(*S*)-Pyroglutamic Acid, (*S*)-Malic Acid, and (*S*)-Serine as Useful Starting Materials in the Synthesis of Enantiopure Hydroxyamidines

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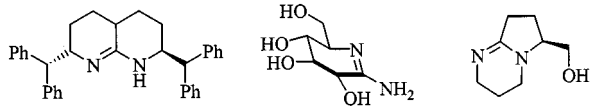
The synthesis of four enantiopure hydroxyamidines is described. One amidine was obtained from (*S*)-pyroglutamic acid. Its key step involved the addition of phenylmagnesium bromide to the corresponding ester, affording the tertiary alcohol without detectable racemization. The second amidine was obtained by coupling of an (*S*)-malic acid derived *N*-acyliminium ion with β-naphthol. The other amidines were obtained from an (*S*)-serine-derived imide which was reduced to two diastereomeric lactams that were eventually transformed into the corresponding amidines.

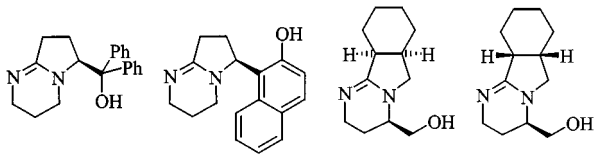
Introduction

The synthesis and properties of amidines are well-documented organic chemistry.[1] However, only a limited number of highly functionalized, enantiopure derivatives are known. Some noteworthy examples follow. The bicyclic amidine **1** was synthesized by the group of Davis and was capable of enantiodifferentiating recognition of chiral carboxylic acids.[2] Ganem synthesized various amidines starting from D-glucose, D-mannose (viz. **2**), and D-galactose; these amidines were evaluated as glycosidase inhibitors.[3]



1 **2** **3**

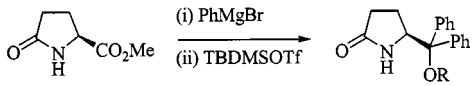
The synthesis and crystal structure of **3** were recently reported by our research group.[4] This enantiopure hydroxyamidine was tested as a chiral base in base-catalysed enantioselective reactions, such as the Michael reaction. In an attempt to increase the asymmetric induction, we designed new highly functionalized enantiopure amidines which, as a result of more steric bulk, might result in better selectivities.[5] Whereas an oxazaborolidine-mediated desymmetrization, developed in our group, was employed as the basis for the synthesis in the latter case, the hydroxyamidines **4**−**7** reported in this article were all synthesized from readily available enantiopure starting materials. Amidine **4**, a diphenyl-substituted analogue of **3**, was synthesized from (*S*)-pyroglutamic acid. Amidine **5** was synthesized with chemistry developed in our group, from (*S*)-malic acid,[6] while amidines **6** and **7** were both prepared from (*S*)-serine.[7] Finally, the enantioselectivity-inducing properties of the amidines were briefly examined in two test reactions.



4 **5** **6** **7**

Results and Discussion

The synthesis of hydroxyamidine **4** commenced with methyl pyroglutamate (**8**), obtained from the acid by treatment with thionyl chloride in methanol.[8] The ester was treated with an excess of phenylmagnesium bromide at −78°C, to afford the tertiary alcohol **9** in 51% yield after recrystallization from Et_2O (Equation 1). The enantiopurity of the product was confirmed by comparison with literature data (ref.[9] $[\alpha]_D = -86.4$). The tertiary alcohol **9** was protected with TBDMSOTf to give the corresponding silyl ether **10** ($[\alpha]_D = -67.1$) in quantitative yield.



(1)

8

9 R = H, 51%
m.p. 191-192 °C, $[\alpha]_D$ –80.8
10 R = TBDMS, 100%

A pathway similar to the one developed for the synthesis of **3** was applied to lactam **10** (Scheme 1).[4] The lactam reacted in a Michael-type fashion with acrylonitrile;[10] **11** was furnished in quantitative yield. The nitrile group was reduced with $NaBH_4$ and $CoCl_2$[11] and the resulting amine was directly treated with $tBoc_2O$ to give the carbamate **12** in 66% yield. The lactam moiety was then activated towards cyclization by conversion into thiolactam **13**,[12] after which the tertiary alcohol was deprotected with tetrabutylammonium fluoride (TBAF) to give alcohol **14** (61% yield over two steps). Next, a three-step, one-pot procedure was applied to perform the cyclization. After treatment of the thi-

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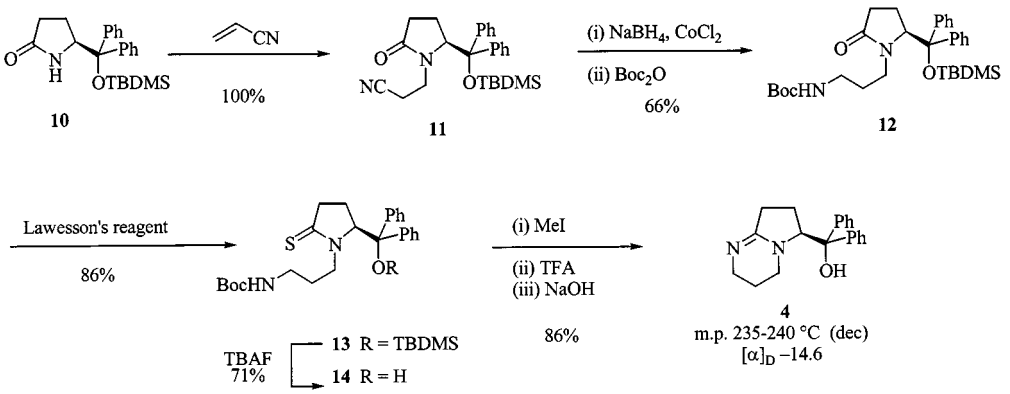
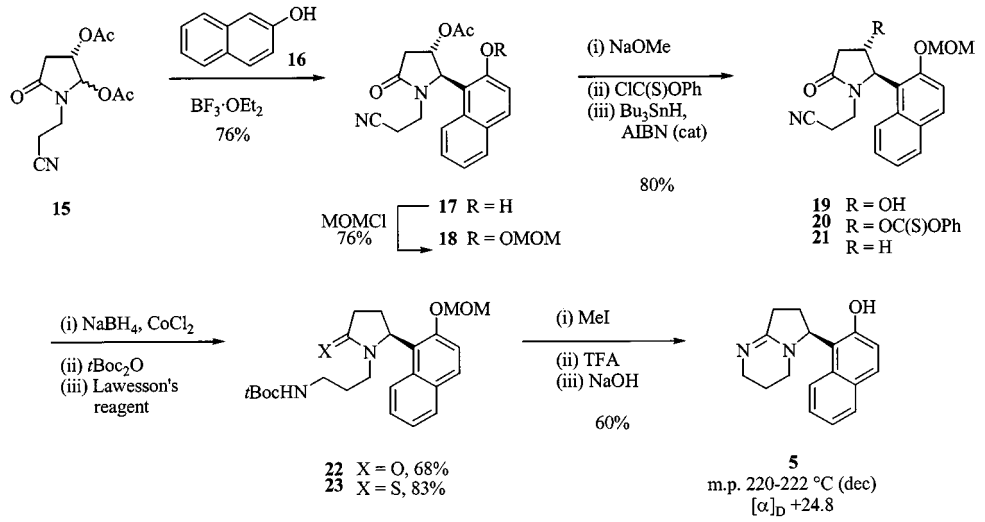


Scheme 1. Synthesis of hydroxyamidine **4**

olactam with MeI and removal of the Boc group with trifluoroacetic acid (TFA), the resulting amine was subjected to various cyclization conditions. Both treatment with Et_3N in CH_2Cl_2[5] or subjection to ion-exchange chromatography (Amberlite IRA 400)[4] did not result in clean product formation. Eventually, treatment of the amine with aqueous NaOH at 0°C, followed by acid/base extraction afforded amidine **4** in good yield (86%) as a white solid which was recrystallized from benzene.

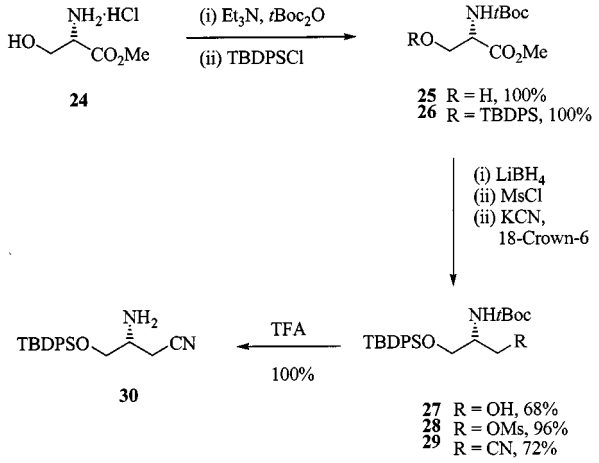
In an earlier paper, we described the synthesis of enantiopure acetoxylactam **15** from (*S*)-malic acid in five steps in 73% yield (5:1 *cis*/*trans* mixture, Scheme 2).[4] Our group investigated aromatic substitution reactions on this and other *N*-acyliminium ion precursors.[13] Treatment of **15** with β-naphthol (**16**) in the presence of $BF_3{\cdot}OEt_2$ provided adduct **17** in 76% yield. This product results from attack of the most nucleophilic α-position of β-naphthol onto the least hindered side of the *N*-acyliminium ion. According to NMR spectroscopy, the *trans* diastereomer was exclusively formed in this reaction. Next, protection of the phenolic alcohol of **17** was investigated. A *tert*-hexyldimethylsilyl group was efficiently introduced (*t*HexMe$_2$SiCl, imidazole, DMF, 96% yield), but appeared to be unstable under the basic nitrile reduction conditions.[14] The methoxymethyl group (MOM) was introduced, in 76% yield, through the reaction with NaH (1.1 equiv) and an excess of MOMCl (2 equiv.) in an 8:1 mixture of THF/DMF. The lactam hydroxy group was removed by saponification of the acetate (cat. NaOMe), followed by the Barton deoxygenation method,[15] which involves reduction of the corresponding thiocarbonate with Bu_3SnH and AIBN in refluxing benzene (80% overall yield). Room-temperature ^{1}H- and ^{13}C-NMR spectra showed that the β-naphthol-substituted compounds mentioned in Scheme 2 consisted of a mixture of two rotamers, due to restricted rotation around the sp^2-sp^3 C−C bond between the aromatic and the lactam moiety. Product **21** was obtained as a solid (m.p. 107−109°C) with satisfactory elemental analysis and ^{1}H- and ^{13}C-NMR spectra, thus confirming the assigned structure. ^{1}H-NMR analysis of the Mosher ester of the deprotected alcohol showed that product **21** was obtained in > 98% enantiomeric excess.[16] This compound was subjected to an identical series of events as that described previously (the aryl−OH was also liberated in the TFA step) to afford the hydroxyamidine **5**.

Finally, the syntheses of amidines **6** and **7** were studied. First, (*S*)-serine had to be converted into an appropriately functionalized amine. For this purpose, the commercially available HCl salt of the methyl ester of (*S*)-serine (**24**) was



Scheme 2. Synthesis of hydroxyamidine **5**

successively treated with $tBoc_2O$ and TBDPSCl to give the *N*- and *O*-protected product **26** in quantitative yield (Scheme 3).[17] The introduction of the nitrile function was performed in a three-step sequence. After reduction of the ester with $LiBH_4$, the resulting primary alcohol **27** was converted into the mesylate by treatment with MsCl. Then, the cyanide group was introduced through KCN and 18-crown-6 in refluxing acetonitrile,[18] to afford the cyanide **29** in good yield. Finally, the *t*Boc group was removed under standard conditions.



