Synthesis of an Enantiomerically Pure Ring A building block for Tolyporphin and Tolyporphin Derivatives

Thesis

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(Dr. rer. nat.)

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von

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Bremen 2005

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2. Referee: Prof. Dr. Wolf-Dieter Stohrer

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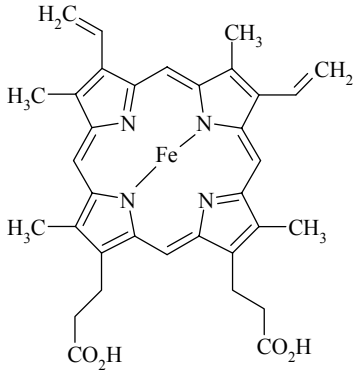
1.1 PORPHYRINOID NATURAL PRODUCTS

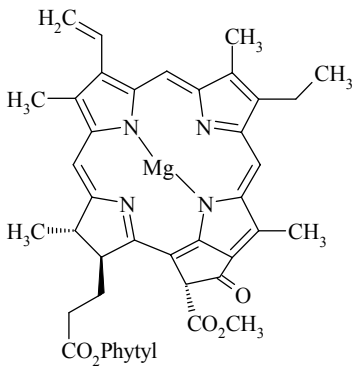
1.1.1 Biological and chemical functions of porphyrinoid natural products

Porphyrinoid natural products are found in nearly all living organisms and they are located primarily in cells and organs that are responsible for energy production, metabolism, and transport functions. The most important and widespread of these porphyrin derivatives are the red blood pigment heme **1**, the green pigment of plant photosynthesis chlorophyll *a* **2**, the bacterial photosynthetic pigment bacteriochlorophyll *a* **3**, and the 'antipernicious' red pigment vitamin B_{12} **4** [1a,b].



1

Heme



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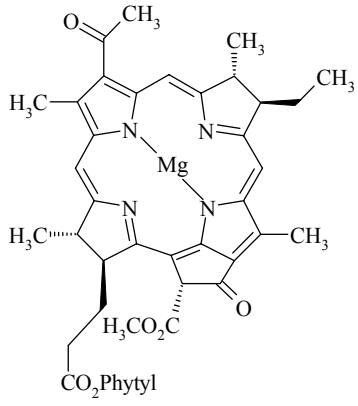
Chlorophyll *a*



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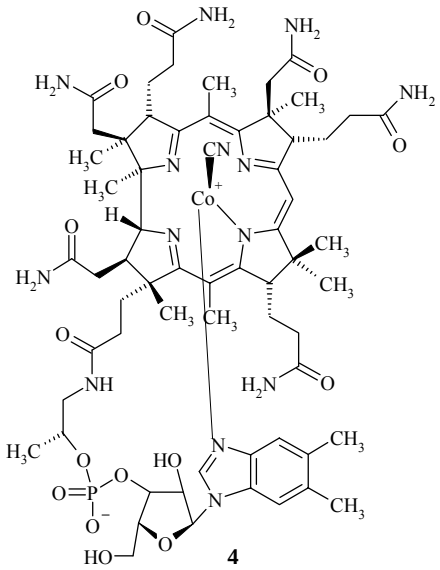
Bacteriochlorophyll *a*

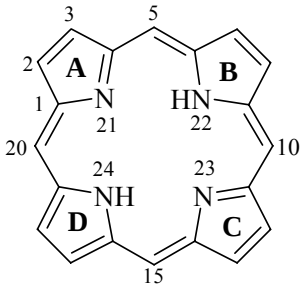


4

Vitamin B_{12}

Figure 1: Heme **1**, chlorophyll *a* **2**, bacteriochlorophyll *a* **3** and vitamin B_{12} **4**

Until the mid-1970s the four classic porphyrinoid and corrinoid structures with their porphyrin **5**, chlorin **6**, bacteriochlorin **7**, isobactriochlorin **8** and corrin **9** skeletons were the only representatives of the class of porphyrinoid natural products (figure 2) [2]. The basic structure of porphyrin **5** consists of four pyrrole units linked by four methine bridges. The porphyrin macrocycle is an aromatic system containing 22 π electrons, but only 18 of them are involved in any one delocalization pathway. Heme **1** belongs to this class of compounds and it is the prosthetic group in hemoglobin and myoglobin, which are responsible for oxygen transport and storage in living tissues [3].



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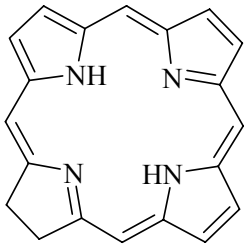
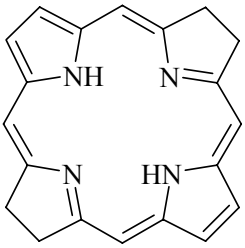
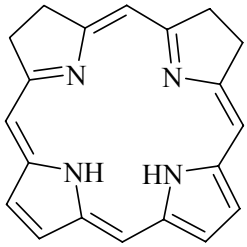
Porphyrin



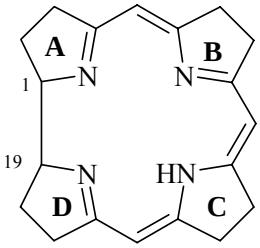
6
Chlorin



7
Bacteriochlorin



8
Isobacteriochlorin



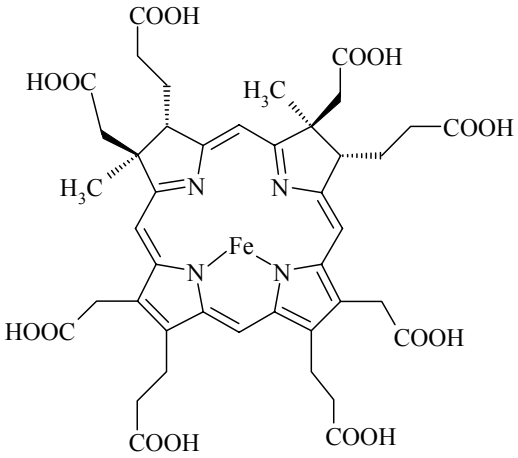
9
Corrin

Figure 2: Porphyrin **1**, chlorin **6**, bacteriochlorin **7**, isobacteriochlorin **8** and corrin **9**

Reduction of one of the pyrrole units on the porphyrin ring leads to chlorin **6** class of compounds. Chlorophyll *a* **2** which is found abundantly in green plants, belongs to this category. It plays very important roles in the process of photosynthesis in green plants [4] due to its structural features and long wavelength absorption [1b]. Chlorins are also of interest in medical applications, for example in photodynamic tumor therapy (PDT) [5].

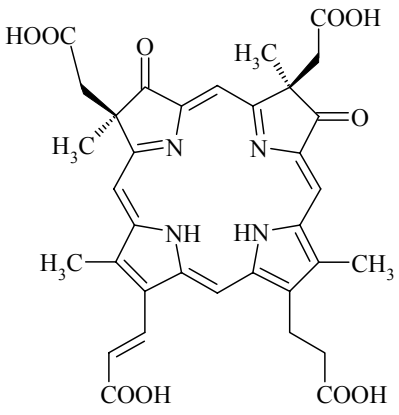
Further reduction of chlorin **2** gives the bacteriochlorin **7**, in which the reduced pyrrole units are diagonally opposite to each other. Bacteriochlorophylls e.g. bacteriochlorophyll *a* **3,** are naturally occurring bacteriochlorins that are found in photosynthetic bacteria [1a]. Tolyporphins (figure 4) are also classified among this group of compounds but they are not involved in bacterial photosynthesis [6, 7a, b].

The constitutional isomers of bacteriochlorins are the isobacteriochlorins **8** which have the reduced pyrrole rings adjacent to each other. Siroheme **10** and heme d_1 **11** are naturally occurring isobacteriochlorins and they play very important role in the sulfur and nitrogen metabolisms of numerous organisms [1a, b].



10

Siroheme



11

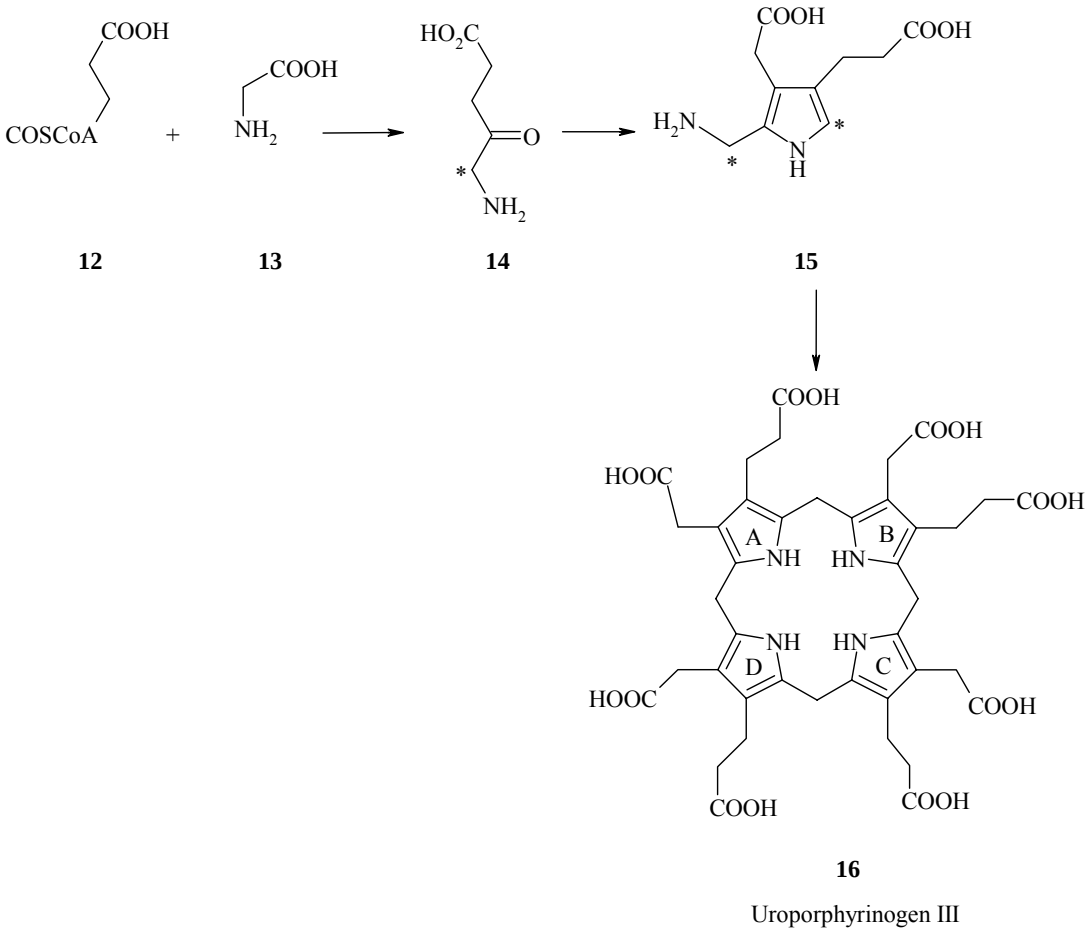
Heme d_1

Figure 3: Siroheme **10**, heme d_1 **11**

Corrin **9** (figure 2) is the chromophoric skeleton of naturally occurring vitamin B_{12} **4** (figure 1) which is important for metabolic process which finally are essential for the formation of red blood cells and the maintenance of the central nervous system [1b]. The striking difference between porphyrinoids and corrins is the direct linkage of the pyrrole rings A and D in the corrin **9** structure originating from the loss of the 20-methine bridge [1b]. Another special feature of the corrin structure is the complete saturation of the β-periphery of the macrocycle and the interrupted cyclic conjugation [1a,b].

1.1.2 Biosynthesis of porphyrinoid natural products

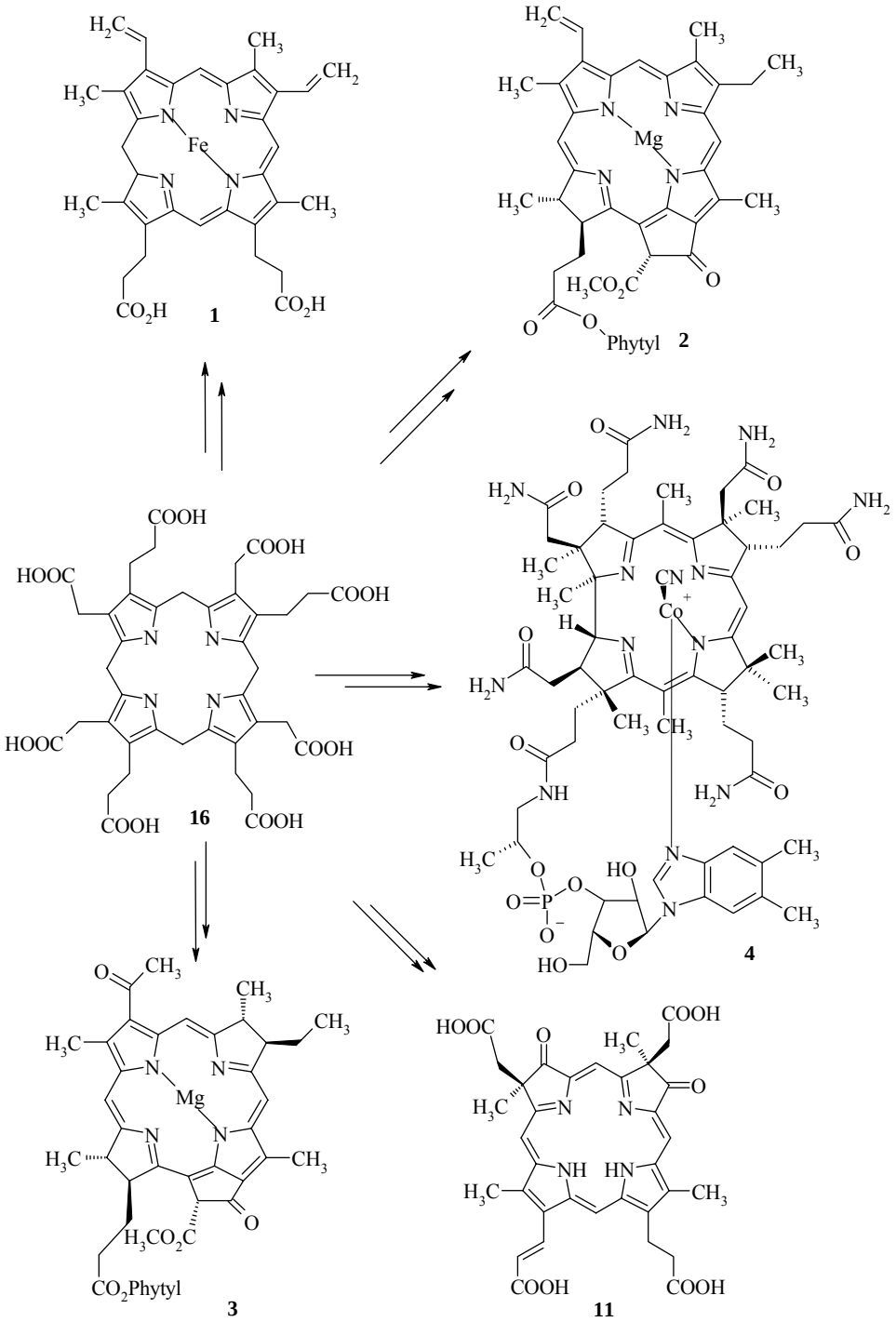
The key building block in the biosynthesis of porphyrinoid natural products is uroporphyrinogen III **16** [10]. The frame work of this key intermediate consists of four isolated pyrrole rings which are linked by methylene bridges. Each of the four pyrrole subunits bears acetic acid and propionic acid side chains at the β-positions. These can be found in sequential pattern on rings A-C but with an inverted substitution pattern on pyrrole ring D [1b].



Scheme 1: Biosynthesis of uroporphyrinogen III **16**

Porphobilinogen **15** which is the building block for uroporphyrinogen III **16** is enzymatically synthesized by paring of two molecules of δ-aminolevulinic acid **14**. Four porphobilinogen **15** molecules are assembled through several reaction steps, controlled by two single enzymes, to generate uroporphyrinogen III **16** [9].

Further enzymatic reaction steps continue from uroporphyrinogen III **16,** with successive enzymatic decarboxylation of the acid side chains, modification of side substituents and the chromophoric skeleton and finally metalation to give the porphyrin and corrin derivatives **1, 2, 3, 4,** and **11.**

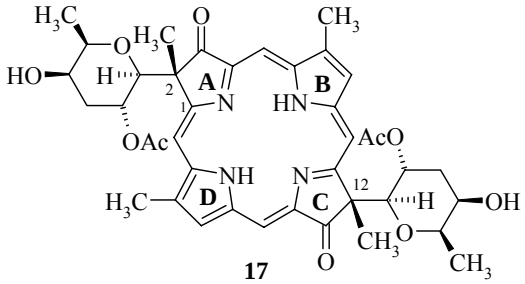


Scheme 2: Biosynthesis of porphyrinoid natural products from uroprophyrinogen III **16**

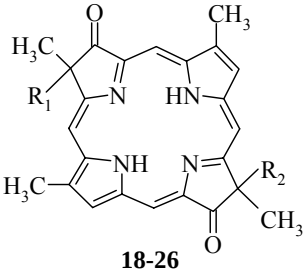
1.2 TOLYPORPHINS

1.1.3 Biological and chemical functions of tolyporphins

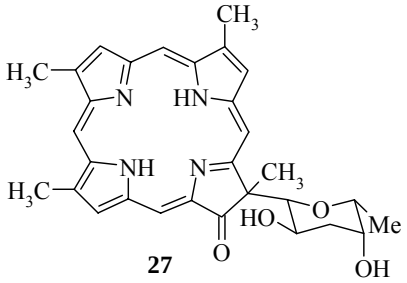
Tolyporphins are naturally occurring bacteriochlorins which were isolated from the lipophilic extract of the terrestrial cyanobacterium, *Tolypothrix nodosa* by Moore, R.E. et. al [6, 7]. Tolyporphin A **17**, the main member of the tolyporphin class of compounds was the first to be isolated in 1992 [6]. Later the isolation and structural elucidation of ten other tolyporphin derivatives, B-K (figure 4) were reported [7] .



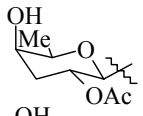
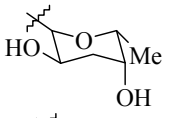
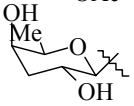
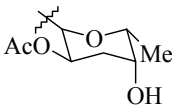
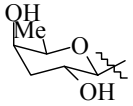
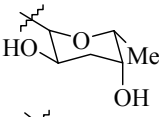
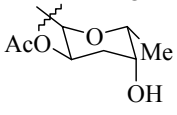
17
Tolyporphin A



18-26
Tolyporphin B-J



27
Tolyporphin K

	R_1	R_2	
B			**18**
C			**19**
D			**20**
E	—OAc		**21**

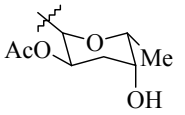
	R_1	R_2	
F	—OH		**22**
G	—OAc	—OH	**23**
H	—OH	—OAc	**24**
I	—OAc	—OAc	**25**
J	—OH	—OH	**26**

Figure 4: Tolyporphin A **17** and tolyporphins B-K **18-27**

Structurally tolyporphins A-J, **17-26** have the bacteriochlorin chromphore and they differ in the residues attached to the geminally disubstituted positions of the saturated rings (figure 4) [7]. Spectroscopic analysis indicates that tolyporphin A **17** contains ketone functions at C-3 and C-13 with two identical β-linked C-glycosides units at C-2 and C-12 (quaternary centers) [6]. From the spectroscopic investigations a configurational formula was assigned in which chirality at C-2 and C-12 was opposite to that of formula **17**. The previous proposed structure for (+)- tolyporphin A had to be revised later based on synthetic studies by Kishi et. al. [23a, 23b, 24]. Tolyporphin K **27** has the chlorin structural unit with a unique macrocyclic ring system of three fully aromatic pyrrole rings [7b].

It was demonstrated in biological experiments that tolyporphin A **17** has the ability to chemosensitize P-glycoprotein overexpressing cells to cytotoxic actions of several anticancer natural product drugs [12b]. P-glycoprotein is a transmembrane protein which utilizes ATP energy to actively pump out cytotoxic drugs including *vinca* alkaloids, actinomycin, anthracyclines, adriamycin, vinblastine and taxol among others [12a,c] from tumor cells. This action is described as multidrug resistance (MDR) and tolyporphins act as antagonists to this activity. Tolyporphins are capable of reversing this MDR activity, by directly binding to P-glycoprotein and then allowing the anticancer drugs to effectively act on the tumor cells [7a, 12a]. Biological experiment showed that the anti-MDR activity of the different tolyporphins varies from each other [7a].

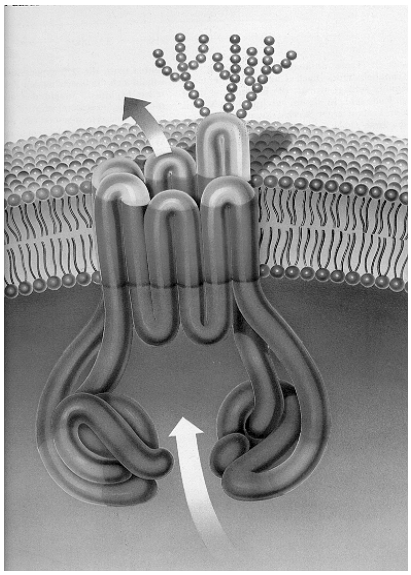
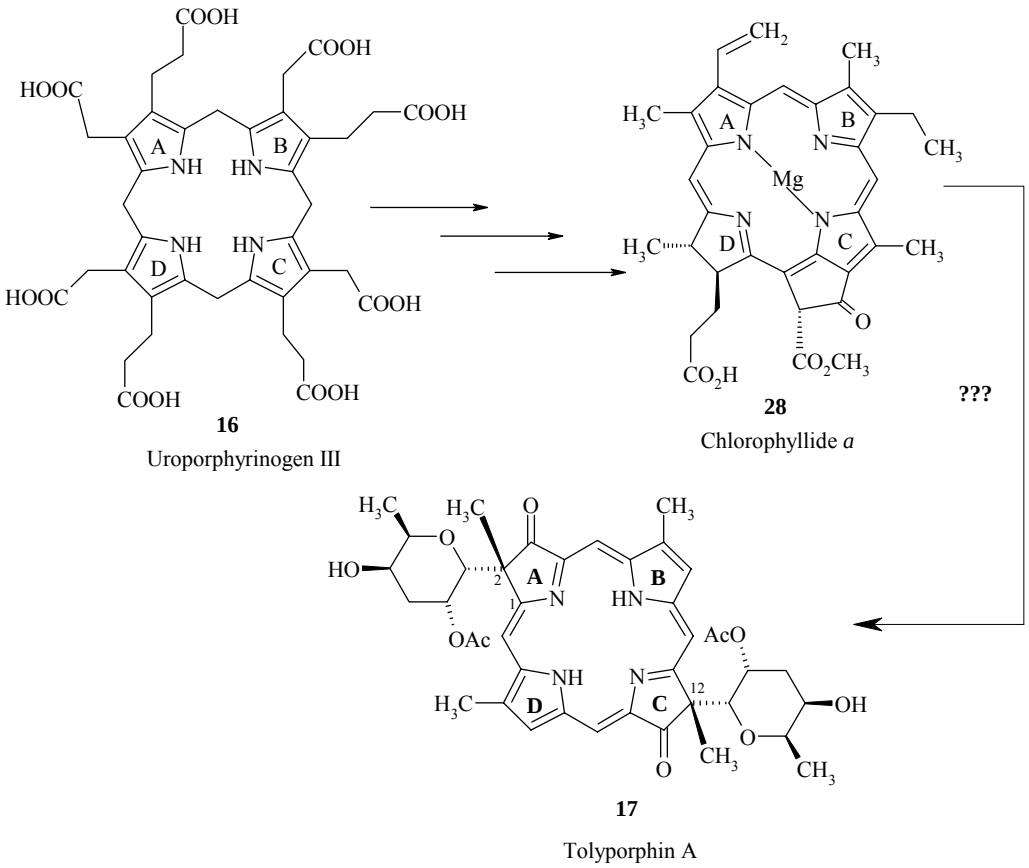


Figure 5: Schematic diagram of p-glycoprotein pump

The tolyporphins also show very potent photosensitizing activity against tumor cells *in vitro* and *in vivo* [12b]. In solution, tolyporphin exhibits a monomer chemical structure with high molar absorbance at 676nm and a relatively high solubility. Preliminary testing indicated strong photokilling activity when tolyporphin was illuminated with red light [12b]. More detailed research was made with EMT-6 tumor cells under *in vivo* conditions and tolyporphin was found to be very effective and could possibly play a useful role in photodynamic therapy (PDT) [12b].

1.1.4 Biosynthesis of Tolyporphins

Whereas elucidation of the biosynthesis of heme **1** and vitamin B_{12} **4** can be considered as more or less completed, the investigation of tolyporphin biosynthesis is still awaiting a breakthrough [1a]. The biosynthetic process may follow that of plant chlorophylls until the formation of chlorophyllide *a* **28** [1b]. The transformation of chlorophyllide *a* **28** into the bacteriochlorins is insufficiently understood and requires further investigations [14].



Scheme 3: Biosynthesis of tolyporphin A **17** from uroporphyrinogen III **16**

Necessary transformations in the biosynthesis of tolyporphin A could be considered by the following modifications of the substitution pattern of **16**.

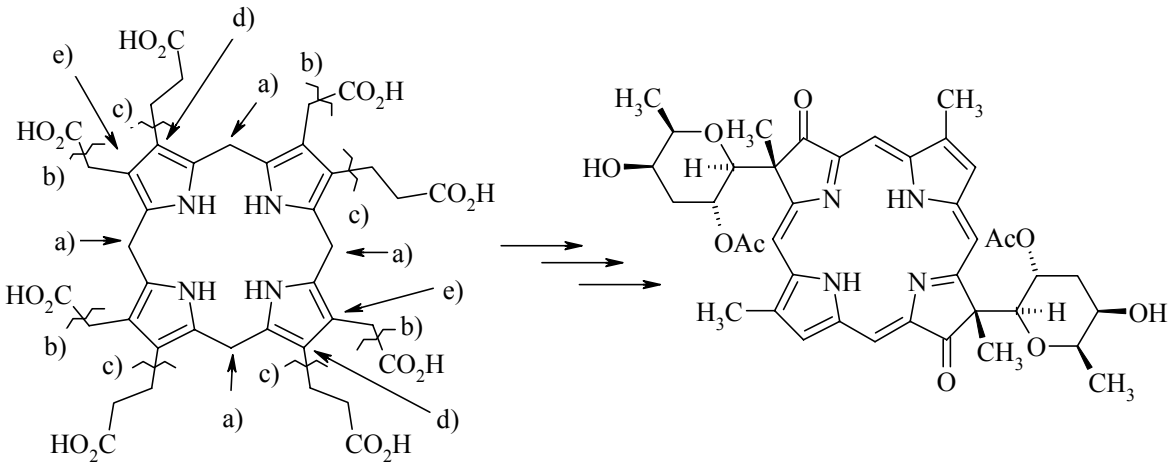
a) Oxidation of the macrocyclic ring.

b) Decarboxylation of the acetic side chains to form the methyl substituents.

c) Complete loss of the propionic acid side chains.

d) Oxidation of the rings A and C to form the ketone functions.

e) Introduction of the tetrahydropyrane rings.



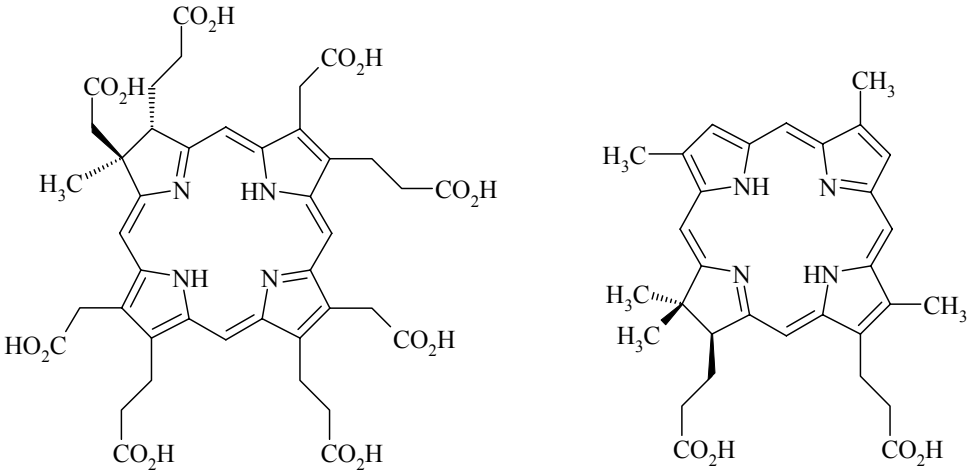
16 **17**

Uroporphyrinogen III Tolyporphin A

Scheme 4: Necesary transformations in the biosynthesis of tolyporphin A **17**

1.3 SYNTHESIS OF CHLORINS

Although methods for the synthesis of chlorins were available when the discovery of novel chlorins like factor I **29** and bonellin **30** began, Woodward's total synthesis of chlorophyll *a* **2** was the only selective pathway for the construction of chlorin **6** [13].



