $CHCl_3$ solutions using a Perkin-Elmer 1310 spectrophotometer and wavelengths (ν) are reported in cm^{-1}. Proton nuclear resonance (^1H NMR) spectra were determined in $CDCl_3$, unless indicated otherwise using a Bruker AC 200 (200 MHz), a Bruker WM 250 (250 MHz) or a Bruker AMX 400 (400 MHz) spectrometer. These instruments were also used for ^{13}C NMR (APT) spectra (50, 63, and 100.6 MHz, respectively) in $CDCl_3$ (unless indicated otherwise). Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Mass spectra and accurate mass measurements were carried out using a VG Micromass ZAB-2HF instrument. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in the indicated solvent at room temperature. Elemental analysis were performed by Dornis u. Kolbe Microanalytisches Laboratorium, Mülheim/Ruhr, Germany. Melting points are uncorrected. Dry CH_2Cl_2, toluene, benzene, triethylamine and DMF were distilled from CaH_2 and stored over 4 Å molecular sieves under an atmosphere of dry nitogen. THF and ether were distilled from sodium benzophenone ketyl prior to use.

(*S*)-1-(2-Cyanoethyl)-3-acetoxysuccinimide (7): A solution of 26.8 g (0.2 mol) of (*S*)-malic acid in 100 mL of acetyl chloride was refluxed for 2 h. After evaporation of the volatiles the residue was dissolved in 25 mL of THF. To this stirred solution was then added at 0-5 °C a solution of 16.1 g of 3-aminopropionitrile (0.23 mol; obtained from 0.3 mol of the commercially available fumarate salt by treatment in THF with 24 g of KOH in 24 mL of water, extraction of the precipitate with THF/ether and concentration in vacuo) in 50 mL of THF. After being stirred for another 2 h at room temperature the reaction mixture was thoroughly concentrated in vacuo. The residue was dissolved in 100 mL of acetyl chloride and refluxed for 5 h. The reaction

mixture was concentrated in vacuo and the residue crystallized from EtOAc to give 23.50 g of product. From the mother liquor an additional crop of 7.03 g of crystals was obtained by flash chromatography (EtOAc) to give a total yield of 30.53 g (76%) of **7**. Mp 84-86 °C. $[\alpha]_D$ -30.6 (*c* 4.27, $CHCl_3$). IR ν 2250 (CN), 1790 and 1720 (imide), 1750 (acetate). ^1H NMR δ 2.15 (s, 3H, acetate), 2.67-2.78 (m, 3H, NCC*H*$_2$ and C=OCH*H*), 3.20 (dd, *J* = 12.5, 8.8 Hz, 1H, C=OC*H*H), 3.70 (td, *J* = 6.8, 1.8 Hz, 2H, NC*H*$_2$), 5.41 (dd, *J* = 4.8, 8.8 Hz, 1H, C*H*OAc).

(4*S*,5*S*)-1-(2-Cyanoethyl)-4,5-diacetoxypyrrolidin-2-one and the (4*S*,5*R*)-isomer (8): To a stirred solution of 4.20 g (20 mmol) of **7** in 80 mL of MeOH, cooled to -40 °C, was added all at once 1.14 g (30 mmol) of powdered $NaBH_4$. The reaction temperature was allowed to rise to 0 °C in 30 min and then kept at 0 °C for 1 h. The mixture was then cooled again to -20 °C and carefully acidified to pH 5 with concentrated aqueous HCl. After concentration in vacuo the residue was filtered over a short silica gel column with EtOAc/aceton 4:1. Removal of the volatiles in vacuo gave the crude hydroxylactam as an oil (4.21 g). The oil was stirred at room temperature with 80 mL of dry toluene, 3.8 mL of acetic anhydride (2 equiv), 5.6 mL of dry triethylamine (2 equiv) and a trace of DMAP for 3 h. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (EtOAc) to give 4.89 g (96%) of a colourless oil, *cis/trans* 5:1. IR ν 2250 (CN), 1750-1690 (br, lactam and acetates). ^1H NMR δ 2.07 and 2.13 (2 × s, acetate C*H*$_3$ *cis*-**8**), 2.09 and 2.03 (2 × s, acetate *CH*$_3$ *trans*-**8**), 2.35-3.00 (m, NCOC*H*$_2$ and C*H*$_2$CN, *cis* and *trans*), 3.45-3.78 (m, NC*H*$_2$ *cis* and *trans*), 5.15 (d, *J* = 1.8 Hz, C*H*OAc *trans*), 5.35 (td, *J* = 8.6, 5.3 Hz, C*H*OAc *cis*), 6.14 (s, NC*H*OAc *trans*), 6.38 (d, *J* = 5.3 Hz, NC*H*OAc *cis*).