Scheme 3. Synthesis of aminonitrile **30**

After the formation of the appropriate serine derivative **30** was established, the syntheses of the hydroxyamidines could be completed (Scheme 4). The first step was the condensation of amine **30** with cyclohexane-1,2-dicarboxylic anhydride at 200°C in the absence of a solvent.[19] This led to the chiral imide **31** in 30% yield after flash chromatography. Next, the removal of one of the imide carbonyls was investigated. Reduction of imide **31** gives four possible ster-

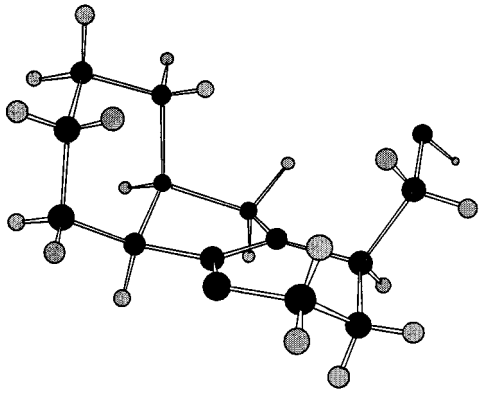
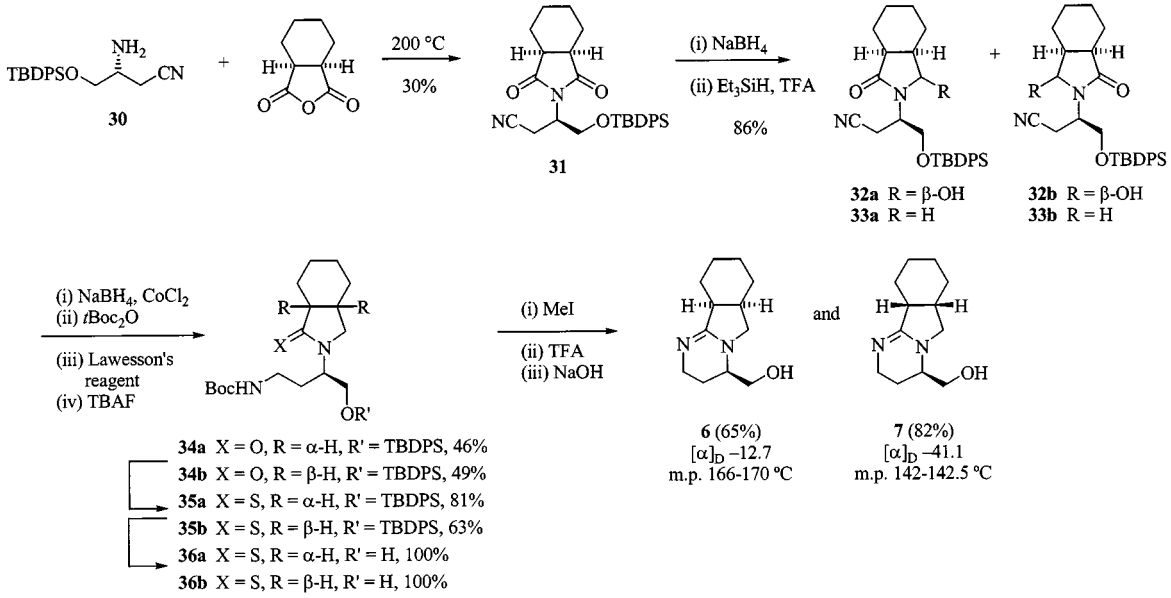


Figure 1. Crystal structure of **6**

eoisomers, resulting from *re* and *si* face attack of each of the carbonyl groups. However, when the reduction was performed with an excess of $NaBH_4$, at −15°C, in EtOH, and in the presence of a catalytic amount of acid,[20] only the kinetic *cis* products **32a** and **32b** were formed. Unfortunately, the isomers could not be separated by column chromatography. Therefore, the mixture of hydroxylactams was treated with TFA and Et_3SiH; in situ reduction of the intermediate *N*-acyliminium ions took place, to generate lactams **33a** and **33b**. At this stage, the diastereomers could be separated by column chromatography, to afford a 45:55 ratio of **33a** and **33b** in good overall yield. It was not possible to assign the structures of the two diastereomeric products solely on the basis of ^{1}H-NMR spectra. Eventually, the X-ray crystal structure of amidine **6** (derived from lactam **33a**, see Figure 1) clearly showed the relative stereochemistry shown in Scheme 4. The lactams were separately subjected to the series of reactions described for amidine **4**, to afford the diastereomeric amidines **6** and **7**. These compounds were purified by recrystallization from benzene. In our hands,

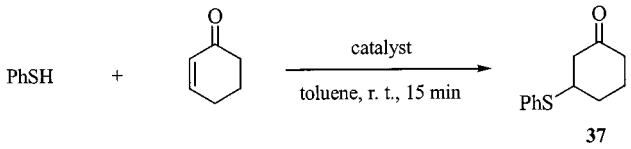


Scheme 4. Synthesis of hydroxyamidines **6** and **7**

only amidine **6** afforded crystals that could be used for an X-ray crystal structure determination. The crystal structure (Figure 1) shows the absolute stereochemistry, i.e., (1*R*,4b*S*,8b*R*); this means that both the hydroxymethyl group (at the 1-position) and the *cis*-fused six-membered ring are on the same (front) face of the amidine ring.

Results on the catalytic activities of the hydroxyamidines **4**−**7** are summarized in Tables 1 and 2. The Michael-type addition of thiophenol to cyclohexenone is a well-studied asymmetric reaction[21] and was chosen as a model system to identify the enantioselective catalytic properties of the four amidines. It was shown that the addition reaction proceeded well in the presence of 2−5% of amidine, to give the thioether **37** in 44−100% yield (Table 1). However, optically active product was only obtained when amidine **4** was used (14% ee, entry 1).

Table 1. Thiophenol addition to cyclohexenone

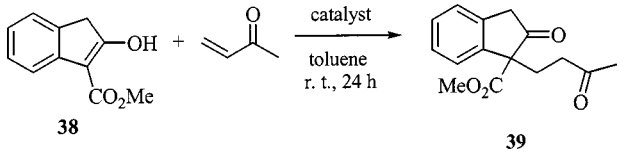


37

Entry	Catalyst	Amount (%)	Yield (%)	$[\alpha]_{578}$	$[\alpha]_{365}$	o. p. (%)[a]
1	**4**	5	44	–14.1		14
2	**5**	2	100	< 0.5		< 3
3	**6**	5	86	+0.8	+6.6	< 3
4	**7**	5	85	–2.0	–14.4	< 3

[a] Determined from the known specific rotation.[21]

Table 2. Michael addition to methyl vinyl ketone



38 **39**

Entry	Catalyst	Amount (%)	Yield (%)	$[\alpha]_D$	ee (%)[a]
1	**4**	10	89	–4.5	17
2	**5**	3	87	–7.1	27
3	**6**	10	100	< 0.5	< 2
4	**7**	10	91	–2.0	8

[a] Determined by chiral HPLC (Chiralpak AS).

A variety of asymmetric amidine-catalysed reactions with carbon nucleophiles such as nitromethane, malonates, and diketones were explored. However, some asymmetric induction was observed only with β-oxo ester **38** (Table 2). In the presence of 3−10% of catalyst, the Michael addition of **38** to methyl vinyl ketone proceeded in excellent yields to give the product **39**. The highest ee was obtained when hydroxyamidine **5** was used (entry 2, 27% ee).

Conclusion

In summary, the hydroxyamidines **4**−**7** were synthesized from the readily available starting materials (*S*)-pyroglutamic acid, (*S*)-malic acid, and (*S*)-serine. The structure of amidine **6** was confirmed by an X-ray crystal structure determination. These compounds represent a new class of chiral functionalized amidines. Preliminary results on the catalytic activities of these hydroxyamidines show that they possess unsatisfactory enantioselectivity-inducing properties. Further studies on hydroxyamidines and other chiral bases will be approached in a combinatorial way, which makes a more rapid discovery of promising structures for catalysis possible

Experimental Section

For general information see ref.[5]

(5*S*)-(Hydroxydiphenylmethyl)pyrrolidin-2-one (9): Phenylmagnesium bromide (90 mL, 270 mmol, 3.0 M solution in Et_2O) was slowly added to a solution of methyl pyroglutamate (**8**)[8] (11.2 g, 78.5 mmol) in THF (100 mL) at −78°C over 30 min. After being stirred for 15 min at −40°C and 30 min at 0°C, the reaction mixture was quenched with a 5% aqueous HCl solution. After extraction of the water layer (CH_2Cl_2, 5 ×), the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The solid residue was recrystallized from Et_2O to give white crystals (11.0 g, 39.7 mmol, 51%), m.p. 191−192°C. − IR ($CHCl_3$): $\tilde{\nu}$ = 3415 cm^{-1}, 1692. − ^1H NMR (400 MHz): δ = 7.48−7.18 (m, 10 H, 2 × Ph), 4.79 (br. s, 1 H, NH), 4.71−4.67 (dd, 1 H, *J* = 8.2, 4.8 Hz, NHCH), 3.95 (br. s, 1 H, OH), 2.37−2.29 [m, 1 H, C(O)CHH], 2.26−2.17 [m, 1 H, C(O)CHH], 2.13−2.04 [m, 1 H, C(O)CH_2CHH], 1.96−1.87 [m, 1 H, C(O)CH_2CHH]. − ^{13}C NMR (100 MHz): δ = 178.0 [s, *C*(O)], 145.2, 143.2 (s, *Ph*), 128.7, 128.2, 127.3, 126.9, 125.7, 125.5 (d, *Ph*), 78.6 [s, *C*(Ph_2OH], 60.5 (d, NH*C*H), 30.1 [t, C(O)*C*H_2], 21.5 [t, C(O)CH_2*C*H_2]. − $[\alpha]_D$ = −80.8 (*c* = 1.3; $CHCl_3$).

(5*S*)-[(*tert*-Butyldimethylsilyloxy)diphenylmethyl]pyrrolidin-2-one (10): *tert*-Butyldimethylsilyl triflate (103 μL, 0.45 mmol) and 2,6-lutidine (70 μL, 0.60 mmol) were slowly added to a solution of alcohol **9** (41 mg, 0.15 mmol) in CH_2Cl_2 (2.0 mL) at 0°C . After being stirred for 17 h at room temp., another portion of TBSOTf (75 μL, 0.30 mmol) and 2,6-lutidine (35 μL, 0.30 mmol) were added. After 5 h at room temp., the reaction mixture was quenched with 5% aqueous HCl. After extraction of the water layer (CH_2Cl_2, 5 ×), the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. After flash chromatography (EtOAc/PE, 1:1), **10** was obtained as a white solid (57 mg, 0.15 mmol, 100%). An analytic sample was recrystallized from EtOAc, m.p. 160.5−161°C. − IR ($CHCl_3$): $\tilde{\nu}$ = 3500 cm^{-1}, 1692. − ^1H NMR (400 MHz): δ = 7.35−7.26 (m, 10 H, 2 × Ph), 6.04 (br. s, 1 H, NH), 4.64−4.61 (dd, 1 H, *J* = 8.4, 3.1 Hz, NHCH), 2.19−2.05 [m, 2 H, C(O)CH_2], 1.87−1.79 [m, 1 H, C(O)CH_2CHH], 1.02−0.90 [m, 1 H, C(O)CH_2CHH], 0.93 [s, 9 H, SiC(CH_3)$_3$], −0.36 and −0.39 [2 × s, 6 H, Si(CH_3)$_2$]. − ^{13}C NMR (100 MHz): δ = 178.5 [s, *C*(O)], 142.8, 142.2 (s, *Ph*), 128.7, 128.5, 128.0, 127.6, 127.5, (d, *Ph*), 82.3 [s, *C*(Ph_2)OSi], 59.7 (d, N*C*H), 28.7 [t, C(O)*C*H_2], 26.0 [q, SiC(*C*H_3)$_3$], 22.2 [t, C(O)CH_2*C*H_2], 18.7 [s, Si*C*(CH_3)$_3$], −3.34 and −3.36 [q, Si(*C*H_3)$_2$]. − $C_{23}H_{31}NO_2Si$ (381.6): calcd. C 72.39, H 8.19, N 3.67; found C 72.46, H 8.19, N, 3.30. − $[\alpha]_D$ = −67.1 (*c* = 1.0; $CHCl_3$).

3-{(2*S*)-[(*tert*-Butyldimethylsilyloxy)diphenylmethyl]-5-oxopyrrolidin-1-yl}propionitrile (11): To a solution of lactam **10** (10.1 g, 25.8 mmol) in THF (70 mL) was added, at room temp, acrylonitrile (2.50 mL, 38.7 mmol) and a catalytic amount of powdered NaOH. After being stirred for 3.5 h at room temp, the reaction mixture was quenched with water. After extraction of the water layer (CH_2Cl_2, 5 ×), the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. After flash chromatography (EtOAc/PE, 1:1.5), **11** was obtained as a yellow foam (11.4 g, 25.8 mmol, 100%). − IR (film): $\tilde{\nu}$ = 2361 cm^{-1}, 1678. − ^1H NMR (400 MHz): δ = 7.46−7.26 (m, 10 H, 2 × Ph), 4.95−4.92 (m, 1 H, NC*H*), 3.75−3.69 (m, 1 H, NC*H*HCH_2), 3.43−3.38 (m, 1 H, NCH*H*CH_2), 2.73−2.65 (m, 1 H, NCH_2CH*H*) 2.37−2.30 (m, 1 H, NCH_2CH*H*), 2.19−2.12 [m, 2 H, C(O)CH_2], 1.74−1.67 [m, 1 H, C(O)CH_2CH*H*], 0.88 [s, 9 H, SiC(CH_3)$_3$], 0.88−0.77 [m, 1 H, C(O)CH_2CH*H*], −0.46 and −0.47 [2 × s, 6 H, Si(CH_3)$_2$]. − ^{13}C NMR (100 MHz): δ = 176.9 [s, *C*(O)], 141.2, 140.0 (s, *Ph*), 129.1, 128.9, 128.5, 128.0, 128.0, 127.7 (d, *Ph*), 118.1 (s, *C*N), 82.3 [s, *C*(Ph_2)OSi], 64.9 (d, N*C*H), 38.1 (t, N*C*H_2CH_2) 28.3 [t, C(O)*C*H_2], 26.1 [q, SiC(*C*H_3)$_3$], 21.8 [t, C(O)CH_2*C*H_2], 18.7 [s, Si*C*(CH_3)$_3$], 15.9 (t, *C*H_2CN), −3.34 and −3.36 (q, Si(*C*H_3)$_2$). − HRMS (FAB+): calcd. for $C_{26}H_{35}N_2O_2Si$ (M + H) 435.2468, found 435.2455. − $[\alpha]_D$ = −34.0 (*c* = 0.98; $CHCl_3$).