29 Factor I

30 Bonellin

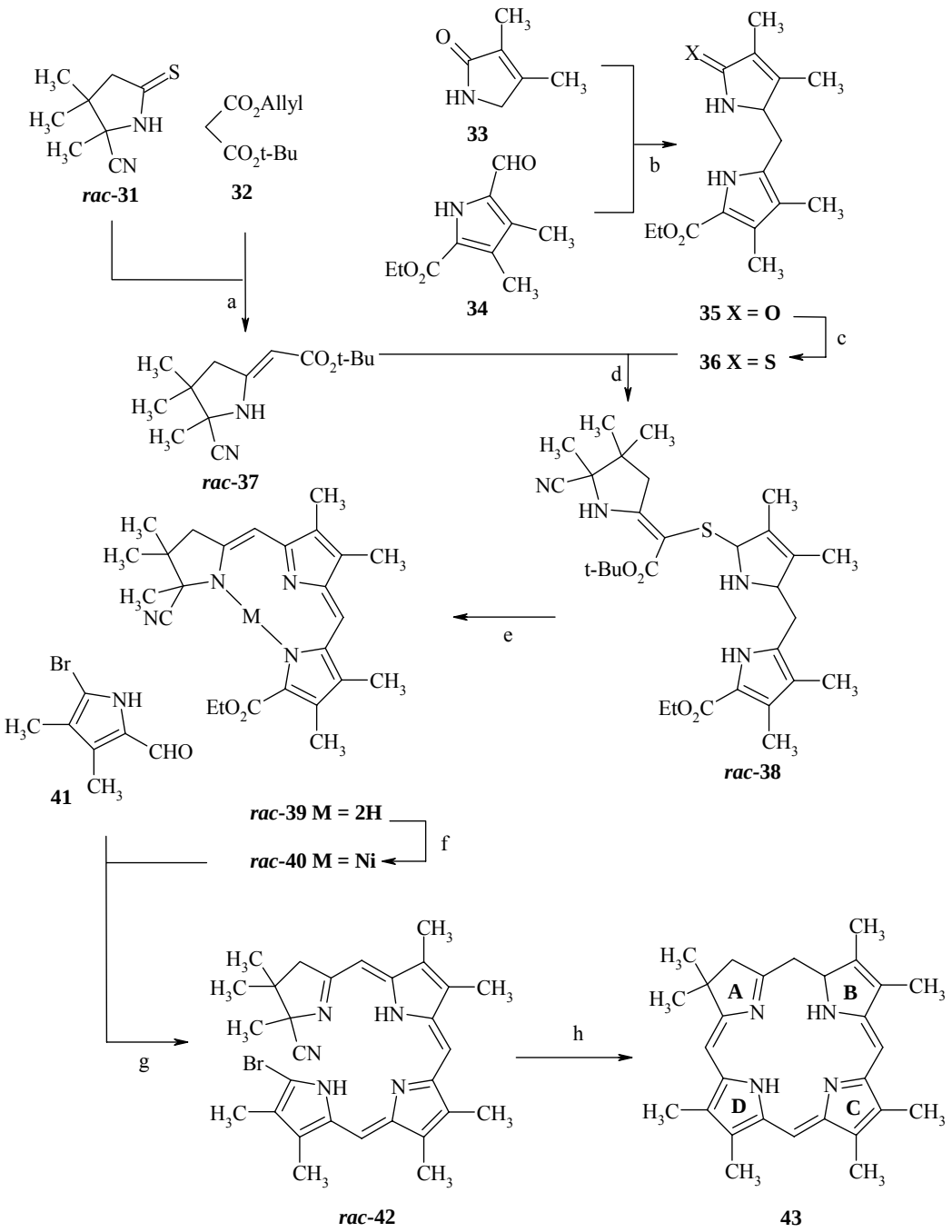
Figure 6: Factor I **30**, bonellin **31**

The laboratories of Battersby [19] and Montforts [18] developed selective methods for the total synthesis of chlorins on model systems, which contain the characteristic dialkylated parts in the saturated five-membered rings of the chlorin system. The knowledge gained from these investigations was later used to synthesize naturally occurring chlorins.

Paramount to the synthesis of chlorin **43** [19] (scheme 5) was the synthesis of the building block precursors *rac*-**31**, **33**, and **34**. The sulphide contraction procedure play a very important role in this synthetic concept. This procedure was devised by Eschenmoser *et al.*[20] while investigating the synthesis of vitamin B_{12} **4** and corrins **9**. Later on the method proved to be extremely efficient for the construction of hydroporphyrinoid structures. With this procedure, the thiolactam *rac*-**31** was able to be connected to the thiolactam bicyclic **36**. The thiolactam *rac*-**31** was converted into the vinylogous urethane *rac*-**37** by reacting with the selectively cleavable malonic ester **32**, *via* sulphide contraction. Under a base-catalyzed reaction, the pyrrolinone **33** and the aldehyde **34** were reacted to give a bicyclic lactam **35**, which was converted into its thio-analogue **36**. Coupling of *rac*-**37** and thiolactam **36** *via* bromination

yielded the tricyclic sulphide *rac*-**38**. Elimination of the *tert*-butylester group on the sulphide *rac*-**38** led to the tricycle *rac*-**39** [21]. The extremely oxygen-sensitive tricycle *rac*-**40** was stabilized by complexation with nickel (II). The nickel in *rac*-**40** also activated the ester function by participating in the complexation, so that a mild selective hydrolysis became possible to cleave the ester function.

The crude product underwent direct acid-catalyzed condensation with the bromopyrrole aldehyde **41**, involving decarboxylation and decomplexation, which gave the tetracycle *rac*-**42**. Reaction with potassium *tert*-butyl alkoxide in the presence of zinc-(II) finally resulted in the cyclization of the linear tetracycle *rac*-**42** to the chlorin **43**. The base liberated an enamine double bond in position 1 by HCN elimination and the enamine cyclized with the loss of bromide. This synthetic concept for chlorin **43** has so far been applied to the syntheses of bonellin **30,** hexadehydrocorrin and chlorin derivatives for inverstigation of artificial photosynthesis [22].



a: 1) DBPO, CH_2CN, 0 °C; 2) $P(OEt)_3$, 80 °C, 2 h; 3) $Pd^0(PPh_3)_4$, THF, 2 h, rt, 20 min; 4) 2 N HCl/CH_2Cl_2, chromatography. **b:** DBU, molecular sieve 3 Å, THF, rt, 8 h. **c:** P_2S_5, $NaHCO_3$, THF, rt. **d:** 1) NBS, CH_2Cl_2, rt, 20 min; 2) DBU, MeCN, rt, 40 min, chromatography **e:** $P(CH_2CH_2CN)_3$, benzol/TFA (10/1), reflux., 20 min, chromatography. **f:** $Ni(OAc)_2.4H_20$, $MeOH/CH_2Cl_2$ (2/1), rt, 20 min. **g**: 1) THF, KOH, $MeOH/H_2O$ (9:l), reflux; 2) *p*-TsOH, $CHC1_3$, reflux. **h:** 1) $Zn(OAc)_2.H_2O$, KOt-Bu, t-BuOH, 70 °C; 2) 25% HCl/CH_2Cl_2.

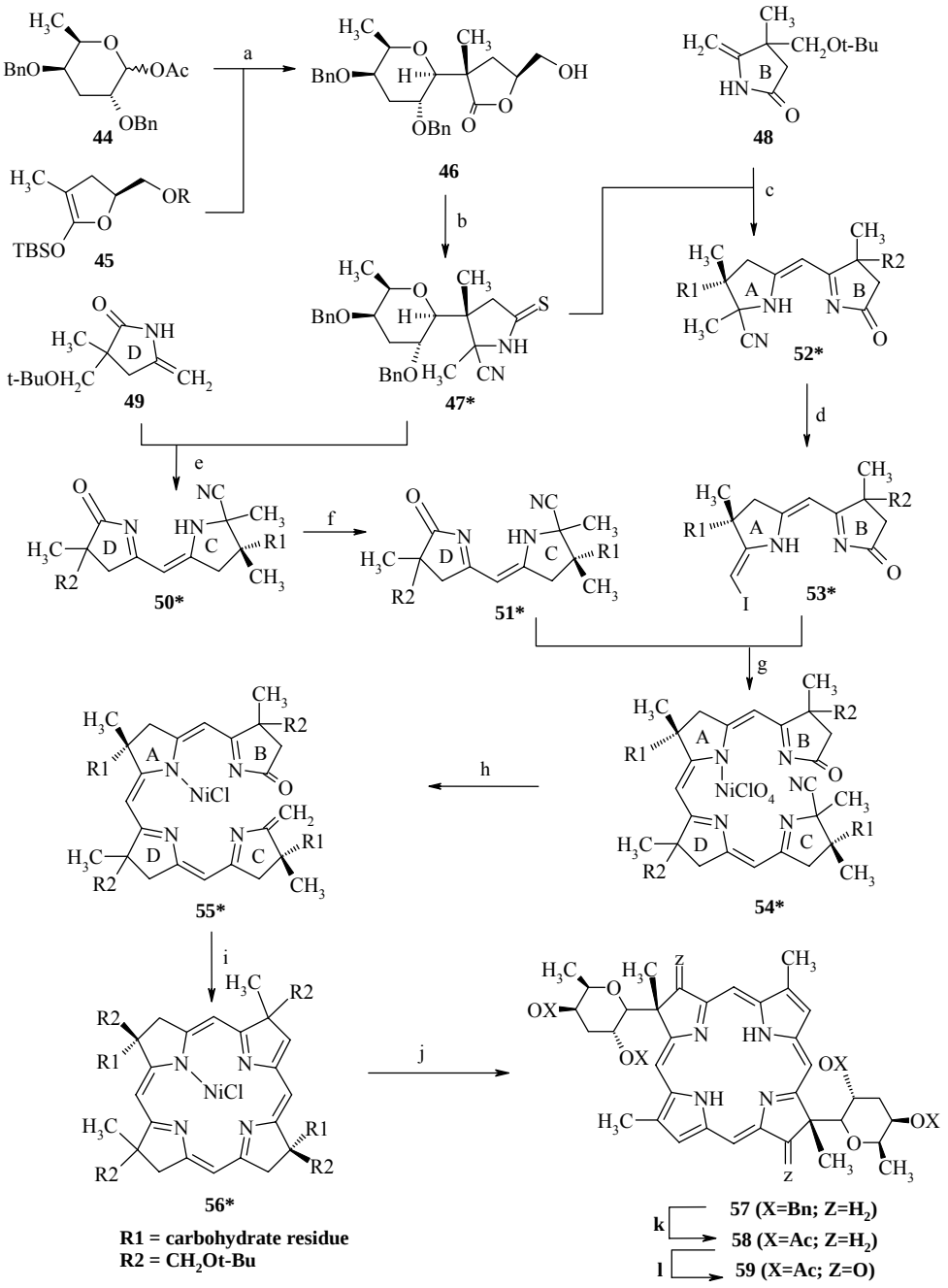
Scheme 5: Synthesis of chlorin **43** on a model system [13, 27, 28]

1.4 SYNTHESIS OF BACTERIOCHLORINS

Methods for the synthesis of bacteriochlorins have not, until recently, been developed. This may be due to the highly sensitivity of bacteriochlorins to various reaction conditions making their chemistry very difficult [1b]. The total synthesis of tolyporphin models, [23c] a tolyporphin stereoisomer [23a] and tolyporphin A **17** [24] have been reported by Kishi using a synthetic route closely related to Eschenmoser's approach for the syntheses of hexahydoporphyrins [23c].

The total synthesis of (+)-tolyporphin A *O,O*-diacetate **59** (scheme 6) involved the assembling of the monocyclic precursors rings A-D **47-49.** The ring-C precursor is identical to the ring-A precursor **47** and this was synthesized *via C*-glycosidation [24].

The precorphin-metal complex **55** was efficiently assembled from **47, 48** [23c] and **49** [23c] by sequential reactions (scheme 6). Transformation of **54** to exo-ene-amide zinc complex **55** was accomplished smoothly by demetalation followed by cyanide elimination and remetalation in one pot reaction. This air-, moisture-, and light-sensitive intermediate was subjected immediately to the iminoester cyclization which gave corphin **56**. Conversion of corphin **56** into tetrahydroporphyrin **57** was done by *tert*-butyl ether deprotection, double-retroaldol reaction/autoxidation, and demetalation. Debenzylation and acetylation at the pyrane moieties of **58** and oxidation at the C-3 and C-13 positions completed the total synthesis of (+)-tolyporphin A *O, O*-diacetate **59** which was identical to tolyporphin A from natural sources.



***The product at this stage was a mixture of diastereomers due to the chiral centers at C-3, C-6, C-12 and /or C-16**

a: 1) TMSOTf, CH_2Cl_2/TFA (10/1), 0 ^oC; 2) TBAF-HOAc, THF; **b**:1) MeLi, THF, -78 ^oC (92%); 2) $Pb(OAc)_4$, CH_2Cl_2 , $NaHCO_3$, rt; 3) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, t-BuOH, H_2O, rt; 4) EtO_2CCl, Et_3N, THF, rt; NH_3, rt; 5) xylene, reflux (70%); 6) KCN, MeOH, 60 ^oC (70%); 7) Lawesson's reagent, toluene, 80 ^oC (98%); **c**: 1) NIS, t-BuOK, t-BuOH, C_6H_6 , rt; 2) $(EtO)_3P$, xylene, 125 ^oC (65% over two steps); **d**:1) t-BuOK, t-BuOH, 85 ^oC; 2) I_2, K_2CO_3, CH_2Cl_2, 0 ^oC (80% over two steps); **e**: 1) NIS, t-BuOK, t-BuOH, C_6H_6 , rt; 2) $(EtO)_3P$, xylene, 125 ^oC (65% over two steps); **f**: Lawesson's reagent, toluene, 80 ^oC (89%); **g**:1) DBU, (4 eq), CH_3CN, rt; 2) Ni $(ClO4)_2$, PPh_3, CH_3CN, rt, (50% over two steps). **h**: 1) KCN, MeOH, rt; 2) t-BuOK, t-BuOH, rt; 3) $Zn(ClO_4)_2$, MeOH, rt; **i**: 1) MeOTf (6.8 eq), pentamethylpiperidine (4.6 eq), CH_2Cl_2, rt, 20 h; MeOH (1.75 eq), rt, 20 h (50%); **j**: 1) TFA, anisole, dimedone, rt; 2) MeOH, rt; 3) t-BuOK, t-BuOH; 4) 20% HCl, rt, (55%); **k**: 1) $ZnCl_2$, EtSH, CH_2Cl_2, rt; 2) Ac_2O, pyridine, rt. (98%). **l**: 1) CrO_3.DMP (0.1M), CH_2Cl_2, 0 ^oC (30 ± 40%).

Scheme 6: Total synthesis of tolyporphin A *O*,*O*-diacetate **59** [23, 24]

2 SYNTHETIC CONCEPTS

2.1 MODEL COMPOUND FOR TOLYPORPHIN A

Due to the unusual structure and important biological activity of natural tolyporphin A **17**, its synthetic studies have a challenging goal. Tolyporphin A is represented by a model compound **60** (figure 7) having the same framework as that of bacteriochlorin **7** but with acetic acid side chains at the stereogenic centers replacing the C-glycoside units. The constitutional arrangement of the substituents and the stereogenic centers correspond to those of the natural tolyporphin A **17.**

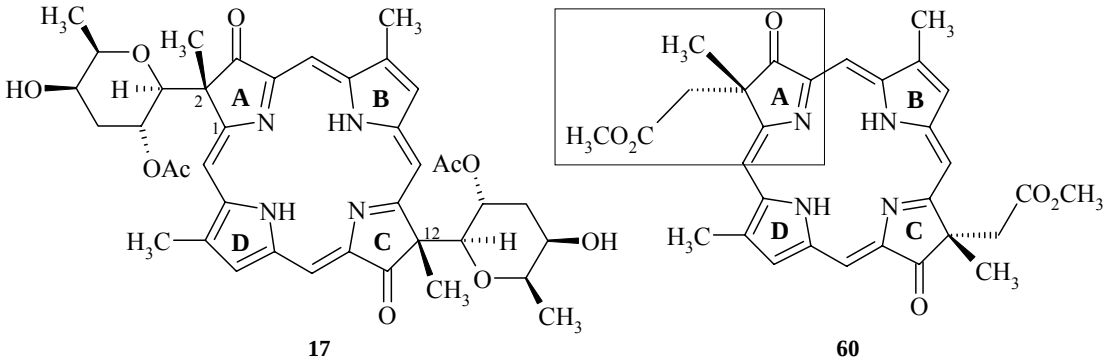
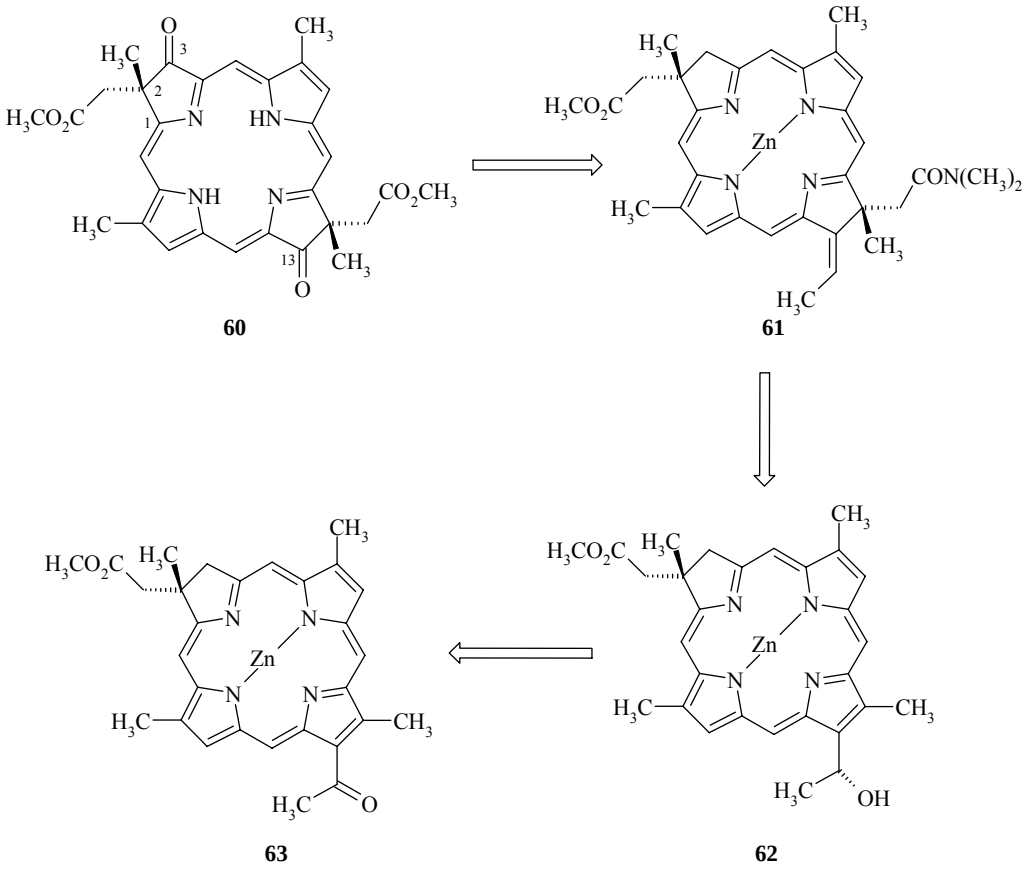


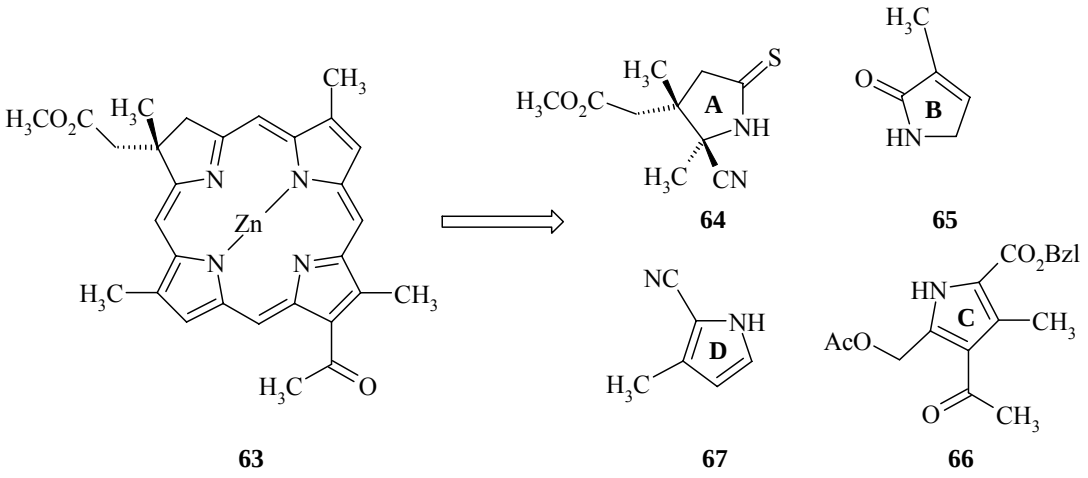
Figure 7: Tolyporphin A **17** and model compound for tolyporphin A **60**

Kishi et.al. described the synthesis of tolyporphin A on a model system from the monocyclic precursors using Eschenmoser's sulphide contraction/iminoester cyclization method [23]. Rings A and C which are the same were synthesized as thiolactam **47** having a quaternary center with a methyl group attached replacing the C-glycoside unit [23c, d].

Retrosynthetic analysis of the model compound **60** indicates that it could be synthesized from acetyl chlorin **63** (scheme 7). A simple route for the synthesis of isobacteriochlorin skeleton by double amide acetal Claisen re-arrangement from hematoporphyrin dimethyl ester could be adopted [29]. *Via* this route the geminally dialkylated structural elements at position C-12 of **61** could be obtained. The hydrolysis of the amide function and splitting of the exocyclic double bond could be accomplished followed by esterification and oxidation of the C-3 and C-13 positions of **61** to give dioxobacteriochlorin dimethylester **60** [29].



Scheme 7: Retrosynthetic analysis of model compound **60**



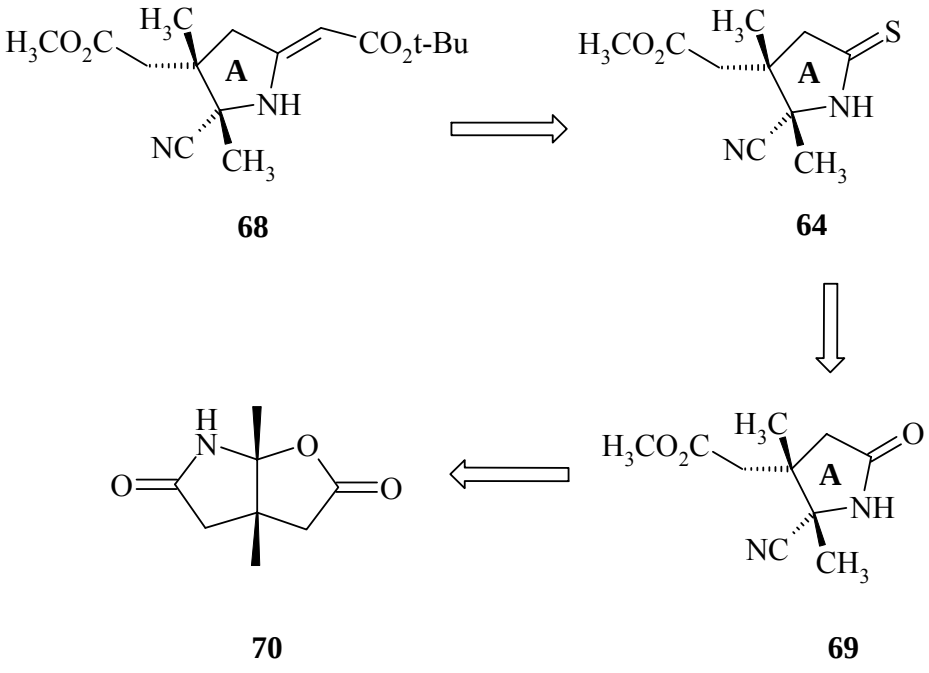
Scheme 8: Disconnection of acetyl chlorin **63**

Complete disconnection of the acetyl chlorin **63** (scheme 8) gives the monocyclic ring precursors A to D. In this case ring A is structurally different from ring C therefore their synthesis would not be the same like the method adopted by Kishi et.al [23].

2.2 SYNTHETIC PLAN FOR RING A

For the total synthesis of the model compound **61** it is of great interest to use an enantiomerically pure ring A-component. The objective of this research work is centered on the synthesis of ring A **64** as a building block, in an enantiomerically pure form. From previous work the ring A precursor **64** was synthesized as a racemic compound [18, 25, 27a] and this has been used as building block for the synthesis of bacteriochlorin and chlorin derivatives [18] . In this work an enantioselective synthetic route was adopted to produce an enantiomerically pure ring A **64** building block which could be used in the synthesis of enantiomerically pure tolyporphin models.

In order to introduce a methine bridge between rings A **64** to B **65** during coupling, it would be better to synthesize the ring A as a pyrrolidine diester **68**. This could be done by coupling **64** with a selectively cleavable malonic ester derivative. The thiocyano lactam **64** could be prepared by the reaction of Lawesson's reagent with cyano lactam **69**. Ring opening of the unsubsituted lactam-lactone **70** by a methanolic cyanide solution followed by esterficaton could be done to form **69** (scheme 9)

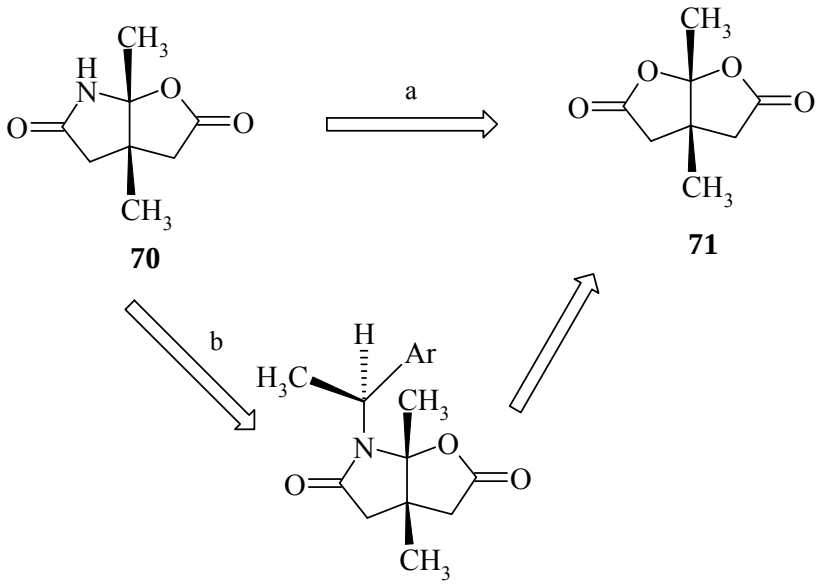


68 **64**

70 **69**

Scheme 9: Retrosynthetic analysis of pyrrolidine diester **68**

Unsubstituted lactam-lactone **70** has been used as a main building block for the synthesis of thiocyano lactam **64** in our laboratory. Previous work on the synthesis of this building block yielded a racemic mixture [25, 26]. Retrosynthetic analysis of **70** *via* two possible routes are shown in scheme 10. Route *a* is the functional group interconversion of **70** to the bislactone **71**. In order to obtain an enantiomerically pure lactam-lactone **70**, a stereoselective disconnection of **70** could be considered (route *b*) and this could give substituted lactam-lactone diastereomers **72** which could be converted by the removal of the aryl amine to the bislactone **71**. Based on this, an enantioselective synthetic approach would be applied in this synthesis and this would involve the use of an aromatic chiral amine [25] which is commercially available. The bislactone precursor **71** could be synthesized from commercially available malononitrile and butane-2,3-dione.



70 **71** **72**

Scheme 10: Retrosynthetic analysis of unsubstituted lactam-lactone **70**

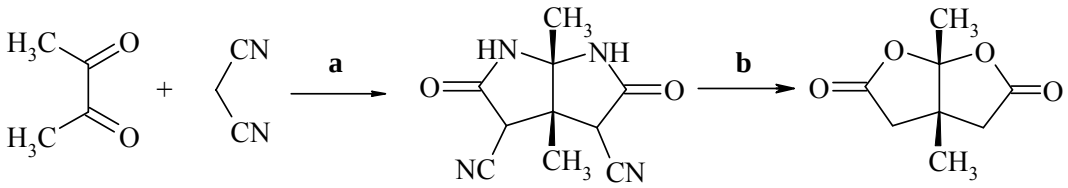
3 SYNTHETIC PROCESS

3.1 SYNTHESIS OF ENANTIOMERICALLY PURE LACTAM-LACTONE BUILDING BLOCK

It is of great importance to synthesize an enantiomerically pure building block for the synthesis of enantiomerically pure ring A. Enantiomerically pure unsubstituted lactam-lactone **70** was used as the main building block for the synthesis of ring A. In our research group [25] and also from literature [26], unsubstituted lactam-lactone was synthesized using aqueous ammonia solution but this resulted into a racemic mixture, *rac*-**70**. To avoid the formation of racemate lactam-lactone, a stereoselective synthetic pathway was adopted which was a deviation from the known synthetic method used (scheme 12a).

3.1.1 Synthesis of bislactone 75

The synthetic route started with the synthesis of bislactone **71.** As quoted in literature, [26] bislactone **71** was synthesized from diacetyl **73** and malononitrile **74** in the presence of sodium ethoxide as catalyst which gave dinitrile dilactam **75**. Hydrolysis of **75** with 48 % hydrogen bromide under reflux afforded bislactone **71**.



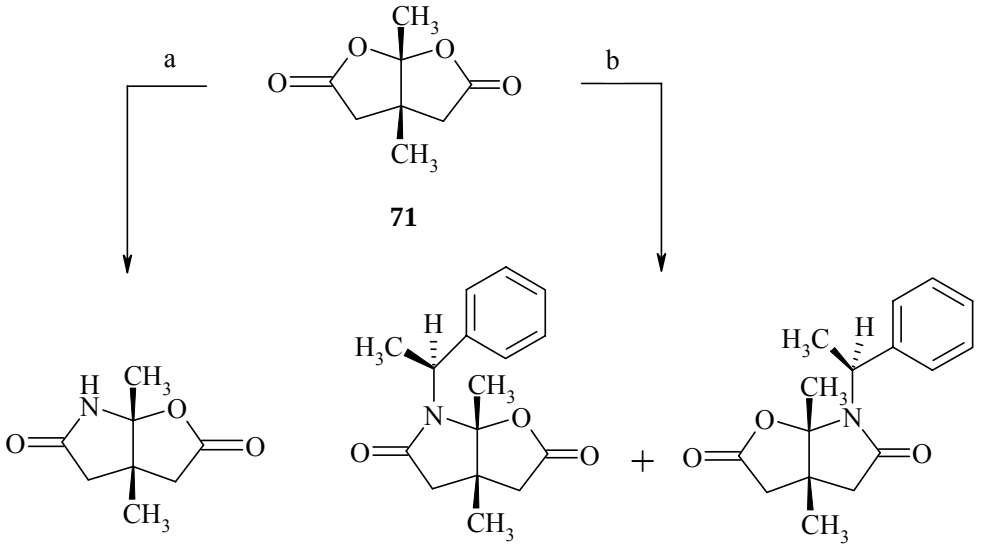
73 **74** **75** **71**

a: 1) EtOH, NaOEt, 0 °C, 4 h; 2) Conc. HCl, pH 1, rt, 1 h, 32%. **b:** 48 % HBr, reflux, 45 min, 60 %.

Scheme 11: Synthesis of bislactone **71** [25, 26]

3.1.2 Synthesis of N-alkylated phenyl ethyl lactam-lactone diastereomers

Asymmetric synthesis was performed on bislactone **71** using a chiral amine namely (S)-(-)-henyl ethyl amine under argon atmosphere. This reaction was TLC controlled and a mixture of N-alkylated lactam-lactone diastereomers **76a** and **76b** was produced (scheme 12b).

