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Synthesis of an Enantiomerically Pure Building Block for the Synthesis of Hydroporphyrins

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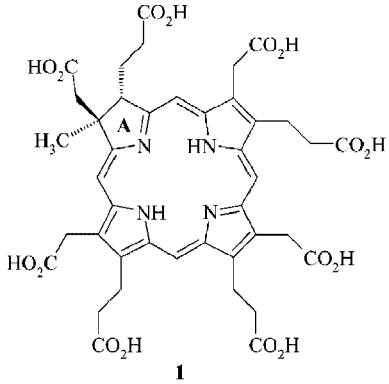
Dedicated to Professor Burchard Franck on the occasion of his 80th birthday

Keywords: Hydroporphyrins / Nitrogen heterocycles / Chiral resolution / Circular dichroism

The enantiomerically pure pyrrolidine diester **4** is a useful building block for the synthesis of chiral hydroporphyrin compounds. Treatment of optically active aromatic amines with bislactone **5** gave pairs of *N*-alkylated lactam-lactone diastereomers **6** and **8**. These diastereomers were separated by MPL chromatography and in the case of **8** they could be debenzylated to yield the enantiomerically pure lactam-lactone **7** and its enantiomer. The (–)-lactam-lactone enantiomer **7** was further transformed into building block **4**.

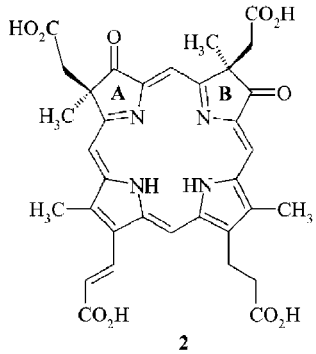
Introduction

Until the mid-1970s the four classical cyclic tetrapyrrolic structures – heme, chlorophyll, bacteriochlorophyll and vitamin B_{12} – were almost the only representatives in the class of porphyrinoid natural products.[1–3] Over the past 30 years, however, many novel hydroporphyrinoid structures have been discovered in marine and terrestrial organisms, in which they participate in essential biochemical processes.[4] Some representatives are Factor I (**1**), heme d_1 (**2**) and tolyporphin A (**3**), belonging to the chlorin (dihydroporphyrin), bacteriochlorin and isobacteriochlorin (tetrahydroporphyrin) families, respectively.



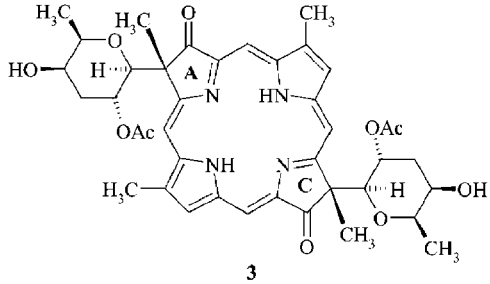
1

Factor I



2

Heme d_1



3

Tolyporphin A

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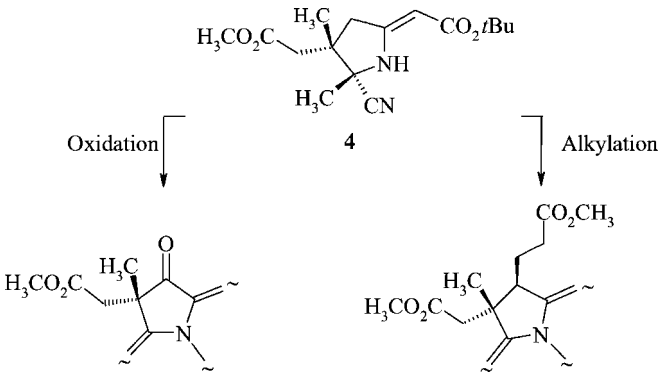
In addition to their biological importance, naturally occurring and synthetic hydroporphyrins are of interest in catalysis, artificial photosynthesis, materials science and medicine.[1b]

A common structural feature of the novel hydroporphyrins is the presence of geminally dialkylated structural com-

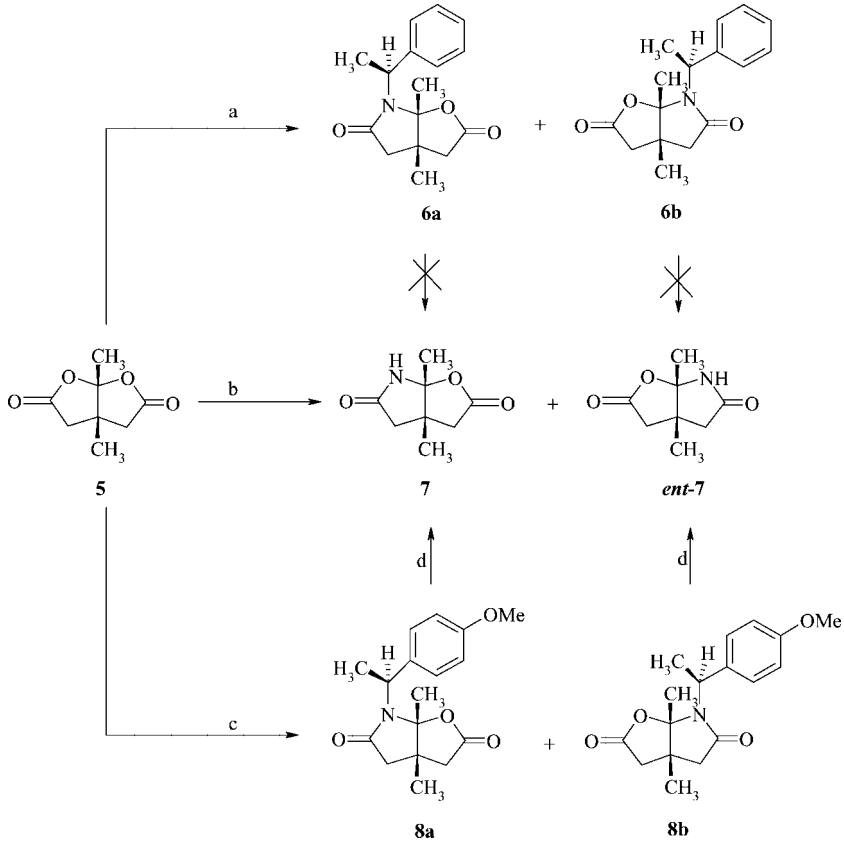


ponents in the reduced rings, creating quaternary stereogenic centres. The presence of these centres makes the synthesis of hydroporphyrins more complicated than the preparation of porphyrins, and selective synthetic routes to hydroporphyrins have been developed in the laboratories of Battersby, Eschenmoser, Kishi, Lindsey and Montforts.[3c,4a,c,5–10] Different pyrrolidine building blocks have been used in several routes for construction of the reduced rings of the target tetramacrocyclic structures. Here we describe a simple route to the enantiomerically pure pyrrolidine building block **4**, which could be further transformed to provide the special structural features present in naturally occurring hydroporphyrins such as **1**, **2** etc. Pyrrolidine building blocks with the same functionality as in **4** have been successfully applied in syntheses of hydroporphyrins, corrins and vitamin B_{12}.[4a,c,7,8]

