Chiral cyclic derivatives of C_2-symmetrical butanedioic acids

Ton Vries

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STICHTING DRUKKERIJ REGENBOOG

RIJKSUNIVERSITEIT GRONINGEN

Chiral cyclic derivatives of C_2- symmetrical butanedioic acids

PROEFSCHRIFT

ter verkrijging van het doctoraat in de
Wiskunde en Natuurwetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus Dr. F. van der Woude
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door

Ton René Vries

geboren op 28 september 1963
te Baflo

Promotor: Prof. Dr. R.M Kellogg

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" I was just mixing up some chemicals."

John Hiatt

Ter herinnering aan mijn ouders

Voorwoord

Het voorwoord is het laatste deel van het proefschrift dat ik schrijf. Na een aantal jaren van deeltijd promoveren is het boekje eindelijk af. Hoewel promoveren grotendeels een solistische aangelegenheid is, zijn er toch veel mensen bij het werk betrokken geweest, die ik met name wil bedanken.

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CHAPTER 1

INTRODUCTION

1.1 Symmetry and chirality

Chiral molecules are often considered by definition to be asymmetric[1]. This is not true, chiral molecules can be symmetrical. This assumption is based upon a misunderstanding that has been present in stereochemistry since the discovery of chirality by Pasteur. Pasteur was awarded the Rumford medal for his outstanding work in the study of "Dissymmetrie Moleculaire"[2], in 1856 by the Royal Society of London. However, in translation the term "dissymmetric" became asymmetric. Unfortunately Pasteur's dissymmetry became confused with asymmetry. We will briefly try to explain the differences between dissymmetry and asymmetry.

The term asymmetry can be used when a molecule or figure lacks all symmetry elements (except for C_1-axes, which are always present). This is, however, not a comprehensive criterion for a molecule or figure to be chiral. A chiral molecule or figure may contain symmetry elements. This is illustrated in figure 1, which shows enantiomeric four-bladed windmills. The figures are dissymmetric, but not asymmetric because of their four fold axis of symmetry (C_4-axes).[3]

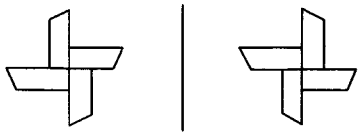

Figure 1. Enantiomeric four-bladed windmills (dissymmetric but not asymmetric).

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1 "I call any geometrical figure, or group of points, chiral and say it has chirality, if its mirror image in a plane mirror, ideally realized, cannot be brought to coincide with itself" Quoted by Whyte, L.L. *Nature*, **1957**, *180*, 513 and *Nature*, **1958**, *182*, 198.

2 "[two hemihedral forms] were dissymmetric, that is, could not be superposed on each other, but each could be superposed on the image of the other in a mirror" Proc. Roy. Soc. London **1857**, *8*, 254.

3 For an introduction to symmetry see: Heilbronner, E.; Dunitz, J.D. *Reflections on symmetry; In chemistry ... and elsewhere.* Verlag Helvetica Chimica Acta; Basel 1993

In a review article on chiral organic molecules containing high symmetry elements, Nakazaki[4] gives another and very clear classification of molecular symmetry. A molecule is either chiral (dissymmetric) or achiral (non-dissymmetric). Chiral molecules can be divided in asymmetric chiral molecules and high symmetry chiral molecules ($> C_2$-symmetry).

So, the existence of high symmetry chiral molecules is accounted for. Chiral molecules containing symmetry elements were known very early in the history of stereochemistry. In fact, the discovery of chirality by Pasteur was accomplished with a C_2-symmetrical compound, tartaric acid. We will see that symmetrical chiral molecules play a very important role in stereochemistry.[5,6]

1.2 Symmetrical chiral molecules in stereochemistry

In this section we will briefly discuss the role of chiral symmetrical molecules in stereochemistry. A number of molecules listed in scheme 1.1 will be mentioned. Although the majority of optically active natural products are asymmetric some beautiful symmetric ones are known. Among these are tartaric acid (C_2-symmetry)[7], cyclo-[tri-L-prolyl] (C_3-symmetry)[8] and α-cyclodextrine (C_6-symmetry).[9] Another striking example is the C_2-symmetrical structure of HIV-protease, an enzyme, which is the most important target for AIDS chemotherapy.[10] The symmetry of the enzyme has inspired many research groups to develop C_2-symmetrical inhibitors.[11] Although chiral symmetrical molecules do appear in nature, by far the most have been designed and synthesized by organic chemists, for different purposes such as chiral ligands and chiral auxiliaries[11], chiral derivatizing agents[12], resolving agents[13], building blocks in host-guest chemis-

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4 a) Nakazaki, M., in E.L. Eliel, S. Wilen, N.L. Allinger (Eds.): "Topics in stereochemistry", John Wiley & Sons, New York, **1984**, *15*, 199. b) Farina, M. and Morandi, C. *Tetrahedron*, **1974**, *30*, 1819.

5 a) Whitesell, J.K. *Chem. Rev.*, **1989**, *89*, 581 b) references throughout this thesis. c) First high symmetrical chiral molecule: a) Mc Casland, G.E.; Proskow, S. *J. Am. Chem. Soc.* **1955**, *77*, 4688. b) Ibid **1956**, *78*, 5646.

6 A short explanation on the notation of symmetry; When a molecule possesses n identical asymmetric units disposed $2\alpha/n$ apart around an axis, it has C_n-symmetry. When a molecule possesses one C_n-axis and n C_2-axis perpendicular to it, it has D_n-symmetry.

7 See section 1.4.

8 Druyan, M.E.; Coulter, C.L.; Walter, R.; Teartha, G.; Ambacly, G.K. *J. Am. Chem Soc.* **1976**, *98*, 5496.

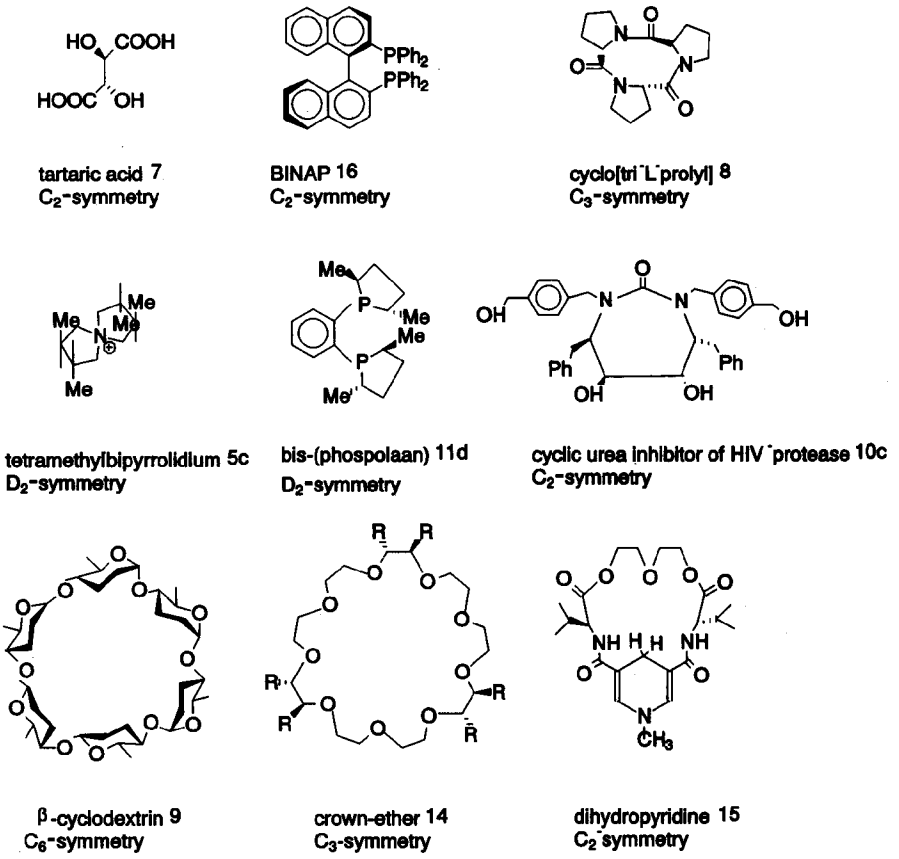
9 Noltemeyer, M.; Saenger, W. *J. Am. Chem. Soc.* **1980**, *102*, 2710.

10 a) Peynan, A; Budt, K.H.; Spanig, J.; Ruppert, D. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1720. b) Enders, D.; Jegelha, U.; Dücker, B. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 423. c) Laxm, P.Y.S.; Erickson-Vitanen, S. *et. al., Science* **1994**, *263*, 380.

11 a) see ref. 5.a. b) Brunner, H. Topics in stereochemistry, Eliel, E.L.; Wilen, S.H., Eds.; Wiley: New York 1988; vol. 18 129. c) Blaser, H.U. *Chem. Rev.* **1992**, *92*, 935. d) Burk, M.J.; Feaster, J.E.; Nugent, W.A.; Harlow, R.L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.

12 For CDA's see chapter 3 and references cited within.

try[14] and enzyme mimics[15]. We have listed some natural and designed high symmetry chiral molecules in scheme 1.1.



Scheme 1.1. High symmetrical chiral molecules.

It is not easy to explain the enormous success of especially C_2-symmetrical compounds in stereochemistry. A first explanation, probably the most important one, is that symmetry simplifies things. Symmetry elements within chemistry make it easier to

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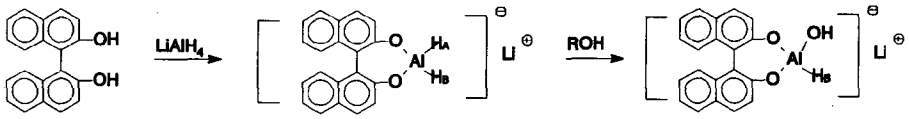
[13] For resolving agents see: a) Jacques, J.; Collet, A.; Wilen, S. *Enantiomers, racemates and resolutions*, Wiley, New York, 1981. b) van der Haest, A.D. *PhD. Thesis* Groningen, **1992**.

[14] a) Stoddart, J.F. *Chem. Soc. Rev.* **1979**, *8*, 85-142. b) Webb, T.H.; Wilcox, C.S. *Chem. Soc. Rev.* **1993**, *22*, 383.

[15] Van Keulen, B.J.; Kellogg, R.M. *J. Am. Chem. Soc.* **1984**, *106*, 6029.

understand the interaction between molecules, which is what chemistry is about. We will illustrate this simplifying idea in the case of stereoselective synthesis. The presence of a C_2-symmetry axis within a chiral auxiliary or chiral ligand can serve the important function of dramatically reducing the number of possible competing diastereomeric transition states. The reaction of optically pure bis-ß-naphthol with $LiAlH_4$ (scheme1.2) in 1:1 ratio provides an adduct in which the two atoms H_A and H_B are homotopic, therefore the successive reaction with an achiral alcohol gives rise to the same reducing agent in solution. On the contrary, a chiral diol possessing only C_1-symmetry would make the atoms H_A and H_B diastereotopic and the reaction with an alcohol would provide two different species.[16] Whereas the C_1-symmetrical molecule will give rise to two possible transition states, the C_2-symmetrical analogue will only give one. This symmetry principle simplifies the understanding of a reaction to a great extent. Results obtained with C_2-symmetrical ligands are often explained in terms of reducing possible competing transition states. A second reason which might explain the success of C_2-symmetrical molecules is more an artistic than a scientific one. Symmetry is often associated with beauty. We are all struck by symmetrical objects such as, snow-flakes, flowers, crystals, butterflies, paintings, sculptures, buildings, etc. Also in chemistry symmetrical compounds, such as benzene, bucky balls, calixarenes, porphyrins, adamantanes, cubanes and the symmetrical structure of diamond and graphite are often referred to as artistically beautiful. Although at first sight trivial, this 'beauty' aspect may play an important role in the broad applicability of symmetrical molecules.

A third and more practical reason lies in the fact that symmetrical molecules are often crystalline which makes purification easy. Just keep in mind the great differences between the melting point of benzene (5°C) and toluene (-95°C). More than 80% of the C_2-symmetrical compounds described in this thesis were purified by crystallisation.



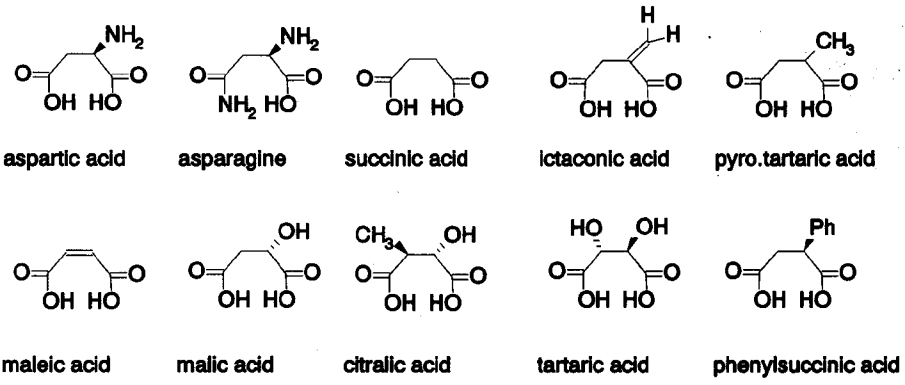
Scheme 1.2.

[16] a) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187. b) Rosini, C.; Franzini, L; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503.

1.3 *Butanedioic acids*

In this section we will briefly discuss the use and synthesis of butanedioic acids in organic chemistry. Butanedioic acids are among a group of important organic (natural) products.

The parent compound, trivial name succinic acid, was discovered by Agricola in 1546.[17] Succinic acid is a constituent of almost all plants and animal tissues. It is used in medicines, preservatives, flavouring agents, in textile, photography, cosmetics and detergents. We have summarised some common butanedioic acids in scheme 1.3.



Scheme 1.3. Butanedioic acids.

These butanedioic acids are not only important biologically compounds, but also valuable (starting) materials for the synthesis of natural products,[18] the design of enantioselective catalyst and auxiliaries,[19] resolving agents[20] and industrial products.[21] There are several methods for preparation of substituted butanedioic acids. They involve

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[17] a) The Merck Index, 11th ed. 8840, 1989 Merck & co. inc. b) Kirck-Othner, *Concise Encyclopedia of Chemical Technology*, Wiley & Sons, Inc., 1985, 1117.

[18] a) The use of tartaric acid is discussed in Section 1.4. b) Also see: Seebach, D. in *Modern Synthetic Methods*, Scheffold, R. (Ed.), Otto Salle Verlag, Frankfurt, 1980, p. 91. c) Seebach D.; Aebi, J.; Wasmuth, D. *Org. Synth. Coll. Vol.* **1990**, 153. d) Koot, W.J.; van Ginkel, R.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Modenaar, M.J.; Speckamp, W.N. *Tetrahedron Lett.* **1991**, *32*, 401.

[19] a) van Aken, E. Ph. D. Thesis Groningen, 1992, Chapter 6. b) see Section 1.3

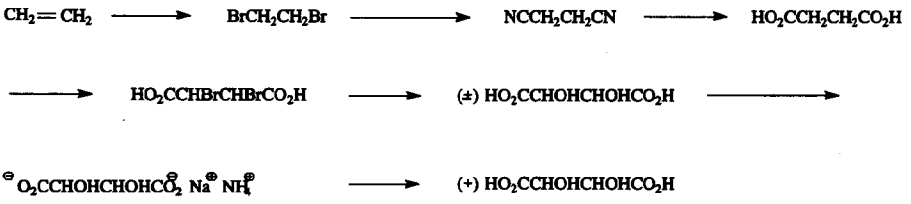
[20] See ref. 13.

[21] Aspartame: Oyana, K.; Kihara, K. *Chemtech.* **1989**, 100-104.

alkylation of butanedioic acid,[22] hydrolysis of nitrile intermediates,[23] oxidative dimerization of enolate anions,[24] condensation of butanedioic esters with aldehydes and ketones (the Stobbe reaction)[25] and hydrolysis of oxetanones.[26] Most of the methods mentioned above will be discussed in more detail throughout this thesis, together with the synthesis of several derivatives of butanedioic acids

1.4 Tartaric acid a C_2-symmetrical butanedioic acid

In this section we will combine aspects of the two previous sections, that is: symmetry and butanedioic acids. Tartaric acid is an unique compound, it has played an essential role in the events that led to the classical structural and stereochemical theory of organic chemistry. A nice description of the role of tartaric acid in organic chemistry in general can be found in an article by Robinson entitled "studies of the structure of tartaric acid before 1874"[27]. In this article it is also mentioned that (+)-tartaric acid was the first chiral natural product to be synthesized. The synthesis is outlined in scheme 1.4 and starts with ethylene.



Scheme 1.4. Total synthesis of (+) tartaric acid; the first synthesis of a chiral natural product

(*R,R*)-(+)-Tartaric acid, the so-called natural compound, is obtained in large quantities from potassium hydrogen tartrate, a waste product of wineries, which crystallize it from wine before bottling. The d,l also called racemic form is synthesized on large industrial scale from maleic anhydride and hydrogen peroxide. Resolution is possible either by crystallization or enzymatic conversions of the racemic acid. It is not widely

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[22] a) Kofron, W.G.; Wideman, L.G. *J. Org. Chem.* **1972**, *37*, 555. b) see ref. 18 c).

[23] a) Allen, C.F.H.; Johnson, H.B. *Org. Synth. vol 4*, **1963**, 804. b) Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 9735.

[24] a) Ratke, M.W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605. b) Belletire, J.L.; Spletzer, E.G.; Pinhas, A.R. *Tetrahedron Lett.* **1984**, 5469. c) Ebberson, L. *Acta Chem. Scand.* **1959**, *13*, 4549.

[25] Johnson, J.W.; Daub, G.H. *Org. React. 6*, **1951**, 1-73.

[26] a) Wynberg, H.; Staring, E.G.J. *J. Am. Chem. Soc.* **1982**, *104*, 166. b)idem, *J. Org. Chem.* **1985**, *50*, 1977.

[27] Robinson, M.J.T. *Tetrahedron* **1974**, *30*, 1499.

known that the enantiomeric (*S,S*)-(-)tartaric acid is also a natural product. Three Frenchmen discovered in 1936-1938 that the dry leaves of the bush plant Bauhinia[28] contains (-)tartaric acid, which can simply be isolated by hot water extraction. Thus tartaric acid is one of the few compounds of which both enantiomers occur in nature, other examples being lactic acid, camphor and citronellol.

The current prices for tartaric acid are approximately $3/kg for the (*R,R*) enantiomer and $100/kg for the (*S,S*) one. It is probably one of the cheapest chiral molecules in which both enantiomers are available on a multi-ton scale. This combination of accessibility and low price make that tartaric acid is the most used starting material in stereoselective synthesis. Also note that the C_2-axis within the molecule turns it into a very practical starting material. Its four functionalized carbon atoms are pairwise homotopic. So any transformation, by which only one of the groups reacts, creates four different functional groups. This allows the synthesis of a variety of valuable chiral building blocks, which in turn can be used in the synthesis of natural products.[28] The C_2-axis within the molecule also allows the design and synthesis of a variety of highly selective C_2-symmetrical auxiliaries and catalysts.[29]

Except for proline, tartaric acid is the single most important starting material for a variety of highly efficient catalysts in stereoselective synthesis,[30] the best known example being the Sharpless epoxidation.[29c] For the resolutions of bases, tartaric acid and its derivatives are among the most applied chiral acids.[13] Tartaric acid is also often used in industrial processes, either as resolving agent, catalyst or chiral auxiliary.[31] We have summarized several derivatives of tartaric acid in scheme 1.5. This might give an idea of the broad applicability of tartaric acid.

32 33 34 35 36 37 38 39

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[28] Seebach, D in *Modern Synthetic Methods*, Scheffold, R.(Ed.) Otto Salle Verlag, Frankfurt, **1980**, 91-171.

[29] a) Blaser, H.U. *Chem. Rev.* **1992**, *92*, 935. b) Brunner, H. *Topics in stereochemistry*, **1988**, *18*, 129. c) Pfenniger, A. *Synthesis*, **1986**, 89.

[30] see ref. 29 a).

[31] a) Sheldon, R.A. *Chirotechnology* **1993**, Marcell Dekker, Inc.

[32] a) Stoddart, J.F. *Chem. Soc. Rev.* **1979**, *18*, 85. b) Behr, J.P.; Lehn, J.M.; Moras, D.; Thierry, J-C. *J. Am. Chem. Soc.* **1981**, *103*, 701.

[33] Review: Beck, A.K.; Bastani, B.; Plattner, A.; Petler, W.; Seebach, D.; Braunschweiger, H.; Gysi, P.; La Vechia, L. *Chimia* **1991**, *45*, 238.

[34] Chapuis, C.; Jurczak, J. *Helv. Chim. Acta.* **1987**, *70*, 436.

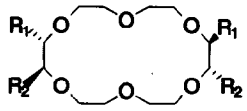
[35] a) Ref. 29 c). b) Izumi, Y. *Adv. Catal.* **1983**, *32*, 15. c) Roush, W.R.; Halterman, R.L. *J. Am. Chem. Soc.* **1986**, *108*, 294.

[36] a) Kagan, H.B.; Dang, T.P.J. *J. Am. Chem. Soc.* **1972**, *94*, 6429. b) Kagan, H. In "*Asymmetric Synthesis*" Morrison, J.D., Ed., Academic Press: New York **1983**, vol. 2-11-39.

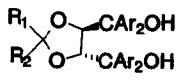
[37] Kolosa, T.;p Miller, M.J. *J. Org. Chem.* **1986**, *51*, 3055.

[38] a) Dener, J.M.; Hart, D.J.; Ranesh, S. *J. Org. Chem.* **1988**, *53*, 6022. b) Yoda, H.; Kitayama, H.; Yamada, W.; Katagari, T.; Takabi, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1951.

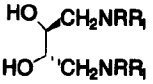
[39] Mori, K.; Takigawa, T.; Matsui, H. *Tetrahedron Lett.* **1976**, 3953



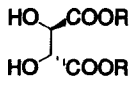
R_1=R_2=CONHR
R_1=COO^- , R_2=CONHAr
Host-Guest chemistry[32]



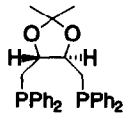
chiral auxiliary, ligand, resolving agent[33]



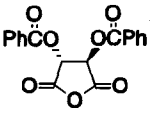
chiral ligand 34



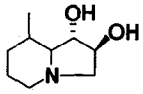
chiral ligand, auxiliary 35



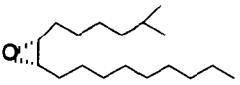
chiral ligand 36



chiral derivatizing agent[37]



R=H Lentiginosine
R=OH Swainsonine
natural products[38]



disparlure
natural product[39]

Scheme 1.5. Derivatives of tartaric acid, used in stereochemistry

1.4 Aim and survey of the contents of this thesis

Before we will give a brief survey of the contents of this thesis, we present a short introduction how the work in this thesis was accomplished. We started working on this thesis in october 1988. The work was sponsored by Unilever and involved the remote functionalisation of fatty acids, by intra-molecular bromination with substituted *N*-bromosuccinimides (see chapter 5). After six months, however, the military service interfered with our plans and the author was called to serve his country and the contract with Unilever was stopped. After 1½ years the author returned to the laboratory to work for Syncom, the company of Prof. Wynberg doing contract research for the pharmaceutical industry, in combination with the work described in this thesis. Because we were

already involved in the synthesis of chiral succinimides (cyclic derivatives of butanedioic acids), we decided to further investigate the synthesis and use of chiral cyclic derivatives of butanedioic acids. Two observations made by us were important for the work described in this thesis. Firstly, despite the wide scope of tartaric acid in stereochemistry only a few other C_2-symmetrical butanedioic acids have been applied in stereoselective synthesis, imparticular 2,3-dimethylbutanedioic acid and 2,3-diphenylbutanedioic acid.[40] Secondly, despite the wide use of tartaric acid in stereoselective synthesis, relatively few cyclic derivatives of the acid part on the molecule have been used.[41] Nagel *et al.* synthesized 3,4-bis(diphenylphosphino)pyrrolidine from tartaric acid and used it as a ligand in rhodium catalyzed hydrogenations.[41a] Other examples are, 3,4-diaminopyrrolidine,[41b] and 3,4-dihydroxy-1-phenylpyrrolidine as building block for chiral push-pull azobenzenes.[41c]In this thesis we will describe the synthesis and use of chiral cyclic derivatives of C_2-symmetrical butanedioic acids.

This chapter was used as a brief introduction in the field of high symmetry chiral molecules and the connection to butanedioic acids. The aim of the research described in this thesis was to develop chiral cyclic derivatives of C_2-symmetrical butanedioic acid and study possible applications in stereoselective synthesis. Chapter 2 of this thesis deals with the synthesis of C_2-symmetrical *N*-hydroxysuccinimides derived from tartaric acid and their use as chiral derivatizing agent. It turned out that these compounds can be used in the determination of the enantiomeric excess of carboxylic acids by means of ^{1}H-NMR. In chapter 3, several strategies for the synthesis of C_2-symmetrical 3,4-disubstituted pyrrolidines derived from the corresponding butanedioic acids will be discussed. These easily accessible chiral cyclic amines may find application in the field of resolving agents, chiral auxiliaries or building blocks for chiral ligands. This latter application is more explored in chapter 4, which deals with the synthesis and application of highly symmetrical (C_2, D_2, D_3 and C_4) nitrogen based chiral ligands. A variety of ligands has been synthesised and their complexation behaviour with transition metals studied. A first application of these ligands in enantioselective synthesis is also described in chapter 4. The final chapter will explain how we became interested in cyclic derivatives of C_2-symmetrical butanedioic acids. It deals with the synthesis of chiral *N*-bromosuccinimides, and their use in the remote functionalisation of fatty acids and enantioselective brominations.

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[40] a) The use of 2,3-dimethylbutanedioic acid is described in ref. 5 c). b) The use of 2,3-diphenylbutanedioic acid is described in chapter 3.

[41] a) Nagel, U.; Kinzel, E.; Andrade, J.; Prescher, G. *Chem. Ber.* **1986**, *119*, 3326; b) Nagel, U.; Trink, T. *Chem. Ber.* **1995**, *128*, 309. b) Reddy, D.D.; Thorton, R.E.; *J. Chem. Soc. Chem. Commun.* **1992**, 172. c) Hulshof, J. Ph. D. Thesis Groningen, **1995**.

CHAPTER 2

C_2-SYMMETRICAL *N*-HYDROXYSUCCINIMIDES AS CHIRAL DERIVATIZING AGENTS

2.1 Introduction

There is a constant need for methods to determine the ratio of enantiomers in chiral non-racemic compounds. Before the mid-1960's, enantiomeric purity was usually assessed by using chiroptical methods. This involved measuring the optical rotation of a sample with a polarimeter. This value, called optical purity, is then compared to the known rotation for an enantiomerically pure sample. It is still a widely used method in organic chemistry. However, there are several sources of error in using this method. If the maximum rotation is unknown, it must be determined by some means. The literature is poisoned with examples of incorrect optical rotations for compounds considered to be enantiomerically pure.[1] A second problem with optical purity is the potential presence of a chiral impurity, which will cause an unsuspected error in the observed rotation. This is particularly serious when the impurity has a high rotation.

Therefore, simple and more reliable methods for determining enantiomeric purity have been developed. Although impressive progress has been made in developing sensitive and accurate GC and HPLC methods,[2] many organic chemists prefer to use NMR methods.[3] NMR analysis may be performed with chiral complexing reagents,[4] chiral lanthanide shift reagents[5] and chiral derivatizing agents (CDA's).[3]

Among the various chiral derivatizing agents, Mosher's reagent, table 2.1, is widely used.[6] The α-methoxy-α(trifluoromethyl)phenylacetic acid derivatives can be analyzed with ^1H, ^{13}C and ^{19}F NMR. The acid chloride of Mosher's reagent reacts with primary and secondary alcohols or amines to form diastereomeric esters or amides.

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1 Weinges, K.; Dietz, V.; Oeser, T.; Irngartinger, H. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 680.

2 a) Schurig,V.; Nowotny, A.P. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 939. b) Okamato, Y.; Hatada, K. *J. Chromatogr.* **1987**, *389*, 95. c) Allenmark, S.G. *Chromatographic enantioseparation: Methods and Applications*, Ellis Horwood: Chichester, **1988**.

3 For some review articles on this issue see: a) Yamaguchi, S. In Morrison, J.D. *Asymmetric Synthesis*: Academic Press: New York, **1983**; vol. 1, chapter 7. b) Parker, D. *Chem. Rev.* **1991**, *91*, 1441. c) Hulst, R. Ph. D. Thesis Groningen, **1994**. d) Hulst, R.; Kellogg, R.M.; Feringa, B.L. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 115.

4 a) Shapiro, M.J.; Archinal, A.E.; Jarena, M.A. *J. Org. Chem.* **1989**, *54*, 5826 and references sited therein. b) Parker, D.; Fulwood, R. *Tetrahedron: Asymmetry* **1992**, *3*, 25.

5 Fraser, R.R. In Morrison, J.D. *Asymmetric Synthesis*; Academic Press: New York, **1983**: Vol. 1 Chapter 9.

6 a) Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543. b) Dale, J.A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

Despite the success of Mosher's reagent as CDA, several new CDA's have been developed. A selection of commonly used CDA's is summarized in table 2.1. The enantiomeric purity is determined via ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR methods. Several of the examples listed in table 2.1 have been developed in our laboratory.