***tert*-Butyl (3-{(2*S*)-[(*tert*-Butyldimethylsilyloxy)diphenylmethyl]-5-oxopyrrolidin-1-yl}propyl)carbamate (12):** To a vigorously stirred, purple solution of $CoCl_2{\cdot}H_2O$ (12.1 g, 50.9 mmol) in MeOH (50 mL) was added, at 0°C, $NaBH_4$ (480 mg, 12.7 mmol). The deep-black solution was stirred for 15 min at room temp and cooled again. Then a solution of cyanide **11** (11.3 g, 25.5 mmol) in 2% NH_3 in MeOH (100 mL) was added dropwise. $NaBH_4$ pellets (19.2 g, 509 mmol) were added in portions over 5 h, during which hydrogen gas evolved. After being stirred another 1 h at 0°C, the reaction mixture was quenched with H_2O and filtered through Celite. The Celite was washed (MeOH/H_2O, 9:1, 3 ×). The solution was concentrated in vacuo and the residue was taken up in 5% aqueous NH_3. After extraction of the water layer (EtOAc, 5 ×), drying of the combined organic layers (Na_2SO_4) and concentration in vacuo, the crude product was obtained as a purple oil (9.85 g, 22.2 mmol, 89%). To a solution of this amine (9.5 g, 21.2 mmol) in CH_2Cl_2 (40 mL) was added Boc_2O (9.3 g, 42.4 mmol) and a catalytic amount of DMAP. After being stirred for 1 h at room temp., the reaction mixture was concentrated in vacuo and purified by flash chromatography (EtOAc/PE, 1:2); the product was obtained as a white foam (9.21 g, 16.8 mmol, 66% from **11**). − IR (film): $\tilde{\nu}$ = 3500 cm^{-1}, 1687, 1673. − ^1H NMR (400 MHz): δ = 7.48−7.26 (m, 10 H, 2 × Ph), 5.20 (br. s, 1 H, N*H*Boc), 4.71−4.68 (d, 1 H, *J* = 9.0 Hz, NC*H*), 3.76−3.65 (m, 1 H, NC*H*HCH_2), 3.28−3.25 (m, 1 H, C*H*HNHBoc), 2.77−2.69 (m, 2 H, NCH*H*CH_2CH*H*NH), 2.22−2.12 [m, 2 H, C(O)CH_2], 2.08−1.97 [m, 1 H, C(O)CH_2CH*H*], 1.78−1.60 (m, 2 H, NCH_2CH_2), 1.39 [s, 9 H, CO_2C(CH_3)$_3$], 0.90 [s, 9 H, SiC(CH_3)$_3$], 0.86−0.80 [m, 1 H, C(O)CH_2CH*H*], −0.45 and −0.49 [2 × s, 6 H, Si(CH_3)$_2$]. − ^{13}C NMR (100 MHz): δ = 177.5 [s, N*C*(O)], 155.9 [s, NH*C*(O)], 141.9, 139.8 (s, *Ph*), 129.1, 129.0, 128.7, 127.9, 127.7, 127.4 (d, *Ph*), 82.4 [s, *C*(Ph_2)OSi], 78.7 [s, $CO_2C(CH_3)_3$], 63.1 (d, N*C*H), 38.3 and 36.9 (t, N*C*$H_2CH_2CH_2$NHBoc), 28.5 [t, C(O)*C*H_2], 28.3 [q, CO_2C(*C*H_3)$_3$], 27.0 (t, NCH_2CH_2), 26.1 [q, SiC(*C*H_3)$_3$], 21.5 [t, C(O)CH_2CH_2], 18.8 [s, Si*C*(CH_3)$_3$], −3.1 and −3.4 [q, Si(*C*H_3)$_2$]. − HRMS (FAB+): calcd. for $C_{31}H_{47}N_2O_4Si$ (M + H) 539.3305, found 539.3283. − $[\alpha]_D$ = −76.0 (*c* = 1.1; $CHCl_3$).

***tert*-Butyl (3-{(2*S*)-[(*tert*-Butyldimethylsilyloxy)diphenylmethyl]-5-thioxopyrrolidin-1-yl}propyl)carbamate (13):** A solution of lactam **12** (190 mg, 0.35 mmol) and Lawesson's reagent (77 mg, 0.19 mmol) in toluene (2 mL) was heated at 90°C for 40 min. After concentration of the reaction mixture in vacuo, the residue was chromatographed (EtOAc/PE, 1:3); **13** was obtained as a green foam (170 mg, 0.30 mmol, 86%). − IR (film): $\tilde{\nu}$ = 3500 cm^{-1}, 1709, 1692. − ^1H NMR (400 MHz): δ = 7.46−7.26 (m, 10 H, 2 × Ph), 5.13 (br. s, 1 H, N*H*Boc), 5.05−5.03 (d, 1 H, *J* = 9.1 Hz, NC*H*), 4.48−4.41 (dt, *J* = 14.1, 7.4 Hz, 1 H, NC*H*HCH_2), 3.25−3.21 (br. m, 2 H, NCH*H*CH_2C*H*HNH), 2.86−2.82 (m, 1 H, CH*H*NHBoc), 2.42−2.35 [dd, 1 H, *J* = 18.3, 9.6 Hz, C(S)C*H*H], 2.24−2.06 [m, 2 H, C(S)CH*H*C*H*H], 1.80−1.77 (m, 2 H, NCH_2CH_2), 1.42 [s, 9 H, $CO_2C(CH_3)_3$], 1.33−1.23 [m, 1 H, C(S)CH_2CH*H*], 0.90 [s, 9 H, SiC(CH_3)$_3$], −0.45 and −0.46 [2 × s, 6 H, Si(CH_3)$_2$]. − ^{13}C NMR (100 MHz): δ = 205.4 [s, N*C*(S)], 155.5 [s, NH*C*(O)], 141.0, 139.4 (s, *Ph*), 128.9, 128.7, 128.6, 128.1, 128.0, 127.7 (d, *Ph*), 83.0 [s, *C*(Ph_2)OSi], 78.9 [s, $CO_2C(CH_3)_3$], 71.5 (d, N*C*H), 44.0 and 42.6 (t, N*C*$H_2CH_2CH_2$NH), 37.2 [t, C(S)*C*H_2], 28.3 [q, CO_2C(*C*H_3)$_3$], 26.4 (t, NCH_2CH_2), 26.1 [q, SiC(*C*H_3)$_3$], 23.4 [t, C(S)CH_2CH_2], 18.8 [s, Si*C*(CH_3)$_3$], −3.0 and −3.3 [q, Si(*C*H_3)$_2$]. − HRMS (FAB+): calcd. for $C_{31}H_{47}N_2O_3SSi$ (M + H) 555.3077, found 555.3050. − $[\alpha]_D$ = −91.2 (*c* = 1.0; $CHCl_3$).

***tert*-Butyl (3-[(2*S*)-(Hydroxydiphenylmethyl)-5-thioxopyrrolidin-1-yl]propyl)carbamate (14):** To a solution of **13** (5.32 g, 9.4 mmol) in THF (40 mL) was added TBAF (10 mL, 10 mmol, 1.0 M solution in THF) at room temp. After 1 h, another portion of TBAF (5 mL, 5 mmol, 1.0 M solution in THF) was added. After being stirred for 50 min, the reaction mixture was quenched with H_2O. After extraction of the water layer (CH_2Cl_2, 5 ×), the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. After flash chromatography (EtOAc/PE, 1:1), **14** was obtained as a white foam (3.01 g, 6.7 mmol, 71%). − IR (film): $\tilde{\nu}$ = 3450 cm^{-1}, 1703, 1693. − ^1H NMR (400 MHz): δ = 7.46−7.24 (m, 10 H, 2 × Ph), 5.08−5.06 (d, 1 H, *J* = 8.6 Hz, NC*H*), 4.84 (br. s, 1 H, N*H*Boc), 4.29−4.22 (dt, 1 H, *J* = 14.3, 7.4 Hz, NC*H*HCH_2), 3.12−3.09 (m, 1 H, C*H*HNHBoc), 2.96 (br. s, 1 H, −O*H*), 2.83−2.68 (m, 2 H, NCH*H*CH_2CH*H*NH), 2.50−2.48 [m, 1 H, C(S)C*H*H], 2.22−2.16 [m, 1 H, C(S)CH*H*], 2.07−2.01 [m, 1 H, C(S)CH_2C*H*H], 1.74−1.60 (m, 2 H, NCH_2CH_2), 1.42 [m, 10 H, $CO_2C(CH_3)_3$ and C(S)CH_2CH*H*]. − ^{13}C NMR (100 MHz): δ = 207.4 [s, N*C*(S)], 155.9 [s, NH*C*(O)], 144.0, 143.7 (s, *Ph*), 128.6, 128.4, 127.7, 127.6, 126.2, 125.9 (d, *Ph*), 80.6 [s, *C*(Ph_2)OH], 79.1 [s, $CO_2C(CH_3)_3$], 72.0 (d, N*C*H), 44.8 and 43.6 (t, N*C*$H_2CH_2CH_2$NHBoc), 37.3 [t, C(S)*C*H_2], 28.3 [q, CO_2C(*C*H_3)$_3$], 26.0 (t, NCH_2CH_2), 24.6 [t, C(S)CH_2CH_2]. − HRMS (FAB+): calcd. for $C_{25}H_{33}N_2O_3S$ (M + H) 441.2212, found 441.2207. − $[\alpha]_D$ = +6.8 (*c* = 1.0; $CHCl_3$).

[(6*S*)-2,3,4,6,7,8-Hexahydropyrrolo[1,2-a]pyrimidin-6-yl]diphenylmethanol (4): A solution of **14** (2.9 g, 6.5 mmol) in MeI (15 mL) was stirred for 17 h at room temp in the dark. After concentration in vacuo, a pale yellow powder was obtained (3.8 g, 6.5 mmol, 100%). This iodine salt (1.32 g, 2.27 mmol) was dissolved in 50% TFA in CH_2Cl_2 (12 mL) at 0°C. After being stirred for 4.5 h at this temperature, the product was extracted (H_2O, 3 ×). The combined aqueous extracts were made basic with solid NaOH and the product was extracted (CH_2Cl_2, 3 ×). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The product (600 mg, 1.96 mmol, 86%, white powder) was recrystallized from benzene as white crystals, m.p. 235−240°C (decomposition). − IR ($CHCl_3$): $\tilde{\nu}$ = 3300 cm^{-1}, 1650. − ^1H NMR (400 MHz): δ = 7.58−7.57 (d, 2 H, *J* = 1.3 Hz, *Ph*), 7.56−7.51 (m, 2 H, *Ph*), 7.49−7.19 (m, 6 H, *Ph*), 4.59−4.56 (dd, 1 H, *J* = 8.6, 3.6 Hz, NC*H*), 3.36−3.32 (b dt, 1 H, *J* = 14.6 Hz, C=NC*H*H), 3.10−3.05 (b t, 1 H, *J* = 9.9 Hz, C=NCH*H*), 2.75−2.70 (m, 1 H, C−NC*H*H), 2.43−2.18 (m, 3 H, C−NCH*H*, N=CCH_2), 2.17−1.95 (m, 2 H, N=CCH_2C*H*H and −O*H*), 1.90−1.82 (m, 1 H, N=CCH_2CH*H*),

1.64−1.56 (m, 1 H, C=NCH$_2$CHH), 1.49−1.39 (m, 1 H, C=NCH$_2$CHH). − ^{13}C NMR (100 MHz): δ = 162.5 (s, *C*=N), 145.9, 144.9 (s, *Ph*), 128.1, 128.0, 126.8, 126.7, 125.8, 125.7 (d, *Ph*), 79.0 [s, *C*(Ph)$_2$OH], 71.0 (d, N*C*H), 45.5, 43.4 (t, *C*H$_2$N=C−N*C*H$_2$), 30.3 (t), 23.4 (t), 20.8 (t). − $C_{20}H_{22}N_2O$ (306.4): calcd. C 78.40, H 7.24, N 9.14; found C 78.60, H 7.18, N 9.08. − $[\alpha]_D$ = −14.6 (*c* = 0.5; $CHCl_3$).