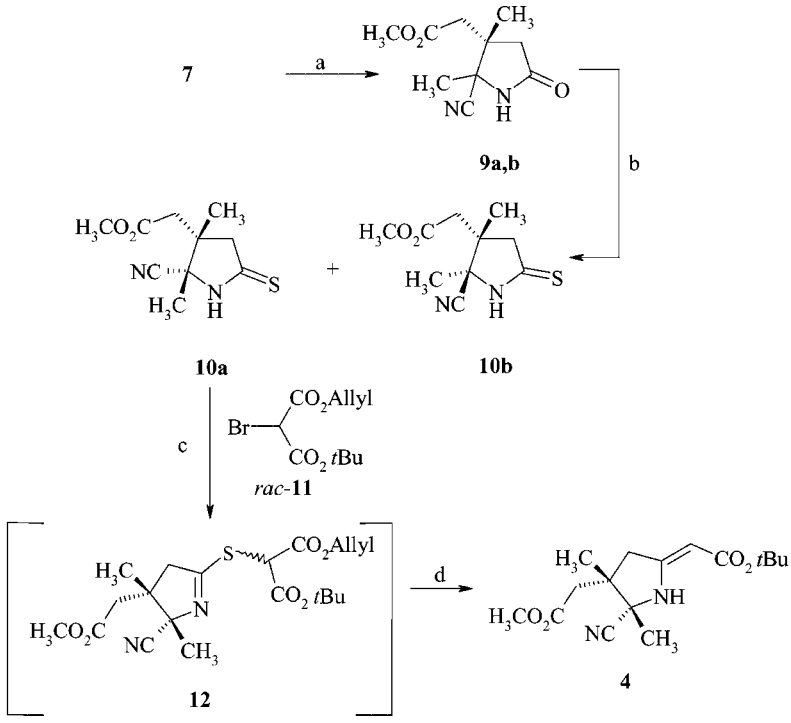
Result and Discussion

The transformation of bislactone **5** (Scheme 1) into the racemic lactam-lactone mixture **7**/*ent*-**7** by treatment with aqueous ammonia was known from the work of Harke.[11] In order to obtain enantiomerically pure **7** or *ent*-**7**, (*S*)-(–)-phenylethylamine was used instead of ammonia, resulting in a mixture of *N*-alkylated lactam-lactone diastereomers **6a** and **6b**. Though no potential for diastereoselectivity could be observed in the reaction, separation of the diastereomeric mixture was achieved by medium pressure liquid chromatography (MPLC). Attempts to cleave the phenyl groups in **6a** or **6b** were unsuccessful,[12] probably due to the steric hindrance around the nitrogen-phenyl bond.

Use instead of an electron-rich benzylamine derivative – namely, (*S*)-(–)-(4-methoxyphenyl)ethylamine – provided a new set of *N*-alkylated lactam-lactone diastereomers **8a** and **8b**, which could also be separated by MPLC (Scheme 1). Methoxy-substituted benzylamines are known to be susceptible to oxidative cleavage,[12,13] and debenzylation of diastereomers **8a** and **8b** by treatment with aqueous ammo-



Scheme 1. a) (*S*)-(–)-$(C_6H_5)CH_3CHNH_2$, $CHCl_3$, 25 °C, 82%. b) Aqueous NH_3 solution, room temp., 86%. c) (*S*)-(–)-$(4\text{-}CH_3OC_6H_4)_3$-$CHNH_2$, $CHCl_3$, 25 °C, 70%. d) 1) $[(NH_4)_2Ce(NO_3)_6]$ [2.1 equiv.] in H_2O, MeCN/H_2O (4:1), 25 °C; 2) $NaHCO_3$, 65%.



Scheme 2. a) 1) KCN, MeOH, 25 °C; 2) CH_2N_2, MeOH, 0 °C, 80%. b) Lawesson's reagent, THF, 40 °C, 25 °C, 88%. c) 1) *rac*-**11**,[15] DBU, MeCN, 0 °C; 2) $P(OC_2H_5)_3$, 80 °C; 3) Pd $[PPh_3]_4$, piperidine, 25 °C, 67%.

nium cerium(IV) nitrate (CAN) gave the lactam-lactones **7** and *ent*-**7**, respectively.

Treatment of **7** with potassium cyanide in methanol induced cleavage of the γ-lactone ring to furnish a diastereomeric mixture of intermediates **9a** and **9b** after esterification of the formed acetic acid side chain with diazomethane (Scheme 2). Conversion of the lactams **9a** and **9b** into the corresponding thiolactams **10a** and **10b** was achieved by treatment with Lawesson's reagent [2,4-bis(*p*-methoxyphenyl)-1,3-dithiaphosphetane 2,4-disulfide] under reflux.[14]

The mixture of diastereomers **10a** (77%) and **10b** (23%) was separated by chromatography for purposes of characterization and for simplification of further transformations, but both diastereomers are synthetically useful. The synthesis continued with the major cyanothiolactam diastereomer **10a**, which was transformed by the sulfide contraction method[15,16] into the desired building block **4**: the thiolactam **10a** was coupled with the bromomalonic diester *rac*-**11**[10b] in the presence of DBU to yield intermediate **12**, crude **12** was treated with triethyl phosphite for sulfur extrusion, and the formed diester intermediate was also allowed to react further, without purification and characterization, to provide **4**,[10b] the allylic ester function being selectively cleaved with tetrakis(triphenylphosphane)palladium(0) in the presence of piperidine to yield a monocarboxylic acid intermediate, which decarboxylated spontaneously under the reaction conditions. The pyrrolidine building block **4** is formed exclusively with the (*Z*) configuration about the double bond, due to a stabilizing intramolecular hydrogen bond between NH in the pyrrolidine ring and the ester carbonyl function. Over the whole synthetic route, pyrrolidine diester **4** is formed in five reaction steps starting from bislactone **5** in an overall yield of 21%. The simplicity of the reaction conditions for each step should readily allow synthetic scaling up.

