

Département de Chimie
Université de Fribourg (Suisse)

**Absolute Configuration Determination of the Dihydroxyethyl Moiety
of *Hordeum Vulgare* Chlorophyll Catabolites**

**Enantiomeric Excess Determination of α -Amino Acids by ^{19}F NMR
Spectroscopy with a New Fluorinated Organometallic Chiral
Derivatizing Agent**

THESE

présentée à la faculté des sciences de l'Université de Fribourg (Suisse)
Pour l'obtention du grade de *Doctor rerum naturalium*

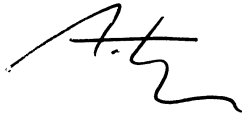
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BY ^{19}F NMR SPECTROSCOPY WITH A NEW FLUORINATED
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ABBREVIATIONS AND ACRONYMS

AA	Amino acid
ABC	ATP binding cassette
APS	Ammonium peroxydisulfate
CAN	Ceric ammonium nitrate
CCDA	Coordinative chiral derivatizing agent
CDA	Chiral derivatizing agent
Chl	Chlorophyll
Chlide	Chlorophyllide
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMP	2,2-Dimethoxypropane
dmphea	<i>N,N</i> -Dimethyl-1-phenylethan-1-amine
FCC	Fluorescent chlorophyll catabolite
HMDS	Hexamethyldisilazane
KP	Potassium phosphate buffer
MA	Maleic anhydride
MVK	Methyl vinyl ketone
NCC	Non-fluorescent chlorophyll catabolite
PaO	Pheophorbide <i>a</i> oxygenase
Phegly	Phenylglycine
Pheo	Pheophorbide
PS	Photosystem
RCC	Red chlorophyll catabolite
RCCR	Red chlorophyll catabolite reductase
RDB	Sodium dihydrobis(2-methoxyethoxy)-aluminate
TMB	3,3',5,5'-Tetramethylbenzidine
TMPDA	<i>N,N,N',N'</i> -Tetramethyl-1,3-propanediamine
TosMIC	Tosylmethyl isocyanide

All other abbreviations or acronyms used in this work are common in chemistry and biochemistry (see for example ^[1]).

SUMMARY

During senescence, chlorophyll of higher plants is degraded into linear tetrapyrrolic catabolites. Their *in vitro* oxidation with chromic acid furnishes the constituting pyrrolic moieties as maleimides fragments. The substitution patterns of the isolated maleimides are related to the catabolites structures. All maleimides bear the characteristic methyl group of the former chlorophyll as well as a modified side chain acquired during the metabolic process. It can also be considered that these maleimides are formed enzymically *in vivo* in some plants – like *Ginkgo biloba* or *Heracleum mantegazzianum* – in which no linear tetrapyrrolic catabolites have been found so far. Synthesis of 3-substituted-4-methylmaleimides should allow, by means of spectroscopy or chromatography, the characterization of chlorophyll catabolites, but also an easy detection of these in senescing plants extracts.

In this work, synthesis of 3-substituted-4-methylmaleimides was carried out following three different ways. In the first, 4-methyl-1*H*-pyrroles were oxidized in maleimides with different reagents. Unfortunately, the high redox potential necessary to carry out this transformation restricts the substrates to simple pyrroles with aliphatic side chains. In the second way, maleimides were prepared by quantitative conversion of the corresponding maleic anhydrides in presence of hexamethyldisilazane and methanol. These maleic anhydrides were synthesized *via* 2-hydroxy-*N*-pyridin-2-ylamides. In the third strategy, several maleimides were synthesized by spontaneous cyclization of (*Z*)-maleamates prepared by Wittig reactions between functionalized α -ketoesters and the dialkylphenylphosphonium salt of 2-bromopropionamide. Both latter methods allowed the use of natural compounds such as α -amino acids or ascorbic acid as starting material.

Chemical oxidation of senescing barley leaves extracts allows the isolation of optically active 3-(1,2-dihydroxyethyl)maleimide with an unknown absolute configuration. This specific fragment derives from the pyrrolic A cycle of the plant chlorophyll catabolites previously isolated from *Hordeum vulgare*. In this research project, the absolute configuration of the single chiral center was determined by correlation with synthetic 3-[(1*R*)-1,2-dihydroxyethyl]maleimide obtained by an enantiomeric pure compound synthesis using ascorbic acid from the natural chiral

pool. A comparison of the circular dichroism spectra of the synthetic product and the product coming from the natural source demonstrated that both compounds have a negative Cotton effect of comparable amplitude. These results permitted the unambiguous absolute configuration assignment of the unknown maleimide fragment and, therefore, of the intact catabolites; all are (*R*) configured.

In the second part of this research a new method of α -amino acids enantiomeric excess determination has been developed – taking in account the advantages of ^{19}F NMR spectroscopy. Hence, di- μ -chloro-bis[*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-2-*C,N*]palladium(II) has been synthesized and resolved with (*R*)-phenylglycine to serve as coordinative chiral derivatizing agent. The relative configuration of one of the separated phenylglycinate diastereomeric complexes has been determined by X-ray diffraction allowing the absolute configuration assignment of the chiral derivatizing agent. This was used to determine the enantiomeric excess of seven natural α -amino acids. As expected, only two peaks, one for each diastereomer, were observed. In each of the amino acid investigated the magnitude of the diastereomeric peaks separation was excellent, allowing a clean integration of each resonance signals.

RÉSUMÉ

Durant la sénescence, la chlorophylle des plantes supérieures est catabolisée en tétrapyrroles linéaires. L'oxydation *in vitro* de ces catabolites avec de l'acide chromique fournit des dérivés monopyrroliques appelés maléimides. Ceux-ci portent aussi bien le groupe méthyle caractéristique des dérivés de la chlorophylle qu'une chaîne latérale spécifique formée pendant le processus métabolique. Il peut également être envisagé que ces maléimides sont formés enzymatiquement *in vivo* dans certaines plantes – comme *Ginkgo biloba* ou *Heracleum mantegazzianum* – dans lesquelles aucun tétrapyrrole linéaire dérivé de la chlorophylle n'a été détecté. La synthèse de 4-méthylmaléimides substitués en position C(3) doit permettre, par comparaison spectroscopique ou chromatographique, la caractérisation des catabolites de la chlorophylle, mais aussi une détection aisée de ces derniers dans des extraits de plantes sénescents.

Dans ce travail, la synthèse de 4-méthylmaléimides substitués en position C(3) a été effectuée de trois manières différentes. Premièrement, des 4-méthyl-1*H*-pyrroles ont été oxydés en maléimides avec différents réactifs. Malheureusement, le haut potentiel rédox nécessaire pour faire cette transformation limite le choix de substrats aux pyrroles avec des substituants aliphatiques. Deuxièmement, des maléimides ont été préparés par conversion quantitative des anhydrides maléiques correspondants en présence de hexaméthylsilazane et de méthanol. Ces anhydrides maléiques ont été synthétisés préalablement *via* des 2-hydroxy-*N*-pyridin-2-ylamides. Troisièmement, des maléimides ont été synthétisés par cyclisation spontanée de (*Z*)-maléamates préparés par des réactions de Wittig entre des α -cétoesters fonctionnalisés et le sel de dialkylphénylphosphonium de la 2-bromopropionamide. Ces deux dernières méthodes permettent l'utilisation comme précurseurs de produits naturels, comme des acides aminés ou l'acide ascorbique.

L'oxydation d'extraits de feuilles sénescents d'orge a permis l'isolation du 3-(1,2-dihydroxyéthyl)maléimide optiquement actif, mais de configuration absolue inconnue. Ce fragment spécifique provient du cycle A des catabolites de la chlorophylle de cette plante. Dans ce projet de recherche, la configuration absolue du centre chiral de ce maléimide a été déterminé par corrélation avec un 3-[(1*R*)-1,2-

dihydroxyéthyl]maléimide synthétique obtenu à partir d'acide ascorbique. La comparaison par dichroïsme circulaire de ces deux produits a permis d'assigner la configuration (*R*) à la fois à ce maléimide, mais aussi, par corrélation, au groupe dihydroxyéthyle des deux catabolites de l'orge connus jusqu'à ce jour.

Dans la deuxième partie de ce travail, une nouvelle méthode de détermination de l'excès énantiomérique des acides α -aminés – prenant en compte les avantages de la spectroscopie ^{19}F RMN – a été développée. Pour ce faire, di- μ -chloro-bis[*N,N*-diméthyl-(2,2,2-trifluoro-1-phényléthyl)amine-2-*C,N*]palladium(II) a été synthétisé et résolu avec de la (*R*)-phénylglycine pour servir d'agent de dérivation chirale. La configuration absolue d'un complexe diastéréomérique de phénylglycine a été déterminée par diffraction de rayons X, permettant ainsi d'assigner par corrélation celle de l'agent de dérivation chirale. Celui-ci a ensuite été utilisé pour déterminer l'excès énantiomérique de sept acides α -aminés naturels. Comme attendu, les spectres ne montraient que deux pics, un pour chaque diastéréoisomère. Dans chaque cas la séparation des pics étaient excellentes, permettant une intégration aisée des signaux de résonance.

Part A

ABSOLUTE CONFIGURATION DETERMINATION OF THE DIHYDROXYETHYL MOIETY OF *HORDEUM VULGARE* CHLOROPHYLL CATABOLITES

THEORETICAL PART

1. CHLOROPHYLL BREAKDOWN IN HIGHER PLANTS AND ALGAE

1.1. Introduction

The disappearance of Chls and emergence of the autumnal colors in the foliage of deciduous trees is one of the most manifest and fascinating natural phenomena. The Chls have a special position among the natural porphyrins, due to their unique roles in the biological transformation of solar energy, essential to the evolved living world.^[2] Indeed, the seasonal appearance and disappearance of the green pigments is probably the most visible sign of life on earth, observable even from outer space. It is estimated that more than 10^9 tons of Chl is biosynthesized and degraded every year on land and in the oceans.^[3] Although considerable work has been done on the biosynthesis of the Chls,^[4, 5] there has been a lack of information on the fate of the green plant pigments. This gap is all the more surprising because Chl breakdown is so visible and of obvious ecological and economic importance.

Research on Chl breakdown can be dated from 1910 when R. Willstaetter and A. Stoll discovered chlorophyllase and the enzymic hydrolysis of Chl to Chlide and phytol.^[6, 7] Except for this early work, there was rather little progress in understanding of degreening in plants during the most of the past century. The publication, in 1987, of a review entitled "The degradation of chlorophyll – a biological enigma" marks a revival of interest in the subject.^[8] In the last 15 years the situation has changed as the chemistry, biochemistry and biology underlying catabolism of Chl during developmental processes, such as leaf senescence and fruit ripening, gradually have been elucidated (for reviews see^[8-18]).

1.2. Pathway of Chlorophyll Breakdown

The skeleton of Chl including the isocyclic ring is called phorbin. The most frequently encountered numbering and nomenclature is given by IUPAC-IUB 1979. The numbers start from 1 to 24 and the methine bridges are indicated as 5, 10, 15 and 20. The five rings are named A, B, C, D and E (Scheme 1). The same numbering system was applied and used in this work to the linear tetrapyrroles which have not lost the C(5) atom.^[19]

The pathway of Chl breakdown depicted in figure 1 is built on the studies over several senescing leaves and ripening fruits, but also from unicellular green algae which are common phylogenetic ancestors of higher plants. In this latter case, the catabolism is, as expected, less evolved.

The breakdown pathway comprises at least six reactions. The hydrophobic phytol chain of Chl *a* (**1a**) is first hydrolyzed to Chlide *a* (**2a**) by the action of chlorophyllase and subsequently the magnesium atom is removed by Mg dechelatase. The product of this reaction, Pheo *a* (**3**), is the last green colored intermediate of the pathway. The key process is the oxygenolytic ring opening of the phorbin macrocycle in a two step reaction in which the red catabolite RCC (**4**) is an intermediate. The product is a fluorescent tetrapyrrole which can exist at least in two primary epimeric forms pFCC-1 (**5a**) and pFCC-2 (**5b**). This sequence is catalyzed by the joint action of two enzymes, Pheo *a* oxygenase (PaO) and RCC reductase (RCCR). Depending on the plant species, the side chains of pFCCs can be modified but two reactions remains common : the enzymic hydroxylation at the C(8²) position and a non-enzymic tautomerization in vacuoles which transforms modified FCCs into non-fluorescent catabolites of chlorophyll, NCCs. These latter are the last recognized breakdown products. Sometimes, the conversion of Chl *b* (**1b**) to Chlide *a* (**2a**) catalyzed by Chl *b* reductase is considered to be the first stage of the breakdown because, in higher plants, Chl *b* (**1b**) can not be degraded without a prior reduction to Chl *a* (**1a**).

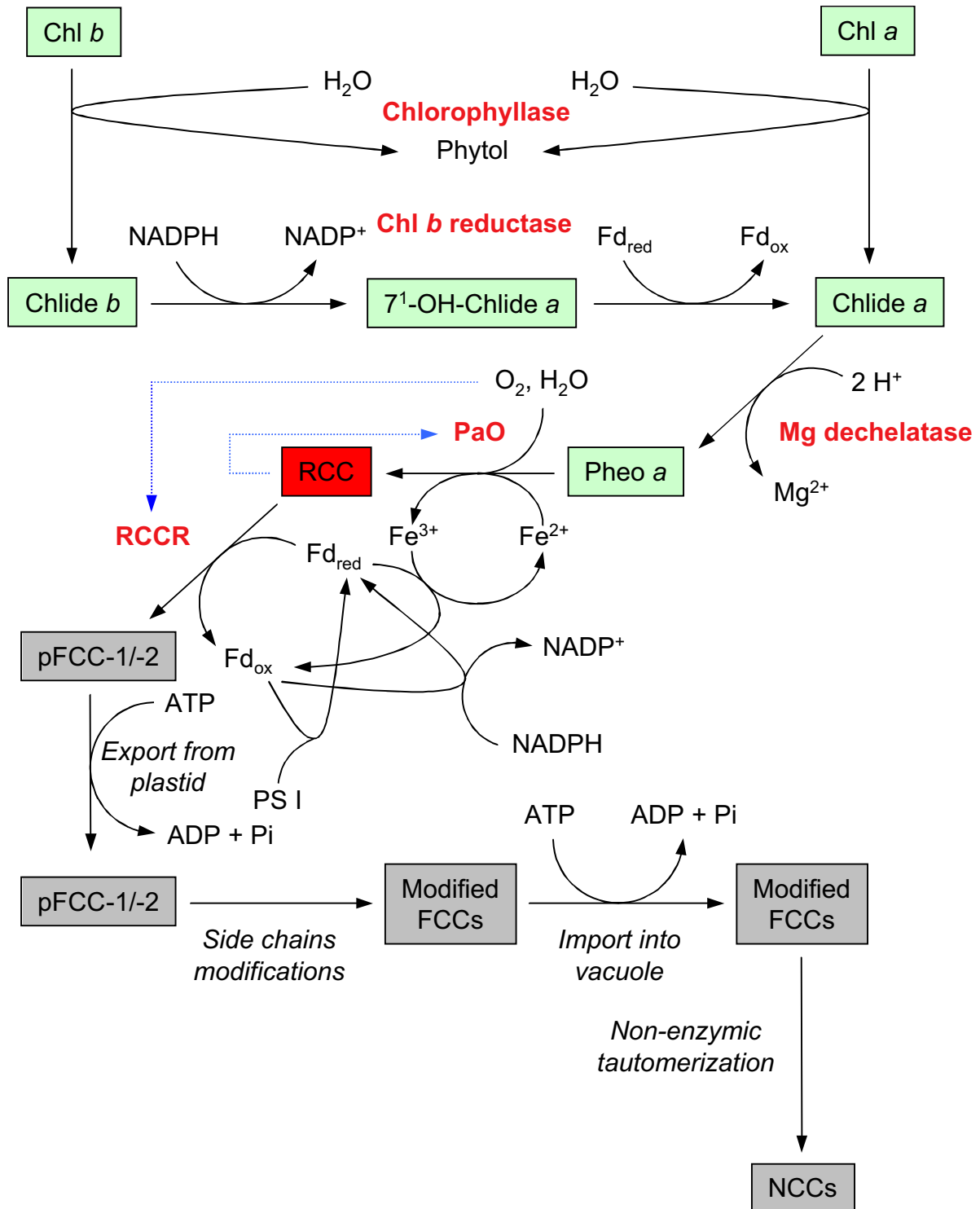


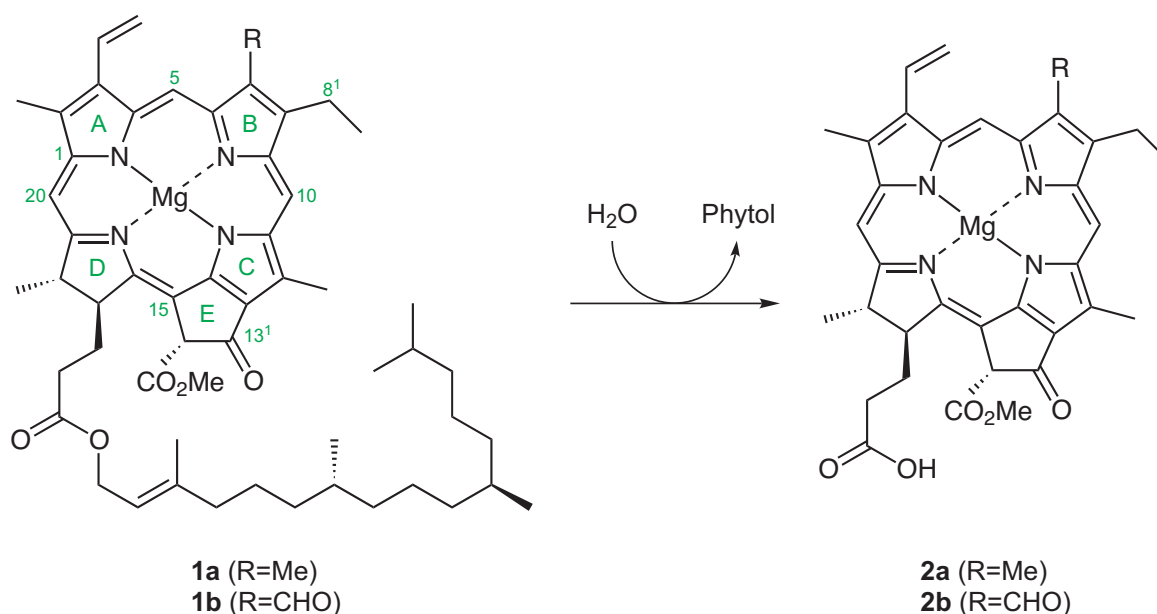
Figure 1. Pathway of Chl breakdown in the green tissues of higher plants. Chl catabolites are framed, enzymes are written in red and competitive inhibitions are indicated by blue arrows.

Because the basic structures of FCCs and NCCs can be modified in different plant species, the following nomenclature has been proposed:^[20] a prefix indicates the plant species (e.g. *Hv* for *Hordeum vulgare*) and the individual compounds are

numbered according to their decreasing polarity during reverse phase HPLC – e.g. *Bn*-NCC-1 (**6d**) represents the most polar non-fluorescent catabolites of *Brassica napus*, or, *Hv*-FCC-4 is the less polar fluorescent catabolite of *Hordeum vulgare*. Both catabolites and biochemical reactions of the pathway are described in details in the following sections.

Dephytylation by Chlorophyllase

Commonly, the hydrolysis of Chl *a* (**1a**) and Chl *b* (**1b**) to Chlide *a* (**2a**) and Chlide *b* (**2b**), respectively, catalyzed by chlorophyllase is regarded as the first step of Chl breakdown (Scheme 1). Since its discovery in 1910,^[6, 7] this enzyme has been vastly investigated (for reviews see^[21-23]), but its role in Chl breakdown has remained partially unknown. Chlorophyllase recognizes only porphyrinic substrates having a reduced ring D,^[24] such as Chl *a* (**1a**), Chl *b* (**1b**) or pheophytins.^[25]



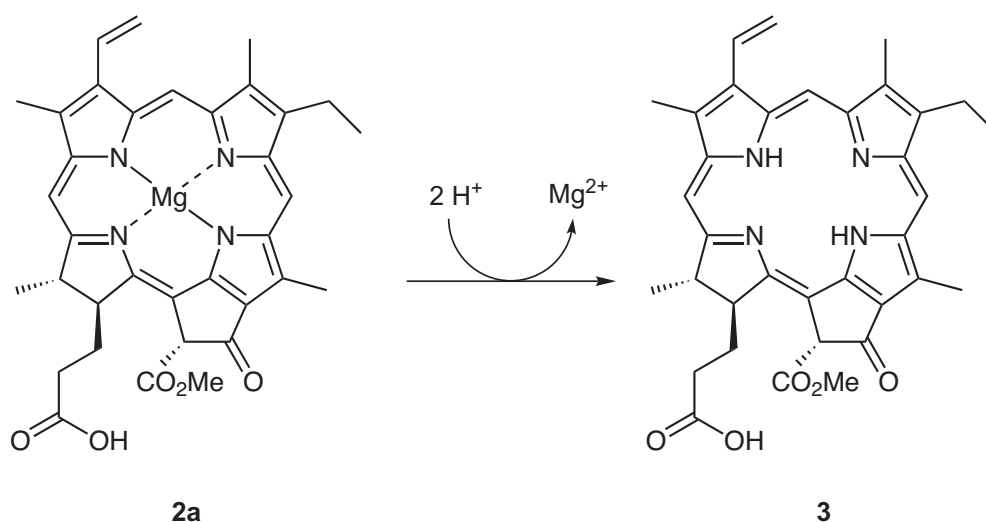
Scheme 1. Enzymic hydrolysis of the hydrophobic phytol ester group by the action of chlorophyllase.

A typical feature of chlorophyllase is its latency, although it is constitutive.^[26] The localization of this enzyme in the inner envelope of chloroplasts^[26, 27] – at least in *Citrus sinensis* and in barley – may explain its structural latency by its compartmental separation with its substrate Chl in the thylakoid membranes of green tissues. This latency remains during senescence suggesting that a biochemical process is needed

to establish the connection between chlorophyllase and Chl.^[26] Nevertheless, enzymic activity is modulated by factors affecting leaf and fruit senescence, such as ethylene and kinetin.^[28-30]

Removal of the Central Mg Atom by Mg Dechelataase

The existence of a Mg dechelating activity has been deduced indirectly by the presence of Pheo pigments during senescence,^[31, 32] in a stay-green genotype mutant of *Festuca pratensis*,^[33] and during Chl catabolism in algae,^[34] in photosynthetic bacteria,^[35] and in *Euglena*.^[36] Removal of the central Mg atom of Chlide *a* (**2a**) is catalyzed enzymically by Mg dechelataase (Scheme 2).

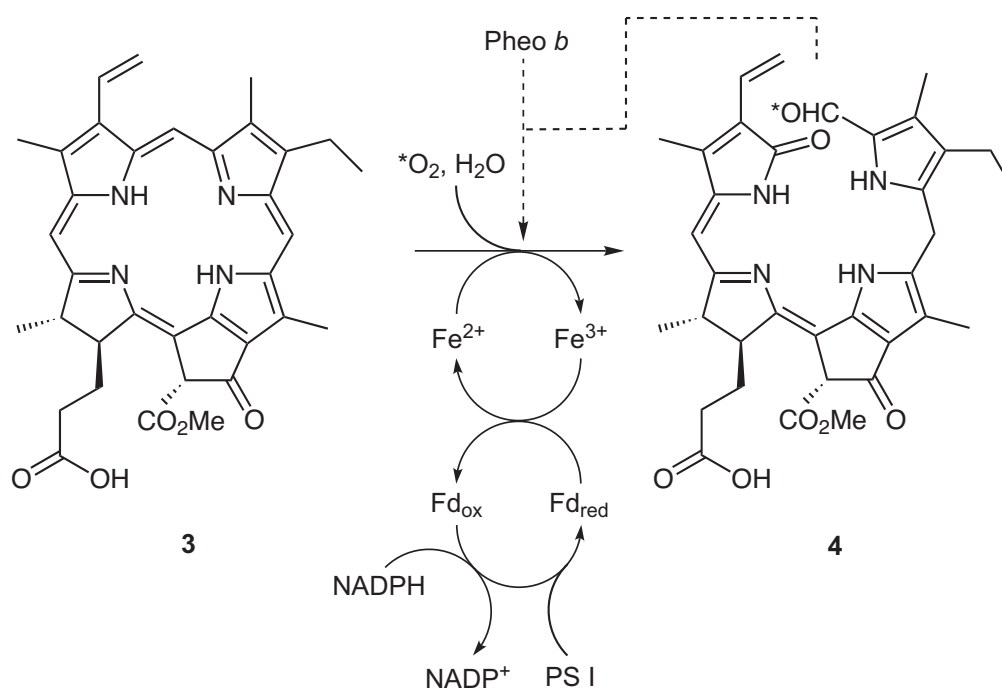


Scheme 2. Removal of the central Mg atom by the action of Mg dechelataase.

The activity of Mg dechelataase is associated with chloroplast membranes and, like chlorophyllase, seems to be constitutive.^[37, 38] This enzyme is active in senescent as well as presenescent leaf tissue of rape^[39] or barley.^[38] Attempts to purify Mg dechelataase revealed that its activity is heat-stable and is associated with a low molecular weight compound, referred to Mg dechelating substance, rather than with a protein. Recently, the Mg dechelataase activity in strawberry fruit has been also associated with such a compound which is sensitive to proteinase K.^[40] It indicates that it is probably a polypeptide. But, it remains to clarify if this Mg dechelating substance is a catalytic cofactor of a genuine Mg dechelataase enzyme.^[40, 41]

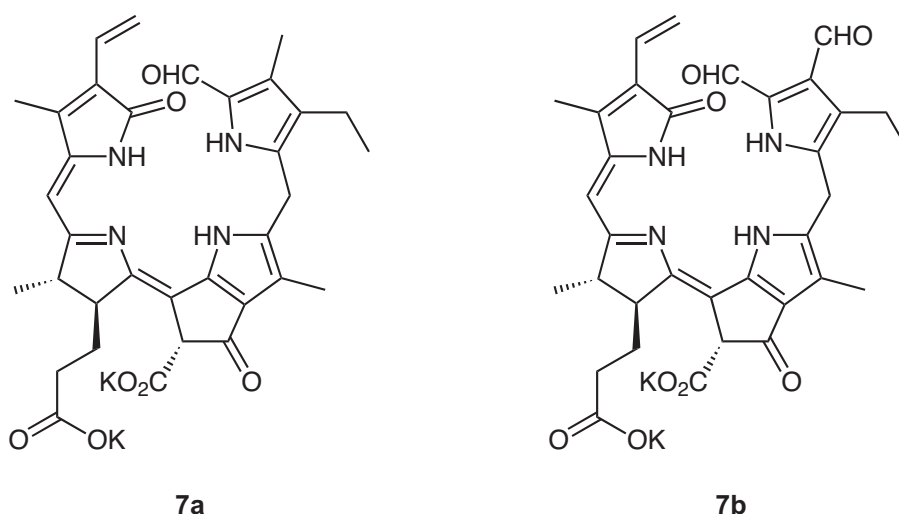
Oxygenolytic Ring Opening of the Phorbins Macrocycle by PaO

The macrocycle of Pheo *a* (**3**) is oxygenolytically opened, regiospecifically at the C(4)/C(5) position (Scheme 3). This reaction is catalyzed by PaO. Formally, two mole equivalents of oxygen and of hydrogen are incorporated into Pheo *a* (**3**). Incorporation studies in *Brassica napus* in the presence of $^{18,18}\text{O}_2$ indicated that only the formyl oxygen arises from molecular oxygen, whereas the lactam one is probably derived from water.^[42] Thus, PaO has been assumed to be a monooxygenase with a non-heme prosthetic group that requires reduced ferredoxin and specifically accepts Pheo *a* (**3**) as substrate.^[43] PaO seems to be inhibited by its own product, RCC (**4**) indicating that it does not accumulate but it is further metabolized in the presence of RCCR (see next section). Pheo *b* is a competitive inhibitor of the reaction, which explains why no Chl *b* derived catabolites have been found in higher plants so far. PaO is located in the envelope of senescent chloroplasts, also called gerontoplasts,^[44] and its activity is exclusively present in senescent tissue,^[45] indicating that it is senescence specifically regulated.



Scheme 3. Oxygenolytic opening of the macrocycle by the non-heme monooxygenase PaO. Competitive inhibitions are indicated by dashed arrows.

As in higher plants, PaO of the chlorophyte *Chlorella protothecoides* is a monooxygenase which also incorporates molecular oxygen to the formyl group.^[46, 47] A chemical mechanism has been proposed in which the initial step is a regioselective C(4)/C(5) epoxide formation followed by an hydrolysis and a subsequent retro-aldol cleavage.^[47] Despite this, there is also considerable differences between the higher plant PaO and its algal ancestor. Chl breakdown in *Chlorella protothecoides* is terminated by the action of the oxygenase, and RCC-type catabolites (**7a,b**) are released into the culture medium (Scheme 4).^[48-52] This oxygenase appears less specific, as suggested by the finding of the Chl *b* derived catabolite **7b**.^[52, 53]

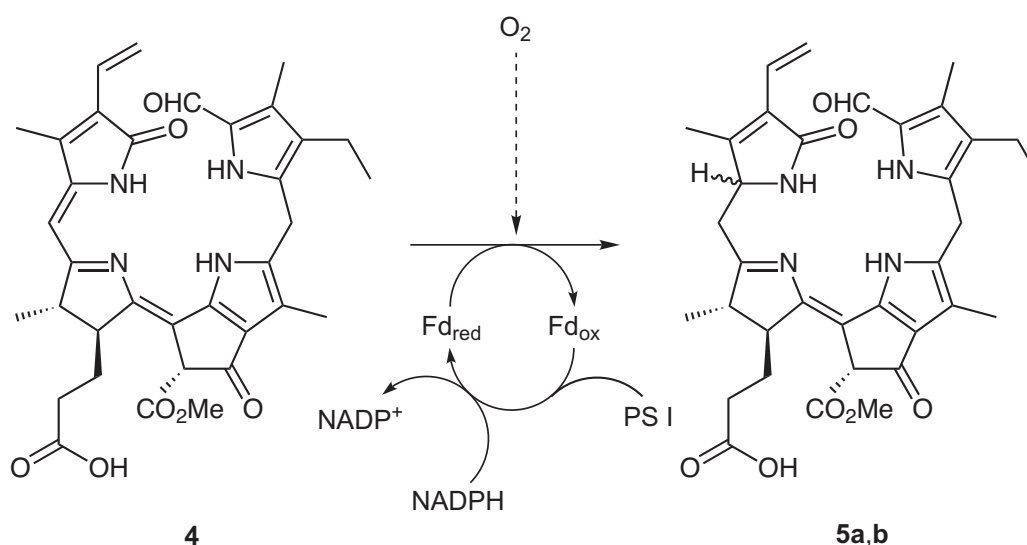


Scheme 4. Structures of both final RCC-type catabolites of *Chlorella protothecoides* derived from Chl a (**1a**) and Chl b (**1b**), respectively.

Reduction of RCC Catalyzed by RCC Reductase

RCCR catalyzes the regiospecific C(1)/C(20) reduction of RCC (**4**) to FCC (**5a,b**), requiring reduced ferredoxin as source of electrons.^[54] This is kept in the reduced state either by NADPH or directly through light-dependent reduction at photosystem I (Scheme 5). FCCs (**5a,b**) are blue fluorescent and have been previously isolated from etiolated barley primary leaves,^[55] in rape^[43] and in *Phaseolus vulgaris*.^[56] Such a compound derived from rape has been synthesized enzymically *in vitro* from Pheo a (**3**) and has been termed as pFCC-1 (**5a**).^[43, 57, 58] pFCC-2 (**5b**) has been isolated from *Capsicum annuum* and is slightly less polar than pFCC-1 (**5a**).^[59] The only difference between this two products is the absolute configuration at the epimeric

C(1) center. Which absolute configuration corresponds to which epimer remains still unknown. Besides pFCC-1 (**5a**) and pFCC-2 (**5b**) which represent identifiable cleavage product of Pheo *a* (**3**), additional FCCs have been found in several species. For example, in barley, four FCCs have been identified (*Hv*-FCC-1-4), the most apolar of which (*Hv*-FCC-4) representing pFCC-1 (**5a**).^[45] These FCCs are perhaps processed forms of pFCC-1 (**5a**), which are eventually also further degraded to the final breakdown products of Chl.



Scheme 5. RCC (**4**) reduction by RCCR to provide one of the two C(1)-epimers pFCC-1 (**5a**) or pFCC-2 (**5b**). Competitive inhibition is signaled by a dashed arrow.

RCCR is a soluble protein localized in the stroma.^[45, 57] It is not senescence specific, and enzyme activity has been found in all stages of leaf development, including etiolated leaves, and also in roots.^[57] The surprising discovery that an enzyme involved in Chl breakdown is also present in non-green tissues leads on to think to an additional function in the metabolism. This enzyme has been purified from senescent barley leaves, and its properties were analyzed.^[57] When a chemically synthesized RCC (**4**)^[60] was employed as substrate, three different FCCs were formed and two of them were identified as pFCC-1 (**5a**) and pFCC-2 (**5b**) found in *Capsicum annuum*.^[61] The structure of the third remains unclear.^[54] An interesting property of RCCR is its sensitivity toward oxygen: when this enzyme is tested in an *in vitro* assay with RCC (**4**) as substrate, pFCCs are obtained only under anoxic conditions.^[54, 57] In contrast, the coupled PaO-RCCR assay from Pheo *a* (**3a**) to pFCCs (**5a,b**) is possible only in

presence of oxygen.^[42] Thus, it is tempting to postulate that in the metabolic channelling of these two reactions, PaO creates an oxygen-depleted micro-environment which allows the reaction of RCCR. Another important feature is that the reduction catalyzed by RCCR is enantioselective only if the two enzymes are associated. In the absence of PaO, in an *in vitro* assay, both pFCC-1 (**5a**) and pFCC-2 (**5b**) are formed simultaneously.^[54] *In vivo*, which one of the two is formed depends on the source of the RCCR enzyme. Within a family of plants, all genera and species produce the same isomer.^[62] After screening of more than sixty plants, it can be assumed that type 2 RCCR, which furnishes pFCC-2 (**5b**), is the more ancient and that a change in selectivity has evolved several times in unrelated lineages.

FCCs Side Chains Modifications

The only common modification of all final Chl catabolites isolated from higher plants so far is the C(8²) hydroxylation. There is no direct proof of an enzymic activity responsible for this reaction, but an indirect evidence for the production of a hydroxylated FCC has been given by radiolabelling of a polar FCC present in senescent chloroplasts of *Brassica napus*.^[20, 58] Isolation of the further catabolized *Bn*-NCC-1 (**6d**) and *Bn*-NCC-2 (**6e**) indicates that the hydroxylated C(8²) position can be conjugated as a malonyl ester or even glucosylated.^[20, 63, 64] Malonyl transferase activity has been demonstrated in protein extracts of rape cotyledons with malonyl-CoA as cosubstrate. It is constitutive and specifically accepts Chl catabolites with a C(8²) hydroxyl group as substrates.^[65] Glucosyl transferase activity necessary for the formation of *Bn*-NCC-2 (**6e**) has not been identified up to now. These modifications resembles to features of the detoxification of xenobiotics and herbicides.^[66] It would not be surprising, therefore, to find that pFCC hydroxylation is catalysed by a P₄₅₀-dependent monooxygenase, known to be involved in detoxification processes of higher plants.^[67]

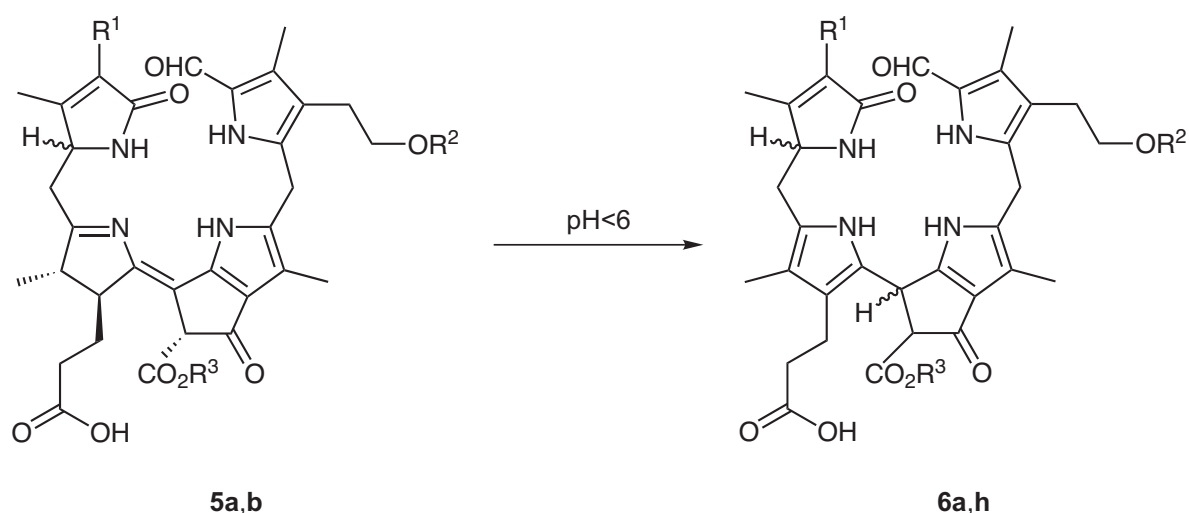
C(13⁴)-demethylated Chl catabolites have been found so far only from rape^[64] and from *Chlorella protothecoides* (**7 a,b**).^[52] These were first isolated as their decarboxylated pyro form,^[50, 68] but it has been demonstrated that they were an artefact of the isolation method.^[52] Hydrolysis of the C(13²) methyl ester of pFCC-1 (**5a**) is catalyzed by a soluble, most probably cytosolic, enzyme from rape

cotyledons.^[69] It is specific for FCCs, and NCCs, like *Cj*-NCC (**6c**), are not hydrolyzed.^[16]

Dihydroxylations at the C(3¹)/C(3²) vinyl group are also encountered in Chl catabolites of barley^[70] and spinach.^[71] As in the case of C(8²) hydroxylation, there are no biochemical data available for the catalysis of this reaction.

Vacuolar Tautomerization of FCCs to NCCs

NCCs (**6a-h**) are exclusively localized in vacuoles of senescent mesophyll cells^[72-74] and the system responsible for the sequestration at the tonoplast has been identified as member of the family of ATP binding cassette (ABC) transporters. Structural analysis of pFCC-1 (**5a**) has led to the presumption that NCCs (**6a-h**) are derived from FCCs through non-enzymic tautomerization under the acidic conditions of vacuoles.^[16] This hypothesis can be verified synthetically by transformation of a pyro RCC-type catabolite of *Chlorella protothecoides* to the basic skeleton of NCCs in propionic acid.^[52, 75] Another proof is the tautomerization *in vitro* of purified pFCC-1 (**5a**)^[69] to an NCC upon incubation at pH 4.^[16] Therefore, it can be said that tautomerization of FCCs to NCCs (**6a-h**) most likely occurs non-enzymically after disposal of FCCs into the vacuole (Scheme 6).



Scheme 6. Non-enzymic tautomerization of modified FCCs (**5a,b**) to NCCs (**6a-h**) into the vacuole. See table 1.

Product ^a	Species	NCC	R ¹	R ²	R ³
6a	<i>Liquidambar styraciflua</i>	Ls-NCC	Vinyl	H	Me
6b	<i>Liquidambar orientalis</i>	Lo-NCC	Vinyl	H	Me
6c	<i>Cercidiphyllum japonicum</i>	Cj-NCC	Vinyl	H	Me
6d	<i>Brassica napus</i>	Bn-NCC-1	Vinyl	Malonyl	H
6e		Bn-NCC-2	Vinyl	Glucosyl	H
6f		Bn-NCC-3	Vinyl	H	H
6g	<i>Hordeum vulgare</i>	Hv-NCC-1	Dihydroxyethyl	H	Me
6h	<i>Spinacia oleracea</i>	So-NCC-2	Dihydroxyethyl	H	Me

^aSee scheme 6 for chemical structures.

Table 1. Chemical constitutions of NCCs (**6a-h**) from higher plants.

NCCs were first identified in 1990 in barley as compounds that were present only in senescent but not in presenescent primary leaves. In the native form these catabolites were colorless, but they were readily oxidized in air to rust-colored pigments of which the most abundant was referred as RP14.^[55, 72] In the meantime, several NCCs have been isolated from various plant species but their chemical structures were not determined.^[20, 56, 61] The first elucidated structure is this of *Hv*-NCC-1 (**6g**) in 1991,^[70] followed by others from various plant species (Table 1).^[63, 64, 71, 76, 77] *Ls*-NCC (**6a**), *Lo*-NCC (**6b**) and *Cj*-NCC (**6c**) have the basic skeleton of these final catabolites. In these species, the total amount of Chl is totally degraded to a single type of NCC.^[76, 77] In contrast, additional modifications occur in other species (Table 1). Whereas the three rape NCCs (**6d-f**) correspond to the total Chl amount of mature cotyledons broken down,^[16] radiolabelling in barley has demonstrated the presence of more than ten additional NCCs whose chemical structure have not been elucidated.^[55]

Conversion of Chlorophyll *b* to the pool of *a*-Forms

In the photosystems of higher plants, algae and some photosynthetic procaryotes, Chl *b* (**1b**) is a component of the antenna complexes and occurs at variable ratios to Chl *a* (**1a**).^[78, 79] During senescence, Chl *b* (**1b**) has to be reduced first to Chl *a* type compound before the oxygenolytic opening of the porphine macrocycle by PaO. Different features seem to prove this conversion : I) PaO reacts exclusively with Pheo *a* (**3**), and Pheo *b* is a competitive inhibitor;^[43, 61] II) the interruption of Chl breakdown at level of PaO results in the accumulation of both forms of Chlide (**2a,b**) but only in the *a* type of Pheo (**3**);^[33, 39, 80] III) all the NCCs (**6a-h**) identified up to now are derived from Chl *a* (**1a**);^[63, 64, 70, 76, 77, 81] and IV) the total amount of NCCs synthesised during senescence represents the totality of Chl degraded.^[20, 77] The funneling of Chl *b* (**1b**) into the pool of *a*-forms during senescence remains subject to investigations. Reports remain contradictory whether the reduction, catalyzed by Chl *b* reductase, takes place before the action of chlorophyllase – e.g. Chl *b* (**1b**) is converted to Chl *a* (**1a**) in the Chl cycle^[82] – or after – e.g. Chlide *b* (**2b**) is transformed into Chlide *a* (**2a**).^[52, 83, 84] A proof for the proposition that the conversion is done at the stage of Chlide is the specificity of Chl *b* reductase for dephytylated compounds.^[83] This enzyme appears to be constituted of two components, an NADPH-dependent enzyme producing a 7¹-hydroxy intermediate (**8**)^[85] and a second reductase that is dependent on reduced ferredoxin (Scheme 7).^[86]

current knowledges of the compartmentation and transport systems during the Chl breakdown.

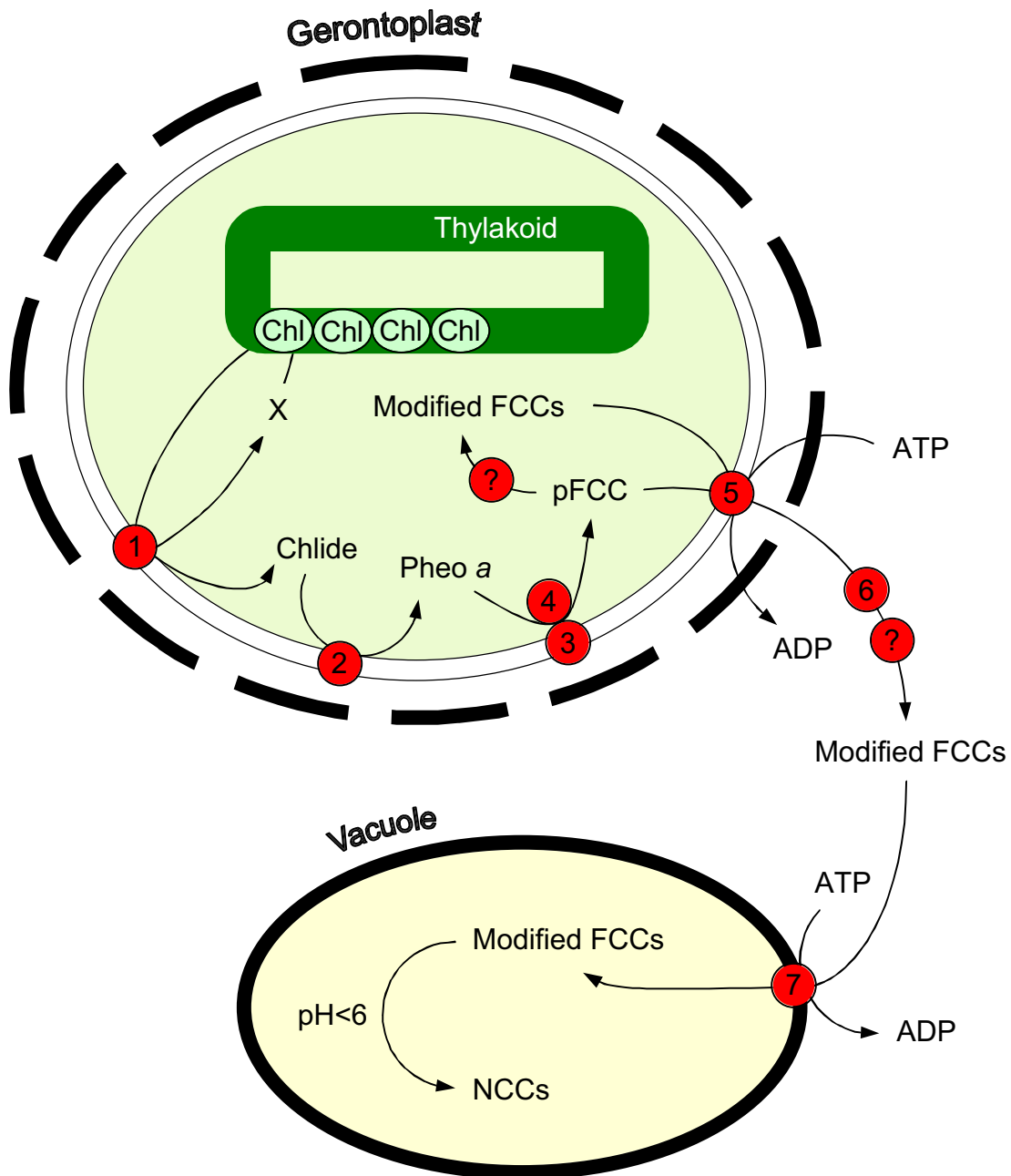
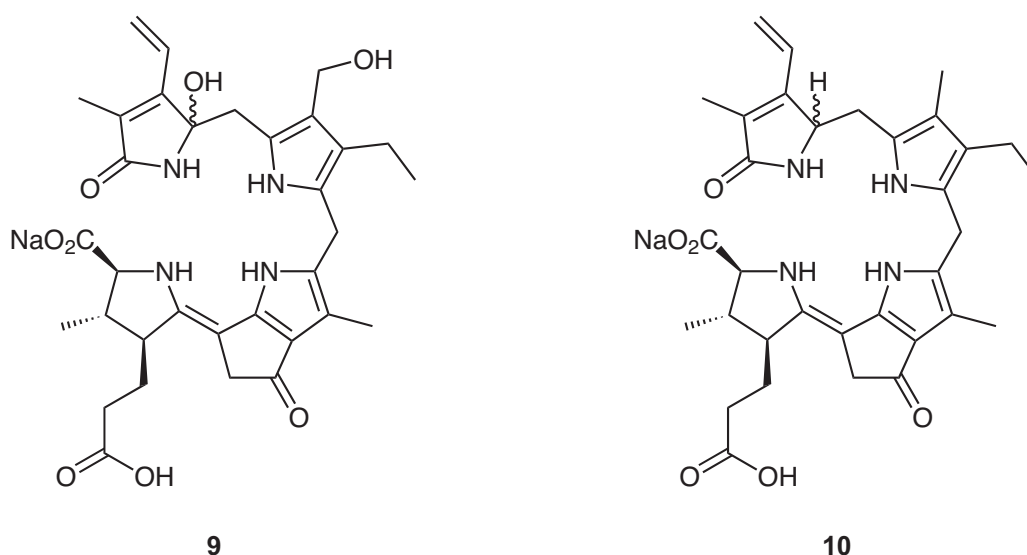


Figure 2. Model of compartmentation during Chl breakdown. X) unidentified factor responsible for the removal of Chl from the thylakoid. 1) Chlorophyllase 2) Mg dechelataase 3) PaO 4) RCCR 5) Catabolite translocator 6) Malonyl transferase 7) ABC transporter.

The first steps of Chl catabolism take place within gerontoplasts^[58, 87] – which represent a senescent form of chloroplasts – by the action of chlorophyllase,^[26] PaO^[44] and, probably, Mg dechelataase in the inner envelope membrane,^[37] whereas RCCR is a soluble protein in the stroma.^[57] It has been speculated that a specific transport protein for Chl or plastoglobules plays a role in shuttling pigment molecules between thylakoids and the chloroplast envelope.^[12, 88] It acts upstream from chlorophyllase and is newly synthesized during senescence. The nature of this factor remains unknown, but recently, a water-soluble apoprotein of Chl, located in plastids, has been cloned and characterized from cauliflower. This protein is able to remove Chl from pigment-protein complexes when incubated together with thylakoid membranes,^[89] and thus possesses the properties to be candidate of a putative shuttle for Chl between thylakoids and chlorophyllase. Export of FCCs is due to an ATP-dependent transport protein in the envelope of gerontoplasts.^[90] The structures of *Bn-FCC-1*,^[58] *Hv-FCC-1* and *Hv-FCC-2*^[87] have not been yet determined, but their occurrence in gerontoplasts suggests that, in addition to the ring cleavage reaction catalyzed by PaO and RCCR, other reactions in the pathway may also be localized within gerontoplasts. In rape, the presence of glucosylated and malonylated NCCs (**6d,e**) requires the presence of enzymes catalyzing their respective modifications. Transmalonylation has been demonstrated to be probably of cytosolic origin.^[65] The final catabolites of Chl breakdown are localized in the vacuole of senescent cells, and a specific carrier of the tonoplast is responsible for this transport. It is a member of the family of ATP binding cassette (ABC) transporters.^[74]

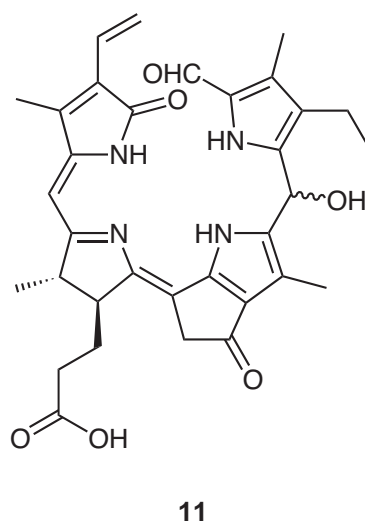
1.4. Miscellaneous Breakdown Products of Chlorophyll

The first structural elements of Chl breakdown products arised in 1980 by the isolation of two fluorescent tetrapyrroles from *Euphausia pacifica* (**9**)^[91] and *Pyrocystis lunula* (**10**),^[92] which are responsible for bioluminescence in these two dinoflagellates (Scheme 8). Their chemical structures have been elucidated later and differ from the other classical Chl catabolites by a phorbine macrocycle opening at the C(20)/C(1) position.^[93-95]



Scheme 8. Structures of the two fluorescent Chl catabolites from *Euphausia pacifica* (**9**) and *Pyrocystis lunula* (**10**).

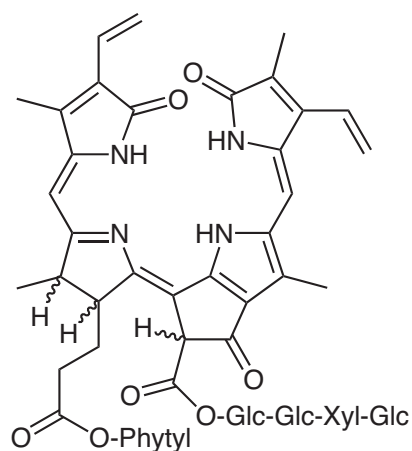
The green alga *Chlorella Kessleri* degrades Chl in a similar way than *Chlorella protothecoides* (see section 1.2.), excreting also a red catabolite (**11**) when submitted to bleaching conditions.^[10] The only structural difference is the presence of a hydroxyl group at the C(10) position (Scheme 9).^[96]



Scheme 9. Structure of the Chl catabolite isolated from the green alga *Chlorella kessleri*.

Water-soluble red Chl catabolites – with properties of bile pigments – have also been isolated from the alga *Bryopsis maxima* (**12**)^[97, 98] and from a Chl *b*-less mutant of

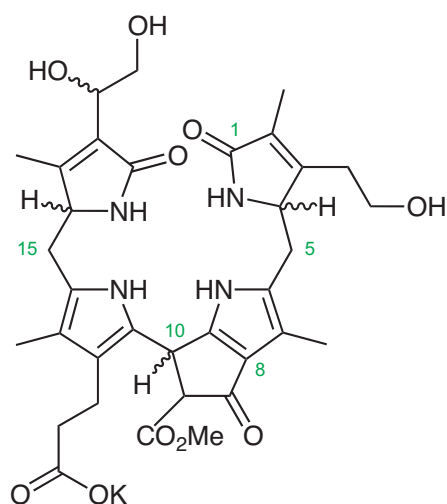
Chlamydomonas reinhardtii.^[99] Only the structure of the first has been proposed (Scheme 10).



12

Scheme 10. Chemical structure of the Chl catabolite isolated from *Bryopsis maxima*.

Recently, a bilin-type Chl catabolite (**13**) has also been isolated from barley (Scheme 11). It remains unclear if this compound is a further catabolized form of *Hv*-NCC-1 (**6g**) but a mechanism was proposed where **6g** was transformed into **13** via a C(6)-hydroxy intermediate.^[100]



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Scheme 11. New urobilinogenoidic catabolite isolated from *Hordeum vulgare*.

1.5. Significance of Chlorophyll Breakdown^[15]

The amount of mobilizable material, principally nitrogen and magnesium, invested in the Chl molecules is small relative to that available from other salvaged cells constituents. For example, if all the nitrogen in the 240-kDa PS II core complex – which is associated with about 36 Chl *a* (**1a**) molecules – is mobilized, less than 6% will be contributed by Chl. Thus, Chl is degraded not because its products are reusable but primarily because otherwise it would block access to more valuable materials. The nitrogen and carbon from which Chl is constructed remain in the cell for good. This is the price the plant pays for access to thylakoid proteins and lipids. The notion of Chl catabolism as being essential for salvage while not itself being a salvage process leads to a conclusion that may make sense for other aspects of the pathway. Not only is the Chl macrocycle converted immediately into non-photodynamic linear forms, these are irreversibly transported to the vacuole and sequestered as oxidized and conjugated by-products.^[74, 101] In a sense, Chl is not so much catabolized as detoxified.

1.6. Evolution of Chlorophyll Breakdown^[18]

There are reports of Chl breakdown processes in a range of microalgae and macroalgae,^[50, 99, 102-105] as well as many terrestrial cryptogams.^[106-111] Catabolites identified in these species include Chlide, Pheo-pigments and their pyro-forms^[34, 103, 105, 112] and both chlorophyllase^[22, 113] and Mg dechelataase^[34, 114] activities have been measured. Evidence for the capacity of pre-tracheophytes to open the macrocycle is much more limited, but linear tetrapyrroles chemically related to the RCC, FCC and NCC structures of angiosperms have been described.^[52, 98, 99] The main Chl *a* catabolite of *Chlorella protothecoides* (**7a**) is chemically identical to the intermediary product of Pheo *a* (**3**) to pFCC-1 (**5a**) or pFCC-2 (**5b**) in angiosperms.^[54] Moreover, the mechanism of oxygen incorporation across the methine bond that opens the phorbins macrocycle is the same in *Chlorella protothecoides* and *Brassica napus*,^[42, 47] making it likely that the angiosperm Chl breakdown pathway evolved from that of green algal progenitors.^[115] RCCs are photodynamic. Multicellular terrestrial plants do not have *Chlorella*'s option of terminating Chl catabolism by simply excreting these products into the external medium. It has been proposed that addition of the part of

the catabolic pathway from RCCR onward was one of the physiological innovations required for the evolutionary step from the unicellular aquatic stage to multicellular land plants. RCCR is detectable in ancient terrestrial species, such as *Selaginella*.^[62] The presence of RCCR, or something very like it, in roots^[116] and mitochondria^[117] suggests it has another, as yet unknown, function and may have become secondarily recruited to the cause of detoxifying RCCs. Assembling the machinery of Chl catabolism, equipping it with regulatory mechanisms and integrating it into the cellular organization were likely to have been key elements in the evolution of plants well adapted to life on land and to sophisticated interactions with animal pollinators and dispersers.