(2*S*,3*S*)-1-(2-Cyanoethyl)-2-(2-hydroxynaphthalen-1-yl)-5-oxopyrrolid-3-yl Acetate (17): To a solution of lactam **16** (2.54 g, 10 mmol) in CH_2Cl_2 (150 mL) were added at 0°C β-naphthol (2.88 g, 20 mmol) and BF_3·OEt_2 (7.5 mL, 60 mmol). After being stirred at room temp for 48 h, the reaction mixture was quenched with aqueous saturated $NaHCO_3$. After extraction of the water layer (CH_2Cl_2, 2 ×), the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The product (2.57 g, 7.60 mmol, 76%) was obtained as a white solid after flash chromatography (EtOAc). An analytical sample was recrystallized from EtOAc, m.p. 214−219°C. − IR (KBr): $\tilde{\nu}$ = 2950 cm^{-1}, 2140, 1750, 1645. − ^{1}H NMR (400 MHz, major rotamer): δ = 7.64 (s, 1 H, −O*H*), 8.04−7.16 (m, 6 H, *Naph*), 5.72 (s, 1 H, NC*H*), 5.47 (br. d, 1 H, *J* = 8.2 Hz, C*H*OAc), 3.61 (dt, 1 H, *J* = 13.9, 6.6 Hz, NC*H*H), 2.96 (dt, 1 H, *J* = 13.9, 7.5 Hz, NCH*H*), 3.33 [dd, 1 H, *J* = 18.1, 8.2 Hz, C(O)C*H*H], 2.62 [dd, 1 H, *J* = 18.1, 2.1 Hz, C(O)CH*H*], 2.65 (m, 1 H, C*H*HCN), 2.29 (dt, 1 H, *J* = 16.9, 5.6 Hz, CH*H*CN), 2.13 [s, 3 H, C(O)CH_3]. − ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 172.4, 170.1 [s, 2 × *C*(O)], 154.2, 133.4, 128.1, 113.7 (s, *Naph*), 130.6, 128.8, 127.2, 122.7, 121.3, 118.5 (d, *Naph*), 118.9 (s, *C*N), 72.9 (d, *C*HOAc), 61.4 (d, N*C*H), 38.4 (t, N*C*H$_2$), 36.2 t, [C(O)*C*H$_2$], 20.0 [q, C(O)*C*H$_3$], 15.8 (t, *C*H$_2$CN). − $C_{19}H_{18}N_2O_4$ (338.4): calcd. C 67.43, H 5.37, N 8.28; found C 67.52, H 5.40, N 8.25. − $[\alpha]_D$ = +42.4 (*c* = 0.65; MeOH).

(2*S*,3*S*)-1-(2-Cyanoethyl)-2-(2-methoxymethylnaphthalen-1-yl)-5-oxopyrrolid-3-yl Acetate (18): A solution of alcohol **17** (3.38 g, 10 mmol) in DMF (25 mL) was added at 0°C to a solution of NaH (0.42 g, 11 mmol) in THF (200 mL). After the reaction mixture was stirred at this temperature for 30 min, MOMCl (1.45 mL, 20 mmol) was added. After being stirred at room temp for 18 h, the reaction mixture was diluted with EtOAc (200 mL) and concentrated in vacuo. The product (2.78 g, 7.60 mmol, 76%) was obtained as a light purple foam after flash chromatography (CH_2Cl_2/acetone, 4:1). − ^{1}H NMR (250 MHz, major rotamer, selected signals): δ = 5.74 (d, 1 H, *J* = 1.9 Hz, NC*H*), 5.43 (dt, 1 H, *J* = 8.2, 2.4 Hz, C*H*OAc), 5.28 (AB d, 1 H, *J* = 7.1 Hz, OC*H*HO), 5.22 (AB d, 1 H, *J* = 7.1 Hz, OCH*H*O), 3.60 (dt, 1 H, *J* = 12.8, 5.4 Hz, NC*H*H), 3.45 (s, 3 H, OCH_3), 3.22 [dd, 1 H, *J* = 18.1, 8.4 Hz, C(O)C*H*H], 2.60 [dd, 1 H, *J* = 18.1, 2.5 Hz, C(O)CH*H*], 2.09 [s, 3 H, C(O)CH_3].

3-[(2*S*,3*S*)-3-Hydroxy-2-(2-methoxymethylnaphthalen-1-yl)-5-oxopyrrolidin-1-yl]propionitrile (19): To a solution of acetate **18** (10.3 g, 28.1 mmol) in MeOH (100 mL) was added, at 0°C, NaOMe (1.4 mL, 1.4 mmol, 1.0 M in MeOH). After the reaction mixture was stirred for 45 min at this temperature, another portion of NaOMe (1.4 mL, 1.4 mmol, 1.0 M in MeOH) was added. After being stirred for 1 h at 0°C, the reaction mixture was quenched with aqueous saturated NH_4Cl. The product (8.37 g, 24.4 mmol, 87%) was isolated by filtration and purified by recrystallization from EtOAc; white crystals were obtained, m.p. 164−166°C. − IR ($CHCl_3$): $\tilde{\nu}$ = 3407 cm^{-1}, 2250, 1681. − ^{1}H NMR (400 MHz, mixture of rotamers): δ = 8.2−7.4 (m, 12 H, *Naph*), 5.84 (d, 1 H, *J* = 6.0 Hz, NC*H*), 5.64 (d, 1 H, *J* = 2.2 Hz, NC*H*), 5.35 (AB d, 1 H, *J* = 6.7 Hz, OC*H*HO), 5.32 (AB d, 1 H, *J* = 6.7 Hz, OCH*H*O), 5.22 (AB d, 1 H, *J* = 7.0 Hz, OC*H*HO), 5.20 (AB d, 1 H, *J* = 6.7 Hz, OCH*H*O), 4.91 (m, 1 H, C*H*OH), 4.66 (m, 1 H, C*H*OH), 3.81 (m, 1 H, NC*H*H), 3.65 (ddd, 1 H, *J* = 13.2, 6.1, 5.4 Hz, NC*H*H), 3.54 (s, 3 H, OCH_3), 3.45 (s, 3 H, OCH_3), 3.14−2.26 (m, 6 H). − ^{13}C NMR (50 MHz, mixture of rotamers): δ = 174.5, 172.9 [s, *C*(O)], 154.8, 153.5, 132.9, 131.6, 130.3, 129.2, 117.7, 117.2 (s, *Naph*), 131.3, 130.8, 129.3, 128.8, 127.6, 127.3, 124.4, 124.0, 121.9, 121.4, 116.5, 114.9 (d, *Naph*), 116.8 (s, *C*N), 96.0, 94.2 (t, O*C*H$_2$O), 70.7, 70.3 (d, N*C*H), 65.9, 62.6 (d, *C*HOH), 56.5, 56.2 (q, O*C*H$_3$), 41.2, 39.9 (t, N*C*H$_2$), 36.6, 36.4 [t, C(O)*C*H$_2$], 16.0, 15.3 [t, *C*H$_2$CN). − $C_{19}H_{20}N_2O_4$ (296.3): cacld. C 67.03, H 5.93, N 8.23; found C 67.14, H 5.93, N 8.21. − $[\alpha]_D$ = +113 (*c* = 1.1; MeOH].

***O*-{(2*S*,3*S*)-[1-(2-Cyanoethyl)-2-(2-methoxymethylnaphthalen-1-yl)-5-oxopyrrolidin-3-yl] *O*-Phenyl Thiocarbonate (20):** To a solution of alcohol **19** (3.42 g, 10.0 mmol) and DMAP (2.44 g, 20 mmol) in CH_2Cl_2 (60 mL) was added, at 0°C, a solution of phenyl chlorothionoformate (1.73 mL, 12.5 mmol) in CH_2Cl_2 (10 mL). After being stirred for 2 h at this temperature, the reaction mixture was concentrated in vacuo. The product (4.61 g, 9.7 mmol, 97%) was purified by column chromatography (EtOAc); it formed a pink foam. − ^{1}H NMR (200 MHz, major rotamer): δ = 8.24−6.97 (m, 11 H, *Naph*), 5.95 (s, 1 H, NC*H*), 5.91 [dd, 1 H, *J* = 8.2, 2.2 Hz C*H*OC(S)], 5.30 (s, 2 H, OCH_2O), 3.59 (m, 1 H, NC*H*H), 3.49 (s, 3 H, OCH_3), 3.38 [dd, 1 H, *J* = 18.4, 8.2 Hz, C(O)C*H*H], 2.93 (m, 1 H, NCH*H*), 2.62 (dt, 1 H, *J* = 16.8, 7.5 Hz, C*H*HCN), 2.85 [dd, 1 H, *J* = 18.4, 2.5 Hz, C(O)CH*H*], 2.30 (dt, 1 H, *J* = 16.8, 6.2 Hz, CH*H*CN).

3-[(2*S*)-(2-Methoxymethylnaphthalen-1-yl)-5-oxopyrrolidin-1-yl]propionitrile (21): A solution of **20** (4.61 g, 9.7 mmol), Bu_3SnH (5.38 mL, 19.4 mmol) and AIBN (cat) in benzene (50 mL) was refluxed for 1.5 h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (EtOAc) and recrystallization (Et_2O/PE), to give the product (2.99 g, 9.22 mmol, 95%) as white crystals, m.p. 107−109°C. − IR ($CHCl_3$): $\tilde{\nu}$ = 2250 cm^{-1}, 1675. − ^{1}H NMR (400 MHz, mixture of rotamers): δ = 8.15−7.34 (m, 12 H, *Naph*), 6.04 (t, 1 H, *J* = 8.6 Hz, NC*H*), 5.90 (dd, 1 H, *J* = 9.2, 4.3 Hz, NC*H*), 5.31 (AB d, 1 H, *J* = 6.9 Hz, OC*H*HO), 5.29 (AB d, 1 H, *J* = 6.9 Hz, OCH*H*O), 5.244 (AB d, 1 H, *J* = 7.1 Hz, OC*H*HO), 5.240 (AB d, 1 H, *J* = 7.1 Hz, OCH*H*O), 3.75 (dt, 1 H, *J* = 13.9, 6.9 Hz, NC*H*H), 3.64 (dt, 1 H, *J* = 13.9, 6.6 Hz, NC*H*H), 3.53 (s, 3 H, OCH_3), 3.45 (s, 3 H, OCH_3), 2.82−2.70 (m, 14 H). − ^{13}C NMR (63 MHz, mixture of rotamers): δ = 176.1, 175.3 [s, *C*(O)], 154.2, 154.0, 132.9, 131.6, 130.5, 129.4, 119.9, 118.6 (s, *Naph*), 131.1, 130.6, 129.5, 129.0, 127.6, 127.2, 124.2, 124.0, 122.4, 121.2, 116.1 (d, *Naph*), 118.1, 117.6 (s, *C*N), 95.8, 94.5 (t, O*C*H$_2$O), 56.5, 56.4 (d, N*C*H), 55.2, 54.3 (q, O*C*H$_3$), 37.1, 37.0 (t, N*C*H$_2$), 30.8, 30.7 [t, C(O)*C*H$_2$], 24.7, 24.5 [t, C(O)CH$_2$*C*H$_2$], 16.3, 15.5 (t, *C*H$_2$CN). − $C_{19}H_{20}N_2O_3$ (324.4): calcd. C 70.34, H 6.22, N 8.64; found C 70.52, H 6.23, N 8.65. − $[\alpha]_D$ = +86.9 (*c* = 1.4; MeOH). − $[\alpha]_{365}$ +338.

