THE USE OF THE CROSSED ALDOL MUKAIYAMA REACTION FOR THE PREPARATION OF ADVANCED INTERMEDIATES FOR THE SYNTHESIS OF RHAZINILAM ANALOGUES

Thesis presented to the Faculté de Science,
Institut de chimie of Université de Neuchâtel for the award of degree of
Doctor of Science

By

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University of Neuchâtel

2008

Université de Neuchâtel

FACULTE DES SCIENCES
Secrétariat-Décanat de la faculté
- Rue Emile-Argand 11
- CP 158
- CH-2009 Neuchâtel

IMPRIMATUR POUR LA THESE

The Use of the Crossed Aldol Mukaiyama Reaction for the Preparation of Advanced Intermediates for the Synthesis of Rhazinilam Analogues

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Neuchâtel, le 8 mai 2008

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Acknowledgment

This PhD work was accomplished from August 2003 to April 2008 in the Laboratory of synthetic organic chemistry, Institute of Chemistry, University of Neuchâtel under the guidance of Prof. Reinhard NEIER. Special thanks go to him for the opportunity that he gave to me to work in his group on a wonderful topic, for his advices for being a better chemist, but also for life, for giving me the independence to apply my ideas (not always the best, but always very fruitful for my experience), to guide me to learn more during the seminars and conferences.

I sincerely acknowledge Prof. Philippe Renaud, Prof. Thomas Ward and Prof. Robert Deschenaux for being the jury experts of my thesis, for taking their time to correct my manuscript and giving me an interesting discussion and a wonderful remembrance from my exam.

I thank the group members: Dr. Olivier Vallat (uff, working with a girl…who is not able to understand “3 grains of DMAP”…), Dr. Vallinayagam Ramakrishnan (Valli – for sharing all our good and bad times of the four years working together), Dr. François Loiseau, “not yet, but almost Dr.” Beat Herzog, Dr. Valeria Blangy, Dr. Sébastien Lanaspèze, Dr. Sabine Gacond, Dr. Sylvain Burger, Damien Thevent (a wonderful colleague and friend, but a frightful Poker player), Inga Zaitseva, Vsevolov Khlebnikov, Gurba Patrice (also a very good friend).

I thank Mrs. Jocelyne Tissot for all administrative help she made, Mr. Maurice Binggeli and Mrs. Claire Rosset, Mr. Heinz Bursian, Julien Furrer, Jean-Denis Bernard, Armelle Vallat for their analytical services and to Mr. Pierre Tissot for all his help in informatics problems.

My special thanks for making my life at Neuchatel very enjoyable go to my friends Claudia and Iulian and to their little princes Ania, Sabina, Cristina and Adrian, Mustapha, Julieta, Olha, Magdalina, Yolanda, Mona and Julien, Dalila, Cristi and their angel Amalia, Florin, Gabi and to my best friend from the first year of University till today, Corina.

My greatest thanks go to my parents, Maria and Neculai, to my brother, Nicu, and to my grandparents for all their support and wishes.

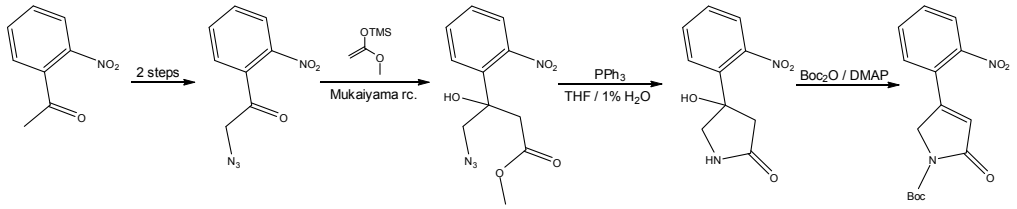
To Marc

Key words:

Rhazinilam, Rhazinilam analogues, Crossed Aldol Mukaiyama reaction, Stereoselectivity of the Mukaiyama reaction.

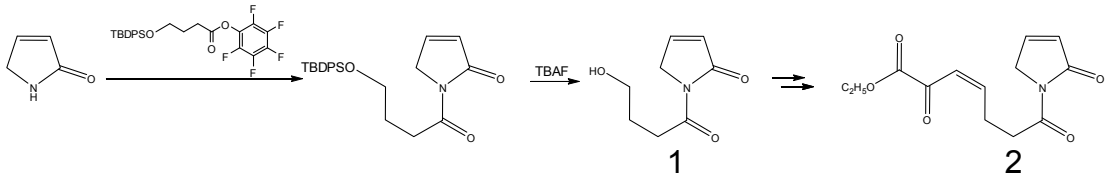
Resume

L'étude des précédents exemples de synthèse totale du rhazinilam et de ses analogues, nous a conduit à élaborer notre propre approche basée sur une réaction d'aldolisation croisée de Mukaiyama comme étape clé. La voie de synthèse est décrite (en partie) ci-dessous :

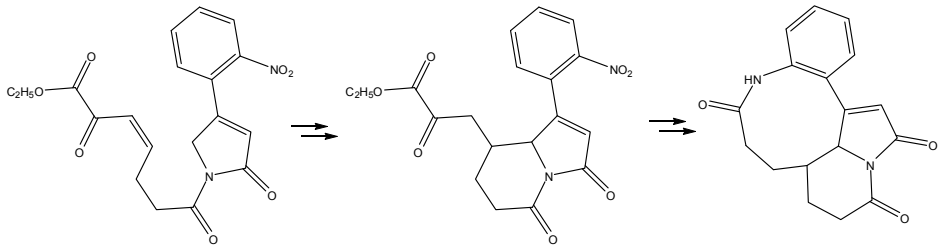


La détermination de la diastéréosélectivité des reactions concernées est realizée par analyse des structures par diffractométrie de rayons-X.

Les étapes suivantes ont été étudiées sur un modèle simplifié. Le composé **1** est obtenu par N-acylation du 1H-pyrrole-2(5H)-one suivie de la déprotection de la fonction alcool. L'oxydation controlée de la fonction alcool de **1** en aldéhyde suivie d'une réaction de Wittig permet d'obtenir le composé **2**.

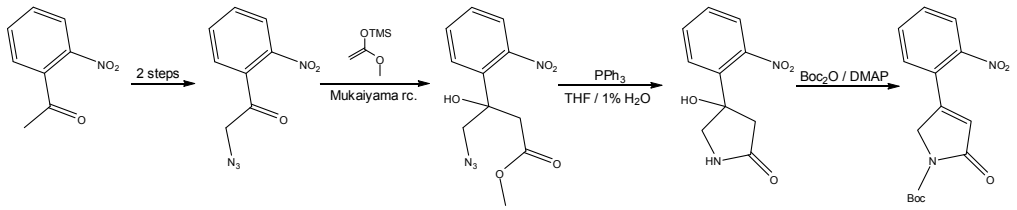


La méthodologie envisagée pour aboutir à la synthèse des analogues du rhazinilam est la suivante : on forme le cycle à six chaînons par une réaction d'addition de Michael suivie de la réduction du groupement nitro et, enfin, une réaction de lactamisation permet de former le cycle à neuf chaînons.



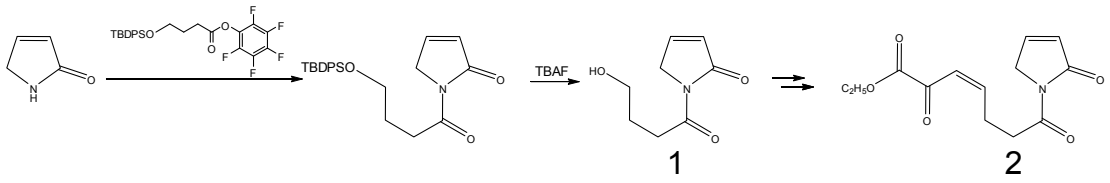
Abstract

Having studied the previous total syntheses of rhazinilam and of its analogues, we developed our own strategy based the crossed aldol Mukaiyama reaction as the key step. The synthetic pathway is depicted below:

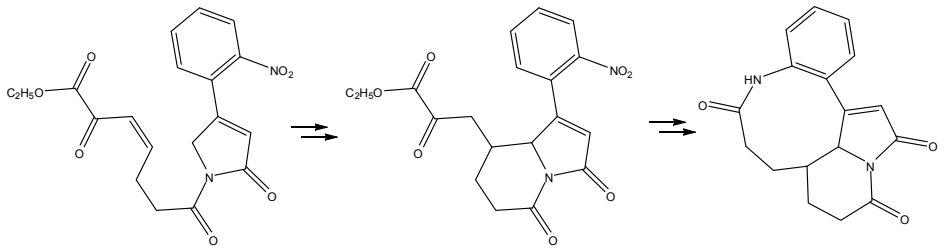


The determination of the diastereoselectivity of the reactions reported above could be achieved with the help X-ray structures.

Working with model molecules, by acylation of 1*H*-pyrrole-2(*5H*)-one to nitrogen, cleavage of hydroxyl group protection, we could obtain 1-(4-hydroxybutanoyl)-1*H*-pyrrol-2(*5H*)-one (**1**). The oxidation of product **1** to aldehyde followed by Wittig reaction will lead to the compound **2**.



The last steps planed for the synthesis of the rhazinilam analogues are: six membered ring formation by Michael reaction, reduction of nitro group and cyclisation to nine membered ring.



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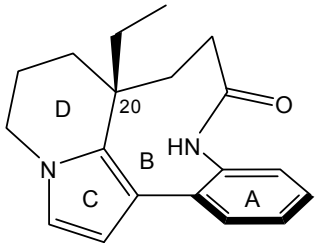
1. Introduction

1.1. (-)-Rhazinilam: biosynthetic origins, semi-synthesis and structural elucidation

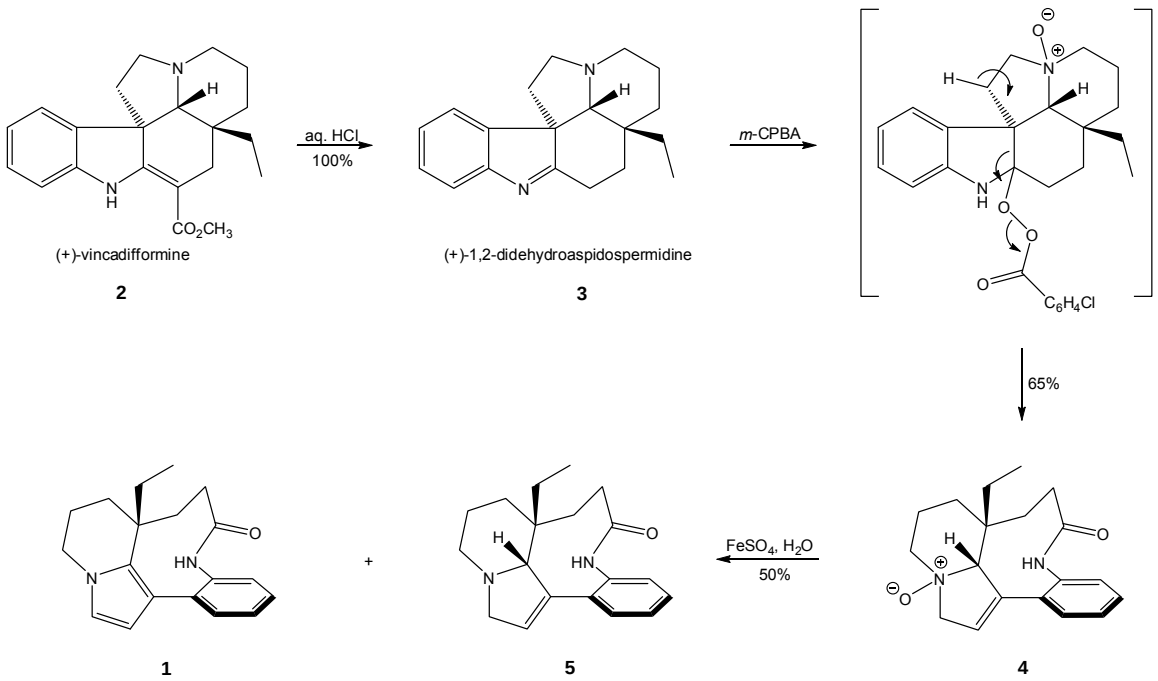
(-)-Rhazinilam, a natural product, was isolated for the first time from *Melodinus australis* in 1965[1]. Later it has been found in other South-east Asian members of the specific family Apocynaceae[2]: *Rhazya stricta*, *Aspidosperma quebracho-blanco*, *Leuconotis eugenifolia*, *Kopsia singapurensis* and *Kopsia teoi*. More recently, (-)-rhazinilam was isolated from intergeneric somatic hybrid cell culture of two members of the same family: *Rauvolfia serpentine* and *Rhazia stricta*.



(-)-rhazinilam (**1**)

The structure of (-)-rhazinilam **1** was initially established through spectroscopic analysis and chemical degradation studies[3] then confirmed using X-ray crystallographic techniques[4]. Compound **1** is characterized by the presence of four rings: the phenyl A-ring, the nine-membered lactam B-ring, the pyrrole C-ring and the piperidine D-ring. Through X-ray analysis, it was determined that the A-C dihedral angle of rhazinilam is ca. 90°, the amide bond possesses a *cis* conformation and the median ring adopts a boat-chair conformation. This molecule bears two stereogenic elements: the quaternary carbon atom C-20 and the phenyl-pyrrole chirality axis. Unfortunately, it was not possible to determine the absolute configuration (*R*, a*R*) by X-ray analysis. Instead, it was established *via* semi-synthesis of **1** from an aspidosperma alkaloid (+)-1,2-didehydroaspidospermidine (**3**)[5]. (-)-Rhazinilam is considered now as an artefact of the isolation procedure employed during the extraction from the source plant.

The naturally occurring indole alkaloid (+)-1,2-didehydroaspidospermidine (**3**) was sequentially treated with *m*-CPBA and ferrous sulfate to give (-)-rhazinilam in ca. 30% yield (Scheme 1).



Scheme 1: Semi-synthesis of (-)-rhazinilam

The mechanism of this stepwise conversion was first proposed by Smith and later confirmed by Baudoin[6, 7]. The reaction sequence begins with the acid-catalysed removal of the ester group in (+)-vincadifformine (**2**) providing (+)-1,2-didehydroaspidospermidine (**3**) quantitatively. The next step is *m*-CPBA oxidative cleavage of the C2-C3 indoline bond to produce the nine-membered ring in **4** in 65% yield. By treatement with Fe(II), compound **4** was reduced to a 9:1 mixture of rhazinilam (**1**) and 5,21-dihydrorhazinilam (**2**) (itself giving rhazinilam upon exposure to air for several days). This slow conversion **5**→**1** suggested that the formation of rhazinilam from compound **4** occurred *via* a Polonovski-type reaction. Indeed, it was found that subjecting compound **4** to acetic anhydride and Et_3N (standard Polonovski conditions) afforded (-)-rhazinilam (**1**) in 81%. These observations led to the conclusion that, in the plant, the direct biogenetic precursor of **1** is almost certainly the air-sensitive 5,21-dihydrorhazinilam (**5**). Nevertheless, since (+)-1,2-didehydroaspidospermidine (**3**) has never been found to co-occur *in vivo* with alkaloids **1** or **5**, the question if **3** is the actual biogenetic precursor of the compound **5** remains an open one. Since the absolute configuration of (+)-vincadifformine (**2**) had been unambiguously determined, this semi-synthesis provided the first experimental evidence of the absolute configuration of (-)-rhazinilam (**1**).

Other alkaloids possessing the same tetracyclic-system as rhazinilam have been isolated from various members of the family Apocynaceae: 3-oxo-rhazinilam (**6**) (rhazinicine), 3-oxo-14,15-dehydrorhazinilam (**7**), (-)-leuconolam (**8**) and rhazinal (**9**).

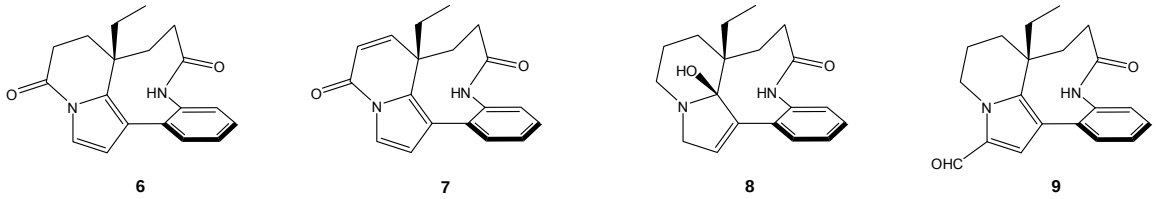


Figure 1: Natural analogues of (-)-rhazinilam 1

Such alkaloids are also likely to be derived from 5,21-dihydrorhazinilam (**5**) *via* oxidative pathways.

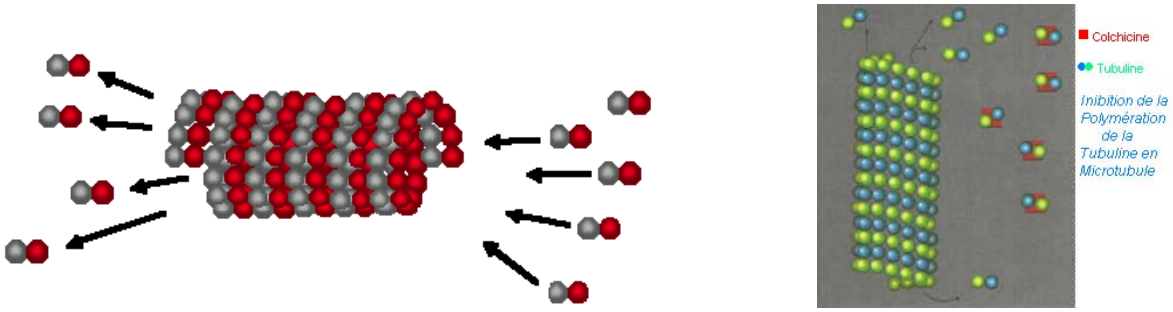
Rhazinal (**9**) has a particular interest because it possesses similar properties to those of (-)-rhazinilam (**1**). **9** was prepared *via* Vilsmeier-Haack formylation of (-)-rhazinilam as part of a structure-activity relationship (SAR) study around this family of compounds. In 1998, Kam and co-workers[8] reported the isolation of (-)-rhazinal (**9**) from stem extracts of a Malayan member of the Apocynaceae, *Kopsia teoi*, a plant that also produces (-)-rhazinilam (**1**).

1.2. Biological activity of rhazinilam and its analogues

Cancer is a class of diseases in which a group of cells shows uncontrolled growth (growth and division beyond the normal limits), invasion (intrusion on and destruction of adjacent tissues) and, sometimes, metastasis (spread to other locations in the body via lymph or blood)[9]. This disease causes about 13% of all deaths. According to the American Cancer Society[10], about 565'650 Americans are expected to die of cancer in 2008 (more than 1500 people a day). Cancer can be treated by surgery, chemotherapy, radiation therapy, immunotherapy, photodynamic therapy, monoclonal antibody therapy or other methods. The choise of therapy depends upon the location and grade of the tumor[11] and the stage of the disease, as well as the general state of the patient.

Chemotherapy is the treatment of cancer with drugs that can destroy cancer cells. The term "chemotherapy" usually refers to the use cytotoxic drugs which affect rapidly dividing cells in general, in contrast with targeted therapy. Chemotherapy drugs interfere with cell division in various possible ways: the duplication of DNA or the separation of newly formed chromosomes (mitosis). Most targets of chemotherapy are rapidly dividing cells and chemotherapy is usually not specific for cancer cells. Some degree of specificity may come from the inability of many cancer cells to repair DNA damage, while normal cells generally can. Hence, chemotherapy has the potential to harm healthy tissue, especially those tissues that have a high rate of cell division (e.g.: hair). These cells usually repair themselves after chemotherapy.

Cell division is facilitated by the formation of the mitotic spindle apparatus which is constructed from a complex and ordered network of microtubules. Microtubules are themselves formed through the reversible dimerisation of a protein called tubulin. In mitotic process, a dynamic interconversion of tubulin and microtubules is required. Consequently, small molecules that disrupt the assembly (vinblastine, colchicine) (Figure 2) or disassembly (paclitaxel, also known as Taxol, and docetaxel) of microtubules have shown a remarkable ability to suppress cell proliferation. Many of these molecules are derived from natural sources and, indeed, some of them, have been successfully employed in the treatment of certain cancers (Figure 3)[12].



A **B**

Figure 2: (A) Normal assembly of the tubulin (dynamic instability)[13]; (B) Colchicine inhibits polymerization of tubuline in microtubules[14].

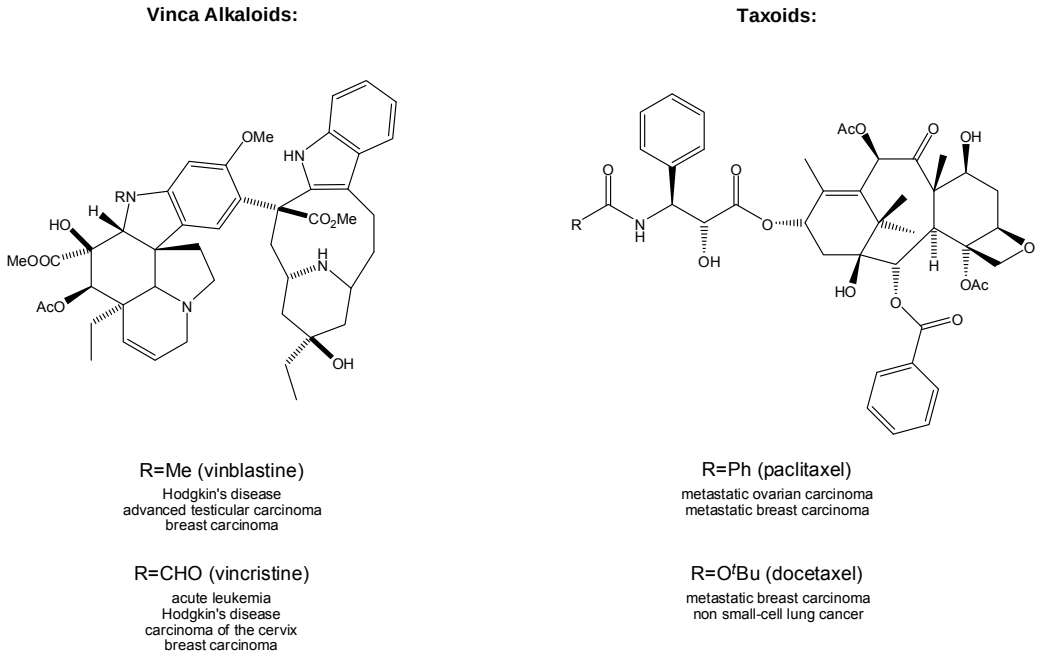


Figure 3

The discovery of the tubulin-binding properties of rhazinilm was made through the screening of a number of Malaysian plant extracts by the Poitier group in Gif sur Yvette[15]. Indeed, this group established that (-)-rhazinilam mimics the effect of both vinblastin and paclitaxel: it exerts a vinblastine-like effect by inducing the non-reversible assembly (spiralisation) of tubulin, as well as inhibiting the cold-induced disassembly of microtubules in the same manner as the taxoids[16].(-)-Rhazinilam has also demonstrated a similarity to Taxol by inducing the formation of anomalous tubulin assemblies (Figure 4)[17].

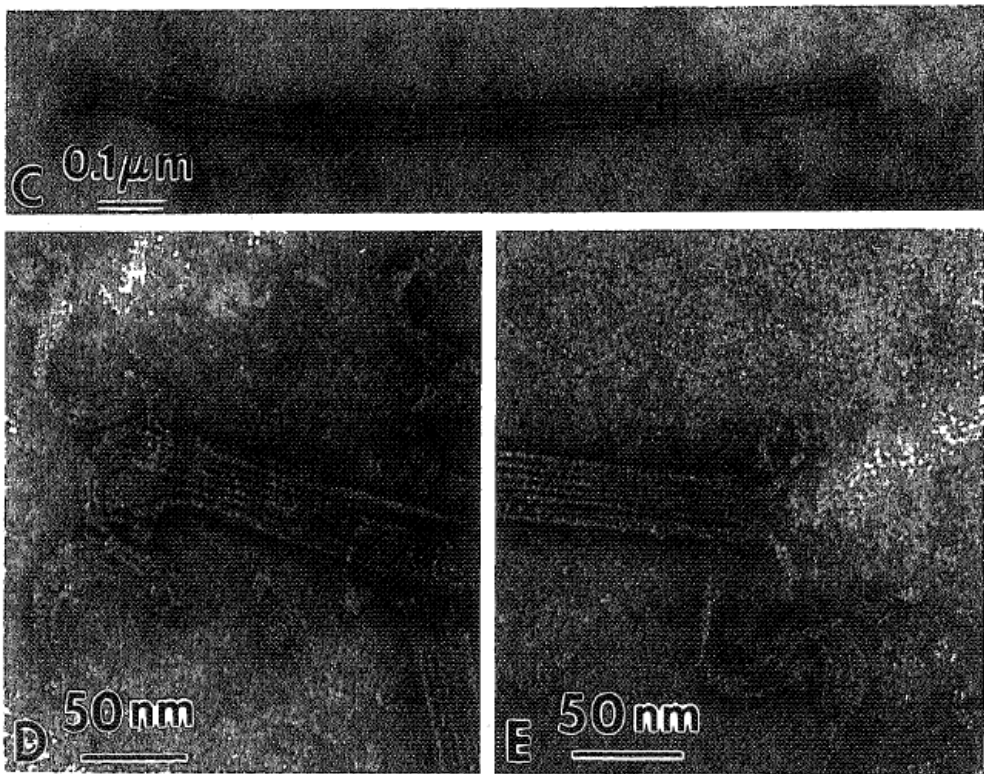
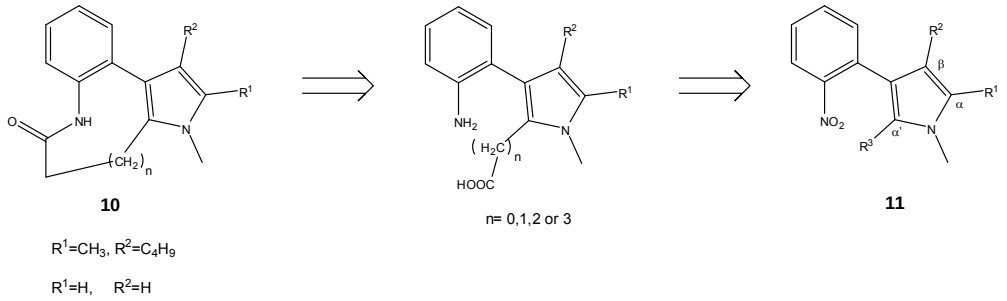


Figure 4: Presence of spirals at the two extremities of a microtubule preincubated at 37 °C in the presence of rhazinilam (125 μM) and further submitted to a 30 min. treatment at 0 °C[17]

As a consequence of its tubulin-binding properties, (-)-rhazinilam shows moderate cytotoxicity towards KB cell lines, with IC_{50}values in the range 7 μM[6, 16].

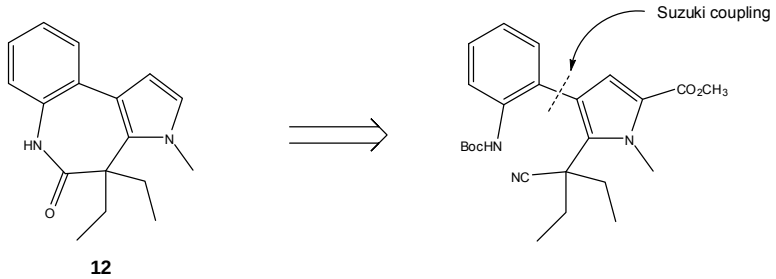
Observing the novel mode of interaction of (-)-rhazinilam with tubullin, several structure-activity relationship (SAR) studies seeking to identify analogues with improved pharmacological properties have been conducted. The analogues were prepared by semi-synthesis from (-)-rhazinilam itself or by "total" synthesis. Thus, for exemple, semi-synthetic routes related to those employed for producing useful quantities of (-)-rhazinilam have also been used for the generation of its enantiomer (+)-rhazinilam, from the alkaloid (-)-tabersonine[15]. Significantly, the (+)-rhazinilam enantiomer failed to inhibit tubulin polymerization due to a lack of binding affinity for this protein.

The Thal group was the first to conduct SAR studies[2] by total synthesis of phenyl-pyrrole analogues[18, 19]. To study the role of the lactame B-ring of rhazinilam, they synthesized a number of achiral phenyl-pyrrole lacking this ring or having different lactame ring size (6 o 9-membered):



Scheme 2: Precursors of phenyl-pyrrole analogues

Substituted phenyl-pyrrole such as **11** were prepared using the Barton-Zard[20] or the Gupton[21] methods. Functionalisation of the R^3 chain and cyclisation afforded various tricyclic lactam **10**. The fact that all intermediates such as **11** lacking the lactam B-ring were inactive on tubulin was confirmed in subsequent studies. Tricyclic analogues, including those having a 9-membered lactame ring such as rhazinilam showed a 200 times smaller activity compared to rhazinilam. These important results provided the first evidence that both the lactame B-ring and the substitution at C-20 atom were essential for the interaction with tubulin. The presence of bulky substituents at C-20 induces the lactam ring of rhazinilam a rigid boat-chair conformation which is the active species in the term of the tubulin binding process.

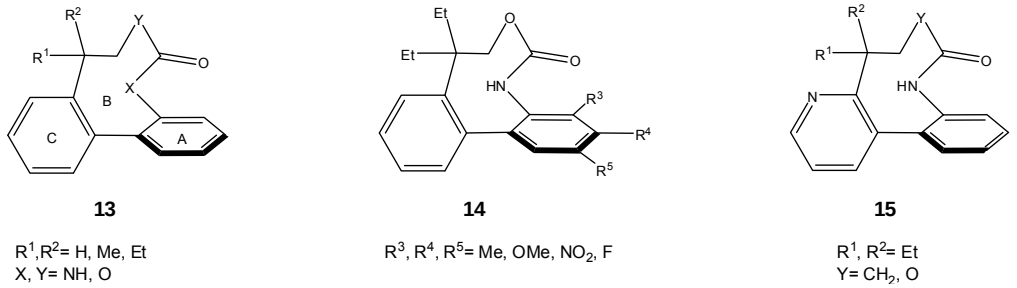


Scheme 3: Synthesis of phenyl-pyrrole analogues

An achiral tricyclic 7-membered lactam **12** was inactive on the cold-induced disassembly of microtubules. It showed inhibition of tubulin polymerization with an IC_{50} value of 27 µM (IC_{50} = 7 µM for rhazinilam and a significant toxicity towards KB cells (IC_{50} = 7 µM, 1/14 compared to rhazinilam).

Studies aimed at replacing the pyrrole C-ring of rhazinilam by other aromatic rings have been undertaken. In the first place, a number of racemic biphenyl analogues having the general structure **13** have been synthesized using a strategy similar to that leading to **12**,

with construction of the biphenyl bond by a Stille or Suzuki-Miyaura coupling and final cyclisation to form the bridging ring[2].



13 **14** **15**

R^1,R^2= H, Me, Et
X, Y= NH, O

R^3, R^4, R^5= Me, OMe, NO_2, F

R^1, R^2= Et
Y= CH_2, O

Figure 5

Some analogues like **13A**, having the structure closest to rhazinilam, but with no D-ring, were less active than the natural product. Decreasing the size and the number of alkyl substituents R^1 and R^2 (entries 2 and 3, Table 1) a dramatic decrease of the antitubulin activity in accordance with observation from Thal and co-workers was observed. Replacing the lactam by a lactone (entry 4) or by urea (entry 5) proved unfruitful, but the replacement by a carbamate (entry 6) was particulary interesting. Indeed racemic compound (**13F**) was equipotent to rhazinilam on the inhibition of both microtubule assembly and disassembly and was twice less cytotoxic towards KB and MCF7 cells. It was shown also that the presence of a cyclohexane ring fused with C-ring as in rhazinilam (entry 7) is not essential.

The next attempt was the optimization of the structure **13F**. To this purpose, a synthetic sequence based on a one-pot borylation Suzuki coupling strategy was proposed[16]. Racemic biaryl analogues **14** bearing substituents on the A-ring were thus synthesized in a direct procedure from substituted anilines. But all these analogues (entries 8-12) were less active than unsubstituted **13F** on tubulin, pointing out the negative influence of increasing the steric bulk on this ring. The naphthyl-phenyl product **14F** was more cytotoxic than (-)-rhazinilam and the most active analogue **13F** towards the MCF7 cell line (entry 13), but its effect on tubulin could not be determined.

Pyridine-phenyl analogues have been synthesized by Rocca and colaborators[22]. Unfortunately, these analogues (entries 14-15) were less active than their surrogates probably due to the basicity of the pyridine.

entry	No. product	IMD	IMA	CT-KB	CT-MCF7
1	**13A**	1/8		1/11	
2	**13B**	1/21		inact.	
3	**13C**	1/17		1/26	
4	**13D**	inact.		1/11	
5	**13E**	1/15		1/40	
6	**13F**	1	1	1/2	1/1.5
7	**13G**	1/3		1/10	
8	**14A**	inact.	1/24	1/5	1/4
9	**14B**	inact.	1/28	<1/30	1/5
10	**14C**	1/55	1/15	1/18	1/1.6
11	**14D**	1/1.7	1/1.8	1/6	1/2
12	**14E**	1/5	1/11	1/7	1/2
13	**14F**			1/9	1/3
14	**15A**	1/10			
15	**15B**	1/6		1/8	

Table 1

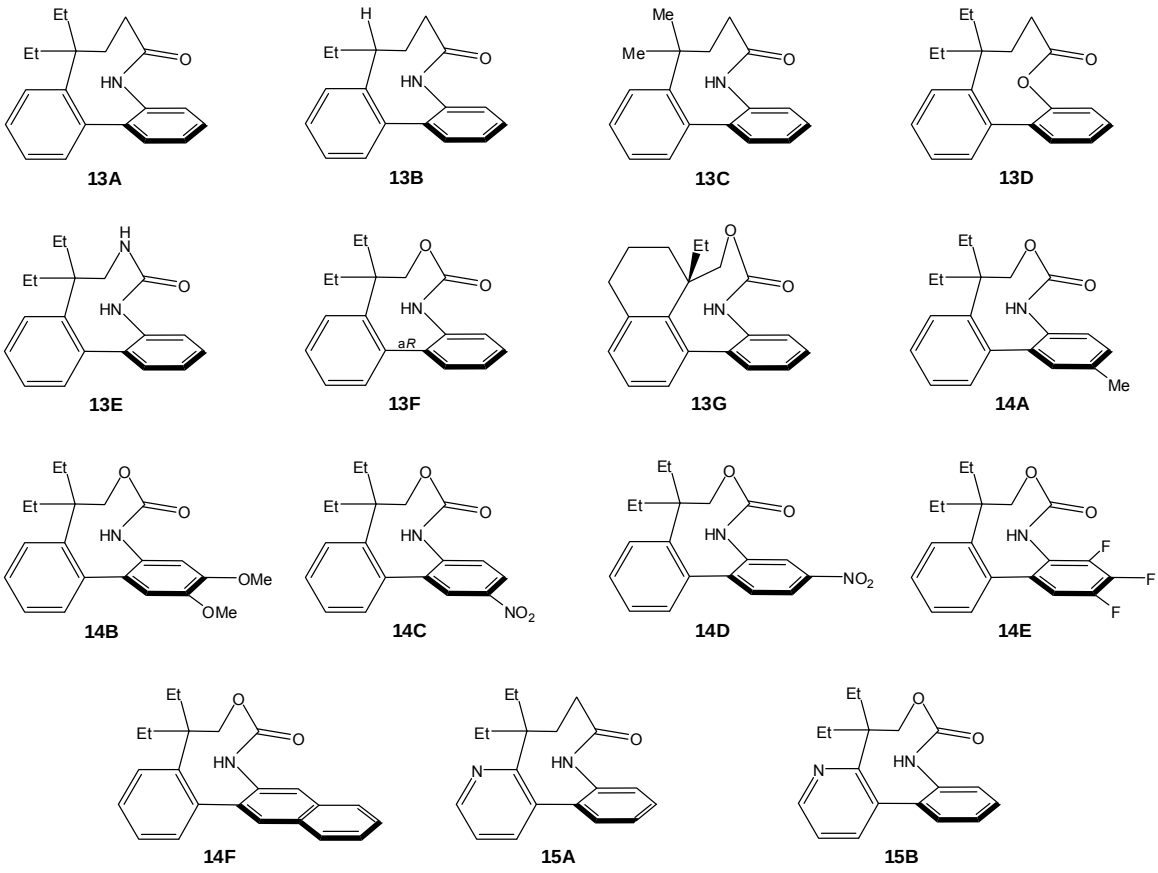


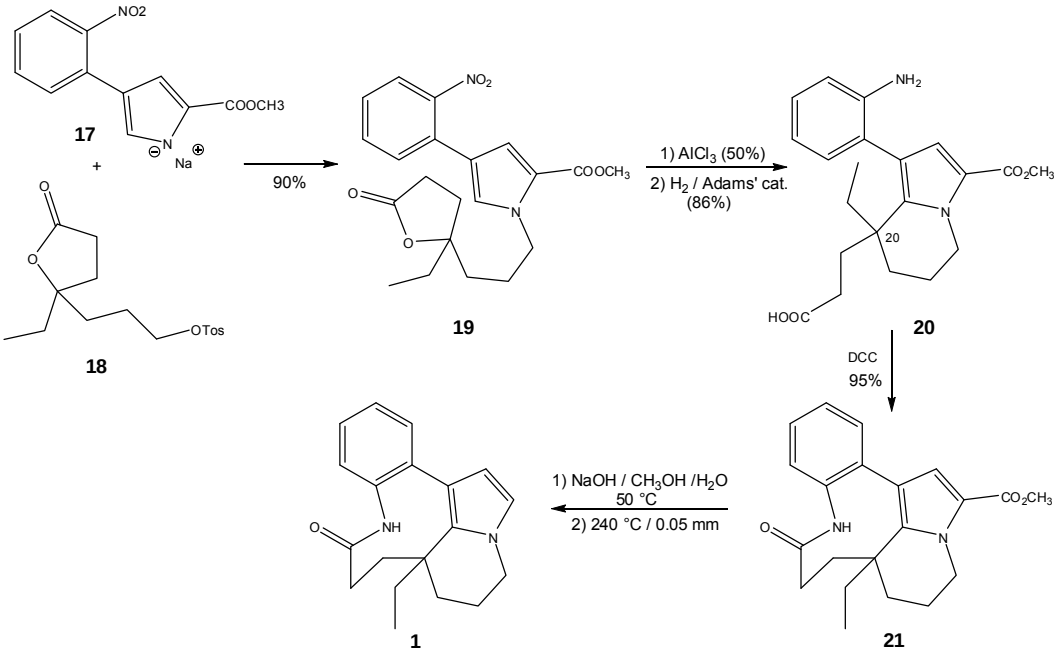
Figure 6

(-)-Rhazinilam is a natural product with unique tubullin-binding properties. For this reason and due to its intriguing molecular structure, several synthetic groups were interested in synthesizing and studying the structure-activity relationship of rhazinilam analogues[16, 19, 23-26]. These total synthesis are discussed in the following section.

1.3. Previous total syntheses

From the first extraction of Rhazinilam in 1965 till our days, seven total syntheses of rhazinilam have been reported: three of the racemic (±)-rhazinilam and four of the natural product or (-)-enantiomer. More than any medicinal chemistry issue, the main purpose of these studies was the synthetic challenge posed by the structure of this compound. The A-C biaryl axis of chirality, the quaternary-carbon centre at C-20, the 5,6,7,8-tetrahydroindolizine C-D rings substructure and the nine-membered lactam B ring are all structural elements that present a significant challenge to those considering a new assembly of this intriguing natural product.

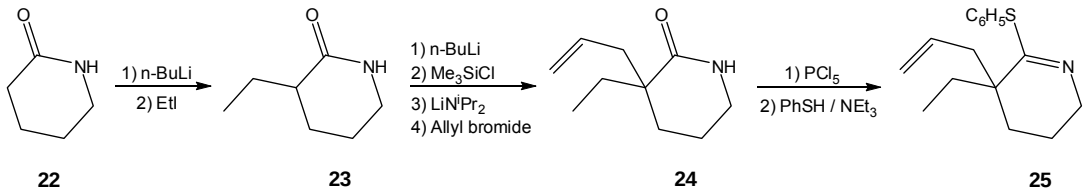
The first total synthesis of the racemic (±)-rhazinilam was reported by G. F. Smith et al in 1973[5]. The key step was the N-alkylation of 2-methoxycarbonyl-4-(2'-nitrophenyl)-pyrrole **17** as the sodium salt by the tosyl derivative of 5-ethyl-5-(3-hydroxypropyl)dihydrofural-2(3*H*)-one **18** to provide pyrrole **19** in 90%.



Scheme 4: Smith's total synthesis of (±)-rhazinilam (1973)

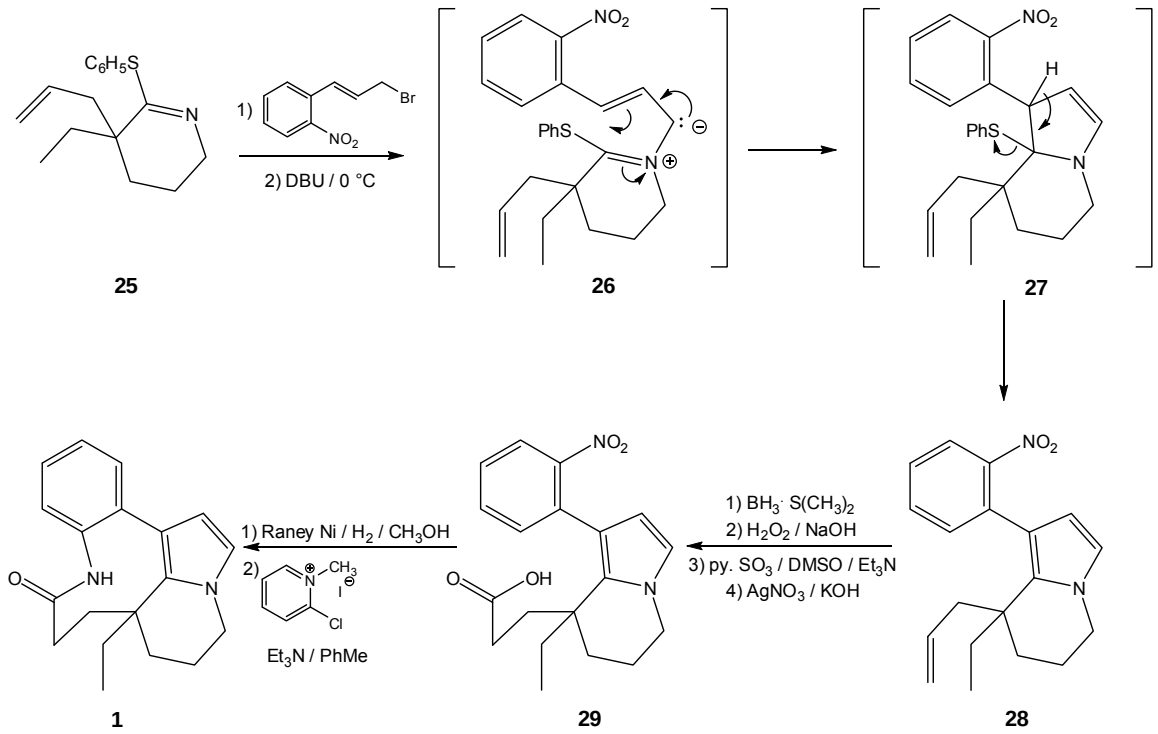
This intermediate, containing all the carbons present in the target molecule plus an additional methyl ester group at the pyrrolic C-5 position, was then treated with aluminium chloride in nitromethane gave tetrahydroindolizine derivative in 50%. Subsequent reduction of the nitro-group on the phenyl ring using Adams' catalyst afforded the corresponding aniline **20** in 86%. Lactamisation of intermediate **20** was effected with DCC at room temperature to provide compound (±)-**21** in 95%. The synthesis was complete via a two-step procedure: saponification of the ester group to give the corresponding acid and then, subsequent thermally-induced decarboxylation of this acid to provide (±)-rhazinilam (**1**) in 86% yield over these final two steps. The identity of the racemic product with (-)-rhazinilam from *Rhazya stricta* was established by complete identity of their UV, IR, 100 MHz NMR and mass spectra, together with identical TLC behavior in four different systems.

In 2001, a straightforward and very elegant synthesis of (±)-rhazinilam was reported by Philip Magnus and Trevor Rainey[27]. Beginning with 2-piperidinone, two sequential α-alkylation reactions provided the product **24**. Thiophenyl iminoether **25** was then generated, by conventional means, from the 2-piperidinone derivate **24** in two steps and 81% yield (Scheme 5).



22 **23** **24** **25**

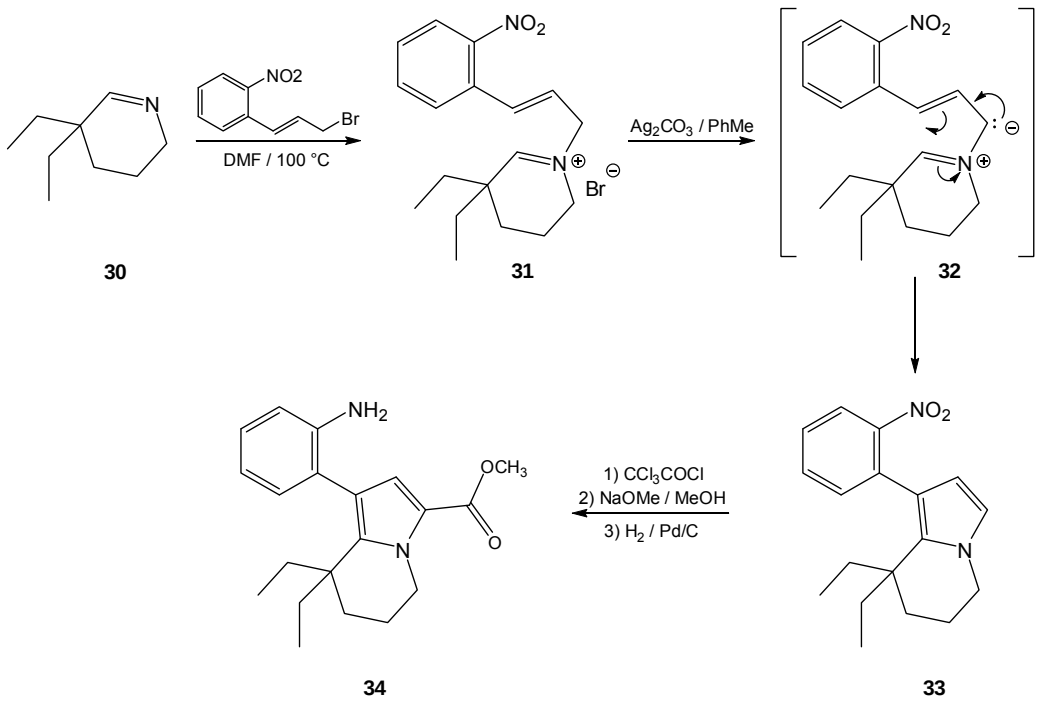
Scheme 5: Preparation of thiophenyl iminoether 25



Scheme 6: Magnus' total synthesis of (±)-rhazinilam (2001)

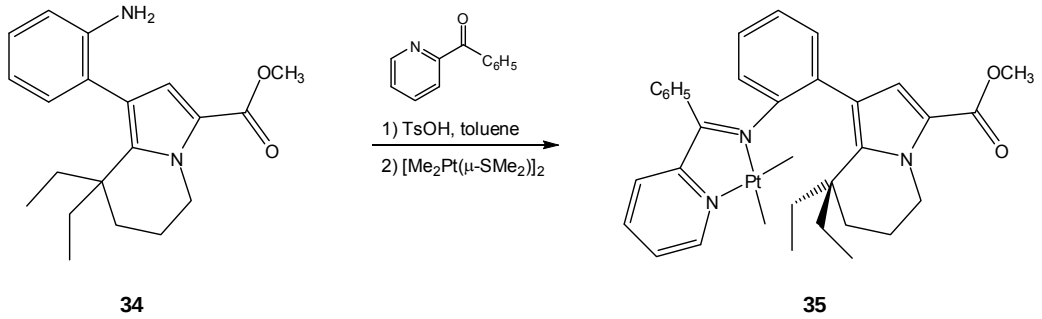
N-alkylation of compound **25** with 1-(3—bromoprop-1-enyl)-2-nitrobenzene produced, after treatment with base, the ylide **26** which engaged in a Grigg-type 1,5-electrocyclisation reaction[28], leading to intermediate **27** that subsequently underwent thiophenol elimination to generate compound **28** in 71% yield from imine **26**. This intermediate, now containing all carbons necessary for the final target, was converted into the alcohol using standard hydroboration reaction conditions followed by oxidation work-up. Attempts to oxidize the alcohol to the acid using silver nitrate under alkaline conditions converted in **29** without any complications. Finally, Raney nickel reduction of the nitro group and lactamisation under Mukaiyama conditions afforded (±)-rhazinilam (**1**).

Two other very elegant total syntheses of (-)-rhazinilam were reported, first in 2000 by Sames and co-workers[29]. Initial work was directed towards the preparation of the racemate and then, in 2002, an adaptation of this work leading to the natural (-)-enantiomer, the first asymmetric total synthesis reported in the literature[30]. Both syntheses proceed through the achiral intermediate **34** which contain the three A-B-C rings present in (-)-rhazinilam.



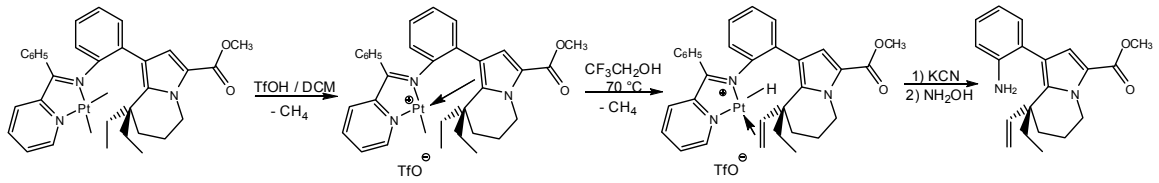
Scheme 7: Synthesis of the achiral intermediate 34

Compound **34** was synthesized in an efficient sequence as depicted in Scheme 7. Iminium salt **31** was generated from readily available imine **30**[31] and 1-(3—bromoprop-1-enyl)-2-nitrobenzene. Heating of **31** in the presence of silver carbonate accomplished both cyclisation and aromatization yielding pyrrole intermediate **32** in 70% yield. The methyl carboxylate group was then installed as a temporary protection to stabilize the sensitive pyrrole ring, followed by reduction of the nitro group to furnish the amine **34**. The completion of the synthesis of the racemic (±)-rhazinilam involved Schiff base condensation of compound **34** with an achiral ketone.



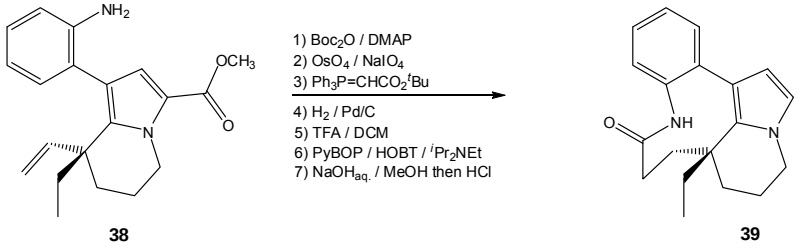
Scheme 8: Preparation of the Pt-complex 35

The stereocontrol in the asymmetric version of the total synthesis was provided by Schiff base formation using the enantiopure ketone as a chiral auxiliary. Complexation of the ensuing imine with the dimethyl platinum reagent $[Me_2Pt(\mu\text{-}SMe_2)]_2$ afforded the complex **35** in 29% yield over the two steps. Addition of triflic acid to the complex led to the rapid formation of the intermediate **36** with concomitant loss of methane.



Scheme 9: Synthesis of the chiral intermediate 38

The thermolysis gave the platinum alkene-hybrid complex **37** as a mixture of diastereomers. The platinum metal was subsequently removed *via* treatment with aqueous potassium cyanide, followed by hydrolysis of the resulting Schiff base in the presence of hydroxylamine. To complete the total synthesis of (-)-rhazinilam, a one-

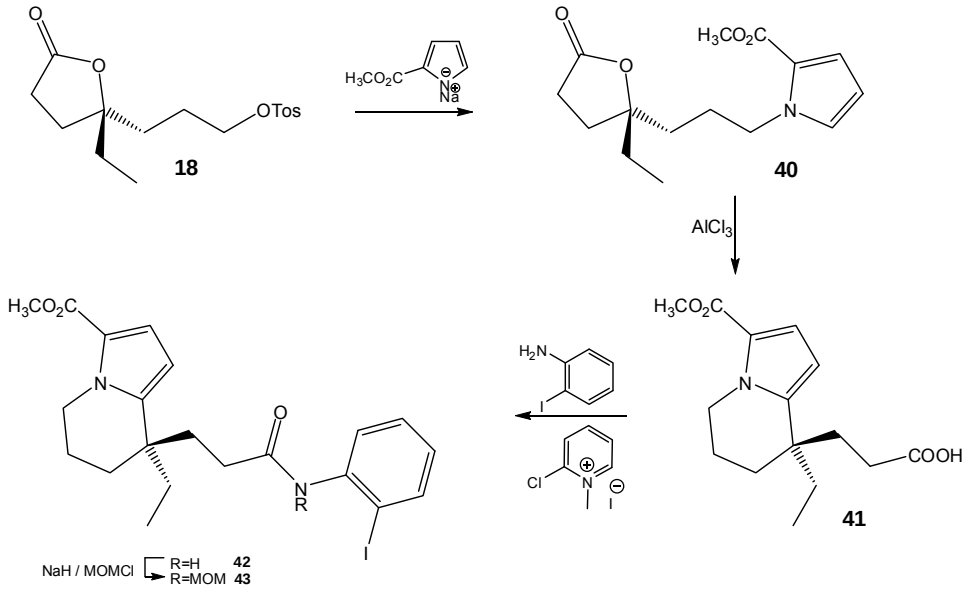


Scheme 10: Final steps in the Sames' total synthesis of (-)-rhazinilam

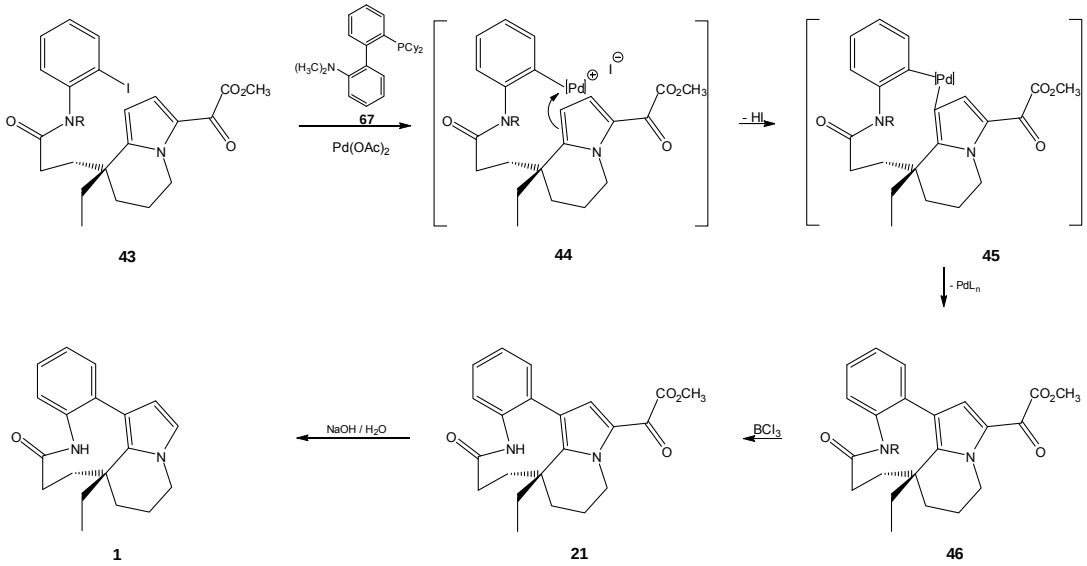
carbon extention of the vinyl group and the subsequent macrocycle closure was then carried out in a standard fashion. Transformation of the double bond of **38** to an aldehyde was followed by Horner-Emmons reaction, catalytic hydrogenation and, finally, a macrolactam formation.

In 2005, Trauner and co-workers published the second total synthesis of enantiomer (±)-rhazinilam[32] (the fifth total synthesis of rhazinilam reported till now in literature). They used an intramolecular Heck-type reaction as the key step. The starting compounds are

the same as in synthesis of Smith[5], enantiomer *R* of tosyl derivative of 5-ethyl-5-(3-hydroxypropyl)dihydrofural-2(3*H*)-one. The tosyloxy group of **18** was readily displaced by the sodium salt of carbomethoxy pyrrole to give the N-alkylated pyrrole **40** in 94% yield. In an analogous fashion to the second transformation used in Smith's total synthesis, compound **40** underwent an intramolecular Friedel-Crafts alkylation upon the treatment with aluminium chloride to afford, in 55% yield, tetrahydroindolizine carboxylic acid **41**, a compound now bearing the requisite quaternary-stereocenter associated with final product rac-rhazinilam. Coupling of **41** with 2-iodoaniline under Mukaiyama's conditions afforded amide **42** . Protection of the amide **42** as a methoxymethyl (MOM) derivative then gave key intermediate **43** in 85% yield. Heating of **43** with 10% of Buchwald's "DavePhos" ligand **67** and $Pd(OAc)_2$ in the presence of a base resulted in the clean formation of the strained, nine-membered lactam **46** in 47% yield. The removal of the methoxymethyl amide-protecting group was effected by treatment of intermediate **46** with a large excess of boron trichloride at low temperature and thus afforded the previously reported ester **21**[30] in 60% yield. Saponification of the ester moiety in compound **21** followed by immediate acid-catalysed decarboxylation, then gave the (-)-rhazinilam (**1**) in 85% yield.