2. SYNTHESIS OF CHLOROPHYLL RELATED 3-SUBSTITUTED-4-METHYLMALEIMIDES

During senescence of higher plants, Chls are degraded in NCCs (**6a-h**) (Scheme 6). Their *in vitro* oxidation with chromic acid leads to several monopyrrole derivatives called maleimides, each of them originating from the pyrrole rings of the Chl core (For an example see scheme 18). These maleimides still bear the characteristic methyl group of Chl derivatives as well as a specific side chain which allows the identification of the catabolite structure.

It should also be taken into consideration that these maleimides are formed enzymically *in vivo* in some plants like *Ginkgo biloba* or *Heracleum mantegazzianum* in which no NCC have been found so far, representing a more processed form of Chl catabolites.

Based on these findings, it was reasoned that chemical synthesis of 3-substituted-4-methylmaleimides would be a useful tool for a correct identification and at the same time characterization of Chl catabolites by means of spectroscopy and/or chromatography. That should allow as well as an easier detection of maleimides in senescing plant extracts. The present study deals with synthesis of some Chl related 3-substituted-4-methylmaleimides and additional topics as polymers containing maleimides substructures or photochemical applications were not considered.

This section concerns the strategies and procedures developed for synthesis of 3-substituted-4-methylmaleimides up to date. The best known route is the oxidation of pyrroles or pyrroles derivatives. Another approach involves the conversion of maleic acid derivatives into maleimides. Interesting alternatives are the oxygen induced conversion of monothiomaleimides into maleimides, as well as the maleimide core formation by Wittig reactions, a method previously developed to synthesize a C-glycosyl nucleoside antibiotic.

2.1. Preparation of 3-Substituted-4-methylmaleimides by Oxidation of Pyrroles and Pyrroles Derivatives

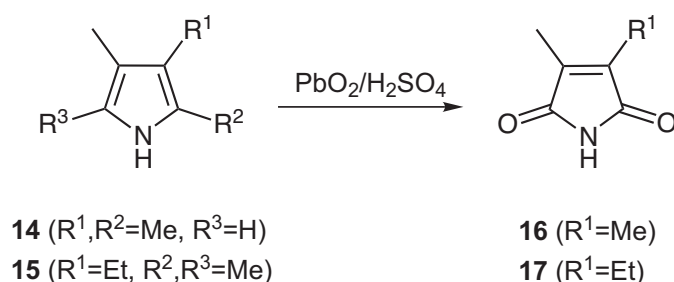
Synthesis of 3-substituted-4-methylmaleimides by oxidation of the corresponding pyrroles, pyrrolin-2-ones, dipyrromethenes or tetrapyrroles have been developed almost exclusively at the beginning of the last century. As the publications from that time are not readily available, the following sections will be just a non-exhaustive review of the extensive work done in this field.

Preparation of 3-Substitued-4-methylmaleimides by Oxidation of Pyrroles

Pyrroles are a class of well-known and studied compounds and most of them can be easily prepared by various synthetic ways (for a review see^[118]). Their oxidation to the corresponding maleimides can be effected using different reagents. All the methods require vigorous reaction conditions, and the yields are generally rather low.

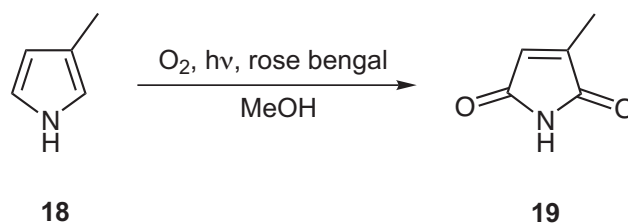
The pyrroles **14** and **15** were oxidized to 3,4-dimethylmaleimide (**16**) and 3-ethyl-4-methylmaleimide (**17**) respectively, with lead dioxide / sulfuric acid (Scheme 12).^{[119,}

120]



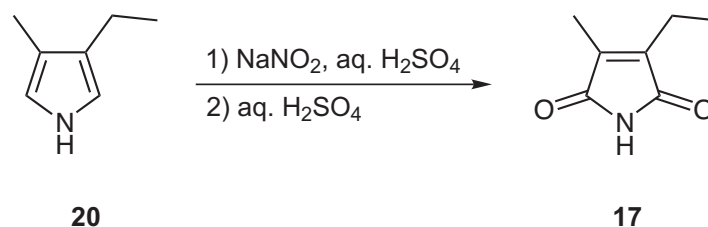
Scheme 12. Oxidation of pyrroles with lead dioxide / sulfuric acid.

Dye-sensitized photooxygenations of pyrroles have been extensively investigated by several groups.^[121, 122] Unfortunately, this type of reaction affords complicated reaction mixtures from which the maleimides were difficult to isolate. Hence the yields remained very low.^[123] For example, 3-methyl-1*H*-pyrrole (**18**) has been converted into 3-methylmaleimide (**19**) in only 13% yield (Scheme 13).^[124]



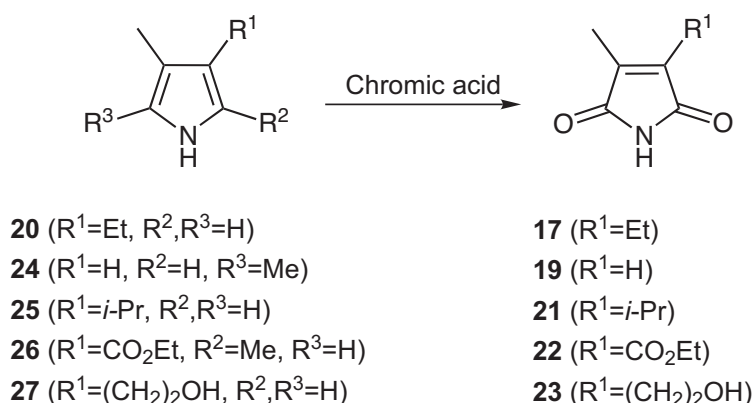
Scheme 13. Photooxidation of 3-methyl-1*H*-pyrrole (**18**).

Another way to transform pyrroles into maleimides involves first the formation of a maleimide-monooxime in the presence of sodium nitrite in aqueous sulfuric acid. In a second step, it was hydrolyzed to the desired compound. Following this procedure, 3-ethyl-4-methylmaleimide (**17**) has been prepared from 3-ethyl-4-methyl-1*H*-pyrrole (**20**) (Scheme 14).^[125, 126]



Scheme 14. Synthesis of 3-ethyl-4-methylmaleimide (**17**) via its monooxime.

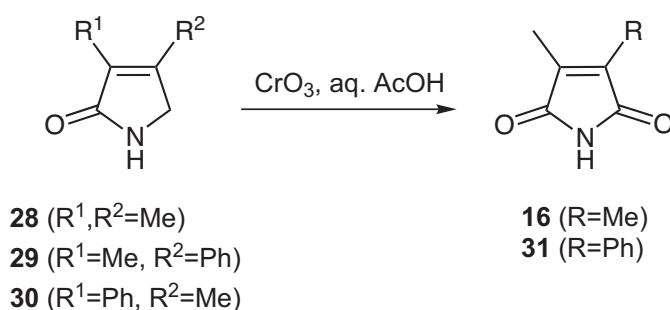
Chromic acid is the most common oxidizing agent used for the oxidation of pyrroles to maleimides. It is commonly generated from chrome trioxide and diluted aqueous sulfuric acid or, eventually, acetic acid. This reagent has been used to synthesize a wide variety of maleimides, like 3-ethyl-4-methylmaleimide (**17**),^[127-129] 3-methylmaleimide (**19**),^[130] 3-isopropyl-4-methylmaleimide (**21**),^[131] 3-ethoxycarbonyl-4-methylmaleimide (**22**)^[132] or 3-(2-hydroxyethyl)-4-methylmaleimide (**23**),^[128] from the corresponding pyrroles **20**, **24-27** (Scheme 15).



Scheme 15. Synthesis of different maleimides by oxidation of pyrroles with chromic acid.

Preparation of 3-Substituted-4-methylmaleimides by Oxidations of Pyrrolin-2-ones

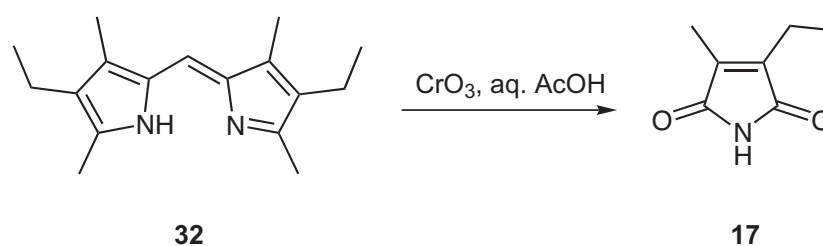
Another way to prepare maleimides is the oxidation of pyrrolin-2-ones with chromic acid. These precursors can be synthesized either from the alkylated ethyl acetoacetate in several steps *via* reduction of the cyanohydrine intermediate,^[133] or by oxidation with hydrogen peroxide of the corresponding α -formyl-pyrrole.^[134] Only two maleimides have been synthesized using this type of starting materials. The first example was the oxidation of 3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (**28**) to 3,4-dimethylmaleimide (**16**)^[135] and the second are the conversion of either 3-methyl-4-phenyl-1,5-dihydro-2*H*-pyrrol-2-one (**29**) or 4-methyl-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one (**30**) to 3-phenyl-4-methylmaleimide (**31**) in 54% and 30% yield, respectively (Scheme 16).^[129]



Scheme 16. Oxidations of pyrrolin-2-ones to maleimides.

Preparation of 3-Substituted-4-methylmaleimides by Oxidation of Dipyrrromethenes

Another type of precursors for the preparation of maleimides are dipyrrromethenes. The oxidizing agent used to carry out this transformation is also chromic acid obtained by dissolving chrome trioxide in aqueous acetic acid. Using this strategy, only 3-ethyl-4-methylmaleimide (**17**) has been prepared from the dipyrrromethene **32** (Scheme 17).^[136]



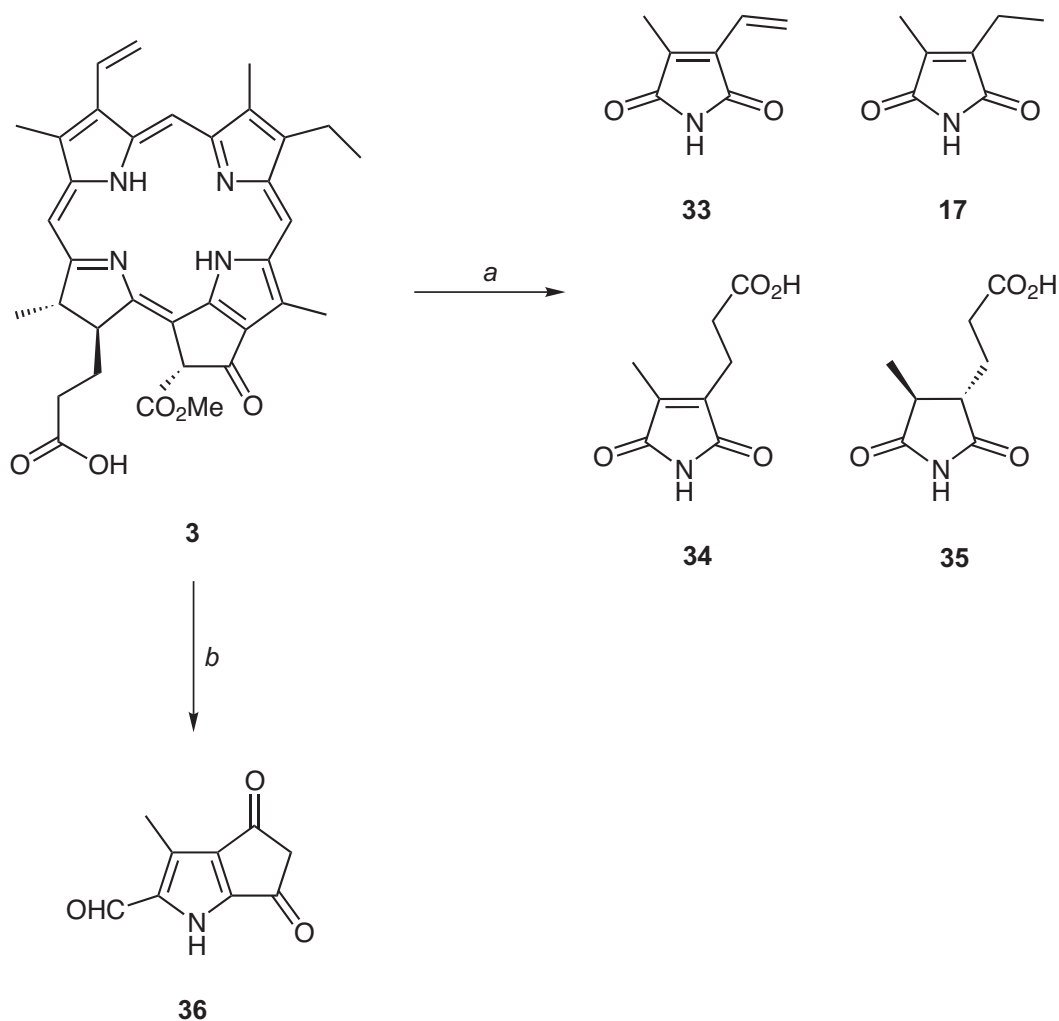
Scheme 17. Oxidation of dipyrrromethene to maleimide.

Preparation of 3-Substituted-4-methylmaleimides by Oxidation of Tetrapyrroles

Numerous oxidizing agents have been used for the oxidation of a wide variety of tetrapyrroles to maleimides. As in the case of pyrroles, pyrrolin-2-ones or dipyrrromethenes, the most employed were chromic acid,^[137-142] lead dioxide in sulfuric acid^[143-145] or their combinations.^[143] Sometimes, the tetrapyrrole oxidative fragmentation was carried out by photooxidation,^[146-148] using sodium nitrite in acetic acid,^[149, 150] lead tetraacetate^[151] or thallium triacetate.^[151] But these routes to maleimides suffer from two major limitations. One is the difficulty to obtain sufficiently high yields – the same is true for all the oxidative preparations of maleimides – and the other one is the fact that porphyrins are not easily available in high yields. Many 3-substituted-4-methylmaleimides – mainly those having an aliphatic group at the C(3) position – have been isolated or detected using this method. Despite the fact that porphyrins side chains synthetical modifications are well-known, their disadvantages make the method less efficient from a synthetic point of views.

The oxidative degradation of natural tetrapyrroles has been used to determine their structure,^[141, 152-154] because the thus formed maleimides still bear the side chains of

the macrocycle. This technique allowed particularly the determination of the absolute configuration of the two Chl a (**1a**) C(17) and C(18) stereocenters.^[155-157]



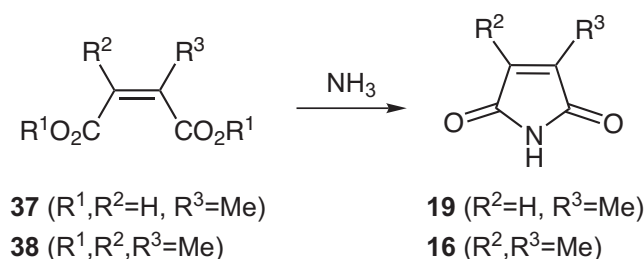
Scheme 18. Oxidation of Pheo a (**3**). Method a : 1% chrome trioxide in 2 N aqueous sulfuric acid. Method b : 1% chrome trioxide in 1% aqueous potassium bisulfate (pH 1.7).

A method for determining the tetrapyrrole side chains has been developed by coupling this type of oxidation with chromatographic techniques.^[158] The maleimides resulting from oxidation of a small amount of tetrapyrrole and still carrying the side chains can be compared on a TLC plate with synthetic reference materials. Thus, oxidation of Pheo a (**3**) with chromic acid reveals the presence of four spots in the TLC (developed with chlorine / TMB), corresponding to 3-vinyl-4-methylmaleimide (**33**), 3-ethyl-4-methylmaleimide (**17**), hematinic acid (**34**) and (2S,3S)-2,3-dihydro-hematinic acid (**35**). Oxidation with chromium trioxide in a bisulfate solution at pH 1.7

affords the aldehyde **36**, which clearly derived from the C pyrrole unit bearing the E isocycle (Scheme 18).^[159]

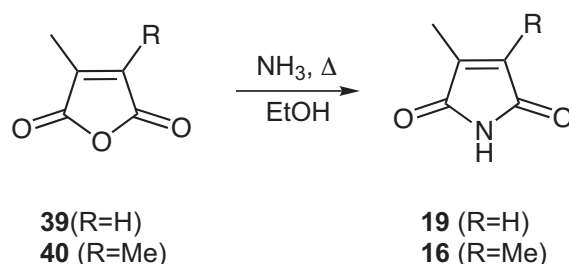
2.2. Synthesis of 3-Substituted-4-methylmaleimides from Maleic Acid Derivatives

3-Substituted-4-methylmaleimides have been prepared also from disubstituted maleic acid – or maleic diesters – in presence of ammonia.^[160-162] The reaction occurs through a maleamic acid – or maleamate – intermediate, which quickly cyclizes to the corresponding maleimide. Despite the fact that disubstituted maleic esters can be synthesized efficiently either by stereoselective Horner-Emmons condensations of α -ketoesters^[163] or by tandem vicinal difunctionalization of dimethyl acetylenedicarboxylate,^[164, 165] only two maleimides were synthesized so far by this method: 3-methylmaleimide (**19**) from citraconic acid (**37**)^[160, 161] and 3,4-dimethylmaleimide (**16**)^[162] from dimethyl 2,3-dimethylmaleate (**38**) (Scheme 19).



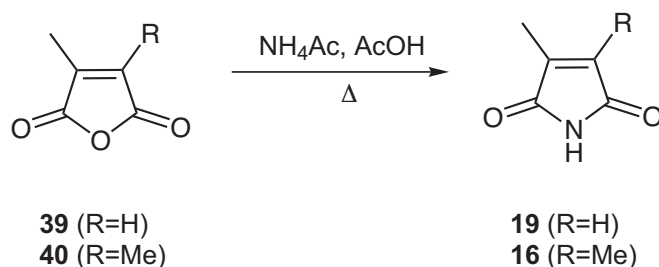
Scheme 19. Synthesis of maleimides from their corresponding maleic acid derivatives.

Conversion of maleic anhydrides is one of the most efficient method for the preparation of maleimides. Dialkylated maleic anhydrides were subject of extensive studies and, very recently, the first general synthetic route to these molecules was established by using a versatile copper-mediated tandem vicinal difunctionalization of dimethyl acetylenedicarboxylate.^[165] The first reported conversion of maleic anhydrides into maleimides was performed at high temperature in presence of alcoholic ammonia and occurred with low yields (<30%).^[166, 167] Using this method, citraconic anhydride (**39**) and 3,4-dimethylmaleic anhydride (**40**) have been converted into 3-methylmaleimide (**19**) and 3,4-dimethylmaleimide (**16**), respectively (Scheme 20).



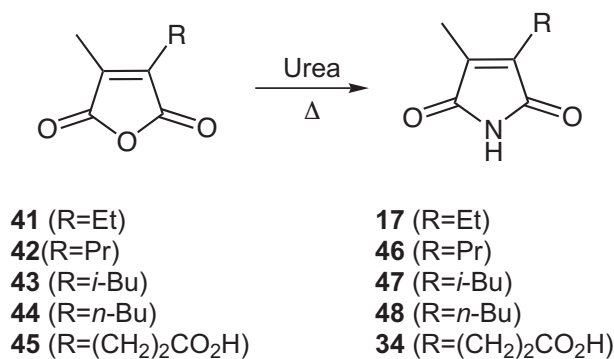
Scheme 20. Conversion of maleic anhydrides to maleimides with alcoholic ammonia.

Latter, several different better procedures have been developed based on the *in situ* formation of ammonia. In one example, ammonia was generated by heating ammonium acetate in acetic acid. With this method, yields obtained for conversions of citraconic anhydride (**39**) and 3,4-dimethylmaleic anhydride (**40**) to 3-methylmaleimide (**19**) and 3,4-dimethylmaleimide (**16**), respectively, were between 20% and 85% (Scheme 21).^[168-172]



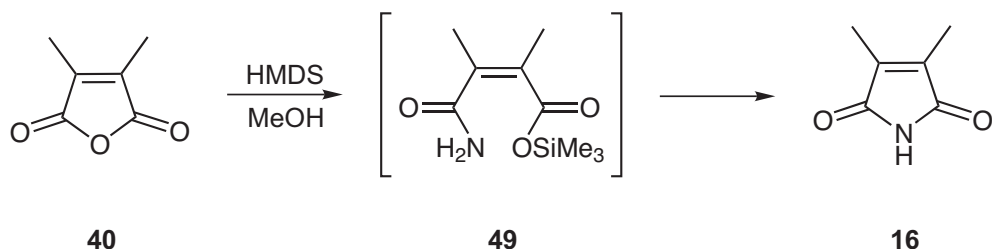
Scheme 21. Conversions with ammonia generated *in situ* by heating ammonium acetate in acetic acid.

In a second approach ammonia was generated by decomposition of urea at high temperature.^[139, 173] Several maleic anhydrides **41-45** have been converted to their corresponding 3-substituted-4-methylmaleimide **17, 34, 46-48** with yields up to 75% (Scheme 22). However, these conditions were neither convenient nor mild and proved to be not applicable to maleimides containing sensitive functionalities, like nitriles or esters.



Scheme 22. Conversion with ammonia generated in situ by thermal decomposition of urea.

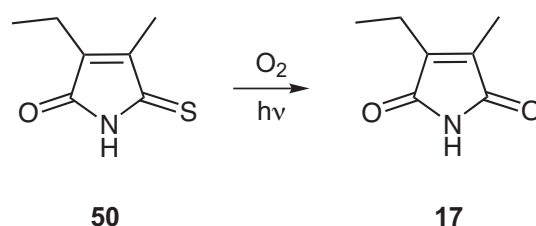
The reaction of maleic anhydrides with ammonia proceeds *via* a maleamic acid which cyclizes to the corresponding maleimide in a generally slow rate determining step. A new strategy has been elaborated in order to increase the efficiency of this type of reactions :^[174] the maleamic acid was activated by conversion into a silyl ester *in situ*. This conversion should be also possible in the presence of ammonia due to the greater strength of the Si-O bond versus the Si-N bond. Thus a new reagent which contained both ammonia and the silylating agent was prepared. The procedure consists in the addition of methanol to HMDS, leading to a mixture of methoxytrimethylsilane, ammonia and some residual HMDS. This procedure allows a very efficient conversion of maleic anhydrides, bearing reactive functionalities, into maleimides in almost quantitative yields. For example, 3,4-dimethylmaleimide (**16**) has been prepared from 3,4-dimethylmaleic anhydride (**40**) in 93% yield *via* the activated maleamic acid **49** (Scheme 23).



Scheme 23. Conversion with HMDS / methanol.

2.3. Oxygen Induced Conversion of Monothiomaleimides to Maleimides

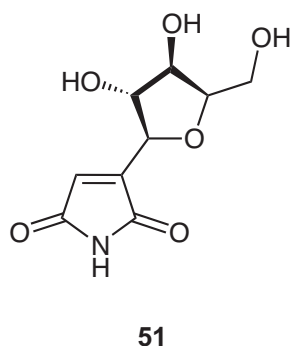
A special case among the maleimides syntheses is the spontaneous oxygen induced conversion of 3-ethyl-2-methyl-1-monothiomaleimide (**50**) – prepared in several steps from methyl acetoacetate and methyl 2-bromopropionate – to 3-ethyl-4-methylmaleimide (**17**).^[175] This reaction seems to proceed with oxygen *via* a six-membered ring intermediate, which collapses, forming the maleimide **17** and molecular sulfur (Scheme 24).



Scheme 24. Spontaneous oxygen induced conversion of 3-ethyl-2-methyl-1-monothiomaleimide (**50**) to 3-ethyl-4-methylmaleimide (**17**).

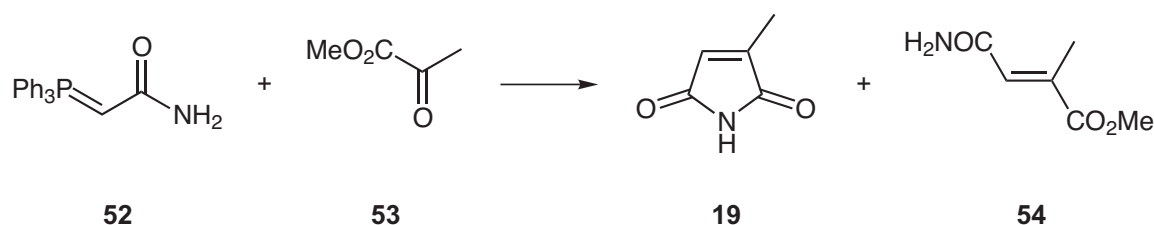
2.4. Condensations of α -Ketoesters and Phosphoranes in Wittig Type Reactions

Extensive studies undertaken *en route* to showdomycin (**51**) – a C-glycosyl nucleoside antibiotic isolated from *Streptomyces showdoensis* –^[176] and its derivatives provided a new approach to the maleimide ring system (Scheme 25).^[177, 178]



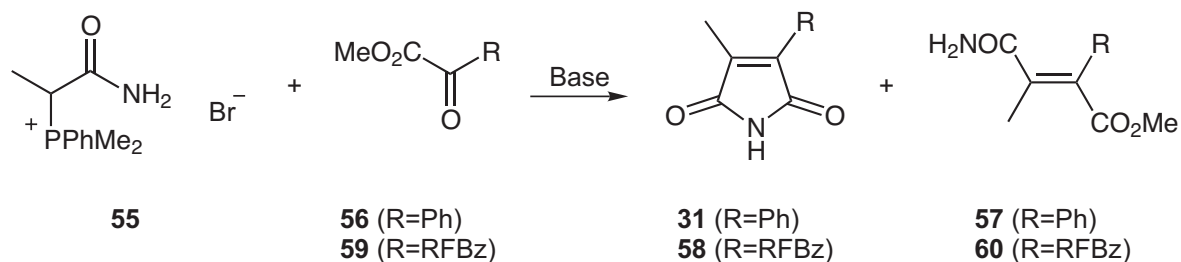
Scheme 25. Chemical structure of the natural C- β -D-ribofuranosyl nucleoside antibiotic showdomycin (**51**).

Condensation of α -ketoesters and the appropriate 1-carbamoylphosphorane in a Wittig type reaction affords a mixture of two (*E*)/(*Z*) stereoisomers of which the (*Z*)-form cyclizes spontaneously to the desired maleimide. Unfortunately, this method suffers from a major limitation : the reaction is not (*Z*)-stereoselective and variable amounts of the undesired (*E*)-form are always produced depending on the size of the substituents.^[179] Three 3-substituted-4-methylmaleimides have been synthesized this way. The Wittig type reaction between the preliminarily prepared carbamoylmethyltriphenylphosphorane (**52**) and methyl pyruvate (**53**) furnished 3-methylmaleimide (**19**) and methyl 2-methylfumaramate (**54**) in 9% and 53% yields, respectively (Scheme 26).^[178]



Scheme 26. Synthesis of 3-methylmaleimide (**19**) by a Wittig type reaction.

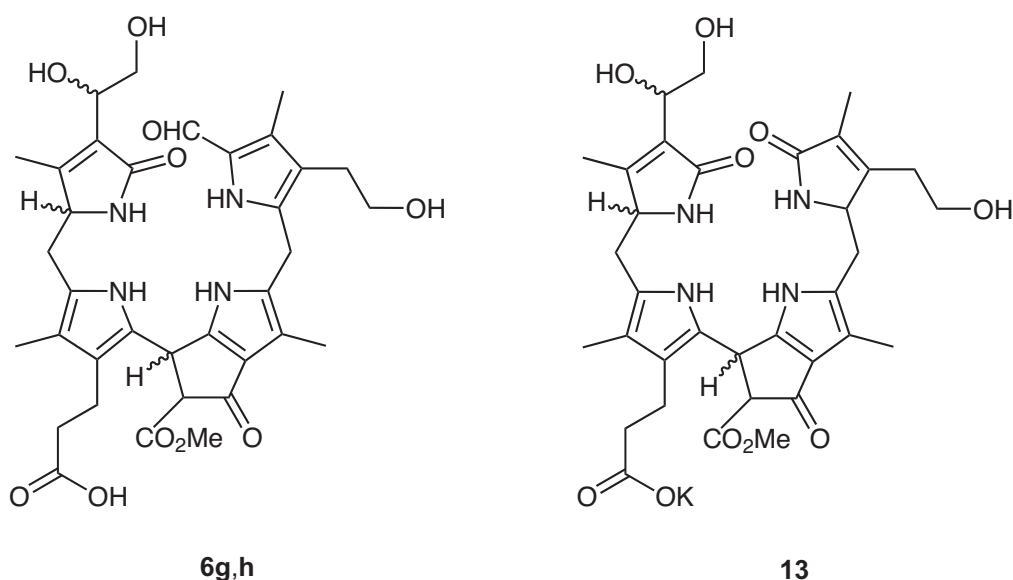
Deprotonation of the phosphonium salt **55** with DBN followed by condensation with methyl phenylglyoxylate (**56**) provided a 1 : 1 mixture of 3-phenyl-4-methylmaleimide (**31**) and methyl 3-methyl-2-phenylfumaramate (**57**) in 35% overall yield.^[178] Finally, the protected 4-methylshowdomycin **58** has been prepared in 30% yield from the corresponding α -ketoester **59** and the deprotonated phosphonium salt **55** (Scheme 27). Unfortunately, no further details on the fumaramate **60** were provided. It remains unclear whether it was isolated or only detected.^[178]



Scheme 27. Reaction between the phosphonium salt **55** and α -ketoesters. The base used can be either sodium hydride or DBN. RFBz is the abbreviation for 2,3,5-tri-O-benzyl- β -D-ribofuranosyl.

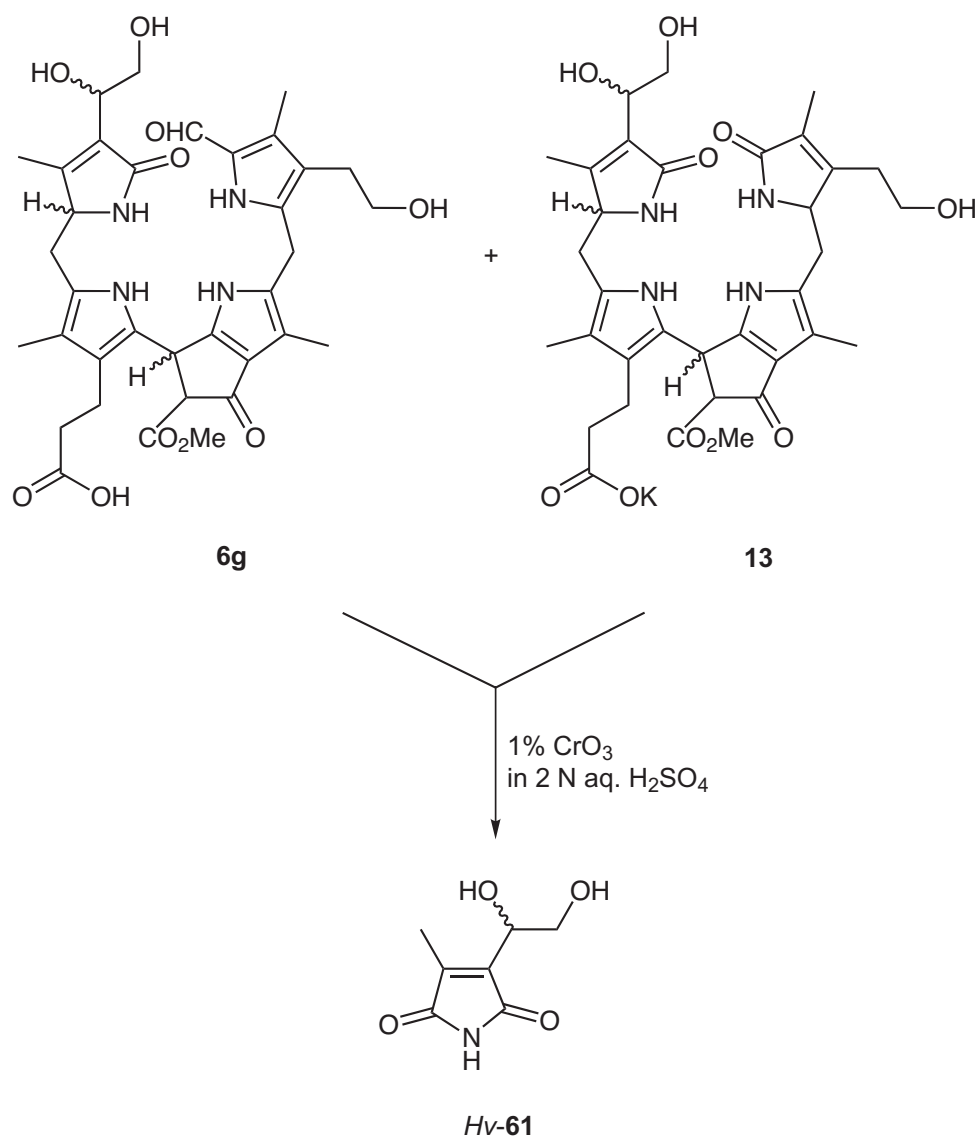
AIM OF THIS WORK

The chemical constitution of NCCs exhibits at least two centers of chirality with unknown configurations at the C(1) and C(15) positions, whereas C(13²) is prone to epimerization (Scheme 28).^[24, 180] Moreover, Hv-NCC-1 (**6g**),^[181] So-NCC-2 (**6h**)^[71] and the new bilin-type catabolite of barley (**13**)^[100] have an additional chiral center of undetermined absolute configuration, since their vinyl group has been probably enzymically dihydroxylated during Chl breakdown.



Scheme 28. Chemical structures of the Chl catabolites showing a dihydroxyethyl group in the C(3¹)/C(3²) position. Hv-NCC-1 (**6g**) and So-NCC-2 (**6h**) are C(1)-epimers.

Oxidation of senescing barley leaves extracts with chromic acid allowed the isolation of the Chl catabolites derived 3-(1,2-dihydroxyethyl)-4-methylmaleimide (*Hv-61*).^[128] Its circular dichroism spectrum shows a negative Cotton effect indicating that it is enantiomerically enriched. The biochemical dihydroxylation of the vinyl group during Chl breakdown thus probably proceeds enantioselectively (Scheme 29).



Scheme 29. Oxidation with chromic acid of senescent barley leaves extracts containing the two Chl final catabolites (**6g**, **13**) isolated from this plant so far. One of the product obtained in this manner is 3-(1,2-dihydroxyethyl)-4-methylmaleimide (*Hv-61*) which still contains the desired chiral group.

One aim of this work was the development of a suitable method for the preparation of 3-substituted-4-methylmaleimide, and to apply this route for the total synthesis of one

enantiomer of 3-(1,2-dihydroxyethyl)-4-methylmaleimide (**61**). A comparison of its chiroptic properties with the maleimide derived from barley Chl catabolites should allow the determination of the absolute configuration of its dihydroxyethyl moiety.

Moreover, a novel, facile synthetic access to 3-substituted-4-methylmaleimides should allow a more convenient future detection of Chl catabolites in natural extracts and should facilitate more intensive studies of structural modifications during Chls degradation.

RESULTS AND DISCUSSION

3. PREPARATION OF 3-SUBSTITUTED-4-METHYLMALEIMIDES BY OXIDATION OF PYRROLES

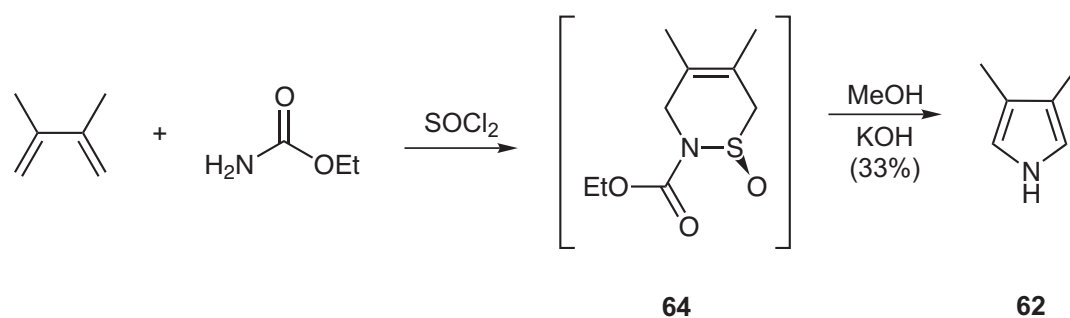
3.1. Use of Ceric Ammonium Nitrate as Oxidizing Agent

Cerium(IV) compounds represent the most important oxidants among lanthanide reagents. In particular, CAN has been extensively used for a wide variety of transformations, like oxidations of aromatic and benzylic systems, alcohols, olefins, ketones and aldehydes and nitroalkanes. Notably, α -methyl-1*H*-pyrroles have been converted to α -formyl-1*H*-pyrroles.^[182, 183] As one might expect for very powerful one-electron oxidants, the chemistry of cerium(IV) oxidation reactions of the organic groups cited above is dominated by radical and radical cation chemistry. The fate of these reactive intermediates determines the nature of the organic oxidation product isolated.^[184]

The following sections show the different approaches used to synthesize 3,4-dimethyl-1*H*-pyrrole (**62**) and 3,4-dimethyl-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole (**63**) – used as model compounds – and the optimization procedures of CAN mediated oxidations leading to maleimides.

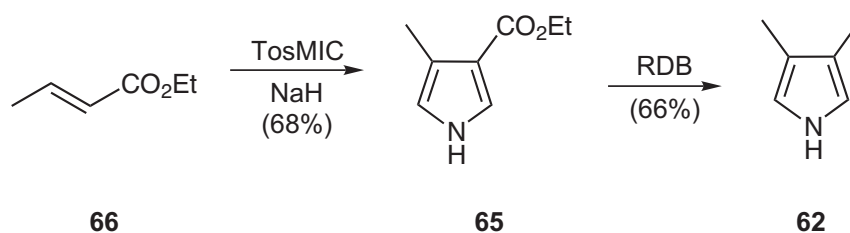
Preparation of Pyrroles Used as Model Substrates

3,4-Dimethyl-1*H*-pyrrole (**62**) has been prepared following three different synthetic approaches. Thus, treatment of a *N*-sulfinyl compound with 2,3-dimethylbutadiene gave a cycloadduct **64** which, by heating in a strongly alkaline methanolic solution, afforded the desired pyrrole **62** in 33% yield (Scheme 30).^[185]



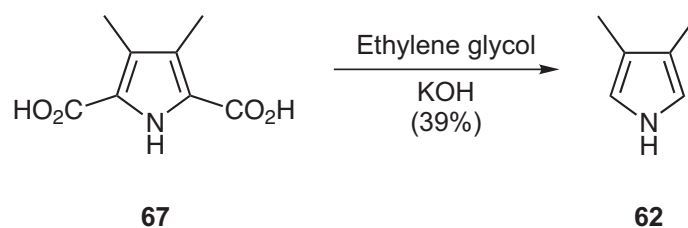
Scheme 30. Synthesis of 3,4-dimethyl-1*H*-pyrrole (**62**) via the cycloadduct **64**.

A two step procedure can also be used to prepare 3,4-dimethyl-1*H*-pyrrole (**62**):^[186] 3-carboethoxy-4-methyl-1*H*-pyrrole (**65**), prepared from ethyl crotonate (**66**) and TosMIC, was reduced with RDB to give the target compound **62** in 45% overall yield (Scheme 31).



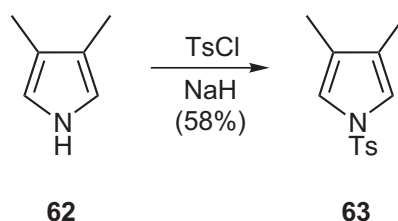
Scheme 31. Preparation of 3,4-dimethyl-1*H*-pyrrole (**62**) in a two steps synthesis via 3-carboethoxy-4-methyl-1*H*-pyrrole (**65**).

The decarboxylation of 3,4-dimethyl-1*H*-pyrrole-2,5-dicarboxylic acid (**67**) in presence of potassium hydroxide and ethylene glycol was the third method to afford the desired product **62** in 39% yield (Scheme 32).



Scheme 32. Decarboxylation of 3,4-dimethyl-1H-pyrrole-2,5-dicarboxylic acid (**67**) to give 3,4-dimethyl-1H-pyrrole (**62**).

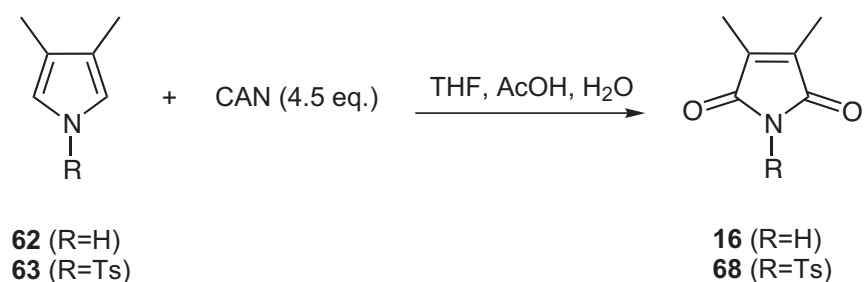
3,4-Dimethyl-1H-pyrrole (**62**) was treated with tosyl chloride to afford the *N*-tosyl pyrrole **63** in 58% yield (Scheme 33). This served as a general model for the oxidation of *N*-protected pyrroles encountered later in the attempts to prepare 3-(1,2-dihydroxyethyl)-4-methylmaleimide (*rac*-**61**) (see section 3.3.).



Scheme 33. Protection of the amino group of 3,4-dimethyl-1H-pyrrole (**62**).

Oxidations of Pyrroles with Ceric Ammonium Nitrate under Stoichiometric Conditions

Preliminary assays – using the conditions described by Thyran *et al.* to oxidize α -methylpyrroles to α -formylpyrroles –^[182] indicated that CAN is a potent oxidizing agent for the conversion of α, α' -free pyrroles to maleimides. Hence, more exhaustive studies have been carried out to evaluate the potential of CAN for this conversion (Scheme 34).



Scheme 34. Oxidations of pyrroles with CAN in stoichiometric amount. See table 2.

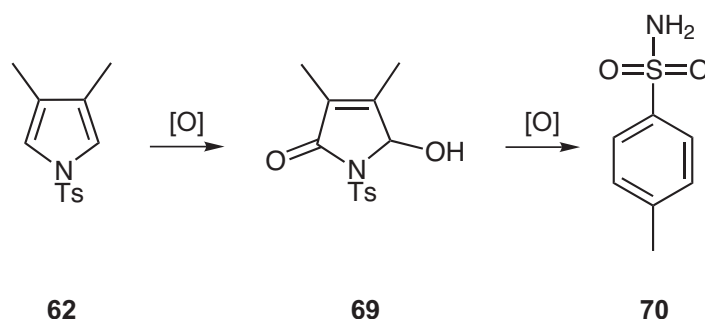
Oxidation of 3,4-dimethyl-1*H*-pyrrole (**62**) with 4.5 molar equivalents of CAN at room temperature for 1 hour furnished, after quenching the reaction with a great amount of water (250 ml for 1 mmol reagent), 3,4-dimethylmaleimide (**16**) in only 14% yield (Table 2, entry 1). This result can be explained by the partial solubility of **16** in water. As expected, when the reaction was quenched with less water (20 ml for 1 mmol reagent) and even with a smaller reaction time, the yield went up to 23% (Table 2, entry 2). No notable difference was observed if the conversion was done at room temperature or at 0°C (Table 2, entries 2 and 3). However, when the reaction was carried out at reflux temperature, the yield significantly increased (Table 2, entry 4). Increasing the reaction time did not lead to a higher yield, indicating that 1 hour is sufficient to carry out this reaction to completion (Table 2, entries 4 and 5).

Entry	Substrate	Time	Temperature	Product	Yield (%)
1	62	1 hour	rt	16	14 ^a
2	62	20 minutes	rt	16	23
3	62	20 minutes	0°C	16	29
4	62	1 hour	reflux	16	57
5	62	4 hours	reflux	16	55
6	63	up to 3 days	rt	68	--
7	63	1 day	reflux	68	-- ^b

^aReaction was quenched with water (250 ml for 1 mmol **62**) during work-up. ^bThe isolated product was 5-hydroxy-3,4-dimethyl-1-[(4-methylphenyl)sulfonyl]-1,5-dihydro-2*H*-pyrrol-2-one (**69**) in 37% yield (Scheme 35).

Table 2. Oxidations of pyrroles with CAN in stoichiometric amounts. See scheme 34.

Oxidation of the *N*-tosylpyrrole **63** with CAN did not afford the desired target compound **68** either at room temperature or at reflux (Table 2, entries 6 and 7). At room temperature no reaction took place while at reflux the only product formed was 5-hydroxy-3,4-dimethyl-1-[(4-methylphenyl)sulfonyl]-1,5-dihydro-2*H*-pyrrol-2-one (**69**) in 37% yield. Moreover, a photooxidation of **63** provided the same product **69** in 25% yield. In an attempt to oxidize **69** further to **68** with manganese dioxide led surprisingly to 4-methylbenzenesulfonamide (**70**) in nearly quantitative yield (Scheme 35). The difference of reactivity between **62** and **63** can certainly be explained by the electron-attracting effect of the tosyl group that reduces the electronic density of the pyrrole ring and thus affects its sensitivity toward oxidative processes.

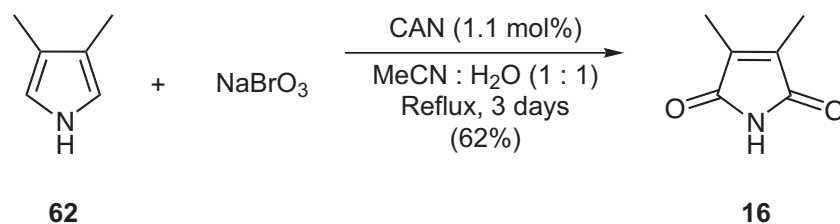


Scheme 35. Oxidation of the *N*-tosylpyrrole **62**.

The fact that CAN is unable to oxidize *N*-tosylpyrroles to maleimides is not the only limitation of this method since oligomerization – or polymerization – of 1*H*-pyrroles occurs under acidic conditions affording an insoluble dark powder named “black pyrrole”.^[187] Hence, yields of oxidations with CAN – which controls certainly the release of protons in the reaction medium – will be greatly decreased. Another major limitation to the use of CAN is the large quantities of reagents being required due to its high molecular weight.

Oxidation of Pyrroles with Ceric Ammonium Nitrate under Catalytic Conditions

The use of a great amount of reagent was a major limitation of the pyrroles oxidation with CAN. Hence, a procedure in which CAN was utilized in catalytic amount was studied. The Ce(IV) species was continuously replenished by the action of sodium bromate, a lighter and cheaper multi-electron oxidant.^[188]



Scheme 36. Oxidation of 3,4-dimethyl-1H-pyrrole (**62**) with CAN in catalytic amount.

In initial investigations the solvents system used was the same as the one used in the oxidation with CAN employing stoichiometric amounts, *i. e.* a mixture of THF, acetic acid and water. But, when 3,4-dimethyl-1H-pyrrole (**62**) was heated at reflux for 4 hours in this mixture in presence of 1.1 mol% CAN and 8 molar equivalents of sodium bromate two inseparable products were isolated : the target compound 3,4-dimethylmaleimide (**16**) and γ -butyrolactone, in a 1 : 5 ratio. With 4 molar equivalents of sodium bromate this ratio decreased to 1 : 2.5, indicating that the by-product was undoubtedly derived from a direct oxidation of THF by the co-oxidant. In addition, it has been shown that sodium bromate itself is able to oxidize THF to γ -butyrolactone in presence of a catalytic amount of hydrobromic acid.^[189] Therefore, a new solvents mixture has been used to avoid this unnecessary depletion of co-oxidant. By heating the pyrrole **62** with 16 molar equivalents of sodium bromate and 1.1 mol% CAN at reflux for 3 days in a mixture of acetonitrile and water , the desired maleimide **16** could be obtained in 62% yield (Scheme 36). The yield is roughly the same as obtained for the oxidation with CAN using stoichiometric conditions, but with a clearly longer reaction time (see previous section). Another experiment was carried out in order to learn wheter sodium bromate itself is able to oxidize pyrroles to maleimides. Using the same conditions described above but without the ceric catalyst, 3,4-dimethylmaleimide (**16**) was detected by TLC after a few days concomitantly with the disappearance of 3,4-dimethyl-1H-pyrrole (**62**). However, this conversion seems to be too slow to indicate that sodium bromate alone was responsible for the oxidation of **62** to **16** in the catalytic system described herein.

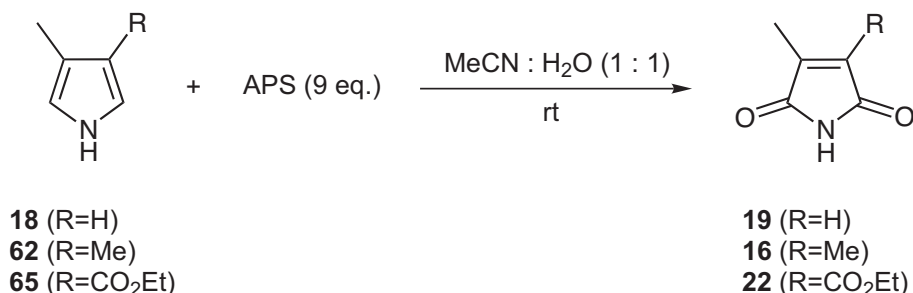
Two main factors alter the efficiency of this catalytic procedure for pyrrole oxidation to maleimides. The first is – as in the case of the oxidation under stoichiometric conditions of CAN – the oligomerization of α,α' -free pyrroles in the conditions used to

carry out the reaction, affording the insoluble compound “black pyrrole”. The incomplete oxidation of 3,4-dimethyl-1*H*-pyrrole (**62**), as indicated by the detection by TLC of 3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (**28**), is another problem which was present in all experiments carried out.

3.2. Peroxydisulfate Oxidation of Pyrroles to Maleimides

Peroxydisulfate ions are capable of oxidizing virtually all functional groups, even hydrocarbons. Mechanistic studies have shown that there are two fundamentally different ways in which this species reacts. At low temperatures (25°C) and in the absence of a catalyst, its reaction is fast only with strong nucleophiles and this proceeds *via* a simple polar mechanism. Many other functional groups react so slowly under these conditions and thus are essentially inert. At higher temperatures – and/or in the presence of a catalyst – rapid radical reactions occur involving a sulfate ion radical formation.^[190]

Due to its great standard redox potential, the peroxydisulfate ion $S_2O_8^{2-}$ has been tested as potential reagent to oxidize pyrroles to maleimides (Scheme 37). Preparation of model pyrroles **62** and **65** were described (see section 3.1.) whereas **18** is available in our laboratory.^[128] 3,4-Dimethyl-1*H*-pyrrole (**62**) has been stirred in presence of 9 molar equivalents of APS at room temperature for 30 minutes to give 3,4-dimethylmaleimide (**16**) in 38% yield (Table 3, entry 1). Increasing the reaction time to 3 days provided a higher yield of 70% for the same conversion (Table 3, entry 2).



Scheme 37. Peroxydisulfate oxidations of pyrroles to maleimides. See table 3.

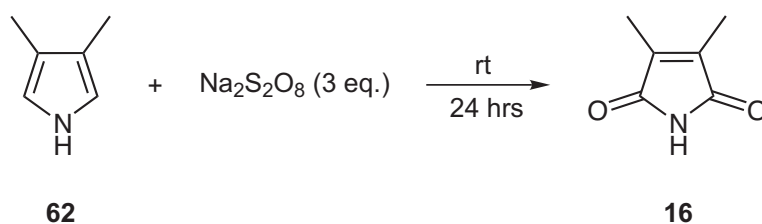
As in the case of CAN mediated oxidations of model pyrroles **62** and **63** (see section 3.1.), the formation of the oligomeric “black pyrrole” was a main limitation of these oxidations with peroxydisulfate. Astonishingly, a de-oligomerization – indicated by the loss of the reaction medium black colour – seemed to have occurred during this latter assay, but, unfortunately, this experiment was not reproducible any more (Table 3, entry 2). Using the same conditions, 3-methyl-1*H*-pyrrole (**18**) furnished the corresponding maleimide in only 26% yield (Table 3, entry 3), whereas oxidation of the pyrrole **65** did not allow neither the isolation nor the detection by TLC of any maleimide (Table 3, entry 4).

Entry	Substrate	Time	Product	Yield (%)
1	62	30 min.	16	38
2	62	3 days	16	70 ^a
3	18	3 days	19	26
4	65	3 days	22	--

^aDe-oligomerization of “black pyrrole” seemed to have occurred during the reaction.

Table 3. Peroxydisulfate oxidations of pyrroles to maleimides. See scheme 37.

The oligomer formation has been studied in more details. Peroxydisulfate oxidations assays have been carried out with different pH conditions and pyrrole addition rates. “Black pyrrole” generation was determined *de visu*, whereas the maleimides were detected by TLC specifically with chlorine / TMB. The acidity of the APS ammonium counterion could be a possible factor able to trigger the oligomerization. That is why sodium peroxydisulfate has been used as oxidant instead of APS in the conversion of 3,4-dimethyl-1*H*-pyrrole (**62**) to 3,4-dimethylmaleimide (**16**) (Scheme 38, table 4).



Scheme 38. Peroxydisulfate oxidation assays to study the formation of the oligomere “black pyrrole” as well as this of 3,4-dimethylmaleimide (**16**). See table 4.