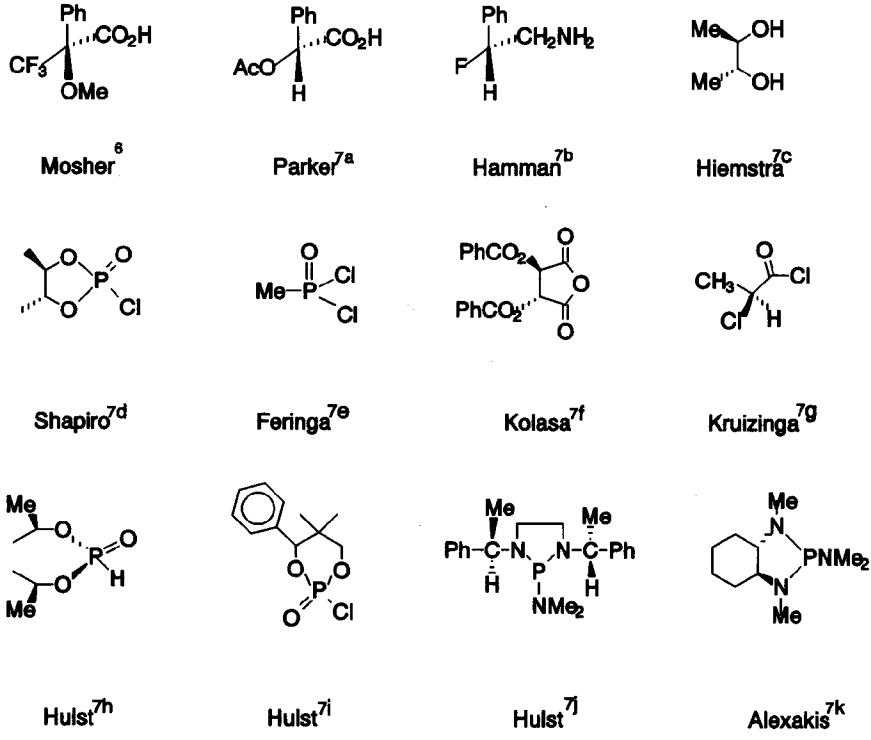

Table 2.1. Common chiral derivatizing agents

7

[7] a) Parker, D.J. *J. Chem. Soc. Perkin Trans 2* **1983**, 83. b) Hamman, S.J. *J. Fluorine Chem.* **1989**, *45*, 377. c) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183. d) Anderson, R.C.; Shapiro, N.J. *J. Org. Chem.* **1984**, *49*, 1304. e) Feringa, B.L.; Smaardijk, A.; Wynberg, H. *J. Am. Chem. Soc.* **1985**, *107*, 4798. f) Kolosa, T.; Miller, M.J. *J. Org. Chem.* **1986**, *51*, 3055. g) Kruizinga, W.H.; Bolser, J.; Kellogg, R.M.; Kamphuis, J.; Boesten, W.H.J.; Meÿer, E.M.; Schoenmaker, H.E. *J. Org. Chem.* **1988**, *53*, 1826. h) Hulst, R.; de Vries, K.; Feringa, B.L. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1092. i) Hulst, R.; Zijlstra, R.W.J.; Feringa, B.L.; de Vries, N.K.; ten Hoeve, W.; Wynberg, H. *Tetrahedron Lett.* **1993**, *34*, 1339. j) Hulst, R.; de Vries, N.K.; Feringa, B.L. *Tetrahedron: Asymmetry* **1994**, *5*, 699. k) Alexakis, A.; Mutti, S.;

It is noteworthy that many of the CDA's are developed for analysis of chiral amines or alcohols, but there are relatively few reports of useful CDA's for carboxylic acids.[8] Chiral derivatizing agents based on α-phenylethylamine or α-naphtylethylamine have been reported, but these methods often require in addition an achiral shift reagent. More useful are (S)-methylmandelate[9] and 2-fluoro-2-phenylethylamine.[7b] But no good, reliable CDA for determining the enantiomeric purity of carboxylic acids is available.[10] Our intention was to develop a generally applicable CDA for the determination of enantiomeric purity of carboxylic acids. The combination of dibenzoyltartaric acid anhydride as CDA for amines, hydroxylamines, amino acids and peptides[7f] and the use of *N*-hydroxysuccinimides in peptide synthesis[11] made us realize that chiral *N*-hydroxysuccinimides derived from tartaric acid, such as **201** might serve as CDA, figure 2.1. The corresponding diacetoxy derivative of **201** has been used in enantioselective peptide synthesis [11a].

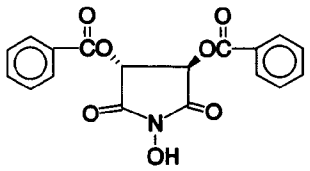

Figure 2.1 N-hydroxy-3,4-dibenzoyl-2,5-pyrrolidinedione 201

We will discuss the synthesis and use of these novel chiral C_2-symmetrical *N*-hydroxysuccinimides as CDA for the enantiomeric purity determination of carboxylic acids by means of ^{1}H-NMR.

2.2 Synthesis of N-hydroxysuccinimides derived from tartaric acid

We synthesized two novel chiral *N*-hydroxysuccinimides as outlined in scheme 2.1. Cyclisation of tartaric acid with 3.2 equivalents of the appropriate acid chloride afforded

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Mangeney, D. *J. Org. Chem.* **1992**, *57*, 1224.

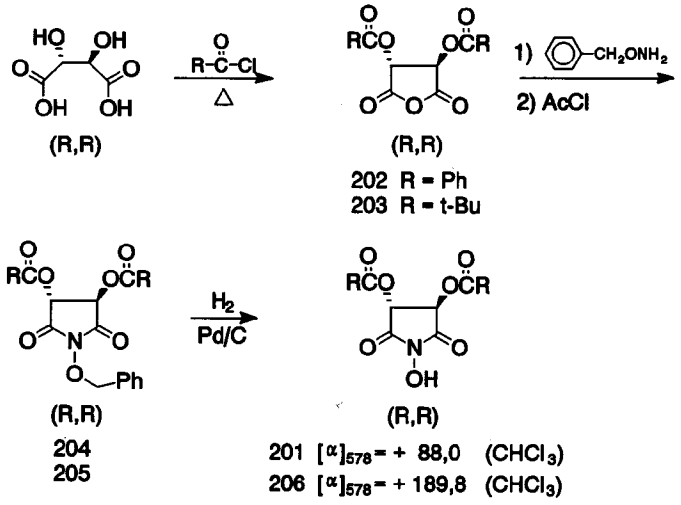
[8] a) Feringa, B.L.; Wynberg, H. *J. Org. Chem.* **1981**, *46*, 2547. b) Moorlag, H.; Kruizinga, W.H.; Kellogg, R.M. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 479.

[9] a) Brown, J.M.; Parker, D. *J. Org. Chem.* **1982**, *97*, 2722. b) Baker, K.V.; Brown, J.M.; Cooley, N.A.; Hughes, G.D.; Taylor, R.J. *J. Organometal. Chem.* **1989**, *370*, 397.

[10] a) Parker has used 1,2-diphenyl-diaminoethane as a chiral solvating agent for direct NMR assay of enantiomeric purity of carboxylic acids. Fulwood, R.; Parker, D. *Tetrahedron: Asymmetry* **1992**, *3*, 25. b) Recently another CDA has been developed: Brown, E.; Chevalier, C.; Huet, F.; Le Grumelec, C.L.; Lézé, A.; Touet, J. *Tetrahedron Asymmetry* **1994**, *5*, 1191.

[11] a) Teramoto, T.; Dequchi, M; Kurosaki, T. *Tetrahedron lett.* **1981**, *22*, 1109. b) Anderson, G.W.; Zimmerman, J.E.; Callahan, F. *J. Am. Chem. Soc.* **1963**, *85*, 3039.

the corresponding anhydrides **202** and **203** in high yield, following a literature procedure[12]. Treatment of these anhydrides with benzyloxyamine in THF at 0°C gave the half amide, which on cyclisation with acetyl chloride furnished imides **204** and **205**. The *O*-benzyl protected *N*-hydroxysuccinimides are highly crystalline compounds. Deprotection with H_2/Pd/C afforded the *N*-hydroxysuccinimides **201** and **206** as white solids.



Scheme 2.1. Synthesis of N-hydroxysuccinimides derived from tartaric acid

The synthesis is easily performed on a molar scale. The starting materials are readily available and all intermediates are crystalline compounds, which makes purification easy. The *N*-hydroxysuccinimides **201** and **206** are stable compounds and can be stored for years without decomposition.

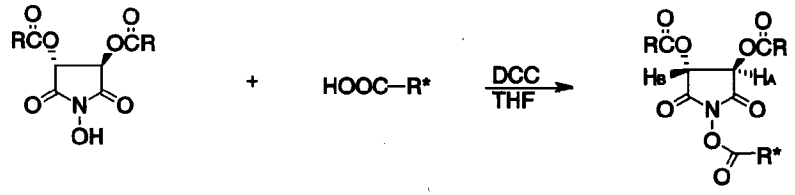
2.3 N-hydroxysuccinimides 201 and 206 as CDA for carboxylic acids

The formation of esters used in the ee determination of chiral carboxylic acids must, for obvious reasons, occur under conditions which exclude the possibility of racemization[13] or kinetic resolution. The formation should proceed without using high temperature, long reaction times or tedious reaction conditions. Work-up has to be easy and the esters may not be purified by crystallization. The coupling reaction of *N*-

[12] a) Shriner, R.L; Furrow, R. *Org. Synth. Coll. Vol. IV.* **1963**, 242. b) Bulter, C.L.; Cretcher, L.H. *J. Am. Chem. Soc.* **1933**, *55*, 2605. c) Duhamel, L.; Angibaud, P.; Ple, G.; Desmurs, J.R. *Synth. Commun.* **1993**, *23*, 2423.

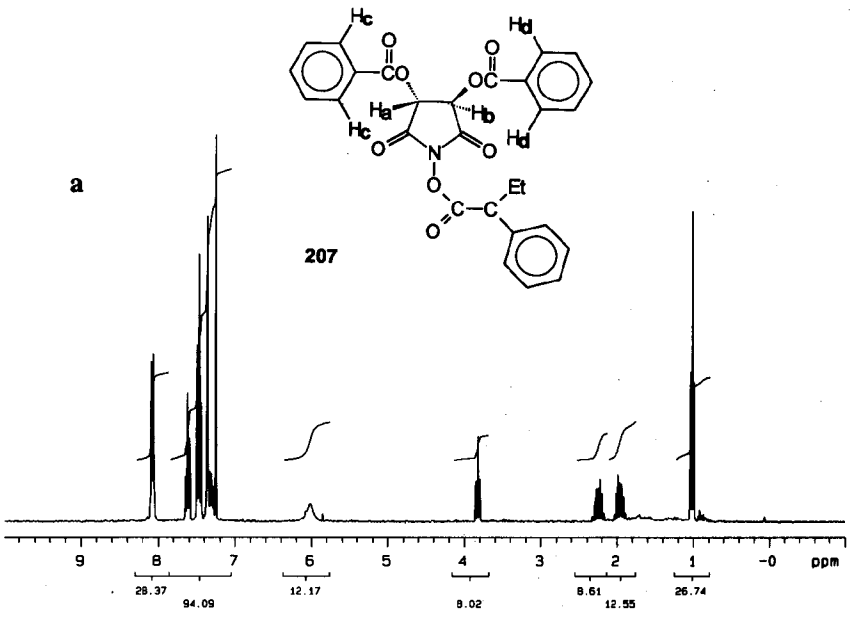
[13] *N*-Hydroxysuccinimide is used in peptide synthesis to prevent racemization of amino acids.

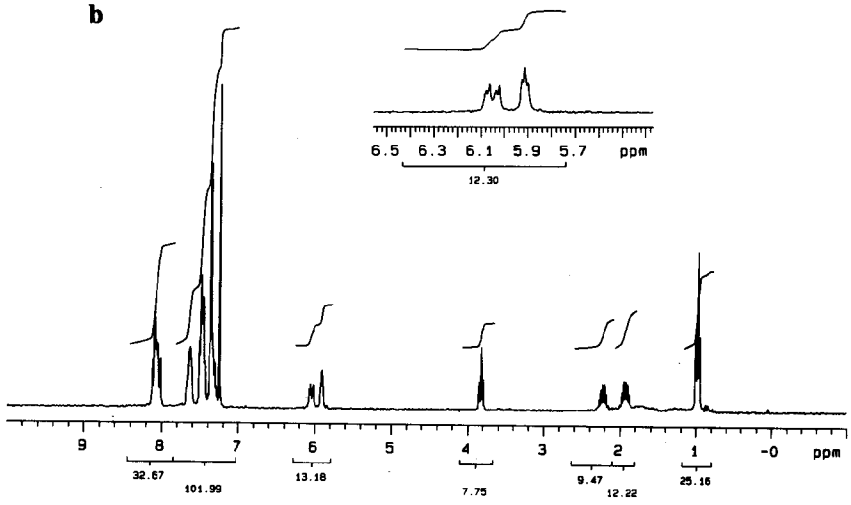
hydroxysuccinimides **201** and **206** with carboxylic acids providing esters **207** and **208** is depicted in scheme 2.2. The procedure is straightforward: a mixture of one equivalent of carboxylic acid, one equivalent N-hydroxysuccinimide **201** or **206** and dicyclohexylcarbodiimide(DCC) in THF is stirred for one hour. The dicyclohexylurea (DHU) is removed by filtration over silica and the solvent is evaporated. In all cases, the esters **207** and **208** were obtained as white solids, in quantitative yield.

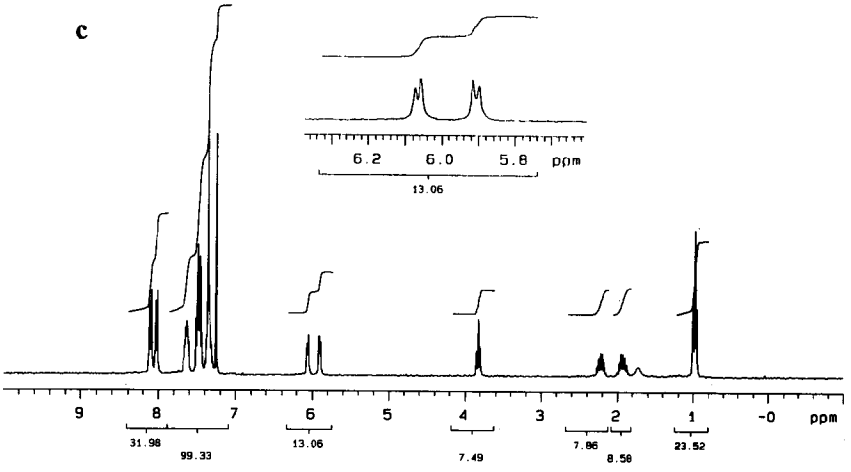


Scheme 2.2. Coupling reaction of N-hydroxysuccinimides 201 or 206 with chiral acids

The first acid we examined was 2-phenylbutyric acid. All three possible esters (racemic, R(-) and S(+)) were prepared in quantitative yield and analyzed by ^{1}H-NMR. Figure 2.3a shows the ^{1}H-NMR of racemic 2-phenylbutyric acid coupled to (3R,4R)-3,4-bisbenzoyl-*N*-hydroxysuccinimide (**201**) at room temperature.




b
6.5 6.3 6.1 5.9 5.7 ppm
12.30
9 8 7 6 5 4 3 2 1 -0 ppm
32.67
101.99
13.18
7.75
9.47
12.22
25.16


c
6.2 6.0 5.8 ppm
13.06
9 8 7 6 5 4 3 2 1 -0 ppm
31.98
99.33
13.06
7.49
7.86
8.58
23.52

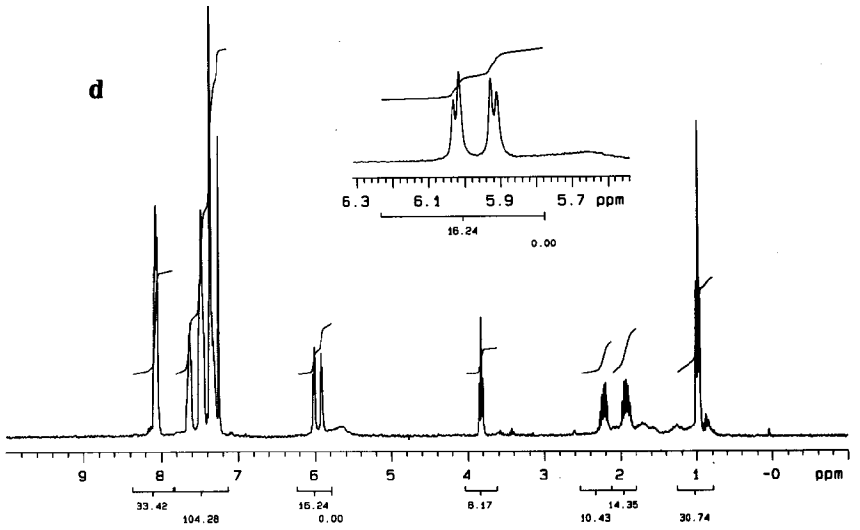
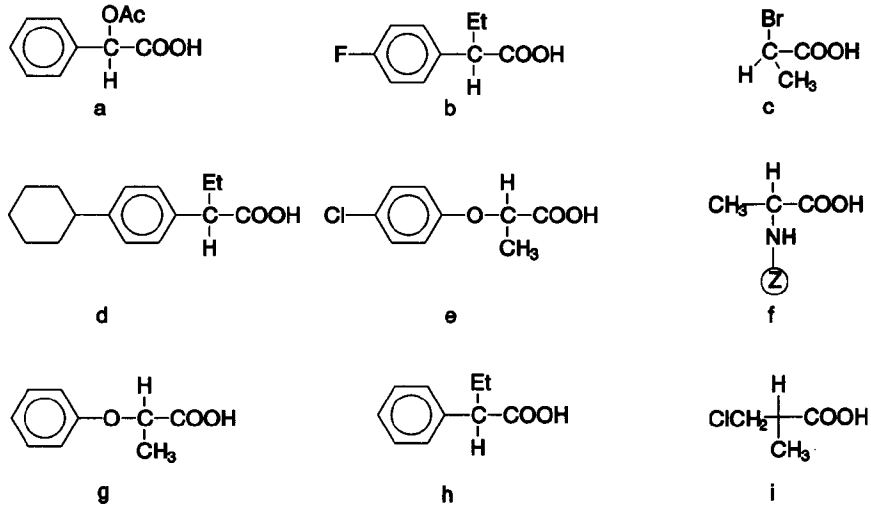


Figure 2.3 ^{1}H-NMR spectra of 2-phenylbutyric acid coupled to CDA 201 in $CDCl_3$; a) racemic 2-phenylbutyric acid at RT; b) racemic 2-phenylbutyric acid at -30°C; c) (R)-2-phenylbutyric acid at -30°C d) (S)-2-phenylbutyric acid at -30°C.

It is noticed that the signal for the H_A and H_B protons in **207**, at δ 6 ppm is very broad,figure 2.3a. Raising the temperature to 60°C a sharp singlet was observed. On lowering the temperature to -30°C a totally different spectrum was obtained, figure 2.3b. The whole system is conformational locked and the signals for the H_A and H_B protons are split into a double AB system. Distortion of the C_2-symmetry of the pyrrolidinedione ring system created by reaction with a chiral acid has made the homotopic protons H_A and H_B heterotopic.[14] The singlet observed in **201** is changed into an double AB system for **207**. The double AB system in figure 2.3b is created by the two diastereoisomers formed. The ^{1}H-NMR spectra recorded of -30°C of optically pure (R) and (S)-2-phenylbutyric acid coupled to **201** are shown in figure 2.3c and 2.3d respectively. In these cases an AB system for the H_A and H_B protons is observed. Integration of the two separate doublets at δ 6.08 and 6.02 ppm for the (R) and (S) enantiomer respectively allows the determination of the enantiomeric purity of 2-phenylbutyric acid. The ^{1}H-NMR shows another remarkable fact, namely that the ortho protons H_C and H_D of the phenyl ring at δ 8.15 ppm also become hetereotopic, creating double doublets for the optically pure esters, figure 2.3c and 2.3d and four doublets for the racemic ester, figure 2.3b. Even although

[14] When recording a ^{1}H-NMR of **201** or **206** at -30°C, only one signal was observed for the homotopic protons H_A and H_B, proving the C_2-symmetry.

the chiral centra in ester **207** are separated by 5 bonds, both diastereoisomers can be observed by ^{1}H-NMR at -30°C.



Scheme 2.3. Carboxylic acids used in the ^{1}H-NMR analysis with CDA's 201 and 206

The results obtained with a variety of carboxylic acids are summarized in table 2.2. Although the best results were obtained at -30°C, some entries (1,15 and 17) also gave peak separation at room temperature. The chemical shift differences of the doublets, observed for the H_A and H_B resonances generally ranges from 0.03 to 0.2 ppm, but are always baseline separated. Other resonances within the esters **207** and **208** may also provide diastereomeric peak separation. No significant differences were observed between CDA's **201** and **206**.

These observations indicate that, within NMR detection limits, the chiral C_2-symmetrical N-hydroxysuccinimides **201** and **206** can be used in the determination of the enantiomeric excess of carboxylic acids by ^{1}H-NMR.[15]

[15] We checked this by comparison of samples with known enantiomeric composition determined by polarimetry and ^{1}H-NMR.

Table 2.2. **^{1}H-NMR data for diastereoisomeric esters 207 and 208.**

entry	CDA	substrate	δ(ppm)	Δδ(ppm)
1	**206**	a (rac)	5.58-5.66	0.08
2	**206**	a (-)	5.58	
3	**206**	b (rac)	5.72-5.76	0.04
4	**206**	b (+)	5.76	
5	**206**	b (-)	5.72	
6	**206**	d (rac)	5.67-5.70	0.03
7	**206**	d (+)	5.70	
8	**206**	d (-)	5.67	
9	**206**	e (rac)	5.67-5.77	0.1
10	**201**	f (rac)	6.08-6.15	0.07
11	**201**	f (-)	6.08	
12	**201**	h (rac)	6.02-6,08	0.06
13	**201**	h (+)	6.08	
14	**201**	h (-)	6.02	
15	**201**	a (rac)	6.00-6.08	0.08
16	**201**	a (-)	6.00	
17	**201**	g (rac)	5.94-6.14	0.2
18	**201**	c (rac)	6.04-6.08	0.04
19	**201**	i (rac)	6.07-6.10	0.03

The indices refer to scheme 2.3; entries 12,13 and 14 refer to the spectra in figure 2.3; the resonances observed are for the H_A and H_B protons.

2.4 Conclusions

We have described a convenient method for the synthesis of C_2-symmetrical chiral *N*-hydroxysuccinimides derived from tartaric acid. These compounds **201** and **206** are useful chiral derivatives agent for the determination of the enantiomeric excess of carboxylic acids by ^{1}H-NMR. The method is quite attractive because, a) the esters are easily prepared and b) the NMR signals appear in an area of the spectrum (δ 5.5-6.2 ppm) generally unobscured by other resonances.

2.5 *Experimental section*

General remarks

All experiments were performed under an inert (N_2) atmosphere when necessary. All solvents were used without further purification, unless otherwise noted. All commercially available chemicals were obtained from Janssen Chimica (Acros), Aldrich or Fluka and were used without further purification. Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope. Optical rotations were determined at room temperature using a Perkin-Elmer 241 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. All rotation were determined with a concentration of c=1. ^{1}H-NMR spectra were recorded on a Varian Gemini-200 (200MHz) or on a Varian VXR-300 spectrometer (at 300 MHz). For 200 and 300 MHz spectra the ^{1}H-NMR and ^{13}C-NMR chemical shifts are determined relative to the solvent ($CDCl_3$, unless otherwise noted) and converted to the TMS scale using $\delta(CDCl_3)$ = 7,26 ppm and 76,9 ppm. ^{13}C-NMR spectra were recorded in the APT mode on either a Varian Gemini 200 (50.32 MHz) or Varian VXR-300 (75.48 Hz) spectrometer. Splitting patterns for ^{1}H-NMR are designed as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet) and br (broad). For ^{13}C-NMR the spectra are designed giving a positive value for the C and CH_2 peaks and a negative value for the CH and CH_3 peaks. Exact mass determinations were carried out on an AFJ-MS-902 spectrometer by Mr. A. Kieviet. Elemental analyses were performed in the micro analytical section of our department by Mr. H. Draaijer, Mr. J. Ebels and Mr. J. Hommes. The X-ray analysis was performed by Mr. F. van Bolhuis.

(3*R*,4*R*)-3,4-Dibenzoyloxydihydro-2,5-furandione (202) was prepared according to the procedure described in chapter 5. Yield 93%; mp 192-193°C (lit.[12] 173°C); ^{1}H-NMR: δ 6.1 (s,2H), 7.5 (t,4H), 7.6 (t,2H), 8.1 (d,4H); ^{13}C-NMR: δ 72.79 (CH), 127.04 (C), 128.69 (CH), 130.23 (CH), 134.53 (CH), 163.33 (C=O), 165.32 (C=O).

(3*R*,4*R*)-3,4-Dipivaloyloxydihydro-2,5-furandione (203) was prepared according to the procedure described in chapter 5. Yield 80%; ^{1}H-NMR: δ 1.25 (s,18H), 5.6 (s,2H); ^{13}C-NMR: δ 26.64 (CH_3), 72.18 (CH), 163.46 (C=O), 170.61 (C=O).

(3*R*,4*R*)-*N*-Benzyloxy-3,4-dibenzoyloxy-2,5-pyrrolidinedione (204)
A mixture of benzyloxyamine·HCl (25 g, 0,156 mol) and diethylamine (50 ml) in THF (200 ml) was stirred vigorously for 3 hours and filtered. The diethylamine·HCl salt was washed with THF (100 ml). The combined filtrates were cooled in a ice-water bath and anhydride **202** (53,04 g, 0,156 mol) was added portionwise. The resulting solution was stirred for 5 hours and concentrated to afford a white solid. To this solid was added AcCl (300 ml), the mixture was refluxed for 3 hours and excess AcCl was removed. The crude product was dissolved in EtOAc, washed with H_2O, 10% $NaHCO_3$ and dried (Na_2SO_4). Evaporation and crystallization from MeOH yielded 53,4 g (75%) of **204**. mp 105,7-

106,4°C; $[\alpha]_D$= + 147° (CH_2Cl_2); ^{1}H-NMR: δ 5,18 (dd,2H), 5,64 (s,2H), 7,25-7,6 (m,11H), 8,0 (d,4H); ^{13}C-NMR: δ 71,50 (CH), 79,3 (CH_2), 127,68 (C), 128,5 (CH), 129,5 (CH), 129,99 (CH), 130,08 (CH), 132,75 (C), 134,08 (CH), 169,52 (C=O), 165,3 (C=O); Anal. calc. for $C_{25}H_{19}O_7N$: C 67.40; H 4.30; N 3.15 Found: C 67.41; H 4.43; N 3.15; HRMS calc. for $C_{25}H_{19}O_7N$: 445,116 Found: No exact mass could be determined due to elimination of the benzoyl group (105) as indicated by the M/e 340 peak.

(3*R*,4*R*)-*N*-Benzyloxy-3,4-dipivaloyloxy-2,5-pyrrolidinedione (205) was prepared in the same as described for **204**. Yield 85%; mp 113,5-114,2°C; $[\alpha]_{578}$= +108,6° (CH_2Cl_2); ^{1}H-NMR: δ 1,2 (s,18H), 5,1 (dd,2H), 5,25 (s,2H), 7,35-7,45 (m,5H); ^{13}C-NMR δ: 26,74 (CH_3), 38,69 (C), 70,93 (CH), 79,17 (CH_2), 128,46 (CH), 129,47 (CH), 129,93 (CH), 132,74 (C), 164,63 (C=O), 177,18 (C=O); Anal. calc. for $C_{21}H_{27}NO_7$: C 62.19; H 6.72; N 3.46 Found: C 62.57; H 6.78; N 3.39; HRMS calc. for $C_{21}H_{27}O_7N$: 404,171 Found: No exact mass could be determined due to elimination of the pivaloyl group (91).

(3*R*,4*R*)-*N*-Hydroxy-3,4-dibenzoyloxy-2,5-pyrrolidinedione (201)
A suspension of imide **202** (15 g, 33 mmol) and Pd/C (10%)(1 g) in MeOH (200 ml) was hydrogenated for 2 hours. The catalyst was removed by filtration and the filtrate evaporated. The crude product was crystallized from CH_2Cl_2/octane to afford **201** as a white solid. Yield 11,5 g (98%); mp 150-152°C; $[\alpha]_{578}$= + 189,9° ($CHCl_3$); ^{1}H-NMR: δ 5,8 (s,2H), 6,4-7,0 (br,OH), 7,25-7,6 (m,6H), 8,0 (d,4H); ^{13}C-NMR: δ 66,64 (CH), 123,47 (CH), 125,12 (CH), 128,9 (CH), 160,43 (C), 160,52 (C=O); Anal. calc. for $C_{18}H_{13}O_7N$: C 60.83; H 3.69; N 3.94. Found: C 60.63; H 3.80; N 3.91; HRMS calc. for $C_{18}H_{13}O_7N$: 335,069 Found: No exact mass could be determined due to elimination of the benzoylgroup.