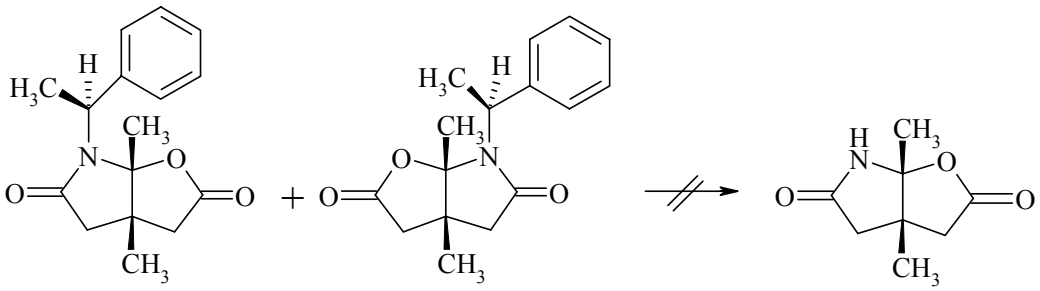


a: aqueous NH_3 solution, rt, 20 h, 86 %. **b:** (S)-(-)-$C_6H_4CH_3CHNH_2$, $CHCl_3$, rt, argon 24 h, 82%

Scheme 12: Synthesis of racemic unsubstituted lactam-lactone, *rac*-**70** and N-alkylated phenyl ethyl lactam-lactones **76a** and **76b** [25]

3.1.3 Debenzylation of N-alkylated phenyl ethyl lactam-lactone

Attempts to cleave the benzyl group from these diastereomers **76a** and **76b** were unsuccessful. Many authors have commented that N-benzylamine groups can be difficult to hydrogenolysis and attempts to overcome this problem require higher catalyst loading, more acidic medium, higher pressure and /or high temperature [39]. A series of reductive reactions was performed both under mild and drastic conditions (table 1) but none was successful. In almost all the reactions performed, only the starting material was recovered. The reaction with Na/liq.NH_3 [33] resulted in decomposition of the starting material. The table below gives a summary of the reactions performed with the specific reagents and conditions. All the reactions were monitored by TLC and ^{1}H-NMR spectra measurements were done in all the products but the N-H signal of the unsubstituted lactam-lactone ***rac*-70** was not seen on any of the spectrum. After trying all these reactions without success it was concluded that steric hinderance around the N-benzyl bond might be the main factor for the problem.



76a **76b** ***rac*-70**

Scheme 13: Debenzylation of N-alkylated phenyl ethyl lactam-lactone diastereomers **76a** and **77b** (refer to table 1 for reagents and conditions)

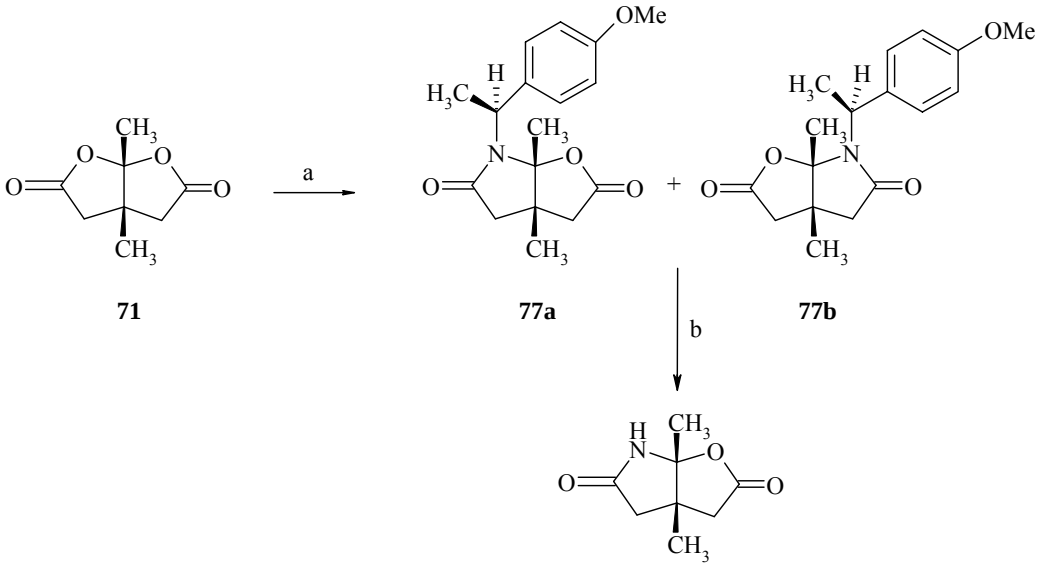
Entry	Reagent	Catalyst	Solvent	Time	Temp	Comments [x]
1	H_2	Pd / C	THF	24 h	r.t.	Starting material isolated
2	H_2 (2 bar)	Pd/C	HOAc	6 days	r.t.	
3 [30]	H_2	$Pd(OH)_2/C$ 20%	HOAc	36 h	r.t.	
4	H_2	$Pd(OH)_2/C$ 20%	MeOH/HOAc	36 h	r.t.	
5 [31]	H_2N-$NH_2.H_2O$	Pd/C	MeOH	30 min.	reflux	
6 [32]	TFA / H_2O 4:1	-	-	1 h	r.t.	
7 [34]	TFA	-	-	96 h	r.t	
8 [35]	H_2 (3 bar)	$Pd(OH)_2/C$	MeOH/HOAc	120 h	60 °C	
9 [33]	TFA / anisole	-	-	23 h	r.t	
10	H_2 (2 bar)	$Pd(OH)_2/C$	HOAc	36 h	r.t.	
11[41]	$Ce(NH_4)_2(NO_3)_6$	-	MeCN/H_2O	20 h	r.t.	
12 [36]	Na / NH_3	-	-	1 h	-78 °C	Decomposition of the starting material
13 [37]	a, HBr 48% b, 0.1M NaOH	-	-	2 h	reflux 100 °C	

Table 1: Reactions conditions for debenzylation studies on N-alkylated phenyl ethyl lactam-lactones **76a** and **76b.** [x] all the reactions were performed under argon atmosphere and monitored by TLC

3.1.4 Synthesis of (S)-(-)-(4-methoxyphenyl) ethyl lactam-lactone

Due to the difficulty in the cleavage of the benzyl group from the diastereomeric mixture of **76a** and **76b**, a new set of N-alklylated lactam-lactone diastereomers **77a** and **77b** was synthesized this time using an electron rich benzyl amine, namely (S)-(-)-(4-methoxy phenyl) ethyl amine. Reaction conditions were kept the same, under argon atmosphere with dry chloroform and the reaction was monitored with TLC. Purification was achieved by repeated column chromatography on silica gel followed by preparative HPLC.

Cleavage of the methoxy-benzyl group can be selectively achieved using an aqueous solution of ceric ammonium nitrate (CAN) [41]. This oxidative cleavage was applied to the mixture of **77a** and **77b** which cleaved the methoxy benzyl group into the phenyl ketone and the lactam-lactone moiety hydrogenated. The reaction was TLC controlled and it took 20 hours after starting material was completely consumed. After purification by column chromatography, ^{1}H-NMR measurements showed that methoxy phenyl ketone and unsubstituted lactam-lactone ***rac*-70** were formed. The reaction was then optimized and repeated on the pure diastereomers **77a** and **77b** respectively.



a: (S)-(-)-(4-MeOC$_6$H$_4$) CH$_3$CHNH$_2$, CHCl$_3$, rt, argon, 24 h, 70% **b:** 1) Ce(NH$_4$)$_2$(NO$_3$)$_6$ [2.1eq.] in H$_2$O, MeCN/ H$_2$O [4:1], rt, 17 h.; 2) NaHCO$_3$ 15 min, 65%.

Scheme 14: Synthesis and oxidative debenzylation of 4-methoxy phenyl ethyl lactam-lactones **77a** and **77b** [41]

3.1.5 Configurational analysis of substituted lactam-lactone derivatives

In effect two pairs of N-alkylated lactam-lactone diastereomeric mixtures **76a** and **76b**, **77a** and **77b** respectively were synthesized. These mixtures of diastereomers were separated and purified by preparative HPLC into four pure diastereomers. These were characterized spectroscopically and analytically. The absolute configurations were determined for these diastereomers by circular dichroism (CD) spectroscopic measurement and by X-ray structural analysis.

The CD spectrum for **76a** showed a positive cotton effect (figure 8) whilst that of **76b** exhibited a negative cotton effect (figure 9). Structure **77a** showed similar CD absorption spectrum (figure 10) as that of **76a**. Likewise **77b** and **76b** showing similar CD absorption spectra. Based on these results it can be concluded that **76a** and **77a** have the same absolute configuration and also **76b** and **77b**.

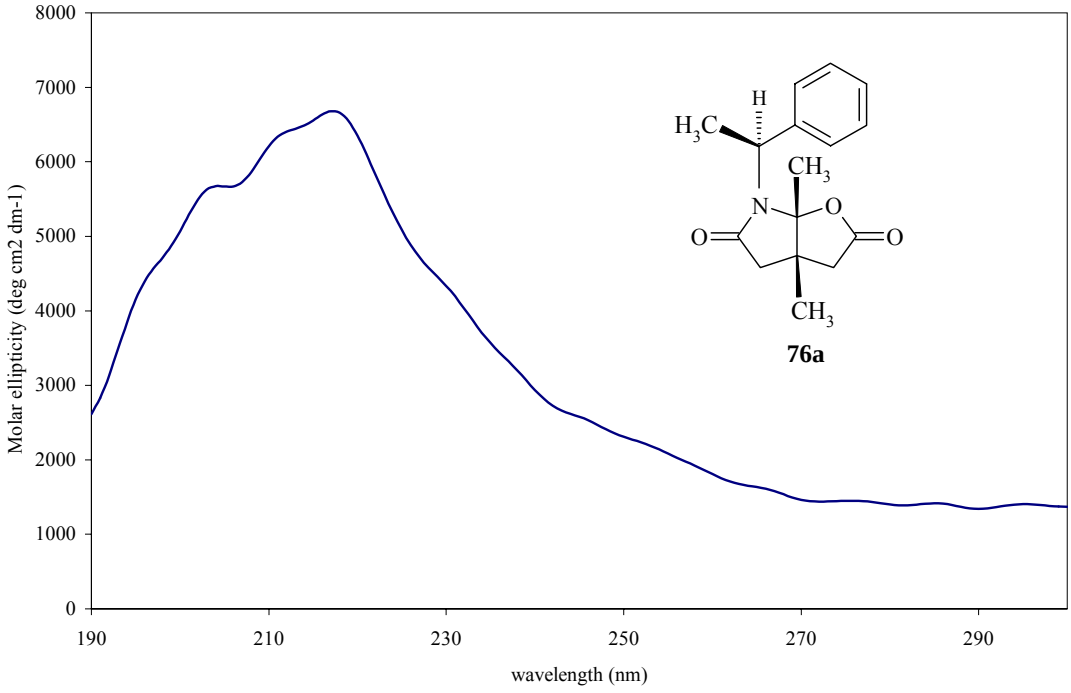


Figure 8: CD spectrum of diastereomer **76a**

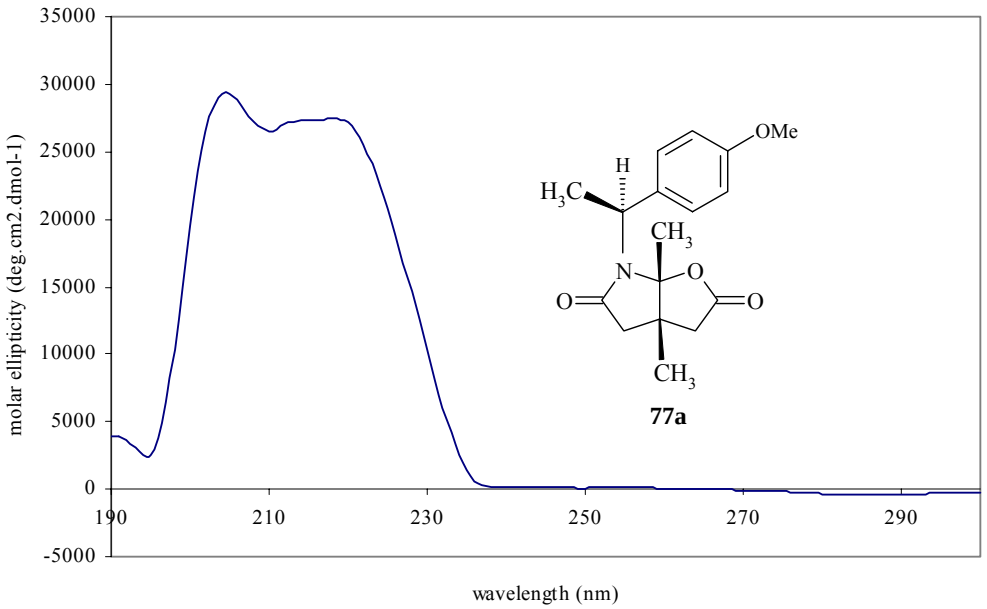


Figure 9: CD spectrum of diastereomer **77a**

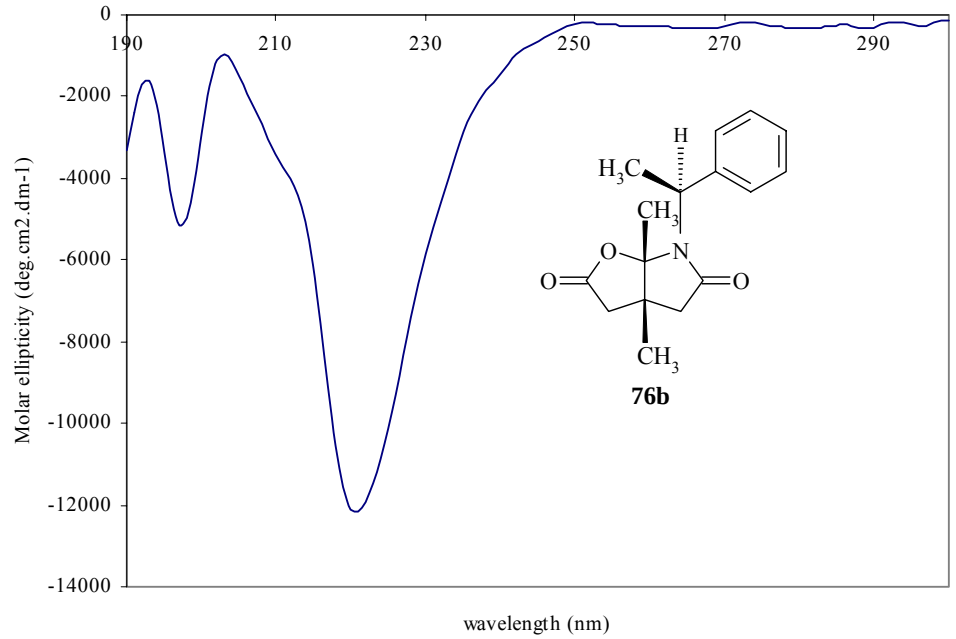


Figure10: CD spectrum of diastereomer **76b**

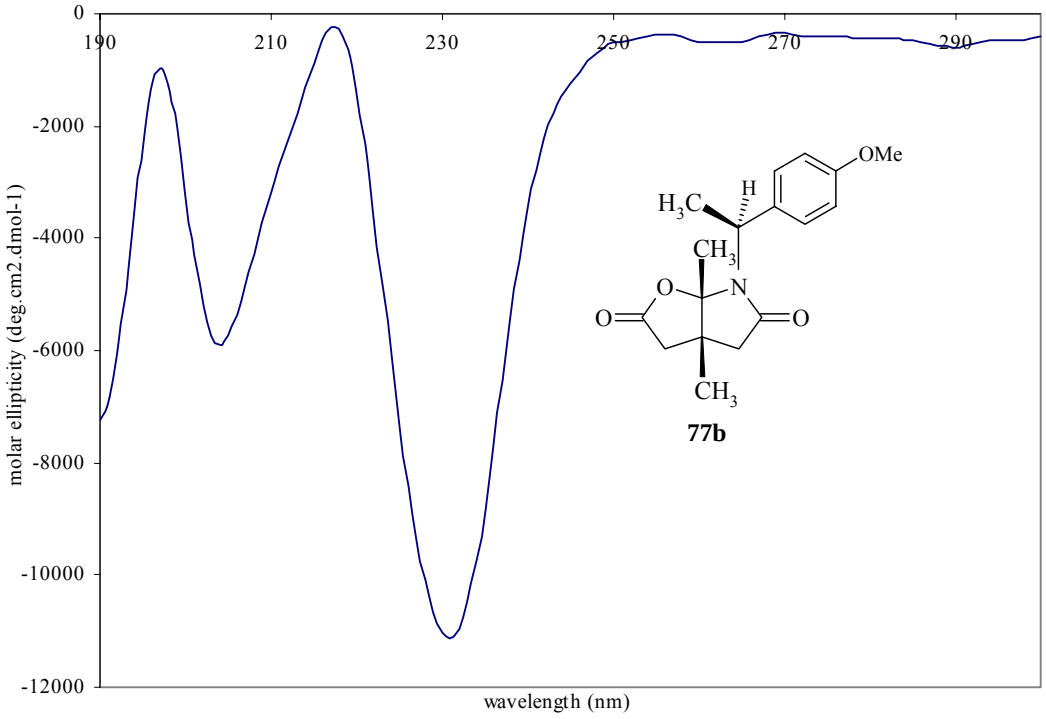


Figure 11: CD spectrum of diastereomer **77b**

X-ray structural measurements were taken for two of the pure diastereomers, **76a** (figure 12) and **77a** (figure 13). Both crystal structures were found to have three chiral centers at C-3, C-6, and C-7. The configurations at these chiral centers were found to be the same for **76a** and **77a**. Across the bridge of both structures are two chiral centers, C-3 and C-6. The center of chirality at position C-3 of both structures have the *S*-configuration and C-6 positions have the *R*-configuration. The stereogenic center at position *C*-7 of **76a** and **77a** have the *S*-configuration. With absolute configuration of **76a** and **77a** determined by X-ray structural measurement, the absolute configuration of **76b** and **77b** were also fixed.

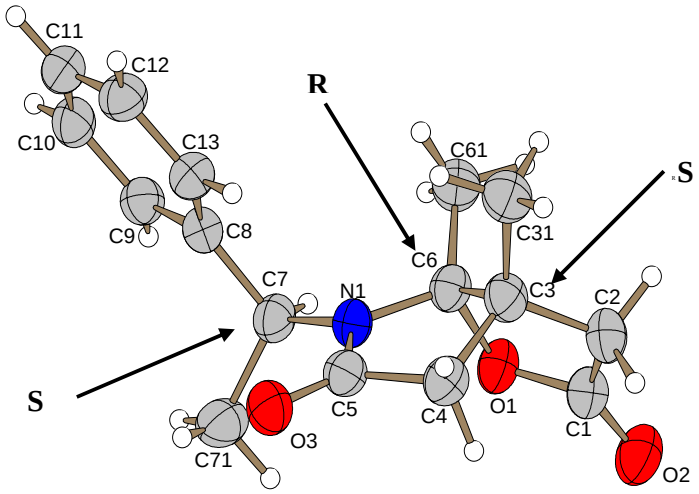


Figure 12: X–ray structures of diastereomer **76a**

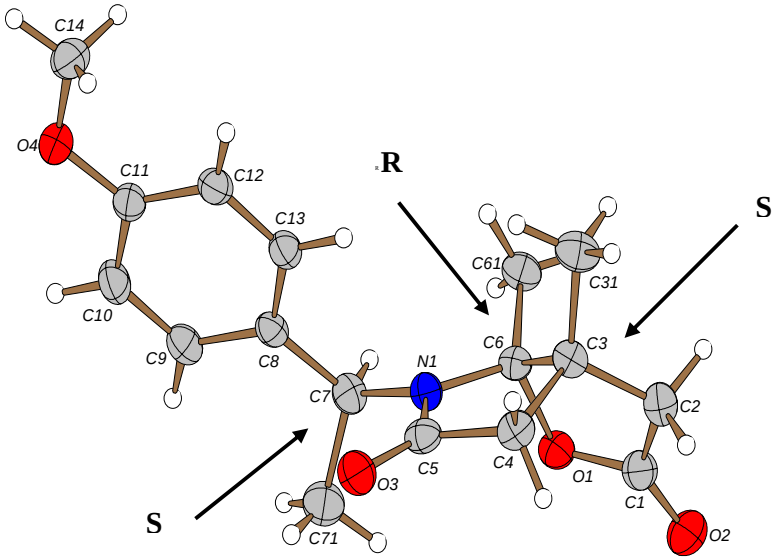


Figure 13: X-ray structure of diastereomer **77a**

3.1.6 Chromatographic separation of substituted lactam-lactone diastereomers

Further analysis was carried out on the methoxy benzyl diastereomers **77a** and **77b** since they were susceptible to debenzylation into the unsubstituted lactam-lactone building block **71**. Separation of this diastereomeric mixture by normal gradient column chromatography using different solvent systems was difficult. Medium pressure liquid chromatographic (MPLC) technic was used to separate this mixture. The MPLC set up consists of an HPLC Kauer pump 64, a column (49 x 460mm) filled with matrex silica (20-45µm 60 Å). Petroleum ether/ethyl acetate (1:1) was the best solvent system for this separation though solubility of the mixture was a problem. The chromatographic fractions from the MPLC separation were analyzed by HPLC and combined conveniently.

The HPLC chromatograms (figure 14) showed the elution pattern of the diastereomeric samples. Diastereomer **77a** was eluted first as fraction A which was followed by fractions B, C and D as mixtures but of different ratios. Fraction E was pure **77b**. The pure chromatographic fractions A and E were concentrated and dried. The intermediate fractions B, C and D were re-chromatographed on the MPLC. The yield of **77a** after the MPLC separation was 57% while **77b** was 27% with the mixture of both diastereomers, 15%.

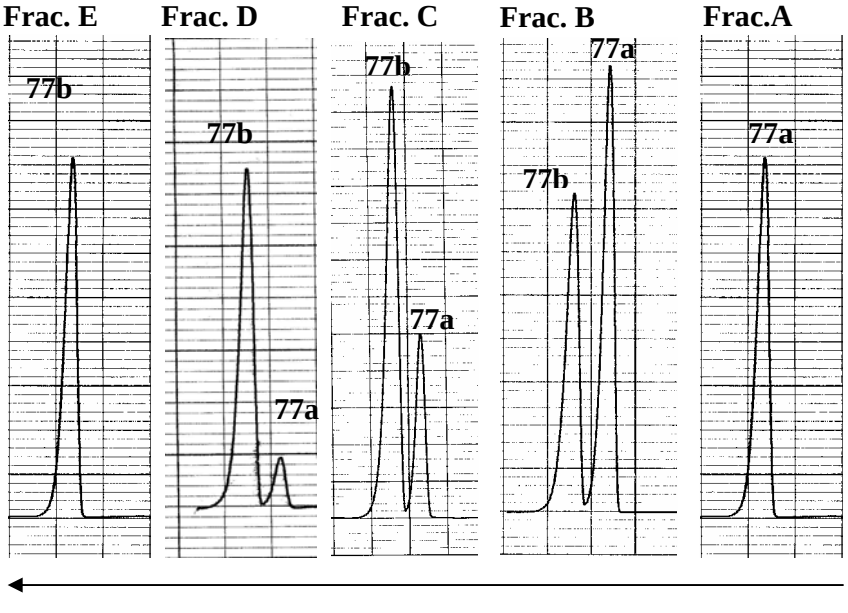
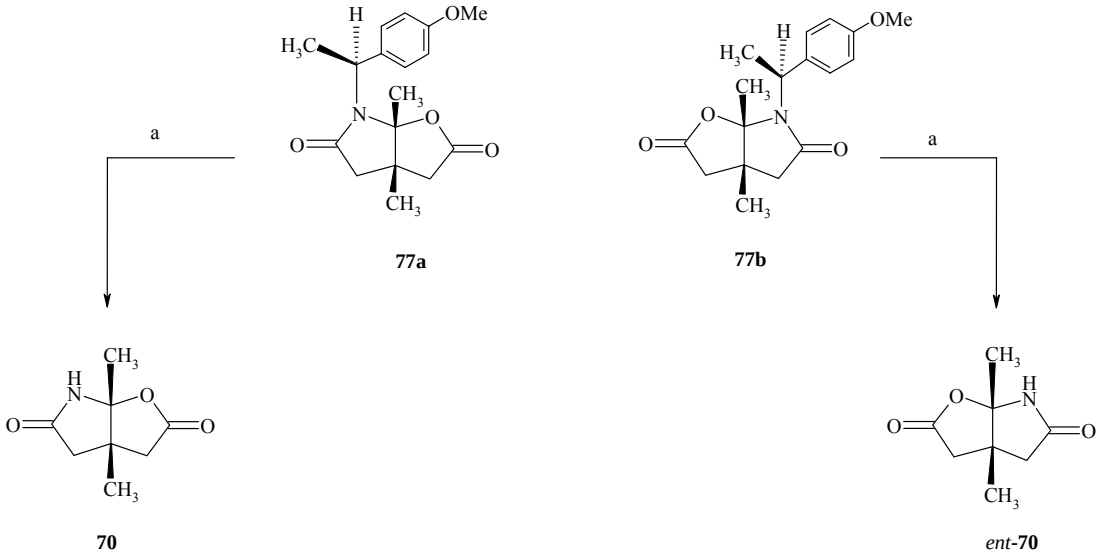


Figure 14: HPLC chromatograms of diastereomers **77a** and **77b**, (Frac. = fraction).

3.1.7 Synthesis of unsubstituted lactam-lactone enantiomers

Oxidative debenzylation with ceric (IV) ammonium nitrate CAN [41] was carried out separately on both diastereomers **77a** and **77b** giving enantiomerically pure unsubstituted lactam-lactone **70** and *ent*-**70** (scheme 15). These were characterized and analyzed spectroscopically. The optical rotations of these enantiomers were measured and **70** was found to be the (-) enantiomer and *ent*-**70** is the (+) enantiomer.



(-) lactam-lactone
$[\alpha]^{20}_D$ = - 82.308 ^{o}ml g^{-1} dm^{-1}

(+) lactam-lactone (*ent*)
$[\alpha]^{20}_D$ = + 82.308 ^{o}ml g^{-1} dm^{-1}

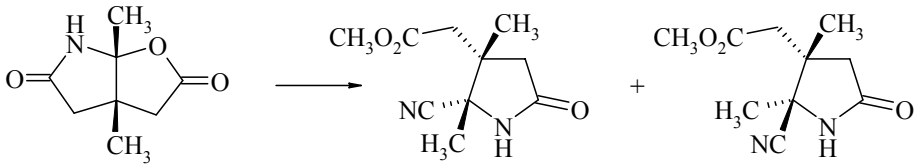
a: 1) $Ce(NH_4)_2(NO_3)_6$ [2.1eq.] in H_2O, MeCN/H_2O [4:1], rt, 17 h; 2) $NaHCO_3$ 15 min, 66%.

Scheme 15: Synthesis of enantiomerically pure lactam-lactone isomers **70** and *ent*-**70** [41]

3.2 SYNTHESIS OF CYANO LACTAM ISOMERS

Synthesis proceeded with **70** since its precursor **77a** was more after the MPLC separation. The (-)-enantiomer **70** was subjected to ring opening of the lactone ring to form cyano lactam **69.** This is a well know reaction from the synthesis of vitamin B_{12} by Eschenmoser et. al. [16]. In this reaction, **70** was treated with methanolic cyanide solution at room temperature and this selectively opened the lactone ring which formed a free carboxylic acid cyano lactam. The free carboxylic acid group was then esterified with diazomethane yielding the methyl ester. A

mixture of *cis*- and *trans*-cyano lactam isomers **69a** and **69b** was formed**.** These isomers were purified by column chromatography for analytical purposes. But they were used together for the next reaction.



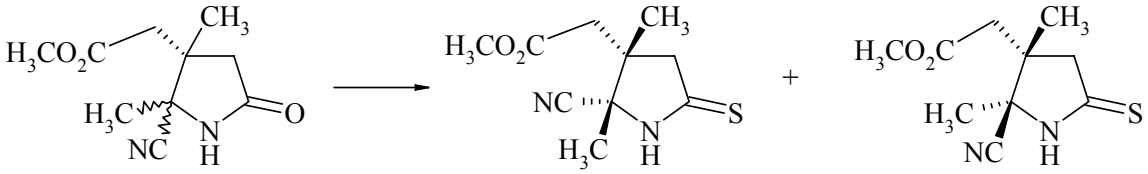
70 ***cis*-69a** ***trans*-69b**

b: 1) KCN, MeOH, rt, 20 h; 2) CH_2N_2, MeOH, 0 °C, 15 min., **80 %**

Scheme 16: Synthesis of *cis*- and *trans*-cyano lactam diastereomers **69a** and **69b**

3.3 SYNTHESIS OF THIOCYANO LACTAM ISOMERS

The isomeric mixture of the cyano lactam **69a** and **69b** was treated with Lawesson reagent [42, 43] in dry THF at 40 °C under argon atmosphere for 15 minutes and then stirred at room temperature for 4hrs. This formed the *cis*- and *trans*- thiocyano lactam isomeric mixture of **64a** and **64b**. These isomers were purified by a normal column chromatography and then further separated on a 'stepped column' (Stufensäule) into pure **64a** and **64b.** The first isomer that came from the 'stepped column' was crystalline **64a**, 77% yield. The second isomer **64b** formed in 23% yield was gelly-like. Both isomers were subjected to analytical and spectroscopic measurements.



69a,b ***cis*-64a** ***trans*-64b**

a: Lawesson-reagent, THF*, 40 °C, 15 min, rt, 4 h, 88 %.