Configuration Analysis of the Substituted Lactam-Lactone Derivatives

The absolute configurations of the diastereomers **6a** and **8a** were determined by X-ray structural analysis and independently by comparison of circular dichroism (CD) spectra (Figure 1 and Figure 2). Because the absolute configura-

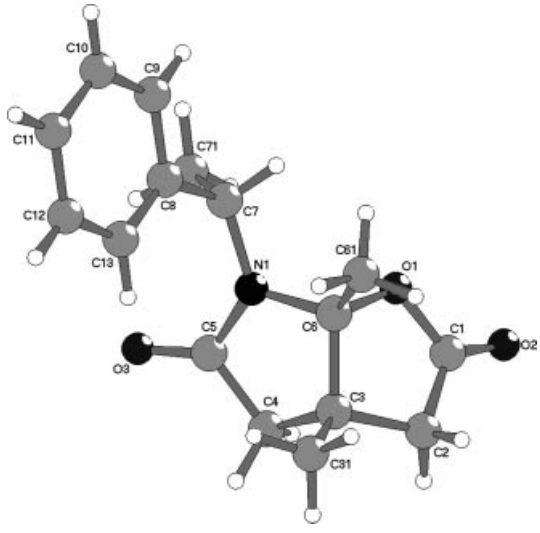


Figure 1. Crystal structure of **6a**.

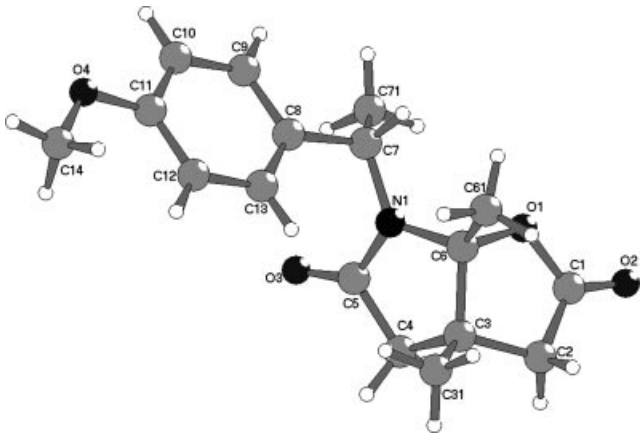


Figure 2. Crystal structure of **8a**.

tions of the phenylethyl substituents were already known, the configurations of the stereogenic centres in the bicyclic lactam-lactone moieties of **6a** and **8a** follow from their relative spatial orientations to the known centres of chirality. The absolute configurations of the stereogenic centres in diastereomers **6b** and **8b** could also be deduced from this observation.

CD spectroscopic measurements for both pairs of diastereomers **6a**/**6b** and **8a**/**8b** are also in agreement with the X-ray structural investigations. Compounds **6a** and **8a**, with the same absolute configurations at all stereogenic centres, show positive Cotton effects, whereas the other diastereomeric pair of compounds exhibits negative Cotton effects (Figure 3). The only difference in the CD spectra of **6a**/**6b** and **8a**/**8b** is an expected bathochromic shift of the absorption bands of **6a**/**6b** in relation to **8a**/**8b**. Although the absolute configurations of all lactam-lactone structures had in this case undoubtedly been established by the X-ray diffraction experiments, the CD relationships between the different lactam-lactone derivatives could be useful tools for further structural investigations of lactam-lactone derivatives synthesized in the future.

Configuration and Spectroscopic Analysis of *cis*- and *trans*-Thiocyanolactams

Transformation of the lactam-lactones **7** into the cyanolactams **9** and further into the cyanothiolactams **10** resulted in diastereomers, and the configurations of these isomers were established by NOE experiments on **10a** and **10b**. NOE measurements for **10a** revealed that the two methyl groups were in close proximity to each other: irradiation of the 4-C**H**$_3$ protons enhanced the peak signal of the 5-C**H**$_3$ protons and, vice versa, irradiation of the 5-C**H**$_3$ protons enhanced the 4-**CH$_3$** protons as well as one of the diastereotopic 4′-C**H$_2$** protons (Figure 4), which suggests the

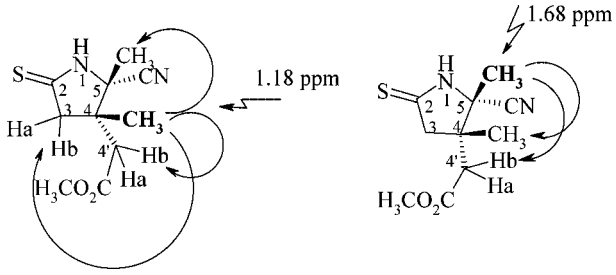


Figure 4. NOE correlation pattern for **10a**.

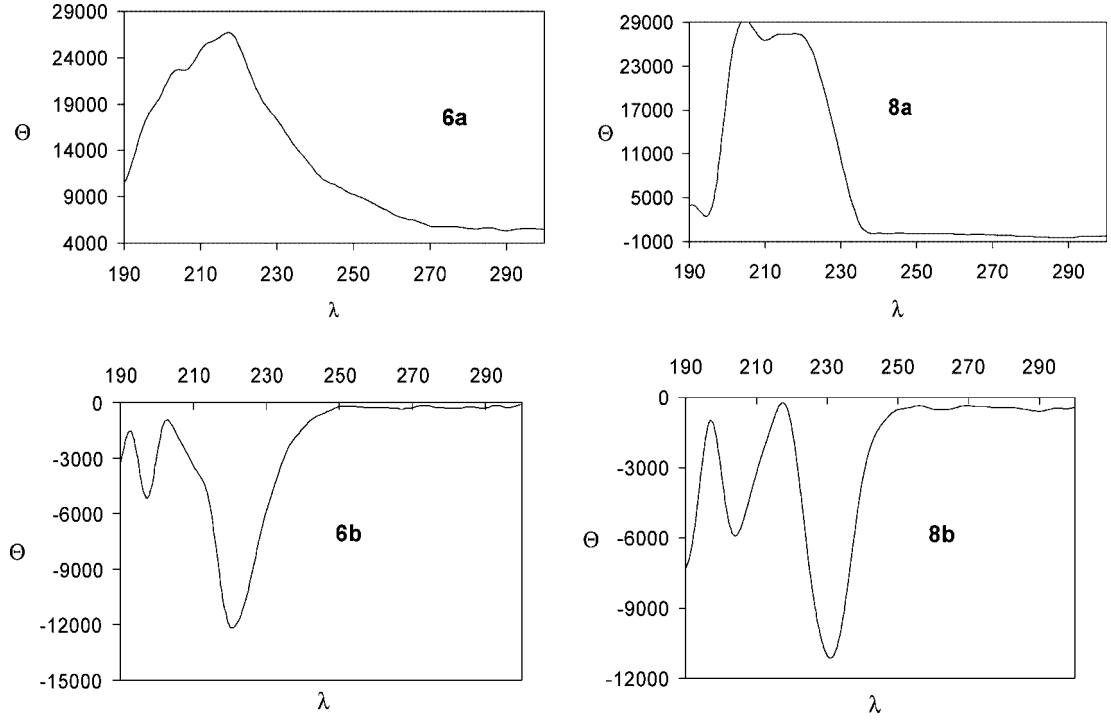


Figure 3. CD spectra of **6a**, **6b**, **8a** and **8b**; Θ [molar ellipticity, deg cm^2 dm^{-1}], λ [wavelength, nm].

cis configuration for **10a**. In the case of **10b**, the *trans* configuration was assigned because NOE spectra showed enhancement of the 4′-C**H**$_2$ and 3-**H**$_a$ signals on irradiation of the 5-C**H**$_3$ protons (Figure 5), while irradiation of the 4-C**H**$_3$ protons had no influence on the 5-C**H**$_3$ proton signals.