(3*R*,4*R*)-*N*-Hydroxy-3,4-dipivaloyloxy-2,5-pyrrolidinedione (206) was
prepared in the same manner as described for **201**. Yield (90%);mp 171-174°C; $[\alpha]_{578}$= +88° ($CHCl_3$); ^{1}H-NMR: δ 1,25 (s,18H), 5,4 (s,2H), 7,4-8,0 (br,1H); ^{13}C-NMR: δ 26,78 (CH_3), 38 (CH), 71,05 (CH), 165,6 (C=O), 178 (C=O); Anal. calc. for$C_{14}H_{21}O_7N$: C 53.33; H 6.71; N 4.44 Found: C 53.14; H 6.79; N 4.40; HRMS calc. for $C_{14}H_{21}O_7N$: 315,132 Found: 315,132.

Typical procedure for the determination of the enantiomeric excess of carboxylic acids by use of reagents 201 and 206.
To a solution of carboxylic acid (1 eq.) and reagent **201** or **206** (1 eq.) in THF was added DCC (1 eq.). The mixture was stirred for an hour and the DHU was removed by filtration over silica. The filtrate was evaporated to afford **207** or **208** as white solids. The solid was dissolved in $CDCl_3$ and a ^{1}H-NMR was taken at -30°C to determine the enantiomeric excess.

Spectroscopic data for representative example of **207.** Ester depicted in figure 2.3 (-)2-phenylbutyric acid . mp 162-164°C; ^{1}H-NMR: see figure 2.3; ^{13}C-NMR: 11,71 ($CHCl_3$; 26,93 (CH_2); 50,27 (CH); 71,30 (CH); 127,56 (C); 127,8 (CH); 127,85 (CH); 128,46

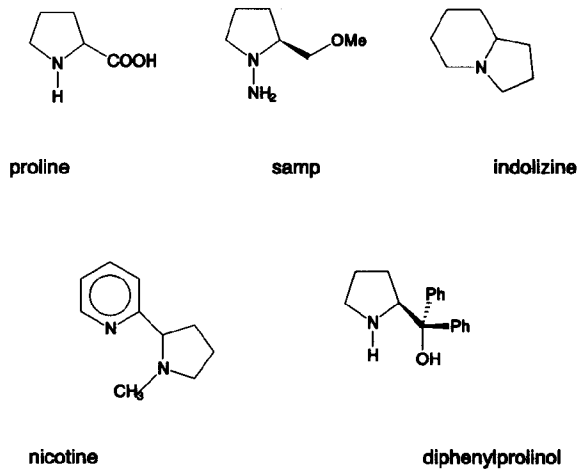
(CH); 128,7 (CH); 130,11 (CH); 134,04 (CH), 136,18 (C); 162,61 (C=O); 165,02 (C=O); 168,77 (C=O); HRMS calc. for 501,142 Found: 501,142.

CHAPTER 3

C_2 - SYMMETRICAL 3,4-DIDUBSTITUTED PYRROLIDINES

3.1 Introduction

The pyrrolidine ring system is common to many naturally occurring[1] and medicinally important compounds.[2] Furthermore, chiral auxiliaries,[3] chiral bases,[4] and chiral ligands[5] for enantioselective synthesis often employ this heterocyclic moiety. Proline, 2-carboxypyrrolidine, is the most important starting material for a variety of highly selective chiral agents.[3b,6] Some important molecules containing the pyrrolidine ring system are listed in scheme 3.1.



Scheme 3.1.

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1 (a) Jones, T.H.; Blum, N.S., Fales, H.M. *Tetrahedron* **1982**, *38*, 1949. (b) Stevens, R.V. *Acc. Chem. Res.* **1977**, *10*, 193.

2 Silverman, R.B; Nanavati, S.M. *J. Med. Chem.* **1990**, *33*, 931.

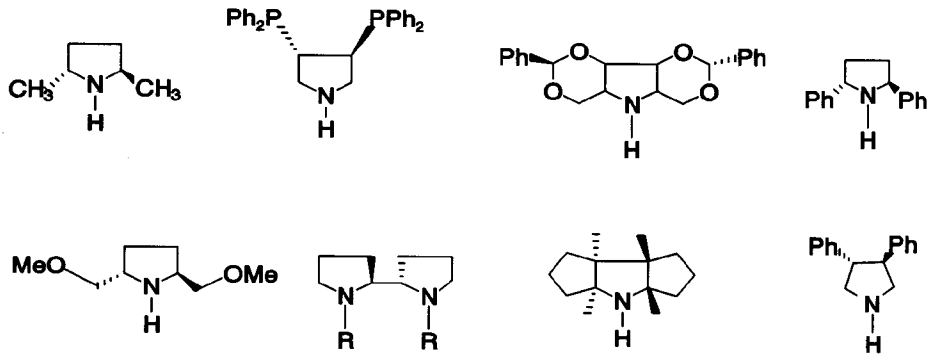
3 (a) Whitesell, J.K. *Chem. Rev.* **1989**, *89*, 1581-1590. (b) Blaser, H.U. *Chem. Rev.* **1992**, *92*, 935.

4 Tomioka, K. *Synthesis* **1990**, 541.

5 See chapter 4

6 Also see: Enders, D.; Fey, P; Kipphardt, H. *Org. Synth.*, **1987**, *65*, 173 and 183 and references cited therein.

There are several procedures for the synthesis of substituted pyrrolidines.[7] C_2-symmetrical pyrrolidines are a special class, which are often applied as chiral auxiliaries or chiral ligands[8,9] in asymmetric synthesis. Scheme 3.2 summarizes some of these C_2-symmetrical pyrrolidines.



Scheme 3.2. Some C_2 -symmetrical pyrrolidines used in asymmetric synthesis

These cyclic C_2-symmetrical amines are used in a variety of stereoselective reactions; the enantiomeric excesses obtained with these molecules can be very high (> 90% ee).There are probably two main reasons why these molecules are so successful in asymmetric synthesis. First, the presence of a C_2-symmetry axis within the chiral auxiliary or ligand can dramatically reduce the number of possible competing diastereomeric transition states, for an example see chapter 1. Secondly, as pointed out by Blaser[10], molecules with a cyclic structure have more chance to act as a successful ligand and auxiliary. Because of the rigid structure of the pyrrolidine ring, the number of transition states will again be reduced.

A major problem with chiral C_2-symmetrical pyrrolidines (and chiral C_2-symmetrical molecules in general) is their synthesis. Many investigations of possible applications have been seriously hampered by the difficulty of preparing these cyclic

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7 Burgess, L.E.; Meyers, A.I. *J. Org. Chem.* **1992**, *57*, 1656 and references cited therein.

8 Whitesell, J.K. *Chem. Rev.* **1989**, *89*, 1581.

9 (a) Veit, A.; lenz, R.; Seiler, M.E.; Neuberger, M.; Zehnder, M.; Giese, B. *Helv. Chim. Acta.* **1993**, *76*, 441. (b) Porter, N.A.; Scott, D.M.; Rosenstein, J.; Giese, B.; Veit, A; Zeitz, H.G. *J. Am. Chem. Soc.* **1991**, *113*, 1791. (c) Nasaki, S.; Oda, H.; Kzatu, K.; Usui, A.; Akichiko, I.; Xu, F. *Tetrahedron Lett.* **1992**, *33*, 5089. (d) Whitesell, J.K.; Ninton, M.A.; Chen, K.N. *J. Org. Chem.* **1988**, *53*, 5283. (e) Tomioka, K.; Nkajima, M; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213. (f) Chong, J.M.; Clake, I.S.; Koch, I.; Olbach, P.C.; Taylor, N.J. *Tetrahedron: Asymmetry* **1995**, *6*, 409. (g) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniouchi, Y.; Katsuki, T.; Yamaquchi,M. *Tetrahedron Lett.* **1984**, *25*, 857.

10 Blaser, H.U. *Chem. Rev.* **1992**, *92*, 935.

amines.[11] Part of the problem associated with the synthesis is the result of a preference for many reactions to form the cis (thus meso) isomer. Several syntheses, described in the literature[12] are very tedious, or will only produce one enantiomer. To explore fully the possibilities of C_2-symmetrical pyrrolidines it is desirable to prepare both enantiomers on a multi-gram scale.

In this chapter we will describe a convenient synthesis for the preparation of chiral C_2-symmetrical 3,4-disubstituted pyrrolidines, derived from the corresponding succinimides. Although the chiral centre is further away from the nitrogen atom, compared to the 2,5-disubstituted pyrrolidines these cyclic amines may be applied as chiral auxiliaries,[13] chiral ligands,[14] resolving agents and for incorporation into organic materials for nonlinear optical applications.[15]

3.2 (R,R)- and (S,S)-3,4-Diphenylpyrrolidine

3.2.1 Introduction

Optically pure 3,4-diphenylpyrrolidine was first synthesized by Tomioka[13a] in 1987. The experimental data, however, were published only in 1993.[13b,c] This is the only available route described for the synthesis of optically pure 3,4-diphenylpyrrolidine. The synthesis is outlined in scheme 3.3. Racemic 2,3-diphenylbutanedioic acid[16] is easily converted to the cyclic anhydride by reaction with acetyl chloride. This anhydride is converted into the half ester by reaction with (-)-menthol.[17] The two diastereomeric half acids can be separated via their potassium salts. The half ester is reduced with $LiAlH_4$ to (*R,R*)-3,4-diphenyl-1,4-butanediol. The corresponding ditosylate is transformed into *N*-benzylpyrrolidine by reaction with benzylamine in xylene. Deprotection with H_2/Pd/C gives enantiomerically pure (*R,R*)-3,4-diphenylpyrrolidine ($[\alpha]_D^{20}$ = -226°($CHCl_3$)). The overall yield, starting with racemic 2,3-diphenylbutanedioic acid is approximately 15%.

In this section we will describe several novel routes to optically pure (*R,R*)- and (*S,S*)-3,4-diphenyl pyrrolidine starting with 2,3-diphenylbutanedioic acid.

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[11] See ref. 3

[12] (a) Short,R.P.; Kennedy, R.M.; Nasanume,S. *J. Org. Chem.* **1989**, *54*, 17755. (b) See ref. 9(e-f) (c) Yanazaki, T.; Giori, R.; Welch, J.T. *Synlett.* **1991**., 573. (d) See ref. 9(d)

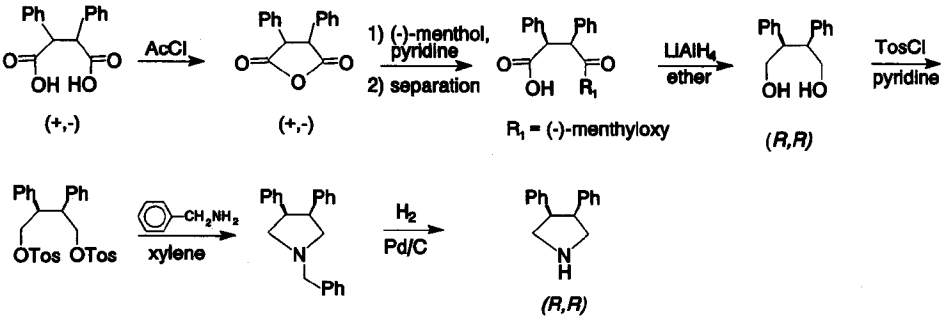
[13] (a) Tomioka, K.; Nakajima, M.; Koga, K. *Chem. Lett.* **1987**, 63. b) Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 9735.(c) Very recently a enantioselective synthesis of 3,4 diphenylpyrrolidine using asymmetric nitroalkene cycloadditions has been described. Denmark, S.E.; Marcin, L.R. J. Org. Chem. **1995**, *54*, 3221.

[14] (a) Tomioka, K.; Nokajima, M.; Koga, K. *Tetrahedron lett.* **1990**, *31*, 1741. (b) Kubota, H.; Koga, K. *Tetrahedron Lett.* **1994**, *35*, 6689.

[15] See ref. 9(d)

[16] (a) Wren, H.; Still, Ch.J. *J. Chem. Soc.* **1915**, 444. (b) Wren, H.; Still, Ch.J. *J. Chem. Soc.* **1915**, 1449. (c) Wren, H.; Still, Ch.J. *J. Chem. Soc.* **1915**, 513.

[17] Berova, N.D.; Kurtev, B.J. *Tetrahedron* **1969**, *25*, 2301.



Scheme 3.3. Synthesis of (3R,4R) diphenyl pyrrolidine

3.2.2 Synthesis of 2,3-diphenylbutanedioic acid

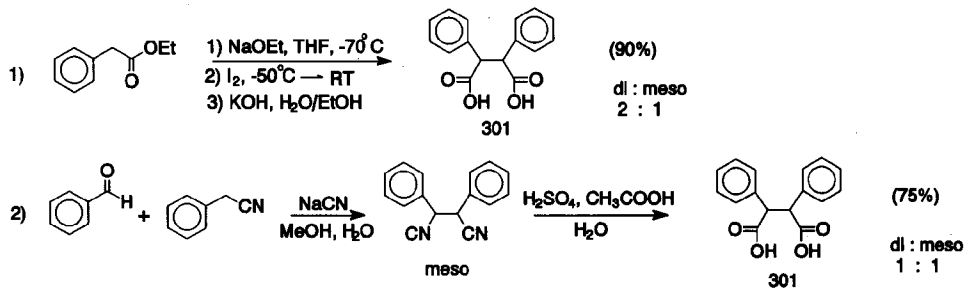
Starting material for all approaches is 2,3-diphenylbutanedioic acid (**301**), which was first described by Wren and Still.[16] The best route to trans 2,3-diphenylbutanedioic acid is described by Belletire[18] and involves the oxidative coupling of the dianion of phenylacetic acid with iodine. The diacid is formed in an 11:1 dl/meso isomer ratio. This reaction, however, needs large amounts of n-BuLi, which makes larger scale preparation of 2,3-diphenylbutanedioic acid expensive. We have used two other methods[19] for the large scale synthesis of 2,3-diphenylbutanedioic acid. Both methods are outlined in scheme 3.4 and will be discussed briefly. Ethyl phenylacetate is deprotonated with NaOEt in THF at -70°C. The resulting ester enolate undergoes an oxidative coupling reaction with iodine to give in high yield (>95%) the diester. This diester is without isolation converted to the diacid **301** by saponification with KOH in water/ethanol. The diacid is obtained as a meso/dl (1:2) mixture. The synthesis is easily performed on a two mole scale. The second method involves hydrolysis of meso 1,2-dicyano-1,2-diphenyl ethane[19b] with H_2SO_4/ acetic acid/water. Although the yield is good, we prefer the route starting with ethyl phenyl acetate, since the second route requires large amounts of NaCN. The meso/d,l mixture of acid **301** can be separated via their barium salts. The d,l acid can be resolved with brucine[16] or 2-amino-1-(*p*-nitrophenyl)-propane-1,3-diol.[20] Several other optically active derivatives of 2,3-diphenylbutanedioic acid have been described in the

[18] Belletire, J.L.; Spletzer, E.G.; Pinhas, A.R. *Tetrahedron Lett.* **1984**, 5969.

[19] (a) Saltiel, J.; Shannon, P.T.; Zafiriou, O.C.; Uriarte, A.K. *J. Am. Chem. Soc.* **1980**, *102*, 6799. (b) Davis, R.B.; Ward, J.A. *Org. Synth. Coll. Vol. IV* **1962**, 392. (c) Wawzonek, S. *J. Am. Chem. Soc.* **1990**, *62*, 745.

[20] Krause, H.W.; Meinicke, C. *J. Prakt. Chem.* **1985**, *327*, 1023.

literature.[21] Very recently an enantioselective synthesis of 2,3-diphenylbutanedioic acid has been described which makes use of the oxidative homo coupling of optically active 3-acyl-2-oxazolidones.[21f]



Scheme 3.4. Synthesis of 2,3-diphenylbutanedioic acid

3.2.3 Resolution of 3,4-diphenyldihydro-2,5-furandione with (α)-phenylethylamine

Our first approach for the synthesis of optically pure 3,4-diphenylpyrrolidine **305** is outlined in scheme 3.5. Ring closure of the crude 2,3-diphenylbutanedioic acid (**301**, meso/d,l) mixture in boiling acetic anhydride provided to our pleasant surprise pure d,l anhydride **302**. Both the melting point (115-116°C, lit[17] 115-116°C, meso[21(a)] 170-175°C) and ^{1}H-NMR indicate that during the cyclization an epimerization takes place to the more stable trans anhydride. This epimerization is of great advantage, because the d,l and meso acids do not need to be separated.

Ring opening with (*S*)-α-phenylethylamine in THF gave a 1:1 diastereomeric mixture of amid acid **303**. The two diastereomeric acids were easily separated by one crystallisation from 2-butanone, providing the (*R,R,S*) isomer in 35% yield. The diastereomeric excess was higher than 95%, as followed from ^{1}H-NMR. Ring closure of the (*R,R,S*) amid acid **303** to the corresponding imide **304** under a variety of circumstances (Ac_2O, AcCl, $SOCl_2$) gave extensive epimerisation. However, when we used concentrated HCl in AcOH the imide **304** was obtained in reasonable yield and high diastereomeric purity. Reduction with $LiAlH_4$ in THF and subsequent hydrogenation gave in 80% yield optically pure (*R,R*)-3,4-diphenylpyrrolidine (**305**). The same sequence was also performed starting with (*R*)-α-phenylethylamine and optically pure (*S,S*)-3,4-diphenylpyrrolidine was obtained in the same overall yield as described for the (*R,R*) enantiomer. Thus both enantiomers of 3,4-diphenylpyrrolidine are available via this route, which includes resolution of the cyclic anhydride **302** with α-phenylethylamine.

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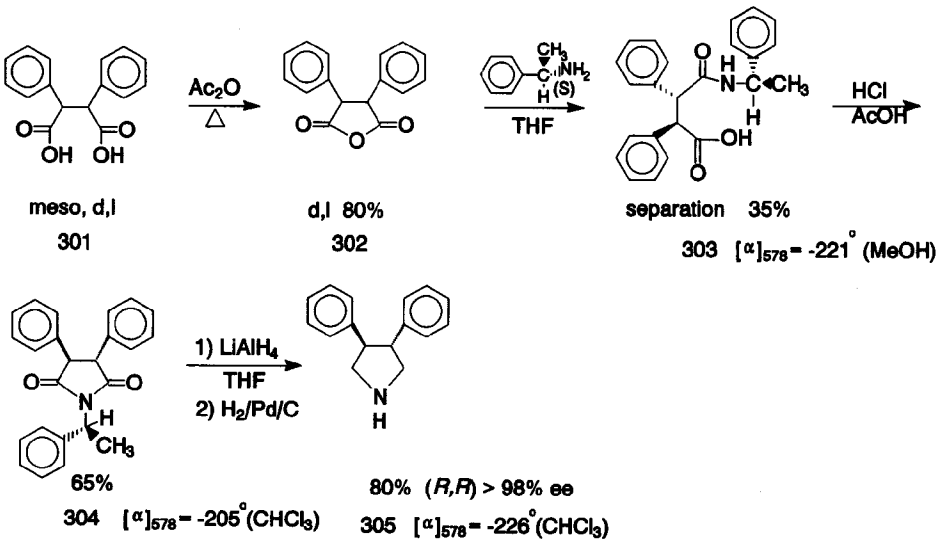
[21] (a) see ref. 16 (b) Buchan, R.; Watson, M.B. *J. Chem. Soc. CC* **1968**, 2465. (c) Ogura, F.; Nakao, A.; Nakagana, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 291. (d) see ref. 17. (e) *J. of Organomet. Chemistry* **1992**, *423*, 270. (f) Kise, N.; Tokioka, K.; Aoyama, Y. *J. Org. Chem.* **1995**, *60*, 1100.



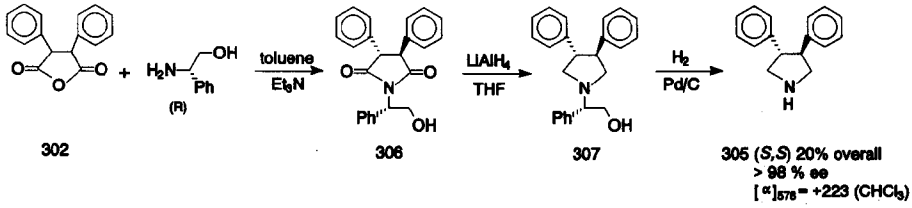
Scheme 3.5. Synthesis of (3R,4R)-3,4-diphenylpyrrolidine via amide acid approach

3.2.4 Resolution of 3,4-diphenyldihydrofuran-2,5-dione with (R)-phenylglycinol

The second route to optically pure 3,4-diphenylpyrrolidine (**305**) makes use of another chiral auxiliary, phenylglycinol. This simple amino alcohol is prepared from phenylglycine by reduction with $LiAlH_4$ without racemisation.[22] Since both enantiomers of phenylglycine are commercially available and cheap, both enantiomers of phenylglycinol are easily accessible. The synthesis of (*S,S*)-3,4-diphenylpyrrolidine (**305**), with (*R*)-phenylglycinol as chiral auxiliary is described in scheme 3.6. Cyclization of cyclic anhydride **302** with (*R*)-phenylglycinol in boiling toluene with a catalytic amount of Et_3N[23] produces a 1:1 mixture of diastereomers. After two crystallizations from EtOH, the (*S,S,R*) diastereomer (**306**) [24] was isolated in 30%. The (*S,S,R*) diastereomer **306** was obtained in more than 95% diastereomeric purity, as determined by ^{1}H-NMR.[25] After being converted to the corresponding pyrrolidine **307**, reduction with $LiAlH_4$ in THF, the chiral auxiliary was removed by hydrogenation over Pd/C 10%. The overall

[22] Meyers, A.I.; Dideman, D.A.; Bailey, T.R. *J. Am. Chem. Soc.* **1985**, *107*, 7974.
[23] Meyers, A.I.; Lefker, B.A.; Sowin, T.J.; Westrum, L.J. *J. Org. Chem.* **1989**, *54*, 4243.
[24] Configuration related to 3S,4S-diphenylpyrrolidine
[25] No other diastereoisomer could be detected by 200 MHz ^{1}H-NMR.

yield of (*S,S*)-3,4-diphenylpyrrolidine (**305**) was 20%.[26] Both enantiomers of 3,4-diphenylpyrrolidine are available via this relatively easy route in good yield.



Scheme 3.6. Synthesis of (3S,4S)-3,4-diphenylpyrrolidine via (R)-phenylglycinol

3.2.5 Resolution of d,l-3,4-diphenylpyrrolidine

In our group much research has been carried out on resolutions and resolving agents.[27,28,29] Especially, a series of cyclic phosphoric acids have received much attention and have proven to be valuable resolving agents. In this section we will describe the synthesis of optically pure 3,4-diphenylpyrrolidine via resolution of the racemic amine. The synthesis of racemic 3,4-diphenylpyrrolidine is given in in scheme 3.7. Reaction of the (meso,d,l) acid **301** with urea at 185°C provided d,l 3,4-diphenyl-2,5-pyrrolidinedione **308** in 95% yield. During the reaction, as in the case of anhydride **302**, an epimerisation takes place. This was easily proved with ^{1}H-NMR (one signal for H_a protons) and melting point (197-199°C).[30] We performed this reaction on a 1 mol scale, simply by heating the diacid with 2.5 eq. of urea at 185°C, without a solvent. The imide is obtained as a white solid, which can be crystallized from EtOH, to form beautiful crystals[31]. Reduction of succinimide **308** with $LiAlH_4$ in THF, gave in 60% yield racemic 3,4-diphenylpyrrolidine, as a yellow oil. This is a very simple and effective route to racemic 3,4-diphenylpyrrolidine. The synthesis starts with cheap chemicals, is scaled up without difficulty and has a good overall yield (60% after distillation).

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[26] See ref. 13 $[\alpha]_d^{20}$ = -226° ($CHCl_3$) for 3R,4R enantiomer, $[\alpha]_D^{20}$ = +223° ($CHCl_3$) for 3S,4S enantiomer. The e.e. is also determined by NMR methods, see section 4.3.

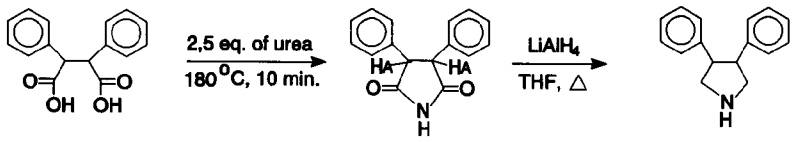
[27] For a good introduction in the field of resolutions see: ref. 32b.

[28] *Tables of resolving agents and optical resolutions;* Wilen, S.H.; University of Notre Dame Press, 1972.

[29] (a) Ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* **1985**, *50*, 4508. (b) Van der Haest, A.D. *Ph. D. Thesis* **1992**, Groningen.

[30] Hargreaves, M.K.; Pritchard, J.G.; Dave, H.R. *Chem. Rev.* **1970**, *70*, 439.

[31] All these C_2-symmetrical derivatives of diphenylbutanedioic acid are crystalline compounds and thus easy to purify.



301 meso, d, l 308 95 % 305 (60% after bulb-to-bulb distillation)

Scheme 3.7. Synthesis of racemic 3,4-diphenylpyrrolidine

With 3,4-diphenylpyrrolidine (**305**), we first did some small-scale trial resolutions. These resolutions were carried out by heating a mixture of 1 mmol racemic base (**305**) with 1 mmol enantiomerically pure acid in an appropriate solvent[32]. When salts crystallized from these mixtures, the amine (**305**) was isolated via acid/base extraction, and the optical purity was determined. The results are listed in Table 3.1.

Table 3.1. Small scale resolutions of 3,4-diphenylpyrrolidine

resolving agent	result	$[\alpha]_{578}$ amine	nr.of cryst.	o.p.
(*S*)-(+)-mandelic acid	++	- 215 °	2	95%
(*R*)-(+)-chlocyphos	-	-	-	-
(*S*)-(+)-phencyphos	++	- 220 °	2	97%
(*R,R*)-(+)-tartaric acid	+	- 160 °	1	71%
(*S*)(+)-10-camphersulfonic acid	++	- 215 °	2	95%
(*R,R*)-(-)-2,3-di-*p*-toluoyltartaric acid	+	- 150 °	2	66%

Optically pure (R,R)-3,4-diphenylpyrrolidine $[\alpha]_{578}$= -226°($CHCl_3$); No or bad resolution, -; some resolution, +; excellent resolution, ++; Phencyphos, 5,5-dimethyl-2-hyroxy-4-phenyl-1,3,2-dioxophosphorinane-2-oxide; Chlocyphos, 5,5-dimethyl-2-hydroxy-4-(2-chlorophenyl)-1,3,2-dioxaphosphorinane-2-oxide; lit.[29a].

[32] a) See Ph.D. Thesis Van der Haest, A.D., 1992, Groningen. b) Wilen, S.H.; Collet, A.; Jacques, J. *Tetrahedron* **1977**, *33*, 2725. c) In all cases described in this thesis, we used 2-butanone as solvent. When the salt was not soluble in 2-butanone, EtOH was added until a clear solution was obtained.

The results depicted in table 3.1 show that 3,4-diphenylpyrrolidine is resolved by five of the six optically active acids used. These results indicate that optically pure 3,4-diphenylpyrrolidine might serve as a resolving agent.[33] To further verify the use 3,4-diphenylpyrrolidine (**305**) as a resolving agent we performed a series of small scale resolution experiments with five racemic acids and (*R,R*)-3,4-diphenylpyrrolidine.[34] The structures of the acids used are listed in figure 3.1

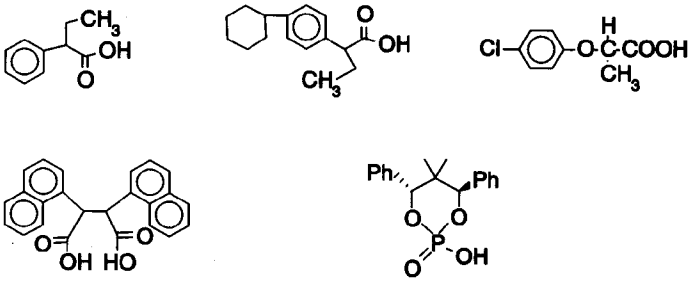


Figure 3.1. Racemic acids used in resolution experiments

After one crystallization of the salts obtained, all five acids listed in figure 3.1 gave to some extent resolution. This was demonstrated by measuring the optial rotation of the free acids. Although we have not further investigated the use of 3,4-diphenylpyrrolidine as a resolving agent, these results, together with the results listed in table 3.1 strongly indicate that the amine might serve as a resolving agent. [35]

We performed the resolution of racemic 3,4-diphenylpyrrolidine (**305**) on a preparative scale, with 5,5-dimethyl-2-hydroxy-4-phenyl-1,3,2-dioxophosphorinane-2-oxide (phencyphos). We used this acid because both enantiomers are available in large quantities (Syncom BV) and the acid is easily recovered. The resolution is outlined in scheme 3.8. When the resolution is performed on a 0.4 mole scale, with (*S*)-(+)-phencyphos, the (*S,R,R*)-salt is obtained in 25% yield after two crystallizations from 2-butanone, $[\alpha]_{578}$= -53° (MeOH). Acid-base extraction of the more soluble (*S,S,S*)-salt, gave the enriched (*S,S*) enantiomer, which was further purified with (*R*)-(+)-phencyphos. After crystallization from 2-butanone the (*R,S,S*) salt was isolated in 27% yield, $[\alpha]_{578}$= +59° (MeOH) The optically pure enantiomers were isolated after treatment of the salts with 10% KOH/ether. The (*R,R*)-(-) and (*S,S*)-(+) enantiomers were isolated in 20% and 22% yield respectively. In both cases optically pure 3,4-diphenylpyrrolidine is obtained as an oil which solidifies on standing and can be crystallized from hexane. This route allows large scale synthesis of both enantiomers of 3,4-diphenylpyrrolidine (**305**) in optically pure form.