(*S*)-1-(2-Cyanoethyl)-4-acetoxypyrrolidin-2-one (9): To a stirred solution of 4.38 g (19 mmol) of **8** in 70 mL of dry dichloromethane was successively added at -70 °C 2.81 mL (1.2 equiv) of freshly distilled $BF_3{\cdot}OEt_2$ over 10 min and 15.4 mL (5 equiv) of dry triethylsilane over 10 min. The temperature was gradually raised to room temperature in 3 h. After being stirred for another 18 h at room temperature the mixture was poured onto ice and excess Na_2CO_3. The water layer was extracted with dichloromethane (2 ×). The combined organic layers were dried and concentrated in vacuo. Purification by flash chromatography (EtOAc) gave 548 mg (11%) of *trans*-**8** and 2.67 g (80%) of **9**. Mp 71-73 °C (EtOAc). $[\alpha]_D$ -44.7 (*c* 4.39, MeOH). IR ν 2250 (cyano), 1740 (acetate), 1690 (lactam). ^1H NMR δ 2.06 (s, 3H, acetate), 2.46 (dd, *J* = 7.9 2.3 Hz, 1H, C(O)C*H*H), 2.62 (t, *J* = 6.4 Hz, 2H, C*H*$_2$CN), 2.77 (dd, *J* = 7.9, 7.0 Hz, 1H, C=OC*H*H), 3.50-3.60 (m, 3H, NC*H*$_2$ and NC*H*HCOAc), 3.91 (dd, *J* = 11.3, 5.7 Hz, 1H, NC*H*HCOAc), 5.29 (dddd, *J* = 7.0, 5.7, 2.3, 2.0 Hz, C*H*OAc). ^{13}C NMR δ 16.4 (*C*CN), 20.9 (*CH*$_3$ acetate), 37.4 and 38.7 (*N*CCCN and C=O*C*), 54.1 (*N*CCOAc), 66.9 (*C*OAc), 117.7 (*C*N), 170.4 (*N*CO), 172.2 (*C*=O acetate). Anal. calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17. Found: C, 55.00; H 6.05.

(*S*)-1-(2-Cyanoethyl)-4-hydroxypyrrolidin-2-one (10): A solution of 392 mg (2 mmol) of **9** in 5 mL of 10% methanolic ammonia was stirred at room temperature for 110 h. Concentration in vacuo and purification of the residue by flash chromatography (EtOAc/MeOH 9:1) gave 271 mg (94%) of **10** as an oil which was slightly contaminated with acetamide. IR ν 3400 (OH), 2250 (CN), 1685 (lactam). ^1H NMR δ 2.35 (dd, *J* = 17.4, 2.0 Hz, 1H, C=OC*H*), 2.46-2.71 (3H), 3.40 (dd, *J* = 10.6, 1.6 Hz, 1H, NC*H*COH), 3.54 (td, *J* = 6.4, 2.8 Hz, 2H, NC*H*$_2$CH$_2$), 3.74 (dd, *J* = 10.6, 5.3 Hz, 1H, NC*H*COH), 4.35 (OH), 4.48 (m, 1H, C*H*OH).