Scheme 17: Synthesis of *cis*- and *trans*- thiocyano lactam diastereomers **64a** and **64b** [43

3.3.1 Configurational and spectroscopical analysis of *cis*- and *trans*-thiocyano lactams

The configurations of these isomers were established by NOE experiments. NMR spectra measurements were taken for both isomers **64a** and **64b** independently. Figure 15 shows the ^{1}H-NMR spectrum for **64a** with the methyl protons absorbing around 1.18ppm (4-C**H**$_3$) and 1.68ppm (5-C**H**$_3$). The two AB systems absorb around 4-C**H**$_2$ (2.83-2.68ppm) and 3-C**H**$_2$ (3.15-2.95ppm). The NOE spectra (figure 16) for **64a** reveal that the two methyl groups are in close proximity to each other. Irradiating the 4-C**H**$_3$ protons enhanced the peak signal of the 5-C**H**$_3$ protons (1.68ppm) which is shown seen clearly in the spectrum (figure 16). The peak signals for the protons that are in close vicinity were also enhanced (figure 16 and table 2) and these are 4'-C**H**$_2$b (2.72-2.68ppm) and 3-C**H**$_2$b (3.00-2.95ppm). Irradiating the 5-C**H**$_3$ protons enhanced the 4-C**H**$_3$ protons (1.18ppm) very well including the 4-C**H**$_2$b protons (2.72-2.68ppm). Figure 17 shows the NOE correlation pattern between the individual protons. The *cis*- configuration is therefore suggested for **64a**

In the case of **64b**, the ^{1}H-NMR spectrum (figure 18) showed a difference compared to **65a** in the AB system. The 3-C**H**$_2$ protons showed the AB system quartet signals (3.10-2.86ppm) but the 4-C**H**$_2$ protons appeared as a singlet (2.48ppm). With the NOE spectra (figure 19), the peak enhancement was seen with the 4-C**H**$_2$ protons which gave a pronounced peak signal when 5-C**H**$_3$ protons were irradiated. Other signals were also enhanced but not as high in intensity as the 4-C**H**$_2$ protons. The intensity of 4-C**H**$_3$ proton peak was quite low likewise that of 3-C**H**$_2$a and b protons. This means that the methyl group at C-5 is in close vicinity with 4-C**H**$_2$ than with the methyl group at C-4 position. Irradiation of the 4-C**H**$_3$ protons gave a good enhancement of the signals at 4-C**H**$_2$ and 3-C**H**$_2$b, medium at 5-C**H**$_3$ and very low for 3-C**H**$_2$a (table 3). Figure 20 shows the NOE correlation pattern between the individual protons. The *trans*-configuration would be favored more by these studies for **64b**.

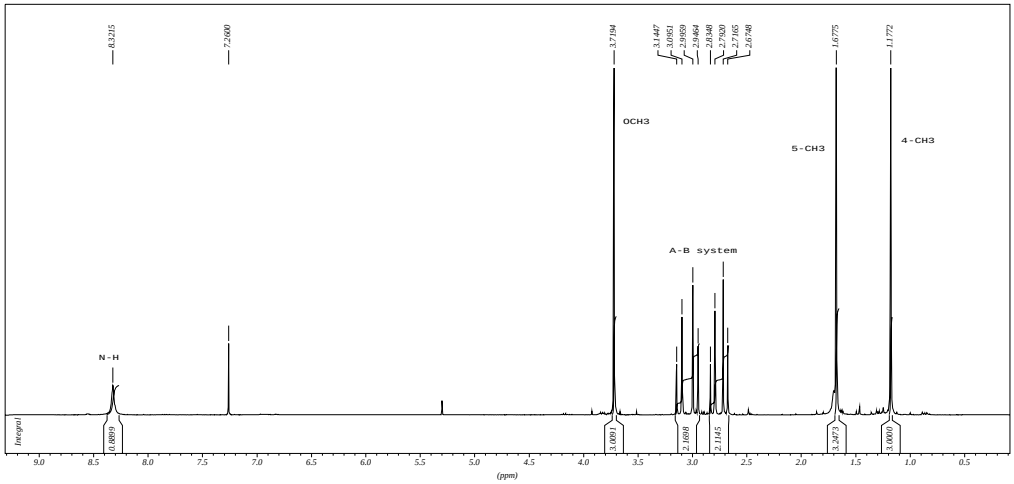


Figure 15: ^{1}H-NNMR spectrum for compound **64a**

IRRADIATION		OBSERVATION-NOE	
δ [ppm]	Assignment	δ [ppm]	Assignment
1.18	**4-CH_3**	1.68	**5-CH_3**
		3.00 / 2.95	**3-CH_2b**
		2.72 / 2.67	4'-CH_2b
1.68	**5-CH_3**	1.18	**4-CH_3**
		2.72 / 2.67	4-CH_2b

Table 2: NOE data on **64a**

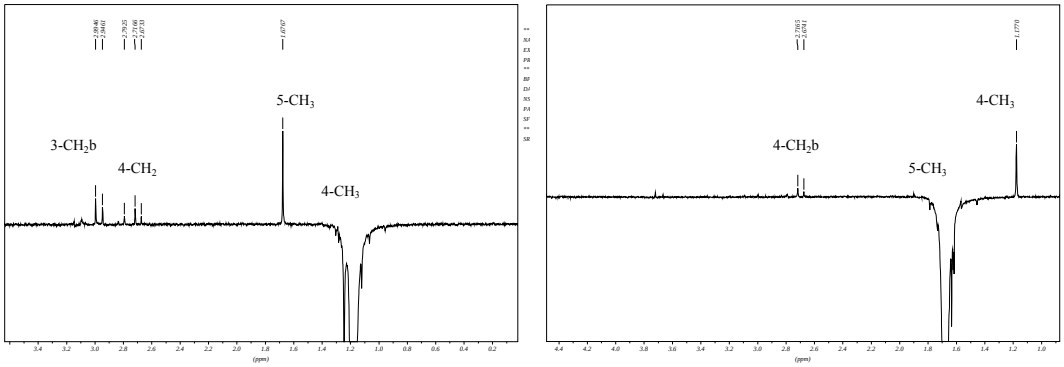


Figure 16: ^{1}H-NOE spectra for compound **64a**

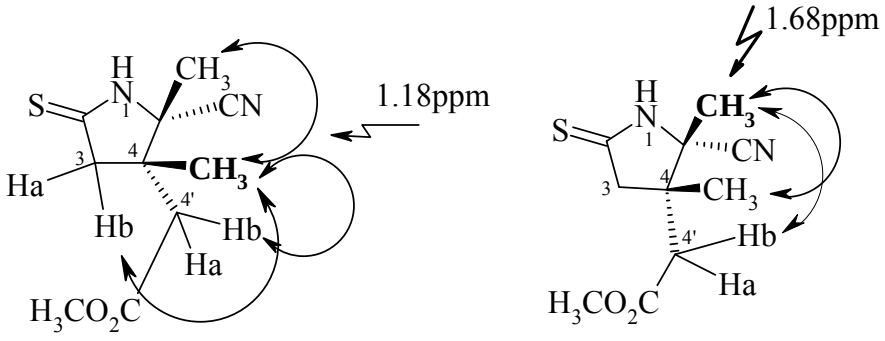


Figure 17: NOE correlation pattern of **64a** showing how the individual protons relate with each other.

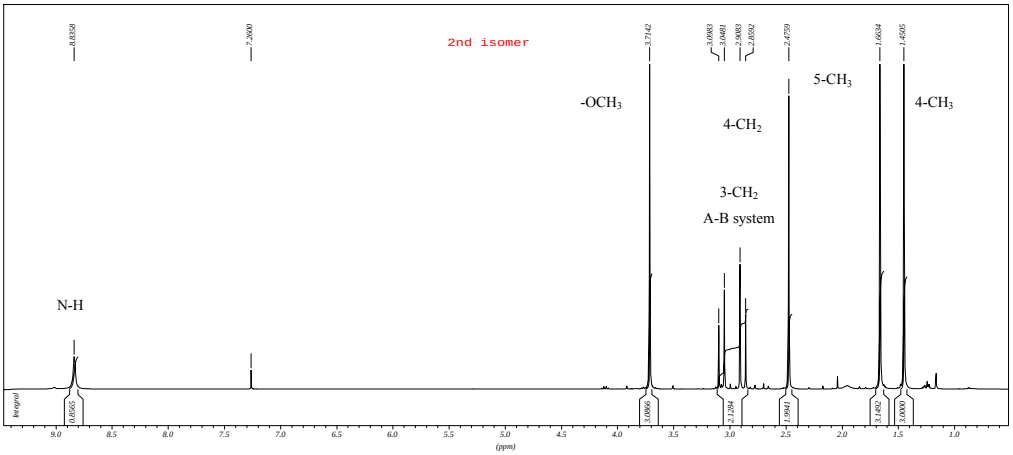


Figure 18: ^{1}H-NMR spectrum for compound **64b**

IRRADIATION		OBSERVATION - NOE	
δ [ppm]	Assignment	δ [ppm]	Assignment
1.46	**4-CH_3**	2.91 / 2.86	**3-CH_2b**
		2.48	**4'-CH_2**
		1.66	5-CH_3
1.66	**5-CH_3**	2.48	**4'-CH_2**
		2.91 / 2.86	3-CH_2b
		3.10 / 3.05	3-CH_2a
		8.32	N-H

Table 3: NOE data on **64b**

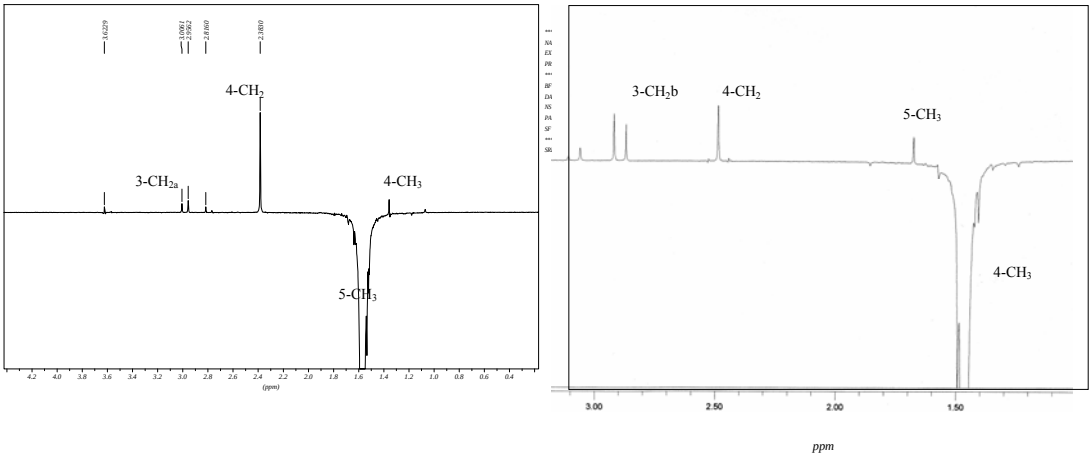


Figure 19: ^{1}H-NOE spectrum for compound **64b**

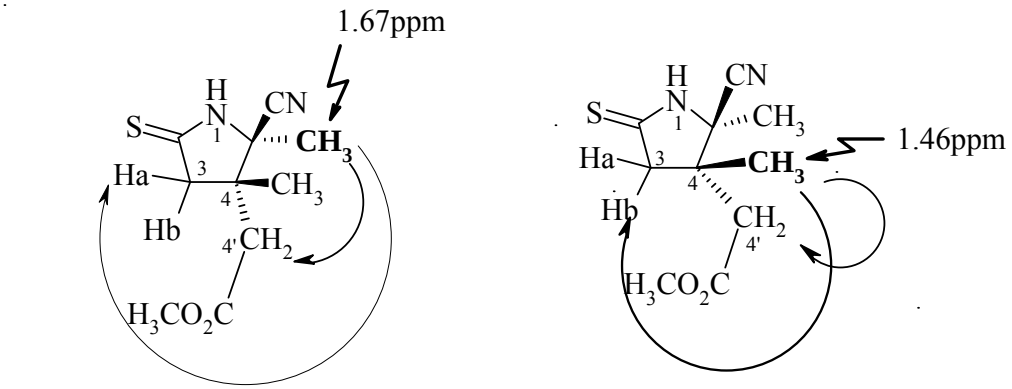


Figure 20: NOE correlation pattern of **64b** showing how the individual protons relate with each other.

An X-ray crystal structural measurement was performed only for **64a** since it formed suitable crystals. Isomer **64b** was gelly-like. Inspection of the crystal structure **64a** for which is formed as the major stereomer (figure 21) confirms that is has the *cis*-configuration. The configurations at the stereogenic centers, C-2 and C-3 are *R*- and *S*- respectively.

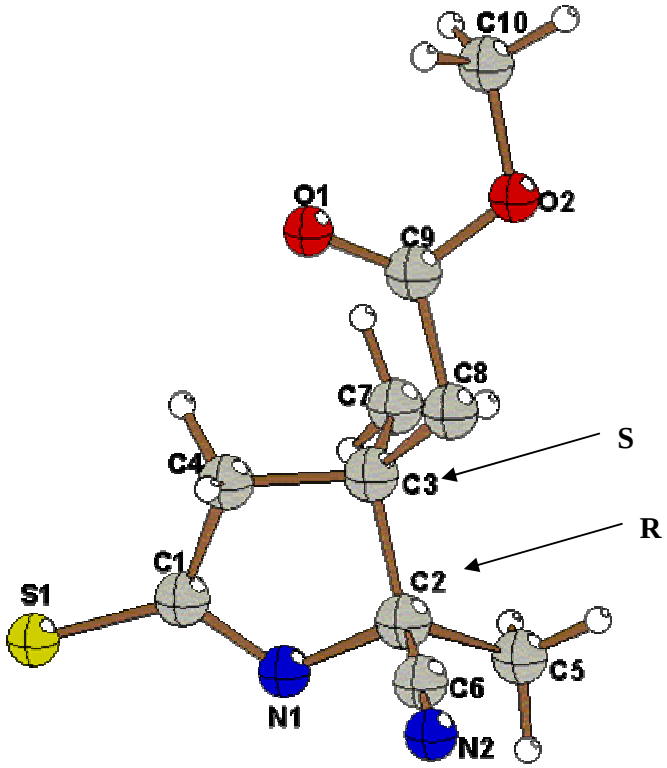


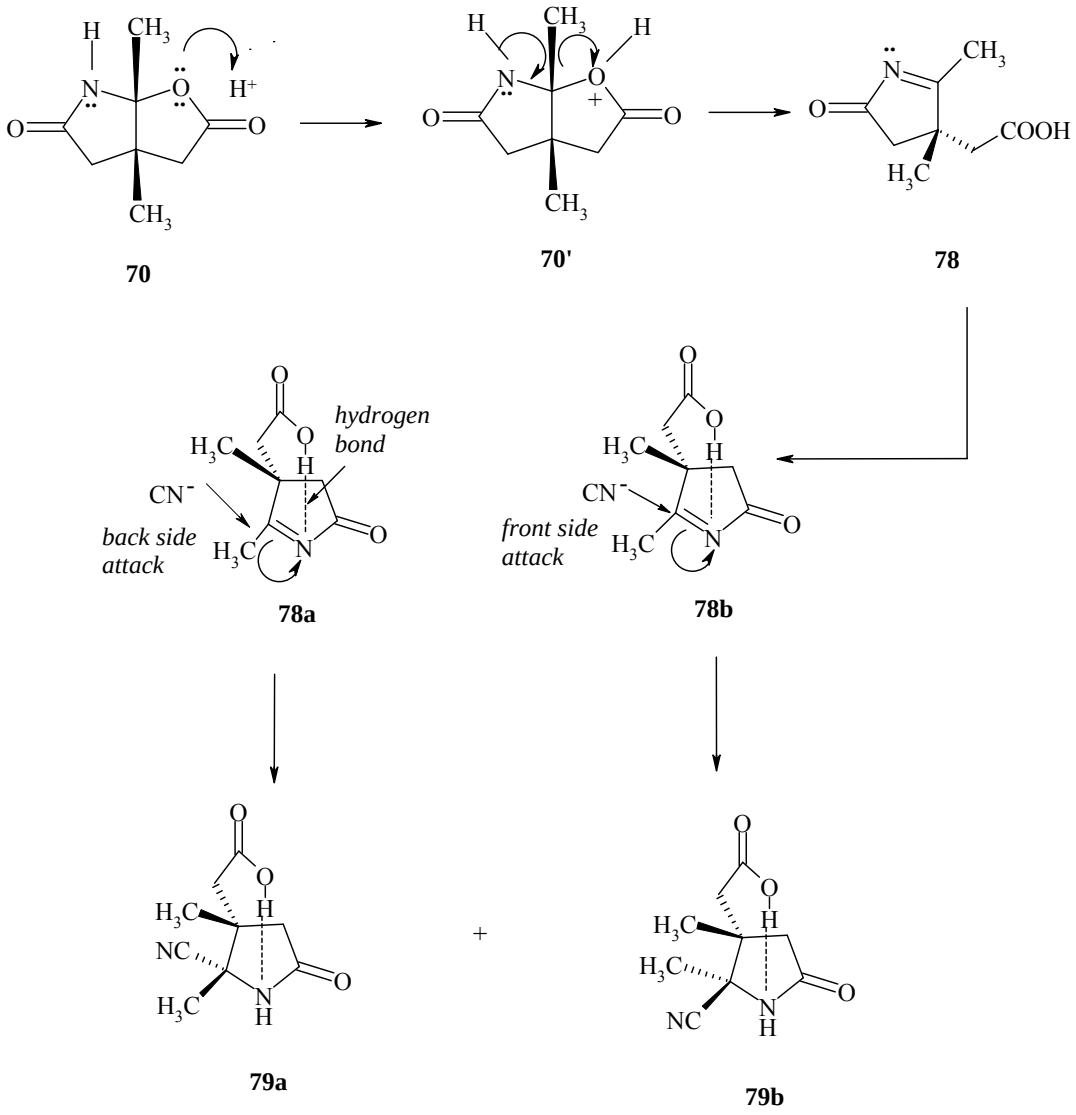
Figure 21: X-ray crystal structure of 64a

3.3.2 Theoretical analysis

Theoretical calculations were carried out to understand and to confirm why the major *cis*-product was formed. The *trans*-configuration was expected for the major product but after the NOE spectra analysis and X-ray measurement, it was clear that the major product had the *cis*-configuration. The mechanistic course of cyano lactam formation (scheme 16) is as follows: First the lactone ring of the lactam-lactone **70** is opened to form an imine carboxylic acid intermediate **78** (scheme 18). The carboxylic hydrogen of **78** could form an intramolecular H-bond with the nitrogen of the imine moiety. Secondly, the cyanide ion then attack the imine. The cyanide anion can attack the imine structure from the back side **78a** where the acetic acid substituent is located giving the *cis*-intermediate **79a** with a stronger H-bond. Alternatively, the cyanide can also attack from the front side **78b** where the 4-methyl group stands yielding the *trans*-intermediate **79b**. The transition state (TS) energies of these intermediate structures were determined by ab initio calculation[*].

From these calculation, the thermodynamical energy difference between the *trans*-intermediate **79b** (-2660 kcal/mol) and the *cis*-intermediate **79a** (-2659 kcal/mol) was calculated as only 1 kcal/mol. But at the transition states (figure 22), the *cis*-intermediate was found to have an energy of -2635 kcal/mol whereas the *trans*-intermediate with an energy of -2628 kcal/mol, was 7 kcal/mol less stable. These could explain why the major product **64a** had the *cis*-configuration.

[*] Geometry Optimization of transition state and minima on the Born-Oppenheimer surface; Semiempirical Method (PM3); HyperChem, Hypercube, Inc.



Scheme 18: Possible mechanism showing the two ways of the cyanide attack on the intermediate imine **78**

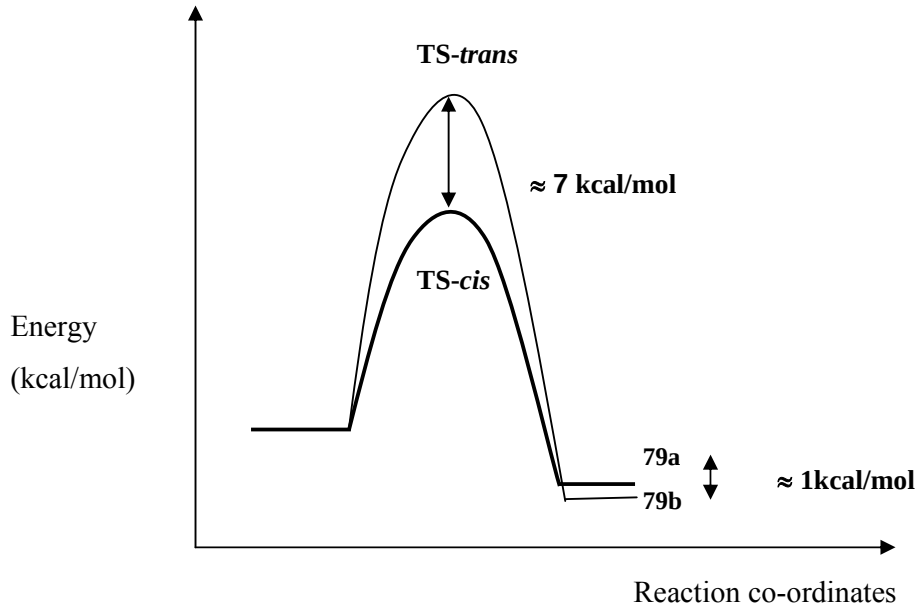
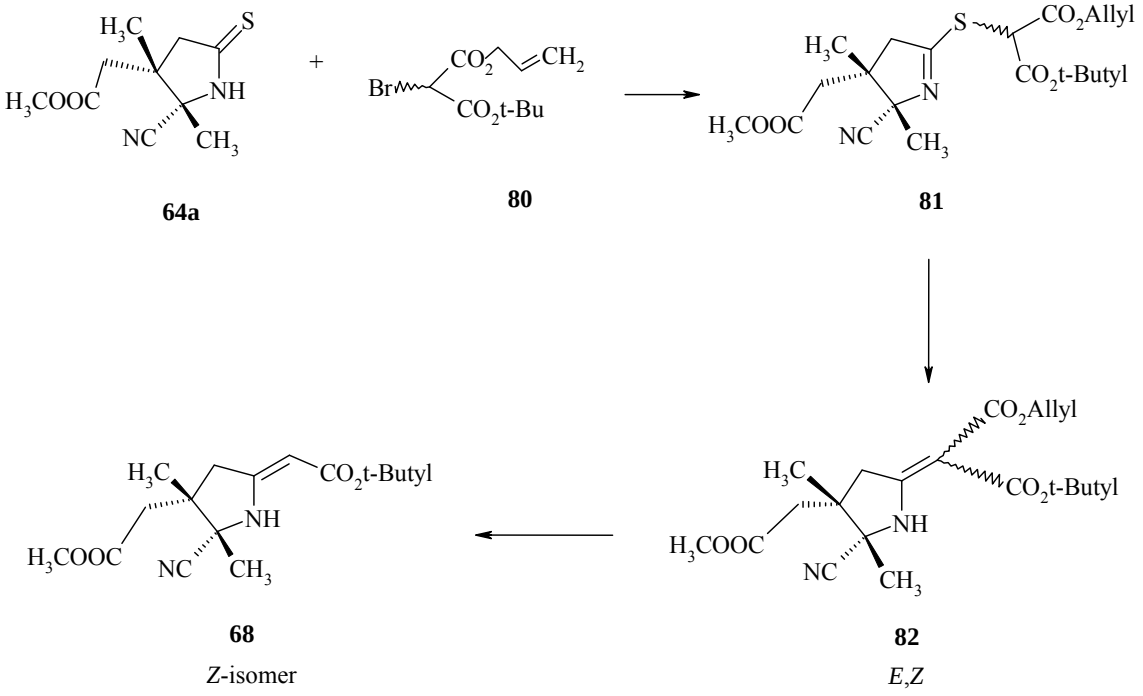


Figure 22. Energy diagram showing the transition states energy levels of the *trans*- and *cis*-intermediates

3.4 SYNTHESIS OF ENANTIOMERICALLY PURE PYRROLIDINE DIESTER

The synthesis of pyrrolidine diester **68** was carried out by coupling of *cis*-thiocyano lactam **64a** with bromomalonic diester **80** according to the sulphid contraction method [24]. This step of synthesis is necessary since coupling of ring A **64a** to ring B **65** requires a methine bridge which should be provided by the ring A.

Three steps were involved in the synthetic procedure. First step was the coupling of bromomalonic diester **80** in the presence of DBU with *cis*-thiocyano lactam **64a** giving intermediate **81**. The second step was the sulphur contraction itself [28] of the crude intermediate **81** using triethlyposphite. This gave a mixture of *E*,*Z*-intermediate **82**. Without purification and separation, *E*,*Z*-**82** was treated with tetrakis triphenylphospine palladium (0) catalyst in the presence of piperidine to remove selectively the allyl ester group forming mono-ester **68** having exclusively the Z-configuration.

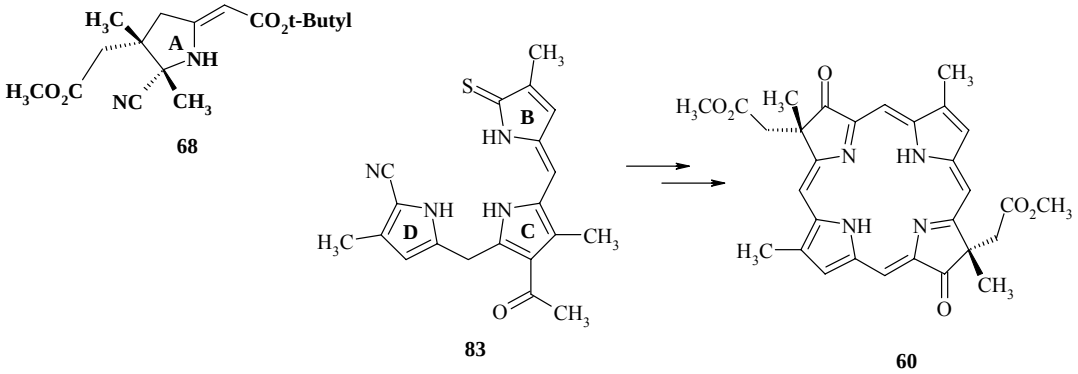


1) *rac*-**80**, DBU*, CH_3CN*, 0 °C, 20 min; 2) $P(OC_2H_5)_3$, 80 °C, 18 h; 3) Pd $[PPh_3]_4$, piperidin*, rt, 2 h, **67 %**.

Scheme 19: Synthesis of pyrrolidine diester **68**

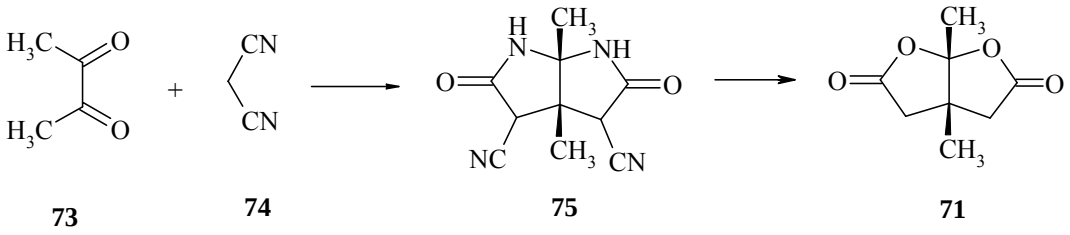
4 SYNTHETIC OVERVIEW

This research work mainly focused on the synthesis of an enantiomerically pure ring A **68** building block which should be used for the total synthesis of an enantiomerically pure tolyporphin like **60**.



Scheme 20: Coupling of enantiomerically ring A to B-C-D tricycle **83**

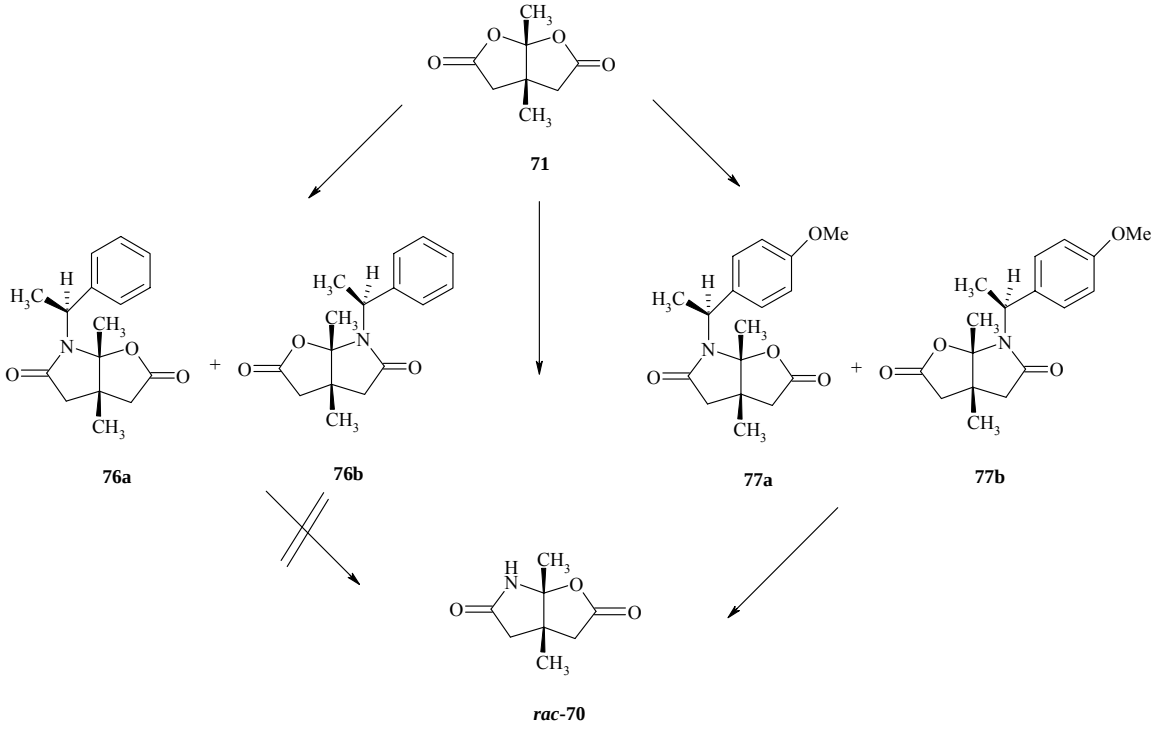
Ring A building blocks were synthesized in our research group using racemic lactam-lactone *rac*-**70** as the key building block. A modified synthetic approach was used to synthesize an enantiomerically pure lactam-lactone **70** for the ring A. Synthesis started with the preparation of bislactone **71** from malononitril and diacetyl which with sodium ethoxide catalysis formed the dinitrile dilactam **74.** On hydrolysis with hydrobromic acid, **74** yielded the desired bislactone **75**.



73 **74** **75** **71**

Scheme 21: Synthesis of bislactone **71**

Treatment of bislactone with ammonia solution resulted in a racemic lactam-lactone but if an optically active amine compound was used instead a substituted lactam-lactone was produced as diastereomeric mixture (**76a** and **76b**) which could be separated by preparative HPLC. Debenzylation of these diastereomers was not possible due to steric hinderance around the N-benzyl bond. An electron rich benzyl amine was then used in the reaction with bislactone to yield another pair of diastereomers **77a** and **77b**. After separation of this pair of diastereomers, oxidative debenzylation yielded enantiomerically pure lactam-lactones **70** and *ent*-**70**.



Scheme 22: Synthesis of N-alkylated lactam-lactone derivatives (**76a, 76b, 77a** and **77b**) and unsubstituted lactam-lactone ***rac*-70**

The diastereomers were separated and purified by HPLC and their absolute configurations were determined by CD spectroscopy and X-ray crystal analysis. Diastereomers **76a** and **77a** were found to have positive cotton effects while **76b** and **77b** exhibit negative cotton effects. X-ray crystal analysis for **76a** and **77a** showed that both have the same configurations at the stereogenic centers.