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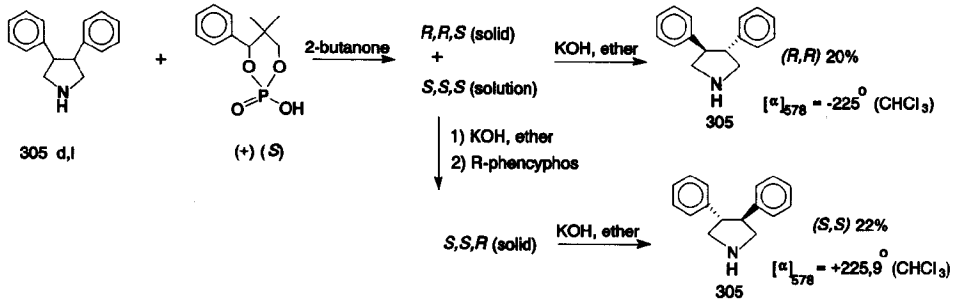
[33] Many C_2-symmetrical compounds are known to be good resolving agents, see chapter 1.

[34] The acids were kindly supplied by Syncom BV and the phosphoric acid by Drs. B. Dros.

[35] We also performed the resolution on a preparative scale with (S)(+)-10-camphorsulfonic acid, see experimental section.



Scheme 3.8 Resolution of 3,4-diphenylpyrrolidine with phencyphos

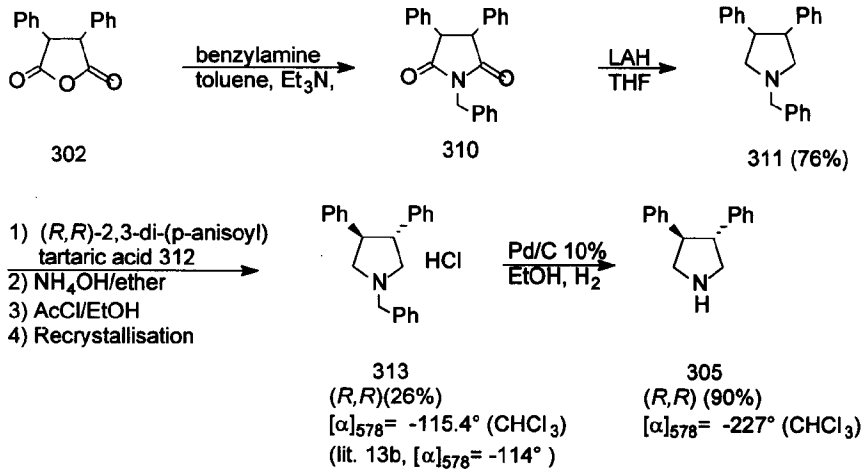
3.2.6. Resolution of N-1-phenylmethyl-3,4-diphenylpyrrolidine

In section 3.2.5 we have described the synthesis and resolution of 3,4-diphenylpyrrolidine. In this section we will discuss the synthesis and resolution of 1-(phenylmethyl)-3,4-diphenylpyrrolidine (**311**) and the conversion to optically pure (*R,R*)-3,4-diphenylpyrrolidine (**305**). Reaction of anhydride **302** with benzylamine in toluene with azeotropic removal of the water formed gave the corresponding succinimide **310** in high yield, scheme 3.9. Crude imide **310** was reduced with $LiAlH_4$ in THF to afford racemic *N*-(phenylmethyl)-3,4-diphenylpyrrolidine **311** in 76% overall yield.

With the racemic tertiary amine **311** we performed some small scale resolution experiments, and found that the C_2-symmetrical amine **311** could be resolved with C_2-symmetrical (*R,R*)-2,3- di-(*p*-dianisoyl)tartaric acid (**312**).[36] Other chiral acids did not provide crystalline salts. When the resolution was performed on a 200 mmol scale, a white salt was obtained in 40% yield. This salt was treated with NH_4OH and (*R,R*) **311** was converted to the HCl salt.[37] Recrystallisation of the HCl salt **313** gave optically pure (*R,R*)-1-(phenylmethyl)-3,4-diphenylpyrrolidine hydrochloride (**313**) in 26% overall yield. Hydrogenation with Pd-C(10%) in EtOH gave in 90% yield optically pure (*R,R*)-3,4-diphenylpyrrolidine (**305**). The procedure described in scheme 3.9 provides optically pure 3,4-diphenylpyrrolidine in reasonable overall yield (17%) and can be performed on a multi-gram scale.

[36] Synthesized from L-tartaric acid in 65% yield according to Rabe, P. *Justus Liebigs Ann. Chem.* **1932**, *492*, 242.

[37] (R,R)-2,3-di-(*p*-anisoyl)tartaric acid can be recovered in high yield after acidification of the basic water layer.



Scheme 3.9 Synthesis and resolution of N-phenylmethyl-3,4-diphenylpyrrolidine 311

3.2.7 Determination of the enantiomeric excess of 3,4-diphenylpyrrolidine using ^{1}H- NMR and ^{31}P-NMR.

Determination of the enantiomeric exces using NMR techniques is well documented.[38,39] We decided to determine the enantiomeric purity of 3,4-diphenyl-pyrrolidine via two chiral derivatizing agents, scheme 3.10. (*R*)-2-acetoxy-2-phenylacetyl chloride (**320**) was synthesized via a literature procedure[40]. The corresponding acid has been used as CDA[41]. The acid chloride easily reacts with secondary amines in ether/Et_3N[42] to give the corresponding amide **322**. The ee is determined by ^{1}H-NMR, the isolated H_A proton which gives two singlets (at δ 6.02 and 6.14 ppm) for the racemic amide (**322**), integration of the H_A proton will provide the enantiomeric excess. The other

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38 (a) Parker, D. *Chem. Rev.* **1991**, *91*, 1441. (b) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224. (c) Hulst, R.; *Ph.D. Thesis*, **1994**, Groningen. (d) See also chapter 2 for chiral derivatizing agents.

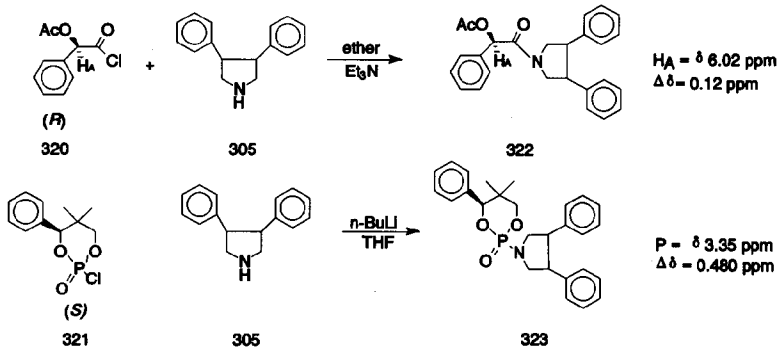
39 Dale, J.A.; Dull, J.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543.

40 Schmidlin, T.; Wallach, D. *Helv. Chim. Acta* **1984**, *67*, 1998.

41 Parker, D. *J. Chem. Soc. Perkin Trans 2* **1983**, 83.

42 The acid chloride was also used to determine the ee of some chiral primary amines. Although CDA **320** might be sensitive to racemisation we have not observed racemisation. We checked this by also preparing the amids from the corresponding acid and the amines with DCC. The results were identical.

CDA **321**, was introduced by Hulst[43]. The chloride of phencyphos **321** reacts with 3,4-diphenylpyrrolidine, to form phosphoramide (**323**). The ee is determined via ^{31}P-NMR, which gives two resonances (δ 3.38 and 2.91 ppm). Integration of these singlets will provide the ee of 3,4-diphenylpyrrolidine. Both methods gave satisfactory results and allow the determination of the enantiomeric excess via NMR. The ee of 3,4-diphenyl pyrrolidine was also determined by chiral HPLC of the 1-(4-methylphenylsulfonyl) derivative of 3,4-diphenylpyrrolidine (Chiralpak AD), see section 3.6, and was consisted with the ee obtained by NMR (HPLC >99% ee, NMR > 95% ee). In summary, we have developed four novel routes to optically pure 3,4-diphenylpyrrolidine (**305**). The third route, described in section 3.2.5, the resolution of trans-3,4-diphenylpyrrolidine, made it possible to synthesize the enantiomerically pure amine on a large scale. When smaller amounts are needed, the other three routes may be used.



Scheme 3.10. The determination of the enantiomeric excess of 3,4- diphenylpyrrolidine by NMR

3.3 The synthesis of novel 3,4-diarylpyrrolidines

3.3.1 Introduction

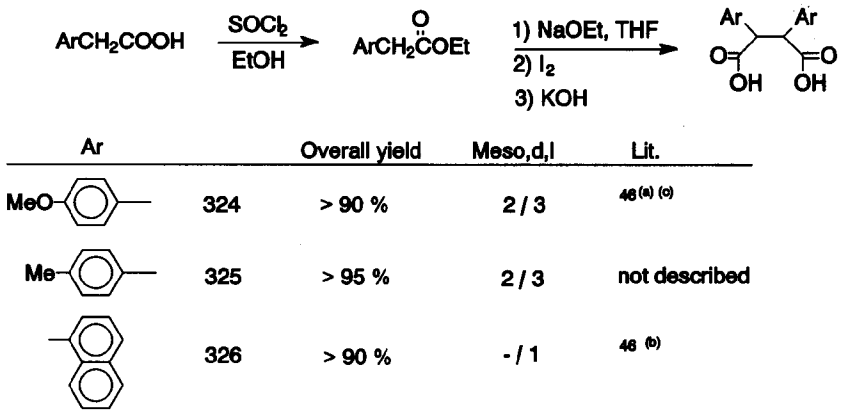
The question arises whether the synthetic methods described in section 3.2 leading to enantiomerically pure 3,4-diphenylpyrrolidine (**305**) are of general applicability. This appears to be the case. Three aspects of the synthesis of **305** were taken into account. 1: are other diarylbutanedioic acids also isomerized to the all trans cyclic anhydrides and imides? 2: is it possible to transform these anhydrides and imides to enantiomerically pure 3,4-diarylpyrrolidines? 3: can we determine the enantiomeric purity and absolute configuration of these 3,4-diarylpyrrolidines? Only one 3,4-diarylpyrrolidine other than **305**

[43] Hulst, R.; Zijlstra, R.W.J.; Feringa, B.L.; de Vries, N.K.; Ten Hoeve, W.; Wynberg, H. *Tetrahedron Lett.* **1993**, *34*, 1339.

has been described, by Tomioka *et al.*[44]. It is used as chiral ligand in the dihydroxylation reaction of olefins with osmium tetraoxide[45]. We will discuss the synthesis of three novel 3,4-diarylpyrrolidines in the next section.

3.3.2 Synthesis and resolution of novel 3,4-diarylpyrrolidines

Starting materials for the synthesis of 3,4-diarylpyrrolidines are the corresponding arylacetic acids, which are commercially available. They were converted to the C_2-symmetrical 2,3-diarylbutanedioic acids by the procedure described in scheme 3.4, section 3.2, that is by the oxidative condensation of two molecules of the arylacetic ester by iodine in the presence of sodium ethoxide. The synthesis and results are outlined in scheme 3.11.



Ar		Overall yield	Meso,d,l	Lit.
MeO	324	> 90 %	2 / 3	46(a) (c)
Me	325	> 95 %	2 / 3	not described
	326	> 90 %	- / 1	46 (b)

Scheme 3.11. Synthesis of 2,3-diarylbutanedioic acids

The yields are excellent, much better than in the known literature procedures. The di(1-naphthyl) analog **326** is fully isomerized during the saponification with KOH in EtOH to the d,l acid. Butanedioic acids **324** and **325** are obtained as meso/d,l mixtures.[46b] The diarylbutanedioic acids **324-326** were converted to the corresponding cyclic anhydrides **327-329** and succinimides **330-332** by the previously described procedure, schemes 3.5 and 3.8. The results are summarized in scheme 3.12.
Like in the case of anhydride **302** and succinimide **308** anhydrides **327-329** and succinimides **330-332** were obtained as d,l compounds. The products, both the anhydrides and the imides, were purified by crystallization.Reduction of the imides **330-332** with $LiAlH_4$ in

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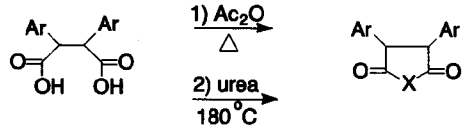
[44] Tomioka, K.; Nakajima, M.; Koga, K. *Chem. Lett.* **1987**, 63
[45] Tomioka, K.; Nokijima, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 1741.
[46] (a) Huang; Kun. Tatt. L *J. Chem. Soc.* **1955**, 4229 (b) King, F.E.; Henshall, T. *J. Chem. Soc.* **1945**, 417 (c) Belletire, J.L.; Spletzer, E.G.; Pinhas, A.R. *Tetrahedron Lett.* **1984**, *25*, 5969

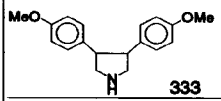
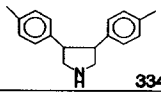
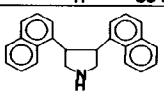


X = O, Ar = *p*-methoxyphenyl 327; *p*-methylphenyl 328; 1-naphthyl 329; yields ca 65%

X = NH, Ar = *p*-methoxyphenyl 330; *p*-methylphenyl 331; 1-naphthyl 332; yields ca 85%

Scheme 3.12. Conversion of 2,3-diarylsuccinic acids to cyclic derivatives 327-332

THF provided the corresponding racemic 3,4-diarylpyrrolidines **333-335** in high yield (>85%)[47]. With these amines we performed small scale trial resolution experiments. The results are outlined in Table 3.2[48].

pyrrolidine	resolving agent*	$[\alpha]_{578}$ (salt)	$[\alpha]_{578}$ (amine)	yield	e.e.
 333	(S)-(+) Phencyphos	-51 0 (MeOH)	-169⁰ (CHCl3)	22%	>95%
	(R)-(-) Phencyphos	+49 0	+164 0	12%	>95%
 334	(S)-(+) Phencyphos	-	+198 0	10%	>95%
	(R)-(-) Phencyphos	-	+190 0	11%	>95%
 335	(2S,3S)-(+) Di-p-toluoyltartaric acid	-92.5 0 (DMF)	-117⁰	30%	>95%
	(2R,3R)-(-) Di-p-toluoyltartaric acid	+75 0	+118 0	29%	>95%

* compounds 333 and 334 could also be resolved with di-p-toluoyltartaric acid, although more crystallizations were needed. Pyrrolidine 335 was to some extend resoved with (S) - malic acid.

Table 3.2. Resolution of 3,4 diarylpyrrolidines 333 - 335.

[47] When after the reduction of imide **332**, excess $LiAlH_4$ was destroyed with ethyl acetate, we isolated *N*-ethyl-3,4-di(1-naphthyl)pyrrolidine, formed via reaction of the lithiumamide of **332** with ethylacetate and subsequent reduction with $LiAlH_4$. This amine was resolved with (R)-(+) chlocyphos to afford the (-) enantiomer $[\alpha]_{578}$= -68° ($CHCl_3$), in 36% yield.

[48] Only the resolution used on a preparative scale is given. The other resolving agents, see table 3.1 did not form salts or no resolution of the amine was observed.

All three pyrrolidines, 3,4-di(*p*-methoxyphenyl)pyrrolidine (**333**), 3,4-di(*p*-methylphenyl)pyrrolidine (**334**) and 3,4-di(1-naphthyl)pyrrolidine (**335**) could be resolved. Looking at the results of the resolution experiments of compounds **305**, **333**, **334** and **335** with enantiomerically pure acids, tables 3.1 and 3.2, two results should be emphasized. First, all amines (**305, 333, 334** and **335**) were to some extent resolved with di-*p*-toluoyltartaric acid. In chapter 4, two C_2- and D_2-symmetrical diamines are also resolved with tartaric acid derivatives. These C_2-symmetrical bases seem to form crystalline salts with C_2-symmetrical carboxylic acids, which can be explained by assuming a better ordering in the crystal lattices of the diastereomeric salts.[49] Second, the resolution of amines **305**, **333** and **334** with (*S*)-(+) phencyphos in all three cases gave the (-) enantiomer of the pyrrolidine. Since the absolute configuration of (-)-3,4-diphenylpyrrolidine is (*R,R*) this might imply that (-)-**333** and (-)-**334** also posses the (*R,R*) configuration. We will examine this in more detail in section 3.3.4.

3.3.3 Alternative routes to enantiomerically pure 3,4-diarylpyrrolidines 333-345

We also tried to obtain C_2-symmetrical pyrrolidines **333-335** via alternative pathways. The attempts are depicted in schemes 3.13, 3.14 and 3.15. We synthesised the 1,3,4-trisubstituted succinimide **336** by a cyclisation reaction of anhydride **327** with (*R*)-glycinol in toluene, scheme 3.13. The diastereomeric mixture was crystallized three times from EtOH, to obtain (*S,S,R*) diastereomer in 20% yield. The diastereomeric purity was checked by ^{1}H-NMR. Reduction with $LiAlH_4$ in THF followed directly by hydrogenolyse afforded (*S,S*)-3,4-di(*p*-methoxyphenyl)pyrrolidine (**333**) in overall modest yield (10%). Although enantiomerically pure material is obtained via this route, the overall yield is not good enough for multigram purpose. Therefore, we also examined the approach of resolving anhydride **327** with (*S*)-α-phenylethyl amine. Cyclisation of anhydride **327** with (*S*)-α-phenylethylamine in toluene provided in 60% yield, based upon one diastereomer, the (*S,S,S*) isomer **337** after crystallisation from 2-butanone/ethylacetate, scheme 3.13.[50] The succinimide derivative **337** was reduced with $LiAlH_4$ in THF and subsequently hydrogenated with H_2/Pd/C 10% to afford enantiomerically pure (*S,S*)-3,4-di(*p*-methoxy)-phenylpyrrolidine (**333**) in 50% yield. This method allows the synthesis of optically pure **333** on a multigram scale.

The same approach was also applied for the synthesis of enantiomerically pure 3,4-di(*p*-tolyl)pyrrolidine **334**, scheme 3.14. Reaction of anhydride **328**, with (*S*)-α-phenylethylamine in toluene and subsequent crystallization from 2-butanone afforded the (*S,S,S*) succinimide **338** in 50% yield. The succinimide derivative was converted to the

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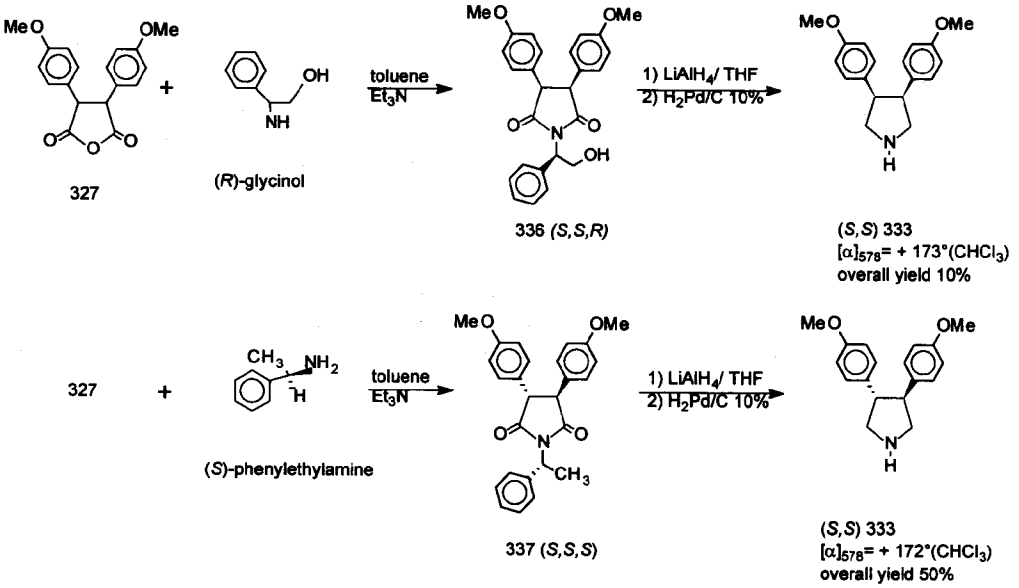
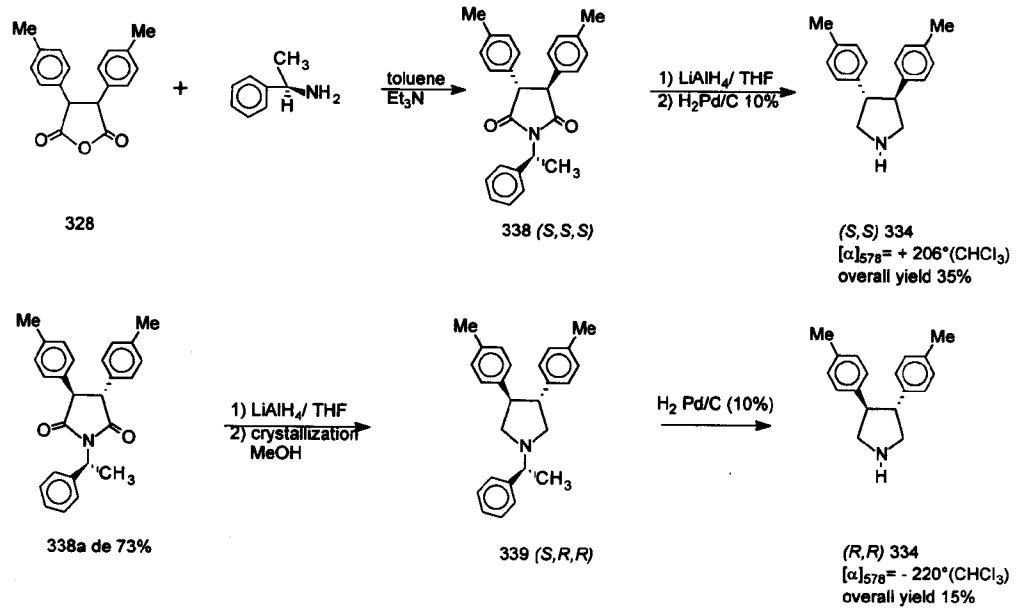
[49] Many C_2-symmetrical amines have been resolved with tartaric acid (a) 2,3-diaminobutane, Dickey, F.H.; Fickett, W.; Lucas, H.J. *J. Am Chem. Soc.* **1952**, *74*, 944 (b) 3,4-dimethylpyrrolidine, Mc Gasland, G.E.; Proskov, S. *J. Am. Chem. Soc.* **1956**, *78*, 5646 (c) 1,2-diaminocyclohexane, Asperger, R.G.; Liu, C.F. *Inorg. Chem.* **1965**, *4*, 1492 (d) Stilbenediamine, Hulst, R. *Ph. D. Thesis*, Groningen, **1994**. (e) N-1-(4-methoxyphenyl)-ethyl-α-(4-methoxyphenyl)ethylamine, v/d Haest, *Ph.D. Thesis*, Groningen, **1992**.

[50] From the mother liquor the (*S,R,R*) diastereoisomer can be obtained with a d.e. of 90% after tituration with ether.



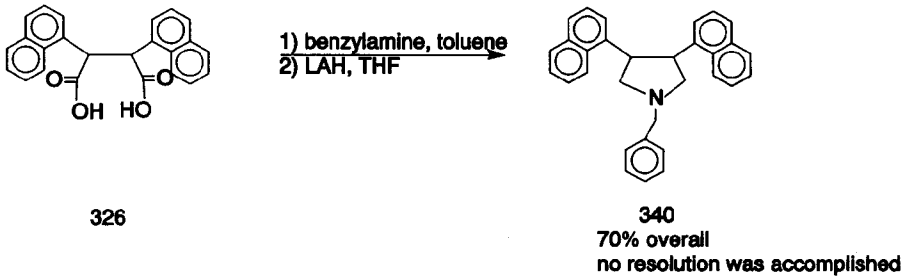
Scheme 3.13 Synthesis of enantiomerically pure 3,4-di(p-methoxyphenyl)pyrrolidine 333



Scheme 3.14 Synthesis of enantiomerically pure 3,4-di-(p-tolyl)pyrrolidine 334

desired (*S,S*)-pyrrolidine **334** by the same procedure as described for the synthesis of **333**. The mother liquor of the (*S,S,S*) succinimide **338** contained the (*S,R,R*) isomer **338a** with a d.e. of 73% (determined by ^{1}H-NMR). When this material was reduced with $LiAlH_4$ in THF, the crude pyrrolidine **339** could be crystallized to afford the diastereomerically pure (*S,R,R*) pyrrolidine **339**, which was converted to (*R,R*) pyrrolidine **333** after hydrogenation. Both enantiomers of 3,4-di-(*p*-tolyl)pyrrolidine are thus available by separation of diastereoisomers obtained by reaction of anhydride **328** with (S)-α-phenylethylamine.

We tried to obtain optically pure 3,4-di-(1-naphthyl)pyrrolidine (**335**), by resolution of racemic of *N*-benzyl-3,4-di(1-naphthyl)pyrrolidine (**340**), which was obtained via condensation of d,l 2,3-di-(1-naphthyl)butanedioic acid (**340**) with benzylamine in toluene, followed by reduction with $LiAlH_4$ in THF, scheme 3.15. The crude amine **340** was isolated after crystallization as a solid in 70% yield. However, all small scale resolution experiments with a variety of chiral acids, see tables 3.1 and 3.2, failed.



326

340
70% overall
no resolution was accomplished

Scheme 3.15 Synthesis of racemic N-benzyl-3,4-di-(1-naphthyl)pyrrolidine

The best route to obtain enantiomerically pure 3,4-disubstituted pyrrolidines **333** and **334** is via resolution of the corresponding *N*-1-(phenylethyl)-2,5-pyrrolidinediones. Subsequent reduction and removal of the chiral auxiliary provides the pyrrolidines **333** and **334** in reasonable yield (35-50%).

3.3.4 Determination of enantiomeric purity and absolute configurations of pyrrolidines 333-335

Since the pyrrolidines described in this section are new compounds, it was necessary to determine the enantiomeric excess and absolute configuration.

The enantiomeric excess was checked by ^{1}H- and ^{31}P-NMR, after derivatization with (*R*)-2-acetoxy-2-phenylacetic acid, or the corresponding acid chloride **320** and (*S*)-phencyphoschloride (**321**), in the same manner as described for 3,4-diphenylpyrrolidine (**305**) in section 3.2.7. The results are summarized in table 3.3

Table 3.3. Determination of the enantiomeric purity of C_2-symmetrical 3,4-diarylpyrrolidines

Entry	Amine	CDA	Chemical shifts ^{1}H-NMR or ^{31}P-NMR*	$[\alpha]_{578}$ ($CHCl_3$) of amine	ee
1	**305**(+)	**320**	6.14	+ 225°	> 95%
2	**305**(-)	**320**	6.02	- 226°	> 95%
3	**333**(+)	**320**	6.11	+ 172°	> 95%
4	**333**(-)	**320**	6.03	- 173°	> 95%
5	**334**(+)	**320**	6.16	+ 206°	> 95%
6	**334**(-)	**320**	6.04	- 220°	> 95%
7	**335**(+)	**320**	6.18	+ 115°	> 95%
8	**335**(-)	**320**	6.05	- 118.3°	> 95%
9	**305**(+)	**321**	3.38	- 223°	> 95%
10	**305**(-)	**321**	2.91	- 225°	> 95%
11	**335**(+)	**321**	3.7	+ 115°	> 95%
12	**335**(-)	**321**	2.6-7	- 118.3°	> 95%

* *In the case of CDA **320** the ee was determined via integration of the resonances observed for the isolated H proton at δ 6 ppm, see scheme 3.10. In the case of CDA **321** the ee was determined via integration of the phosphorous resonances at δ 3 ppm. In both cases the chemical shift differences were large enough to distinguish between both enantiomers.*

As can be seen from table 3.3 the enantiomeric purity of the amines **305**, **333**, **334** and **335** was determined by ^{1}H-NMR and ^{31}P-NMR. But can also the absolute configurations of amines **334**, **334** and **335** be established by relation to the known absolute configuration of 3,4-diphenylpyrrolidine (**305**), (*RR*,-) and (*SS*,+) ? Several examples are known in the literature which permit the assignment of the absolute configuration of alcohols and amines by NMR configurational correlation schemes.[51] When looking at table 3.3 it is noticed that proton H_A of (*R*)-*O*-acetylmandelicamide resonates at 6.14 ppm

[51] (a) Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Trost, B.M.; Belletire, J.L.; Godleske, S.; Mc Dougal, P.; Balkovec, J.M.; Baldwin, J.J.; Christy, M.E.; Ponticello, G.S.; Varga, S.L.; Springer, J.P. *J. Org. Chem.* **1986**, *51*, 2370. (c) Trost, B.M.; Van Vranken, D.L.; Bingel, C.J. *J. Am. Chem. Soc.* **1992**, *114*, 9327.

and 6.02 ppm for, respectively, (*SS*,+) and (*RR*,-) 3,4-diphenylpyrrolidine, entries 1 and 2. To relate the chemical shift differences to the absolute configuration it is necessary to examine the conformation of the 3,4-diphenylpyrrolidine (**305**) coupled to CDA **320**. The conformations depicted in figure 3.3, are translated to a Newman projection where the central amide linkage is omitted. If the proton (H_A) on the mandelic part of the molecule is on the same side as the phenyl ring of the pyrrolidine part, it is shielded and its chemical shift is upfield (δ H_A 6.02 ppm) with respect to the other diastereomer (δ H_A 6.14 ppm).