(*S*)-1-(2-Cyanoethyl)-4-(thexyldimethylsilyloxy)pyrrolidin-2-one (11): To a solution of 117 mg (0.76 mmol) of **10** in 1.5 mL of dry DMF was added thexyldimethylsilyl chloride (0.225 mL, 1.5 equiv) and imidazole (129 mL, 2.5 equiv). The mixture was stirred for 16 h at room temperature and poured onto ice. It was extracted with hexanes (2 ×) and ether (4 ×). The organic layers were washed with brine, dried and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexanes 1:4) yielding 190 mg (84%) of **11** as a colourless oil. IR ν 2250 (CN), 1680 (lactam). ^1H NMR δ 0.08 (s, 6H, C*H*$_3$Si), 0.80 (s, 6H C*H*$_3$CSi), 0.83 (d, *J* = 6.9 Hz, 6H, C*H*$_3$CCSi), 1.57 (sept, *J* = 6.9 Hz, 1H, C*H*CSi), 2.30 (dd, *J* = 17.0, 3.7 Hz, 1H, C=OC*H*), 2.51-2.66 (3H), 3.33 (dd, *J* = 9.9, 3.1 Hz, 1H, NC*H*COSi), 3.54 (t, *J* = 6.6 Hz, 2H, NC*H*$_2$CH$_2$), 3.72 (dd, *J* = 9.9, 5.9 Hz, 1H, NC*H*COSi), 4.46 (m, 1H, C*H*OSi).

(*S*)-1-{(3-*tert*-Butoxycarbonylamino)propyl}-4-(thexyldimethylsilyloxy)pyrrolidin-2-one (13): To a vigorously stirred ice-cold solution of 952 mg (4 mmol) of $CoCl_2{\cdot}6H_2O$ in 4 mL of MeOH under a hydrogen atmosphere was added 38 mg (1 mmol) of $NaBH_4$. The black suspension was stirred for 10 min at room temperature and then cooled again. To the ice-cold mixture was added dropwise in 5 min a solution of 592 mg (2 mmol) of **11** in 16 mL of 3% methanolic ammonia. At the same temperature 380

mg of $NaBH_4$ was added in portions over a period of 15 min. After being stirred for 2.5 h another 380 mg of $NaBH_4$ was added in portions. After being stirred for an additional 1 h the reaction was complete according to TLC. Water (2 mL) was added and the reaction mixture was filtered over Celite. The filter was washed with MeOH/water 9:1. The filtrates were concentrated in vacuo. The residue was dissolved in EtOAc and 10% aqueous ammonia. The water layer was extracted with EtOAc (2 ×). The combined organic layers were washed with 10% aqueous ammonia (3 ×) and brine, dried and concentrated in vacuo to give 556 mg of impure **12** as a light-brown oil. This oil was stirred for 30 min with 6 mL of dry dichloromethane, 872 mg of di-*tert*-butyl dicarbonate (4 mmol) and a catalytic amount of DMAP. The reaction mixture was concentrated in vacuo and purified by flash chromatography (EtOAc) to afford 475 mg (59%) of **13** as a light-yellow oil. IR ν 3450 (NH), 1700 (C=O carbamate), 1670 (C=O lactam). ^{1}H NMR δ 0.08 (s, 6H, C*H*$_3$Si), 0.80 (s, 6H, C*H*$_3$CSi), 0.84 (d, *J* = 6.8 Hz, 6H, C*H*$_3$CCSi), 1.42 (s, 9H, *tert*-butyl), 1.51-1.96 (3H), 2.31 (dd, *J* = 16.9, 3.4 Hz, 1H, C=OC*H*), 2.61 (dd, *J* = 16.9, 6.5 Hz, 1H, C=OC*H*), 2.97-3.25 (4H), 3.38-3.57 (1H), 3.53 (dd, *J* = 10.2 5.8 Hz, 1H NC*H*COSi), 4.43 (m, 1H, C*H*OSi), 5.31 (br s, 1H, N*H*).