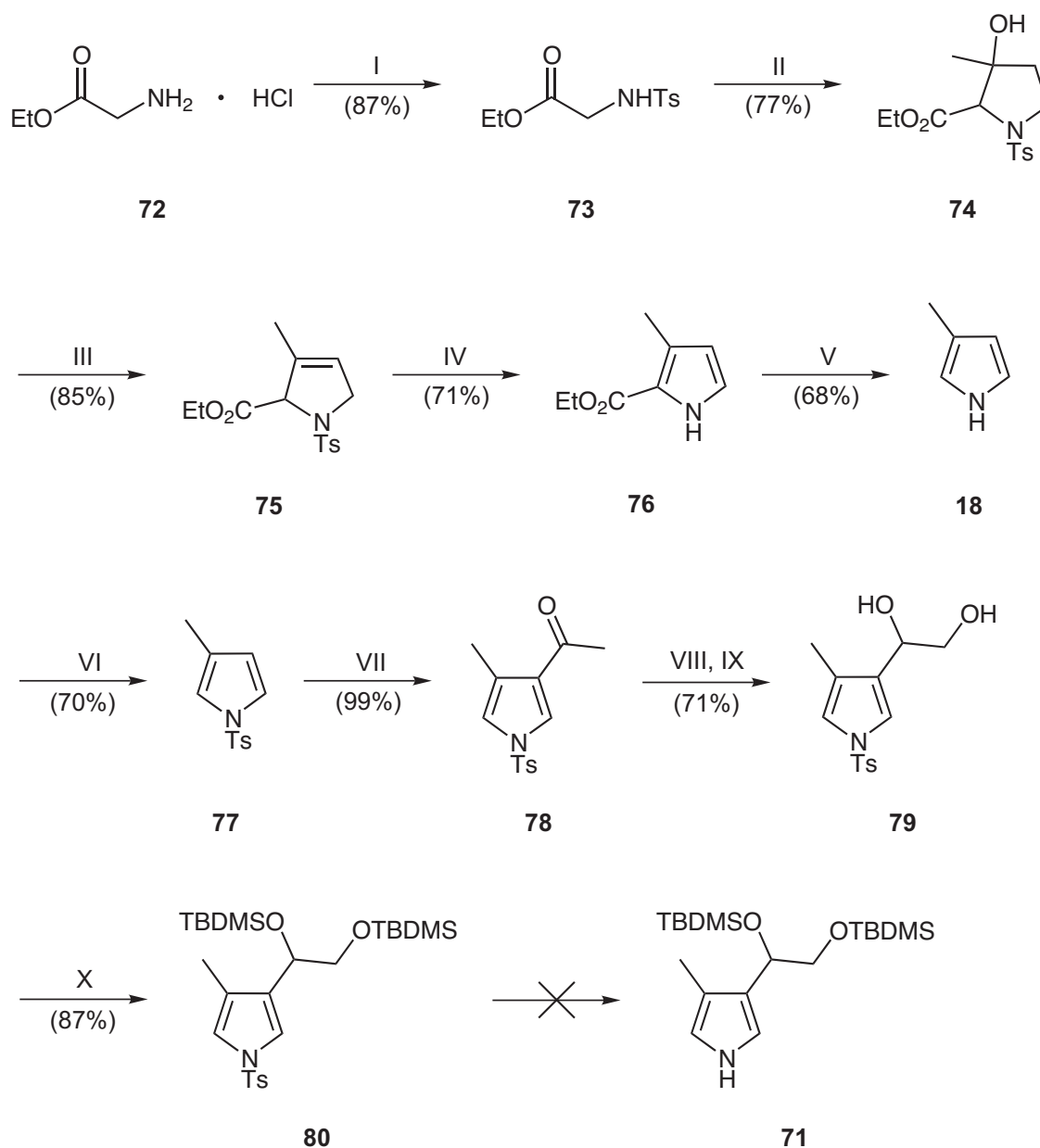
Entry	Solvent	pH ^a	Method ^b	16 ^c	“Black pyrrole” ^d
1	MeCN : H ₂ O (1 : 1)	7.2	a	+	+
2	MeCN : 4.5 M aq. NaOH (1 : 1)	14	a	-	-
3	MeCN : 0.4 M aq. KP (1 : 3)	7.2	a	+	+
4	MeCN : 1 M aq. H ₂ SO ₄ (1 : 1)	1	a	+	+
5	MeCN : 0.4 M aq. KP (3 : 2)	7.2	b	+	+
6	MeCN : 0.4 M aq. KP (3 : 2)	7.2	c	+	+

^aAccording to the pH of the aqueous component of the solvents mixture before the reaction. ^b(a) addition of the pyrrole in one block to the reaction mixture, (b) addition of the pyrrole over 5 hours and (c) addition of the pyrrole over 24 hours. ^cDetected by TLC. ^dDetected *de visu*.

Table 4. Peroxydisulfate oxidation assays to study the formation of “black pyrrole” and maleimides. See scheme 38.

The use of sodium peroxydisulfate, which bears a neutral counterion, did not avoid the problem of oligomerization (Table 4, entries 1 and 3-6). In each case, the formation of “black pyrrole” was concomitant with the formation of the maleimide **16** – except in alkaline medium where no reaction took place at all (Table 4, entry 2). The generation of hydrogen sulfate ions during the oxidative process could explain the formation of “black pyrrole”. Surprisingly, oligomerization occurred also in a KP buffer without decrease of the pH value, thus allowing to postulate that perhaps the oxidation of the pyrrole itself is sufficient to trigger it (Table 4, entry 3). Furthermore, addition over many hours of a diluted solution of the pyrrole **62** to a concentrated one of the oxidizing agent was not able to avoid this problem of oligomerization (Table 4, entries 5 and 6).

reductive deprotection with magnesium was also tried, but without success thus not allowing the completion of the synthesis of **71**.^[128]



Scheme 40. Synthesis of pyrroles precursors of 3-(1,2-dihydroxyethyl)-4-methylmaleimide (rac-**61**). I) TsCl, Na₂CO₃, H₂O, rt, 3 hrs. II) MVK, DBU, THF, rt, o/n. III) Py, POCl₃, rt, o/n. IV) DBU, THF, reflux, o/n. V) KOH, ethylene glycol, H₂O, 200°C. VI) NaH, TsCl, THF, rt, o/n. VII) Ac₂O, AlCl₃, 1,2-dichloroethane, rt, o/n. VIII) SeO₂, dioxane, H₂O, reflux, 5 hrs. IX) NaBH₄, EtOH, 0°C, 1 hr. X) TBDMSCl, Im, DMF, rt, 3 hrs.

Application of CAN mediated - or peroxydisulfate oxidation as the key step of the preparation of 3-(1,2-dihydroxyethyl)-4-methylmaleimide (*rac*-**61**) was not possible since the *N*-deprotected pyrrole **71** was not available. Furthermore, the oxidative conversion of pyrrole to maleimide has been tried before the deprotection of the amino group. But, as expected for this type of compounds, oxidations of *N*-tosylpyrroles **79** and **80** with chromic acid did not furnish the desired maleimides.^[191]

3.4. Scope and Limitations

The main advantage for the preparation of 3-substituted-4-methylmaleimides by oxidation of the corresponding pyrroles lies in the fact that their syntheses are well documented and give access to a wide variety of compounds with substituents in the C(3) position. Furthermore, the use of CAN – in stoichiometric or catalytic amount – or APS as oxidizing agents allows the preparation of maleimides with aliphatic side chains in yields up to 70%.

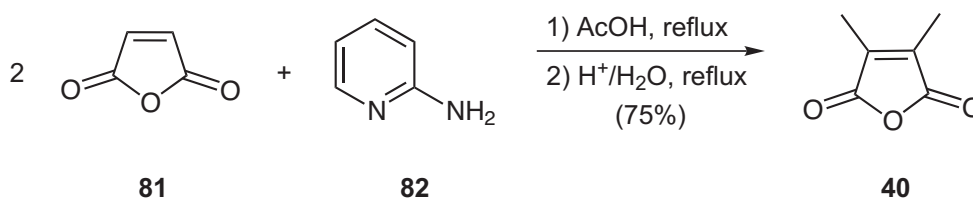
Despite this, the method suffers from substantial disadvantages. The redox potential needed for the conversion of pyrroles to maleimides should be very high, hence the use of strong oxidizing conditions restricting its application to less functionalized substrates. Moreover, when they are subjected to this type of reactions, pyrroles undergo spontaneously oligomerization to give an insoluble product named “black pyrrole”. Total synthesis of optically active 3-(1,2-dihydroxyethyl)-4-methylmaleimide (**61**) – which was the main purpose of this work – with an oxidative key step was not accomplished since the preparation of the corresponding pyrrole **71** was unsuccessful.

4. REACTIVE 2-OXO-3H-IMIDAZO[1,2- α]PYRIDINIUM COMPOUNDS AS KEY INTERMEDIATES IN A GENERAL WAY TO MALEIMIDES

The strategy depicted in this section consists in preparing 3-substituted-4-methylmaleimides from their corresponding disubstituted maleic anhydrides. These are synthesized based on the method described by Baumann *et al.*,^[192-194] which finally would allow the preparation of the enantiopure 3-[(1*R*)-1,2-dihydroxyethyl]-4-methylmaleimide ((*R*)-**61**). The conversion of maleic anhydrides to maleimides is well-known, and can be carried out very efficiently and smoothly using the conditions described by Davis *et al.* (see section 2.4.).^[174]

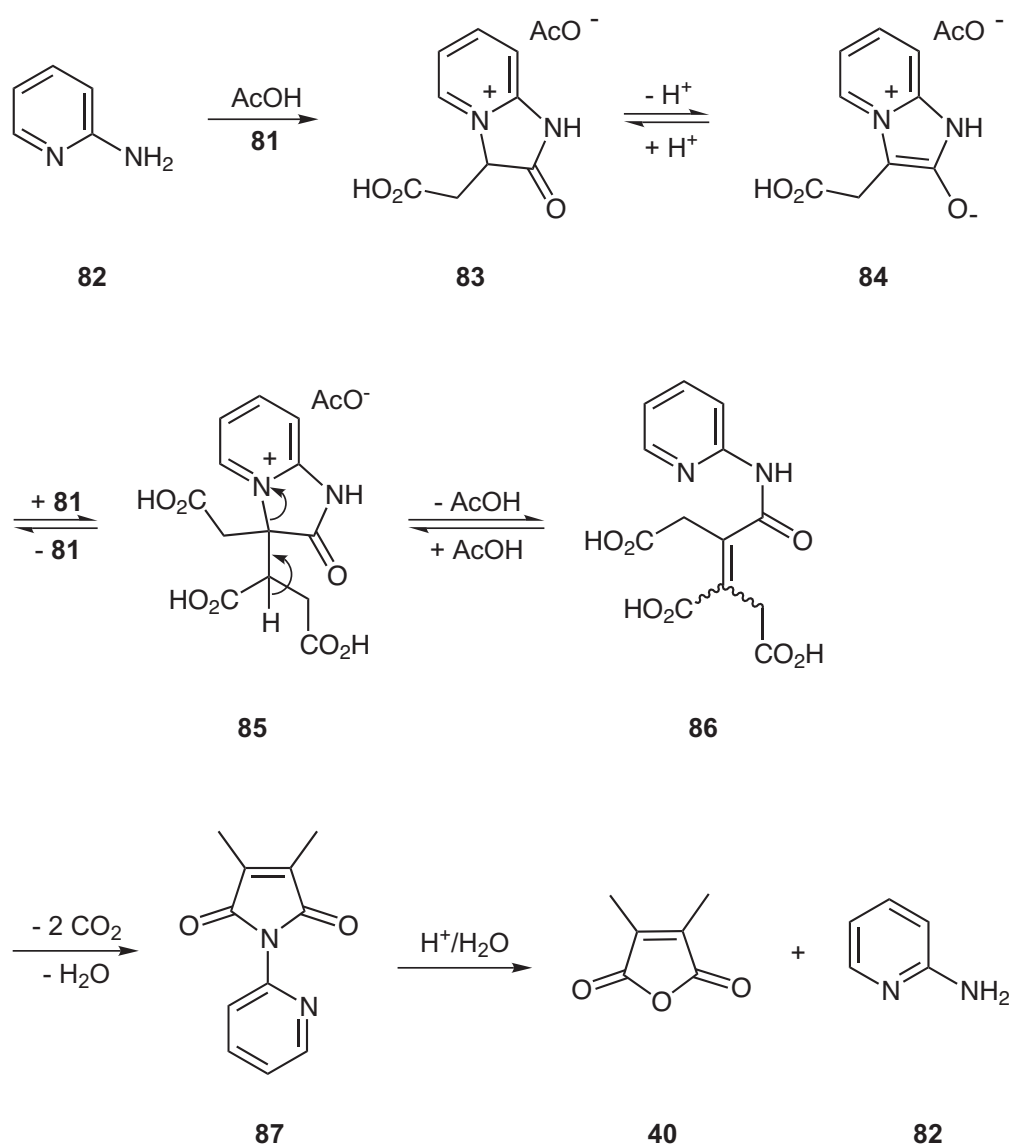
4.1. Synthesis of Substituted Maleic Anhydrides from 2-Oxo-3*H*-imidazo[1,2- α]pyridinium Compounds

In 1978, Baumann *et al.* described a method for the synthesis of 3,4-dimethylmaleic anhydride (**40**) by decarboxylative dimerization of MA (**81**) in presence of 2-aminopyridine (**82**) in 75% yield (Scheme 41).^[192]



Scheme 41. Decarboxylative dimerization of MA (**81**) in presence of 2-aminopyridine (**82**).

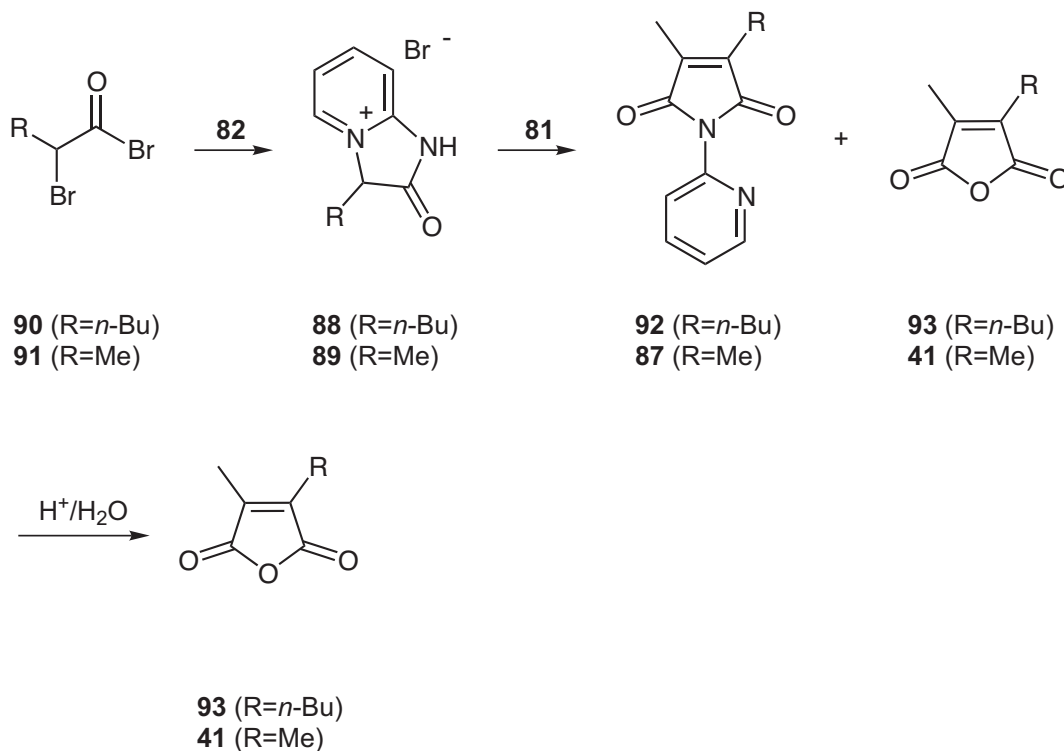
Mechanistic studies showed that the imidazopyridinium salt **83** is formed first from MA (**81**) and 2-aminopyridine (**82**), it is in equilibrium with its deprotonated form **84** on account of its high acidity, comparable with these of carboxylic acids (Scheme 42).^[194] Michael addition of MA (**81**) leads to the tricarboxylic acid (**85**) which undergoes β -elimination and ring opening to give the intermediate **86**, followed by a double decarboxylation and cyclization leading to 3,4-dimethyl-*N*-pyridin-2-ylmaleimide (**87**). This is hydrolyzed in acidic medium to afford 3,4-dimethylmaleic anhydride (**40**).



Scheme 42. Mechanism proposed for the decarboxylative dimerization of MA (**81**) in presence of 2-aminopyridine (**82**).

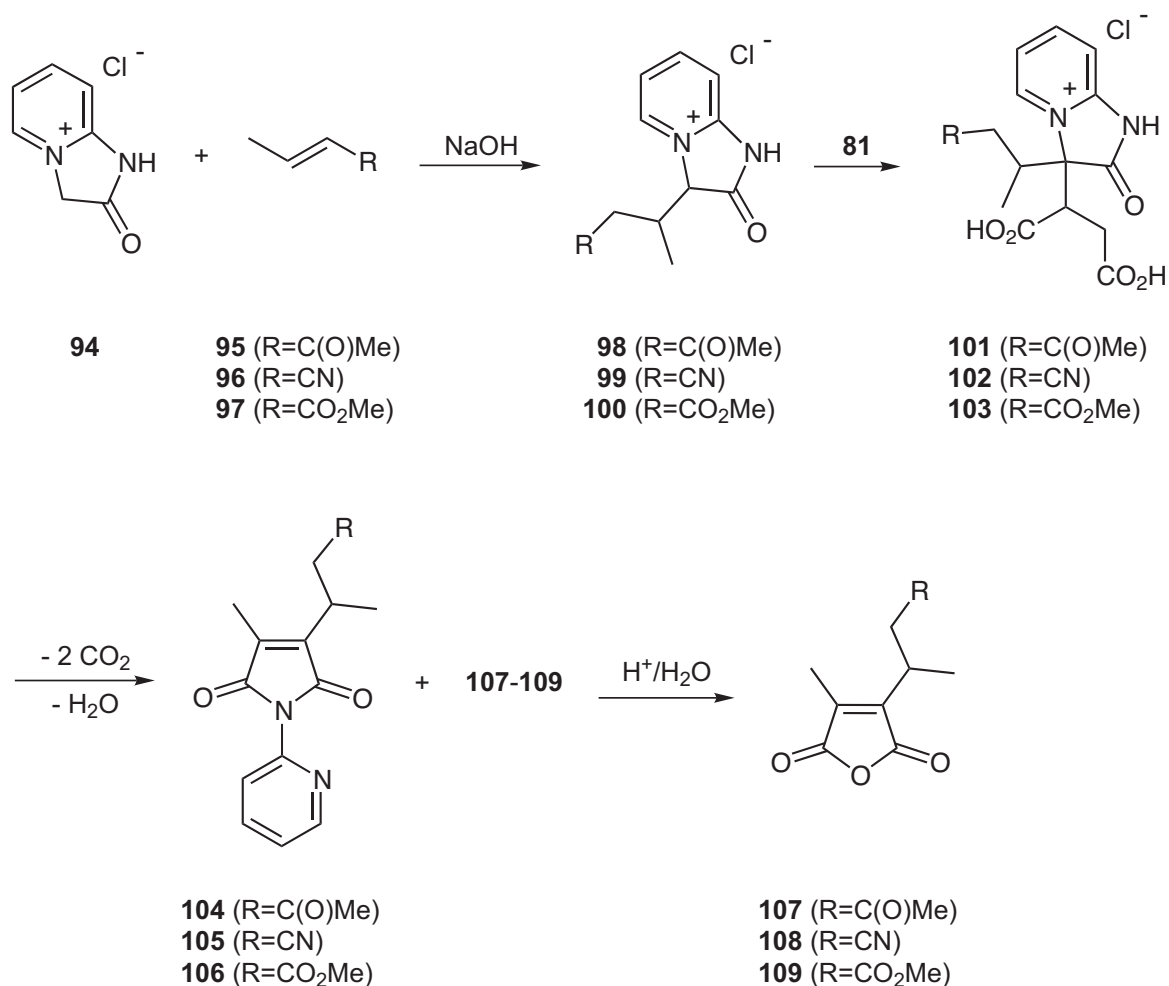
This method was improved in order to allow syntheses of various 3-substituted-4-methylmaleic anhydrides, most of them bearing additional functional groups in their side chain.^[194] Three different strategies have been elaborated. Firstly, the imidazopyridinium intermediates (**88**, **89**) were formed by reaction between 2-aminopyridine (**82**) and α -bromoacyl bromides (**90**, **91**) followed by subsequent Michael addition of MA (**81**) to afford a mixture of the corresponding 3-substituted-4-methyl-1-pyridin-2-ylmaleimides (**87**, **92**) and 3-substituted-4-methylmaleic

anhydrides (**40**, **93**). After acidic hydrolysis, **40** and **93** were isolated in yields up to 60% (Scheme 43).



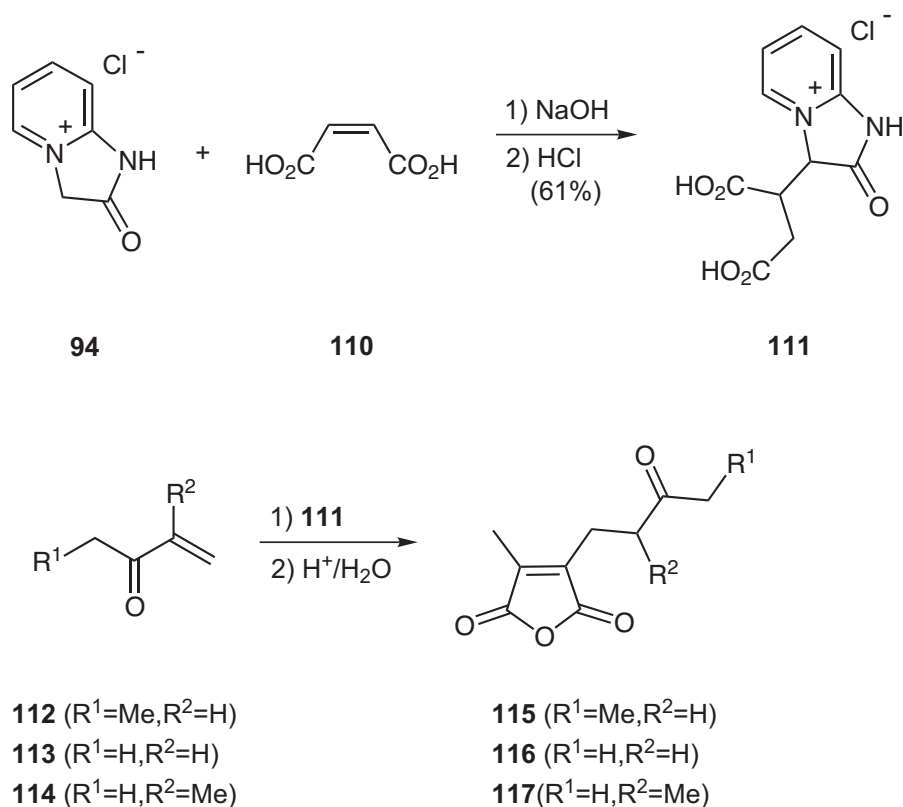
Scheme 43. Preparation of 2-oxo-3H-imidazo[1,2-*a*]pyridinium bromides (**88**, **89**) by reaction between 2-aminopyridine (**82**) and α -bromo-acyl bromides (**90**, **91**), followed by their reaction with MA (**81**) and by an acidic hydrolysis leading to maleic anhydrides (**41**, **93**).

The second strategy involved first the alkylation of the imidazopyridinium **94** – prepared from chloroacetyl chloride and 2-aminopyridine (**82**) – with β -substituted Michael acceptors (**95-97**) to give the intermediates **98-100**. Michael acceptors must bear a β -substituent in order to avoid a double alkylation of **94**. Then, a second alkylation with MA (**81**), which proceeded via **101-103**, afforded a mixture of 1-pyridin-2-ylmaleimides (**104-106**) and maleic anhydrides **104-106**. An acidic hydrolysis of them furnished the target compounds **104-106** in yields comprised between 41% and 45% (Scheme 44).^[194]



Scheme 44. Preparation of maleic anhydrides (**107-109**) via a first alkylation with Michael acceptors (**95-97**) and a second with MA (**81**).

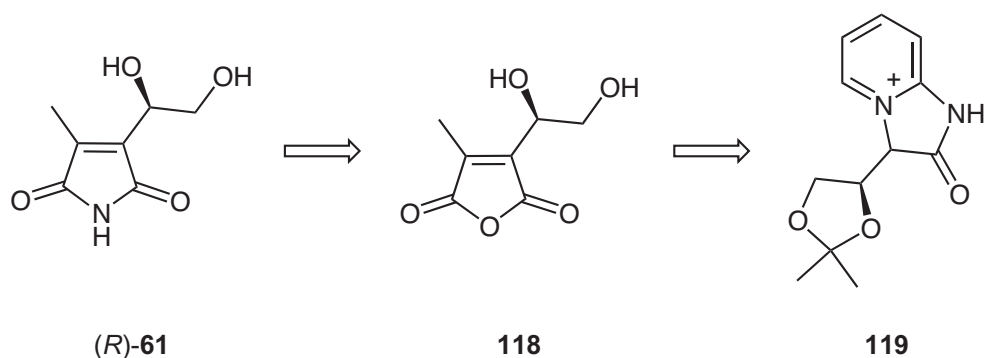
The third strategy involved an inversion of the alkylation sequence allowing thus the use of acceptors with a terminal double bond. Here the alkylation of **94** was first carried out with maleic acid (**110**) to give the imidazopyridinium **111** in 61% yield. This was alkylated with various Michael acceptors (**112-114**) and provided, following the procedure described above, 3-substituted-4-methylmaleic anhydrides (**115-117**) in yields of up to 47% (Scheme 45).^[194]



Scheme 45. Preparation of maleic anhydrides (**115-117**) by alkylating first the imidazopyridinium **94** with maleic acid (**110**).

4.2. Proposed Strategy for the Preparation of 3-Substituted-4-methylmaleic Anhydrides

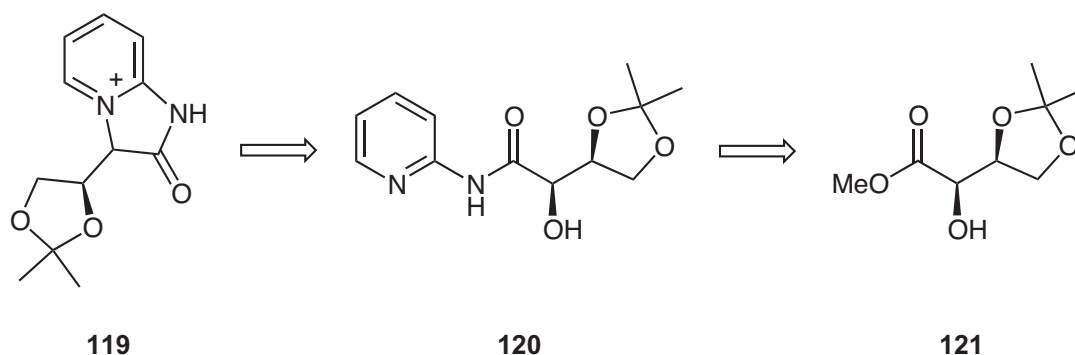
The method for the synthesis of maleic anhydrides described by Baumann *et al.* (see section 4.1.) is not applicable for the preparation of the optically active **118** which is a key intermediate in the retrosynthetic way of 3-[(1*R*)-1,2-dihydroxyethyl]-4-methylmaleimide ((*R*)-**61**) (Scheme 46).



Scheme 46. Strategy for the preparation of (R)-**61** via the imidazopyridinium intermediate **119**.

To our knowledge no Michael acceptor is able to introduce a precursor of such a dihydroxyethyl group into the imidazopyridinium **94**. Another possibility would be the preparation of a correspondingly substituted imidazopyridinium **119** by reaction between 2-aminopyridine (**82**) and α -bromoacyl bromide bearing the desired dihydroxyethyl function. But, the conditions necessary for the formation of this compound are too vigorous to be practical.

In order to avoid these problems, another approach would be to form first the amido group of the imidazopyridinium **119** by reaction of 2-aminopyridine (**82**) with the optically active α -hydroxyester **121**. The following cyclization has then to be carried out by intramolecular nucleophilic substitution induced by the activation of the hydroxyl group (Scheme 47).



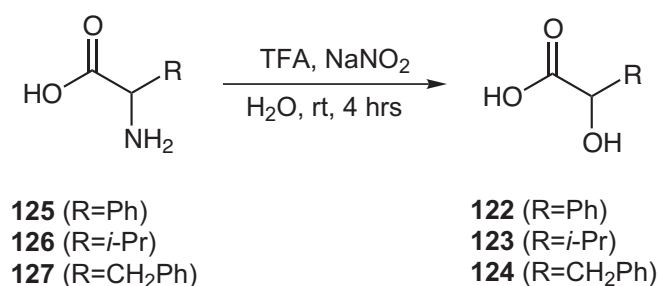
Scheme 47. Strategy for the preparation of the imidazopyridinium **119** via the 2-hydroxy-N-pyridin-2-ylamide **120**.

The strategy depicted here for the preparation of 3-[(1*R*)-1,2-dihydroxyethyl]-4-methylmaleimide ((*R*)-**61**) is not restricted to this single compound, but constitutes an efficient and versatile method for syntheses of a great number of maleimides with various substituents at the C(3) position.

4.3. Preparation of 2-Hydroxy-*N*-pyridin-2-ylamides

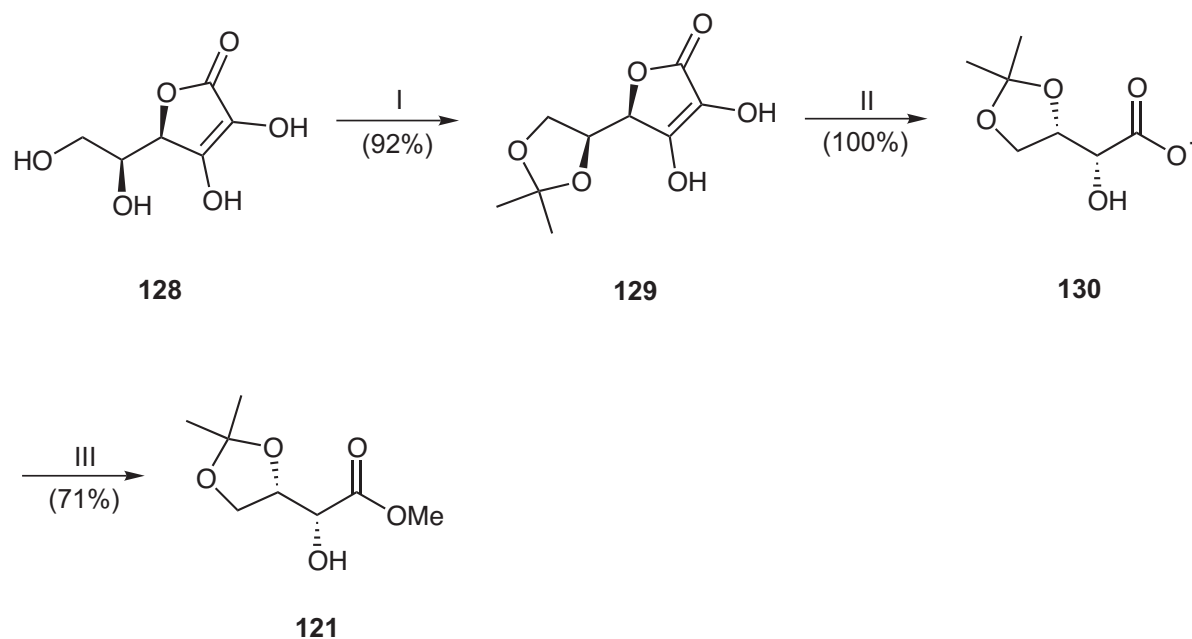
The synthetic strategy depicted in the section 4.2. needs the preparation of 2-hydroxy-*N*-pyridin-2-ylamides. This is not well documented^[195, 196] and it appears that the only general method known up to now involves the direct condensation of an α -hydroxyacid – or an α -hydroxyester – with 2-aminopyridine (**82**).^[195]

α -Hydroxyacids can be easily obtained from their corresponding AA by nitrous acid deamination. For examples, mandelic acid (**122**), 2-hydroxy-3-methylbutanoic acid (**123**) and 2-hydroxy-3-phenylpropanoic acid (**124**) were prepared in good yields from Phegly (**125**), Val (**126**) and Phe (**127**), respectively (Scheme 48).



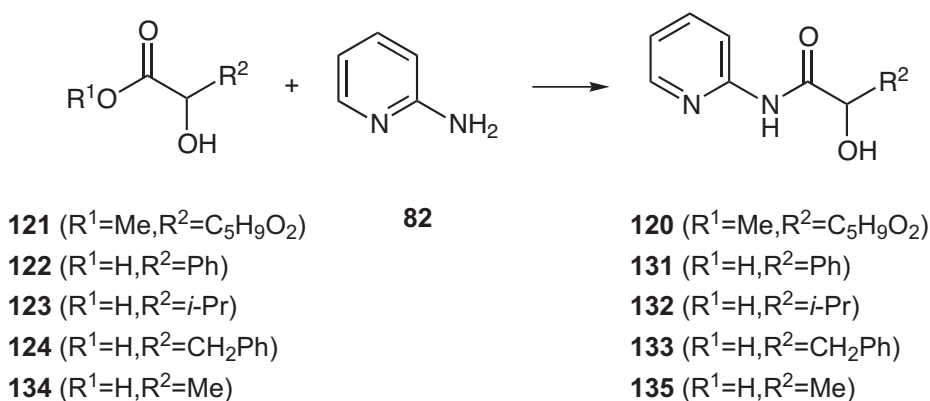
Scheme 48. Preparation of α -hydroxyacids (**122-124**) by deamination of their corresponding AA (**125-127**).

Ascorbic acid (**128**) is the naturally occurring chiral precursor of the α -hydroxyester **121** necessary for the synthesis of 3-[(1*R*)-1,2-dihydroxyethyl]-4-methylmaleimide ((*R*)-**61**).^[197, 198] Its dihydroxyethyl moiety was first protected with DMP in acetone and in presence of catalytic amounts of tin(II) chloride to give **129** in 92% yield. Oxidation with hydrogen peroxide provided the calcium salt of the threonic acid derivative **130** which was subsequently transformed to the desired methyl ester **121** in 71% yield by treatment with dimethyl sulfate in an aqueous sodium bicarbonate solution (Scheme 49).



Scheme 49. Preparation of the α -hydroxyester **121** involved in the synthetic strategy leading to **119**. I) DMP, SnCl₂, acetone, reflux, 6 hrs. II) CaCO₃, H₂O₂, H₂O, 40°C, 2 hrs. III) Dimethyl sulfate, NaHCO₃, H₂O, 40°C, 7 hrs.

Two different procedures were applied successfully to the preparation of a number of 2-hydroxy-*N*-pyridin-2-ylamides (Scheme 50, Table 5). The first involved a condensation at high temperature in a sealed Schlenk tube. It was applied to the preparation of **120** and also to the AA derived amides **131** and **133**. The latter was carried out in somewhat larger amounts in a Dean-Stark apparatus in presence of toluene and served to transform the commercially available lactic acid (**134**) and also **123** to their corresponding 2-hydroxy-*N*-pyridin-2-ylamides **135** and **132**, respectively.^[195] Results are summarized in table 5.



Scheme 50. Synthesis of 2-hydroxy-N-pyridin-2-ylamides (**120**, **131-133**, **135**). See table 5.

Entry	Substrate	Temperature	Time	Method ^a	Product	Yield (%)
1	121	110°C	48 hrs	1	120 ^b	32
2	121	110°C	72 hrs	1	120 ^c	49
3	121	140°C	24 hrs	1	120 ^d	23
4	121	120°C	7 hrs	2	120	--
5	121	rt	24 hrs	2	120	--
6	122	160°C	4 hrs	1	131	41
7	123	120°C	24 hrs	3	132	55
8	124	160°C	4 hrs	1	133	25
9	134	120°C	20 hrs	3	135	58

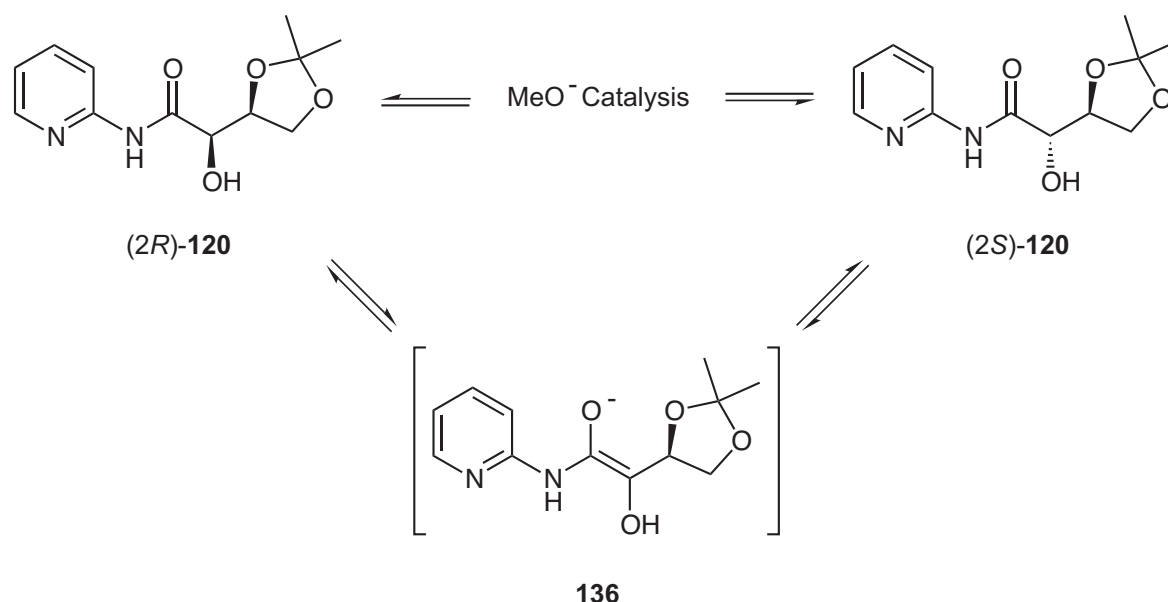
^aMethods (1) condensation in a sealed Schlenk tube; (2) deprotonation of **82** with sodium methoxide prior to the condensation; (3) condensation in a Dean-Stark apparatus. ^b70% *de.* ^c56% *de.* ^d16% *de.*

Table 5. Formation of 2-hydroxy-N-pyridin-2-ylamides. See scheme 50.

The synthesis of the 2-hydroxy-N-pyridin-2-ylamide **120** by direct condensation of 2-aminopyridine (**82**) and the ester **121** was carried out first at 110°C for 48 hours in 32% yield (Table 5, entry 1). Increasing the reaction time to 72 hours afforded a better yield of 49% (Table 5, entry 2). These poor yields can be explained by the great number of by-products generated during the reaction. When the temperature was increased to 140°C from 110°C the reaction went faster to completion but the side-reactions were greatly favoured and thus the yield was of only 23% (Table 5,

entry 3). Moreover, a deprotonation of **82** with sodium methoxide prior to the condensation reaction did not allow the isolation nor the detection of the desired product **120** (Table 5, entries 4 and 5). Other attempts to prepare **120** from 2-aminopyridine (**82**) and the calcium salt of the threonic acid derivative **130** with the help of coupling reagents like BOP, PyBOP or DPPA have also failed certainly because these were inactivated by water which co-crystallized with **130**. 2-Hydroxy-*N*-pyridin-2-ylamides **131** and **133** were prepared in low yields from their corresponding α -hydroxyacids (**123**, **125**) (Table 5, entries 6 to 8). 2-Hydroxy-*N*-pyridin-2-ylamides **135** and **132** were synthesized in substantial amount by condensation in a Dean-Stark apparatus in yields up to 58%.

^1H NMR experiments showed that **120** was present in two diastereomeric forms (*2R*)-**120** and (*2S*)-**120**. A most likely hypothesis is that the methoxide ion liberated during the condensation of 2-aminopyridine (**82**) with the α -hydroxyester **121** catalyzed slowly this isomerization (Scheme 51) *via* the enolate **136**.



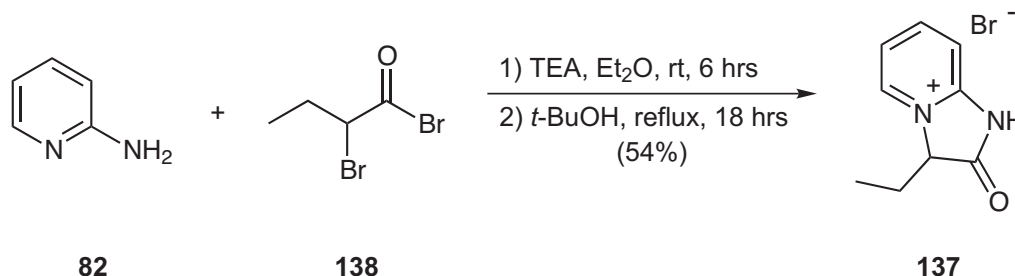
Scheme 51. Isomerization of **120** catalyzed by a methoxide ion.

The diastereomeric excess, determined by ^1H NMR, rose to 70% when the reaction was carried out at 110°C for 48 hours (Table 5, entry 1). As expected, with a reaction

time of 72 hours, the *de* decreased to 56% (Table 5, entry 2). The isomerization rate was greatly enhanced when the condensation was effectuated at 140°C; after 24 hours, the *de* was 16% (Table 5, entry 3). However, this isomerization did not play a major role in the synthetic approach to 3-[(1*R*)-1,2-dihydroxyethyl]-4-methylmaleimide ((*R*)-**61**) because it proceeded without loss of the chiral information in the dihydroxyethyl moiety.

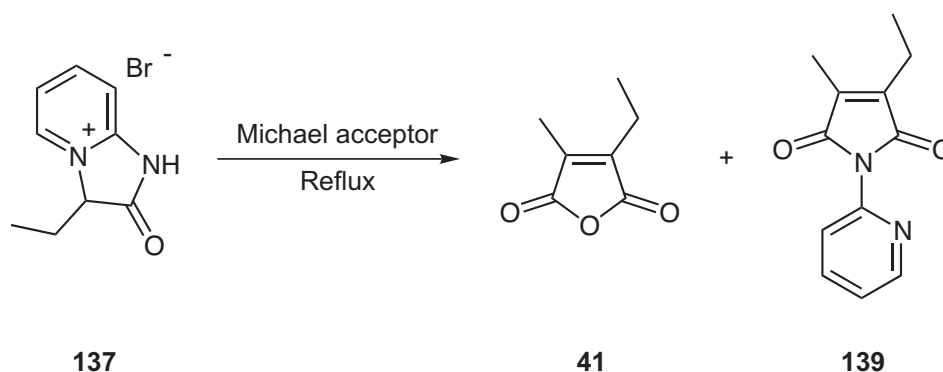
4.4. Cyclization and Decarboxylation of Alkylated Reactive 2-Oxo-3*H*-imidazo[1,2- α]pyridinium Compounds

The transformation of alkylated imidazopyridiniums in 1-pyridin-2-ylmaleimides and 4-methylmaleic anhydrides needs a second alkylation with either MA (**81**) or maleic acid (**110**) followed by a cyclization and decarboxylation at high temperature. This step has been investigated in more detail with the help of 3-ethyl-2-oxo-1*H*,2*H*,3*H*-imidazo[1,2- α]pyridin-4-ium bromide (**137**). This was prepared from 2-aminopyridine (**82**) and 2-bromobutyryl bromide (**138**) according to a single step procedure described by Baumann *et al.* (Scheme 52).^[199]



Scheme 52. Preparation of the imidazopyridinium **137** used as model compound for the cyclization and decarboxylation process.

The thus prepared imidazopyridinium derivative **137** served as model compound to test different conditions, especially alkaline ones for its transformation to **41** and **139** (Scheme 53). Table 6 summarizes these different reaction conditions.



Scheme 53. Transformation of **137** to **41** and **139**. See table 6.

Entry	Michael acceptor	Base	Solvent	Time	Products ratio ^a	Yield (%)
					(41 : 139)	
1	81	AcONa (1 eq.)	AcOH	3 hrs	24 : 76	94
2	81	--	<i>n</i> -BuOH	48 hrs	--	--
3	110	--	<i>n</i> -BuOH	5 hrs	--	--
4	110	MeONa (1 eq.)	<i>n</i> -BuOH	5 hrs	33 : 67	54
5	110	MeONa (1 eq.)	<i>n</i> -BuOH	15 hrs	24 : 76	58
6	110	<i>n</i> -BuONa (1 eq.)	<i>n</i> -BuOH	5 hrs	7 : 93	60
7	110	<i>n</i> -BuONa (2 eq.)	<i>n</i> -BuOH	5 hrs	0 : 100	31
8	110	<i>n</i> -BuOK (4 eq.)	<i>n</i> -BuOH	5 hrs	--	--

^abased upon isolated yields.

Table 6. Alkylation of **137** leading to **41** and **139**.

Treatment of **137** with MA (**81**) in an acidic medium furnished a mixture of **41** and **139** in a 76 : 24 ratio and with an excellent yield of 94% (Table 6, entry 1). However, since **120** – which is the precursor of (*R*)-**61** – bears an acid sensitive isopropylidene ketal protective group requires the development of a similar method but under neutral or alkaline conditions. Hence, *n*-butanol was chosen as solvent due to its high boiling point, allowing the reaction medium to reach a sufficient high temperature for the decarboxylation step. The reaction was tried first by treating **137** with MA (**81**) or maleic acid (**110**) in the absence of a base (Table 6, entries 2 and 3). In both cases

no formation of the desired products **41** and **139** was detected. By addition of 1 molar equivalent of commercially available sodium methoxide, **41** and **139** were obtained after 5 hours in a 33 : 67 ratio with an overall yield of 54% (Table 6, entry 4). An increase of the reaction time to 15 hours did not afford a better yield but the product ratio increased to 24 : 76 (Table 6, entry 5). The reaction became much more selective when a molar equivalent of sodium *n*-butoxide generated *in situ* was employed and became even completely selective when 2 molar equivalents were used (Table 6, entries 6 and 7). However, in this case, the yield decreased to only 31%. In presence of 4 molar equivalents of potassium *n*-butoxide – used instead of sodium *n*-butoxide because this is insoluble in *n*-butanol at the desired concentration – no desired product was either detected nor isolated suggesting that these conditions were too alkaline for the reaction (Table 6, entry 8).

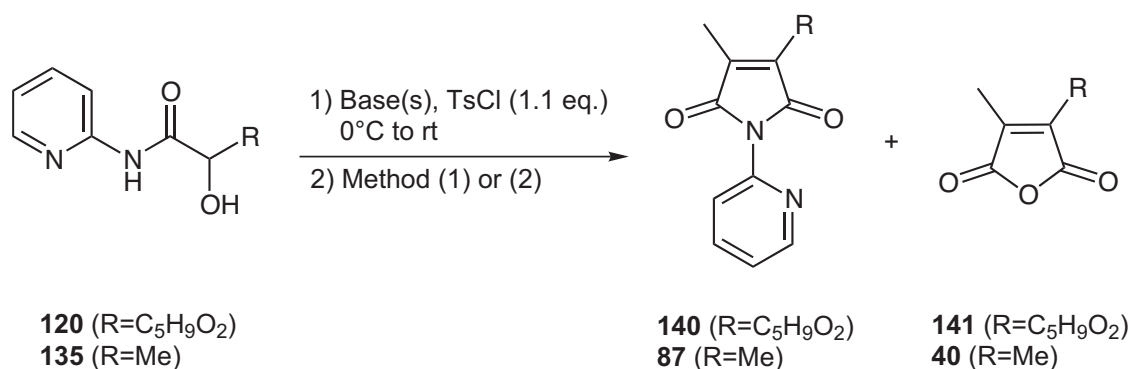
Baumann *et al.* postulated that 1-pyridin-2-ylmaleimides are direct products of the reaction. Nevertheless, they left it open whether these are products of the reaction between corresponding maleic anhydrides and 2-aminopyridine (**82**) released in the medium during the ring closure process.^[193] The fact that an increase of the reaction time led to a decrease in the relative amounts of **41** seems to verify this hypothesis (Table 6, entries 4 and 5). This was also corroborated by the reactions carried out in alkaline medium (Table 6, entries 6 and 7). In these cases, released 2-aminopyridine (**82**) was immediately deprotonated and thus became more nucleophilic allowing an efficient transformation of **41** in the 1-pyridin-2-ylmaleimide **139**. In order to prove that maleic anhydrides are probably direct precursors of 1-pyridin-2-ylmaleimides, the following reaction was carried out : the maleic anhydride **41** was heated at reflux for 3 hours in acetic acid and in presence of sodium acetate and 2-aminopyridine (**82**). As expected, a mixture of **41** and **139** was isolated in a 54 : 46 ratio allowing to postulate that 1-pyridin-2-ylmaleimides are, at least partially, derived from their corresponding maleic anhydrides.

4.5. Generation of Reactive 2-Oxo-3*H*-imidazo[1,2- α]pyridinium Intermediates *via* a Tosylation Mediated Cyclization

The considered approach to form imidazopyridinium intermediates from 2-hydroxy-*N*-pyridin-2-ylamides was to generate the cyclization by intramolecular nucleophilic

substitution induced by activation of the hydroxyl moiety. Its transformation to a tosyl group was chosen upon the following rationales : I) tosyl functionalities are good leaving groups and should certainly be easily substituted by the pyridinyl moiety to furnish the desired intermediates; II) tosylations are generally carried out in alkaline medium allowing the use of starting compounds bearing acid sensitive functionalities; and III) Yoshida *et al.* published in 1999 a procedure employing a catalytic amount of TMPDA.^[200] It provides an efficient and mild tosylation and circumvents the undesirable substitution side reaction with a chloride ion.

Therefore, a two step - one pot procedure was developed to prepare 1-pyridin-2-ylmaleimides and maleic anhydrides. First, the tosylation of 2-hydroxy-*N*-pyridin-2-ylamides was investigated. Secondly, imidazopyridinium intermediates were alkylated either with MA (**82**) or maleic acid (**110**) to give, after decarboxylation and ring closure, the desired products as described in section 4.4. (Scheme 54).



Scheme 54. Preparation of 1-pyridin-2-ylmaleimides (**87**, **140**) and their corresponding maleic anhydrides (**40**, **141**) from 2-hydroxy-*N*-pyridin-2-ylamides (**120**, **135**) via a tosylation induced nucleophilic substitution. Method (1) : MA (**82**), AcONa, AcOH, reflux, 3 hrs (Table 6, entry 1). Method (2) : Maleic acid (**110**), *n*-BuONa, *n*-BuOH, reflux, 5 hrs (Table 6, entry 6). See table 7.

2-Hydroxy-*N*-pyridin-2-ylpropanamide (**135**) has been chosen as model reagent to study this reaction because it is easily available in large amounts from commercially available lactic acid (**134**) (see section 4.3.). It was first tosylated in ether for 4 hours with 1.1 molar equivalents of TsCl in presence of a stoichiometric amount of TEA. An orange oil was obtained which was subsequently subjected to alkylation with MA (**81**)

in acetic acid – the best method obtained for this transformation (Table 6, entry 1) – to provide the two desired products **87** and **40** in a 81 : 19 ratio with a modest yield of 31% (Table 7, entry 1). The use of toluene rather than ether for a longer reaction time (24 hours) afforded a yield of 50% with a similar ratio (Table 7, entry 2). On the other hand, when the method described by Yoshida *et al.* was utilized for the tosylation step yields were cleanly better with similar products ratios.^[200] Thus 66% were obtained with a stoichiometric amount of TMPDA and 77% when this was used as catalyst together with 1.1 molar equivalents of TEA (Table 7, entries 3 and 4).

Next, this method was applied to the 2-hydroxy-*N*-pyridin-2-ylamide **120** which is a precursor of 3-[(1*R*)-1,2-dihydroxyethyl]-4-methylmaleimide ((*R*)-**61**). The first step of the reaction was carried out with TMPDA as catalyst in toluene for 24 hrs. The second step was carried out in the alkaline conditions described in the previous section (Table 6, entry 6) due to the presence of the acid sensitive isopropylidene ketal protective group. Unfortunately, neither **140** nor **141** could be isolated among the great number of side products (Table 7, entry 5). And when the second step was made in acidic medium the same problem was encountered, no desired – eventually deprotected – products could be isolated (Table 7, entry 6). On the other hand, one of the side products was identified as 3,4-dimethyl-1-pyridin-2-ylmaleimide (**87**). This is usually the product of the reaction between MA (**81**) and 2-aminopyridine (**82**) indicating that either the imidazopyridinium intermediate **119** or the 2-hydroxy-*N*-pyridin-2-ylamide **120** was decomposed during one of the two steps of the reaction. ¹H NMR analysis of **119** could not provide a proof for its existence because the spectral pattern was complicated by the presence of two diastereomers and several potential organic counterions.

Entry	Reagent	Base		Solvent	Method ^a	Products ratio ^b	Yield (%)
		TEA	TMPDA				
1	135	1.1 eq.	--	Ether	1	81 : 19	31 ^c
2	135	1.1 eq.	--	Toluene	1	78 : 22	50 ^d
3	135	--	1.1 eq.	Toluene	1	65 : 35	66 ^d
4	135	1.1 eq.	10 mol%	Toluene	1	72 : 28	77 ^d
5	120	1.1 eq.	10 mol%	Toluene	2	--	-- ^d
6	120	1.1 eq.	10 mol%	Toluene	1	--	-- ^d

^aMethod (1) : MA (**82**), AcONa, AcOH, reflux, 3 hrs (Table 6, entry 1). Method (2) : Maleic acid (**110**), *n*-BuONa, *n*-BuOH, reflux, 5 hrs (Table 6, entry 6). ^bRatio 1-pyridin-2-ylmaleimide : maleic anhydride.

^cReaction time : 4 hrs. ^dReaction time : 24 hrs.

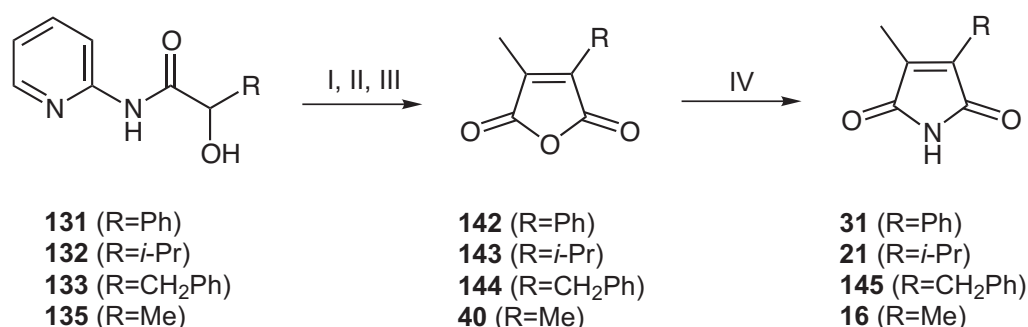
Table 7. Preparation of 1-pyridin-2-ylmaleimides and their corresponding maleic anhydrides from 2-hydroxy-N-pyridin-2-ylamides. See scheme 54.

4.6. Chemical Transformations of Maleimides Precursors

Two synthetical routes are conceivable to transform 1-pyridin-2-ylmaleimides to maleimides. The first is a hydrolysis furnishing the corresponding maleic anhydrides which must be next converted to maleimides according to known methods, while the second consists in carrying out a direct conversion with ammonia.^[139, 167-174]

The acidic hydrolysis of **139** at reflux for 8 hours provided 3-ethyl-4-methylmaleic anhydride (**41**) with an excellent yield of 86%. But, alkaline hydrolysis with 10% aqueous potassium hydroxide at reflux did not furnish the desired compound **41**. Direct conversion with ammonia generated *in situ* from ammonium acetate gave 3-ethyl-4-methylmaleimide (**17**) in 51% yield. On the other hand, when ammonia was generated from HMDS and methanol in DMF the yield decreased to 11%. In absence of DMF and when HMDS and methanol were used as solvents the desired target compound **17** was not formed. Conversion of **41** using the conditions described by Davis *et al.* furnished the maleimide **17** in quantitative yield.^[174] These results indicates obviously that the best way to obtain maleimides from their corresponding

affording 2-oxo-3*H*-imidazo[1,2- α]pyridinium intermediates. These were next alkylated *in situ* with MA (**81**) furnishing intermediates which after decarboxylated were ring closed to mixtures of 1-pyridin-2-ylmaleimide and maleic anhydride. Its acidic hydrolysis provided then exclusively the corresponding maleic anhydride. Finally, the conversion leading to the desired maleimide was effectuated in DMF under the conditions described by Davis *et al.* in presence of HMDS and methanol.^[174]



Scheme 56. Preparation of 3-substituted-4-methylmaleimides from 2-hydroxy-N-pyridin-2-ylamides in a four steps sequence. I) TsCl, TEA (1.1 eq.), TMPDA (10 mol%), toluene, rt, 24 hrs. II) MA (**81**), AcONa, AcOH, reflux, 3 hrs. III) 6 M aq. H₂SO₄ : THF (1 : 1), reflux, 8 hrs. IV) HMDS, MeOH, DMF, rt, 16 hrs. See table 9.

Entry	Reagent	Maleic anhydride	Yield (%)	Maleimide	Yield (%)	Overall yield (%)
1	131	142	--	31	--	--
2	132	143	--	21	--	--
3	133	144	25	145	100	25
4	135	40	67	16	100	67

Table 9. Some examples for the application of the method developed in the section 4.. See scheme 56.