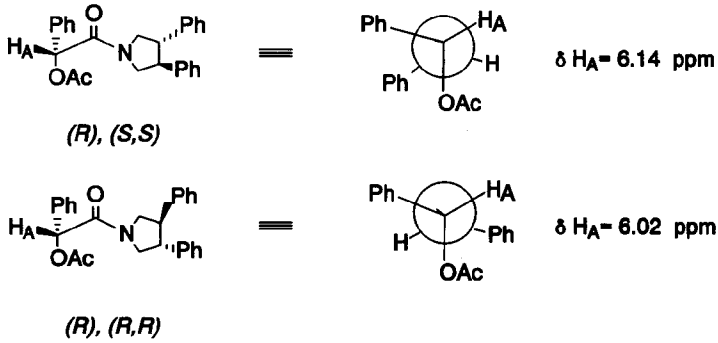


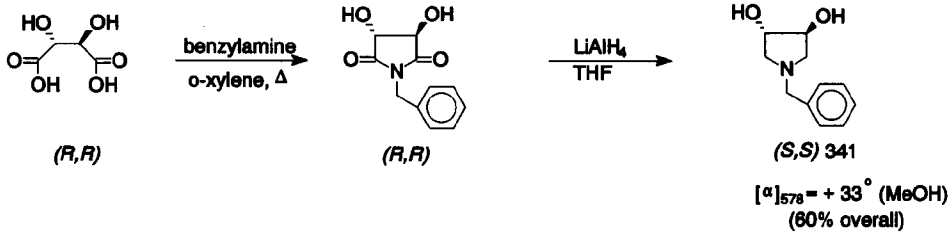
Figure 3.3

This effect is observed in all four 3,4-diarylpyrrolidines **305** (entries 1 and 2), **333** (entries 3 and 4), **334** (entries 5 and 6), **335** (entries 7 and 8), see table 3.3. That prompted us to conclude that the (-)-diarylpyrrolidines possess the (*R,R*) configuration and thus the (+)-diarylpyrrolidines the (*S,S*) configuration.This conclusion is further supported by two other observations. The only other known 3,4-diarylpyrrolidine[44], see section 3.3.1 possesses the same configuration as 3,4-diphenylpyrrolidine (**305**). Furthermore the (-)-pyrrolidines **333** and **334** like (*RR*,-)-3,4-diphenylpyrrolidine **305** are obtained by resolution with (*S*)-(+)-phencyphos.

3.4 C_2-Symmetrical pyrrolidines derived from tartaric acid

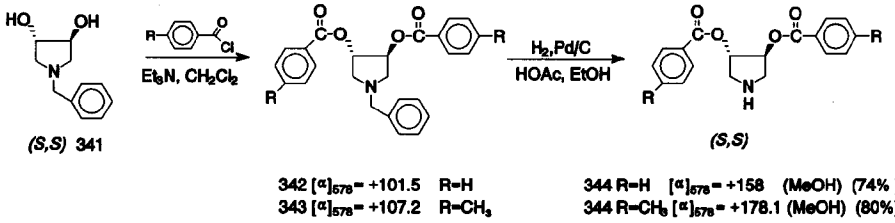
As mentioned in section 3.1, C_2-symmetrical pyrrolidines are widely used in stereoselective chemistry. In sections 3.2 and 3.3 we have described several convenient general routes to C_2-symmetrical 3,4-diarylpyrrolidines. In this section we will describe the synthesis of another class of C_2-symmetrical 3,4-disubstituted pyrrolidines derived from tartaric acid. Like the diarylbutandioic acids described in section 3.2 and 3.3, tartaric acid is also a C_2-symmetrical butanedioic acid, which should make it possible to convert it into the corresponding pyrrolidine, via reduction of the succinimide derivative, scheme 3.16. The dihydroxy moiety can then be used to synthesize a variety of 3,4-disubstituted

pyrrolidines. This idea is not new, two examples are known where C_2-symmetrical pyrrolidines derived from tartaric acid are used as chiral ligands in stereoselective synthesis[52]. Both reports use *N*-benzyl-3,4-dihydroxypyrrolidine (**341**) as starting material. Pyrrolidine **341** is synthesized in 65% overall yield from tartaric acid as outlined in scheme 3.16. Tartaric acid is converted to *N*-benzyl-3,4-dihydroxy-2,5-pyrrolidinedione



Scheme 3.16 Synthesis of (S,S)-N-1-benzyl-3,4-dihydroxypyrrolidine

340 by reaction with benzylamine in xylene. Reduction with BH_3 or $LiAlH_4$ provides pyrrolidine **341** in high overall yield. We used amine **341** as starting material for two new 3,4-disubstituted pyrrolidines, **344** and **345**, which might also be used as chiral auxiliary, chiral ligand or resolving agent. The dihydroxy moiety of **341** is converted into the bis-3,4-benzoyl ester **342** by reaction with benzoylchloride in CH_2Cl_2 and Et_3N. An analogous reaction with *p*-toluoylchloride gave the corresponding pyrrolidine **343**. Cleavage of the benzyl group with H_2 afforded the C_2-symmetrical pyrrolidines **344** and **355** in 50% overall yield. All amines **342**, **343**, **344**, **345** are crystalline compounds, and thus easily purified. The synthesis is depicted in scheme 3.17.



Scheme 3.17 Synthesis of 3,4-disubstituted pyrrolidines derived from tartaric acid

[52] (a) (*R,R*)-3,4-bis(diphenylphosphino)-pyrrolidine; Nagel, U.; Kinzel, E.; Andrade, J.; Prescher, G. *Chem. Ber.* **1986**, *119*, 3326. (b) (*R,R*)-3,4-diaminopyrrolidine; Reddy, D.D.; Thorton R.E. *J. Chem. Soc. Chem. Common.* **1992**, 172.

We also synthesized the bis-p-chlorine derivative, but upon reduction cleavage of the benzyl group also removed the chlorine atoms. However, with this methodology it should be possible to synthesize a variety of C_2-symmetrical pyrrolidines. One might consider these compounds as the amine analogues of the (*O,O*)-diacyltartaric acid derivatives, which have proven to be succesfull resolving agents. We have used both amines **344** and **345** in small resolutions of racemic carboxylic acids[53]. Although salts were formed no significant resolution was obtained.

3.5 Conclusions

In the first part of this chapter, we have described the synthesis of optically pure 3,4-diphenylpyrrolidine (**305**). Four different methods were used, all starting from 2,3-diphenylbutanedioic acid. The best route seems to be the resolution of racemic 3,4-diphenylpyrrolidine with 'phencyphos'. This approach allows the synthesis of optically pure 3,4-diphenylpyrrolidine on a multigram scale without difficulty. The second part of this chapter deals with the synthesis of three other 3,4-diarylpyrrolidines. The same methods applied for to synthesis of **305** seem to be of broad applicability. The methods applied, include resolution of racemic pyrrolidines or separation of diastereomeric succinimide derivatives. Although the different pyrrolidines can be synthesized by various routes, each amine has its own preferred synthesis. Optically pure 3,4-di-(*p*-methoxyphenyl)-pyrrolidine (**333**) and 3,4-di-(*p*-methylphenyl)pyrrolidine (**334**) are best prepared by resolution of the corresponding *N*-phenylmethylsuccinimides. Resolution of racemic 3,4-di-(1-naphthyl)pyrrolidine (**335**) was accomplished with 3,4-di-(*p*-toluoyl)tartaric acid. The enantiomeric excess of these four pyrrolidines was determined by ^{1}H-NMR and ^{31}P-NMR.

The last part of this chapter, deals with the synthesis of two novel 3,4-disubstituted pyrrolidines derived from tartaric acid. A simple and convenient procedure is described, which allows the synthesis of a new type of C_2-symmetrical pyrolidines. The C_2-symmetrical pyrrolidines described in this chapter may find use as chiral auxiliary, chiral ligand or resolving agent.

[53] The acids we used were; a) 2-(p-chlorophenyl)propanoic acid. b) 2-phenylbutyric acid. c) phenylglycine and d) 2-(chlorophenoxy)propanoic acid.

3.6 Experimental section

General remarks see chapter two, experimental section.

Meso and d,l 2,3-diphenylbutanedioic acid (301) method 1
To a mechanically stirred suspension of NaH (80 g, 2.0 mol 65% in mineral oil) in THF (400 ml), previously cooled in an ice-water bath was added EtOH (92 g, 2.0 mol) in 30 minutes. The whole mixture was cooled to -70°C and ethylphenylacetate (328g, 2.0 mol) was added over a 15 minutes period, maintaining the temperature below -50°C. To this suspension was added a pre-cooled solution (0°C) of iodine (252 g, 1.0 mol) in THF (600 ml) over a 20 minutes period (exothermic reaction). The yellow suspension was stirred for another 20 minutes, allowing the temperature to rise to RT. Unreacted iodine was treated with 5% sodiumsulfite (200 ml) and most of the THF was removed. To the resulting suspension was added KOH (162 g, 2.5 mol) in water (400 ml) and EtOH (200 ml). The resulting mixture was refluxed for 4 hours, and after being cooled to RT water (400 ml) was added. The water layer is extracted with toluene (200 ml) and acidified with conc. HCl. After cooling the precipitate was collected, washed with cold water and dried to afford **301** as an off-white solid. Yield 255 g (94%); mp 180-210°C (lit.[21e] 175-210°C); ^{1}H-NMR(DMSO-d6): δ 4,2 (s,2H), 7.2-7.6 (m,10H), 12.2 (s,2H); ^{13}C-NMR (DMSO-d6): δ 53.08 (CH_3), 126.82 (CH), 128.03 (CH), 128.26 (CH), 136.43 (C), 173.76 (C=O).

Meso and d,l 2,3-diphenylbutanedioic acid (301) method 2
Meso 1,2-dicyano-1,2-diphenylethane was prepared on a 2 mol scale according to ref. 18b in 90% yield. mp °C (lit.[18b] °C). A mixture of meso-1,2-dicyano-1,2-diphenylethane (232 g, 1.o mol) in 1200 ml H_2SO_4 (50%) and 300 ml AcOH was refluxed during 40 hours. The mixture was cooled and added 2 l of water and the acid collected by suction to yield a mixture of meso and d,l 2,3-diphenylbutanedioic acid **301** as a white solid (90%). Spectroscopic data were identical with those of method 1.

d,l 3,4-Diphenyldihydro-2,5-furandione (302)
A suspension of cis/trans **301** (166 g, 0.61 mol) in acetic anhydride (200 ml) was refluxed for 2 hours. The clear solution was evaporated and to the resulting oil was added ether (600 ml). After cooling the crystals were collected and washed with ether (cold) to afford **302** as a white solid. Yield 116 g (75%); mp 113-115°C (lit.[17] 115-116°C); ^{1}H-NMR: δ 4.4 (s,2H), 7.2 (m,4H), 7.3-7.4 (m,6H); ^{13}C-NMR δ 54.86 (CH), 127.62 (CH), 128.49 (CH), 129.17 (CH), 133.31 (C), 170.18 (C=O).

(2*R*,3*R*,α*S*)-*N*-(α-phenylethyl)-2,3-diphenylsuccinamic acid (303)
To a solution of anhydride **302** (104 g, 0.413 mol) in THF (400 ml) was added at 0°C (*S*)-α-phenylethylamine (51 g, 0.413 mol, 96% ee) over a 10 minutes period. The resulting mixture was stirred for an additional hour and evaporated to dryness. The solid obtained was recrystallised from 2-butanone (600 ml) and stirred overnight. The crystals were collected to afford **303** as a white solid. Yield 54 g (35%); mp 206-208°C; $[\alpha]_{578}$= -221° (MeOH); ^{1}H-NMR(DMSO-d6): δ 1.16 (d,3H), 4.25 (dd,2H), 4.82 (m,1H), 7.0-7.4 (m,15H), 8.5 (d,1H); ^{13}C-NMR(DMSO-d6): δ 22.21 (CH_3), 47.62 (CH), 53.55 (CH), 53.97 (CH), 125.94 (CH), 126.52 (CH), 126.84 (CH), 127.87 (CH), 127.91 (CH), 128.03 (CH), 128.16 (CH), 128.22 (CH), 128.35 (CH), 137.17 (C), 138.00 (C), 144.31 (C), 171.16 (C=O), 173.95 (C=O); Anal. calc. for $C_{24}H_{23}NO_3$: C 77.19, H 6.12, N 3.75 Found: C 76.24, H 6.19, N 3.72.

(2*R*,3*R*,α*S*)-*N*-(α-Phenylethyl)-2,3-diphenylsuccinimide (304)
A mixture of **303** (50 g, 134 mmol) in conc. HCl (150 ml) and acetic acid (400 ml) was stirred under reflux for 5 hours. The solution was poured on ice-water (2000 ml) and the solid collected and recrystallized from EtOH to afford **304** as white solid. Yield (31 g, 65%); mp 87.1-89°C; $[\alpha]_{578}$= -205° ($CHCl_3$); ^{1}H-NMR: δ 1.9 (d,3H), 4.0 (s,2H), 5.6 (q,2H), 7.0-7.6 (m,15H); ^{13}C-NMR: δ 18.20 (CH_3), 50.71 9CH), 55.13 (CH), 127.54 (CH), 127.9 (CH), 128.49 (CH), 129.21 (CH), 136.0 (C), 139 (C), 176 (C=O); HRMS calc. for $C_{24}H_2NO_2$: 355.157 found: 355.157; Anal. calc. for $C_{24}H_2NO_2$: C 81.10, H 5.96, N 3.94 Found: C 78.93, H 5.98, N 3.82.

(3*R*,4*R*)-3,4-Diphenylpyrrolidine (305)
To a suspension of $LiALH_4$ (3.8 g, 100 mmol) in THF (100 ml) was added a solution of **304** (17 g, 47 mmol) in THF (300 ml). The mixture was refluxed for an additional hour, cooled to RT and treated with 10% KOH (10 ml) (exothermic). The salts were filtered of and washed with THF/toluene (200 ml). The combined filtrates were evaporated and (3*R*,4*R*,α*S*)-*N*-(α-phenylethyl)-3,4-diphenylpyrrolidine was obtained as a yellow oil, which was used without further purification. Yield 13.2 g (85%).
The protected amine was dissolved in MeOH (150 ml) and formic acid (5 ml) together with 10% Pd/C (1.3 g) were added. This mixture was hydrogenated for 16 hours. The catalyst was removed by filtration and the filtrate evaporated. After addition of 15% NaOH (30 ml) the mixture was extracted with ether. The organic layer was dried (Na_2SO_4) and evaporated to afford **305** as a colourless oil which solidifies on standing. Yield 8.4 g (95%); mp 56-57°C (lit.[13b] 58-59°C); $[\alpha]_{578}$= -226° ($CHCl_3$) (lit.[13b] $[\alpha]_D$= -227^0); ^{1}H-NMR: δ 2.2 (br,1H), 3.05-3.2 (m,2H), 3.2-3.4 (m,2H), 3.5 (m,2H), 7.1-7.3 (m,10H); ^{13}C-NMR: δ 54.03 (CH), 55.82 (CH_2), 126.27 (CH), 127.26 (CH), 128.36 (CH), 142.30 (C); HRMS calc. for $C_{16}H_{17}N$: 223.136 found: 223.136

(2*S*,3*S*,α*R*)-*N*-(α-phenyl-2-hydroxymethyl)-2,3-diphenylsuccinimide (306)
A mixture of (*R*)-phenylglycinol* (2.7 g, 19.8 mmol), **202** (5 g, 19.8 mmol), Et_3N (1 ml) in toluene (120 ml) was refluxed for 16 hours. The clear solution was evaporated and the resulting oil was crystallized three times from EtOH to afford **306** as a white solid. Yield 2.2 g (30%); mp 188-191°C; $[\alpha]_{578}$= +156.3° ($CHCl_3$); ^{1}H-NMR: δ 2.5 (br,OH), 4.07

(s,2H), 4.1 (dd,1H), 4.68 (t,1H, 5.45 (dd,1H), 7.1-7.5 (m,15H); ^{13}C-NMR: δ 55.44 (CH), 58.73 (CH), 61.60 (CH_2), 127.65 (CH), 127.98 (CH), 128.05 (CH), 128.39 (CH), 128.80 (CH), 129.25 (CH), 136.5 (C), 136.61(C), 177 (C=O); Anal. calc. for C 77.61, H 5.70, N 3.77 found: C 76.91, H 5.76, N 3.71.

* obtained by reduction of (*R*)-phenylglycine with $LiAlH_4$.
Meyers, A.I.; Dideman, D.A.; Bailey, I.R. *J. Am. Chem. Soc.* **1985**, *107*, 7974.

(3*S*,4*S*)-3,4-Diphenylpyrrolidine (305), via reduction of 306 and hydrogenation of 307
To a suspension of $LiAlH_4$ (400 mg, 10.5 mmol) in THF (30 ml) is added **306** (1.7 g, 4.6 mmol) in THF (10 ml). The mixture was refluxed for two hours and hydrolysed with 10% KOH. The salts were removed by filtration and the filtrate evaporated to afford (3*S*,4*S*,α*S*)-*N*-(α-phenyl-2-hydroxymethyl)-3,4-diphenylpyrrolidine **307** as an oil. Yield 1.34 g (85%). The crude product was used without further purification. The crude amine **307** (1.34 g, 3.4 mmol) was dissolved in MeOH (50 ml) and ammoniumformate (3 g, 34 mmol) was added, followed by Pd/C (10%)(500 mg). The resulting slurry was stirred overnight at RT and the catalyst was removed by filtration. The filtrate was evaporated and treated with 15% NaOH/ether (50:50 ml) mixture. The organic layer was dried (Na_2SO_4) and evaporated to afford (3*S*,4*S*)-**305** as a colourless oil which solidifies on standing. Yield 740 mg (85%); $[\alpha]_{578}$= + 225.9° ($CHCl_3$); Spectroscopic data identical to those previously described.

d,l 3,4-Diphenylsuccinimide (308)
A mechanically stirred mixture of cis/trans acid **301** (250 g, 0.93 mol) and urea (173 g, 2.9 mol) were slowly heated until the temperature reached 180°C (at 120°C the reaction starts with evolution of NH_3). The clear solution was heated for an additional 20 minutes at 180°C and poured on a solution of 5% $NaHCO_3$ (800 ml) with vigorous stirring. The solid was collected, washed with water and dried to afford **308** as a slightly yellow solid. Yield 210 g (90%). An pure sample was obtained after crystallisation from EtOH. mp 197-200°C (lit.[30] 197-199°C); ^{1}H-NMR(DMSO-d6): δ 4.35 (s,2H), 7.2-7.4 (m,10H), 11.45 (br,N-H); ^{13}C-NMR(DMSO-d6): δ 55.10 (CH), 127.19 (CH), 128.25 (CH), 128.39 (CH), 136.3 (C), 177.25 (C=O).

d,l 3,4-Diphenylpyrrolidine (305)
A suspension of $LiAlH_4$ (54 g, 1.42 mol) in THF (200 ml) was cooled in an ice-water bath and a suspension of imide **308** (170 g, 0.68 mol) in THF (1000 ml) was added over a 90 minutes period. The green mixture was refluxed for an additional hour and cooled in an ice-water bath. A 10% KOH solution was added slowly until complete hydrolysis has takes place. The salts were removed by filtration over Celite and washed several times with toluene. The combined filtrates were concentrated and the crude amine was purified via bulb-to-bulb distillation (0.1 mmHg-150°C). The racemic amine was isolated as an yellow oil which solidifies on standing. Yield 95 g (63%). Spectroscopic data identical with those of (3*S*,4*S*)-3,4-diphenyl pyrrolidine.

Resolution of 3,4-diphenylpyrrolidine with phencyphos*,**
To a solution of racemic amine **305** (64.0 g, 287 mmol) in 2-butanone (800 ml) and MeOH (60 ml) was added (-)-phencyphos (69.4 g, 287 mmol). The mixture is refluxed and the clear solution was allowed to cool to RT overnight. The solid was collected and recrystallized from 2-butanone/MeOH (11:1) to afford a white salt. Yield 43 g (32%): $[\alpha]_{578}$= + 53° (MeOH). The combined mother liquors are evaporated and treated with 10% KOH (250 ml) and toluene (250 ml). After being stirred for 1 hour, the organic layer is dried (Na_2SO_4) and evaporated to afford enriched (-)-**305**. This amine (40 g) was dissolved in 2-butanone (600 ml) and (+)phencyphos (43 g) was added. The mixture was refluxed and MeOH was added until a clear solution was obtained. The solution was allowed to cool to RT overnight, the solid was collected and recrystallized from 2-butanone/MeOH (12:1) to afford a white solid. Yield 42 g (31 %): $[\alpha]_{578}$= -58° (MeOH).

* Phencyphos was obtained from Syncom BV.
** In all resolution experiments, the optically pure acid is recovered by acidifying the basic water layers with HCl.

(3*S*,4*S*)-3,4-Diphenylpyrrolidine (305) was obtained by treating the salt ($[\alpha]_{578}$= +53°) with a 10% KOH/ether mixture. After being stirred for 1 hour the water layer was extracted two times with ether. The combined layers were dried (Na_2SO_4) and evaporated to afford (3S,4S) **305** as a colourless oil which solidifies on standing. Yield 18 g (28 %, based upon racemic **305**); $[\alpha]_{578}$= + 225.9° ($CHCl_3$). Spectroscopic data identical with those previously described.

(3*R*,4*R*)-3,4-Diphenylpyrrolidine was obtained by treating the other salt identical as described above. Yield 17 g (27 %, based upon racemic **305**): $[\alpha]_{578}$= - 226° ($CHCl_3$).

Resolution of 305 with d(+)-camphorsulfonic acid
Racemic amine **305**, can also be resolved with d-(+)-camphorsulfonic acid. After three crystallisations from abs. EtOH a salt was obtained with $[\alpha]_{578}$= -96.8 (MeOH). Treatment of this salt with 10% KOH/ether gave optically pure (3*R*,4*R*) **305**. Yield 25%: Spectroscopic data identical with those previously described.

1-Phenylmethyl-3,4-diphenylpyrrolidine (311)
A mixture of anhydride **302** (100 g, 400 mmol), benzylamine (43 g, 400 mmol), Et_3N (3 ml) in toluene (500 ml) was refluxed overnight, with azeotropic removal of the water formed. The mixture was cooled and washed with water, 10 % HCl and saturated $NaHCO_3$. The organic layer was dried and concentrated. The crude imide was dissolved in THF (500 ml) and slowly added to a suspension of $LiAlH_4$ (38 g, 1 mol) in 200 ml THF. The mixture was refluxed for 3 hours and hydrolysed with 10 % KOH. The mixture was filtered over Celite and washed with toluene. The combined organic layers were concentrated to afford amine **311** as an orange oil. Yield 95 g (76 %). This material was used without further purification. ^{1}H-NMR: δ 3.05 (dd,2H), 3.35 (dd,2H), 3.55 (m,2H), 3.9 (dd,2H), 7.3-7.7 (m,15H).

Resolution of 1-phenylmethyl-3,4-diphenylpyrrolidine (411) with (2*R*,3*R*)-2,3-(di-*p*-anisoyl)-tartaric acid

A mixture of racemic **311** (70 g, 224 mmol) and (2*R*,3*R*)-2,3-di-(*p*-anisoyl)tartaric acid (94 g, 224 mmol) in 2-butanone (400 ml) and MeOH (20ml) was heated to reflux. To the clear solution were added some seed crystals and the mixture was allowed to cool to RT. The crystals were collected, washed with 2-butanone and dried to yield 65 g (40 %) of a white solid. $[\alpha]_{578}$= -136° (MeOH).The salt was treated with ether (300 ml) and 10% NH_4OH (300 ml) for thirty minutes. The organic layer was dried (Na_2SO_4) and concentrated to provide (3*R*,4*R*)-1-phenylmethyl-3,4-diphenylpyrrolidine as a yellow oil. $[\alpha]_{578}$= -73°($CHCl_3$). This material was dissolved in EtOH (100 ml), cooled to 5°C and treated with AcCl (30 ml). The mixture was concentrated and the crude HCl salt recrystallized from EtOH/ether (9:1) to give (3*R*,4*R*)-1-phenylmethyl-3,4-diphenylpyrrolidine hydrochloride (**312**) as a white solid. Yield 20 g (26%);mp 254-255° (lit.[13b] 256-257°) $[\alpha]_{578}$= -115.4° ($CHCl_3$) (lit.[13b] $[\alpha]_{578}$= -114° ($CHCl_3$)); ^{1}H-NMR: δ 3.2 (m,1H), 3.6 (m,2H), 4.0 (m,3H, 4.4 (m,2H), 7.0-7.8 (m,15H); ^{13}C-NMR: δ 50.2 (CH), 59.22 (CH_2), 127.63 (CH), 127.80 (CH), 128.91 (CH), 129.41 (CH), 129.99 (CH), 130.62 (CH).

(3*R*,4*R*)-3,4-Diphenylpyrrolidine (305)

A mixture of **312** (20 g, 57 mmol) and Pd-C (10%, 5 g) in EtOH was hydrogenated for 2 days in a Parr-Apparatus. After the catalyst was removed by filtration, the filtrate was evaporated and treated with 15% NaOH and the mixture was extracted three times with ether. The organic layer was dried and evaporated to give **305** as a colourless oil which solidifies on standing. Yield 11.5 g (90%): $[\alpha]_{578}$= -227° ($CHCl_3$); All spectroscopic data were identical with those previously described.

The determination of the enantiomeric excess of 305 with (2*R*)-2-acetoxy-2-phenylacetyl chloride (320)

To a solution of amine **305** (0.1 mmol) in ether (3 ml) was added one equivalent of Et_3N, followed by (2*R*)-2-acetoxy-2-phenylacetylchloride* (0.1 mmol). The mixture was stirred for 1 hour and 10% HCl is added. The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue **322** was dissolved in $CDCl_3$ (2 ml) and a ^{1}H-NMR was recorded. For spectroscopic data, see scheme 3.10.

* Synthesized according to Smidlin, T.; Wallach, D. *Helv. Chim. Acta* **1984**, *67*, 1998.$[\alpha]_{578}$= -192° ($CHCl_3$) (lit. $[\alpha]_D$= +186° ($CHCl_3$); ^{1}H-NMR: δ 2.2 (s,3H), 6.15 (s,1H), 7.25-7.55 (m,5H).

The determination of the enantiomeric excess of 305 with (*R*)-2-chloro-2-oxo-5,5-dimethyl-4-(R)-phenyl-1,3,2-dioxophosphorinane (321)[43]

To a solution of amine **305** (0.1 mmol) in 3 ml THF was added 1 equivalent of n-BuLi. After stirring the mixture for 15 minutes at RT the derivatizing reagent **321** (0.1 mmol) was added. The reaction was allowed to stir for 30 minutes. The mixture was evaporated and the residue **323** was dissolved in $CDCl_3$ (2 ml) and the solution was analyzed using ^{31}P-NMR. For spectroscopic data, see scheme 3.10.