(*S*)-1-{(3-*tert*-Butoxycarbonylamino)propyl}-4-(thexyldimethylsilyloxy)pyrrolidin-2-thione (14): A solution of 106 mg (0.265 mmol) of **13** and 64 mg (0.16 mmol) of Lawesson's reagens in 3 mL of dry toluene was stirred for 2 h at 100 °C. After concentration in vacuo the residue was purified by flash chromatography (EtOAc/hexanes 1:3) to yield 99 mg (90%) of **14** as a yellow oil. IR ν 3450 (NH), 1700 (C=O carbamate), 1500 (C=S). ^{1}H NMR δ 0.08 (s, 6H, C*H*$_3$Si), 0.79 (s, 6H, C*H*$_3$CSi), 0.83 (d, *J* = 6.9 Hz, 6H, C*H*$_3$CCSi), 1.42 (s, 9H, *tert*-butyl), 1.57 (sept, *J* = 6.9 Hz, 1H, C*H*CSi), 1.78 (m, 2H, NCC*H*$_2$CN), 2.85-3.21 (4H), 3.52 (dd, *J* = 11.8, 2.1 Hz, 1H, NC*H*COSi), 3.63 (dt, *J* = 13.6, 6.6 Hz, 1H, C=SNC*H*), 3.80 (dd, *J* = 11.8, 5.3 Hz, 1H, NC*H*COSi), 4.00 (dt, *J* = 13.7, 6.8 Hz, 1H C=SNC*H*), 4.45 (m, 1H, C*H*OSi), 5.36 (br s, 1H, N*H*). ^{13}C NMR δ -1.8 (*C*H$_3$Si), 18.3 (*C*H$_3$CSi), 19.9 (*C*H$_3$CCSi), 24.6 (NC*C*CN), 26.5 (NC=S*C*), 28.2 (*tert*-butyl), 33.9 (*C*HCSi), 36.7 (*C*Si), 44.4 (NCC*C*NBoc), 54.4 (C(S)N*C*), 62.8 (N*C*COSi), 66.2 (*C*OSi), 78.8 (*tert*-butyl), 155.8 (*C*=O), 199.5 (*C*=S).

(*S*)-8-Thexyldimethylsilyloxy-1,5-diazabicyclo[4.3.0]non-5-ene (15): A solution of 264 mg (0.63 mmol) of **14** in 1 mL of freshly distilled methyl iodide was stirred for 18 h in the dark. After concentration in vacuo the crude iminium iodide salt was obtained as a yellow foam. ^{1}H NMR (some characteristic signals) δ 0.04 (s), 0.05 (s), 0.71 (s) and 0.74 (d, *J* = 7 Hz, ThMe$_2$Si), 1.32 (s, *tert*-butyl), 2.80 (s, SMe), 4.35 and 4.68 (br AB-system, *J* 19 Hz, NC*H*$_2$COSi), 4.75 (m, C*H*OSi), 5.20 (N*H*). The crude reaction product was dissolved in 6 mL of dry dichloromethane and cooled to 0 °C. Then 0.6 mL of freshly distilled CF_3COOH was added to the stirred solution. After being stirred for 4 h at 0-5 °C the reaction mixture was poured onto ice and 10% aqueous NaOH. The water layer was extracted with dichloromethane (2 ×). The combined organic layers were washed with brine, dried and concentrated in vacuo to yield 216 mg of a colourless oil. The residue was purified on basic alumina by fast elution with EtOAc/MeOH 9:1 and MeOH. In this way 177 mg of a brown-green oil was obtained. The oil became black within a few hours at room temperature or at -20 °C. IR ν 1670 (C=N). ^{1}H NMR δ 0.08 (s, 6H, C*H*$_3$Si), 0.78 (s, 6H, C*H*$_3$CSi), 0.81 (d, *J* = 6.9 Hz, 6H, C*H*$_3$CCSi), 1.22 (sept, 1H, C*H*CCSi), 2.01 (m, 2H), 2.80 (d, *J* = 17.6 Hz, 1H, *H*7b), 3.17-3.49 (6H), 3.84 (dd, *J* = 10.7, 5.6 Hz, 1H, *H*9a), 4.55 (m, 1H, *H*8). ^{1}H NMR (C_6D_6) δ 0.05 and 0.08 (2 × s, 6H, C*H*$_3$Si), 0.81 (s, 6H, C*H*$_3$CSi), 0.87 (d, *J* = 6.9 Hz, 6H, C*H*$_3$CCSi), 1.19 (m, 1H), 1.55 (quint, *J* = 7.0 Hz, 2H, *H*3), 2.42 (dt, *J* = 13.0, 6.5 Hz, 1H, *H*2 or *H*4), 2.86-2.97 (4H), 3.32 (m, 1H, *H*2 or *H*4), 3.57 (dd, *J* = 17.3, 6.4 Hz, 1H, *H*7b), 3.72 (dd, *J* = 9.6, 5.6 Hz, 1H, *H*9b), 4.46 (m, 1H, *H*8). ^{13}NMR, see Table 1.