The reactions sequence depicted herein has been tested for the preparation of four maleimides bearing an AA derived side chain (**16**, **21**, **31**, **145**) (Table 9). Surprisingly, reactions with **131** and **132** were carried out without success (Table 9, entry 1 and 2). On the other hand, this same sequence was applied successfully to

other 2-hydroxy-*N*-pyridin-2-ylamides (**133**, **135**) with yields reaching up to satisfying 67% (Table 9, entries 3 and 4). These results suggests that the preparation of maleic anhydrides di- or tri-substituted at the C(3¹) position is impossible following this route. The impossibility to synthesize **141** is a supplementary proof for this hypothesis (see section 4.5.).

4.8. Scope and Limitations

2-Oxo-3*H*-imidazo[1,2- α]pyridiniums were generated efficiently from 2-hydroxy-*N*-pyridin-2-ylamides by intramolecular nucleophilic substitution induced by tosylation of the hydroxyl group (Scheme 54 and Table 7). These amides were previously prepared by condensation of α -hydroxyacids – or α -hydroxyesters – and 2-aminopyridine (**82**) (Scheme 50 and Table 5). The main advantage of this synthetic method is the great variety of available substrates, including optically active reagents coming from chiral natural products pools like AAs. 2-Oxo-3*H*-imidazo[1,2- α]pyridiniums were next alkylated *in situ* either with MA (**81**) or maleic acid (**110**) to furnish an intermediate which carries out at high temperature a decarboxylation and a ring closure giving a mixture of 1-pyridin-2-ylmaleimide and maleic anhydride. This reaction was modified in order to allow transformation in acidic or in alkaline medium thus accommodating a greater range of substrates. The conversion of 1-pyridin-2-ylmaleimides into maleimides could be effectuated in high yields only with a previous acidic hydrolysis leading to the corresponding maleic anhydride which was next transformed into maleimide in presence of HMDS and methanol in DMF (Scheme 55 and Table 8).

Unfortunately, this method did not allow the preparation of 3-[(1*R*)-1,2-dihydroxyethyl]-4-methylmaleimide ((*R*)-**61**). The corresponding 2-hydroxy-*N*-pyridin-2-ylamide **120** bearing the desired optically active side chain could be synthesized easily, but the two step - one pot reaction of the imidazopyridinium formation and alkylation did not furnish the desired target compounds **140** and **141** (Scheme 54 and Table 7).

5. PREPARATION OF 3-SUBSTITUTED-4-METHYLMALEIMIDES FROM FUNCTIONALIZED α -KETOESTERS

5.1. Strategy

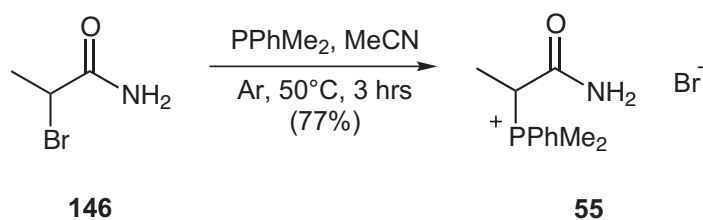
The work described in this section was inspired by a publication by Trummlitz *et al.* in 1975 for the synthesis of showdomycin derivatives (Section 2.5.).^[177, 178] The maleimide heterocycle was formed by spontaneous condensation of a (*Z*)-maleamate formed by a Wittig reaction between a carbamoylphosphorane and substituted α -ketoesters.

5.2. Synthesis of 4-Methylmaleimides with Various C(3)-Substituents

The maleimides formations described by Trummlitz *et al.* led only to poor yields with either simple model compounds or more complex showdomycin derivatives.^[177, 178] Hence the aim of this work was to first optimize the reaction conditions with commercially available α -ketoesters, and then to use them for the synthesis of 3-[(1*R*)-1,2-dihydroxyethyl]-4-methylmaleimide ((*R*)-**61**).

Synthesis of Model Compounds

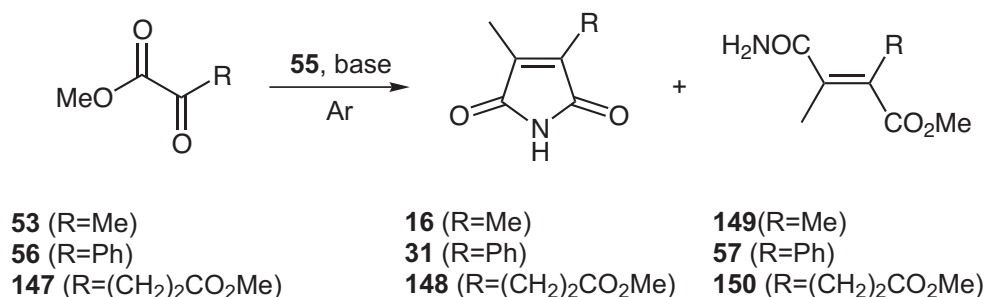
Phosponium salt **55** was prepared from dimethylphenylphosphine and 2-bromopropionamide (**146**) in acetonitrile in 77% yield (Scheme 57).



Scheme 57. Preparation of the phosponium salt **55**.

The use of a less nucleophilic phosphine – like triphenylphosphine – was impossible due to the spontaneous decomposition of the desired product into triphenylphosphine oxide and bromhydric acid *via* an enolphosponium salt.^[177]

Wittig reactions were investigated under different reaction conditions (Scheme 58, Table 10). A phosphorane – or ylid – was prepared *in situ* by deprotonation of the phosphonium salt **55** and was then added to a solution of the α -ketoester. The reaction proceeded unselectively to afford a mixture of both (*E*)- and (*Z*)-isomers. The latter cyclized spontaneously by intramolecular condensation to afford the desired maleimide.



Scheme 58. Wittig reactions to synthesize 3-substituted-4-methylmaleimides. See table 10.

Entry	Substrate	Temperature	Time	Solvent(s)	Base	Products		Ratio (Z) (E) (Z : E)	Yield (%)
						(Z)	(E)		
1	56	65°C	2 hrs	CHCl ₃ /DMSO ^a	DBN	31	57	80 : 20	40
2	56	65°C	6 hrs	CHCl ₃ /DMSO ^a	DBN	31	57	83 : 17	36
3	147	65°C	2 hrs	CHCl ₃ /DMSO ^a	DBN	148	150	--	--
4	147	rt	2 hrs	CHCl ₃ /DMSO ^a	DBN	148	150	100 : 0	5
5	56	65°C	2 hrs	CHCl ₃ /DMSO	DBN	31	57	68 : 32	59
6	56	rt	2 hrs	CHCl ₃ /DMSO	DBN	31	57	73 : 27	40
7	56	rt	8 hrs	CHCl ₃ /DMSO	DBN	31	57	65 : 35	52
8	56	rt	24 hrs	CHCl ₃ /DMSO	DBN	31	57	73 : 27	70
9	147	rt	24 hrs	CHCl ₃ /DMSO	DBN	148	150	100 : 0	2
10	53	rt	24 hrs	CHCl ₃ /DMSO	DBN	16	149	100 : 0	28
11	53	rt	24 hrs	THF/DMSO	LDA	16	149	100 : 0	34
12	147	0°C to rt	24 hrs	THF	LDA	148	150	67 : 33	6

^aSolvents were not previously dried.

Table 10. Maleimides via Wittig reactions : various reaction conditions.

Methyl phenylglyoxylate (**56**) with DBN as a base at 65°C for 2 hours in solvents from the shelf produced a yield of 40% (Table 10, entry 1). The selectivity of the reaction was 80 : 20 in favour of the desired (*Z*)-isomer. Increasing the reaction time did not improve neither the yield nor the selectivity (Table 10, entry 2). The use of methyl α -ketoglutarate – a more functionalized α -ketoester which should be the precursor of hematinic acid methyl ester (**148**), a well-known oxidation product of many naturally occurring porphyrins and phorbins – under the same reaction conditions as previously described, yielded no product (Table 10, entry 3). On the other hand, when this transformation was effectuated at room temperature, the desired maleimide **148** was isolated with a poor yield of 5%, but with a complete selectivity (Table 10, entry 4). With anhydrous solvents, the reaction with methyl phenylglyoxylate (**56**) furnished the expected products **31** and **57** in a higher yield but with a slightly less selectivity (Table 10, entry 5). When this same reaction was carried out at room temperature for 2 hours the yield decreased to 40% (Table 10, entry 6), but when the reaction time was increased up to 24 hrs the yield increased to 70% (Table 10, entry 7 and 8). Changes in the α -ketoester caused a drastic decrease in the yield, but in these cases, the selectivity was complete (Table 10, entries 9 and 10). Substitution of DBN by the lithiated base LDA for the ylid formation and the use of THF instead of chloroform did not cause any drastic change in the case of the reaction with methyl pyruvate (**53**) (Table 10, entry 11). This change of base was also tested for the reaction with methyl α -ketoglutarate (**147**) in THF at 0°C. Here the selectivity decreased to a ratio of 67 : 33 (Table 10, entries 4, 9 and 12).

Explanations for the stereochemical outcome of the Wittig reaction are complex and many factors – such as solvents, temperature, type of phosphorous ylids, additives, *etc* ... – intervene.^[179, 201, 202] That is the reason why no explanation about the selectivity of these reactions – based on the aforementioned results – are proposed in this section.

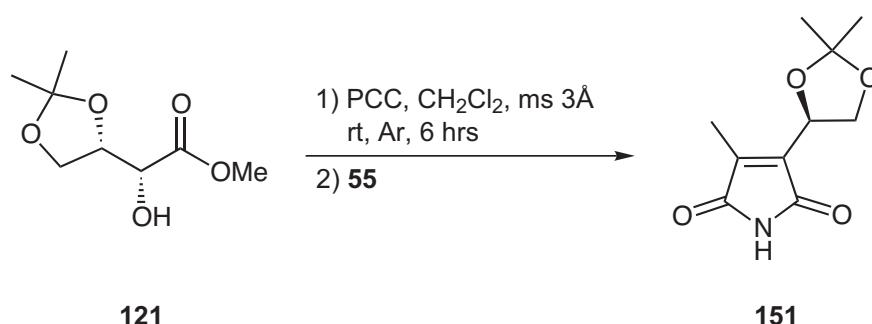
5.3. Synthesis of 3-[(1*R*)-1,2-Dihydroxyethyl]-4-methylmaleimide

The aim of this section is the synthesis of the chiral 3-[(1*R*)-1,2-dihydroxyethyl]-4-methylmaleimide ((*R*)-**61**) with a Wittig reaction as key step. The reaction conditions

The presence of molecular sieves 3 Å during oxidation with PCC was necessary for two main reasons:^[204] I) molecular sieves trapped water formed during the reaction, which could hydrate the α -ketoester **152**; and II) this water scavenging served also as driving force of the reaction. In the absence of molecular sieves no reaction occurred, as no α -hydroxyester **121** consumption could be observed.

Due to its moisture sensitivity, **152** was not purified nor spectroscopically characterized, but immediately employed in the next step of the synthetic sequence, the Wittig reaction, which is the key step of the procedure.

Attempts to perform the Wittig reaction under the same conditions as with the model compound **16** failed (Table 10, entry 8) (Scheme 60). The desired product could neither be isolated nor detected by TLC (Table 11, entry 1). Use of the lithiated base LDA in THF to deprotonate the phosphonium salt **55**, and running the reaction at -35°C for 1 hours and 13 hours at room temperature afforded the desired maleimide **151**, but only in 1% yield (Table 11, entry 2). A short screening of the reaction allowed us to establish the optimale reaction conditions. Decreasing the reaction temperature to -78° with slightly longer reaction times, the maleimide **151** was finally isolated in 10% yield and with nearly complete selectivity (Table 11, entry 3). Even if some traces of (*E*)-maleamate were detected (<0.1%) their amount was too small to be isolated.



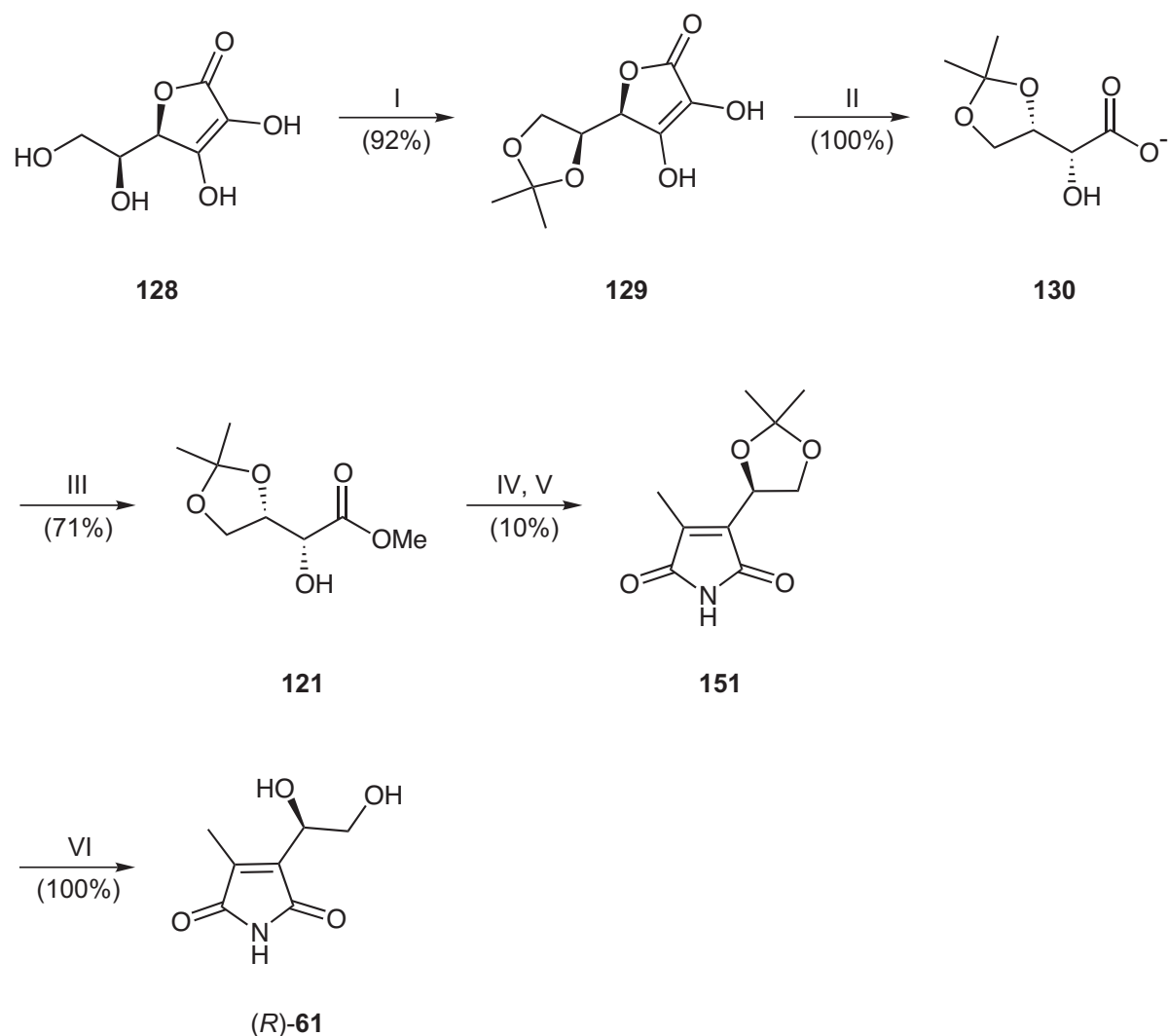
Scheme 60. Wittig reaction affording the maleimide **151**. See table 11.

Entry	Temperature	Time	Solvent(s)	Base	Yield (%)
1	rt	18 hrs	CHCl ₃ /DMSO	DBN	--
2	-35°C to rt	14 hrs	THF	LDA	1
3	-78°C to rt	24 hrs	THF	LDA	10

Table 11. Different conditions for the synthesis of **155** via a Wittig reaction. See scheme 62.

The rather low yield obtained (10%) could have a variety of reasons. First, as explained before, the α -ketoester **152** hydrated very fast which leads to a loss of active substrate since only the keto form is able to react with the ylid generated by deprotonation of **55**. Secondly, the yields obtained with the model compounds were never excellent, especially in the case of the functionalized α -ketoester **147**.

Finally, deprotection of **151** occurred quantitatively in the presence of TFA in aqueous THF, at 50°C for 16 hours and afforded pure 3-[(1*R*)-1,2-dihydroxyethyl]-4-methylmaleimide ((*R*)-**61**). The complete synthetic route is depicted in scheme 61.



Scheme 61. Total synthesis of 3-[(1R)-1,2-dihydroxyethyl]-4-methylmaleimide ((R)-**61**). I) DMP, SnCl₂, acetone, reflux, 6 hrs. II) CaCO₃, H₂O₂, H₂O, 40°C, 2 hrs. III) Dimethyl sulfate, NaHCO₃, H₂O, 40°C, 7 hrs. IV) PCC, *ms* 3 Å, CH₂Cl₂, rt, 6 hrs. V) **55**, LDA, THF, -78°C to rt, 24 hrs. VI) TFA, H₂O, THF, 50°C, 16 hrs.

5.4. Scope and Limitations

Wittig reactions between an ylid generated by deprotonation of **55** and α -ketoesters were successfully applied to form the 3-substituted-4-methylmaleimide core. Spontaneous ring closure of the intermediate (Z)-maleamate obtained by this way afforded directly the desired compound. The poor yields obtained, particularly in the case of functionalized α -ketoesters make the procedure less attractive from preparative point of view. The advantage is the high selectivity, which was always in

favour of the maleimide, although in some cases, the (*E*)-maleamates were isolated in up to 35% ratio.

Despite this inconvenience, the method presents many advantages. Only two steps – formation of the phosphonium salt **55** and the Wittig reaction itself – were necessary to prepare maleimides from commercially available α -ketoesters. In addition, many α -ketoesters can be synthesized in the laboratory *via* known procedures.^[205] Furthermore, this method is the only one with sufficiently mild reaction conditions to allow preparations of more functionalized maleimides.

This procedure represents also the key step in the synthesis of 3-[(1*R*)-1,2-dihydroxyethyl]-4-methylmaleimide ((*R*)-**61**). Even if the yield was poor it is the unique reaction known up to date which allows preparation of this very important compound.

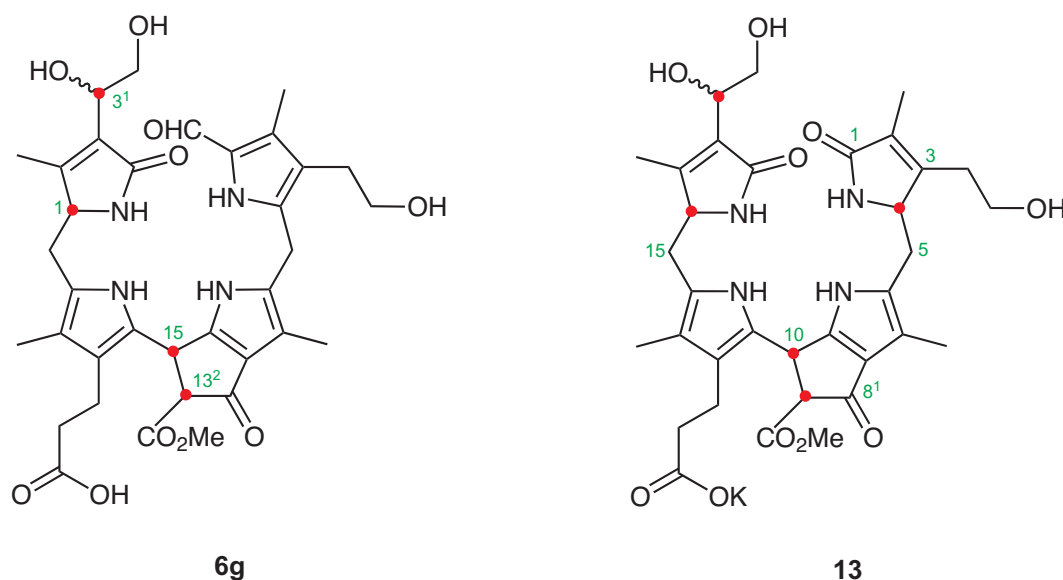
Future development of the procedure involves screening of the reaction conditions for the base, phosphine type involved, solvent, temperature, etc ... in order to improve the low yields obtained up to now. Other related procedures – like Wadsworth-Emmons-Horner reactions – should be tested as well. Finally, these investigations should lead to better yields, thus providing a fast, convenient and efficient total synthesis of 3-[(1*R*)-1,2-dihydroxyethyl]-4-methylmaleimide ((*R*)-**61**).

6. ABSOLUTE CONFIGURATION DETERMINATION OF THE DIHYDROXYETHYL MOEITY OF *HORDEUM VULGARE* CHLOROPHYLL CATABOLITES

This part of the thesis is concerned with the determination of the absolute configuration of the dihydroxyethyl group of Chl catabolites (**6g**, **13**) isolated from barley. 3-[(1*R*)-1,2-Dihydroxyethyl]-4-methylmaleimide ((*R*)-**61**) – whose total synthesis was described in section 5.3. – will be used as reference for the product coming from the oxidation of *Hordeum vulgare* Chl catabolites.

6.1. Chirality and Chlorophyll Catabolites

In spite of the fact that NCCs structures are well-known, the absolute configurations of any of their chiral centers are unknown up to now (Scheme 62), especially since no suitable crystals for X-ray investigations were available so far. The carboxymethyl moiety of the E isocycle originated from the Chls, due to the β -ketoester functional group, is prone to epimerization. Thus investigations of this absolute configuration are useless. However, it was demonstrated that *Hv*-NCC-1 (**6g**) and *So*-NCC-2 (**6h**) are C(1)-epimers and that *So*-NCC-2 (**6h**) and *Cj*-NCC (**6c**) have the same configuration at this center.^[71] Moreover, the new urobilinogenoid catabolite isolated from *Hordeum vulgare* was isolated in two C(4)-epimeric forms.^[100]

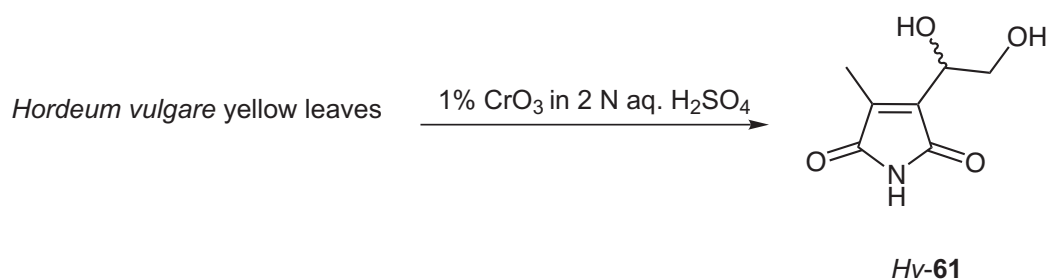


Scheme 62. Structures of both barley Chl catabolites isolated up to now. Their numbering is written in green. Chiral centers are symbolized with a red point.

Proton H(15) arises from the protic solvent during acid-catalyzed pyrroline/pyrrole rearrangement of both geometric isomers of the red Chl catabolite from *Chlorella protothecoides* (**7a**).^[52] Intensive mechanistic-chemical studies showed a remarkable high stereoselectivity for this rearrangement (>98% ee). Because of the stereochemical consequence of aforementioned experiments, to this position was tentatively assigned an (*R*) configuration. The proton at this position is highly resistant, it does not exchange even in boiling acetic acid-*d*¹.^[75]

6.2. Isolation of 3-(1,2-Dihydroxyethyl)-4-methylmaleimide by Chemical Oxidation of Barley Extracts

Chemical oxidation with chromic acid of enriched extracts of barley senescing leaves was previously carried out and allowed the isolation of an optically active 3-(1,2-dihydroxyethyl)-4-methylmaleimide (*Hv-61*) (Scheme 63).^[81, 128] This step was performed by P. Folly during his PhD work.^[128] This oxidation product comes from the A cycle of **6g** and **13** and, perhaps, equally from other Chl catabolites. Indeed, radiolabelling experiments demonstrated the presence of more than ten additional NCCs, which were not isolated nor spectroscopically characterized up to now.^[55] Next, this isolated maleimide *Hv-61* will be compared by chiroptic spectroscopy with the synthesized one ((*R*)-**61**) of known absolute configuration (see section 5.3.).



Scheme 63. Oxidation of barley enriched extracts. Two other maleimides – hematinic acid (**34**) and 3-(2-hydroxyethyl)-4-methylmaleimide (**23**) – were also isolated.

The procedure followed for the bleaching of primary leaves of barley was similar to that described previously except for some additional modifications as follows.^[70] In order to terminate Chl biosynthesis the green intact shoots were left at 25°C for 12 hours in permanent darkness. Afterward, batches of green primary leaves (150 g) were cut 10-15 cm from the apex and immersed with their ends in water (100 ml). The opening of the 1000 ml beakers was covered with punctured aluminium foil in order to allow gas exchange. The leaves were subsequently incubated at 25°C for 7-8 days in permanent darkness. When the green color of the Chls vanished, the yellowish still turgid leaves were collected and stored frozen until use.^[81, 128]

De-greened yellow leaves of *Hordeum vulgare* were next extracted with a desintegration buffer. After centrifugation and evaporation of the solvent mixture, the

residue was filtered through a reversed phase cartridge. After elution, the dark brown aqueous phase was oxidized with 1% chrome trioxide in 2 N aqueous sulfuric acid at room temperature for 24 hours and the product separated from the reaction mixture by continuous extraction with ether. The organic phase was dried with sodium sulfate and evaporated at reduced pressure to dryness. A first purification on TLC silica gel plates followed by a micro-scale column chromatography afforded 1.4 mg of 3-(1,2-dihydroxyethyl)-4-methylmaleimide (*Hv-61*).^[128] Its ¹H NMR, ¹³C NMR and MS data were absolutely identical to those of the synthesized compound (*R*)-**61**.

6.3. Absolute Configuration Assignment of Barley Catabolites Dihydroxyethyl Moiety

Circular dichroism was chosen as chiroptic method to assign the absolute configuration of the 3-(1,2-dihydroxyethyl)-4-methylmaleimide (*Hv-61*) – resulting from oxidation of *Hordeum vulgare* senescing leaves extracts – by comparison with the configuration of the enantiopure compound (*R*)-**61**. Circular dichroism reflects the anisotropic absorption of circularly polarized light by chiral samples containing an excess of one enantiomer. Anisotropic absorption – which is a Cotton effect – occurs in the spectral region where the absorption bands of the isochronic UV/Vis electronic spectrum are located. Comparing the Cotton effect of *Hv-61* whose absolute configuration was to be determined, with the Cotton effect of the synthetic reference material (*R*)-**61** of known absolute configuration allowed the assignment of the absolute configuration of the natural *Hv-61*.

Figure 3 shows the CD spectra of 3-(1,2-dihydroxyethyl)-4-methylmaleimide (*Hv-61*) originating from barley Chl catabolites and the synthetic enantiopure maleimide (*R*)-**61** with the absolute configuration (*R*).

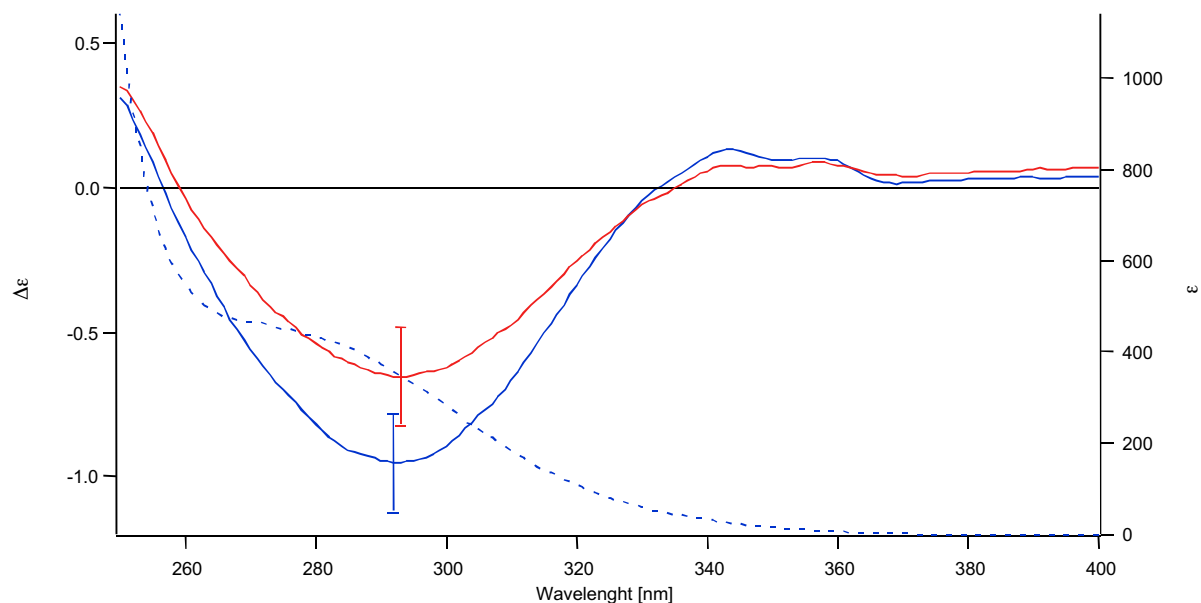
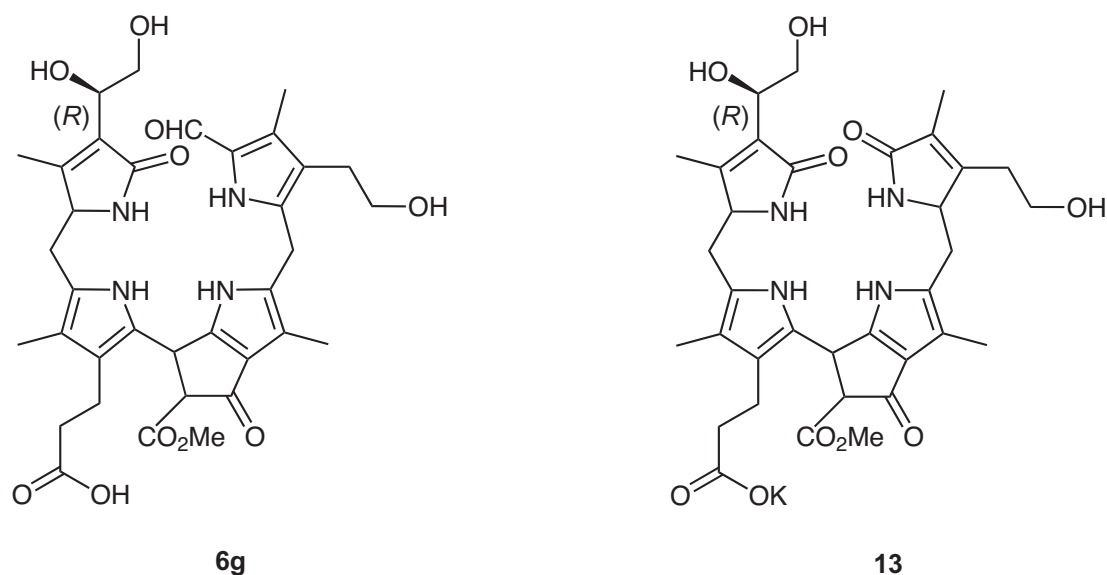


Figure 3. CD spectra of both synthesized maleimide (*R*)-**61** (in blue) and isolated one (*Hv*-**61**) (in red). UV/Vis spectrum of the synthesized compound is depicted by a dashed blue line.

The CD spectra demonstrate unequivocally that *Hv*-**61** has the same absolute (*R*) configuration as the synthesized maleimide (*R*)-**61**. Both Cotton effects at 293 nm have the same direction. However, their amplitudes are slightly different. This fluctuation can be reasonably ascribed to handling errors in the preparation of the solutions. Because **61** is a viscous oil at room temperature and its availability in very small amounts, the quantitative transfer with high accuracy was difficult. In order to minimize both random and systematic errors, the CD spectrum of (*R*)-**61** was measured several times and its average spectrum was calculated from these data as well as the standard deviation. This standard deviation was then used for estimating the amplitude of the error for CD spectra of both *Hv*-**61** and (*R*)-**61**. As obvious from figure 3 the fluctuations observed in CD spectra are only due to handling problems and not to enantiomeric mixtures.

Thus, the (*R*) configuration of *Hv*-**61** determined as aforementioned allows the assignment – by correlation – of the absolute configuration of barley catabolites dihydroxyethyl moiety. Both the C(3¹) center of **6g** and the C(19¹) of **13** have the same (*R*) absolute configuration. The updated chemical structures of these two *Hordeum vulgare* Chl catabolites are shown in scheme 64.



Scheme 64. Modified chemical structures of barley Chl catabolites (**6g**, **13**) with their newly determined chiral center.

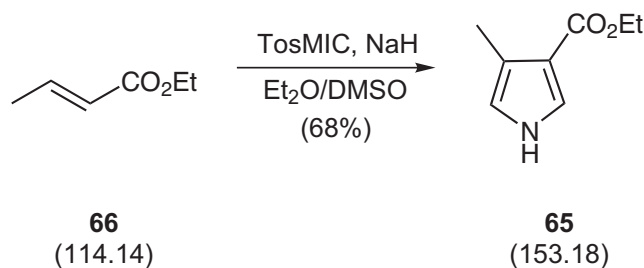
6.4. Perspectives

Determinations of absolute configurations are never a trivial task. The procedure we used in this study for the determination of the absolute configuration of the dihydroxyethyl groups of barley catabolites proved to be a versatile and reliable method, which presumably can be extended to other substrates such as the dihydroxyethyl moiety of *So*-NCC-2 (**6h**). Our work opens new perspectives for investigations, which up to now were beyond reach. The now known absolute configuration of the dihydroxyethyl moiety in **6g** and **13** can be useful for a future X-ray analysis of these catabolites allowing a determination of the absolute configurations of the other chiral centers by diastereomeric relationships. Furthermore, the dihydroxylation mechanism of the vinyl group during senescence might be studied in more details with the aid of isotope labelling experiments, notably for establishing whether the enzyme involved is a mono- or a dioxygenase.

EXPERIMENTAL PART

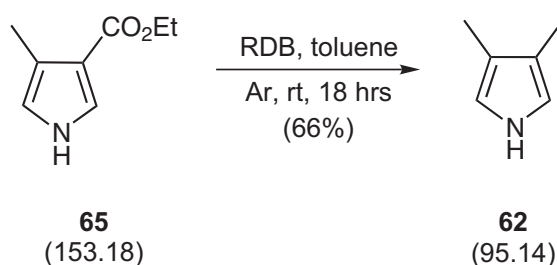
7. GENERAL REMARKS

All chemicals were reagent grade. – Solvents were generally dried and distilled prior to use. – Reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F254 (0.2 mm) precoated aluminium foil ; revelations were done according to known methods ; spottings with TMB were done by placing the plates in a saturated atmosphere of chlorine vapours (formed by mixing a solution of 5 M aq. hydrochloric acid with 1% aq. potassium permanganate) for 1 min, then spraying them with a solution of TMB (750 mg) in 50% aq. ethanol (200 ml) and acetic acid (50 ml) – Column chromatography : Merck silica gel 60 (0.040-0.063 mm, 230-400 mesh) or Fluka silica gel 60 (0.040-0.063 mm, 230-400 mesh). – UV/Vis spectra were recorded on a Perkin-Elmer Lambda 40 spectrometer ; λ_{\max} (log ϵ) in nm. – Circular dichroism (CD) spectra were obtained with a Jasco J-715 spectropolarimeter; λ_{\max} ($\Delta\epsilon$) in nm. – NMR : Bruker Avance DPX 360 (^1H : 360.13 MHz, ^{13}C : 90.55 MHz), Bruker Avance DRX 500 (^1H : 500.13 MHz, ^{13}C : 125.75 MHz) or Varian Gemini 200 (^1H : 200 MHz, ^{13}C : 50.3 MHz); chemical shifts (δ) are given in ppm relative to the TMS signal or to the solvent used, coupling constants J in Hz. – Mass spectra (MS) and high-resolution mass spectra (HR-MS) were measured on a Vacuum Generators Micromass VG 7070 spectrometer or on a FT/ICR mass spectrometer Bruker 4.7T BioApex II by chemical ionization (CI), electronic ionization (EI), fast atomic bombardment (FAB), all in positive mode, or by electrospray ionization in positive (ESI) or in negative (*neg*ESI) mode.

3-Carboethoxy-4-methyl-1H-pyrrole (65)

A solution of ethyl crotonate (**66**, 2.92 g, 25 mmol) and TosMIC (5.00 g, 26 mmol) in ether : DMSO (2 : 1) (120 ml) was added dropwise in a nitrogen atmosphere to a stirred suspension of 55-65% sodium hydride (2.2 g) in ether. After completion of the addition the reaction mixture was stirred 15 minutes then diluted with water (200 ml) and extracted with ether. The combined ether extracts were passed through a short column of alumina (eluting with dichloromethane then ethyl acetate). Evaporation of the solvents gave an oil which solidified on standing. This solid was washed with *n*-hexane and vacuum dried affording yellow crystals of **65** (2.61 g, 68%).

TLC : R_f=0.65 (alumina, dichloromethane, KMnO₄). **¹H NMR** (200 MHz, CDCl₃) : δ 1.34 (t, 3H, CH₂-CH₃), 2.21 (s, 3H, CH₃), 4.27 (q, 2H, CH₂-CH₃), 6.53 (m, 1H, CH), 7.37 (m, 1H, CH), 8.40 (br. s., 1H, NH).

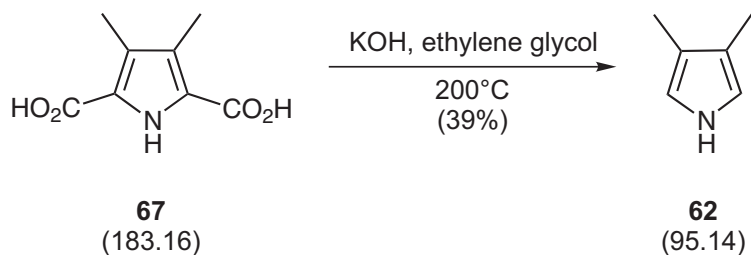
3,4-Dimethyl-1H-pyrrole (62)

A solution of **65** (2.00 g, 13 mmol) in toluene (50 ml) was added dropwise to a solution of 70% RDB in toluene (15.00 g, 52 mmol) at 25°C under an atmosphere of argon. After the reaction mixture had stirred for 18 hours, water (50 ml) was added. The toluene layer was separated, washed with water and dried over sodium sulfate.

The solvent was removed at reduced pressure to give 3,4-dimethyl-1*H*-pyrrole (**62**, 821 mg, 66%).

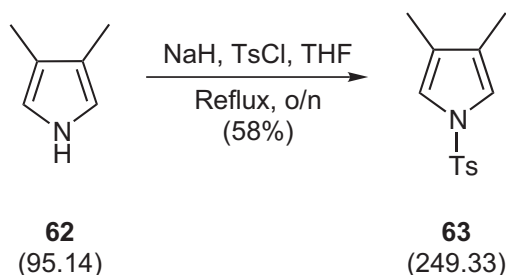
For spectroscopical and physical data, see above.

3,4-Dimethyl-1*H*-pyrrole (**62**)



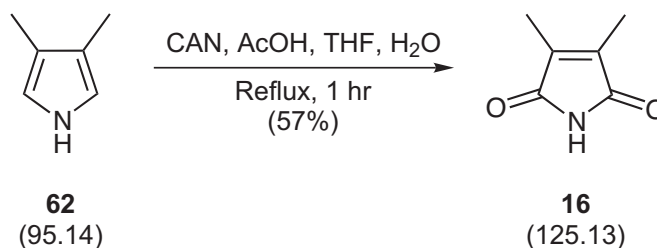
A mixture of 3,4-dimethyl-1*H*-pyrrole-2,5-dicarboxylic acid (**67**, 10 g, 55 mmol) and potassium hydroxide (20 g, 356 mmol) in ethylene glycol (100 ml) was slowly heated to 200°C, while the distillate was collected. The mixture was then cooled, water (100 ml) was added, and heating to 200°C was resumed while the distillate was collected. The pooled distillates were diluted with water (50 ml), and the aqueous mixture was extracted with dichloromethane (3x70 ml). The pooled extracts were dried over sodium sulfate and evaporated at reduced pressure. The residue was distilled *in vacuo* (bp 67-70°C(25 mmHg)) to give 3,4-dimethyl-1*H*-pyrrole (**62**, 2.05 g, 39%).

For spectroscopical and physical data, see above.

3,4-Dimethyl-1-[(4-methylphenyl)sulfonyl]-1H-pyrrole (63)

At 0°C, a solution of 3,4-dimethyl-1H-pyrrole (**62**, 1 g, 11 mmol) in dry THF (7 ml) was added dropwise to a stirred suspension of sodium hydride 55-65% (900 mg) in dry THF (50 ml). The mixture was stirred at room temperature for 1 hr and then *p*-toluenesulfonyl chloride (2.38 g, 12 mmol) in dry THF (10 ml) was added dropwise. The solution was heated at reflux overnight, quenched with methanol and water and extracted with ether. The extracts were dried over sodium sulfate and evaporated at reduced pressure. Column chromatography (silica gel, dichloromethane) furnished 3,4-dimethyl-1-[(4-methylphenyl)sulfonyl]-1H-pyrrole (**63**, 1.44 g, 58%).

¹H NMR (200 MHz, CDCl₃): δ 1.91 (s, 6H, CH₃), 2.39 (s, 3H, PhCH₃), 6.84 (s, 2H, CH), 7.24-7.28 (m, 2H, Ph), 7.68-7.72 (m, 2H, Ph). **MS-EI**: *m/z* 250 ([M+H]⁺, 32%), 249 ([M]⁺, 77%), 185 (38%), 184 (60%), 155 (61%), 139 (24%), 97 (26%), 95 (27%), 94 (60%), 91 (100%), 67 (20%), 65 (52%).

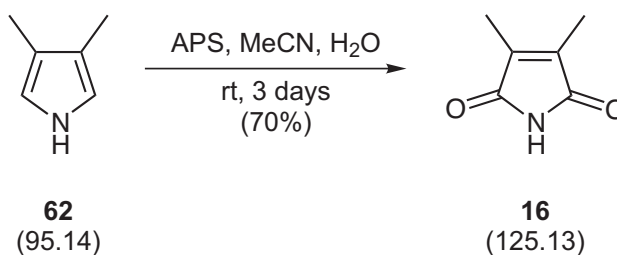
3,4-Dimethylmaleimide (16)

3,4-Dimethyl-1H-pyrrole (**62**, 130 mg, 1.4 mmol) was dissolved, at room temperature, in a solvents mixture of THF (13 ml), acetic acid (15 ml) and water (13 ml). CAN (3.45 g, 6.3 mmol) was added in one portion, then the mixture was heated at reflux for 1 hr.

CH₃), 3.80 (s, 2H, CH₂), 6.91 (br. s., 1H, NH). **MS-EI** : *m/z* 111 ([M]⁺, 100%), 96 ([M-CH₃]⁺, 43%), 82 (22%), 68 (39%), 67 (23%).

8.2. Peroxydisulfate Oxidations of Pyrroles to Maleimides

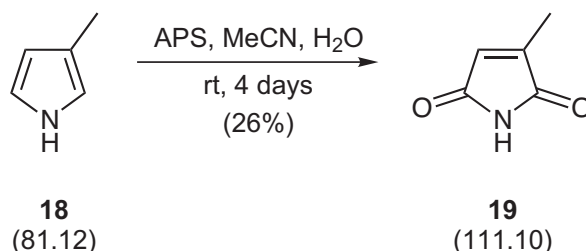
3,4-Dimethylmaleimide (16)



To a solution of APS (2.05 g, 9 mmol) in water (10 ml) was added dropwise a solution of 3,4-dimethyl-1*H*-pyrrole (**62**, 100 mg, 1.1 mmol) in acetonitrile (10 ml). The reaction mixture was stirred at room temperature for 3 days, then extracted with dichloromethane (3x10 ml). The extracts were dried over sodium sulfate and evaporated at reduced pressure. Column chromatography (silica gel, *n*-hexane : acetone (3 : 1)) furnished 3,4-dimethylmaleimide (**16**, 96 mg, 70%).

For spectroscopical and physical data, see section 8.1..

3-Methylmaleimide (19)



To a solution of APS (1.98 g, 8.7 mmol) in water (10 ml) was added dropwise a solution of 3-methyl-1*H*-pyrrole (**18**, 100 mg, 1.2 mmol) in acetonitrile (10 ml). The reaction mixture was stirred at room temperature for 4 days, then extracted with dichloromethane (3x10 ml). The extracts were dried over sodium sulfate and

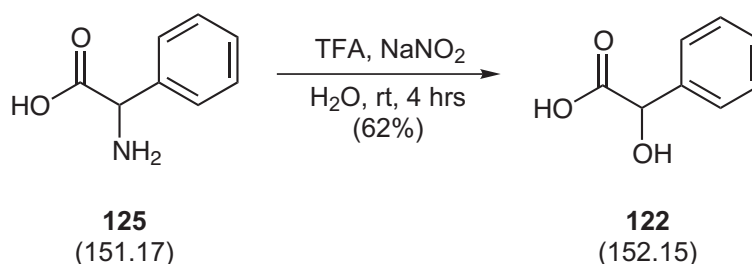
evaporated at reduced pressure. Column chromatography (silica gel, *n*-hexane : acetone (2 : 1)) furnished 3-methylmaleimide (**19**, 34 mg, 26%).

TLC : $R_f=0.31$ (silica gel, *n*-hexane : acetone (2 : 1), chlorine/TMB). **$^1\text{H NMR}$** (360.13 MHz, CDCl_3) : δ 2.08 (s, 3H, CH_3), 6.33 (m, 2H, CH_2).

9. REACTIVE 2-OXO-3H-IMIDAZO[1,2- α]PYRIDINIUM COMPOUNDS AS KEY INTERMEDIATES IN A GENERAL WAY TO MALEIMIDES

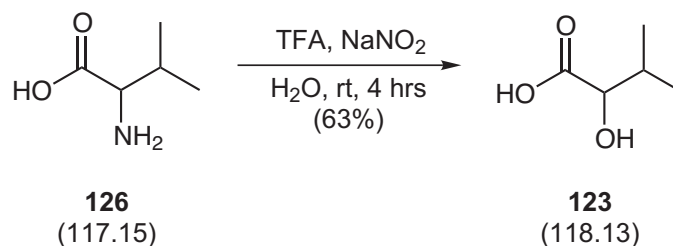
9.1. Preparation of 2-Hydroxy-*N*-pyridin-2-ylamides

Mandelic Acid (**122**)



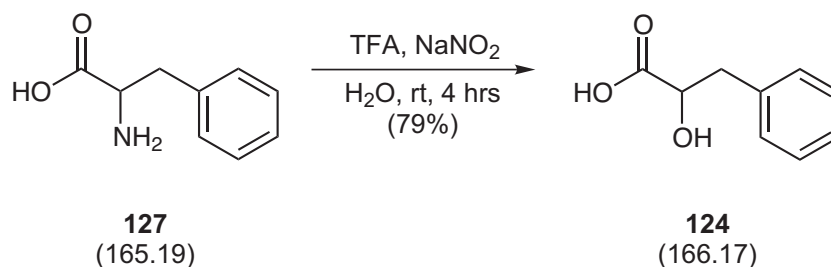
rac-Phegly (**125**, 1.51 g, 10 mmol) and TFA (1.48 g, 13 mmol) were dissolved in water (38 ml). Sodium nitrite (1.03 g, 14.9 mmol) in water (10 ml) was added to the reaction mixture over 3 hrs. Stirring was then continued for another 1 hr and the solution was extracted with ether (5x30 ml). The extracts were washed with a saturated aq. sodium chloride solution (2x60 ml) and dried over sodium sulfate. Evaporation at reduced pressure of the solvent gave a white solid **122** (942 mg, 62%).

Mp : 130-132°C. **$^1\text{H NMR}$** (360.13 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) : δ 5.15 (s, 1H, $\underline{\text{CH}}$ -Ph), 7.29-7.38 (m, 3H, Ph), 7.45-7.47 (m, 2H, Ph). **$^{13}\text{C NMR}$** (90.55 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) : δ 72.71 ($\underline{\text{CH}}$ -Ph), 126.60 (2xPh), 128.25 (Ph), 128.44 (2xPh), 138.71 (C_{quat}), 175.11 ($\text{C}=\text{O}$). **MS-EI** : m/z 152 ($[\text{M}]^+$, 28%), 107 (100%), 105 (26%), 79 (90%), 77 (67%).

2-Hydroxy-3-methylbutanoic acid (123)

rac-Val (**126**, 1.17 g, 10 mmol) and TFA (1.48 g, 13 mmol) were dissolved in water (38 ml). Sodium nitrite (1.03 g, 14.9 mmol) in water (10 ml) was added to the reaction mixture over 3 hrs. Stirring was then continued for another 1 hr and the solution was extracted with ether (5x30 ml). The extracts were washed with a saturated aq. sodium chloride solution (2x60 ml) and dried over sodium sulfate. Evaporation at reduced pressure of the solvent gave the desired product **123** (741 mg, 63%).

Mp : 83°C. ¹H NMR (360.13 MHz, CDCl₃) : δ 0.92-0.94 (d, ³J(H,H)=6.8, 3H, CH₃), 1.06-1.08 (d, ³J(H,H)=7.3, 3H, CH₃), 2.10-2.23 (m, 1H, CH(CH₃)₂), 4.16-4.17 (d, ³J(H,H)=3.6, CH-OH), 6.74 (br. s., 2H, OH and CO₂H). ¹³C NMR (90.55 MHz, CDCl₃) : δ 15.98 (CH₃), 18.90 (CH₃), 32.13 (CH(CH₃)₂), 74.95 (CH-OH), 179.54 (C=O). **MS-EI** : *m/z* 119 ([M+H]⁺, 18%), 91 (17%), 76 ([M-CH(CH₃)₂]⁺, 100%), 73 (90%).

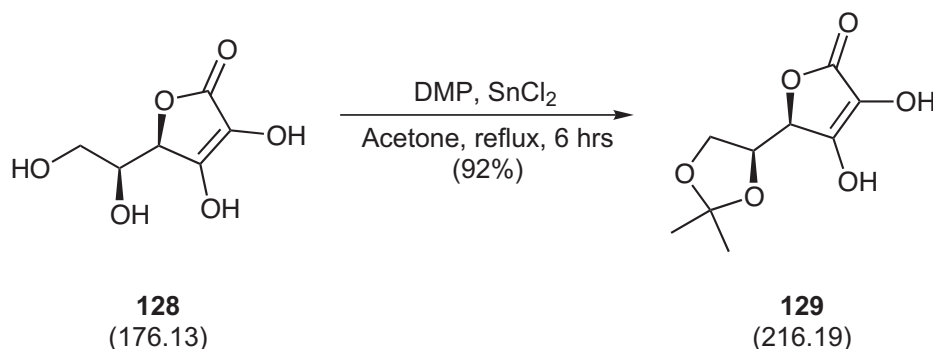
2-Hydroxy-3-phenylpropanoic acid (124)

rac-Phe (**127**, 10 g, 60.5 mmol) and TFA (8.97 g, 78.7 mmol) were dissolved in water (230 ml). Sodium nitrite (6.22 g, 90.2 mmol) in water (60 ml) was added to the reaction mixture over 3 hrs. Stirring was then continued for another 1 hr and the

solution was extracted with ether (5x180 ml). The extracts were washed with a saturated aq. sodium chloride solution (2x360 ml) and dried over sodium sulfate. Evaporation at reduced pressure of the solvent gave a white solid **124** (7.89 g, 79%).

Mp : 98°C. **¹H NMR** (360.13 MHz, CDCl₃/CD₃OD) : δ 2.91-2.97 (dd, $^2J(\text{H,H})=14.1$, $^3J(\text{H,H})=3.8$, 1H, CH-CH₂-Ph), 3.13-3.18 (dd, $^2J(\text{H,H})=14.1$, $^3J(\text{H,H})=4.1$, 1H, CH-CH₂-Ph), 4.38-4.41 (2d, $^3J(\text{H,H})=4.1$, $^3J(\text{H,H})=3.8$, 1H, CH-CH₂-Ph), 7.21-7.32 (m, 5H, CH-CH₂-Ph). **¹³C NMR** (90.55 MHz, CDCl₃/CD₃OD) : δ 40.30 (CH-CH₂-Ph), 71.09 (CH-CH₂-Ph), 126.55 (2xPh), 128.19 (Ph), 129.39 (Ph), 136.95 (C_{quat}), 175.94 (C=O). **MS-EI** : *m/z* 166 ([M]⁺, 8%), 148 (65%), 91 (100%).

(5*R*)-5-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3,4-dihydroxyfuran-2(5*H*)-one (129)

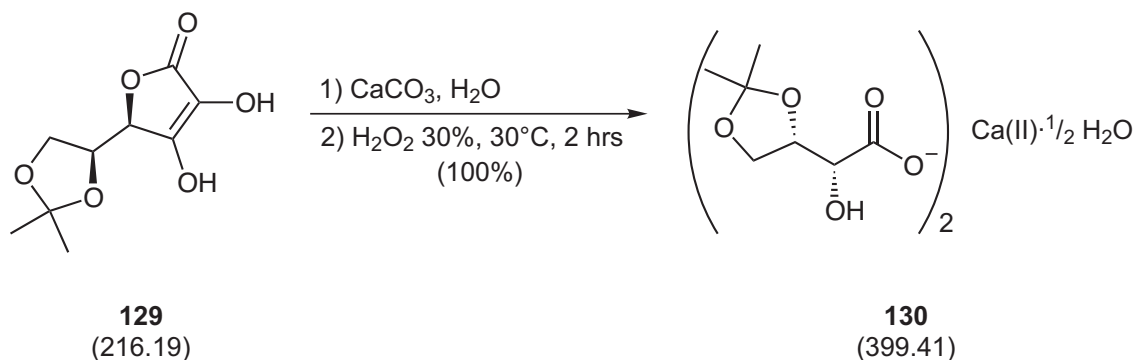


A mixture of ascorbic acid (**128**, 25 g, 142 mmol), DMP (25.13 g, 241 mmol) and tin(II) chloride (1.35 g, 7 mmol) in acetone (125 ml) was heated at reflux for 6 hrs. The product precipitated. It was filtered and washed with cold acetone. The filtrate was concentrated at reduced pressure and the precipitate was filtered and washed with cold acetone. The solids were collected to give (5*R*)-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3,4-dihydroxyfuran-2(5*H*)-one (**129**, 28.26 g, 92%).

Mp : 218-219°C. **TLC** : $R_f=0.36$ (silica gel, dichloromethane : ethyl acetate : ethanol : acetic acid (100 : 20 : 10 : 1), KMnO₄). **¹H NMR** (500.13 MHz, D₂O) : δ 1.38-1.39 (2s, 6H, 2xCH₃), 4.17-4.20 (dd, $^2J(\text{H,H})=9.1$, $^3J(\text{H,H})=5.0$, 1H, CH-CH(O)-CH₂(O)), 4.31-4.34 (dd, $^2J(\text{H,H})=9.1$, $^3J(\text{H,H})=7.2$, 1H, CH-CH(O)-CH₂(O)), 4.59-4.62 (ddd, $^3J(\text{H,H})=7.2$, $^3J(\text{H,H})=5.0$, $^3J(\text{H,H})=2.3$, 1H, CH-CH(O)-CH₂(O)), 4.93-4.94 (d,

$^3J(\text{H,H})=2.3$, 1H, $\underline{\text{CH}}\text{-CH}(\text{O})\text{-CH}_2(\text{O})$). $^{13}\text{C NMR}$ (125.75 MHz, D_2O): δ 24.60 (CH_3), 25.43 (CH_3), 65.71 ($\text{CH-CH}(\text{O})\text{-CH}_2(\text{O})$), 73.56 and 76.48 ($\underline{\text{CH}}\text{-CH}(\text{O})\text{-CH}_2(\text{O})$), 111.44 ($\text{C}(\text{OH})$), 118.55 ($\text{C}(\text{OH})$), 156.09 (C_{quat}), 174.06 ($\text{C}=\text{O}$). **MS-EI**: m/z 216 ($[\text{M}]^+$, 17%), 201 ($[\text{M-CH}_3]^+$, 82%), 141 (50%), 101 (100%).