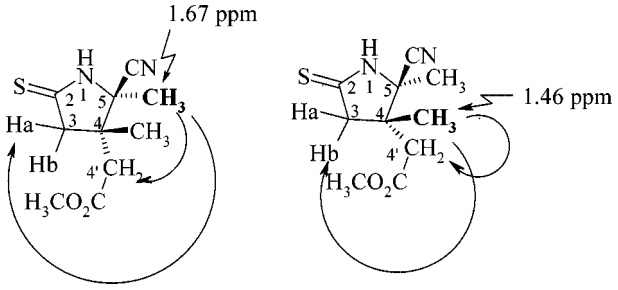


Figure 5. NOE correlation pattern for **10b**.

Independent confirmation of the *cis* arrangement of the 4- and 5-CH$_3$ groups in the major product **10a** was provided by X-ray diffraction analysis of **10a** (Figure 6).

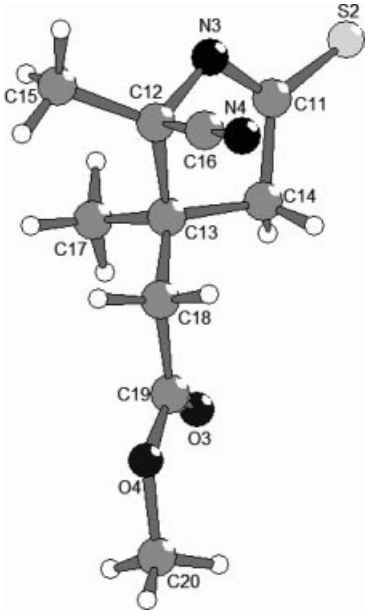
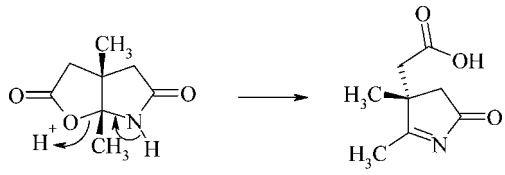


Figure 6. Crystal structure of **10a**.

Theoretical Calculations

The unexpected selectivity of the formation of the major *cis*-products **9a** and **10a** from lactam-lactone **5** was investigated by semiempirical calculations: Geometry Optimization of the transition state and minima on the Born–Oppenheimer surface; Semiempirical Method (PM3); HyperChem, Hypercube, Inc. For that purpose, the geometry of the proposed transition state was optimized. Prior to cyanide addition the γ-lactone of **5** is cleaved to form an imine intermediate **13** (Scheme 3).



7 **13**

Scheme 3. Formation of imine intermediate **13** from lactam-lactone **7**.

The transition state **A** for the *cis* product **14a** was calculated to be –7 kcal mol^{-1} lower in energy than transition **B** for *trans* product **14b**, although the energy difference between the *cis* product **14a** and the *trans* product **14b** was itself calculated as only 1 kcal mol^{-1} in favour of the *trans* isomer. From the transition state **A** it becomes clear that the attack of the nucleophile is directed by the hydrogen bonding between the incoming cyanide and the carboxylic acid functions. The calculations were performed to explain not only the preference for the formation of the *cis* product **14a**, but also other similar cases described in the literature.[10b,16] In cases in which hydrogen bonding to a free carboxylic acid function was possible, the same selectivity for cyanide addition was observed, whereas in the absence of any such possibility for hydrogen bonding the opposite selectivity was observed.[10b,16]

A *Re* attack of cyanide on the imine function of **13** gives the *cis* product **14a** and finally **9a/10a**, whilst *Si* attack gives the *trans* product **14b** and finally **9b/10b** (Figure 7).

Experimental Section

General Remarks: Starting materials were either prepared by literature procedures or purchased from Fluka, Merck or Aldrich and used without further purification. All solvents were purified and dried by standard methods and all reactions were carried out under argon. ^{1}H NMR spectra: Bruker DPX 200 Avance spectrometer; all chemical shifts were referenced to TMS lock signal. MS and HR-MS: Finnigan MAT 8200 spectrometer [EI (70 eV) and DCI (NH_3, 8 mA s^{-1})], Bruker Daltonik Biflex III (MALDI-TOF). IR: Perkin–Elmer Paragon 500 FT-IR spectrometer. UV/Vis: Varian Cary 50 spectrophotometer, ε [L M^{-1} cm^{-1}]. – Column chromatographic separations were performed on silica gel (32–63 μm, 60 Å, ICN). Melting points are uncorrected and were determined on a Reichert Thermovar hot-stage apparatus or Gallenkamp apparatus. – Optical rotation: Perkin–Elmer 243 polarimeter with a water-jacket cell length of 1 dm (concentration *c* given in g/100 mL). CD spectra: JASCO J-600 spectropolarimeter. – HPLC: Knauer HPLC instrument with pump 64, two-channel potentiometer BBC Metrawatt Servogor 120 recorder and Knauer UV spectrometer. – MPLC conditions: separation was carried out on a setup consisting of an HPLC Knauer pump 64, Büchi 660 fraction collector, matrix silica 20–45 μm, 60 Å, column size 49 × 460 mm and mobile phase petroleum ether/EtOAc (50:50), detection was done with a UV lamp (254 nm).