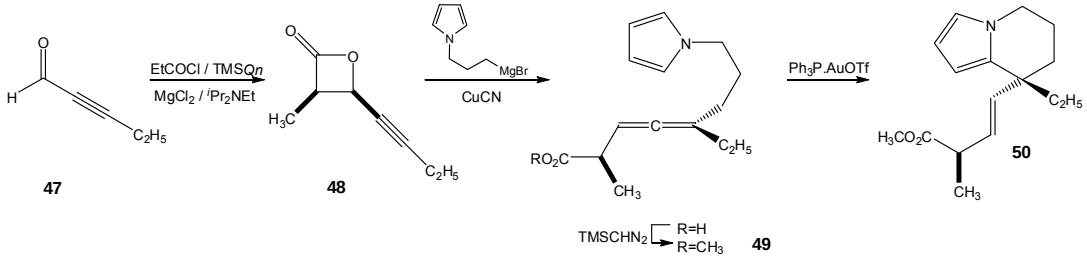


Scheme 11: First steps in the Trauner's total synthesis of (-)-rhazinilam



Scheme 12: Trauner's total synthesis of (-)-rhazinilam (2005)

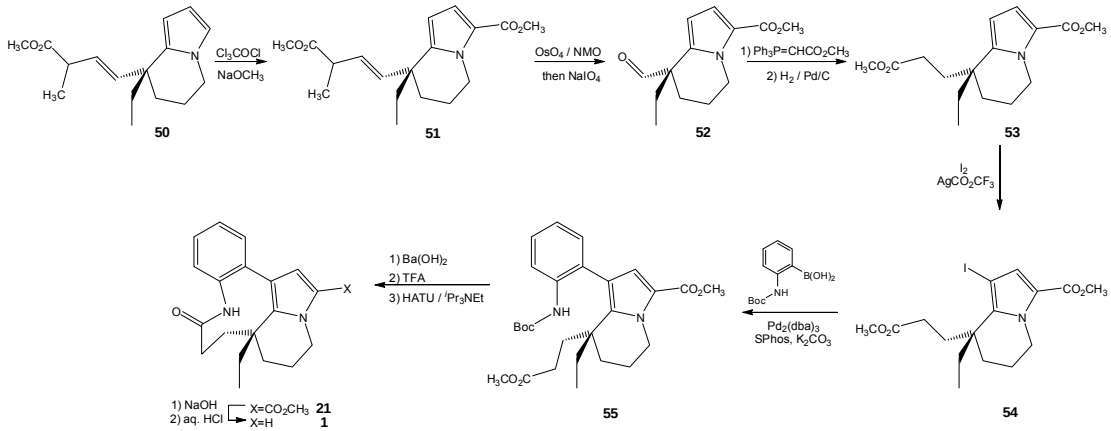
In 2006, Nelson and co-workers reported an elegant and original enantioselective (the 3rd) total synthesis of (-)-rhazinilam[33]. Their strategy was based on the successful application of the Au(I)-catalyzed pyrrole-allene addition. Allenes offer the potential to relay the associated axial chirality to the ensuing bond forming process. The 3,4-cis-disubstituted *β*-lactone **48**, used as starting material, was obtained from propionyl chloride 2-pentynal in 76% yield (99% *ee*). *β*-Lactone ring opening with (3-(1H-pyrrole-1-yl)propyl)magnesium bromide provides the allene **49** as a single diastereomer. To be sure that the methyl-bearing stereocenter had no effect on the stereoselection of the annulation, the methyl ester **49** was subjected to $Ph_3P{\cdot}AuOTf$-catalyzed cyclisation that provided tetrahydroindolizine **50** with nearly complete transmission of allene chirality (92%, 94% *de*).



Scheme 13: First steps in the Nelson's total synthesis of (-)-rhazinilam

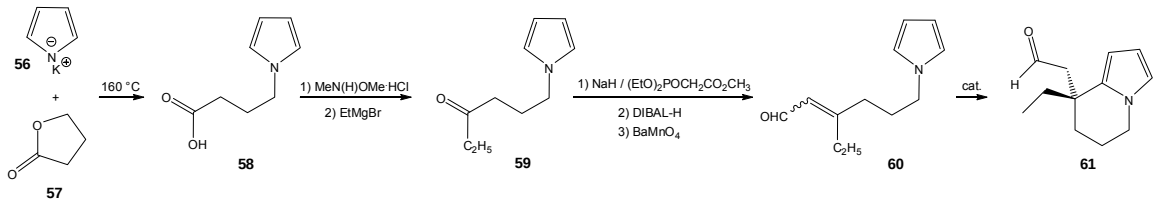
After the construction of the tetrahydroindolizine and the installation of the quaternary carbon in the preparation of **50**, introducing the aniline moiety represented the last

challenge to complete the total synthesis. To circumvent difficulties associated with the oxidation of the heterocycle, pyrrole basicity was effectively attenuated by regioselective carboxylation to provide **51**. Oxidative olefin cleavage, Horner-Wittig homologation and catalyzed dehydrogenation afforded ester **53**. Biaryl bond construction proceeded by regioselective pyrrole iodination (89%) and ensuing Suzuki-Miyaura cross-coupling of iodine **54** with N-Boc aniline boronic ester using Buchwald's SPhos ligand[34] to afford the 3-arylpyrrole **55** in 86% yield. Chemoselective ester saponification and aniline N-deprotection (93% over two steps) induced the lactamisation of the resulting amino acid to deliver 10-(carbomethoxy)rhazinilam **21** in 74% yield over three steps. Pyrrole decarboxylation provided synthetic (-)-rhazinilam (**1**) in 96% yield (94% ee).



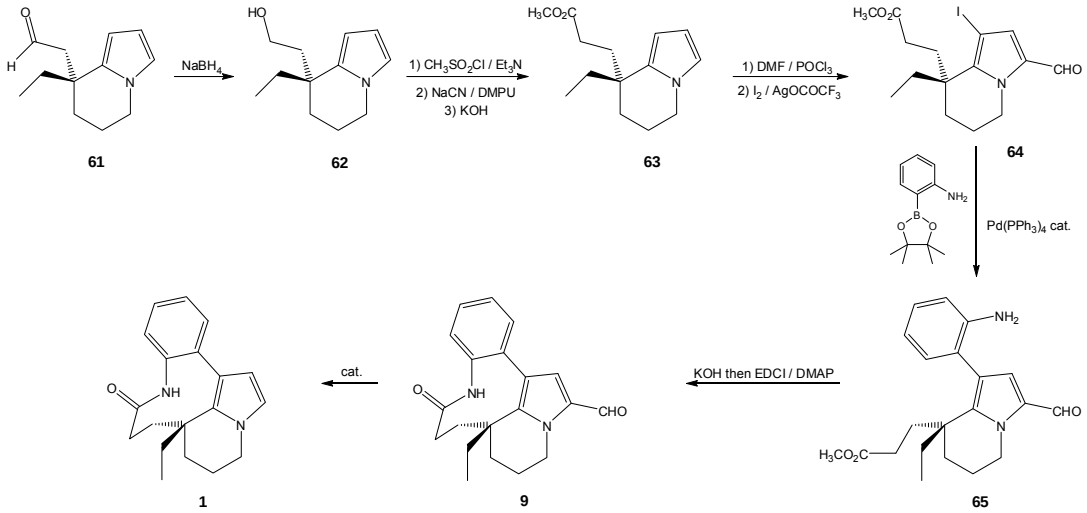
Scheme 14: Nelson's total synthesis of (-)-rhazinilam (2006)

The last total synthesis (the 4th enantioselective synthesis) was reported in 2006 by Banwell et al[35]. Their key step was the intramolecular Michael addition reaction in an enantioselective fashion using MacMillan's first generation organocatalyst ((5*S*)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monotrifluoroacetate). The reaction between potassium salt of pyrrole **56** with γ-butyrolactone **57** afforded, after acidic work up, the acid **58** (60-90%) which was converted into the amide in 87% yield. This amide was then treated with ethyl magnesium bromide giving ethyl ketone **59** (95%). The target aldehyde **61** was synthesized after Horner-Wadsworth-Emmons-type olefination of ketone **59**, reduction with DIBAL-H, the corresponding mixture of allylic alcohol was immediately oxidized with bariummanganate followed by intra-molecular Michael addition. The enantiomeric purity of this cyclisation product was established through its reduction with



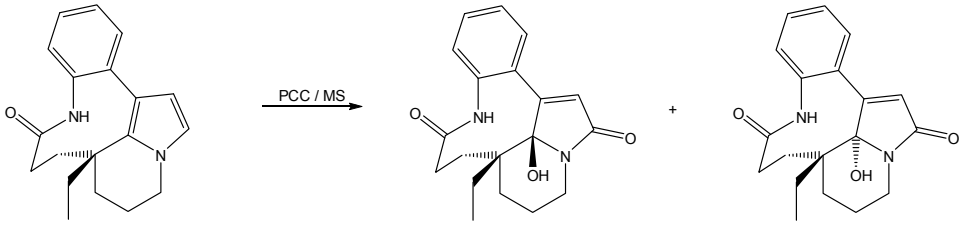
Scheme 15: First steps in the Banwell's total synthesis of (-)-rhazinilam

sodium borohydride to the corresponding alcohol **62** (84%, 74% ee). The mesylate intermediate derived from the alcohol (95%) was subjected to reaction with sodium cyanide in DMPU giving the nitrile which was converted into the corresponding methyl ester **63** in 63% yield by reaction with KOH in aqueous methanol followed by acidic work up and reaction of the ensuing free-acid with DCC in methanol containing catalytic amounts of DMAP. Vilsmeier-Haack formylation of pyrrole **63** then afforded the aldehyde (78%) which was subjected to electrophilic iodination using molecular iodine in the presence of silver (I) trifluoroacetate and thereby affording iodide **64** (quant.) in a completely regioselective manner. Suzuki-Miyaura cross-coupling of **64** with pinacolate ester of o-aminophenylboronic acid afforded the arylated pyrrole **65** (64%) which engaged in a simple two-step lactamisation procedure to deliver synthetic (-)-rhazinal **9** in 68% yield (74% ee). Decarboxylation of (-)-rhazinal was the final step needed for obtaining (-)-rhazinilam (**1**).



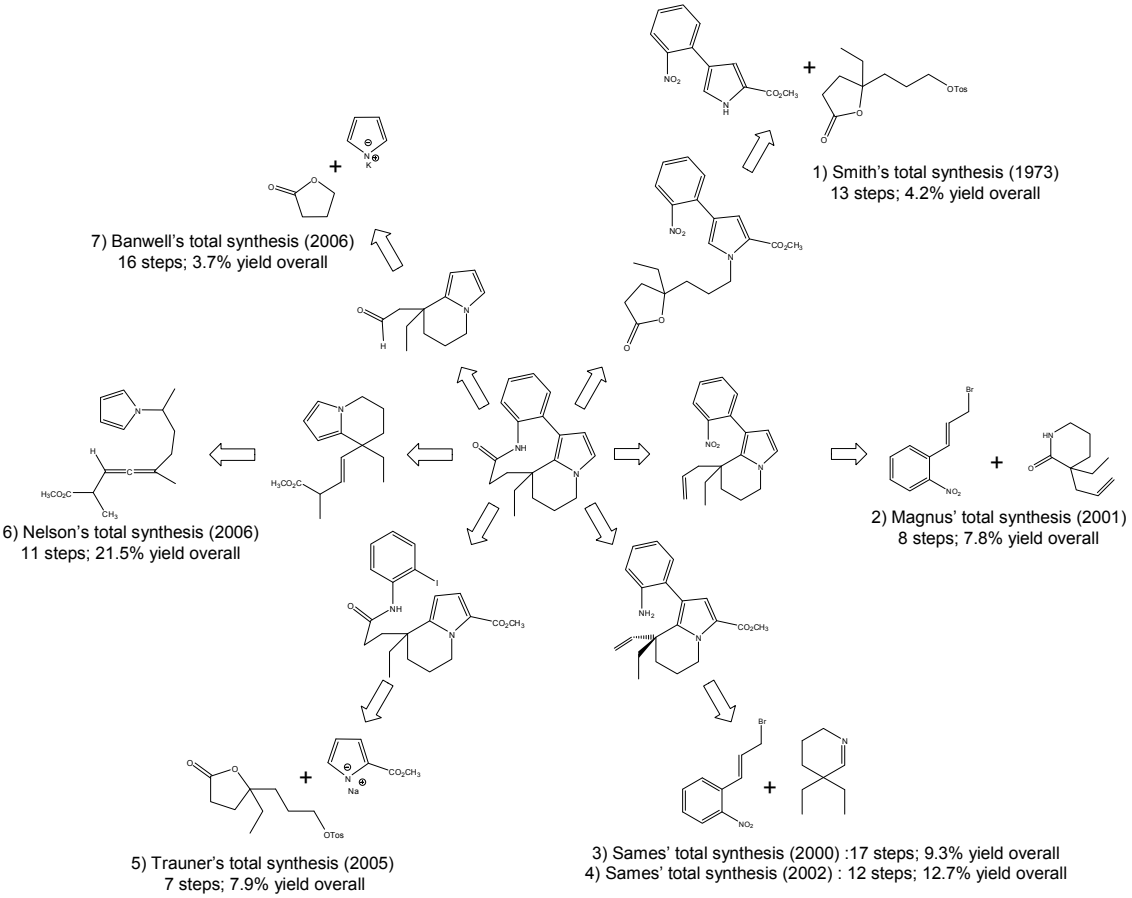
Scheme 16: Banwell's total synthesis of (-)-rhazinilam (2006)

Banwell's strategy is the only one which allows to synthesize rhazinilam's analogues: (-) rhazinal **9**, (-)-leuconolam **8** (28%) and (+)-*epi*-leuconolam **66** (46%).



1 **8** **66**

Scheme 17: Synthesis of rhazinilam analogues by Banwell's strategy



Scheme 18: Survey of total syntheses of rhazinilam

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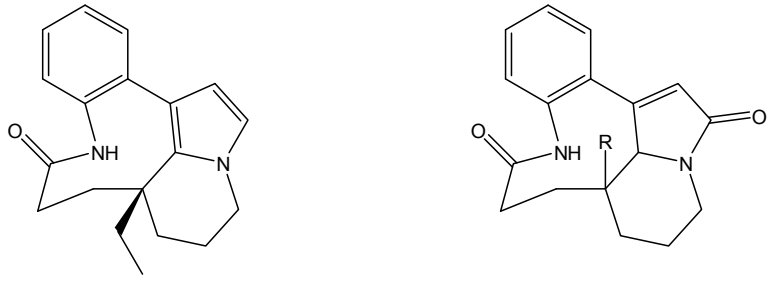
2. Goal

The goal of our work is the development of a novel methodology applicable to the synthesis of simplified analogues of (-)-rhazinilam (**1**). The attractiveness of the unusual tetracyclic structure of (-)-rhazinilam (**1**) lies in its unique biological effects exercised by a relatively simple biaryl structure. (-)-Rhazinilam (**1**) intervenes in mitosis. It resembles to simple biaryl foldamers and can therefore be considered as a mimic to α-helices of peptides. The scientific challenge of this relatively simple natural product is to understand and to explain in structural terms its activity. The chosen strategy must allow the synthesis of many derivatives to check structure activity relationships. It should also take into account sensitivity issues due to the presence of the pyrrole C-ring.



(-)-rhazinilam (1) **rhazinilam analogues**

Figure 7

The retrosynthesis of our target molecule is shown in Figure 8:

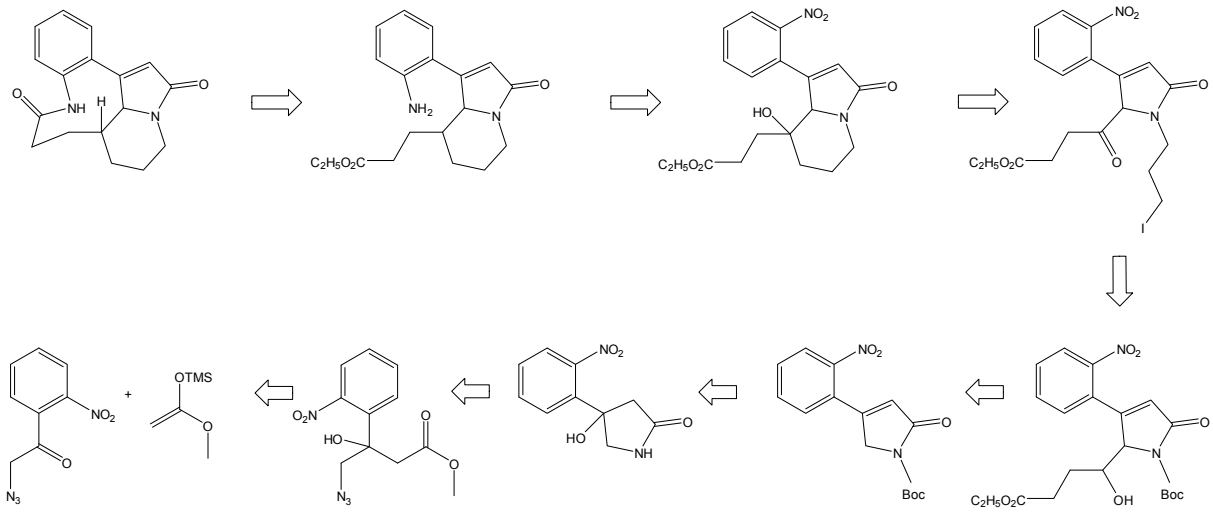


Figure 8:

The retrosynthesis of the target molecule includes the following steps : cyclisation of the nine-membered lactam ring, cyclisation of six-membered D-ring under Molander conditions (SmI_2)[1, 2], N-alkylation of pyrrole, crossed aldol Mukaiyama reaction for introducing all the atom needed for nine-membered ring, dehydroxylation and N-Boc protection in “one-pot” reaction from five-membered lactame ring leadind to the N-protected pyrrole-one, Mukaiyama reaction between 2-azido-1-(2-nitrophenyl)ethanone as electrophile and (1-methoxyvinyloxy)trimethylsilane as nucleophile.

References:

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3. Analysis of the Retrosynthesis of Rhazinilam

In view of the relative simplicity of Rhazinilam it is surprising that only seven total syntheses have been reported so far. Out of the seven total syntheses four syntheses lead to the enantiomerically pure natural products. These four enantioselective syntheses have been reported only during the last five years. In view of the spectacular development of the available synthetic methodologies and of the art of natural products synthesis, the progress around the Rhazinilam synthesis has been slow. The question has to be asked, why is this so?

Analysing the Rhazinilam structure using the classic retrosynthesis approach heralded by Correy, the following elements have to be considered to be challenging: the nine-membered lactam B-ring, the quaternary center α to the pyrrole C-ring, the axial chirality and the enantioselective creation of the asymmetric center C-21. Following the traditional wisdom one would consider the aromatic benzene A-ring and the heterocyclic pyrrole C-ring to be elements which one should be able to introduce without any difficulties.

Analysing the retrosyntheses which lead to successful total syntheses of the natural product **1,** one comes up with a surprising conclusion: all the reported syntheses, with the exception of only one, have to introduce an additional electron attracting auxiliary substituent to the pyrrole C-ring, usually an ester. One of the reported syntheses uses an ester substituted pyrrole ring as starting material. The other syntheses have to introduce the stabilizing substituent in a separate additional step, which prolongs their synthetic approach. This auxiliary, stabilizing substituent is kept in place until one of the final steps. This additional functional group has then to be removed to liberate the structure of the natural product.

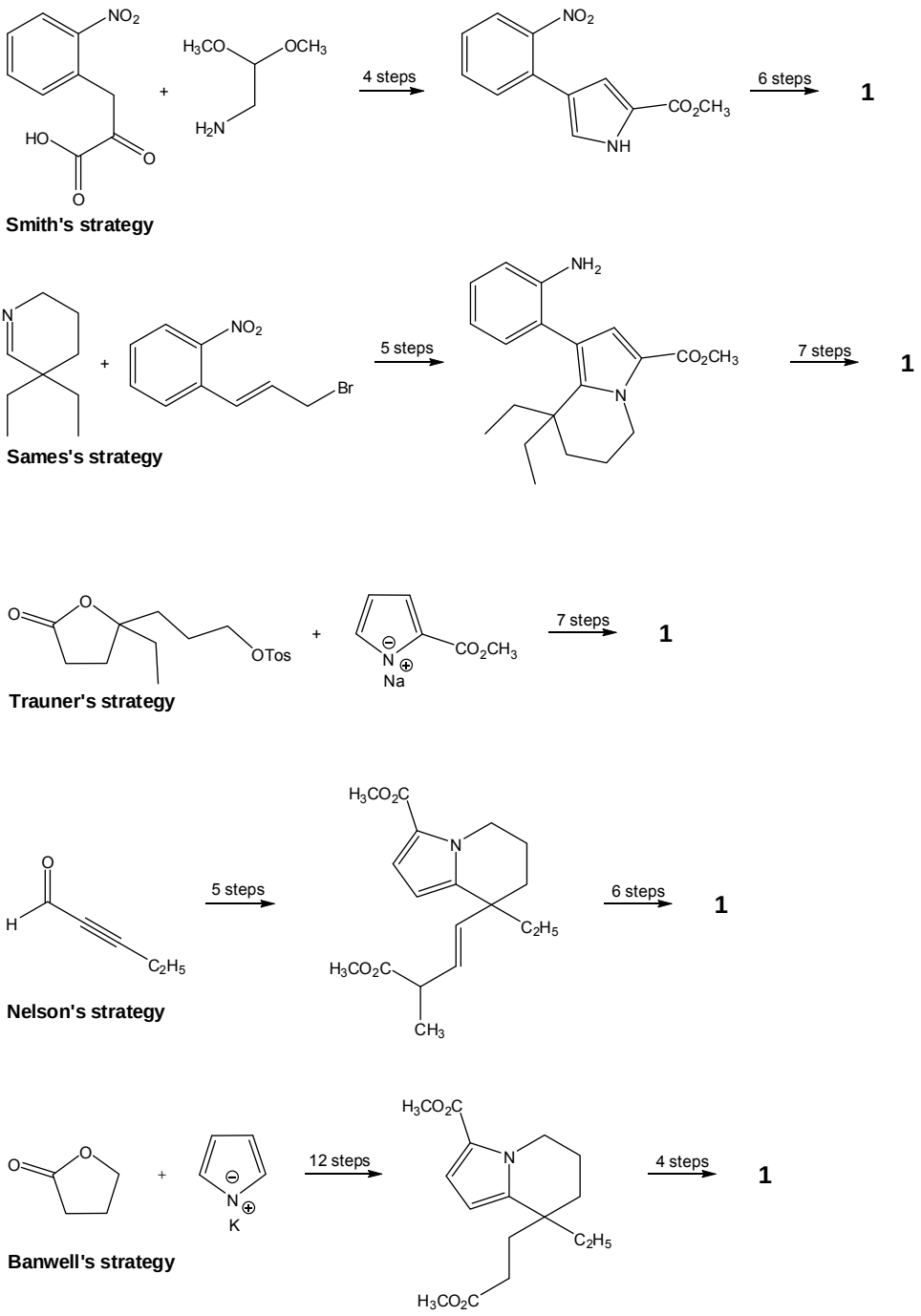
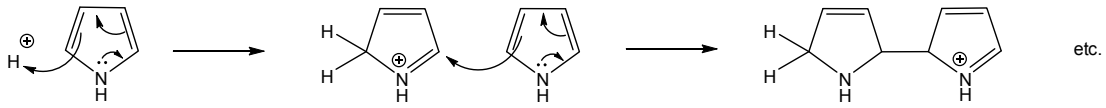


Figure 9: Survey of the introduction of ester or aldehyde function steps on pyrrole ring

In view of today's pressure to create the most efficient synthesis, which often means the shortest possible synthesis, it is surprising that five different groups had to introduce one, two or even three additional steps into their syntheses, which prolong the synthetic pathway without advancing the construction of the skeleton. The chosen protection

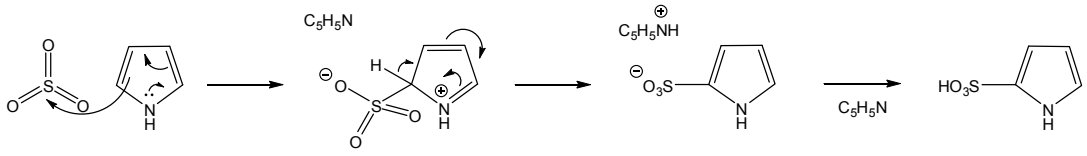
deprotection strategy prolongs most of these syntheses by at least two steps. Avoiding this strategy would considerably shorten the synthetic pathways and thereby increase the yields. Reading the reports it becomes clear that these protection-deprotection strategies were necessary to be able to execute the transformation needed, avoiding side reactions due to the sensitivity of the pyrrole C-ring.

As it is known, the pyrrole is an electron rich heteroaromatic compound (six electrons distributed over five atoms). Without these stabilising substituents the pyrrole ring is easily attacked. Under the influence of small amounts of acids, unstabilised pyrroles are polymerised and autooxidised to give so called pyrrole black[1].



Scheme 19: The behavior of pyrrole in acidic conditions

Pyrrole can also be sulfonated in the 2-position by treatment with the pyridine-sulfur trioxide complex[2]:



Scheme 20: Sulfonation of pyrrole

In conclusion the protection deprotection strategy chosen by the five groups mentioned above is a consequence of the sensitivity of the pyrrole C-ring and the additional steps needed can not be avoided.

In view of the preceding arguments it is surprising that in the synthesis reported by the Magnus group, these protection-deprotection steps could be avoided. This is all the more surprising because the key intermediate reported by Magnus is structurally very similar to the intermediate reported by Sames.

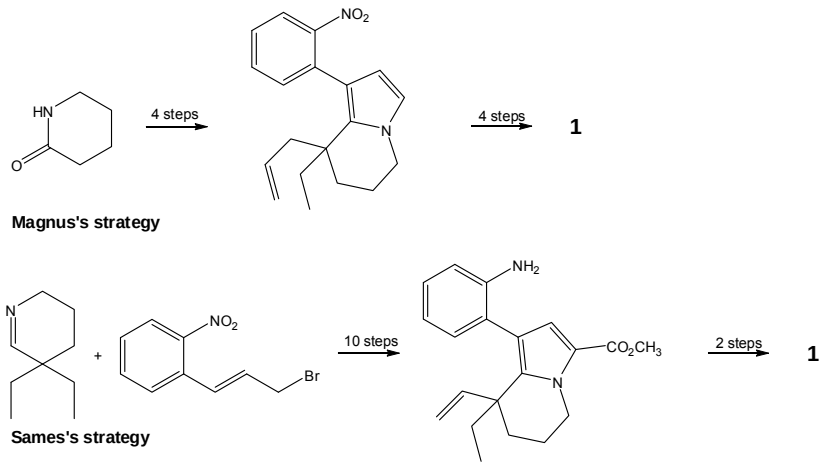
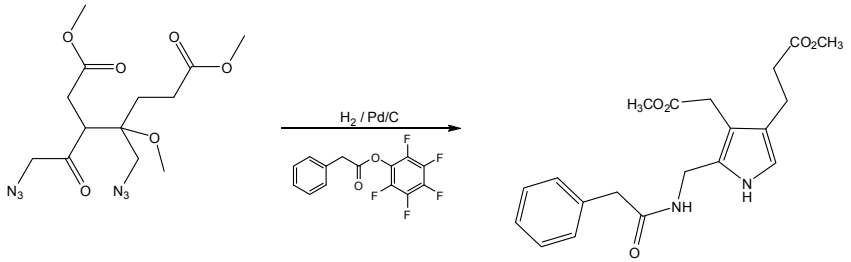


Figure 10: Comparison Magnus – Sames strategies

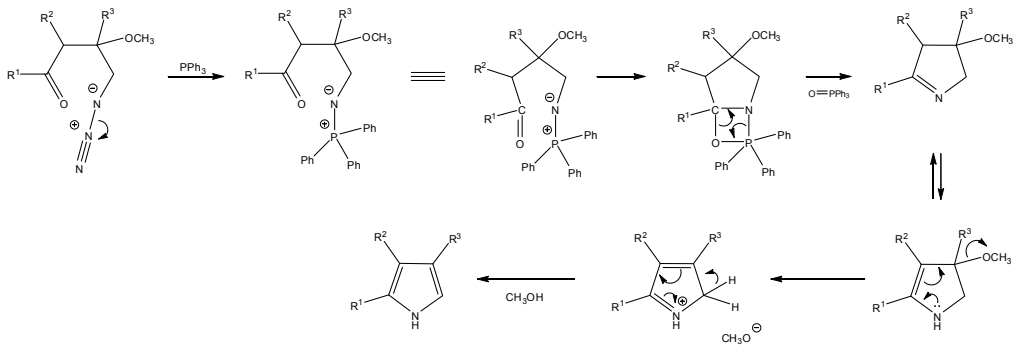
In view of the known sensitivity of pyrroles towards oxidation processes and to the treatment with acids it is highly interesting to observe that Magnus reports three oxidation processes, occurring with high yields. Reading carefully the experimental part it is not evident, how the Magnus group has been able to avoid the side reactions, which are usually induced under such conditions.

Our group has developed a novel synthetic methodology leading in a convergent way to substituted pyrrole rings in the synthesis of phorphobilinogen, a precursor for many natural products. The key transformation is the use of the Mukaiyama crossed aldol reaction to assemble the adequately substituted skeleton, typically followed by (i) reduction using a Pd/C catalyst to transform the azido group into the amino function. The molecule is then set up in such a way that a cascade of reaction steps directly leads to the aromatic pyrrole ring. Once the amino group is set free, it reacts with the δ-keto function. The imine is in equilibrium with the corresponding enamine, which expulses the methoxy group leading to the protonated pyrrole, which is transformed into its tautomeric form, the heterocyclic aromatic pyrrole ring.



Scheme 21: Synthesis of protected porphobilinogen[3]

Or by (ii) the Staudinger reaction:

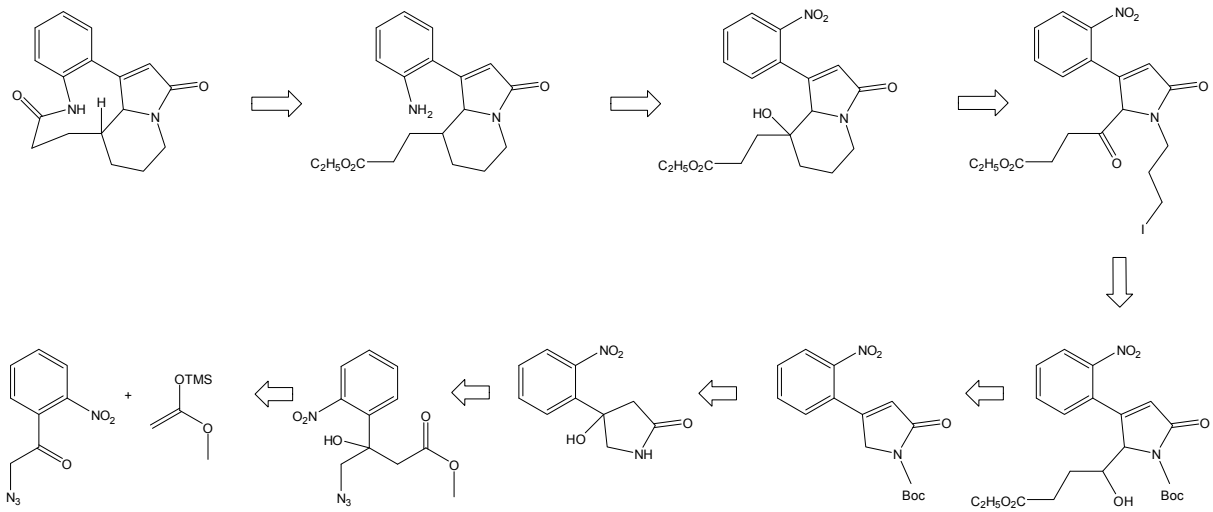


Scheme 22: Staudinger (Aza-Wittig) mechanism

The method used to “deprotect” the azido function has no influence on the final outcome of the reaction sequence.

The advantages of this methodology are the convergency of the sequence used to construct the skeleton, the availability of many easily available building blocks and the mild methodologies used for the formation of the pyrrole ring. Our method is complementary to the known classic literature procedures[4-7]. Mono-, di-, tri- and tetra-alkylpyrroles can be synthesized using this method. The yields are good to excellent and the ease of the final reaction step allows to isolate these sensitive compounds in high purity.

Based on this observation we were interested to test the scope and limitations of our methodology using (-)-rhazinilam as our goal. The hope was that our approach should allow to solve the sensitivity problem, using our mild method and avoiding degradation due to the use of too harsh reaction conditions.



Scheme 23: Retrosynthesis of rhazinilam analogue

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3.1. Towards the Synthesis of the Skeleton of (-)-Rhazinilam: Mukaiyama Crossed Aldol Reaction Followed by the Staudinger Reaction for the Construction of the Pyrrolic C-Ring

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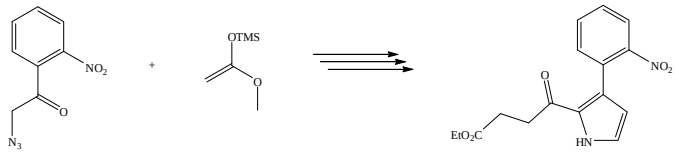


ABSTRACT

As a novel approach to biaryl core structure of rhazinilam different variants of the sequence crossed Mukaiyama aldol reaction followed by the Staudinger reaction were studied. The reaction sequence reacting the adequately substituted acetophenone with the O-methyl-O-trimethylsilyl ketene acetal gave in good to excellent yields the pyrrolidinones **12a** and **12b**. These intermediates could be transformed in four high-yielding steps into the pyrrolic precursor **17** containing all atoms necessary for the construction of the rings A, B and C of rhazinilam.

For a long time the number of natural products containing pyrrole rings as characteristic structural element was comparatively small[1]. The tetrapyrrolic “pigments of life”[2] were an important exception to this empirical observation. They represented on their own a major class of natural products with an impressive variation of the basic structural element and an even more remarkable variety of functions[3]. In contrast to the large number of pyrrole containing macrocyclic compounds found in nature, the simple heterocycle pyrrole itself had been identified only in a limited number of natural products[4-8]. Comparing the relative “rareness” of pyrrolic natural products with the ubiquitous presence of pyridine containing natural products[9-12] can be correlated with the high chemical stability of pyridine and its protonated form. In contrast non stabilized alkyl pyrroles are highly sensitive. Protonation leads to oligomer or polymer formation as was detected already in the 19th century[13]. This high inherent reactivity in the presence

of Broensted acids is used in the third dedicated step of the biosynthesis of the "pigments of life"[2].

The number of pyrrole containing natural products has steadily increased in recent years[1]. This constant increase of identified pyrrole containing natural products is certainly due to the combination of more efficient isolation methods with more sophisticated structure determination procedures[1]. The interest for a new natural product stems from their biological functions, their application in humans and for the chemist from their chemical structure[14]. In this context it is interesting to note, that the world's largest selling drug, Lipitor®, contains a pyrrole as its central aromatic ring in a triaryl structural motive[15, 16].

(-)-Rhazinilam, a mono-pyrrolic natural product, was first isolated by Linde in 1965 from *Melodinus australis* well before the development of modern highly automatized isolation techniques[17]. The structure of (-)-rhazinilam was determined in the early seventies by a combination of chemical, NMR- and X-ray-analysis[18-20]. The structure of this compound isolated from natural sources is unusual in different respects. It contains a biaryl unit composed of a substitued benzene and a pyrrole ring, rings A and C of (-)-rhazinilam. In contrast to many other pyrrole containing natural products the pyrrole ring of (-)-rhazinilam lacks a directly linked electron attracting substituent. The tetracyclic system is unusual, especially the nine membered ring containing the lactam function is an uncommon structural element in natural products[21]. Finally (-)-rhazinilam contains two elements of asymmetry, the chiral center at C(9) and the chiral axis fixed by the restricted conformational flexibility of the nine-membered lactam ring.

Already during the process of isolation and structure determination it became evident that (-)-rhazinilam might be formed during the isolation procedure[22]. The first indication came from the observation that (-)-rhazinilam accumulated *in vitro* in a basic fraction of *Rhazia stricta*[19]. This hypothesis could be confirmed using different natural alkaloids like (+)-1,2-dehydroaspidospermidin as natural precursor. Oxidation followed by hydrolytic ring cleavage lead in acceptable yields to (-)-rhazinilam[23]. Due to these findings (-)-rhazinilam has lost the status of a genuine natural product. It is however possible that small quantities of (-)-rhazinilam could be formed naturally under oxygen stress conditions without human intervention[24]. The usual assumption is that artifacts of the isolation process should not exercise a biological function as these artifacts of isolation do not evolve under the selection pressure of evolution. The change in biological properties generally admitted for artifacts formed by oxidation is an increase in solubility

due to the increased polarity of the oxidation products helping to excrete these degradation products[22]. It is however possible that small quantities of (-)-rhazinilam could be formed naturally under oxygen stress conditions without human intervention.[lit. ref.]

It came therefore as a surprise, when almost twenty years later screening experiments gave evidence for interesting cytotoxic and pharmacological properties of (-)-rhazinilam *in vivo* due to its interference with the tubulin-microtubule equilibrium[25, 26]. A comparison of the mode of the antimitotic action of (-)-rhazinilam with other compounds intervening in this important process showed that (-)-rhazinilam had a specific profile. (-)-Rhazinilam combines a vinblastine-like activity provoking the aggregation of tubulin into spirales with a taxol-like activity inhibiting the disassembly of microtubules[27]. Taxol and vinblastine have structures which are considerably more complex than the tetracyclic structure of (-)-rhazinilam[28, 29]. Colchicine, which represents also a “special” expanded biaryl skeleton[30], is the only known natural product of similar simplicity acting on the mitotic process.

Microtubule formation through the assembly of tubulin must be a highly controlled process. Microtubules form the internal skeleton of cells sustaining their form and volume. More important and more visible is the role of the microtubules during mitosis, where the geometry and the timing of their formation has to be carefully controlled to guarantee the smooth proceeding of the process of cell division. Impressive progress has been made in understanding the structures of tubulin, its association into α-β-heterodimers and the tubulin-microtubule equilibrium controlled by the association with GTP and its hydrolysis product GDP. Wheras the overall process is reasonably well understood on a molecular bases the detailed control elements necessary for the assembly and disassembly of mitotic spindle needed during mitosis are not known. Small molecules interfering with this process are not only excellent tools to provoke cell arrest and can therefore be used as anticancer drugs, but they give valuable hints at the complex control mechanism in charge of this intricate process. (-)-Rhazinilam obviously intervenes with the protein-protein interactions leading to the microtubule formation through the association of tubulin molecules.

The protein-protein interactions are important factors as control elements in many biological processes such as signaling, skeleton formation, gene silencing, gene transcriptions and activation or silencing of enzymes[31, 32]. Studying of the effects of and the site of interaction of small (natural) molecules with these communication processes

has given important clues for the understanding of these processes[33]. In the classification of the crucial elements for the protein-protein interactions proposed by Clackson and used by Hamilton and collaborators one of the simpler recognition elements is the interaction between an α-helix and a protein surface[34, 35]. In a systematic empirical approach to imitate the sequence of recognition elements presented by α-helices Hamilton and his group synthesized specifically substituted biphenyls and terphenyls as analogues imitating α-helices[36]. The biphenyls and terphenyls are used as foldmers which are capable to imitate the geometry of one full or two full turns of substituted α-helices[37-39]. In this approach only two aspects of an α-helix are imitated: the type and polarity of the side chains in positions i and i + 3 and the distance and the dihedral angle viewed along the cylinder axis. In view of the simplicity of the skeleton used to replace an α-helix turn composed of three amino acids bound through peptide bonds the inhibition results obtained by the Hamilton group are truly remarkable[40, 41]. As (-)-rhazinilam is formed during the "artificial" isolation process from plant material, it is not obvious how the biological properties of (-)-rhazinilam could have evolved in a "natural" selection process. At the moment one can not exclude that the structure of (-)-rhazinilam might be a chance finding not related to any "natural" process in the tubulin-microtubule equilibrium. If this should be the case the information one can deduce from (-)-rhazinilam is essentially a structural information, using the reasoning applied to artificial drugs in order to describe the receptor blocked by these drugs. As many small molecules playing the role of natural messengers are formed by oxidation processes[42, 43] one can not exclude the possibility that (-)-rhazinilam is playing the role of a specific recognition element in a protein-protein interaction as proposed by Hamilton and his group for their artificial molecules[40]. As a consequence one would expect (-)-rhazinilam to be an α-helix mimick, which fills a more or less shallow pocket made for a "natural" protein-protein interaction based on the recognition of a natural α-helix element. Assuming this hypothesis to be true, one should be able to find the natural messenger, which is imitated by (-)-rhazinilam. This sort of "retrodesign" has been successfully applied to understand the physiological activities of morphine type molecules, which imitate the natural pharmacophore the endorphins[44-47].

The systematic research undertaken by the group of Guénard to define the pharmacophore responsible for the action of (-)-rhazinilam showed, that the rings A, B and C are necessary for the pharmacological activity[48-51]. In contrast to these three cycles the six-membered ring D is optional. The pyrrolic ring C can be replaced by a

benzene ring without loss of activity[52]. The nine-membered ring B is crucial. The lactam function can be replaced by other functional groups which have similar polarity and hydrogen bond donating and accepting properties like carbamates. These results are compatible with the design principles proposed by Hamilton and his group[40, 41], and thereby add credit to the hypothesis that (-)-rhazinilam acts as an α-helix mimick.

Due to the special pharmacological activities of (-)-rhazinilam the interest to develop total syntheses of this molecule has been kept alive over more than 30 years. Seven total syntheses have been reported so far, three of them leading to racemic rhazinilam and four recent synthesis allow to obtain enantiopure (-)-rhazinilam[22, 53-58].

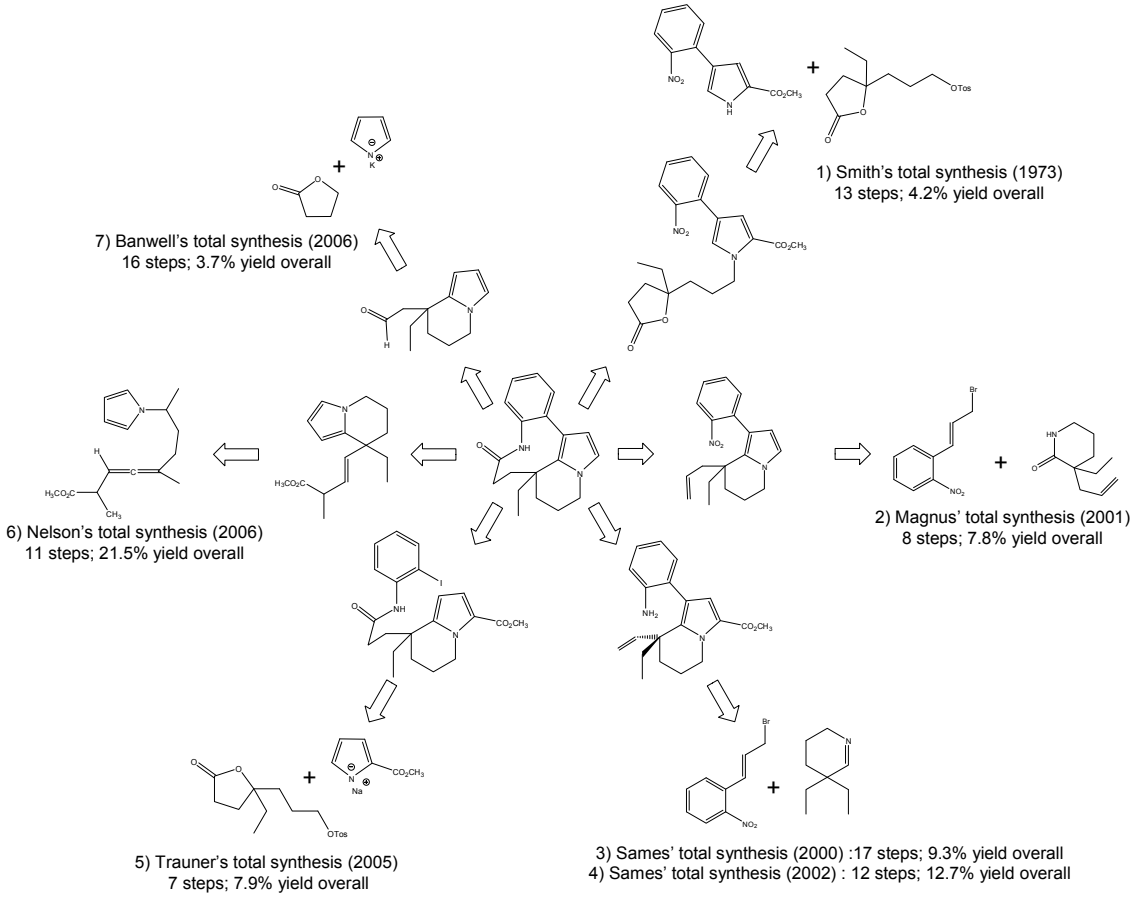


Figure 1.

For obvious reasons the construction of the sensitive pyrrole ring is the key step in three of the reported total synthesis. These three syntheses take care of the sensitivity problem by forming the acid sensitive pyrrole ring relatively late in the synthesis. Introducing the pyrrole ring late, the lack of stability associated with the presence of the pyrrole ring can be avoided during the early steps in the synthesis. The two more recent

total syntheses introduce the pyrrole ring intact[57, 59]. In one approach a chiral auxiliary is fixed to the precursor and the enantiomerically pure intermediate is obtained by an organometallic C-H activation reaction. In the second approach an organocatalytic approach is used to induce an enantioselective Michael addition. We describe our approach to the rhazinilam skeleton synthesizing adequately substituted phenyl-pyrrole ring systems using the sequence developed in our group. The advantage of our approach is the wide variety of starting materials available and the mildness of the pyrrole building step.

Our group has developed a versatile pyrrole synthesis based on the two steps sequence *Mukaiyama* crossed aldol reaction followed by the *Staudinger* reaction[60-63]. Our method allowed the synthesis of sensitive alkyl substituted pyrroles in good to excellent yields, complementing the classical *Knorr* pyrrole synthesis[64]. We decided to investigate a synthetic path towards the rhazinilam skeleton based on our pyrrole synthesis (Figure 2)

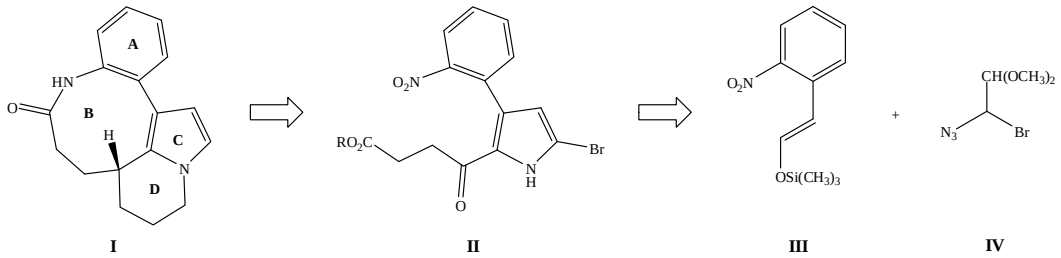
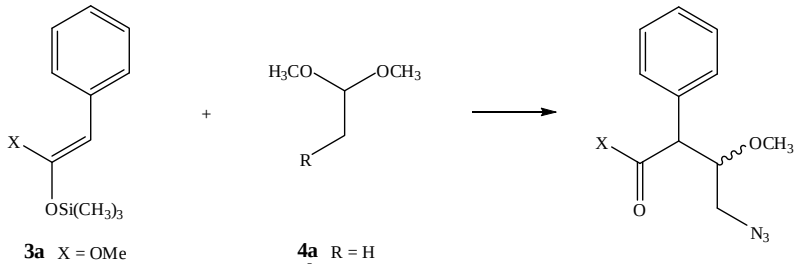


Figure 2.

The key step of our proposed retrosynthesis was a novel variant of our pyrrole synthesis. To test the compatibility of our methodology with the high density of functional groups needed for the application of our strategy to a rhazinilam synthesis was an additional motivation for our studies.

The condensation of **III** with **IV** should lead to the substituted pyrrole **II**, suitably protected. The introduction of the side chain necessary for the formation of ring B should be regioselective using this starting material. In the initial trials we were unable to control the reaction conditions adequately. We mostly isolated polymeric materials, probably due to the high reactivity of the substituted phenylacetaldehyde obtained after the crossed aldol reaction. To avoid this problem we modified the nucleophile, using *O*-alklylketene-*O*-silylacetals of the type **3a** – **3c** instead of the silyl enol ether (Scheme 1).



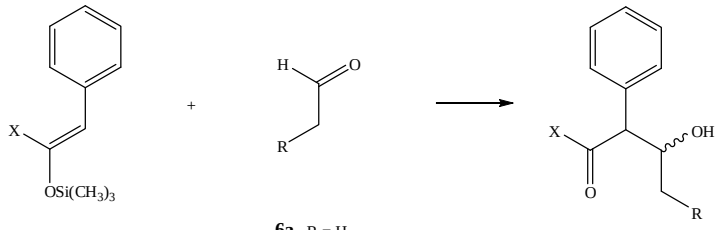
3a X = OMe
3b X = OEt
3c X = SEt

4a R = H
4b R = Br
4c R = N_3

5 X = OMe (20%)

Scheme 1. Reagents and conditions: $TiCl_4$, CH_2Cl_2.

Using the ketene-acetal **3a** and the acetal **4c** we could isolate small amounts of the aldol product **5**. Using the aldehydes **6a** – **6c** improved the yields considerably (Scheme 1 and Table 1). Acetals react smoothly, as shown by Mukaiyama in his previous work[65, 66]. The major advantage of using acetals is the fact that the substituent in the β-position of the aldehyde is an ether, which exhibits a reduced reactivity compared to the β-hydroxy group. However aldehydes show an increased reactivity for these transformations.



3a - 3c

6a R = H
6b R = Cl
6c R = CO_2Et

7a - 7e

Scheme 2. Reagents and conditions: 6 equiv. $TiCl_4$, CH_2Cl_2, -78 °C.

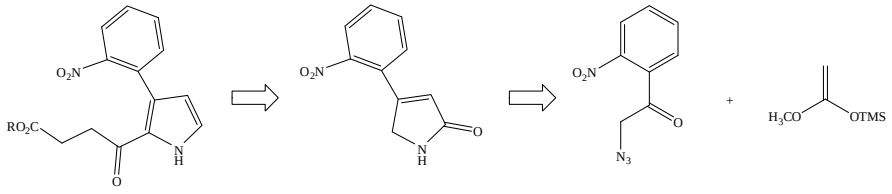
Entry	Substrates		Product	Isolated yield (%)
[a]1	**3a**	**6a**	**7a**	51
[a]2	**3b**	**6a**	**7b**	34
3	**3c**	**6a**	**7c**	70
4	**3c**	**6b**	**7d**	51
5	**3c**	**6c**	**7e**	13

Table 1.

We therefore used simple aldehydes of the type **6a** – **6b** as electrophiles. The yields of the aldol products **7a** – **7d** obtained under these optimized conditions were satisfactory to excellent. Only the *Mukaiyama* reaction between the ketene acetal **3c** and the aldehyde **6c** was unsatisfactory. **6c** was difficult to obtain in anhydrous form and the enolisation of the β-aldehydo ester occurs easily, diminishing the amount of active aldhyde present under the reaction conditions.

In view of these results we decided to keep the retrosynthetic dissection of rhazinilam, but to invert the roles of the two fragments needed for the pyrrole synthesis (Figure 3).

The part introducing the nitro substituted aromatic ring (**VII**) becomes the electrophile, whereas the aliphatic part becomes the nucleophile (**VIII**).



V **VI** **VII** **VIII**

Figure 3.

The inversion of the polarity should also allow to solve the problem of the regioselectivity for the introduction of the aliphatic side chain into the sterically more hindered α-position of the pyrrole ring.

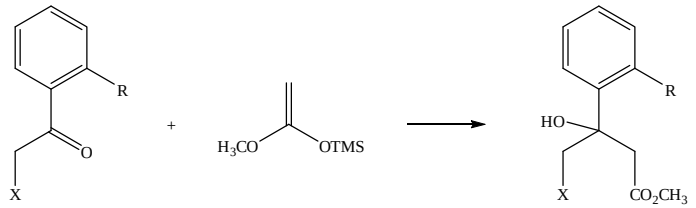
We initially used 6 equivalents of $TiCl_4$ and near stoechiometric amounts of the reagent **9**.

The reaction was initiated at – 78 °C, then allowed to warm up slowly to room temperature. Under these conditions moderate yields of the condensation products **10a** and **10b** were isolated (Table 2,).

Careful studies indicated that the starting materials and the products are unstable if the temperature of the reaction mixture is too high. At temperatures above –10 °C the formation of side products and a corresponding reduction of the yield was observed. The presence of large quantities of the strong Lewis acid $TiCl_4$, which had to be neutralized, rendered the work-up more difficult and lowered the yield.

In a systematic study, the amount of $TiCl_4$ was reduced from 6 equivalents to 0.5 equivalents. The amount of the ketene acetal was increased to 3 equivalents and the

reaction temperature was kept between –30 °C and –15 °C. Under these conditions the reaction time could be kept just under 1 h allowing the isolation of the products in excellent yields of up to 87% (Table 2, entry 2). The reaction was allowed to run for 2 h without significant change in the yield.



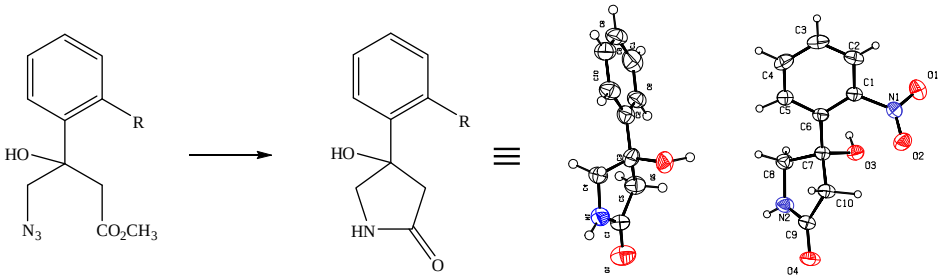
8a - 8e **9** **10a - 10e**

Scheme 3. Reagents and conditions: 0.5 equiv. $TiCl_4$, CH_2Cl_2, -30 °C then -15 °C, 45 min.

Entry		Substrates **8**	Isolated yield **10** (%)
[a]1	**a**	X = Cl, R = H	20
2	**b**	X = Br, R = H	87
3	**c**	X = N_3, R = H	74
[b]4	**d**	X = Br, R = NO_2	48
5	**e**	X = N_3, R = NO_2	80

Table 2.

The *Staudinger* reaction transforming the aldol products **10c** and **10e** into the pyrrolidinones **11a** and **11b** occurred without any problems in good yields using 1.5 equivalents of triphenylphosphine (Scheme 4).



10c R = H
10e R = NO_2

11a R = H (76%)
11b R = NO_2 (80%)

11a **11b**

Scheme 24. Reagents and conditions: PPh_3, H_2O, THF, RT.

The isolation of **11b** was very expedient because the product is not soluble in THF. Just a filtration allowed to isolate the pure product. The X-ray crystallographic analysis of **11b** revealed that all fonctionnal groups are implicated in a dense network of hydrogen bonds (Figure 4).

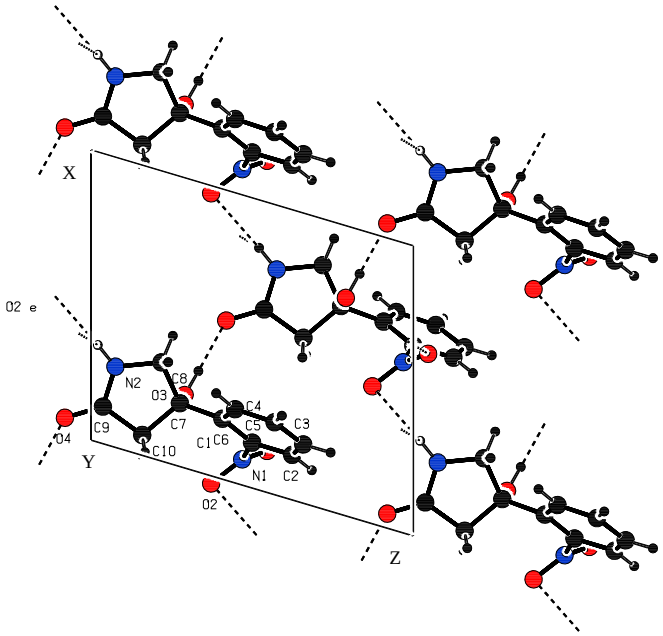


Figure 4.

Two chains of hydrogen bonds cross the whole crystal forming a sheet and further hydrogen bonds extand into the 3rd dimension (not shown in Figure 3). This particular arrangment is in accordance with the low solubility observed.

Entry	Atoms	Distance (Å)	Observation
1	O(3)-H-O(4)	2.72	Normal length
2	N(2)-H-O(1)	3.15	Normal length
3	N(2)-H-O(2)	3.23	Unusual big length

Table 3.

On the opposite the solubility of **11a** in organic solvents is sufficient and does not create any problems for further transformations. The X-ray analysis of **11a** revealed that the

molecules are associated as dimers. A third hydrogen bond links these dimers together into an one-dimensional chain (Figure 5).

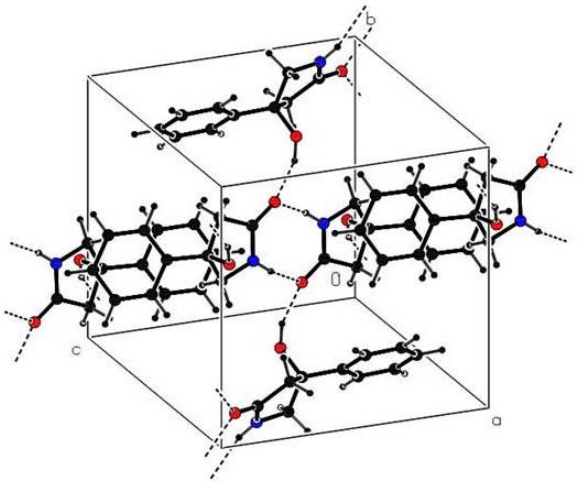
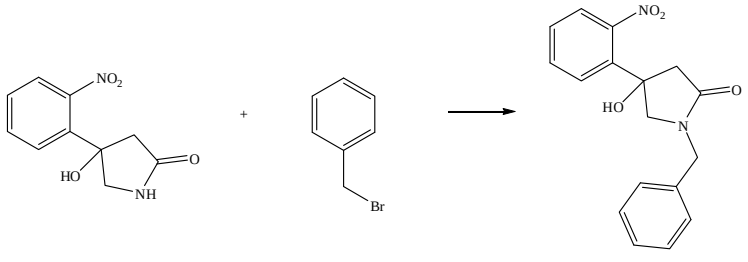


Figure 5.

Whereas **11b** makes 6 hydrogen bonds per molecule the absence of the nitro group onto **11a** reduces this number to 4.

The elimination of the tertiary alcohol was more difficult than we had anticipated. The alcohol reacted only sluggishly, if at all with many of the reagents tried. Part of the problem is the low solubility of compound **11b**.

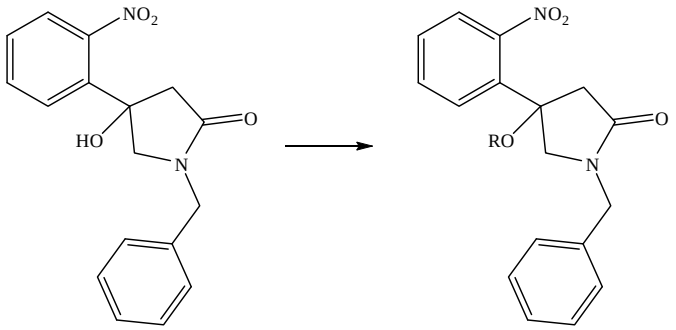
We tried to eliminate the tertiary alcohol of **11b** under acidic conditions but we only observed the degradation of the starting material. Because of the slightly higher reactivity of the lactam compared to the alcohol and the problem of solubility we protected first this fonction with a benzyl group in good yield (Scheme 5).



11b **13**

Scheme 5. Reagents and conditions: NaH, DMF, -20 °C then -10 °C, 60%.

To eliminate the alcohol we decided to introduce a good leaving group. However the tertiary alcohol of **13** was very unreactive and the formation of a derivative could only be observed under very harsh conditions (table 4, entry 7). Only the acetate could be introduced in 73 % yield at 100 °C. No elimination of the acetyl group could be observed under these conditions.