Calcium di{(2R)-2-[(4S)-Dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethanoate} (130)

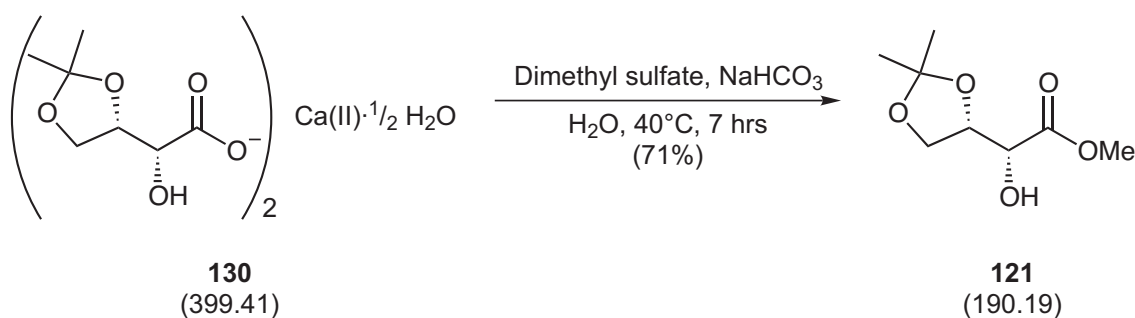


A suspension of (5R)-5-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-3,4-dihydrofuran-2(5H)-one (**129**, 40 g, 185 mmol) in water (460 ml) was treated with calcium carbonate (37.04 g, 370 mmol). The resulting mixture was cooled in an ice bath, and 30% aq. hydrogen peroxide (76 ml, 740 mmol) was added dropwise. After the addition, the mixture was allowed to slowly warm to about 20°C (*Caution!*). When the reaction has subsided, the mixture was heated at 35°C for 2 hrs. To the reaction was added 10% Pd/C (230 mg). It was heated on the oil bath for 30 min. The suspended material was removed by filtration and the filtrate was concentrated at reduced pressure. Crystallization of the residue from water/acetone afforded the title compound **130** as a white solid (36.90 g, 100%).

Mp: >250°C. $^1\text{H NMR}$ (500.13 MHz, D_2O): δ 1.39 (m, 3H, CH_3), 1.46 (m, 3H, CH_3), 3.96-3.98 (dd, $^2J(\text{H,H})=8.6$, $^3J(\text{H,H})=6.8$, 1H, $\text{CH}(\text{OH})\text{-CH}(\text{O})\text{-CH}_2(\text{O})$), 4.00-4.01 (d, $^3J(\text{H,H})=4.5$, 1H, $\underline{\text{CH}}(\text{OH})\text{-CH}(\text{O})\text{-CH}_2(\text{O})$), 4.15-4.19 (dd, $^2J(\text{H,H})=8.6$, $^3J(\text{H,H})=6.8$, 1H, $\text{CH}(\text{OH})\text{-CH}(\text{O})\text{-CH}_2(\text{O})$), 4.43-4.47 (ddd, $^3J(\text{H,H})=6.8$, $^3J(\text{H,H})=6.8$, $^3J(\text{H,H})=4.5$, 1H, $\text{CH}(\text{OH})\text{-CH}(\text{O})\text{-CH}_2(\text{O})$). $^{13}\text{C NMR}$ (125.75 MHz, D_2O): δ 24.53 (CH_3), 25.61 (CH_3), 65.92 ($\text{CH}(\text{OH})\text{-CH}(\text{O})\text{-CH}_2(\text{O})$), 72.57 ($\underline{\text{CH}}(\text{OH})\text{-CH}(\text{O})\text{-CH}_2(\text{O})$), 77.46

(CH(OH)-CH(O)-CH₂(O)), 110.26 (C_{quat}), 178.09 (C=O). **MS-negESI** (H₂O/MeCN) : *m/z* 175.06125 ([C₇H₁₁O₅]⁻). *Calcd mass for* [C₇H₁₁O₅]⁻ : 175.06065.

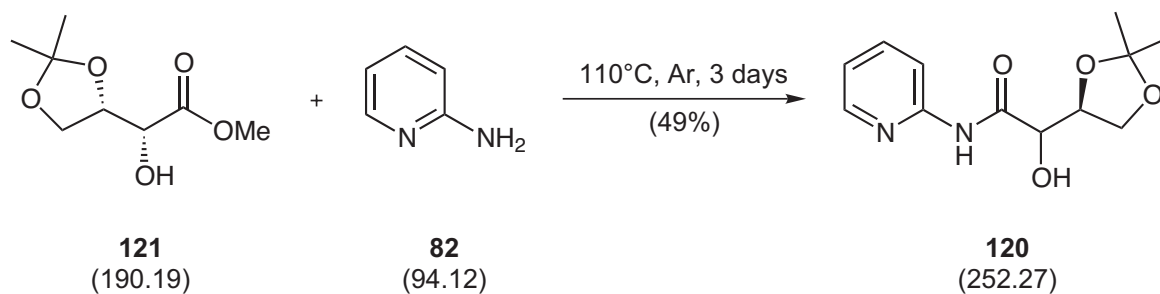
Methyl (2*R*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethanoate (121)



To a suspension of calcium di{(2*R*)-2-[(4*S*)-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethanoate} (**130**, 10 g, 25 mmol) in water (125 ml) was added slowly sodium bicarbonate (18.76 g, 223 mmol) followed by dimethyl sulfate (28.13 g, 223 mmol) (*Caution ! Very toxic !*). The mixture was heated at 40°C for 7 hrs. After the reaction mixture was filtered, the filtrate was extracted with dichloromethane (5x150 ml). The combined extracts were dried over sodium sulfate and the solvent was evaporated at reduced pressure to give methyl (2*R*)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethanoate (**121**, 6.71 g, 71%).

TLC : R_f=0.40 (silica gel, *n*-hexane : acetone (2 : 1), KMnO₄). **¹H NMR** (500.13 MHz, CDCl₃) : δ 1.36 (m, 3H, CH₃), 1.43 (m, 3H, CH₃), 2.92-2.94 (d, ³*J*(H,H)=8.2, 1H, CH(OH)-CH(O)-CH₂(O)), 3.83 (s, 3H, CO₂CH₃), 4.01-4.04 (dd, ²*J*(H,H)=8.3, ³*J*(H,H)=6.8, 1H, CH(OH)-CH(O)-CH₂(O)), 4.08-4.11 (dd, ²*J*(H,H)=8.3, ³*J*(H,H)=6.8, 1H, CH(OH)-CH(O)-CH₂(O)), 4.12-4.14 (dd, ³*J*(H,H)=8.2, ³*J*(H,H)=2.8, 1H, CH(OH)-CH(O)-CH₂(O)), 4.38-4.41 (ddd, ³*J*(H,H)=6.8, ³*J*(H,H)=6.8, ³*J*(H,H)=2.8, 1H, CH(OH)-CH(O)-CH₂(O)). **¹³C NMR** (125.75 MHz, CDCl₃) : δ 25.43 (CH₃), 26.21 (CH₃), 52.90 (CO₂CH₃), 65.73 (CH(OH)-CH(O)-CH₂(O)), 70.46 (CH(OH)-CH(O)-CH₂(O)), 76.40 (CH(OH)-CH(O)-CH₂(O)), 110.16 (C_{quat}), 172.66 (C=O). **MS-EI** : *m/z* 175 ([M-CH₃]⁺, 100%), 133 (82%), 115 (35%), 101 (52%). **MS-ESI** (MeOH) : *m/z* 213.08 ([M+Na]⁺).

(2*R*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-hydroxy-*N*-pyridin-2-ylethanamide
(120)

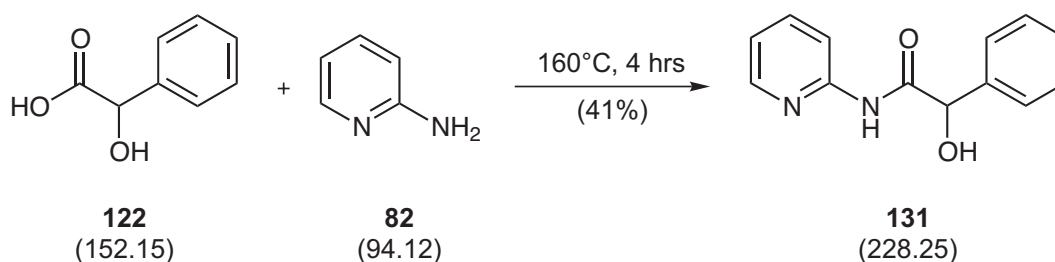


Methyl (2*R*)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethanoate (**121**, 1 g, 5.26 mmol) and 2-aminopyridine (**82**, 1.73 g, 18.4 mmol) were heated at 110°C under argon for 3 days. Column chromatography (silica gel, ethyl acetate) followed by recrystallization from dichloromethane/*n*-hexane furnished the title compound **120** as a white solid (650 mg, 49%).

Mp : 102-103°C. **¹H NMR** (500.13 MHz, CDCl₃, two sets of signals for both C(2)-diastereoisomers) : δ 1.37 (m, 3H, CH₃), 1.39 (s, 0.56H, CH₃), 1.45 (s, 0.56H, CH₃), 1.48 (s, 3H, CH₃), 4.01-4.04 (dd, ²*J*(H,H)=8.3, ³*J*(H,H)=6.5, 0.18H, CH(OH)-CH(O)-CH₂(O)), 4.05-4.08 (dd, ²*J*(H,H)=8.3, ³*J*(H,H)=6.5, 0.18H, CH(OH)-CH(O)-CH₂(O)), 4.11-4.14 (dd, ²*J*(H,H)=8.8, ³*J*(H,H)=6.3, 1H, CH(OH)-CH(O)-CH₂(O)), 4.19-4.22 (dd, ²*J*(H,H)=8.8, ³*J*(H,H)=6.3, 1H, CH(OH)-CH(O)-CH₂(O)), 4.25-4.26 (d, ³*J*(H,H)=6.3, 1H, CH(OH)-CH(O)-CH₂(O)), 4.42-4.46 (ddd, ³*J*(H,H)=6.3, ³*J*(H,H)=6.3, ³*J*(H,H)=6.3, 1H, CH(OH)-CH(O)-CH₂(O)), 4.49-4.50 (d, ³*J*(H,H)=4.9, 0.18H, CH(OH)-CH(O)-CH₂(O)), 4.53-4.57 (ddd, ³*J*(H,H)=6.5, ³*J*(H,H)=6.5, ³*J*(H,H)=4.9, 0.18H, CH(OH)-CH(O)-CH₂(O)), 5.75 (br. s., 1.18H, CH(OH)-CH(O)-CH₂(O)), 7.05-7.08 (m, 2.36H, Py), 7.71-7.74 (m, 1.18H, Py), 8.22-8.29 (s, 0.18H, NH), 9.61 (s, 0.18H, NH), 9.68 (s, 1H, NH). **¹³C NMR** (125.75 MHz, CDCl₃, two sets of signals for both C(2)-diastereoisomers) : δ 25.25 (CH₃), 26.56 (CH₃), 26.71 (CH₃), 64.97 (CH(OH)-CH(O)-CH₂(O)), 66.68 (CH(OH)-CH(O)-CH₂(O)), 71.02 (CH(OH)-CH(O)-CH₂(O)), 73.17 (CH(OH)-CH(O)-CH₂(O)), 76.49 (CH(OH)-CH(O)-CH₂(O)), 76.61 (CH(OH)-CH(O)-CH₂(O)), 109.72 (C_{quat}), 110.04 (C_{quat}), 114.38 (Py), 120.20 (Py), 120.25 (Py), 138.97 (Py), 139.05 (Py), 147.46 (Py), 147.66 (Py), 150.81 (C_{quat}), 169.91 (C=O). **MS-EI** :

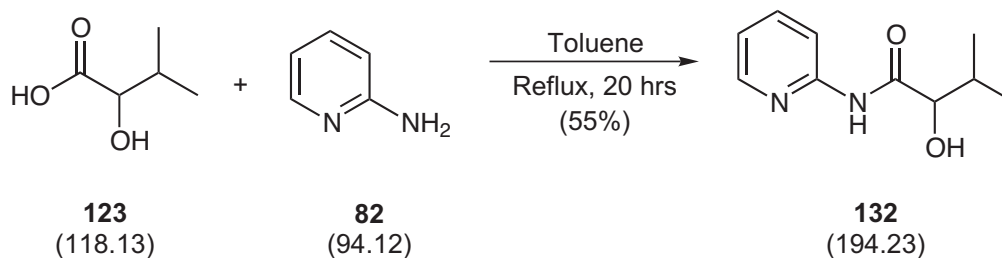
m/z 253 ($[M+H]^+$, 73%), 237 ($[M-CH_3]^+$, 35%), 195 (42%), 177 (27%), 152 (100%), 151 (27%), 121 (40%), 101 (28%), 95 (36%), 78 (21%).

2-Hydroxy-2-phenyl-*N*-pyridin-2-ylacetamide (**131**)



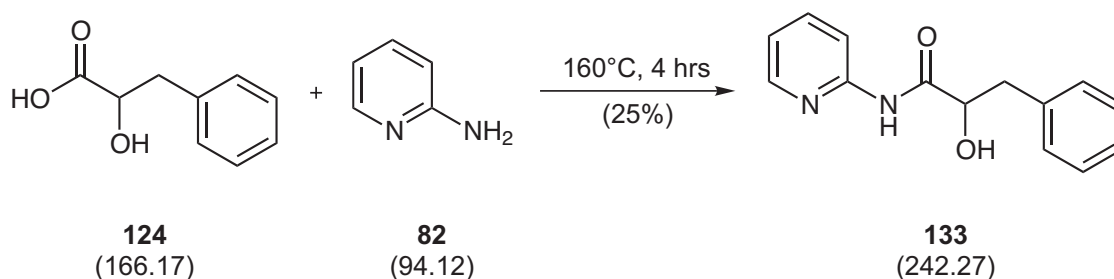
rac-mandelic acid (**122**, 761 mg, 5 mmol) and 2-aminopyridine (**82**, 471 mg, 5 mmol) were heated in a sealed Schlenk tube under argon at 160°C for 4 hrs. Column chromatography (silica gel, *n*-hexane : ethyl acetate (2 : 1)) gave the title compound **131** as a white solid (465 mg, 41%).

Mp : 115-117°C. **¹H NMR** (500.13 MHz, CDCl₃/CD₃OD) : δ 4.98 (s, 1H, CH(OH)-Ph), 6.61-6.62 (d, ³ J (H,H)=8.8, 1H, Py), 6.65-6.68 (m, 1H, Py), 7.24-7.27 (m, 1H, Ph), 7.31-7.34 (m, 2H, Ph), 7.48-7.50 (m, 2H, Ph), 7.60-7.64 (m, 1H, Py), 7.69-7.71 (m, 1H, Py). **¹³C NMR** (125.75 MHz, CDCl₃/CD₃OD) : δ 73.98 (CH(OH)-Ph), 112.19 (Py), 112.50 (Py), 126.62 (Ph), 127.32 (Ph), 128.12 (Ph), 137.96 (Py), 141.56 (C_{quat}), 142.13 (Py), 155.98 (C_{quat}), 179.32 (C=O). **MS-EI** : m/z 228 ($[M]^+$, 17%), 122 (41%), 121 (91), 107 (49%), 91 (100%), 78 (41%).

2-Hydroxy-3-methyl-*N*-pyridin-2-ylbutanamide (132)

In a flask fitted with a Dean-Stark apparatus and a moisture trap were placed 2-aminopyridine (**82**, 12.41 g, 132 mmol) and **123** (15.58 g, 132 mmol) in toluene (120 ml). The mixture was heated at reflux for 20 hrs during which time water was collected. A thick brown oil precipitated. The solvent was evaporated under reduced pressure. Trituration with *n*-hexane furnished slowly the title compound **132** as a brown solid (14.21 g, 55%).

Mp : 66-68°C. **¹H NMR** (360.13 MHz, CDCl₃) : δ 0.89-0.91 (d, ³*J*(H,H)=6.8, 3H, CH(CH₃)₂), 1.06-1.08 (d, ³*J*(H,H)=6.8, 3H, CH(CH₃)₂), 2.11-2.19 (m, 1H, CH(CH₃)₂), 3.96-3.97 (d, ³*J*(H,H)=3.1, 1H, CH(OH)), 6.62-6.70 (m, 2H, Py), 7.59-7.64 (m, 1H, Py), 7.77-7.79 (m, 1H, Py). **¹³C NMR** (90.55 MHz, CDCl₃) : δ 15.99 (CH(CH₃)₂), 16.03 (CH(CH₃)₂), 32.10 (CH(CH₃)₂), 76.02 (CH(OH)), 112.39 (Py), 139.04 (Py), 141.86 (Py), 156.56 (C_{quat}), 181.12 (C=O). **MS-FAB** (NOBA) : *m/z* 195 ([M+H]⁺), 189, 154, 136, 111, 95, 78, 67.

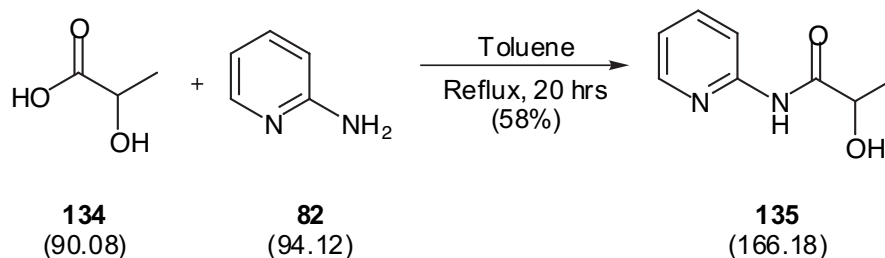
2-Hydroxy-3-phenyl-*N*-pyridin-2-ylpropanamide (133)

2-Hydroxy-3-phenylpropanoic acid (**124**, 831 mg, 5 mmol) and 2-aminopyridine (**82**, 471 mg, 5 mmol) were heated in a sealed Schlenk tube under argon at 160°C for 4

hrs. Column chromatography (silica gel, *n*-hexane : ethyl acetate (3 : 2) followed by recrystallization from THF/*n*-hexane gave the title compound **133** as a white solid (302 mg, 25%).

Mp : 173-174°C. **¹H NMR** (360.13 MHz, CDCl₃) : δ 2.83-2.90 (dd, ³*J*(H,H)=14, ³*J*(H,H)=10, 1H, CH(OH)-CH₂-Ph), 3.47-3.51 (dd, ³*J*(H,H)=14, ³*J*(H,H)=2.6, 1H, CH(OH)-CH₂-Ph), 4.47-4.51 (dd, ³*J*(H,H)=10, ³*J*(H,H)=2.6, 1H, CH(OH)-CH₂-Ph), 6.17 (s, 1H, OH), 6.88-6.91 (m, 1H, Py), 7.26-7.27 (m, 1H, Py), 7.28-7.37 (m, 5H, Ph), 7.66-7.71 (m, 1H, Py), 8.27-8.30 (d, ³*J*(H,H)=8.6, 1H, Py), 9.71 (s, 1H, NH). **¹³C NMR** (90.55 MHz, CDCl₃) : δ 41.24 (CH(OH)-CH₂-Ph), 73.40 (CH(OH)-CH₂-Ph), 114.26 (Ar), 119.81 (Ar), 126.95 (Ar), 128.91 (Ar), 129.84 (Ar), 138.03 (C_{quat}), 139.05 (Ar), 147.20 (Ar), 150.87 (C_{quat}), 171.83 (C=O). **MS-EI** : *m/z* 243 ([M+H]⁺, 25%), 151 (100%).

2-Hydroxy-*N*-pyridin-2-ylpropanamide (**135**)

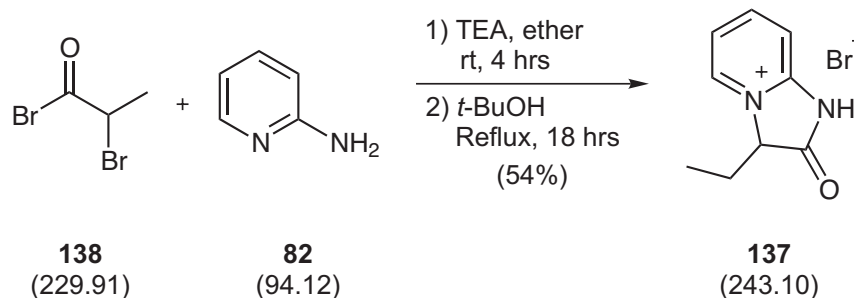


In a flask fitted with a Dean-Stark apparatus and a moisture trap were placed 2-aminopyridine (**82**, 18.82 g, 200 mmol) and *rac*-lactic acid (**134**, 18.02 g, 200 mmol) in toluene (120 ml). The mixture was heated at reflux for 20 hrs during which time water was collected. A thick orange oil precipitated. The solvent was evaporated under reduced pressure. Column chromatography (silica gel, dichloromethane : ethyl acetate : ethanol : acetic acid (100 : 20 : 10 : 1)) followed by recrystallization from *n*-hexane/dichloromethane furnished the title compound **135** as a white powder (19.3 g, 58%).

Mp : 86-87°C. **¹H NMR** (360.13 MHz, CDCl₃) : δ 1.56-1.58 (d, ³J(H,H)=6.8, 3H, CH(OH)-CH₃), 4.42-4.48 (q, ³J(H,H)=6.8, 1H, CH(OH)-CH₃), 6.02 (br. s., 1H, OH), 7.06-7.10 (m, 1H, Py), 7.73-7.77 (m, 1H, Py), 8.23-8.29 (m, 1H, Py), 8.29-8.32 (d, ³J(H,H)=8.2, 1H, Py), 9.61 (br. s., 1H, NH). **¹³C NMR** (90.55 MHz, CDCl₃) : δ 21.23 (CH(OH)CH₃), 68.62 (CH(OH)CH₃), 114.42 (Py), 120.14 (Py), 139.21 (Py), 147.18 (Py), 151.05 (C_{quat}), 173.77 (C=O). **MS-EI** : *m/z* 167 ([M+H]⁺, 30%), 166 ([M]⁺, 23%), 121 (21%), 95 (22%), 94 (100%), 78 (39%), 67 (56%).

9.2. Cyclization and Decarboxylation of Alkylated Reactive 2-Oxo-3H-imidazo[1,2- α]pyridinium Compounds

3-Ethyl-2-oxo-1H,2H,3H-imidazo[1,2- α]pyridin-4-ium bromide (**137**)

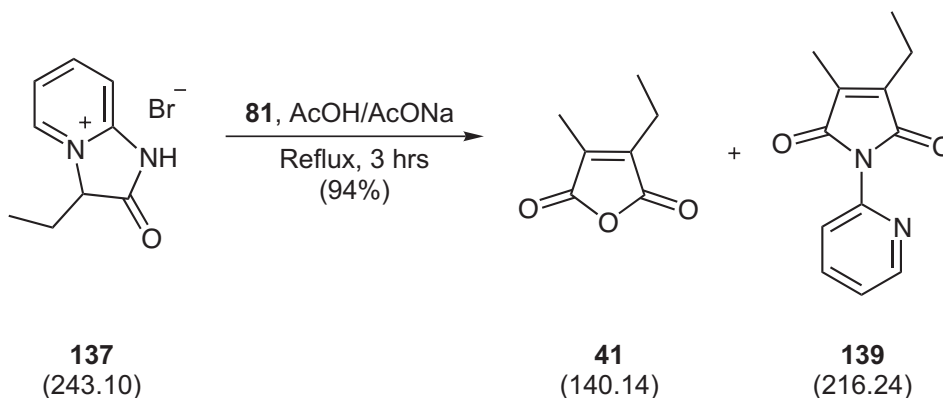


2-Bromobutyryl bromide (**138**, 24.43 g, 106 mmol) dissolved in dry ether (40 ml) was added dropwise under argon at 0°C to a stirred solution of TEA (10.75 g, 106 mmol) and 2-aminopyridine (**82**, 10 g, 106 mmol) in dry ether (50 ml). Then the mixture was stirred at room temperature for 4 hrs. The precipitate was filtered and washed with ether. The filtrate was evaporated at reduced pressure providing a yellow oil which was then heated at reflux in *t*-butanol (30 ml) for 18 hrs. The product precipitated. It was filtered and washed with ether to give a white solid **137** (13.9 g, 54%).

Mp : >200°C (decomp.) **¹H NMR** (500.13 MHz, DMSO-*d*⁶) : δ 0.81-0.84 (t, ³J(H,H)=7.5, 3H, CH-CH₂-CH₃), 2.19-2.33 (m, 2H, CH-CH₂-CH₃), 5.29-5.31 (m, 1H, CH-CH₂-CH₃), 7.54-7.56 (d, ³J(H,H)=8.6, 1H, Py), 7.60-7.63 (m, 1H, Py), 8.39-8.42 (m, 1H, Py), 8.82-8.83 (m, 1H, Py), 13.17 (br. s., 1H, NH). **¹³C NMR** (125.75 MHz, DMSO-*d*⁶) : δ 7.31 (CH-CH₂-CH₃), 23.62 (CH-CH₂-CH₃), 65.70 (CH-CH₂-CH₃),

111.06 (Py), 119.15 (Py), 138.17 (Py), 147.03 (Py), 152.80 (C_{quat}), 172.11 (C=O).
MS-ESI (H₂O/MeCN) : *m/z* 163.09 ([M-Br]⁺).

3-Ethyl-4-methylmaleic Anhydride (**41**) and 3-Ethyl-4-methyl-1-pyridin-2-ylmaleimide (**139**)



A mixture of 3-ethyl-2-oxo-1*H*,2*H*,3*H*-imidazo[1,2- α]pyridin-4-ium bromide (**137**, 5 g, 20.6 mmol), MA (**81**, 2.02 g, 20.6 mmol) and sodium acetate (1.69 g, 20.6 mmol) in acetic acid (40 ml) was refluxed for 3 hrs. Then, the solvent was evaporated at reduced pressure. Column chromatography (silica gel, *n*-hexane : ethyl acetate (2 : 1)) furnished 3-ethyl-4-methylmaleic anhydride (**41**, 660 mg, 23%) and 3-ethyl-4-methyl-1-pyridin-2-ylmaleimide (**139**, 3.16 g, 71%).

3-Ethyl-4-methylmaleic Anhydride (**41**) :

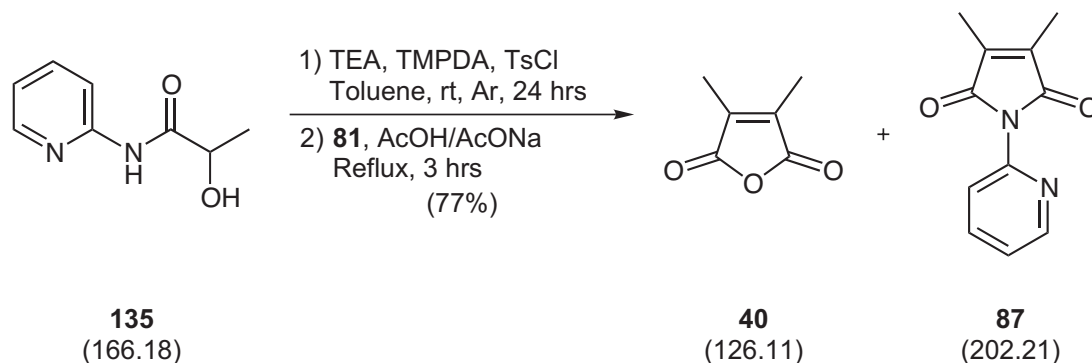
TLC : *R_f*=0.63 (silica gel, *n*-hexane : ethyl acetate (2 : 1), KMnO₄). **¹H NMR** (500.13 MHz, CDCl₃) : δ 1.19-1.22 (t, ³*J*(H,H)=7.6, 3H, CH₂-CH₃), 2.08 (t, ⁵*J*(H,H)=0.8, 3H, CH₃), 2.47-2.52 (qq, ³*J*(H,H)=7.6, ⁵*J*(H,H)=0.8, 2H, CH₂-CH₃). **¹³C NMR** (125.75 MHz, CDCl₃) : δ 9.49 (CH₃), 12.16 (CH₃), 18.03 (CH₂-CH₃), 140.23 (C_{quat}), 145.82 (C_{quat}), 165.86 (C=O), 166.43 (C=O). **MS-EI** : *m/z* 140 ([M]⁺, 13%), 112 (45%), 68 (58%), 67 (100%).

3-Ethyl-4-methyl-1-pyridin-2-ylmaleimide (**139**) :

TLC : *R_f*=0.28 (silica gel, *n*-hexane : ethyl acetate (2 : 1), UV_{254nm}). **¹H NMR** (500.13 MHz, CDCl₃) : δ 1.19-1.22 (t, ³*J*(H,H)=7.6, 3H, CH₂-CH₃), 2.07 (t, ⁵*J*(H,H)=0.8, 3H,

9.3. Generation of Reactive 2-Oxo-3*H*-imidazo[1,2- α]pyridinium Intermediates *via* a Tosylation Mediated Cyclization

3,4-Dimethylmaleic Anhydride (40) and 3,4-Dimethyl-1-pyridin-2-ylmaleimide (87)



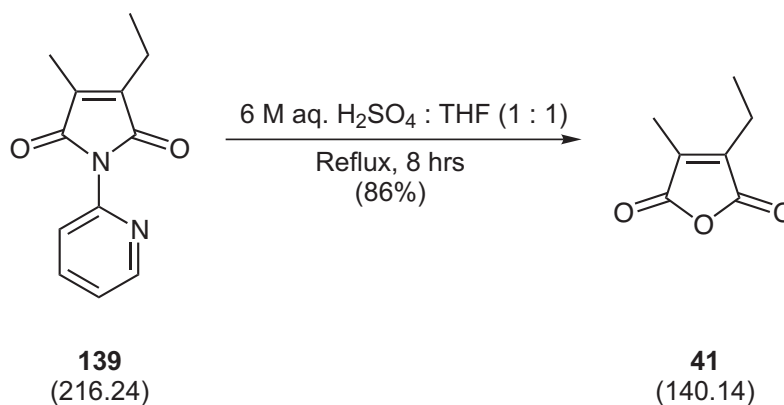
Under argon, TEA (670 mg, 6.62 mmol) in dry toluene (2 ml) and TMPDA (78 mg, 0.602 mmol) in dry toluene (1 ml) were added to a solution of 2-hydroxy-*N*-pyridin-2-ylpropanamide (**135**, 1 g, 6.02 mmol) in dry toluene (3 ml). The reaction was cooled at 0°C and then *p*-toluenesulfonyl chloride (1.26 g, 6.62 mmol) dissolved in dry toluene (6 ml) was added dropwise over 30 min. The solution became yellow. The reaction was stirred at room temperature for another 24 hrs. The precipitate was filtered and the solvent evaporated at reduced pressure to give a yellow oil which was dissolved in acetic acid (12 ml). Sodium acetate (494 mg, 6.02 mmol) and MA (**81**, 590 mg, 6.02 mmol) were added, then the reaction mixture was heated at reflux for 3 hrs. The solvent was evaporated at reduced pressure. Column chromatography (silica gel, *n*-hexane : ethyl acetate (2 : 1)) furnished 3,4-dimethylmaleic anhydride (**40**, 160 mg, 21%) and 3,4-dimethyl-1-pyridin-2-ylmaleimide (**87**, 680 mg, 56%).

3,4-Dimethylmaleic Anhydride (40) :

MP : 93-95°C. **TLC** : R_f =0.69 (silica gel, *n*-hexane : ethyl acetate (1 : 1), KMnO_4). **^1H NMR** (360.13 MHz, CDCl_3) : δ 2.08 (s, 6H, CH_3). **^{13}C NMR** (90.55 MHz, CDCl_3) : δ 9.64 (CH_3), 140.90 (C_{quat}), 166.26 ($\text{C}=\text{O}$). **MS-EI** : m/z 126 ($[\text{M}]^+$, 90%), 82 (100%).

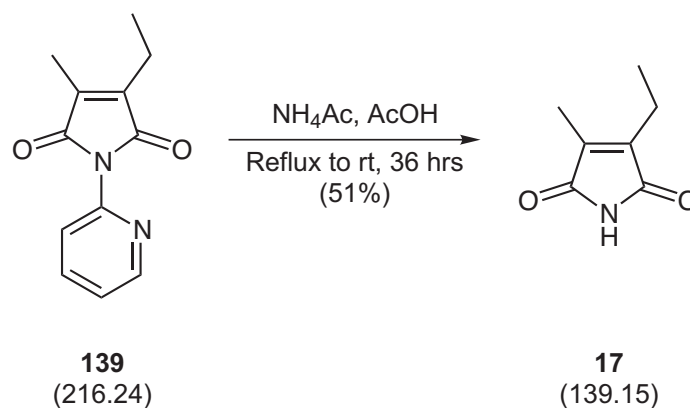
3,4-Dimethyl-1-pyridin-2-ylmaleimide (87) :

Mp : 119-123°C. **TLC** : $R_f=0.52$ (silica gel, *n*-hexane : ethyl acetate (1 : 1), UV_{254nm}). **1H NMR** (360.13 MHz, $CDCl_3$) : δ 2.06 (s, 6H, CH_3), 7.29-7.35 (m, 2H, Py), 7.80-7.85 (m, 1H, Py), 8.61-8.62 (m, 1H, Py). **^{13}C NMR** (90.55 MHz, $CDCl_3$) : δ 8.97 (CH_3), 121.21 (Py), 122.93 (Py), 137.94 (C_{quat}), 138.25 (Py), 146.33 (C_{quat}), 149.49 (Py), 170.30 (C=O). **MS-EI** : m/z 202 ($[M]^+$, 83%), 171 (66%), 159 (39%), 146 (37%), 145 (73%), 121 (32%), 120 (31%), 92 (30%), 78 (69%), 65 (22%), 51 (100%).

9.4. Chemical Transformations of Maleimides Precursors**3-Ethyl-4-methylmaleic Anhydride (41)**

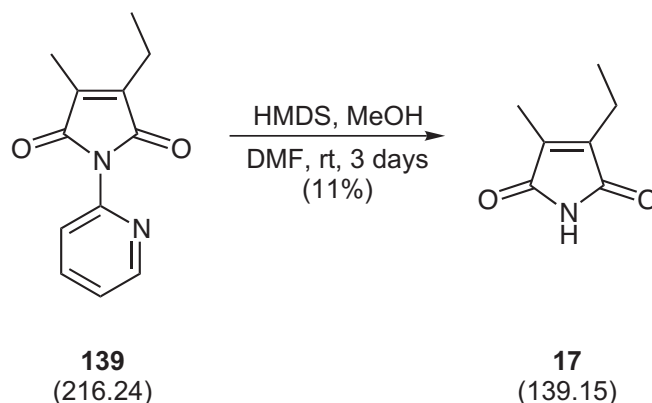
3-Ethyl-4-methyl-1-pyridin-2-ylmaleimide (**87**, 202 mg, 0.93 mmol) was dissolved in 6 M aq. sulfuric acid : THF (1 : 1) (1 ml) and heated at reflux for 8 hrs. The reaction was cooled at room temperature, diluted with water and extracted with dichloromethane. The extracts were dried over sodium sulfate and evaporated at reduced pressure to give 3-ethyl-4-methylmaleic anhydride (**41**, 112 mg, 86%).

For spectroscopical and physical data, see section 9.2..

3-Ethyl-4-methylmaleimide (17)

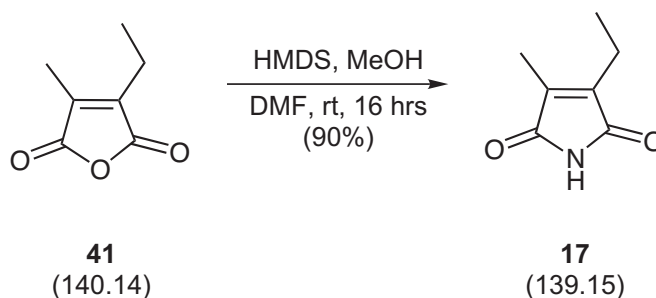
3-Ethyl-4-methyl-1-pyridin-2-ylmaleimide (**139**, 200 mg, 0.92 mmol) and ammonium acetate (356 mg, 4.62 mmol) were dissolved in acetic acid (3 ml) and heated at reflux for 6 hrs. The reaction mixture was then stirred at room temperature overnight. Another portion of ammonium acetate (356 mg, 4.62 mmol) were added and the reaction mixture was heated at reflux for 6 hrs, then stirred at room temperature overnight. The solvent was evaporated under reduced pressure. Column chromatography (silica gel, *n*-hexane : ethyl acetate (2 : 1)) furnished 3-ethyl-4-methylmaleimide (**17**, 65 mg, 51%).

Mp : 65-66°C. **TLC** : $R_f=0.76$ (silica gel, dichloromethane : ethyl acetate : ethanol : acetic acid (100 : 20 : 10 : 1), chlorine/TMB). **¹H NMR** (360.13 MHz, CDCl₃) : δ 1.12-1.17 (t, $^3J(\text{H,H})=7.7$, 3H, CH₂-CH₃), 1.97 (s, 3H, CH₃), 2.37-2.44 (q, $^3J(\text{H,H})=7.7$, 2H, CH₂-CH₃), 7.33 (br. s., 1H, NH). **¹³C NMR** (90.55 MHz, CDCl₃) : δ 8.56 (CH₂-CH₃), 12.74 (CH₃), 17.15 (CH₂-CH₃), 137.80 (C_{quat}), 143.51 (C_{quat}), 171.85 (C=O), 172.25 (C=O). **MS-EI** : m/z 139 ([M]⁺, 100%), 121 (29%), 96 (20%), 67 (96%).

3-Ethyl-4-methylmaleimide (17)

3-Ethyl-4-methyl-1-pyridin-2-ylmaleimide (**139**, 200 mg, 0.92 mmol), HMDS (1.04 g, 6.43 mmol) and methanol (103 mg, 3.21 mmol) in DMF (2 ml) were stirred at room temperature for 3 days. Column chromatography (silica gel, *n*-hexane : ethyl acetate (2 : 1)) furnished 3-ethyl-4-methylmaleimide (**17**, 10 mg, 11%).

For spectroscopical and physical data, see above.

3-Ethyl-4-methylmaleimide (17)

A solution of 3-ethyl-4-methylmaleic anhydride (**41**, 1.01 g, 7.19 mmol) in DMF (14 ml) was treated with a mixture of HMDS (11.61 g, 71.9 mmol) and methanol (1.15 g, 36.0 mmol). After 16 hrs at room temperature the mixture was poured into water (90 ml) and extracted with ethyl acetate (4x90 ml). The combined extracts were dried over sodium sulfate. Removal of the solvent at reduced pressure gave 3-ethyl-4-methylmaleimide (**17**, 897 mg, 90%).

For spectroscopical and physical data, see above.

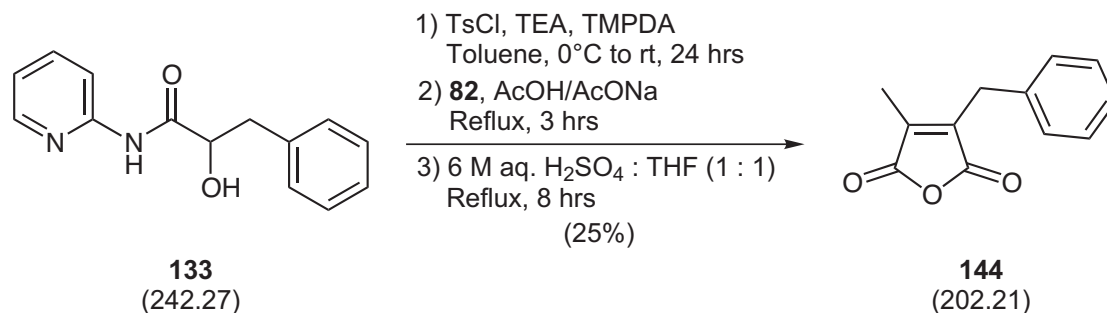
9.5. Further Examples for the Versatility of the Method

General Procedure for the Preparation of Maleic Anhydrides from 2-Hydroxy-*N*-pyridin-2-ylamides

Under an atmosphere of argon, 2-hydroxy-*N*-pyridin-2-ylamide (5 mmol) was suspended in dry toluene (3 ml). TEA (557 mg, 5.5 mmol) in dry toluene (2 ml) then TMPDA (65 mg, 0.5 mmol) in dry toluene (1 ml) were added to the suspension. The reaction mixture was cooled to 0°C and tosyl chloride (1.05 g, 5.5 mmol) in dry toluene (5 ml) was added dropwise over 15 minutes. The reaction mixture was stirred at room temperature for 24 hours, the precipitate was filtered and the solvent evaporated at reduced pressure affording an orange oil.

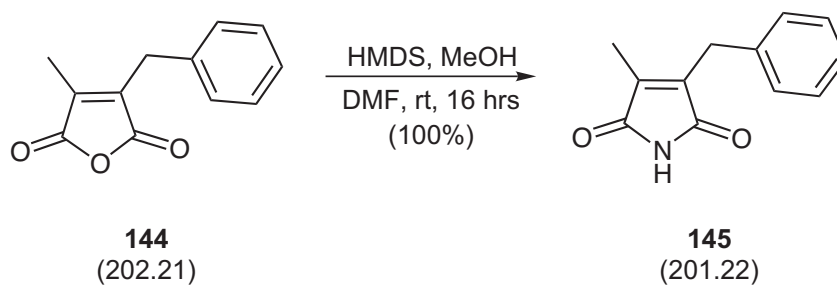
This orange oil was diluted in acetic acid (10 ml), MA (**81**, 490 mg, 5 mmol) and sodium acetate (410 mg, 5 mmol) were added and the solution was heated at reflux for 3 hrs. Then, acetic acid was evaporated at reduced pressure and the residue was filtered over silica gel (eluting with ethyl acetate). The solvent was removed at reduced pressure.

The residue was dissolved in THF : 6 M aq. H₂SO₄ (1 : 1) (20ml) and then heated at reflux for 15 hours. The reaction mixture was cooled to room temperature, water (50 ml) was added and an extraction with dichloromethane (4x30 ml) followed by drying over sodium sulfate and evaporation of the solvent at reduced pressure furnished crude maleic anhydride. This was next purified by column chromatography (silica gel, *n*-hexane : ethyl acetate (3 : 1) to afford the pure maleic anhydride.

3-Benzyl-4-methylmaleic Anhydride (144)

The general procedure was followed for the synthesis of **144** (250 mg, 25%).

$^1\text{H NMR}$ (360.13 MHz, CDCl_3) : δ 2.04 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 7.21-7.34 (m, 5H, Ph). **$^{13}\text{C NMR}$** (90.55 MHz, CDCl_3) : δ 9.83 (CH_3), 30.49 (CH_2), 127.58 (ArH), 128.90 (ArH), 129.24 (ArH), 135.26 (C_{quat}), 141.16 (C_{quat}), 142.77 (C_{quat}), 165.91 ($\text{C}=\text{O}$), 166.26 ($\text{C}=\text{O}$). **MS-EI** : m/z 202 ($[\text{M}]^+$, 100%), 174 (44%), 156 (31%), 145 (20%), 131 (39%), 128 (56%), 115 (32%).

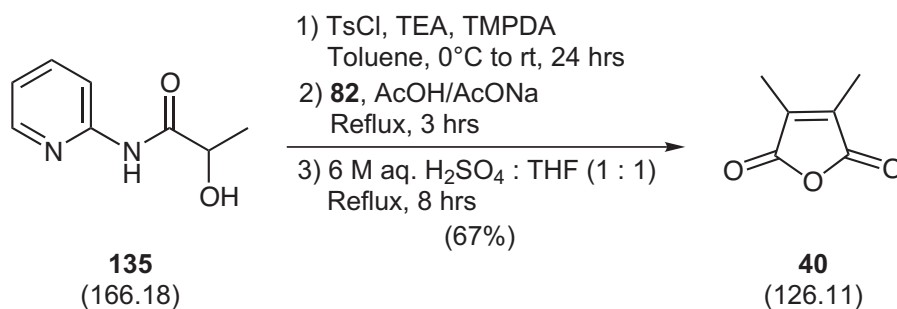
3-Benzyl-4-methylmaleimide (145)

A solution of 3-benzyl-4-methylmaleic anhydride (**144**, 142 mg, 0.7 mmol) in DMF (2 ml) was treated with a mixture of HMDS (1.13 g, 7 mmol) and methanol (112 g, 3.5 mmol). After 16 hrs at room temperature the mixture was poured into water (20 ml) and extracted with ethyl acetate (4x20 ml). The combined extracts were dried over sodium sulfate. Removal of the solvent at reduced pressure gave 3-benzyl-4-methylmaleimide (**145**, 141 mg, 100%).

$^1\text{H NMR}$ (360.13 MHz, CDCl_3) : δ 1.96 (s, 3H, CH_3), 3.71 (s, 2H, CH_2), 7.21-7.32 (m, 5H, Ph), 7.84 (br. s., 1H, NH). **$^{13}\text{C NMR}$** (90.55 MHz, CDCl_3) : δ 8.93 (CH_3), 29.58

(CH₂), 126.98 (ArH), 128.84 (ArH), 128.96 (ArH), 136.81 (C_{quat}), 138.97 (C_{quat}), 140.35 (C_{quat}), 171.85 (C=O). **MS-EI** : *m/z* 201 ([M]⁺, 100%), 155 (27%), 130 (21%), 129 (32%), 128 (28%), 115 (22%).

3,4-Dimethylmaleic Anhydride (**40**)



The general procedure was followed for the synthesis of **40** (424 mg, 67%).

For spectroscopical and physical data, see section 9.3..

3,4-Dimethylmaleimide (**16**)



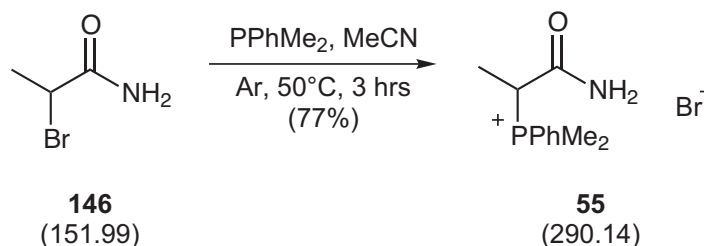
A solution of 3,4-dimethylmaleic anhydride (**40**, 250 mg, 1.98 mmol) in DMF (7 ml) was treated with a mixture of HMDS (3.20 g, 19.8 mmol) and methanol (318 mg, 9.91 mmol). After 16 hrs at room temperature the mixture was poured into water (30 ml) and extracted with ethyl acetate (3x30 ml). The combined extracts were dried over sodium sulfate. Removal of the solvent at reduced pressure gave 3,4-dimethylmaleimide (**16**, 230 mg, 93%).

For spectroscopical and physical data, see section 8.1..

10. PREPARATION OF 3-SUBSTITUTED-4-METHYLMALEIMIDES FROM FUNCTIONALIZED α -KETOESTERS

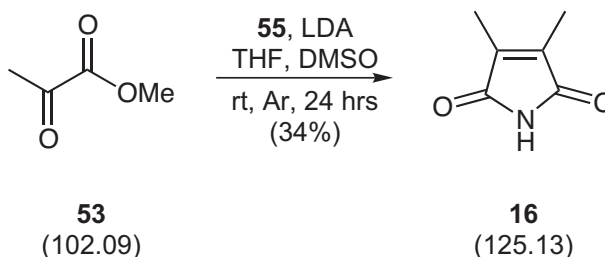
10.1. Synthesis of 4-Methylmaleimides with Various C(3)-Substituents

(2-Amino-1-methyl-2-oxoethyl)(dimethyl)phenylphosphonium Bromide (**55**)



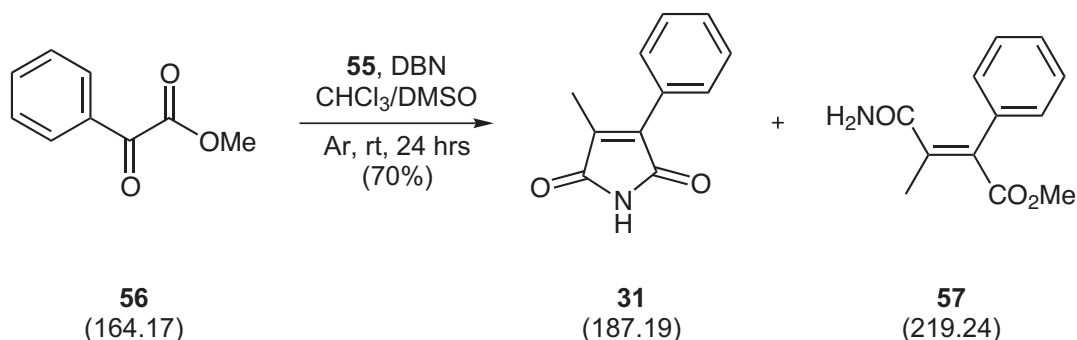
Dimethylphenylphosphine (2.73 g, 19.74 mmol) was added dropwise under argon to a solution of 2-bromopropionamide (**146**, 3 g, 19.74 mmol) in acetonitrile (22 ml) at 50°C and then held at this temperature for 3 hrs. The mixture was diluted with ethyl acetate (100 ml) and extracted with water (3x80 ml). Following evaporation at reduced pressure of the water, the residue was coevaporated with toluene. Crystallization from acetonitrile/ethyl acetate gave the desired product **55** (4.43 g, 77%).

Mp : 192-193°C. **¹H NMR** (500.13 MHz, DMSO-*d*⁶) : δ 1.32-1.37 (dd, $^3J(\text{H,P})=18.9$, $^3J(\text{H,H})=7.3$, 3H, CH-CH₃), 2.27-2.31 (2d, $^2J(\text{H,P})=14.5$, $^2J(\text{H,P})=14.4$, 6H, PPh(CH₃)₂), 3.78-3.85 (qd, $^2J(\text{H,P})=12.6$, $^3J(\text{H,H})=7.3$, 1H, CH-CH₃), 7.52 (br. s., 1H, NH₂), 7.67-7.72 (m, 2H, PPh(CH₃)₂), 7.79-7.82 (m, 1H, PPh(CH₃)₂), 7.84 (br. s., 1H, NH₂), 7.94-7.98 (m, 2H, PPh(CH₃)₂). **¹³C NMR** (125.75 MHz, DMSO-*d*⁶) : δ 4.88-5.31 (d, $^1J(\text{C,P})=54.6$, PPh(CH₃)₂), 5.40-5.83 (d, $^1J(\text{C,P})=54.0$, PPh(CH₃)₂), 11.41-11.44 (d, $^2J(\text{C,P})=3.3$, CH-CH₃), 37.00-37.43 (d, $^1J(\text{C,P})=54.0$, CH-CH₃), 119.71-120.38 (d, $^1J(\text{C,P})=84.6$, C_{quat}), 129.32-129.42 (d, $J(\text{C,P})=12.2$, PPh(CH₃)₂), 132.03-132.11 (d, $J(\text{C,P})=10.0$, PPh(CH₃)₂), 134.08-134.10 (d, $^4J(\text{C,P})=3.3$, PPh(CH₃)₂), 169.37-169.39 (d, $^2J(\text{C,P})=2.8$, C=O). **MS-ESI** (H₂O/MeOH) : *m/z* 210.10 ([C₁₁H₁₇NOP]⁺).

3,4-Dimethylmaleimide (16)

Freshly prepared LDA (1.13 ml of a 0.69 M solution in THF, 0.78 mmol) was added under argon at -78°C to a solution of the phosphonium salt **55** (250 mg, 0.86 mmol) in dry THF (0.7 ml) and dry DMSO (1.5 ml) and then stirred at room temperature for 30 min. A solution of methyl pyruvate (**53**, 80 mg, 0.78 mmol) in dry THF (7 ml) was added dropwise to the mixture. After stirring for 24 hrs, the reaction mixture was diluted with ethyl acetate (50 ml) and washed with water (3x20 ml). The organic layer was dried over sodium sulfate and evaporated at reduced pressure. Column chromatography (silica gel, *n*-hexane : acetone (3 : 1)) furnished only 3,4-dimethylmaleimide (**16**, 33 mg, 34%).

For spectroscopical and physical data, see section 8.1..

3-Methyl-4-phenylmaleimide (31) and Methyl (*E*)-4-Amino-3-methyl-4-oxo-2-phenyl-2-butenate (57)

Under argon, a solution of DBN (97 mg, 0.78 mmol) in dry chloroform (0.5 ml) was added to a solution of the phosphonium salt **55** (250 mg, 0.86 mmol) in dry DMSO

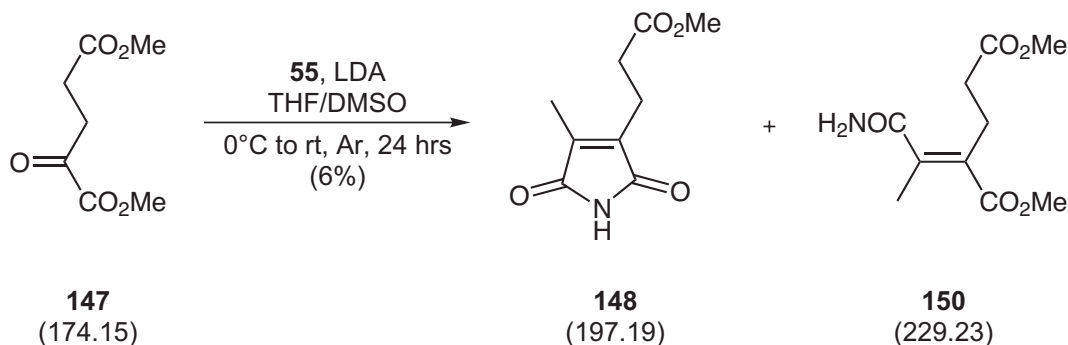
(1.6 ml) and stirred at room temperature for 30 min. The resulting solution was added to a solution of methyl phenylglyoxylate (**56**, 128 mg, 0.78 mmol) in dry chloroform (8 ml) and then stirred at room temperature for 24 hrs. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with water (3x20 ml). The organic layer was dried over sodium sulfate and evaporated at reduced pressure. Column chromatography (silica gel, *n*-hexane : ether (2 : 1) then ether) furnished 3-methyl-4-phenylmaleimide (**31**, 74 mg, 51%) and methyl (*E*)-4-amino-3-methyl-4-oxo-2-phenyl-2-butenolate (**57**, 32 mg, 19%).

3-Methyl-4-phenylmaleimide (31) :

Mp : 181-183°C. **TLC** : $R_f=0.33$ (silica gel, *n*-hexane : ether (2 : 1), UV_{254nm}). **1H NMR** (360.13 MHz, $CDCl_3$) : δ 2.20 (s, 3H, CH_3), 7.42-7.51 (m, 3H, Ph), 7.56-7.59 (m, 2H, Ph), 7.71 (br. s., 1H, NH). **^{13}C NMR** (90.55 MHz, $CDCl_3$) : δ 9.99 (CH_3), 128.76 (Ph), 128.81 (C_{quat}), 129.62 (Ph), 129.90 (Ph), 137.65 (C_{quat}), 138.26 (C_{quat}), 171.06 (C=O), 171.87 (C=O). **MS-EI** : m/z 187 ($[M]^+$, 100%), 116 (64%), 115 (61%).

Methyl (*E*)-4-amino-3-methyl-4-oxo-2-phenyl-2-butenolate (57) :

Mp : 160-161°C. **TLC** : $R_f=0.68$ (silica gel, ether, UV_{254nm}). **1H NMR** (360.13 MHz, $CDCl_3$) : δ 2.19 (s, 3H, CH_3), 3.76 (s, 3H, CO_2CH_3), 5.12 (br. s., 1H, NH_2), 5.50 (br. s., 1H, NH_2), 7.30-7.35 (m, 5H, Ph). **^{13}C NMR** (90.55 MHz, $CDCl_3$) : δ 18.47 (CH_3), 52.46 (CO_2CH_3), 128.50 (Ph), 128.74 (Ph), 128.84 (Ph), 133.72 (C_{quat}), 135.47 (C_{quat}), 139.21 (C_{quat}), 168.53 (C=O), 171.67 (C=O). **MS-EI** : m/z 219 ($[M]^+$, 19%), 202 (85%), 187 (51%), 117 (22%), 116 (25%), 115 (100%).