(1*RS*,5*SR*)-1,5-Dimethyl-2-oxa-8-azabicyclo[3.3.0]octane-3,7-dione (*rac*-7):[11] A suspension of *cis*-1,5-dimethyl-2,8-dioxabicyclo[3.3.0]-octane-3,7-dione (**5**,[11] 1.53 g, 8.99 mmol) in aqueous ammonia solution (25%, 45 mL, 0.6 mol) was prepared at room temperature

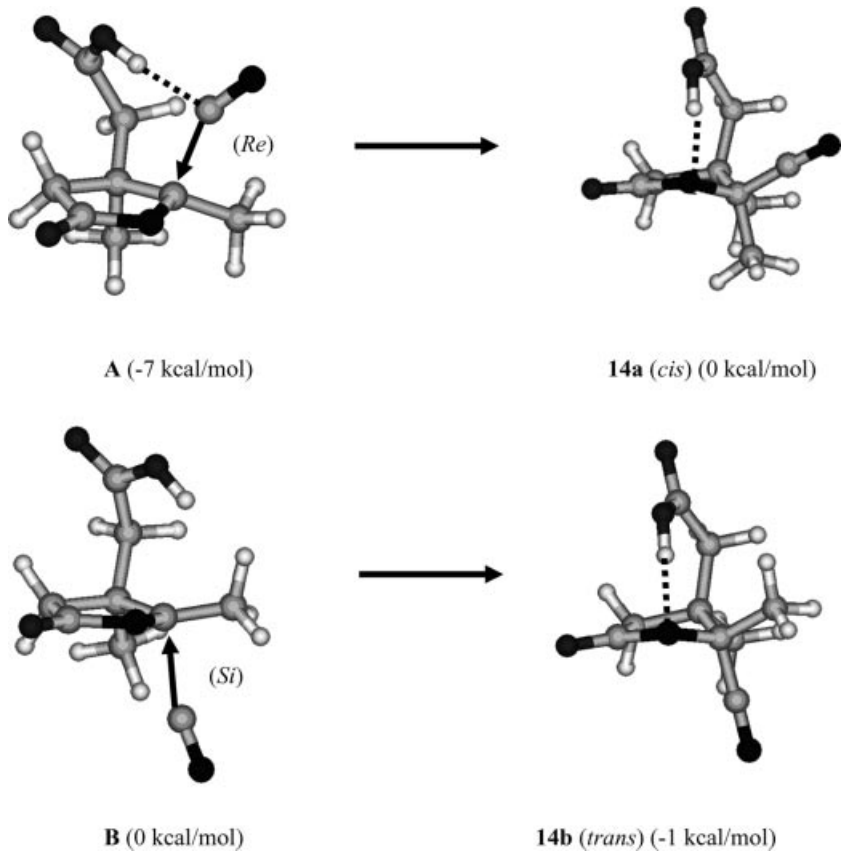


Figure 7. Ball and stick drawings of the calculated alternative transition states and of products of cyanide addition to **13**.

under argon. After 24 h reaction time, the reaction mixture was concentrated under reduced pressure, and the crude yellowish residue was purified by column chromatography over silica gel with CH_2Cl_2/MeOH (95:5) as eluting solvent. Drying under high vacuum gave *rac*-**7** as colourless crystals. Yield: 1.31 g (7.74 mmol, 86%). M.p. 192 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.35 (s, 3 H, C-5-CH_3), 1.62 (s, 3 H, C-1-CH_3), 2.36–2.82 (2 AB systems, from both enantiomers) 4 H, 2×–CH_2–), 6.41 (s, 1 H, NH) ppm. IR (KBr): $\tilde{\nu}$ = 3212, 3109, 2975, 2969, 2854, 1779, 1698, 1443, 1390, 1369, 1302, 1240, 1213, 1116, 1115, 1065 cm^{-1}. MS (EI, 70 eV, direct inlet): *m*/*z* (%) = 170 (3) $[M + H]^+$, 126 (4), 125 (45), 124 (4), 111 (8), 110 (100) $[M - C_2H_3O_2]^+$, 96 (7), 83 (7), 82 (40), 69 (4), 68 (4), 67 (3), 57 (8), 56 (6), 55 (13), 54 (5), 53 (6), 43 (43), 42 (34), 41 (12), 40 (5), 39 (13).

General Procedure A. Synthesis of the Diastereomeric *N*-Alkylated Lactam-Lactones 6a/6b and 8a/8b: A solution of the bislactone **5** in dry chloroform was prepared under argon at room temperature, the optically active amine was added, and the reaction mixture was stirred at room temperature for 20 h until the starting material had been completely consumed (TLC). The reaction mixture was saturated with NaCl solution, the product was extracted three times with CH_2Cl_2, the combined CH_2Cl_2 extracts were dried by filtration through cotton wool, and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel to afford diastereomeric mixtures of *N*-alkylated lactam-lactones **6a/6b** or **8a/8b** as colourless solids.

(1*R*,5*S*,1′*S*)-1,5-Dimethyl-8-phenylethyl-2-oxa-8-azabicyclo[3.3.0]-octane-3,7-dione (6a) and (1*S*,5*R*,1′*S*)-1,5-Dimethyl-8-phenylethyl-2-oxa-8-azabicyclo[3.3.0]octane-3,7-dione (6b): Procedure A. Bislactone **5** (0.34 g, 2.00 mmol) and (*S*)-(–)-phenylethylamine (0.24 g, 2.00 mmol) gave the *N*-alkylated lactam-lactone diastereomeric mixture **6a/6b**. It was separated by preparative HPLC.

Mixture 6a/6b: Yield: 450 mg (1.65 mmol, 82%). IR (KBr): $\tilde{\nu}$ = 3005, 2990, 2945, 2910, 2875, 1780, 1710, 1540, 1495, 1460, 1420, 1395, 1375, 1350, 1305, 1290, 1235, 1195, 1105, 1055, 1010, 900, 850, 830 cm^{-1}. UV/Vis (methanol): λ_{max} (rel. intensity) = 258 (0.02), 205 (1) nm. MS (EI, 70 eV, direct inlet): *m*/*z* (%) = 274 (27) $[M + H]^+$, 273 (55) $[M]^+$, 161 (43), 160 (57), 146 (65), 132 (12), 125 (18), 120 (17), 111 (16), 110 (36), 106 (25), 105 (100), 104 (48), 103 (22), 83 (11), 79 (25), 78 (16), 77 (40), 55 (29), 54 (5), 53 (12), 51 (13), 43 (65), 42 (15), 40 (23). HRMS ($C_{16}H_{19}NO_3$) calcd. 273.13649; found 273.136889.

Compound 6a: HPLC: Nucleosil 50–10 Si, PE/EtOAc (1:1), 1.5 mL min^{-1}, t_R = 8 min, 48 s. M.p. 162.3 °C. $[\alpha]_D^{20}$ = +5.3 (*c* = 0.45 in CH_2Cl_2). CD (MeOH, *c* = 0.057 mg mL^{-1}): Θ (λ) = 26700 (217 nm). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 [s, 3 H, C(1)-CH_3], 1.51 [s, 3 H, C(5)-CH_3], 1.83 [d, ^3J = 6.9 Hz, 3 H, C(8′)-CH_3], 2.35–2.77 [2×AB system, 4 H, C(4)-H_2, C(6)-H_2], 4.71 [q, ^3J = 6.9 Hz, 1 H, C(8′)-H], 7.30–7.43 (m, 5 H, C_6H_5) ppm.