(*S*)-1-(2-Cyanoethyl)-5-(thexyldimethylsilyloxymethyl)pyrrolidin-2-one (21): To a solution of 1.028 g (4 mmol) of **20** in 10 mL of THF were added at room temperature a trace of powdered NaOH and 0.31 mL (5 mmol) of freshly distilled acrylonitrile. After being stirred for 1 h at room temperature another trace of NaOH was added. Stirring was continued for another hour. The reaction was quenched by adding 1 N $NaHSO_4$. The water layer was extracted with ether (4 ×). The combined organic layers were successively washed with a saturated aqueous $NaHCO_3$ and brine, dried and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc) to give 1.192 g (96%) of **21** as a colourless oil. $[\alpha]_D$ +28.3 (*c* 1.04, MeOH). IR ν 2250 (CN), 1675 (lactam). ^{1}H NMR δ 0.11 (s, 6H, C*H*$_3$Si), 0.83 (s, 6H, C*H*$_3$CSi), 0.86 (d, *J* = 6.9 Hz, 6H, C*H*$_3$CCSi), 1.60 (sept, *J* = 6.9 Hz, 1H, C*H*CCSi), 1.79 (m, 1H, C=OCCH), 2.05-2.49 (3H), 2.65 (ddd, *J* = 16.7, 6.9, 5.6 Hz, 1H, C=OC*H*), 2.77 (dt, *J* = 16.7, 7.4 Hz, C=OC*H*), 3.45 (dt, *J* = 13.7, 7.3 Hz, 1H, NC*H*H), 3.57 (dd, *J* = 10.9, 5.0 Hz, 1H, C*H*OSi), 3.71-3.87 (3H). ^{13}C NMR δ -3.1 (*C*H$_3$Si), 16.2 (NC*C*CN), 18.2 (*C*H$_3$CSi), 19.9 (*C*H$_3$CCSi), 21.2 (C=OC*C*), 24.9 (*C*Si), 29.7 (C=O*C*), 33.8 (*C*HCSi), 37.4 (N*C*H$_2$), 59.7 (N*C*H), 64.4 (*C*H$_2$O), 117.8 (*C*N), 175.7 (N*C*=O). Mass spectrum (EI) no molecular ion peak observed, *m/e* 225 (48%, M^+ - C_6H_{13}), 172 (100%, M^+ - C_6H_{13} - C_3H_4N).

(*S*)-1-{(3-*tert*-Butoxycarbonylamino)propyl}-5-(thexyldimethylsilyloxymethyl)-pyrrolidin-2-one (22): According to the procedure as described for **13**, 4.404 g (14.21 mmol) of **21** was transformed into 4.21 g of **22** (70%). Mp 48-52 °C. $[\alpha]_D$ -0.47 (*c* 1.29, MeOH). IR ν 3450 (NH), 1700 (carbamate), 1760 (lactam). ^{1}H NMR δ 0.06 and 0.07 (2 × s, 6H, C*H*$_3$Si), 0.81 (s, 6H, C*H*$_3$CSi), 0.84 (d, *J* = 6.8 Hz, 6H, C*H*$_3$CCSi), 1.41 (s, 9H, *tert*-butyl), 1.45-1.69 (3H), 1.84 and 2.05 (2 × m, 2H, C=OCC*H*$_2$), 2.21-2.49 (m, 2H, C=OC*H*$_2$), 2.95 (m, 1H, C=ONC*H*), 3.15 (m, 2H, C*H*$_2$NBoc), 3.51-3.71 (m, 4H), 5.39 (br s, 1H, N*H*). ^{13}C NMR δ -3.6 (*C*H$_3$Si), 18.5 (*C*H$_3$CSi), 20.3 (*C*H$_3$CCSi), 21.5 (NC=O*C*C), 25.1 (NC*C*H$_2$CN), 27.7 (NC=O*C*), 28.5 (*tert*-butyl), 30.3 (*C*H$_2$NBoc), 34.2 (*C*HCSi), 37.2 (*C*Si), 37.8 (C=ONCH$_2$), 59.4 (N*C*HCOSi), 63.6 (NC*C*H$_2$OSi), 78.9 (*tert*-butyl), 156.1 (*C*=O, carbamate), 176.2 (*C*=O lactam). Anal. calcd for $C_{21}H_{42}N_2SiO_4$: C, 60.83; H, 10.21. Found: C, 60.95; H, 10.28.