Hematinic Acid Methyl Ester (148) and Dimethyl 2-[(E)-2-Amino-1-methyl-2-oxoethylidene]pentanedioate (150)


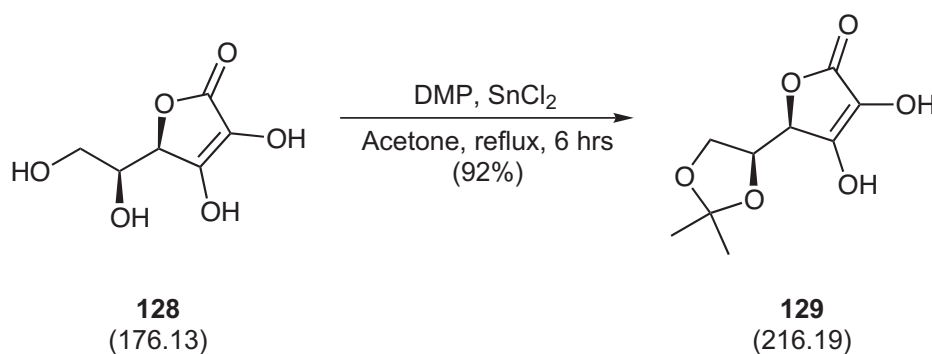
Freshly prepared LDA (1.13 ml of a 0.69 M solution in THF, 0.78 mmol) was added under argon at -78°C to a solution of the phosphonium salt **55** (250 mg, 0.86 mmol) in dry THF (2 ml) and dry DMSO (1 ml) and then stirred at room temperature for 2 hrs. A solution of dimethyl 2-oxoglutarate (**147**, 136 mg, 0.78 mmol) in dry THF (3 ml) was added dropwise at 0°C to the mixture. After stirring for 24 hrs, the reaction mixture was diluted with ethyl acetate (50 ml) and washed with water (3x20 ml). The organic layer was dried over sodium sulfate and evaporated at reduced pressure. Column chromatography (silica gel, dichloromethane : ethyl acetate (1 : 1)) furnished methyl 3-(4-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)propanoate (**148**, 6 mg, 4%) and dimethyl 2-[(E)-2-amino-1-methyl-2-oxoethylidene]pentanedioate (**150**, 3 mg, 2%).

Hematinic Acid Methyl Ester (148) :

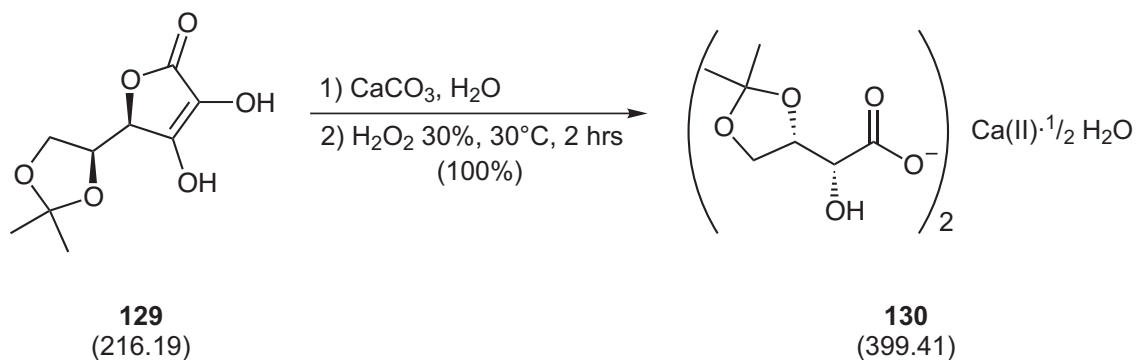
Mp : $64\text{--}65^\circ\text{C}$. **TLC** : $R_f=0.48$ (silica gel, dichloromethane : ethyl acetate (7 : 3), chlorine/TMB). **$^1\text{H NMR}$** (500.13 MHz, CDCl_3) : δ 2.01 (s, 3H, CH_3), 2.64 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CO}_2\text{CH}_3$), 2.70 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CO}_2\text{CH}_3$), 3.68 (s, 3H, $\text{CH}_2\text{-CH}_2\text{-CO}_2\text{CH}_3$), 7.36 (br. s., 1H, NH). **$^{13}\text{C NMR}$** (50.3 MHz, CDCl_3) : δ 9.10 (CH_3), 19.81 ($\text{CH}_2\text{-CH}_2\text{-CO}_2\text{CH}_3$), 32.15 ($\text{CH}_2\text{-CH}_2\text{-CO}_2\text{CH}_3$), 140.16 (C_{quat}), 140.24 (C_{quat}), 171.25 (C=O), 171.41 (C=O), 172.50 (C=O). **MS-Cl** (CH_4) : m/z 198 ($[\text{M}+\text{H}]^+$, 62%), 166 (100%).

Dimethyl 2-[(E)-2-Amino-1-methyl-2-oxoethylidene]pentanedioate (150) :

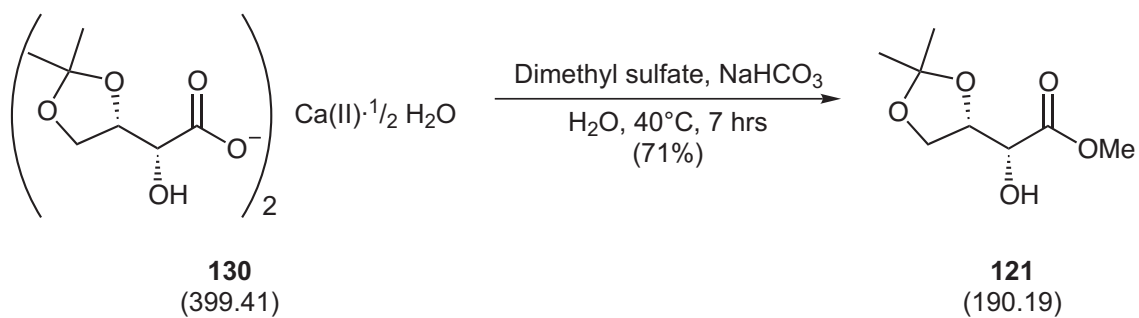
TLC : $R_f=0.17$ (silica gel, dichloromethane : ethyl acetate (2 : 1), KMnO_4). **$^1\text{H NMR}$** (500.13 MHz, CDCl_3) : δ 2.11 (2d, $^5J(\text{H,H})=1.1$, $^5J(\text{H,H})=0.8$, 3H, CH_3), 2.53-2.56 (t, $^3J(\text{H,H})=6.9$, 2H, $\text{CH}_2\text{-CH}_2\text{-CO}_2\text{CH}_3$), 2.72-2.75 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CO}_2\text{CH}_3$), 3.67 (s, 3H, CO_2CH_3), 3.78 (s, 3H, CO_2CH_3), 5.60 (br. s., 1H, NH_2), 7.12 (br. s., 1H, NH_2). **$^{13}\text{C NMR}$** (125.75 MHz, CDCl_3) : δ 18.51 (CH_3), 26.16 (CH_2), 31.88 (CH_2), 51.97 (CO_2CH_3), 52.05 (CO_2CH_3), 129.43 (C_{quat}), 140.48 (C_{quat}), 168.34 ($\text{C}=\text{O}$), 172.11 ($\text{C}=\text{O}$), 174.25 ($\text{C}=\text{O}$). **MS-EI** : m/z 230 ($[\text{M}+\text{H}]^+$, 5%), 212 (67%), 197 (38%), 180 (50%), 166 (55%), 153 (47%), 152 (42%), 139 (21%), 138 (100%), 125 (20%), 124 (27%).

10.2. Synthesis of 3-[(1R)-1,2-Dihydroxyethyl]4-methylmaleimide**(5R)-5-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3,4-dihydroxyfuran-2(5H)-one (129)**

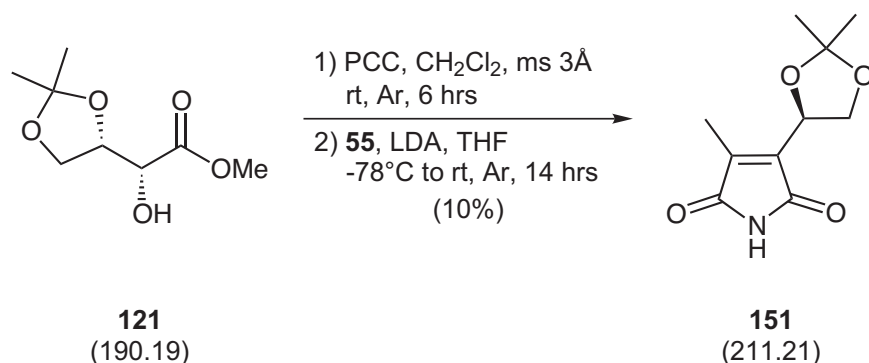
See section 9.1..

Calcium di{(2R)-2-[(4S)-Dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethanoate} (130)

See section 9.1..

Methyl (2R)-2-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethanoate (121)

See section 9.1..

3-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-methylmaleimide (**151**)

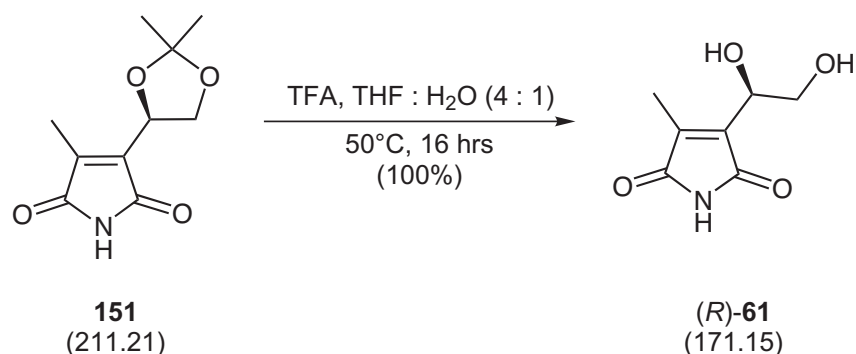
Methyl (2*R*)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethanoate (**121**, 1.79 g, 9.4 mmol), PCC (8.11 g, 37.6 mmol), and freshly activated powdered 3Å molecular sieves (18 g) were stirred in dry dichloromethane (35 ml) under argon at room temperature for 6 hrs. After dilution with dry ether (35 ml), column chromatography (silica gel, dry ether) furnished crude methyl 2-[(4'*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxoacetate **152** (*Caution ! Moisture very sensitive !*) which was immediately stored in dry THF (32 ml) under argon.

Freshly prepared LDA (13.62 ml of a 0.69 M solution in THF, 9.4 mmol) was added under argon at -78°C to a solution of the phosphonium salt **55** (3 g, 10.34 mmol) in dry THF (25 ml) and then stirred at this temperature for 2 hrs. The freshly prepared solution of methyl 2-[(4'*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxoacetate **152** (see above) was added dropwise at -78°C to the mixture. After stirring for 2 hrs at this temperature and 24 hrs at room temperature, water (250 ml) was added and the reaction mixture was extracted with ether (5x120 ml). The organic layer was dried over sodium sulfate and evaporated at reduced pressure. Column chromatography (silica gel, *n*-hexane : acetone (5 : 1), then (3 : 1)) furnished 3-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-methylmaleimide (**151**, 190 mg, 10%).

Mp : 91-92°C. **TLC** : R_f=0.45 (silica gel, *n*-hexane : acetone (2 : 1), chlorine/TMB). **¹H NMR** (500.13 MHz, CDCl₃) : δ 1.43 (m, 3H, C(CH₃)₂), 1.49 (m, 3H, C(CH₃)₂), 2.15-2.16 (d, ⁵J(H,H)=1.3, 3H, CH₃), 3.83-3.86 (dd, ²J(H,H)=8.2, ³J(H,H)=8.0, 1H, CH(O)-CH₂(O)), 4.34-4.37 (dd, ²J(H,H)=8.2, ³J(H,H)=6.8, 1H, CH(O)-CH₂(O)), 5.00-5.04 (ddq, ³J(H,H)=8.0, ³J(H,H)=6.8, ⁵J(H,H)=1.3, 1H, CH(O)-CH₂(O)), 7.36 (br. s., 1H,

NH). ^{13}C NMR (125.75 MHz, CDCl_3) : δ 9.17 (CH_3), 25.52 ($\text{C}(\underline{\text{C}}\text{H}_3)_2$), 26.06 ($\text{C}(\underline{\text{C}}\text{H}_3)_2$), 68.88 ($\underline{\text{C}}\text{H}(\text{O})\text{-CH}_2(\text{O})$), 70.81 ($\text{CH}(\text{O})\text{-}\underline{\text{C}}\text{H}_2(\text{O})$), 110.47 (C_{quat}), 137.16 (C_{quat}), 140.72 (C_{quat}), 170.41 ($\text{C}=\text{O}$), 171.27 ($\text{C}=\text{O}$). **MS-Cl** (*iso*-butane) : m/z 212 ($[\text{M}+\text{H}]^+$), 196, 154. **HR-MS** (Cl, *iso*-butane) : m/z 212.09194. *Calcd mass for* $[\text{C}_{10}\text{H}_{13}\text{NO}_4+\text{H}]^+$: 212.09227. **UV/Vis** (CH_2Cl_2) : 278 (2.78). **CD** (CH_2Cl_2) : 281 (-1.78), 335 (+0.74).

3-[(1*R*)-1,2-Dihydroxyethyl]-4-methylmaleimide ((*R*)-**61**)



3-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-methylmaleimide (**151**, 21 mg, 0.1 mmol) was dissolved in THF : water (4 : 1) (5 ml). TFA (200 μl , 2.61 mmol) was added and the reaction mixture was stirred at 50°C for 16 hrs. Evaporation of the solvents at reduced pressure furnished the desired product (*R*)-**61** (17 mg, 100%).

^1H NMR (500.13 MHz, CD_3OD) : δ 2.06 (d, $^5J(\text{H},\text{H})=0.8$, 3H, CH_3), 3.67-3.75 (m_{ABX} , $^2J_{\text{AB}}(\text{H};\text{H})=11.3$, $^3J_{\text{AX}}(\text{H},\text{H})=6.2$, $^3J_{\text{BX}}(\text{H},\text{H})=4.9$, 2H, $\text{CH}(\text{OH})\text{-}\underline{\text{C}}\text{H}_2(\text{OH})$), 4.66-4.69 (m_{ABX} , $^3J_{\text{AX}}(\text{H},\text{H})=6.2$, $^3J_{\text{BX}}(\text{H},\text{H})=4.9$, $^5J(\text{H},\text{H})=0.8$, 1H, $\underline{\text{C}}\text{H}(\text{OH})\text{-CH}_2(\text{OH})$). ^{13}C NMR (125.75 MHz, CD_3OD) : δ 8.84 (CH_3), 65.64 ($\text{CH}(\text{OH})\text{-}\underline{\text{C}}\text{H}_2(\text{OH})$), 68.58 ($\underline{\text{C}}\text{H}(\text{OH})\text{-CH}_2(\text{OH})$), 140.24 (C_{quat}), 141.92 (C_{quat}), 173.74 ($\text{C}=\text{O}$), 174.41 ($\text{C}=\text{O}$). **MS-Cl** (*iso*-butane) : m/z 172 ($[\text{M}+\text{H}]^+$), 102. **HR-MS** (Cl, *iso*-butane) : m/z 172.06074. *Calcd mass for* $[\text{C}_7\text{H}_9\text{NO}_4+\text{H}]^+$: 172.06098. **UV/Vis** (MeOH) : 274 (2.61). **CD** (MeOH) : 292 (-0.79), 342 (+0.13), 351 (+0.09).

Part B

ENANTIOMERIC EXCESS DETERMINATION OF α -AMINO ACIDS BY ^{19}F NMR SPECTROSCOPY WITH A NEW FLUORINATED ORGANOMETALLIC CHIRAL DERIVATIZING AGENT

THEORETICAL PART

11. INTRODUCTION

For the determination of their enantiomeric excess, chiral AAs generally have to be chemically modified and subjected to chromatographic separations or NMR spectroscopy. In gas chromatography, AAs are first converted to their corresponding *N*-acyl esters, then separated on a chiral stationary phase.^[206, 207] Liquid chromatographic analysis are effectuated with AAs derived with chiral isothiocyanates in normal phase conditions on an achiral stationary phase,^[208] or with free AAs in reversed phase in presence of chiral auxiliaries either in the mobile or in the stationary phase.^[209-211] Analysis by capillary electrophoresis is accomplished after derivatization with *o*-phthaldialdehyde cysteine.^[212] NMR-based methods of analysis are widely used for the determination of enantiomeric purity of organic compounds.^[213, 214] Particularly, AAs are derivatized with chiral carboxylic acid chlorides or with chiral phosphonates prior to their NMR analysis.^[215-219] It is also possible to determine their enantiomeric excess with chiral lanthanoid shift reagents, but, often, line broadening due to paramagnetic relaxation are observed.^[220-223]

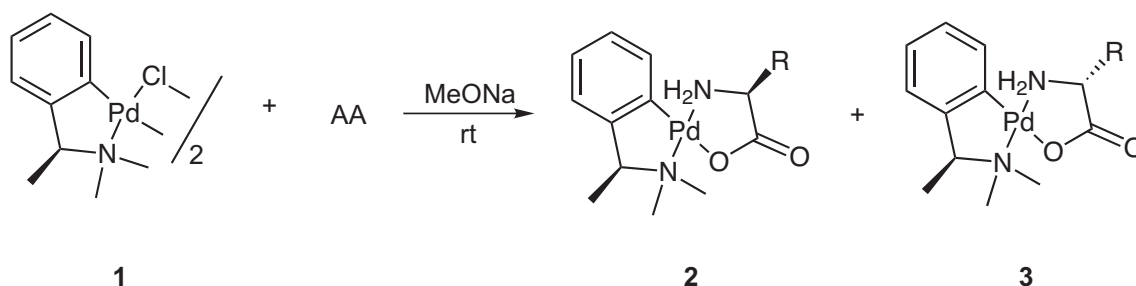
A promising method to determine the enantiomeric excess of AAs involves conversion of the enantiomers into a mixture of diastereomers by coordinative bond formation with a palladium ion bearing an enantiopure auxiliary ligand. Integration of the separated resonance signals of (an) appropriate diastereotopic group(s) then allows the calculation of the enantiomeric composition of the original mixture. The choice of the NMR nucleus observed is important. If the compound has a complex ¹H NMR spectrum, then ¹⁹F or ³¹P analysis should be considered – particularly with CDAs which usually contain only one or two different F or P atoms.

12. DETERMINATION OF THE ENANTIOMERIC EXCESS OF AMINO ACIDS WITH ORGANOPALLADATED CHIRAL DERIVATIZING AGENTS

The determination of the enantiomeric excess of AAs by ^1H or ^{13}C NMR techniques has already been achieved with palladium complexes, but in some cases complex ^1H NMR spectra were obtained in which overlapping signals hampered reliable integration.^[224, 225] Another method was developed using a CCDA with a P^* -chiral auxiliary ligand taking advantage of ^{31}P NMR spectroscopy.^[226] A short description of these experiments are given in the following sections.

12.1. Derivatization with a *N,N*-Dimethyl-*N*-[(1*S*)-1-phenylethyl]amine Palladium Complex

The (*S*)-dmphea orthometallated palladium complex **1** was used as a reagent for the determination of the enantiomeric ratio of AAs.^[224] Diastereomers **2** and **3** of the corresponding α -amino acidato complexes were obtained by reaction of **1** with mixtures of several (*R*)- and (*S*)-amino carboxylates (Scheme 1). The base used for this purpose was sodium methoxide.



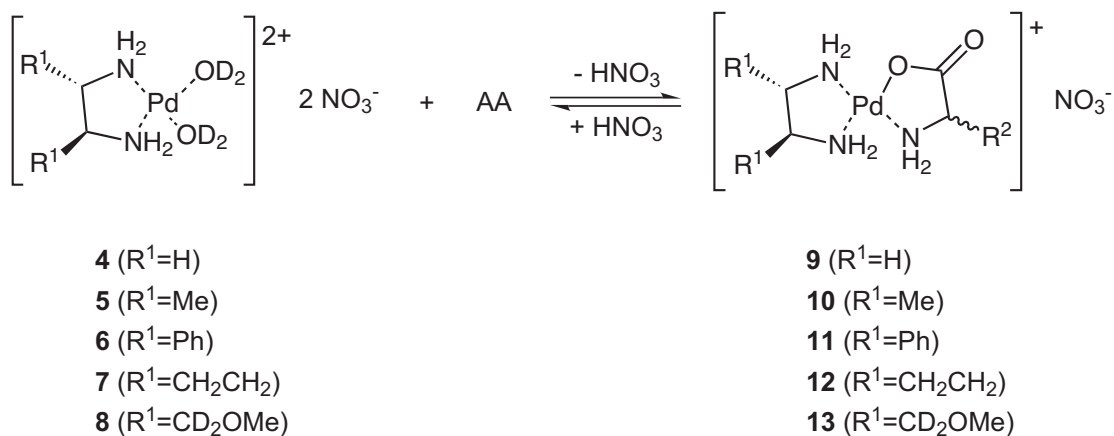
Scheme 1. Derivatization of AAs with the palladium complex **1**. AAs tested were Ala, Val, Leu, Phegly, Phe, Pro and Thr.

These diastereomeric complexes were analyzed by ^1H NMR. Spectra showed a duplication of the signals for both diastereomers, which, unfortunately, overlapped sometimes. The best resolved signals – Ph-CH(Me)NMe₂ or Ph-CH(Me)NMe₂ – were chosen to be integrated thus affording the *de*. Studies with weighed amounts of both enantiomers showed that this method was efficient and reliable even in the case

of Phegly which is known to racemize in alkaline mediums.^[227] Regrettably, nothing is mentioned about the nonequivalence of the chemical shifts.

12.2. Determination of the Enantiomeric Ratio of Unprotected Amino Acids with C₂-Chiral Palladium Compounds

Starting from optically active C₂-chiral 1,2-diamines, Staubach *et al.* prepared aqueous solutions of the chiral palladium compounds **4-8** and subsequently treated them with AAs to give the diastereomeric palladium complexes **9-13**.^[225] The ¹H NMR analysis of the diastereomeric complexes yielded the enantiomeric ratio of the AAs directly (Scheme 2).



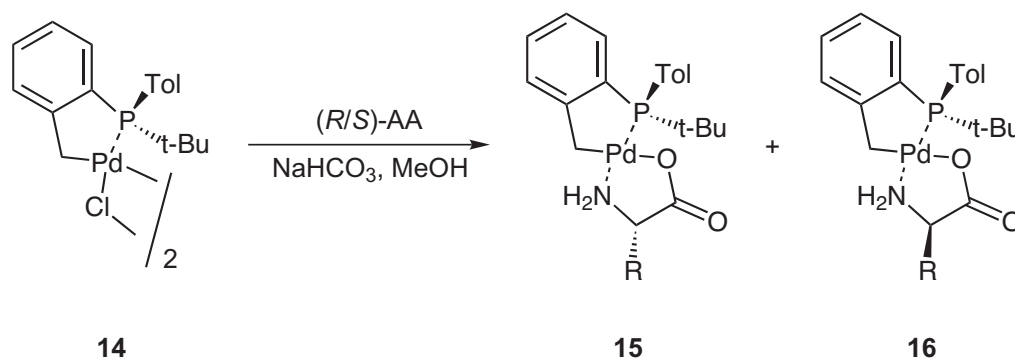
Scheme 2. Derivatization of AAs with palladium complexes (**4-8**). AAs used were Pro, His, Thr, Trp, Val, Ser, β -aminobutyric acid, methylphenylglycine, γ -fluoraminobutyric acid and α -thienylglycine.

The main disadvantage of this method was that ¹H NMR analysis of a mixture of *rac*-AAs gave four sets of signals for the diamine residue whereas AA lead to two sets of signals. To test the ability of chiral palladium complexes (**4-8**) as suitable auxiliaries, Ala with different (*R*)/(*S*) ratios was prepared by weighing the pure enantiomers and examining the products of the reaction with **7**. NMR analysis gave the same ratio within the experimental error. The influence of the substituent in the chiral diamine was investigated by derivatizing *rac*-Ala with complexes **4-8**. All diastereomeric peak separations were measured between 0.02 ppm and 0.06 ppm, the worst for **8** and the best for **6**. Finally, several natural α -AAs, three artificial α -AAs (one of them alkylated

in α -position) and one β -AA, all of them unprotected, were investigated and provided similar results as for Ala.

12.3. P*-Chiral Phosphopalladacycle as Coordinative Chiral Derivatizing Agent

Dunina *et al.* used a P*-chiral phosphopalladacycle as CCDA for a series of α -AAs.^[226] The transformation of AAs enantiomers into a mixture of diastereomers included the complexation of an α -amino acidate ligand with a homochiral cyclopalladated dimer (**14**) (Scheme 3).



Scheme 3. Derivatization of AAs with a chiral P*-phosphopalladacycle. AAs used were Phegly, Val, Ala, Pro and Leu.

The presence of the ^{31}P nucleus in the reagent **14** offered the opportunity to employ the $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy for the control of the diastereomeric composition of the mixtures of α -amino acidate adducts **15** and **16** formed. The advantages of ^{31}P NMR spectroscopy for enantiomeric purity determination are well-known.^[213] They include : I) a large dispersion of chemical shifts facilitating the integration of the anisochronic signals; II) extremely simple spectral picture which is independent on the C,H-complexity of the molecule examined; and III) the possibility to avoid the spectral complications caused by a presence of the reagent excess or non-phosphorus admixtures.

A major limitation of the method developed by Dunina *et al.* resided in the fact that spectra were complicated to some extent due to the (Z)/(E)-isomery of

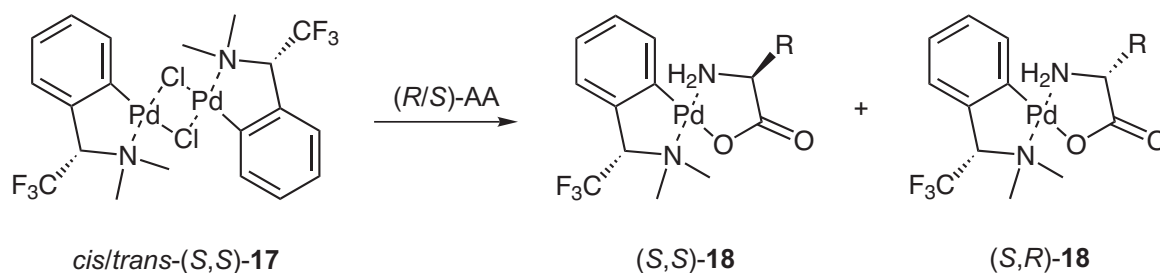
diastereomeric mononuclear adducts **15** and **16** caused by the similar *trans*-influences of the C- and P-donor centers of the phosphopalladacycle and unsymmetrical nature of *N,O*-coordinated α -amino acidate ligands.^[226]

The magnitude of the diastereomeric peak separation represented as the difference in chemical shifts of diastereomeric complexes **15** and **16** were measured for five α -AAs (Scheme 3). These values were generally much greater for the isomers of geometric (*E*)-configuration (0.88-2.01 ppm). In the case of the (*Z*)-isomers they were inside the range 0.09-0.48 ppm, with the exception of 1.578 ppm found for the Pro derivative.

In order to demonstrate the practicality of this method, artificial mixtures of known enantiomeric composition using racemic and optically active Val in defined ratios were prepared and analyzed by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy. The comparison of the magnitudes of the *ee* determined with the values based on the weighing method showed that the deviation did not exceed 2% that is the natural limit of NMR spectroscopy possibilities.

AIM OF THIS WORK

C,N-Cyclopalladated complexes have been already used as CCDAs to determine by ^1H NMR spectroscopy the enantiomeric purity of AAs as well as of other functional groups.^[224, 228-232] The aim of this work was first to synthesize and resolve a new trifluoromethyl-palladacycle (*cis/trans*-(*S,S*)-**17**) and next to apply it for the derivatization of α -AAs. The formed diastereomers (*S,S*)-**18** and (*S,R*)-**18** should be analyzed by ^{19}F NMR spectroscopy in order to determine their *ee* (Scheme 4).



Scheme 4. Strategy considered to determine the ee of natural α-AAs by means of ¹⁹F NMR spectroscopy.

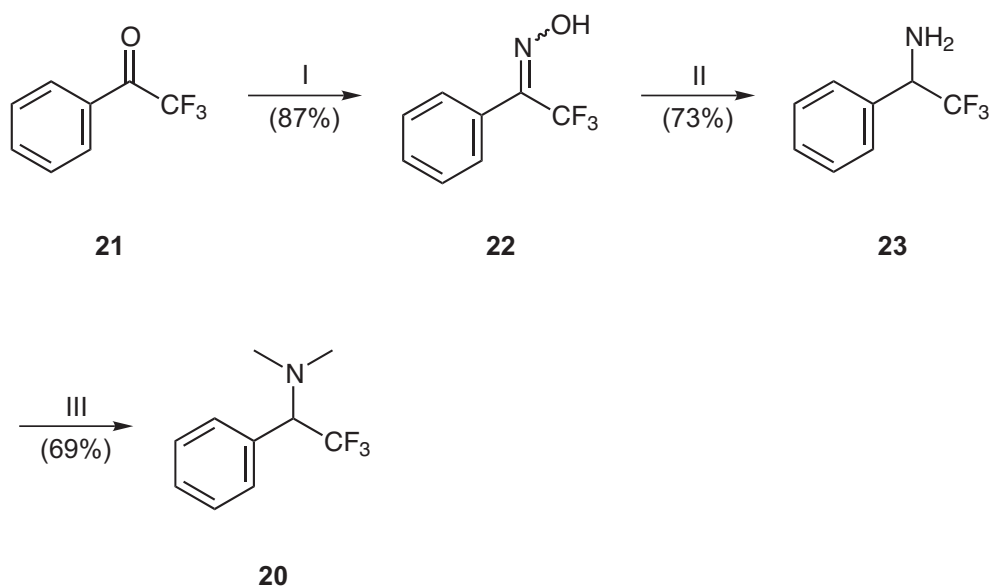
RESULTS AND DISCUSSION

13. SYNTHESIS OF THE HOMOCHIRAL C,N-CYCLOPALLADATED COMPLEX USED AS COORDINATIVE CHIRAL DERIVATIZING AGENT

Cis/trans-(*S,S*)-**17** – used as CCDA in this work – was prepared first by synthesizing the racemic fluorinated ligand **20**, followed by an *ortho*-palladation affording an isomeric mixture of the corresponding dimer **17**. These were resolved into their constituent enantiomers (*cis/trans*-(*R,R*)-**17**) and (*cis/trans*-(*S,S*)-**17**) by flash column chromatography of their (*R*)-phenylglycinate diastereomers (*R,R*)-**19** and (*S,R*)-**19**. Their subsequent treatment with diluted hydrochloric acid yielded both *cis/trans*-(*S,S*)-**17** and *cis/trans*-(*R,R*)-**17**.

13.1. Synthesis of the Fluorinated Auxiliary Ligand

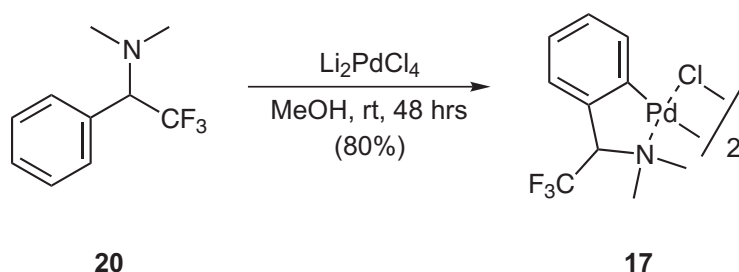
The auxiliary ligand *N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine (**20**) was synthesized in a simple three step sequence starting from commercially available 2,2,2-trifluoroacetophenone (**21**). Transformation of **21** into the corresponding oxime **22**,^[233, 234] and subsequent reduction with LAH afforded 2,2,2-trifluoro-1-phenylethylamine (**23**) in 64% overall yield.^[235] Reductive methylation of **23** under Eschweiler-Clarke conditions gave the desired *N,N*-dimethylamine **20** in 69% yield (Scheme 5).



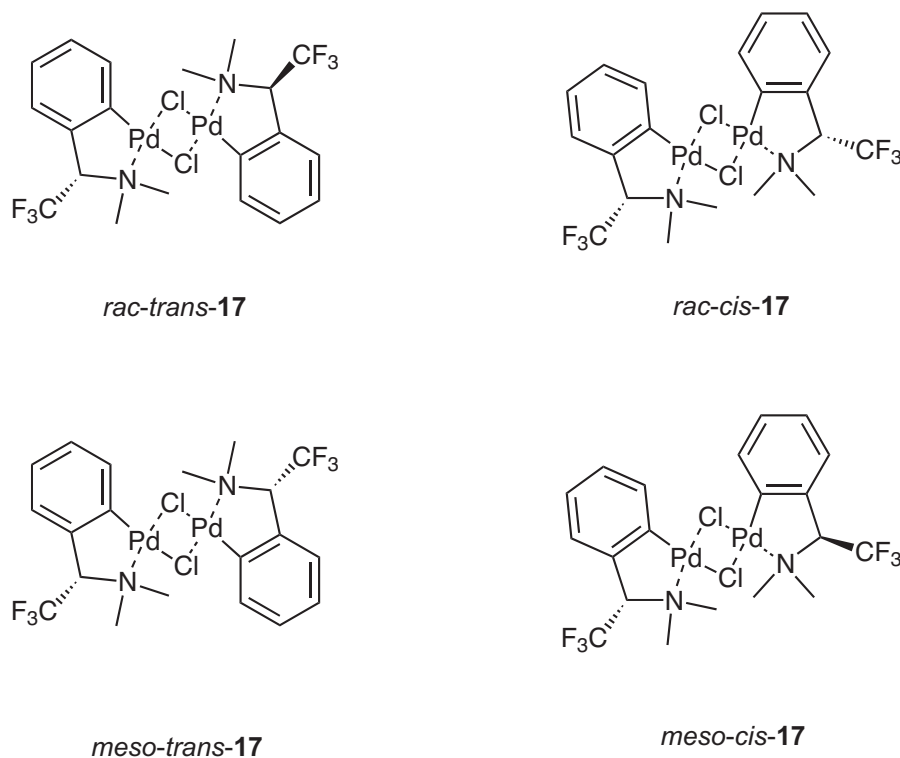
Scheme 5. Preparation of the auxiliary ligand. I) Hydroxylamine hydrochloride, AcONa, EtOH, H₂O, 80°C, 14 hrs. II) LAH, ether, rt, 3 hrs. III) 37% aq. Formaldehyde, formic acid, 90°C, 40 hrs.

13.2. Preparation of the Homochiral Palladium Complex

ortho-Palladation of *N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine (**20**) with lithium tetrachloropalladate(II) was carried out in methanol at room temperature and afforded dimer **17** as a yellow air-stable powder in 80% yield (Scheme 6).^[236] According to the ¹⁹F and ¹H NMR spectra **17** consists of a mixture of four diastereomers such as *rac-trans*, *rac-cis*, *meso-trans* and *meso-cis* (Scheme 7). Unfortunately, the signals are broad and insufficiently resolved to allow reliable assignment and integration.



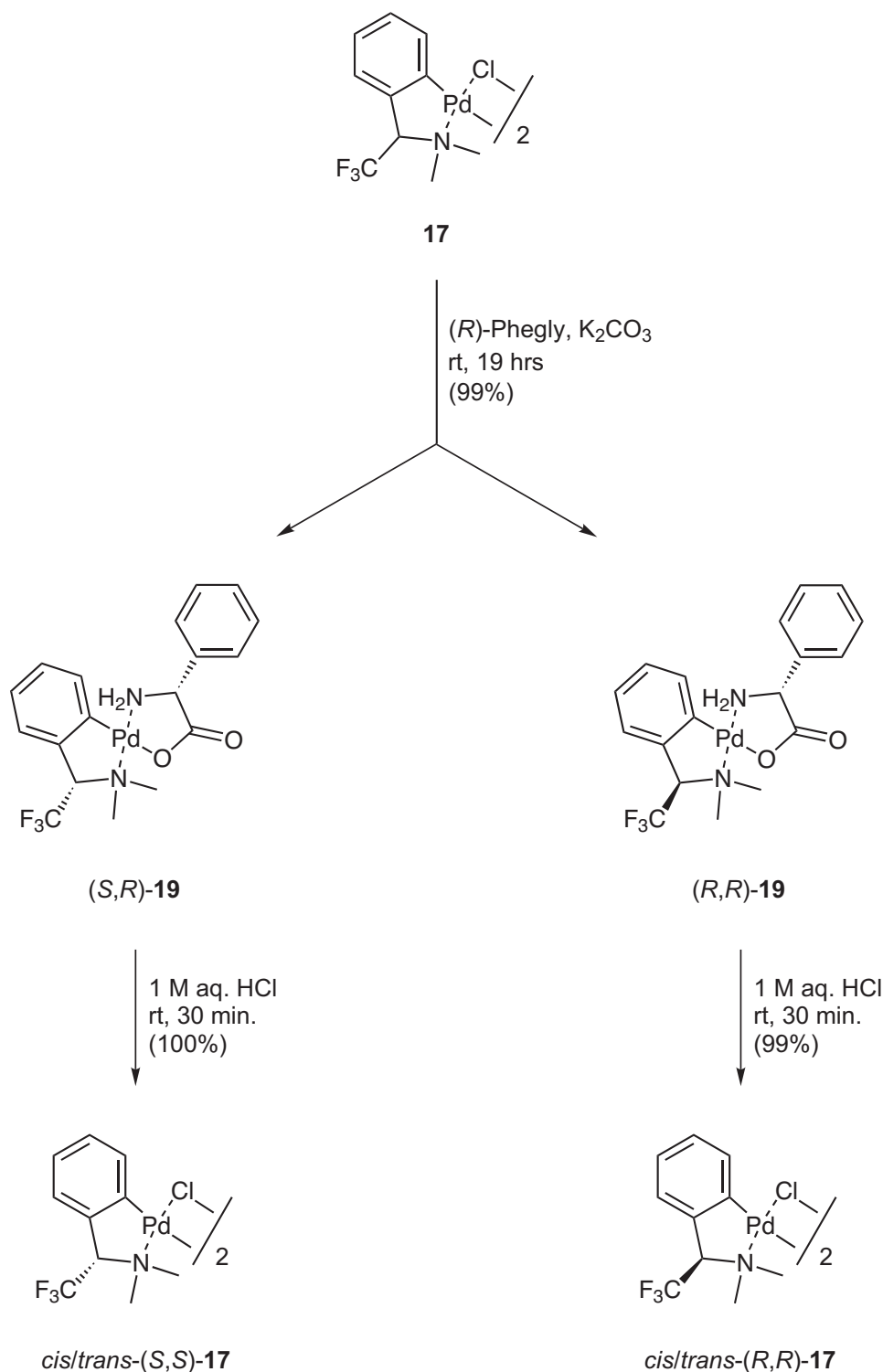
Scheme 6. *ortho*-Palladation affording **17** in a mixture of diastereomers.



Scheme 7. Isomeric forms of the dimer **17** obtained by ortho-palladation of **20**.

Resolution of the Isomeric Dimer in its Enantiomeric Constituents

Dimer **17** was resolved into its constituent enantiomers by flash column chromatography of its (*R*)-Phenylglycinate complexes (*S,R*)-**19** and (*R,R*)-**19** prepared with (*R*)-Phegly according to a procedure described by Ambach *et al.*^[237] Compound (*S,R*)-**19** was the more polar migrating more slowly than (*R,R*)-**19** on a silica gel stationary phase. Subsequent treatment of each of the separated complexes with dilute aqueous hydrochloric acid yielded quantitatively both *cis/trans*-(*S,S*)-**17** and *cis/trans*-(*R,R*)-**17** (Scheme 8).



Scheme 8. Resolution of the isomeric dimer **17** in its enantiomeric constituents.

^{19}F NMR spectra of the separated diastereomeric complexes **(S,R)-19** and **(R,R)-19** showed that both enantiomers were completely resolved, providing an *de* >99% in

both cases. As their conversion to the resolved dimers proceeded with complete retention of the configuration an *ee* >99% could be assigned for CCDAs *cis/trans*-(*S,S*)-**17** and *cis/trans*-(*R,R*)-**17**.

Determination of the Absolute Configuration of the (*R*)-Phenylglycinate Diastereomers

An X-ray structure determination of the less polar (*R*)-phenylglycinate derivative (*R,R*)-**19** was carried out in order to elucidate its absolute configuration. A suitable crystal was grown by diffusion of *n*-hexane into an ethyl acetate solution of the complex. In the crystal two independent molecules per asymmetric unit exist together with one water molecule. The crystal belongs to the orthorhombic system. The complex revealed a *trans*-relationship between the two nitrogen donor atoms and an *anti*-relationship between both hydrogen atoms connected to the stereogenic carbon atoms. Considering that the absolute configuration of the AA center is known to be (*R*) – from (*R*)-Phegly – the absolute configuration of the second stereogenic center was assigned as (*R*). The resulting structure is shown in figure 1. As dimer *cis/trans*-(*R,R*)-**17** was directly derived from (*R,R*)-**19** (Scheme 8) the configuration of its two stereogenic centers could be unambiguously assigned to be (*R*).

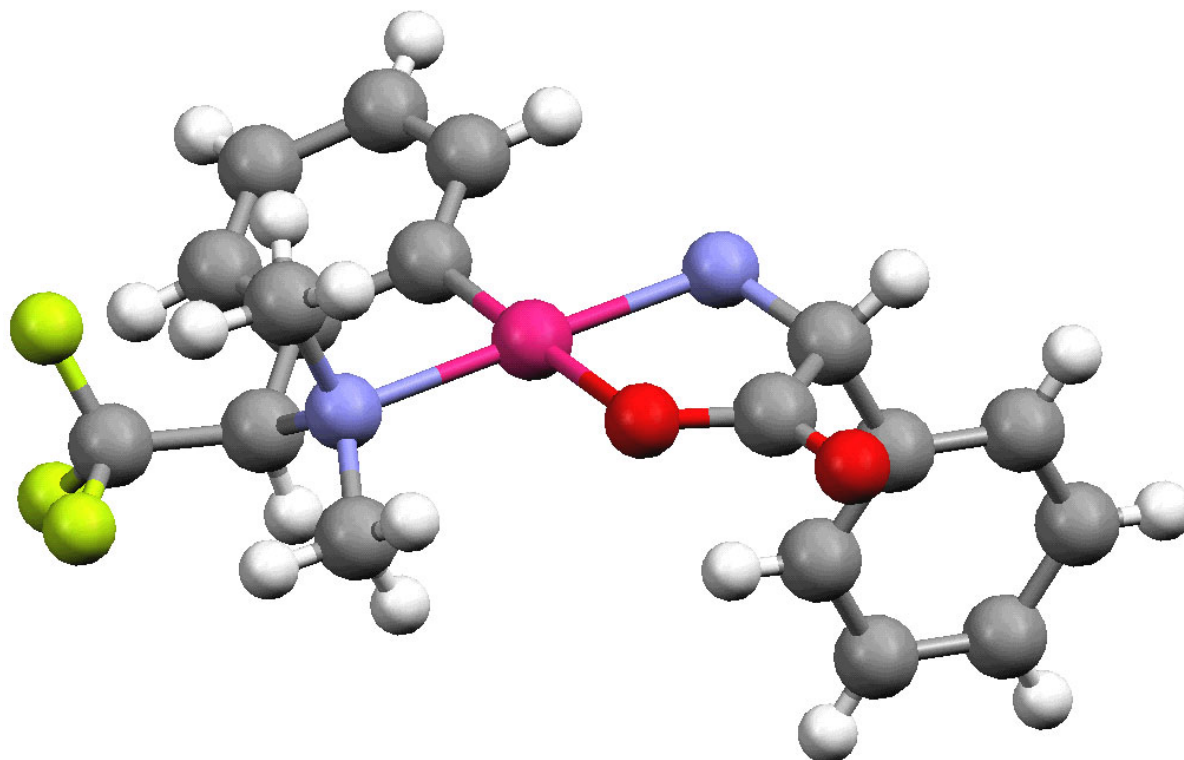


Figure 1. Structure of the (*R*)-phenylglycinate complex (*R,R*)-**19**, determined from X-ray scattering. The atomic coordinates correspond to the absolute configuration in which both asymmetric C-atoms have the (*R*) configuration. C-atoms are depicted in grey, H-atoms in white, O-atoms in red, N-atoms in blue, F-atoms in green and Pd-atom in purple.

Figure 2 shows the UV/Vis and CD spectra of both *cis/trans*-(*S,S*)-**17** and *cis/trans*-(*R,R*)-**17** in dichloromethane solution, respectively. As expected, both compounds show Cotton effects of opposite signs thus proving that they are enantiomers.

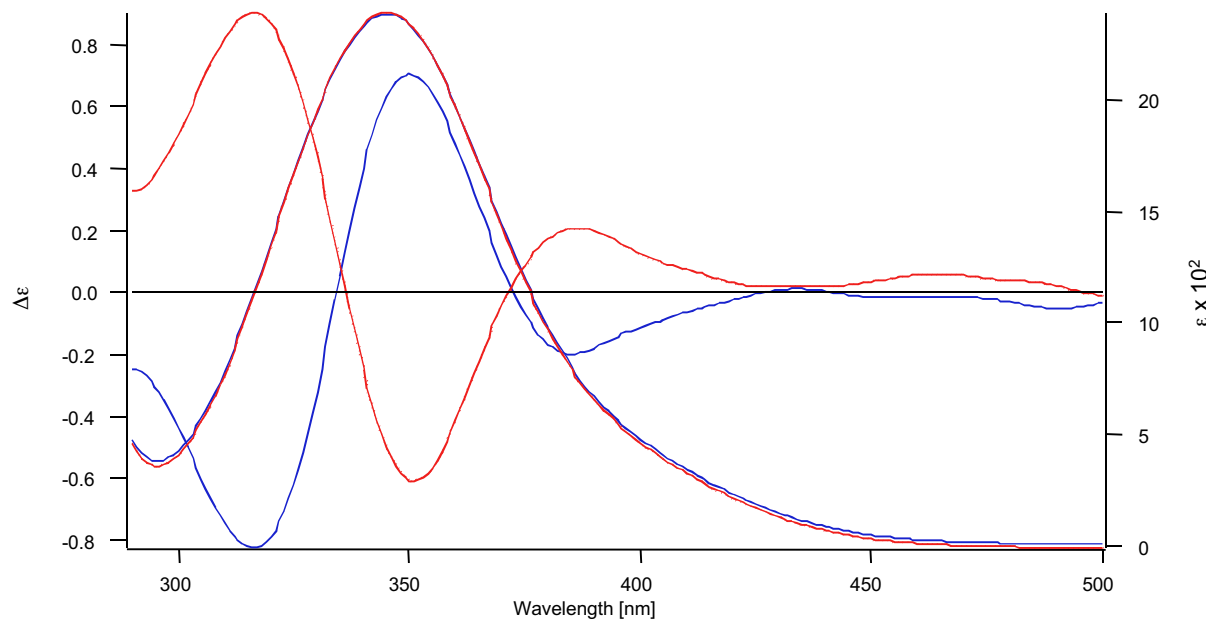


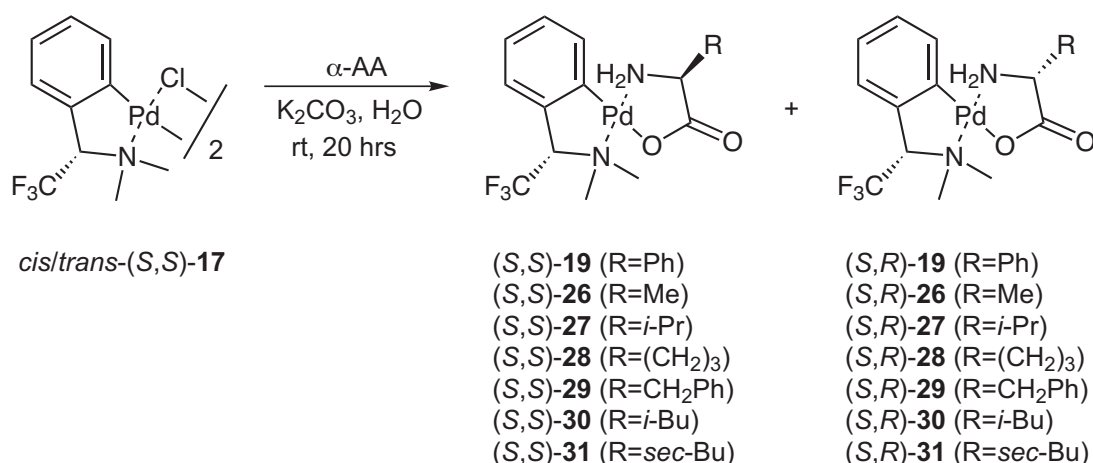
Figure 2. Superimposed UV/Vis and CD spectra of *cis/trans*-(*S,S*)-**17** (in red) and *cis/trans*-(*R,R*)-**17** (in blue) in dichloromethane.

14. ENANTIOMERIC EXCESS DETERMINATION OF α -AMINO ACIDS BY ^{19}F NMR SPECTROSCOPY

The transformation of natural α -AAs into diastereomers was performed by complexation with *cis/trans*-(*S,S*)-**17** in water in the presence of potassium carbonate according to a method used by Ambach *et al.* (Scheme 9).^[237] All AA complexes (**19**, **26-31**) were isolated and characterized by ^1H , ^{13}C ^{19}F NMR and FAB mass spectroscopy (see section 19.2.).

The reaction time for complexation varied depending on the substitution pattern of the α -AA. The transformation was complete when the yellow color of the palladated complex disappeared. Reaction time of 20 hrs was generally sufficient for quantitative complexation of an unknown α -AA sample; the isolated yields were almost quantitative.

Spectroscopy



Scheme 9. Conversion of mixtures of α -AAs into diastereomers with the help of the CCDA *cis/trans*-(*S,S*)-17.

For the determination of the magnitudes of the diastereomeric peak separation ($\Delta\delta$) and to demonstrate the applicability of the method a mixture of AAs enantiomers of known enantiomeric ratio – weighed with an accuracy of 0.001 mg – was derivatized with the CCDA *cis/trans*-(*S,S*)-17. A small excess of CCDA was used (1%) to ensure that both enantiomers of the AA under investigation were complexed. The isolated mixture of diastereomers was dissolved in 0.75 ml dichloromethane- d_2 and analyzed by ^{19}F NMR spectroscopy at 470.50 MHz. The results from seven AAs using this method are shown in table 1.

The ^{19}F nucleus for NMR-based chiral analysis of AAs was chosen upon the following rationales : I) ^{19}F is the only naturally occurring isotope of fluorine; II) the ^{19}F shift range is considerably wider when compared with that for ^1H NMR spectra; III) the spectra are simple and independent of the complexity of the AA complex; IV) the spectroscopic sensitivity of ^{19}F NMR is 83% that of ^1H NMR; and V) multiple fluorine are readily incorporated – for example the trifluoromethyl group – and would additionally increase the sensitivity of the method.

Entry	Substrate	Diastereomeric Products	Chemical Shifts (δ , ppm) ^a		Diastereomeric Peak Separation $ \Delta\delta $
			(S,S)	(S,R)	
1	Phegly	19	-64.57	-64.42	0.15
2	Ala	26	-64.27	-64.57	0.30
3	Val	27	-64.42	-64.63	0.21
4	Pro	28	-63.87	-65.33	1.46
5	Phe	29	-64.45	-64.24	0.21
6	Leu	30	-64.42	-64.63	0.21
7	Ile	31	-64.55	-64.78	0.23

^aFluorotrichloromethane was used as internal reference $\delta=0.00$ ppm.

Table 1. ¹⁹F NMR chemical shifts of α -AAs analysis with the help of the CCDA *cis/trans*-(S,S)-17.

All of the AAs tested showed diastereomeric peak separation, allowing clean integration of the resonance signals. As expected, each AA exhibited two signals, one for each diastereomer. The formation of the corresponding *cis*-diastereomers was never detected. Line splitting of the signals were observed and attributed to ³J couplings with the neighboring proton. Figure 3 and 4 show ¹⁹F NMR spectra of a mixture of Pro (Table 1, entry 4) – the best diastereomeric shift obtained – and a mixture of Phegly (Table 1, entry 1) – the worst diastereomeric shift measured – respectively.

Spectroscopy

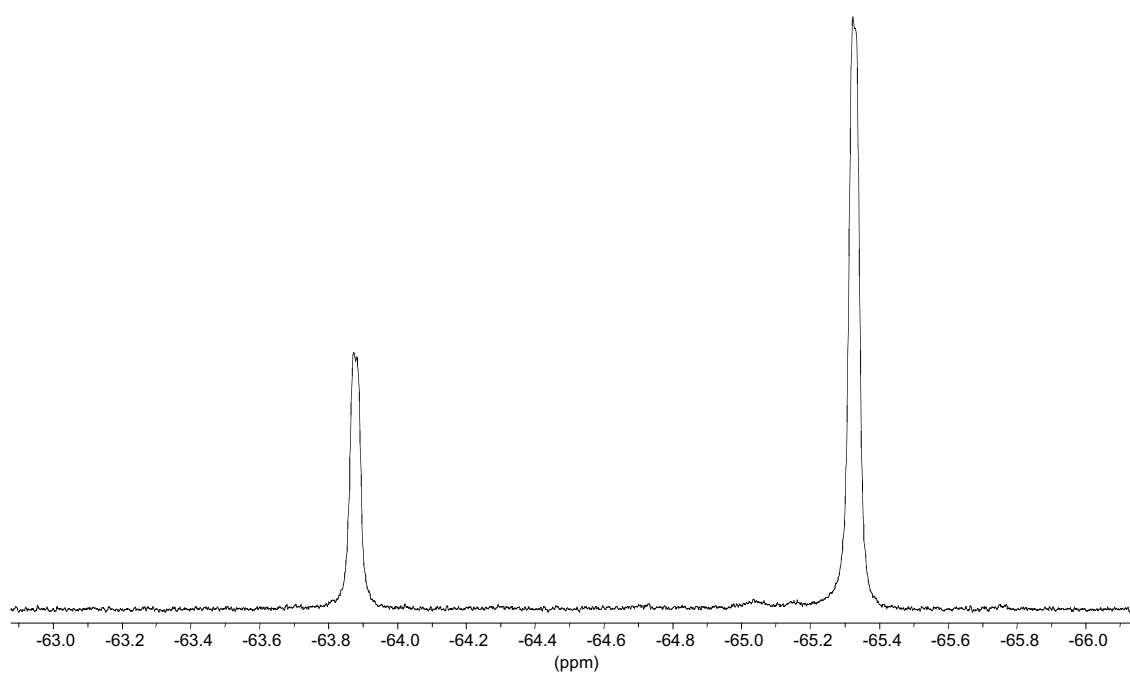


Figure 3. ^{19}F NMR spectrum obtained from an artificial (R)/(S)-Pro mixture after complexation with cis/trans-(S,S)-17.