Compound 6b: HPLC: Nucleosil 50–10 Si, PE/EtOAc (1:1), 1.5 mL min^{-1}, t_R = 10 min. M.p. 145 °C. $[\alpha]_D^{20}$ = –3.2 (*c* = 0.28 in CH_2Cl_2). CD (MeOH, *c* = 0.055 mg mL^{-1}): Θ (λ) = –5160 (197 nm), –12160 (221 nm). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.22 [s, 3 H, C(1)-CH_3], 1.30 [s, 3 H, C(5)-CH_3], 1.78 [d, ^3J = 6.4 Hz, 3 H, C(8′)-CH_3], 2.38–2.68 [2×AB system, 4 H, C(4)-H_2, C(6)-H_2], 5.27–5.38 [q, ^3J = 6.41 Hz, 1 H, C(8′)-H], 7.34–7.43 (m, 5 H, C_6H_5) ppm.

(1*R*,5*S*,1′*S*)-8-[1-(4-Methoxyphenyl)ethyl]-1,5-dimethyl-2-oxa-8-azabicyclo[3.3.0]octane-3,7-dione (8a) and (1*S*,5*R*,1′*S*)-8-[1-(4-

Methoxyphenyl)ethyl]-1,5-dimethyl-2-oxa-8-azabicyclo[3.3.0]octane-3,7-dione (8b): Procedure A. Treatment of bislactone **5** (1.02 g, 5.99 mmol) with (*S*)-(–)-(4-methoxyphenyl)ethylamine (906 mg, 6.02 mmol) gave the *N*-alkylated lactam-lactone pair **8a/8b**. The diastereomeric mixture was separated by MPLC.

Mixture 8a/8b: Yield: 1.27 g (4.19 mmol, 70%). IR (KBr): $\tilde{\nu}$ = 3005, 2990, 2945, 2910, 2875, 1780, 1710, 1540, 1495, 1460, 1420, 1395, 1375, 1350, 1305, 1290, 1235, 1195, 1145, 1105, 1080, 1055, 1010, 950, 900, 850, 830, 795, 780, 760, 725, 700 cm^{-1}. UV/Vis (MeOH): λ_{max} (rel. intensity) = 275 (0.12), 227 (1), 203 (0.99) nm. MS (EI, 70 eV, direct inlet): *m/z* (%) = 304 (16) $[M + H]^+$, 303 (98) $[M]^+$, 288 (12), 191 (12), 190 (24), 177 (10), 176 (100), 160 (32), 149 (9), 136 (18), 135 (68), 134 (20). MS (DCI negative, NH_3, direct inlet): *m/z* (%) = 605 (16) $[2M + H]^+$, 338 (20) $[M + Cl]^-$, 303 (26) $[M]^-$, 302 (100) $[M – H]^+$, 275 (15), 231 (14), 168 (56), 127 (5), 120 (71), 109 (11). MS (DCI positive, NH_3, direct inlet): *m/z* (%) = 305 (21) $[M + 2H]^+$, 304 (100) $[M + H]^+$, 303 (18) $[M]^+$, 176 (13), 170 (9), 160 (6), 136 (6), 135 (32), 134 (4). HRMS (DCI^-) $C_{17}H_{20}NO_4$: calcd. 302.13923, found 302.13922.

Compound 8a: Yield: 764 mg (2.52 mmol, 60%). M.p. 135 °C. $[\alpha]_D^{20}$ = –3.4 (*c* = 1 in CH_2Cl_2). TLC [silica gel, CH_2Cl_2/EtOAc (99:1)]: R_f = 0.45. HPLC: Nucleosil 50–10 Si, PE/EtOAc (1:1), 2.0 mL min^{-1}, 254 nm, t_R = 11 min. CD (MeOH, *c* = 0.062 mg mL^{-1}): Θ (λ) = 29300 (205 nm), 27400 (218 nm). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.28 [s, 3 H, C(1)-CH_3], 1.53 [s, 3 H, C(5)-CH_3], 1.79 [d, ^3J = 6.9 Hz, 3 H, C(8′)-CH_3], 2.32–2.76 [2 × AB system, 4 H, C(4)-H_2, C(6)-H_2], 4.63–4.73 [q, ^3J = 6.9 Hz, 1 H, C(8′)-H], 6.85, 7.36 (2 × d, 4 H, C_6H_4) ppm.

Compound 8b: Yield: 509 mg (1.68 mmol, 40%). M.p. 149 °C. $[\alpha]_D^{20}$ = –11.2 (*c* = 1 in CH_2Cl_2). TLC [silica gel, CH_2Cl_2/EtOAc (99:1)]: R_f = 0.44. HPLC: Nucleosil 50–10 Si, PE/EtOAc (1:1), 1.5 mL min^{-1}, detector UV 254 nm, t_R = 12 min. CD (MeOH, *c* = 0.060 mg mL^{-1}): Θ (λ) = –5900 (204 nm), –11100 (231 nm). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.21 [s, 3 H, C(1)-CH_3], 1.32 [s, 3 H, C(5)-CH_3], 1.75 [d, ^3J = 6.4 Hz, 3 H, C(8′)-CH_3], 2.35–2.66 [m, 4 H, C(4)-H_2, C(6)-H_2], 5.20 [q, ^3J = 6.4 Hz, 1 H, C(8′)-H], 6.85, 7.34 (2 × d, 4 H, C_6H_4) ppm.

(1*R*,5*S*)-1,5-Dimethyl-2-oxa-8-azabicyclo[3.3.0]octane-3,7-dione (7) and (1*S*,5*R*)-1,5-Dimethyl-2-oxa-8-azabicyclo[3.3.0]octane-3,7-dione (*ent*-7): A solution of ammonium cerium(IV) nitrate (1.14 g, 2.08 mmol) in water (30 mL) was added in portions to a stirred mixture of the *N*-alkylated lactam-lactone **8a** (300 mg, 0.99 mmol) in a solution of MeCN and water (4:1, 25 mL). The mixture was allowed to react at room temperature for 17 h, quenched by the addition of saturated aqueous $NaHCO_3$ solution and stirred vigorously for 15 min. The solution was then extracted three times with CH_2Cl_2 and the combined organic extracts were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was chromatographed on silica gel with elution with CH_2Cl_2/MeOH (95:5), giving the lactam-lactone **7** as colourless crystals after removal of the eluent. The same procedure was used with **8b** to yield *ent*-**7**.