13 **14**

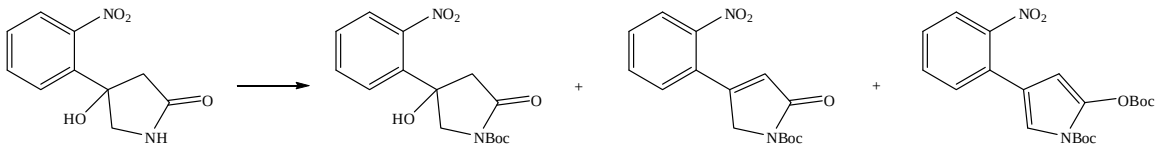
Scheme 6.

Entry	Reagents	T (°C)	Isolated yield (%)
1	Pyridine, Ac_2O	rt	-
2	NaH, Ac_2O, DMF	-20 then rt	-
3	Et_3N, TMSCl, toluene	rt	-
4	Pyridine,MsCl	rt	-
5	Pyridine, Tf_2O	rt	-
6	NaH, Tf_2O, CH_2Cl_2	-20 then rt	-
7	Ac_2O	100	73%

Table 4.

However treating **11b** with 2 equivalents of Boc-anhydride in the presence of DMAP using THF as a solvent introduced the Boc-protecting group on the lactam nitrogen and effected at the same time the elimination of the tertiary alcohol in almost quantitative yield to give the product **16b**. This one-pot procedure was an elegant solution of the solubility and the correlated reactivity problem.

A systematic study of this reaction revealed that we were able to isolate 3 different products changing the amount of Boc_2O (Table 5).



11b **15** **16b** **17**

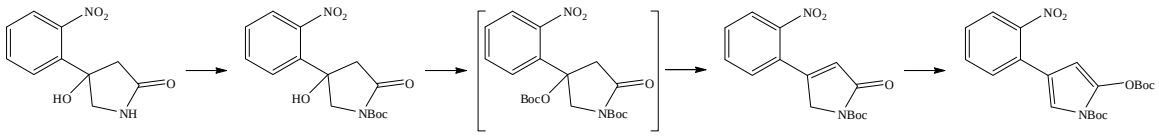
Scheme 7. Reagents and conditions: x equiv. Boc_2O, DMAP, RT.

Entry	Boc_2O (eq.)	Solvent	Reaction time (h)	**15**	**16b**	**17**	Isolated yield (%)
1	1	DMF	1	75	25	-	-
2	2.1	THF	24	-	98	2	98%
3	3	DMF	2	-	-	100	93%
4	3	THF	2	-	-	100	82-93%

Table 5.

With one equivalent of Boc_2O we isolated a mixture of **15** and **16b**. These conditions were not optimized. If **11b** was treated with 3 equivalents of Boc_2O we isolated the pyrrolic tautomer **17** in almost quantitative yield. We initially made this reaction in DMF because of the low solubility of **11b**. However using THF as solvent the reaction has the same efficiency and the purification is easier.

This study suggests that the first step is the *N*-bocylation followed by the *O*-bocylation. The elimination with the help of the third equivalent of Boc_2O will produce the aromatic compound **17** (Scheme 8).

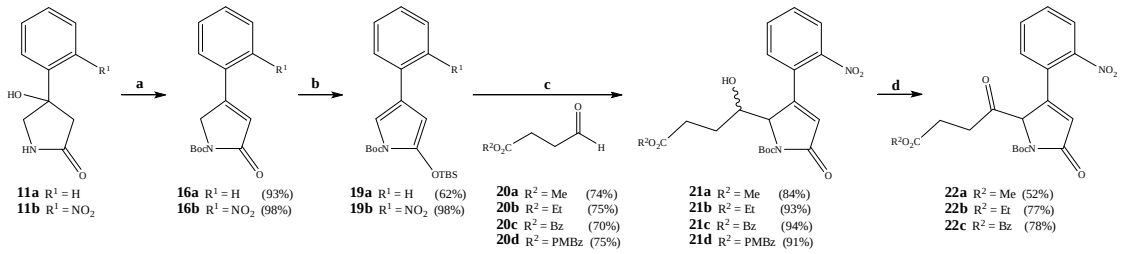


11b **15** **18** **16b** **17**

Scheme 8.

In spite of our efforts we never isolated or observed the compound **18**. Applying the same strategy for **11a** we isolated **16a** in almost quantitative yield (Scheme 9). The nitro group on the phenyl ring seems to have no direct impact on this reaction.

In order to introduce the four carbon side chain, the pyrrolinone was first silylated forming **19a** and **19b**, which correspond to a protected form of the pyrrolic tautomer of the pyrrolidinone[67, 68]. The compound **19a** was more sensitive to hydrolysis than **19b**. Whereas we were able to purify **19b** by flash chromatography on silica gel, **19a** was not stable under these conditions. We had to purify **19a** by distillation to prevent any hydrolysis. The side chain was introduced using the aldehyde **20a-d** as electrophile and BF_3 etherate as catalyst[69-71]. The aldehyde **20a** was obtained using a procedure described in literature[72]. Hydrolysis and esterification of γ-butyrolactone followed by Swern oxidation gave the ethyl derivative **20b** in 75% yield over two steps. The derivatives **20c** and **20b** were synthesized using an equivalent strategy compare to **20b**. First the hydrolysis of γ-butyrolactone followed by the esterification to give the corresponding alcohol which was oxidized using a Swern procedure. The respective yields over 3 steps were 70 and 75%.



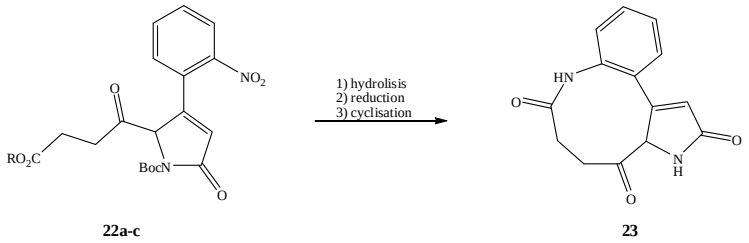
Scheme 9. Reagents and conditions: (a) Boc_2O, DMAP, THF, RT; (b)TBSOTf, 2,6-lutidine, CH_2Cl_2; (c) BF_3OEt_2, CH_2Cl_2, -78 °C; (d) PDC, CH_2Cl_2, 0 °C.

84 to 94% yield of aldol products **21a-d** were obtained starting with the compound **19b**. The diastereoselectivity of the reaction controlling the two newly formed chiral centers was low. In the next step the alcohols **21a-c** were oxidized using PDC in the presence of molecular sieves.

No.	R	PDC (equiv.)	Conc.(M)	Temp.(°C)	Time (h)	MS4Å (g)	Yield(%)
1	Me	3.4	$2.4\ 10^{-2}$	RT	1	2	23
2	Me	2.5	$1.6\ 10^{-2}$	RT	3	2	52
3	Et	1.8	$1.6\ 10^{-2}$	RT	3	2	43
4	Et	1.1	$1.6\ 10^{-2}$	RT	3	2.5	35
5	Et	1.1	$1.4\ 10^{-2}$	0	6	2	45
6	Et	2	$9\ 10^{-3}$	0	7	2	77
7	Bz	2	$1\ 10^{-2}$	0	7	2	78

Table 6.

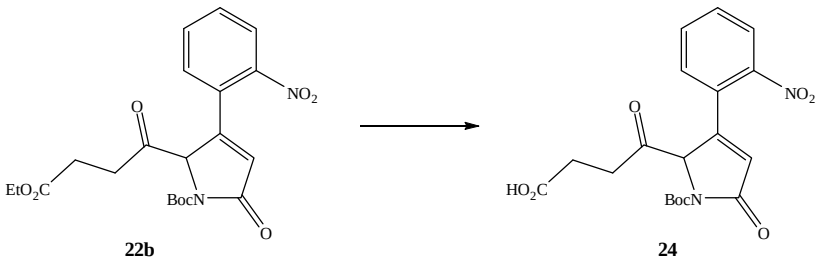
The compounds **22a-c** contain all the carbons necessary to form the 9 membered ring **B** (Scheme 10) .



22a-c **23**

Scheme 10.

The hydrolysis of **22b** under basic conditions gave the corresponding acid **24** but in moderate yield (Scheme 11).



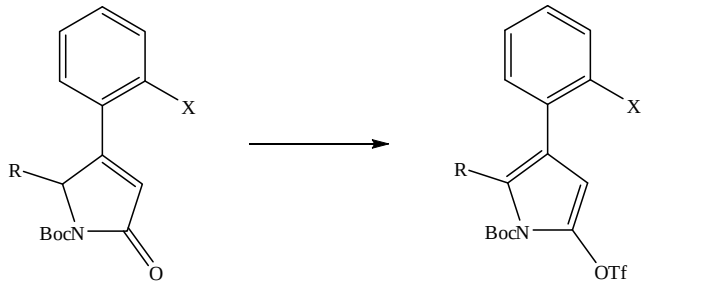
22b **24**

Scheme 11. Reagents and conditions: MeOH, NaOH (50%), 1 h, RT, 40%.

We were not able to improve this result changing the parameters of this procedure. Part of the problem could be the high acidity of the proton in position 5 of the pyrrolidinone. The best conditions for basic hydrolysis found were the treatment of **22b** with and an excess of aqueous sodium hydroxide and MeOH at room temperature. The hydrolysis

under acidic conditions gave no better results. Compounds **22a-c** were too sensitive to acids. Different other procedures as enzymatic hydrolysis or hydrogenation (**22c**) were tried to optimize this step but without any significant result.

To reduce the pyrrolidinone **22b** to the needed pyrrole we developed a method using Pd^0 as catalyst starting from the triflate derivative **25d** for the reductive elimination. We synthesized in good to moderate yields 4 different triflate derivatives (**25a-d**) (Scheme 12).



16a-b, 22a-b

25a R = H, X = H (82%)
25b R = H, X = NO_2 (61%)
25c R = $MeCO_2(CH_2)_2CO$, X = NO_2 (21%)
25d R = $EtCO_2(CH_2)_2CO$, X = NO_2 (74%)

Scheme 12. Reagents and conditions: Tf_2O, Base, CH_2Cl_2.

The choice of the base is critical for this reaction. By analogy with the synthesis of **19a,b** we used 1,3-lutidine as base for the non substituted pyrrolidinones **16a,b** giving the corresponding triflate **25a,b** in good yield. But in presence of the side chain this base gave a moderate yield only (**25c**). Changing 1,3-lutidine for Et_3N allowed to improve this reaction and to obtain **25d** in good yield.

We observed for all the compounds **25a-d** a ^6J coupling in the ^{1}H-NMR between H(3) and the fluorines of the triflate group (Figure 5). The ^{1}H-NMR of H(3) is a doublet of quadruplets. The coupling constant of the doublet is a classical ^4J for pyrrole rings between H(3) and H(5) with a typical coupling constant of 2.3 Hz. The coupling constant of the quadruplet is much smaller (0.8 Hz) and is correlated with the coupling constant of the doublet (0.7 Hz) observed in ^{19}F-RMN.

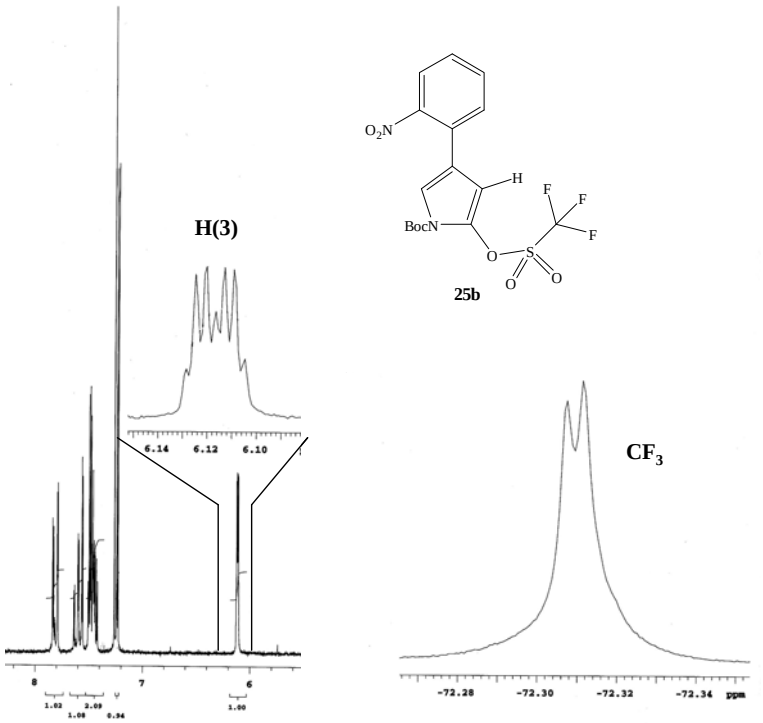


Figure 6.

The X-ray analysis of the derivative **25a** revealed that the triflate group is not in the same plane than the pyrrole ring (Figure 7). This conformation brings the fluorines into close van der Waals contact with H(3).

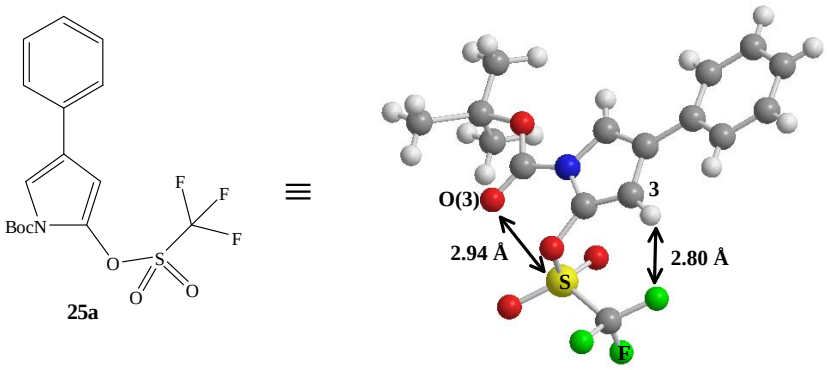


Figure 7.

The distance between H(3) and the nearest fluorine atom is rather short (2.80 Å). The triflate group in **25a** is turned out of conjugation with the π-system of the adjacent pyrrole ring to avoid strong steric contact with the *N*-Boc group. The same conformation was observed for the *O*-Boc group in compound **17**. The comparison of the X-ray analysis of

17 and **25a** revealed the same 3D arrangement for the two different *O*-substituants (Figure 8).

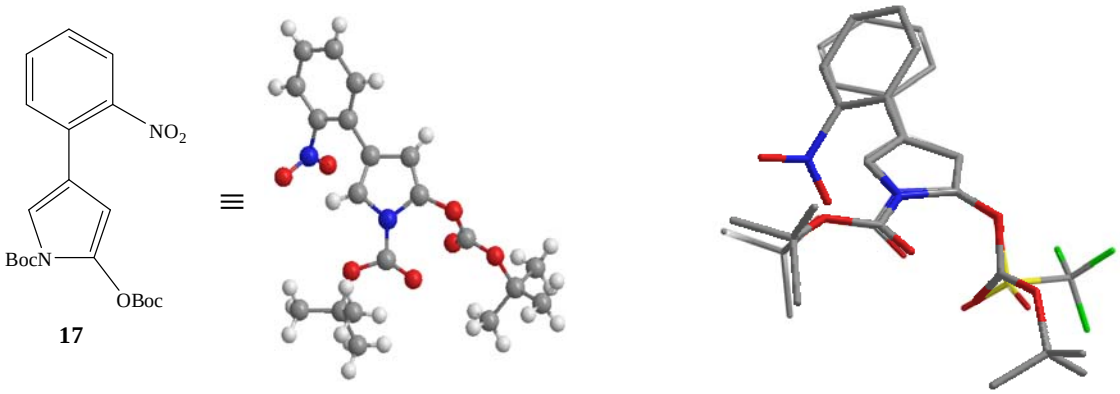
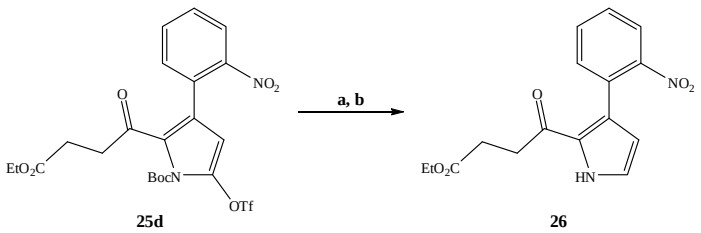


Figure 11.

The superposition of the structures **17** and **25a** shows that the substituants on the nitrogen and the oxygen of the pyrrole ring have the same geometry. The bulky Boc-group on the pyrrole nitrogen is in the plane of the pyrrole ring. This arrangement maximizes the overlap between the lone pair of the pyrrole nitrogen and the carbonyl of the Boc-group. To avoid the steric hindrance, the substituents on the vicinal oxygen of **17** and **25a** are pushed out of the plane. The oxygen Boc-group in **17** is arranged in a zig-zag conformation in the plane which is almost orthogonal to the plane of the pyrrole ring. The triflate on the oxygen does not show a streched conformation but the trifluoromethyl group is turned towards the pyrrole ring.

The reduction of **25d** using Et_3SiH in the presence of $Pd(OAc)_2$ and dppf as catalyst afforded the expected pyrrole in good yield (Scheme 13). This reduction was very fast at room temperature (less than 1 min.) and we had to lower the temperature to be able to control it.



25d **26**

Scheme 13. Reagents and conditions: (a) 2.5 equiv. Et_2SiH, 5% $Pd(OAc)_2$, dppf, DMF, -10 °C (64%); (b) TFA, CH_2Cl_2, RT (88%).

Finally the deprotection of the Boc group under standard conditions using TFA in CH_2Cl_2 gave the compound **26** in 88% yield.

In conclusion we have developed the synthesis of compound **26**, an advanced synthetic intermediate for the rhazinilam analogue **I**. The total yield of **26** starting from **10e** is 22%. The approach is convergent, starting from simple, inexpensive materials and allows to obtain structural variations of the skeleton. Further efforts towards the synthesis of the rhazinilam analogue are in progress.

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3.2. Supporting Material

General procedure for 3a,b,c:

A solution of LHMDS 1M in THF (15 mmol, 1.2 equiv.) is diluted in dry THF (50 mL) under N_2. Ester (12.4 mmol, 1 equiv.) is added dropwise. After 15 min. at RT, the reaction is cooled to -78 °C and TMSCl (72.1 mmol, 5.8 equiv.) is added slowly. The reaction is kept under stirring at this temperature for 1 h. The solvent is evaporated under vacuum and salts are precipitated with pentane. The solution is filtered over celite and the solved is evaporated. Purification by distillation (P=0.07 mbar, T=76 °C) (93%).

Synthesis of (1-methoxy-2-phenylvinyloxy)trimethylsilane (3a)

A solution of LHMDS 1M in THF (34 mL, 34 mmol) is diluted in dry THF (100 mL) under N_2. Methyl 2-phenylacetate (4.28 g, 28.6 mmol) is added dropwise. After 15 min. at RT, the reaction is cooled to -78 °C and TMSCl (18.02 g, 165.9 mmol) is added slowly. The reaction is kept under stirring at this temperature for 1 h. The solvent is evaporated under vacuum and salts are precipitated with pentane. The solution is filtered over celite and the solvent is evaporated. Purification by distillation (P=0.055 mbar, T=64-65 °C) (92%).

^{1}H-NMR (400 MHz, $CDCl_3$) : **isomer *E*** : 7.44 (*dd*, ^3J(4,5) = 8.1, ^4J(4,6) = 1.3, 2H, H(4)), 7.26 (*tripletoide*, ^3J(5,4) = 8.1, ^3J(5,6) = 7.4, 2H, H(5)), 7.04 (*tt*, ^3J(6,5) = 7.4, ^4J(6,4) = 1.3, 1H, H(6)), 4.70 (*s*, 1H, H(2), 3.72 (*s*, 3H, H(1')), 0.35 (*s*, 9H, H(1'')).

^{1}H-NMR (400 MHz, $CDCl_3$) : **isomer *Z*** : 7.44 (*dd*, ^3J(4,5) = 8.1, ^4J(4,6) = 1.3, 2H, H(4)), 7.26 (*dd*, ^3J(5,4) = 8.1, ^3J(5,6) = 7.4, 2H, H(5)), 7.04 (*tt*, ^3J(6,5) = 7.4, ^4J(6,4) = 1.3, 1H, H(6)), 4.62 (*s*, 1H, H(2)), 3.71 (*s*, 3H, H(1')), 0.31 (*s*, 9H, H(1'')).

^{13}C-NMR (100 MHz, $CDCl_3$) : 158.0 (C(1)) ; 137.2 (C(3)) ; 128.3 (C(5)) ; 126.5 (C(4)) ; 123.7 (C(6)) ; 78.8 (C(2)) ; 55.3 (C(1')) ; 0.6 (C(1'')).

ESI-MS : $[M + H + TFA]^+$ = 337.4

Synthesis of (1-ethoxy-2-phenylvinyloxy)trimethylsilane (3b)

A solution of LHMDS 1M in THF (15 mL, 15 mmol) is diluted in dry THF (50 mL) under N_2. Ethyl 2-phenylacetate (2.03 g, 12.4 mmol) is added dropwise. After 15 min. at RT,

the reaction mixture is cooled to -78 °C and TMSCl (7.84 g, 72.1 mmol) is added slowly. The reaction mixture is kept under stirring at this temperature for 1 h. The solvent is evaporated under vacuum and salts are precipitated with pentane. The solution is filtered over celite and the solvent is evaporated. Purification by distillation (P=0.07 mbar, T=76 °C) (88%).

^{1}H-NMR (400 MHz, $CDCl_3$) **: isomer *E*** : 4.72 (*s*, 1H, H(2)), 4.18 (*q*, ^{3}J(1',2') = 7.1, 2H, H(1')), 1.28 (*t*, ^{3}J(2',1') = 7.1, 3H, H(2')).

Note : the signals for protons 4, 5, 6 et 1'' are hided by the majority isomer *Z*

^{13}C-NMR (100 MHz, $CDCl_3$) **:isomer *E* :** 128.5 (C(5)); 126.6 (C(4)); 123.8 (C(6)); 86.5 (C(2)); 62.7 (C(1')); 15.2 (C(2')).

Note : the signals for protons 4, 5, 6 et 1'' are hided by the majority isomer *Z*

^{1}H-NMR (400 MHz, $CDCl_3$) : **isomer *Z*** : 7.45 (*dd*, ^{3}J(4,5) = 8.0, ^{4}J(4,6) = 1.3, 2H, H(4)), 7.26 (*dd*, ^{3}J(5,6) = 7.5, ^{3}J(5,4) = 8.2, 2H, H(5)), 7.03 (*tt*, ^{3}J(6,5) = 7.4, ^{4}J(6,4) = 1.3, 1H, H(6)), 4.59 (*s*, 1H, H(2)), 3.94 (*q*, ^{3}J(1',2') = 7.1, 2H, H(1')), 1.39 (*t*, ^{3}J(2',1') = 7.1, 3H, H(2')), 0.33 (*s*, 9H, H(1'')).

^{13}C-NMR (100 MHz, $CDCl_3$) : **isomer *Z*** : 157.0 (C(1)) ; 137.4 (C(3)) ; 128.2 (C(5)) ; 126.4 (C(4)) ; 123.5 (C(6)) ; 79.2 (C(2)) ; 63.8 (C(1')) ; 14.6 (C(2')) ; 0.7 (C(1'')).

ESI-MS : $[M + H]^+$ = 237.1

Synthesis of (1-ethylthio-2-phenylvinyloxy)trimethylsilane (3c)

A solution of LHMDS 1M in THF (15 mL 15 mmol) is diluted in dry THF (50 mL) under N_2. Ethyl 2-phenylacetate (2.03 g, 12.4 mmol) is added dropwise. After 15 min. at RT, the reaction is cooled at -78 °C and TMSCl (7.84 g, 72.1 mmol) is added slowly. The reaction is kept under stirring at this temperature for 1 h. The solvent is evaporated under vacuum and salts are precipitated with pentane. The solution is filtered over celite and the solvent is evaporated. Purification by distillation (P=0.08 mbar, T=80-82 °C) (92%).

^{1}H-NMR (200 MHz, $CDCl_3$, 298 K) : **isomer *E***: 7.54-7.15 (*m*, 5H, H(ar)), 6.06 (*s*, 1H, H(2)), 2.79 (*q*, ^{3}J(1',2') = 7.3, 2H, H(1')), 1.34 (*t*, ^{3}J(2',1') = 7.3, 3H, H(2')).

^{1}H-NMR (200 MHz, $CDCl_3$, 298 K) : **isomer *Z***: 7.54-7.15 (*m*, 5H, H(ar)), 5.88 (*s*, 1H, H(2)), 2.79 (*q*, ^{3}J(1',2') = 7.3, 2H, H(1')), 1.28 (*t*, ^{3}J(2',1') = 7.3, 3H, H(2')).

Synthesis of 2-azido-1,1-dimethoxyethane (4c)

NaN_3 (3.00 g, 46.2 mmol) and KI (0.50 g, 3.0 mmol) are mixed in a flask with DMF (50 mL). 2-bromo-1,1-dimethoxyethane (5.00 g, 29.6 mmol) is added and the solution is heated at 95 °C. After 6 h, the solution is cooled and H_2O (100 mL) is added. The aqueous phase is extracted with Et_2O. The combined organic phases are dried over $MgSO_4$. The solvent is evaporated and a red oil is recuperated (79%).

Synthesis of methyl 4-azido-3-methoxy-2-phenylbutanoate (5)

$TiCl_4$ (6.60 mL, 59.7 mmol) is added to a solution of acetal **4c** (532 mg, 4.1 mmol) in dry CH_2Cl_2 (20 mL) under Ar. **3a** (902 mg, 4.5 mmol) is then added dropwise. The mixture becomes green and is stirred at this temperature. After 1 h, H_2O (100 mL) is added and phases are separated. Aqueous phase is extracted 3 times with CH_2Cl_2. The organic phases are successively washed with water and brine and dried over $MgSO_4$. After concentration the residue is purified by flash chromatography (silica gel, EtOAc/hexane 1:3) to give 200 mg of **5** (20%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.38-7.24 (*m*, 5H, H(ar)), 4.37-4.34 (*m (X part of the system ABX* (partially solved)), ^3J(3,2) ≈ 9.6, ^3J(X,A) ≈ 5.6, ^3J(X,B) ≈ 2.9, 1H, H(3)), 3.81 (*d*, ^3J(2,3) = 9.6, 1H, H(2)), 3.76 (*s*, 3H, H(2')), 3.70 (*s*, 3H, H(1')), 3.25, 3.24, 3.05 and 3.03 (*2xdd system ABX*, ^2J = 12.8, ^3J(A,X) = 5.6, ^3J(B,X) = 2.9, 2H, H(4)),

Note : the signal due to an impurity: 7.38-7.24 (m, H(ar)) double intensity of integrals)

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 173.2 (C(1)) ; 138.1 (C(arq)) ; 129.3 (C(ar)) ; 128.7 (C(ar)) ; 128.5 (C(ar)) ; 72.6 (C(3)) ; 54.8 (C(2)) ; 53.5 (C(4)) ; 52.4 (C(2')) ; 52.4 (C(1')).

Note : the signal due to an impurity: for C(ar) the difference between product and impurity is not well difined

ESI-MS : $[M - H + H_2O]^-$ = 265.3; [[M + H + H_2O] + H_3COOH] = 278.4; [[M + H] + H_3COOH] = 296.3

General procedure for 7a,b:

$TiCl_4$ (60.8 mmol, 14.8 equiv.) is added to a solution of acetaldehyde **6a** (4.1 mmol, 1 equiv.) in dry CH_2Cl_2 (20 mL) under N_2 at -78 °C. The enol **3a,b** (4.1 mmol, 1 equiv.) dissolved in dry CH_2Cl_2 (8 mL) is then added dropwise over 30 min. After 4 h water is added to the mixture until complete dissolution of the solid. The aqueous phase is

extracted 3 times with CH_2Cl_2 and the combined organic phases are washed 3 times with water and once with brine. After having dried the organic phase over $MgSO_4$ and concentrated the mixture, the residue is purified by flash chromatography (silica gel, 40% EtOAc in hexane) to afford **7a,b** as a yellow oil.

Synthesis of methyl 3-hydroxy-2-phenylbutanoate (7a)

Acetaldehyde (200 mg, 4.5 mmol) is dissolved in dry CH_2Cl_2 (20 mL) and $TiCl_4$ (7.3 mL, 66.1 mmol) is added at -78 °C under Ar. 1-Methoxy-2-phenyl-vinyloxy)trimethylsilane (1.00 g, 4.5 mmol) is added dropwise to the reaction. The solution becomes green and is kept at this temperature for 1 h, than H_2O (100 mL) is added. The aqueous phase is extracted 3 times with CH_2Cl_2 and the combined organic phases are washed succesively with water and brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product is purified by flash chromatography (EtOAc/Hexane 2:3) (51%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.37-7.30 (*m*, 5H, H(ar)), 4.40-4.34 (*m* (partially solved), ^3J(3,2) ≈ 6.6, ^3J(3,4) = 6.2, 1H, H(3)), 3.69 (*s*, 3H, H(1')), 3.55 (*d*, ^3J(2,3) = 6.8, 1H, H(2)), 2.41 (*s*, 1H, OH)), 1.21, (*d*, ^3J(4,3) = 6.2, 3H, H(4)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 173.4 (C(1)) ; 135.0 (C(ar)) ; 129.1 (C(ar)) ; 128.6 (C(ar)) ; 127.8 (C(ar)) ; 68.5 (C(3)) ; 58.6 (C(2)) ; 52.0 (C(1')) ; 20.4 (C(4)).

ESI-MS : $[M+Na]^+$ = 217.3

Synthesis of Ethyl 3-hydroxy-2-phenylbutanoate (7b)

Acetaldehyde (0.20 mL, 4.1 mmol) is dissolved in dry CH_2Cl_2 (20 mL) and $TiCl_4$ (6.7 mL, 60.8 mmol) freshly distilled over polyvinylpyridine is added to the reaction at -78 °C under Ar. The solution becomes yellow. (1-Ethoxy-2-phenyl-vinyloxy)trimethylsilane (976.5 mg, 4.1 mmol) dissolved in CH_2Cl_2 (8 mL) is added dropwise (during aproximatively 30 min.) to the reaction. After 4 h at -78 °C under stirring, 100 mL water are added. The aqueous phase is extracted 3×30 mL with CH_2Cl_2 and the combined organic phases are washed succesively 3×30 mL with water and 1×30 mL brine, dried over $MgSO_4$ and concentrated under vacuum. The crude yellow product is purified by flash chromatography (EtOAc/Hexane 2:3) (34%).

^{1}H-NMR (400 MHz, $CDCl_3$) : **isomer 1** : 7.40-7.24 (*m*, 5H, H(ar)), 4.39 (*dq*, ^3J(3,2) = 6.5, ^3J(3,4) = 6.3), 1H, H(3)), 4.24, 4.22, 4.21 and 4.20 (*dxdq (ABX$_3$, system)* ^2J = 10.8, ^3J(A,X$_3$)(B,X$_3$) = 7.2, 2H, H(1')), 3.53 (*d*, ^3J(2,3) = 6.7, 1H, H(2)), 2.35 (*sbr*, 1H, OH), 1.24

(*t (X$_3$ part of the system ABX$_3$)*, ^3J(X$_3$,A)(X$_3$,B) = 7.1, 3H, H(2')), 1.23 (*d*, ^3J(4,3) = 6.3, 3H, H(4)).

^{1}H-NMR (400 MHz, $CDCl_3$) : **isomer 2** : 7.40-7.24 (*m*, 5H, H(ar)), 4.35 (*dq*, ^3J(3,2) = 9.1, ^3J(3,4) = 6.3), 1H, H(3)), 4.15, 4.14, 4.12 and 4.11 (*dxdq (ABX$_3$ system)* ^2J = 10.8, ^3J(A,X$_3$)(B,X$_3$) = 7.1, 2H, H(1')), 3.51 (*d*, ^3J(2,3) = 9.1, 1H, H(2)), 1.22 (*t (X$_3$ part of the system ABX$_3$)* ^3J(X$_3$,A)(X$_3$,B) = 7.1, 3H, H(2')), 1.07 (*d*, ^3J(4,3) = 6.3, 3H, H(4)).

^{13}C-NMR (100 MHz, $CDCl_3$) : **isomer 1 :** 173.7 (C(1)) ; 136.4 (C(ar)) ; 128.8 (C(ar)) ; 128.7 (C(ar)) ; 127.8 (C(ar)) ; 68.6 (C(3)) ; 61.1 (C(1')) ; 58.7 (C(2)) ; 20.3 (C(4)) ; 14.0 (C(2')).

^{13}C-NMR (100 MHz, $CDCl_3$) : **isomer 2 :** 173.1 (C(1)) ; 135.1 (C(ar)) ; 129.1 (C(ar)) ; 128.3 (C(ar)) ; 127.6 (C(ar)) ; 69.7 (C(3)) ; 61.0 (C(1')) ; 60.2 (C(2)) ; 20.4 (C(4)) ; 14.0 (C(2')).

ESI-MS : $[M + H]^+$ = 231.2

General procedure for 7c-e:

$TiCl_4$ (24 mmol, 6 equiv.) is added to a solution of aldehyde **6a-c** (4 mmol, 1 equiv.) in dry CH_2Cl_2 (20 mL) under N_2 at -78 °C. The enol **3c** (4 mmol, 1 equiv.) dissolved in dry CH_2Cl_2, (6 mL) is added dropwise over 30 min. After 1 h at this temperature, a saturated aqueous solution of $NaHCO_3$ (50 mL) is added to the cold mixture and the aqueous phase is extracted 3 times with CH_2Cl_2. The combined organic phases are washed 3 times with water and once with brine. After having dried the organic phase over $MgSO_4$ and concentrated the mixture, the residue is purified by flash chromatography (silica gel, EtOAc/hexane 1:3) to afford **7c-e**.

Synthesis of *S*-ethyl 3-hydroxy-2-phenylbutanethioate (7c)

Acetaldehyde (0.23 mL, 4.1 mmol) is dissolved in dry CH_2Cl_2 (20 mL) and $TiCl_4$ (2.70 mL, 24 mmol) freshly distilled over polyvinylpyridine is added to the reaction at -78 °C under Ar. (1-Ethylsulfanyl-2-phenyl-vinyloxy)trimethylsilane (1 g, 4 mmol) dissolved in CH_2Cl_2 (6 mL) is added dropwise to the reaction. The solution becomes dark orange. After 1 h at -78 °C under stirring, sat. $NaHCO_3$ (50 mL) is added to the cold solution. The aqueous phase is extracted 3 times with CH_2Cl_2 and the combined organic phases are washed succesively with water and brine, dried over $MgSO_4$ and concentrated under vacuum. The crude yellow product is purified by flash chromatography (EtOAc/Hexane 1:3) (70%)

^{1}H-NMR (400 MHz, CD_3OD, 298 K) : **isomère 1** : 7.42-7.29 (*m*, 5H, H(ar)), 4.49-4.42 (*m* (partially solved), ^{3}J(2,3) = 9.1, ^{3}J(3,4) = 6.3, 1H, H(3)), 3.72 (*d*, ^{3}J(2,3) = 9.0, 1H, H(2)), 2.88 (*q*, ^{3}J(1',2') = 7.4, 2H, H(1')), 2.29 (*s*, 1H, OH), 1.24 (*d*, ^{3}J(4,3) = 6.18, 3H, H(4)),1.22 (*t*, ^{3}J(2',1') = 7.4, 3H, H(2')).

Note : OH signal of the 2nd isomer is hidden under H(1') signal

^{1}H-NMR (400 MHz, CD_3OD, 298 K) : **isomer 2** : 7.42-7.29 (*m*, 5H, H(ar)), 4.49-4.42 (*m* (partially solved), ^{3}J(2,3) ≈ 6.8, ^{3}J(3,4) = 6.3, 1H, H(3)), 3.70 (*d*, ^{3}J(2,3) = 7.1, 1H, H(2)), 2.87 (*q*, ^{3}J(1',2') = 7.5, 2H, H(1')), 2.29 (*s*, 1H, OH)), 1.21 (*t*, ^{3}J(2',1') = 7.4, 3H, H(2')), 1.03 (*d*, ^{3}J(4,3) = 6.3, 3H, H(4)).

^{13}C-NMR (100 MHz, CD_3OD, 298 K) : **isomer 1** : 201.3 (C(1)) ; 136.1 (C(arq)) ; 128.8 (C(ar)) ; 128.7 (C(ar)) ; 127.8 (C(ar)) ; 68.7 (C(3)) ; 68.2 (C(2)) ; 23.5 (C(1')) ; 20.6 (C(4)) ; 14.3 (C(2')).

^{13}C-NMR (100 MHz, CD_3OD, 298 K) : **isomer 2** : 199.9 (C(1)) ; 134.9 (C(arq)) ; 129.1 (C(ar)) ; 128.5 (C(ar)) ; 127.9 (C(ar)) ; 69.7 (C(3)) ; 67.3(C(2)) ; 23.6 (C(1')) ; 20.5 (C(4)) ; 14.3 (C(2')).

ESI-MS : $[M + Na]^+$ = 247.3

Synthesis of *S*-ethyl 4-chloro-3-hydroxy-2-phenylbutanethioate (7d)

Chloro-acetaldehyde (306 mg, 3.9 mmol) is dissolved in dry CH_2Cl_2 (20 mL) and $TiCl_4$ (2.6 mL, 23.4 mmol) freshly distilled over polyvinylpyridine is added to the reaction at -78 °C under Ar. 1-(Ethylsulfanyl-2-phenyl-vinyloxy)trimethylsilane (0.98 g, 3.9 mmol) dissolved in CH_2Cl_2 (6 mL) is added dropwise to the reaction. The solution becomes dark orange. After 1 h at -78 °C under stirring, sat. $NaHCO_3$ (50 mL) is added to the cold solution. The aqueous phase is extracted 3 times with CH_2Cl_2 and the combined organic phases are washed succesively 3 times with water and brine, dried over $MgSO_4$ and concentrated under vacuum. The crude yellow product is purified by flash chromatography (EtOAc/Hexane 1:3) (51%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.42-7.34 (*m*, 5H, H(ar)), 4.57-4.52 (*m (X part of the system ABX* (partially solved)), ^{3}J(X,A) ≈ 5.5, ^{3}J(3,OH) ≈ 3.9, 1H, H(3)), 4.10 (*d*, ^{3}J(2,3) = 6.4, 1H, H(2)), 3.58, 3.57, 3.52 et 3.51 (*2xdd (ABX system)*, ^{2}J = 11.3, ^{3}J(A,X) = 5.6, ^{3}J(B,X) = 5.1, 2H, H(4)), 2.94, 2.91, 2.89 et 2.87 (*2xdq (ABX$_3$ system)*, ^{2}J = 13.4, ^{3}J(A,X$_3$)(B,X$_3$) = 7.4, 2H, H(1')), 2.67 (*d*, ^{3}J(OH,3) = 4.0, 1H, H(OH)), 1.24 (*t (X$_3$ part of the system ABX$_3$)*, ^{3}J(X$_3$,A)(X$_3$,B) = 7.4, 3H, H(2')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 199.9 (C(1)) ; 133.7 (C(arq)) ; 129.4 (C(ar)) ; 128.9 (C(ar)) ; 128.3 (C(ar)) ; 71.9 (C(3)) ; 62.0 (C(2)) ; 46.4 (C(4)) ; 23.7 (C(1')) ; 14.3 (C(2')).
ESI-MS : $[M + Na]^+$ = 281.1

Synthesis of ethyl 5-(ethylthio)-3-hydroxy-5-oxo-4-phenylpentanoate (7e)

Ethyl 3-oxopropanoate (1.50 mL, 4 mmol) is dissolved in dry CH_2Cl_2 (20 mL) and $TiCl_4$ (2.60 mL, 23.4 mmol) freshly distilled over polyvinylpyridine is added to the reaction at -78 °C under Ar. (1-Ethylsulfanyl-2-phenyl-vinyloxy)trimethylsilane (1.00 g, 4 mmol) dissolved in CH_2Cl_2 (6 mL) is added dropwise to the reaction. The solution becomes dark orange. After 1 h at -78 °C under stirring, sat. $NaHCO_3$ (50 mL) is added to the cold solution. The aqueous phase is extracted 3 times with CH_2Cl_2 and the combined organic phases are washed succesively 3 times with water and brine, dried over $MgSO_4$ and concentrated under vacuum. The crude yellow product is purified by flash chromatography (EtOAc/Hexane 1:3) (13%).
^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : **isomer 1** : 7.42-7.28 (*m*, 5H, H(ar)), 4.80-4.4.71 (*m (X part of the system ABX* (partially solved)), ^{3}J(3,2) = 9.6, ^{3}J(X,A) ≈ 8.2, ^{3}J(X,B) ≈ 4.2, 1H, H(3)), 4.14 (*q*, ^{3}J(1'',2'') = 7.1, 2H, H(1'')), 3.89 (*d*, ^{3}J(2,3) = 9.6, 1H, H(2)), 2.94, 2.91, 2.90 and 2.87 (*2xdq (ABX$_3$ system)*, ^{2}J = 13.3, ^{3}J(A,X_3)(B,X_3) = 7.5, 2H, H(1')), 2.56, 2.53, 2.50 and 2.46 (*2xdd (ABX system)*, ^{2}J = 16.3, ^{3}J(A,X) = 8.2, ^{3}J(B,X) = 4.2, 2H, H(4)), 1.24 (*t*, ^{3}J(2'',1'') = 7.1, 3H, H(2'')), 1.23 (*t (X_3 part of the system ABX$_3$)*, ^{3}J(X_3,A)(X_3,B) = 7.4, 3H, H(2')).
^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : **isomer 2** : 7.42-7.28 (*m*, 5H, H(ar)), 4.80-4.4.71 (*m (X part of the system ABX* (partially solved)), ^{3}J(3,2) = 7.8, ^{3}J(X,A) ≈ 7.2, ^{3}J(X,B) ≈ 4.8, 1H, H(3)), 4.13 (*q*, ^{3}J(1'',2'') = 7.2, 2H, H(1'')), 3.91 (*d*, ^{3}J(2,3) = 7.7, 1H, H(2)), 2.90, 2.87, 2.84 and 2.83 (*2xdq (ABX$_3$ system)*, ^{2}J = 11.7, ^{3}J(A,X_3)(B,X_3) = 7.5, 2H, H(1')), 2.31 and 2.26 (*2xdd (ABX system)*, ^{2}J = 16.5, ^{3}J(A,X) = 7.5, ^{3}J(B,X) = 4.6, 2H, H(4)), 1.24 (*t*, ^{3}J(2'',1'') = 7.1, 3H, H(2'')), 1.22 (*t (X_3 part of the system ABX$_3$)*, ^{3}J(X_3,A)(X_3,B) = 7.4, 3H, H(2')).
^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : **isomer 1** : 199.6 (C(1)) ; 172.0 (C(5)) ; 135.1 (C(arq)) ; 129.3 (C(ar)) ; 128.7 (C(ar)) ; 128.1 (C(ar)) ; 69.9 (C(3)) ; 65.6 (C(2)) ; 60.8 (C(1'')) ; 38.9 (C(4)) ; 24.7 (C(1')) ; 14.1 (C(2')) ; 14.1 (C(2'')).
^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : **isomer 2** : 199.6 (C(1)) ; 171.9 (C(5)) ; 134.6 (C(arq)) ; 129.0 (C(ar)) ; 128.5 (C(ar)) ; 128.1 (C(ar)) ; 69.0 (C(3)) ; 64.5 (C(2)) ; 60.8 (C(1'')) ; 38.7 (C(4)) ; 23.7 (C(1')) ; 14.1 (C(2')) ; 14.1 (C(2'')).

ESI-MS : $[M + Na]^+ = 319.1$

Synthesis of 2-azido-1-phenylethanone (8c)

2-Bromo-1-phenylethanone (7.84 g, 39.3 mmol) dissolved in MeOH (27.7 mL) is added to a solution of NaN_3 (3.93 g, 60.3 mmol) in H_2O (11 mL). After 15 h under mechanical stirring at 4 °C, the solution is extracted 3 times with Et_2O and the combined organic phases are wash succesively 3 times with water and brine, dried over $MgSO_4$ and concentrated under vacuum. The crude yellow product is purified by flash chromatography (CH_2Cl_2/Hexane 7:3) (91%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.86-7.83 (*m*, 2H, H(2')), 7.60-7.55 (*m*, 1H, H(4')), 7.46-7.42 (*m*, 2H, H(3')), 4.52 (*s*, 2H, H(2)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 193.1 (C(1)) ; 134.0 (C(1')) ; 133.9 (C(3')) ; 128.7 (C(4')) ; 127.6 (C(2')) ; 54.6 (C(2)).

Synthesis of 2-Bromo-1-(2-nitrophenyl)ethanone (8d)

1-(2-nitrophenyl)ethanone (1.00 g, 6 mmol) and $AlCl_3$ (25 mg) are dissolved in dry Et_2O at 0 °C . Bromine (0.31 mL, 6 mmol) is added dropwise. When the addition is completed, the temperature is brought to RT. After 3 h at this temperature, the organic phases are washed succesively 3 times with water and brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product is purified by flash chromatography (CH_2Cl_2/Hexane 7:3) (73%)

^{1}H-NMR (200 MHz, $CDCl_3$, 298 K) : 8.24 (*dd*, ^3J(5,6) = 8.1, ^4J(5,7) = 1.3, 1H, H(5)), 7.80 (*dt*, ^3J(7,6)= ^3J(7,8) = 7.4, ^4J(7,5) = 1.3, 1H, H(7)), 7.68 (*ddd*, ^3J(6,5) = 8.2, ^3J(6,7) = 7.5, ^4J(6,8) = 1.6, 1H, H(6)), 7.51 (*dd*, ^3J(8,7) = 7.5, ^4J(8,6) = 1.6, 1H, H(6)), 4.30 (*s*, 2H, H(2)).

^{13}C-NMR (50 MHz, $CDCl_3$, 298 K) : 194.3 (C(2)) ; 145.6 (C(4)) ; 134.9 (C(3)) ; 134.7 (C(7)) ; 131.2 (C(7)) ; 129.1 (C(6)) ; 124.4 (C(5)) ; 33.8 (C(1)).

Synthesis of 2-bromo-1-(2-nitrophenyl)ethanone (8e)

2-Bromo-1-(-2-nitrophenyl)ethanone (1.00 g, 4.1 mmol) dissolved in MeOH (20 mL) is added to a solution of NaN_3 (0.40 g, 6.1 mmol) in H_2O (11 mL). After 48 h under mechanical sttiring at 6 °C, the solution is extracted 3 times with Et_2O and the combined

organic phases are washed succesively 3 times with water and brine, dried over $MgSO_4$ and concentrated under vacuum. The crude yellow product is purified by flash chromatography (CH_2Cl_2) (92%).

^{1}H-NMR (200 MHz, $CDCl_3$, 298 K) : 8.24 (*dd*, ^3J(5,6) = 8.1, ^4J(5,7) = 1.5, 1H, H(5)), 7.81 (*dt*, ^3J(7,6)= ^3J(7,8) = 7.7, ^4J(7,5) = 1.5, 1H, H(7)), 7.70 (*ddd*, ^3J(6,5) = 8.1, ^3J(6,7) = 7.7, ^4J(6,8) = 1.7, 1H, H(6)), 7.43 (*dd*, ^3J(8,7) = 7.7, ^4J(8,6) = 1.7, 1H, H(6)), 4.32 (*s*, 2H, H(2)).

^{13}C-NMR (50 MHz, $CDCl_3$, 298 K) : 197.1 (C(2)) ; 135.0 (C(3)) ; 134.8 (C(7)) ; 131.4 (C(7)) ; 127.7 (C(6)) ; 124.5 (C(5)) ; 57.7 (C(1)).

Synthesis of (1-methoxyvinyloxy)trimethylsilane (9)

A solution of LHMDS 1M in THF (16.20 mL, 16.2 mmol) is diluted in dry THF (10 mL) and cooled to -78 °C. Methyl acetate (1.00 g,13.5 mmol) in THF (6 mL) is added dropwise. After 30 min. TMSCl (1.75 g, 16.2 mmol) is added and the resulting mixture is stirred for 1.5 h. The solvent is evaporated and the salts are precipitated with pentane. The solution is filtered over celite and the solvent is evaporated. Purification by distillation (P=45 mmHg, T=48-50 °C) (92%).

^{1}H-NMR (200 MHz, $CDCl_3$, 298 K) : 3.54 (*s*, 3H, H(1')), 3.21 and 3.11 (2x*d (AB system)*, 2H, ^2J = 2.6, H(2)), 0.22 (*s*, 9H, H(2')).

^{13}C-NMR (50 MHz, $CDCl_3$, 298 K) : 162.1 (C(1)) ; 59.9 (C(2)) ; 55.1 (C(1')) ; 2.5 (C(2')).

General procedure for 10a-e:

A solution of compound **8a-e** (2.4 mmol, 1 equiv.) in dry CH_2Cl_2 (15 mL) is added to a solution of keten acetal **9** (7.3 mmol, 3 equiv.) in dry CH_2Cl_2 (15 mL) at -30 °C under Ar. A solution of $TiCl_4$ (1.2 mmol, 0.5 equiv.), freshly distilled over polyvinylpyridine, in dry CH_2Cl_2 (4 mL) is added slowly. The solution becomes immediately red and then dark red. The reaction mixture is stirred at –30 °C for 15 min and then at –15 °C for 30 min. The cold mixture is poured into an aqueous solution of NaOH 2N (2.4 mL) and is extracted with $CHCl_3$. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, CH_2Cl_2) followed by crystallization (ether/hexane) afford **10a-10e** as a white solid.

Synthesis of methyl 4-chloro-3-hydroxy-3-phenyl)butanoate (10a)

To a solution of (1-methoxyvinyloxy)trimethylsilane (**9**) (1.00 g, 6.5 mmol)) in dry CH_2Cl_2 (20 mL), 2-chloro-1-phenylethanone (2.90 g, 19.5 mmol) is added at -78 °C. $TiCl_4$ (4.30 mL, 39.0 mmol), frashly distilled over polyvinylpyridine, dissolved in CH_2Cl_2 (6 mL) is added dropwise. After 1 h the temperature is rised to -40 °C and stirred for 20 h. The reaction is quenched with NaOH 2M (78 mL), the aqueous phase is extracted with $CHCl_3$, dried over $MgSO_4$ and concentrated under vacum. Purification by chromatography (CH_2Cl_2) (20%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.30-7.51 (*m*, 5H, H(ar)), 4.53 (*s*, 1H, OH), 3.78 and 3.70 (*2xd (AB system)*, ^2J = 11.5, 2H, H(4)), 3.63 (*s*, 3H, H(1')), 3.19 and 3.08 (*2xd (AB system)*, ^2J = 16.2, 2H, H(2)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 173.2 (C(1)) ; 142.9 (C(ar)) ; 128.9 (C(ar)) ; 128.4 (C(ar)) ; 125.7 (C(ar)) ; 75.0 (C(3)) ; 53.4 (C(4)) ; 52.5 (C(1')) ; 42.0 (C(2)).

ESI-MS : $[M(^{37}Cl) + Na]^+$ = 253.0, $[M(^{35}Cl) + Na]^+$ = 251.1.

Synthesis of methyl 4-bromo-3-hydroxy-3-phenylbutanoate (10b)

2-Bromo-1-phenylethanone (1.00 g, 6.2 mmol) is dissolved in dry CH_2Cl_2 (20 mL) and the solution is cooled to -78 °C and (1-methoxyvinyloxy)trimethylsilane (**9**) (2.20 g, 18.6 mmol) is added to the solution. $TiCl_4$ (4.10 mL, 39.0 mmol), frashly distilled over polyvinylpyridine, dissolved in CH_2Cl_2 (6 mL) is added dropwise. After 1 h the temperature is rised to -25 °C and stirred for 6 h. The reaction is quenched with NaOH 2M (74.4 mL), the aqueous phase is extracted with $CHCl_3$, dried over $MgSO_4$ and concentrated under vacum. Purification by chromatography (CH_2Cl_2) (39%)

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.28-7.50 (*m*, 5H, H(ar)), 4.53 (*s*, 1H, OH), 3.68 et 3.63 (*2xd (AB system)*, ^2J = 10.9, 2H, H(4)), 3.63 (*s*, 3H, H(1')), 3.24 et 3.09 (*2xd (AB system)*, ^2J = 16.2, 2H, H(2)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 173.2 (C(1)) ; 142.9 (C(ar)) ; 129.0 (C(ar)) ; 128.4 (C(ar)) ; 125.6 (C(ar)) ; 74.3 (C(3)) ; 52.5 (C(1')) ; 43.0 (C(4)) ; 42.9 (C(2)).

ESI-MS : $[M(^{81}Br) + Na]^+$ = 296.9, $[M(^{79}Br) + Na]^+$ = 295.1, $[M(^{81}Br) - H_2O]^+$ = 256.9, $[M(^{79}Br) - H_2O]^+$ = 255.1.

HR-MS : $[M + Na]^+$:calc. 294.9946; found 294.9931

Synthesis of methyl 4-azido-3-hydroxy-3-phenylbutanoate (10c)

To a solution of (1-methoxyvinyloxy)trimethylsilane (**9**) (1.06 g, 7.3 mmol)) in dried CH_2Cl_2 (15 mL), 2-azido-1-phenylethanone (0.50 g, 2.4 mmol) is added at -30 °C. $TiCl_4$ (0.13 mL, 1.2 mmol), frashly distilled over polyvinylpyridine, dissolved in CH_2Cl_2 (4 mL) is added dropwise. After 15 min. the temperature is rised to -16 °C for 30 min. more. The reaction is quenched with NaOH 2M (2.4 mL), the aqueous phase is extracted with $CHCl_3$, dried over $MgSO_4$ and concentrated under vacum. Purification by chromatography (CH_2Cl_2) (74%)

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.48-7.43 (*m*, 2H, H(6)), 7.41-7.36 (*m*, 2H, H(7)), 7.33-7.29 (*m*, 1H, H(8)), 4.64 (*d*, ^4J(OH,4) ≅ 1.4, 1H, OH), 3.62 (*s*, 3H, H(1')), 3.51 and 3.27 (*1xd* et *1xdd (AB system)*, ^2J = 12.7, ^4J(4,OH) ≅ 1.3, 2H, H(4)), 3.10 and 3.00 (*2xd (AB system)*, ^2J = 16.2, 2H, H(2)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 173.0 (C(1)) ; 142.7 (C(5)) ; 128.6 (C(7)) ; 127.8 (C(8)) ; 125.0 (C(6)) ; 75.7 (C(3)) ; 60.7 (C(4)) ; 52.0 (C(1')) ; 41.2 (C(2)).

ESI-MS : $[M + Na]^+$ = 258.1

CHN : calc. : 56.16; H: 5.57; N: 17.86; found : 55.69; H: 5.57; N: 17.81

Synthesis of Methyl 4-bromo-3-hydroxy-3-(2-nitrophenyl)butanoate (10d)

To a solution of (1-methoxyvinyloxy)trimethylsilane (**9**) (0.90 g, 6.2 mmol)) in dry CH_2Cl_2 (6 mL), 2-bromo-1-phenylethanone (0.50 g, 2.1 mmol) is added at -30 °C. $TiCl_4$ (0.11 mL, 1.0 mmol), frashly distilled over polyvinylpyridine, dissolved in CH_2Cl_2 (4 mL) is added dropwise. After 1 h the temperature is risedd to -13 °C and stirred for 4.5 h. The reaction is quenched with NaOH 2M (2mL), the aqueous phase is extracted with $CHCl_3$, dried over $MgSO_4$ and concentrated under vacum. Purification by chromatography (CH_2Cl_2) (84%)

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.44-7.56 (*m*, 4H, H(ar)), 4.74 (*s*, 1H, OH), 3.95 (*s*, 2H, H(4)), 3.67 (*s*, 3H, H(1')), 3.27 and 3.24 (*2xd (AB system)*, ^2J = 16.6, 2H, H(2)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 172.7 (C(1)) ; 150.6 (C(ar)) ; 134.5 (C(ar)) ; 131.2 (C(ar)) ; 129.7 (C(ar)) ; 128.9 (C(ar)) ; 124.8 (C(ar)) ; 74.9 (C(3)) ; 52.8 (C(1')) ; 42.5 (C(2)) ; 40.7 (C(4)).

HR-MS : $[M + Na]^+$: calc. 339.9797; found 339.9790

Synthesis of methyl 4-azido-3-hydroxy-3-(2-nitrophenyl)butanoate (10e)

To a solution of (1-methoxyvinyloxy)trimethylsilane (**9**) (1.06 g, 7.3 mmol)) in dry CH_2Cl_2 (15 mL), 2-azido-1-(2-nitrophenyl)ethanone (0.50 g, 2.4 mmol) is added at -30 °C. $TiCl_4$ (0.13 mL, 1.2 mmol), frashly distilled over polyvinylpyridine, dissolved in CH_2Cl_2 (6 mL) is added dropwise. After 15 minutes the temperature is riseed to -15 °C and stirred for 30 min. The reaction is quenched with NaOH 2M (2.4 mL), the aqueous phase is extracted with $CHCl_3$, dried over $MgSO_4$ and concentrated under vacum. Purification by chromatography (CH_2Cl_2) (76%)

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.43-7.56 (*m*, 4H, H(ar)), 4.86 (*s*, 1H, OH), 3.67 (*s*, 3H, H(1')), 3.82 and 3.59 (*2xd (AB system)*, ^2J = 12.8, 2H, H(4)), 3.18 and 3.08 (*2xd (AB system)*, ^2J = 16.7, 2H, H(2)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 173.0 (C(1)) ; 150.7 (C(ar)) ; 134.8 (C(ar)) ; 131.4 (C(ar)) ; 129.7 (C(ar)) ; 128.3 (C(ar)) ; 124.7 (C(ar)) ; 76.4 (C(3)) ; 59.4 (C(4)) ; 52.8 (C(1')) ; 41.2 (C(2)).

ESI-MS ; $[M + Na]^+$ = 303.0

CHN: calc. : C: 47.15; H: 4.32; N: 19.99; found : C: 47.15; H: 4.39; N: 19.76

General procedure for 11a-b:

PPh_3 (5.4 mmol, 1.5 equiv.) is added to a solution of azido **10c,e** (3.6 mmol, 1 equiv.) in THF (15 mL). 0.15 mL of water (1%) is added and the mixture is stirred at RT for 3 days. The solution is concentrated and MeOH (10 mL) is added. The mixture is stirred at reflux for 30 min. The suspension is cooled to –20 °C overnight, filtered and the white powder is washed with EtOAc and dried to afford **11a-b**.