***tert*-Butyl {3-[(2*S*)-(2-Methoxymethylnaphthalen-1-yl)-5-oxopyrrolidin-1-yl]propyl}carbamate (22):** According to the procedure described for **12**, 1.73 g of **21** (5.32 mmol) was transformed into 1.55 g (3.62 mmol, 68%, white foam) of **22**. − IR ($CHCl_3$): $\tilde{\nu}$ = 3452 cm^{-1}, 1703, 1666. − ^{1}H NMR (400 MHz, mixture of rotamers): δ = 8.10−7.33 (m, 12 H, *Naph*), 5.89 (t, 1 H, *J* = 8.6 Hz, NC*H*), 5.71 (dd, 1 H, *J* = 9.1, 4.8 Hz, NC*H*), 5.25 (m, 2 H, N*H*Boc), 5.293 (AB d, 1 H, *J* = 6.9 Hz, OC*H*HO), 5.290 (AB d, 1 H, *J* = 6.9 Hz, OCH*H*O), 5.25 (AB d, 1 H, *J* = 7.0 Hz, OC*H*HO), 5.22 (AB d, 1 H, *J* = 7.0 Hz, OCH*H*O), 3.68−3.55 (m, 2 H, NC*H*H), 3.51 (s, 3 H, OCH_3), 3.46 (s, 3 H, OCH_3), 2.88−2.19 (m, 10 H), 1.40 (m, 4 H, NCH$_2$CH_2), 1.38, 1.37 [2 × s, 18 H, CO$_2$C(CH_3)$_3$]. − ^{13}C NMR (63 MHz, mixture of rotamers): δ = 175.9, 175.4 [s, N*C*(O)], 155.9 [s, NH*C*(O)], 154.0, 153.8, 132.9, 131.9, 130.4, 129.4, 120.4, 119.1

(s, *Naph*), 130.7, 130.3, 129.3, 129.0, 127.3, 126.9, 124.1, 123.8, 122.6, 121.1, 115.9, 115.5 (d, *Naph*), 95.6, 94.5 (t, O*C*H$_2$O), 78.8 [s, CO$_2$*C*(CH$_3$)$_3$], 56.4, 56.3 (d, N*C*H), 54.4, 53.8 (q, O*C*H$_3$), 37.7 (t, *C*H$_2$NHBoc), 37.5, 37.3 (t, N*C*H$_2$), 30.9, 31.2 [t, C(O)*C*H$_2$], 28.4 [q, CO$_2$C(*C*H$_3$)$_3$], 27.4, 26.8 (t, NCH$_2$*C*H$_2$), 24.6, 24.4 [t, C(O)CH$_2$*C*H$_2$]. − HRMS (FAB+): calcd. for C$_{24}$H$_{33}$N$_2$O$_5$ (M + H) 429.2389, found 429.2284. − [α]$_D$ = +41.6 (*c* = 1.3; MeOH).

***tert*-Butyl {3-[(2*S*)-(2-Methoxymethylnaphthalen-1-yl)-5-thioxopyrrolidin-1-yl]propyl}carbamate (23)**: According to the procedure described for **13**, 8.82 g of **22** (20.6 mmol) was transformed into 7.63 g (17.1 mmol, 83%, colourless foam) of **23**. − IR (CHCl$_3$): ṽ = 3450 cm^{-1}, 1695, 1490. − ^{1}H NMR (250 MHz, mixture of rotamers): δ = 8.07−7.34 (m, 12 H, *Naph*), 6.18 (t, 1 H, *J* = 9.2 Hz, NC*H*), 5.99 (dd, 1 H, *J* = 9.2, 5.7 Hz, NC*H*), 5.3 (m, 2 H, N*H*Boc), 5.32 (s, 2 H, OC*H*HO), 5.27 (AB d, 1 H, *J* = 7.1 Hz, OCH*H*O), 5.20 (AB d, 1 H, *J* = 7.1 Hz, OCH*H*O), 4.5−4.1 (m, 2 H, NC*H*H), 3.52 (s, 3 H, OC*H*$_3$), 3.47 (s, 3 H, OC*H*$_3$), 3.5−1.5 (m, 14 H), 1.39, 1.38 [2 × s, 18 H, CO$_2$C(C*H*$_3$)$_3$]. − ^{13}C NMR (100 MHz, mixture of rotamers): δ = 201.5, 201.1 [s, N*C*(S)], 155.7, 155.6 [s, NH*C*(O)], 153.9, 153.6, 132.4, 131.4 130.1, 129.2, 118.6, 117.4 (s, *Naph*), 131.2, 130.8, 129.3, 128.9, 127.5, 127.4, 124.1, 123.8, 122.0, 120.8, 115.5, 115.2 (d, *Naph*), 95.3, 94.4 (t, O*C*H$_2$O), 78.8 [s, CO$_2$*C*(CH$_3$)$_3$], 62.3, 61.3 (d, N*C*H), 56.4, 56.3 (q, O*C*H$_3$), 45.0, 44.2 (t, N*C*H$_2$), 42.8, 42.6 (t, *C*H$_2$NHBoc), 28.2 [q, CO$_2$C(*C*H$_3$)$_3$], 26.8 [t, C(S)*C*H$_2$], 26.6, 26.1 (t, NCH$_2$*C*H$_2$), 25.9, 25.7 [t, C(S)CH$_2$*C*H$_2$]. − HRMS (FAB+): calcd. for C$_{24}$H$_{33}$N$_2$O$_5$ (M + H) 429.2389, found 429.2284. − [α]$_D$ = +70.1 (*c* = 0.60; MeOH). − [α]$_{365}$ = +106.7.

1-[(6*S*)-2,3,4,6,7,8-Hexahydropyrrolo[1,2-a]pyrimidin-6-yl]naphthalen-2-ol (5): Accoding to the procedure described for the synthesis of **4**, **23** (1.30 g, 4.89 mmol, 60%) was obtained as colourless crystals after recrystallization from a MeOH/*i*PrOH mixture, m.p. 220−220°C (decomposition). − IR (CHCl$_3$): ṽ = 3100 cm^{-1}, 1665. − ^{1}H NMR (400 MHz, CD$_3$OD, mixture of rotamers): δ = 8.01−7.04 (m, 12 H, *Naph*), 6.23 (t, 1 H, *J* = 8.8 Hz, C−NC*H*), 5.95 (dd, 1 H, *J* = 9.2, 5.6 Hz, C−NC*H*), 3.42−2.80 (m, 12 H), 2.61 (m, 2 H, C−NCHC*H*$_2$), 2.48 (m, 2 H, C−NCHC*H*$_2$), 1.95 (m, 2 H, C−NCH$_2$C*H*$_2$), 1.86 (m, 2 H, C−NCH$_2$C*H*$_2$). − ^{13}C NMR (100 MHz): δ = 165.3 (s, *C*=N), 152.8 (s, *Naph*), 132.8 (s, *Naph*), 131.6 (d, *Naph*), 129.3 (d, *Naph*), 129.1 (s, *Naph*), 127.8 (d, *Naph*), 123.7 (d, *Naph*), 120.3 (d, *Naph*), 118.2 (d, *Naph*), 113.1 (s, *Naph*), 62.4 (d, NC*H*), 40.6, 38.4, (d, C=N*C*H$_2$ and C−N*C*H$_2$), 30.8 (t, N=C*C*H$_2$), 25.2 (t, N=CCH$_2$*C*H$_2$), 18.4 (t, C−NCH$_2$*C*H$_2$). − [α]$_D$ = +24.8 (*c* = 0.91; MeOH).

***tert*-Butyl [(1*R*)-2-(*tert*-Butyldiphenylsilyloxy)-1-(hydroxymethyl)-ethyl]carbamate (27):** LiBH$_4$ (2.0 g, 93.8 mmol) was added, at 0°C, to a solution of ester **26** (30.7 g, 67.0 mmol) in Et$_2$O (300 mL). After being stirred for 20 min at 0°C and 40 min at room temp, the reaction mixture was carefully poured into 2% aqueous HCl. The water layer was extracted (CH$_2$Cl$_2$, 2 ×). The combined organic layers were dried (MgSO$_4$) and concentrated in vacuo. The product (19.7 g, 45.8 mmol, 68%) was obtained after flash chromatography as a white solid. An analytical sample of colourless needles was recrystallized from PE. M.p. 73−74°C. − IR (CHCl$_3$): ṽ = 3444 cm^{-1}, 1704. − ^{1}H NMR (400 MHz): δ = 7.67−7.64 (m, 4 H, *Ph*), 7.47−7.37 (m, 6 H, *Ph*), 5.09 (br. s, 1 H, N*H*Boc), 3.84−3.67 (m, 5 H, SiOC*H*$_2$C*H*C*H*$_2$), 2.41 (br. s, 1 H, −O*H*), 1.45 [s, 9 H, CO$_2$C(C*H*$_3$)$_3$], 1.08 [s, 6 H, SiC(C*H*$_3$)$_3$]. − ^{13}C NMR (100 MHz): not observed [*C*O$_2$C(CH$_3$)$_3$], δ = 135.4 (d, *Ph*), 132.8 (s, *Ph*), 132.7 (s, *Ph*), 129.8 (d, *Ph*), 127.8 (d, *Ph*), 79.5 [s, CO$_2$*C*(CH$_3$)$_3$], 64.0 (t, *C*H$_2$OSi), 53.0 (d, *C*HNHBoc), 28.7 [q, CO$_2$C(*C*H$_3$)$_3$], 26.8 [q, SiC(*C*H$_3$)$_3$], 19.1 [s, Si*C*(CH$_3$)$_3$]. − C$_{24}$H$_{35}$NO$_4$Si (429.6): cacld. C 67.10, H 8.21, N 3.26; found C 67.24, H 8.17, N 3.24. − [α]$_D$ = +4.7 (*c* = 1.2; CHCl$_3$).

(2*S*)-2-(*tert*-Butoxycarbonylamino)-3-(*tert*-butyldiphenylsilyloxy)propyl Methanesulfonate (28): To a solution of alcohol **27** (4.69 g, 11.0 mmol) in CH$_2$Cl$_2$ (50 mL) were added Et$_3$N (1.55 mL, 11.5 mmol) and mesyl chloride (0.90 mL, 11.5 mmol) at 0°C. After being stirred at 0°C for 0.5 h, the reaction mixture was washed (H$_2$O, 2 ×), dried (MgSO$_4$), and concentrated in vacuo. The crude product (5.33 g, 10.5 mmol, 96%) was obtained as a yellow oil which was pure according to ^{1}H NMR. − IR (film): ṽ = 3384 cm^{-1}, 1713. − ^{1}H NMR (400 MHz): δ = 7.65−7.63 (m, 4 H, *Ph*), 7.46−7.36 (m, 6 H, *Ph*), 4.87−4.85 (br. d, 1 H, *J* = 7.9 Hz, N*H*Boc), 4.39−4.29 (m, 2 H, C*H*$_2$OMs), 4.0 (br. m, 1 H, C*H*NH), 3.80−3.77 (ABX dd, 1 H, *J* = 10.3, 4.0 Hz, C*H*HOSi), 3.71−3.67 (ABX dd, 1 H, *J* = 10.3, 5.7 Hz, CH*H*OSi), 2.96 (s, 3 H, SO$_2$C*H*$_3$), 1.43 [s, 9 H, CO$_2$C(C*H*$_3$)$_3$], 1.07 [s, 9 H, SiC(C*H*$_3$)$_3$]. − ^{13}C NMR (100 MHz): δ = 155.0 [*C*O$_2$C(CH$_3$)$_3$], 135.4 (d, *Ph*), 135.3 (s, *Ph*), 132.5 (s, *Ph*), 129.9 (d, *Ph*), 127.8 (d, *Ph*), 79.9 [s, CO$_2$*C*(CH$_3$)$_3$], 67.7 (t, *C*H$_2$OMs), 61.9 (t, *C*H$_2$OSi), 50.6 (d, *C*HNH), 37.1 (q, SO$_2$*C*H$_3$), 28.1 [q, CO$_2$C(*C*H$_3$)$_3$], 26.7 [q, SiC(*C*H$_3$)$_3$], 19.1 [s, Si*C*(CH$_3$)$_3$]. − [α]$_D$ = −3.1 (*c* = 1.2; CHCl$_3$).