Compound 7: Yield: 108 mg (0.64 mmol, 65%). M.p. 188 °C. $[\alpha]_D^{20}$ = –104.5 (*c* = 1 in CH_2Cl_2). TLC [silica gel, CH_2Cl_2/EtOAc (9+1)]: R_f = 0.61. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.35 [s, 3 H, C(5)-CH_3], 1.62 [s, 3 H, C(1)-CH_3], 2.36–2.82 (m, 4 H, –CH_2–), 6.19 (s, 1 H, NH) ppm. IR (KBr): $\tilde{\nu}$ = 3212, 3070, 3010, 2990, 2926, 1769, 1703, 1495, 1442, 1417, 1347, 1309, 1300, 1280, 1240, 1231, 1213, 1176, 1145, 1105, 1054, 1023, 951, 914, 850, 824, 760, 725, 700 cm^{-1}. MS (EI, 70 eV, direct inlet): *m/z* (%) = 170 (2) $[M + H]^+$, 126 (4) $[M – CHNO]^+$, 125 (46) $[M – CO_2]^+$, 124 (3), 111 (8) $[M – C_2H_4NO]^+$, 110 (100) $[M – C_2H_3O_2]^+$, 96 (6), 83 (10), 82 (54), 57 (7), 56 (7), 55 (12), 54 (5), 53 (4), 44 (2) $[CO_2]$, 43 (42) $[CHNO]^+$, 42 (32), 41 (10), 40 (4).39 (12), 29 (8). HRMS (CI): $C_8H_{10}NO_3$ calcd.168.06607; found 168.06571.

Compound *ent*-7: Yield: 100 mg (0.59 mmol, 59%). TLC [silica gel, CH_2Cl_2/EtOAc (99:1)]: R_f = 0.55. M.p. 183.5 °C. $[\alpha]_D^{20}$ = +101.9 (*c* = 1 in CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.35 [s, 3 H, C(5)-CH_3], 1.63[s, 3 H, C(1)-CH_3], 2.36–2.82 (m, 4 H, –CH_2–), 6.20 (s, 1 H, NH) ppm. IR (KBr): $\tilde{\nu}$ = 3212, 3070, 3010, 2990, 2926, 1769, 1703, 1495, 1442, 1417, 1347, 1309, 1300, 1280, 1240, 1231, 1213, 1176, 1145, 1105, 1054, 1023, 951, 914, 850, 824, 760, 725, 700 cm^{-1}. MS (EI, 70 eV, direct inlet): *m/z* (%) = 170 (2) $[M + H]^+$, 126 (4) $[M – CHNO]^+$, 125 (46) $[M – CO_2]^+$, 124 (3), 111 (8) $[M – C_2H_4NO]^+$, 110 (100) $[M – C_2H_3O_2]^+$, 96 (6), 83 (10), 82 (54), 57 (7), 56 (7), 55 (12), 54 (5), 53 (4), 44 (2) $[CO_2]$, 43 (42) $[CHNO]^+$, 42 (32), 41 (10), 40 (4).39 (12), 29 (8). HRMS (DCI): $C_8H_{10}NO_3$ calcd. 168.06607; found 168.06571.

Synthesis of Methyl [(2′*R*,3′*R*)-2′-Cyano-2′,3′-dimethyl-5′-oxopyrrolidin-3′-yl]acetate (9): Potassium cyanide (130.2 mg, 2.00 mmol) was added to a solution of lactam-lactone **7** (169 mg, 1.0 mmol) and dry methanol (20 mL). The reaction was stirred at room temperature under argon for 20 h, after which about three quarters of the solvent was removed in vacuo. A solution of NaH_2PO_4 (2 N, 15 mL) was added to the remaining reaction mixture and it was cooled in an ice bath, concentrated H_3PO_4 was carefully added to the cooled reaction mixture until pH 2 was reached (caution: evolution of hydrogen cyanide gas!), and saturated NaCl solution was then added to the reaction mixture, after which the product was extracted three times with ethyl acetate. The combined organic extracts were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo, and the colourless, oily residue was dried in vacuo (oil pump) and dissolved in methanol (5 mL). This solution was cooled in an ice bath, after which a solution of ethereal diazomethane (0.5 M, 10 mL) was added, the ice bath was removed, and the reaction mixture was stirred at room temperature for 15 min. The mixture was concentrated in vacuo (a small amount of acetic acid was added to the receiver flask during the concentration to neutralize the excess diazomethane) and the residue was chromatographed on silica gel with elution with CH_2Cl_2/MeOH (95:5). A mixture of colourless *cis*-, *trans*-cyano lactam crystals **9** was obtained. Yield: 168 mg (0.80 mmol, 80%). M.p. 127 °C. TLC: [silica gel, CH_2Cl_2/MeOH (9:1)]: R_f = 0.62. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.22 [s, 3 H, C(3′)-CH_3], 1.63 [s, 3 H, C(2′)-CH_3], 2.38–2.90 [2 × AB system, 4 H, C(4)-H_2, C(3)-CH_2], 3.74 (s, 3 H, CO_2CH_3), 5.94 (s, 1 H, NH) ppm. IR (KBr): $\tilde{\nu}$ = 3172, 3115, 3001, 2976, 2955, 2915, 2848, 2230, 1732, 1725, 1668, 1450, 1440, 1389, 1351, 1329, 1297, 1280, 1236, 1214, 1185, 1159, 1150, 1091, 1000, 925, 900, 885, 865, 840, 780, 760, 720 cm^{-1}. MS (EI, 70 eV, direct inlet): *m/z* (%) = 210 (18) $[M]^+$, 179 (37) $[M – OCH_3]^+$, 178 (5) $[M – CH_4O]^+$, 168 (7), 152 (7), 142 (22), 141 (13), 137 (23), 136 (3), 137 (23), 124 (10), 115 (8), 114 (100),113 (10), 110 (28), 109 (6), 108 (9), 99 (8), 86 (26), 83 (15), 82 (86), 81 (7), 72 (11), 71 (28), 69 (23), 68 (5), 67 (12), 59 (36), 56 (6), 55 (50), 54 (15), 53 (15), 43 (24), 42 (19), 41 (6), 40 (7), 39 (26), 29 (9), 28 (19), 27(16). HRMS (EI): $C_{10}H_{14}N_2O_3$ calcd. 210.10044; found 210.09981.

Methyl [(2′*R*,3′*S*)-2′-Cyano-2′,3′-dimethyl-5′-thioxopyrrolidin-3′-yl]acetate (10a) and Methyl [(2′S,3′*S*)-2′-Cyano-2′,3′-dimethyl-5′-thioxopyrrolidin-3′-yl]acetate (10b): Lawesson's reagent (247 mg, 0.62 mmol) was added to a solution of lactam **9** (106 mg, 0.51 mmol) in THF (10 mL) under argon, and the reaction mixture was heated at 40 °C with stirring for 30 min and then at room temperature for 3½ h. The reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel laminated with

a slice of 2 cm of alox with elution with CH_2Cl_2/EtOAc (9:1). A mixture of **10a** and **10b** was obtained as a colourless, oily product, which crystallized out after some time. This mixture was rechromatographed on a silica gel "stepped column" (in German: Stufensäule) with elution with CH_2Cl_2/EtOAc (95:5). This gave pure isomers **10a** as colourless crystals and **10b** as a gel-like product.