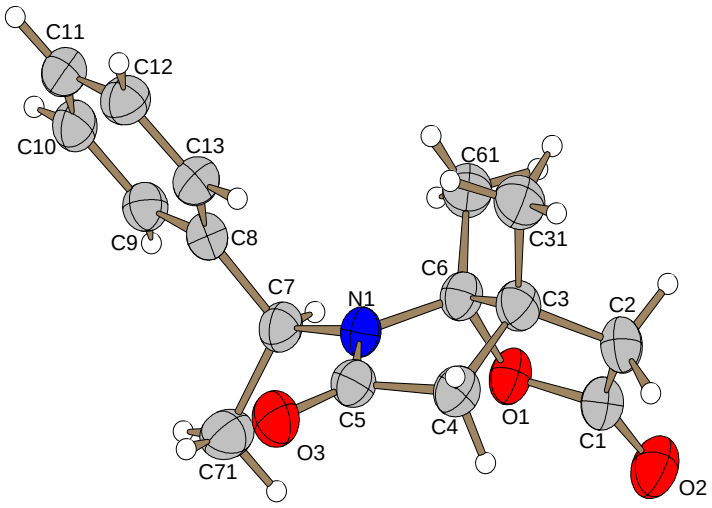


Figure 23: X-ray structure of **76a**

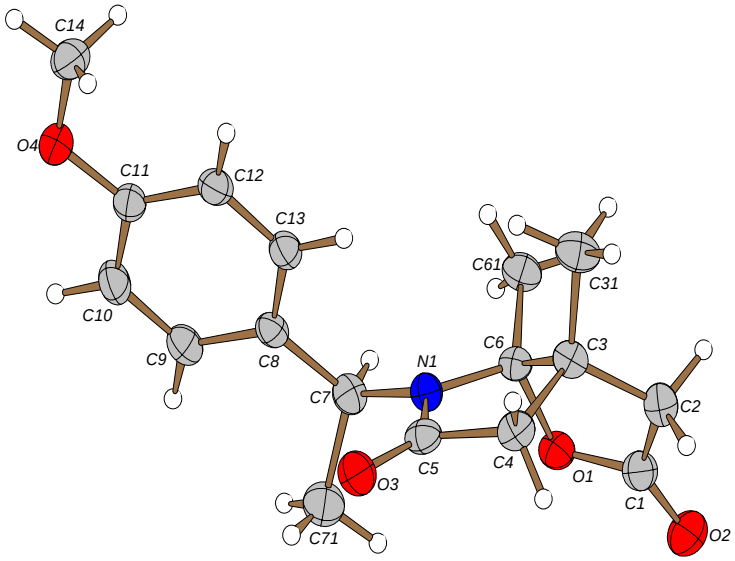
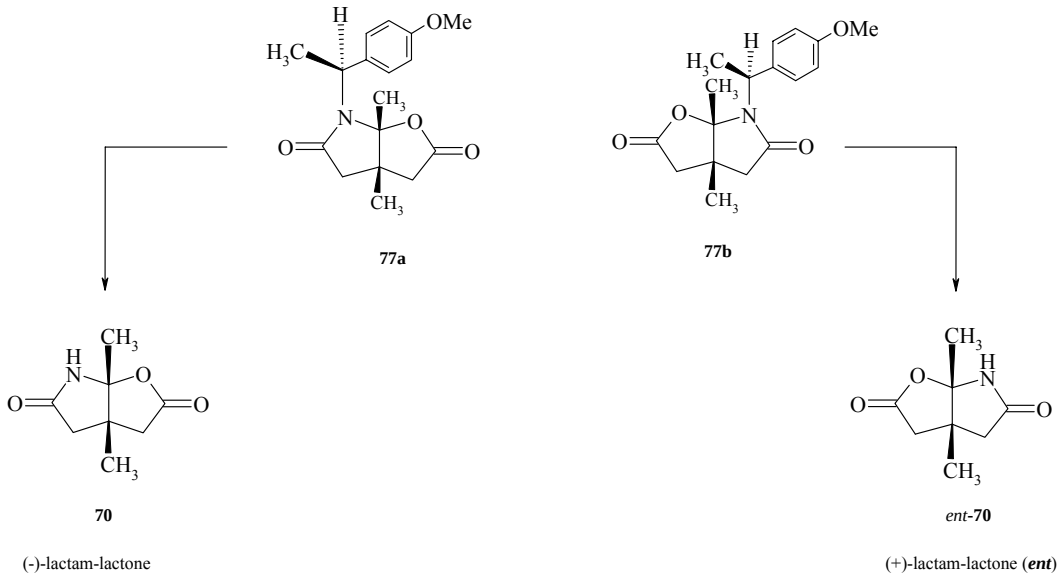


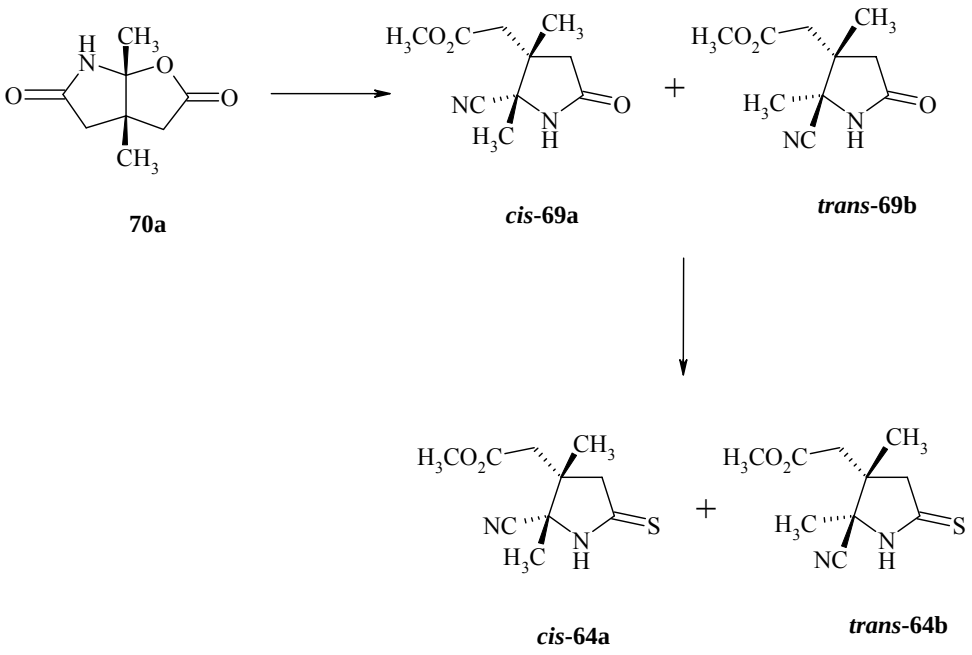
Figure 24: X-ray structure of **77a**

On a preparative scale MPLC was used to produce sufficient amounts of pure diastereomers. These were debenzylated separately into **70** and *ent*-**70** respectively.



Scheme 23: Synthesis of enantiomerically pure lactam-lactone isomers **70a** and **70b**

Enantiomer **70** was the major product from MPLC separation and was therefore treated with methanolic cyanide solution yielding a mixture of *cis*- and *trans*-cyano lactam isomers **69a** and **69b**. Without separation the mixture of isomers was sulphonated with Lawesson's reagent into a mixture of thiocyano lactam **64a** and **64b**. Separation of this mixture was possibly on a 'stepped column' (Stufensäule). Diastereomer **64a** was the major product.



Scheme 24: Synthesis of *cis*- and *trans*-thiocyano lactam **64a** and **64b**

NOE spectra measurement performed on the pure isomers revealed *cis*-configuration for **64a** and and *trans*-configuration for **64b**. An X-ray crystal analysis of **64a** confirmed it's *cis*-configuration.

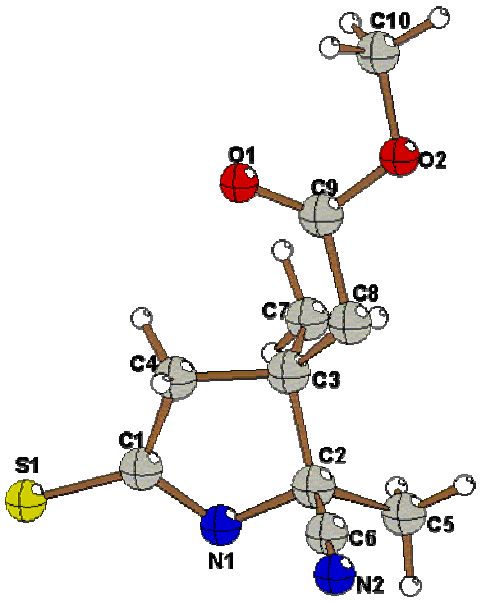
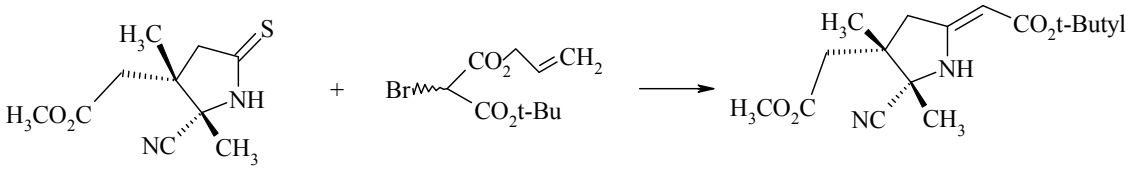


Figure 25: X-ray crystal structure for *cis*-thiocyano lactam **64a**

The transition state (TS) energies of the *cis*- and *trans*-intermediates formed during this synthesis were determined by ab initio calculations. The lowest energy transition state led to the *cis*- product.

Finally the enantiomerically pure *cis*-thiocyano lactam **64a** was coupled with bromomalonic diester **80** which underwent sulpur contraction and loss of allyl ester group to form pyrrolidine diester **68**.



64a **80** **68**

Z-isomer

Scheme 25: Synthesis of pyrrolidine diester **68**

5 EXPERIMENTAL DETAILS

5.1 GENERAL EXPERIMENTAL CONDITIONS

5.1.1 Quality of useful chemicals and solvents

Reagents and solvents:

Unless otherwise stated, all the reagents were obtained commercially from the following chemical companies, Fluka, Merck, Merck Schuchart, Lancaster, Aldrich, Janssen or Riedel de Haen. And they were used without further purification. Special pre-treated reactants or reagents used in the experiment are described in the write-up. Ethereal diazomethane was prepared from diazald (*N*-nitroso-*N*-methyl-4-toluenesulphonamide) according to the manufacturer's instructions and stored over potassium hydroxide at -20 ^{0}C.

Solvents used for the thin layer and column chromatography were distilled prior to use. Solvents and reagents marked with (*) were dried and freshly distilled under argon before use according to literature procedures mentioned as follows.

Preparation of dry solvents and /or reagents marked with (*)

Acetonitrile	dried over P_4O_{10}
Ammonia	dried over potassium hydroxide
Chloroform	dried over P_4O_{10}
DBU	dried over calcium hydride
Dichloromethane	dried over P_4O_{10}
Diethyl ether	dried over sodium
DMF	dried over calcium hydride
Ethanol	dried over calcium oxide
Methanol	dried over calcium oxide
Piperidine	Stored over molecular sieve 4 Å and freshly distilled using ‘Kugelrohr’ distillation apparatus
Pyridine	dried over calcium hydride
THF	dried over sodium / benzophenone

5.1.2 Analytical instruments

Melting points:

Melting points are uncorrected and were determined on a Reichert Thermovar hot-stage apparatus and Gallenkamp apparatus.

Nuclear Magnetic Resonance Spectroscopy NMR (^{1}H and ^{13}C-NMR, 1D-COSY, DEPT-135, HSQC, HMBC, and NOE experiments):

NMR spectra were recorded on a Bruker-Daltonik DPX-200, AM-360 or DRX-600 spectrometer in the deuteriated solvent indicated in each case, in an NMR tube of 5mm in diameter. The "lock in" was done on the solvent signal. All chemical shifts (δ) were quoted in parts par million (ppm) and were referenced to the deuterium lock signal. The following abbreviations were used to describe the signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal etc.; the coupling constants (^{x}J, where x = number of bonds between the coupling nuclei) refer to ^{1}H-^{1}H couplings; the designation of the spin systems took place after the usual convention.

Mass Spectrometry (MS):

The MS measurements were done using double focusing sector field mass spectrometers MAT 8200 and MAT 95 respectively of the company Finnigan MAT, Bremen. The samples were measured done by direct inlet method. With the electron-impact ionization (EI) method, the electron energy was 70 eV and the source temperature, if not differently indicated, was 200 °C. With the direct chemical ionisation (DCI), ammonia gas was used as the reactant gas. The current filament of the DCI thread was increased linearly with a heating rate of 8 mA/s. The mass spectra were continuously registered. The best molecular groups were determined by analysis of the mass spectra.

Highly Resolution-Mass Spectrometry (HR-MS):

The determination of the accurate mass took place at the double focusing sector field mass spectrometers MAT 8200 and MAT 95 respectively by the Finnigan MAT company, Bremen according to the ‘peak matching’ method. Perfluorkerosine (PFK) was used as reference substance. The resolution R at which the ‘peak-matching’ was done was stated.

Infrared Spectroscopy (IR):

Infrared spectra were recorded on a Perkin-Elmer Paragon 500 FT-IR. Liquids were run as films on NaCl plates and solids as KBr discs. The relative intensity of the bands are characterised as s (strong), m (middle) and w (weak).Only the characteristic peaks are quoted in cm^{-1}.

Ultraviolet spectroscopy (UV/VIS):

The measurements were taken on a Cary 50 spectrophotometer by the Varian Company. Concentration of the samples is approximately 10^{-5} molar solution in the solvent, λ_{max} = maximum absorption, sh = shoulder

Polarimeter:

Optical rotation were measured with a Perkin-Elamer 243 polarimter with a water-jacket cell length of 1 dm. The concentration were quoted in g/ml. The optical rotations were given in units of degree (^{o}).

CD Spectroscopy:

The CD spectra were taken on JASCO J-600 spectropolarimeter at a temperature of 20 ^{o}C using solutions of the products in methanol with concentrations between 2.1x 10^{-4} to 1.9x10^{-4}M. The molar ellipticity [Θ] was computed according to the following formula:

$$[\Theta] = \frac{\Theta \text{ Mwt}}{100\, l\, .c}$$

where Θ(λ) = ellipticity

c = concentration (mg/l)

l = **cell** length (cm)

Mwt = molecular weight

5.1.3 Chromatography

Thin Layer Chromatography (TLC):

This was performed on precoated plates with the following specifications; silica gel 60 F_{254}, 20 x 20 cm, layer thickness 0.2 mm by Riedel de Haen and Fluka. Spots on the sheets were visualized by UV lamp 254 nm or in iodine chamber.

Flash Chromatography:

Flash chromatography was done on silica gel 32 - 63 µm 60 Å (ICN Biomedicales); Packing of the column was by the Slurry method with pressure; the separation took place with normal pressure or with slightly high pressure.

Column Chromatography:

Purification of compounds were carried out by column chromatography on silica gel 32 - 63 µm 60 Å (ICN Biomedicales). Packing of the column was by the slurry method using the solvent system.

High Performance Liquid Chromatography (HPLC):

Knauer HPLC instrument with pump 64, two-channel potentiometer BBC Metrawatt Servogor 120 recorder and UV-spectrometer from Knauer was used. The appropriate data was given in the following sequence: stationary phase, mobile phase, and flow rate and detection method.

Medium Pressure Liquid Chromatography (MPLC):

MPLC separation was carried out on a set up which consist of an HPLC Knauer pump 64, Büchi 660 fraction collector, a solvent tank and a column (49 x 460mm) containing matrex silica 20-45µm 60 Å as the stationary phase. The column was filled the matrex silica using the dry-filling method under nitrogen pressure and it was conditioned with the solvent system before sample injection.

5.1.4 Formulae and Abbreviations

The used abbreviations are general and accepted by the *Gesellschaft Deutscher Chemiker* (GDCh) published in *Angewandte Chemie.* [Instruction for authors, *Angew. Chem*. **2000**, 112, 19-23] Other abbreviations used are mentioned below:

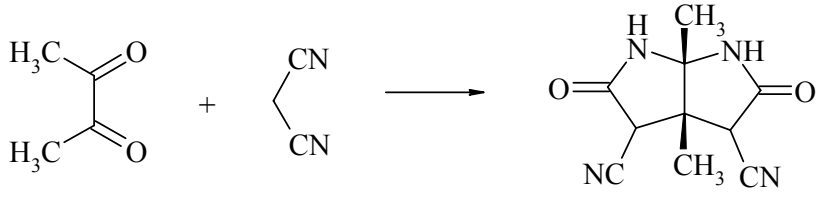
com.	computered
BRN	Beilstein-Registration Number
Bzl	benzyl
CAS-Nr.	CAS Registration number
CH_2Cl_2	Dichloromethane
DBU	1,8-diazabicyclo [5.4.0] undec-7-ene
decom.	decomposition
DMF	*N*, *N*-dimethylformamid
EtOAc	ethyl acetate
ether	diethyl ether
eq	equivalent(s)
Lit.	Literature
MeOH	Methanol
Pet. ether	Petroleum ether
rel.	relative
sat.	saturated
sol.	solution
THF	tetrahydrofuran
Th.	theoretical
TEA	triethylamine

References to the CAS and BRN numbers:

The respective numbers are indicated at the end of the analytic data of a substance. If no number is noted, then the substances were at the time of the literature search of 25.05.2004 not in the MDL Beilstein Crossfire Commander V6 (version 5.0, data base BS 0302). -

5.2 SYNTHESIS OF ENANTIOMERICALLY PURE LACTAM-LACTONE 70

5.2.1 Synthesis of 1,5-dimethyl-3,7-dioxo-2,8-diaza-*cis*-bicyclo[3.3.0]octan-4,6-dinitril (75) [25, 26]



73 **74** **75**

$C_4H_6O_2$ $C_3H_5N_2$ $C_{10}H_{10}N_4O_2$

86.09 66.06 218.22

A solution of 2.3 g (100 mmol) of sodium in 250 ml ethanol* was prepared at 0 °C under argon atmosphere after which a solution of diacetyl **73** (8.6 g, 100 mmol) and malononitril **74** (13.2 g, 200 mmol) in 100 ml ethanol* was added dropwise from a dropping funnel with stirring at 0 °C. The resulting solution was stirred for 4 hours under argon atmosphere and at a temperature below 5 °C. After 4 hours of reaction, the reaction mixture was acidified with concentrated HCl solution until pH 1. The product **75** precipitated out and this was left for 1 hour. The reaction mixture was filtered by suction and the precipitate (dinitrile dilactam) was washed with enough water. The dinitrile dilactam **75** was dried and analyzed spectroscopically.

Yield: 6.89 g (32 mmol, 32 % Th.).-

Melting point: >220°C (decom.).-

IR (KBr): $\tilde{\nu}$ = 3312 cm^{-1} (s, >N-H), 3235 (m), 2986 (w, C-H), 2910 (s, C-H), 2257 (s, -CN), 1750 (s, 5-ring-lactam), 1705 (s, 5-ring-lactam), 1626 (s), 1470 (m), 1469 (m), 1430 (s), 1390 (s, $-CH_3$), 1345 (s), 1286 (s), 1250 (w), 1196 (m), 1152 (s), 1116 (m), 1100 (w), 1030 (m), 965 (w), 915 (w), 890 (w), 780 (w), 725 (m), 710 (s), 685 (m), 650 (m).-

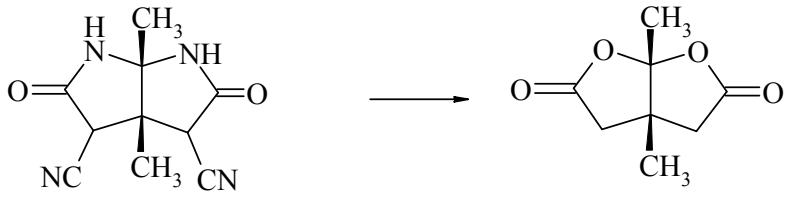
^{1}H-NMR (200 MHz, d_6-DMSO): δ = 1.29 (s, 3H, C-5-C**H**$_3$), 1.33 (s, 3H, C-1-C**H**$_3$), 4.50 (s, 1H, >C**H**CN), 4.89 (s, 1H, >C**H**CN), 9.19 (s, 1H, N**H**), 9.32 (s, 1H, N**H**).-

MS (EI, 70 eV, direct inlet): m/z (% relative intensity) = 218 (2) [M^+], 217 (2) [M^+-H], 203 (3) [M^+-CH_3], 176 (10), 175 (93), 160 (24), 148 (6), 147 (22), 136 (8), 135 (19), 134 (19), 121 (3), 111 (7), 110 (36), 109 (16), 108 (12), 107 (8), 106 (14), 105 (10), 94 (45), 93 (11), 92 (5), 91 (6), 84 (6), 81 (6), 80 (8), 79 (9), 78 (10), 77 (5), 68 (19), 67 (31), 66 (17), 65 (13), 64 (13), 63 (8), 53 (9), 52 (12), 51 (9), 44 (51), 43 (14), 42 (100), 41 (33), 40 (22), 39 (22), 38 (15), 37 (7).-

BRN: 918679.-

CAS-NR: 57825-21-5, 125276-45-1.-

5.2.2 Synthesis of 1,5-dimethyl-2,8-dioxa-*cis*-bicyclo[3.3.0]octan-3,7-dion (71) [25, 26]



75

$C_{10}H_{10}N_4O_2$

218.22

71

$C_8H_{10}O_4$

170.17

Aqueous hydrogen bromide solution (48%, 250 ml) was heated and 4.4 g (20 mmol) of dinitrildilactam **75** was carefully added. This was refluxed for 45 minutes after which the HBr solution was distilled out under reduced pressure leaving a gelly-like residue. The residue was allowed to cool down and washed 4 times, each time with 50 ml CH_2Cl_2. The CH_2Cl_2 extract was filtered, dried over cotton wool and concentrated *in vacuo*. The crude product was purified by the column chromatography on 60 g silica gel with CH_2Cl_2 / MeOH (95+5) as solvent system. The bislactone **71** crystallizes out as a colorless crystal and this was subjected to spectroscopic analysis.

Yield: 2.04 g (12.0 mmol, 60% Th.).-

Melting point: 128 °C ($CHCl_3$/n-Pentane).-

TLC [silica gel, CH_2Cl_2/MeOH (95+5)]: R_f = 0.78.-

IR (KBr): $\tilde{\nu}$ = 2993 cm^{-1} (s, C-H), 2955 (s, C-H), 2935 (s, C-H), 1795 (s, C=O, lactone), 1780 (s, C=O, lactone), 1641 (w), 1552 (w), 1540 (w), 1470 (m), 1420 (m), 1394 (s), 1280 (s), 1265 (s), 1220 (m), 1170 (m), 1140 (m), 1115 (m), 1080 (s), 980 (m), 935 (s), 900 (s), 870 (m), 860 (m), 730 (m), 710 (m), 670 (w), 640 (m), 610 (m), 600 (m), 535 (w), 505 (w), 480 (w).-

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.39 ppm (s, 3H, C-5-C**H**$_3$), 1.71 (s, 3H, C-1-C**H**$_3$), 2.71 (AB-System, 4H, 2x -C**H**$_2$-).-

^{13}C-NMR (200 MHz, $CDCl_3$): δ = 18.06 ppm (C-5-**C**H_3), 19.60 (C-1-**C**H_3), 40.27 (**C**-5), 43.53 (2x -**C**H_2-), 113.56 (**C**-1), 170.12 (2x >**C**=O).-

MS (EI, 70 eV, direct inlet): m/z (% relative intensity) = 171 (24) [M^++H], 127 (14) [M^+-CO_2], 126 (13) [M^+-CO_2], 113 (16), 111 (13), 100(26), 99 (5), 98 (30), 83 (15), 82 (7), 72 (4), 69 (17), 56 (14), 55 (73), 54 (16), 53 (3), 44 (100), 43 (7), 42 (62), 41 (69), 40 (15), 39 (2), 38 (11), 29 (8), 28 (3), 27 (8). -

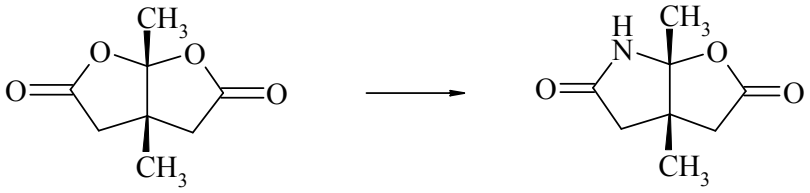
MS (DCI negative, NH_3, 8 mA/s): m/z (% relative intensity) = 170 (13) [M^-], 169 (100) [M-H]$^-$, 124 (11).-

MS (DCI positive, NH_3, 8 mA/s): m/z (% relative intensity) = 359 (18), 358 (80), 327 (42), 326 (88), 316 (22), 206 (16), 205 (87) [M+$N_2H_7^+$], 190 (27), 189 (88), 188 (100) [M+NH_4^+], 171 (21) [M+H^+], 170 (10) [M^+] , 130 (36), 126 (10), 98 (54), 83 (10), 69 (22).-

BRN: 1366316.-

CAS-NR: 57825-22-6, 100378-81-2.-

5.2.3 Synthesis of (1*RS*,5*SR*)-1,5-dimethyl-2-oxa-8-aza-*cis*-bicyclo[3.3.0] octan-3,7-dion (*rac*-70) [25, 26]



71

$C_8H_{10}O_4$

170.17

rac-**70**

$C_8H_{11}NO_3$

169.18

A suspension of 1.53 g (9 mmol) bislactone **71** in 45 ml aqueous ammonia solution (25 %) was prepared at ambient temperature under argon atmosphere. A solution was formed after some time during stirring which continued for the next 24 hours at room temperature. The reaction mixture was concentrated under reduced pressure after which the crude yellowish material was purified by column chromatography over 70 g silica gel using CH_2Cl_2/MeOH (95+5) as solvent system. The product came as colorless racemic crystals *rac*-**70**.

Yield: 1.31 mg (7.75 mmol, 86 % Th.).-

Melting point: 190 °C ($CHCl_3$/n-Pentane).-

TLC [silica gel, CH_2Cl_2/MeOH (95+5)]: R_f = 0.52.-

IR (KBr): $\tilde{\nu}$ = 3212 cm^{-1} (s, N-H), 3109 (s), 2975 (s, C-H), 2969 (s, C-H), 2854 (s, C-H), 1779 (s, C=O, lactone), 1698 (s, C=O, lactam), 1443 (m), 1407(w), 1390 (s), 1369 (s), 1302 (m), 1290 (w), 1240 (s), 1213 (s), 1116 (s), 1150 (w), 1115 (s), 1065 (s), 1000 (w), 952 (w) 914 (s), 895 (s), 849(m), 805 (w), 790 (m), 735 (m), 700 (s), 635 (w), 610 (s), 595 (m), 565 (w), 530 (w).-

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.35 ppm (s, 3H, C-5-C**H**$_3$), 1.62 (s, 3H, C-1-C**H**$_3$), 2.36-2.82 (2AB-Systems[1] , 4H, 2x –C**H**$_2$-), 6.41(s, br, 1H, N**H**).-

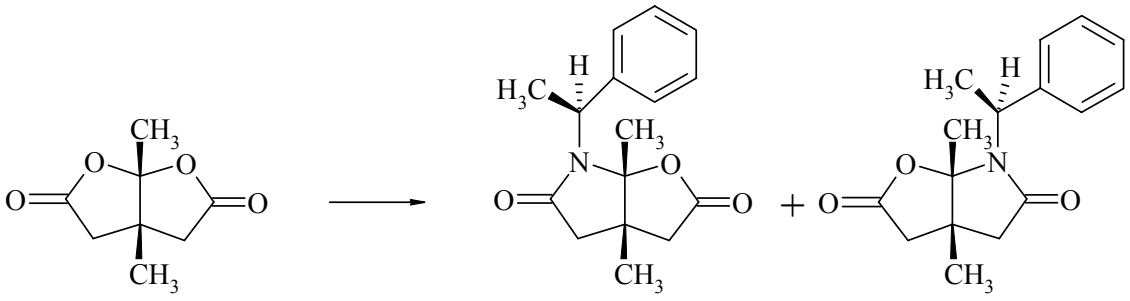
[1] The 2 AB-Systems are from both enantiomers

MS (EI, 70 eV, direct inlet): m/z (% relative Intensity) = 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).-

BRN: 4937697.-

CAS-NR: 57825-28-2.-

5.2.4 Synthesis of (1*R*,5*S*,1'*S*)-1,5-dimethyl-8-phenyl ethyl-2-oxa-8-aza-*cis*-bicyclo[3.3.0]octan-3,7-dion (76a) and (1*S*,5*R*,1'*S*)-1,5-dimethyl-8-phenyl ethyl-2-oxa-8-aza-*cis*- bicyclo[3.3.0]octan-3,7-dion (76b) [25]



71

$C_8H_{10}O_4$

170.17

76a

$C_{16}H_{19}NO_3$

273.33

76b

$C_{16}H_{19}NO_3$

273.33

A solution of 340 mg (2 mmol) bislactone **71** and 4 ml chloroform* was prepared under argon atmosphere at room temperature. The reaction was stirred for some time after which 242 mg (2 mmol) (S)-(-)-phenyl ethylamine was added. Stirring continued at room temperature under argon atmosphere for 20 hours. Thin layer chromatography was used to monitor the reaction until almost all the bislactone had been consumed. Saturated solution of NaCl (10 ml) was added to the reaction mixture and 20 ml each of CH_2Cl_2 was used to extract the product three times. The CH_2Cl_2 extract was dried over cotton wool and the solvent was removed *in vacuo*. The product was purified by column chromatography on 50 g silica gel (CH_2Cl_2/MeOH [95+5]). A mixture of diastereomers **76a** and **76b** was obtained in colorless crystal form. These were separated by preparative HPLC and subjected to spectra analysis. CD spectra and x-ray crystal measurement were taken to determine the absolute configurations.