Synthesis of 3-hydroxy-3-phenylpyrrolidine-2-one (11a)

P(*n*-Bu)$_3$ (2.10 g, 8.55 mmol.) is added to a solution of methyl 4-azido-3-hydroxy-3-phenylbutanoate (2.59 g, 12.8 mmol) in THF (30 mL). 0.3 mL of water (1%) is added and the resulting mixture is stirred at RT for 3 days. The solution is concentrated and MeOH (10 mL) is added. The mixture is stirred at reflux for 30 min. The suspension is cooled at –20 °C overnight, filtered and the white powder is washed with EtOAc (76%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.55-7.52 (*m*, 2H, HC(7)), 7.42-7.37 (*m*, 2H, HC(8)), 7.32-7.28 (*m*, 1H, HC(9)), 3.58 and 3.75 (2x*d (AB system)*, ^2J = 10.1, 2H, H_2C (3)), 2.58 and 2.96 (2x*d (AB system)*, ^2J = 16.9, 2H, H_2C (5)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 177.62 (C(2)) ; 144.28 (C(6)) ; 128.46 (2C(7)) ; 127.56 (C(9)) ; 125.21(2C(8)) ; 77.69 (C(4)) ; 57.13 (C(3)) ; 46.38 (C(5)).
CHN: calc. : C: 67.78; H: 6.26; N: 7.90; found : C: 67.66; H: 6.37; N: 7.57

Synthesis of 3-hydroxy-3-(2-nitrophenyl)pyrrolidin-2-one (11b)

PPh_3 (1.4 g, 5.4 mmol,) is added to a solution of methyl 4-azido-3-hydroxy-3-(-2nitrophenyl)butanoate (1.00 g, 3.6 mmol) in THF (15 mL). 0.15mL of water (1%) is added and the mixture is stirred at RT for 3 days. The solution is concentrated and MeOH (10 mL) is added. The mixture is stirred at reflux for 30 min. The suspension is cooled at –20 °C overnight, filtered and the white powder is washed with EtOAc and dried.
^{1}H-NMR (400 MHz, DMSO-d6, 298 K) : 7.79 (*sbr*, 1H, H(1)), 7.49-7.67 (*m*, 4H, H(ar)), 6.08 (*s*, 1H, OH), 3.66 and 3.46 (*2xd (AB system)*, ^{2}J = 10.7, 2H, H(5)), 2.97 and 2.42 (*2xd (AB system)*, ^{2}J = 16.6, 2H, H(3)).
^{13}C-NMR (100 MHz, DMSO-d6, 298 K) : 174.7 (C(2)) ; 151.0 (C(arq)) ; 137.8 (C(arq)) ; 132.1 (C(ar)) ; 129.6 (C(ar)) ; 128.3 (C(ar)) ; 124.8 (C(ar)) ; 77.2 (C(4)) ; 56.3 (C(5)) ; 46.5 (C(3)).
CHN: calc. : C: 54.06; H: 4.54; N: 12.61; found : C: 54.00; H: 4.63; N: 12.50

Synthesis of 1-benzyl-4-hydroxy-4-(2-nitrophenyl)pyrrolidin-2-one (13)

4-Hydroxy-4-phenyl-pyrrolidine-2-one (0.10 g, 0.4 mmol) is dissolved in DMF (1 mL) under Ar at -20 °C. NaH (0.013 g, 0.5 mmol) suspension in DMF (0.5 mL) is added. After 15 min., bromoethyl-benzen (92.4 mg, 0.5 mmol) is added. In 10 min., the resulting mixture is cooled to -10 °C and the reaction mixture is stirred this temperature for 1 h. The solvent is evaporated. Purification of the crude product is made by chromatography (EtOAc/CH_2Cl_2 6:4) (60%).
^{1}H-NMR (400 MHz, CD_3OD, 298 K) : 7.62 (*m* (patially solved), ^{3}J(11,10) = 7.8, ^{4}J(11,9) = 1.4, 1H, H(11)), 7.61 (*m* (partially solved), ^{4}J(8,10) = 1.8, 1H, H(8)), 7.58 (*dxtripletoide*, ^{3}J(9,8) = 8.0, ^{3}J(9,10) = 7.1, ^{4}J(9,11) = 1.4, 1H, H(9)), 7.50 (*ddd*, ^{3}J(10,11) = 7.8, ^{3}J(10,9) = 7.1, ^{4}J(10,8) = 1.7, 1H, H(10)), 7.39-7.28 (*m*, 5H, H(ar)), 4.57 (*2xd (AB system)*, ^{2}J = 16.00, 2H, H(1')), 3.82 and 3.61 (*2xd (AB system)*, ^{2}J = 11.0, 2H, H(5)), 3.28 and 2.79 (*2xd (AB system)*, ^{2}J = 17.2, 2H, H(3)).

^{13}C-NMR (100 MHz, CD_3OD, 298 K) : 173.4 (C(2)) ; 150.5 (C(6)) ; 137.0 (C(arq)) ; 136.2 (C(arq)) ; 131.7 (C(9)) ; 129.1 (C(10)) ; 128.8 (C(ar)) ; 128.1(C(ar)) ; 128.1 (C(ar)) ; 127.8 (C(11)) ; 127.5 (C(ar)) ; 124.6 (C(8)) ; 74.0 (C(4)) ; 60.8 (C(5)) ; 46.7 (C(3)) ; 46.2 (C(6)).
ESI-MS : $[M + Na]^+$ = 335.1, $[M + H]^+$ = 313.2

Synthesis of 1-benzyl-3-(2-nitrophenyl)-5-oxopyrrolidin-3-yl acetate (14)

1-Benzyl-4-hydroxy-4-(2-nitrophenyl)pyrrolidin-2-one (100 mg, 0.3 mmol) is added to acetic anhydride (15 mL) under Ar and the temperature is brought to 100 °C. After 2 h at this temperature, the excess of acetic anhydride is evaporated and the crude product is purified by chromatography (EtOAc/Hexane 6:4) (73%).
^{1}H-NMR (400 MHz, CD_3OD, 298 K) : 7.57-7.49 (*m*, 3H, H(ar)); 7.40-7.28 (*m*, 6H, H(ar)), 4.56 (*s*, 2H, H(6)), 4.08 and 3.87 (*2xd (AB system)*, ^{2}J = 11.8, 2H, H(5)), 3.37 and 3.24 (*2xd (AB system)*, ^{2}J = 17.6, 2H, H(3)), 1.93 (*s*, 3H, H(2')).
^{13}C-NMR (100 MHz, CD_3OD, 298 K) : 172.6 (C(1')) ; 171.0 (C(2)) ; 150.1 (C(arq)) ; 137.0 (C(arq)) ; 134.4 (C(arq)) ; 132.7 (C(ar)) ; 130.7 (C(ar)) ; 129.9 (C(ar)) ; 129.4 (C(ar)) ; 129.1 (C(ar)) ; 127.5 (C(ar)) ; 125.2 (C(ar)) ; 80.9 (C(4)) ; 58.7 (C(5)) ; 46.9 (C(6)) ; 45.6 (C(3)) ; 20.6 (C(2')).

Synthesis of *tert*-butyl 4-hydroxy-4-(2-nitrophenyl)-2-oxopyrrolidine-1-carboxylate (15)

4-Hydroxy-4-(2-nitrophenyl)-pyrrolidine-2-one (0.10 g, 0.5 mmol) is dissolved in DMF (2 mL) under Ar. DMAP (0.023 g, 0.2 mmol) and Boc_2O (0.1 m, 0.5 mmol) are added successively to the reaction. After 24 h at RT, the solvent is evaporated and the crude product is purified by chromatography (EtOAc/CH_2Cl_2 8:2).
^{1}H-NMR (200 MHz, CD_3OD, 298 K) : 7.65-7.47 (*m*, 4H, H(ar)), 4.11 and 5.05 (*2xd (AB system)*, ^{2}J = 12.6, 2H, H(5)), 3.43 and 2.75 (*1xd* and *1xdd (AB system)*, ^{2}J = 17.0, ^{4}J(3b,OH) = 0.9, 2H, H(3)), 1.54 (*s*, 9H, H(3')).

General procedure for 16a-b:

DMAP (0.023 mg, 0.2 mmol) and Boc_2O (0.20 g, 1.0 mmol) are added to a supension of lactam **11a-b** (0.5 mmol) in dry THF (10 mL) under Ar. The solution becomes clear immediately. The solution is stirred at RT for at least 2 h. After the removal of the

solvent, the residue is purified by flash chromatography (silica gel, 1% MeOH in CH_2Cl_2) to afford **12a-b** as a white solid.

Synthesis of *tert*-butyl 2-oxo-4-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxylate (16a)

DMAP (0.50 g, 4.1 mmol) and Boc_2O (0.43 g, 2.0 mmol) are added to a supension of 3-hydroxy-3-phenylpyrrolidine-2-one (0.16 g, 1.0 mmol) in dry THF (24 mL) under Ar. The solution becomes clear immediately. The solution is stirred at RT for 24 h. After the removal of the solvent, the residue is purified by flash chromatography (silica gel, 1% MeOH in CH_2Cl_2) (93%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.55-7.30 (*m*, 5H, HC(7, 8, 9)); 6.42 (*t*, ^4J(3,5) = 1.5, 1H, H(3)); 4.72 (*d*, ^4J(5,3) = 1.5, 2H, H(5)); 1.63 (*s*, 9H, H(3')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 169.9 (C(2)) ; 156.1 (C(1')) ; 149.7 (C(6)) ; 131.3 (C(4)); 131.2 (2C(7)) ; 129.2 (C(9)) ; 126.2 (2C(8)) ; 119.8 (C(3)) ; 83.0 (C(2')) ; 51.0 (C(5)) ; 28.2 (3C(3')).

ESI-MS : $[M + Na]^+$ = 282.0

Synthesis of *tert*-butyl 2-oxo-4-(2-nitrophenyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (16b)

DMAP (0.02 g, 0.2 mmol) and Boc_2O (0.20 g, 1.0 mmol) are added to a supension of 3-hydroxy-3-(2-nitrophenyl)pyrrolidine-2-one (0.10 g, 0.5 mmol) in dry THF (10 mL) under Ar. The solution becomes clear immediately. The solution is stirred at RT for 2 h. After the removal of the solvent, the residue is purified by flash chromatography (silica gel, 1% MeOH in CH_2Cl_2) (98%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 8.10 (*dd*, ^3J (8,9) = 8.1, ^4J (8,10) = 1.3, 1H, H(8)), 7.72 (*dt*, ^3J (10, 11)= ^3J(10, 9) = 7.6, ^4J (10, 8) = 1.3, 1H, H(10)), 7.63 (*dxtripletoide*, ^3J (9, 10) = 7.6, ^3J (9, 8) = 8.1, ^4J (9, 11) = 1.5, 1H, H(9)), 7.41 (*dd*, ^3J (11, 10) = 7.6, ^4J (11, 9) = 1.5, 1H, H(11)), 6.13 (*t*, ^4J (3, 5) = 1.6, 1H, H(3)), 4.55 (*d*, ^4J (5, 3) = 1.6, 2H, H(5)), 1.56 (*s*, 9H, H(3')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 168.0 (C(2)) ; 155.3 (C(1')) ; 149.2 et 147.4 (C(6) et C(7)) ; 133.7 (C(10)) ; 130.7 (C(9)) ; 130.3 (C(11)) ; 128.3 (C(4)) ; 125.0 (C(8)) ; 124.9 (C(3)) ; 83.3 (C(2')) ; 53.0 (C(5)) ; 28.1 (C(3')).

CHN : calc. C: 59.21; H: 5.30; N: 9.21; found : C: 59.23; H: 5.39; N: 9.11.

Synthesis of *tert*-butyl 2-(*tert*-butoxycarbonyloxy)-4-(2- nitrophenyl)-1*H*-pyrrole-1-carboxylate (17)

4-Hydroxy-4-(2-nitrophenyl)pyrrolidine-2-one (0.10 g, 0.5 mmol) is dissolved in dry THF (3mL) under Ar and a suspension is formed. DMAP (0.023 g, 0.2 mmol) and Boc_2O (0.30 g, 1.4 mmol) are added. The solution becomes clear. After 1 h at RT, the solvent is evaporated and the crude product is purified by chromatography (Hexane/EtOAc 7:3) (93%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.76 (*ddd*, ^3J (8, 9) = 8.1, ^4J (8, 10) = 1.3, ^5J (8,11) = 0.5, 1H, H(8)), 7.64 (*dxtripletoide*, ^3J (10, 11) = 7.8, ^3J (10, 9) = 7.1, ^4J (10, 8) = 1.3, 1H, H(10)), 7.60 (*ddd*, ^3J (11, 10) = 7.8, ^4J (11, 9) = 1.8, ^5J (11,8) = 0.5, 1H, H(11)), 7.49 (*ddd*, ^3J (9, 8) = 8.1, ^3J (9, 10) = 7.1, ^4J (9, 11) = 1.8, 1H, H(9)), 7.16 (*d*, ^4J (5, 3) = 2.3, 1H, H(5)), 5.97 (*d*, ^4J (3, 5) = 2.3, 1H, H(3)), 1.62 (*s*, 9H, H(3')), 1.55 (*s*, 9H, H(3'')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 151.2 (C(1'')) ; 149.6 (C(1')) ; 147.7 et 137.9 (C(6) et C(7)) ; 132.2 (C(10)) ; 131.1 (C(11)) ; 128.2 (C(9)) ; 128.0 (C(4)) ; 123.6 (C(8)) ; 119.3 (C(2)) ; 114.5 (C(5)) ; 100.6 (C(3)) ; 85.2 (C(2')) ; 84.7 (C(2'')) ; 27.1 (C(3') ; 26.8 (C(3'').

ESI-MS : $[M + Na]^+ = 426.9$

CHN: calc: C: 59.40; H: 5.98; N: 6.93; found: C: 59.66; H: 6.16; N: 6.89.

General procedure for 19a-b:

2,6-Lutidine (0.20 mL, 1.7 mmol, 3.4 equiv.) and TBSOTf (0.5 mmol, 1 equiv.) are added at RT under Ar to a solution of pyrrolidinone **12a-b** (0.5 mmol, 1 equiv.) in dry CH_2Cl_2 (5 mL). The mixture is stirred for 1 h. After the removal of the solvent, purification of the residual oil by filtration over silica gel (20% EtOAc in hexane) afford silyl enol **13a-b** as an orange oil.

Synthesis of *tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-4-phenyl-1*H*-pyrrole-1-carboxylate (19a)

2,6-Lutidine (0.38 mL, 3.3 mmol) and TBSOTf (0.28 mL, 1.2 mmol) are added at RT under Ar to a solution of *tert*-butyl 2-oxo-4-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxylate (0.28 g, 1.1 mmol) in dry CH_2Cl_2 (2.50 mL). After 40 min. of stirring at RT, the salts are

precipitated with pentane, filtered over celite and 2,6-lutidine is removed by bulb-to-bulb distillation (P=0.06 torr, T=60 °C). (62%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.50 (*m*, 2H, H(7,11)), 7.36 (*m*, 2H, H(8,10)), 7.23 (*m*, 1H, H(9)), 7.04 (*d*, ^{4}J(5, 3) = 2.3, 1H, H(5)), 5.63 (*d*, ^{4}J(3, 5) = 2.3, 1H, H(3)), 1.63 (*s*, 9H, H(3')), 1.06 (*s*, 9H, H(3'')), 0.31 (*s*, 6H, H(1'')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 148.1 (C(1')) ; 144.1 (C(6)) ; 134.6 (C(8,10)) ; 128.5 (C(4)) ; 126.2 (C(9)) ; 125.0 (C(7,11)) ; 123.3 (C(2)) ; 108.6 (C(5)) ; 91.2 (C(3)) ; 83.0 (C(2')) ; 28.1 (C(3')) ; 25.7 (C(3'')) ; 18.4 (C(2'')) ; -4.7 (C(1'')).

Synthesis of *tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-4-(-nitrophenyl)-1*H*-pyrrole-1-carboxylate (19b)

2,6-Lutidine (0.2 mL, 1.7 mmol) and TBSOTf (1.27 mL, 0.5 mmol) are added at RT under Ar to a solution of *tert*-butyl 2-oxo-4-(2-nitrophenyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (0.14 g, 0.5 mmol) in dry CH_2Cl_2 (5 mL). The mixture was stirred for 1 h. After the removal of the solvent, purification of the residual oil by filtration over silica gel (20% EtOAc in hexane) affords the product as an orange oil (80%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.69 (*dd*, ^{3}J (8, 9) = 8.1, ^{4}J (8, 10) = 1.2, 1H, H(8)), 7.53 (*dxtripletoide*, ^{3}J (10, 11) = 7.8, ^{3}J (10, 9) = 6.9, ^{4}J (10, 8) = 1.3, 1H, H(10)), 7.50 (*dd*, ^{3}J (11, 10) = 7.8, ^{4}J (11, 9) = 2.0, 1H, H(11)), 7.37 (*ddd*, ^{3}J (9, 8) = 8.1, ^{3}J (9, 10) = 6.9, ^{4}J (9, 11) = 1.9, 1H, H(9)), 6.91 (*d*, ^{4}J (5, 3) = 2.3, 1H, H(5)), 5.31 (*d*, ^{4}J (3, 5) = 2.3, 1H, H(3)), 1.61 (*s*, 9H, H(3')), 1.02 (*s*, 9H, H(3'')), 0.27 (*s*, 6H, H(1'')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 149.1 (C(1')) ; 147.8 et 144.0 (C(6) et C(7)) ; 131.8 (C(10)) ; 130.8 (C(11)) ; 129.3 (C(4)) ; 127.2 (C(9)) ; 123.6 (C(8)) ; 118.7 (C(2)) ; 111.1 (C(5)) ; 92.4 (C(3)) ; 83.5 (C(2')) ; 28.1 (C(3')) ; 25.7 (C(3'')) ; 18.4 (C(2'')) ; -4.8 (C(1'')).

Synthesis of methyl 4-oxobutanoate (20a)

Methyl 4,4-dimethoxybutanoate (1.87 g, 11.5 mmol) is dissolved in acetone (10 mL) and a solution of $HCl_{conc.}/H_2O$ 0.5:21 is added to the reaction. The mixture is stirred at RT. After 1 h, the aqueous phase is extracted once with CH_2Cl_2 and 3 times with a mixture of acetone/CH_2Cl_2 (1:2). The combined organic phases are washed with sat. K_2CO_3 and dried over $MgSO_4$. After vacuum concentration, a light-yellow oil is obtained (87%).

^{1}H-NMR (200 MHz, $CDCl_3$, 298 K) : 9.82 (*s*, 1H, H(4)), 3.70 (*s*, 3H, H(1')), 2.85-2.76 (*m*, 4H, H(2,3)).

Synthesis of ethyl 4-oxobutanoate (20b)

Oxalyl dichloride (11.71 mL, 134.5 mmol) is dissolved in dry CH_2Cl_2 (110 mL) under Ar and the solution is cooled to -78 °C. DMSO (12.45 mL, 179.4 mmol) in CH_2Cl_2 (110 mL) is added to the reaction. After 10 min. at -78 °C, ethyl 4-hydroxybutanoate (11.84 g, 89.7 mmol) in CH_2Cl_2 (350 mL) is added followed by Et_3N (37.40 mL, 269.1 mmol). After 10 min. the temperature is rised to 0 °C and kept fixed for 2 h. Water (50 mL) is added to the solution and the aqueous phase is extracted with CH_2Cl_2. The combined organic phases are dried over $MgSO_4$, the solvent evaporated and the crude product is purified by chromatography (EtOAc/hexane 6:4) (82%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 9.82 (*t*, ^3J(4,3) = 0.7, 1H, H(4)), 4.10 (*q*, ^3J(1',2') = 7.1, 2H, H(1')), 2.75 (*m* (partially solved), ^3J(3,2) ≈ 6.6, ^3J(3,4) ≈ 0.6, 2H, H(3)), 2.57 (*t*, ^3J(2,3) ≈ 6.7, 2H, H(2)), 1.21 (*t*, ^3J(2'1') = 7.1, 3H, H(2')).
^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 200.0 (C(4)) ; 172.2 (C(1)) ; 60.7 (C(1')) ; 38.4 (C(3)) ; 26.5 (C(2)) ; 14.0 (C(2')).

Synthesis of benzyl 4-oxobutanoate (20c)

Oxalyl dichloride (2.69 mL, 30.9 mmol) is dissolved in dry CH_2Cl_2 (28 mL) under Ar and the solution is cooled to -78 °C. DMSO (2.86 mL, 41.2 mmol) in CH_2Cl_2 (110 mL) is added to the reaction. After 10 min. at -78 °C benzyl 4-hydroxybutanoate (4.00 g, 20.6 mmol) in CH_2Cl_2 (100 mL) is added followed by Et_3N (8.60 mL 61.9 mmol). After 10 min. the temperature is rised to 0 °C and kept fixed for 2 h. Water (50 mL) is added to the solution and the aqueous phase is extracted with CH_2Cl_2. The combined organic phases are dried over $MgSO_4$, the solvent is evaporated and the crude product is purified by chromatography (EtOAc/hexane 1:1) (86%).
^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 9.82 (*t*, ^3J(4,3) = 0.7, 1H, H(4)), 7.40-7.31 (*m*, 5H, H(3', 4' et 5')), 5.14 (*s*, 2H, H(1')), 2.82 (*m* (partially solved), ^3J(3,2) ≈ 6.8, ^3J(3,4) ≈ 0.7, 2H, H(3)), 2.69 (*m* (partially solved), ^3J(2,3) ≈ 6.9, 2H, H(2)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 199.9 (C(4)) ; 172.1 (C(1)) ; 135.7 (C(2')) ; 128.6 (C(3')) ; 128.3 (C(5')) ; 128.2 (C(4')) ; 66.6 (C(1')) ; 38.5 (C(3)) ; 26.6 (C(2)).

Synthesis of 4-methoxybenzyl 4-oxobutanoate (20d)

Oxalyl dichloride (1.96 mL, 22.5 mmol) is dissolved in dry CH_2Cl_2 (20 mL) under Ar and the solution is cooled to -78 °C. DMSO (2.08 mL, 30.0 mmol) in CH_2Cl_2 (20 mL) is added to the reaction. After 10 min. at -78 °C benzyl 4-hydroxybutanoate (3.36 g, 15.0 mmol) in CH_2Cl_2 (65 mL) is added followed by Et_3N (6.26 mL, 45.0 mmol). After 10 min. the temperature is rised to 0 °C and kept fixed for 2 h. Water (50 mL) is added to the solution and the aqueous phase is extracted with CH_2Cl_2. The combined organic phases are dried over $MgSO_4$, the solvent is evaporated and the crude product is purified by chromatography (EtOAc/hexane 1:1) (79%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 9.82 (*t*, ^{3}J(4,3) = 0.7, 1H, H(4)), 7.31 et 6.91 (*AA'XX'system* (partially solved), *J*(A,X) = 8.4, *J*(A'X) = 0.3, 4H, H(AA'XX')), 5.08 (*s*, 2H, H(1')), 3.82 (*s*, 3H, H(6')), 2.81 (*m* (partially solved), ^{3}J(3,2) ≈ 6.8, ^{3}J(3,4) ≈ 0.7, 2H, H(3)), 2.67 (*m* (partially solved), ^{3}J(2,3) ≈ 6.9, 2H, H(2)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 199.9 (C(4)) ; 172.1 (C(1)) ; 159.6 (C(5')) ; 130.1 (C(AA')) ; 127.8 (C(2')) ; 113.9 (C(XX')) ; 66.4 (C(1')) ; 55.2 (C(6')) ; 38.5 (C(3)) ; 26.6 (C(2)).

ESI-MS : $[M + Na]^+$ = 245.0

Synthesis of *tert*-butyl 2-(4-methoxy-1-hydroxy-4-oxobutyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (21a)

Methyl 4-oxobutanoate (0.35 g, 3.0 mmol) and $BF_3{\cdot}OEt_2$ (0.38 mL, 2.3 mmol) are added dropwise to a solution of silyl enol **19b** (0.96 g, 2.3 mmol) in dried CH_2Cl_2 (20 mL) at -78 °C under Ar. The colour of the solution changes from yellow to light yellow. The mixture is stirred at -78 °C for 1 h. The reaction mixture is quenched with saturated aqueous solution of $NaHCO_3$ (15 mL) at -78 °C and the aqueous layer is extracted with CH_2Cl_2. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, EtOAc/Ether 3:7) affords the aldol product as a white solid (84%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : **isomer 1** : 8.05 (*dd*, ^{3}J(12,13) = 8.1, ^{4}J(12,14) = 1.2, 1H, H(12)), 7.69 (*dt*, ^{3}J(14,13)= ^{3}J(14,15) = 7.6, ^{4}J(14,12) = 1.3, 1H, H(14)), 7.59

(*dxtripletoide*, ^{3}J(13,12) = 8.1, ^{3}J(13,14) = 7.5, ^{4}J(13,15) = 1.5, 1H, H(13)), 7.47 (*dd*, ^{3}J(15,14) = 7.7, ^{4}J(15,13) = 1.4, 1H, H(15)), 6.20 (*d*, ^{4}J(3,5) = 1.2, 1H, H(3)), 5.15 (*t*, ^{3}J(5,6) = 1.2, ^{4}J(5,3) = 1.2, 1H, H(5)), 4.11 (*m*, 1H, H(6)), 3.60 (*s*, 3H, H(1')), 2.72 (m, 1H, OH), 2.45-2.29 (*m*, 2H, H(8)), 1.71 (*dtd*, ^{2}J(7a,7b) ≈ 14.3, ^{3}J(7a,8) ≈ 6.9, ^{3}J(7a,6) ≈ 2.4, 1H, H(7a)), 1.57 (*s*, 9H, H(3'')), 1.53-1.41 (*m*, 1H, H(7b)).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : **isomer 2** : 8.14 (*dd*, ^{3}J(12,13) = 8.2, ^{4}J(12,14) = 1.2, 1H, H(12)), 7.74 (*dt*, ^{3}J(14,13)= ^{3}J(14,15) = 7.6, ^{4}J(14,12) = 1.3, 1H, H(14)), 7.64 (*dxtripletoide*, ^{3}J(13,12) = 8.2, ^{3}J(13,14) = 7.5, ^{4}J(13,15) = 1.5, 1H, H(13)), 7.51 (*dd*, ^{3}J(15,14) = 7.6, ^{4}J(15,13) = 1.4, 1H, H(15)), 6.08 (*d*, ^{4}J(3,5) = 1.2, 1H, H(3)), 5.14 (*t*, ^{3}J(5,6) = 1.2, ^{4}J(5,3) = 1.2, 1H, H(5)), 4.27 (*d*, ^{3}J(OH,6) = 8.5, 1H, OH), 3.86 (*m* (partially solved), ^{3}J(6,OH) ≈ 8.4, 1H, H(6)), 3.59 (*s*, 3H, H(1')), 2.42 and 2.33 (*dd*x(AB system), ^{2}J(8a,8b) = 16.7, ^{3}J(8ab,7a) = ^{3}J(8b,7b) = 7.5, ^{3}J(8a,7b) = 6.1, 2H, H(8ab)), 1.60 (*s*, 9H, H(3'')), 1.59-1.51 (*m* (partially solved), ^{3}J(7a,8ab) ≈ 7.6, 1H, H(7a)), 1.33-1.23 (*m* (partially solved), ^{3}J(7b,8b) ≈ 7.5, ^{3}J(7b,8a) = 6.2, 1H, H(7b)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : **isomer 1** : 174.2 (C(9)) ; 168.2 (C(2)) ; 159.0 (C(1'')) ; 149.6 and 148.0 (C(10) and (C(11)) ; 133.6 (C(14)) ; 131.3 (C(15)) ; 130.6 (C(13)) ; 129.3 (C(4)) ; 125.9 (C(3)) ; 124.9 (C(12)) ; 83.8 (C(2'')) ; 70.4 (C(6)) ; 65.9 (C(5)) ; 51.8 (C(1')) ; 31.1 (C(8)) ; 28.1 (C(3'')) ; 26.5 (C(7)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : **isomer 2** : 173.6 (C(9)) ; 167.6 (C(2)) ; 157.7 (C(1'')) ; 151.4 and 147.2 (C(10) and (C(11)) ; 133.9 (C(14)) ; 131.5 (C(15)) ; 130.8 (C(13)) ; 128.5 (C(4)) ; 125.5 (C(3)) ; 125.1 (C(12)) ; 84.5 (C(2'')) ; 70.8 (C(6)) ; 69.2 (C(5)) ; 51.5 (C(1')) ; 30.3 (C(8)) ; 28.1 (C(3'')) ; 26.6 (C(7)).

HR-MS : $[M + Na]^+$: calc. 443.1430; found 443.1423

Synthesis of *tert*-butyl 2-(4-ethoxy-1-hydroxy-4-oxobutyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (21b)

Ethyl 4-oxobutanoate (0.76 g, 5.8 mmol) and $BF_3{\cdot}OEt_2$ (0.87 mL, 6.9 mmol) are added dropwise to a solution of silyl enol **19b** (2.22 g, 5.3 mmol) in dry CH_2Cl_2 (50 mL) at –78 °C under Ar. The colour of the solution changes from yellow to pale yellow. The mixture is stirred at –78 °C for 1 h. The reaction mixture is quenched with saturated aqueous solution of $NaHCO_3$ (15 mL) at -78 °C and the aqueous layer is extracted with CH_2Cl_2. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, CH_2Cl_2/EtOAc 6:4) afford the aldol product as a white solid (55%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : **isomer 1** : 8.05 (*dd*, ^3J(12,13) = 8.1, ^{4}J(12,14) = 1.2, 1H, H(12)), 7.69 (*dt*, ^3J(14,13)= ^3J(14,15) = 7.6, ^4J(14,12) = 1.3, 1H, H(14)), 7.59 (*ddd*, ^3J(13,12) = 8.1, ^3J(13,14) = 7.5, ^4J(13,15) = 1.5, 1H, H(13)), 7.47 (*dd*, ^3J(15,14) = 7.7, ^4J(15,13) = 1.4, 1H, H(15)), 6.21 (*d*, ^4J(3,5) = 1.2, 1H, H(3)), 5.15 (*dd*, ^3J(5,6) = 3.8, ^4J(5,3) = 1.2, 1H, H(5)), 4.12 (*m* (partially solved), ^3J(6,OH) ≈ 5.7, ^3J(6,5) ≈ 3.8, 1H, H(6)), 4.05 (*q*, ^3J(1',2') = 7.2, 2H, H(1')), 2.78 (*d*, ^3J(OH,6) = 5.7, 1H, OH), 2.36 and 2.33 (*t*x(AB system), ^2J(8a,8b) = 16.7, ^3J(8ab,7a) ≈ ^3J(8ab,7b) ≈ 6.5, 2H, H(8a,8b)), 1.71-1.65 (*m* (partially solved), ^2J(7a,7b) ≈ 14.4, ^3J(7a,8ab) ≈ 7.0, 1H, H(7a)), 1.57 (*s*, 9H, H(3'')), 1.50-1.42 (*m* (partially solved), ^2J(7b,7a) ≈ 14.3, 1H, H(7b)), 1.19 (*t*, ^3J(2',1') = 7.2, 3H, H(2')).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : **isomer 2** : 8.14 (*dd*, ^3J(12,13) = 8.2, ^4J(12,14) = 1.2, 1H, H(12)), 7.73 (*dt*, ^3J(14,13)= ^3J(14,15) = 7.6, ^4J(14,12) = 1.3, 1H, H(14)), 7.64 (*ddd*, ^3J(13,12) = 8.2, ^3J(13,14) = 7.5, ^4J(13,15) = 1.5, 1H, H(13)), 7.53 (*dd*, ^3J(15,14) = 7.6, ^4J(15,13) = 1.4, 1H, H(15)), 6.05 (*d*, ^4J(3,5) = 1.3, 1H, H(3)), 5.09 (*t*, ^3J(5,6)(5,3) = 1.2, 1H, H(5)), 4.40-4.20 (*br*, 1H, OH), 4.02 (*q*, ^3J(1',2') = 7.1, 2H, H(1')), 3.93 (*m*, 1H, H(6)), 2.36 and 2.32 (*AB*x*dd* (partially solved), ^2J(8a,8b) = 16.6, ^3J(8a,7ab) ≈ 7.7, ^3J(8b,7ab) = 6.1, 2H, H(8a,8b)), 1.57 (*s*, 9H, H(3'')), 1.52-1.44 (*m*, 1H, H(7a)), 1.26-1.20 (*m*, 1H, H(7b)), 1.16 (*t*, ^3J(2',1') = 7.2, 3H, H(2')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : **isomer 1** : 173.9 (C(9)) ; 168.2 (C(2)) ; 159.0 (C(1'')) ; 149.5 and 148.0 (C(10) and C(11)) ; 133.6 (C(14)) ; 131.3 (C(15)) ; 130.5 (C(13)) ; 129.3 (C(4)) ; 125.9 (C(3)) ; 124.9 (C(12)) ; 83.8 (C(2'')) ; 70.5 (C(6)) ; 65.9 (C(5)) ; 60.7 (C(1')) ; 31.4 (C(8)) ; 28.1 (C(3'')) ; 26.4 (C(7)) ; 14.1 (C(2')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : **isomer 2** : 173.1 (C(9)) ; 167.9 (C(2)) ; 157.9 (C(1'')) ; 150.8 and 147.1 (C(10) and C(11)) ; 134.0 (C(14)) ; 131.7 (C(15)) ; 130.7 (C(13)) ; 128.7 (C(4)) ; 125.5 (C(3)) ; 125.0 (C(12)) ; 84.2 (C(2'')) ; 70.7 (C(6)) ; 69.1 (C(5)) ; 60.3 (C(1')) ; 30.6 (C(8)) ; 28.6 (C(3'')) ; 26.9 (C(7)) ; 14.1 (C(2')).

HR-MS : $[M + Na]^+$: calc. 457.1587; found 457.1584

Synthesis of *tert*-butyl 2-(4-benzyloxy)-1-hydroxy-4-oxobutyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (21c)

Benzyl 4-oxobutanoate (0.68 g, 3.6 mmol) and $BF_3{\cdot}OEt_2$ (0.54 mL, 3.2 mmol) are added dropwise to a solution of silyl enol **19b** (1.25 g, 3.0 mmol) in dry CH_2Cl_2 (25 mL) at –78 °C under Ar. The colour of the solution changes from yellow to light yellow. The mixture is stirred at –78 °C for 1 h. The reaction mixture is quenched at with saturated aqueous

solution of $NaHCO_3$ (15 mL) at -78 °C and the aqueous layer is extracted with CH_2Cl_2. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, EtOAc/Ether 2:8) affords the aldol product as a white solid (55%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : **isomer 1** : 8.04 (*dd*, ^3J(12,13) = 8.1, ^4J(12,14) = 1.3, 1H, H(12)), 7.66 (*dt*, ^3J(14,13)= ^3J(14,15) = 7.6, ^4J(14,12) = 1.3, 1H, H(14)), 7.57 (*dxtripletoide*, ^3J(13,12) ≈ 7.9, ^3J(13,14) ≈ 7.7, ^4J(13,15) = 1.5, 1H, H(13)), 7.45 (*dd*, ^3J(15,14) = 7.6, ^4J(15,13) = 1.5, 1H, H(15)), 7.36-7.27 (*m*, 5H, H(3',4',5')), 6.19 (*d*, ^4J(3,5) = 1.1, 1H, H(3)), 5.16 (*dd*, ^3J(5,6) = 3.7, ^4J(5,3) = 1.1, 1H, H(5)), 5.03 (*s*, 2H, H(1')), 4.12 (*m*, 1H, H(6)), 2.89 (*m*, 1H, OH), 2.41 (*t*, ^3J(8,7) = 7.0, 2H, H(8)), 1.72 (*dtd*, ^2J(7a,7b) ≈ 14.3, ^3J(7a,8) ≈ 7.0, ^3J(7a,6) ≈ 2.3, 1H, H(7a)), 1.55 (*s*, 9H, H(3'')), 1.49 (*dtd*, ^2J(7b,7a) ≈ 14.4, ^3J(7b,8) ≈ 7.2, ^3J(7b,6) ≈ 3.5, 1H, H(7b)).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : **isomer 2** : 8.13 (*dd*, ^3J(12,13) = 8.2, ^4J(12,14) = 1.2, 1H, H(12)), 7.69 (*dt*, ^3J(14,13)= ^3J(14,15) = 7.6, ^4J(14,12) = 1.4, 1H, H(14)), 7.60 (*dxtripletoide*, ^3J(13,12) = 8.0, ^3J(13,14) = 7.6, ^4J(13,15) = 1.5, 1H, H(13)), 7.48 (*dd*, ^3J(15,14) = 7.7, ^4J(15,13) = 1.4, 1H, H(15)), 7.37-7.31 (*m*, 2H, H(3')), 7.30-7.27 (*m*, 3H, H(4',5')), 6.08 (*d*, ^4J(3,5) = 1.4, 1H, H(3)), 5.15 (*m*, 1H, H(5)), 5.03 (*s*, 2H, H(1')), 3.84 (*m*, 1H, H(6)), 2.53-2.35 (*m*, 2H, H(8)), 1.59-1.54 (*m*, 1H, H(7a)), 1.59 (*s*, 9H, H(3'')), 1.36-1.27 (*m*, 1H, H(7b)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : **isomer 1** : 173.5 (C(9)) ; 168.2 (C(2)) ; 159.0 (C(1'')) ; 149.5 and 147.9 (C(10) and (C(11)) ; 135.6 (C(2')) ; 133.6 (C(14)) ; 131.3 (C(15)) ; 130.5 (C(13)) ; 129.2 (C(4)) ; 128.5 (C(3')) ; 128.2 (C(5')) ; 128.2 (C(4')) ; 125.8 (C(3)) ; 124.8 (C(12)) ; 83.8 (C(2'')) ; 70.3 (C(6)) ; 66.4 (C(1')) ; 65.9 (C(5)) ; 31.2 (C(8)) ; 28.0 (C(3'')) ; 26.5 (C(7)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : **isomer 2** : 173.0 (C(9)) ; 167.5 (C(2)) ; 157.6 (C(1'')) ; 151.5 and 147.2 (C(10) and (C(11)) ; 135.8 (C(2')) ; 133.9 (C(14)) ; 131.4 (C(15)) ; 130.8 (C(13)) ; 128.5 (C(3')) ; 128.3 (C(4)) ; 128.1 (C(5)) ; 125.5 (C(3)) ; 125.1 (C(12)) ; 84.5 (C(2'')) ; 70.9 (C(6)) ; 69.1 (C(5)) ; 66.2 (C(1')) ; 30.6 (C(8)) ; 28.0 (C(7,3'')).

HR-MS : $[M + Na]^+$: calc. 519.1743; found 519.1739

Synthesis of *tert*-butyl 2-(1-hydroxy-4-(4-methoxybenzyloxy)-4-oxobutyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (21d)

4-Methoxybenzyl 4-oxobutanoate (0.75 g, 3.4 mmol) and $BF_3{\cdot}OEt_2$ (0.43 mL, 3.4 mmol) are added dropwise to a solution of silyl enol **19b** (1.29 g, 3.1 mmol) in dry CH_2Cl_2 (25 mL) at -78 °C under Ar. The colour of the solution changes from yellow to light yellow. The mixture is stirred at -78 °C for 1 h. The reaction mixture is quenched with saturated aqueous solution of $NaHCO_3$ (15 mL) at -78 °C and the aqueous layer is extracted with CH_2Cl_2. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, CH_2Cl_2/Ether 3:7) affords the aldol product as a white solid (91%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : **isomer 1** : 8.06 (*dd*, ^3J(12,13) = 8.1, ^4J(12,14) = 1.3, 1H, H(12)), 7.69 (*dt*, ^3J(14,13)= ^3J(14,15) = 7.6, ^4J(14,12) = 1.3, 1H, H(14)), 7.60 (*dxtripletoide*, ^3J(13,12) = 8.1, ^3J(13,14) = 7.5, ^4J(13,15) = 1.5, 1H, H(13)), 7.47 (*dd*, ^3J(15,14) = 7.6, ^4J(15,13) = 1.4, 1H, H(15)), 7.24 and 6.87 (*AA'XX' system* (partially solved), J(A,X) = 8.4, J(A'X) = 0.4, 4H, H(AA'XX')), 6.21 (*d*, ^4J(3,5) = 1.2, 1H, H(3)), 5.17 (*dd*, ^3J(5,6) = 3.7, ^4J(5,3) = 1.2, 1H, H(5)), 4.98 (*s*, 2H, H(1')), 4.13 (*m*, 1H, H(6)), 3.81 (*s*, 3H, H(6')), 2.79 (*m*, 1H, OH), 2.39 (*t*x(AB system), ^2J(8a,8b) = 13.8, ^3J(8ab,7a) ≈ ^3J(8ab,7b) ≈ 6.9, 2H, H(8ab)), 1.75-1.69 (*m* (partially solved), ^2J(7a,7b) ≈ 14.3, ^3J(7a,8ab) ≈ 6.9, 1H, H(7a)), 1.57 (*s*, 9H, H(3'')), 1.50-1.42 (*m*, 1H, H(7b)).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : **isomère 2** : 8.13 (*dd*, ^3J(12,13) = 8.2, ^4J(12,14) = 1.3, 1H, H(12)), 7.73 (*dt*, ^3J(14,13)= ^3J(14,15) = 7.5, ^4J(14,12) = 1.3, 1H, H(14)), 7.62 (*dxtripletoide*, ^3J(13,12) = 8.1, ^3J(13,14) = 7.5, ^4J(13,15) = 1.5, 1H, H(13)), 7.50 (*dd*, ^3J(15,14) = 7.6, ^4J(15,13) = 1.5, 1H, H(15)), 7.24 et 6.87 (*AA'XX'system* (partially solved), J(A,X) = 8.4, J(A'X) = 0.4, 4H, H(AA'XX')), 6.09 (*d*, ^4J(3,5) = 1.3, 1H, H(3)), 5.15 (*dd*, ^3J(5,6) = 1.2, ^4J(5,3) = 1.2, 1H, H(5)), 4.98 (*s*, 2H, H(1')), 3.88 (*m*, 1H, H(6)), 3.82 (*s*, 3H, H(6')), 2.53-2.24 (*m*, 2H, H(8)), 1.60 (*s*, 9H, H(3'')), 1.58-1.54 (*m*, 1H, H(7a)), 1.33-1.29 (*m*, 1H, H(7b)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : **isomer 1** : 173.7 (C(9)) ; 168.2 (C(2)) ; 159.6 (C(5')) ; 159.0 (C(1'')) ; 149.5 and 147.9 (C(10) and (C(11)) ; 133.6 (C(14)) ; 131.3 (C(15)) ; 130.5 (C(13)) ; 130.1 (C(AA')) ; 129.3 (C(4)) ; 127.6 (C(2')) ; 125.9 (C(3)) ; 124.8 (C(12)) ; 113.9 (C(XX')) ; 83.8 (C(2'')) ; 70.4 (C(6)) ; 66.3 (C(1')) ; 65.9 (C(5)) ; 55.2 (C(6')) ; 31.4 (C(8)) ; 28.0 (C(3'')) ; 26.5 (C(7)).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : **isomer 2** : 173.0 (C(9)) ; 167.6 (C(2)) ; 159.5 (C(5')) ; 157.7 (C(1'')) ; 151.3 and 147.2 (C(10) and (C(11)) ; 133.9 (C(14)) ; 131.5 (C(15)) ; 130.8 (C(13)) ; 129.9 (C(AA')) ; 128.4 (C(4)) ; 127.9 (C(2')) ; 125.5 (C(3)) ; 125.1 (C(12)) ; 113.9 (C(XX')) ; 85.5 (C(2'')) ; 70.8 (C(6)) ; 69.1 (C(5)) ; 66.0 (C(1')) ; 55.2 (C(6')) ; 30.6 (C(8)) ; 28.0 (C(3'')) ; 26.7 (C(7)).
HR-MS : $[M + Na]^+$ calc. 549.1849; found 549.1842

Synthesis of *tert*-butyl 2-(4-methoxy-4-oxobutanoyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (22a)

tert-Butyl 2-(4-methoxy-1-hydroxy-4-oxobutyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (3.64 g, 8.7 mmol) is dissolved in dry CH_2Cl_2 (500 mL) under Ar with MS 4Å (3g). The suspension is cooled to 0 °C and PDC (6.31 g, 17.4 mmol) is added to the reaction mixture. After 6 h, the solution is filtered over a mixture of celite:silice:celite. The solvent is evaporeted under vacum and the crude product is purified by chromatography (CH_2Cl_2/Et_2O 3:7) (76%).
^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 8.13 (*dd*, ^{3}J(12,13) = 8.1, ^{4}J(12,14) = 1.2, 1H, H(12)), 7.68 (*dt*, ^{3}J(14,13)= ^{3}J(14,15) = 7.5, ^{4}J(14,12) = 1.3, 1H, H(14)), 7.62 (*dxtripletoide*, ^{3}J(13,12) = 8.1, ^{3}J(13,14) = 7.6, ^{4}J(13,15) = 1.5, 1H, H(13)), 7.32 (*dd*, ^{3}J(15,14) = 7.5, ^{4}J(15,13) = 1.4, 1H, H(15)), 6.18 (*d*, ^{4}J(3,5) = 1.7, 1H, H(3)), 5.42 (*d*, ^{4}J(5,3) = 1.7, 1H, H(5)), 3.58 (*s*, 3H, H(1')), 2.83 (*dt*, ^{2}J(7a,7b) ≈ 19.1, ^{3}J(7a,8) ≈ 6.4, 1H, H(7a)), 2.55 (*ddd*, ^{2}J(7b,7a) ≈ 19.0, ^{3}J(7b,8b) ≈ 7.0, ^{3}J(7b,8a) ≈ 5.7, 1H, H(7b)), 2.41 and 2.39 (*dd*x(*AB system*) (partially solved), ^{2}J(8a,8b) ≈ 17.3, ^{3}J(8a,7b) ≈ 5.7, ^{3}J(8b,7a) ≈ 6.3, 2H, H(8ab)), 1.53 (*s*, 9H, H(3'')).
^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 201.3 (C(6)) ; 172.2 (C(9)) ; 167.3 (C(2)) ; 153.8 (C(1'')) ; 148.6 and 147.2 (C(10) and (C(11)) ; 133.8 (C(14)) ; 131.2 (C(15)) ; 131.1 (C(13)) ; 126.7 (C(4)) ; 125.8 (C(3)) ; 125.2 (C(12)) ; 84.7 (C(2'')) ; 71.9 (C(5)) ; 51.8 (C(1')) ; 32.9 (C(7)) ; 27.9 (C(3'')) ; 26.8 (C(8)).
ESI-MS : $[M + Na]^+$ = 440.9

Synthesis of *tert*-butyl 2-(4-ethoxy-4-oxobutanoyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (22b)

tert-Butyl 2-(4-ethoxy-1-hydroxy-4-oxobutyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (0.22 g, 0.5 mmol) is dissolved in dry CH_2Cl_2 (60 mL) under Ar with MS 4Å (2g). The suspension is cooled to 0 °C and PDC (0.39 g, 1.0 mmol) is added to

the reaction. After 6 h, the solution is filtered over a mixture of celite:silice:celite. The solvent is evaporeted under vacum and the crude product is purified by chromatography (CH_2Cl_2/Et_2O 3:7) (77%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 8.15 (*dd*, ^3J(12,13) = 8.1, ^4J(12,14) = 1.4, 1H, H(12)), 7.70 (*dt*, ^3J(14,13)= ^3J(14,15) = 7.5, ^4J(14,12) = 1.4, 1H, H(14)), 7.63 (*dxtripletoide*, ^3J(13,12) = 8.0, ^3J(13,14) = 7.6, ^4J(13,15) = 1.5, 1H, H(13)), 7.34 (*dd*, ^3J(15,14) = 7.5, ^4J(15,13) = 1.5, 1H, H(15)), 6.20 (*d*, ^4J(3,5) = 1.7, 1H, H(3)), 5.44 (*d*, ^4J(5,3) = 1.7, 1H, H(5)), 4.05 (*q*, ^3J(1',2') = 7.1, 2H, H(1')), 2.84 (*dt* (partially solved), ^2J(7a,7b) ≈ 19.0, 1H, H(7a)), 2.55 (*ddd*, ^2J(7b,7a) ≈ 19.0, ^3J(7b,8b) ≈ 7.1, ^3J(7b,8a) ≈ 5.7, 1H, H(7b)), 2.41 and 2.40 (*ddx(AB system)* (partially solved), ^2J(8a,8b) ≈ 17.2, ^3J(8a,7b) ≈ 5.7, ^3J(8a,7a) ≈ 6.7, ^3J(8b,7a) ≈ 6.2, ^3J(8b,7b) ≈ 6.8, 2H, H(8a and b)), 1.55 (*s*, 9H, H(3'')), 1.19 (*t*, ^3J(2',1') = 7.2, 3H, H(2')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 201.4 (C(6)) ; 171.8 (C(9)) ; 167.3 (C(2)) ; 153.8 (C(1'')) ; 148.7 and 147.2 (C(10) and (C(11)) ; 133.8 (C(14)) ; 131.3 (C(15)) ; 131.1 (C(13)) ; 126.7 (C(4)) ; 125.8 (C(3)) ; 125.2 (C(12)) ; 84.7 (C(2'')) ; 71.9 (C(5)) ; 60.7 (C(1')) ; 32.9 (C(7)) ; 27.9 (C(3'')) ; 27.1 (C(8)) ; 14.1 (C(2')).

HR-MS : $[M + Na]^+$ calc. 455.1430; found 455.1427.

Synthesis of *tert*-butyl 2-(4-benzoxy-4-oxobutanoyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (22c)

tert-Butyl 2-(4-benzoxy-1-hydroxy-4-oxobutyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (0.30 g, 0.6 mmol) is dissolved in dry CH_2Cl_2 (70 mL) under Ar with MS 4Å (3g). The suspension is cooled to 0 °C and PDC (0.45 g, 1.2 mmol) is added to the reaction mixture. After 6 h, the solution is filtered over a mixture of celite:silice:celite. The solvent is evaporeted under vacuum and the crude product is purified by chromatography (Ether) (78%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 8.14 (*dd*, ^3J(12,13) = 7.6, ^4J(12,14) ≈ 1.8, 1H, H(12)), 7.64 (*dt*, ^3J(14,13)=^3J(14,15) = 7.5, ^4J(14,12) ≈ 1.6, 1H, H(14)), 7.60 (*dt*, ^3J(13,12)=^3J(13,14) = 7.6, ^4J(13,15) = 1.7, 1H, H(13)), 7.36-7.27 (*m*, 6H, H(15,Bn)), 6.20 (*d*, ^4J(3,5) = 1.7, 1H, H(3)), 5.46 (*d*, ^4J(5,3) = 1.7, 1H, H(5)), 5.06 and 5.03 (*2xd (AB system)*, ^2J = 12.4, 2H, H(1')), 2.87 (*dt* (partially solved), ^2J(7a,7b) ≈ 18.8, 1H, H(7a)), 2.57 (*ddd* (partially solved), ^2J(7b,7a) ≈ 18.5, 1H, H(7b)), 2.50-2.46 (*m*, 2H, H(8)), 1.54 (*s*, 9H, H(3'')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 201.3 (C(6)) ; 171.7 (C(9)) ; 167.3 (C(2)) ; 153.9 (C(1'')) ; 148.7 and 147.2 (C(10) and (C(11)) ; 135.7 (C(2')) ; 133.8 (C(14)) ; 131.3 (C(15)) ; 131.1 (C(13)) ; 128.5 (C(3')) ; 128.2 (C(5')) ; 128.0 (C(4')) ; 126.7 (C(4)) ; 125.8 (C(3)) ; 125.2 (C(12)) ; 84.7 (C(2'')) ; 71.9 (C(5)) ; 66.5 (C(1')) ; 33.0 (C(7)) ; 27.9 (C(3'')) ; 27.1 (C(8)).

HR-MS : $[M + Na]^+$ calc. 517.1587; found 517.1577.

Synthesis of 4-(1-(*tert*-butoxycarbonyl)-3-(2-nitrophenyl)-5-oxo.2,5-dihydro-1*H*-pyrrol-2-yl)-4-oxobutanoic acid (24)

Tert-Butyl 2-(4-ethoxy-4-oxobutanoyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (0.70 g, 1.6 mmol) is dissolved in MeOH (40 mL) and NaOH 50% (3 mL) is added. The solution becomes red and than dark brown. After 1 h, the aqueous phase is extracted once with Et_2O, acidified with HCl 3.5N to pH ~ 1. The aqueous phase is extracted then 3 times with Et_2O. The combined organic phases are dried over $MgSO_4$ and crude product is purified by chromatography (CH_2Cl_2/MeOH 95:5) (40%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 8.15 (*dd*, ^{3}J(12,13) = 8.0, ^{4}J(12,14) = 1.4, 1H, H(12)), 7.68 (*dt*, ^{3}J(14,13)=^{3}J(14,15) = 7.4, ^{4}J(14,12) = 1.5, 1H, H(14)), 7.63 (*ddd*, ^{3}J(13,12) = 8.0, ^{3}J(13,14) = 7.6, ^{4}J(13,15) = 1.6, 1H, H(13)), 7.29 (*dd*, ^{3}J(15,14) = 7.5, ^{4}J(15,13) = 1.6, 1H, H(15)), 6.22 (*d*, ^{4}J(3,5) = 1.7, 1H, H(3)), 5.46 (*d*, ^{4}J(5,3) = 1.7, 1H, H(5)), 1.55 (*s*, 9H, H(3')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 201.1 (C(6)) ; 177.1 (C(9)) ; 167.3 (C(2)) ; 153.9 (C(1')) ; 148.7 and 147.2 (C(10) and (C(11)) ; 133.9 (C(14)) ; 131.3 (C(15)) ; 131.3 (C(13)) ; 126.5 (C(4)) ; 125.8 (C(3)) ; 125.3 (C(12)) ; 84.8 (C(2')) ; 71.6 (C(5)) ; 32.7 (C(7)) ; 27.9 (C(3')) ; 26.7 (C(8)).

ESI-MS : $[M - H]^-$ = 403.1

Synthesis of *tert*-butyl 4-phenyl-2-(trifluoromethylsulfonyloxy)-1*H*-pyrrole-1-carboxylate (25a)

tert-Butyl 2-oxo-4-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxylate (0.10 g, 0.4 mmol) is dissolved in dry CH_2Cl_2 (15 mL) at RT. 2,6-Lutidine (0.09 mL, 0.8 mmol) is added to the solution followed by Tf_2O (0.07 mL, 0.4 mmol). After 10 min. under stirring, the solution is washed with water and the aqueous phase is extracted with CH_2Cl_2. The combined

organic phases are dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, (i) EtOAc/hexane 1:4, (ii) CH_2Cl_2) (82%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.55 (*m*, 2H, H(7,11), 7.44 (*m*, 2H, H(8,10), 7.41 (*d*, ^4J(5,3) = 2.3, 1H, H(5)), 7.34 (*m*, 1H, H(9)), 6.43 (*m*, ^4J(3,5) = 2.3, ^6J(3,-F_3) ≈ 0.8, 1H, H(3)), 1.72 (*s*, 9H, H(3')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 147.0 (C(1')) ; 133.4 (C(6)) ; 132.8 (C(4)) ; 128.8 (C(9)) ; 127.2 (C(2)) ; 125.3 (C(8,10)) ; 123.8 (C(7,11)) ; 118.7 (*q*, C(1'')) ; 114.0 (C(5)) ; 100.4 (C(3)) ; 86.5 (C(13)) ; 27.9 (C(14)).

ESI-MS : $[M + Na]^+$ = 413.9

.**Synthesis of *tert*-butyl 4-(2-nitrophenyl)-2-(trifluoromethylsulfonyloxy)-1*H*-pyrrole-1-carboxylate (25b)**

tert-Butyl 4-(2-nitrophenyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (0.10 g, 0.3 mmol) is dissolved in dry CH_2Cl_2 (15 mL) and the solution is cooled to 0 °C. 2,6-Lutidine (0.11 mL, 1.0 mmol) is added to the solution followed by Tf_2O (0.07 mL, 0.4 mmol). After 2 h, the temperature is allowed to reach the RT. The solution is quenched with sat. $NaHCO_3$ (15 mL) and the aqueous phase is extracted with CH_2Cl_2. The combined organic phases are dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, CH_2Cl_2) (61%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 7.80 (*dd*, ^3J(8,9) ≈ 8.2, ^4J(8,10) ≈ 1.5, 1H, H(8)), 7.61 (*ddd* (partially solved), ^3J(10,9) and ^3J(10,11) ≈ 7.1 and 7.6, ^4J(10,8) ≈ 1.5, 1H, H(10)), 7.47-7.43 (*m* (partially solved), ^3J(9,10) ≈ 7.8, ^4J(9,11) ≈ 1.5, 2H, H(9,11)), 7.23 (*d*, ^4J(5,3) = 2.3, 1H, H(5)), 6.12 (*dq*, ^4J(3,5) = 2.3, ^6J(3,CF_3) = 0.8, 1H, H(3)), 1.64 (*s*, 9H, H(3')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 148.9 (C(1')) ; 146.7 (C(7)) ; 133.1 (C(6)) ; 132.4 (C(10)) ; 131.3 (C(11)) ; 128.5 (C(9)) ; 127.7 (C(4)) ; 124.1 (C(8)) ; 119.2 (C(2)) ; 118.7 (*q*, ^1J(C,F) = 321.5, CF_3) ; 116.6 (C(5)) ; 102.9 (C(3)) ; 87.0 (C(2')) ; 27.8 (C(3')).

^{19}F-NMR (188 MHz, $CDCl_3$, 298 K) : -72.3 (*d*, ^6J(CF_3,3) = 0.7, 3F, CF_3).

ESI-MS : $[M + Na]^+$ = 458.7

Synthesis of *tert*-butyl 2-(4-methoxy-4-oxobutanoyl)-3-(2-nitrophenyl)-5-(trifluoromethyl sulfonyloxy)-1*H*-pyrrole-1-carboxylate (25c)

tert-Butyl 2-(4-methoxy-4-oxobutanoyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (0.11 g, 0.3 mmol) is dissolved into dry CH_2Cl_2 (15 mL) at RT. 2,6-Lutidine

(0.09 mL, 0.8 mmol) is added to the solution followed by Tf_2O (0.07 mL, 0.4 mmol). After 2 h under stirring, the solution is washed with water and the aqueous phase is extracted with CH_2Cl_2. The combined organic phases are dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, EtOAc/hexane 4:6) (21%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 8.06 (*dd*, ^3J(12,13) = 8.0, ^4J(12,14) = 1.2, 1H, H(12)), 7.69 (*td*, ^3J(14,15)= ^3J(14,13) = 7.5, ^4J(14,12) = 1.4, 1H, H(14)), 7.61 (*ddd*, ^3J(13,12) = 8.1, ^3J(13,14) = 7.5, ^4J(13,15) = 1.6, 1H, H(13)), 7.48 (*dd*, ^3J(15,14) = 7.5, ^4J(15,13) ≈ 1.5, 1H, H(15)), 5.03 (*m* (partially solved), ^6J(3,CF_3) ≈ 0.6, 1H, H(3)), 3.62 (s, 3H, H(1')), 2.64-2.60 (*m*, 2H, H(7)), 2,54-2.51 (*m*, 2H, H(8)), 1.64 (*s*, 9H, H(3'')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 190.0 (C(6)) ; 172.5 (C(9)) ; 149.0 (C(1'')) ; 146.3 (C(11)) ; 135.1 (C(10)) ; 133.0 (C(15)) ; 132.8 (C(14)) ; 129.9 (C(13)) ; 127.9 (C(4)) ; 126.8 (C(5)) ; 124.6 (C(2)) ; 124.5 (C(12)) ; 120.7 (*q*, ^1J(C,F) = 322.4, CF_3) ; 101.9 (C(3)) ; 88.2 (C(2'')) ; 51.7 (C(1')) ; 36.4 (C(7)) ; 27.8 (C(8)) ; 27.4 (C(3'')).

ESI-MS : $[M + K]^+$ = 588.8, $[M + Na]^+$ = 572.8

Synthesis of *tert*-butyl 2-(4-ethoxy-4-oxobutanoyl)-3-(2-nitrophenyl)-5-(trifluoromethyl sulfonyloxy)-1*H*-pyrrole-1-carboxylate (25d)

tert-Butyl 2-(4-ethoxy-4-oxobutanoyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (1.52 g, 3.5 mmol) is dissolved into dry CH_2Cl_2 (80 mL) and the solution is cooled to -10 °C. Et_3N (0.71 mg, 7.04 mmol) is added to the solution followed by Tf_2O (0.83 mL, 4.9 mmol). The reaction is followed by TLC until complete disappearing of the starting material. Then a saturated solution of $NaHCO_3$ (40 mL) is added and the organic phase is washed with brine, dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, 40% EtOAc in hexane) affords the product as a slightly orange oil (71%).