The determination of the enantiomeric excess of 305 by chiral HPLC*
(3*R*,4*R*)-3,4-diphenylpyrrolidine (**305**) (1mmol) was dissolved in CH_2Cl_2 (5ml) and cooled to 0^0C, and triethylamine (1mmol) was added followed by TsCl (1mmol). The mixture was allowed to stir for 30 min., and washed with 10% HCl and brine. The organic layer was dried and concentrated. The crude product was purified by column chromatography (silica, EtOAc/hexane 1:6) to afford (3*R*,4*R*)-1-[(4-methylphenyl)sulfonyl]-3,4-dipenylpyrrolidine as a white solid. ^{1}H-NMR: δ 2.5 (s,3H), 3.4 (m,4H), 3.9 (m,2H), 7.0 (4,H), 7.2 (m,6H), 7.4 (d,2H), 7.8 (d,2H); Chiral HPLC (column: Chiralpak AD (hexane/EtOH, 80/20), 1.0 ml/min., 240 nm), t_r (*R,R*) 22.09 min. 99.5%, t_r (*S,S*) 9.64 min. 0.5%; 99% ee. * According to; Denmark, S.E.; Marcin, L.R. *J. Org. Chem.* **1995**, *60*, 3221.

meso and d,l 2,3-Bis-(*p*-methoxyphenyl)succinic acid (324) was prepared from ethyl-*p*-methoxyphenylacetate* in the same way as described for **301**, with the exception that the saponification was performed in ethylene glycol. Thus starting with *p*-methoxyphenylacetic acid 100 g (0.6 mol), 2,3-bis-(*p*-methoxyphenyl)succinic acid (**324**) was obtained as a yellow solid. Yield 90%; mp 207-215°C (lit[46a] 214-215°C); ^{1}H-NMR(DMSO-d6): δ 3.72 and 3.76 (2s,6H), 4.06 and 4.12 (2s,2H), 6.7 and 7.0 (2d,4H), 7.2 and 7.4 (2d,4H), 12.2 (b,2H); ^{13}C-NMR(DMSO-d6): δ 52.83 (CH), 53.61 (CH), 54.82 (CH), 55.00 (CH), -133.6 (CH), -133.78 (CH), 128.51 (C), 128.6 (C), 129,3 (CH), 129.40 (C), 158 (C), 158.1 (C), 172.65 (C=O, 174,37 (C=O).

meso and d,l 2,3-Bis-(*p*-methylphenyl)succinic acid (325) was prepared from ethyl *p*-methylphenylacetate* in the same way as described for **301**. Thus starting with *p*-methylphenylacetic acid 25 g (0.17 mol), 2,3-bis-(*p*-methylphenyl)succinic acid (**325**) was obtained as a white solid. Yield 90%; ^{1}H-NMR(DMSO-d6): δ 2.13 and 2.25(2s,6H, 4.09 and 4.13 (2s,2H), 7.0-7.11 (m,8H), 7.15 (d,4H), 7.33 (d,4H); ^{13}C-NMR(DMSO-d6): δ 20.51 (CH), 53.20 (CH), 53.40 (CH), 128.10 (CH), 128,25 (CH), 128.82 (CH), 128.98 (CH), 133.53 (C), 133.9 (C), 135.9 (CH), 136.1 (CH), 172.8 (C=O), 174.2 (C=O); HRMS calc. for $C_{18}H_{18}O_4$: 298.120 Found: 298.120

d,l 2,3-Bis-(1-naphtyl)succinic acid (326) was prepared from ethyl 1-naphthylacetate* in the same way as described for **301**. Thus starting with 1-naphtylacetic acid 186 g (1 mol), d,l 2,3-bis-(1-naphtyl)succinic acid was obtained as a white solid. Yield 92%. A pure sample was obtained after crystallisation from acetone. mp 245-246^{0}C (lit. [46b] 247°C); ^{1}H-NMR(DMSO-d6): δ 4.13 (s,2H), 7.0-8.0 (m,14H); ^{13}C-NMR (DMSO-d6): δ 123.8 (CH),125.2 (CH), 125.4 (CH), 126.0 (CH), 127.8 (CH), 128.2 (CH), 131.5 (C_), 133.3 (C), 133.8 (C), 174 (C=O).

* In all three cases the esters were prepared form the corresponding acid via standard procedures (EtOH, $SOCl_2$). The esters were used without further purification.

d,l -2,3-Bis-(*p*-methoxyphenyl)succinic anhydride (327) was prepared from the corresponding succinic acid **324** in the same way as described for **302**. Yellow solid. Yield 65%; mp 107-108°C; ^{1}H-NMR: δ 3.8 (s,6H), 4.35 (s,2H), 6.9 (d,2H), 7.15

(d,2H); ^{13}C-NMR: δ 54.74 (CH_3), 55.32 (CH), 114.8 (CH), 125.48 (C), 128.86 (CH), 160.0 (C), 171 (C=O); HRMS calcd. for $C_{18}H_{16}O_5$: 312.100 Found: 312.100.

d,l -2,3-Bis-(*p*-methylphenyl)succinic anhydride (328) was prepared from the corresponding succinic acid **325** in the same way as described for **302**. White solid. Yield 60%; mp 150.8-151.3°C; ^{1}H-NMR: δ 2.4 (s,6H), 4.35 (s,2H), 7.16 (d,4H), 7.25 (d,4H); ^{13}C-NMR: δ 21.09 (CH_3), 55.00 (CH), 127.54 (CH), 130.08 (CH), 130.65 (C), 138.67 (C), 165.60 (C=O); HRMS calcd. $C_{18}H_{16}O_3$: 280.110 Found: 280.110.

d,l -2,3-Bis-(1-naphthyl)succinic anhydride (329) was prepared from the corresponding succinic acid **326** in the same way as described for **302**. White solid. Yield 63%. mp 160-161°C(lit.[46b], 162°C); ^{1}H-NMR: δ 5.1 (s,2H); 7.0-7.5 (m,10H), 7.8 (d,4H); ^{13}C-NMR: δ 53.8 (CH), 122.3 (CH), 125.8 (CH), 126.5 (CH), 129.7 (CH), 129.8 (CH), 130.5 (C), 130.6 (C), 134 (C), 170.8 (C=O).

d,l -2,3-Bis-(*p*-methoxyphenyl)succinimide (330) was prepared from the corresponding succinic acid **324** in the same way as described for **308**. Slightly yellow solid. Yield 85%. A pure sample was obtained by crystallisation from EtOH. ^{1}H-NMR(DMSO-d6): δ 3.75 (s,6H), 4.2 (s,2H), 6.8 (d,4H), 7.2 (d,4H), 11.2 (br, NH); ^{13}C-NMR(DMSO-d6): δ 55.64 (CH), 113.92 (CH), 129.59 (C), 131.11 (CH), 158.47 (C), 177.93 (C=O); HRMS calcd. for $C_{18}H_{17}NO_4$: 311.116 Found: 311.116.

d,l -2,3-Bis-(*p*-methylphenyl)succinimide (331) was prepared form succinic acid **325** in the same way as described for **308**. White solid. A pure sample was obtained by crystallisation from EtOH. ^{1}H-NMR(DMSO-d6): δ 2.25 (s,6H), 4.2 (s,2H), 5.4 (br,1H), 7.2-7.4 (m,8H); ^{13}C-NMR(DMSO-d6): 20.58 (CH_3), 55.05 (CH), 128.34 (CH), 129.09 (CH), 133.43 (C), 136.51 (C), 177.77 (C=O); HRMS calc. for $C_{18}H_{17}NO_2$: 279.126 Found: 279.126.

d,l -2,3-Bis-(1-naphthyl)succinimide (332) was prepared from the corresponding trans succinic acid **326** in the same way as described for **308**. White solid. Yield 95%. A pure sample was obtained by crystallisation from EtOH. mp 124-125°C; ^{1}H-NMR(DMSO-d6): δ 5.36 (s,2H), 7.0-8.0 (m,14H), 7.6 (br,1H); ^{13}C-NMR(DMSO-d6): δ 56.0 (CH), 123.33 (CH), 125.53 (CH), 125.72 (CH), 126.26 (CH), 128.06 (CH), 128.64 (CH), 131.8 (C), 132.92 (C), 133.43 (C), 177.92 (C=O); HRMS calcd. for $C_{24}H_{17}NO_2$: 315.126 Found: 351.126.

Preparation of racemic 2,3-bisarylpyrrolidines (333-335)

Racemic pyrrolidines **333-335** were prepared from the corresponding imides **330-332** in the same way as described for **305**. The crude amines were used in the resolution step without further purification. The pyrrolidines were obtined as brown oils which were pure by ^{1}H-NMR.

Resolution of 3,4-bis-(*p*-methoxyphenyl)pyrrolidine (333) using phencyphos
To a solution of racemic amine **333** (21 g, 74 mmol) in 2-butanone (250 ml) was added (+) phencyphos (17 g,74 mmol). The mixture was heated to reflux and the clear resolution was stirred overnight at RT. The solid was collected and recrystallised twice from 2-butanone, to afford 5 g (13%) of a salt with $[\alpha]_{578}$= -51° (MeOH). The mother liquors were treated with 10% KOH/ether and the resulting amine (16 g) treated with (-) phencyphos (13 g) in 2-butanone. After three crystallisations a salt was obtained with $[\alpha]_{578}$= +49° (MeOH). Yield 5 g (13%). Treatment of the salt with $[\alpha]_{578}$= -51° with 10% KOH/ether afforded (*R,R*)-**333** as a colorless oil, yield 2.56 g (12%, based upon racemic **333**); $[\alpha]_{578}$= -166° ($CHCl_3$); ^{1}H-NMR: δ 2.2 (br,NH), 3.0-3.7 (m,4H), 3.5-3.6 (m,2H), 3.8 (s,6H, 6.75 (d,4H), 7.15 (d,4H); ^{13}C-NMR: δ 53.31 (OCH_3), 55.16 (CH), 55.80 (CH_2), 113.82 (CH), 128.27 (CH), 134.20 (C), 157.95 (C); HRMS calcd. for $C_{18}H_{21}O_2N$: 283.157 Found: 283.157.
Treatment of the salt with $[\alpha]_{578}$= +49° with 10% KOH/ether afforded (*S,S*)-**332** as a colorless oil. Yield 2.5 g (12%, based upon racemic **333**); $[\alpha]_{578}$= +164° ($CHCl_3$). Spectroscopic data identical with those of (*R,R*)-**333**.

Resolution of 3,4-bis-(*p*-methylphenyl)pyrrolidine (334) using phencyphos
Same procedure as described above. With (+) phencyphos, (*R,R*)-**334** was obtained as a colorless oil. Yield (10%, based upon racemic amine **334**); $[\alpha]_{578}$= -198° ($CHCl_3$); ^{1}H-NMR: δ 2.31 (s,6H), 3.0-3.2 (m,2H), 3.2-3.4 (m,2H), 3.5-3.7 (m,2H), 7.27 (s,8H); ^{13}C-NMR: 21.0 (CH_3), 53.59 (CH), 55.98 (CH_2), 127.23 (CH), 129.13 (CH), 135.79 (C), 139.25 (C); HRMS calcd. for $C_{18}H_{21}N$ 251.167 Found: 251.167.
(*S,S*)-**334** was obtained as a colorless oil. Yield (10%, based upon racemic amine **334**); $[\alpha]_{578}$= +190° ($CHCl_3$). Spectroscopic data identical with those of (*R,R*) **334**.

Resolution of 3,4-bis-(1-naphtyl)pyrrolidine 335 using di-*p*-toluoyltartaric acid
A solution of racemic amine **335** (32.3 g, 0.10 mol) in 2-butanone (2 l.) was heated to reflux and (2*S*,3*S*) (+)-di-*p*-toluoyltartaric acid (40.4 g, 0.10 mol) was added. The mixture was refluxed and the clear solution was allowed to cool to 30°C and the precipitate was filtered, to afford a salt (26 g, 37%) with $[\alpha]_{578}$= -92.5° (DMF). The moter liquors were treated with 10% $NH_4OH/CHCl_3$ and the enriched (+) amine 335 was treated with (2*R*,3*R*)(-)-di-*p*-toluoyltartaric acid to afford a salt (24 g, 35%) with $[\alpha]_{578}$= +75° (DMF). Treatment of the salt with $[\alpha]_{578}$= -92.5° with $NH_4OH/CHCl_3$ afforded (*R,R*)-**335** as a yellow solid. Yield 30%; $[\alpha]_{578}$= -122° ($CHCl_3$); ^{1}H-NMR: δ 2.4 (br,NH), 3.2 (dd,2H), 3.85 (dd, 2H), 4.5 (m,2H), 7.2-7.5 (m,8H), 7.6 (d,2H), 7.8 (m,2H), 8.1 (m,2H); ^{13}C-NMR: δ 46.48 (CH), 55.00 (CH_2), 122.83 (CH), 123.45 (CH), 125.47 (CH), 125.64 (CH), 125.94 (CH), 126.98 (CH), 128.87 (CH), 132.36 (C), 133.92 (CH), 138.03 (C); HRMS calcd. for $C_{24}H_{21}N$ 323.167 Found: 323.167.
Treatment of the salt with $[\alpha]_{578}$= +75° with $NH_4OH/CHCl_3$ afforded (*S,S*)-**335** as a yellow solid. Yield 29%; $[\alpha]_{578}$= +118.3° ($CDCl_3$). Spectroscopic data identical with those of (*R,R*) **335**.

The determination of the enantiomeric excess of pyrrolidines 333-335 with CDA's 320 or 321 was performed as described for pyrrolidine **305**. The results are summarized in table 3.3.

(2*S*,3*S*,1*R*)-*N*-(1-Phenyl-2-hydroxymethyl)-2,3-bis-(*p*-methoxyphenyl)succinimide (336) was prepared in the same way as described for **306**. Thus starting with anhydride **327** (5.0 g,16 mmol) and (*R*)-phenylglycinol (2.19 g,16 mmol), (*S,S,R*)-**336** was obtained diastereomerically pure after three crystallizations from EtOH as a white solid. Yield 1.2 g (16%); $[\alpha]_{578}$= +104°($CHCl_3$); mp 193-198.5°C; ^{1}H-NMR: δ 2.0-2.4 (br,OH), 3.8 (s,6H), 4.0 (s,2H), 4.15 (dd,1H), 4.65 (t,1H), 5.45 (dd,1H), 6.85 (d,4H), 7.1 (d,4H), 7.3-7.5 (m,5H); ^{13}C-NMR: δ 54.80 (CH_3), 55.27 (CH), 58.30 (CH), 61.5 (C), 114.59 (CH), 127.95 (CH), 128.33 (CH), 128.77 (CH), 128.00 (C), 136 (C), 154 (C), 178 (C=O); HRMS calcd. for $C_{26}H_{25}NO_5$ 431.173 Found: 431.173.

(3*S*,4*S*)-3,4-Bis-(*p*-methoxyphenyl)pyrrolidine (333) was prepared in the same way as described for **305**. Thus starting with imide **336** (1.2 g) reduction with $LiAlH_4$, followed by hydrogenation with ammonium formate Pd/C 10% afforded (*S,S*)-**333**. Yield 10% (based upon anhydride **327**); $[\alpha]_{578}$= +175° ($CHCl_3$). Spectroscopic data identical with those previously described.

(2*S*,3*S*,α*S*)-*N*-(α-Phenylethyl)-2,3-bis(*p*-methoxyphenyl)succinimide (337)
A mixture of anhydride **327** (30 g,96 mmol), (S)-α-phenylethylamine (12.2 g, 96 mmol), Et_3N (2 ml) in toluene (300 ml) was refluxed for 24 hours. The solvent was evaporated and the residue crystallized from 2-butanone/EtOAc (4:1, 600 ml) to afford (*S,S,S*)-**337** as a white solid. Yield 12 g (30%); mp 229-232°C, $[\alpha]_{578}$= +128° ($CHCl_3$); ^{1}H-NMR: δ 1.8 (d,CH_3), 3.8 (s,6H), 3.8 (s,2H), 5.1 (q,1H), 6.85 (d,4H), 7.0 (d,4H), 7.3-7.5 (m,5H; ^{13}C-NMR: 18.5 (CH_3), 52.0 (CH), 54.55 (CH), 55.27 (CH), 114.55 (CH), 127.38 (CH), 127.80 (CH), 128.48 (CH), 128.81 (CH), 128.9 (C), 159,0 (C), 177 (C=O); HRMS calcd. $C_{26}H_{25}NO_4$: 415.178 Found: 415.178.
Anal. calc. for $C_{26}H_{25}NO_4$: C 75.15 H 6.07 N 3.37 Found: C 72.82 H 5.97 N 3.37
The mother liquors were evaporated and treated with ether to afford 10 g (25%) of the (*R,R,S*) diastereomer with a d.e. of 80%.

(2*S*,3*S*,α*S*)-*N*-(α-Phenylethyl)-2,3-bis(*p*-methylphenyl)succinimide (337)
A mixture of anhydride **328** (12.6 g, 45 mmol), (*S*)-α-phenylethylamine (5.44 g, 45 mmol 96% ee), Et_3N (1 ml) in toluene (200 ml) was refluxed for 8 hours. The solvent was concentrated and the residue was crystallized from 2-butanone to afford (*S,S,S*) **437** as a white solid. Yield 4.3 g (25%); mp 184-187.9°C; $[\alpha]_{578}$= +114° ($CHCl_3$); ^{1}H-NMR: δ 1.93 (d,3H), 2.33 (s,6H), 3.95 (s,2H), 5.55 (q,1H), 7.0 (d,4H), 7.1 (d,4H), 7.2-7.6 (m,5H); ^{13}C-NMR: δ 16.86 (CH_3), 21.04 (CH_3), 50.90 (CH), 54.90 (CH), 127.37 (CH), 127.79 (CH), 128.46 (CH), 129.82 (CH), 133.83 (C), 137.66 (C), 139.9 (C), 177 (C=O); Anal. calcd. for $C_{26}H_{25}NO_2$: C 81.42 H 6.58 N 3.65 Found: C 77.78 H 6.38 N 3.60; HRMS calcd. for $C_{26}H_{25}NO_2$: 383.188 Found: 383.188.
The mother liquors were concentrated to afford the (*R,R,S*)-**337a** diastereomer with a de of 73% (determined via ^{1}H-NMR).

(3*S*,4*S*)-3,4-Bis-(*p*-methylphenyl)pyrrolidine (334) was prepared according to the same procedure as described for **305**. Thus starting with (*S,S,S*)-**338** (4.7 g, 12.2 mmol), (*S,S*)-**334** was obtained as a colourless oil. Yield 2.8 g (91 %); $[\alpha]_{578}$= +206° ($CHCl_3$). Spectroscopic data identical with those previously described.

(3*R*,4*R*)-3,4-Bis-(*p*-methylphenyl)pyrrolidine (334)
Reduction of (*R,R,S*) **337a** (73% de) with $LiALH_4$ in THF afforded diastereomerically pure (3*R*,4*R*,α*S*)-*N*-(α-phenylethyl)-3,4-bis(*p*-methylphenyl)pyrrolidine **339** after crystallisation from MeOH. Yield 3.1 g (20%); ^{1}H-NMR: δ 1.45 (d,3H), 2.31 (s,6H), 2.7 (m,2H), 3.2-3.5 (m,5H), 7.1 (dd,8H), 7.2-7.5 (m,5H); ^{13}C-NMR: δ 20.97 (CH_3), 23.26 (CH_3), 52.29 (CH), 61.56 (CH_2), 65.82 (CH), 126.82 (CH), 127.10 (CH), 127.31 (CH), 128.32 (CH), 129.01 (CH), 135.63 (C), 142 (C), 145.9 (C).
Hydrogenation with ammoniumformate (10 g) and Pd/C 10% (1.1 g) in MeOH/THF (8:1)(45 ml) afforded (*R,R*) **334** as a colorless oil. Yield 1.9 g; $[\alpha]_{578}$= -220° ($CHCl_3$). Spectroscopic data identical to those previously described.

d,l *N*-Benzyl-3,4-bis-(1-naphthyl)pyrrolidine (340)
A mixture of acid **326** (10 g, 27 mmol), benzylamine (2 g, 27 mmol) in o-xylene (200 ml) was refluxed for 2 hours with constant removal of the water formed. The clear solution was evaporated, dissolved in CH_2Cl_2 (100 ml) washed with 10% HCl, H_2O, 5% $NaHCO_3$, H_2O, dried ($NaSO_4$) and concentrated to afford a brown oil which was used in the next step without further purification. The oil was dissolved in THF (50 ml) and added to a suspension of $LiAlH_4$ (1.9 g, 50 mmol) in THF (50 ml). The mixture was refluxed for 2 hours and hydrolysed with 10% KOH. The salts obtained were filtered over Celite and washed with toluene (100 ml). The combined filtrates were concentrated and the yellow oil was crystallised from ether/hexane to afford amine **340** as a yellow solid. Yield 8.6 g (70%). ^{1}H-NMR: δ 3.0 (dd,2H), 3.5 (dd,2H), 3.8 (dd,2H), 4.5 (m,2H), 7.0-7.5 (m,11H), 7.6 (dd,4H), 7.75 (d,2H), 7.9 (d,2H); ^{13}C-NMR: δ 46.86 (CH), 60.70 (CH_2), 62.92 (CH_2), 123.71 (CH), 125.28 (CH), 125.63 (CH), 126.86 (CH), 127.0 (CH), 128.30 (CH), 128.30 (CH), 128.68 (CH), 132.05 (C), 133.85 (C), 183,5 (C), 139.5 (C).
Small scale resolutions experiments with various optically pure acids failed.

(3*S*,4*S*)-*N*-Benzyl-3,4-dihydroxypyrrolidine (341)
An suspension of (3*R*,4*R*)-3,4-dihydroxysuccinimide* (75 g, 340 mmol) in THF (500 ml) was slowly added to $LiAlH_4$ (27 g, 700 mmol) in THF (400 ml). The resulting mixture was refluxed for 3 hours and hydrolysed with 10% KOH. The THF is evaporated and the salts are extracted for five days with ether. The combined THF and ether layers were evaporated and the crude product recrystallised from EtOAc to afford amine **341** as a white solid. Yield 40 g (60%). mp 98-99°C (lit. 52a, 99°C); $[\alpha]_{578}$= +31° (MeOH) (lit. [52a], $[\alpha]_D$= +32.4° (MeOH))

* Obtained according to the procedure described by Nagel[52a] in 70% yield. mp 196-198.2 °C (lit. [52a], 196-198°C).

(3*S*,4*S*)-*N*-Benzyl-3,4-bisbenzoyloxypyrrolidine (342)
A solution of **341** (16.5 g, 86 mmol), Et_3N (20 ml) in CH_2Cl_2 (250 ml) was cooled in an ice-bath. Benzoylchloride (20 ml), 172 mmol) was added over a 10 minutes period. The mixture was stirred for an additional 2 hours and water was added. The organic layer was washed with 5% $NaHCO_3$, dried (Na_2SO_4) and concentrated to afford **342** as a white solid, which was used in the next step without further purification. An analytically pure sample was obtained by crystallisation from MeOH. mp 112.3-113.2°C; $[\alpha]_{578}$= +101.5° ($CHCl_3$); ^{1}H-NMR: δ 2.8 (dd,2H), 3.34 (dd,2H), 3.75 (dd,2H), 5.6 (t,2H0, 7.2-7.7 (m,11H), 8.1 (d,4H); ^{13}C-NMR: δ 57.83 (CH_2), 59.30 (CH_2), 77.89 (CH), 126.78 (CH), 127.90 (CH), 128.30 (CH), 129.27 (C), 132.70 (CH), 137.23 (C), 165.52 (C=O); Anal. calc. for $C_{25}H_{23}NO_4$ C 74.80,H 5.77,N 3.49 found: C 74.60, H 5.80, N 3.41

(3*S*,4*S*)-3,4-Bisbenzoyloxopyrrolidine (344)
Crude **301** was dissolved in EtOH (200 ml) and HOAc (30 ml). Palladium on carbon (10%) (1.5 g) was added and the mixture was hydrogenated for 2 days. The catalyst was removed by filtration and the residue dissolved in CH_2Cl_2 and treated with 10% NH_4OH. The organic layer was washed with water, dried (Na_2SO_4) and concentrated in vacuo. The crude product was crystallised from ether/hexane to afford **344** as a white solid. Yield 20 g (74%, overall); mp 60°C; $[\alpha]_{578}$= +158° (MeOH); ^{1}H-NMR: δ 2.5 (br,1H), 3.1 (dd,2H), 3.5 (dd,2H), 5.5 (m,2H), 7.5 (m,6H), 8.0 (d,4H); ^{13}C-NMR: δ 52.46 (CH_2), 79.34 (CH), 128.40 (CH), 129.66 (CH), 133.25 (CH), 165.62 (C=O); No exact mass could be determined due to elimination of the benzoyl group[(m=105).

(3*S*,4*S*)-*N*-Benzyl-3,4bis-*p*-toluoyloxypyrrolidine (343) was prepared from **341** in the same way as described for **342**. Thus starting with **341** (9 g, 47 mmol) and *p*-toluoylchloride (12.4 ml, 94 mmol) amine **343** was obtained in quantitive yield. An analytically pure sample was obtained by crystallisation from MeOH. mp 77.1-78.5°C; $[\alpha]_{578}$= +107.2° ($CDCl_3$); ^{1}H-NMR: δ 2.43 (s,6H), 2.75 (dd,2H), 3.33 (dd,2H), 3.72 (dd,2H), 5.55 (t,2H), 7.28 (d,4H), 7.2-7.4 (m,5H), 8.0 (d,4H); ^{13}C-NMR: δ 21.71 (CH_3), 58.30 (CH_2), 59.82 (CH_2), 78.23 (CH), 127.03 (C), 127.25 (CH), 128.37 (CH), 128.81 (CH), 129.10 (CH), 129.83 (CH), 137.76 (C), 145.88 (C), 166.07 (C=O);Anal. calc. for $C_{27}H_{27}NO_4$ C 75.50, H 6.34, N 3.26 found: C 75.40, H 6.40, N 3.18

(3*S*,4*S*)-3,4-Bis-*p*-toluoyloxypyrrolidine (345) was prepared from **343** in the same way as described for **344**. Yield 80% (overall); mp 80.8-82°C; $[\alpha]_{578}$= +178.1° (MeOH); ^{1}H-NMR: δ 2.2 (br,1H), 2.4 (s,6H), 3.1 (dd,2H), 3.5 (dd,2H), 5.5 (m,2H), 7.2 (d,4H), 7.9 (d,4H); ^{13}C-NMR: δ 21.66 (CH_3), 52.55 (CH_2),,79.15 (CH), 126.87 (C), 129.12 (CH), 129.70 (CH), 144.01 (C), 165.75 (C=O).No exact mass could be determined due to elimination of the toluoyl group (119)

CHAPTER 4

HIGHLY SYMMETRICAL MULTI-DENTATE NITROGEN LIGANDS BASED UPON 3,4-DISUBSTITUTED PYRROLIDINES

4.1 Introduction

Over the last decade catalytic enantioselective synthesis has been established as a tool of common practice. The number of catalytic enantioselective processes is steadily increasing, as well as the capability for directing such processes.[1] The catalysts used in enantioselective synthesis can be divided into three groups. First, natural products, of which the cinchona alkaloids are frequently used members.[2] Secondly, enzymes play an increasingly important role in enantioselective synthesis.[3] But the most successful type of enantioselective catalysts, developed over the last ten years, are catalysts with a metal center surrounded by a chiral ligand.[4] The metal is used as the catalytic core, which binds both the chiral ligand and the substrate, thus creating a chiral environment, in which the enantioselectivity is determined. The ultimate goal in such systems is to restrict the system to one and only one transition state, thus ensuring a single enantiomeric product. Limiting the number of available transition states in the enantiodetermining step entails restriction of the number of degrees of freedom in the ligand-metal-substrate complex. Especially the development and investigation of tailor-made, chiral mono- and bidentate phosphines has led to a greater understanding of the prerequisites for chirality transfer.[5] It has become important to design chiral ligands specifically for enantioselective control of metal-catalyzed reactions. New catalysts to be developed should be accessible via relatively easy synthesis and should be easily modified. Recent interest in metal-catalyzed asymmetric reactions has focussed attention on the development of chiral cyclic nitrogen ligands.[6] Although much progress has been made in the rational design of chiral ligands,[7] it is difficult to predict whether a catalytic system will be successful or

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1 Enantioselective synthesis; Issue of: *Chem. Rev.* **1992**, *92*, 739-1190.

2 Wynberg, H., *Topics in Stereochemistry*, Eliel, E.L.; Wilen, S.H. and Allinger, N.L., Eds. Intersc. Publ., John Wiley & Sons, Inc., *vol. 16*, 87, New York 1986.

3 *Enzymes in organic chemistry: Tetrahedron: Asymmetry* **1993**, *4*, 757-1037.

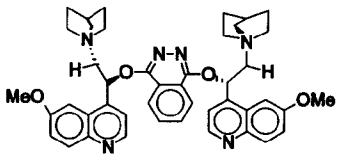
4 a) Brunner, H. "Enantioselective synthesis of organic compounds with optically active transition metal catalysts in substochiometric quantities", *Topics Stereochem.* **1988**, *18*, 129. b) Noyori, R.; Kitamura, "Enantioselective Catalysis with metal complexes" An overview in *Modern Synthetic Methods* **1989**, Ed. R. Scheffold, Springer, Berlin-Heidelberg, 115-198.

5 a) König, K.E., *The applicability of asymmetric homogeneous catalytic hydrogenation*, 71-101 and Halpern, J. *Asymmetric Catalytic hydrogenation Mechanism and origin of enantioselection*, 41-69 in Morrison, J.D., Ed., *Asymmetric synthesis, Chiral Catalysis*, Academic Press, Orlando Florida, **1985**, *vol. 5*.

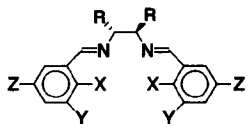
6 a) Bolm, C. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 542. b) For an excellent review see: Togni, A.; Venanzi, L.M. *Angew. Chem. Int. Ed. Eng.* **1994**, *33*, 497.