***tert*-Butyl [(*R*)-2-Cyano-1-(*tert*-butyldiphenylsilyloxy)ethyl]carbamate (29):** To a solution of mesylate **28** (4.62 g, 9.10 mmol) in CH$_3$CN (30 mL) were added KCN (1.18 g, 18.2 mmol) and 18-crown-6 (2.40 g, 9.10 mmol) at room temp. After being refluxed for 2 h, the reaction mixture was concentrated in vacuo. The product (2.89 g, 6.59 mmol, 72%) was obtained as a yellow oil after column chromatography (EtOAc/PE, 1:5). − IR (film): ṽ = 3500 cm^{-1}, 2250, 1716. − ^{1}H NMR (400 MHz): δ = 7.75−7.72 (m, 1 H, *Ph*), 7.67−7.64 (m, 3 H, *Ph*), 7.49−7.35 (m, 6 H, *Ph*), 4.87−4.85 (br. d, 1 H, *J* = 7.9 Hz, N*H*Boc), 4.00 (br. m, 1 H, C*H*NH), 3.81−3.77 (ABX bdd, 1 H, *J* = 10.5, 4.0 Hz, C*H*HOSi), 3.72−3.68 (ABX dd, 1 H, *J* = 10.4, 5.4 Hz, CH*H*OSi), 2.73−2.71 (d, 2 H, *J* = 5.4 Hz, C*H*$_2$CN), 1.45 [s, 9 H, CO$_2$C(C*H*$_3$)$_3$], 1.10 [s, 9 H, SiC(C*H*$_3$)$_3$]. − ^{13}C NMR (100 MHz): δ = 154.8 [s, *C*O$_2$C(CH$_3$)$_3$], 135.4 (d, *Ph*), 134.7 (s, *Ph*), 132.3 (s, *Ph*), 129.5 (d, *Ph*), 127.9 (d, *Ph*), 127.6 (d, *Ph*), 117.1 (s, *C*N), 80.2 [s, CO$_2$*C*(CH$_3$)$_3$], 63.9 (t, *C*H$_2$OSi), 48.5 (d, *C*HNH), 28.2 [q, CO$_2$C(*C*H$_3$)$_3$], 26.7 [q, SiC(*C*H$_3$)$_3$], 19.2, 18.9 [t, *C*H$_2$CN, s, Si*C*(CH$_3$)$_3$]. − HRMS (EI+): calcd. for C$_{25}$H$_{34}$N$_2$O$_3$Si 438.2339, found 438.2335. − [α]$_D$ = −7.4 (*c* = 1.0; CHCl$_3$).

(3*R*)-Amino-4-(*tert*-butyldiphenylsilyloxy)butyronitrile (30): Cyanide **29** (2.89 g, 6.59 mmol) was dissolved in freshly distilled trifluoroacetic acid (15 mL) at 0°C. After being stirred for 1 h at 0°C, the reaction mixture was concentrated in vacuo. The residue was dissolved in aqueous saturated NaHCO$_3$. The water layer was extracted (CH$_2$Cl$_2$, 5 ×) and the combined organic layers were dried (MgSO$_4$) and concentrated in vacuo. The product (2.23 g, 6.59 mmol, 100%) was obtained as a yellow oil. − IR (film): ṽ = 3500 cm^{-1}, 2240. − ^{1}H NMR (400 MHz): δ = 7.74−7.71 (m, 1 H, *Ph*), 7.68−7.63 (m, 3 H, *Ph*), 7.59−7.32 (m, 6 H, *Ph*), 3.66−3.57 (m, 2 H, C*H*$_2$OSi), 3.21−3.15 (quint, 1 H, *J* = 5.4 Hz, C*H*NH$_2$), 2.58−2.53 (ABX dd, 1 H, *J* = 16.6, 5.4 Hz, C*H*HCN), 2.49−2.43 (ABX dd, 1 H, *J* = 16.6, 6.9 Hz, CH*H*CN), 2.03 (br. s, 2 H, N*H*$_2$), 1.08 [s, 9 H, SiC(C*H*$_3$)$_3$]. − ^{13}C NMR (100 MHz): δ = 135.4 (d, *Ph*), 134.7 (s, *Ph*), 132.7 (s, *Ph*), 129.9 (d, *Ph*), 127.8 (d, *Ph*), 127.6 (d, *Ph*), 117.9 (s, *C*N), 66.9 (t, *C*H$_2$OSi), 49.9 (d, *C*HNH$_2$), 26.7 [q, SiC(*C*H$_3$)$_3$], 19.1, 18.9 [t, *C*H$_2$CN, s, Si*C*(CH$_3$)$_3$]. − HRMS (FAB+): calcd. for C$_{20}$H$_{26}$N$_2$OSiNa (M + Na) 361.1712, found 361.1682. − [α]$_D$ = +3.6 (*c* = 0.73; CHCl$_3$).

(3*R*)-4-(*tert*-Butyldiphenylsilyloxy)-3-(1,3-dioxooctahydroisoindol-2-yl)butyronitrile (31): A mixture of amine **30** (2.23 g, 6.59 mmol) and

powdered *cis*-1,2-cyclohexanedicarboxylic anhydride (1.0 g, 6.59 mmol) was heated at 200°C for 10 min. The product was purified by column chromatography (EtOAc/PE, 1:4); a yellow oil (951 mg, 2.0 mmol, 30%) was obtained. − IR (film): $\tilde{\nu}$ = 2260 cm^{-1}, 1713. − ^1H NMR (400 MHz): δ = 7.66−7.59 (m, 4 H, *Ph*), 7.46−7.33 (m, 6 H, *Ph*), 4.60−4.54 (m, 1 H, C*H*N), 3.97−3.92 (dd, 1 H, *J* = 10.2, 7.8 Hz, C*H*HOSi), 3.84−3.79 (dd, 1 H, *J* = 10.1, 6.8 Hz, CH*H*OSi), 3.18−3.11 (dd, 1 H, *J* = 16.9, 10.9 Hz, C*H*HCN), 2.85−2.78 [m, 2 H, C(O)C*HCH*], 2.76−2.71 (dd, 1 H, *J* = 16.8, 5.2 Hz, C*H*HCN), 1.85−1.81 (m, 4 H), 1.44−1.42 (m, 4 H), 1.03 [s, 9 H, SiC(CH_3)$_3$]. − ^{13}C NMR (100 MHz): δ = 179.1 [s, *C*(O)], 135.4 (d, *Ph*), 135.3 (s, *Ph*), 132.4 (s, *Ph*), 132.3 (d, *Ph*), 130.0 (d, *Ph*), 129.9 (d, *Ph*), 127.8 (d, *Ph*), 127.7, (d, *Ph*), 116.6 (s, *C*N), 61.9 (t, *C*H_2OSi), 49.2 (d, *C*HN), 39.6, 39.5 [d, C(O)*C*H*C*H], 26.6 [q, SiC(*C*H_3)$_3$], 23.9, 23.7, 21.6 [t, −(*C*H_2)$_4$−], 18.9 and 17.0 [t, *C*H_2CN, s, Si*C*(CH$_3$)$_3$]. − HRMS (FAB+): calcd. for $C_{28}H_{34}N_2O_3SiNa$ (M + Na) 497.2236, found 497.2236. − $[\alpha]_D$ = −2.0 (*c* = 0.86; $CHCl_3$).

(3*R*)-4-(*tert*-Butyldiphenylsilyloxy)-3-(1-hydroxy-3-oxooctahydroisoindol-2-yl)butyronitrile (32): $NaBH_4$ (325 mg, 8.60 mmol) was added at −15°C to a solution of imide **31** (812 mg, 1.72 mmol) in EtOH (10 mL). Three drops of a 0.5 M solution of H_2SO_4 in EtOH were added every 15 min. After being stirred for 1.5 h at −15°C, the reaction mixture was poured into aqueous saturated $NaHCO_3$. The water layer was extracted (CH_2Cl_2, 5 ×) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The products (773 mg, 1.64 mmol, 95%) were obtained as a white foam. An analytical sample was purified by column chromatography (EtOAc/PE, 1:3). The products could not be separated. − IR ($CHCl_3$): $\tilde{\nu}$ = 3365 cm^{-1}, 2270, 1668. − ^1H NMR (400 MHz, mixture of diastereomers): δ = 7.68−7.31 (m, 28 H, *Ph*), 5.28−5.26 (br. d, 1 H, *J* = 3.7 Hz, C*H*OH), 5.18 (br. s, 1 H, C*H*OH), 4.17−4.11, 4.01−3.97 and 3.93−3.80 (3 × m, 7 H, C*H*N, CH_2OSi and −O*H*), 3.13−3.03 (m, 2 H, C*H*HCN), 2.68−2.56 (m, 2 H, CH*H*CN), 2.48−2.45 (m, 2 H), 2.41 (m, 3 H), 1.97−1.89 (m, 2 H), 1.74−1.57 (m, 7 H), 1.49−1.21 (m, 12), 1.08 [s, 18 H, SiC(CH_3)$_3$]. − HRMS (FAB+): calcd. for $C_{28}H_{36}N_2O_3SiNa$ (M + Na) 499.2393, found 499.2372.

(3*R*)-4-(*tert*-Butyldiphenylsilyloxy)-3-(1-oxooctahydroisoindol-2-yl)butyronitrile (33): A mixture of trifluoroacetic acid (10 mL) and triethylsilane (10 mL) in CH_2Cl_2 (10 mL) was added at −15°C to a solution of hydroxylactams **32** (2.50 g, 5.25 mmol) in CH_2Cl_2 (25 mL). After being stirred for 2 h at −15°C, the reaction mixture was poured into aqueous saturated $NaHCO_3$. The water layer was extracted (CH_2Cl_2, 5 ×) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The products **33a** (1.0 g, 2.17 mmol, 41%) and **33b** (1.2 g, 2.61 mmol, 50%) were obtained separately, as colourless oils, after purification by column chromatography (EtOAc/PE, 1:3).

(3a*R*,7a*S*) Isomer 33a: IR (film): $\tilde{\nu}$ = 2260 cm^{-1}, 1699. − ^1H NMR (250 MHz): δ = 7.64−7.61 (m, 4 H, *Ph*), 7.47−7.38 (m, 6 H, *Ph*), 4.40−4.35 (m, 1 H, C*H*N), 3.80−3.78 (dd, 2 H, *J* = 5.9, 1.1 Hz, CH_2OSi), 3.42−3.38 (ABX dd, 1 H, *J* = 9.2, 5.8 Hz, NC*H*H), 3.05−3.02 (ABX dd, 1 H, *J* = 9.3, 2.2 Hz, NCH*H*), 2.80−2.74 (ABX dd, 1 H, *J* = 16.9, 8.1 Hz, C*H*HCN), 2.69−2.63 (ABX dd, 1 H, *J* = 16.9, 5.5 Hz, CH*H*CN), 2.46−2.42 [m, 1 H, C(O)C*H*], 2.32−2.29 [m, 1 H, C(O)CHC*H*H], 2.06−2.02 (m, 1 H, NCH$_2$C*H*), 1.72−1.69 (m, 1 H), 1.58−1.47 (m, 3 H), 1.30−1.15 (m, 3 H), 1.06 [s, 9 H, SiC(CH_3)$_3$], 0.91−0.82 (m, 1 H). − ^{13}C NMR (50 MHz): δ = 176.3 [s, *C*(O)], 135.4 (d, *Ph*), 132.3 (s, *Ph*), 130.0 (d, *Ph*), 127.8 (d, *Ph*), 117.3 (s, *C*N), 63.1 (t, *C*H_2OSi), 50.0 (d, *C*HN), 49.1 (t, N*C*H_2), 41.8 [d, C(O)*C*H], 32.6 [d, C(O)CH*C*H], 26.7 [q, SiC(*C*H_3)$_3$], 27.6, 23.4, 23.2, 22.7 [t, −(*C*H_2)$_4$−], 19.0, 17.6, [t, *C*H_2CN, s, Si*C*(CH$_3$)$_3$]. − HRMS (FAB+): calcd. for $C_{28}H_{37}N_2O_2Si$ (M + H) 461.2624, found 461.2638. − $[\alpha]_D$ = +6.2 (*c* = 0.41; $CHCl_3$).

(3a*S*,7a*R*) Isomer 33b: IR (film): $\tilde{\nu}$ = 2260 cm^{-1}, 1694. − ^1H NMR (250 MHz): δ = 7.65−7.62 (m, 4 H, *Ph*), 7.48−7.38 (m, 6 H, *Ph*), 4.33−4.30 (m, 1 H, C*H*N), 3.88−3.84 (ABX dd, 1 H, *J* = 10.6, 6.0 Hz, C*H*HOSi), 3.81−3.77 (ABX dd, 1 H, *J* = 10.6, 5.7 Hz, CH*H*OSi), 3.50−3.46 (ABX dd, 1 H, *J* = 9.1, 5.9 Hz, NC*H*H), 3.11−3.08 (ABX dd, 1 H, *J* = 9.2, 2.6 Hz, NCH*H*), 2.84−2.78 (ABX dd, 1 H, *J* = 16.9, 8.1 Hz, C*H*HCN), 2.69−2.64 (ABX dd, 1 H, *J* = 16.9, 5.6 Hz, CH*H*CN), 2.48−2.45 [m, 1 H, C(O)C*H*], 2.35−2.32 [m, 1 H, C(O)CHC*H*H], 2.00−1.96 (m, 1 H, NCH$_2$C*H*), 1.67−1.65 (m, 1 H), 1.56−1.45 (m, 3 H), 1.28−1.18 (m, 3 H), 1.07 [s, 9 H, SiC(CH_3)$_3$], 0.85 (m, 1 H). − ^{13}C NMR (50 MHz): δ = 176.4 [s, *C*(O)], 135.4 (d, *Ph*), 135.3 (s, *Ph*), 132.3 (s, *Ph*), 130.0 (d, *Ph*), 127.8 (d, *Ph*), 117.4 (s, *C*N), 63.1 (t, *C*H_2OSi), 50.3 (d, *C*HN), 49.5 (t, N*C*H_2), 41.8 [d, C(O)*C*H], 32.6 [d, C(O)CH*C*H], 26.7 [q, SiC(*C*H_3)$_3$], 27.6, 23.3, 23.2, 22.7 [t, −(*C*H_2)$_4$−], 19.0, 17.7, [t, *C*H_2CN, s, Si*C*(CH$_3$)$_3$]. − HRMS (FAB+): calcd. for $C_{28}H_{37}N_2O_2Si$ (M + H) 461.2624, found 461.2604. − $[\alpha]_D$ = +1.5 (*c* = 1.1; $CHCl_3$).