^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 8.02 (*ddd*, ^3J(12,13) = 8.1, ^4J(12,14) = 1.4, ^5J(12,15) = 0.3, 1H, H(12)), 7.65 (*td*, ^3J(14,15)= ^3J(14,13) = 7.5, ^4J(14,12) = 1.4, 1H, H(14)), 7.57 (*ddd*, ^3J(13,12) = 8.1, ^3J(13,14) = 7.5, ^4J(13,15) = 1.6, 1H, H(13)), 7.43 (*ddd*, ^3J(15,14) = 7.5, ^4J(15,13) = 1.6, ^5J(15,12) = 0.3, 1H, H(15)), 5.99 (*m* (partially solved), ^6J(3,CF_3) ≈ 0.7, 1H, H(3)), 4.02 (*q*, ^3J(1',2') = 7.2, 2H, H(1')), 2.58-2.54 (*m*, 2H, H(7)), 2,48-2.45 (*m*, 2H, H(8)), 1.60 (*s*, 9H, H(3'')), 1.16 (*t*, ^3J(2',1') = 7.2, 3H, H(2')).

^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 190.0 (C(6)) ; 172.0 (C(9)) ; 148.9 (C(1'')) ; 146.2 (C(11)) ; 135.1 (C(10)) ; 133.0 (C(15)) ; 132.8 (C(14)) ; 129.9 (C(13)) ; 127.9 (C(4)) ;

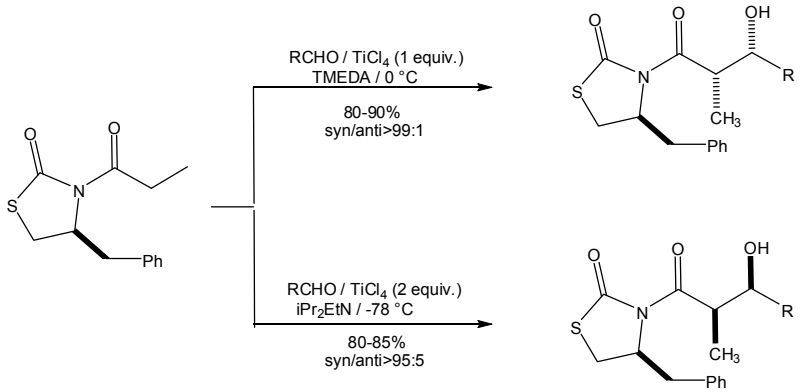
126.7 (C(5)) ; 124.5 (C(2)) ; 124.5 (C(12)) ; 118.6 (*q*, ^{1}J(C,F) = 321.1, CF_3) ; 101.9 (C(3)) ; 88.1 (C(2'')) ; 60.5 (C(1')) ; 36.3 (C(7)) ; 28.1 (C(8)) ; 27.3 (C(3'')) ; 14.1 (C(2')).
ESI-MS : $[M + Na]^+$ = 586.8

Synthesis of ethyl 4-(3-(2-nitrophenyl)-1*H*-pyrrole-2-yl)-4-oxobutanoate (26)

tert-Butyl 2-(4-ethoxy-4-oxobutanoyl)-3-(2-nitrophenyl)-1*H*-pyrrole-1-carboxylate (0.37 g, 0.9 mmol) is dissolved in CH_2Cl_2 (10 mL) and TFA (2 mL) is added to the mixture at RT. After 20 min. the mixture is treated with a saturated solution of $NaHCO_3$ (10 mL) and the organic phase is washed with brine, dried over $MgSO_4$ and concentrated (88%).
^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) : 9.73 (*s br*, 1H, H(NH)), 7.95 (*dd*, ^{3}J(12,13) = 8.1, ^{4}J(12,13) = 1.3, 1H, H(12)), 7.64 (*dt*, ^{3}J(14,13)(14,15) = 7.5, ^{4}J(14,12) = 1.4, 1H, H(14)), 7.55 (*dxtripletoide*, ^{3}J(13,12) = 8.1, ^{3}J(13,14) = 7.5, ^{4}J(13,15) = 1.6, 1H, H(13)), 7.50 (*dd*, ^{3}J(15,14) = 7.5, ^{4}J(15,13) = 1.6, 1H, H(15)), 7.02 (*tripletoide*, ^{3}J(2,NH) = 3.0, ^{3}J(2,3) = 2.6, 1H, H(2)), 6.20 (*t*, ^{3}J(3,2)= ^{3}J(3,NH) = 2.7, 1H, H(3)), 4.07 (*q*, ^{3}J(1',2') = 7.1, 2H, H(1')), 2.57-2.51 (*m*, 4H, H(7,8)), 1.20 (*t*, ^{3}J(2',1') = 7.1, 3H, H(2')).
^{13}C-NMR (100 MHz, $CDCl_3$, 298 K) : 188.5 (C(6)) ; 172.7 (C(9)) ; 149.7 (C(11)) ; 132.8 (C(15)) ; 132.3 (C(14)) ; 130.9 (C(10)) ; 128.9 (C(13)) ; 128.8 (C(5)) ; 125.8 (C(4)) ; 124.0 (C(12)) ; 123.0 (C(2)) ; 112.8 (C(3)) ; 60.5 (C(1')) ; 33.7 (C(7)) ; 28.0 (C(8)) ; 14.1 (C(2')).
HR-MS : $[M + Na]^+$ calc. 339.0957; found 339.0952

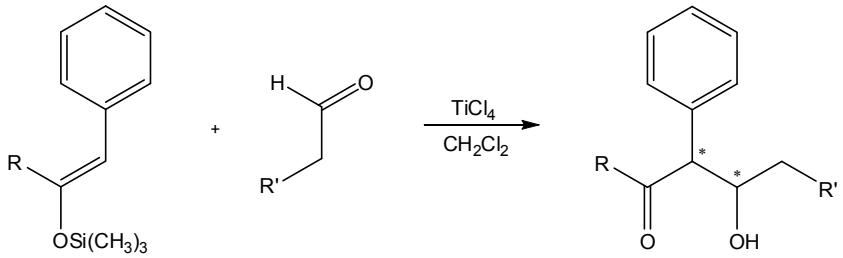
4. X-Ray Analysis of Some Synthetic Intermediates

During our studies towards the development of an efficient synthetic methodology of rhazinilam and rhazinilam analogues, the crossed Mukaiyama aldol reaction played a crucial role. This process has been widely used in synthesis and allows to create regioselectively carbon-carbon bonds. The importance of this process is increased by the fact that two asymmetric carbon centers are created. The relative configuration of the two newly formed asymmetric centers can often be controlled. Additional chiral centers in one of the two starting materials or chiral centers present in both starting materials exercice a high control over the newly formed centers.



Scheme 25: Stereodivergent route to both *syn*-aldol from the same chiral reagent[1]

At several points in our synthetic endeavour we created aliphatic intermediates using a Mukaiyama type reaction containing two newly formed asymmetric centers.

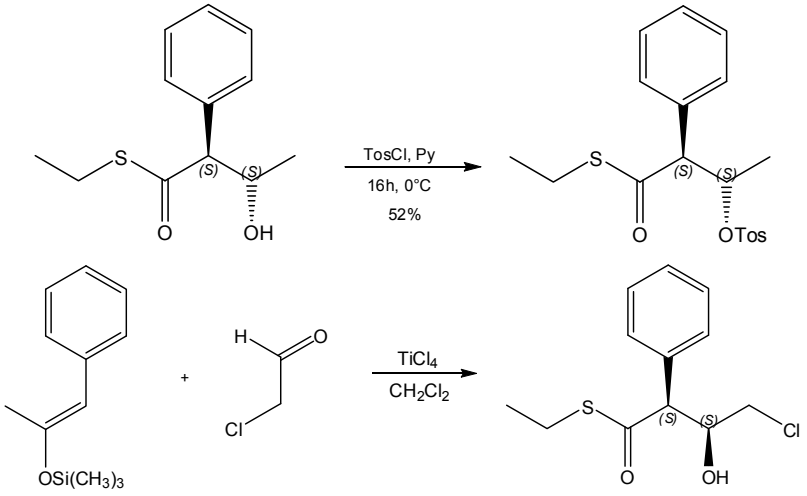


Scheme 26: Mukaiyama type reaction

The diastereoselectivity of this process was of no importance for the continuation of our synthetic plan because we intended to transform the asymmetric centers in later states of the synthesis into sp^2 hybridized carbon atoms. In view of the lack of direct impact on

the continuation of our synthetic plans, the determination of the diastereoselectivity of these processes has not been discussed extensively before.

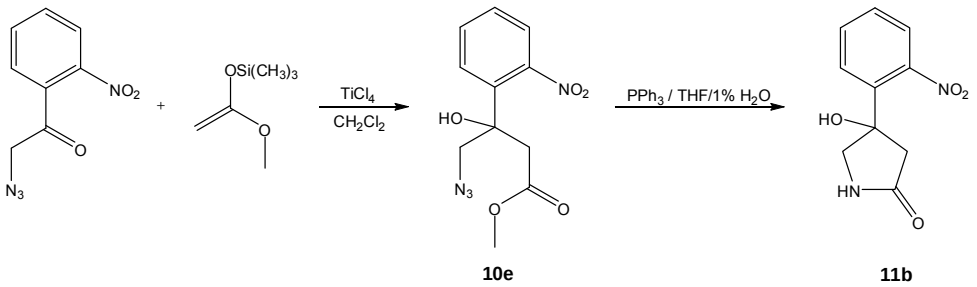
Another problem in this context is that despite the accumulation of a huge body of experimental data on the diastereoselectivity, extrapolation from the known to the unknown is often very difficult. Finally the attribution of the relative configuration of such compounds is not easy. Traditional NMR analysis often does not allow to attribute the relative configuration of the obtained diastereoisomers unequivocally. The coupling constants, which are usually the best experimental parameter to assign the dihedral angles between adjacent substituents on a carbon chain, depend often crucially on the solvent used, the sort and strength of the intra- versus intermolecular hydrogen bonds and sometimes also on the character of the other subtituents present. In view of this difficulty, we decided to determine the relative configuration of the series of compounds obtained during our synthetic studies with the help of X-ray diffraction studies on the crystals obtained from the reaction seen in the first publication in Acta Crystallographica. The result of the X-ray analysis confirms that the Mukaiyama type process using an unsubstituted aldehyde as electrophile gives the *anti* product as expected. Changing the electrophile to the chloro-acetaldehyde induces a switch of the diastereoselectivity to the *syn* product.



Scheme 27: The relative configuration of the Mukaiyama reaction products

In our second generation approach to the phenyl-pyrrole intermediates we encountered a major difficulty to induce seemingly simple reactions after the formation of the γ-lactam

ring. The difficulty to bring these intermediates to react is probably to do with the lack of solubility of our intermediates.



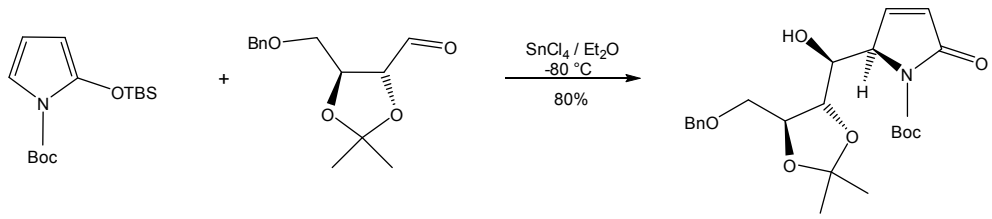
10e **11b**

Scheme 28: Synthesis of lactam (unsoluble)

The structure determination of the compounds **11a** and **11b** (Full Paper) showed that the molecules formed highly ordered networks of intermolecular hydrogen bonds. The individual molecule of nitro compound **11b** in the crystal is connected with hydrogen bonds to all surrounding molecules and is therefore firmly held in place. We interpreted this arrangement as the major factor limiting the solubility of these compounds and obstructing the reactivity of these molecules.

The precursors of the lactam, the aldol products **10c,e** are crystalline as well, but they are considerably more soluble. We therefore decided to determine the X-ray solid state structure of one of these compounds, molecule **10e** in order to have a point of comparison. The major observation is, that the aldol product **10e** shows only an intramolecular hydrogen bond, fixing the conformation of the chain between the tertiary alcohol function and the ester, whereas the lactams showed exclusively intermolecular hydrogen bonds. The intramolecular hydrogen bond of the aldol product forms a six membered ring between the alcohol hydrogen and the ester oxygen in an arrangement which corresponds to a boat-like conformation. These observations are compatible with the differences in solubility observed, even if the strength of the involved hydrogen bonds can not be quantified.

One of the methods we have studied to introduce the side chain needed for the formation of the B-ring was the nucleophilic addition of activated equivalent of 2-hydroxypyrroles **19a,b** (Full Papers) to aldehydes. This type of reaction has been systematically studied by the group of Rassu.



Scheme 29: Diastereoselectivity in Rassu's strategy towards carbasugars[2]

This reaction is nothing else than the condensation of a deprotonated pyrrolinone with an aldehyde creating two new asymmetric centers, one α to the nitrogen and one at the exocyclic carbon. The group of Rassu has used these compounds for a series of elegant synthesis of natural products. To the best of our knowledge no reports have appeared where the 2-silyloxypyrrole was substituted by a phenyl ring. The phenyl ring in our compounds is positioned next to the newly formed chiral center. We thereby can not exclude an interaction of this bystanding substituend on the reaction process. The reports in the literature indicate also that the diastereoselectivity depends highly on the reaction conditions used, especially the Lewis acid added to induce the aldol type reaction can exercice a big influence on the diastereoselectivity. It is therefore not evident if we can extrapolate the synthetic and mechanistic results reported in the literature so far for this process.

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4.1. Rac-(2*R,3*R**)-*S*-ethyl 4-chloro-3-hydroxy-2-phenylbuthanethioate and Rac-(2*R**,3*R**)-*S*-ethyl 2-phenyl-3-(tosyloxy)buthanethioate: The dichotomy of the stereoselectivity of the Mukaiyama reaction**

Submitted to *Acta Cryst. C*

rac-(2*R**,3*R**)-*S*-ethyl 4-chloro-3-hydroxy-2-phenylbuthanethioate and rac-(2*R**,3*R**)-*S*-ethyl 2-phenyl-3-(tosyloxy)buthanethioate: The dichotomy of the stereoselectivity of the Mukaiyama reaction

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Abstract

The title compounds, $C_{12}H_{15}ClO_2S$ (I) and $C_{19}H_{22}O_4S_2$ (III), are both compossed of a *S*-ethyl 2-phenylbutanethioate moiety which have different geometries. Compound I is substituted in the 4 and 3 positions by a chlorine atom and an hydroxyl group, respectively. In compound III the hydroxyl group in the 3 position has been tosylated in order to obtain suitable crystals for X-ray analysis. In compound I the phenyl substituent and the hydroxyl group have a *syn* arrangement whereas in the tosylate derivative of II, *i.e.* compound III, they have an anti arrangement. In the crystal structure of I centrosymmetric hydrogen bonded dimers are formed *via* O—H···O hydrogen bonds involving the hydroxyl group and the carbonyl O-atom. In the crystal structure of III symmetry related molecules are connect *via* a C—H···O interaction, involving a tosylate O-atom and a phenyl H-atom, so forming a zigzag chain extending in the c direction.

Comment

The number of pyrrole containing natural products has steadily increased in recent years certainly due to the application of more sophisticated isolation procedures (Gossauer, 2003). (-)-Rhazinilam, a natural product whose unusual structure was determined in the early seventies (De Silva *et al.*, 1972), showed interesting cytotoxic and pharmaceutical properties due to its interference with the tubuline-microtubule equilibrium (David *et al.*, 1994; Thoison *et al.*, 1987). The crystal structure of (-) Rhazinilam and a t-butoxycarbonyl derivative, have been reported recently (Decor *et al.*, 2006). We are studying the scope and the applicability of our pyrrole synthesis based on the two step sequence Mukaiyama cross-aldol reaction followed by the Staudinger reaction (Vallat, 2004). To assemble the key elements, we studied the Mukaiyama crossed aldol reaction between the silyl enol ether of *S*-ethyl 2-phenylethanethioate and simple aldehydes like acetaldehyde and 2-chloroacetaldehyde (Scheme 1). This modified version allowed us to obtain the condensation products needed for our planed rhazinilam synthesis in reasonable to good yields, whereas the use of the silyl enol ether of 2-phenylacetaldehyde has only lead to the formation of polymers.

The crystal structures of the title condensation products, rac-(2*R**,3*R**)-*S*-ethyl 4-chloro-3-hydroxy-2-phenylbuthanethioate (I), and rac-(2*R**,3*R**)-*S*-ethyl 2-phenyl-3-(tosyloxy)buthanethioate (III) [compound II in its derivatized crystalline form] were carried out in order to ascertain the relative configuration of the two newly created chiral centers at C7 and C11. The product of the reaction described in Scheme 1 using 6 equivalents of $TiCl_4$ lead to the formation of compound I with a

yield of 51%. Compound II was obtained in a higher yield, 70%, also using 6 equivalents of $TiCl_4$. In order to obtain crystals suitable for X-ray analysis compound II was tosylated (Scheme 2) to give compound III.

The molecular structure of compound I is illustrated in Fig. 1. The bond lengths and angles (Table 1) are in the normal ranges (Allen *et al.*, 1987). The phenyl ring and the hydroxyl group are directed to the opposite side of the molecule with respect to the Chlorine atom and the methyl group of the buthanethiolate moiety. The phenyl substituent at C7 and the hydroxyl group at C11 have a *syn* arrangement In the crystal structure of I centrosymmetric hydrogen bonded dimers are formed *via* O—H···O hydrogen bonds involving the hydroxyl group (O2) and the thioate O-atom O1 (Table 2 and Fig 2).

The molecular structure of compound III is illustrated in Fig. 3. Again the bond lengths and angles (Table 3) are in the normal ranges (Allen. 1987). In compound III the phenyl substituent at C7 and the tosylated hydroxyl group at C11 have an anti arrangement. In the crystal structure of III symmetry related molecules are connect *via* a C—H···O interaction forming a zigzag chain extending in the c direction (Table 4 and Fig 2).

The *syn*/anti stereo descriptors clearly indicate that the stereoselectivity of the Mukaiyama aldol reaction has switched from an anti-selective process for the reaction with acetaldehyde (Scheme 2) to a *syn*-selective process for the reaction using 2-chloroacetaldehyde (Scheme 1). This dichotomy is compatible with the predictions based on the Cornforth transition state model (Evans *et al.*, 2003; Marco *et al.*, 2003) and the polar Felkin-Anh model (Evans *et al.*, 2006) as has been discussed recently in the literature.

Experimental

Compound I was prepared by dissolving Chloro-acetaldehyde (306 mg, 3.9 mmol) in dry CH_2Cl_2 (20 ml) and $TiCl_4$ (2.6 ml, 23.4 mmol), freshly distilled over polyvinylpyridine, were added to the reaction at −78°C under Ar. 1-Ethylsulfanyl-2-phenyl-vinyloxy)trimethylsilane (0.983 g, 3.9 mmol) dissolved in CH_2Cl_2 (6 ml) was added dropwise to the reaction mixture. The solution became dark orange. After 1 h at −78°C under stirring, sat. $NaHCO_3$ (50 ml) was added to the cold solution. The aqueous phase was extracted three times with CH_2Cl_2. The organic phases were collected together and washed three times with water and brine, then dried over $MgSO_4$ and concentrated under vacuum. The crude yellow product obtained was purified by flash chromatography (AcOEt/Hexane 1:3) (Yield 51%). Crystals suitable for X-ray analysis were obtained from ether/hexane (v:v = 1.1)

rac-(2*R*,3*R*)-*S*-ethyl 2-phenyl-3-(tosyloxy)buthanethioate (II): *p*-TosCl (680 mg, 3.57 mmol) dissolved in Pyridine (5 ml) and *S*-ethyl 3-hydroxy-2-phenylbutanethioate (391 mg, 1.74 mmol) were added to the reaction reaction vessel at 0°C. The reaction was kept under stirring at this temperature for 16 h. 10 ml of water were added to the reaction mixture and the aqueous phase was extracted three times with CH_2Cl_2. The organic phases were collected together, washed twice with 1*M* HCl and then with a saturated $NaHCO_3$ solution, and then dried over MgSO4 and concentrated under vacuum. The crude yellow product was purified by flash chromatography (AcOEt/Hexane 1:3) (Yield 52%). Crystals suitable for X-ray analysis were obtained from ether/hexane (v:v = 1.1)

Refinement

The hydroxyl H-atom in I was located from a difference Fourier map and freely refined: O—H = 0.77 (3) Å. The remainde of the H-atoms in both structures were included in calculated positons and treated as riding atoms: C—H = 0.93 − 0.98 Å in I, and 0.95 − 1.00 Å in II; with U_{iso}(H) = 1.2 or 1.5U_{eq}(parent C-atoms).

Computing details

Data collection: STADI4 (Stoe & Cie, 1997) for (I); *EXPOSE* (Stoe & Cie, 2000) for (III). Cell refinement STADI4 for (I); *CELL* (Stoe & Cie, 2000) for (III). Data reduction: *X-RED* (Stoe & Cie, 1997) for (I); *INTEGRATE* (Stoe & Cie, 2000) for (III). For both compounds, program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008) program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3* (Farrugia, 1997), Mercury (Macrea, 2006) & *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*

Figures

Figure 1. Molecular structure of compound I, showing the atom labelling scheme and the displacement ellipsoids drawn at the 50% probability level.
Figure 2. A view along the *b* axis of the crystal packing of compound I, showing the intermolecular hydrogen bonds as dashed lines (see Table 2 for details).
Figure 3. Molecular structure of compound III, showing the atom labelling scheme and the displacement ellipsoids drawn at the 50% probability level.
Figure 4. A view along the *a* axis of the crystal packing of compound III, showing the intermolecular hydrogen bonds as dashed lines (see Table 2 for details).

(I)

Crystal data

$C_{12}H_{15}ClO_2S$	V = 1261.3 (4) Å^3
M_r = 258.75	Z = 4
Monoclinic, $P2_1/c$	Cu $K\alpha$
a = 11.2422 (19) Å	μ = 4.09 mm^{-1}
b = 5.4674 (11) Å	T = 293 (2) K
c = 20.685 (4) Å	0.53 × 0.46 × 0.19 mm
β = 97.236 (14)°	

Data collection

STOE AED2 4-circle diffractometer	R_{int} = 0.048
Absorption correction: part of the refinement model (ΔF) DELrefABS in PLATON (Spek, 2003)	θ_{max} = 59.7°
T_{min} = 0.075, T_{max} = 0.459	2 standard reflections
3624 measured reflections	every 60 min
1833 independent reflections	intensity decay: <2%

1719 reflections with $I > 2\sigma(I)$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.041$	151 parameters
$wR(F^2) = 0.111$	H atoms treated by a mixture of independent and constrained refinement
$S = 1.05$	$\Delta\rho_{max} = 0.18$ e Å^{-3}
1833 reflections	$\Delta\rho_{min} = -0.27$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °)

Cl1—C9	1.784 (2)	O1—C8	1.424 (3)
S1—C10	1.763 (2)	O2—C10	1.207 (3)
S1—C11	1.809 (3)		
C10—S1—C11	100.71 (11)	S1—C10—O2	121.80 (19)
O1—C8—C7	108.37 (17)	O2—C10—C7	123.0 (2)
O1—C8—C9	108.41 (18)	S1—C10—C7	115.10 (16)
Cl1—C9—C8	111.59 (16)	S1—C11—C12	112.7 (2)

Table 2
Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1O···O2^{i}	0.77 (3)	2.06 (3)	2.832 (3)	176 (3)
C7—H7···O1^{ii}	0.98	2.59	3.393 (3)	139

Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $x, y-1, z$.

(III)

Crystal data

$C_{19}H_{22}O_4S_2$	$V = 1953.8$ (3) Å^3
$M_r = 378.49$	$Z = 4$
Monoclinic, $P2_1/n$	Mo $K\alpha$
$a = 5.7792$ (5) Å	$\mu = 0.29$ mm^{-1}
$b = 20.0506$ (14) Å	$T = 153$ (2) K
$c = 17.0331$ (16) Å	0.40 × 0.40 × 0.20 mm
$\beta = 98.151$ (11)°	

Data collection

STOE IPDS diffractometer	3546 independent reflections
Absorption correction: none	2461 reflections with $I > 2\sigma(I)$
16245 measured reflections	$R_{int} = 0.059$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.035$	229 parameters
$wR(F^2) = 0.087$	H-atom parameters constrained
$S = 0.91$	$\Delta\rho_{max} = 0.31$ e Å^{-3}
3546 reflections	$\Delta\rho_{min} = -0.37$ e Å^{-3}

Table 3
Selected geometric parameters (Å, °)

S1—C8	1.7551 (17)	S2—O4	1.4271 (15)
S1—C9	1.810 (3)	S2—C13	1.7509 (17)
S2—O2	1.5857 (13)	O1—C8	1.213 (2)
S2—O3	1.4237 (16)	O2—C11	1.472 (2)
C8—S1—C9	100.83 (10)	S1—C8—O1	124.36 (13)
O2—S2—O3	106.97 (8)	S1—C8—C7	112.80 (12)
O2—S2—O4	108.27 (8)	O1—C8—C7	122.80 (15)
O2—S2—C13	101.30 (7)	S1—C9—C10	111.9 (2)
O3—S2—O4	119.15 (9)	O2—C11—C7	103.87 (12)
O3—S2—C13	109.59 (8)	O2—C11—C12	109.63 (14)
O4—S2—C13	110.01 (9)	S2—C13—C14	119.05 (14)
S2—O2—C11	120.08 (10)	S2—C13—C18	120.31 (14)

Table 4
Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C4—H4···O4^{i}	0.95	2.44	3.180 (3)	135

Symmetry codes: (i) $x-1/2, -y+3/2, z+1/2$.

Acknowledgements

This work was partially financed by the Swiss National Science Foundation.

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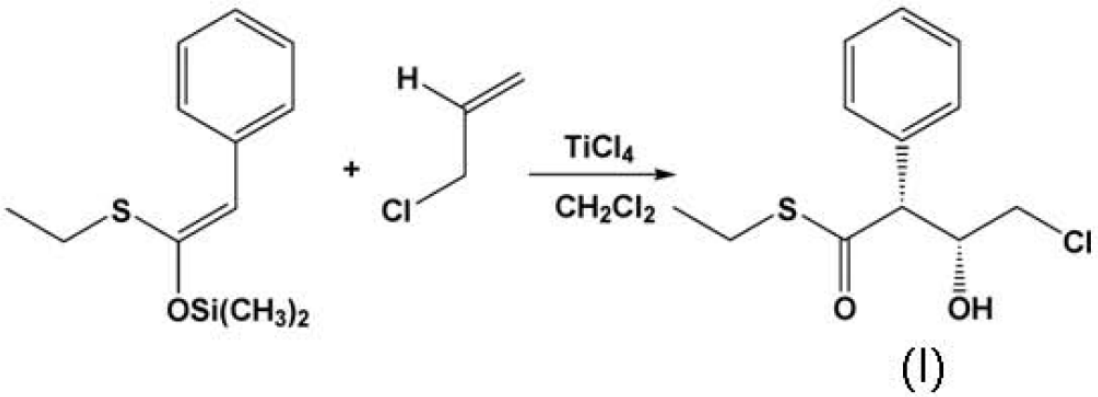


(I)

Scheme 1

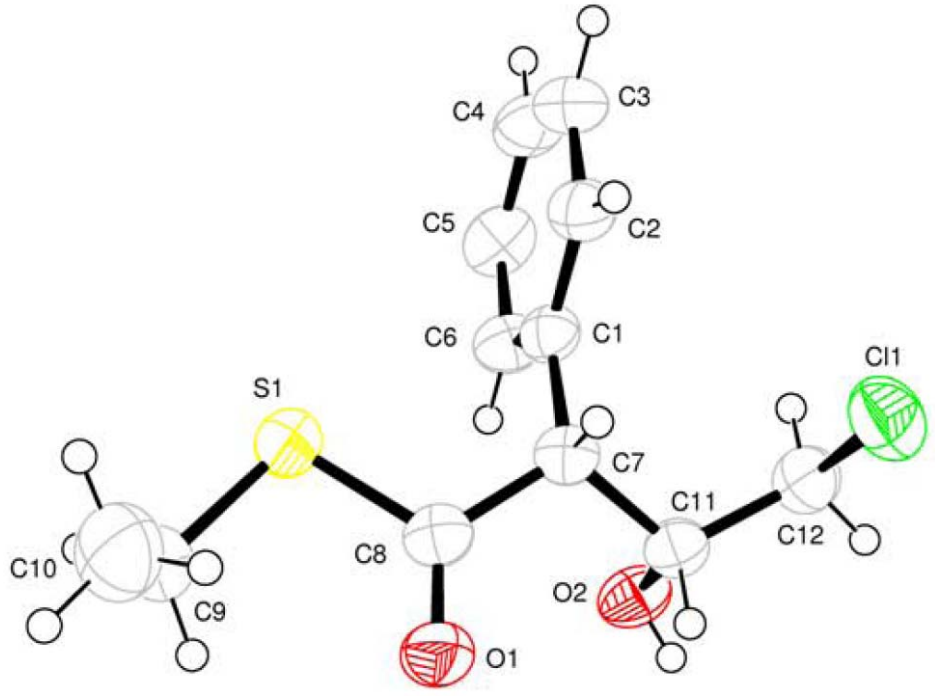


Fig. 1. The molecular structure of compound I, showing the atomic labelling scheme and displacement ellipsoids drawn at the 50% probability level.

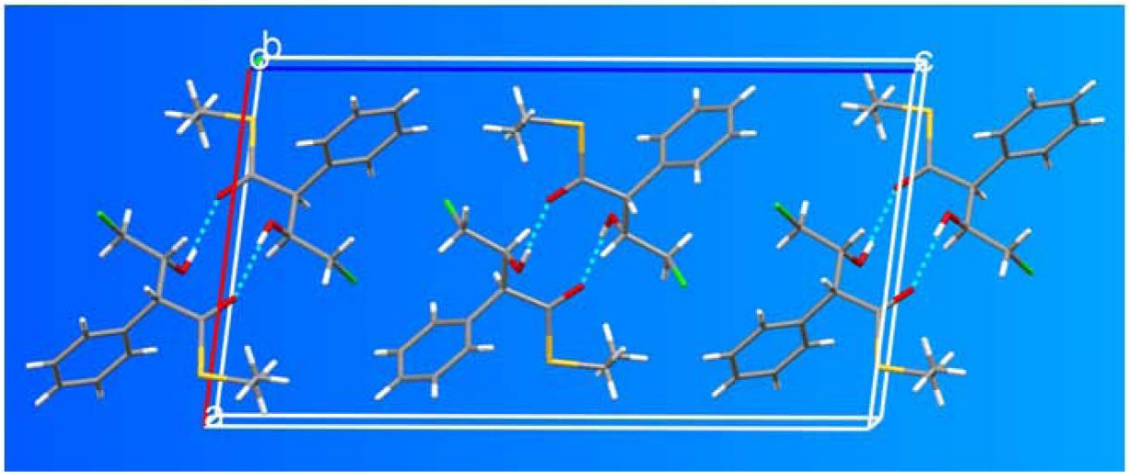
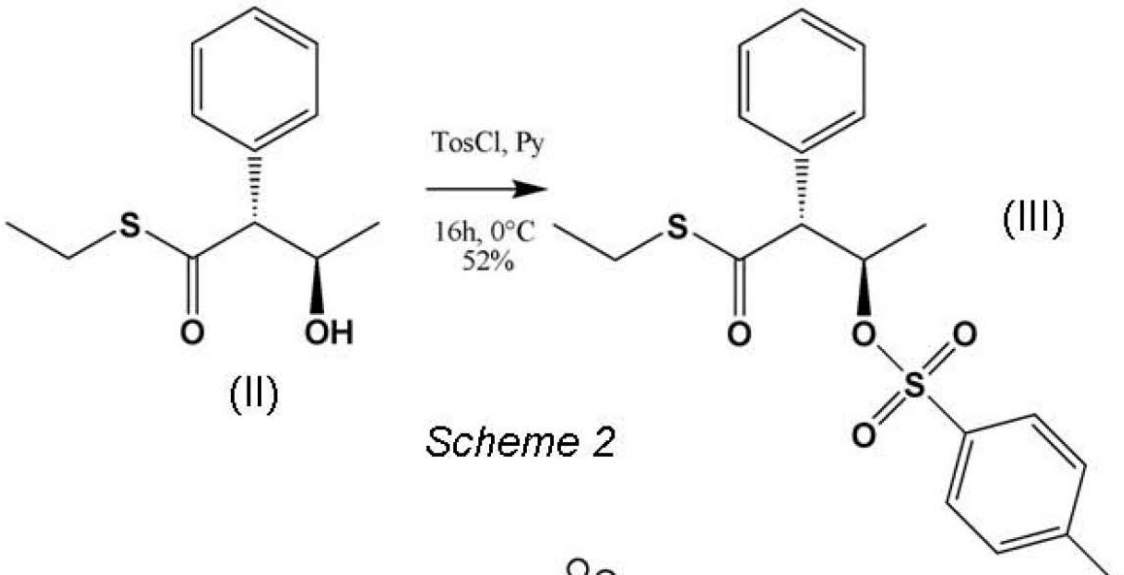


Fig. 2. Crystal packing viewed along the b axis of compound I, showing the formation of the centrosymmetric O-H…O hydrogen bonded dimers (hydrogen bonds are shown as dashed blue lines).



Scheme 2

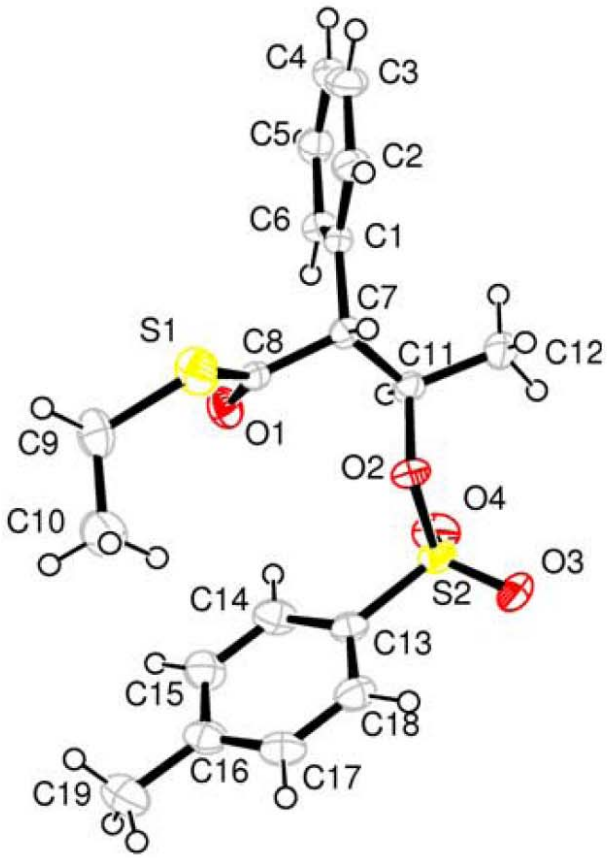


Fig. 3. Molecular structure of compound III, showing the atomic numbering Scheme and the displacement ellipsoids drawn at the 505 probability level.

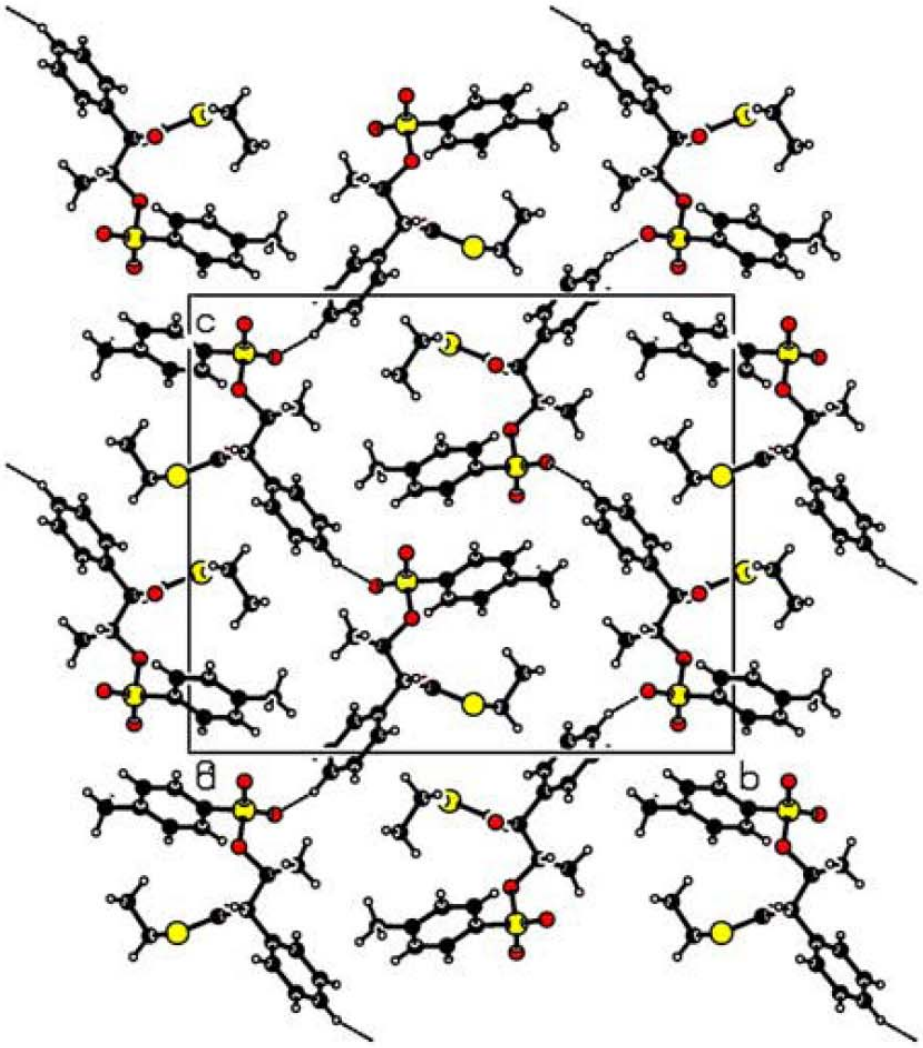


Fig. 4. Crystal packing viewed along the a axis of compound III, showing the formation of the zig-zag C-H…O hydrogen bonded chain (hydrogen bonds shown as dashed lines).

supplementary materials

rac-(2*R**,3*R**)-*S*-ethyl 4-chloro-3-hydroxy-2-phenylbuthanethioate and rac-(2*R**,3*R**)-*S*-ethyl 2-phenyl-3-(tosyloxy)buthanethioate: The dichotomy of the stereoselectivity of the Mukaiyama reaction

Olivier Vallat[a], Ana-Maria Buciumas[a], Reinhard Neier[a] and Helen Stoeckli-Evans[b]

(I)

Crystal data

$C_{12}H_{15}ClO_2S$	F_{000} = 544
M_r = 258.75	D_x = 1.363 Mg m^{-3}
Monoclinic, $P2_1/c$	Cu $K\alpha$ radiation λ = 1.54186 Å
Hall symbol: -P 2ybc	Cell parameters from 25 reflections
a = 11.2422 (19) Å	θ = 12.5–32.9°
b = 5.4674 (11) Å	μ = 4.09 mm^{-1}
c = 20.685 (4) Å	T = 293 (2) K
β = 97.236 (14)°	Rod, colourless
V = 1261.3 (4) Å^3	0.53 × 0.46 × 0.19 mm
Z = 4	

Data collection

STOE AED2 4-circle diffractometer	R_{int} = 0.048
Radiation source: fine-focus sealed tube	θ_{max} = 59.7°
Monochromator: graphite	θ_{min} = 4.0°
T = 293(2) K	h = −12→12
2θ/ω scans	k = −6→6
Absorption correction: part of the refinement model (ΔF) DELrefABS in PLATON (Spek, 2003)	l = −23→23
T_{min} = 0.075, T_{max} = 0.459	2 standard reflections
3624 measured reflections	every 60 min
1833 independent reflections	intensity decay: <2%
1719 reflections with $I > 2\sigma(I)$	

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)]$ = 0.041	$w = 1/[\sigma^2(F_o^2) + (0.0535P)^2 + 0.5447P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2)$ = 0.111	$(\Delta/\sigma)_{max} < 0.001$

S = 1.05	$\Delta\rho_{max}$ = 0.18 e Å^{-3}
1833 reflections	$\Delta\rho_{min}$ = −0.27 e Å^{-3}
151 parameters	Extinction correction: SHELXL, $Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
Primary atom site location: structure-invariant direct methods	Extinction coefficient: 0.0023 (6)
Secondary atom site location: difference Fourier map	

Special details

Geometry. Bond distances, angles *etc*. have been calculated using the rounded fractional coordinates. All su's are estimated from the variances of the (full) variance-covariance matrix. The cell e.s.d.'s are taken into account in the estimation of distances, angles and torsion angles

Refinement. Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
Cl1	0.60274 (6)	0.14886 (14)	0.69152 (3)	0.0667 (3)
S1	0.15565 (5)	0.07674 (13)	0.50791 (3)	0.0540 (3)
O1	0.42724 (16)	0.6080 (3)	0.56344 (9)	0.0508 (6)
O2	0.36791 (15)	0.1546 (3)	0.47359 (8)	0.0574 (6)
C1	0.27352 (18)	0.2730 (4)	0.63479 (10)	0.0393 (7)
C2	0.2633 (2)	0.1268 (4)	0.68829 (12)	0.0492 (8)
C3	0.1848 (2)	0.1881 (6)	0.73239 (13)	0.0615 (9)
C4	0.1168 (2)	0.3943 (5)	0.72338 (14)	0.0611 (10)
C5	0.1255 (2)	0.5412 (5)	0.67063 (13)	0.0580 (9)
C6	0.2034 (2)	0.4831 (4)	0.62629 (12)	0.0480 (8)
C7	0.36266 (18)	0.2039 (4)	0.58871 (10)	0.0387 (7)
C8	0.47006 (19)	0.3791 (4)	0.58967 (11)	0.0410 (7)
C9	0.5349 (2)	0.4223 (4)	0.65734 (12)	0.0499 (8)
C10	0.3090 (2)	0.1550 (4)	0.51849 (12)	0.0426 (7)
C11	0.1371 (2)	−0.0241 (6)	0.42394 (12)	0.0605 (9)
C12	0.1621 (3)	−0.2903 (6)	0.41729 (16)	0.0805 (12)
H1O	0.481 (3)	0.673 (6)	0.5514 (14)	0.063 (9)*
H2	0.30960	−0.01420	0.69480	0.0590*
H3	0.17870	0.08810	0.76820	0.0740*
H4	0.06440	0.43520	0.75310	0.0730*
H5	0.07860	0.68150	0.66460	0.0700*
H6	0.20900	0.58460	0.59070	0.0580*
H7	0.39690	0.04750	0.60490	0.0460*
H8	0.52680	0.31130	0.56210	0.0490*
H9A	0.47840	0.48320	0.68530	0.0600*
H9B	0.59610	0.54590	0.65530	0.0600*

H11A	0.05560	0.00960	0.40460	0.0730*
H11B	0.19070	0.06870	0.40000	0.0730*
H12A	0.24260	−0.32490	0.43640	0.1210*
H12B	0.10690	−0.38350	0.43920	0.1210*
H12C	0.15290	−0.33380	0.37200	0.1210*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl1	0.0683 (5)	0.0739 (5)	0.0552 (5)	0.0078 (3)	−0.0031 (3)	0.0070 (3)
S1	0.0473 (4)	0.0640 (5)	0.0511 (4)	−0.0080 (3)	0.0078 (3)	−0.0045 (3)
O1	0.0521 (10)	0.0385 (9)	0.0641 (11)	−0.0046 (8)	0.0164 (9)	0.0097 (8)
O2	0.0570 (10)	0.0699 (12)	0.0479 (10)	−0.0149 (9)	0.0173 (8)	−0.0116 (8)
C1	0.0416 (12)	0.0337 (11)	0.0429 (12)	−0.0046 (9)	0.0069 (9)	0.0012 (9)
C2	0.0500 (13)	0.0478 (13)	0.0502 (14)	−0.0031 (11)	0.0081 (11)	0.0064 (11)
C3	0.0592 (15)	0.0773 (19)	0.0504 (15)	−0.0080 (14)	0.0169 (12)	0.0120 (14)
C4	0.0517 (15)	0.0751 (19)	0.0606 (17)	−0.0038 (13)	0.0234 (12)	−0.0081 (14)
C5	0.0535 (14)	0.0480 (14)	0.0746 (18)	0.0065 (12)	0.0166 (13)	−0.0054 (13)
C6	0.0509 (13)	0.0388 (12)	0.0563 (14)	0.0039 (11)	0.0143 (11)	0.0065 (11)
C7	0.0443 (12)	0.0307 (11)	0.0417 (12)	0.0011 (9)	0.0079 (9)	0.0011 (9)
C8	0.0416 (12)	0.0382 (12)	0.0445 (13)	0.0003 (9)	0.0101 (10)	−0.0008 (9)
C9	0.0507 (13)	0.0488 (13)	0.0507 (14)	−0.0040 (11)	0.0089 (11)	−0.0080 (11)
C10	0.0479 (13)	0.0331 (11)	0.0480 (14)	−0.0003 (10)	0.0112 (11)	0.0005 (10)
C11	0.0555 (15)	0.0733 (18)	0.0513 (15)	−0.0072 (14)	0.0018 (11)	−0.0002 (14)
C12	0.082 (2)	0.080 (2)	0.080 (2)	−0.0108 (18)	0.0123 (17)	−0.0250 (18)

Geometric parameters (Å, °)

Cl1—C9	1.784 (2)	C11—C12	1.492 (5)
S1—C10	1.763 (2)	C2—H2	0.9300
S1—C11	1.809 (3)	C3—H3	0.9300
O1—C8	1.424 (3)	C4—H4	0.9300
O2—C10	1.207 (3)	C5—H5	0.9300
O1—H1O	0.77 (3)	C6—H6	0.9300
C1—C2	1.382 (3)	C7—H7	0.9800
C1—C7	1.515 (3)	C8—H8	0.9800
C1—C6	1.392 (3)	C9—H9A	0.9700
C2—C3	1.388 (3)	C9—H9B	0.9700
C3—C4	1.362 (4)	C11—H11A	0.9700
C4—C5	1.368 (4)	C11—H11B	0.9700
C5—C6	1.383 (3)	C12—H12A	0.9600
C7—C8	1.539 (3)	C12—H12B	0.9600
C7—C10	1.525 (3)	C12—H12C	0.9600
C8—C9	1.513 (3)		
C10—S1—C11	100.71 (11)	C4—C5—H5	120.00
C8—O1—H1O	107 (2)	C6—C5—H5	120.00
C2—C1—C6	118.4 (2)	C1—C6—H6	120.00
C6—C1—C7	122.36 (19)	C5—C6—H6	120.00

C2—C1—C7	119.20 (19)	C1—C7—H7	105.00
C1—C2—C3	120.7 (2)	C8—C7—H7	105.00
C2—C3—C4	120.2 (3)	C10—C7—H7	105.00
C3—C4—C5	120.0 (2)	O1—C8—H8	109.00
C4—C5—C6	120.6 (2)	C7—C8—H8	109.00
C1—C6—C5	120.1 (2)	C9—C8—H8	109.00
C1—C7—C8	114.62 (18)	Cl1—C9—H9A	109.00
C8—C7—C10	109.69 (17)	Cl1—C9—H9B	109.00
C1—C7—C10	115.43 (17)	C8—C9—H9A	109.00
O1—C8—C7	108.37 (17)	C8—C9—H9B	109.00
C7—C8—C9	113.25 (18)	H9A—C9—H9B	108.00
O1—C8—C9	108.41 (18)	S1—C11—H11A	109.00
Cl1—C9—C8	111.59 (16)	S1—C11—H11B	109.00
S1—C10—O2	121.80 (19)	C12—C11—H11A	109.00
O2—C10—C7	123.0 (2)	C12—C11—H11B	109.00
S1—C10—C7	115.10 (16)	H11A—C11—H11B	108.00
S1—C11—C12	112.7 (2)	C11—C12—H12A	109.00
C1—C2—H2	120.00	C11—C12—H12B	110.00
C3—C2—H2	120.00	C11—C12—H12C	109.00
C2—C3—H3	120.00	H12A—C12—H12B	109.00
C4—C3—H3	120.00	H12A—C12—H12C	109.00
C3—C4—H4	120.00	H12B—C12—H12C	109.00
C5—C4—H4	120.00		
C11—S1—C10—O2	6.8 (2)	C3—C4—C5—C6	−0.3 (4)
C11—S1—C10—C7	−168.92 (18)	C4—C5—C6—C1	0.3 (4)
C10—S1—C11—C12	89.0 (2)	C1—C7—C8—O1	−67.6 (2)
C6—C1—C2—C3	0.1 (3)	C1—C7—C8—C9	52.8 (2)
C7—C1—C2—C3	178.3 (2)	C10—C7—C8—O1	64.2 (2)
C2—C1—C6—C5	−0.2 (3)	C10—C7—C8—C9	−175.52 (18)
C7—C1—C6—C5	−178.4 (2)	C1—C7—C10—S1	−22.2 (2)
C2—C1—C7—C8	−111.5 (2)	C1—C7—C10—O2	162.2 (2)
C2—C1—C7—C10	119.6 (2)	C8—C7—C10—S1	−153.47 (15)
C6—C1—C7—C8	66.7 (3)	C8—C7—C10—O2	30.9 (3)
C6—C1—C7—C10	−62.2 (3)	O1—C8—C9—Cl1	−175.09 (15)
C1—C2—C3—C4	−0.1 (4)	C7—C8—C9—Cl1	64.6 (2)
C2—C3—C4—C5	0.2 (4)		

Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1O···O2^{i}	0.77 (3)	2.06 (3)	2.832 (3)	176 (3)
C6—H6···O1	0.93	2.59	3.052 (3)	111
C7—H7···Cl1	0.98	2.80	3.233 (2)	108
C7—H7···O1^{ii}	0.98	2.59	3.393 (3)	139
C11—H11B···O2	0.97	2.40	2.841 (3)	107

Symmetry codes: (i) −*x*+1, −*y*+1, −*z*+1; (ii) *x*, *y*−1, *z*.

(III)

Crystal data

$C_{19}H_{22}O_4S_2$	F_{000} = 800
M_r = 378.49	D_x = 1.287 Mg m^{-3}
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation λ = 0.71073 Å
Hall symbol: -P 2yn	Cell parameters from 8000 reflections
a = 5.7792 (5) Å	θ = 2.0–25.9°
b = 20.0506 (14) Å	μ = 0.29 mm^{-1}
c = 17.0331 (16) Å	T = 153 (2) K
β = 98.151 (11)°	Plate, colourless
V = 1953.8 (3) Å^3	0.40 × 0.40 × 0.20 mm
Z = 4	

Data collection

STOE IPDS diffractometer	3546 independent reflections
Radiation source: fine-focus sealed tube	2461 reflections with $I > 2\sigma(I)$
Monochromator: graphite	R_{int} = 0.059
Detector resolution: 0.81Å pixels mm^{-1}	θ_{max} = 25.9°
T = 153(2) K	θ_{min} = 2.0°
phi oscillation scans	$h = -7 \rightarrow 7$
Absorption correction: none	$k = -24 \rightarrow 24$
16245 measured reflections	$l = -20 \rightarrow 20$

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)]$ = 0.035	H-atom parameters constrained
$wR(F^2)$ = 0.087	$w = 1/[\sigma^2(F_o^2) + (0.0556P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
S = 0.91	$(\Delta/\sigma)_{max}$ = 0.001
3546 reflections	$\Delta\rho_{max}$ = 0.31 e Å^{-3}
229 parameters	$\Delta\rho_{min}$ = −0.37 e Å^{-3}
Primary atom site location: structure-invariant direct methods	Extinction correction: none

Special details

Geometry. Bond distances, angles *etc*. have been calculated using the rounded fractional coordinates. All su's are estimated from the variances of the (full) variance-covariance matrix. The cell e.s.d.'s are taken into account in the estimation of distances, angles and torsion angles

Refinement. Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$)

	x	*y*	*z*	U_{iso}*/U_{eq}
S1	0.73279 (11)	1.02202 (2)	0.39427 (3)	0.0443 (2)
S2	0.74375 (9)	0.89906 (2)	0.12561 (3)	0.0293 (1)
O1	1.0337 (2)	0.93690 (6)	0.34781 (8)	0.0345 (5)
O2	0.6377 (2)	0.90896 (6)	0.20573 (7)	0.0260 (4)
O3	0.5524 (3)	0.89859 (7)	0.06297 (7)	0.0403 (5)
O4	0.8985 (3)	0.84326 (6)	0.13506 (8)	0.0409 (5)
C1	0.6593 (3)	0.84717 (8)	0.41423 (10)	0.0225 (5)
C2	0.4830 (3)	0.84742 (10)	0.46223 (11)	0.0319 (6)
C3	0.4943 (4)	0.80380 (11)	0.52563 (12)	0.0407 (7)
C4	0.6775 (4)	0.75989 (10)	0.54203 (11)	0.0356 (7)
C5	0.8550 (4)	0.76013 (9)	0.49556 (11)	0.0316 (6)
C6	0.8459 (3)	0.80349 (8)	0.43186 (11)	0.0277 (6)
C7	0.6428 (3)	0.89399 (8)	0.34345 (10)	0.0231 (5)
C8	0.8333 (3)	0.94702 (8)	0.35808 (10)	0.0247 (6)
C9	0.9935 (5)	1.07284 (11)	0.40025 (14)	0.0536 (9)
C10	0.9988 (6)	1.11344 (14)	0.32597 (16)	0.0764 (13)
C11	0.6667 (3)	0.85662 (8)	0.26693 (10)	0.0252 (5)
C12	0.4840 (4)	0.80297 (10)	0.24621 (12)	0.0395 (7)
C13	0.9034 (3)	0.97292 (8)	0.12181 (10)	0.0274 (6)
C14	1.1256 (4)	0.97676 (10)	0.16348 (13)	0.0369 (7)
C15	1.2508 (4)	1.03548 (10)	0.16218 (13)	0.0399 (7)
C16	1.1568 (4)	1.09051 (10)	0.11940 (12)	0.0351 (7)
C17	0.9353 (4)	1.08466 (10)	0.07635 (12)	0.0391 (7)
C18	0.8069 (4)	1.02677 (9)	0.07742 (12)	0.0352 (7)
C19	1.2934 (4)	1.15439 (11)	0.12021 (15)	0.0494 (8)
H2	0.35530	0.87750	0.45140	0.0380*
H3	0.37390	0.80420	0.55820	0.0490*
H4	0.68190	0.72950	0.58510	0.0430*
H5	0.98350	0.73050	0.50730	0.0380*
H6	0.96820	0.80330	0.40000	0.0330*
H7	0.48700	0.91660	0.33710	0.0280*
H9A	1.13300	1.04370	0.40880	0.0640*
H9B	1.00020	1.10320	0.44630	0.0640*
H10A	0.98750	1.08360	0.28000	0.1150*

H10B	0.86670	1.14460	0.31930	0.1150*
H10C	1.14550	1.13850	0.33040	0.1150*
H11	0.82650	0.83670	0.27050	0.0300*
H12A	0.32770	0.82260	0.24340	0.0590*
H12B	0.50370	0.76820	0.28700	0.0590*
H12C	0.50230	0.78340	0.19470	0.0590*
H14	1.19220	0.93950	0.19280	0.0440*
H15	1.40370	1.03820	0.19100	0.0480*
H17	0.87050	1.12140	0.04540	0.0470*
H18	0.65450	1.02380	0.04820	0.0420*
H19A	1.32470	1.17150	0.17460	0.0740*
H19B	1.20270	1.18740	0.08630	0.0740*
H19C	1.44170	1.14590	0.10030	0.0740*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0562 (4)	0.0276 (3)	0.0510 (3)	−0.0002 (2)	0.0146 (3)	−0.0098 (2)
S2	0.0371 (3)	0.0294 (2)	0.0222 (2)	0.0028 (2)	0.0073 (2)	−0.0014 (2)
O1	0.0260 (9)	0.0338 (7)	0.0428 (8)	−0.0026 (6)	0.0015 (7)	0.0008 (6)
O2	0.0299 (8)	0.0281 (6)	0.0207 (6)	0.0066 (5)	0.0063 (6)	0.0041 (5)
O3	0.0508 (10)	0.0449 (8)	0.0225 (6)	−0.0071 (7)	−0.0037 (7)	−0.0026 (6)
O4	0.0533 (10)	0.0314 (7)	0.0418 (8)	0.0110 (6)	0.0203 (8)	−0.0018 (6)
C1	0.0241 (11)	0.0223 (8)	0.0209 (9)	−0.0024 (7)	0.0021 (8)	−0.0004 (7)
C2	0.0228 (12)	0.0435 (11)	0.0296 (10)	0.0022 (8)	0.0049 (9)	0.0040 (8)
C3	0.0302 (13)	0.0633 (14)	0.0298 (11)	−0.0076 (10)	0.0085 (10)	0.0094 (9)
C4	0.0384 (14)	0.0405 (11)	0.0260 (10)	−0.0132 (9)	−0.0017 (10)	0.0087 (8)
C5	0.0346 (12)	0.0270 (9)	0.0314 (10)	0.0025 (8)	−0.0015 (9)	0.0033 (8)
C6	0.0305 (12)	0.0278 (9)	0.0254 (9)	0.0026 (7)	0.0056 (9)	0.0012 (7)
C7	0.0212 (10)	0.0252 (8)	0.0223 (8)	0.0038 (7)	0.0013 (8)	0.0013 (7)
C8	0.0300 (12)	0.0252 (9)	0.0180 (8)	−0.0005 (7)	0.0002 (8)	0.0039 (7)
C9	0.0726 (19)	0.0324 (11)	0.0544 (14)	−0.0167 (11)	0.0042 (13)	−0.0118 (10)
C10	0.113 (3)	0.0654 (16)	0.0545 (16)	−0.0431 (17)	0.0250 (17)	−0.0127 (13)
C11	0.0296 (11)	0.0230 (8)	0.0217 (9)	0.0025 (7)	−0.0004 (8)	0.0039 (7)
C12	0.0502 (15)	0.0350 (10)	0.0308 (11)	−0.0124 (9)	−0.0028 (10)	0.0006 (8)
C13	0.0300 (12)	0.0316 (9)	0.0224 (9)	0.0044 (8)	0.0099 (9)	0.0019 (7)
C14	0.0320 (14)	0.0371 (11)	0.0422 (11)	0.0078 (8)	0.0075 (11)	0.0122 (9)
C15	0.0271 (13)	0.0477 (12)	0.0447 (12)	0.0003 (9)	0.0048 (10)	0.0073 (10)
C16	0.0379 (14)	0.0370 (11)	0.0340 (10)	0.0016 (8)	0.0173 (10)	0.0021 (8)
C17	0.0464 (15)	0.0351 (10)	0.0366 (11)	0.0060 (9)	0.0089 (11)	0.0127 (9)
C18	0.0357 (13)	0.0413 (11)	0.0279 (10)	0.0038 (9)	0.0021 (9)	0.0065 (8)
C19	0.0523 (16)	0.0427 (12)	0.0570 (15)	−0.0058 (10)	0.0207 (13)	0.0042 (10)

Geometric parameters (Å, °)

S1—C8	1.7551 (17)	C16—C19	1.504 (3)
S1—C9	1.810 (3)	C17—C18	1.379 (3)
S2—O2	1.5857 (13)	C2—H2	0.9500
S2—O3	1.4237 (16)	C3—H3	0.9500

S2—O4	1.4271 (15)	C4—H4	0.9500
S2—C13	1.7509 (17)	C5—H5	0.9500
O1—C8	1.213 (2)	C6—H6	0.9500
O2—C11	1.472 (2)	C7—H7	1.0000
C1—C2	1.394 (2)	C9—H9A	0.9900
C1—C6	1.389 (2)	C9—H9B	0.9900
C1—C7	1.520 (2)	C10—H10A	0.9800
C2—C3	1.384 (3)	C10—H10B	0.9800
C3—C4	1.375 (3)	C10—H10C	0.9800
C4—C5	1.382 (3)	C11—H11	1.0000
C5—C6	1.386 (3)	C12—H12A	0.9800
C7—C8	1.525 (2)	C12—H12B	0.9800
C7—C11	1.527 (2)	C12—H12C	0.9800
C9—C10	1.508 (4)	C14—H14	0.9500
C11—C12	1.514 (3)	C15—H15	0.9500
C13—C14	1.379 (3)	C17—H17	0.9500
C13—C18	1.389 (3)	C18—H18	0.9500
C14—C15	1.384 (3)	C19—H19A	0.9800
C15—C16	1.390 (3)	C19—H19B	0.9800
C16—C17	1.387 (3)	C19—H19C	0.9800
C8—S1—C9	100.83 (10)	C4—C5—H5	120.00
O2—S2—O3	106.97 (8)	C6—C5—H5	120.00
O2—S2—O4	108.27 (8)	C1—C6—H6	120.00
O2—S2—C13	101.30 (7)	C5—C6—H6	120.00
O3—S2—O4	119.15 (9)	C1—C7—H7	109.00
O3—S2—C13	109.59 (8)	C8—C7—H7	109.00
O4—S2—C13	110.01 (9)	C11—C7—H7	109.00
S2—O2—C11	120.08 (10)	S1—C9—H9A	109.00
C2—C1—C6	119.03 (16)	S1—C9—H9B	109.00
C2—C1—C7	119.61 (15)	C10—C9—H9A	109.00
C6—C1—C7	121.36 (16)	C10—C9—H9B	109.00
C1—C2—C3	119.86 (18)	H9A—C9—H9B	108.00
C2—C3—C4	120.9 (2)	C9—C10—H10A	109.00
C3—C4—C5	119.62 (18)	C9—C10—H10B	109.00
C4—C5—C6	120.13 (19)	C9—C10—H10C	109.00
C1—C6—C5	120.48 (17)	H10A—C10—H10B	109.00
C1—C7—C8	109.77 (14)	H10A—C10—H10C	109.00
C1—C7—C11	111.77 (13)	H10B—C10—H10C	109.00
C8—C7—C11	109.33 (14)	O2—C11—H11	110.00
S1—C8—O1	124.36 (13)	C7—C11—H11	110.00
S1—C8—C7	112.80 (12)	C12—C11—H11	110.00
O1—C8—C7	122.80 (15)	C11—C12—H12A	109.00
S1—C9—C10	111.9 (2)	C11—C12—H12B	109.00
O2—C11—C7	103.87 (12)	C11—C12—H12C	109.00
O2—C11—C12	109.63 (14)	H12A—C12—H12B	110.00
C7—C11—C12	113.79 (15)	H12A—C12—H12C	109.00
S2—C13—C14	119.05 (14)	H12B—C12—H12C	109.00
S2—C13—C18	120.31 (14)	C13—C14—H14	120.00
C14—C13—C18	120.65 (17)	C15—C14—H14	120.00

C13—C14—C15	119.36 (19)	C14—C15—H15	119.00
C14—C15—C16	121.2 (2)	C16—C15—H15	119.00
C15—C16—C17	118.22 (19)	C16—C17—H17	119.00
C15—C16—C19	120.4 (2)	C18—C17—H17	119.00
C17—C16—C19	121.39 (19)	C13—C18—H18	120.00
C16—C17—C18	121.48 (19)	C17—C18—H18	120.00
C13—C18—C17	119.1 (2)	C16—C19—H19A	109.00
C1—C2—H2	120.00	C16—C19—H19B	109.00
C3—C2—H2	120.00	C16—C19—H19C	109.00
C2—C3—H3	120.00	H19A—C19—H19B	109.00
C4—C3—H3	120.00	H19A—C19—H19C	110.00
C3—C4—H4	120.00	H19B—C19—H19C	110.00
C5—C4—H4	120.00		
C9—S1—C8—O1	4.56 (18)	C1—C2—C3—C4	−0.1 (3)
C9—S1—C8—C7	−177.61 (13)	C2—C3—C4—C5	1.2 (3)
C8—S1—C9—C10	93.19 (19)	C3—C4—C5—C6	−1.3 (3)
O3—S2—O2—C11	117.18 (12)	C4—C5—C6—C1	0.2 (3)
O4—S2—O2—C11	−12.39 (14)	C1—C7—C8—S1	−97.03 (14)
C13—S2—O2—C11	−128.08 (12)	C1—C7—C8—O1	80.8 (2)
O2—S2—C13—C14	83.32 (16)	C11—C7—C8—S1	140.03 (12)
O2—S2—C13—C18	−96.65 (16)	C11—C7—C8—O1	−42.1 (2)
O3—S2—C13—C14	−163.91 (16)	C1—C7—C11—O2	177.94 (13)
O3—S2—C13—C18	16.13 (18)	C1—C7—C11—C12	58.8 (2)
O4—S2—C13—C14	−31.08 (18)	C8—C7—C11—O2	−60.32 (16)
O4—S2—C13—C18	148.96 (15)	C8—C7—C11—C12	−179.47 (15)
S2—O2—C11—C7	156.24 (11)	S2—C13—C14—C15	−178.57 (16)
S2—O2—C11—C12	−81.82 (16)	C18—C13—C14—C15	1.4 (3)
C6—C1—C2—C3	−1.0 (3)	S2—C13—C18—C17	179.12 (16)
C7—C1—C2—C3	178.47 (17)	C14—C13—C18—C17	−0.9 (3)
C2—C1—C6—C5	0.9 (3)	C13—C14—C15—C16	−0.2 (3)
C7—C1—C6—C5	−178.50 (16)	C14—C15—C16—C17	−1.4 (3)
C2—C1—C7—C8	111.90 (18)	C14—C15—C16—C19	178.6 (2)
C2—C1—C7—C11	−126.61 (17)	C15—C16—C17—C18	2.0 (3)
C6—C1—C7—C8	−68.7 (2)	C19—C16—C17—C18	−178.0 (2)
C6—C1—C7—C11	52.8 (2)	C16—C17—C18—C13	−0.9 (3)

Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C4—H4···O4^{i}	0.95	2.44	3.180 (3)	135
C9—H9A···O1	0.99	2.41	2.888 (3)	109
C11—H11···O4	1.00	2.41	2.787 (2)	102
C18—H18···O3	0.95	2.60	2.954 (2)	102

Symmetry codes: (i) *x*−1/2, −*y*+3/2, *z*+1/2.