7 For an illustrative example see: Trost, B.M.; van Vranken, D.L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.

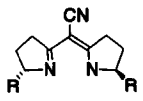
not. Each chemical transformation demands its own type of chiral ligand that has the ability to activate the substrate on the one hand and control the stereochemistry on the other. But as stated by Blaser[8], there are structural elements that are common to many of the best ligands and that are often beneficial for obtaining high enantioselectivities. We want to discuss them briefly. First, the position of the asymmetric centre, which should be as close as possible to the reacting centre. Secondly, ligands that can form chelates (bidentate and tridentate) are preferred over monodentate ones.[9] A better defined surrounding is created by using bi- and tridentate ligands. Thirdly, C_2-symmetrical chiral ligands seem to be more successful then non-symmetrical. In fact, as pointed out by Kagan,[10] when a C_2-symmetrical ligand is bound to a metal centre, the substrate feels the same situation, independent of its manner of approach. The number of possible transition states is reduced by the introduction of C_2-symmetry. Fourthly, bidentate ligands with a cyclic backbone have probably the best chance to give good results. The resulting bicyclic chelate complexes are better defined, because of the rigidness of the cyclic backbone, which reduces the number of conformations. The last structural element, that is important for success, is the influence of bulky or aromatic substituents. They will lead to a better defined environment. On the other hand, too much bulk will decrease the accessibility to the metal centre and thus reduce the activity. In table 4.1 we have listed some chiral ligands that match the criteria stated above and have proven to be successful in stereoselective reactions.



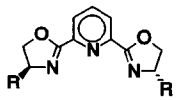
Sharpless[11]



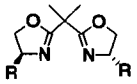
Jacobsen[12]



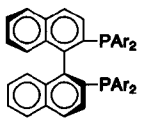
Pfaltz[13]



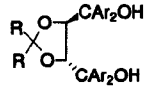
Nishiyama[14]



Corey & Evans[15]



Noyori[16]



Seebach[17]

Table 4.1. Chiral ligands in enantioselective synthesis

11 12 13 14 15 16 17

[8] Blaser, H.U. *Chem. Rev.* **1992**, *92*, 935.

[9] For a discussion concerning coordination chemistry, see Busch, D. H. *Chem. Rev.* **1993**, *93*, 847.

[10] Kagan, H.B.; Dang, T.J. *J. Am. Chem. Soc.* **1972**, *94*, 6429.

[11] Sharpless, K.B.; Amberg, W.; Bennani, K.; Crispino, G.A., Hartung, J.; Jeong, K.S.; Kwong, H.L.; Wang, Z.M.; Xu, D.; Zhang, X.L. *J. Org. Chem.* **1992**, *57*, 2768.

All these ligands have in common that structural changes within the ligand are easy to perform. The ligands can therefore be specifically modified for enantioselective control of the reaction they are used in. They also match the five criteria stated above. It is noteworthy to realize that many of the successful ligands used in stereoselective reactions are C_2-symmetrical. The usefulness of the introduction of C_2-symmetry within a ligand is very clearly indicated (see also chapter 1) by the work of Sharpless concerning the dihydroxylation of olefins with alkaloid derivatives.[11] With the introduction of C_2-symmetry in their ligands, see table 4.1, the enantiomeric excess has raised significantly.

As mentioned before nitrogen-containing ligands are acquiring increasing importance in this field. In chapter 3 we have described the synthesis of C_2-symmetrical 3,4-disubstituted pyrrolidines. They might serve as building block for nitrogen-containing ligands, since they consist of a rigid ring structure, and are easily modified. Furthermore, the C_2-symmetry element within these molecules will provide a D_2 or D_3-symmetry element within the bi- and tridentate ligands derived from these pyrrolidines. Despite the great success with C_2-symmetric ligands, chiral ligands possessing elements of higher symmetry have been ignored to a large extent.

In this chapter we describe the synthesis of a variety of nitrogen-containing ligands with high symmetry, and different chelate ring size. The scope, complexation with transition metals and use in enantioselective synthesis will be discussed.

4.2 C_2- and D_2-symmetrical TMEDA analogues

The well known activation of organo-metallic reagents by complexation with tetramethylethylenediamine (TMEDA) suggests that chiral derivatives might serve as chiral ligands in asymmetric reactions. Chiral C_2- and D_2-symmetrical TMEDA analogs were introduced by Cram et al. [18] These compounds allow the enantioselective addition of alkyllithiums to benzaldehydes; the phenylalkylalcohols were obtained in 23-95% ee. The synthesis of these diamines was accomplished by separation of the d,l and meso mixture and subsequent resolution with dibenzoyltartaric acid.

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[12] a) Jacobsen, E.W.; Zhang, W.; Muci, A.R.; Ecker, J.R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. b) Zhen, L.; Conser, K.R.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1993**, *115*, 5326.

[13] Pfaltz, A. *Chimia* 1990, *44*, 201. b) von Matt, P.; Pfaltz, A. *Tetrahedron: Asymmetry* **1991**, *2*, 691.

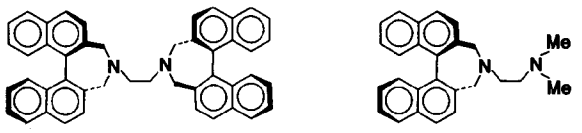
[14] a) Nishiyama, H.; Yanaguchi, S.; Kondo, M.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 4306. b) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223.

[15] Corey, E.J.; Inai, N.; Zhang, H.Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. b) Evans, D.A.; Faul, M.M.; Bilodeau, M.T.; Anderson, B.A.; Barnes, D.M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.

[16] Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245.

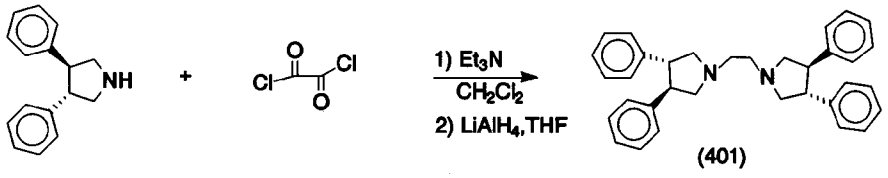
[17] Schmidt, B.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 99.

[18] Mazaleyrat, J.P; Cram, D.J. *J. Am. Chem. Soc.* **1981**, *103*, 4585.



D_2- and C_2- symmetrical diamines introduced by Cram

Tomioka *et al.* synthesized the D_2-symmetrical diamine **401** as shown in scheme 4.1 and used the diamine as ligand in the addition of Grignard reagents to benzaldehyde-[19a,c] (enantiomeric excesses up to 75 % were obtained) and the dihydroxylation reaction of olefins with OsO_4[19b] (ee's up to 99% were obtained in the case of trans stilbene).



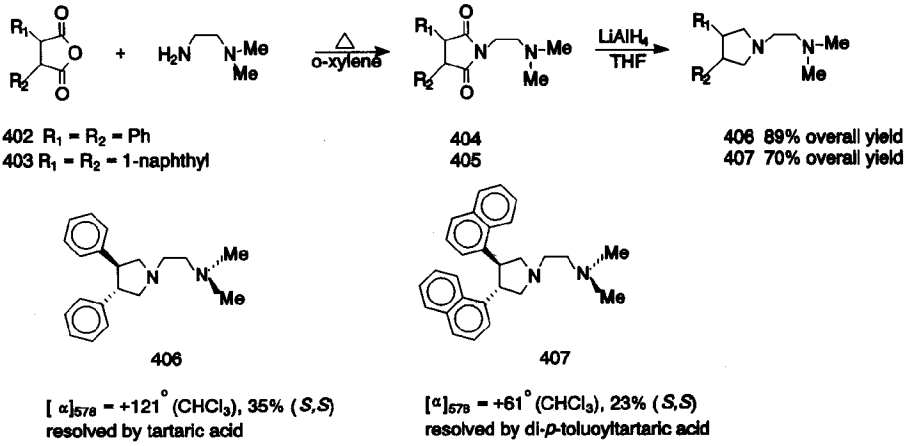
Scheme 4.1. Synthesis of D_2-symmetrical TMEDA analogue

4.2.1 Synthesis of 1-(3,4-diphenylpyrrolidine)-2-dimethylaminoethane (406) and 1-(3,4-di-1-naphthylpyrrolidine)-2-dimethylaminoethane (407)

We decided to synthesize C_2- and D_2-symmetrical TMEDA analogues based on diarylpyrrolidines by resolution of the racemic diamines with tartaric acid derivatives. The syntheses of C_2-symmetrical diamines are outlined in scheme 4.2. The trans 3,4-diarylanhydrides (**402** and **403**) (see chapter 3) were converted to the corresponding imides (**404** and **405**) by reaction with *N,N*-dimethyldiaminoethane in refluxing *o*-xylene. These aminosuccinimides were reduced with $LiAlH_4$ in THF and gave in high overall yield racemic diamines **406** and **407**. With these diamines in hand we did some small-scale trial resolutions with tartaric acid derivatives. The results were very satisfactory; both amines, the diphenylpyrrolidine analogue **406** and the di(1-naphthyl)pyrrolidine **407** were resolved with tartaric acid and di-*p*-toluoyltartaric acid, respectively. Both resolutions required only one crystallization to obtain optically pure amines **406** and **407** in 35%

[19] a) Tomioka, K.; Nakajima, M.; Koga, K. *Chem. Lett.* **1987**, 65. b) Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* 1990, *31*, 1741. c) Nakjima, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 9751.

and 23% yield, respectively.



Scheme 4.2. Synthesis and resolution of C_2-symmetrical diamines

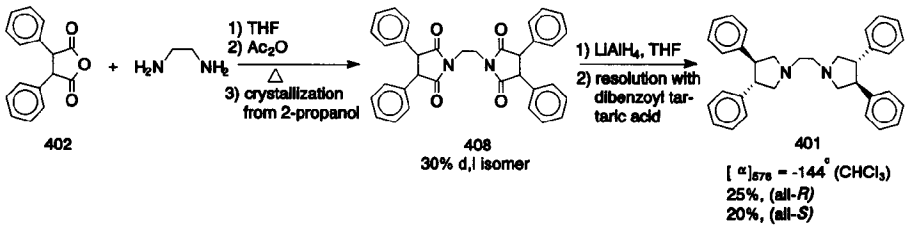
The enantiomeric purity of compound **406** was determined by ^{1}H-NMR of the di-*p*-toluoyltartaric acid amine salt. For the racemic amine two resonances were found at δ 2.48 and 2.52 ppm for the methyl protons of the amine. Enantiomerically pure amine **406**, gave one signal only at δ 2.48 ppm. This is one of the few examples in which the enantiomeric excess of a chiral amine can directly be determined by analysis of the ^{1}H-NMR of the diastereomeric salt.

4.2.2 Synthesis of 1,2-bis(3,4-diphenylpyrrolidine)ethane (401)

The D_2-symmetrical diamine **401** consists of two 3,4-diphenylpyrrolidine units linked by an ethylene bridge. Because of the easy resolution of C_2-symmetrical amines **406** and **407** with tartaric acid derivatives, we also wanted to examine this approach for the synthesis of diamine **401**. The synthesis of racemic diamine **401** is depicted in scheme 4.3. Anhydride **402** is converted to diimide **408** by reaction with ethylenediamine in toluene. This diimide consists of a 1:1 mixture of the d,l and meso compound.[20] One crystallization from this mixture from 2-propanol afforded the d,l isomer in ca. 30% yield, the meso isomer being insoluble. Reduction of this racemic diimide afforded the racemic diamine **401** in 65% yield. The diamine **401** was, as expected, easily resolved with dibenzoyltartaric acid to afford optically pure diamine **401** in reasonable overall

[20] This was confirmed by ^{1}H-NMR. Two resonances were observed for the H_2 and H_3 protons (at δ 4.15 and 4.25 ppm) of the succinimide ring, accounting for the d,l and meso isomer, respectively.

yield.[21] This is a very short synthetic route to chiral diamine **401**, a compound which has proven its applicability as chiral ligand.[19]



Scheme 4.3. Synthesis and resolution of D_2-symmetrical diamine 401

The tertiary diamines described in this section are connected via an ethylene bridge. When coordinated to a metal they will form a five-membered chelate ring. Ligands forming a five-membered chelate ring are widely applied in asymmetric synthesis.[22]

4.3 D_2-symmetrical bidentate nitrogen ligands

In section 4.2 we have described the synthesis of C_2- and D_2-symmetrical bidentate nitrogen ligands obtained via resolution of the corresponding d,l-diamines with tartaric acid derivatives. In the following sections we will describe the synthesis of high symmetrical nitrogen ligands derived from chiral 3,4-disubstituted pyrrolidines. The methodology we will use is depicted, by way of example, in figure 4.1. The chiral 3,4-disubstituted pyrrolidine **[A]** is converted into a diamide **[B]**, which is reduced to form the corresponding nitrogen ligand **[C]**. This methodology has several features which makes it attractive. First, the reaction of an acid chloride with an amine proceeds in high yield and often produces crystalline intermediates. Secondly, the reduction proceeds without racemisation,[21] and thirdly variations in the backbone **[D]** is easy since acid chlorides are widely available.

4.3.1 Synthesis of 3-bis(3,4-diphenylpyrrolidine)-2,2'-dimethylpropane (411)

Bidentate nitrogen ligands forming a six-membered chelate ring are widely used in enantioselective synthesis. Reactions involving enantioselective Diels-Alder reactions, enantioselective aziridination and cyclopropanation of olefins and the asymmetric

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[21] $[\alpha]_D = -143^{\circ}$ for the all (*R*) enantiomer, we found $[\alpha]_{578} = -144^{\circ}$ Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron*, **1993**, *49*, 9735. They prepared diamine **401** according to scheme 4.1, without racemisation.

[22] For a review on chiral ligands see; Tomioka, K. *Synthesis* **1990**, 541.

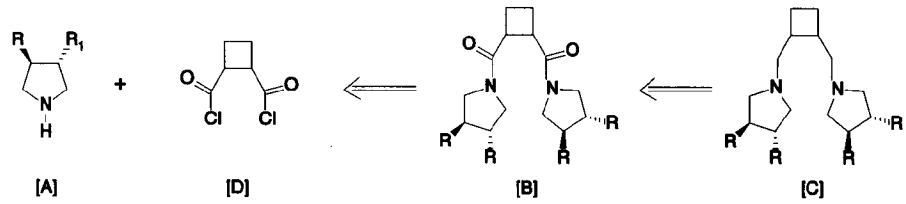
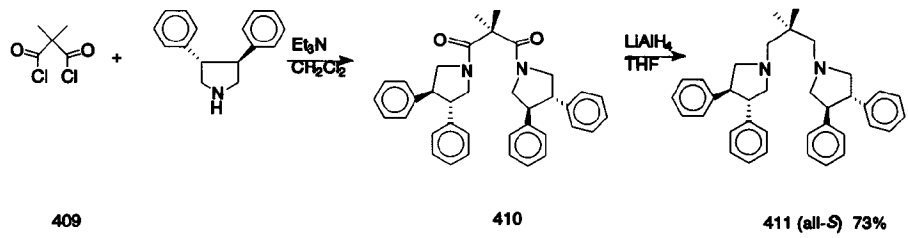


Figure 4.1.

reduction of α,ß-unsaturated carboxylic esters and amides all proceed with high induction.[23]

The first 3,4-disubstituted pyrrolidine analogue of these bidentate nitrogen ligands was synthesized according to scheme 4.4. Dimethylmalonyl dichloride (**409**) was reacted with 2 equivalents of (*S,S*)-3,4-diphenylpyrrolidine to form the diamide **410**. The diamide was crystallized from EtOH and reduced with $LiAlH_4$ in THF. The (all-*S*) diamine **411** was isolated in 73% overall yield. That the reduction proceeds without racemization was checked by ^{1}H-NMR; no signals for the meso compound were detected. The high symmetry of the ligand was confirmed by ^{13}C-NMR, in which only nine signals were observed. This in sharp contrast with the diamide, in which fiveteen signals were found, due to the rotation barrier created by the amide bond. The (all-*R*) diamine **411** was prepared in the same way.



Scheme 4.4. Synthesis of D_2-symmetrical diamine 411

The starting material, dimethylmalonyl dichloride, was synthesized according to a literature procedure starting with diethylmalonate.[24] Diamine **411** will form six-membe-

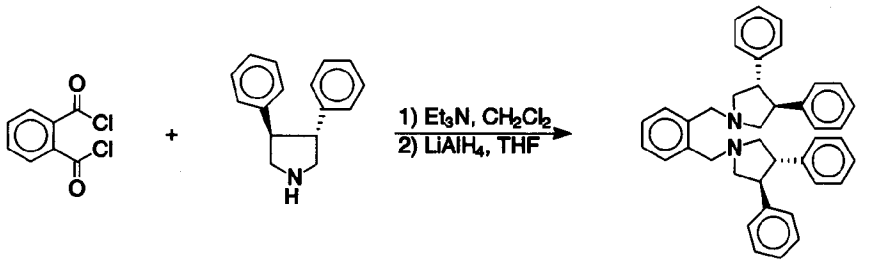
[23] a) See ref. 7 and references cited within. b) Corey, E.J.; Wang, Z. *Tetrahedron Lett.* **1993**, *34*, 4001. c) Evans, D.A.; Faul, M.M.; Bilodeau, M.T.; Anderson, B.A.; Barnes, D.M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. d) For a review on nitrogen heterocycles in asymmetric catalysis see: Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.

[24] Corey, E.J.; Imay, N.; Zhang, H.Y. *J. Am. Chem. Soc.* **1991**, *113*, 728.

red rings when coordinated with a metal. The two methyl groups will provide extra steric hindrance within this ligand, see section 4.7.

4.3.2 Synthesis of 1,2-bis[(3,4-diphenylpyrrolidine)methyl]benzene (412)

A chiral ligand, which will form seven membered rings with metals was formed by starting with commercially available phthaloyl chloride. Reaction with (*R,R*)-3,4-diphenylpyrrolidine provided the diamide, which was purified by crystallization from EtOH. Reduction with $LiAlH_4$ in THF gave in 65% overall yield, D_2-symmetrical diamine **412**, see scheme 4.5.



412, all (*R*) 65 %

Scheme 4.5. Synthesis of D_2-symmetrical diamine 412

Diamine **412** shows great similarity to the 1,2-bis(2-oxazolinyl)benzene ligands, introduced by Bolm *et al.*[25] They synthesized the 1,2-, 1,3- and 1,4-bis(2-oxazolinyl)benzenes by condensation of the corresponding dinitriles with chiral amino alcohols. By the procedure outlined in scheme 4.5, it is of course, possible to synthesize a variety of di-substituted benzene analogues of amine, **412**. The two examples discussed in this section show that D_2-symmetrical bidentate nitrogen ligands are available via "acylation and reduction" of chiral diarylpyrrolidines.

4.4 D_2- and D_3-symmetrical tridentate ligands

A third ligating atom within a chiral ligand might define a better chiral environment. Burk *et al.* have designed D_2-symmetrical chiral bidentate diphospholane ligands.[26a,b] They proposed that introduction of a third binding atom in the backbone of these phosphine ligands dramatically affects the mode of binding to transition metals. A similar idea was introduced by Nishiyama *et al.* in the synthesis and use of tridentate chiral bis(oxazolinyl)pyridine ligands,[26c] see figure 4.2.

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[25] Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173.

[26] a) Burk, M.J.; Feaster, J.E.; Harlow, R.L. *Tetrahedron: Asymmetry* **1991**, *2*, 569. b) Burk, M.J.; Feaster, J.E.; Nugent, W.A.; Harlow, R.L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. c) see ref. 14.

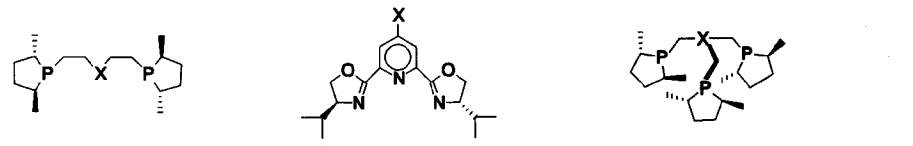


Figure 4.2. High symmetry tridentate ligands

Burk *et al.* also introduced the concept of C_3-symmetric tridentate phosphanes (3 C_2-axes), see figure 4.2.[26a] They proposed that the high optical yields obtained with C_2-symmetrical ligands must be attributed to a reduction of possible diastereomeric transition states. This is the case in reactions involving an intermediate square-planar metal complex, since a 180° rotation of a transitionstate intermediate is an identity operation. But also octahedral intermediates are known to be involved in many transition-metal-catalyzed reactions. In this case, see figure 4.3, a chiral C_2-symmetrical bidentate ligand **A** offers two non-equivalent coordination sites [axial(a) and equatorial(b)]. A similar tridentate C_3-symmetrical ligand **B** offers one coordination site only; since all sites are homotopic.

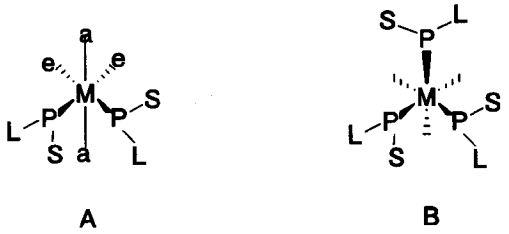


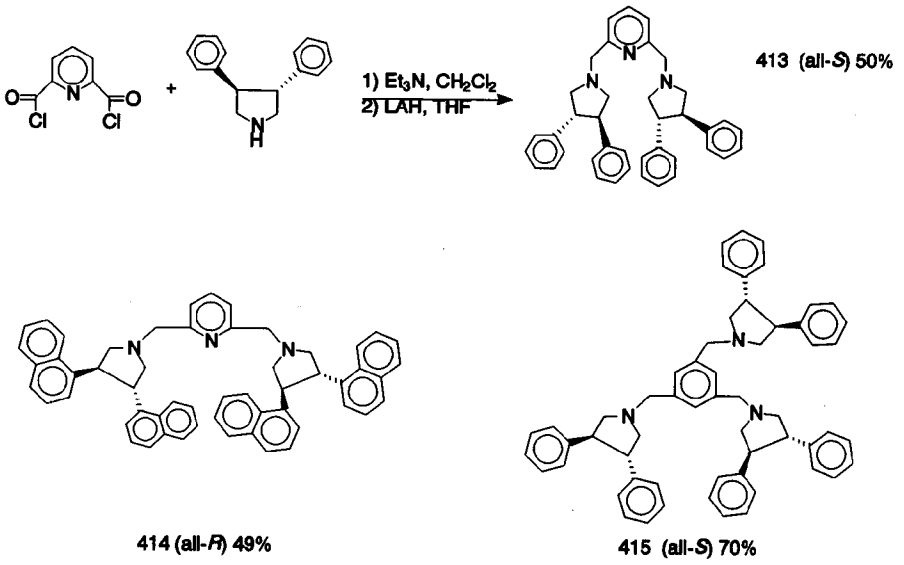
Figure 4.3. Octahedral complexes of C_2-versus C_3-symmetrical ligands

The reduced number of competing asymmetric environments should lead to higher enantioselectivity. We also introduced within our ligand system, the concept of a third binding site and the concept of D_3-symmetry.

4.4.1 Synthesis of 2,6-bis[(3,4-diarylpyrrolidine)methyl]pyridines (413) and (414), 1,3,5-tris[(3,4-diphenylpyrrolidine)methyl]benzene (415), 1-hydroxy-2,6-bis[(3,4-diphenylpyrrolidine)methyl]benzene (419) and 1-bromo-2,6-bis[(3,4-diphenylpyrrolidine)methyl]benzene (420)

The D_2-symmetrical tridentate nitrogen ligand **413** (scheme 4.6) was synthesized from pyridine-2,6-dicarboxylic acid and (*S,S*)-3,4-diphenylpyrrolidine according to the method described for **411**. The crystalline diamide **413a** was reduced with $LiAlH_4$ in THF. After purification by chromatography the (all-*S*) triamine **413** was isolated in 50% overall yield. The other enantiomer of **413** (all-*R*) was prepared in the same way starting with (*R,R*)-3,4-diphenylpyrrolidine. The same approach was also applied to the synthesis of the (all-*R*)-3,4-bis-(1-naphthyl)pyrrolidine derivative **414**. The triamine was purified by column-chromatography and was isolated in 50% overall yield.

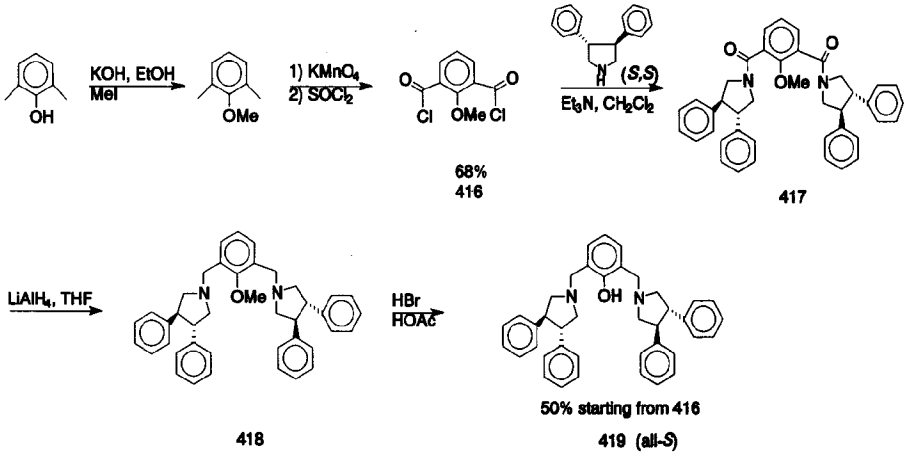
The D_3-symmetrical tridentate nitrogen ligand **415** was prepared in a similar way. Starting with 1,3,5-benzene tricarboxylic acid the ligand **415** was obtained in 72% yield. The high symmetry was clearly indicated by ^{1}H-NMR and ^{13}C-NMR, which exhibited only nine signals.



Scheme 4.6. Synthesis of D_2 - and D_3 -symmetrical tridentate nitrogen ligands

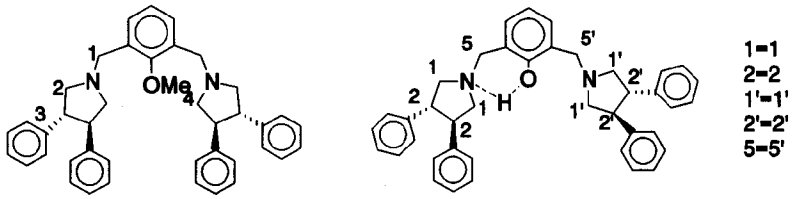
We also wanted to synthesize a tridentate dipyrrolidine ligand with an oxygen atom as extra binding site. 1-Methoxybenzene-2,6-dicarboxylic acid (**416**) seemed to be an appropriate starting material. We synthesized this compound by alkylation of 2,6-dimethylphenol with MeI and subsequent oxidation with $KMnO_4$. The acid was isolated in 60% overall yield. Reaction of the diacid chloride **416** with (*S,S*)-3,4-diphenylpyrrolidine

afforded the diamide **417** in 90% yield. Reduction with $LiAlH_4$ in THF gave the corresponding diamine **418**. The methyl ether was cleaved with HBr in acetic acid, affording the desired ligand **418**. The complete synthesis is depicted in scheme 4.7.



Scheme 4.7 Synthesis of D_2-symmetrical tridentate ligand 419

A strange effect was observed on examination of the ^{1}H-NMR and ^{13}C-NMR spectra of compounds **418** and **419**. The ^{13}C-NMR of ligand **418** consists of 4 signals in the non-aromatic part, proving the C_2-symmetry. This symmetry is also observed in the ^{1}H-NMR, only three resonances are observed for the protons of the pyrrolidine ring. However, the ^{1}H-NMR and ^{13}C-NMR spectra of ligand **419** lack this symmetry. Five signals are observed in the ^{13}C-NMR in the non-aromatic part, where three are expected, two for the pyrrolidine carbons and one for the benzylic carbon. Also the ^{1}H-NMR does not show C_2-symmetry. An explanation for this non-symmetrical behaviour is that the hydroxy proton forms a hydrogen bond with one of the nitrogen atoms, thus disturbing the C_2-symmetry within the molecule, see figure 4.4.



418
4 signals observed in ^{13}C-NMR

419
5 signals observed in ^{13}C-NMR

Figure 4.4. Non-symmetrical behaviour of tridentate ligand 419

Recently a paper appeared[27] in which use of organonickel (II) complexes containing aryl ligands with chiral pyrrolidines as catalysts for the Kharash addition reaction was described.[28] The catalysts used are listed in figure 4.5.