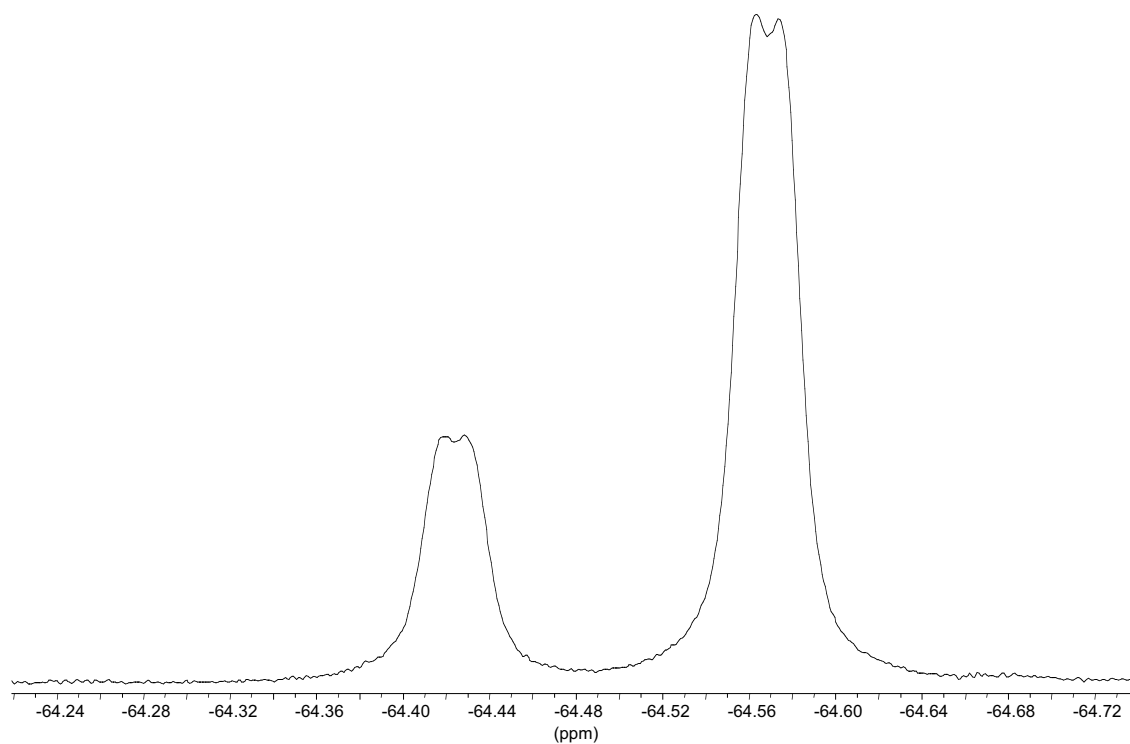


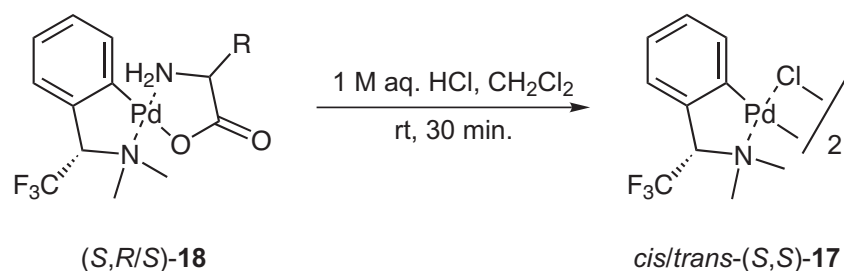
Figure 4. ^{19}F NMR spectrum obtained from an artificial (R)/(S)-Phegly mixture after complexation with cis/trans-(S,S)-17.

In the case of the Pro diastereomers (figure 3), the two signals were integrated and the ratios were used as a basis for the calculation of enantiomeric purities. The calculated ee took into account the purity of *cis/trans*-(*S,S*)-**17** (>99% ee) and the purity of the AA (99% ee). The determined value did not differ more than 1.8% from these calculated.

In order to prove that no racemization of the CCDA *cis/trans*-(*S,S*)-**17** or the amino acidate ligand occurred during derivatization under the mild alkaline conditions used, an (*S*)-Phegly chemical probe – which is well-known to racemize easily in alkaline medium –^[227] was subjected to the derivatization method in presence of deuterated water. In the ¹H NMR spectrum of this (*S*)-Phegly derivative only the peaks for the two amino protons showed reduction in their relative integration values, and all other signals showed no diminution relative to the aromatic protons used as internal reference. A similar experience with a (*S*)-Ala sample yielded the same results.

15. RECOVERY OF THE COORDINATIVE CHIRAL DERIVATIZING AGENT AFTER ANALYSIS

One advantage of the method described herein is that the CCDA *cis/trans*-(*S,S*)-**17** can be recovered quantitatively and with a total retention of the configuration after analysis of mixtures of AAs. The method used was the same as for the preparation of enantiomerically pure CCDA *cis/trans*-(*S,S*)-**17** and *cis/trans*-(*R,R*)-**17** from their separated (*R*)-phenylglycinate diastereomers (*S,R*)-**19** and (*R,R*)-**19**, respectively, and implied treatment with diluted hydrochloric acid in a two layers system with dichloromethane (Scheme 10).



Scheme 10. CCDA recovery after analysis of a mixture of α -AAs.

16. SCOPE AND LIMITATIONS

Di- μ -chloro-bis[*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-2-*C,N*]palladium(II) **17** was easily synthesized in four steps and resolved after derivatization with (*R*)-Phegly. The absolute configuration of the phenylglycinate complex (*R,R*)-**19** was determined by X-ray diffraction allowing thus the absolute configuration determination of *cis/trans*-(*R,R*)-**17** and *cis/trans*-(*S,S*)-**17**. In this work, *cis/trans*-(*S,S*)-**17** was used as CCDA for the *ee* determination of seven natural α -AAs. The magnitude of the diastereomeric peak separation was excellent in all cases, allowing the integration of both resonance signals. The applicability of the method was validated by measuring the *ee* for mixtures of AAs of exactly known composition.

A future development of this analytical method can be envisaged for the determination of enantiomeric ratios in other types of optically active compounds like α -alkylated- α -AAs, β -AAs, 1,2-diamines or dicarboxylic acids. Another possibility is the use of other fluorinated homochiral ligands with different magnetic environment providing possibly better diastereomeric shift separations.

EXPERIMENTAL PART

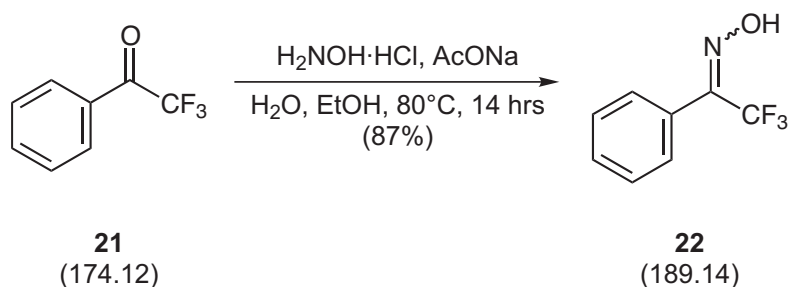
17. GENERAL REMARKS

All chemicals were reagent grade. – Solvents were generally dried and distilled prior to use. – Reactions were monitored by TLC on Merck silica gel 60 F254 (0.2 mm) precoated aluminium foil ; revelations were done according to known methods. – Column chromatography : Merck silica gel 60 (0.040-0.063 mm, 230-400 mesh) or Fluka silica gel 60 (0.040-0.063 mm, 230-400 mesh). – UV/Vis spectra were recorded on a Perkin-Elmer Lambda 40 spectrometer ; λ_{\max} (log ϵ) in nm. – Circular dichroism (CD) spectra were obtained with a Jasco J-715 spectropolarimeter; λ_{\max} ($\Delta\epsilon$) in nm. – NMR : Bruker Avance DPX 360 (^1H : 360.13 MHz, ^{13}C : 90.55 MHz) or Bruker Avance DRX 500 (^1H : 500.13 MHz, ^{13}C : 125.75 MHz and ^{19}F : 470.50 MHz) ; chemical shifts (δ) are given in ppm downfield from the TMS peak or downfield from the CFCl_3 peak for ^{19}F NMR; coupling constants J in Hz. – Mass spectra (MS) were measured on a Vacuum Generators Micromass VG 7070 spectrometer by chemical ionization (CI), electronic ionization (EI), fast atomic bombardment (FAB), all in positive mode ; mass spectra using electrospray ionization technique (positive mode) were recorded on a FT/ICR mass spectrometer Bruker 4.7T BioApex II.

18. SYNTHESIS OF THE HOMOCHIRAL C,N-CYCLOPALLADATED COMPLEX USED AS COORDINATIVE CHIRAL DERIVATIZING AGENT

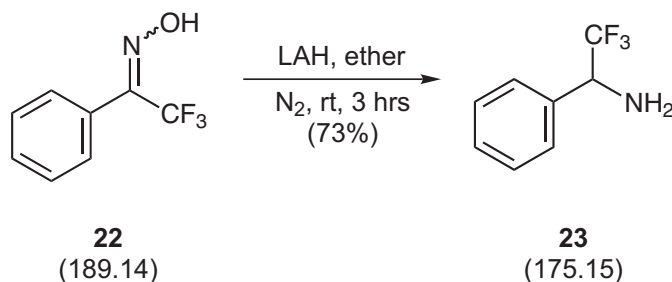
18.1. Synthesis of the Fluorinated Auxiliary Ligand

2,2,2-Trifluoro-1-phenylethan-1-one oxime (22)



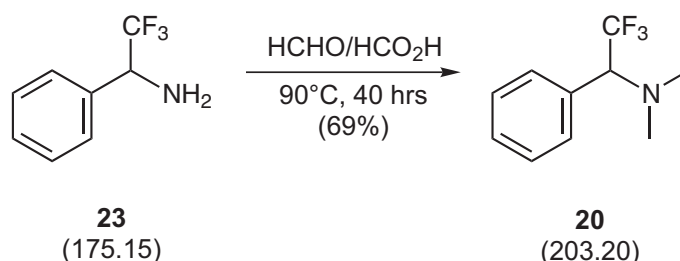
2,2,2-trifluoroacetophenone (**21**, 38.81 g, 223 mmol), hydroxylamine hydrochloride (20.90 g, 301 mmol) and sodium acetate (25.68 g, 313 mmol) were mixed in water (90 ml). Ethanol was added to give a homogeneous solution. The solution was heated at 80°C for 14 hrs allowing a total evaporation of ethanol. The solution was cooled to room temperature. The two layers were separated and the lower crystallized. The product was washed with water to obtain white crystals **22** (36.86 g, 87%).

Mp : 79-81°C. **TLC** : $R_f=0.59$ (silica gel, CH_2Cl_2 , $\text{UV}_{254\text{nm}}$). **^1H NMR** (500.13 MHz, CDCl_3) : δ 7.46-7.53 (m, 5H, Ph), 9.13 (br. s., 1H, OH). **^{13}C NMR** (125.75 MHz, CDCl_3) : δ 117.31-123.86 (q, $^1J(\text{C},\text{F})=275$, CF_3), 125.93 (Ph), 128.59 (Ph), 128.63 (Ph), 130.69 (Ph), 147.38-148.15 (q, $^2J(\text{C},\text{F})=32$, $\text{C}=\text{N}(\text{OH})$). **MS-EI** : m/z 189 ($[\text{M}]^+$, 100%), 127 (27%), 120 ($[\text{M}-\text{CF}_3]^+$, 33%), 91 (24%), 92 (28%), 78 (67%), 77 (74%), 76 (27%), 69 (27%). **MS-CI** (CH_4) : m/z 190 ($[\text{M}+\text{H}]^+$, 100%), 172 (79%), 170 (57%), 101 (13%).

2,2,2-Trifluoro-1-phenylethylamine (23)

To a stirred suspension of LAH (12.43 g, 328 mmol) in dry ether (400 ml) was added dropwise under nitrogen 2,2,2-trifluoro-1-phenylethan-1-one oxime (**22**, 38 g, 201 mmol) in dry ether (400 ml). After stirring for 2 hrs at room temperature, the reaction mixture was treated dropwise with a saturated sodium sulfate solution (100 ml). The solution was stirred for additional 2 hrs and dried over potassium carbonate. The solvent was evaporated at reduced pressure. The residue was distilled *in vacuo* (bp 32°C (1.9 mbar)) to give the desired product **23** as a colorless oil (25.78 g, 73%).

TLC : $R_f=0.50$ (silica gel, CH_2Cl_2 , $\text{UV}_{254\text{nm}}$). **$^1\text{H NMR}$** (500.13 MHz, CDCl_3) : δ 1.77 (br. s., 2H, NH_2), 4.35-4.41 (q, $^3J(\text{H},\text{F})=7.5$, 1H, $\underline{\text{C}}\text{H}(\text{NH}_2)\text{-CF}_3$), 7.36-7.40 (m, 5H, Ph). **$^{13}\text{C NMR}$** (125.75 MHz, CDCl_3) : δ 57.56-58.27 (q, $^2J(\text{C},\text{F})=29.7$, $\underline{\text{C}}\text{H}(\text{NH}_2)\text{-CF}_3$), 122.29-129.00 (q, $^1J(\text{C},\text{F})=281$, $\text{CH}(\text{NH}_2)\text{-}\underline{\text{C}}\text{F}_3$), 127.77 (Ph), 128.64 (Ph), 128.92 (Ph), 135.42 (Ph). **MS-CI** (CH_4) : m/z 176 ($[\text{M}+\text{H}]^+$, 93%), 159 ($[\text{M}-\text{NH}_2]^+$, 75%), 106 ($[\text{M}-\text{CF}_3]^+$, 100%), 98 (28%).

2,2,2-Trifluoro-*N,N*-dimethyl-1-phenylethylamine (20)

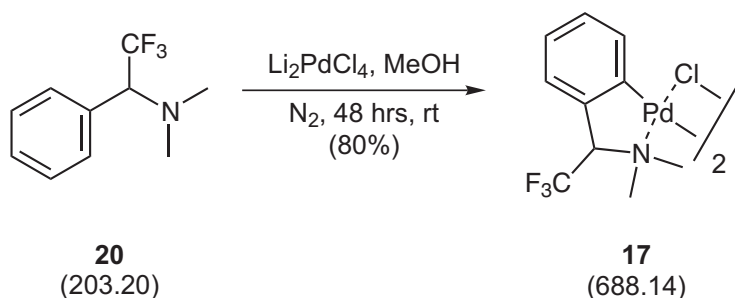
To 2,2,2-trifluoro-1-phenylethylamine (**23**, 10 g, 57 mmol) were added formic acid (9.20 g, 200 mmol) and 37% aq. formaldehyde (11.6 g, 143 mmol). After being

heated for 40 hours at 90°C the solution was cooled and 6 M aq. hydrochloric acid (20 ml) was added. The resulting solution was extracted with ether (3x30 ml). The aqueous layer was made alkaline with 25% aq. sodium hydroxide and was extracted with ether (3x30 ml). The combined extracts were dried over sodium sulfate and the solvent was removed at reduced pressure. The residue was distilled *in vacuo* (bp 34°C (1.9 mbar)) to obtain a colorless oil **20** (8.00 g, 69%).

TLC : $R_f=0.69$ (silica gel, CH_2Cl_2 , $\text{UV}_{254\text{nm}}$). **$^1\text{H NMR}$** (500.13 MHz, CDCl_3) : δ 2.33 (q, $^5J(\text{H},\text{F})=0.9$, 6H, $\text{CH}(\text{N}(\underline{\text{C}}\text{H}_3)_2)\text{-CF}_3$), 3.91-3.96 (q, $^3J(\text{H},\text{F})=8.6$, 1H, $\underline{\text{C}}\text{H}(\text{N}(\text{CH}_3)_2)\text{-CF}_3$), 7.33-7.37 (m, 5H, Ph). **$^{13}\text{C NMR}$** (125.75 MHz, CDCl_3) : δ 43.13 ($\text{CH}(\text{N}(\underline{\text{C}}\text{H}_3)_2)\text{-CF}_3$), 70.46-71.12 (q, $^2J(\text{C},\text{F})=27$, $\underline{\text{C}}\text{H}(\text{N}(\text{CH}_3)_2)\text{-CF}_3$), 122.49-129.27 (q, $^1J(\text{C},\text{F})=284$, $\text{CH}(\text{N}(\text{CH}_3)_2)\text{-CF}_3$), 128.38 (Ph), 128.58 (Ph), 129.34 (Ph), 132.10 (Ph). **MS-EI** : m/z 203 ($[\text{M}]^+$, 14%), 135 (30%), 134 ($[\text{M}-\text{CF}_3]^+$, 100%), 118 (21%), 109 (61%), 91 (52%). **MS-CI** (CH_4) : m/z 204 ($[\text{M}+\text{H}]^+$, 62%), 181 (66%), 131 (100%), 126 (24%).

18.2. Preparation of the Homochiral Palladium Complex

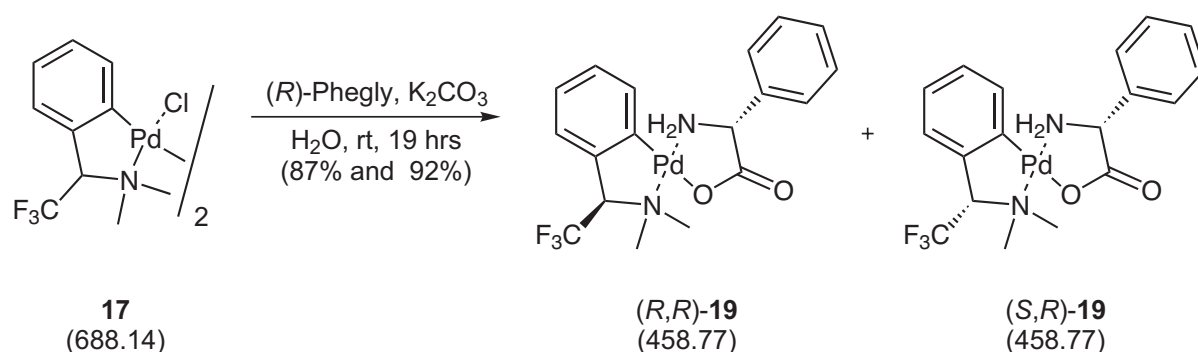
di- μ -Chloro-bis[*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-2-*C,N*]dipalladium(II) (**17**)



Under nitrogen, lithium tetrachloropalladate(II) (1 g, 3.81 mmol) was dissolved in methanol (40 ml). 2,2,2-Trifluoro-*N,N*-dimethyl-1-phenylethan-1-amine (**20**, 3.1 g, 15.3 mmol) in methanol (20 ml) was added. The solution was stirred at room temperature for 48 hrs. The yellow precipitate was then filtered. The desired product **17** was obtained as yellow crystals (1.05 g, 80%).

Mp : 200°C (decomp.). **¹H NMR** (500.13 MHz, CDCl₃) : δ 2.93-2.97 (m, 6H, CH(N(CH₃)₂)-CF₃), 3.11-3.13 (m, 6H, CH(N(CH₃)₂)-CF₃), 4.14-4.23 (m, 2H, CH(N(CH₃)₂)-CF₃), 6.95-7.05 (m, 6H, Ph), 7.17-7.23 (m, 2H, Ph). **¹³C NMR** (125.75 MHz, CDCl₃) : δ 48.66 (CH(N(CH₃)₂)-CF₃), 49.06-49.11 (m, CH(N(CH₃)₂)-CF₃), 54.28 (m, CH(N(CH₃)₂)-CF₃), 54.55 (m, CH(N(CH₃)₂)-CF₃), 78.74-79.52 (m, CH(N(CH₃)₂)-CF₃), 120.22-126.99 (q, ¹J(C,F)=284, CH(N(CH₃)₂)-CF₃), 124.86 (Ph), 124.96 (Ph), 127.01 (Ph), 127.03 (Ph), 133.17 (Ph), 133.20 (Ph), 133.68 (Ph), 133.72 (Ph), 141.63 (Ph), 141.73 (Ph), 143.15 (Ph), 143.27 (Ph). **¹⁹F NMR** (470.50 MHz, CDCl₃) : δ -64.98 - -64.81 (m). **MS-ESI** (MeCN) : *m/z* 994.94 ([³/₂M-Cl+H]⁺), 735.02, 693.99 ([M-Cl+CH₃CN+H]⁺), 652.96 ([M-Cl+H]⁺). *Calcd average mass for [M-Cl+H]⁺* : 652.94. **MS-FAB** (NOBA) : *m/z* 652.7 ([M-Cl]⁺). **UV/Vis** (CH₂Cl₂) : 345 (3.40).

Diastereomeric (*R*)-Phenylglycinate Complexes (*R,R*)-19 and (*S,R*)-19 Synthesis and Separation



(*R*)-Phegly (615 mg, 4.07 mmol) and potassium carbonate (562 mg, 4.07 mmol) were dissolved in water (40 ml). **17** (700 mg, 1.02 mmol) was added and the mixture was stirred for 19 hrs at room temperature. Then, water (200 ml) was added and the resulting solution was extracted with dichloromethane (4x150 ml). The organic layer was dried over sodium sulfate and the solvent was removed at reduced pressure to give the desired mixture of diastereomers as a white solid (922 mg, 99%). The two diastereomers were separated by flash column chromatography (silica gel, ethyl acetate : methanol (15 : 1), then (1 : 1)). The desired fractions were evaporated to dryness. The products were isolated by addition of *n*-hexane to the concentrated solution of the complex in dichloromethane to give the diastereomer (*R,R*)-**19** as a

white solid (399 mg, 87%), and the diastereomer (*S,R*)-**19** as a white solid (425 mg, 92%).

Diastereomer (R,R)-19 :

Mp : 180°C (decomp.). **TLC** : $R_f=0.53$ (silica gel, ethyl acetate : methanol (9 : 1), UV_{254nm}). **1H NMR** (500.13 MHz, $CDCl_3$) : δ 2.70-2.72 (m, 1H, \underline{NH}_2), 3.02 (s, 3H, $CH(N(\underline{CH}_3)_2)-CF_3$), 3.18 (s, 3H, $CH(N(\underline{CH}_3)_2)-CF_3$), 4.34-4.38 (q, $^3J(H,F)=7.2$, 1H, $\underline{CH}(N(\underline{CH}_3)_2)-CF_3$), 4.59-4.62 (m, 1H, \underline{NH}_2), 4.74-4.76 (m, 1H, $\underline{CH}-Ph(\text{Phegly})$), 6.62-6.64 (m, 1H, Ph), 6.96-7.00 (m, 1H, Ph), 7.04-7.07 (m, 1H, Ph), 7.12-7.13 (m, 1H, Ph), 7.32-7.39 (m, 3H, Ph(Phegly)), 7.69-7.71 (m, 2H, Ph(Phegly)). **^{13}C NMR** (125.75 MHz, $CDCl_3$) : δ 47.45 ($CH(N(\underline{CH}_3)_2)-CF_3$), 53.41 ($CH(N(\underline{CH}_3)_2)-CF_3$), 63.91 ($\underline{CH}-Ph$), 77.87-78.50 (q, $^2J(C,F)=27$, $\underline{CH}(N(\underline{CH}_3)_2)-CF_3$), 120.57-127.36 (q, $^1J(C,F)=285$, $CH(N(\underline{CH}_3)_2)-\underline{CF}_3$), 124.82 (Ph), 125.24 (Ph), 127.05 (Ph), 127.47 (Ph(Phegly)), 128.68 (Ph(Phegly)), 129.23 (Ph(Phegly)), 131.82 (Ph), 139.13 (C_{quat}), 142.90 (C_{quat}), 145.14 (C_{quat}), 178.29 (C=O). **^{19}F NMR** (470.50 MHz, $CDCl_3$) : δ -64.45. **MS-FAB** (NOBA) : m/z 767.9 ($[2M-\text{Phegly}]^+$), 458.9 ($[M]^+$), 413.9, 307.9 ($[M-\text{Phegly}]^+$).

Diastereomer (S,R)-19 :

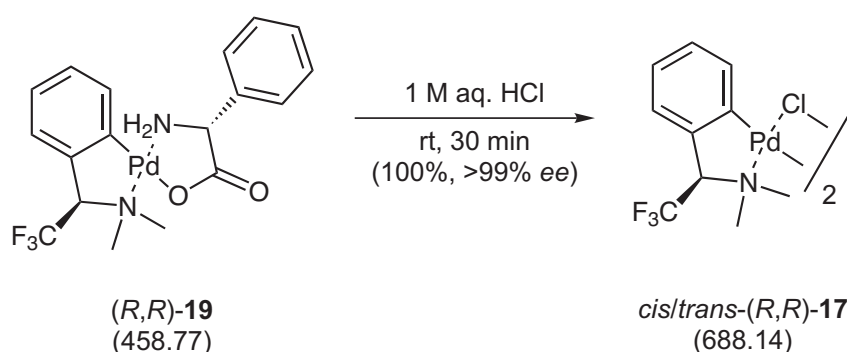
Mp : 80°C (decomp.). **TLC** : $R_f=0.25$ (silica gel, ethyl acetate : methanol (9 : 1), UV_{254nm}). **1H NMR** (500.13 MHz, $CDCl_3$) : δ 2.79-2.81 (m, 1H, \underline{NH}_2), 3.02-3.05 (m, 6H, $CH(N(\underline{CH}_3)_2)-CF_3$), 4.08-4.12 (q, $^3J(H,F)=6.9$, 1H, $\underline{CH}(N(\underline{CH}_3)_2)-CF_3$), 4.67-4.70 (m, 1H, \underline{NH}_2), 4.77-4.79 (m, 1H, $\underline{CH}-Ph$), 6.64-6.66 (m, 1H, Ph), 6.96-6.99 (m, 1H, Ph), 7.04-7.07 (m, 1H, Ph), 7.11-7.12 (m, 1H, Ph), 7.33-7.40 (m, 3H, Ph(Phegly)), 7.82-7.84 (m, 2H, Ph(Phegly)). **^{13}C NMR** (500.13 MHz, $CDCl_3$) : δ 47.98 ($CH(N(\underline{CH}_3)_2)-CF_3$), 53.44 ($CH(N(\underline{CH}_3)_2)-CF_3$), 64.12 ($\underline{CH}-Ph$), 78.14-78.78 (q, $^2J(C,F)=27$, $\underline{CH}(N(\underline{CH}_3)_2)-CF_3$), 120.41-127.18 (q, $^1J(C,F)=283$, $CH(N(\underline{CH}_3)_2)-\underline{CF}_3$), 124.84 (Ph), 125.53 (Ph), 127.06 (Ph), 127.36 (Ph(Phegly)), 128.75 (Ph(Phegly)), 129.18 (Ph(Phegly)), 131.85 (Ph), 138.59 (C_{quat}), 142.97 (C_{quat}), 145.18 (C_{quat}), 178.32 (C=O). **^{19}F NMR** (470.50 MHz, $CDCl_3$) : δ -64.96. **MS-FAB** (NOBA) : m/z 768.0 ($[2M-\text{Phegly}]^+$), 458.9 ($[M]^+$), 415.9, 307.9 ($[M-\text{Phegly}]^+$).

X-Ray Crystal Structure Analysis of $\{[(R)\text{-Phenylglycinato-}N,O][(\text{R})\text{-}N,N\text{-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-C,N}]\text{palladium(II)}\}$ ((R,R) -19)

Suitable crystals of (R,R) -19 were grown by diffusion of *n*-hexane into an ethyl acetate solution giving pale yellow blocks. Intensity data were collected at 153K on a Stoe Image Plate Diffraction system using MoK α graphite monochromated radiation. Image plate distance 70mm, ϕ oscillation scans 0 - 200°, step $\Delta\phi = 1.0^\circ$, 2θ range 3.27 – 52.1°, $d_{\text{max}} - d_{\text{min}} = 12.45 - 0.81 \text{ \AA}$. The structure was solved by direct methods using the programme SHELXS-97.^[238] The refinement and all further calculations were carried out using SHELXL-97.^[239] The water H-atoms were located from Fourier difference maps and refined with $U_{\text{eq}} = 1.5 \times U_{\text{eq}}(\text{Ow})$. The remainder of the H-atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. The non-H atoms were refined anisotropically, using weighed full-matrix least-squares on F^2 . An empirical absorption correction was applied using DIFABS3, Transmission factors $T_{\text{min}}/T_{\text{max}} = 0.356/0.773$.

There is two independent molecules per asymmetric unit together with one water molecule. The atomic coordinates correspond to the absolute structure of the molecules in the crystal. Atoms C7, C12 (Molecule A) and atoms C27, C32 (Molecule B) all have the (R) configuration. The bond lengths and angles are normal within experimental error.

di- μ -Chloro-bis $[(R)\text{-}N,N\text{-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-2-C,N}]\text{dipalladium(II)}$ (*cis/trans*- (R,R) -17)

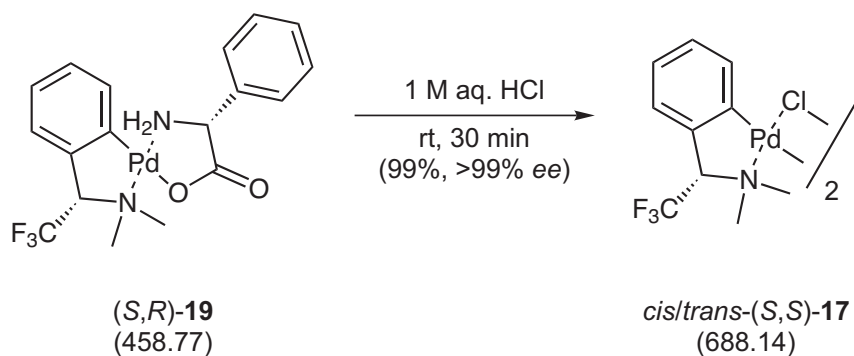


A solution of (R,R) -19 (352 mg, 0.77 mmol) in dichloromethane (35 ml) was vigorously shaken with 1 M aq. hydrochloric acid (35 ml) for 30 min. The organic layer was separated and dried over sodium sulfate and then evaporated to dryness.

The product *cis/trans*-(*R,R*)-**17** was obtained as a yellow powder (264 mg, 100%, >99% ee according to the ^{19}F NMR data for the (*R*)-phenylglycinate derivative (*R,R*)-**19**).

Mp : 200°C (decomp.). $^1\text{H NMR}$ (500.13 MHz, CDCl_3 , two sets of signals from *cis/trans* isomers) : δ 2.92 and 2.97 (2s, 3H, $\text{CH}(\text{N}(\underline{\text{C}}\text{H}_3)_2)\text{-CF}_3$), 3.11 and 3.13 (2s, 3H, $\text{CH}(\text{N}(\underline{\text{C}}\text{H}_3)_2)\text{-CF}_3$), 4.17-4.21 (q, $^3J(\text{H},\text{F})=6.8$, 1H, $\underline{\text{C}}\text{H}(\text{N}(\text{CH}_3)_2)\text{-CF}_3$), 6.95-7.05 (m, 3H, Ph), 7.13-7.23 (m, 1H, Ph). $^{13}\text{C NMR}$ (125.75 MHz, CDCl_3 , two sets of signals from *cis/trans* isomers) : δ 48.66 and 49.03 ($\text{CH}(\text{N}(\underline{\text{C}}\text{H}_3)_2)\text{-CF}_3$), 54.30 and 54.50 ($\text{CH}(\text{N}(\underline{\text{C}}\text{H}_3)_2)\text{-CF}_3$), 78.17-79.55 (2q, $\underline{\text{C}}\text{H}(\text{N}(\text{CH}_3)_2)\text{-CF}_3$), 120.22-127.00 (q, $^1J(\text{C},\text{F})=284$ Hz, $\text{CH}(\text{N}(\text{CH}_3)_2)\text{-CF}_3$), 124.85 (Ph), 124.96 (Ph), 126.99 (Ph), 127.04 (Ph), 133.20 (Ph), 133.68 (Ph), 141.63 (Ph), 141.73 (Ph), 143.14 (Ph), 143.25 (Ph). $^{19}\text{F NMR}$ (470.50 MHz, CDCl_3) : δ -64.86 - -64.82. **UV/Vis** (CH_2Cl_2) : 345 (3.35). **CD** (CH_2Cl_2) : 317 (-0.86), 349 (+0.75), 384 (-0.22). **CHN** : Anal. calcd for $\text{C}_{20}\text{H}_{22}\text{Cl}_2\text{F}_6\text{N}_2\text{Pd}_2$: C, 34.91; H, 3.22; N, 4.07. Found: C, 34.87; H, 3.35; N, 4.03.

di- μ -Chloro-bis[(*S*)-*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-2-*C,N*]dipalladium(II) (*cis/trans*-(*S,S*)-17**)**



A solution of (*S,R*)-**19** (404 mg, 0.88 mmol) in dichloromethane (35 ml) was vigorously shaken with 1 M aq. hydrochloric acid (35 ml) for 30 min. The organic layer was separated and dried over sodium sulfate and then evaporated to dryness. The product *cis/trans*-(*S,S*)-**17** was obtained as a yellow powder (299 mg, 99%, >99% ee according to the ^{19}F NMR data for the (*R*)-phenylglycinate derivative (*S,R*)-**19**).

Mp : 200°C (decomp.). **¹H NMR** (500.13 MHz, CDCl₃, two sets of signals from *cis/trans* isomers) : δ 2.92 and 2.97 (2s, 3H, CH(N(CH₃)₂)-CF₃), 3.11 and 3.13 (2s, 3H, CH(N(CH₃)₂)-CF₃), 4.17-4.21 (q, ³J(H,F)=6.8 Hz, 1H, CH(N(CH₃)₂)-CF₃), 6.95-7.05 (m, 3H, Ph), 7.13-7.23 (m, 1H, Ph). **¹³C NMR** (125.75 MHz, CDCl₃, two sets of signals from *cis/trans* isomers) : δ 48.64 and 49.01 (CH(N(CH₃)₂)-CF₃), 54.28 and 54.48 (CH(N(CH₃)₂)-CF₃), 78.69-79.54 (2q, CH(N(CH₃)₂)-CF₃), 120.19-126.97 (q, ¹J(C,F)=284, CH(N(CH₃)₂)-CF₃), 124.83 (Ph), 124.94 (Ph), 126.97 (Ph), 127.02 (Ph), 133.18 (Ph), 133.65 (Ph), 141.61 (Ph), 141.71 (Ph), 143.13 (Ph), 143.23 (Ph). **¹⁹F NMR** (470.50 MHz, CDCl₃) : δ -64.85 - -64.83. **UV/Vis** (CH₂Cl₂) : 345 (3.37). **CD** (CH₂Cl₂) : 318 (+0.93), 351 (-0.66), 386 (+0.22). **CHN** : *Anal. Calcd for* C₂₀H₂₂Cl₂F₆N₂Pd₂: C, 34.91; H, 3.22; N, 4.07. *Found*: C, 34.80; H, 3.37; N, 4.12.

19. SYNTHESIS AND ANALYSIS OF AMINO ACIDS DIASTEREOMERIC MIXTURES

19.1. Procedure for Enantiomeric Purity Determination

AA (0.05 mmol) and potassium carbonate (6.91 mg, 0.05 mmol) were dissolved in water (2 ml). *cis/trans*-(*S,S*)-**17** (17.4 mg, 0.025 mmol) was added and the mixture was stirred for 20 hrs at room temperature. Then, water (6 ml) was added and the resulting solution was extracted with dichloromethane (4x10 ml). The organic layer was dried over sodium sulfate and the solvent was removed at reduced pressure. The products were dissolved in 0.75 ml dichloromethane-*d*₂, transferred to a NMR tube and measured at room temperature.

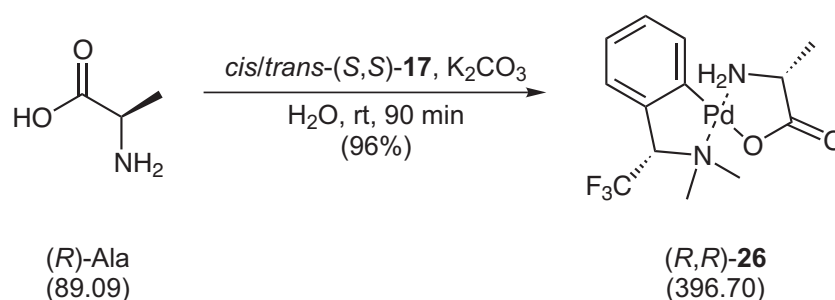
19.2. Preparation of the Amino Acids Diastereomeric Complexes

General Procedure for the Synthesis of {[Amino acidato-*N,O*][(S)-*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C,N*]palladium(II)}

AA (0.14 mmol) and potassium carbonate (21 mg, 0.14 mmol) were dissolved in water (2 ml). *cis/trans*-(*S,S*)-**17** (25 mg, 0.036 mmol) was added and the mixture was stirred for 20 hrs at room temperature. Then, water (6 ml) was added and the resulting solution was extracted with dichloromethane (4x10 ml). The organic layer was dried over sodium sulfate and the solvent removed at reduced pressure. The

desired product was isolated by addition of *n*-hexane to the concentrated solution of the complex in dichloromethane and removal of the solvents at reduced pressure.

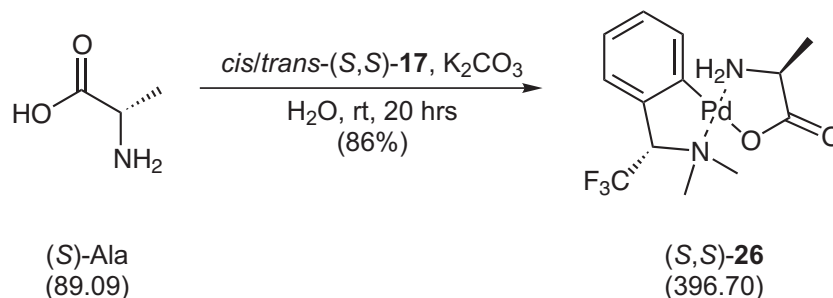
{[(*R*)-Alaninato-*N,O*][(*S*)-*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C,N*]palladium(II)} ((*S,R*)-26)



A slight modification of the generale procedure (use of 20 mg *cis/trans*-(*S,S*)-**17** and adapted amounts for the other reactants, for a reaction time of 90 min.) was followed for the synthesis of the desired compound (*S,R*)-**26** as a white solid (22 mg, 96%).

Mp : 160°C (decomp.) **TLC** : $R_f=0.15$ (silica gel, ethyl acetate : methanol (9 : 1), UV_{254nm}). **1H NMR** (500.13 MHz, $CDCl_3$) : δ 1.62-1.64 (d, $^3J(H,H)=7.0$, 3H, $\underline{CH-CH_3}$), 2.96 (d, $^4J(H,H)=1.3$, 3H, $\underline{CH(N(CH_3)_2)-CF_3}$), 3.01-3.04 (m, 4H, $\underline{CH(N(CH_3)_2)-CF_3}$ and $\underline{NH_2}$), 3.76-3.82 (m, 1H, $\underline{CH-CH_3}$), 4.11-4.15 (q, $^3J(H,F)=7.0$, $\underline{CH(N(CH_3)_2)-CF_3}$), 4.36-4.39 (m, 1H, $\underline{NH_2}$), 6.80-6.82 (m, 1H, Ph), 7.01-7.10 (m, 3H, Ph). **^{13}C NMR** (125.75 MHz, $CDCl_3$) : δ 47.88 ($\underline{CH(N(CH_3)_2)-CF_3}$), 53.50 ($\underline{CH(N(CH_3)_2)-CF_3}$), 56.35 ($\underline{CH-CH_3}$), 78.15-78.79 (q, $^2J(C,F)=26.9$, $\underline{CH(N(CH_3)_2)-CF_3}$), 120.83-127.63 (q, $^1J(C,F)=285$, $\underline{CH(N(CH_3)_2)-CF_3}$), 125.11 (Ph), 125.65 (Ph), 127.37 (Ph), 132.62 (Ph), 143.25 (Ph), 145.59 (Ph), 181.42 (C=O). **^{19}F NMR** (470.50 MHz, $CDCl_3$) : δ -64.61. **MS-FAB** (NOBA): m/z 703.8 ($[2M-Ala]^+$), 396.9 ($[M]^+$), 306.9 ($[M-Ala]^+$).

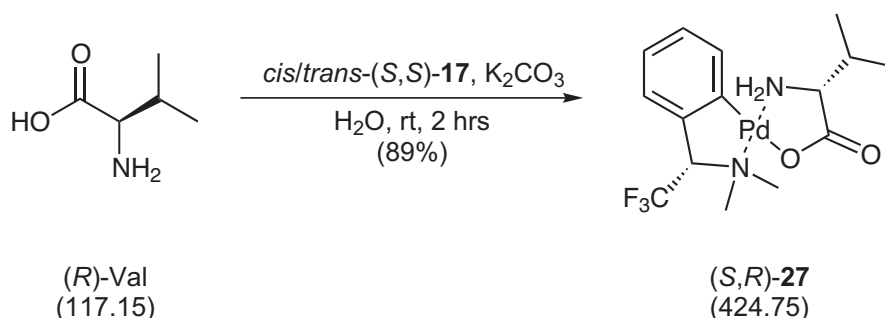
{[(S)-Alaninato-N,O][[(S)-N,N-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-C,N]palladium(II)]} ((S,S)-26)



The general procedure was followed for the synthesis of the desired compound (S,S)-26 as a white solid (25 mg, 86%).

Mp : 160°C (decomp.). **TLC** : $R_f=0.10$ (silica gel, ethyl acetate : methanol (9 : 1), UV_{254nm}). **1H NMR** (500.13 MHz, $CDCl_3$) : δ 1.59 (d, $^3J(H,H)=7.1$, 3H, CH-CH₃), 2.96 (s, 3H, CH(N(CH₃)₂)-CF₃), 3.00-3.03 (m, 1H, NH₂), 3.07 (s, 3H, CH(N(CH₃)₂)-CF₃), 3.77-3.83 (m, 1H, CH-CH₃), 4.18-4.24 (m, 2H, NH₂ and CH(N(CH₃)₂)-CF₃), 6.77-6.78 (m, 1H, Ph), 7.01-7.11 (m, 3H, Ph). **^{13}C NMR** (125.75 MHz, $CDCl_3$) : δ 46.90 (CH(N(CH₃)₂)-CF₃), 52.59 (CH(N(CH₃)₂)-CF₃), 55.34 (CH-CH₃), 77.20-77.84 (q, $^2J(C,F)=27$, CH(N(CH₃)₂)-CF₃), 120.06-126.86 (q, $^1J(C,F)=285$, CH(N(CH₃)₂)-CF₃), 124.28 (Ph), 124.72 (Ph), 126.53 (Ph), 131.68 (Ph), 142.40 (Ph), 144.78 (Ph), 180.31 (C=O). **^{19}F NMR** (470.50 MHz, $CDCl_3$) : δ -64.46. **MS-FAB** (NOBA) : m/z 705.8 ([2M-Ala]⁺), 396.9 ([M]⁺), 307.8 ([M-Ala]⁺).

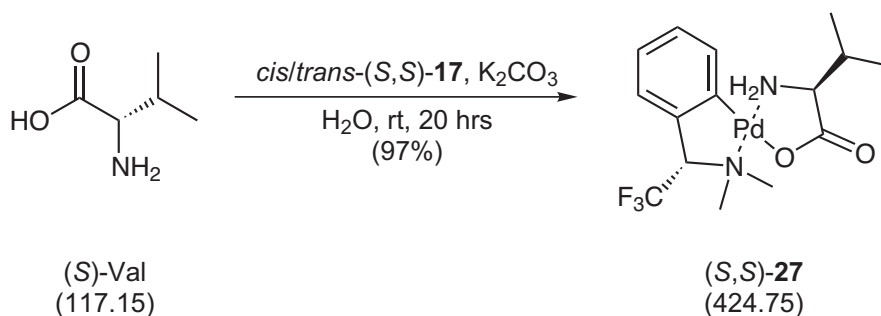
{[(*R*)-Valinato-*N*,*O*][(*S*)-*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C,N*]palladium(II)} ((*S,R*)-27)



A slight modification of the generale procedure (use of 20 mg *cis/trans*-(*S,S*)-17 and adapted amounts for the other reactants, for a reaction time of 2 hours) was followed for the synthesis of the desired compound (*S,R*)-27 as a white solid (22 mg, 89%).

Mp : 125°C (decomp.). **TLC** : $R_f=0.17$ (silica gel, ethyl acetate : methanol (9 : 1), UV_{254nm}). **1H NMR** (500.13 MHz, $CDCl_3$) : δ 1.18-1.19 (d, $^3J(H,H)=6.9$, 3H, $CH-CH(CH_3)_2$), 1.21-1.22 (d, $^3J(H,H)=7.0$, 3H, $CH-CH(CH_3)_2$), 2.45-2.51 (m, 1H, $CH-CH(CH_3)_2$), 2.57-2.59 (m, 1H, NH_2), 2.96 (d, $^4J(H,H)=1.5$, 3H, $CH(N(CH_3)_2)-CF_3$), 3.01 (s, 3H, $CH(N(CH_3)_2)-CF_3$), 3.53-3.55 (m, 1H, $CH-CH(CH_3)_2$), 3.99-4.03 (q, $^3J(H,F)=7.1$, $CH(N(CH_3)_2)-CF_3$), 4.32-4.36 (m, 1H, NH_2), 6.76-6.81 (m, 1H, Ph), 7.03-7.11 (m, 3H, Ph). **^{13}C NMR** (125.75 MHz, $CDCl_3$) : δ 18.13 ($CH-CH(CH_3)_2$), 19.92 ($CH-CH(CH_3)_2$), 31.87 ($CH-CH(CH_3)_2$), 47.96 ($CH(N(CH_3)_2)-CF_3$), 53.36 ($CH(N(CH_3)_2)-CF_3$), 65.75 ($CH-CH(CH_3)_2$), 77.91-78.54 (q, $^2J(C,F)=26.5$, $CH(N(CH_3)_2)-CF_3$), 120.83-127.62 (q, $^1J(C,F)=284$, $CH(N(CH_3)_2)-CF_3$), 125.23 (Ph), 125.69 (Ph), 127.38 (Ph), 132.13 (Ph), 143.36 (Ph), 145.67 (Ph), 179.78 (C=O). **^{19}F NMR** (470.50 MHz, $CDCl_3$) : δ -64.57. **MS-FAB** (NOBA): m/z 734.0 ($[2M-Val]^+$), 425.0 ($[M]^+$), 382.0, 307.0 ($[M-Val]^+$).

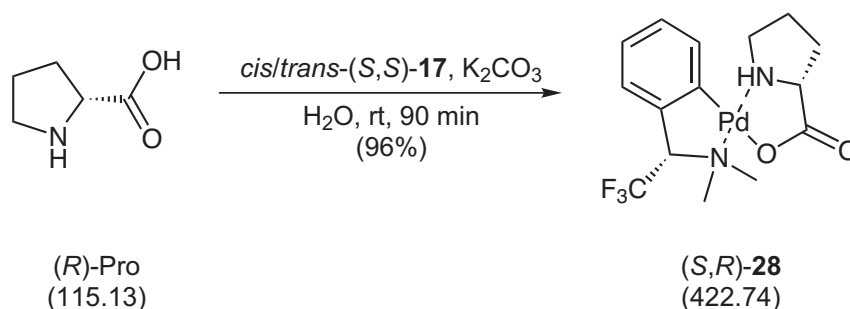
{[(S)-Valinato-N,O][[(S)-N,N-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-C,N]palladium(II)]} ((S,S)-27)



The general procedure was followed for the synthesis of the desired compound (S,S)-27 as a white solid (30 mg, 97%).

Mp : 90°C (decomp.). **TLC** : $R_f=0.41$ (silica gel, ethyl acetate : methanol (9 : 1), UV_{254nm}). **1H NMR** (500.13 MHz, $CDCl_3$) : δ 1.11-1.15 (m, 6H, $CH-CH(CH_3)_2$), 2.43-2.51 (m, 2H, $CH-CH(CH_3)_2$ and NH_2), 2.98 (d, $^4J(H,H)=1.6$, $CH(N(CH_3)_2)-CF_3$), 3.09 (s, 3H, $CH(N(CH_3)_2)-CF_3$), 3.50-3.53 (m, 1H, $CH-CH(CH_3)_2$), 3.83-3.86 (m, 1H, NH_2), 4.25-4.30 (q, $^3J(H,F)=7.1$, $CH(N(CH_3)_2)-CF_3$), 6.71-6.75 (m, 1H, Ph), 7.05-7.09 (m, 2H, Ph), 7.12-7.15 (m, 1H, Ph). **^{13}C NMR** (125.75 MHz, $CDCl_3$) : δ 17.72 ($CH-CH(CH_3)_2$), 19.85 ($CH-CH(CH_3)_2$), 31.71 ($CH-CH(CH_3)_2$), 47.87 ($CH(N(CH_3)_2)-CF_3$), 53.73 ($CH(N(CH_3)_2)-CF_3$), 65.59 ($CH-CH(CH_3)_2$), 78.32-78.96 (q, $^2J(C,F)=26.7$, $CH(N(CH_3)_2)-CF_3$), 120.86-127.65 (q, $^1J(C,F)=284$, $CH(N(CH_3)_2)-CF_3$), 125.14 (Ph), 125.69 (Ph), 127.46 (Ph), 132.10 (Ph), 143.31 (Ph), 145.86 (Ph), 179.59 (C=O). **^{19}F NMR** (470.50 MHz, $CDCl_3$) : δ -64.61. **MS-FAB** (NOBA): m/z 733.9 ($[2M-Val]^+$), 425.0 ($[M]^+$), 378.9, 307.9 ($[M-Val]^+$).

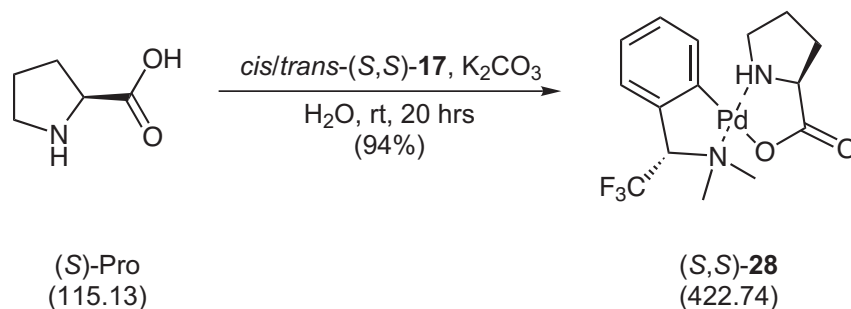
{[(*R*)-Prolinato-*N,O*][(*S*)-*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C,N*]palladium(II)} ((*S,R*)-28)



A slight modification of the generale procedure (use of 20 mg *cis/trans*-(*S,S*)-17 and adapted amounts for the other reactants, for a reaction time of 90 min.) was followed for the synthesis of the desired compound (*S,R*)-28 as a white solid (24 mg, 96%).

Mp : 180°C (decomp.). **TLC** : $R_f=0.12$ (silica gel, ethyl acetate : methanol (9 : 1), UV_{254nm}). **1H NMR** (500.13 MHz, CD_2Cl_2) : δ 1.68-1.74 (m, 1H, $CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 1.92-1.99 ($CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 2.15-2.20 (m, 2H, $CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 2.91 (s, 3H, $CH(N(CH_3)_2)-CF_3$), 2.93-2.94 (m, 3H, $CH(N(CH_3)_2)-CF_3$), 3.21-3.34 (m, 2H, $CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 4.01-4.08 (m, 2H, $CH_2(NH)-CH_2-CH_2-CH(CO_2)$ and $CH(N(CH_3)_2)-CF_3$), 4.34-4.38 (m, 1H, NH), 6.98-7.01 (m, 1H, Ph), 7.03-7.06 (m, 2H, Ph), 7.10-7.12 (m, 1H, Ph). **^{13}C NMR** (125.75 MHz, CD_2Cl_2) : δ 25.79 ($CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 30.56 ($CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 48.31 ($CH(N(CH_3)_2)-CF_3$), 53.59 ($CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 53.91 ($CH(N(CH_3)_2)-CF_3$), 65.93 ($CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 78.83-79.47 (q, $^2J(C,F)=26.9$, $CH(N(CH_3)_2)-CF_3$), 120.75-127.50 (q, $^1J(C,F)=283$ Hz, $CH(N(CH_3)_2)-CF_3$), 124.61 (Ph), 125.87 (Ph), 127.27 (Ph), 133.19 (Ph), 143.41 (Ph), 147.79 (Ph), 180.76 (C=O). **^{19}F NMR** (470.50 MHz, CD_2Cl_2) : δ -67.26. **MS-FAB** (NOBA) : m/z 843.8 ($[2M]^+$), 731.8 ($[2M-Pro]^+$), 422.9 ($[M]^+$), 376.9, 306.9 ($[M-Pro]^+$).

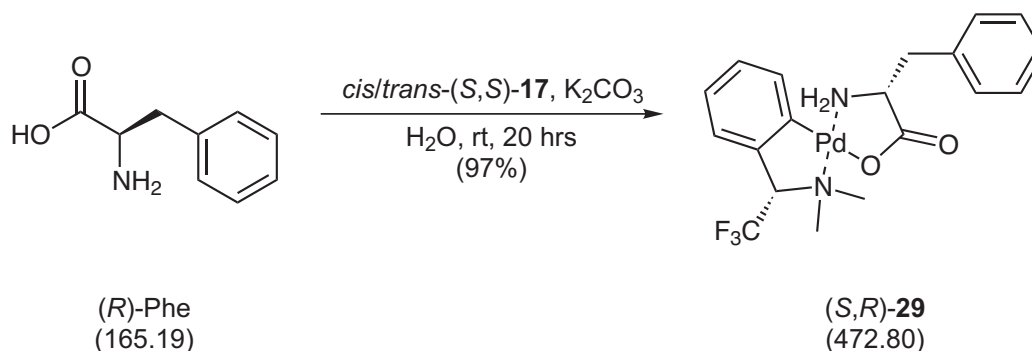
[[*(S)*-Prolinato-*N,O*][*(S)*-*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C,N*]palladium(II)] (*(S,S)*-28)



The general procedure was followed for the synthesis of the desired compound (*(S,S)*-28 as a white solid (29 mg, 94%).

Mp : 118°C (decomp.). **TLC** : $R_f=0.20$ (silica gel, ethyl acetate : methanol (9 : 1), UV_{254nm}). **1H NMR** (500.13 MHz, CD_2Cl_2) : δ 1.66-1.74 (m, 1H, $CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 1.87-1.94 (m, 1H, $CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 2.08-2.23 (m, 2H, $CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 2.89-2.90 (m, 3H, $CH(N(CH_3)_2)-CF_3$), 3.11 (s, 3H, $CH(N(CH_3)_2)-CF_3$), 3.20-3.27 (m, 1H, $CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 3.34-3.40 (m, 1H, $CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 4.04-4.09 (m, 1H, $CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 4.38-4.43 (m, 2H, $CH(N(CH_3)_2)-CF_3$ and NH), 6.97-7.01 (m, 1H, Ph), 7.03-7.08 (m, 2H, Ph), 7.11-7.14 (m, 1H, Ph). **^{13}C NMR** (125.75 MHz, CD_2Cl_2) : δ 25.44 ($CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 30.23 ($CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 47.42 ($CH(N(CH_3)_2)-CF_3$), 53.08 ($CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 53.13 ($CH(N(CH_3)_2)-CF_3$), 66.08 ($CH_2(NH)-CH_2-CH_2-CH(CO_2)$), 77.77-78.40 (q, $^2J(C,F)=26$, $CH(N(CH_3)_2)-CF_3$), 121.18-127.99 (q, $^1J(C,F)=285$, $CH(N(CH_3)_2)-CF_3$), 124.70 (Ph), 125.18 (Ph), 127.11 (Ph), 133.24 (Ph), 143.29 (Ph), 147.08 (Ph), 180.32 (C=O). **^{19}F NMR** (470.50 MHz, CD_2Cl_2) : δ -63.87. **MS-FAB** (NOBA): m/z 731.2 ($[2M-Pro]^+$), 422.1 ($[M]^+$), 378.1, 307.0 ($[M-Pro]^+$).

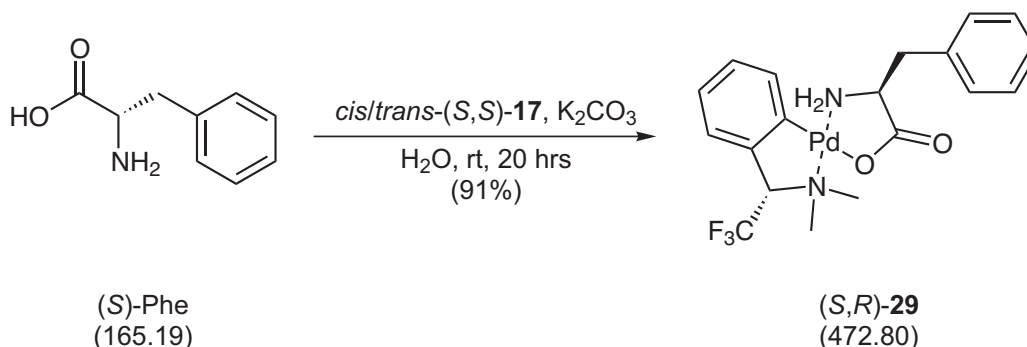
{[(*R*)-Phenylalaninato-*N,O*][(*S*)-*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C,M*]palladium(II)} ((*S,R*)-29)



A slight modification of the generale procedure (use of 15 mg *cis/trans*-(*S,S*)-**17** and adapted amounts for the other reactants) was followed for the synthesis of the desired compound (*S,R*)-**29** as a white solid (20 mg, 97%).