Yield: 450 mg (1.65 mmol, 82 %).-

TLC: [silica gel, CH_2Cl_2/MeOH (95+5)]: R_f = 0.75.-

UV/VIS (Methanol): λ_{max} (rel. intensity) = 258 nm (0.02), 205 (0.84).-

IR (KBr): $\tilde{\nu}$ = 3005 cm^{-1} (s), 2990 (s, C-H), 2945 (m, C-H), 2910 (m, C-H), 2875 (m), 1780 (s, C=O, lactone), 1710 (s, C=O, lactam), 1540 (w), 1495 (m), 1460 (m), 1420 (s), 1395 (s), 1375 (m), 1350 (s), 1305 (s), 1290 (m), 1235 (s), 1195 (s), 1145 (w), 1105 (m), 1080 (m), 1055 (s), 1010 (m), 950 (w), 900 (s), 850 (m), 830 (w), 795 (w), 780 (m), 760 (s), 725 (w), 700 (s), 670 (m), 650 (w), 640 (w), 620 (w), 580 (m), 540 (m), 515 (w), 505 (w).-

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.22 ppm (s, 3H, C-1-C**H**$_3$) [2], 1.30 (s, 6H, C-5-C**H**$_3$), 1.52 (s, 3H, C-1-C**H**$_3$), 1.78-1.82 (d, ^3J = 6.36 Hz, 3H, CH-C**H**$_3$), 1.82-1.86 (d, ^3J = 6.41 Hz, 3H, CH-C**H**$_3$), 2.36-2.80 (m, 8H, C-4-C**H**$_2$, C-6-C**H**$_2$), 4.71 (q, ^3J = 6.38 Hz, 1H, C**H**-CH_3), 5.27-5.38 (q, ^3J = 6.38 Hz, 1H, C**H**-CH_3), 7.34 (m, 10H, C_6**H**$_5$).-

MS (EI, 70 eV, direct inlet): m/z (% relative intensity) = 274 (27) [M^++H], 273 (55) [M^+], 161 (43), 160 (57), 146 (65), 132 (12), 125 (18), 120 (17), 119 (7), 111 (16), 110 (36), 106 (25), 105 (100), 104 (48), 103 (22), 91 (7), 83 (11), 82 (7), 79 (25), 78 (16), 77 (40), 69 (6), 56 (5), 55 (29), 54 (5), 53 (12), 51 (13), 44 (4), 43 (65), 42 (15), 41 (5), 40 (23).-

HS-MS $C_{16}H_{19}NO_3$ Calculated 273.13649
Founded. 273.136889 (R = 1000).-

Spectroscopic data for (1*R*,5S,1´*S*)-1,5-dimethyl-8-phenyl ethyl-2-oxa-8-aza-*cis*-bicyclo [3.3.0] octan-3,7-dion (76 a)

Melting Point: 162.3 °C.-

Optical rotation: $[\alpha]_D^{20}$ = +00.650 (c = 0.004/ml in MeOH).-

TCL [Silica gel, CH_2Cl_2 / EtOAc (9+1)]: R_f = 0.61.-

HPLC: Nucleosil 50-10 Si, Pet. ether / EtOAc (50+50), 1.5 ml/min., detector UV 254 nm, t_R = 8 min. 48 sec.-

[2] Diastereomeic mixture was measured.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.29 ppm (s, 3H, C(1)-C**H**$_3$), 1.51 (s, 3H, C(5)-C**H**$_3$), 1.82-1.85 (d, ^3J = 6.95 Hz, 3H, CH-C**H**$_3$), 2.35-2.77 (2x AB-System, 4H, C(4)-C**H**$_2$, C(6)-C**H**$_2$), 4.4.66-4.77 (q, ^3J = 6.95 Hz, 2H, C**H**-CH_3), 7.34 (m, 5H, C_6**H**$_5$).-

CD (MeOH): c = 0.05713 mg/ml, λ_{max} (Θ) = 295 nm (2.9355), 285 (2.9631), 217 (13.9636).-

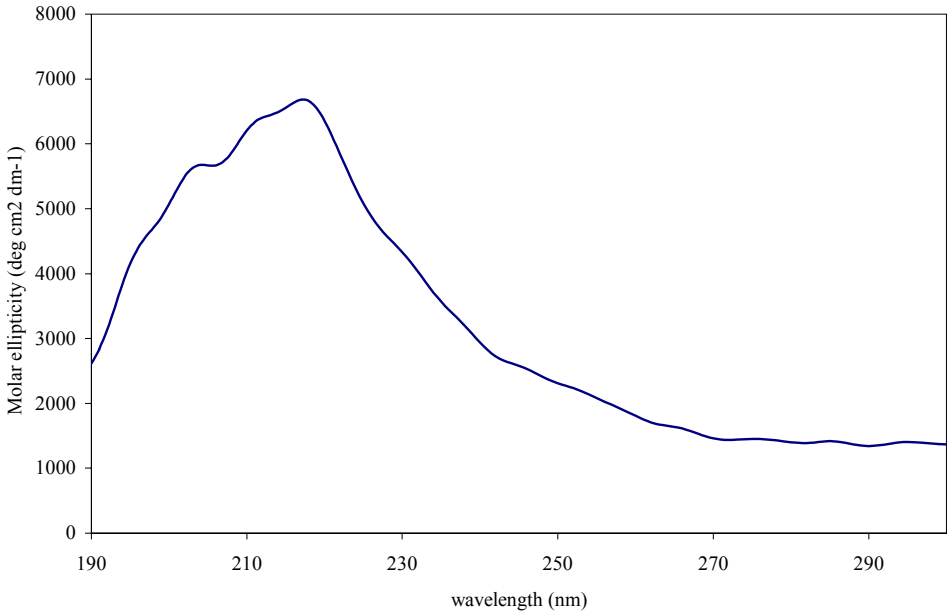


Figure 26: CD spectrum for (1*R*,5*S*,1'*S*)1,5-dimethyl-8-phenyl ethyl-2-oxa-8-aza-*cis*-bicyclo bicyclo [3.3.0]octan-3,7-dion (**76a**)

Spectroscopic data for (1*S*,5R,1´*S*)-1,5-dimethyl-8-phenyl ethyl-2-oxa-8-aza-*cis*-bicyclo [3.3.0] octan-3,7-dion (76b)

TLC [Silica gel, CH_2Cl_2 / EtOAc (9+1)]: R_f = 0.55.-

Melting Point : 145 °C.-

Optical rotation: $[\alpha]_D^{20}$ = -00.601 (c = 0.004/ml in MeOH).-

HPLC: Nucleosil 50-10 Si, Pet. ether/ EtOAc (50+50), 1.5 ml/min., detector UV 254 nm, t_R = 10 min.-

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.22 ppm (s, 3H, C(1)-C**H**$_3$), 1.30 (s, 3H, C(5)-C**H**$_3$), 1.78 (d, ^3J = 6.41 Hz, 3H, CH-C**H**$_3$), 2.38 - 2.68 (2x AB-System, 4H, C(4)-C**H**$_2$, C(6)-C**H**$_2$), 5.27-5.38 (q, ^3J = 6.41 Hz, 1H, C**H**-CH_3), 7.34 (m, 5H, C_6**H**$_5$).-

CD (MeOH): c = 0.0552 mg/ml, λ_{max} (Θ) = 299 nm (-0.2934), 296 (-0.5581), 289 (-0.6499), 282 (-0.6533), 273 (-0.3416), 267 (-0.6947), 255 (-0.4933), 240 (-2.8553), 221 (-24.5888), 203 (-1.9208), 197 (-10.4385), 193 (-3.2199), 190 (-6.6783).-

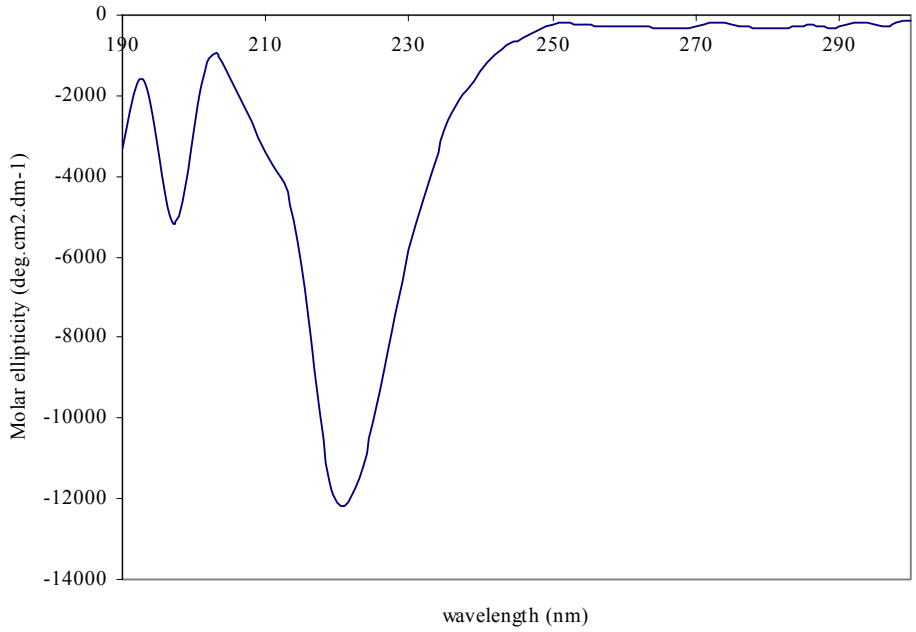
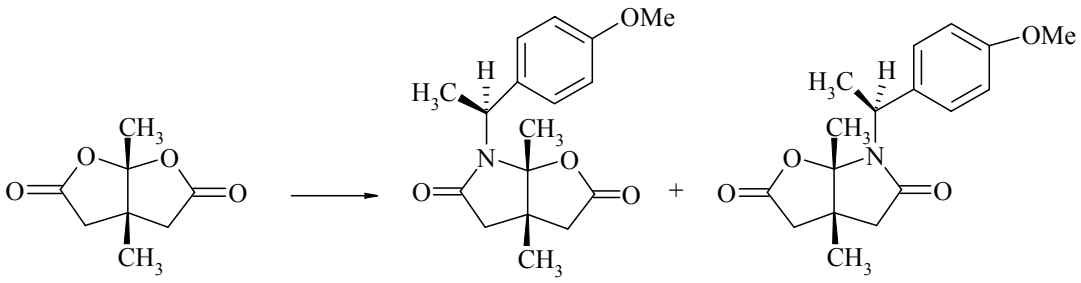


Figure 27: CD spectrum for (1*S*,5R,1'S) 1,5-dimethyl-8-phenyl ethyl-2-oxa-8-aza-*cis* bicyclo[3.3.0]octan-3,7-dion (**76b**)

5.2.5 Synthesis of (1*R*,5*S*,1'*S*)1,5-dmethyl-8-(4-methoxyphenyl) ethyl-2-oxa-8-aza-*cis*-bicyclo[3.3.0]octan-3,7-dion (77a) and (1*S*,5*R*,1'*S*)1,5-dmethyl-8-(4-methoxyphenyl)ethyl-2-oxa-8-aza-*cis*-bicycle[3.3.0]octan-3,7-dion (77b)



71	**77a**	**77b**
$C_8H_{10}O_4$	$C_{16}H_{19}NO_3$	$C_{16}H_{19}NO_3$
170.17	303.33	303.33

A solution of 340 mg (2 mmol) bislactone **71** in 10 ml chloroform* was prepared at room temperature and under argon atmosphere. To this solution was added 302 mg (2 mmol) of (S)-(-)-(4-methoxyphenyl) ethylamine and the reaction stirred for 20 hours at room temperature under argon atmosphere. The reaction was monitored with TLC until almost all the bislactone was consumed. Saturated solution of NaCl (10 ml) was added to the reaction mixture and 20 ml each of CH_2Cl_2 was used to extract the product three times. The bulked CH_2Cl_2 extract was dried over cotton wool and the solvent was removed under reduce pressure. The product was purified by column chromatography on 50 g silica gel (CH_2Cl_2/EtOAc [95+5]). A mixture of diastereomers **77a** and **77b** was obtained as colorless crystals. MPLC was then used to further separate this diastereomeric mixture into pure forms and the chromatography fractions were analyzed by HPLC. The fractions were combined conveniently, concentrated and recrystalized from ethyl acetate into pure colorless crystals, **77a** and **77b** respectively. These pure diastereomers **77a** and **77b** were characterized by spectra analysis.

Yield: 424 mg (1.4 mmol, 70 %).-

TLC [silica gel, CH_2Cl_2/EtOAc (95+5)]: $R_f = 0.75$.-

UV/VIS (MeOH): λ_{max} (rel. intensity) = 275 nm (0.13), 227 (1.06), 203 (1.05).-

IR (KBr): $\tilde{\nu}$ = 3005 cm^{-1} (s), 2990 (s, C-H), 2945 (m, C-H), 2910 (m, C-H), 2875 (m), 1780 (s, C=O, lactone), 1710 (s, C=O, lactam), 1540 (w), 1495 (m), 1460 (m), 1420 (s), 1395 (s), 1375 (m), 1350 (s), 1305 (s), 1290 (m), 1235 (s), 1195 (s), 1145 (w), 1105 (m), 1080 (m), 1055 (s), 1010 (m), 950 (w), 900 (s), 850 (m), 830 (w), 795 (w), 780 (m), 760 (s), 725 (w), 700 (s), 670 (m), 650 (w), 640 (w), 620 (w), 580 (m), 540 (m), 515 (w), 505 (w).-

^{1}H-NMR (200 MHz, CD_3Cl): δ = 1.21 ppm (s, 3H, C-5-C**H**$_3$)[3], 1.28 (s, 6H, C-5-C**H**$_3$), 1.32 (s, 3H, C-1-C**H**$_3$), 1.53 (s, 3H, C-1-C**H**$_3$), 1.74 (d, ^3J = 6.36 Hz, 3H, CH-C**H**$_3$), 1.83 (d, ^3J = 6.41 Hz, 3H, CH-C**H**$_3$), 2.32-2.76 (m, 8H, C-4-C**H**$_2$, C-6-C**H**$_2$), 4.63-4.73 (q, ^3J = 6.38 Hz, 1H, C**H**-CH_3), 5.19-5.32 (q, ^3J = 6.38 Hz, 1H, C**H**-CH_3), 6.84-6.89 (d, 2H, C_6**H**$_5$), 7.35 (d, 2H, C_6**H**$_5$).-

MS (EI, 70 eV, direct inlet): m/z (% relative intensity) = 304 (16) [M^++H], 303 (98) [M^+], 288 (12), 260 (8), 232 (2), 191 (12), 190 (24), 177 (10), 176 (100), 160 (32), 149 (9), 136 (18), 135 (68), 134 (20), 111 (6), 105 (5), 91 (5), 77 (4), 55 (5), 43 (7), 41 (2), 39(1).-

MS (DCI negative, NH_3, direct inlet): m/z (% relative intensity) = 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 (% relative intensity) = 305 (21) [M+2H], 304 (100) [M+H], 303 (18) [M^+], 176 (13), 170 (9), 160 (6), 136 (6), 135 (32), 134 (4).-

HR-MS (DCI) $C_{17}H_{21}NO_4$ Calculated 303.14706
Founded 302.13922 (R = 3000)

MPLC conditions: Column size: 49 x 460 mm, stationary phase: matrex silica 20-45 µm 60 Å, eluent: Pet. ether/EtOAc (50:50), back pressure: 00.1– 00.2 MPa, flow rate: 6 ml/min, weight of sample: 604.70 mg, injection volume: 30 ml, detection: UV lamp-254 nm, chromatographic fractions were analysed by HPLC.-

[3] Diastereomeric mixture was measured.

Yield (from MPLC separation):

Chromatographic fractions	Weight (mg)	Yield (%)
77a	344.079	57
mixture of **77a** and **77b**	90.700	15
77b	163.269	27

Spectroscopic data for (1*R*,5S,1'S) 1,5-dimethyl-8-(4-methoxyphenyl) ethyl-2-oxa-8-aza-*cis* bicyclo [3.3.0] octan-3, 7-dion (77a)

Melting Point: 135 ^{0}C.-

Optical rotation: : $[\alpha]_D^{20}$ = -00.258 ° (c = 0.002 g/ml in MeOH).-

TCL [Silica gel, CH_2Cl_2/ EtOAc (99+1)]: R_f = 0.45.-

HPLC: Nucleosil 50-10 Si, Pet. ether / EtOAc (50+50), 2.0 ml/min, detector UV 254 nm, t_R = 11 min.-

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.28 ppm (s, 3H, C(1)-C**H**$_3$), 1.53 (s, 3H, C(5)-C**H**$_3$), 1.79 (d, ^3J = 6.95 Hz, 3H, CH-C**H**$_3$), 2.32-2.76 (2x AB-System, 4H, C(4)-C**H**$_2$, C(6)-C**H**$_2$), 4.63-4.73 (q, ^3J = 6.95 Hz, 1H, C**H**-CH$_3$), 6.68 / 7.34 (m, 4H, C$_6$**H**$_5$).-

CD (MeOH): c = 0.06164mg/ml, λ_{max} (Θ) = 290 nm (-0.9458), 253 (0.2691), 246 (0.2978), 218 (55.7008), 214 (55.6367), 205 (59.6334), 191 (8.0683).-

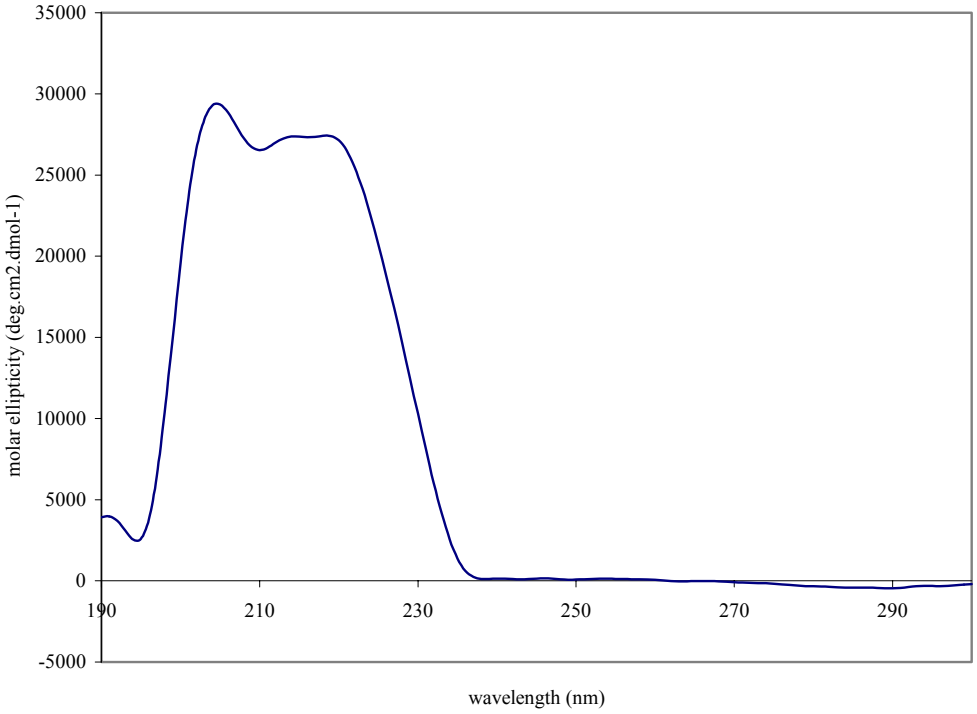


Figure 28: CD spectrum for (1*R*, 5S, 1'S) 1, 5-dimethyl-8-(4-methoxyphenyl) ethyl-2-oxa-8-aza-*cis*-bicyclo [3.3.0] octan-3, 7-dion (**77a**)

Spectroscopic data for (1*S*,5R,1´*S*)-1,5-dimethyl-8-(4-methoxyphenyl) ethyl-2-oxa-8-aza-*cis*-bicyclo [3.3.0] octan-3,7-dion (77b)

TLC [Silica gel, CH_2Cl_2 / ethyl acetate (99+1)]: R_f = 0.44.-

Melting Point: 149 ^{0}C.-

Optical rotation: $[\alpha]_D^{20}$ = + 00.214 ^{0} (c = 0.002g /ml in MeOH).-

HPLC: Nucleosil 50-10 Si, Pet. ether/EtOAc (50+50), 1.5 ml/min., detector UV 254 nm, t_R = 12 min.-

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.21 ppm (s, 3H, C(1)-C**H**$_3$), 1.32 (s, 3H, C(5)-C**H**$_3$), 1.75 (d, ^3J = 6.41 Hz, 3H, CH-C**H**$_3$), 2.35 - 2.66 (m, 4H, -C**H**$_2$-), 5.19-5.30 (q, ^3J = 6.41 Hz, 1H, C**H**-CH_3), 6.84 / 7.34 (m, 4H, C_6**H**$_5$).-

CD (MeOH): c = 0.06022 mg/ml, λ_{max} (Θ) = 290 nm (-1.1725), 270 (-0.6818), 262 (-1.0276), 256 (-0.6988), 231 (-22.0727), 217 (-0.4753), 204 (-11.7219), 197 (-1.9251).-

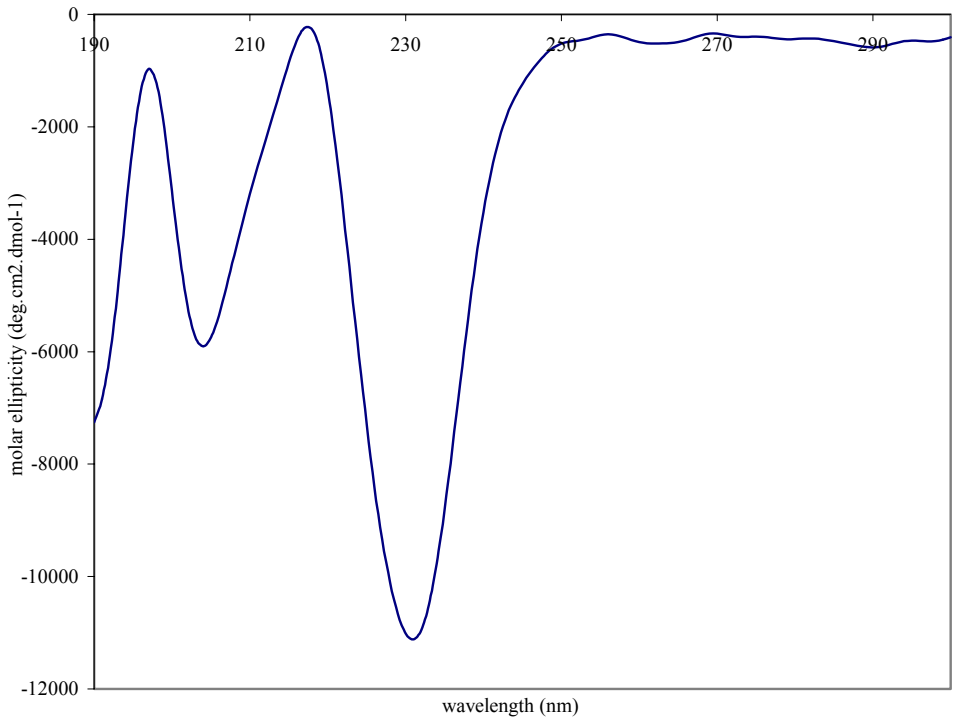
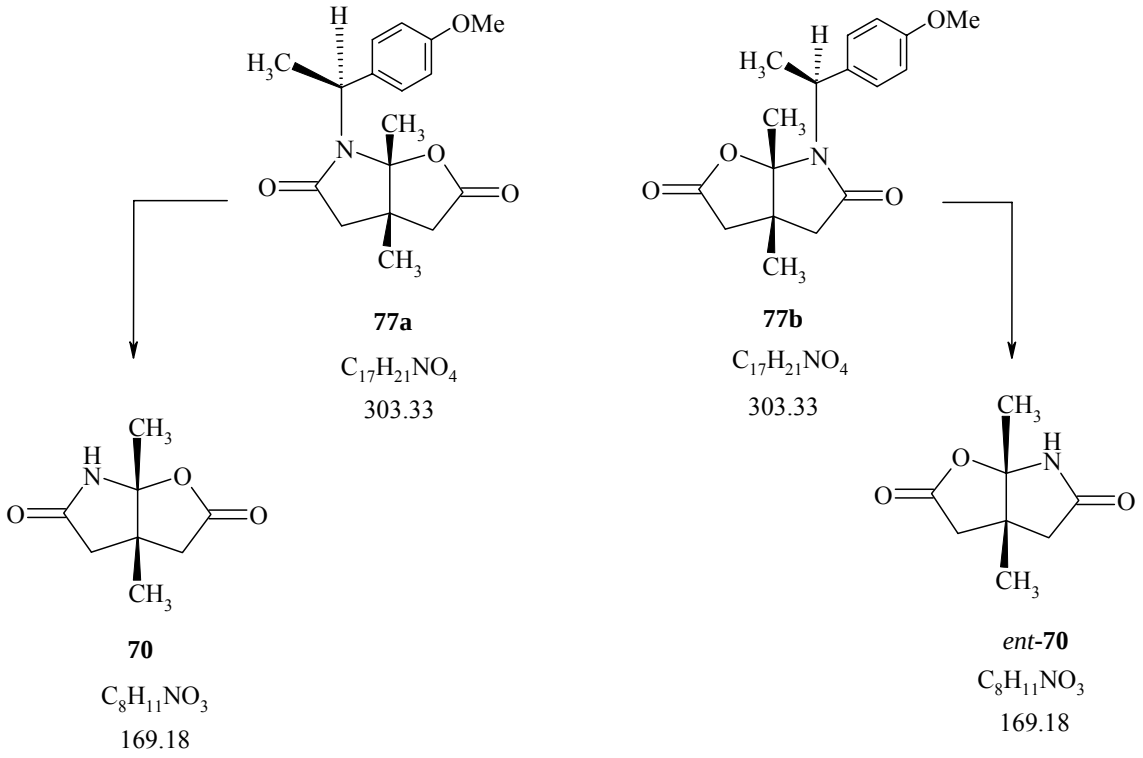


Figure 29: CD spectrum for (1*S*, 5R, 1'S)-1, 5-dimethyl-8-(4-methoxyphenyl) ethyl-2-oxa-8-aza-*cis*-bicyclo [3.3.0] octan-3, 7-dion (**77b**)

5.2.6 Synthesis of (1*R*,5*S*)-1,5-dimethyl-2-oxa-8-aza-*cis*-bicyclo [3.3.0] octan- 3, 7-dion (70) and (1*S*,5*R*)-1,5-dimethyl-2-oxa-8-aza-*cis*-bicyclo [3.3.0]octan-3, 7-dion (*ent*-70) [41]



A solution of 2.1 eq. ceric (IV) ammonium nitrate in 30 ml water was added portionwise to a stirred mixture of 300 mg (0.989 mmol) **77a** in 25 ml of a 4:1 solution of MeCN and water. The mixture was allowed to react at room temperature for 17 hours. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution and stirred vigorously for 15 minutes. The product was extracted with CH_2Cl_2 three times and the bulked organic extracts were dried over anhydrous $NaSO_4$. This was filtered and concentrated *in vacuo*. The product **70** was purified by column chromatography on 40 g silica gel using CH_2Cl_2/MeOH (95+5) as solvent system. Colorless crystal were obtained which were characterized by spectra analysis. The same reaction procedure was repeated on **77b** with the same conditions and reagents and this gave *ent*-**70**.

Analytical and spectroscopic data for (1*R*,5*S*)-1,5-dimethyl-2-oxa-8-aza-*cis*-bicyclo [3.3.0] octan-3,7-dion (70)

Yield: 108mg (6.4 mmol, 65 % Th.).-

Melting Point: 188 ^{o}C.-

Optical rotation: $[\alpha]_D^{20}$ = - 00.214 ^{o} (c = 0.003 g/ml in MeOH).-

TCL [Silica gel, CH_2Cl_2 / EtOAc (9+1)]: R_f = 0.61.-

IR (KBr): $\tilde{\nu}$ = 3212 cm^{-1} (s, N-H), 3070 (w), 3010 (m), 2990 (m, C-H), 2926 (m, C-H), 1769 (s, C=O, lactone), 1703 (s, C=O, lactam), 1495 (m), 1442 (m), 1417 (s), 1347 (s), 1309 (s), 1300 (w), , 1280 (w), 1240(s), 1231 (s, C-O), 1213 (s, C-O), 1176 (s), 1145 (w), 1105 (m), 1054 (s), 1023 (m), 951 (m), 914 (s), 850 (m), 824 (m), 760 (s), 725 (w), 700 (s).-

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.35 ppm (s, 3H, C (5)-C**H**$_3$), 1.62 (s, 3H, C (1)-C**H**$_3$), 2.36 - 2.82 (m, 4H, -C**H**$_2$-), 6.19 (s, br, 1H, N**H**).-

MS (EI, 70 eV, direct inlet): m/z (% relative intensity) = 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).-

HS-MS (CI) - $C_8H_{11}NO_3$ Calculated 169.07389
Founded 168.06571 R = 3000

Analytical and spectroscopic data for (1*S*,5*R*)-1, 5-dimethyl-2-oxa-8-aza-*cis*-bicyclo [3.3.0] octan-3,7-dion (*ent*-70)

Yield: 100 mg (5.9 mmol, 59.8 % Th.).-

TLC [Silica gel, CH_2Cl_2 / EtOAc (99+1)]: R_f = 0.55.-

Melting Point: 183.5 ^{o}C.-

Optical rotation: $[\alpha]_D^{20}$ = + 00.214 ^{o} (c = 0.003 g /ml in MeOH).-

IR (KBr): $\tilde{\nu}$ = 3212 cm^{-1} (s, N-H), 3070 (w), 3010 (m), 2990 (m, C-H), 2926 (m, C-H), 1769 (s, C=O, lactone), 1703 (s, C=O, lactam), 1495 (m), 1442 (m), 1417 (s), 1347 (s), 1309 (s), 1300 (w), , 1280 (w), 1240(s), 1231 (s, C-O), 1213 (s, C-O), 1176 (s), 1145 (w), 1105 (m), 1054 (s), 1023 (m), 951 (m), 914 (s), 850 (m), 824 (m), 760 (s), 725 (w), 700 (s).-

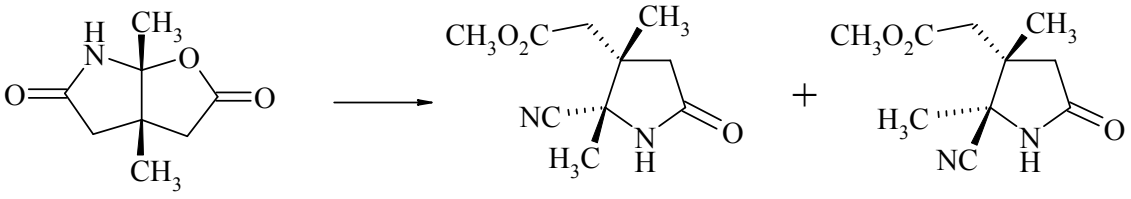
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.35 ppm (s, 3H, C (5)-C**H**$_3$), 1.63 (s, 3H, C (1)-C**H**$_3$), 2.36 - 2.82 (m, 4H, -C**H**$_2$-), 6.20 (s, br, 1H, N**H**).-

MS (EI, 70 eV, direct inlet): m/z (% relative intensity) = 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).-

HS-MS (DCI) - $C_8H_{11}NO_3$ Calculated 169.07389
Founded 168.06571 R = 3000

5.3 SYNTHESIS OF ENANTIOMERICALLY PURE PYRROLIDINE DIESTER 68

5.3.1 Synthesis of methyl [(2´*R*,3´*R*)-2´-cyano-2´,3´-dimethyl-5´-oxo-pyrrolidin-3´-yl] acetate (69a) and methyl [(2´S,3´*R*)-2´-cyano-2´, 3´-dimethyl-5´-oxo-pyrrolidin-3´-yl] acetate (69b)



70
$C_8H_{11}NO_3$
169.18

69a
$C_{10}H_{14}N_2O_3$
210.23

69b
$C_{10}H_{14}N_2O_3$
210.23

To a solution of 169 mg (1 mmol) **70** in 20 ml of methanol* was added 130.2 mg (2 mmol, 2 eq.) of potassium cyanide. The reaction was stirred at room temperature under argon atmosphere for 20 hours. About three-fourth of the solvent was removed *in vacuo*. A solution of 2 N NaH_2PO_4 (15 ml) was added to the remaining reaction mixture and was cooled in an ice bath. Concentrated H_3PO_4 was carefully added to the cooled reaction mixture until pH 2. (Caution: evolution of hydrogen cyanide gas!). Saturated NaCl solution was then added to the reaction mixture after which the product was extracted each time with 20 ml ethyl acetate three times. The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* The colorless oily crude product was dried on an oil vacuum-pump for some time.