Mixture 10a/10b: Yield: 100 mg (0.44 mmol, 86%). IR (KBr): $\tilde{\nu}$ = 3091, 2985, 2955, 2360, 2235, 1747, 1734, 1698, 1506, 1438, 1411, 1390, 1385, 1350, 1335, 1300, 1285, 1245, 1214, 1210, 1170, 1145, 1138, 1105, 1086, 1012, 755 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) = 270 nm (13424). MS (EI, 70 eV, direct inlet): *m/z* = 227 (9) $[M + H]^+$, 226 (68) $[M]^+$, 211 (3) $[M - CH_3]^+$, 199 (7) $[M - HCN]^+$, 196 (3), 195 (24) $[M - CH_3O]^+$, 184 (4), 167 (5) $[M - C_2H_3O_2]^+$, 166 (4), 157 (15), 155 (5), 154 (9), 153 (100) $[M - C_3H_5O_2]^+$, 126 (30), 125 (16), 120 (15), 119 (6), 112 (10), 41 (15), 40 (11). HRMS (EI): $C_{10}H_{14}N_2O_2S$ calcd. 226.07760; found 226.07716.

Compound 10a: Yield: 76.8 mg (0.34 mmol, 77%). M.p. 118 °C. TLC [silica gel, CH_2Cl_2/EtOAc (95:5)]: R_f = 0.78. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.18 [s, 3 H, C(3′)-CH_3], 1.68 [s, 3 H, C(2′)-CH_3], 2.68–2.84 [AB system, 2 H, C(2)-CH_2], 2.95–3.15 [AB system, 2 H, C(4′)-CH_2], 3.72 (s, 3 H, CO_2CH_3), 8.32 (s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.7 [C(3′)-CH_3], 18.3 [C(2′)-CH_3], 39.9 [C(2)], 45.1 [C(3′)], 50.7 (O-CH_3), 54.4 [C(4′)], 64.8 [C(2′)], 116.6 (-CN), 168.9 (C=O), 203.3 (C=S) ppm.

Compound 10b: Yield: 23 mg (0.10 mmol, 23%). TLC [silica gel, CH_2Cl_2/EtOAc (95:5)]: R_f = 0.70. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.44 [s, 3 H, C(3′)-CH_3], 1.66 [s, 3 H, C(2′)-CH_3], 2.48 [s, 2 H, C(4′)-CH_2], 2.96 [AB system, 2 H, C(2)-CH_2], 3.71 (s, 3 H, CO_2CH_3), 9.18 (s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.7 [C(3′)-CH_3], 18.3 [C(2′)-CH_3], 39.9 [C(2)], 45.1 [C(3′)], 50.7 (O-CH_3), 54.4 [C(4′)], 64.8 [C(2′)], 116.6 (-CN), 168.9 (C=O), 203.2 (C=S) ppm.

Methyl [(2′*S*,3′*S*,5′*Z*)-5′-(2′-*tert*-Butoxy-2-oxoethylidene)-2′-cyano-2′,3′-dimethylpyrrolidin-3′-yl]acetate (4): A solution of the thiolactam **10a** (130 mg, 0.57 mmol) and *rac*-**11** 270 mg, 0.99 mmol) in acetonitrile (4 mL) was prepared under argon and freshly distilled DBU (132 mg, 0.13 mL, 0.87 mmol) in dry acetonitrile (3 mL) was added. [The ratio between the brominated and unbrominated malonic ester *rac*-**11** was determined by ^{1}H NMR just before the reaction was performed (the mixture contained about 12% of unbrominated malonic diester). The bromomalonic diester[10b] was freshly distilled by kugelrohr distillation in vacuo at 120–130 °C.] The reaction mixture was stirred for 20 min at 0 °C under argon, after which it was diluted with CH_2Cl_2 (10 mL) and transferred into a separating funnel. The organic layer was washed with a saturated solution of $NaHCO_3$ (15 mL), the aqueous phase was again extracted twice with CH_2Cl_2 (10 mL), and the combined organic extracts were dried by filtration through cotton wool and concentrated under reduced pressure. The crude product was thoroughly dried in vacuo and then treated with triethylphosphite (2.9 g, 3 mL, 17.49 mmol) for 18 h under argon at 80 °C for sulfur extrusion. Excess triethylphosphite was removed by kugelrohr distillation under reduced pressure, the yellowish brown, oily crude residue was dissolved in dry THF (4 mL) under argon, and piperidine (0.4 mL, 345 mg, 4.05 mmol) was added. Tetrakis triphenylphosphane palladium(0) catalyst (ca. 50 mg) was quickly added and the reaction mixture was stirred for 2 h at room temperature, treated with ice-chilled hydrochloric acid (2 N, 10 mL) and then extracted three times with CH_2Cl_2 (10 mL). The combined organic extracts were neutralized with saturated aqueous $NaHCO_3$ solution, separated and dried by filtration through cotton wool, the solvent was removed under reduced pressure, and the crude product was chromatographed on silica gel laminated with a slice of 2 cm of alumina with elution with CH_2Cl_2/EtOAc (9:1). The product crystallized from chloroform. Yield: 121.4 mg (0.39 mmol, 69%). M.p. 120 °C. TLC [silica gel CH_2Cl_2/EtOAc (9:1)]: R_f = 0.69. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.09 [s, 3 H, C(3′)-CH_3], 1.47 [s, 9 H, C-$(CH_3)_3$], 1.58 [s, 3 H, C(2′)-CH_3], 2.56–3.21 (m, 4 H, 2 × –CH_2–), 3.72 (s, CO_2CH_3), 4.64 [s, 1 H, C(2)-H], 7.90 (s, 1 H, NH) ppm. IR (KBr): $\tilde{\nu}$ = 3330, 2974, 2929, 2360 2235, 1747, 1738, 1664, 1615, 1480, 1443, 1421, 1392, 1362, 1343, 1298, 1273, 1229, 1178, 1134, 1090, 1040, 1008, 995, 974, 924, 860, 797 cm^{-1}. MS (EI, 70 eV, direct inlet): *m/z* (%) = 308 (20) $[M]^+$, 253 (10) $[M - C_4H_7]^+$, 252 (65) $[M - C_4H_8]^+$, 235 (35) $[M - C_2H_5O_2]^+$, 226 (6), 225 (36), 221 (22) $[M - C_3H_7O_2]^+$, 210 (11), 208 (16), 180 (11), 179 (100), 161 (60), 153 (10), 152 (62), 134 (15), 84 (14), 79 (12), 77 (10), 69 (7), 67 (11), 66 (12), 59 (16) $[C_3H_3O_2]^+$, 57 (60) $[C_4H_9]^+$, 55 (14), 54 (11), 53 (10), 41 (26), 29 (17). HRMS: (EI) $C_{16}H_{24}N_2O_4$ calcd. 308.17361 found 308.17282.

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