Mp : 125°C (decomp.). **TLC** : $R_f=0.19$ (silica gel, ethyl acetate : methanol (9 : 1), UV_{254nm}). **1H NMR** (360.13 MHz, CD_2Cl_2) : δ 2.67-2.69 (m, 1H, \underline{NH}_2), 2.90 (s, 3H, $\underline{CH(N(CH_3)_2)-CF_3}$), 2.94 (s, 3H, $\underline{CH(N(CH_3)_2)-CF_3}$), 3.26-3.33 (m, 1H, $\underline{CH-CH_2-Ph(Phe)}$), 3.42-3.47 (m, 1H, $\underline{CH-CH_2-Ph(Phe)}$), 3.75-3.81 (m, 1H, $\underline{CH-CH_2-Ph(Phe)}$), 3.94-4.00 (q, $^3J(H,F)=7.1$, $\underline{CH(N(CH_3)_2)-CF_3}$), 4.29-4.33 (m, 1H, \underline{NH}_2), 6.59-6.61 (m, 1H, Ph), 6.96-7.00 (m, 1H, Ph), 7.04-7.10 (m, 2H, Ph), 7.25-7.34 (m, 5H, Ph(Phe)). **^{13}C NMR** (90.55 MHz, CD_2Cl_2) : δ 41.28 ($\underline{CH-CH_2-Ph(Phe)}$), 47.97 ($\underline{CH(N(CH_3)_2)-CF_3}$), 53.37 ($\underline{CH(N(CH_3)_2)-CF_3}$), 62.22 ($\underline{CH-CH_2-Ph(Phe)}$), 77.76-78.63 (q, $^2J(C,F)=26.3$, $\underline{CH(N(CH_3)_2)-CF_3}$), 120.12-129.57 (q, $^1J(C,F)=285$, $\underline{CH(N(CH_3)_2)-CF_3}$), 125.51 (Ph), 125.86-125.89 (q, $^4J(C,F)=2.7$ Hz, Ph), 127.58 (Ph), 128.16 (Ph(Phe)), 129.90 (Ph(Phe)), 130.19 (Ph(Phe)), 132.87 (Ph), 137.51 (C_{quat}), 143.83 (C_{quat}), 145.88 (C_{quat}), 179.58 (C=O). **^{19}F NMR** (470.50 MHz, CD_2Cl_2) : δ -64.01. **MS-FAB** (NOBA): m/z 782.0 ($[2M-Phe]^+$), 473.0 ($[M]^+$), 429.0, 308.0 ($[M-Phe]^+$).

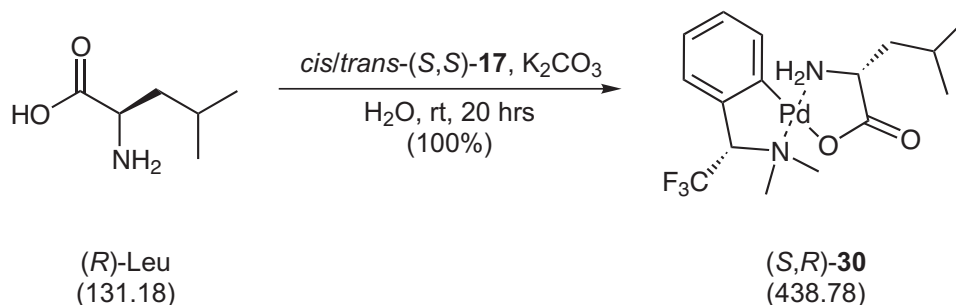
{[(S)-Phenylalaninato-*N,O*][(S)-*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C,M*]palladium(II)} ((S,S)-29)



The general procedure was followed for the synthesis of the desired compound (S,S)-29 as a white solid (31 mg, 91%).

Mp : 180°C (decomp.). **TLC** : $R_f=0.32$ (silica gel, ethyl acetate : methanol, UV_{254nm}). **1H NMR** (500.13 MHz, CD_2Cl_2) : δ 2.86-2.88 (m, 1H, \underline{NH}_2), 2.92 (d, $^4J(H,H)=1.8$, 3H, $CH(N(\underline{CH}_3)_2-CF_3)$), 2.99 (s, 3H, $CH(N(\underline{CH}_3)_2-CF_3)$), 3.20-3.25 (m, 1H, $CH-\underline{CH}_2-Ph(Phe)$), 3.38-3.41 (m, 1H, $CH-\underline{CH}_2-Ph(Phe)$), 3.72-3.75 (m, 1H, \underline{NH}_2), 3.81-3.86 (m, 1H, $\underline{CH}-CH_2-Ph(Phe)$), 4.17-4.21 (q, $^3J(H,F)=7.2$, $\underline{CH}(N(CH_3)_2-CF_3)$), 6.56-6.58 (m, 1H, Ph), 6.95-6.99 (m, 1H, Ph), 7.03-7.06 (m, 1H, Ph), 7.10-7.11 (m, 1H, Ph), 7.27-7.34 (m, 5H, Ph(Phe)). **^{13}C NMR** (CD_2Cl_2 , 125.75 MHz) : δ 40.68 ($CH-\underline{CH}_2-Ph(Phe)$), 47.82 ($CH(N(\underline{CH}_3)_2-CF_3)$), 53.54 ($CH(N(\underline{CH}_3)_2-CF_3)$), 61.34 ($\underline{CH}-CH_2-Ph(Phe)$), 78.22-78.85 (q, $^2J(C,F)=26.7$, $\underline{CH}(N(CH_3)_2-CF_3)$), 120.88-127.41 (q, $^1J(C,F)=284$, $CH(N(CH_3)_2-\underline{CF}_3)$), 124.86 (Ph), 125.67 (Ph), 127.13 (Ph), 127.63 (Ph(Phe)), 129.42 (Ph(Phe)), 129.88 (Ph(Phe)), 132.20 (Ph), 137.27 (C_{quat}), 143.40 (C_{quat}), 145.81 (C_{quat}), 178.81 (C=O). **^{19}F NMR** (CD_2Cl_2 , 470.50 MHz) : δ -64.60. **MS-FAB** (NOBA) : m/z 781.9 ($[2M-Phe]^+$), 472.9 ($[M]^+$), 307.9 ($[M-Phe]^+$).

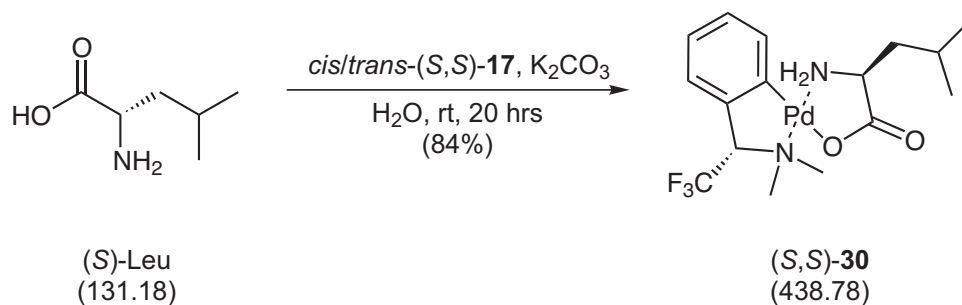
{[(*R*)-Leucinato-*N,O*][(*S*)-*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C,N*]palladium(II)} ((*S,R*)-30)



A slight modification of the generale procedure (use of 15 mg *cis/trans*-(*S,S*)-**17** and adapted amounts for the other reactants) was followed for the synthesis of the desired compound (*S,R*)-**30** as a white solid (19 mg, 100%).

Mp : 170°C (decomp.). **TLC** : $R_f=0.19$ (silica gel, ethyl acetate : methanol (9 : 1), UV_{254nm}). **1H NMR** (360.13 MHz, $CDCl_3$) : δ 0.96-0.98 (d, $^3J(H,H)=6.8$, 3H, CH-CH₂-CH(CH₃)₂), 1.01-1.02 (d, $^3J(H,H)=6.4$, 3H, CH-CH₂-CH(CH₃)₂), 1.74-1.92 (m, 2H, CH-CH₂-CH(CH₃)₂), 2.01-2.08 (m, 1H, CH-CH₂-CH(CH₃)₂), 2.65-2.67 (m, 1H, NH₂), 2.97 (s, 3H, CH(N(CH₃)₂)-CF₃), 3.05 (s, 3H, CH(N(CH₃)₂)-CF₃), 3.68-3.73 (m, 1H, CH-CH₂-CH(CH₃)₂), 4.07-4.13 (q, $^3J(H,F)=7.1$, 1H, CH(N(CH₃)₂)-CF₃), 4.20-4.24 (m, 1H, NH₂), 6.73-6.75 (m, 1H, Ph), 7.01-7.12 (m, 3H, Ph). **^{13}C NMR** (90.55 MHz, $CDCl_3$) : δ 22.09 (CH-CH₂-CH(CH₃)₂), 23.58 (CH-CH₂-CH(CH₃)₂), 25.29 (CH-CH₂-CH(CH₃)₂), 44.20 (CH-CH₂-CH(CH₃)₂), 47.97 (CH(N(CH₃)₂)-CF₃), 53.54 (CH(N(CH₃)₂)-CF₃), 59.05 (CH-CH₂-CH(CH₃)₂), 78.01-78.96 (q, $^2J(C,F)=27.0$, CH(N(CH₃)₂)-CF₃), 119.49-128.94 (q, $^1J(C,F)=285$, CH(N(CH₃)₂)-CF₃), 125.21 (Ph), 125.76 (Ph), 127.40 (Ph), 132.23 (Ph), 143.34 (Ph), 145.57 (Ph), 181.00 (C=O). **^{19}F NMR** (470.50 MHz, $CDCl_3$) : δ -64.70. **MS-FAB** (NOBA): m/z 748.0 ([2M-Leu]⁺), 439.0 ([M]⁺), 394.0, 307.9 ([M-Leu]⁺).

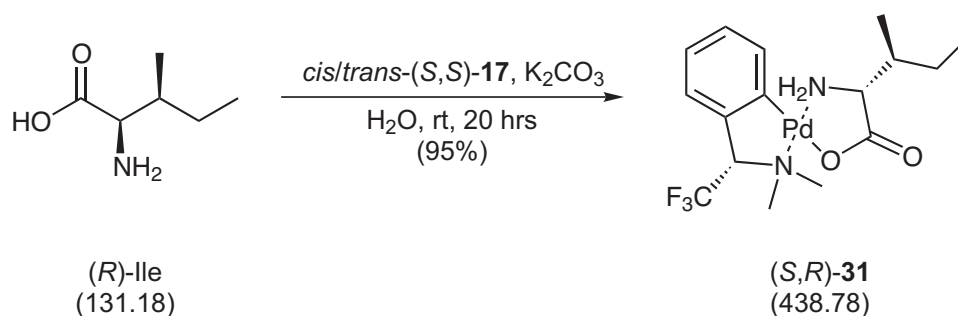
{[(S)-Leucinato-N,O][(S)-N,N-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-C,N]palladium(II)} ((S,S)-30)



The general procedure was followed for the synthesis of the desired compound (S,S)-30 as a white solid (27 mg, 84%).

Mp : 112°C (decomp.). **TLC** : $R_f=0.43$ (silica gel, ethyl acetate : methanol (9 : 1), UV_{254nm}). **1H NMR** (500.13 MHz, $CDCl_3$) : δ 0.97-0.98 (d, $^3J(H,H)=6.4$, 3H, $CH-CH_2-CH(CH_3)_2$), 1.01-1.02 (d, $^3J(H,H)=6.4$, 3H, $CH-CH_2-CH(CH_3)_2$), 1.68-1.74 (m, 1H, $CH-CH_2-CH(CH_3)_2$), 1.76-1.83 (m, 1H, $CH-CH_2-CH(CH_3)_2$), 1.99-2.04 (m, 1H, $CH-CH_2-CH(CH_3)_2$), 2.52-2.53 (m, 1H, NH_2), 2.98 (s, 3H, $CH(N(CH_3)_2)-CF_3$), 3.10 (s, 3H, $CH(N(CH_3)_2)-CF_3$), 3.65-3.69 (m, 1H, $CH-CH_2-CH(CH_3)_2$), 3.95 (m, 1H, NH_2), 4.26-4.31 (q, $^3J(H,F)=7.0$, $CH(N(CH_3)_2)-CF_3$), 6.68-6.70 (m, 1H, Ph), 7.04-7.13 (m, 3H, Ph). **^{13}C NMR** (125.75 MHz, $CDCl_3$) : δ 21.96 ($CH-CH_2-CH(CH_3)_2$), 23.58 ($CH-CH_2-CH(CH_3)_2$), 25.18 ($CH-CH_2-CH(CH_3)_2$), 44.33 ($CH-CH_2-CH(CH_3)_2$), 47.83 ($CH(N(CH_3)_2)-CF_3$), 53.60 ($CH(N(CH_3)_2)-CF_3$), 58.79 ($CH-CH_2-CH(CH_3)_2$), 78.23-78.87 (q, $^2J(C,F)=26.5$, $CH(N(CH_3)_2)-CF_3$), 120.90-127.69 (q, $^1J(C,F)=285$, $CH(N(CH_3)_2)-CF_3$), 125.17 (Ph), 125.67 (Ph), 127.45 (Ph), 132.16 (Ph), 143.31 (Ph), 145.73 (Ph), 180.76 (C=O). **^{19}F NMR** (470.50 MHz, $CDCl_3$) : δ -64.51. **MS-FAB** (NOBA): m/z 745.1 ($[2M-Leu]^+$), 439.1 ($[M]^+$), 396.1, 308.0 ($[M-Leu]^+$).

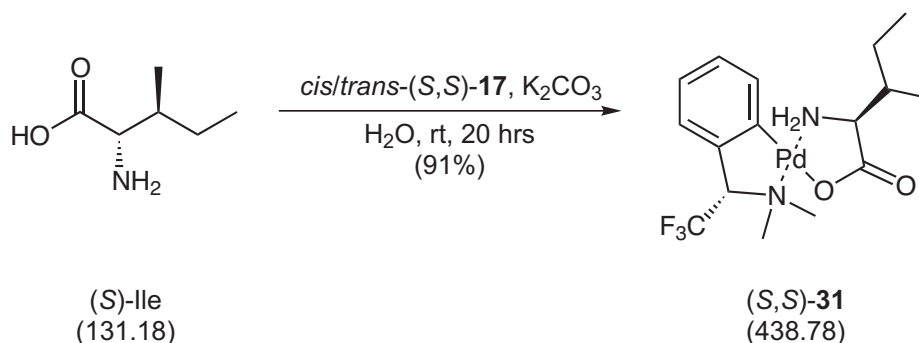
{[(*R*)-Isoleucinato-*N,O*][(*S*)-*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C,N*]palladium(II)} ((*S,R*)-31)



A slight modification of the generale procedure (use of 15 mg *cis/trans*-(*S,S*)-17 and adapted amounts for the other reactants) was followed for the synthesis of the desired compound (*S,R*)-31 as a white solid (18 mg, 95%).

Mp : 143°C (decomp.). **TLC** : $R_f=0.14$ (silica gel, ethyl acetate : methanol (9 : 1), UV_{254nm}). **1H NMR** (360.13 MHz, $CDCl_3$) : δ 0.95-1.00 (t, $^3J(H,H)=7.5$, 3H, $CH-CH(CH_3)-CH_2-CH_3$), 1.18-1.20 (d, $^3J(H,H)=7.3$, 3H, $CH-CH(CH_3)-CH_2-CH_3$), 1.43-1.54 (m, 1H, $CH-CH(CH_3)-CH_2-CH_3$), 1.75-1.86 (m, 1H, $CH-CH(CH_3)-CH_2-CH_3$), 2.13-2.20 (m, 1H, $CH-CH(CH_3)-CH_2-CH_3$), 2.54-2.56 (m, 1H, NH_2), 2.98 (s, 3H, $CH(N(CH_3)_2)-CF_3$), 3.01 (s, 3H, $CH(N(CH_3)_2)-CF_3$), 3.60-3.65 (m, 1H, $CH-CH(CH_3)-CH_2-CH_3$), 3.99-4.04 (q, $^3J(H,F)=7.0$, 1H, $CH(N(CH_3)_2)-CF_3$), 4.21-4.26 (m, 1H, NH_2), 6.76-6.78 (m, 1H, Ph), 7.02-7.11 (m, 3H, Ph). **^{13}C NMR** (90.55 MHz, $CDCl_3$) : δ 11.89 ($CH-CH(CH_3)-CH_2-CH_3$), 16.13 ($CH-CH(CH_3)-CH_2-CH_3$), 24.86 ($CH-CH(CH_3)-CH_2-CH_3$), 38.35 ($CH-CH(CH_3)-CH_2-CH_3$), 47.63 ($CH(N(CH_3)_2)-CF_3$), 53.05 ($CH(N(CH_3)_2)-CF_3$), 64.72 ($CH-CH(CH_3)-CH_2-CH_3$), 77.64-78.28 (q, $^2J(C,F)=26.6$, $CH(N(CH_3)_2)-CF_3$), 120.41-127.20 (q, $^1J(C,F)=285$, $CH(N(CH_3)_2)-CF_3$), 124.79 (Ph), 125.33 (Ph), 126.97 (Ph), 131.70 (Ph), 142.97 (Ph), 145.37 (Ph), 179.40 (C=O). **^{19}F NMR** (470.50 MHz, $CDCl_3$) : δ -64.67. **MS-FAB** (NOBA): m/z 747.9 ($[2M-Ile]^+$), 439.0 ($[M]^+$), 396.0, 307.9 ($[M-Ile]^+$).

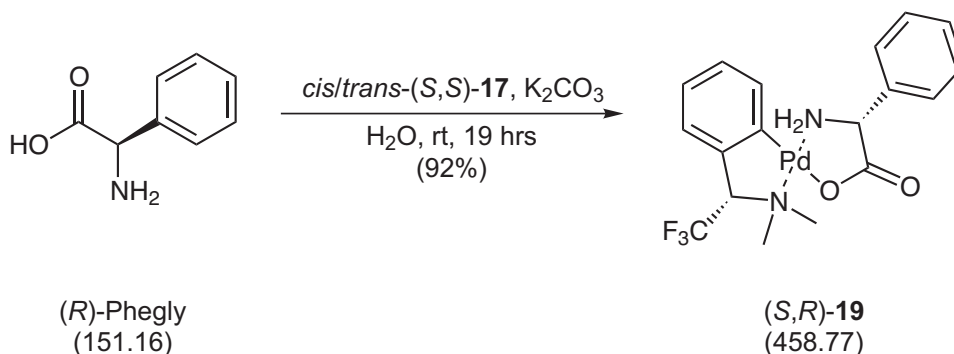
{[(S)-Isoleucinato-N,O][[(S)-N,N-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-C,N]palladium(II)]} ((S,S)-31)



The general procedure was followed for the synthesis of the desired compound (S,S)-31 as a white solid (29 mg, 91%).

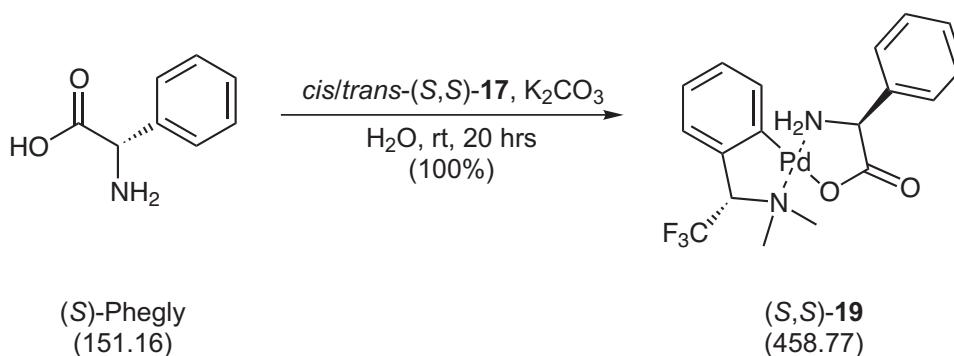
Mp : 85°C (decomp.). **TLC** : $R_f=0.46$ (silica gel, ethyl acetate : methanol (9 : 1), UV_{254nm}). **1H NMR** (500.13 MHz, $CDCl_3$) : δ 0.96-0.99 (t, $^3J(H,H)=7.3$, 3H, CH-CH(CH₃)-CH₂-CH₃), 1.14-1.16 (d, $^3J(H,H)=6.9$, 3H, CH-CH(CH₃)-CH₂-CH₃), 1.32-1.41 (m, 1H, CH-CH(CH₃)-CH₂-CH₃), 1.66-1.74 (m, 1H, CH-CH(CH₃)-CH₂-CH₃), 2.10-2.17 (m, 1H, CH-CH(CH₃)-CH₂-CH₃), 2.44-2.46 (m, 1H, NH₂), 2.98 (s, 3H, CH(N(CH₃)₂)-CF₃), 3.10 (s, 3H, CH(N(CH₃)₂)-CF₃), 3.57-3.60 (m, 1H, CH-CH(CH₃)-CH₂-CH₃), 3.87-3.91 (m, 1H, NH₂), 4.27-4.31 (q, $^3J(H,F)=7.1$, 1H, CH(N(CH₃)₂)-CF₃), 6.70-6.73 (m, 1H, Ph), 7.04-7.12 (m, 3H, Ph). **^{13}C NMR** (125.75 MHz, $CDCl_3$) : δ 12.32 (CH-CH(CH₃)-CH₂-CH₃), 16.47 (CH-CH(CH₃)-CH₂-CH₃), 25.02 (CH-CH(CH₃)-CH₂-CH₃), 38.67 (CH-CH(CH₃)-CH₂-CH₃), 47.83 (CH(N(CH₃)₂)-CF₃), 53.71 (CH(N(CH₃)₂)-CF₃), 65.01 (CH-CH(CH₃)-CH₂-CH₃), 78.29-78.93 (q, $^2J(C,F)=26.9$, CH(N(CH₃)₂)-CF₃), 120.88-127.68 (q, $^1J(C,F)=285$, CH(N(CH₃)₂)-CF₃), 125.12 (Ph), 125.64 (Ph), 127.44 (Ph), 132.09 (Ph), 143.31 (Ph), 145.94 (Ph), 179.59 (C=O). **^{19}F NMR** (470.50 MHz, $CDCl_3$) : δ -64.56. **MS-FAB** (NOBA): m/z 744.4 ([2M-Ile]⁺), 439.2 ([M]⁺), 396.2, 308.1 ([M-Ile]⁺).

{[(*R*)-Phenylglycinato-*N,O*][(S)-*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C,N*]palladium(II)} ((*S,R*)-19)



See section 18.2..

{[(*S*)-Phenylglycinato-*N,O*][(S)-*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C,N*]palladium(II)} ((*S,S*)-19)



A slight modification of the general procedure (use of 15 mg *cis/trans*-(*S,S*)-17 and adapted amounts for the other reactants) was followed for the synthesis of the desired compound (*S,S*)-19 as a white solid (20 mg, 100%).

Mp : 180°C (decomp.). **TLC** : $R_f=0.32$ (silica gel, ethyl acetate : methanol (9 : 1), UV_{254nm}). **1H NMR** (360.13 MHz, $CDCl_3$) : δ 2.69-2.71 (m, 1H, NH₂), 3.01 (s, 3H, CH(N(CH₃)₂)-CF₃), 3.17 (s, 3H, CH(N(CH₃)₂)-CF₃), 4.34-4.40 (q, $^3J(H,F)=7.1$, 1H, CH(N(CH₃)₂)-CF₃), 4.73-4.81 (m, 2H, NH₂ and CH-Ph(Phegly)), 6.63-6.65 (m, 1H, Ph), 6.95-6.99 (m, 1H, Ph), 7.03-7.07 (m, 1H, Ph), 7.11-7.13 (m, 1H, Ph), 7.30-7.39 (m, 3H, Ph(Phegly)), 7.69-7.70 (m, 2H, Ph(Phegly)). **^{13}C NMR** (90.55 MHz, $CDCl_3$) : δ

47.78 (CH(N(CH₃)₂)-CF₃), 53.75 (CH(N(CH₃)₂)-CF₃), 64.29 (CH-Ph(Phegly)), 78.06-78.94 (q, ²J(C,F)=26.6, CH(N(CH₃)₂)-CF₃), 119.65-129.09 (q, ¹J(C,F)=285, CH(N(CH₃)₂)-CF₃), 125.16 (Ph), 125.54 (Ph), 127.42 (Ph), 127.88 (Ph(Phegly)), 129.02 (Ph(Phegly)), 129.57 (Ph(Phegly)), 132.32 (Ph), 139.52 (C_{quat}), 143.24 (C_{quat}), 145.54 (C_{quat}), 178.91 (C=O). ¹⁹F NMR (470.50 MHz, CDCl₃) : δ -64.38. **MS-FAB** (NOBA) : *m/z* 768.2 ([2M-Phegly]⁺), 459.1 ([M]⁺), 416.1, 308.0 ([M-Phegly]⁺).

APPENDIX

Crystallographic Data for (R,R)-19 :

Table 1. Crystal data table for (R,R)-19.

Identification code	ne-01
Crystal shape	plate
Crystal colour	pale_yellow
Crystal size	0.50 x 0.35 x 0.20 mm
Empirical formula	C18 H18 F3 N2 O2 Pd . 1/2H ₂ O
Formula weight	465.74
Crystal system	Orthorhombic
Space group	P 2 ₁ 2 ₁ 2 ₁
Unit cell dimensions	a = 9.8302(7) Å alpha = 90 deg. b = 12.4839(8) Å beta = 90 deg. c = 29.280(3) Å gamma = 90 deg.
Volume	3593.3(5) Å ³
Cell refinement parameters	
Reflections	7998 (plus equivalents)
Angle range	2.14 < theta < 25.87
Z	8
Density (calculated)	1.722 g/cm ³
Radiation used	MoK α
Wavelength	0.71073 Å
Linear absorption coefficient	1.081 mm ⁻¹
Temperature	293(2) K

Table 2. Data Collection Details for (R,R)-19.

Diffractometer	STOE Image Plate Diffraction System
Scan method	phi oscillation

Absorption correction	Empirical_DIFABS
Max. and min. transmission	0.773 and 0.356
Number of Reflections measured	27843
Number of Independent reflections	6786
Number of observed reflections	5288
Criterion for recognizing	>2sigma(I)
R(int) =	0.1380
Theta range for data collection	2.14 to 25.87 deg.
Index ranges	-12<=h<=12, -14<=k<=14, -35<=l<=35
Number of standards	0
Intensity variation	0 %
F(000)	1864

Table 3. Refinement Details for (R,R)-**19**.

Refinement method	Full-matrix least-squares on F ²
Final R indices [I>2sigma(I)]	R1 = 0.0536, wR2 = 0.1165
R indices (all data)	R1 = 0.0749, wR2 = 0.1241
R1 [=SUM(Fo - Fc)/SUM Fo]	
wR ² { = [SUM(w(Fo ² -Fc ²) ²)/SUM(wFo ⁴)] ^{1/2} }	
Number of reflections used	6786
Number of L.S. restraints	0
Number of refined Parameters	484
Goodness-of-fit on F ²	0.999
S { = [SUM w(Fo ² -Fc ²) ²]/(n-p) ^{1/2} }, n= number of reflections, p= Parameters used.	
calc w=1/[s ² (Fo ²)+(0.0586P) ² +0.0000P] where P=(Fo ² +2Fc ²)/3	
Maximum delta/sigma	0.001
Maximum e-density	0.811 e.A ⁻³
Minimum e-density	-0.667 e.A ⁻³

Table 4. Computer Programs used for (R,R)-**19**.

Data collection program	EXPOSE (Stoe & Cie GmbH, Darmstadt, 1997)
Cell refinement program	CELL (Stoe & Cie GmbH, Darmstadt, 1997)
Data reduction program	INTEGRATE (Stoe & Cie GmbH, Darmstadt, 1997)
Structure Solving Program	SHELXS-97 (Sheldrick, 1990)
Structure Refinement Program	SHELXL-97 (Sheldrick, 1997)
Pictures drawn with	PLATON/PLUTON (Spek, 1990)
Tables made with	SHELXL-97 (Sheldrick, 1997)
Absolute structure parameter	-0.01(5)

Table 5. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for (R,R)-**19**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U (eq)
Pd(1)	-4041 (1)	-4614 (1)	-506 (1)	15 (1)
N(1)	-3974 (7)	-3656 (6)	69 (2)	16 (1)
N(2)	-4127 (7)	-5557 (6)	-1092 (2)	14 (1)
O(1)	-5282 (6)	-3368 (5)	-742 (2)	18 (1)
O(2)	-6465 (5)	-1954 (6)	-502 (2)	25 (1)
F(1)	-3838 (6)	-8500 (5)	-1172 (2)	31 (1)
F(2)	-2288 (5)	-7468 (5)	-1444 (2)	29 (1)
F(3)	-4347 (5)	-7357 (5)	-1693 (2)	30 (1)
C(1)	-2860 (7)	-5771 (7)	-283 (3)	17 (2)
C(2)	-1935 (9)	-5734 (7)	79 (3)	22 (2)
C(3)	-1164 (9)	-6592 (8)	190 (3)	25 (2)
C(4)	-1260 (9)	-7538 (9)	-49 (3)	27 (2)
C(5)	-2170 (8)	-7590 (8)	-409 (3)	21 (2)
C(6)	-2936 (7)	-6714 (7)	-541 (3)	18 (2)
C(7)	-3952 (9)	-6696 (7)	-942 (3)	19 (2)
C(8)	-3598 (9)	-7496 (9)	-1315 (3)	26 (2)
C(9)	-2965 (9)	-5167 (8)	-1388 (3)	24 (2)
C(10)	-5419 (9)	-5388 (10)	-1337 (3)	31 (2)
C(11)	-5659 (7)	-2658 (7)	-435 (3)	16 (2)
C(12)	-5086 (8)	-2824 (8)	53 (3)	19 (2)
C(13)	-6253 (7)	-3185 (7)	365 (3)	16 (2)
C(14)	-7023 (8)	-4051 (8)	252 (3)	20 (2)
C(15)	-8076 (8)	-4392 (7)	542 (3)	25 (2)
C(16)	-8285 (9)	-3865 (9)	949 (3)	30 (2)
C(17)	-7484 (11)	-3005 (10)	1068 (3)	35 (2)
C(18)	-6465 (9)	-2649 (9)	776 (3)	28 (2)
Pd(2)	-3125 (1)	-1980 (1)	1932 (1)	17 (1)
N(21)	-1628 (7)	-2808 (6)	1581 (2)	20 (2)
N(22)	-4471 (7)	-1068 (6)	2315 (2)	19 (2)
O(21)	-2726 (6)	-3200 (6)	2418 (2)	26 (2)
O(22)	-1525 (6)	-4672 (6)	2510 (2)	32 (2)
F(21)	-1903 (6)	-6 (5)	2405 (2)	39 (2)
F(22)	-3260 (8)	814 (5)	2861 (2)	47 (2)
F(23)	-2738 (6)	1535 (5)	2215 (2)	39 (2)
C(21)	-3527 (8)	-866 (8)	1477 (3)	20 (2)
C(22)	-3460 (8)	-910 (8)	999 (3)	18 (2)
C(23)	-3902 (9)	-84 (7)	735 (3)	23 (2)
C(24)	-4402 (9)	876 (8)	931 (3)	26 (2)
C(25)	-4485 (8)	946 (9)	1399 (3)	24 (2)
C(26)	-4075 (8)	71 (7)	1668 (3)	16 (2)
C(27)	-4275 (9)	85 (7)	2184 (3)	21 (2)
C(28)	-3019 (11)	572 (9)	2415 (3)	33 (2)
C(29)	-4371 (11)	-1267 (9)	2815 (3)	32 (2)
C(30)	-5905 (10)	-1349 (10)	2176 (3)	36 (2)
C(31)	-1945 (9)	-3936 (7)	2275 (3)	20 (2)
C(32)	-1526 (9)	-3905 (8)	1768 (3)	25 (2)
C(33)	-2436 (8)	-4674 (9)	1511 (3)	20 (2)
C(34)	-2069 (10)	-5729 (8)	1481 (3)	27 (2)
C(35)	-2884 (10)	-6502 (9)	1268 (3)	34 (2)
C(36)	-4138 (11)	-6159 (8)	1077 (3)	30 (2)
C(37)	-4561 (10)	-5099 (9)	1117 (3)	31 (3)
C(38)	-3679 (8)	-4389 (8)	1327 (3)	21 (2)
O(1W)	-602 (9)	-6762 (8)	2824 (3)	49 (2)

Table 6. Bond lengths [\AA] and angles [deg] for (R,R)-**19**.

Pd(1)-C(1)	1.965 (8)
Pd(1)-N(1)	2.068 (6)
Pd(1)-N(2)	2.083 (6)
Pd(1)-O(1)	2.094 (6)
N(1)-C(12)	1.509 (11)
N(2)-C(10)	1.473 (11)
N(2)-C(7)	1.499 (11)

N (2) -C (9)	1.513 (11)
O (1) -C (11)	1.316 (10)
O (2) -C (11)	1.200 (10)
F (1) -C (8)	1.342 (11)
F (2) -C (8)	1.342 (10)
F (3) -C (8)	1.340 (10)
C (1) -C (2)	1.398 (11)
C (1) -C (6)	1.400 (12)
C (2) -C (3)	1.351 (12)
C (3) -C (4)	1.376 (14)
C (4) -C (5)	1.385 (12)
C (5) -C (6)	1.383 (12)
C (6) -C (7)	1.541 (11)
C (7) -C (8)	1.521 (13)
C (11) -C (12)	1.548 (11)
C (12) -C (13)	1.534 (11)
C (13) -C (14)	1.360 (12)
C (13) -C (18)	1.395 (12)
C (14) -C (15)	1.405 (12)
C (15) -C (16)	1.377 (13)
C (16) -C (17)	1.376 (15)
C (17) -C (18)	1.388 (14)
Pd (2) -C (21)	1.965 (10)
Pd (2) -N (21)	2.070 (7)
Pd (2) -N (22)	2.075 (7)
Pd (2) -O (21)	2.122 (6)
N (21) -C (32)	1.478 (12)
N (22) -C (29)	1.488 (11)
N (22) -C (27)	1.502 (12)
N (22) -C (30)	1.509 (12)
O (21) -C (31)	1.269 (11)
O (22) -C (31)	1.221 (11)
F (21) -C (28)	1.314 (12)
F (22) -C (28)	1.362 (10)
F (23) -C (28)	1.366 (12)
C (21) -C (26)	1.403 (12)
C (21) -C (22)	1.403 (12)
C (22) -C (23)	1.361 (12)
C (23) -C (24)	1.418 (14)
C (24) -C (25)	1.374 (13)
C (25) -C (26)	1.406 (13)
C (26) -C (27)	1.524 (11)
C (27) -C (28)	1.533 (14)
C (31) -C (32)	1.542 (12)
C (32) -C (33)	1.512 (13)
C (33) -C (34)	1.369 (15)
C (33) -C (38)	1.382 (11)
C (34) -C (35)	1.400 (14)
C (35) -C (36)	1.420 (15)
C (36) -C (37)	1.393 (15)
C (37) -C (38)	1.384 (13)
C (1) -Pd (1) -N (1)	97.8 (3)
C (1) -Pd (1) -N (2)	83.2 (3)
N (1) -Pd (1) -N (2)	178.9 (3)
C (1) -Pd (1) -O (1)	179.3 (3)
N (1) -Pd (1) -O (1)	81.8 (2)
N (2) -Pd (1) -O (1)	97.2 (2)
C (12) -N (1) -Pd (1)	110.5 (5)
C (10) -N (2) -C (7)	112.2 (7)
C (10) -N (2) -C (9)	109.1 (7)
C (7) -N (2) -C (9)	112.7 (6)
C (10) -N (2) -Pd (1)	110.8 (5)
C (7) -N (2) -Pd (1)	106.8 (4)
C (9) -N (2) -Pd (1)	105.0 (5)
C (11) -O (1) -Pd (1)	116.1 (5)
C (2) -C (1) -C (6)	118.2 (8)
C (2) -C (1) -Pd (1)	127.7 (7)
C (6) -C (1) -Pd (1)	114.0 (6)
C (3) -C (2) -C (1)	121.3 (8)
C (2) -C (3) -C (4)	121.3 (8)
C (3) -C (4) -C (5)	118.1 (9)
C (6) -C (5) -C (4)	121.8 (9)
C (5) -C (6) -C (1)	119.0 (7)
C (5) -C (6) -C (7)	125.2 (7)
C (1) -C (6) -C (7)	115.7 (7)

N (2) -C (7) -C (8)	116.0 (7)
N (2) -C (7) -C (6)	108.2 (7)
C (8) -C (7) -C (6)	113.0 (7)
F (3) -C (8) -F (1)	106.4 (7)
F (3) -C (8) -F (2)	107.0 (7)
F (1) -C (8) -F (2)	106.3 (8)
F (3) -C (8) -C (7)	112.5 (8)
F (1) -C (8) -C (7)	110.4 (7)
F (2) -C (8) -C (7)	113.8 (8)
O (2) -C (11) -O (1)	124.5 (8)
O (2) -C (11) -C (12)	119.3 (8)
O (1) -C (11) -C (12)	116.0 (7)
N (1) -C (12) -C (13)	108.7 (7)
N (1) -C (12) -C (11)	112.6 (6)
C (13) -C (12) -C (11)	108.4 (6)
C (14) -C (13) -C (18)	120.5 (8)
C (14) -C (13) -C (12)	120.4 (7)
C (18) -C (13) -C (12)	119.0 (8)
C (13) -C (14) -C (15)	120.3 (8)
C (16) -C (15) -C (14)	119.2 (8)
C (15) -C (16) -C (17)	120.4 (9)
C (16) -C (17) -C (18)	120.5 (9)
C (17) -C (18) -C (13)	119.0 (10)
C (21) -Pd (2) -N (21)	99.3 (3)
C (21) -Pd (2) -N (22)	81.4 (3)
N (21) -Pd (2) -N (22)	174.3 (3)
C (21) -Pd (2) -O (21)	178.8 (3)
N (21) -Pd (2) -O (21)	81.0 (3)
N (22) -Pd (2) -O (21)	98.5 (2)
C (32) -N (21) -Pd (2)	109.2 (5)
C (29) -N (22) -C (27)	113.7 (7)
C (29) -N (22) -C (30)	106.8 (7)
C (27) -N (22) -C (30)	105.9 (7)
C (29) -N (22) -Pd (2)	113.5 (5)
C (27) -N (22) -Pd (2)	107.8 (5)
C (30) -N (22) -Pd (2)	108.8 (6)
C (31) -O (21) -Pd (2)	114.2 (5)
C (26) -C (21) -C (22)	116.7 (8)
C (26) -C (21) -Pd (2)	113.4 (6)
C (22) -C (21) -Pd (2)	129.6 (7)
C (23) -C (22) -C (21)	121.5 (9)
C (22) -C (23) -C (24)	121.4 (8)
C (25) -C (24) -C (23)	118.6 (9)
C (24) -C (25) -C (26)	119.5 (9)
C (21) -C (26) -C (25)	122.3 (8)
C (21) -C (26) -C (27)	117.0 (8)
C (25) -C (26) -C (27)	120.6 (8)
N (22) -C (27) -C (26)	105.0 (7)
N (22) -C (27) -C (28)	111.8 (8)
C (26) -C (27) -C (28)	109.7 (7)
F (21) -C (28) -F (22)	106.8 (8)
F (21) -C (28) -F (23)	107.8 (8)
F (22) -C (28) -F (23)	104.6 (8)
F (21) -C (28) -C (27)	116.4 (8)
F (22) -C (28) -C (27)	111.7 (8)
F (23) -C (28) -C (27)	108.9 (8)
O (22) -C (31) -O (21)	124.3 (8)
O (22) -C (31) -C (32)	118.1 (8)
O (21) -C (31) -C (32)	117.6 (7)
N (21) -C (32) -C (33)	111.4 (7)
N (21) -C (32) -C (31)	111.1 (7)
C (33) -C (32) -C (31)	107.8 (7)
C (34) -C (33) -C (38)	117.1 (9)
C (34) -C (33) -C (32)	119.1 (8)
C (38) -C (33) -C (32)	123.6 (9)
C (33) -C (34) -C (35)	122.8 (9)
C (34) -C (35) -C (36)	117.6 (10)
C (37) -C (36) -C (35)	120.9 (10)
C (38) -C (37) -C (36)	117.3 (10)
C (33) -C (38) -C (37)	124.2 (10)

Table 7. Torsion-angles for (R,R)-**19**.

C (1) -Pd (1) -N (1) -C (12)	-165.2 (5)
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N(2)-Pd(1)-N(1)-C(12)	24(16)
O(1)-Pd(1)-N(1)-C(12)	15.4(5)
C(1)-Pd(1)-N(2)-C(10)	151.7(7)
N(1)-Pd(1)-N(2)-C(10)	-38(16)
O(1)-Pd(1)-N(2)-C(10)	-28.8(6)
C(1)-Pd(1)-N(2)-C(7)	29.3(5)
N(1)-Pd(1)-N(2)-C(7)	-160(15)
O(1)-Pd(1)-N(2)-C(7)	-151.2(5)
C(1)-Pd(1)-N(2)-C(9)	-90.6(5)
N(1)-Pd(1)-N(2)-C(9)	80(15)
O(1)-Pd(1)-N(2)-C(9)	88.8(5)
C(1)-Pd(1)-O(1)-C(11)	-63(26)
N(1)-Pd(1)-O(1)-C(11)	-10.2(5)
N(2)-Pd(1)-O(1)-C(11)	170.0(5)
N(1)-Pd(1)-C(1)-C(2)	-18.8(8)
N(2)-Pd(1)-C(1)-C(2)	161.0(8)
O(1)-Pd(1)-C(1)-C(2)	34(26)
N(1)-Pd(1)-C(1)-C(6)	164.5(6)
N(2)-Pd(1)-C(1)-C(6)	-15.6(6)
O(1)-Pd(1)-C(1)-C(6)	-143(25)
C(6)-C(1)-C(2)-C(3)	-2.2(13)
Pd(1)-C(1)-C(2)-C(3)	-178.7(7)
C(1)-C(2)-C(3)-C(4)	-0.2(14)
C(2)-C(3)-C(4)-C(5)	0.2(13)
C(3)-C(4)-C(5)-C(6)	2.2(13)
C(4)-C(5)-C(6)-C(1)	-4.6(12)
C(4)-C(5)-C(6)-C(7)	178.9(8)
C(2)-C(1)-C(6)-C(5)	4.4(11)
Pd(1)-C(1)-C(6)-C(5)	-178.6(6)
C(2)-C(1)-C(6)-C(7)	-178.7(7)
Pd(1)-C(1)-C(6)-C(7)	-1.7(9)
C(10)-N(2)-C(7)-C(8)	74.4(9)
C(9)-N(2)-C(7)-C(8)	-49.2(9)
Pd(1)-N(2)-C(7)-C(8)	-164.0(6)
C(10)-N(2)-C(7)-C(6)	-157.5(6)
C(9)-N(2)-C(7)-C(6)	78.9(8)
Pd(1)-N(2)-C(7)-C(6)	-36.0(7)
C(5)-C(6)-C(7)-N(2)	-157.2(7)
C(1)-C(6)-C(7)-N(2)	26.2(9)
C(5)-C(6)-C(7)-C(8)	-27.4(11)
C(1)-C(6)-C(7)-C(8)	156.0(7)
N(2)-C(7)-C(8)-F(3)	-44.1(10)
C(6)-C(7)-C(8)-F(3)	-169.8(7)
N(2)-C(7)-C(8)-F(1)	-162.8(7)
C(6)-C(7)-C(8)-F(1)	71.5(9)
N(2)-C(7)-C(8)-F(2)	77.8(10)
C(6)-C(7)-C(8)-F(2)	-47.9(11)
Pd(1)-O(1)-C(11)-O(2)	-172.8(6)
Pd(1)-O(1)-C(11)-C(12)	2.2(8)
Pd(1)-N(1)-C(12)-C(13)	101.6(6)
Pd(1)-N(1)-C(12)-C(11)	-18.5(8)
O(2)-C(11)-C(12)-N(1)	-173.6(7)
O(1)-C(11)-C(12)-N(1)	11.1(10)
O(2)-C(11)-C(12)-C(13)	66.1(10)
O(1)-C(11)-C(12)-C(13)	-109.2(8)
N(1)-C(12)-C(13)-C(14)	-68.6(9)
C(11)-C(12)-C(13)-C(14)	54.1(10)
N(1)-C(12)-C(13)-C(18)	108.0(9)
C(11)-C(12)-C(13)-C(18)	-129.3(8)
C(18)-C(13)-C(14)-C(15)	2.4(12)
C(12)-C(13)-C(14)-C(15)	178.9(8)
C(13)-C(14)-C(15)-C(16)	-2.4(13)
C(14)-C(15)-C(16)-C(17)	0.8(14)
C(15)-C(16)-C(17)-C(18)	0.8(16)
C(16)-C(17)-C(18)-C(13)	-0.9(15)
C(14)-C(13)-C(18)-C(17)	-0.7(13)
C(12)-C(13)-C(18)-C(17)	-177.3(9)
C(21)-Pd(2)-N(21)-C(32)	-158.4(6)
N(22)-Pd(2)-N(21)-C(32)	106(3)
O(21)-Pd(2)-N(21)-C(32)	20.4(5)
C(21)-Pd(2)-N(22)-C(29)	-161.0(7)
N(21)-Pd(2)-N(22)-C(29)	-64(3)
O(21)-Pd(2)-N(22)-C(29)	20.2(7)
C(21)-Pd(2)-N(22)-C(27)	-34.1(5)
N(21)-Pd(2)-N(22)-C(27)	63(3)
O(21)-Pd(2)-N(22)-C(27)	147.1(5)

C (21) -Pd (2) -N (22) -C (30)	80.2 (6)
N (21) -Pd (2) -N (22) -C (30)	177 (3)
O (21) -Pd (2) -N (22) -C (30)	-98.6 (6)
C (21) -Pd (2) -O (21) -C (31)	94 (16)
N (21) -Pd (2) -O (21) -C (31)	-8.4 (6)
N (22) -Pd (2) -O (21) -C (31)	177.3 (6)
N (21) -Pd (2) -C (21) -C (26)	-155.2 (6)
N (22) -Pd (2) -C (21) -C (26)	19.1 (6)
O (21) -Pd (2) -C (21) -C (26)	103 (16)
N (21) -Pd (2) -C (21) -C (22)	31.1 (8)
N (22) -Pd (2) -C (21) -C (22)	-154.6 (8)
O (21) -Pd (2) -C (21) -C (22)	-71 (16)
C (26) -C (21) -C (22) -C (23)	0.1 (11)
Pd (2) -C (21) -C (22) -C (23)	173.7 (7)
C (21) -C (22) -C (23) -C (24)	2.5 (13)
C (22) -C (23) -C (24) -C (25)	-2.6 (13)
C (23) -C (24) -C (25) -C (26)	0.1 (12)
C (22) -C (21) -C (26) -C (25)	-2.7 (12)
Pd (2) -C (21) -C (26) -C (25)	-177.3 (6)
C (22) -C (21) -C (26) -C (27)	174.4 (7)
Pd (2) -C (21) -C (26) -C (27)	-0.2 (9)
C (24) -C (25) -C (26) -C (21)	2.6 (13)
C (24) -C (25) -C (26) -C (27)	-174.4 (8)
C (29) -N (22) -C (27) -C (26)	166.8 (7)
C (30) -N (22) -C (27) -C (26)	-76.3 (8)
Pd (2) -N (22) -C (27) -C (26)	40.0 (7)
C (29) -N (22) -C (27) -C (28)	47.9 (9)
C (30) -N (22) -C (27) -C (28)	164.9 (7)
Pd (2) -N (22) -C (27) -C (28)	-78.8 (7)
C (21) -C (26) -C (27) -N (22)	-27.3 (10)
C (25) -C (26) -C (27) -N (22)	149.9 (7)
C (21) -C (26) -C (27) -C (28)	93.0 (9)
C (25) -C (26) -C (27) -C (28)	-89.8 (10)
N (22) -C (27) -C (28) -F (21)	45.9 (11)
C (26) -C (27) -C (28) -F (21)	-70.2 (11)
N (22) -C (27) -C (28) -F (22)	-77.1 (9)
C (26) -C (27) -C (28) -F (22)	166.8 (8)
N (22) -C (27) -C (28) -F (23)	167.9 (6)
C (26) -C (27) -C (28) -F (23)	51.8 (9)
Pd (2) -O (21) -C (31) -O (22)	175.3 (7)
Pd (2) -O (21) -C (31) -C (32)	-6.0 (10)
Pd (2) -N (21) -C (32) -C (33)	91.5 (7)
Pd (2) -N (21) -C (32) -C (31)	-28.6 (8)
O (22) -C (31) -C (32) -N (21)	-157.4 (8)
O (21) -C (31) -C (32) -N (21)	23.7 (11)
O (22) -C (31) -C (32) -C (33)	80.3 (10)
O (21) -C (31) -C (32) -C (33)	-98.5 (10)
N (21) -C (32) -C (33) -C (34)	150.7 (8)
C (31) -C (32) -C (33) -C (34)	-87.2 (9)
N (21) -C (32) -C (33) -C (38)	-33.9 (11)
C (31) -C (32) -C (33) -C (38)	88.3 (9)
C (38) -C (33) -C (34) -C (35)	1.2 (13)
C (32) -C (33) -C (34) -C (35)	176.9 (8)
C (33) -C (34) -C (35) -C (36)	0.1 (14)
C (34) -C (35) -C (36) -C (37)	-2.6 (14)
C (35) -C (36) -C (37) -C (38)	3.5 (14)
C (34) -C (33) -C (38) -C (37)	-0.1 (13)
C (32) -C (33) -C (38) -C (37)	-175.6 (8)
C (36) -C (37) -C (38) -C (33)	-2.2 (13)

Table 8. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for (R,R)-**19**. The anisotropic displacement factor exponent takes the form: $-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
Pd(1)	13(1)	18(1)	15(1)	0(1)	-1(1)	2(1)
N(1)	13(3)	10(4)	25(3)	-5(3)	5(3)	5(3)
N(2)	14(3)	12(4)	16(3)	0(3)	3(3)	9(3)
O(1)	20(3)	15(4)	18(3)	0(2)	-3(2)	6(2)
O(2)	20(3)	32(4)	24(3)	2(3)	1(2)	0(3)
F(1)	45(3)	15(3)	33(3)	-3(2)	-6(3)	3(3)

F(2)	22(2)	36(4)	29(3)	-12(2)	9(2)	3(2)
F(3)	34(3)	33(4)	24(3)	-7(2)	-6(2)	4(2)
C(1)	8(4)	18(5)	24(4)	4(3)	0(3)	2(3)
C(2)	25(4)	21(6)	19(4)	1(3)	-7(3)	4(4)
C(3)	21(4)	32(6)	22(4)	1(4)	-4(3)	2(4)
C(4)	24(5)	30(6)	26(5)	7(4)	0(4)	4(4)
C(5)	18(4)	24(5)	20(4)	3(3)	5(3)	3(3)
C(6)	12(4)	19(5)	22(4)	-2(4)	7(3)	-6(3)
C(7)	19(4)	17(5)	21(4)	2(3)	-1(3)	1(4)
C(8)	29(5)	23(6)	24(5)	0(4)	-3(3)	-6(4)
C(9)	36(5)	16(6)	20(4)	-1(3)	5(4)	-7(4)
C(10)	31(4)	40(7)	21(4)	-7(5)	-7(3)	6(5)
C(11)	13(4)	6(5)	29(5)	7(3)	2(3)	2(3)
C(12)	14(4)	25(6)	18(4)	-5(4)	1(3)	-3(4)
C(13)	13(4)	14(5)	19(4)	3(3)	-1(3)	3(3)
C(14)	10(4)	27(6)	24(4)	-3(4)	-2(3)	0(4)
C(15)	22(4)	28(6)	23(4)	6(4)	0(4)	-9(4)
C(16)	21(5)	36(7)	34(5)	8(4)	10(4)	7(4)
C(17)	48(6)	32(7)	26(5)	-6(5)	11(4)	6(6)
C(18)	32(5)	25(6)	27(5)	-7(4)	2(4)	15(4)
Pd(2)	18(1)	17(1)	17(1)	1(1)	2(1)	2(1)
N(21)	21(4)	13(5)	26(4)	4(3)	11(3)	9(3)
N(22)	29(4)	13(5)	14(3)	2(3)	5(3)	8(3)
O(21)	32(3)	28(4)	17(3)	-1(3)	2(2)	9(3)
O(22)	36(3)	35(5)	24(3)	8(3)	2(3)	12(3)
F(21)	30(3)	46(4)	42(3)	-13(3)	-7(3)	-4(3)
F(22)	78(4)	42(4)	20(3)	-12(2)	1(3)	-9(4)
F(23)	50(4)	25(4)	42(3)	-2(3)	0(3)	-13(3)
C(21)	18(4)	15(5)	28(5)	-3(4)	1(3)	-6(3)
C(22)	16(4)	23(5)	15(4)	8(3)	1(3)	-3(3)
C(23)	23(4)	28(6)	18(4)	0(3)	3(3)	0(4)
C(24)	28(5)	27(6)	22(4)	9(4)	-1(3)	-3(4)
C(25)	21(4)	26(6)	26(5)	4(4)	0(3)	-4(4)
C(26)	14(3)	14(5)	20(4)	-4(3)	2(3)	-6(3)
C(27)	24(5)	15(5)	24(4)	-5(3)	3(3)	1(3)
C(28)	41(5)	32(7)	27(5)	-14(4)	4(4)	11(5)
C(29)	48(6)	25(6)	23(5)	4(4)	8(4)	11(5)
C(30)	19(4)	45(7)	44(6)	3(5)	8(4)	3(5)
C(31)	27(4)	14(5)	19(4)	6(3)	-6(4)	-8(4)
C(32)	31(5)	25(6)	18(4)	0(4)	-4(3)	5(4)
C(33)	19(4)	29(6)	12(4)	7(4)	4(3)	1(4)
C(34)	28(5)	22(6)	30(5)	-2(4)	0(4)	0(4)
C(35)	38(6)	22(6)	43(6)	-6(4)	8(4)	7(4)
C(36)	40(5)	25(6)	25(5)	-4(4)	5(4)	-4(5)
C(37)	28(5)	36(7)	29(5)	4(4)	-2(4)	-10(4)
C(38)	17(4)	12(6)	34(5)	8(4)	-3(3)	-6(3)
O(1W)	52(5)	36(6)	59(5)	-1(4)	-23(4)	14(4)

Table 9. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for (R,R)-**19**.

	x	y	z	U (eq)
H(2)	-1849	-5106	247	26
H(3)	-556	-6541	432	30
H(4)	-728	-8126	29	32
H(5)	-2269	-8232	-567	25
H(7)	-4830	-6922	-817	23
H(9C)	-2945	-5571	-1667	36
H(9B)	-2122	-5261	-1228	36
H(9A)	-3093	-4422	-1457	36
H(10C)	-5440	-5830	-1605	46
H(10B)	-5495	-4649	-1424	46
H(10A)	-6165	-5575	-1141	46
H(12)	-4726	-2141	166	23
H(14)	-6852	-4419	-18	24
H(15)	-8625	-4968	461	30
H(16)	-8972	-4090	1145	36
H(17)	-7625	-2659	1345	42
H(18)	-5932	-2062	855	33
H(22)	-3105	-1518	860	21
H(23)	-3875	-150	419	28

H (24)	-4668	1447	748	31
H (25)	-4811	1567	1536	29
H (27)	-5088	500	2263	25
H (29C)	-5016	-824	2973	48
H (29B)	-3468	-1098	2918	48
H (29A)	-4563	-2007	2877	48
H (30C)	-6536	-932	2352	54
H (30B)	-6064	-2097	2230	54
H (30A)	-6026	-1197	1857	54
H (32)	-582	-4149	1741	29
H (34)	-1245	-5942	1607	32
H (35)	-2613	-7215	1253	41
H (36)	-4683	-6649	923	36
H (37)	-5403	-4877	1007	37
H (38)	-3940	-3674	1346	25
H (1WA)	-370 (160)	-7100 (140)	2620 (50)	74
H (1WB)	-60 (150)	-6050 (130)	2670 (50)	74

Table 10. Hydrogen-bonds for (*R,R*)-**19** [Å and deg.] .

D-H...A	d(D-H)	d(H...A)	d(D...A)	< (DHA)
O (1W)-H (1WB) ... F (21) #1	1.13 (16)	2.34 (16)	3.363 (12)	150 (11)

Symmetry transformations used to generate equivalent atoms:

#1 -x, y-1/2, -z+1/2

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