4.2. 4-Azido-3-hydroxy-3-(2-nitro-phenyl)-butyric acid methyl ester

Submitted to *Acta Cryst. E*

4-Azido-3-hydroxy-3-(2-nitro-phenyl)-butyric acid methyl ester

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Abstract

In the title compound, $C_{11}H_{12}N_4O_5$, the hydroxyl group is involved in bifurcated hydrogen bonds. The first is an intramolecular O—H···O hydrogen bond involving the ester substituent carbonyl O-atom. The conformation of the intramolecular hydrogen bonded chelate ring is boat-like. The second is an intermolecular O—H···N hydrogen bond involving the first N-atom of the azide group of a symmetry related molecule. This leads to the formation of a polmer chain running extending in the c direction. The best plane throught the nitro substituent on the benzene ring is inclined to the best plane throught the benzene ring by 85.8 (2)°, presumably to avoid steric interactions with the *ortho* substituents.

Related literature

For related literature, see: Alazard *et al.* (1996); Baudoin *et al.* (2002); Bonneau *et al.* (2007); Decor *et al.* (2006); Dupont *et al.* (1999, 2000); Mukaiyama *et al.* (1974); Vallat (2004).

Computing details

Data collection: *EXPOSE* (Stoe & Cie, 2000); cell refinement: *CELL* (Stoe & Cie, 2000); data reduction: *INTEGRATE* (Stoe & Cie, 2000); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: ORETP3 (Farugia, 1997), Mercury (Macrae, 2006) & *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

(I)

Crystal data

$C_{11}H_{12}N_4O_5$	$V = 1272.4\ (2)$ Å^3
$M_r = 280.25$	$Z = 4$
Monoclinic, $P2_1/n$	Mo $K\alpha$
$a = 9.4772\ (11)$ Å	$\mu = 0.12$ mm^{-1}
$b = 14.0710\ (12)$ Å	$T = 153\ (2)$ K
$c = 10.1861\ (12)$ Å	$0.40 \times 0.30 \times 0.30$ mm

β = 110.496 (13)°

Data collection

STOE IPDS diffractometer	2451 independent reflections
Absorption correction: none	1587 reflections with $I > 2\sigma(I)$
8743 measured reflections	$R_{int} = 0.074$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.036$	230 parameters
$wR(F^2) = 0.088$	All H-atom parameters refined
$S = 0.87$	$\Delta\rho_{max} = 0.23$ e Å^{-3}
2451 reflections	$\Delta\rho_{min} = -0.21$ e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H3O···N2^{i}	0.825 (19)	2.27 (2)	2.9193 (18)	135.6 (18)
C10—H10B···O4^{ii}	0.95 (2)	2.557 (19)	3.350 (2)	141.0 (15)
C11—H11B···O1^{iii}	0.95 (3)	2.57 (2)	3.268 (3)	130.9 (16)

Symmetry codes: (i) $x+1/2, -y+1/2, z+1/2$; (ii) $x-1/2, -y+1/2, z-1/2$; (iii) $x-1/2, -y+1/2, z+1/2$.

Acknowledgements

This work was partially financed by the Swiss National Science Foundation.

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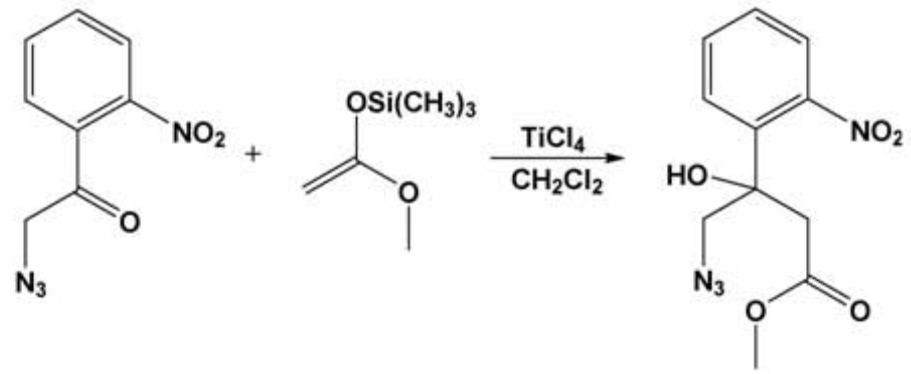

Scheme

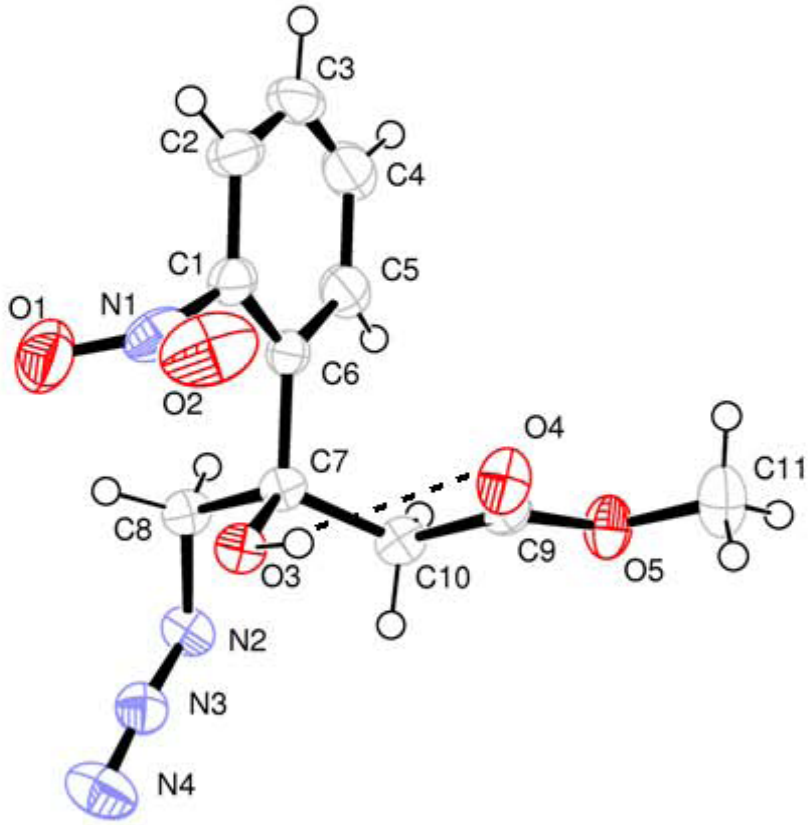

Fig. 1. Molecular structure of compound (I), showing the atom labelling scheme and displacement ellipsoids drawn at the 50% probability level. The intra-molecular O-H...O hydrogen bond is shown as a dashed line.

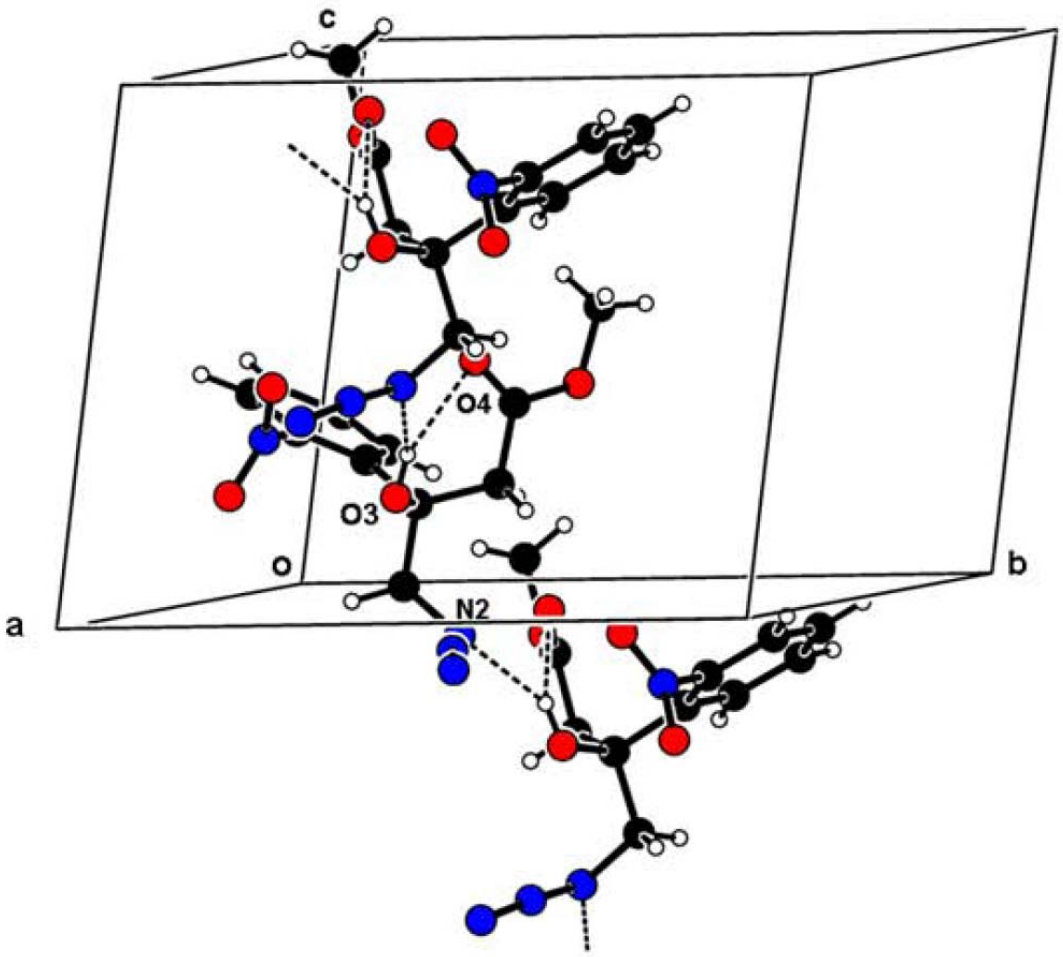

Fig. 2. Crystal packing of compound (1), showing the formation of the hydrogen bonded (dashed lines) polymer extending in the c direction.

supplementary materials

4-Azido-3-hydroxy-3-(2-nitro-phenyl)-butyric acid methyl ester

Olivier Vallat[a], Ana-Maria Buciumas[a], Reinhard Neier[a] and Helen Stoeckli-Evans[b]

Comment

Rhazinilam is a natural product with antitumoral properties. It induces in vitro spiralization of microtubules [vinblastin effect] and inhibits the disassembly of these microtubules [paclitaxel effect](Bonneau *et al.*, 2007). It shows significant *in vitro* cytotoxicity towards various cancer cells, but it is not active *in vivo*. Several groups have been interested in synthesizing and studying the structure-activity relationship of rhazinilam analogues (Decor *et al.*, 2006; Baudoin *et al.*, 2002; Ghosez *et al.*, 2002; Rubia *et al.*, 2001; Dupont *et al.*, 2000; Dupont *et al.*, 1999; Alazard *et al.*, 1996).

In the synthesis of Rhazinilam analogues developed in our group the Mukaiyama reaction, a versatile synthetic tool in organic chemistry, is the key step reaction (Mukaiyama *et al.*, 1974). In the third generation of our retrosynthetic approach (1-methoxyvinyloxy)trimethysilane has been used as a nucleophile, 2-azido-1-(2-nitrophenyl)ethanone as an electrophile and $TiCl_4$ as a Lewis acid, to synthesize the title compound hydroxyester, (I), in high yield (Scheme). This hydroxyester is a suitable precursor for the formation of the pyrrolinone required for the next step in the synthesis of the Rhazinilam analogues (Vallat, 2004; Vallat *et al.*, 2008).

The molecular structure of the title compound (I) is illustrated in Fig. 1, and selected bond distances and angles are given in Table 1. There is an intramolecular hydrogen bond in the molecule involving the hydroxyl substituent (O3) and the ester carbonyl O-atom, O4 (Table 2). The conformation of the resulting hydrogen bonded chelate ring is boat-like. The thermal motion of the nitro group is larger than that of neighbouring atoms. The best plane through this group is inclined to the best plane through the benzene ring by 85.8 (2)°, presumably to avoid steric interactions with the *ortho* substituents.

In the crystal structure of I symmetry related molecules are linked by O—H···N hydrogen bonds involving the hydroxyl substiuent (O3) and the first N-atom of the azide group (Table 2). This leads to the formation of a polymer chain extending in the c direction. (Fig. 2). There are also two weak intermolecular C—H···O interactions involving atoms O1 and O4 and the hydrogen atoms of the butyric acid moiety (Table 2).

Experimental

Under an atmosphere of Ar, (1-methoxyvinyloxy)trimethylsilane (1.06 g, 7.3 mmol) was dissolved in dry CH_2Cl_2 (15 ml) and the temperature lowered to −30 °C. 2-Azido-1- (2-nitrophenyl)ethanone (0.5 g, 2.4 mmol) dissolved in drx CH_2Cl_2 (6 ml) was added to the reaction mixture dropwise. A solution of $TiCl_4$ (0.13 ml, 1.2 mmol), freshly distilled over polyvinylpyridine, in dry CH_2Cl_2 (4 ml) was added slowly. The solution became immediately red and then dark red. The reaction mixture was stirred at −30°C for 15 min and then at −15°C for 30 min. The cold mixture was then poured into an aqueous solution of 2 N of NaOH (2.4 ml) and extracted with chloroform. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash chromatography (silica gel, CH_2Cl_2) followed by crystallization (ether/hexane) gave a white solid (Yield 76%). Colourless plate-like crystals, suitable for X-ray analysis, were obtained by slow evaporation of a solution in ether/hexane (v:v = 1:1)

Refinement

The H-atoms were located from difference Fourier maps and freely refined: O—H = 0.825 (19) Å, C—H = 0.91 (3) − 1.02 (2) Å.

Figures

Figure 1. Molecular structure of compound I, showing the atom labelling scheme and the displacement ellipsoids drawn at the 50% probability level. The intra-molecular O—H···O hydrogen bond is shown as a dashed line.
Figure 2. A view along the *a* axis of the crystal packing of compound I, showing the intra- and inter molecular hydrogen bonds as dashed lines (see Table 2 for details).

(I)

Crystal data

$C_{11}H_{12}N_4O_5$	F_{000} = 584
M_r = 280.25	D_x = 1.463 Mg m^{-3}
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation λ = 0.71073 Å
Hall symbol: -P 2yn	Cell parameters from 5300 reflections
a = 9.4772 (11) Å	θ = 2.6–25.8°
b = 14.0710 (12) Å	μ = 0.12 mm^{-1}
c = 10.1861 (12) Å	T = 153 (2) K
β = 110.496 (13)°	Plate, colourless
V = 1272.4 (2) Å^3	0.40 × 0.30 × 0.30 mm
Z = 4	

Data collection

STOE IPDS diffractometer	2451 independent reflections
Radiation source: fine-focus sealed tube	1587 reflections with $I > 2\sigma(I)$
Monochromator: graphite	R_{int} = 0.074
Detector resolution: 0.81Å pixels mm^{-1}	θ_{max} = 25.9°
T = 153(2) K	θ_{min} = 2.5°
phi oscillation scans	h = −11→11
Absorption correction: none	k = −17→17
8743 measured reflections	l = −12→12

Refinement

Refinement on F^2	Hydrogen site location: difference Fourier map
Least-squares matrix: full	All H-atom parameters refined
$R[F^2 > 2\sigma(F^2)]$ = 0.036	$w = 1/[\sigma^2(F_o^2) + (0.0487P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2)$ = 0.088	$(\Delta/\sigma)_{max} < 0.001$

S = 0.87	$\Delta\rho_{max}$ = 0.23 e Å^{-3}
2451 reflections	$\Delta\rho_{min}$ = −0.21 e Å^{-3}
230 parameters	Extinction correction: SHELXL, $Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
Primary atom site location: structure-invariant direct methods	Extinction coefficient: 0.0087 (18)
Secondary atom site location: difference Fourier map	

Special details

Geometry. Bond distances, angles *etc*. have been calculated using the rounded fractional coordinates. All su's are estimated from the variances of the (full) variance-covariance matrix. The cell e.s.d.'s are taken into account in the estimation of distances, angles and torsion angles

Refinement. Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.32528 (17)	−0.00702 (10)	0.18798 (17)	0.0599 (6)
O2	0.39794 (16)	0.06178 (11)	0.39169 (15)	0.0653 (5)
O3	0.20867 (11)	0.19457 (8)	0.17217 (12)	0.0272 (4)
O4	0.13982 (13)	0.26155 (8)	0.41688 (11)	0.0370 (4)
O5	−0.07815 (12)	0.34053 (9)	0.35528 (11)	0.0372 (4)
N1	0.30233 (17)	0.02628 (11)	0.28967 (16)	0.0424 (5)
N2	−0.03288 (14)	0.22705 (10)	−0.10334 (13)	0.0321 (4)
N3	0.08103 (17)	0.25861 (10)	−0.12165 (13)	0.0340 (5)
N4	0.17267 (19)	0.29547 (14)	−0.15016 (17)	0.0535 (6)
C1	0.1474 (2)	0.01792 (12)	0.29231 (16)	0.0330 (5)
C2	0.1235 (3)	−0.06299 (14)	0.35997 (18)	0.0472 (7)
C3	−0.0179 (3)	−0.07913 (17)	0.3639 (2)	0.0574 (9)
C4	−0.1334 (3)	−0.01579 (16)	0.3016 (2)	0.0524 (8)
C5	−0.1057 (2)	0.06436 (14)	0.23568 (19)	0.0391 (6)
C6	0.03622 (18)	0.08457 (11)	0.22890 (15)	0.0277 (5)
C7	0.05471 (16)	0.17238 (11)	0.14778 (15)	0.0253 (5)
C8	−0.01067 (19)	0.14495 (13)	−0.00855 (16)	0.0293 (5)
C9	0.02297 (16)	0.28584 (12)	0.32851 (16)	0.0263 (5)
C10	−0.02665 (18)	0.25954 (13)	0.17665 (17)	0.0293 (5)
C11	−0.0434 (3)	0.36959 (19)	0.4988 (2)	0.0489 (8)
H2	0.210 (2)	−0.1090 (17)	0.404 (2)	0.062 (6)*
H3	−0.039 (3)	−0.1301 (18)	0.409 (2)	0.071 (7)*
H3O	0.242 (2)	0.2153 (14)	0.253 (2)	0.043 (6)*
H4	−0.235 (3)	−0.0267 (16)	0.307 (2)	0.064 (6)*
H5	−0.183 (2)	0.1080 (15)	0.186 (2)	0.053 (6)*
H8A	0.0553 (19)	0.0951 (13)	−0.0298 (16)	0.032 (4)*

H8B	−0.113 (2)	0.1209 (12)	−0.0262 (17)	0.035 (4)*
H10A	−0.0016 (19)	0.3118 (13)	0.1284 (17)	0.037 (5)*
H10B	−0.133 (2)	0.2515 (14)	0.1442 (19)	0.047 (5)*
H11A	−0.035 (3)	0.315 (2)	0.560 (3)	0.084 (8)*
H11B	−0.128 (3)	0.4060 (17)	0.497 (2)	0.067 (7)*
H11C	0.044 (3)	0.4065 (17)	0.525 (2)	0.062 (6)*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0611 (9)	0.0464 (10)	0.0834 (11)	0.0058 (7)	0.0395 (8)	−0.0098 (8)
O2	0.0494 (8)	0.0595 (10)	0.0596 (9)	0.0016 (7)	−0.0151 (7)	0.0141 (8)
O3	0.0215 (6)	0.0308 (7)	0.0259 (6)	−0.0016 (5)	0.0039 (4)	−0.0006 (5)
O4	0.0298 (6)	0.0426 (8)	0.0307 (6)	0.0080 (5)	0.0006 (5)	−0.0054 (5)
O5	0.0262 (6)	0.0445 (8)	0.0401 (7)	0.0067 (5)	0.0108 (5)	−0.0081 (5)
N1	0.0440 (9)	0.0276 (9)	0.0482 (10)	0.0104 (7)	0.0069 (8)	0.0091 (7)
N2	0.0236 (7)	0.0413 (9)	0.0279 (7)	−0.0005 (6)	0.0048 (5)	0.0044 (6)
N3	0.0352 (8)	0.0377 (9)	0.0257 (7)	0.0053 (7)	0.0063 (6)	0.0049 (6)
N4	0.0431 (10)	0.0645 (12)	0.0571 (10)	−0.0023 (9)	0.0228 (8)	0.0169 (9)
C1	0.0452 (10)	0.0269 (10)	0.0264 (8)	−0.0012 (8)	0.0118 (7)	−0.0025 (7)
C2	0.0829 (15)	0.0269 (11)	0.0336 (10)	−0.0010 (11)	0.0226 (10)	0.0010 (8)
C3	0.109 (2)	0.0334 (13)	0.0435 (12)	−0.0247 (13)	0.0437 (13)	−0.0082 (9)
C4	0.0721 (15)	0.0475 (14)	0.0494 (12)	−0.0280 (12)	0.0360 (11)	−0.0173 (10)
C5	0.0432 (10)	0.0397 (11)	0.0370 (9)	−0.0133 (9)	0.0174 (8)	−0.0097 (9)
C6	0.0341 (9)	0.0255 (9)	0.0229 (7)	−0.0046 (7)	0.0091 (7)	−0.0049 (6)
C7	0.0201 (7)	0.0260 (9)	0.0269 (8)	−0.0015 (6)	0.0045 (6)	0.0003 (6)
C8	0.0272 (9)	0.0297 (10)	0.0272 (8)	−0.0021 (7)	0.0047 (7)	−0.0003 (7)
C9	0.0230 (8)	0.0223 (9)	0.0322 (8)	−0.0018 (7)	0.0080 (7)	0.0002 (7)
C10	0.0226 (8)	0.0299 (10)	0.0304 (9)	0.0017 (7)	0.0032 (7)	0.0012 (7)
C11	0.0456 (12)	0.0569 (15)	0.0476 (12)	0.0028 (11)	0.0207 (10)	−0.0157 (11)

Geometric parameters (Å, °)

O1—N1	1.224 (2)	C5—C6	1.400 (3)
O2—N1	1.221 (2)	C6—C7	1.530 (2)
O3—C7	1.426 (2)	C7—C10	1.531 (2)
O4—C9	1.206 (2)	C7—C8	1.542 (2)
O5—C9	1.330 (2)	C9—C10	1.497 (2)
O5—C11	1.441 (2)	C2—H2	1.02 (2)
O3—H3O	0.825 (19)	C3—H3	0.91 (2)
N1—C1	1.483 (3)	C4—H4	1.00 (3)
N2—C8	1.473 (2)	C5—H5	0.95 (2)
N2—N3	1.240 (2)	C8—H8A	1.012 (19)
N3—N4	1.133 (2)	C8—H8B	0.983 (19)
C1—C6	1.389 (2)	C10—H10A	0.959 (18)
C1—C2	1.390 (3)	C10—H10B	0.95 (2)
C2—C3	1.374 (4)	C11—H11A	0.98 (3)
C3—C4	1.382 (4)	C11—H11B	0.95 (3)
C4—C5	1.384 (3)	C11—H11C	0.93 (3)

C9—O5—C11	116.57 (15)	O4—C9—C10	125.11 (15)
C7—O3—H3O	105.2 (14)	C7—C10—C9	113.54 (14)
O1—N1—O2	125.32 (18)	C1—C2—H2	119.6 (12)
O2—N1—C1	117.49 (15)	C3—C2—H2	121.7 (12)
O1—N1—C1	117.11 (15)	C2—C3—H3	122.3 (18)
N3—N2—C8	116.57 (14)	C4—C3—H3	117.5 (18)
N2—N3—N4	171.07 (18)	C3—C4—H4	120.1 (13)
N1—C1—C6	122.19 (15)	C5—C4—H4	120.3 (13)
C2—C1—C6	123.7 (2)	C4—C5—H5	122.8 (13)
N1—C1—C2	114.10 (18)	C6—C5—H5	114.6 (12)
C1—C2—C3	118.7 (2)	N2—C8—H8A	111.1 (10)
C2—C3—C4	120.3 (2)	N2—C8—H8B	104.2 (10)
C3—C4—C5	119.6 (3)	C7—C8—H8A	109.8 (9)
C4—C5—C6	122.56 (19)	C7—C8—H8B	106.8 (10)
C1—C6—C7	125.77 (16)	H8A—C8—H8B	111.5 (15)
C5—C6—C7	118.97 (15)	C7—C10—H10A	106.5 (11)
C1—C6—C5	115.17 (16)	C7—C10—H10B	112.4 (12)
O3—C7—C6	112.72 (13)	C9—C10—H10A	107.2 (10)
O3—C7—C10	110.15 (13)	C9—C10—H10B	107.4 (11)
C6—C7—C8	105.96 (13)	H10A—C10—H10B	109.6 (16)
O3—C7—C8	104.56 (13)	O5—C11—H11A	111.3 (17)
C8—C7—C10	110.58 (13)	O5—C11—H11B	104.1 (12)
C6—C7—C10	112.49 (13)	O5—C11—H11C	108.2 (13)
N2—C8—C7	113.22 (14)	H11A—C11—H11B	109 (2)
O4—C9—O5	123.38 (14)	H11A—C11—H11C	113 (2)
O5—C9—C10	111.52 (14)	H11B—C11—H11C	111 (2)
C11—O5—C9—O4	−1.0 (3)	C4—C5—C6—C1	0.5 (3)
C11—O5—C9—C10	179.32 (17)	C4—C5—C6—C7	177.10 (16)
O1—N1—C1—C2	91.99 (19)	C1—C6—C7—O3	−15.3 (2)
O1—N1—C1—C6	−86.4 (2)	C1—C6—C7—C8	98.52 (18)
O2—N1—C1—C2	−84.7 (2)	C1—C6—C7—C10	−140.54 (16)
O2—N1—C1—C6	96.86 (19)	C5—C6—C7—O3	168.49 (14)
N3—N2—C8—C7	78.29 (18)	C5—C6—C7—C8	−77.74 (18)
N1—C1—C2—C3	−177.75 (16)	C5—C6—C7—C10	43.21 (19)
C6—C1—C2—C3	0.6 (3)	O3—C7—C8—N2	−73.41 (17)
N1—C1—C6—C5	177.43 (15)	C6—C7—C8—N2	167.29 (14)
N1—C1—C6—C7	1.1 (2)	C10—C7—C8—N2	45.12 (19)
C2—C1—C6—C5	−0.8 (2)	O3—C7—C10—C9	−69.34 (17)
C2—C1—C6—C7	−177.19 (15)	C6—C7—C10—C9	57.34 (19)
C1—C2—C3—C4	0.0 (3)	C8—C7—C10—C9	175.59 (14)
C2—C3—C4—C5	−0.3 (3)	O4—C9—C10—C7	19.8 (2)
C3—C4—C5—C6	0.1 (3)	O5—C9—C10—C7	−160.54 (14)

Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H3O···O4	0.825 (19)	2.30 (2)	2.9439 (16)	135.5 (18)
O3—H3O···N2^{i}	0.825 (19)	2.27 (2)	2.9193 (18)	135.6 (18)

C10—H10B···O4^{ii}	0.95 (2)	2.557 (19)	3.350 (2)	141.0 (15)
C11—H11B···O1^{iii}	0.95 (3)	2.57 (2)	3.268 (3)	130.9 (16)

Symmetry codes: (i) $x+1/2, -y+1/2, z+1/2$; (ii) $x-1/2, -y+1/2, z-1/2$; (iii) $x-1/2, -y+1/2, z+1/2$.

4.3. 5-Hydroxyalkyl Derivatives of *tert*-Butyl 2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate

Submitted to *Acta Cryst. C*

5-Hydroxyalkyl Derivatives of *tert*-Butyl 2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate

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Abstract

The title compounds, $C_{17}H_{20}N2O_6$ (3), $C_{20}H_{24}N2O_8$ (4) and $C_{13}H_{20}BrNO_4$ (5), are 5-hydroxyalkyl derivatives of *tert*-butyl 2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate. The synthetic procedure used lead to a *syn* configuration of the two newly created chiral centers in all three compounds. The *tert*-butyl-carboxylate unit is orientated in the same manner in all three compounds with respect to the best plane through the 2-oxo-2,5-dihydro-1*H*-pyrrole ring. In compounds 3 and 4 the phenyl ring of the *o*-nitrophenyl substituent is inclined to the best plane through the 2-oxo-2,5-dihydro-1*H*-pyrrole ring by 52.47 (6)° in 3 and 71.25 (11)° in 4. The best plane through the nitro group is inclined to the phenyl ring by 33.95 (13)° in 3 but by only 11.4 (2)° in 4. The hydroxyl substituent at one of the newly created chiral centers is *trans* with respect to the oxo group of the pyrrole ring in 3, synthesized using acetaldehyde. When a larger aldehyde was used, as in the case of compounds 4 and 5, the same arrangement is *cis*. In the crystal structure of compound 3 O—H···O hydrogen bonding leads to an extremely interesting hexagonal arrangement of symmetry related molecules. In the crystal structures of compounds 4 and 5, the hydroxyl groups have bifurcated O—H···O hydrogen bonds, and centrosymmetric hydrogen bonded dimers are formed.

Comment

The natural product (-)-Rhazinilam was first isolated by Linde in 1965 from Melodinus Australis (Baudoin *et al.*, 2004). The tetracyclic structure was determined by a combination of X-ray analysis and chemical studies seven years later (De Silva *et al.*, 1972). Screening experiments have given evidence for interesting pharmacological properties of (-)-rhazinilam due to its interference in the tubuline-microtubule equilibrium during mitosis. (-)-Rhazinilam showed significant *in vitro* cytotoxicity, but, unfortunately, no activity *in vivo* (Baudoin *et al.*, 2004). Several groups have reported their studies on the synthesis of the natural product and its analogues (Decor *et al.*, 2006; Buadoin *et al.*, 2002; Ghosez *et al.*, 2001; Rubio *et al.*, 2001; Dupont *et al.*, 2000; Alazard *et al.*, 1996). Our synthetic strategy was to replace the pyrrole ring by a corresponding pyrrole-2(5*H*)- ring or its protected 2-hydroxy-pyrrole tautomer (Vallat *et al.*, 2008). In order to introduce the missing side chain needed for the formation of ring B of rhazinilam we tested the known aldol reaction of the protected 2-hydroxy-pyrrole with different aldehydes.

The Mukaiyama crossed aldol type reaction was successfull when using the *o*-nitrophenyl substituted hydroxy-pyrrole (1), or the unsubstituted hydroxy-pyrrole (2), and boron trifluoride diethyl ether as catalyst. The relative configuration at the two newly formed chiral centers could not be determined unequivocally using NMR methods. A literature search showed that the Boc-protected TBS-silyloxy-pyrrole (2) had been used in a series of very elegant natural product synthesis (Battistini

et al., 2004; Rassu *et al.*, 2002; Rassu *et al.*, 2003; Barnes *et al.*, 2002; Casiraghi *et al.*, 1992; DeGoey *et al.*, 2002). The diastereoselectivity of the reaction with a series of chiral aldehydes and imines has been carefully studied. The diastereoselectivity of most of the reported processes is *syn*, however the reaction using the imine has been reported to be anti selective (Barnes *et al.*, 2002; DeGoey *et al.*, 2002). The diastereoselectivity of the crossed aldol type reaction using a phenyl substituted pyrrole has not been reported previously to our knowledge. Here we report on the crystal structure analyses of *tert*-Butyl 2-(1-hydroxyethyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-\ carboxylate (3), 2-(1-hydroxyethyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1- carboxylate (4) and 2-(4-bromo-1-hydroxybutyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (5). They were studied in order to determine the diastereoselectivity of the Mukaiyama crossed aldol type reaction.

The molecular structures of compounds 3, 4 and 5, and the crystallographic numbering schemes, are illustrated in Figs. 1, 3 and 5, respectively. The crystal packing in compounds 3, 4 and 5, also showing the hydrogen bonding, are illustrated in Figs. 2, 4, and 6, respectively. The bond lengths and angles (Tables 1, 3 and 5) in all three compounds are in normal ranges (Allen *et al.*, 1987). Details of the hydrogen bonding are given in Tables 2, 4 and 6.

All three compounds contain an oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate unit that has a very similar geometry. In compounds 3 and 4 the *o*-nitrophenyl substituent at C3 is inclined to the best plane through the 2,5-dihydro-1*H*-pyrrole ring by 52.47 (6)° and 71.25 (11)°, respectively. In compound 3 the nitro group is inclined to the phenyl ring by 33.95 (13)°, but in 4 it is inclined to the phenyl ring by only 11.4 (2)%. The orientation of the hydroxyl substituent (at C10, see Figs. 1, 3 and 5) in compound 3 is different to that in compounds 4 and 5. In 3 it lies *trans* with respect to the 2,5-dihydro-1*H*-pyrrole ring, and bond C10—O4 makes an angle of 1.16 (9)° with the best plane through the pyrrole ring. In compounds 4 and 5, however, it is *cis* with respect to the pyrrole ring, and here the C10—O4 bonds is inclined to the best plane through the pyrrole ring by 55.22 (11)° in 4 and 56.08 (11)° in 5.

In the crystal structures of all three compounds O—H···O hydrogen bonds play an important role. In the crystal structure of compound 3 an hexagonal arrangement of symmetry related molecules if formed (Fig. 2 and Table 2). In compounds 4 and 5 the hydroxyl group is involved in bifurcated O—H···O hydrogen bonds and in both crystal structures centrosymmetric hydrogen bonded dimers are formed (Figs. 4 and 6, and Tables 4 and 6, respectively).

The relative stereochemistry of the newly created chiral centers in compound 3 (at C4 and C10) is *R*,*R*. When a larger aldehyde was used, as in the case of compounds 4 and 5, the relative stereochemistry of the newly created chiral centers is *R*,*S*. The synthetic procedure used lead to a *syn* configuration of the two newly created chiral centers in all three compounds, in close analogy to the reports in the literature (battistini *et al.*, 2004; Rassu *et al.*, 2002; Rassu *et al.*, 2003; Casiraghi *et al.*, 1992). Changing the Lewis acid, using BF_3 instead of $SnCl_4$, and introducing an aryl substituent at the carbon next to the nucleophilic center does not influence the diastereoselectivity of the process. An extended transition state respecting the Bürgi-Dunitz angle is compatible with these results.

Experimental

tert-Butyl 2-(1-hydroxyethyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1- carboxylate (3): Acetaldehyde (0.18 ml, 3.20 mmol) and $BF_3{\cdot}OEt_2$ (0.47 ml, 3.78 mmol) were added dropwise to a solution of *tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-4-(2-nitrophenyl)-1*H*-pyrrole-1-carboxylate (1.22 g, 2.91 mmol) in dry CH_2Cl_2 (30 ml) at −78°C under argon. The colour of the solution changed from yellow to light yellow. The mixture was stirred at −78°C for 1 h. The reaction

mixture was quenched at −78°C with a saturated aqueous solution of $NaHCO_3$ (20 ml) and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, AcOEt/DCM 4:6) afforded the aldol product (3) as a white solid(Yield 0.53 g, 52%). Crystals suitable for X-ray analysis were otained by slow evaporation of an ether/hexane (1:1) solution.

tert-Butyl 2-(1-hydroxyethyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1- carboxylate (4): Methyl 4-oxobutanoate (348 mg, 3.0 mmol) and $BF_3{\cdot}OEt_2$ (0.38 ml, 2.3 mmol) were added dropwise to a solution of *tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-4-(2-nitrophenyl)-1*H*-pyrrole-1- carboxylate (966 mg, 2.3 mmol) in dry CH_2Cl_2 (20 ml) at −78°C under argon. The colour of the solution changed from yellow to light yellow. The mixture was stirred at −78°C for 1 h. The reaction mixture was quenched at −78°C with a saturated aqueous solution of $NaHCO_3$ (15 ml) and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, AcOEt/Ether 3:7) afforded the aldol product (4) as a white solid (Yield 815 mg, 93%). Crystals suitable for X-ray analysis were otained by slow evaporation of an ether/hexane (1:1) solution.

tert-Butyl 2-(4-bromo-1-hydroxybutyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (5): 4-Bromobutanal (0.35 g, 2.31 mmol) and BF~3~·OEt~2~ (0.29 ml, 2.31 mmol) were added dropwise to a solution of *tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-1*H*-pyrrole-1-carboxylate (0.68 g, 2.31 mmol) in dry CH_2Cl_2 (20 ml) at −78°C under argon. The colour of the solution changed from yellow to light yellow. The mixture was stirred at −78°C for 1 h. The reaction mixture was quenched at − 78°C with a saturated aqueous solution of $NaHCO_3$ (15 ml) and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, AcOEt/DCM 3:7) afforded the aldol product (5) as a white solid (Yield 0.30 g, 39%). Crystals suitable for X-ray analysis were otained by slow evaporation of an ether/hexane (1:1) solution.

Refinement

In compound 3 the hydroxyl H-atom was located from a difference Fourier map and freely refined: O—H = 0.852 (18) Å. For compounds 4 and 5 the hydroxyl H-atoms were included in the calculated positions and treated as a riding atom: O—H = 0.84 with U_{iso}(H) = 1.2U_{eq}(O). The C-bound H-atoms in all three compounds were included in calculated positions and treated as riding atoms: C—H = 0.95 − 1.00 Å with U_{iso}(H) = 1.2 or 1.5U_{eq}(C)

Computing details

Data collection: *X-AREA* V1.35 (Stoe & Cie, 2006) for (5), (cpd3); *X-AREA* V1.17 (STOE & Cie, 2002) for (4). Cell refinement: *X-AREA* V1.35 for (5), (cpd3); *X-AREA* V1.17 for (4). Data reduction: *X-RED32* V1.31 (Stoe & Cie, 2006) for (5), (cpd3); *X-RED32* V1.04 (STOE & Cie, 2002) for (4). For all compounds, program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008). Molecular graphics: *ORTEP-3* (Farrugia, 1997), Mercury (Macrea, 2006) and *PLATON* (Spek, 2003) for (cpd3); *ORTEP-3* (Farrugia, 1997)and Mercury (Macrea, 2006) for (5), (4). For all compounds, software used to prepare material for publication: *SHELXL97*

Figures

Figure 1. Molecular structure of compound 3, showing the atom labelling scheme and the displacement ellipsoids drawn at the 50% probability level.

Figure 2. A view along the *a* axis of the crystal packing of compound 3, showing the formation of the hexagonal arrangement of symmetry related hydrogen bonded molecules (see Table 2 for details). Hydrogen bonds are shown as dotted blue lines and hydrogen atoms not involved in hydrogen bonding have been removed for clarity.
Figure 3. Molecular structure of compound 4, showing the atom labelling scheme and the displacement ellipsoids drawn at the 50% probability level.
Figure 4. A view along the *a* axis of the crystal packing of compound 4, showing the bifurcated hydrogen bonds and the formation of the centrosymmetric hydrogen bonded dimers (see Table 4 for details). Hydrogen bonds are shown as dotted blue lines and hydrogen atoms not involved in hydrogen bonding have been removed for clarity.
Figure 5. Molecular structure of compound 5, showing the atom labelling scheme and the displacement ellipsoids drawn at the 50% probability level.
Figure 6. A view along the *a* axis of the crystal packing of compound 5, showing the bifurcated hydrogen bonds and the formation of the centrosymmetric hydrogen bonded dimers (see Table 6 for details). Hydrogen bonds are shown as dotted blue lines and hydrogen atoms not involved in hydrogen bonding have been removed for clarity.

(cpd3)

Crystal data

$C_{17}H_{20}N_2O_6$	$\gamma = 120°$
$M_r = 348.35$	$V = 7845.0\ (5)$ Å^3
Trigonal, $R\overline{3}$	$Z = 18$
$a = 21.1117\ (8)$ Å	Mo $K\alpha$
$b = 21.1117\ (8)$ Å	$\mu = 0.10$ mm^{-1}
$c = 20.3244\ (9)$ Å	$T = 173\ (2)$ K
$\alpha = 90°$	0.45 × 0.45 × 0.45 mm
$\beta = 90°$	

Data collection

STOE IPDS-2 diffractometer	4718 independent reflections
Absorption correction: none	4041 reflections with $I > 2\sigma(I)$
39673 measured reflections	$R_{int} = 0.089$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.039$	235 parameters
$wR(F^2) = 0.098$	H atoms treated by a mixture of independent and constrained refinement
$S = 1.05$	$\Delta\rho_{max} = 0.27$ e Å^{-3}
4718 reflections	$\Delta\rho_{min} = -0.17$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °)

O1—C1	1.2098 (18)	O6—N2	1.2230 (16)
O2—C5	1.1945 (18)	N1—C1	1.3990 (15)
O3—C5	1.3271 (15)	N1—C5	1.3923 (16)
O3—C6	1.4788 (15)	N1—C4	1.4694 (17)

O4—C10	1.4164 (18)	N2—C17	1.4604 (13)
O5—N2	1.2234 (15)		
C5—O3—C6	121.44 (11)	N1—C4—C3	101.58 (8)
C1—N1—C5	123.85 (11)	O2—C5—N1	123.91 (11)
C4—N1—C5	124.37 (10)	O3—C5—N1	108.86 (11)
C1—N1—C4	111.29 (10)	O2—C5—O3	127.24 (12)
O5—N2—O6	123.86 (10)	O3—C6—C7	109.05 (10)
O6—N2—C17	118.15 (10)	O3—C6—C9	101.81 (11)
O5—N2—C17	117.93 (10)	O3—C6—C8	110.67 (11)
O1—C1—N1	126.66 (12)	O4—C10—C11	109.46 (11)
N1—C1—C2	105.79 (11)	O4—C10—C4	106.69 (10)
O1—C1—C2	127.56 (10)	N2—C17—C16	115.68 (10)
N1—C4—C10	112.45 (10)	N2—C17—C12	120.69 (10)

Table 2
Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H4O···O1^{i}	0.852 (18)	1.930 (19)	2.7600 (15)	164.3 (19)
C10—H10···O2^{i}	1.00	2.50	3.1765 (17)	124
C11—H11B···O5^{ii}	0.98	2.60	3.3871 (19)	138
C14—H14···O4^{iii}	0.95	2.52	3.3120 (15)	140

Symmetry codes: (i) $y, -x+y, -z$; (ii) $-x+y+1/3, -x+2/3, z-1/3$; (iii) $y+1/3, -x+y+2/3, -z-1/3$.

(4)

Crystal data

$C_{20}H_{24}N_2O_8$	$V = 4090.3\ (6)$ Å^3
$M_r = 420.41$	$Z = 8$
Orthorhombic, *Pbca*	Mo $K\alpha$
$a = 9.1439\ (7)$ Å	$\mu = 0.11$ mm^{-1}
$b = 20.7113\ (18)$ Å	$T = 153\ (2)$ K
$c = 21.598\ (2)$ Å	0.50 × 0.45 × 0.10 mm

Data collection

STOE IPDS-2 diffractometer	3856 independent reflections
Absorption correction: none	2605 reflections with $I > 2\sigma(I)$
16666 measured reflections	$R_{int} = 0.078$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.044$	277 parameters
$wR(F^2) = 0.110$	H-atom parameters constrained
$S = 0.95$	$\Delta\rho_{max} = 0.18$ e Å^{-3}

3856 reflections | $\Delta\rho_{min} = -0.22$ e Å^{-3}

Table 3
Selected geometric parameters (Å, °)

O1—C1	1.223 (2)	O6—C14	1.442 (3)
O2—C5	1.205 (2)	O7—N2	1.228 (3)
O3—C5	1.3384 (19)	O8—N2	1.231 (2)
O3—C6	1.491 (2)	N1—C4	1.477 (2)
O4—C10	1.422 (2)	N1—C5	1.385 (3)
O5—C13	1.202 (3)	N1—C1	1.411 (2)
O6—C13	1.335 (3)	N2—C20	1.462 (3)
C5—O3—C6	121.15 (14)	O2—C5—O3	126.62 (17)
C13—O6—C14	115.78 (19)	O2—C5—N1	124.21 (15)
C1—N1—C4	111.13 (15)	O3—C5—N1	109.15 (16)
C1—N1—C5	123.74 (16)	O3—C6—C7	108.81 (16)
C4—N1—C5	124.32 (13)	O3—C6—C8	110.62 (14)
O7—N2—O8	122.9 (2)	O3—C6—C9	101.08 (16)
O7—N2—C20	118.69 (16)	O4—C10—C11	108.73 (16)
O8—N2—C20	118.38 (19)	O4—C10—C4	111.62 (13)
O1—C1—C2	128.47 (15)	O5—C13—C12	125.1 (2)
N1—C1—C2	105.86 (15)	O6—C13—C12	111.7 (2)
O1—C1—N1	125.67 (17)	O5—C13—O6	123.0 (2)
N1—C4—C10	112.77 (15)	N2—C20—C19	117.34 (17)
N1—C4—C3	101.48 (13)	N2—C20—C15	120.29 (18)

Table 4
Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H4O···O1^{i}	0.84	2.15	2.903 (2)	149
O4—H4O···O2^{i}	0.84	2.33	2.9696 (16)	134
C8—H8C···O7^{ii}	0.98	2.55	3.410 (3)	146
C19—H19···O5^{iii}	0.95	2.43	3.152 (3)	132

Symmetry codes: (i) −*x*+2, −*y*+2, −*z*+2; (ii) *x*+1, *y*, *z*; (iii) *x*−1, *y*, *z*.

(5)

Crystal data

$C_{13}H_{20}BrNO_4$	$\gamma = 101.367$ (8)°
$M_r = 334.21$	$V = 719.57$ (12) Å^3
Triclinic, $P\overline{1}$	$Z = 2$
$a = 8.8340$ (9) Å	Mo $K\alpha$
$b = 9.0750$ (9) Å	$\mu = 2.87$ mm^{-1}
$c = 10.7283$ (10) Å	$T = 173$ (2) K
$\alpha = 104.176$ (7)°	0.50 × 0.50 × 0.50 mm

β = 113.759 (7)°

Data collection

STOE IPDS-2 diffractometer	3862 independent reflections
Absorption correction: multi-scan MULscanABS in PLATON (Spek, 2003)	3587 reflections with $I > 2\sigma(I)$
T_{min} = 0.307, T_{max} = 0.472	R_{int} = 0.031
9956 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.027	177 parameters
$wR(F^2)$ = 0.066	H-atom parameters constrained
S = 1.05	$\Delta\rho_{max}$ = 0.43 e Å^{-3}
3862 reflections	$\Delta\rho_{min}$ = −0.78 e Å^{-3}

Table 5
Selected geometric parameters (Å, °)

Br1—C13	1.9575 (19)	O4—C10	1.413 (2)
O1—C1	1.213 (2)	N1—C4	1.4691 (19)
O2—C5	1.2015 (19)	N1—C5	1.388 (2)
O3—C5	1.331 (2)	N1—C1	1.402 (2)
O3—C6	1.477 (2)		
C5—O3—C6	121.31 (12)	O2—C5—N1	124.16 (17)
C1—N1—C4	111.34 (13)	O3—C5—N1	108.81 (13)
C4—N1—C5	123.47 (14)	O2—C5—O3	127.03 (16)
C1—N1—C5	124.00 (13)	O3—C6—C7	109.20 (16)
O1—C1—N1	126.53 (15)	O3—C6—C8	110.36 (15)
N1—C1—C2	105.51 (14)	O3—C6—C9	101.43 (14)
O1—C1—C2	127.96 (17)	O4—C10—C11	108.24 (13)
N1—C4—C10	112.27 (12)	O4—C10—C4	111.18 (15)
N1—C4—C3	101.63 (14)	Br1—C13—C12	111.00 (12)

Table 6
Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H4O···O1^{i}	0.84	2.17	2.9138 (16)	148
O4—H4O···O2^{i}	0.84	2.28	2.9225 (18)	134
C13—H13A···O4^{ii}	0.99	2.54	3.339 (2)	138

Symmetry codes: (i) −*x*+1, −*y*, −*z*+1; (ii) −*x*+2, −*y*+1, −*z*+2.

Acknowledgements

This work was partially financed by the Swiss National Science Foundation.

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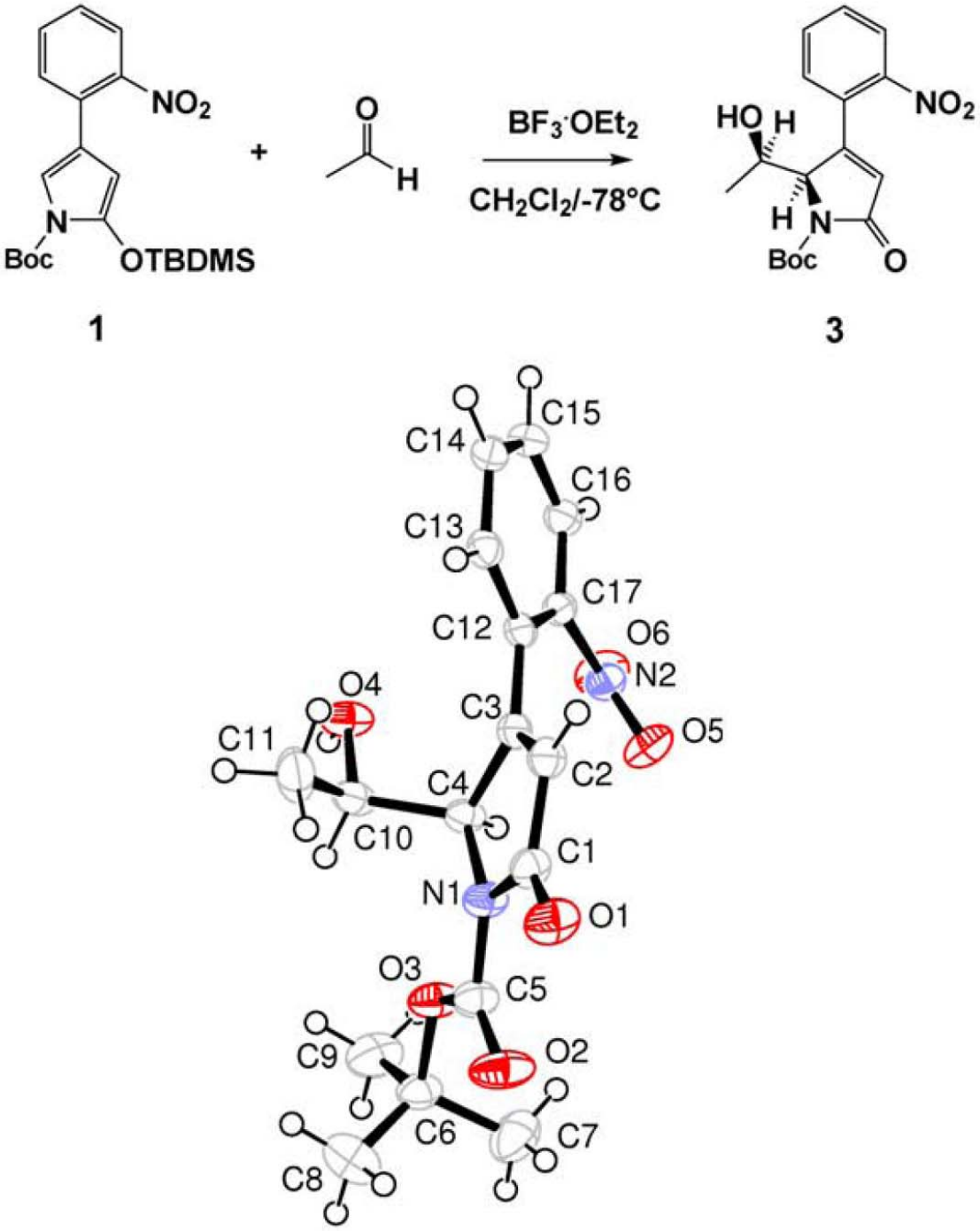


Fig. 1. Molecular structure of compound **3**, showing the atom numbering scheme and displacement ellipsoids drawn at the 50% probability level.