The crude product was dissolved in 5ml methanol and cooled in an ice bath. About 5-10 ml ethereal diazomethane solution* (0.5 M) was added after which the ice bath was removed and the solution stirred at room temperature for 15 minutes. The excess diazomethane was removed by rotary evaporation (some amount of acetic acid was put into the receiver flask during the concentration to prevent explosion). The crude product was purified on the column chromatography with 20g silica gel and CH_2Cl_2 / MeOH (95+5) as solvent system. This gave a mixture of *cis*-, *trans*-cyano lactam isomers as colorless crystals.

Yield: 168 mg (0.99 mmol, 80 % Th.).-

Melting point: 127 °C ($CHCl_3$/n-Pentan).-

TLC: [Silica gel, CH_2Cl_2 / MeOH (9+1)]: R_f = 0.62.-

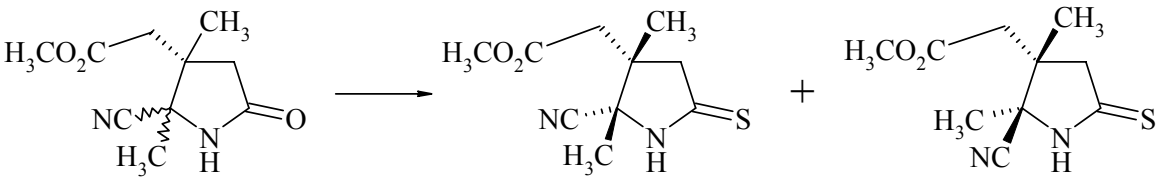
IR (KBr): $\tilde{\nu}$ = 3172 cm^{-1} (s, N-H), 3115 (s, N-H), 3001 (s), 2976 (s, C-H), 2955 (s, C-H), 2915 (m, C-H), 2848 (m, C-H), 2230 (m, -CN), 1732 (s, C=O, ester), 1725 (s, C=O, lactam), 1668 (s), 1450 (s), 1440 (s), 1389 (s), 1351 (s), 1329 (s), 1297 (m), 1280 (w), 1236 (s), 1214 (s), 1185 (s), 1159 (s), 1150 (s), 1091 (m), 1000 (s), 925 (w), 900 (w), 885 (w), 865 (m), 840 (w), 780 (m), 760 (m), 720 (s), 655 (w), 630 (m), 600 (w), 540 (s), 510 (w), 500 (m).-

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.22 ppm (s, 6H, C-3´-C**H**$_3$), 1.63 (s, 6H, C-2´-C**H**$_3$), 2.38-2.90 (2 x AB-System, 8H, C-4´-C**H**$_2$, C-2-C**H**$_2$), 3.74 (s, 6H, 2 x O-C**H**$_3$), 5.94 (s, br, 1H, N**H**).-

MS (EI, 70 eV, direct inlet): m/z (% relative intensity) = 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).-

HS-MS (EI)- $C_{10}H_{14}N_2O_3$ Calculated 210.10044
Founded 210.09981 R = 1000

5.3.2 Synthesis of methyl [(2´*R*,3´*S*)-2´-cyano-2´, 3´-dimethyl-5´-thioxo-pyrrolidin-3´-yl] acetate (64a) and methyl [(2´S,3´*S*)-(2´-cyano-2´, 3´-dimethyl-5´-thioxo-pyrrolidin-3´-yl] acetate (64b) [42, 43]



69a,b

$C_{10}H_{14}N_2O_3$

210.23

64a

$C_{10}H_{14}N_2O_2S$

226.30

64b

$C_{10}H_{14}N_2O_2S$

226.30

The isomeric mixture of cyano lactam **69a,b** (106 mg 0.51 mmol) was dissolved in 10 ml THF * and 247 mg (0.615 mmol, 1.2 eq.) Lawesson's reagent[4] added under argon atmosphere. The reaction mixture was heated up to about 40 ^oC with stirring for 30 minutes and then allowed to go on at room temperature under argon atmosphere for 3 hours 30 minutes. The reaction mixture was concentrated and the crude product purified by column chromatography on 30g silica gel. The silica gel was over-laminated with 2 cm thick alox before the raw product was transferred onto the column. Solvent system was CH_2Cl_2/EtOAc (9+1). A mixture of *cis*- and *trans*-thiocyano lactam isomers was obtained as colourless oily product which crystallized out after some time. The isomers were separated on a 'stepped column'[5] over 50 g silica gel with CH_2Cl_2/EtOAc (95+5). The first isomer that was eluted was **64a** (70%) and then came a mixture of both **64a** and **64b** (9%). The second isomer **64b** was only 20%. The mixture was re-chromatographed and added to the respective isomers. Yield for isomer **64a** was 77% and that of **64b** was 22%. Both **64a** and **64b** were recrystallized from $CHCl_3$ and **65a** came out as colourless crystals and **64b** was gelly-like in nature.

[4] Lawesson-reagent: 2,4-bis (*p*-methoxyphenyl)-1,3-dithiaphosphetan-2,4-disulphide

[5] Stufensäule (Three stepped column of different diameters).

Yield: 100 mg (0.44 mmol, 88 % Th.).-

UV/VIS ($CHCl_3$): λ_{max} = 270 nm.-

IR (KBr): $\tilde{\nu}$ = 3091 cm^{-1} (s, N-H), 2985 (m, C-H), 2955 (s, C-H), 2360 (m), 2235 (w, -CN), 1747 (m), 1734 (s, C=O, Ester), 1698 (w), 1506 (s, C=S, thiolactam), 1438 (s), 1411 (w), 1390 (m), 1385 (w), 1350 (s), 1335 (s), 1300 (w), 1285 (m), 1245 (m), 1214 (s, C-O), 1210 (s, C-O), 1170 (m), 1145 (s), 1138 (s), 1105 (s), 1086 (m), 1012 (s), 985 (w), 920 (w), 860 (w), 850 (w), 835 (w), 795 (w), 755 (m), 700 (w), 670 (w), 645 (w), 616 (w), 590 (w), 530 (w), 509 (w).-

MS (EI, 70 eV, direct inlet): m/z (% relative intensity) = 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^+-$C_3H_5O_2$], 152 (4), 151 (3), 140 (6), 139 (5), 138 (2), 137 (5), 136 (3), 129 (8), 128 (6), 127 (7), 126 (30), 125 (16), 124 (6), 121 (5), 120 (15), 119 (6), 112 (10), 111 (5), 110 (2), 108 (6), 99 (8), 98 (9), 97 (9), 94 (8), 93 (4), 85 (7), 80 (3), 74 (7), 73 (3), 71 (8), 67 (6), 66 (5), 65 (8), 59 (11), 58 (9), 55 (9), 53 (8), 45 (8), 43 (8), 42 (9), 41 (15), 40 (11).-

HS-MS (EI) $C_{10}H_{14}N_2O_2S$ Calculated 226.07760
Founded 226.07716 R = 1000

Spectroscopic data for methyl [(2´*R*,3´*S*)-2´-cyano-2´,3´-dimethyl-5´-thioxo pyrrolidin-3´-yl] acetate (64a)

Yield: 76.8mg (0.34mmol, 77% Th.).-

Melting point: 118 °C ($CHCl_3$ / n-Pentan).-

TLC [silica gel, CH_2Cl_2 / EtOAc (95+5)]: R_f = 0.78.-

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.18 ppm (s, 3H, C(3´)-C**H**$_3$), 1.68 (s, 3H, C(2´)-C**H**$_3$), 2.68-2.84 (AB-System, 2H, C(2)-C**H**$_2$), 2.95-3.15 (AB-System, 2H, C(4´)-C**H**$_2$), 3.72 (s, 3H, O-C**H**$_3$), 8.32 (s, br, 1H, N**H**).-

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 17.67 ppm (C(3´)-**C**H$_3$), 18.32(C(2´)-**C**H$_3$), 39.94 (**C**(2)), 45.10 (**C**(3´)), 50.71 (O-**C**H$_3$), 54.40 (**C**(4´)), 64.81 (**C**(2´)), 116.60 (-**C**N), 168.97 (**C**=O), 203.26 (**C**=S).-

NOE experimental data:

IRRADIATION		OBSERVATION-NOE	
δ [ppm]	Assignment	δ [ppm]	Assignment
1.18	4-CH_3	1.68	**5-CH_3**
		3.00/2.95	**3-CH_2b**
		2.72 / 2.67	4'-CH_2b
1.68	5-CH_3	1.18	**4-CH_3**
		2.72 / 2.67	**4-CH_2b**

Spectroscopic daten for methyl[(2´S,3´*S*)-2´-cyano-2´,3´-dimethyl-5´-thioxo pyrrolidin-3´-yl] acetate (64b)

Yield: 23mg (0.102mmol, 23%)

TLC [silica gel, CH_2Cl_2 / EtOAc (95+5)]: R_f = 0.70.-

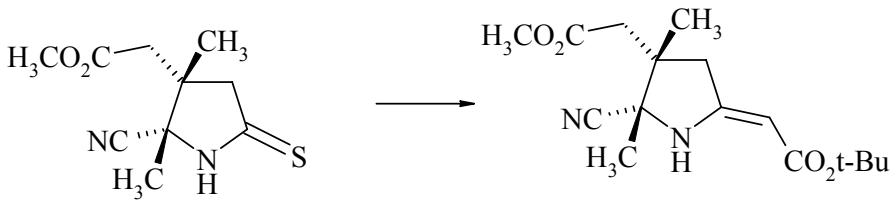
^{1}H-NMR (200 MHz, $CDCl_3$): δ=1.44 ppm (s, 3H, C(3´)-C**H**$_3$), 1.66 (s, 3H, C(2´)-C**H**$_3$), 2.48 (s, 2H, C(4´)-C**H**$_2$), 2.96 (AB-System, 2H, C(2)-C**H**$_2$), 3.71 (s, 3H, O-C**H**$_3$), 9.18 (s, br, 1H, N**H**).-

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 17.67 ppm (C(3´)-**C**H$_3$), 18.32(C(2´)-**C**H$_3$), 39.94 (**C**(2)), 45.10 (**C**(3´)), 50.71 (O-**C**H$_3$), 54.40 (**C**(4´)), 64.81 (**C**(2´)), 116.60 (-**C**N), 168.97 (**C**=O), 203.26 (**C**=S).-

NOE experimental data:

IRRADIATION		OBSERVATION-NOE	
δ [ppm]	Assignment	δ [ppm]	Assignment
1.46	4-CH_3	2.91 / 2.86	**3-CH_2b**
		2.48	**4'-CH_2**
		1.66	5-CH_3
1.66	5-CH_3	2.48	**4'-CH_2**
		2.91 / 2.86	3-CH_2b
		3.10 / 3.05	3-CH_2a
		8.32	N-H

5.3.2 Synthesis of methyl[(2´S,3´S,5´Z)-5´-(2'-tert-butoxy-2-oxoethylidene)-2´-cyano-2´,3´-dimethyl-pyrrolidin-3´-yl]-acetate 68



64a

$C_{10}H_{14}N_2O_2S$

226.30

68

$C_{16}H_{24}N_2O_4$

308.38

A solution of 100 mg (0.44 mmol) *cis*-thiocyano lactam **64a** in 4 ml acetonitrile* was prepared under argon atmosphere and 135 mg (0.49 mmol, 1.1 eq.) a 88% (7:1 product/reactant)[6] of bromine malonic diester mixture *rac*-**80** [7] was added. DBU * (81 mg, 0.070 ml, 0.528 mmol, 1.2 eq.) was then added and the reaction was stirred for 20 minutes at 0 °C under argon atmosphere. The reaction mixture was transferred into a separating funnel and 20 ml CH_2Cl_2 was added. Saturated aqueous solution of $NaHCO_3$ (50 ml) was used to wash the organic solution and separated. The aqueous phase was treated twice with 20 ml CH_2Cl_2 and the bulked organic phase was dried over cotton wool and concentrated under reduce pressure. The crude intermediate product was dried completely on a vacuum pump.

Without purification, the crude product was desulphonated with 5 ml triethylphosphite for 18 hours under argon atmosphere at 80 °C reflux. The excess desulphonating reagent was distilled out on a kugelrohr distillation apparatus under reduced pressure. The yellowish brown oily crude product without purification was solved in 1.5 ml THF * under argon atmosphere and 0,246 ml piperidin * was added.

---

[6] The relationship between the brominated and non –brominated malonic ester was determined by ^{1}H-NMR before the reaction (This contained about 12 % malonic diester **33**).

[7] The bromomalonic diester [44] was freshly distilled on the kugelrohr distillation apparatus with an oil pump vacuum at 120-130 °C.

Two spatula full tetrakis triphenylphosphine palladium (0) catalyst were carefully and quickly added and the reaction was stirred for 2 hours at room temperature. The yellowish red reaction mixture was treated with 20 ml ice chilled 2 N hydrochloric acid and then extracted three times with 20 ml CH_2Cl_2. The bulked organic phase was neutralized with saturated aqueous $NaHCO_3$ solution, separated and then dried over cotton wool. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on 20 g silica gel. The top of the silica gel was over laminated, 5 cm thick, with alox and the product was eluted with CH_2Cl_2/EtOAc (9+1) as solvent system. The product **68** was isolated as creamish crystals which were recrystalized in $CHCl_3$. Spectroscopic analysis was used to characterize the product.

Yield: 231 mg (0.75 mmol, 67 % Th.).-

Melting point: 120 ^oC .-

TLC [silica gel CH_2Cl_2/EtOAc (9+1)]: R_f = 0.69.-

IR (KBr): $\tilde{\nu}$ = 3330 cm^{-1} (s, N-H), 2974 (m, C-H), 2929 (s, C-H), 2360 (m), 2235 (w, -CN), 1747 (m), 1738 (s, C=O, methyl ester), 1664 (w, C=O tert-butyl ester), 1615 (s), 1480(w), 1443 (s), 1421 (w), 1392 (m), 1362 (s), 1343 (w), 1298 (w), 1273 (s), 1229 (m), 1178 (m), 1134 (s, C-O), 1090 (m), 1040 (s), 1008 (w), 995 (w), 974 (w), 924 (w), 860 (w), 797 (s), 704 (w), 663(w), 608 (w), 583 (w), 541 (w).-

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.09 ppm (s, 3H, C(3´)-C**H**$_3$), 1.47 (s, 9H, C-(C**H**$_3$)$_3$), 1.58 (s, 3H, C(2´)-C**H**$_3$), 2.75 (m, 4H, 2x -C**H**$_2$-), 3.72 (s, 3H, O-C**H**$_3$), 4.64 (s, 1H, =C**H**-), 7.90 (s, br, 1H, N**H**).-

MS (EI, 70 eV, direct inlet): m/z (% relative intensity) = 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^+-$C_3H_7O_2$], 220 (5), 219 (9), 210 (11), 208 (16), 205 (7), 203 (8), 180 (11), 179 (100), 178 (8), 175 (8), 161 (60), 154 (9), 153 (10), 152 (62), 149 (5), 148 (5), 147 (8), 146 (7), 145 (9), 138 (5), 135 (8), 134 (15), 133 (8), 120 (7), 108 (8), 107 (7), 106 (6), 94 (8), 84 (14), 80 (6), 79 (12), 77 (10), 69 (7), 67 (11), 66 (12), 59 (16) [$C_3H_3O_2^+$], 58 (5), 57 (60) [$C_4H_9^+$], 56 (5), 55 (14), 54 (11), 53 (10), 43 (7), 42 (8), 41 (26), 29 (17).-

HR-MS: **(EI)** $C_{16}H_{24}NO_4$ Calculated 308.17361
Founded 308.17282 (R = 10000).-

5.4 X-RAY STRUCTURAL DATA FOR 64A, 76A AND 77A

Table 7. Crystal data and structure refinement for methyl [(2´R, 3´S)-2´-cyano- 2´, 3´-dimethyl-5´-thioxo pyrrolidin-3´-yl] acetate (**64a**)

Identification code	**64a**	
Empirical formula	$C_{10} H_{13} N_2 O_2 S$	
Formula weight	225.28	
Temperature	173(2) K	
Wavelength	71.073 pm	
Crystal system	Monoclinic	
Space group	C 2	
Unit cell dimensions	a = 2231.9(4) pm	α= 90°.
	b = 878.0(3) pm	β= 98.440(10)°.
	c = 1207.1(2) pm	γ = 90°.
Volume	2.3398(10) nm^3	
Formula unit per cell Z	8	
Density (calculated)	1.279 Mg/m^3	
Absorption coefficient	0.260 mm^{-1}	
F (000)	952	
Crystal size	1.00 x 0.30 x 0.15 mm^3	
Theta range for data collection	2.69 to 27.49°.	
Index ranges	$-28 \leq h \leq 28$, $-1 \leq k \leq 10$, $-15 \leq l \leq 15$	
Reflections collected	6477	
Independent reflections	3367 [R (int) = 0.0414]	
Completeness to theta = 27.49°	99.0 %	
Absorption correction	None	
Max. and min. transmission	0.9621 and 0.7813	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3367 / 1 / 279	
Goodness-of-fit on F^2	1.014	
Final R indices [I>2sigma (I)]	R1 = 0.0458, wR2 = 0.0972	
R indices (all data)	R1 = 0.0638, wR2 = 0.1046	

Absolute structure parameter	0.05(10)
Largest diff. peak and hole	0.327 and -0.242 e.Å^{-3}

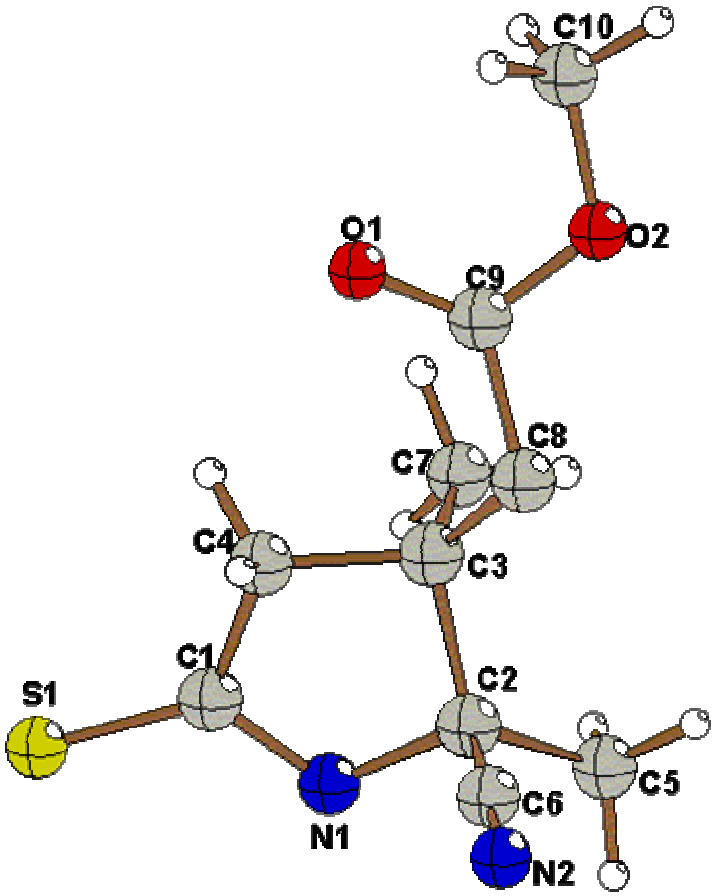


Figure 30: X-ray crstal structure for **64a**

Table 8: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (pm^2x 10^{-1}) for **64a**. U (eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	2195(1)	1714(1)	8028(1)	46(1)
C(1)	2754(1)	1459(4)	7270(3)	31(1)
N(1)	2947(1)	99(4)	7005(2)	30(1)
C(2)	3485(1)	166(4)	6414(3)	27(1)
C(3)	3426(1)	1817(5)	5903(2)	28(1)
C(4)	3123(1)	2659(5)	6804(3)	32(1)
C(5)	3504(2)	-1158(5)	5612(3)	36(1)
C(6)	4029(1)	26(4)	7288(3)	27(1)
N(2)	4434(1)	-126(4)	7981(2)	37(1)
C(7)	2995(2)	1802(6)	4791(3)	42(1)
C(8)	4048(2)	2470(5)	5726(3)	33(1)
C(9)	3995(2)	4068(5)	5283(3)	39(1)
O(1)	3727(2)	5075(5)	5645(4)	97(2)
O(2)	4295(1)	4271(4)	4431(2)	50(1)
C(10)	4293(2)	5819(6)	4011(4)	65(1)
S(2)	2845(1)	-3206(1)	8260(1)	42(1)
C(11)	2113(1)	-3411(5)	8391(2)	29(1)
N(3)	1866(1)	-4745(4)	8566(2)	32(1)
C(12)	1207(1)	-4671(4)	8574(3)	27(1)
C(13)	1121(1)	-2928(4)	8843(3)	25(1)
C(14)	1639(1)	-2203(5)	8304(3)	32(1)
C(15)	999(2)	-5846(5)	9362(3)	34(1)
C(16)	905(1)	-5036(5)	7410(3)	32(1)
N(4)	677(1)	-5310(5)	6521(2)	46(1)
C(17)	1242(2)	-2686(5)	10110(2)	37(1)
C(18)	484(1)	-2385(5)	8345(3)	32(1)
C(19)	348(1)	-737(5)	8543(3)	30(1)
O(3)	698(1)	237(4)	8874(2)	47(1)
O(4)	-249(1)	-499(3)	8242(3)	49(1)
C(20)	-451(2)	1072(6)	8326(4)	55(1)

Table 9: Bond lengths [pm] and angles [°] for **64a**.

S(1)-C(1)	166.6(3)	C(6)-C(2)-C(5)	107.0(3)	O(3)-C(19)-O(4)	123.8(4)
C(1)-N(1)	132.6(5)	N(1)-C(2)-C(3)	101.4(3)	O(3)-C(19)-C(18)	127.4(3)
C(1)-C(4)	149.7(5)	C(6)-C(2)-C(3)	111.5(3)	O(4)-C(19)-C(18)	108.7(3)
N(1)-C(2)	148.5(4)	C(5)-C(2)-C(3)	117.7(3)	C(19)-O(4)-C(20)	115.6(3)
C(2)-C(6)	149.2(4)	C(7)-C(3)-C(8)	110.0(3)		
C(2)-C(5)	151.7(5)	C(7)-C(3)-C(4)	109.7(3)		
C(2)-C(3)	157.3(6)	C(8)-C(3)-C(4)	114.4(3)		
C(3)-C(7)	153.2(4)	C(7)-C(3)-C(2)	110.0(3)		
C(3)-C(8)	154.5(5)	C(8)-C(3)-C(2)	111.7(3)		
C(3)-C(4)	154.9(5)	C(4)-C(3)-C(2)	100.7(3)		
C(6)-N(2)	114.6(4)	C(1)-C(4)-C(3)	104.4(3)		
C(8)-C(9)	150.0(6)	N(2)-C(6)-C(2)	177.1(4)		
C(9)-O(1)	118.6(5)	C(9)-C(8)-C(3)	111.8(3)		
C(9)-O(2)	132.0(5)	O(1)-C(9)-O(2)	121.8(4)		
O(2)-C(10)	145.0(6)	O(1)-C(9)-C(8)	125.8(3)		
S(2)-C(11)	167.4(3)	O(2)-C(9)-C(8)	112.4(4)		
C(11)-N(3)	132.4(5)	C(9)-O(2)-C(10)	115.0(4)		
C(11)-C(14)	149.0(5)	N(3)-C(11)-C(14)	109.5(2)		
N(3)-C(12)	147.2(4)	N(3)-C(11)-S(2)	123.0(3)		
C(12)-C(16)	150.1(5)	C(14)-C(11)-S(2)	127.5(3)		
C(12)-C(15)	152.2(5)	C(11)-N(3)-C(12)	113.6(3)		
C(12)-C(13)	158.2(5)	N(3)-C(12)-C(16)	107.3(3)		
C(13)-C(17)	152.8(4)	N(3)-C(12)-C(15)	111.8(3)		
C(13)-C(18)	153.6(4)	C(16)-C(12)-C(15)	107.7(3)		
C(13)-C(14)	154.6(4)	N(3)-C(12)-C(13)	101.3(3)		
C(16)-N(4)	114.4(4)	C(16)-C(12)-C(13)	110.3(3)		
C(18)-C(19)	150.4(5)	C(15)-C(12)-C(13)	118.0(3)		
C(19)-O(3)	118.8(5)	C(17)-C(13)-C(18)	111.5(3)		
C(19)-O(4)	134.5(4)	C(17)-C(13)-C(14)	109.3(3)		
O(4)-C(20)	145.9(6)	C(18)-C(13)-C(14)	114.5(3)		
N(1)-C(1)-C(4)	109.0(3)	C(17)-C(13)-C(12)	109.3(3)		
N(1)-C(1)-S(1)	123.4(3)	C(18)-C(13)-C(12)	110.7(3)		
C(4)-C(1)-S(1)	127.6(3)	C(14)-C(13)-C(12)	101.0(2)		
C(1)-N(1)-C(2)	113.3(3)	C(11)-C(14)-C(13)	104.1(3)		
N(1)-C(2)-C(6)	106.7(2)	N(4)-C(16)-C(12)	179.6(4)		
N(1)-C(2)-C(5)	112.1(3)	C(19)-C(18)-C(13)	115.7(3)		

Table 10: Anisotropic displacement parameters ($pm^2 x\ 10^{-1}$) for **64a**. The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	35(1)	32(1)	76(1)	-9(1)	25(1)	1(1)
C(1)	25(1)	29(2)	36(2)	-4(2)	-1(1)	2(1)
N(1)	21(1)	29(2)	39(1)	-9(2)	4(1)	3(1)
C(2)	26(1)	25(2)	31(2)	0(2)	7(1)	-2(1)
C(3)	31(1)	25(2)	29(2)	1(2)	3(1)	1(2)
C(4)	33(2)	28(2)	33(2)	-1(2)	0(1)	5(2)
C(5)	39(2)	29(2)	42(2)	-11(2)	11(2)	-3(2)
C(6)	31(2)	21(2)	33(2)	3(2)	13(1)	5(1)
N(2)	32(1)	36(2)	43(2)	7(2)	5(1)	3(1)
C(7)	46(2)	44(2)	32(2)	6(2)	-3(1)	4(2)
C(8)	39(2)	26(2)	34(2)	7(2)	11(1)	2(2)
C(9)	46(2)	30(2)	43(2)	3(2)	16(2)	2(2)
O(1)	160(4)	35(2)	122(3)	18(3)	106(3)	25(3)
O(2)	76(2)	34(2)	43(2)	6(2)	26(1)	5(2)
C(10)	102(4)	46(3)	50(3)	13(3)	28(2)	-2(3)
S(2)	23(1)	40(1)	64(1)	9(1)	11(1)	2(1)
C(11)	26(1)	32(2)	28(1)	3(2)	4(1)	1(2)
N(3)	25(1)	32(2)	41(2)	-1(2)	8(1)	1(1)
C(12)	23(1)	28(2)	30(2)	-3(2)	7(1)	2(1)
C(13)	21(1)	26(2)	30(2)	0(2)	6(1)	1(1)
C(14)	25(1)	30(2)	41(2)	5(2)	6(1)	1(2)
C(15)	34(2)	28(2)	41(2)	6(2)	8(1)	2(2)
C(16)	33(2)	27(2)	38(2)	-4(2)	14(1)	1(2)
N(4)	49(2)	53(2)	39(2)	-11(2)	10(1)	-2(2)
C(17)	44(2)	37(2)	29(2)	0(2)	4(1)	0(2)
C(18)	23(1)	32(2)	40(2)	-4(2)	5(1)	3(2)
C(19)	29(2)	28(2)	33(2)	5(2)	6(1)	3(2)
O(3)	39(1)	30(2)	69(2)	-6(2)	-2(1)	2(1)
O(4)	28(1)	33(2)	85(2)	2(2)	7(1)	10(1)
C(20)	44(2)	44(3)	78(3)	6(3)	10(2)	22(2)

Table 11: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (pm^2x 10^{-1}) for **64a**.

	x	y	z	U(eq)
H(4A)	3432	3081	7397	41(4)
H(4B)	2863	3499	6466	41(4)
H(5A)	3532	-2117	6033	53(3)
H(5B)	3857	-1054	5223	53(3)
H(5C)	3134	-1159	5063	53(3)
H(7A)	2616	1298	4896	53(3)
H(7B)	3184	1248	4228	53(3)
H(7C)	2910	2851	4538	53(3)
H(8A)	4324	2457	6448	41(4)
H(8B)	4226	1814	5193	41(4)
H(10A)	3883	6086	3654	53(3)
H(10B)	4574	5898	3462	53(3)
H(10C)	4420	6518	4634	53(3)
H(14A)	1500	-1933	7511	41(4)
H(14B)	1795	-1275	8715	41(4)
H(15A)	1072	-6872	9092	53(3)
H(15B)	565	-5713	9388	53(3)
H(15C)	1225	-5709	10115	53(3)
H(17A)	1637	-3123	10410	53(3)
H(17B)	925	-3187	10458	53(3)
H(17C)	1243	-1593	10274	53(3)
H(18A)	427	-2568	7527	41(4)
H(18B)	183	-3018	8662	41(4)
H(20A)	-415	1364	9116	53(3)
H(20B)	-875	1160	7977	53(3)
H(20C)	-199	1746	7941	53(3)

Table 12: Torsion angles [°] for **64a**.