(*S*)-1-{(3-*tert*-Butoxycarbonylamino)propyl}-5-thexyldimethylsilyloxymethyl-pyrrolidin-2-thione (23): According to the procedure as described for **14**, 2.97 g (7.17 mmol) of **22** was transformed into 2.75 g (89%) of **23**. Mp 50-53 °C. $[\alpha]_D$ +6.36 (*c* 1.10, MeOH). IR ν 3450 (NH), 1700 (carbamate), 1495 (C=S). ^{1}H NMR δ 0.05 (s, 6H, C*H*$_3$Si), 0.78 (s, 6H, *CH*$_3$CSi), 0.81 (d, *J* = 6.9 Hz, 6H, C*H*$_3$CCSi), 1.40 (s, 9H, *tert*-butyl), 1.54 (sept, *J* = 6.9 Hz, 1H, C*H*CSi), 1.71-1.93 (3H), 2.08 (m, 1H, C=SCC*H*), 2.82-3.09 (3H), 3.21 (m, 1H, C=SC*H*), 3.38 (dt, *J* = 13.4, 5.9 Hz, 1H, C=SNC*H*), 3.58 and 3.76 (2 × dd, *J* = 11.1, 3.7 Hz, 2H, m, C*H*$_2$OSi), 3.94 (m, 1H, NC*H*COSi), 4.27 (dt, *J* = 13.4, 7.6 Hz, 1H, C=SNC*H*), 5.25 (br s, 1H, N*H*). ^{13}C NMR δ -3.2 (*C*H$_3$Si), 18.4 (*C*H$_3$CSi), 20.2 (*C*H$_3$CCSi), 23.2 (C=SCCH$_2$), 25.0 (C=SCH$_2$), 26.8 (NCCH$_2$CN), 28.4 (*tert*-butyl), 34.1 (*C*HCSi), 37.4 (*C*Si), 42.9 (C=SNCH$_2$), 43.8 (*C*H$_2$NBoc), 62.8 (*C*H$_2$OSi), 66.9 (N*C*HCOSi), 79.0 (*tert*-butyl), 156.0 (N*C*=O carbamate), 202.8 (*C*=S). Anal. calcd for $C_{21}H_{42}N_2SSiO_3$: C, 58.56; H, 9.83. Found: C, 58.39; H, 9.85.

(*S*)-1-{(3-*tert*-Butoxycarbonylamino)propyl}-5-hydroxymethylpyrrolidin-2-one (24): A solution of 1.505 g (3.5 mmol) of **23** and 0.35 mL of 1 N tetra-*n*-butylammonium fluoride (TBAF) in THF in 25 mL of THF was stirred at room temperature with 406 mg (2 equiv) of potassium fluoride. After 3 h a second portion of 0.35 mL of the TBAF solution was added. After 51 h the reaction was complete. The reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (EtOAc) and recrystallized from EtOAc to yield 816 mg (85%) of **24**. Mp 104-105 °C. $[\alpha]_D$ +36.4 (*c* 0.55, MeOH). IR ν 3400 (OH, NH), 1695 (carbamate), 1500 (C=S). ^{1}H NMR ($CDCl_3$ + D_2O) δ 1.35 (s, 9H, *tert*-butyl), 1.68-2.13 (4H), 2.76-3.18 (4H), 3.46 (dt, *J* = 13.6, 6.6 Hz, 1H, C=SNC*H*), 3.60 (dd, *J* = 12.0 3.9 Hz, 1H, C*H*OH), 3.79 (dd, *J* = 11.0, 3.3 Hz, 1H, C*H*OH), 3.95 (m, 1H, C=SNC*H*COH), 5.36 (br s, 1H, N*H*). ^{13}C NMR δ 23.1 (NCCH$_2$CN), 27.1 (C=SCCH$_2$), 28.5 (*tert*-butyl), 37.9 (C=SCH$_2$), 43.6 and 43.9 (C=SNCH$_2$CCN and C=SNCCCH$_2$N), 62.7 (*C*H$_2$OH), 67.5 (N*C*HCOH), 79.4 (*tert*-butyl), 156.3 (s, carbamate), 203.1 (*C*=S). Anal. calcd for $C_{13}H_{24}N_2SO_3$: C, 54.14; H, 8.39; N, 9.71. Found: C, 54.18; H, 8.44; N, 9.67.