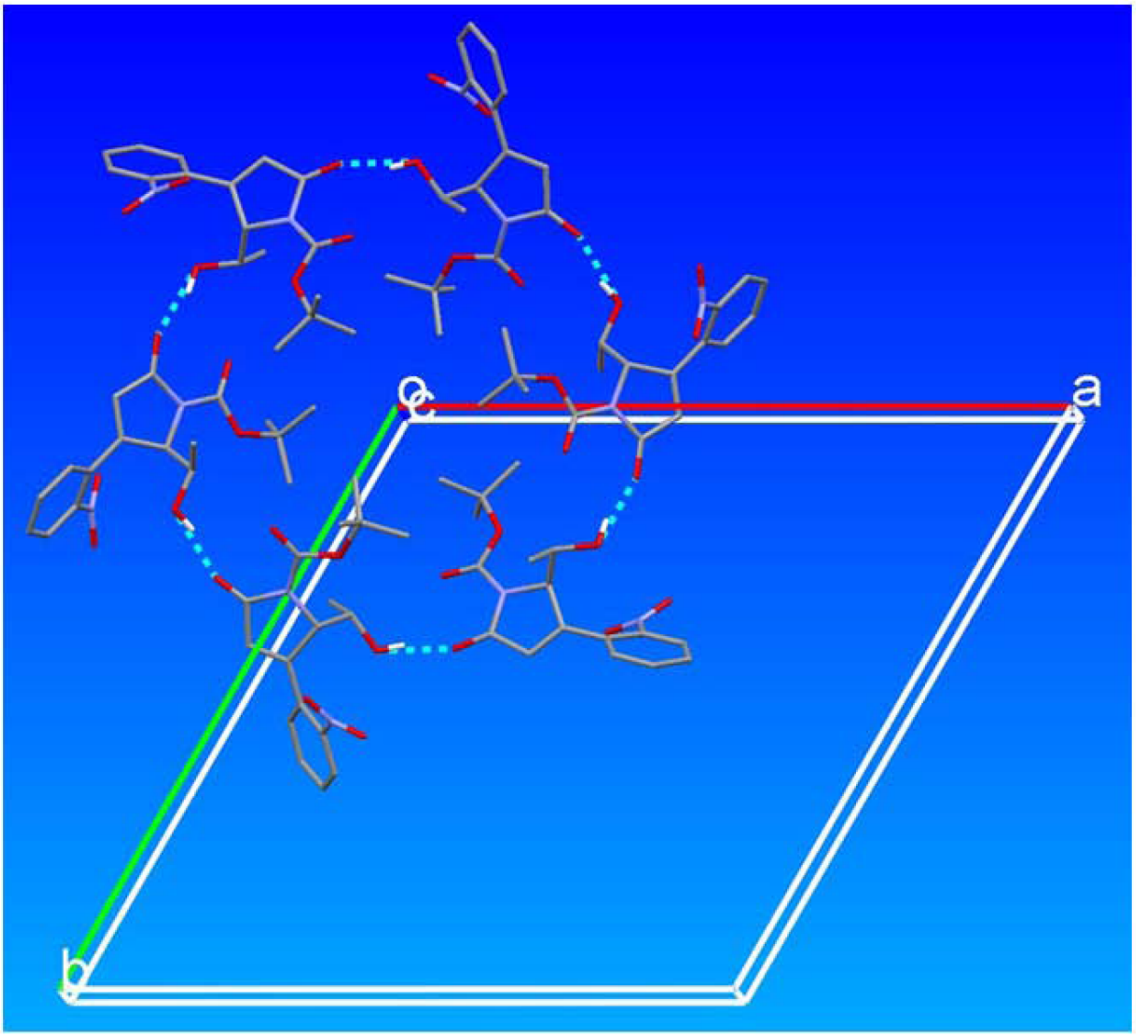
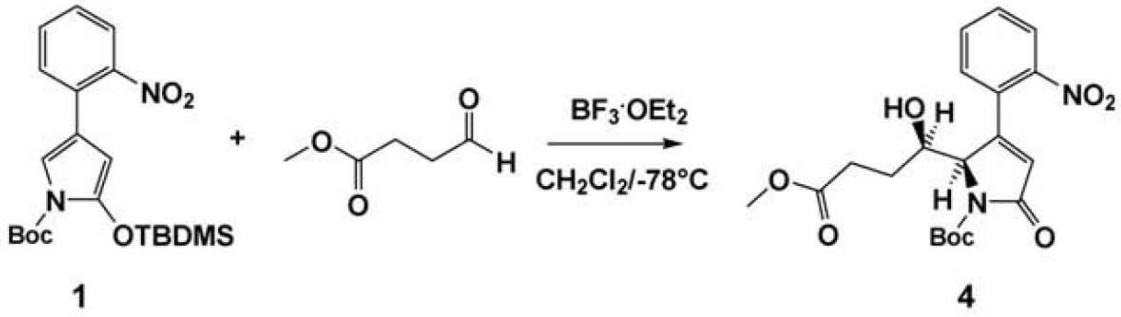


Fig. 2. A partial view, along the c axis, of the crystal packing of compound **3**, showing the hexagonal arrangement of O-H…O hydrogen bonded symmetry related molecules (hydrogen bonds shown as dotted blue lines).



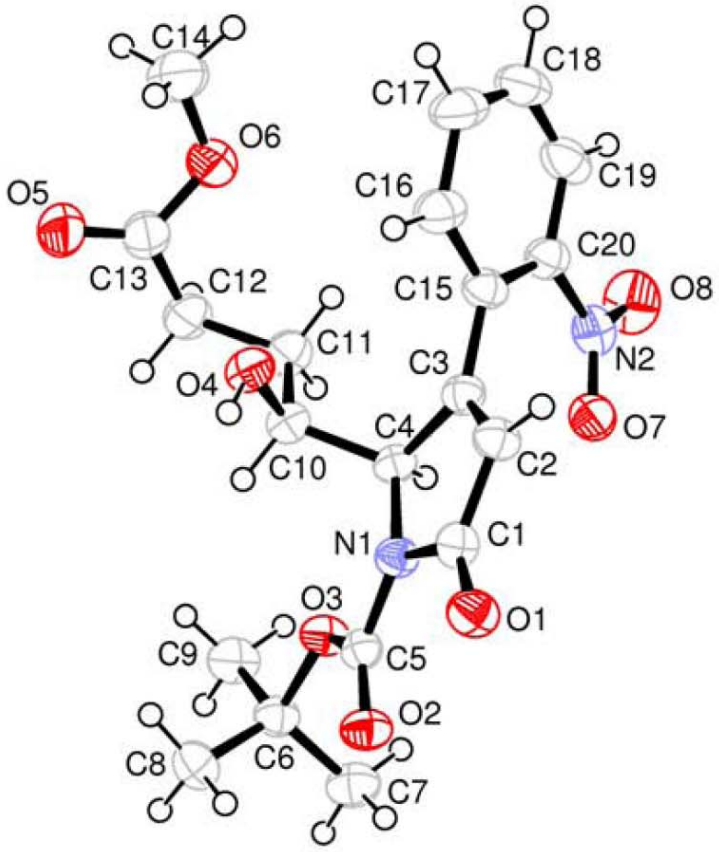


Fig. 3. Molecular structure of compound **4**, showing the atom numbering scheme and displacement ellipsoids drawn a the 50% probability level.

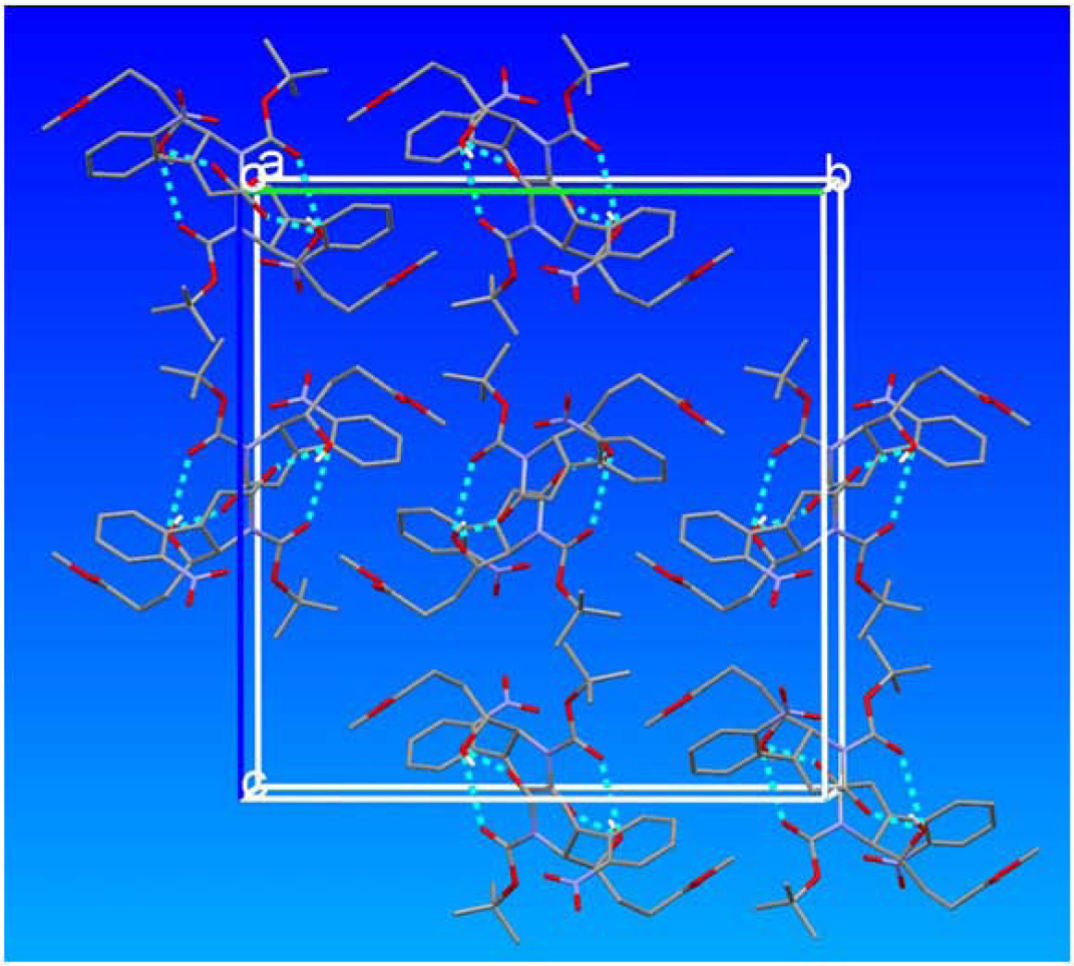
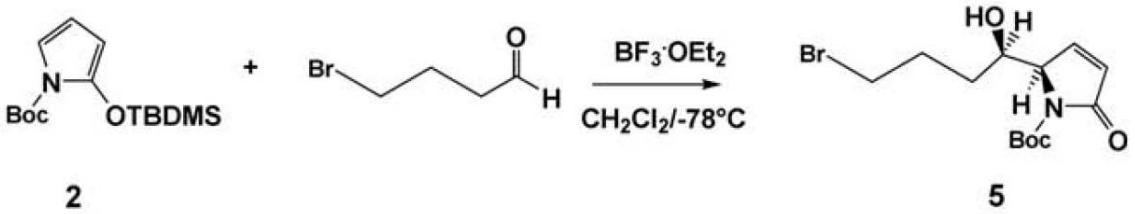


Fig. 4. View of the crystal packing along the a axis of compound 4, showing the formation of the centrosymmetric hydrogen bonded dimers (the hydrogen bonds are shown as dotted blue lines).



2 5

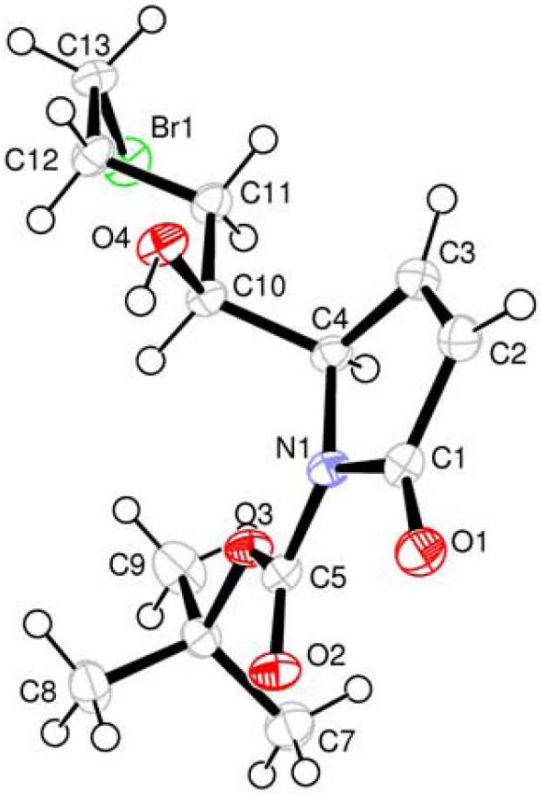


Fig. 5. The molecular structure of compound **5**, showing the atom numbering scheme and the displacement ellipsoids drawn at the 50% probability level.

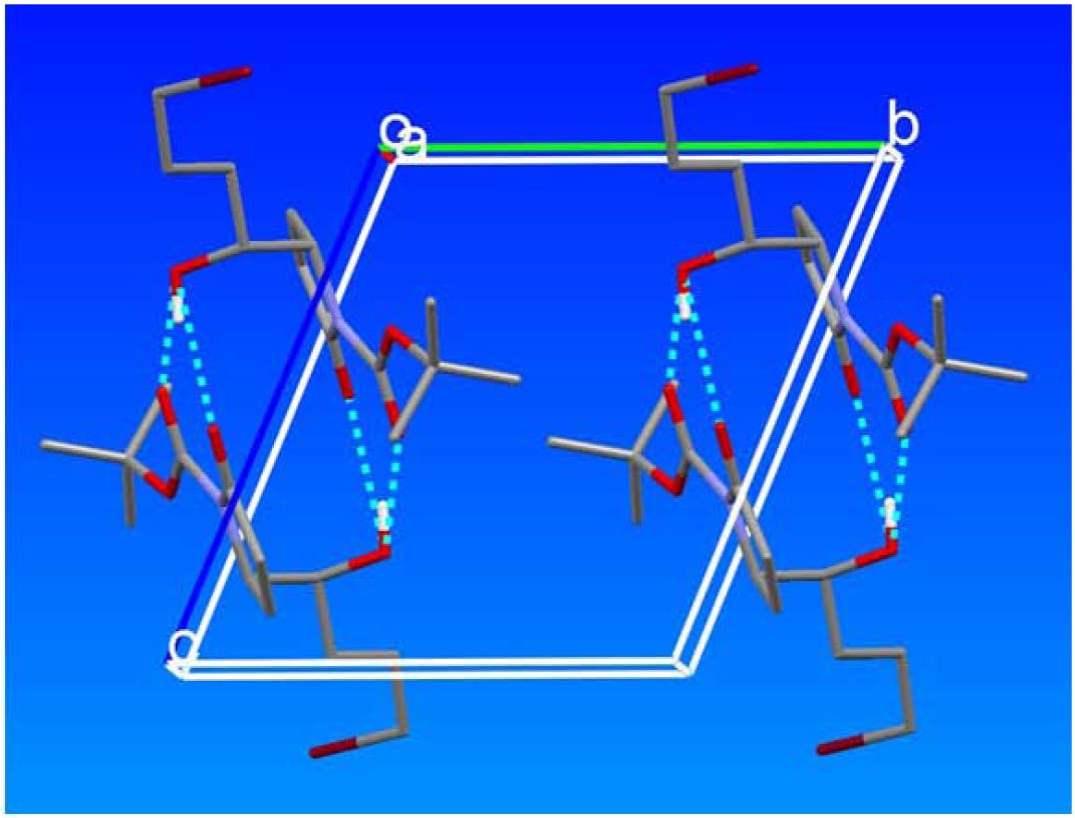


Fig. 6. A view of the crystal packing along the a axis of compound **5**, showing the formation of the centrosymmetric hydrogen bonded dimers (hydrogen bonds are shown as dotted blue lines).

supplementary materials

5-Hydroxyalkyl Derivatives of *tert*-Butyl 2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate

Olivier Vallat[a], Ana-Maria Buciumas[a], Reinhard Neier[a] and Helen Stoeckli-Evans[b]

(cpd3)

Crystal data

$C_{17}H_{20}N_2O_6$	$Z = 18$
$M_r = 348.35$	$F_{000} = 3312$
Trigonal, $R\overline{3}$	$D_x = 1.327$ Mg m^{-3}
Hall symbol: -R 3	Mo $K\alpha$ radiation $\lambda = 0.71073$ Å
$a = 21.1117$ (8) Å	Cell parameters from 37232 reflections
$b = 21.1117$ (8) Å	$\theta = 1.9$–$29.6°$
$c = 20.3244$ (9) Å	$\mu = 0.10$ mm^{-1}
$\alpha = 90°$	$T = 173$ (2) K
$\beta = 90°$	Block, pale violet
$\gamma = 120°$	0.45 × 0.45 × 0.45 mm
$V = 7845.0$ (5) Å^3	

Data collection

STOE IPDS-2 diffractometer	4041 reflections with $I > 2\sigma(I)$
Radiation source: fine-focus sealed tube	$R_{int} = 0.089$
Monochromator: graphite	$\theta_{max} = 29.3°$
$T = 173(2)$ K	$\theta_{min} = 1.9°$
phi & ω scans	$h = -28 \rightarrow 29$
Absorption correction: none	$k = -28 \rightarrow 28$
39673 measured reflections	$l = -25 \rightarrow 27$
4718 independent reflections	

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)] = 0.039$	$w = 1/[\sigma^2(F_o^2) + (0.0345P)^2 + 5.9651P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.098$	$(\Delta/\sigma)_{max} < 0.001$
$S = 1.05$	$\Delta\rho_{max} = 0.27$ e Å^{-3}
4718 reflections	$\Delta\rho_{min} = -0.17$ e Å^{-3}

235 parameters

Primary atom site location: structure-invariant direct methods

Secondary atom site location: difference Fourier map

Extinction correction: SHELXL, $Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$

Extinction coefficient: 0.00059 (14)

Special details

Geometry. Bond distances, angles *etc*. have been calculated using the rounded fractional coordinates. All su's are estimated from the variances of the (full) variance-covariance matrix. The cell e.s.d.'s are taken into account in the estimation of distances, angles and torsion angles

Refinement. Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.29424 (5)	0.41562 (5)	0.00122 (5)	0.0391 (3)
O2	0.21212 (5)	0.28894 (5)	0.07457 (5)	0.0480 (3)
O3	0.25771 (5)	0.21244 (4)	0.06812 (4)	0.0371 (3)
O4	0.41816 (5)	0.23954 (4)	−0.06199 (5)	0.0372 (3)
O5	0.50360 (5)	0.38580 (5)	0.09835 (4)	0.0417 (3)
O6	0.56788 (6)	0.33232 (5)	0.09317 (5)	0.0447 (3)
N1	0.31770 (5)	0.32006 (5)	0.01879 (5)	0.0294 (3)
N2	0.54177 (5)	0.36699 (5)	0.06844 (4)	0.0295 (2)
C1	0.33427 (6)	0.39007 (6)	−0.00134 (5)	0.0287 (3)
C2	0.40944 (6)	0.42536 (5)	−0.02579 (5)	0.0278 (3)
C3	0.43615 (5)	0.38024 (5)	−0.02026 (5)	0.0244 (2)
C4	0.37748 (5)	0.30600 (5)	0.00296 (6)	0.0270 (3)
C5	0.25675 (6)	0.27380 (6)	0.05644 (6)	0.0320 (3)
C6	0.20133 (6)	0.15371 (6)	0.10954 (6)	0.0353 (3)
C7	0.20589 (10)	0.18259 (9)	0.17826 (7)	0.0559 (5)
C8	0.12653 (8)	0.12481 (9)	0.07984 (9)	0.0595 (5)
C9	0.22464 (9)	0.09680 (8)	0.10738 (8)	0.0513 (5)
C10	0.35612 (6)	0.24733 (6)	−0.05118 (6)	0.0342 (3)
C11	0.33351 (8)	0.26656 (8)	−0.11510 (8)	0.0489 (4)
C12	0.51070 (5)	0.39876 (5)	−0.03979 (5)	0.0234 (3)
C13	0.53620 (6)	0.42848 (5)	−0.10190 (5)	0.0273 (3)
C14	0.60600 (6)	0.44736 (6)	−0.12258 (5)	0.0305 (3)
C15	0.65207 (6)	0.43617 (6)	−0.08213 (6)	0.0322 (3)
C16	0.62888 (6)	0.40740 (6)	−0.02006 (5)	0.0286 (3)
C17	0.55966 (5)	0.39000 (5)	−0.00005 (5)	0.0243 (3)
H2	0.43550	0.47360	−0.04310	0.0330*
H4	0.39390	0.29140	0.04350	0.0320*
H4O	0.4094 (9)	0.1984 (10)	−0.0466 (8)	0.050 (4)*
H7A	0.19070	0.21950	0.17780	0.0840*

H7B	0.25630	0.20470	0.19420	0.0840*
H7C	0.17350	0.14230	0.20740	0.0840*
H8A	0.12740	0.11170	0.03370	0.0890*
H8B	0.11250	0.16250	0.08220	0.0890*
H8C	0.09100	0.08140	0.10420	0.0890*
H9A	0.22470	0.08200	0.06170	0.0770*
H9B	0.27390	0.11730	0.12580	0.0770*
H9C	0.19040	0.05410	0.13320	0.0770*
H10	0.31500	0.19980	−0.03470	0.0410*
H11A	0.37550	0.30970	−0.13440	0.0730*
H11B	0.31630	0.22530	−0.14570	0.0730*
H11C	0.29400	0.27720	−0.10680	0.0730*
H13	0.50510	0.43600	−0.13070	0.0330*
H14	0.62230	0.46820	−0.16500	0.0370*
H15	0.69950	0.44820	−0.09700	0.0390*
H16	0.66010	0.39970	0.00840	0.0340*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0436 (5)	0.0381 (4)	0.0497 (5)	0.0309 (4)	0.0099 (4)	0.0058 (4)
O2	0.0417 (5)	0.0501 (5)	0.0662 (6)	0.0334 (5)	0.0241 (4)	0.0187 (5)
O3	0.0361 (4)	0.0315 (4)	0.0479 (5)	0.0200 (3)	0.0182 (4)	0.0127 (3)
O4	0.0361 (4)	0.0246 (4)	0.0577 (5)	0.0203 (3)	0.0199 (4)	0.0106 (4)
O5	0.0480 (5)	0.0603 (6)	0.0284 (4)	0.0358 (5)	0.0067 (3)	−0.0001 (4)
O6	0.0559 (6)	0.0532 (5)	0.0383 (5)	0.0373 (5)	0.0082 (4)	0.0166 (4)
N1	0.0285 (4)	0.0258 (4)	0.0390 (5)	0.0174 (4)	0.0083 (4)	0.0037 (4)
N2	0.0314 (4)	0.0307 (4)	0.0272 (4)	0.0162 (4)	0.0024 (3)	0.0024 (3)
C1	0.0328 (5)	0.0266 (5)	0.0321 (5)	0.0190 (4)	0.0024 (4)	−0.0009 (4)
C2	0.0307 (5)	0.0217 (4)	0.0323 (5)	0.0140 (4)	0.0007 (4)	−0.0005 (4)
C3	0.0256 (4)	0.0212 (4)	0.0262 (4)	0.0115 (4)	−0.0001 (4)	−0.0016 (3)
C4	0.0238 (4)	0.0229 (4)	0.0370 (5)	0.0138 (4)	0.0064 (4)	0.0030 (4)
C5	0.0299 (5)	0.0327 (5)	0.0377 (6)	0.0189 (4)	0.0068 (4)	0.0047 (4)
C6	0.0348 (6)	0.0319 (5)	0.0363 (6)	0.0144 (5)	0.0112 (4)	0.0085 (4)
C7	0.0747 (11)	0.0519 (8)	0.0388 (7)	0.0299 (8)	0.0134 (7)	0.0043 (6)
C8	0.0397 (7)	0.0500 (8)	0.0744 (11)	0.0117 (6)	−0.0006 (7)	0.0060 (7)
C9	0.0609 (9)	0.0384 (7)	0.0585 (9)	0.0278 (6)	0.0215 (7)	0.0177 (6)
C10	0.0249 (5)	0.0208 (5)	0.0546 (7)	0.0098 (4)	0.0100 (4)	−0.0040 (4)
C11	0.0381 (6)	0.0556 (8)	0.0576 (8)	0.0269 (6)	−0.0162 (6)	−0.0285 (7)
C12	0.0242 (4)	0.0170 (4)	0.0269 (5)	0.0088 (3)	0.0010 (3)	−0.0014 (3)
C13	0.0293 (5)	0.0218 (4)	0.0263 (5)	0.0095 (4)	−0.0017 (4)	0.0001 (4)
C14	0.0314 (5)	0.0245 (5)	0.0266 (5)	0.0072 (4)	0.0046 (4)	0.0009 (4)
C15	0.0248 (5)	0.0310 (5)	0.0344 (5)	0.0091 (4)	0.0061 (4)	0.0006 (4)
C16	0.0257 (5)	0.0272 (5)	0.0320 (5)	0.0126 (4)	0.0007 (4)	−0.0002 (4)
C17	0.0265 (5)	0.0204 (4)	0.0249 (4)	0.0109 (4)	0.0024 (3)	0.0003 (3)

Geometric parameters (Å, °)

O1—C1	1.2098 (18)	C13—C14	1.3855 (19)

O2—C5	1.1945 (18)	C14—C15	1.3811 (19)
O3—C5	1.3271 (15)	C15—C16	1.3794 (16)
O3—C6	1.4788 (15)	C16—C17	1.3781 (18)
O4—C10	1.4164 (18)	C2—H2	0.9500
O5—N2	1.2234 (15)	C4—H4	1.0000
O6—N2	1.2230 (16)	C7—H7A	0.9800
O4—H4O	0.852 (18)	C7—H7B	0.9800
N1—C1	1.3990 (15)	C7—H7C	0.9800
N1—C5	1.3923 (16)	C8—H8A	0.9800
N1—C4	1.4694 (17)	C8—H8B	0.9800
N2—C17	1.4604 (13)	C8—H8C	0.9800
C1—C2	1.4622 (18)	C9—H9A	0.9800
C2—C3	1.3323 (16)	C9—H9B	0.9800
C3—C12	1.4738 (16)	C9—H9C	0.9800
C3—C4	1.5074 (14)	C10—H10	1.0000
C4—C10	1.5459 (16)	C11—H11A	0.9800
C6—C8	1.506 (2)	C11—H11B	0.9800
C6—C9	1.510 (2)	C11—H11C	0.9800
C6—C7	1.5077 (19)	C13—H13	0.9500
C10—C11	1.508 (2)	C14—H14	0.9500
C12—C17	1.3950 (16)	C15—H15	0.9500
C12—C13	1.3926 (14)	C16—H16	0.9500
C5—O3—C6	121.44 (11)	C1—C2—H2	125.00
C10—O4—H4O	108.6 (14)	C3—C2—H2	125.00
C1—N1—C5	123.85 (11)	N1—C4—H4	110.00
C4—N1—C5	124.37 (10)	C3—C4—H4	110.00
C1—N1—C4	111.29 (10)	C10—C4—H4	110.00
O5—N2—O6	123.86 (10)	C6—C7—H7A	109.00
O6—N2—C17	118.15 (10)	C6—C7—H7B	109.00
O5—N2—C17	117.93 (10)	C6—C7—H7C	109.00
O1—C1—N1	126.66 (12)	H7A—C7—H7B	110.00
N1—C1—C2	105.79 (11)	H7A—C7—H7C	109.00
O1—C1—C2	127.56 (10)	H7B—C7—H7C	110.00
C1—C2—C3	110.28 (9)	C6—C8—H8A	110.00
C2—C3—C12	124.42 (9)	C6—C8—H8B	109.00
C4—C3—C12	124.99 (9)	C6—C8—H8C	109.00
C2—C3—C4	110.39 (10)	H8A—C8—H8B	109.00
N1—C4—C10	112.45 (10)	H8A—C8—H8C	109.00
C3—C4—C10	111.66 (10)	H8B—C8—H8C	110.00
N1—C4—C3	101.58 (8)	C6—C9—H9A	110.00
O2—C5—N1	123.91 (11)	C6—C9—H9B	110.00
O3—C5—N1	108.86 (11)	C6—C9—H9C	109.00
O2—C5—O3	127.24 (12)	H9A—C9—H9B	109.00
O3—C6—C7	109.05 (10)	H9A—C9—H9C	109.00
O3—C6—C9	101.81 (11)	H9B—C9—H9C	110.00
C7—C6—C8	112.16 (14)	O4—C10—H10	109.00
O3—C6—C8	110.67 (11)	C4—C10—H10	109.00
C8—C6—C9	111.04 (12)	C11—C10—H10	109.00
C7—C6—C9	111.62 (13)	C10—C11—H11A	109.00

O4—C10—C11	109.46 (11)	C10—C11—H11B	110.00
C4—C10—C11	113.72 (10)	C10—C11—H11C	109.00
O4—C10—C4	106.69 (10)	H11A—C11—H11B	109.00
C3—C12—C17	124.93 (9)	H11A—C11—H11C	109.00
C13—C12—C17	116.07 (11)	H11B—C11—H11C	109.00
C3—C12—C13	118.99 (10)	C12—C13—H13	119.00
C12—C13—C14	121.37 (11)	C14—C13—H13	119.00
C13—C14—C15	120.59 (10)	C13—C14—H14	120.00
C14—C15—C16	119.64 (13)	C15—C14—H14	120.00
C15—C16—C17	118.87 (12)	C14—C15—H15	120.00
N2—C17—C16	115.68 (10)	C16—C15—H15	120.00
C12—C17—C16	123.44 (10)	C15—C16—H16	121.00
N2—C17—C12	120.69 (10)	C17—C16—H16	121.00
C6—O3—C5—O2	−2.40 (19)	C1—C2—C3—C12	−179.43 (9)
C6—O3—C5—N1	177.35 (10)	C2—C3—C4—N1	−8.07 (12)
C5—O3—C6—C7	−62.67 (16)	C2—C3—C4—C10	111.98 (11)
C5—O3—C6—C8	61.16 (14)	C12—C3—C4—N1	176.97 (10)
C5—O3—C6—C9	179.26 (11)	C12—C3—C4—C10	−62.99 (14)
C4—N1—C1—O1	175.08 (11)	C2—C3—C12—C13	−49.77 (14)
C4—N1—C1—C2	−4.97 (12)	C2—C3—C12—C17	129.10 (11)
C5—N1—C1—O1	−12.66 (19)	C4—C3—C12—C13	124.51 (11)
C5—N1—C1—C2	167.29 (10)	C4—C3—C12—C17	−56.63 (15)
C1—N1—C4—C3	7.80 (12)	N1—C4—C10—O4	179.54 (9)
C1—N1—C4—C10	−111.70 (10)	N1—C4—C10—C11	58.76 (14)
C5—N1—C4—C3	−164.42 (10)	C3—C4—C10—O4	66.10 (12)
C5—N1—C4—C10	76.09 (14)	C3—C4—C10—C11	−54.68 (15)
C1—N1—C5—O2	0.98 (19)	C3—C12—C13—C14	179.54 (9)
C1—N1—C5—O3	−178.78 (10)	C17—C12—C13—C14	0.57 (14)
C4—N1—C5—O2	172.23 (12)	C3—C12—C17—N2	−5.69 (14)
C4—N1—C5—O3	−7.52 (16)	C3—C12—C17—C16	179.51 (10)
O5—N2—C17—C12	−31.70 (14)	C13—C12—C17—N2	173.20 (9)
O5—N2—C17—C16	143.49 (11)	C13—C12—C17—C16	−1.60 (14)
O6—N2—C17—C12	150.83 (10)	C12—C13—C14—C15	0.89 (16)
O6—N2—C17—C16	−33.99 (14)	C13—C14—C15—C16	−1.41 (17)
O1—C1—C2—C3	179.47 (11)	C14—C15—C16—C17	0.42 (16)
N1—C1—C2—C3	−0.48 (12)	C15—C16—C17—N2	−173.92 (9)
C1—C2—C3—C4	5.58 (12)	C15—C16—C17—C12	1.12 (16)

Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H4O···O1^{i}	0.852 (18)	1.930 (19)	2.7600 (15)	164.3 (19)
C4—H4···O5	1.00	2.44	3.0333 (15)	117
C7—H7A···O2	0.98	2.47	3.0339 (19)	116
C8—H8B···O2	0.98	2.44	3.0037 (19)	116
C10—H10···O3	1.00	2.49	3.0344 (16)	113
C10—H10···O2^{i}	1.00	2.50	3.1765 (17)	124
C11—H11B···O5^{ii}	0.98	2.60	3.3871 (19)	138

C14—H14···O4^{iii}	0.95	2.52	3.3120 (15)	140

Symmetry codes: (i) y, $-x+y$, $-z$; (ii) $-x+y+1/3$, $-x+2/3$, $z-1/3$; (iii) $y+1/3$, $-x+y+2/3$, $-z-1/3$.

(4)

Crystal data

$C_{20}H_{24}N_2O_8$	F_{000} = 1776
M_r = 420.41	D_x = 1.365 Mg m^{-3}
Orthorhombic, *Pbca*	Mo $K\alpha$ radiation λ = 0.71073 Å
Hall symbol: -P 2ac 2ab	Cell parameters from 14223 reflections
a = 9.1439 (7) Å	θ = 1.4–26.0°
b = 20.7113 (18) Å	μ = 0.11 mm^{-1}
c = 21.598 (2) Å	T = 153 (2) K
V = 4090.3 (6) Å^3	Plate, colourless
Z = 8	0.50 × 0.45 × 0.10 mm

Data collection

STOE IPDS-2 diffractometer	2605 reflections with $I > 2\sigma(I)$
Radiation source: fine-focus sealed tube	R_{int} = 0.078
Monochromator: graphite	θ_{max} = 26.0°
T = 153(2) K	θ_{min} = 1.9°
rotation method scans	h = −8→11
Absorption correction: none	k = −17→25
16666 measured reflections	l = −26→26
3856 independent reflections	

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)]$ = 0.044	$w = 1/[\sigma^2(F_o^2) + (0.0615P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2)$ = 0.110	$(\Delta/\sigma)_{max}$ = 0.001
S = 0.95	$\Delta\rho_{max}$ = 0.18 e Å^{-3}
3856 reflections	$\Delta\rho_{min}$ = −0.22 e Å^{-3}
277 parameters	Extinction correction: SHELXL, $Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
Primary atom site location: structure-invariant direct methods	Extinction coefficient: 0.0048 (6)
Secondary atom site location: difference Fourier map	

Special details

Geometry. Bond distances, angles *etc*. have been calculated using the rounded fractional coordinates. All su's are estimated from the variances of the (full) variance-covariance matrix. The cell e.s.d.'s are taken into account in the estimation of distances, angles and torsion angles

Refinement. Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.82338 (16)	1.04916 (7)	1.03743 (5)	0.0398 (4)
O2	0.98587 (16)	1.10030 (7)	0.94111 (5)	0.0377 (4)
O3	0.95859 (15)	1.04336 (7)	0.85188 (5)	0.0355 (4)
O4	0.94241 (16)	0.86269 (7)	0.92957 (5)	0.0381 (4)
O5	1.0951 (2)	0.73288 (9)	0.85235 (9)	0.0652 (7)
O6	0.85174 (18)	0.72804 (8)	0.85811 (7)	0.0503 (5)
O7	0.46800 (17)	0.97641 (8)	0.87432 (6)	0.0426 (5)
O8	0.3128 (2)	0.91739 (10)	0.82448 (6)	0.0618 (7)
N1	0.84959 (18)	1.00760 (8)	0.93705 (6)	0.0314 (5)
N2	0.40953 (19)	0.92421 (10)	0.86356 (7)	0.0405 (6)
C1	0.7897 (2)	1.01036 (10)	0.99720 (7)	0.0330 (6)
C2	0.6820 (2)	0.95899 (10)	1.00009 (7)	0.0345 (6)
C3	0.6746 (2)	0.92758 (10)	0.94629 (7)	0.0321 (6)
C4	0.7851 (2)	0.95408 (9)	0.90103 (7)	0.0309 (5)
C5	0.9383 (2)	1.05520 (10)	0.91219 (7)	0.0308 (6)
C6	1.0587 (2)	1.08406 (10)	0.81389 (7)	0.0354 (6)
C7	0.9866 (3)	1.14807 (11)	0.80216 (9)	0.0455 (7)
C8	1.2068 (2)	1.08975 (12)	0.84463 (9)	0.0428 (7)
C9	1.0704 (3)	1.04371 (12)	0.75502 (8)	0.0459 (7)
C10	0.9001 (2)	0.90391 (10)	0.88007 (7)	0.0343 (6)
C11	0.8398 (3)	0.86263 (11)	0.82758 (8)	0.0404 (7)
C12	0.9515 (3)	0.81462 (11)	0.80205 (9)	0.0460 (7)
C13	0.9772 (3)	0.75551 (12)	0.84067 (10)	0.0459 (7)
C14	0.8654 (3)	0.67016 (13)	0.89480 (11)	0.0604 (9)
C15	0.5813 (2)	0.87049 (10)	0.93627 (7)	0.0347 (6)
C16	0.6175 (3)	0.81437 (11)	0.96806 (9)	0.0439 (7)
C17	0.5335 (3)	0.75894 (12)	0.96383 (10)	0.0541 (8)
C18	0.4101 (3)	0.75838 (13)	0.92703 (10)	0.0546 (8)
C19	0.3711 (3)	0.81283 (12)	0.89444 (9)	0.0483 (7)
C20	0.4561 (2)	0.86762 (10)	0.89889 (8)	0.0367 (6)
H2	0.62450	0.94910	1.03550	0.0410*
H4	0.73330	0.97180	0.86400	0.0370*
H4O	1.00180	0.88220	0.95260	0.0570*
H7A	0.89070	1.14110	0.78300	0.0680*

H7B	1.04790	1.17380	0.77430	0.0680*
H7C	0.97420	1.17110	0.84150	0.0680*
H8A	1.19770	1.11540	0.88250	0.0640*
H8B	1.27540	1.11090	0.81630	0.0640*
H8C	1.24320	1.04660	0.85500	0.0640*
H9A	1.11600	1.00210	0.76470	0.0690*
H9B	1.13020	1.06670	0.72450	0.0690*
H9C	0.97240	1.03640	0.73800	0.0690*
H10	0.98860	0.92740	0.86480	0.0410*
H11A	0.80700	0.89130	0.79360	0.0480*
H11B	0.75340	0.83860	0.84280	0.0480*
H12A	0.91880	0.80070	0.76040	0.0550*
H12B	1.04600	0.83730	0.79680	0.0550*
H14A	0.91600	0.63690	0.87070	0.0910*
H14B	0.76790	0.65460	0.90630	0.0910*
H14C	0.92170	0.67960	0.93230	0.0910*
H16	0.70240	0.81400	0.99340	0.0530*
H17	0.56080	0.72130	0.98620	0.0650*
H18	0.35210	0.72040	0.92420	0.0650*
H19	0.28620	0.81270	0.86910	0.0580*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0431 (8)	0.0422 (8)	0.0341 (6)	−0.0070 (8)	0.0024 (5)	−0.0091 (6)
O2	0.0461 (8)	0.0322 (8)	0.0348 (6)	−0.0067 (7)	−0.0004 (5)	−0.0041 (5)
O3	0.0435 (8)	0.0348 (8)	0.0283 (5)	−0.0078 (7)	0.0027 (5)	−0.0013 (5)
O4	0.0429 (9)	0.0323 (8)	0.0390 (6)	0.0015 (7)	−0.0080 (5)	−0.0012 (5)
O5	0.0419 (10)	0.0490 (12)	0.1047 (13)	0.0032 (9)	−0.0081 (9)	−0.0138 (9)
O6	0.0428 (9)	0.0463 (10)	0.0618 (9)	−0.0045 (8)	−0.0055 (7)	−0.0016 (7)
O7	0.0392 (9)	0.0437 (10)	0.0448 (7)	0.0001 (8)	−0.0008 (6)	0.0071 (6)
O8	0.0570 (11)	0.0812 (14)	0.0473 (8)	0.0047 (10)	−0.0222 (7)	−0.0111 (8)
N1	0.0341 (9)	0.0306 (9)	0.0295 (7)	−0.0022 (8)	0.0010 (6)	−0.0024 (6)
N2	0.0369 (10)	0.0516 (12)	0.0330 (7)	0.0008 (10)	−0.0002 (7)	−0.0043 (7)
C1	0.0338 (11)	0.0356 (11)	0.0295 (8)	0.0016 (9)	−0.0003 (7)	−0.0011 (7)
C2	0.0376 (11)	0.0352 (11)	0.0307 (8)	−0.0043 (10)	0.0017 (7)	−0.0001 (7)
C3	0.0339 (11)	0.0298 (11)	0.0325 (8)	0.0007 (9)	−0.0026 (7)	0.0024 (7)
C4	0.0360 (11)	0.0273 (10)	0.0294 (7)	−0.0012 (9)	−0.0018 (7)	−0.0014 (7)
C5	0.0318 (10)	0.0298 (11)	0.0309 (8)	−0.0002 (9)	−0.0009 (7)	−0.0004 (7)
C6	0.0401 (12)	0.0348 (12)	0.0314 (8)	−0.0047 (10)	0.0033 (7)	0.0026 (7)
C7	0.0577 (14)	0.0386 (13)	0.0402 (9)	−0.0028 (11)	−0.0070 (9)	0.0063 (8)
C8	0.0375 (12)	0.0491 (14)	0.0419 (9)	−0.0042 (11)	0.0032 (8)	0.0002 (9)
C9	0.0576 (14)	0.0474 (14)	0.0327 (8)	−0.0067 (12)	0.0063 (9)	−0.0035 (8)
C10	0.0366 (11)	0.0326 (11)	0.0336 (8)	0.0006 (10)	−0.0007 (7)	−0.0004 (7)
C11	0.0462 (13)	0.0401 (13)	0.0348 (8)	0.0002 (11)	−0.0010 (8)	−0.0077 (8)
C12	0.0509 (14)	0.0398 (13)	0.0474 (10)	−0.0016 (11)	0.0075 (9)	−0.0140 (9)
C13	0.0433 (13)	0.0411 (13)	0.0534 (11)	−0.0016 (12)	−0.0026 (9)	−0.0195 (9)
C14	0.0652 (18)	0.0479 (16)	0.0682 (14)	−0.0051 (14)	−0.0135 (12)	0.0034 (11)

C15	0.0385 (11)	0.0339 (11)	0.0317 (8)	−0.0052 (10)	0.0045 (7)	−0.0005 (7)
C16	0.0511 (13)	0.0362 (12)	0.0445 (10)	−0.0023 (11)	0.0026 (9)	0.0039 (8)
C17	0.0759 (18)	0.0324 (12)	0.0540 (11)	−0.0052 (13)	0.0191 (12)	0.0040 (9)
C18	0.0618 (16)	0.0425 (14)	0.0594 (12)	−0.0201 (13)	0.0246 (12)	−0.0144 (11)
C19	0.0454 (13)	0.0522 (15)	0.0473 (10)	−0.0157 (12)	0.0101 (9)	−0.0156 (10)
C20	0.0408 (12)	0.0350 (12)	0.0342 (8)	−0.0029 (10)	0.0039 (8)	−0.0051 (8)

Geometric parameters (Å, °)

O1—C1	1.223 (2)	C16—C17	1.384 (4)
O2—C5	1.205 (2)	C17—C18	1.380 (4)
O3—C5	1.3384 (19)	C18—C19	1.376 (3)
O3—C6	1.491 (2)	C19—C20	1.379 (3)
O4—C10	1.422 (2)	C2—H2	0.9500
O5—C13	1.202 (3)	C4—H4	1.0000
O6—C13	1.335 (3)	C7—H7A	0.9800
O6—C14	1.442 (3)	C7—H7B	0.9800
O7—N2	1.228 (3)	C7—H7C	0.9800
O8—N2	1.231 (2)	C8—H8A	0.9800
O4—H4O	0.8400	C8—H8B	0.9800
N1—C4	1.477 (2)	C8—H8C	0.9800
N1—C5	1.385 (3)	C9—H9A	0.9800
N1—C1	1.411 (2)	C9—H9B	0.9800
N2—C20	1.462 (3)	C9—H9C	0.9800
C1—C2	1.451 (3)	C10—H10	1.0000
C2—C3	1.333 (2)	C11—H11A	0.9900
C3—C15	1.474 (3)	C11—H11B	0.9900
C3—C4	1.509 (2)	C12—H12A	0.9900
C4—C10	1.546 (3)	C12—H12B	0.9900
C6—C7	1.502 (3)	C14—H14A	0.9800
C6—C8	1.513 (3)	C14—H14B	0.9800
C6—C9	1.525 (3)	C14—H14C	0.9800
C10—C11	1.523 (3)	C16—H16	0.9500
C11—C12	1.528 (3)	C17—H17	0.9500
C12—C13	1.500 (3)	C18—H18	0.9500
C15—C20	1.402 (2)	C19—H19	0.9500
C15—C16	1.390 (3)		
C5—O3—C6	121.15 (14)	N1—C4—H4	110.00
C13—O6—C14	115.78 (19)	C3—C4—H4	110.00
C10—O4—H4O	109.00	C10—C4—H4	110.00
C1—N1—C4	111.13 (15)	C6—C7—H7A	110.00
C1—N1—C5	123.74 (16)	C6—C7—H7B	109.00
C4—N1—C5	124.32 (13)	C6—C7—H7C	109.00
O7—N2—O8	122.9 (2)	H7A—C7—H7B	109.00
O7—N2—C20	118.69 (16)	H7A—C7—H7C	110.00
O8—N2—C20	118.38 (19)	H7B—C7—H7C	109.00
O1—C1—C2	128.47 (15)	C6—C8—H8A	109.00
N1—C1—C2	105.86 (15)	C6—C8—H8B	110.00
O1—C1—N1	125.67 (17)	C6—C8—H8C	109.00

C1—C2—C3	110.77 (15)	H8A—C8—H8B	109.00
C2—C3—C4	110.67 (17)	H8A—C8—H8C	109.00
C2—C3—C15	123.28 (16)	H8B—C8—H8C	109.00
C4—C3—C15	125.74 (14)	C6—C9—H9A	110.00
N1—C4—C10	112.77 (15)	C6—C9—H9B	109.00
C3—C4—C10	113.62 (15)	C6—C9—H9C	109.00
N1—C4—C3	101.48 (13)	H9A—C9—H9B	109.00
O2—C5—O3	126.62 (17)	H9A—C9—H9C	109.00
O2—C5—N1	124.21 (15)	H9B—C9—H9C	109.00
O3—C5—N1	109.15 (16)	O4—C10—H10	109.00
O3—C6—C7	108.81 (16)	C4—C10—H10	109.00
O3—C6—C8	110.62 (14)	C11—C10—H10	109.00
C7—C6—C8	113.46 (19)	C10—C11—H11A	109.00
C7—C6—C9	111.95 (15)	C10—C11—H11B	109.00
C8—C6—C9	110.23 (17)	C12—C11—H11A	109.00
O3—C6—C9	101.08 (16)	C12—C11—H11B	109.00
O4—C10—C11	108.73 (16)	H11A—C11—H11B	108.00
C4—C10—C11	110.42 (16)	C11—C12—H12A	108.00
O4—C10—C4	111.62 (13)	C11—C12—H12B	108.00
C10—C11—C12	113.1 (2)	C13—C12—H12A	108.00
C11—C12—C13	115.79 (18)	C13—C12—H12B	108.00
O5—C13—C12	125.1 (2)	H12A—C12—H12B	107.00
O6—C13—C12	111.7 (2)	O6—C14—H14A	109.00
O5—C13—O6	123.0 (2)	O6—C14—H14B	109.00
C3—C15—C20	126.24 (18)	O6—C14—H14C	110.00
C16—C15—C20	116.32 (19)	H14A—C14—H14B	109.00
C3—C15—C16	117.42 (17)	H14A—C14—H14C	109.00
C15—C16—C17	121.9 (2)	H14B—C14—H14C	110.00
C16—C17—C18	119.9 (2)	C15—C16—H16	119.00
C17—C18—C19	120.0 (2)	C17—C16—H16	119.00
C18—C19—C20	119.5 (2)	C16—C17—H17	120.00
N2—C20—C19	117.34 (17)	C18—C17—H17	120.00
C15—C20—C19	122.36 (19)	C17—C18—H18	120.00
N2—C20—C15	120.29 (18)	C19—C18—H18	120.00
C1—C2—H2	125.00	C18—C19—H19	120.00
C3—C2—H2	125.00	C20—C19—H19	120.00
C6—O3—C5—O2	5.9 (3)	C2—C3—C4—C10	118.35 (18)
C6—O3—C5—N1	−175.48 (15)	C15—C3—C4—N1	−176.71 (17)
C5—O3—C6—C7	−73.9 (2)	C15—C3—C4—C10	−55.4 (2)
C5—O3—C6—C8	51.4 (2)	C2—C3—C15—C16	−67.2 (3)
C5—O3—C6—C9	168.17 (17)	C2—C3—C15—C20	110.8 (2)
C14—O6—C13—O5	2.7 (3)	C4—C3—C15—C16	105.8 (2)
C14—O6—C13—C12	179.15 (18)	C4—C3—C15—C20	−76.2 (3)
C4—N1—C1—O1	179.15 (18)	N1—C4—C10—O4	76.74 (18)
C4—N1—C1—C2	−1.4 (2)	N1—C4—C10—C11	−162.19 (15)
C5—N1—C1—O1	−10.8 (3)	C3—C4—C10—O4	−38.0 (2)
C5—N1—C1—C2	168.65 (17)	C3—C4—C10—C11	83.03 (18)
C1—N1—C4—C3	2.58 (19)	O4—C10—C11—C12	−60.7 (2)
C1—N1—C4—C10	−119.33 (16)	C4—C10—C11—C12	176.57 (16)

C5—N1—C4—C3	−167.39 (17)	C10—C11—C12—C13	77.2 (3)
C5—N1—C4—C10	70.7 (2)	C11—C12—C13—O5	−135.7 (3)
C1—N1—C5—O2	8.1 (3)	C11—C12—C13—O6	48.0 (3)
C1—N1—C5—O3	−170.64 (16)	C3—C15—C16—C17	177.31 (19)
C4—N1—C5—O2	176.79 (18)	C20—C15—C16—C17	−0.9 (3)
C4—N1—C5—O3	−1.9 (2)	C3—C15—C20—N2	2.1 (3)
O7—N2—C20—C15	−10.9 (3)	C3—C15—C20—C19	−176.86 (18)
O7—N2—C20—C19	168.10 (18)	C16—C15—C20—N2	−179.86 (17)
O8—N2—C20—C15	169.43 (17)	C16—C15—C20—C19	1.2 (3)
O8—N2—C20—C19	−11.6 (3)	C15—C16—C17—C18	0.2 (3)
O1—C1—C2—C3	178.8 (2)	C16—C17—C18—C19	0.2 (4)
N1—C1—C2—C3	−0.6 (2)	C17—C18—C19—C20	0.0 (3)
C1—C2—C3—C4	2.3 (2)	C18—C19—C20—N2	−179.74 (19)
C1—C2—C3—C15	176.26 (17)	C18—C19—C20—C15	−0.8 (3)
C2—C3—C4—N1	−3.0 (2)		

Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H4O···O1^{i}	0.84	2.15	2.903 (2)	149
O4—H4O···O2^{i}	0.84	2.33	2.9696 (16)	134
C4—H4···O7	1.00	2.44	2.992 (2)	114
C8—H8A···O2	0.98	2.33	2.911 (2)	117
C8—H8C···O7^{ii}	0.98	2.55	3.410 (3)	146
C10—H10···O3	1.00	2.43	3.000 (3)	115
C11—H11B···O6	0.99	2.48	2.867 (3)	103
C19—H19···O5^{iii}	0.95	2.43	3.152 (3)	132

Symmetry codes: (i) −*x*+2, −*y*+2, −*z*+2; (ii) *x*+1, *y*, *z*; (iii) *x*−1, *y*, *z*.

(5)

Crystal data

$C_{13}H_{20}BrNO_4$	$Z = 2$
$M_r = 334.21$	$F_{000} = 344$
Triclinic, $P\overline{1}$	$D_x = 1.543$ Mg m^{-3}
Hall symbol: -P 1	Mo $K\alpha$ radiation $\lambda = 0.71073$ Å
$a = 8.8340$ (9) Å	Cell parameters from 12982 reflections
$b = 9.0750$ (9) Å	$\theta = 2.2$–$29.7°$
$c = 10.7283$ (10) Å	$\mu = 2.87$ mm^{-1}
$\alpha = 104.176$ (7)°	$T = 173$ (2) K
$\beta = 113.759$ (7)°	Block, colourless
$\gamma = 101.367$ (8)°	0.50 × 0.50 × 0.50 mm
$V = 719.57$ (12) Å^3	

Data collection

STOE IPDS-2 diffractometer	3862 independent reflections
Radiation source: fine-focus sealed tube	3587 reflections with $I > 2\sigma(I)$
Monochromator: graphite	$R_{int} = 0.031$
Detector resolution: 0.81Å pixels mm^{-1}	$\theta_{max} = 29.2°$
$T = 173(2)$ K	$\theta_{min} = 2.2°$
phi & ω scans	$h = -12 \rightarrow 12$
Absorption correction: multi-scan MULscanABS in PLATON (Spek, 2003)	$k = -10 \rightarrow 12$
$T_{min} = 0.307$, $T_{max} = 0.472$	$l = -14 \rightarrow 14$
9956 measured reflections	

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)] = 0.027$	$w = 1/[\sigma^2(F_o^2) + (0.0236P)^2 + 0.4857P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.066$	$(\Delta/\sigma)_{max} = 0.003$
$S = 1.05$	$\Delta\rho_{max} = 0.43$ e Å^{-3}
3862 reflections	$\Delta\rho_{min} = -0.78$ e Å^{-3}
177 parameters	Extinction correction: SHELXL, $Fc^* = kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
Primary atom site location: structure-invariant direct methods	Extinction coefficient: 0.012 (2)
Secondary atom site location: difference Fourier map	

Special details

Geometry. Bond distances, angles *etc*. have been calculated using the rounded fractional coordinates. All su's are estimated from the variances of the (full) variance-covariance matrix. The cell e.s.d.'s are taken into account in the estimation of distances, angles and torsion angles

Refinement. Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
Br1	1.47778 (2)	0.30287 (2)	1.13729 (2)	0.0329 (1)
O1	0.31030 (14)	−0.11093 (15)	0.53882 (12)	0.0262 (3)
O2	0.52777 (14)	−0.25263 (14)	0.45870 (12)	0.0245 (3)

O3	0.80224 (14)	−0.16522 (13)	0.64932 (12)	0.0231 (3)
O4	0.82532 (15)	0.30771 (13)	0.76664 (12)	0.0245 (3)
N1	0.61400 (16)	−0.04621 (15)	0.67145 (13)	0.0192 (3)
C1	0.44905 (19)	−0.03668 (18)	0.64902 (16)	0.0211 (4)
C2	0.4806 (2)	0.0789 (2)	0.78665 (18)	0.0247 (4)
C3	0.6499 (2)	0.13381 (19)	0.88148 (17)	0.0236 (4)
C4	0.75282 (19)	0.06297 (18)	0.81779 (15)	0.0201 (3)
C5	0.63877 (19)	−0.16534 (17)	0.58003 (16)	0.0200 (3)
C6	0.8667 (2)	−0.28116 (19)	0.57988 (17)	0.0230 (4)
C7	0.7644 (3)	−0.4500 (2)	0.5536 (2)	0.0342 (5)
C8	0.8571 (3)	−0.2594 (2)	0.4414 (2)	0.0336 (5)
C9	1.0554 (2)	−0.2308 (3)	0.6973 (2)	0.0385 (6)
C10	0.89225 (19)	0.19009 (18)	0.81204 (16)	0.0200 (3)
C11	1.05272 (19)	0.27493 (19)	0.96104 (16)	0.0229 (4)
C12	1.1980 (2)	0.39234 (19)	0.95675 (17)	0.0240 (4)
C13	1.3675 (2)	0.46521 (19)	1.09855 (17)	0.0244 (4)
H4	0.81030	−0.00080	0.87430	0.0240*
H2	0.39270	0.10970	0.80500	0.0300*
H3	0.69970	0.20910	0.97810	0.0280*
H4O	0.75420	0.26750	0.67690	0.0370*
H7A	0.76700	−0.45500	0.64460	0.0510*
H7B	0.64260	−0.47870	0.47880	0.0510*
H7C	0.81720	−0.52580	0.52020	0.0510*
H8A	0.91190	−0.14520	0.46220	0.0500*
H8B	0.73400	−0.29600	0.36660	0.0500*
H8C	0.91910	−0.32290	0.40610	0.0500*
H9A	1.05770	−0.24010	0.78710	0.0580*
H9B	1.11690	−0.11880	0.71640	0.0580*
H9C	1.11350	−0.30100	0.66420	0.0580*
H10	0.92810	0.13480	0.74120	0.0240*
H11A	1.09730	0.19350	0.99690	0.0270*
H11B	1.01900	0.33430	1.03060	0.0270*
H12A	1.22070	0.33530	0.87830	0.0290*
H12B	1.15710	0.48030	0.93160	0.0290*
H13A	1.34380	0.51190	1.17960	0.0290*
H13B	1.44870	0.55330	1.09370	0.0290*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Br1	0.0263 (1)	0.0349 (1)	0.0359 (1)	0.0131 (1)	0.0108 (1)	0.0149 (1)
O1	0.0180 (5)	0.0296 (6)	0.0238 (5)	0.0047 (4)	0.0064 (4)	0.0070 (4)
O2	0.0204 (5)	0.0215 (5)	0.0212 (5)	0.0046 (4)	0.0046 (4)	0.0024 (4)
O3	0.0186 (5)	0.0209 (5)	0.0226 (5)	0.0066 (4)	0.0059 (4)	0.0032 (4)
O4	0.0232 (5)	0.0194 (5)	0.0223 (5)	0.0052 (4)	0.0036 (4)	0.0080 (4)
N1	0.0166 (5)	0.0175 (6)	0.0187 (5)	0.0038 (4)	0.0058 (5)	0.0049 (4)
C1	0.0195 (6)	0.0202 (7)	0.0233 (7)	0.0056 (5)	0.0095 (6)	0.0096 (5)
C2	0.0230 (7)	0.0248 (7)	0.0267 (7)	0.0071 (6)	0.0130 (6)	0.0086 (6)

C3	0.0248 (7)	0.0225 (7)	0.0211 (7)	0.0061 (6)	0.0104 (6)	0.0062 (6)
C4	0.0186 (6)	0.0184 (6)	0.0174 (6)	0.0037 (5)	0.0050 (5)	0.0050 (5)
C5	0.0196 (6)	0.0166 (6)	0.0220 (6)	0.0047 (5)	0.0088 (5)	0.0073 (5)
C6	0.0227 (7)	0.0252 (7)	0.0238 (7)	0.0106 (6)	0.0122 (6)	0.0091 (6)
C7	0.0444 (10)	0.0237 (8)	0.0413 (10)	0.0149 (7)	0.0235 (8)	0.0141 (7)
C8	0.0353 (9)	0.0419 (10)	0.0295 (8)	0.0121 (8)	0.0191 (7)	0.0164 (7)
C9	0.0250 (8)	0.0576 (13)	0.0313 (9)	0.0190 (8)	0.0114 (7)	0.0128 (8)
C10	0.0192 (6)	0.0176 (6)	0.0195 (6)	0.0044 (5)	0.0069 (5)	0.0060 (5)
C11	0.0185 (6)	0.0232 (7)	0.0209 (7)	0.0033 (5)	0.0057 (5)	0.0076 (6)
C12	0.0198 (7)	0.0222 (7)	0.0244 (7)	0.0035 (6)	0.0067 (6)	0.0087 (6)
C13	0.0207 (7)	0.0193 (7)	0.0265 (7)	0.0053 (5)	0.0081 (6)	0.0042 (6)

Geometric parameters (Å, °)

Br1—C13	1.9575 (19)	C2—H2	0.9500
O1—C1	1.213 (2)	C3—H3	0.9500
O2—C5	1.2015 (19)	C4—H4	1.0000
O3—C5	1.331 (2)	C7—H7A	0.9800
O3—C6	1.477 (2)	C7—H7B	0.9800
O4—C10	1.413 (2)	C7—H7C	0.9800
O4—H4O	0.8400	C8—H8A	0.9800
N1—C4	1.4691 (19)	C8—H8B	0.9800
N1—C5	1.388 (2)	C8—H8C	0.9800
N1—C1	1.402 (2)	C9—H9A	0.9800
C1—C2	1.467 (2)	C9—H9B	0.9800
C2—C3	1.324 (3)	C9—H9C	0.9800
C3—C4	1.491 (3)	C10—H10	1.0000
C4—C10	1.545 (2)	C11—H11A	0.9900
C6—C8	1.517 (3)	C11—H11B	0.9900
C6—C9	1.517 (3)	C12—H12A	0.9900
C6—C7	1.510 (3)	C12—H12B	0.9900
C10—C11	1.516 (2)	C13—H13A	0.9900
C11—C12	1.522 (3)	C13—H13B	0.9900
C12—C13	1.508 (2)		
C5—O3—C6	121.31 (12)	C6—C7—H7B	109.00
C10—O4—H4O	109.00	C6—C7—H7C	109.00
C1—N1—C4	111.34 (13)	H7A—C7—H7B	110.00
C4—N1—C5	123.47 (14)	H7A—C7—H7C	109.00
C1—N1—C5	124.00 (13)	H7B—C7—H7C	109.00
O1—C1—N1	126.53 (15)	C6—C8—H8A	109.00
N1—C1—C2	105.51 (14)	C6—C8—H8B	109.00
O1—C1—C2	127.96 (17)	C6—C8—H8C	109.00
C1—C2—C3	109.86 (17)	H8A—C8—H8B	109.00
C2—C3—C4	111.62 (15)	H8A—C8—H8C	110.00
N1—C4—C10	112.27 (12)	H8B—C8—H8C	110.00
C3—C4—C10	113.40 (14)	C6—C9—H9A	109.00
N1—C4—C3	101.63 (14)	C6—C9—H9B	109.00
O2—C5—N1	124.16 (17)	C6—C9—H9C	109.00
O3—C5—N1	108.81 (13)	H9A—C9—H9B	109.00

O2—C5—O3	127.03 (16)	H9A—C9—H9C	109.00
O3—C6—C7	109.20 (16)	H9B—C9—H9C	109.00
O3—C6—C8	110.36 (15)	O4—C10—H10	109.00
C7—C6—C8	112.91 (14)	C4—C10—H10	109.00
C7—C6—C9	111.11 (17)	C11—C10—H10	109.00
O3—C6—C9	101.43 (14)	C10—C11—H11A	109.00
C8—C6—C9	111.24 (18)	C10—C11—H11B	109.00
O4—C10—C11	108.24 (13)	C12—C11—H11A	109.00
C4—C10—C11	110.71 (13)	C12—C11—H11B	109.00
O4—C10—C4	111.18 (15)	H11A—C11—H11B	108.00
C10—C11—C12	112.01 (13)	C11—C12—H12A	109.00
C11—C12—C13	113.79 (14)	C11—C12—H12B	109.00
Br1—C13—C12	111.00 (12)	C13—C12—H12A	109.00
C1—C2—H2	125.00	C13—C12—H12B	109.00
C3—C2—H2	125.00	H12A—C12—H12B	108.00
C2—C3—H3	124.00	Br1—C13—H13A	109.00
C4—C3—H3	124.00	Br1—C13—H13B	109.00
N1—C4—H4	110.00	C12—C13—H13A	109.00
C3—C4—H4	110.00	C12—C13—H13B	109.00
C10—C4—H4	110.00	H13A—C13—H13B	108.00
C6—C7—H7A	109.00		
C6—O3—C5—O2	−0.7 (3)	C4—N1—C5—O2	−177.97 (16)
C6—O3—C5—N1	179.11 (13)	C4—N1—C5—O3	2.2 (2)
C5—O3—C6—C7	−64.05 (19)	O1—C1—C2—C3	179.65 (18)
C5—O3—C6—C8	60.6 (2)	N1—C1—C2—C3	0.5 (2)
C5—O3—C6—C9	178.60 (16)	C1—C2—C3—C4	0.8 (2)
C4—N1—C1—O1	179.21 (17)	C2—C3—C4—N1	−1.68 (19)
C4—N1—C1—C2	−1.66 (18)	C2—C3—C4—C10	119.01 (16)
C5—N1—C1—O1	−12.9 (3)	N1—C4—C10—O4	72.57 (17)
C5—N1—C1—C2	166.25 (15)	N1—C4—C10—C11	−167.08 (14)
C1—N1—C4—C3	2.02 (17)	C3—C4—C10—O4	−41.91 (17)
C1—N1—C4—C10	−119.46 (16)	C3—C4—C10—C11	78.44 (17)
C5—N1—C4—C3	−165.97 (15)	O4—C10—C11—C12	−62.07 (19)
C5—N1—C4—C10	72.6 (2)	C4—C10—C11—C12	175.84 (14)
C1—N1—C5—O2	15.6 (3)	C10—C11—C12—C13	−173.35 (15)
C1—N1—C5—O3	−164.30 (14)	C11—C12—C13—Br1	68.73 (17)

Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H4O···O1^{i}	0.84	2.17	2.9138 (16)	148
O4—H4O···O2^{i}	0.84	2.28	2.9225 (18)	134
C7—H7B···O2	0.98	2.48	3.044 (3)	116
C8—H8B···O2	0.98	2.45	3.000 (3)	115
C10—H10···O3	1.00	2.50	3.032 (2)	113
C11—H11A···Br1	0.99	2.90	3.3776 (18)	110
C13—H13A···O4^{ii}	0.99	2.54	3.339 (2)	138

Symmetry codes: (i) −*x*+1, −*y*, −*z*+1; (ii) −*x*+2, −*y*+1, −*z*+2.