***tert*-Butyl {(3*R*)-4-(*tert*-Butyldiphenylsilyloxy)-3-[(3a*R*,7a*S*)-1-oxooctahydrohydroisoindol-2-yl]butyl}carbamate (34a):** According to the procedure described for **12**, 1.96 g (4.26 mmol) of **33a** was transformed into **34a** (1.12 g, 1.98 mmol, 46%). − IR (film): $\tilde{\nu}$ = 3400 cm^{-1}, 1685. − ^1H NMR (400 MHz): δ = 7.70−7.62 (m, 4 H, *Ph*), 7.48−7.37 (m, 6 H, *Ph*), 5.44 (br. s, 1 H, N*H*Boc), 4.27−4.20 (m, 1 H, NC*H*), 3.64−3.63 (d, 2 H, *J* = 6.3 Hz, CH_2OSi), 3.37−3.33 (ABX dd and m, 2 H, *J* = 9.4, 5.8 Hz, NC*H*H, C*H*HNHBoc), 2.82−2.74 (ABX d and m, 2 H, *J* = 9.1 Hz, NCH*H*, CH*H*NHBoc), 2.51−2.44 [m, 1 H, C(O)C*H*], 2.33−2.26 [m, 1 H, C(O)CHC*H*H], 2.09−2.04 (m, 1 H, NCH$_2$C*H*), 1.73−1.70 (m, 1 H), 1.58−1.47 (m, 4 H), 1.43 [s, 9 H, CO$_2$C(CH_3)$_3$], 1.39−1.11 (m, 4 H), 1.02 [s, 9 H, SiC(CH_3)$_3$]. − ^{13}C NMR (100 MHz): δ = 176.7 [s, N*C*(O)], 155.9 [s, *C*O$_2$C(CH$_3$)$_3$], 135.5 (d, *Ph*), 135.4 (d, *Ph*), 133.0 (s, *Ph*), 132.9 (s, *Ph*), 129.7 (d, *Ph*), 129.6 (d, *Ph*), 127.6 (d, *Ph*), 78.7 [s, CO$_2$*C*(CH$_3$)$_3$], 64.3 (t, *C*H$_2$OSi), 50.2 (d, N*C*H), 47.4 (t, N*C*H$_2$), 41.9 [d, C(O)*C*H], 36.8 (t, *C*H$_2$NHBoc), 32.3 (d, NCH$_2$*C*H), 28.3 [q, CO$_2$C(*C*H$_3$)$_3$], 28.0 (t, *C*H$_2$CH$_2$NHBoc), 26.7 [q, SiC(*C*H$_3$)$_3$], 28.5, 23.6, 23.4, 22.9 [t, −(*C*H$_2$)$_4$−], 19.0 [q, Si*C*(CH$_3$)$_3$]. − HRMS (FAB+): calcd. for $C_{33}H_{49}N_2O_4Si$ (M + H) 565.3462, found 565.3434. − $[\alpha]_D$ = +22.6 (*c* = 0.87; $CHCl_3$).

***tert*-Butyl {(3*R*)-4-(*tert*-Butyldiphenylsilyloxy)-3-[(3a*S*,7a*R*)-1-oxooctahydrohydroisoindol-2-yl]butyl}carbamate (34b):** According to the procedure described for **12**, 2.25 g (4.88 mmol) of **33b** was transformed into **34b** (1.32 g, 2.41 mmol, 49%). − IR (film): $\tilde{\nu}$ = 3400 cm^{-1}, 1711, 1677. − ^1H NMR (400 MHz): δ = 7.67−7.59 (m, 4 H, *Ph*), 7.48−7.37 (m, 6 H, *Ph*), 5.29 (br. s, 1 H, N*H*Boc), 4.29−4.26 (m, 1 H, NC*H*), 3.74−3.69 (ABX dd, 1 H, *J* = 10.9, 7.5 Hz, C*H*HOSi), 3.65−3.62 (ABX dd, 1 H, *J* = 10.9, 4.4 Hz, CH*H*OSi), 3.36−3.34 (m, 1 H, C*H*HNHBoc), 3.26−3.22 [ABX dd, 1 H, *J* = 9.3, 5.9 Hz, C(O)NC*H*H], 3.09−3.06 [ABX dd, 1 H, *J* = 9.4, 2.6 Hz, C(O)NCH*H*], 2.63−2.61 (m, 1 H, CH*H*NHBoc), 2.50−2.46 [m, 1 H, C(O)C*H*], 2.35−2.28 [m, 1 H, C(O)CHC*H*H], 2.03−1.99 [m, 1 H, C(O)NCH$_2$C*H*], 1.80−1.45 (m, 5 H), 1.42 [s, 9 H, CO$_2$C(CH_3)$_3$], 1.29−1.20 (m, 3 H), 1.04 [s, 9 H, SiC(CH_3)$_3$], 0.89−0.83 (m, 1 H). − ^{13}C NMR (100 MHz): δ = 177.1 [s, N*C*(O)], not observed [*C*O$_2$C(CH$_3$)$_3$], 135.6 (d, *Ph*), 135.5 (d, *Ph*), 133.0 (s, *Ph*), 132.9 (s, *Ph*), 129.8 (d, *Ph*), 129.7 (d, *Ph*), 127.7 (d, *Ph*), 78.7 [s, CO$_2$*C*(CH$_3$)$_3$], 64.5 (t, *C*H$_2$OSi), 50.2 (d, N*C*H), 47.2 (t, N*C*H$_2$), 42.1 [d, C(O)*C*H], 36.8 (t, *C*H$_2$NHBoc), 32.4 (d, NCH$_2$*C*H), 28.4

[q, $CO_2C(CH_3)_3$], 27.6 (t, CH_2CH_2NHBoc), 26.8 [q, $SiC(CH_3)_3$], 28.5, 23.5, 23.4, 22.8 [t, $-(CH_2)_4-$], 19.0 [s, $SiC(CH_3)_3$]. − HRMS (FAB+): calcd. for $C_{33}H_{49}N_2O_4Si$ (M + H) 565.3462, found 565.3453. − $[\alpha]_D$ = +27.0 (*c* = 0.67; $CHCl_3$).

***tert*-Butyl {(3*R*)-4-(*tert*-Butyldiphenylsilyloxy)-3-[(3a*R*,7a*S*)-1-thioxooctahydrohydroisoindol-2-yl]butyl}carbamate (35a):** According to the procedure described for **13**, 1.12 g (1.98 mmol) of **34a** was transformed into **35a** (931 mg, 1.60 mmol, 81%). − IR (film): $\tilde{\nu}$ = 3400 cm^{-1}, 1700. − ^1H NMR (400 MHz): δ = 7.65−7.61 (m, 4 H, *Ph*), 7.47−7.37 (m, 6 H, *Ph*), 5.60 (br. s, 1 H, N*H*Boc), 5.25−5.18 (quint, 1 H, *J* = 6.9 Hz, NC*H*), 3.73−3.68 (m, 2 H, CH_2OSi), 3.60−3.56 [ABX dd, 1 H, *J* = 10.7, 5.9 Hz, C(S)NC*H*H], 3.37−3.36 (m, 1 H, C*H*HNHBoc), 3.17−3.14 [ABX dd, 1 H, *J* = 10.8, 2.3 Hz, C(S)NCH*H*], 2.81−2.69 [m, 2 H, C(S)C*H* and CH*H*NHBoc], 2.38−2.22 [m, 2 H, C(S)CHC*H*H and NCH_2CH], 1.74−1.47 (m, 4 H), 1.43 [s, 9 H, $CO_2C(CH_3)_3$], 1.38−1.11 (m, 4 H), 1.02 [s, 9 H, $SiC(CH_3)_3$], 0.89−0.82 (m, 1 H). − ^{13}C NMR (100 MHz): δ = 206.0 [s, N*C*(S)], not observed [$CO_2C(CH_3)_3$], 135.6 (d, *Ph*), 135.4 (s, *Ph*), 132.9 (s, *Ph*), 132.6 (d, *Ph*), 129.8 (d, *Ph*), 129.7 (d, *Ph*), 127.7 (d, *Ph*), 78.9 [s, $CO_2C(CH_3)_3$], 64.1 (t, CH_2OSi), 55.6 (d, N*C*H), 53.7 [t, C(S)N*C*H_2], 52.7 [d, C(S)*C*H], 36.6 (t, CH_2NHBoc), 34.1 (t, NCH_2CH), 28.3 [q, $CO_2C(CH_3)_3$], 28.1 (t, CH_2CH_2NHBoc), 26.7 [q, $SiC(CH_3)_3$], 27.5, 26.2, 23.5, 22.2 [t, -(CH_2)$_4$-], 19.0 [s, $SiC(CH_3)_3$]. − HRMS (FAB+): calcd. for $C_{33}H_{49}N_2O_3SSi$ (M + H) 581.3233, found 581.3219. − $[\alpha]_D$ = −4.0 (*c* = 0.87; $CHCl_3$). − $[\alpha]_{365}$ = −538.

***tert*-Butyl {(3*R*)-4-(*tert*-Butyldiphenylsilyloxy)-3-[(3a*S*,7a*R*)-1-thioxooctahydrohydroisoindol-2-yl]butyl}carbamate (35b):** According to the procedure described for **13**, 1.32 g (2.41 mmol) of **34b** was transformed into **35b** (876 mg, 1.51 mmol, 63%). − IR (film): $\tilde{\nu}$ = 3400 cm^{-1}, 1712, 1699. − ^1H NMR (400 MHz): δ = 7.69−7.60 (m, 4 H, *Ph*), 7.46−7.38 (m, 6 H, *Ph*), 5.33 (br. s, 1 H, N*H*Boc), 5.25−5.21 (m, 1 H, NC*H*), 3.81−3.76 (ABX dd, 1 H, *J* = 11.1, 7.4 Hz, C*H*HOSi), 3.74−3.70 (ABX dd, 1 H, *J* = 11.1, 4.0 Hz, CH*H*OSi), 3.53−3.45 [m, 2 H, C(S)NCH_2], 3.29 (m, 1 H, C*H*HNHBoc), 2.81−2.77 [m, 1 H, C(S)C*H*], 2.70−2.69 (m, 1 H, CH*H*NHBoc), 2.44−2.43 [m, 1 H, C(S)CHC*H*H], 2.23−2.21 (m, 1 H, NCH_2CH), 1.78−1.69 (m, 2 H), 1.65−1.51 (m, 2 H), 1.42 [s, 9 H, $CO_2C(CH_3)_3$], 1.37−1.20 (m, 4 H), 1.04 [s, 9 H, $SiC(CH_3)_3$], 0.90−0.83 (m, 1 H). − ^{13}C NMR (100 MHz): δ = 206.2 [s, N*C*(S)], 155.8 [s, $CO_2C(CH_3)_3$], 135.6 (d, *Ph*), 135.4 (d, *Ph*), 132.8 (s, *Ph*), 132.6 (s, *Ph*), 129.8 (d, *Ph*), 129.7 (d, *Ph*), 127.7 (d, *Ph*), 78.9 [s, $CO_2C(CH_3)_3$], 64.3 (t, CH_2OSi), 55.4 (d, N*C*H), 53.3 [t, C(S)NCH_2], 53.0 [d, C(S)*C*H], 36.7 (t, CH_2NHBoc), 34.0 (d, NCH_2CH), 28.3 [q, $CO_2C(CH_3)_3$], 28.2 (t, CH_2CH_2NHBoc), 26.7 [q, $SiC(CH_3)_3$], 26.6, 26.1, 23.2, 22.2 [t, -(CH_2)$_4$-], 19.0 [s, $SiC(CH_3)_3$]. − HRMS (FAB+): calcd. for $C_{33}H_{49}N_2O_3SSi$ (M + H) 581.3233, found 581.3223. − $[\alpha]_D$ = +33.2 (*c* = 0.98; $CHCl_3$).