C(4)-C(1)-N(1)-C(2)	4.0(3)	C(11)-N(3)-C(12)-C(15)	-148.2(3)
S(1)-C(1)-N(1)-C(2)	-174.8(2)	C(11)-N(3)-C(12)-C(13)	-21.6(3)
C(1)-N(1)-C(2)-C(6)	93.3(3)	N(3)-C(12)-C(13)-C(17)	-84.8(3)
C(1)-N(1)-C(2)-C(5)	-149.9(3)	C(16)-C(12)-C(13)-C(17)	161.8(3)
C(1)-N(1)-C(2)-C(3)	-23.5(3)	C(15)-C(12)-C(13)-C(17)	37.5(4)
N(1)-C(2)-C(3)-C(7)	-84.2(3)	N(3)-C(12)-C(13)-C(18)	151.9(3)
C(6)-C(2)-C(3)-C(7)	162.6(3)	C(16)-C(12)-C(13)-C(18)	38.6(3)
C(5)-C(2)-C(3)-C(7)	38.4(4)	C(15)-C(12)-C(13)-C(18)	-85.7(3)
N(1)-C(2)-C(3)-C(8)	153.4(3)	N(3)-C(12)-C(13)-C(14)	30.3(3)
C(6)-C(2)-C(3)-C(8)	40.1(4)	C(16)-C(12)-C(13)-C(14)	-83.1(3)
C(5)-C(2)-C(3)-C(8)	-84.1(3)	C(15)-C(12)-C(13)-C(14)	152.6(3)
N(1)-C(2)-C(3)-C(4)	31.5(3)	N(3)-C(11)-C(14)-C(13)	18.4(4)
C(6)-C(2)-C(3)-C(4)	-81.7(3)	S(2)-C(11)-C(14)-C(13)	-163.3(2)
C(5)-C(2)-C(3)-C(4)	154.1(3)	C(17)-C(13)-C(14)-C(11)	85.5(4)
N(1)-C(1)-C(4)-C(3)	17.8(3)	C(18)-C(13)-C(14)-C(11)	-148.7(3)
S(1)-C(1)-C(4)-C(3)	-163.5(2)	C(12)-C(13)-C(14)-C(11)	-29.7(3)
C(7)-C(3)-C(4)-C(1)	85.6(4)	N(3)-C(12)-C(16)-N(4)	-34(94)
C(8)-C(3)-C(4)-C(1)	-150.2(3)	C(15)-C(12)-C(16)-N(4)	-155(100)
C(2)-C(3)-C(4)-C(1)	-30.3(3)	C(13)-C(12)-C(16)-N(4)	75(94)
N(1)-C(2)-C(6)-N(2)	40(8)	C(17)-C(13)-C(18)-C(19)	58.3(4)
C(5)-C(2)-C(6)-N(2)	-80(8)	C(14)-C(13)-C(18)-C(19)	-66.4(4)
C(3)-C(2)-C(6)-N(2)	150(8)	C(12)-C(13)-C(18)-C(19)	-179.7(3)
C(7)-C(3)-C(8)-C(9)	59.9(4)	C(13)-C(18)-C(19)-O(3)	13.1(6)
C(4)-C(3)-C(8)-C(9)	-64.1(4)	C(13)-C(18)-C(19)-O(4)	-169.2(3)
C(2)-C(3)-C(8)-C(9)	-177.7(3)	O(3)-C(19)-O(4)-C(20)	1.0(6)
C(3)-C(8)-C(9)-O(1)	48.2(6)	C(18)-C(19)-O(4)-C(20)	-176.8(4)
C(3)-C(8)-C(9)-O(2)	-133.0(3)		
O(1)-C(9)-O(2)-C(10)	2.6(6)		
C(8)-C(9)-O(2)-C(10)	-176.3(4)		
C(14)-C(11)-N(3)-C(12)	2.5(4)		
S(2)-C(11)-N(3)-C(12)	-175.9(2)		
C(11)-N(3)-C(12)-C(16)	94.0(4)		

Tabel 13: Crystal data and structure refinement for (1R, 5S, 1´S)-1, 5-dimethyl-8-phenyl ethyl-2-oxa-8-aza-*cis*-bicyclo [3.3.0] octan-3, 7-dion (**76a**)

Identification code	**76a**	
Empirical formula	$C_{16}H_{19}NO_3$	
Formula weight	273.32	
Temperature	173(2) K	
Wavelength	71.073 pm	
Crystal system	Monoclinic	
Space group	$P2_1$	
Cell dimension	a = 877.65(18) pm	α= 90°.
	b = 1010.2(2) pm	β = 118.75(3) °.
	c = 900.87(18) pm	γ = 90°.
Volume	0.7003(2) nm^3	
Formula unit per cell Z	2	
Density (calculated)	1.296 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	292	
Crystal size	0.50 x 0.50 x 0.30 mm^3	
Theta range for data collection	2.58 to 26.09°.	
Index ranges	$-10 \le h \le 10$, $-12 \le k \le 12$, $-11 \le l \le 11$	
Reflections collected	8242	
Independent reflections	2727 [R (int) = 0.0451]	
Completeness to theta = 26.09°	98.2 %	
Max. und min. Transmission	0.9737 and 0.9567	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2727 / 1 / 188	
Goodness-of-fit on F^2	1.046	
Final R indices [I>2sigma (I)]	R1 = 0.0393, wR2 = 0.0955	
R indices (all Data)	R1 = 0.0455, wR2 = 0.1024	
Absolute structure parameter	0.0(13)	
Largest diff. Peak and hole	0.158 and -0.154 e.$Å^{-3}$	

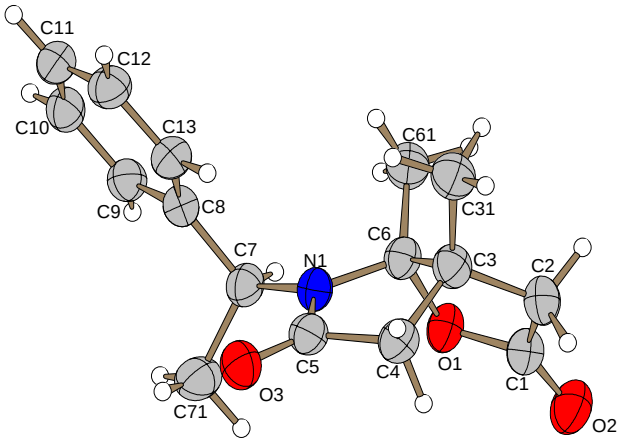


Figure 31: X-ray crystal structure for **76a**

Table 14. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (pm^2x 10^{-1}) for **76a**. U (eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U (eq)
O(1)	1294(2)	1342(2)	6465(2)	42(1)
C(1)	-70(3)	1877(2)	5073(3)	41(1)
O(2)	-49(2)	1945(2)	3743(2)	56(1)
C(2)	-1441(3)	2324(2)	5497(3)	43(1)
C(3)	-517(3)	2382(2)	7423(3)	40(1)
C(31)	-1681(3)	2116(3)	8216(3)	48(1)
C(4)	518(3)	3660(2)	8138(3)	40(1)
C(5)	2228(3)	3221(2)	9576(3)	39(1)
O(3)	3288(2)	3912(2)	10731(2)	50(1)
N(1)	2443(2)	1902(2)	9354(2)	36(1)
C(6)	951(3)	1344(2)	7918(2)	36(1)
C(61)	547(3)	-65(2)	8165(3)	49(1)
C(7)	4087(3)	1155(2)	10282(3)	39(1)
C(71)	5659(3)	1947(3)	10477(3)	55(1)
C(8)	4372(3)	605(2)	11964(2)	36(1)
C(9)	5617(3)	-387(2)	12729(3)	39(1)
C(10)	5980(3)	-930(2)	14277(3)	43(1)
C(11)	5103(3)	-483(2)	15110(3)	44(1)
C(12)	3852(3)	498(2)	14360(3)	44(1)
C(13)	3491(3)	1032(2)	12806(3)	39(1)

Table 15. Bond lengths [pm] and angles [°] for **76a**.

O(1)-C(1)	136.2(3)	C(31)-C(3)-C(4)	110.31(18)
O(1)-C(6)	147.6(2)	C(2)-C(3)-C(6)	102.39(17)
C(1)-O(2)	121.0(3)	C(31)-C(3)-C(6)	113.38(18)
C(1)-C(2)	149.6(3)	C(4)-C(3)-C(6)	101.93(16)
C(2)-C(3)	152.3(3)	C(5)-C(4)-C(3)	105.00(16)
C(3)-C(31)	152.6(3)	O(3)-C(5)-N(1)	125.04(19)
C(3)-C(4)	153.0(3)	O(3)-C(5)-C(4)	126.81(19)
C(3)-C(6)	155.1(3)	N(1)-C(5)-C(4)	108.12(16)
C(4)-C(5)	150.2(3)	C(5)-N(1)-C(6)	112.41(16)
C(5)-O(3)	122.6(3)	C(5)-N(1)-C(7)	125.29(17)
C(5)-N(1)	137.4(3)	C(6)-N(1)-C(7)	121.67(17)
N(1)-C(6)	144.2(2)	N(1)-C(6)-O(1)	108.18(15)
N(1)-C(7)	148.0(3)	N(1)-C(6)-C(61)	114.39(17)
C(6)-C(61)	150.9(3)	O(1)-C(6)-C(61)	106.99(16)
C(7)-C(8)	151.8(3)	N(1)-C(6)-C(3)	105.27(16)
C(7)-C(71)	153.1(3)	O(1)-C(6)-C(3)	103.97(15)
C(8)-C(13)	138.7(3)	C(61)-C(6)-C(3)	117.29(18)
C(8)-C(9)	139.6(3)	N(1)-C(7)-C(8)	113.49(16)
C(9)-C(10)	138.5(3)	N(1)-C(7)-C(71)	112.22(18)
C(10)-C(11)	138.4(3)	C(8)-C(7)-C(71)	111.71(17)
C(11)-C(12)	138.9(3)	C(13)-C(8)-C(9)	117.62(19)
C(12)-C(13)	138.7(3)	C(13)-C(8)-C(7)	124.37(18)
C(1)-O(1)-C(6)	110.62(15)	C(9)-C(8)-C(7)	118.01(18)
O(2)-C(1)-O(1)	120.62(19)	C(10)-C(9)-C(8)	121.8(2)
O(2)-C(1)-C(2)	129.3(2)	C(11)-C(10)-C(9)	119.9(2)
O(1)-C(1)-C(2)	110.08(17)	C(10)-C(11)-C(12)	118.9(2)
C(1)-C(2)-C(3)	104.43(17)	C(13)-C(12)-C(11)	120.8(2)
C(2)-C(3)-C(31)	114.64(19)	C(12)-C(13)-C(8)	120.9(2)
C(2)-C(3)-C(4)	113.30(18)		

Table 16: Anisotropic displacement parameters ($pm^2 x\ 10^{-1}$) for **76a**. The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}]$$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	40(1)	51(1)	31(1)	0(1)	15(1)	8(1)
C(1)	41(1)	45(1)	34(1)	-2(1)	14(1)	0(1)
O(2)	54(1)	75(1)	37(1)	2(1)	21(1)	6(1)
C(2)	34(1)	50(1)	38(1)	-1(1)	12(1)	3(1)
C(3)	34(1)	45(1)	40(1)	2(1)	17(1)	3(1)
C(31)	40(1)	59(1)	50(1)	1(1)	25(1)	2(1)
C(4)	40(1)	38(1)	41(1)	2(1)	20(1)	5(1)
C(5)	42(1)	41(1)	35(1)	-3(1)	20(1)	-3(1)
O(3)	54(1)	48(1)	41(1)	-7(1)	17(1)	-8(1)
N(1)	34(1)	37(1)	33(1)	1(1)	13(1)	4(1)
C(6)	37(1)	39(1)	32(1)	-1(1)	16(1)	2(1)
C(61)	52(1)	42(1)	47(1)	1(1)	18(1)	-3(1)
C(7)	34(1)	48(1)	36(1)	5(1)	16(1)	5(1)
C(71)	40(1)	70(2)	59(1)	24(1)	26(1)	8(1)
C(8)	32(1)	38(1)	34(1)	-1(1)	14(1)	-2(1)
C(9)	37(1)	40(1)	40(1)	1(1)	18(1)	1(1)
C(10)	37(1)	40(1)	43(1)	5(1)	13(1)	2(1)
C(11)	46(1)	44(1)	37(1)	3(1)	16(1)	-5(1)
C(12)	49(1)	46(1)	42(1)	-1(1)	26(1)	-3(1)
C(13)	41(1)	39(1)	39(1)	2(1)	20(1)	2(1)

Table 17. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (pm^2x 10^{-1}) for **76a**.

	x	y	z	U(eq)
H(2A)	-2418	1686	5069	42(3)
H(2B)	-1896	3205	5003	42(3)
H(31A)	-979	2129	9453	64(3)
H(31B)	-2231	1246	7851	64(3)
H(31C)	-2580	2801	7855	64(3)
H(4A)	691	4127	7265	42(3)
H(4B)	-93	4258	8549	42(3)
H(61A)	1508	-642	8313	64(3)
H(61B)	-524	-351	7171	64(3)
H(61C)	396	-117	9173	64(3)
H(7)	3987	372	9561	45(6)
H(71A)	5419	2303	9374	64(3)
H(71B)	6679	1367	10912	64(3)
H(71C)	5886	2678	11272	64(3)
H(9)	6233	-698	12173	53(3)
H(10)	6829	-1608	14766	53(3)
H(11)	5352	-841	16179	53(3)
H(12)	3236	806	14917	53(3)
H(13)	2628	1700	12312	53(3)

Table 18: Torsion angles [°] for **76a**

C(6)-O(1)-C(1)-O(2)	-178.8(2)	C(4)-C(3)-C(6)-N(1)	24.16(19)
C(6)-O(1)-C(1)-C(2)	1.6(2)	C(2)-C(3)-C(6)-O(1)	27.9(2)
O(2)-C(1)-C(2)-C(3)	-162.6(2)	C(31)-C(3)-C(6)-O(1)	151.96(18)
O(1)-C(1)-C(2)-C(3)	16.9(2)	C(4)-C(3)-C(6)-O(1)	-89.50(17)
C(1)-C(2)-C(3)-C(31)	-150.20(19)	C(2)-C(3)-C(6)-C(61)	-89.9(2)
C(1)-C(2)-C(3)-C(4)	82.0(2)	C(31)-C(3)-C(6)-C(61)	34.1(3)
C(1)-C(2)-C(3)-C(6)	-27.0(2)	C(4)-C(3)-C(6)-C(61)	152.65(18)
C(2)-C(3)-C(4)-C(5)	-135.47(18)	C(5)-N(1)-C(7)-C(8)	86.0(2)
C(31)-C(3)-C(4)-C(5)	94.5(2)	C(6)-N(1)-C(7)-C(8)	-103.8(2)
C(6)-C(3)-C(4)-C(5)	-26.2(2)	C(5)-N(1)-C(7)-C(71)	-41.8(3)
C(3)-C(4)-C(5)-O(3)	-162.2(2)	C(6)-N(1)-C(7)-C(71)	128.3(2)
C(3)-C(4)-C(5)-N(1)	19.7(2)	N(1)-C(7)-C(8)-C(13)	-17.1(3)
O(3)-C(5)-N(1)-C(6)	178.0(2)	C(71)-C(7)-C(8)-C(13)	111.0(2)
C(4)-C(5)-N(1)-C(6)	-3.9(2)	N(1)-C(7)-C(8)-C(9)	163.64(18)
O(3)-C(5)-N(1)-C(7)	-11.1(3)	C(71)-C(7)-C(8)-C(9)	-68.3(3)
C(4)-C(5)-N(1)-C(7)	167.08(17)	C(13)-C(8)-C(9)-C(10)	-0.3(3)
C(5)-N(1)-C(6)-O(1)	97.29(18)	C(7)-C(8)-C(9)-C(10)	179.0(2)
C(7)-N(1)-C(6)-O(1)	-74.0(2)	C(8)-C(9)-C(10)-C(11)	-0.4(3)
C(5)-N(1)-C(6)-C(61)	-143.59(18)	C(9)-C(10)-C(11)-C(12)	0.8(3)
C(7)-N(1)-C(6)-C(61)	45.1(2)	C(10)-C(11)-C(12)-C(13)	-0.5(3)
C(5)-N(1)-C(6)-C(3)	-13.4(2)	C(11)-C(12)-C(13)-C(8)	-0.2(3)
C(7)-N(1)-C(6)-C(3)	175.31(16)	C(9)-C(8)-C(13)-C(12)	0.6(3)
C(1)-O(1)-C(6)-N(1)	-130.56(17)	C(7)-C(8)-C(13)-C(12)	-178.7(2)
C(1)-O(1)-C(6)-C(61)	105.7(2)		
C(1)-O(1)-C(6)-C(3)	-19.0(2)		
C(2)-C(3)-C(6)-N(1)	141.57(17)		
C(31)-C(3)-C(6)-N(1)	-94.4(2)		

Table 19. Crystal data and structure refinement for (1R, 5S, 1´S)-1, 5-dimethyl-8-(-4-methoxyphenyl) ethyl-2-oxa-8-aza-*cis*-bicyclo [3.3.0] octan-3, 7-dion (**77a**)

Identification code	**77a**	
Empirical formula	$C_{17}\ H_{21}\ N\ O_4$	
Formula weight	303.35	
Temperature	173(2) K	
Wavelength	71.073 pm	
Crystal system	Monoclinic	
Space group	P 2_1	
Unit cell dimensions	a = 651.40(10) pm	α= 90°.
	b = 738.90(10) pm	β= 93.130(10) °.
	c = 1606.5(2) pm	γ = 90°.
Volume	0.77209(18) nm^3	
Formula unit per cell Z	2	
Density (calculated)	1.305 Mg/m^3	
Absorption coefficient	0.093 mm^{-1}	
F (000)	324	
Crystal size	0.8 x 0.6 x 0.5 mm^3	
Theta range for data collection	2.54 to 27.50°.	
Index ranges	$-8 \le h \le 8$, $-9 \le k \le 9$, $-20 \le l \le 20$	
Reflections collected	7161	
Independent reflections	1907 [R (int) = 0.0311]	
Completeness to theta = 27.50°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1907 / 1 / 208	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2sigma (I)]	R1 = 0.0287, wR2 = 0.0755	
R indices (all data)	R1 = 0.0299, wR2 = 0.0770	
Absolute structure parameter	Not refined, Friedel pairs merged	
Extinction coefficient	0.065(6)	
Largest diff. peak and hole	0.214 and -0.132 e.$Å^{-3}$	

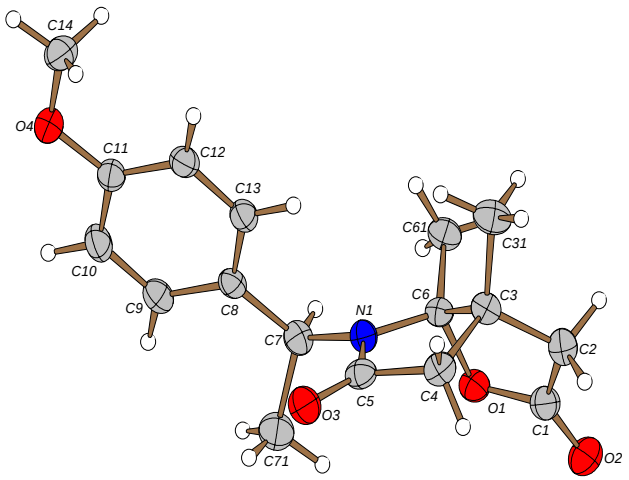


Figure 32: X-ray crstal structure for **77a**

Table 20. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (pm^2x 10^{-1}) for **77a**. U (eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	5418(2)	2659(2)	1055(1)	27(1)
C(1)	4762(3)	2246(2)	268(1)	30(1)
O(2)	5888(2)	2366(2)	-301(1)	44(1)
C(2)	2560(2)	1622(2)	242(1)	31(1)
C(3)	1787(2)	2151(2)	1090(1)	25(1)
C(31)	212(2)	836(3)	1411(1)	35(1)
C(4)	1030(2)	4123(2)	1119(1)	28(1)
C(5)	2084(2)	4945(2)	1890(1)	27(1)
O(3)	1703(2)	6394(2)	2201(1)	36(1)
N(1)	3572(2)	3757(2)	2188(1)	24(1)
C(6)	3812(2)	2232(2)	1652(1)	22(1)
C(61)	4486(2)	494(2)	2084(1)	29(1)
C(7)	5036(2)	4215(2)	2886(1)	27(1)
C(71)	6348(3)	5857(3)	2677(1)	43(1)
C (8)	3938(2)	4399(2)	3699(1)	24(1)
C (9)	4858(2)	5342(2)	4373(1)	31(1)
C (10)	3968(3)	5406(2)	5136(1)	33(1)
C (11)	2114(2)	4527(2)	5248(1)	28(1)
O (4)	1377(2)	4646(2)	6029(1)	35(1)
C (14)	-482(3)	3696(3)	6169(1)	37(1)
C (12)	1149(2)	3599(2)	4583(1)	28(1)
C (13)	2078(2)	3540(2)	3821(1)	27(1)

Table 21: Bond lengths [pm] and angles [°] for **77a**.

O(1)-C(1)	134.8(2)	C(2)-C(3)-C(4)	112.98(14)
O(1)-C(6)	148.98(16)	C(31)-C(3)-C(6)	113.15(13)
C(1)-O(2)	120.57(19)	C(2)-C(3)-C(6)	102.48(12)
C(1)-C(2)	150.5(2)	C(4)-C(3)-C(6)	102.07(12)
C(2)-C(3)	152.9(2)	C(5)-C(4)-C(3)	105.84(12)
C(3)-C(31)	152.3(2)	O(3)-C(5)-N(1)	125.24(16)
C(3)-C(4)	153.9(2)	O(3)-C(5)-C(4)	126.76(15)
C(3)-C(6)	155.79(19)	N(1)-C(5)-C(4)	108.00(13)
C(4)-C(5)	151.1(2)	C(5)-N(1)-C(6)	113.04(12)
C(5)-O(3)	121.3(2)	C(5)-N(1)-C(7)	122.26(14)
C(5)-N(1)	137.4(2)	C(6)-N(1)-C(7)	123.51(12)
N(1)-C(6)	143.2(2)	N(1)-C(6)-O(1)	108.90(12)
N(1)-C(7)	147.16(19)	N(1)-C(6)-C(61)	115.45(12)
C(6)-C(61)	151.3(2)	O(1)-C(6)-C(61)	106.17(11)
C(7)-C(8)	152.8(2)	N(1)-C(6)-C(3)	105.16(12)
C(7)-C(71)	153.2(2)	O(1)-C(6)-C(3)	103.75(11)
C(8)-C(13)	139.1(2)	C(61)-C(6)-C(3)	116.64(13)
C(8)-C(9)	139.6(2)	N(1)-C(7)-C(8)	110.97(12)
C(9)-C(10)	138.5(2)	N(1)-C(7)-C(71)	111.14(14)
C(10)-C(11)	139.2(2)	C(8)-C(7)-C(71)	114.17(14)
C(11)-O(4)	137.11(18)	C(13)-C(8)-C(9)	117.29(14)
C(11)-C(12)	139.0(2)	C(13)-C(8)-C(7)	122.11(13)
O(4)-C(14)	142.8(2)	C(9)-C(8)-C(7)	120.44(14)
C(12)-C(13)	139.5(2)	C(10)-C(9)-C(8)	121.43(15)
C(1)-O(1)-C(6)	110.99(12)	C(9)-C(10)-C(11)	120.42(14)
O(2)-C(1)-O(1)	121.34(16)	O(4)-C(11)-C(12)	124.67(15)
O(2)-C(1)-C(2)	128.33(16)	O(4)-C(11)-C(10)	115.95(14)
O(1)-C(1)-C(2)	110.32(13)	C(12)-C(11)-C(10)	119.37(14)
C(1)-C(2)-C(3)	104.91(13)	C(11)-O(4)-C(14)	117.07(13)
C(31)-C(3)-C(2)	113.52(14)	C(11)-C(12)-C(13)	119.32(14)
C(31)-C(3)-C(4)	111.76(13)	C(8)-C(13)-C(12)	122.16(14)

Table 22: Anisotropic displacement parameters ($pm^2 x\ 10^{-1}$) for **77a.** The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h2\ a^{*2} U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}]$$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	22(1)	28(1)	32(1)	-1(1)	7(1)	0(1)
C(1)	34(1)	25(1)	32(1)	-1(1)	9(1)	4(1)
O(2)	52(1)	44(1)	38(1)	-4(1)	22(1)	-3(1)
C(2)	32(1)	31(1)	30(1)	-4(1)	-1(1)	1(1)
C(3)	21(1)	24(1)	30(1)	1(1)	-1(1)	1(1)
C(31)	23(1)	35(1)	46(1)	5(1)	0(1)	-5(1)
C(4)	25(1)	28(1)	29(1)	4(1)	1(1)	7(1)
C(5)	26(1)	26(1)	29(1)	4(1)	8(1)	3(1)
O(3)	42(1)	26(1)	39(1)	-2(1)	8(1)	9(1)
N(1)	23(1)	23(1)	26(1)	-2(1)	1(1)	3(1)
C(6)	18(1)	22(1)	26(1)	1(1)	4(1)	1(1)
C(61)	27(1)	24(1)	36(1)	4(1)	0(1)	3(1)
C(7)	23(1)	28(1)	31(1)	-3(1)	0(1)	-1(1)
C(71)	40(1)	48(1)	42(1)	-5(1)	10(1)	-19(1)
C(8)	26(1)	19(1)	27(1)	1(1)	-1(1)	1(1)
C(9)	29(1)	28(1)	35(1)	-3(1)	-1(1)	-6(1)
C(10)	38(1)	29(1)	30(1)	-6(1)	-6(1)	-4(1)
C(11)	35(1)	22(1)	25(1)	1(1)	0(1)	3(1)
O(4)	46(1)	33(1)	26(1)	-1(1)	4(1)	-2(1)
C(14)	46(1)	34(1)	33(1)	3(1)	10(1)	1(1)
C(12)	29(1)	25(1)	30(1)	1(1)	0(1)	-4(1)
C(13)	29(1)	24(1)	27(1)	-1(1)	-2(1)	-2(1)

Table 23: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (pm^2x 10^{-1}) for **77a**.

	x	y	z	U(eq)
H(2A)	2472	297	159	45(3)
H(2B)	1743	2229	-214	45(3)
H(31A)	-1032	859	1040	45(2)
H(31B)	-132	1193	1974	45(2)
H(31C)	789	-389	1425	45(2)
H(4A)	1404	4787	614	45(3)
H(4B)	-482	4162	1153	45(3)
H(61A)	5910	618	2306	45(2)
H(61B)	4393	-507	1684	45(2)
H(61C)	3592	247	2542	45(2)
H(7)	5997	3165	2960	30(5)
H(71A)	6797	5739	2107	45(2)
H(71B)	7553	5919	3068	45(2)
H(71C)	5531	6963	2721	45(2)
H(9)	6122	5954	4308	36(3)
H(10)	4628	6053	5586	36(3)
H(14A)	-1616	4231	5827	45(2)
H(14B)	-778	3785	6759	45(2)
H(14C)	-326	2421	6018	45(2)
H(12)	-130	3011	4647	36(3)
H(13)	1418	2893	3371	36(3)

Table 24: Torsion angles [°] for **77a**.

C(6)-O(1)-C(1)-O(2)	-174.53(16)	C(31)-C(3)-C(6)-C(61)	33.03(19)
C(6)-O(1)-C(1)-C(2)	4.34(17)	C(2)-C(3)-C(6)-C(61)	-89.59(16)
O(2)-C(1)-C(2)-C(3)	-167.63(18)	C(4)-C(3)-C(6)-C(61)	153.27(13)
O(1)-C(1)-C(2)-C(3)	13.60(18)	C(5)-N(1)-C(7)-C(8)	67.31(19)
C(1)-C(2)-C(3)-C(31)	-146.86(14)	C(6)-N(1)-C(7)-C(8)	-126.04(14)
C(1)-C(2)-C(3)-C(4)	84.56(15)	C(5)-N(1)-C(7)-C(71)	-60.88(19)
C(1)-C(2)-C(3)-C(6)	-24.49(16)	C(6)-N(1)-C(7)-C(71)	105.77(17)
C(31)-C(3)-C(4)-C(5)	100.46(14)	N(1)-C(7)-C(8)-C(13)	24.3(2)
C(2)-C(3)-C(4)-C(5)	-130.05(13)	C(71)-C(7)-C(8)-C(13)	150.88(16)
C(6)-C(3)-C(4)-C(5)	-20.75(15)	N(1)-C(7)-C(8)-C(9)	-160.37(14)
C(3)-C(4)-C(5)-O(3)	-169.40(15)	C(71)-C(7)-C(8)-C(9)	-33.8(2)
C(3)-C(4)-C(5)-N(1)	10.54(16)	C(13)-C(8)-C(9)-C(10)	0.7(2)
O(3)-C(5)-N(1)-C(6)	-174.34(14)	C(7)-C(8)-C(9)-C(10)	-174.83(15)
C(4)-C(5)-N(1)-C(6)	5.72(17)	C(8)-C(9)-C(10)-C(11)	-0.2(3)
O(3)-C(5)-N(1)-C(7)	-6.4(2)	C(9)-C(10)-C(11)-O(4)	178.98(16)
C(4)-C(5)-N(1)-C(7)	173.64(13)	C(9)-C(10)-C(11)-C(12)	-0.7(2)
C(5)-N(1)-C(6)-O(1)	91.36(14)	C(12)-C(11)-O(4)-C(14)	2.1(2)
C(7)-N(1)-C(6)-O(1)	-76.39(16)	C(10)-C(11)-O(4)-C(14)	-177.60(16)
C(5)-N(1)-C(6)-C(61)	-149.36(13)	O(4)-C(11)-C(12)-C(13)	-178.51(15)
C(7)-N(1)-C(6)-C(61)	42.89(19)	C(10)-C(11)-C(12)-C(13)	1.1(2)
C(5)-N(1)-C(6)-C(3)	-19.31(16)	C(9)-C(8)-C(13)-C(12)	-0.2(2)
C(7)-N(1)-C(6)-C(3)	172.94(13)	C(7)-C(8)-C(13)-C(12)	175.22(15)
C(1)-O(1)-C(6)-N(1)	-131.67(13)	C(11)-C(12)-C(13)-C(8)	-0.7(2)
C(1)-O(1)-C(6)-C(61)	103.42(14)		
C(1)-O(1)-C(6)-C(61)	103.42(14)		
C(1)-O(1)-C(6)-C(3)	-20.05(16)		
C(31)-C(3)-C(6)-N(1)	-96.33(15)		
C(2)-C(3)-C(6)-N(1)	141.05(12)		
C(4)-C(3)-C(6)-N(1)	23.91(15)		
C(31)-C(3)-C(6)-O(1)	149.36(13)		
C(2)-C(3)-C(6)-O(1)	26.74(15)		
C(4)-C(3)-C(6)-O(1)	-90.40(13)		

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