(*S*)-9-Hydroxymethyl-1,5-diazabicyclo[4.3.0]non-5-ene (5): A solution of 174 mg (0.6 mmol) of **24** in 4 mL of freshly distilled methyl iodide was stirred for 18 h in the dark. After concentration of the reaction mixture in vacuo the residue was dissolved in 4 mL of dry dichloromethane. Freshly distilled CF_3COOH (0.4 mL) was added and stirring continued for 4 hr at room temperature. The reaction mixture was extracted with water. The water layer was extracted with dichloromethane (2 ×) and concentrated in vacuo. The residue was dissolved in a small amount of water and run through a short ion exchange column (Amberlite IRA 400) with water. After concentration in vacuo the residue was decanted with hot benzene leaving a yellowish oil. After cooling of the benzene solution 51 mg (55%) of **5** crystallized as white needles. Mp 103-108 °C (benzene). $[\alpha]_D$ -63.9 (*c* 1.45, MeOH). IR ν 3300 (br, OH), 1640 (C=N). ^{1}H NMR (C_6D_6) δ 1.31-1.50 (m, 2H, *H*3), 1.60 and 1.75 (m, 2H, *H*8), 2.32 (ddd, 1H, *H*7), 2.60 (dt, 1H, *H*7), 2.72 (dt, *H*2), 3.14 (m, 1H, *H*2), 3.07 (m, 1H, *H*9), 3.20-3.27 and 3.34-3.39 (2H, *H*4), 4.43 (dd, *J* = 11.4, 3.8 Hz, 1H, *H*10), 3.55 (dd, *J* = 11.4, 4.0 Hz, 1H, *H*10). ^{13}C NMR, see Table 1.

Crystallographic data of **5**: $C_8H_{14}N_2O$, M = 154.2, monoclinic, $P2_1$, *a* = 5.2633(4), *b* = 10.419(2), *c* = 7.804(1) Å, *b* = 104.099(9)°, *V* = 415.1(1) Å^3, z = 2, D_x = 1.23 gcm^{-3}, λ(Cu Kα) = 1.5418 Å, μ(Cu Kα) = 6.3 cm^{-1}, *F*(000) = 168, room temperature. Final R = 0.047 for 912 observed reflections. Experimental procedure: A crystal with dimensions 0.25 × 0.40 × 0.90 mm was used for data collection on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated Cu Kα radiation and ω-2θ scan. A total of 945 reflections were measured within the range -6≤h≤0, 0≤k≤13, -9≤l≤9. Of these, 912 were above the significance level of 2.5 σ(I). The maximum value of (sinθ)/λ was 0.63 Å^{-1}. Two reference reflections (210, $\bar{1}$12) were measured hourly and showed no decrease during the 10 h collecting time. In addition 253 Friedel reflections were measured, which were used in the determination of the absolute configuration. Unit-cell parameters were refined by a least-squares fitting procedure using 23 reflections with 80<2θ<89°. Corrections for Lorenz and polarisation effects were applied. The structure was solved by Direct Methods. The hydrogen atoms were calculated. Full-matrix least-squares refinement on F, anisotropic for the non-hydrogen atoms

and isotropic for the hydrogen atoms, restraining the latter in such a way that the distance to their carrier remained constant at approximately 1.09 Å, converged to R = 0.047, R_w = 0.056, $(\Delta/\sigma)_{max}$ = 0.42. A weighting scheme w = $(5.75 + F_{obs} + 0.0043 \times F_{obs}^2)^{-1}$ was used. An empirical absorption correction (DIFABS)[22] was applied, with coefficients in the range of 0.58-1.20. The secondary isotropic extinction coefficient[23,24] refined to G = 0.025(9). The absolute-structure parameter[25] refined to X_{abs} = 0.14(6), thus indicating the correct enantiomorph. A final difference Fourier map revealed a residual electron density between -0.1 and 0.2 eÅ^{-3}. Scattering factors were taken from Cromer and Mann.[26] All calculations were performed with XTAL,[27] unless stated otherwise.[28]

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