***tert*-Butyl {(3*R*)-4-Hydroxy-3-[(3a*R*,7a*S*)-1-thioxooctahydrohydroisoindol-2-yl]butyl}carbamate (36a):** TBAF (1.4 mL, 1.4 mmol, 1.0 M solution in THF) was added at room temp to a solution of **35a** (751 mg, 1.29 mmol) in THF (10 mL). After 20 min, another portion of TBAF (1.5 mL, 1.5 mmol, 1.0 M solution in THF) was added. After being stirred for 25 min at 40°C (rotavapor bath), the reaction mixture was quenched with H_2O. After extraction of the water layer (CH_2Cl_2, 5 ×), the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. After flash chromatography (EtOAc/PE, 4:1), **36a** was obtained as a yellow oil (448 mg, 1.29 mmol, 100%). − IR ($CHCl_3$): $\tilde{\nu}$ = 3370 cm^{-1}, 1703. − ^1H NMR (400 MHz): δ = 5.46 (br. s, 1 H, N*H*Boc), 5.24−5.17 (m, 1 H, NC*H*), 3.82−3.78 (ABX dd, 1 H, *J* = 11.8, 4.4 Hz, C*H*HOH), 3.73−3.71 [AB d, 1 H, *J* = 9.0 Hz, C(S)NC*H*H], 3.68−3.64 (ABX dd, 1 H, *J* = 10.7, 5.9 Hz, CH*H*OH), 3.39−3.38 (m, 1 H, C*H*HNHBoc), 3.23−3.20 [ABX dd, 1 H, *J* = 10.8, 2.4 Hz, C(S)NCH*H*], 2.89−2.81 [m, 2 H, C(S)C*H* and CH*H*NHBoc], 2.50−2.42 [m, 1 H, C(S)CHC*H*H], 2.34−2.30 (m, 1 H, NCH_2CH), 2.04 (br. s, 1 H, −O*H*), 1.87−1.63 (m, 4 H), 1.62−1.47 (m, 2 H), 1.43 [s, 9 H, $CO_2C(CH_3)_3$], 1.30−1.21 (m, 2 H), 1.11−1.03 (m, 1 H). − ^{13}C NMR (100 MHz): δ = 206.4 [s, N*C*(S)], 156.0 [s, $CO_2C(CH_3)_3$], 79.1 [s, $CO_2C(CH_3)_3$], 62.9 (t, CH_2OH), 55.9 (d, N*C*H), 53.6 [t, C(S)N*C*H_2], 52.8 [d, C(S)*C*H], 36.7 (t, CH_2NHBoc), 33.9 (d, NCH_2CH), 28.4 (t, CH_2CH_2NHBoc), 28.3 [q, $CO_2C(CH_3)_3$], 27.4, 26.1, 23.4, 22.2 [t, $-(CH_2)_4-$]. − HRMS (FAB+): calcd. for $C_{17}H_{31}N_2O_3SSi$ (M + H) 343.2055, found 343.2032. − $[\alpha]_D$ = −24.3 (*c* = 0.93; $CHCl_3$).

***tert*-Butyl {(3*R*)-4-Hydroxy-3-[(3a*S*,7a*R*)-1-thioxooctahydrohydroisoindol-2-yl]butyl}carbamate (36b):** According to the procedure described for **36a**, 33.7 mg (0.058 mmol) of **35b** was transformed into **36b** (20 mg, 0.058 mmol, 100%, yellow solid), which was recrystallized as pale yellow crystals from an EtOAc/PE mixture. M.p. 99−100°C. − IR ($CHCl_3$): $\tilde{\nu}$ = 3400 cm^{-1}, 1703. − ^1H NMR (400 MHz): δ = 5.28−5.21 (m, 2 H, N*H*Boc and NC*H*), 3.84−3.80 (ABX dd, 1 H, *J* = 11.6, 4.4 Hz, C*H*HOH), 3.75−3.71 (m, 1 H, CH*H*OH), 3.54−3.50 [ABX dd, 1 H, *J* = 10.7, 6.2 Hz, C(S)NC*H*H], 3.38−3.34 [ABX dd, 1 H, *J* = 10.8, 3.7 Hz, C(S)NCH*H*], 3.33−3.30 (m, 1 H, C*H*HNHBoc), 2.83−2.79 [m, 2 H, C(S)C*H* and CH*H*NHBoc], 2.47−2.41 [m, 1 H, C(S)CHC*H*H], 2.23−2.18 (m, 1 H, NCH_2CH), 1.97 (br. s, 1 H, −O*H*), 1.79−1.70 (m, 3 H), 1.65−1.58 (m, 1 H), 1.53−1.49 (m, 1 H), 1.42 [s, 9 H, $CO_2C(CH_3)_3$], 1.38−1.33 (m, 4 H). − ^{13}C NMR (100 MHz): δ = 206.8 [s, N*C*(S)], 155.9 [s, $CO_2C(CH_3)_3$], 79.2 [s, $CO_2C(CH_3)_3$], 63.0 (t, CH_2OH), 55.7 (d, N*C*H), 53.1 [d, C(S)*C*H], 53.0 [t, C(S)N*C*H_2], 36.9 (t, CH_2NHBoc), 34.1 (d, NCH_2CH), not observed (CH_2CH_2NHBoc), 28.3 [q, $CO_2C(CH_3)_3$], 26.5, 26.1, 23.1, 22.3 [t, -(CH_2)$_4$-]. − $C_{17}H_{30}N_2O_3S$ (342.4): calcd. C 59.62, H 8.83, N 8.18; found C 59.60, H 8.69, N 8.14. − $[\alpha]_D$ = +45.9 (*c* = 0.93; $CHCl_3$).

(1*R*,4b*S*,8a*R*)-(1,2,3,4b,5,6,7,8,8a,9-Decahydro-4,9a-diazafluoren-1-yl)methanol (6): Accoding to the procedure for **4**, **6** (49.7 mg, 0.24 mmol, 46%) was obtained as white crystals after recrystallization from benzene, m.p. 166−170°C. − IR ($CHCl_3$): $\tilde{\nu}$ = 3300 cm^{-1}, 1647. − ^1H NMR (400 MHz, C_6D_6): δ = 3.63−3.57 (dt, 1 H, *J* = 14.1, 4.2 Hz, C=NC*H*H), 3.42−3.35 (m, 2 H, C=NCH*H*, C*H*HOH), 3.28−3.26 (m, 1 H, CH*H*OH), 3.05−2.96 (m, 1 H, C−NC*H*), 2.88−2.86 (AB d, 1 H, *J* = 8.6 Hz, C−NC*H*H), 2.75−2.71 (ABX dd, 1 H, *J* = 8.6, 5.7 Hz, C−NCH*H*), 2.50−2.44 (m, 2 H), 1.82−1.77 (m, 1 H), 1.66−1.63 (m, 1 H), 1.58−1.50 (m, 1 H), 1.44−1.38 (m, 5 H), 1.18−1.06 (m, 1 H). − ^{13}C NMR (100 MHz, C_6D_6): not observed (*C*=N), δ = 64.1 (t, CH_2OH), 53.7 (d, C−N*C*H), 53.7, 41.5 (t, C=N*C*H_2, C−N*C*H_2), 41.7 (d, N=C*C*H), 33.7 (d, C−NCH_2CH), 27.7, 24.5, 24.0, 22.5, 22.4 [t, $-(CH_2)_4-$, C=NCH_2CH_2]. − $C_{12}H_{20}N_2O$ (208.3): cacld. C 69.19, H 9.68, N 13.45; found C 69.34, H 9.54, N 13.47. − $[\alpha]_D$ = −12.7 (*c* = 0.15; $CHCl_3$).

Crystallographic Data for 6: Orthorhombic, $P2_12_12_1$, *a* = 8.469 (1) *b* = 10.399 (5), *c* = 12.454 (1) Å, *V* = 1096.8 (5) $Å^3$, *S* = 1.03, λ = 0.71073 Å, μ = 0.8 cm^{-1}, *F*(000) = 456. Final *R* = 0.048. The hydrogen bond is between O and N5 of different molecules.[22]

(1*R*,4b*R*,8a*S*)-(1,2,3,4b,5,6,7,8,8a,9-Decahydro-4,9a-diazafluoren-1-yl)methanol (7): According to the procedure for **4**, **7** (70.5 mg, 0.34 mmol, 69%) was obtained as white crystals after recrystallization from benzene, m.p. 142−142.5°C. − IR ($CHCl_3$): $\tilde{\nu}$ = 3300 cm^{-1}, 1653. − ^1H NMR (400 MHz, C_6D_6): δ = 3.76−3.72 (ABX

dd, 1 H, J = 10.7, 5.5 Hz, C*H*HOH), 3.65−3.60 (ABX dd, 1 H, J = 10.7, 6.8 Hz, CH*H*OH), 3.57−3.51 (ABX dt, 1 H, J = 10.6, 4.0 Hz, C=NC*H*H), 3.47−3.40 (m, 2 H, C=NCH*H*, C−NC*H*H), 3.31−3.29 (m, 1 H, C−NC*H*), 2.61−2.57 (ABX dd, 1 H, J = 9.4, 4.4 Hz, C−NCH*H*), 2.55−2.50 (q, 1 H, J = 5.9 Hz, N=CC*H*), 2.11−2.07 (m, 1 H, N=CCHC*H*H), 2.01−1.91 (m, 2 H, C=NCH$_2$CH*H*, C−NCH$_2$C*H*), 1.72−1.65 (m, 1 H, C=NCHCH*H*), 1.55 (m, 2 H), 1.35 (m, 3 H), 1.15 (m, 2 H). − ^{13}C NMR (100 MHz, C_6D_6): δ = 162.0 (s, *C*=N), 63.2 (t, *C*H$_2$OH), 54.9 (d, C−N*C*H), 53.9, 40.9 (t, C=N*C*H$_2$, C−N*C*H$_2$), 41.6 (d, N=C*C*H), 33.9 (t, C−NCH$_2$*C*H), 26.8, 24.5, 23.4, 22.8, 22.0 [t, −(*C*H$_2$)$_4$−, C=NCH$_2$*C*H$_2$]. − $C_{12}H_{20}N_2O$ (208.3): calcd. C 69.19, H 9.68, N 13.45; found C 69.19, H 9.54, N 13.42. − $[\alpha]_D$ = −41.1 (c = 0.19; $CHCl_3$).

Thiophenol Addition (37): A mixture of thiophenol (51.0 mL, 0.29 mmol) and amidine **4** (4.6 mg, 0.015 mmol) was dissolved in toluene (1 mL). Cyclohexenone (43.7 mL, 0.29 mmol) was added and, after being stirred for 20 min at room temp, the reaction mixture was diluted with toluene and washed (5% aqueous HCl, 2 ×). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, yielding the product (41 mg, 0.32 mmol, 44%) as a colourless oil. The spectral data are as reported previously.[21] − $[\alpha]_{578}$ = −14.1 (c = 0.70; CCl_4). − O.p. 14%.[21]

Conjugate Addition Product 39: A mixture of **38** (272 mg, 1.43 mmol) and amidine **5** (11.4 mg, 0.043 mmol) was dissolved in toluene (2 mL). Methyl vinyl ketone (130 μL, 1.57 mmol) was added and, after being stirred for 24 h at room temp, the reaction mixture was diluted with toluene and washed (5% aqueous HCl, 2 ×). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, yielding the product (323 mg, 1.24 mmol, 87%) as a colourless oil. ^{1}H NMR (400 MHz): δ = 7.37−7.25 (m, 4 H, *Ph*), 3.80 [AB d, 1 H, J = 22.7 Hz, C(O)C*H*H], 3.63 (s, 3 H, OC*H*$_3$), 3.58−3.52 [AB d, 1 H, J = 22.8 Hz, C(O)C*H*H], 2.53−2.19 (m, 4 H), 2.03 [s, 3 H, C(O)C*H*$_3$]. ^{13}C NMR (100 MHz): δ = 207.1, 199.1 [2 × *C*(O)], 170.3 (*C*O$_2$Me), 140.2, 136.9, 128.7, 128.0, 125.0, 124.0 (*Ph*), 63.7 (*C*CO$_2$Me), 52.7 (O*C*H$_3$), 43.2 [C(O)*C*H$_2$], 38.2 [C(O)*C*H$_2$CH$_2$] 29.7 [C(O)*C*H$_3$], 27.9 [C(O)CH$_2$*C*H$_2$]. − $[\alpha]_D$ = −7.1 (c = 1; $CHCl_3$). ee: 27% [determined by chiral HPLC (Chiralpak AS)].

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