5. Conclusions

(-)-Rhazinilam (**1**) is a natural product which interfers in the tubulin-microtubule equilibrium. It shows significant *in vitro* cytotoxicity, but, unfortunately, no activity *in vivo*. Due to this reason and to its intriguing molecular structure, this molecule raised the interest in several synthetic groups in the last ten years: a number of synthetic approaches to the natural product and analogues have been reported.

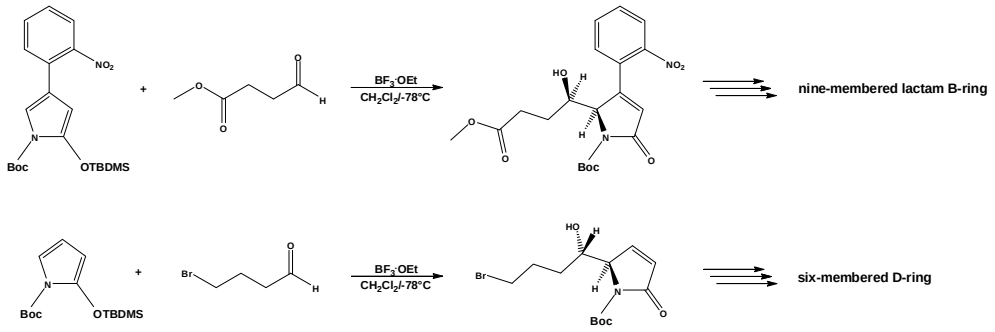
In the absence of structural data regarding the active binding-site, the only way to improve our understanding is the testing of as many structural variants as possible. The goal of this approach is to identify more active structural analogues of rhazinilam. The discrepancy between *in vitro* and *in vivo* activity is not understood so far and new structural variants have the potential to solve this problem.

Our group has developed a new strategy for the synthesis of rhazinilam analogues based on our methodology developed for the synthesis of highly sensitive unstabilized pyrroles. The key step is Mukaiyama reaction, which leads after condensation of the ester with the azido group followed by dehydration to the 1*H*-pyrrole-2(5*H*)-one **16a,b**. In our synthetic strategy, the deprotected pyrrole-one as in **16a,b** will replace the pyrrole C-ring from rhazinilam, hopefully protecting this sensitive element from degradation. At the same time these derivatives can be used to create new analogues and to modify the structure of the natural product.

In the context of our synthetic studies we determined the relative configuration of the aldol products obtained, because the structure determination based on NMR analysis alone was not possible. The diastereoselectivity observed showed an interesting dichotomy as a function of the substituents in the α-position of the aldehyde. This dichotomy is compatible with the mechanistic picture of the Cornforth transition state model and the polar Felkin-Anh model.

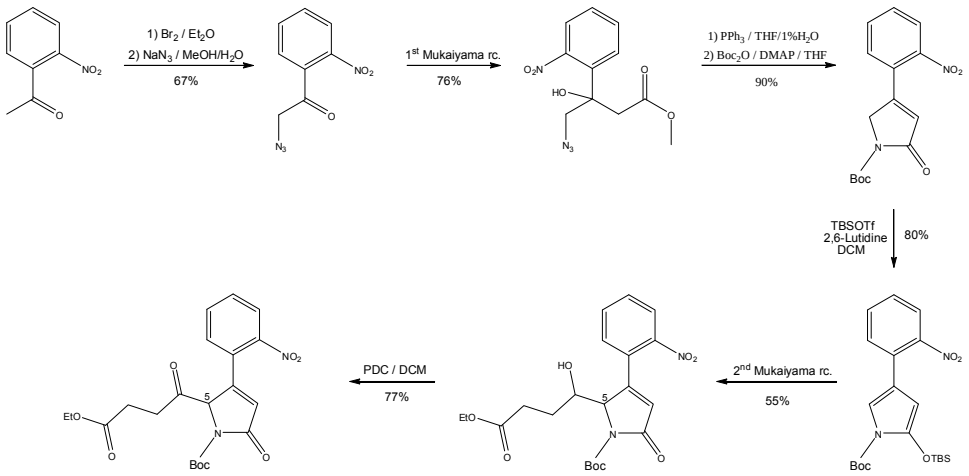
The X-ray analysis of the lactams and one of their precursors showed that the nicely soluble precursor forms intramolecular hydrogen bonds exclusively, whereas the purely insoluble lactams show a maximum number of intermolecular hydrogen bonds. We correlated this observation tentatively with the huge differences in solubility.

Having this key intermediate **16b** in hand, the important challenges were to find good and efficient methodologies to introduce the B-ring and the D-ring as we had the A,B-system firmly put in place. An important part of our efforts was dedicated to study independent methods for either the introduction of ring B or ring D. The goal of these studies was to find out, the best methods and to have in hands empirical data to make a decision on the best sequence for the introduction of the two missing rings.



Scheme 30: Studies towards B- respectively D-ring

The most advanced studies were pursuing the goal to introduce the side chain needed for the creation of the B-ring. A second aldol type Mukaiyama reaction allowed to introduce different side chains to the C-5 on the 1*H*-pyrrole-2(5*H*)-one (the 3rd publication in Acta Crystallographica). The diastereoselectivity of aldol products obtained during our studies could be ascertained based on the X-Ray structures of the crystalline compounds. We could show that for two of the compounds the diastereoselectivity is compatible with the results reported in the literature despite the fact that a phenyl substituent is present in the α-position to one of the newly formed chiral centers. However the third structure determined in this study showed an inversion of the diastereoslectivity. We have not been able to explain this switch of the diastereoselectivity.

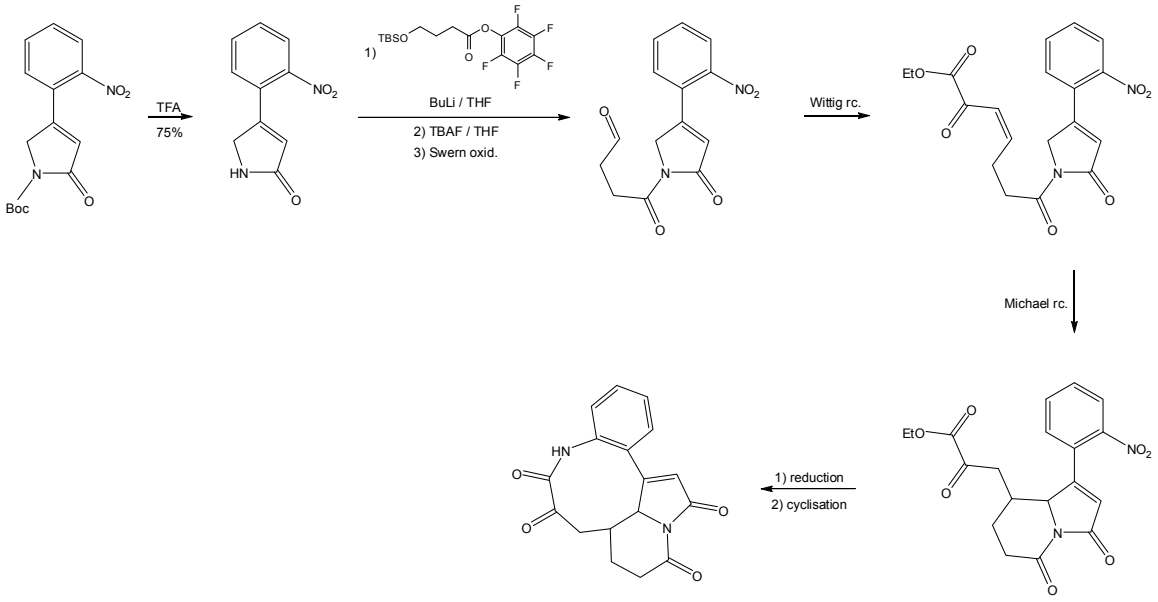


Scheme 31: Synthetic pathway to the formation of lactam B-ring

In conclusion, we have been able to obtain advanced intermediates for the synthesis of rhazinilam and analogues of rhazinilam. Our efforts to synthesize the D-ring have not yet allowed us to develop a reliable methodology. For the synthesis of the B-ring we could introduce all the carbon atoms needed. To transform this intermediate into a simplified version of rhazinilam would require the reduction of the nitro group followed by lactam formation. These two processes have been accomplished in earlier syntheses.

6. Perspectives

Because of the acidity of the proton in C-5, we have faced a lot of difficulties in building the D-ring of rhazinilam (six-membereed ring). Based on these observations our new strategy is N-acylation of 1*H*-pyrrole-2(5*H*)-one followed by Wittig and Michael reactions. Based on literature precedence the last steps will be the reduction of the nitro group and cyclisation of the nine-membered ring (Scheme 32).



Scheme 32: The presumed last steps in synthesis of rhazinilam analogue

7. Experimental Section

7.1. General remarks

Chromatography

Thin layer chromatography

Thin layer chromatography (TLC) was carried out in TLC plates made out of silica gel 60 F_{254} (fluorescence indicator). The TLC plates are of 10 cm length and 0.2 mm thickness. After the elution in the eluent mentioned, the plates were dried, looked under UV lamp (254 nm), marked and then looked for oxidized spots by spraying.

Column chromatography

Silica gel 60 Å, size of 0.04-0.063 mm (230-400 mesh ASTM) (Merck, Darmstadt). Eluent proportions are mentioned in the experimental part.

Gas chromatography

Agilent 6850 Series chromatography. Column used was HP-5 capillary column: long 30 m, interior diameter = 0.32 mm, film thickness = 0.25 μm. Nature of polymer: polysiloxane (crosslinked 5% Ph, Me silixane). Programme: injection at 150 °C or 170 °C, 2 min, 10 °C/min till 290 °C. Helium gas: 1.0 mL/min. Injection temp.: 250 °C Detecto temp. (FID): 300 °C; ChemStation Programme.

Infrared Spectroscopy (IR)

Perkin Elmer Spectrum One version B FT-IR was used for obtained IR spectras with the resolution of 2 cm^{-1}. Software used: Spectrum version 5.0.1. The solid substances and thick oil like substances were analyzed by preparing KBr pellets (KBr – Fluka puriss p.a.).Liquid samples were analyzed as film (sandwich) by applying between two KBr salt plates. The absorption bands between 4000 and 400 cm^{-1} were measured. The intensity

of the spectrum was divided into five equal parts for the abbreviations *vs* (very strong – the maximum intensity), *s* (strong), *m* (medium), *w* (weak), *vw* (very weak) and *br* (broad).

Nuclear Magnetic Spectroscopy (NMR)

The NMR spectras were measured using spectrometer Gemini XL-200 of Varian at 298 K where ^{1}H was measured at frequency of 200 MHz and ^{13}C was measured at frequency of 50 MHz. Also NMR spectras were measured using spectrometer Bruker Avance-400 at 298 K where ^{1}H was measured at frequency of 400 MHz and ^{13}C was measured at frequency of 100 MHz. The NMR solvents were purchased from Cambridge Isotope Laboratories. The internal standards for the spectras of ^{1}H: TMS (d = 0.00 ppm) or $CHCl_3$ (d = 7.26 ppm) or CH_3OH (d = 3.31 ppm) or $(CH_3)_2SO$ (d = 2.50 ppm) or H_2O (d = 4.79). The internal standards for the spectras ^{13}C: TMS (d = 0.00 ppm) or $CHCl_3$ (d = 77.00 ppm) or CH_3OH (d = 49.00 ppm) or $(CH_3)_2SO$ (d = 39.52 ppm). The ^{13}C spectras were measured by decoupling from ^{1}H. The chemical shift is given in ppm in the decreasing order and the coupling constant *J* in Hz. The multiplicity of signals were given abbreviations *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *quint* (quintet), *dt* (doublet of triplet), *br* (broad) and *m* (multiplet). The sign "≈" denotes for the average value of J varying from 0.2 to 0.4 Hz. The ratio of α to β is measured by area integration in the case of ^{1}H and by the intensity (height) of peak in the case of ^{13}C.

Mass Spectrometry

The mass spectra measurements for ESI (electro-spray ionization) and for APCI (atmospheric pressure chemical ionization) were carried out by an instrument ThermoFinnigan LCQ (San Jose, California, USA). Software used: Tune Plus version 1.2. The values given here are average mass of ion with precision in the range of ±0.1 values. The nature of ion pattern is written in parenthesis with intensity. The ion peaks due to deuterium isotope (probably comes from proton exchange by deuterium as some samples were dissolved in deuteriated solvents) were not considered. The mass corresponding to the highest abundant isotope is written.

The high resolution mass spectrometry (HR-MS) was measured at University of Fribourg (Switzerland) in the group of Professor Gossauer by Mr. F. Nydegger. The instrument used was Brucker BioAPEX II daltonics. The ionization used was ESI (electro-spray ionization).

Glass Apparatus

For reactions where Ar or N_2 was used, the glass apparatus were dried by keeping in the hot oven at 150 °C for at least 2 h. The apparatus were removed from hot oven and cooled to ambient temperature with Ar or N_2 atmosphere. For rections at low temperature, ice bath with salt (0 °C to -5 °C) and aacetone/liquid nitrogen bath were used. For reactions of long maintenance hours (2 days) at low temperature, cryostat was used. For heating reactions, PEG bath was used.

Karl-Fischer Titration

For reactions where the moisture content is very critical such as Mukaiyama reaction, the purified solvents, reactants and reagents if possible were checked for moisture content using the Karl-Fischer coulometer (Metler Toledo DL 32). For the moisture critical reactions, reactants and solvents were dried till the moisture content is less than 0.05% and then only reactions were carried out.

Hydrogenation

The hydrogenation reactions were carried out at room temperature under magnetic stirring with hydrogen filled “gas bag” (Aldrich) whose volume is approximately 1 gallon (3.8 L).

Solvents

For the purpose of chromatography and extractions, technical grade solvents were distilled over drying agents:

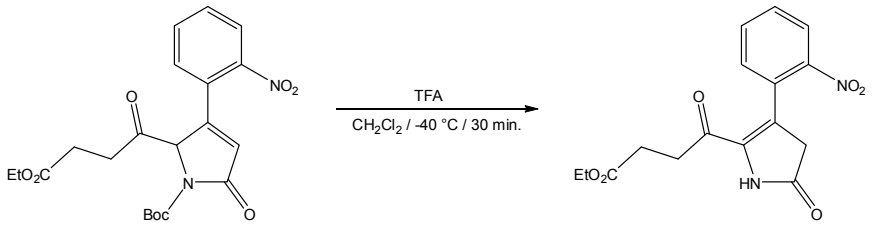
Solvent	**Abbreviation used**	**Drying agent**
Ethyl acetate	EtOAc	K_2CO_3
Hexane	hexane	$CaCl_2$
Dichloromethane	CH_2Cl_2	$CaCl_2$
Diethyl ether	Et_2O	$CaCl_2$
Methanol	MeOH	CaO
Chloroform	$CHCl_3$	$CaCl_2$

Solvents for reactions – with distillation

Solvent	**Abbreviation used**	**Drying agent**
Pentane	Pentane	P_2O_5
Dichloromethane	CH_2Cl_2	P_2O_5
Diethyl ether	Et_2O	$LiAlH_4$
Tetrahydrofurane	THF	potasium/benzophenone

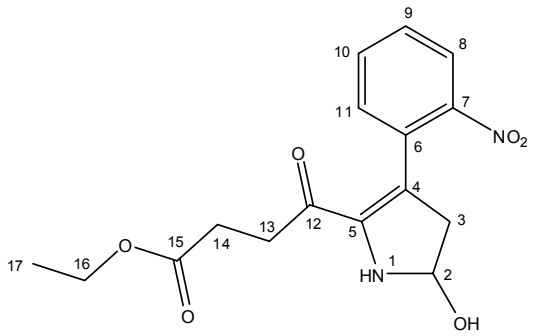
7.2. Syntheses

Synthesis of ethyl 4-(3-(2-nitrophenyl)-5-oxo-4,5-dihydro-1*H*-pyrrole-2-yl)-4-oxobutanoate



432.43 332.32

tert-Butyl 2-(4-ethoxy-4-oxobutanoyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (0.11 g, 0.3 mmol) is dissolved in CH_2Cl_2 (2 mL) and the temperature is brought to -40 °C. Triflouroacetic acid (TFA) (0.02 mL, 0.25 mmol) is added to the reaction. The mixture is kept under stirring to -40 °C for 30 min. The solution is quenched with sat. $NaHCO_3$, the aqueous layers are extracted with CH_2Cl_2 and the solvent is concentrated under vacuum. The crude oil is purified by chromatography (CH_2Cl_2/Et_2O 3:7) (75%).



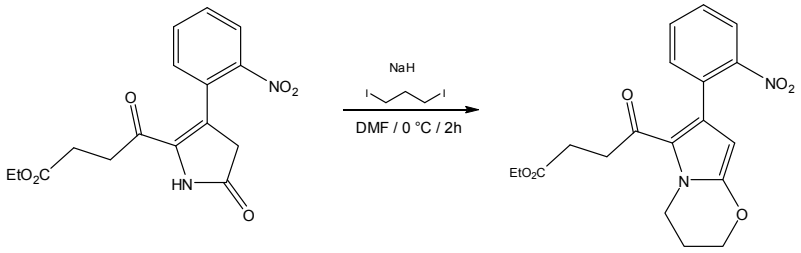
^{1}H-NMR: 8.25(*s*, 1H, NH); 8.20(*dd*, ^3J(8,9)=8.2, ^4J(8,10)=1.2, 1H, H(8)); 7.75(*ddd*, ^3J(10,11)=^3J(10,9)=7.5, ^4J(10,8)=1.2, 1H, H(10)); 7.64(*ddd*, ^3J(9,8)=8.3, ^3J(9,10)=7.4, ^4J(9,11)=1.4, 1H, H(9)); 7.49(*dd*, ^3J(11,10)=7.6, ^4J(11,9)=1.4, 1H, H(11)); 4.06(*q*, ^3J(16,17)=7.1, 2H, H(16)); 3.62(*s*, 2H, H(3)); 2,46(*tripletoid*, ^3J(13a, 14a)=6.0, ^3J(13b, 14b)=6.6, 2H, H(13)); 2.31*(tripletoid*, ^3J(14b, 13b)=6.6, ^3J(14a, 13a)=6.0, 2H, H(19)); 1.19(*t*, ^3J(17,16)=7.1, 3H, H(17));

^{13}C-NMR: 189.8(C(12)); 174.6(C(15)); 172.1(C(2)); 148.1(C(7)); 136.3(C(6)); 134.2(C(10)); 131.8(C(11)); 130.5(C(9)); 129.5(C(5)); 125.5(C(8)); 124.5(C(4)); 60.9(C(16)); 45.0(C(3)); 34.7(C(14)); 27.7(C(13)); 14.2(C(17)).

IR: 3132(*s*); 2927(*w*); 1729(*m*); 1602(*m*); 1574(*w*); 1525(*s*); 1401(*vs*); 1347(*m*).

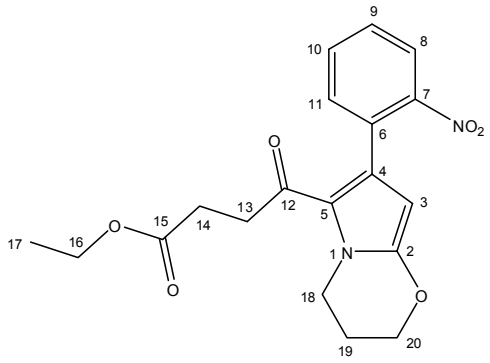
MS-ESI: 331.3$[M-H]^-$

Synthesis of ethyl 4-(7-(2-nitrophenyl)-3,4-dihydro-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-6-yl)-4-oxobutanoate



332.32 372.13

Ethyl 4-(3-(2-nitrophenyl)-5-oxo-4,5-dihydro-1*H*-pyrrole-2-yl)-4-oxobutanoate (0.23 g, 0.69 mmol) is dissolved in DMF (20 mL) and the temperature is brought to 0 °C. NaH (0.02 g, 0.83 mmol) is added to the reaction and resulted mixture is kept under stirring for 15 min. 1,3-diiodopropan (0.20 mL, 1.7 mmol) is added dropwise to the solution. After 2 h, the reaction is diluted with Et_2O (150 mL) and washed with H_2O and sat. $NaHCO_3$. After extraction, the organic solvent is concentrated under vacuum. The crude product is purified by chromatography (Et_2O) (60%).



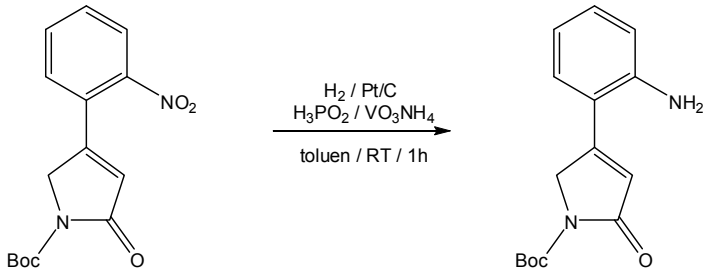
^{1}H-NMR: 7.93(*dd*, ^{3}J(8,9)=8.0, ^{4}J(8,10)=1.3, 1H, H(8)); 7.63(*ddd*, ^{3}J(10,11)=^{3}J(10,9)=7.5, ^{4}J(10,8)=1.3, 1H, H(10)); 7.54(*ddd*, ^{3}J(9,8)=8.0, ^{3}J(9,10)=7.5, ^{4}J(9,11)=1.5, 1H, H(9)); 7.47(*dd*, ^{3}J(11,10)=7.5, ^{4}J(11,9)=1.5, 1H, H(11)); 5.38(*s*, 1H, H(3)); 4.45(*t*, ^{3}J(18,19)=6.0, 2H, H(18)); 4.31(*m*, 2H, H(20)); 4.06(*q*, ^{3}J(16,17)=7.1, 2H, H(16)); 2,54-2.31(*m*, 4H, H(13,14)); 2.19(*m*, 2H, H(19)); 1.20(*t*, ^{3}J(17,16)=7.1, 3H, H(17));

^{13}C-NMR: 187.1(C(12)); 173.4(C(15)); 149.8(C(2)); 149.0(C(7)); 133.0(C(11)); 132.6(C(9)); 132.4(C(6)); 129.3(C(5)); 129.2(C(10)); 124.3(C(8)); 121.5(C(4)); 93.7(C(3)); 65.6(C(20)); 60.7(C(16)); 44.2(C(18)); 34.8(C(14)); 28.8(C(13)); 22,3(C(19)); 14.5(C(17)).

IR: 3125(*s*); 3006(*w*); 2929(*w*); 1733(*m*); 1621(*m*); 1560(*w*); 1502(*m*); 1401(*vs*).

MS-ESI: 373.1$[M+H]^{+}$

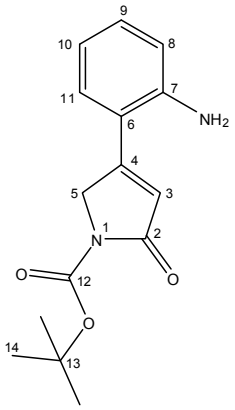
Synthesis of *tert*-butyl 4-(2-aminophenyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate



304.10 274.13

Catalyst pre-treatment: Pt/C 5% (250 mg) and H_2O (5 mL) are mixed in a test tube and an aqueous solution of H_3PO_2 5% (200 mg) is added. The resulting mixture is stirred for 15 min. VO_3NH_4 (7.5 mg) is added and the reaction is stirred for 15 min. more.

tert-Butyl 4-(2-aminophenyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (2.50 g, 8.2 mmol) is dissolved in toluene (50 mL). The pre-treated catalyst is added to the solution. A "gas bag" with hydrogen is added to the installation (the air from flask is replaced by hydrogen). The mixture is kept under stirring at RT for 1 h. The solution is washed with H_2O (100 mL), the aqueous layers are extracted with Et_2O and the solvent is removed under reduced pressure for obtaining a yellow solid (93%).



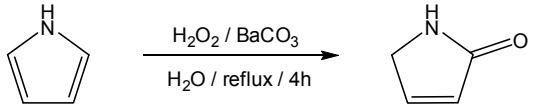
^{1}H-NMR: 7.22(*dd*, ^3J(11,10)=7.9, ^4J(11,9)=1.3, 1H, H(11)) ; 7.12(*m*(*partial solved*), ^3J(9,8)=7.6, ^4J(9,11)=1.4, 1H, H(9)); 6.80(*dd*, ^3J(8,9)=7.7, ^4J(8,10)=0.9, 1H, H(8)); 6.61(*m*(*partial solved*), ^3J(10,9)=7.5, ^4J(10,8)=1.0), 1H, H(10)); 6,36(*s*, 1H, H(3)); 5,47(*s*, 2H, NH_2); 4.70(*d*, ^4J(5,3)=1.1, 2H, H(5)); 1.48(*s*, 9H, H(14)).

^{13}C-NMR: 169.5 (C(2)) ; 155.7 (C(12)) ; 149.5 (C(4)) ; 148.2 (C(7)) ; 131.6 (C(9)) ; 128.6 (C(11) ; 119.9 (C(3)) ; 117.4 (C(8)) ; 116.9 (C(10)) ; 115.7 (C(6)) ; 81.8(C(13)) ; 52.7 (C(5)) ; 28.2 (C(14)).

IR: 3458(*w*), 3344(*m*), 3223(*w*), 3074(*vw*), 3014(*vw*), 2984(*w*), 2930(*w*), 2854(*w*), 2588(*vw*), 2422(*vw*), 1712(*vs*), 1637(*s*), 1608(*s*), 1589(*m*), 1561(*s*), 1499(*m*), 1360(*vs*), 1330(*vs*), 1251(*s*), 1202(*m*), 1165(*s*), 1153(*s*), 1101(*vs*), 750(*m*), 740(*m*).

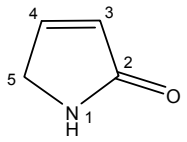
HR-MS: calc. 297.1209; found 297.1199

Synthesis of 1*H*-pyrrole-2(5*H*)-one



67.09 83.09

Pyrrole (5.00 g, 74.5 mmol) in dissolved in H_2O (450 mL). H_2O_2 35% (6.18 mL, 74.5 mmol) and $BaCO_3$ (1.50 g, 7.6 mmol) is added to the reaction. The resulting mixture is kept under reflux for 4 h. The excess of oxidant is removed with small quantity of PbO_2. The solution is filtered and the water is removed under reduced pressure. The crude oil is treated with dioxin till a precipitated is formed. It is filtered and the resulted oil is concentrated under vacuum. Purification under bulb-to-bulb distillation (T=100-130 °C, P=0.5 mmHg) to obtain a light yellow oil (29%).



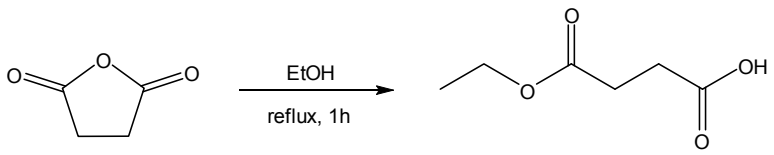
^{1}H-NMR: 6.91(*dq*, ^{3}J(3,4)=5.6, ^{4}J(3,5)=^{4}J(3,1)=1.7, 1H, H(3)); 5.85(*d*×*quadrupletoid*, ^{3}J(4,3)=5.6, ^{3}J(4,5)≈^{4}J(4,1)≈1.9, 1H, H(4)); 3.78(*quadrupletoid*, ^{3}J(5,1)≈^{3}J(5,4)≈^{4}J(5,3) ≈1.8, 2H, H(5)).

^{13}C-NMR: 175.9(C(2)); 146.5(C(3)); 127.6(C(4)); 49.3(C(5)).

IR: 3271(*m*); 1672(*vs*)).

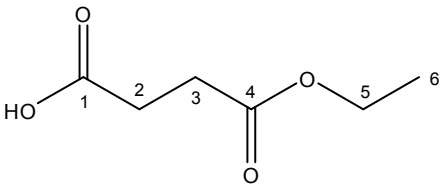
MS-ESI: 84.1$[M+H]^{+}$

Synthesis of 4-ethoxy-4-oxobutanoic acid



100.01 146.05

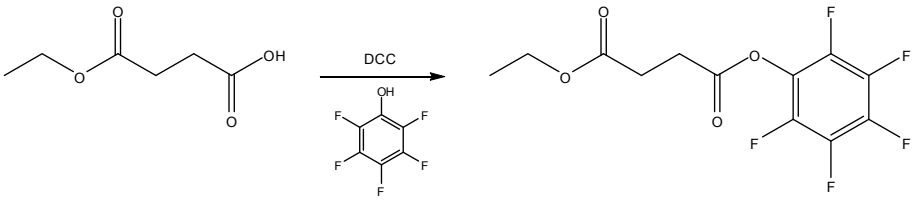
Dihydrofuran-2,5-dione (5.00 g, 50.0 mmol) is dissolved in EtOH (3.50 mL, 60.7 mmol). The reaction is kept 1 h under reflux. The excess of ethanol is removed under vacuum and the product is directly used for the next step.



^{1}H-NMR: 12.1(*br*, 1H, COOH); 4.3(*q*, ^{3}J(5,6)=7.1, 2H, H(5)); 2.50-2.42(*m*, 4H, H(2,3)); 1.15(*t*, ^{3}J(6,5)=7.1, 3H, H(6)).

^{13}C-NMR: 173.8(C(1)); 172.5(C(4)); 60.4(C(5)); 29.1(C(3)); 29.1(C(2)); 14.4(C(6)).

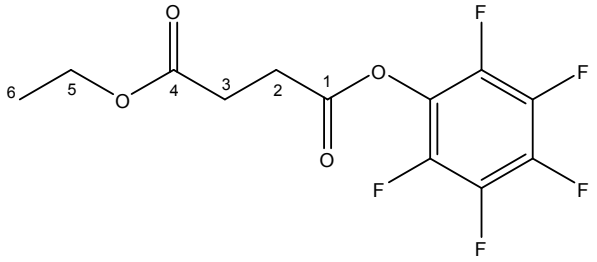
Synthesis of ethyl perflourophenyl succinate



146.14 312.18

4-ethoxy-4-oxobutanoic acid (1.37 g, 9.4 mmol) in CH_2Cl_2 (40 mL) is charged in a dry flusk under Ar atmosphere and cooled to 0 °C. Pentaflourophenol (1.89 g, 10.3 mmol) is added followed by DCC (2.16 g, 10.5 mmol). The reaction is brought to RT and kept fixed overnight. The reaction mass is then filtered over celite bed to get rid off DCC,

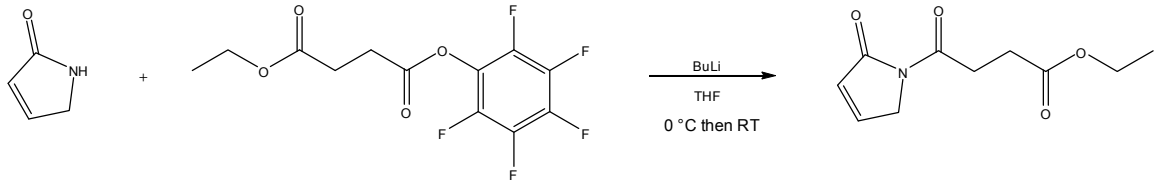
concentrated under vacuum and the crude product is purified by chromatography (hexane/CH_2Cl_2 3:1) (69%).



^{1}H-NMR: 4.16(*q*, ^3J(5,6)=7.1, 2H, H(5)); 2.97(*tripletoid*, ^3J(2,3)≈7.1, 2H, H(2)); 2.73(*tripletoid*, ^3J(3,2)≈7.0, 2H, H(3)); 1.25(*t*, ^3J(6,5)=7.1, 3H, H(6)).

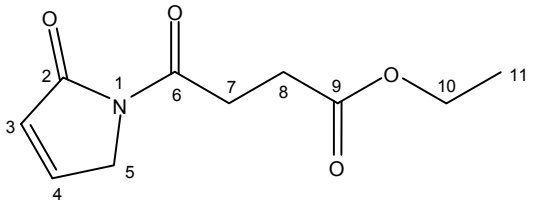
^{13}C-NMR: 171.2(C(4)); 168.4(C(1)); 142.4-142.2(m, $C_{Ar}F$); 140.9-140.5(m, $C_{Ar}F$); 139.9-139.7(m, $C_{Ar}F$); 139.2-138.9(m, $C_{Ar}F$); 138.3-138.1(m, $C_{Ar}F$); 136.7-136.4(m, $C_{Ar}F$); 61.0(C(5)); 28.8(C(3)); 28.3(C(2)); 13.9(C(6)).

Synthesis of 4-oxo-4-(2-oxo-2,5-dihydro-1H-pyrrole-1-yl)butanoate



83.09 312.18 211.21

1*H*-pyrrole 2(5*H*)-one (0.43 g, 5.2 mmol) in THF (80 mL) is cooled to 0 °C under Ar. BuLi 1.6M in hexane (3.61 mL, 5.8 mmol) is added slowly to the reaction. After 80 min. at 0 °C, a solution of ethyl perfluorophenyl succinate (1.84 g, 5.9 mmol) in THF (30 mL) is added. The reaction is kept under stirring at 0 °C for 30 min. more, then the temperature is raided to RT and kept fixed for 2.5 h. The mixture is washed with sat. NH_4Cl (20 mL), the organic layers are extracted with $CHCl_3$ (3 times) and the solvent is evaporated under vacuum. The crude product is purified by chromatography (CH_2Cl_2) (66%).

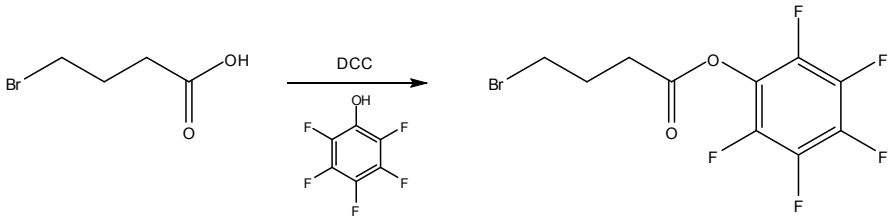


^{1}H-NMR: 7.27(*dt*, ^{3}J(3,4)=6.0, ^{4}J(3,5)=2.0 1H, H(3)); 6.13(*dt*, ^{3}J(4,3)=6.1, ^{3}J(4,5)=1.9, 1H, H(4)); 4.37(*dd*, ^{3}J(5,4)=^{4}J(5,3)=2.0, 2H, H(5)); 4.12(*q*, ^{3}J(10,11)=7.1, 2H, H(10)); 3.24(*t*, ^{3}J(7,8)=6.6, 2H, H(7)); 2.65(*t*, ^{3}J(8,7)=6.6, 2H, H(8)); 1.22(*t*, ^{3}J(11,10)=7.1, 3H, H(11)).

^{13}C-NMR: 172.6(C(9)); 171.7(C(6)); 170.0(C(2)); 127.5(C(4)); 60.6(C(10)); 50.5(C(5)); 31.5(C(7)); 28.2(C(8)); 14.1(C(11)).

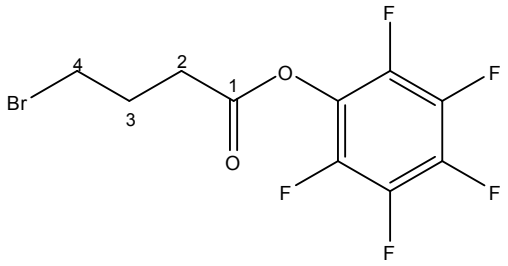
HR-MS: calc. 234.0736; found 234.0731.

Synthesis of perfluorophenyl 4-bromobutanoate



167.0 333.05

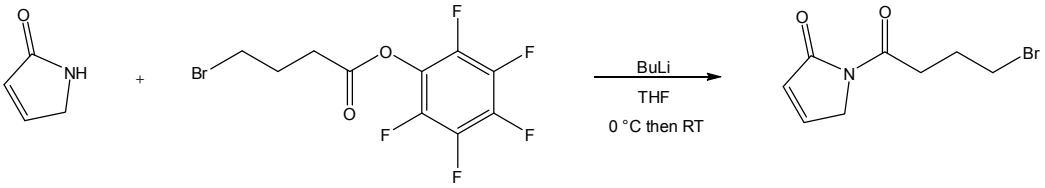
4-bromobutanoic acid (1.67 g, 10.0 mmol) in CH_2Cl_2 (40 mL) is charged in a dry flusk under Ar atmosphere and cooled to 0 °C. Pentaflourophenol (2.02 g, 11.0 mmol) is added followed by DCC (2.31 g, 11.2 mmol). The reaction is brought to RT and kept fixed overnight. The reaction mass is then filtered over celite bed to get rid off DCC, concentrated under vacuum and the crude product is purified by chromatography (hexane/CH_2Cl_2 3:1) (90%).



^{1}H-NMR: 3.53(*t*, ^{3}J(4,3)=6.3, 2H, H(4)); 2.90(*t*, ^{3}J(2,3)=7.1, 2H, H(2)); 2.32(*tt*, ^{3}J(3,2)=7.0, ^{3}J(3,4)=6.5, 2H, H(3)).

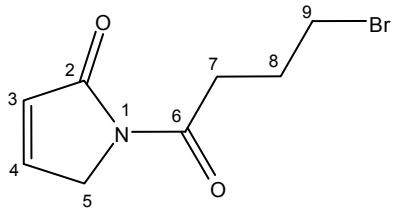
^{13}C-NMR: 168.4(C(1)); 142.4-142.2(m, $C_{Ar}F$); 140.9-140.6(m, $C_{Ar}F$); 139.9-139.7(m, $C_{Ar}F$); 139.2-139.0(m, $C_{Ar}F$); 138.4-138.1(m, $C_{Ar}F$); 136.8-136.4(m, $C_{Ar}F$); 31.6(C(4)); 31.5(C(2)); 27.3(C(3)).

Synthesis of 1-(4-bromobutanoyl)-1*H*-pyrrole-2(5*H*)-one



83.09 331.04 232.07

1*H*-pyrrole 2(5*H*)-one (0.60 g, 7.2 mmol) in THF (100 mL) is cooled to 0 °C under Ar. BuLi 1.6M in hexane (5.00 mL, 8.0 mmol) is added slowly to the reaction. After 80 min. at 0 °C, a solution of perfluorophenyl 4-bromobutanoate (2.73 g, 8.2 mmol) in THF (40 mL). The reaction is kept under stirring at 0 °C for 30 min. more, then the temperature is raided to RT and kept fixed for 2.5 h. The mixture is washed with sat. NH_4Cl (20 mL), the organic layers are extracted with $CHCl_3$ (3 times) and the solvent is evaporated under vacuum. The crude product is purified by chromatography (CH_2Cl_2) (82%).

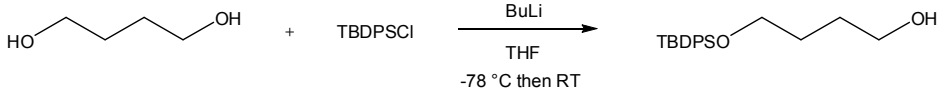


^{1}H-NMR: 7.30(*dt*, ^{3}J(3,4)=6.1, ^{4}J(3,5)=2.0, 1H, H(3)); 6.12(*dt*, ^{3}J(4,3)=6.1, ^{4}J(4,5)=1.9, 1H, H(4)) ; 4.36(*dd*, ^{3}J(5,4)=^{4}J(5,3)=2.0, 2H, H(5)) ; 3.45(*t*, ^{3}J(9,8)=6.6, 2H, H(9)) ; 3.07(*t*, ^{3}J(7,8)=7.0, 2H, H(7)) ; 2.18(*tt*, ^{3}J(8,7)≈^{4}J(8,9)=6.8, 2H, H(8)).

^{13}C-NMR: 171.9(C(6)) ; 170.0(C(2)) ; 147.0(C(3)) ; 127.4(C(4)) ; 50.6(C(5)) ; 34.7(C(7)) ; 32.9(C(9)) ; 27.0(C(8)).

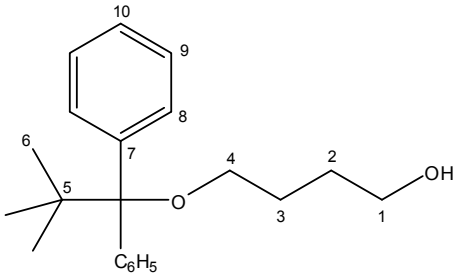
IR: 3363(*w*), 3102(*w*), 2924(*w*), 2687(*vw*), 1727(*vs*), 1693(*vs*), 1598(*w*), 1534(*m*), 1517(*s*), 1441(*m*), 1384(*s*), 1349(*s*), 1335(*vs*), 1286(*m*), 1241(*s*), 1218(*s*), 1015(*m*), 995(*m*), 979(*m*), 806(*s*).

Synthesis of 4-(*tert*-butyldiphenylsilyloxy)butan-1-ol



90.12 274.87 328.53

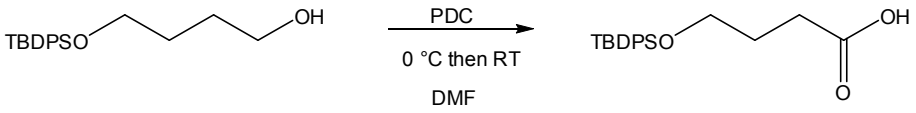
1,4-Butandiol (3.00 g, 33.3 mmol) in dried THF (18 mL) is cooled to -78 °C under Ar. BuLi 1.6M in hexane (7.00 mL, 11.1 mmol) is added dropwise to the white suspension under strong stirring. After 5 min., TBDPSCl (2.88 mL, 11.1 mmol), is added slowly to the solution. The temperature is raised to RT and the reaction is kept under stirring for 40 min. The resulting mixture is washed with H_2O (20 mL) and sat. NaCl (20 mL), the combined organic phases are dried over $MgSO_4$ and the solvent is evaporated under vacuum. The crude product is purified by chromatography (hexane/EtOAc 100:15) (67%).



[1]H-NMR: 7.76-7.73(*m*, 4H, H(8)) ; 7.50-7.42(*m*, 6H, H(9,10)) ; 3.76(*t*, ^{3}J(1,2)=5.7, 2H, H(1)) ; 3.70(*t*, ^{3}J(4,3)=6.0, 2H, H(4)) ; 2.43 (*s*, 1H, OH)) ; 1.78-1.67(*m*, 4H, H(2,3)) ; 1.13 (*s*, 9H, H(6)).

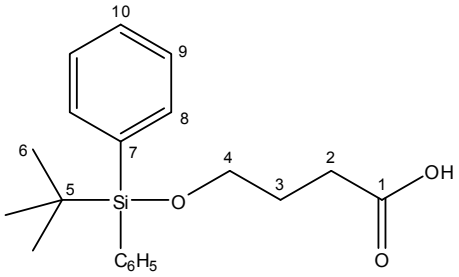
[13]C-NMR: 135.6(C(8)); 133.7(C(7)); 129.7(C(10)); 127.7(C(9)); 64.0(C(1)); 62.7(C(4)); 29.8(C(2)); 29.3(C(3)); 26.9(C(6)); 19.2(C(5)).

Synthesis of 4-(*tert*-butyldiphenylsilyloxy)butanoic acid



328.52 342.50

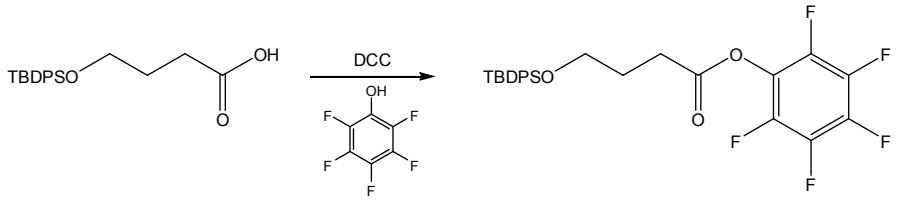
4-(*tert*-Butyldiphenylsilyloxy)butan-1-ol (2.60 g, 7.9 mmol) in DMF (20 mL) is cooled to 0 °C under Ar and treated portionwise with PDC (10.42 g, 27.7 mmol). After 1 h at 0 °C, the temperature is raised at RT and the reaction is kept under stirring at this temperature over night (15 h). The mixture is washed with H_2O (150 mL) and the organic layer is extracted with Et_2O (5 times). The combined organic phases are dried over $MgSO_4$, filtered over celite:silice:celite and concentrated under vacuum giving the pur product (63%).



^{1}H-NMR: 11.51(*br*, 1H, COOH); 7.81-7.78(*m*, 4H, H(8)); 7.55-7.47(*m*, 6H, H(9,10)); 3.83(*t*, ^{3}J(4,3)=6.0, 2H, H(4)); 2.63(*t*, ^{3}J(2,3)=7.3, 2H, H(2)); 2.01(*tt*, ^{3}J(3,2)=7.2, ^{3}J(3,4)=6.0, 2H, H(3)); 1.19(*s*, 9H, H(6)).

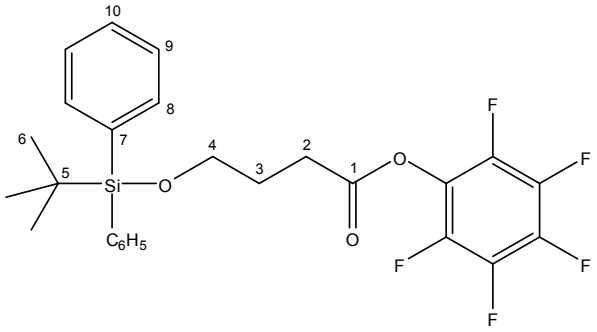
^{13}C-NMR: 180.6(C(1)) ; 135.6(C(8)) ; 133.7(C(7)) ; 129.7(C(10)) ; 127.8(C(9)) ; 62.8(C(4)) ; 30.95(C(2)) ; 27.6(C(3)) ; 26.9(C(6)) ; 19.31(C(5)).

Synthesis of perfluorophenyl 4-(*tert*-butyldiphenylsilyloxy)butanoate



342.50 508.55

4-(*tert*-butyldiphenylsilyloxy)butanoic acid (2.44 g, 7.1 mmol) in CH_2Cl_2 (50 mL) is charged in a dry flusk under Ar atmosphere and cooled to 0 °C. Pentaflourophenol (1.44 g, 7.8 mmol) is added followed by DCC (1.64 g, 8.0 mmol). The reaction is brought to RT and kept fixed overnight. The reaction mass is then filtered over celite bed to get rid off DCC, concentrated under vacuum and the crude product is purified by chromatography (hexane/CH_2Cl_2 3:1) (92%).

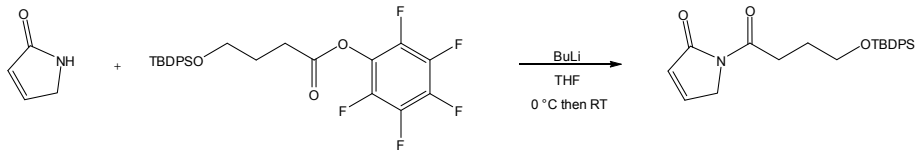


^{1}H-NMR: 7.74-7.72(*m*, 4H, H(8)) ; 7.51-7.42(*m*, 6H, H(9,10)) ; 3.83(*t*, ^{3}J(4,3)=6.0, 2H, H(4)) ; 2.90(*t*, ^{3}J(2,3)=7.3, 2H, H(2)) ; 2.07(*tt*, ^{3}J(3,2)=7.3, ^{3}J(3,4)=6.0, 2H, H(3)) ; 1.13(*s*, 9H, H(6)).

^{13}C-NMR: 169.5(C(1)); 142.5-142.3(m, $C_{Ar}F$); 140.8-140.5(m, $C_{Ar}F$); 240.0-139.8(m, $C_{Ar}F$); 139.3-138.9(m, $C_{Ar}F$); 138.3-138.0(m, $C_{Ar}F$); 136.8-136.4(m, $C_{Ar}F$); 135.5(C(8)); 133.5(C(7)); 129.7(C(10)); 127.7(C(9)); 62.2(C(4)); 29.8(C(2)); 27.5(C(3)); 26.8(C(6)); 19.2(C(5)).

IR: 3391(*vw*); 3235(*vw*); 3072(*w*); 3051(*w*); 2958(*m*); 2932(*m*); 2893(*w*); 2859(*m*); 2668(*vw*); 2459(*vw*); 2143(*vw*); 1959(*vw*); 1891(*vw*); 1791(*s*); 1654(*vw*); 1589(*w*); 1520(*vs*); 1472(*m*); 1428(*m*); 1112(*vs*); 1022(*m*); 1002(*vs*); 823(*m*); 742(*m*); 702(*vs*); 614(*m*); 506(*s*).

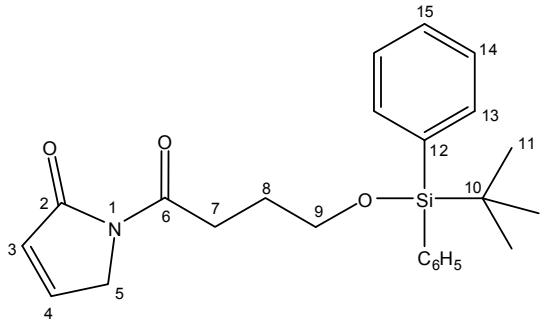
Synthesis of 1-(4-*tert*-butyldiphenylsilyloxy)butanoyl-1*H*-pyrrole-2(5*H*)-one



83.09 508.55 407.57

1*H*-pyrrole 2(5*H*)-one (0.30 g, 3.5 mmol) in THF (50 mL) is cooled to 0 °C under Ar. BuLi 1.6M in hexane (2.40 mL, 3.9 mmol) is added slowly to the reaction. After 80 min. at 0 °C, a solution of perfluorophenyl 4-(*tert*-butyldiphenylsilyloxy)butanoate (2.02 g, 4.0 mmol) in THF (20 mL). The reaction is kept under stirring at 0 °C for 30 min. more, then the temperature is raided to RT and kept fixed for 4.5 h. The mixture is washed with sat. NH_4Cl (20 mL), the organic layers are extracted with $CHCl_3$ (3 times) and the solvent is

evaporated under vacuum. The crude product is purified by chromatography (CH_2Cl_2) (38%).

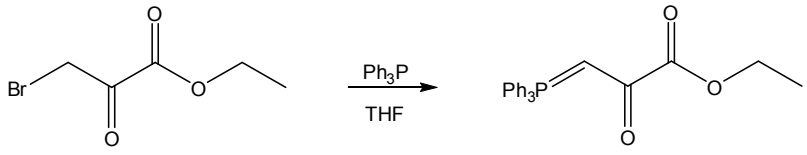


^{1}H-NMR: 7.69-7.65(*m*, 4H, H(13)) ; 7.43-7.35(*m*, 6H, H(14,15)); 7.29(*dt*, ^3J(3,4)=6.0, ^4J(3,5)=2.0, 1H, H(3) ; 6.19(*dt*, ^3J(4,3)=6.0, ^3J(4,5)=1.9, 1H, H(4)); 4.37(*d*d, ^4J(5,3)=^3J(5,4)=2.0, 2H, H(5)); 3.75(*t*, ^3J(9,8)=6.2, 2H, H(9)); 3.09(*t*, ^3J(7,8)=7.3, 2H, H(7)); 1.97(*tt*, ^3J(8,7)=7.3, ^3J(8,9)=6.2, 2H, H(8)); 1.054(*s*, 9H, H(11)).
^{13}C-NMR: 173.0(C(6)); 169.8(C(2)); 146.4(C(3)); 135.6(C(13)); 133.8(C(12)); 129.5(C(15)); 127.7(C(4)); 127.6(C(14)); 63.0(C(9)); 50.6(C(5)); 32.9(C(7)); 26.9(C(8)); 26.87(C(11)); 19.2(C(10)).

IR: 3433(*vs*, H_2O); 3070(*w*); 2930(*s*); 2857(*m*); 1729(*vs*); 1696(*vs*); 1427(*m*); 1385(*s*); 1348(*m*); 1333(*s*); 1260(*m*); 1216(*m*); 1109(*s*); 805(*m*); 702(*s*).

HR-MS: calc. 430.1808; found 430.1800.

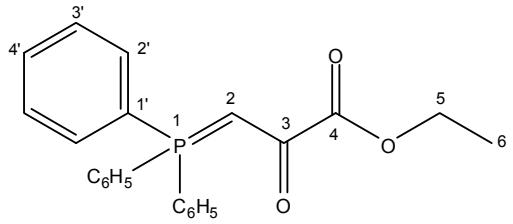
Synthesis of ethyl triphenylphosphoranylidenepyruvate



193.95 376.12

Triphenylphosphine (1.90 g, 7.2 mmol) is dissolved in THF (15 mL). To the stirring solution, ethyl bromopyruvate (0.50 mL, 3.6 mmol) is added. The mixture is stirred at RT for 30 min. and then refluxed under Ar for 2 h. The solvent is removed under reduced pressure and the residue is triturated with Et_2O (3 times), redissolved in water (20 mL)

and extracted with Et_2O. The pH of the aqueous layer is adjusted with sat. $NaHCO_3$ to *ca.* 8 when no more precipitate formed. It is filtered and the filter cake is washed thoroughly with water. After crystallization from EtOH, the yellow solid is obtained (36%).



^{1}H-NMR: 7.69-7.64(*m*, 6H, H(2')) ; 7.61-756(*m*, 3H, H(4')) ; 7.50-7.46(*m*, 6H, H(3')) ; 4.84(*d*, ^{2}J(2,1)=23.3, 1H, H(2)) ; 4.26(*q*, ^{3}J(5,6)=7.1, 2H, H(5)) ; 1.35(*t*, ^{3}J(6,5)=7.1, 3H, H(6)).

^{13}C-NMR: 174.2(d, C(3)) ; 165.8(d, C(4)) ; 133.2(d, C(2')) ; 132.5(d, C(4')) ; 129.1(d, C(3')) ; 125.8(d, C(1')) ; 61.2(C(5)) ; 56.5(d, C(2)) ; 14.2(C(6)).

IR: 3083(*vw*), 3051(*vw*), 2925(*vw*), 1703(*vs*), 1628(*vw*), 1577(*s*), 1558(*vs*), 1481(*m*), 1437(*m*), 1217(*vs*), 1184(*m*), 1103(*s*), 1082(*m*), 754(*m*), 712(*m*), 694(*s*), 511(*m*).

MS-ESI: 377$[M+H]^+$(100%) ; 399$[M+Na]^+$(60%).