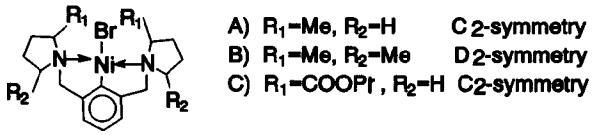


Figure 4.5. Organonickel(II) complexes

The D_2-symmetric catalyst **B**, derived from 2,5-dimethylpyrrolidine showed no catalytic activity due to steric effects. Bulky groups close to the nitrogen atom hinder the formation of an 'encounter complex' with the halocarbon. This problem of steric hindrance can be solved by using 3,4-disubstituted pyrrolidines instead of 2,5-disubstituted pyrrolidines. The bulky phenyl groups are further away from the nitrogen atom, thus reducing steric hindrance, whereas the D_2-symmetry is still present. We synthesized tridentate ligand **420** in a one step procedure[29] starting with 2,6-bis(bromomethyl)bromobenzene[30] and (*R,R*)-

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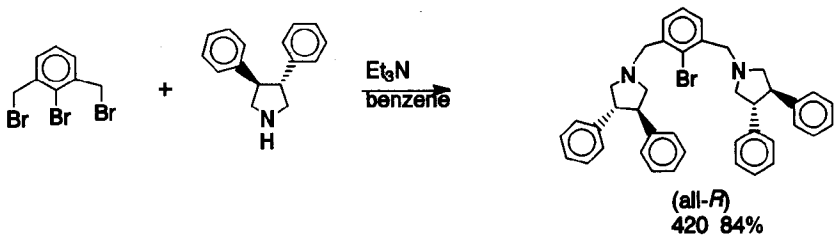
[27] van de Kuil, L.A.; Veldhuizen, Y.S.J.; Grove, D.M.; Zwikker, J.W.; Jenneskens, L.W.; Drenth, W.; Smeets, W.J.J.; Spek, A.L.; van Koten, G. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 267.

[28] The Kharash addition reaction involves the addition of halocarbons to alkene, in which a new C-C and a new C-X bond are formed.

[29] This type of ligands have been studied by van Koten *et al.*; For a review see: van Koten, G. *Pure and Appl. Chem.* **1989**, *61*, 1681.

[30] Vögtle, F. *Chem. Ber.* **1969**, *102*, 1784.

3,4-diphenylpyrrolidine. The D_2-symmetrical diamine **420** was obtained in 84% yield after purification by chromatography. We have not performed the Kharash addition reaction with this ligand.



Scheme 4.8. D_2-symmetrical tridentate ligand 420

4.5 D_2-symmetrical bi- and tetradentate nitrogen ligands

The bidentate 1,10-phenanthroline and 2,2'-bipyridine nucleii are strong chelating agents for a variety of metal ions. Therefore, they are widely used as building blocks for incorporation into host molecules, where a ligated metal atom serves as binding site and catalyst.[31] The 1,10-phenanthroline and 2,2'-bipyridine unit are also effectively used as chiral ligands in metal catalyzed reactions.[32] Two examples of C_2-symmetrical ligands containing these moieties are given in figure 4.5.

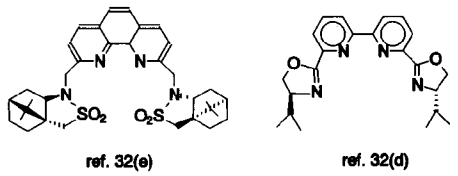


Figure 4.6 C_2-symmetrical 1,10-phenanthroline and 2,2'-bipyridine ligands.

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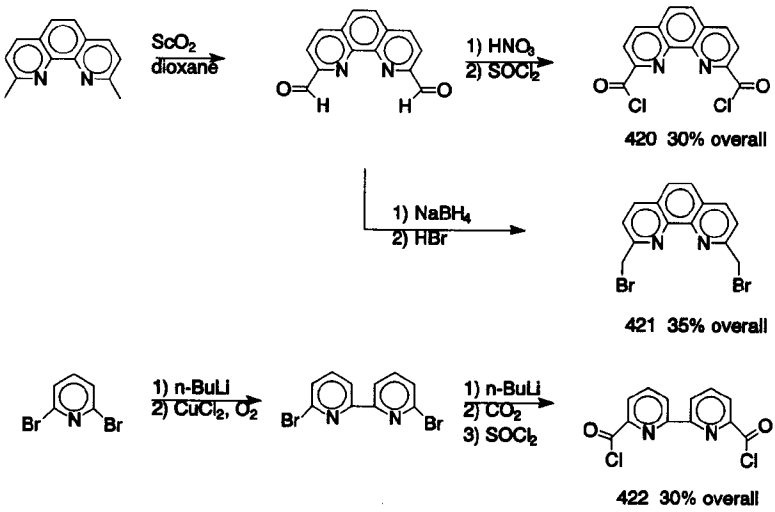
31 a) Weynen, J.G.; Koudijs, A.; Engbersen, J.F.J. *J. Org. Chem.* **1992**, *57*, 7258. b) Newkome, G.R.; Kiefer, G.E.; Puckett, W.E.; Vreeland, T. *J. Org. Chem.* **1983**, *48*, 5112. c) Alpha, B.; Anklan, E.; Deschenaux, R; Lehn, J.M.; Pietraskiewicz, M. *Helv. Chim. Acta.* **1988**, *71*, 1042.

32 a) Botleghi, C.; Scheionato, A.; Chelucci, G.; Brunner, H.; Kürzinger, A.; Oberamn, U. *J. Organomet. Chem.* **1989**, *397*, 17. b) Boln, C.; Ewald, M.; Felder, M.; Schlinloff, G. *Chem. Ber.* **1992**, *125*, 1169. c) Gladiali, S.; Pinna, L.; Melogu, D.G.; Graf, E.; Brunner, H. *Tetrahedron: Asymmetry* **1990**, *1*, 937. d) Wishiyana, H.; Yanaguchi, S,; Park, S.B.; Itoh, K. *Tetrahedron: Asymmetry* **1993**, *4*, 143. e) Kandzia, C.; Steckhan, E.; Knoch, F. *Tetrahedron: Asymmetry* **1993**, *4*, 39.

We also wanted to use these units as building blocks for chiral ligands based upon 3,4-disubstituted pyrrolidines. First, we had to synthesize the appropriate starting materials, which were obtained following literature procedures.[33] 1,10-Phenanthroline-2,9-dicarbonyl chloride (**420**) was synthesized in three steps from commercially available neocuprine. The same starting material was also used to prepare 2,9-bis(bromomethyl)-1,10-phenanthroline (**421**), The diacid chloride **422** of 2,2'-bipyridine-6,6'-dicarboxylic acid was obtained starting with 2,6-dibromopyridine in three steps. The syntheses of these building blocks is outlined in scheme 4.9.



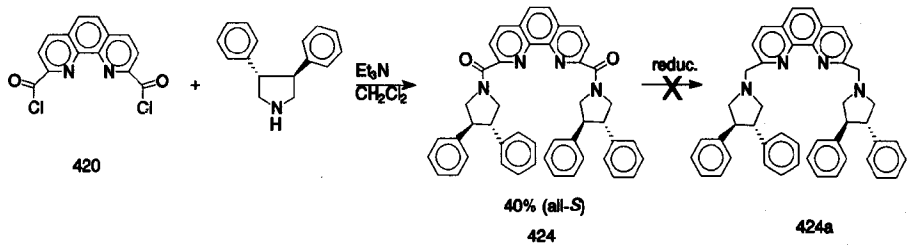
Scheme 4.9. Synthesis of 1,10-phenanthroline and 2,2'-bipyridine building blocks

4.5.1 Attempted synthesis of 2,9-bis[(3,4-diphenylpyrrolidine)methyl]-1,10-phenanthroline (424a) and synthesis of 2,9-bis[(3,4-dibenzoyloxypyrrolidine)methyl]-1,10-phenanthroline (425)

We started with the formation of tetradentate ligand **424a**. Reaction of the diacid chloride **420** with (*S,S*)-3,4-diphenylpyrrolidine afforded in moderate yield the corresponding diamide **424.** Reduction of this diamide with $LiAlH_4$ afforded a mixture of compounds. Some product could was detected by ^{1}H-NMR, but it was not possible to isolate tetramine **424a**, see scheme 4.10. The amide bond is probably cleaved (some aldehyde

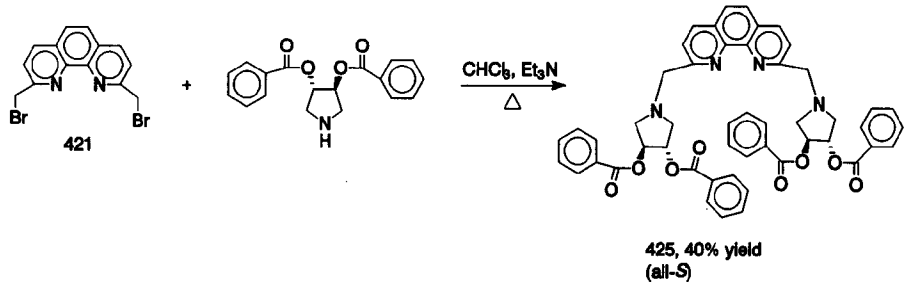
[33] For 1,10-phenanthroline derivatives see: a) Chandler, C.J.; Deady, L.W.; Reiss, J.A.; Tzinos, V. *J. Heterocyclic Chem.* **1982**, *19*, 1017. b) idem, *J. Heterocyclic Chem.* **1981**, *18*, 599.
For 2,2'-bipyridine derivatives see: c) Buhleyer, E.; Wehner, W.; Vögtle, F. *Chem. Ber.* **1978**, *111*, 200. d) Parks, J.E.; Wagner, B.E.; Holm, R.H. *J. Organomet. Chem.* **1973**, *56*, 53.

resonances and 3,4-diphenylpyrrolidine were observed in the crude ^{1}H-NMR) and the lithium and aluminum complexes are difficult to hydrolyse. This approach was therefore not successful and reduction with other reagents, such as BH_3 and AlH_3 gave rise to the same problems.



Scheme 4.10. Attempted synthesis of tetradentate ligand 424a

Another approach to synthesize D_2-symmetrical tetradentate ligands is outlined in scheme 4.11. Reaction of the dibromide **421** with two equivalents of (*S,S*)-3,4-dibenzoyloxopyrrolidine (see chapter 3) in chloroform and triethylamine afforded after chromatography the desired tetramine **425**. A similar attempt with 3,4-diphenylpyrrolidine was unsuccessful, only about 10% conversion to tetramine **424** had taken place after 3 days. The bisaroylpyrrolidines are clearly more reactive towards alkylation than the corresponding diarylpyrrolidines.



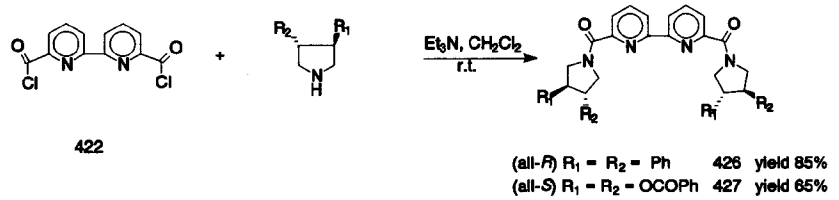
Scheme 4.11. Synthesis of D $_2$-symmetrical tetradentate ligand 425

The high symmetry of ligand **425** was again, established from the ^{1}H-NMR and ^{13}C-NMR spectrum, as expected only 14 signals are observed in the ^{13}C-NMR spectrum.

The synthesis of tetradentate phenantroline ligands containing 3,4-disubstituted pyrrolidines, using alkylation and acylation/reduction methods, is limited. Only one compound (**425**) could be synthesized.

4.5.2 *Synthesis of 2,6-bis[(3,4-diphenylpyrrolidine)oxo]-2,2'-bipyridine (426) and 2,6-bis[(3,4-dibenzoyloxopyrrolidine)oxo]-2,2'-bipyridine (427)*

The same problem observed with the reduction of the diamide of 1,10-phenanthroline, scheme 4.10 might of course also occur with the corresponding 2,2'-bipyridine analogues. However, we realized that diamides of 2,2'-bipyridine-2,6-dicarboxylic acid, might also serve as tetradentate ligands, since well-defined cavities will be created when the dichloride **423** is converted to C_2-symmetrical diamides (**426** and **427**). The syntheses of these ligands, **426** and **427**, is depicted in scheme 4.12.



Scheme 4.12. Synthesis of C_2-symmetrical diamides 426 and 427

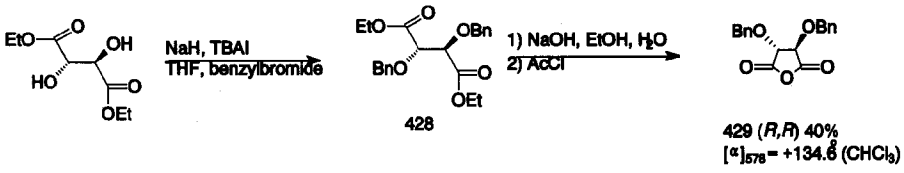
Both the ligands were isolated as crystalline solids. The reduction of ligand **426** with $LiAlH_4$ again gave too a large extent cleavage of the amide bond. Although the desired tetradentate ligand could be detected by ^{1}H-NMR, also aldehyde resonances were observed. Apparently, this is not a suitable approach for the synthesis of tetradentate nitrogen ligands with a 2,2'-bipyridine nucleus.

4.6 *D_2- and C_4-symmetrical bi- and hexadentate nitrogen ligands based upon tartaric acid*

In the previous sections we have described the synthesis of high symmetrical nitrogen ligands. Most of these ligands were based upon 3,4-diphenylpyrrolidine. Only two ligands were based upon 3,4-dibenzoyloxypyrrolidines, that is compounds **425** and **427**, which were prepared via alkylation. The reason that we did not use more 3,4-diaroyloxopyrrolidines is that the methodology we used most, acylation followed by reduction is not suitable for these amines because they possess an ester moiety, which is of course cleaved during the reduction step. In this section we will describe a methodology which will allow the synthesis of high symmetrical nitrogen ligands based upon chiral 3,4-disubstituted pyrrolidines derived from tartaric acid. We decided to use (2*R*,3*R*)-2,3-bis((benzyl)oxy)butanedioic acid diethylester (**428**) as starting material. The diester is readily available from diethyl tartrate following literature procedure.[34] The diester **428** was converted to the corresponding cyclic anhydride **429** via saponification and cyclisati-

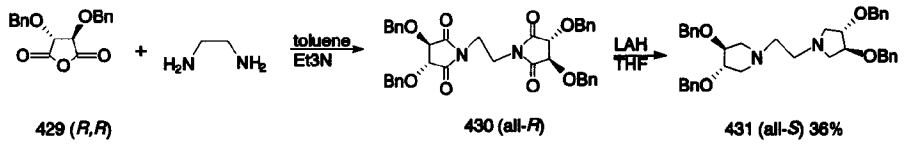
[34] Nemoto, H.; Takamatsu, S.; Yamamato, Y. *J. Org. Chem.* **1991**, *56*, 1321.

on with acetyl chloride, see scheme 4.13. The anhydride is a crystalline compound which hydrolysis very rapidly to the corresponding acid. The overall yield starting from diethyl tartrate is 40%.



Scheme 4.13. Synthesis of (R,R)-2,3-bis-(benzyloxy)succinic anhydride 429

Anhydride **429** was converted with primary amines to the corresponding imides, which after reduction provides the desired pyrrolidines. This approach was also used in section 4.2 for the synthesis of chiral TMEDA derivatives. Thus condensation of anhydride **429** with ethylene diamine afforded the diimide **430** in moderate yield after flash chromatography. The diimide **430** was converted to all (*S*)-1,2-bis-(3,4-dibenzyloxy)pyrrolidine)ethane (**431**) after reduction with $LiAlH_4$ in THF, see scheme 4.14. Purification by chromatography provided the D_2-symmetrical diamine in 36% overall yield.

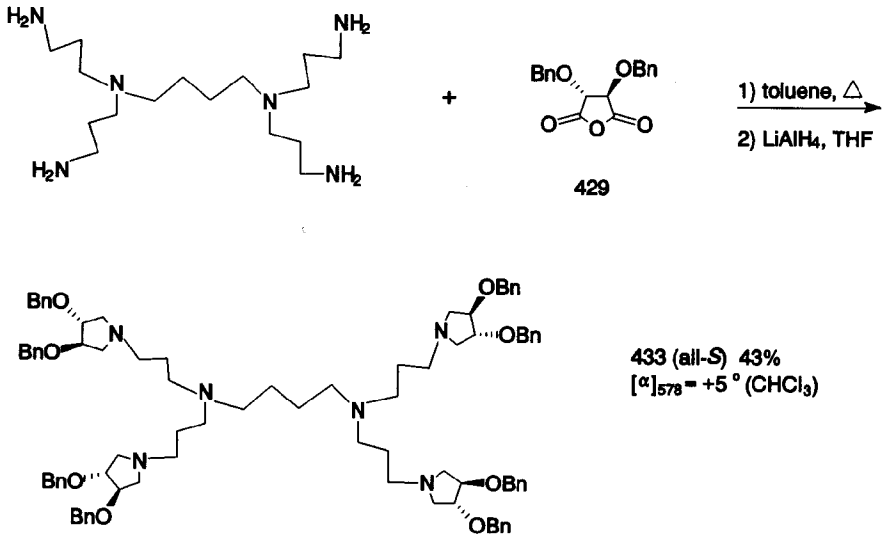


Scheme 4.14. Synthesis of D_2-symmetrical diamine 431

We extended this very straightforward synthesis of highly symmetrical nitrogen ligands derived from tartaric acid to the synthesis of the C_4-symmetrical hexadentate nitrogen ligand **433**. The synthesis is outlined in scheme 4.15. Condensation of hexamine 432 $(DAB(PA)_4)$[35a,b](which means a dendrimer with DiAminoButane as core with four PropylAmino groups attached to the nitrogens) with four equivalents **429** in toluene afforded the corresponding imide. Subsequent reduction with $LiAlH_4$ in THF provided the C_4-symmetrical hexamine **433** in 50% yield after purification (chromatography (silica, CH_2Cl_2, MeOH, NH_4OH)) as a viscous oil. The high symmetry of **433** was established by both ^1H- and ^{13}C-NMR. The ^{13}C-NMR consists of only twelve signals. Hexamine **433** is one of the few examples of a chiral dendrimer which is obtained by attaching chiral end

[35] a) Poly amines of this type are dendrimers which recently have attracted much attention, see: Mekelburger, H.B.; Jaworeke, W.; Vögtle, F. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 571. b) For the preparation of $DAB(PA)_4$ and higher dendrimers see: De Brabander van den Berg, E.M.M.; Meyer, E.W. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1308.

groups to a dendrimer.[36] We also looked at the reaction of $DAB(PA)_{16}$, a dendrimer with sixteen primary amine end groups with anhydride **429**. Although the corresponding chiral dendrimer could be prepared, purification via chromatography proved to be impossible.



Scheme 4.15. C_4-symmetrical hexaamine

4.7 *Metal complexes of multidentate nitrogen ligands possessing C_2-symmetrical pyrrolidines*

In this chapter we have described the synthesis of chiral a series multi-dentate nitrogen ligands based upon C_2-symmetrical pyrrolidines. We now want to apply these compounds as ligands in enantioselective synthesis. For a successful application of these ligands they should have a high affinity especially for (transition) metal ions (and create a well-defined cavity). In this section we will show that the ligands described in this chapter show a high affinity towards (transition) metal ions and form stable chelate complexes.[37]

---

[36] For a discussion on chiral dendrimers see: a) Seebach, D.; Lapierre, J.M.; Skobridis, K; Greivelolinger, G. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 440. b) Kremers, J.A.; Meyer, E.W. *J. Org. Chem.* **1994**, *59*, 4262. For other chiral dendrimers with chiral end groups see; a) Jansen, J.F.G.A.; den Brabander-van den Berg; Meyer, E.W. *Science*, **1994**, *266*, 1226. b) Newkome, G.R.; Lin, X.; Weis, C.D. *Tetrahedron Asymmetry* **1991**, *2*, 957.

[37] For a review on coordination chemistry and factors determining ligand-metal binding see: Busch, D.H. *Chem. Rev.* **1993**, *93*, 847.

From the work of Tomioka[19], it is known that diamine **401** forms complexes with both Mg^{2+} and Os^{8+}. The X-ray structure of a ternary complex consisting of diamine **401**, OsO_4 and trans-stilbene (the alkene to be hydroxylated) has been determined.[38] The structure clearly shows that the four phenyl substituents of diamine **401** create a well-defined asymmetric environment within the metal-substrate-ligand complex.[39]

We examined briefly the reactivity of our ligands towards (transition)-metal ions in a series of experiments with $CoCl_2$, $ZnCl_2$, $Zn(OAc)_2$, $Cu(OAc)_2$, $Ni(COD)_2$, and $RhCl_3$ in organic solvents such as methanol, ethanol, acetonitrile, and tetrahydrofuran. The complexes examined in these experiments are; **401**.$ZnCl_2$, **401**.$CoCl_2.6H_2O$, **406**.$Zn(OAc)_2$, **406**.$CoCl_2$, **411**.$ZnCl_2$, **412**.$Zn(OAc)_2$, **413**.$RhCl_3.xH_2O$, **415**.$ZnCl_2$, **419**.$Cu(OAc)_2$, **420**.$Ni(COD)_2$ and **426**.$ZnCl_2$. In all cases NMR analysis or a characteristic color change indicated spontaneous complex formation. Most of the complexes were isolated by simple crystallization[40] and proved to be stable even to air and moisture. The ligands form 1:1 complexes with most of the (transition) metals used. This was easily demonstrated by ^{1}H-NMR studies. We performed these experiments by adding solutions of $ZnCl_2$ (0,25 eq.) in acetonitrile (d3) to a solution of one equivalent of the appropriate ligand in acetonitrile (d3). Upon addition of substochiometric amounts of $ZnCl_2$, extensive broadening of the ^{1}H-NMR signals, as well as large chemical shift indicated interaction of the Zn atom with the nitrogens of the pyrrolidine ring. After the addition of one equivalent of $ZnCl_2$, immediate sharpening of the signals was observed. Line shape and chemical shifts did not change upon the addition of more $ZnCl_2$. These results indicate the formation of 1:1 complexes in solution.

^{1}H-NMR studies further indicate that the complexes formed still are highly symmetrical. Two examples will clarify this. In figure 4.8 both the ^{1}H-NMR of the bidentate nitrogen ligand **411** (all-*S*) (top) and its $ZnCl_2$ complex (bottom) are shown. The ^{1}H-NMR of **411** (all-*S*) shows that the molecule is high symmetrical. The spectrum shows only five resonances, at δ 1 ppm (CH_3,s 6H), 2.55 ppm (CH_2, AB 4H), 3.1 ppm (CH, m 4H), 3.2-3.4 (CH, m 8H), 7.2 (ArH, m 20H). This clearly indicates that the C_2-symmetrical pyrrolidine ring is free to rotate (three resonances are observed for twelve protons). The $ZnCl_2$ complex of **411** (all-*S*) consists of a six membered ring fused with two five membered rings. From the ^{1}H-NMR it becomes clear that most of the resonances are shifted downfield, δ 1.1 (CH_3, s 6H), 2.8 (CH, dd 2H), 3.1 (CH_2, s 4H), 3.5 (CH, m 4H), 4.2 (CH, m 4H), 4.4 (CH, dd 2H) and, 7.1-7.4 ppm (ArH, m 20H). From this spectrum it also becomes clear that the system is C_2-symmetric. The ^{1}H-NMR indicates that the five membered rings are locked; six resonances are observed for the pyrrolidine protons. The six membered ring however is not locked, and the two methyl groups as well as the two CH_2 resonances appear as singlets. Temperaturedependent measurements (-50°C to 50°C) did not provide evidence for conformational changes.

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[38] Tomioka, K.; Nakajima, M.; Itaka, Y.; Koga, R. *Tetrahedron Lett.* **1988**, *29*, 573.

[39] Jorgensen, K.A. *Tetrahedron: Asymmetry* **1991**, *2*, 515.

[40] The complex ***413***.$RhCl_3$ was purified by columnchromatography.

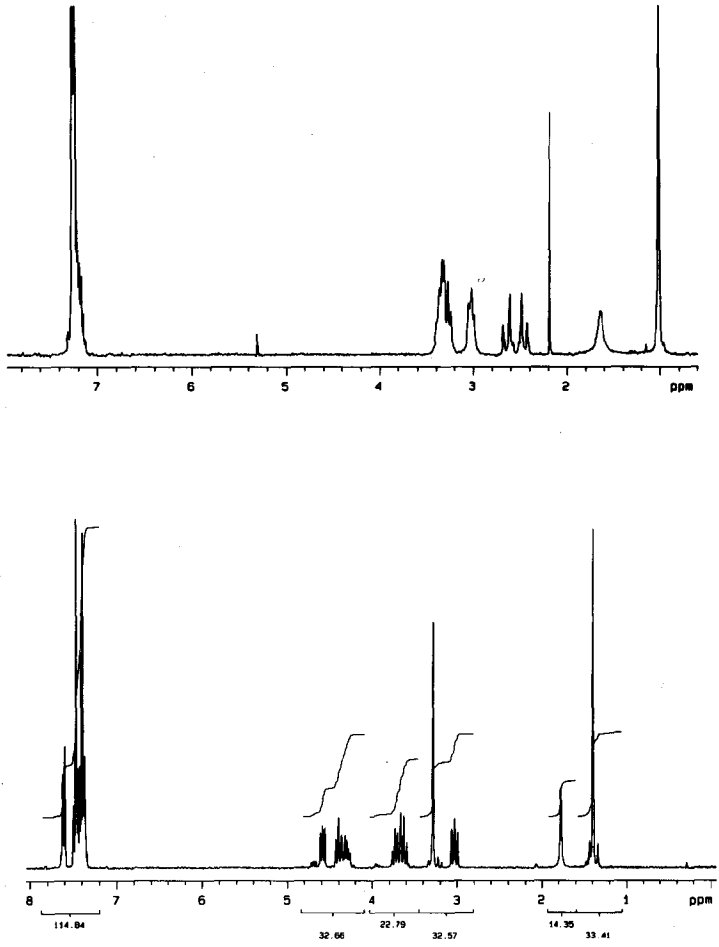


Figure 4.8 ^{1}H-NMR spectra of **411** (top) and **411**.$ZnCl_2$ (bottom) in $CDCl_3$.

That the six membered ring does appear in two conformations (chair, boat) was proven by X-ray analysis of the $ZnCl_2$ complex of **411**. Suitable crystals of **411**.$ZnCl_2$ were grown by slow evaporation of a THF/EtOH mixture. The molecular structure of **411**·$ZnCl_2$ is shown in figure 4.9.[41] The -C-$(CH_3)_2$ group is disordered and has two configurations C_{20}-C_{19}-C_{21} and C_{20}-C_{190}-C_{210}, respectively, with C_{20} in common. The atoms C_{19}-C_{190} and C_{21}-C_{210} have an occupancy of 0.5. This means that in the solid state two conformations are present. The zinc atom is tetrahedrally surrounded by two chlorine atoms and the two nitrogen atoms from the pyrrolidine rings. The distances between the metal and the nitrogen atoms are 2.110(9) and 2.078(9) angstrom, respectively. The selected interatomic distances and angles are listed in the experimental section.

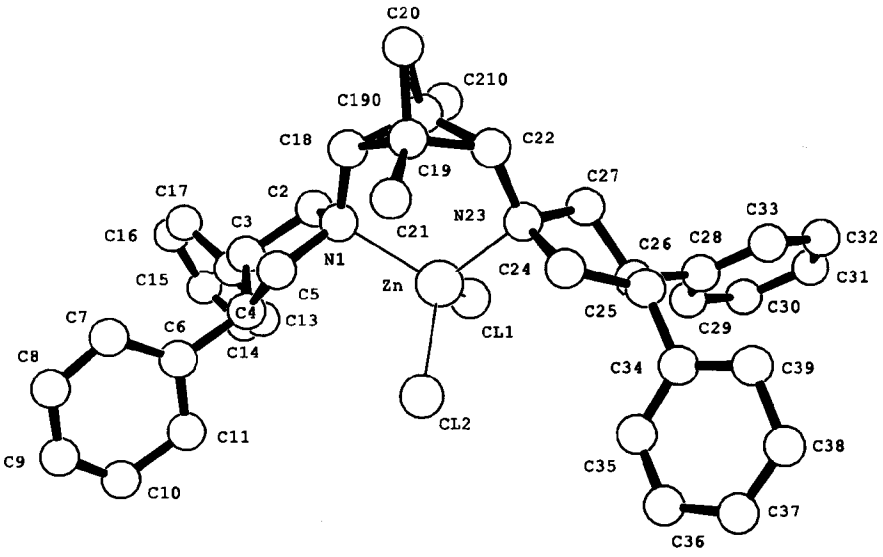


Figure 4.9 Crystal structure of **411**.$ZnCl_2$

A second example which proves the high symmetry of the ligand-metal complexes is shown in figure 4.10, which shows both the ^{1}H-NMR spectra of tridentate nitrogen ligand **413** (all S) and the $RhCl_3$ complex. The ^{1}H-NMR of **413** (top) is very simple. The pyrrolidine ring shows three resonances (at δ 3.0, 3.3 and 3.5 ppm) proving the high

[41] Crystals of the complex were monoclinic and from systematic absences the space group was determined to be P_2. Z=2 with unit cell parameters a=11.424(1)Å, b=12.504(2)Å, c=11.722(2)Å, ß=92.48(2)°, V=1672.9(4)Å, R=0.083 and R=0.090 (w=1). The structure was solved by direct methods. Hydrogen atoms were not included and could be revealed from succeeding Fourier difference synthesis.

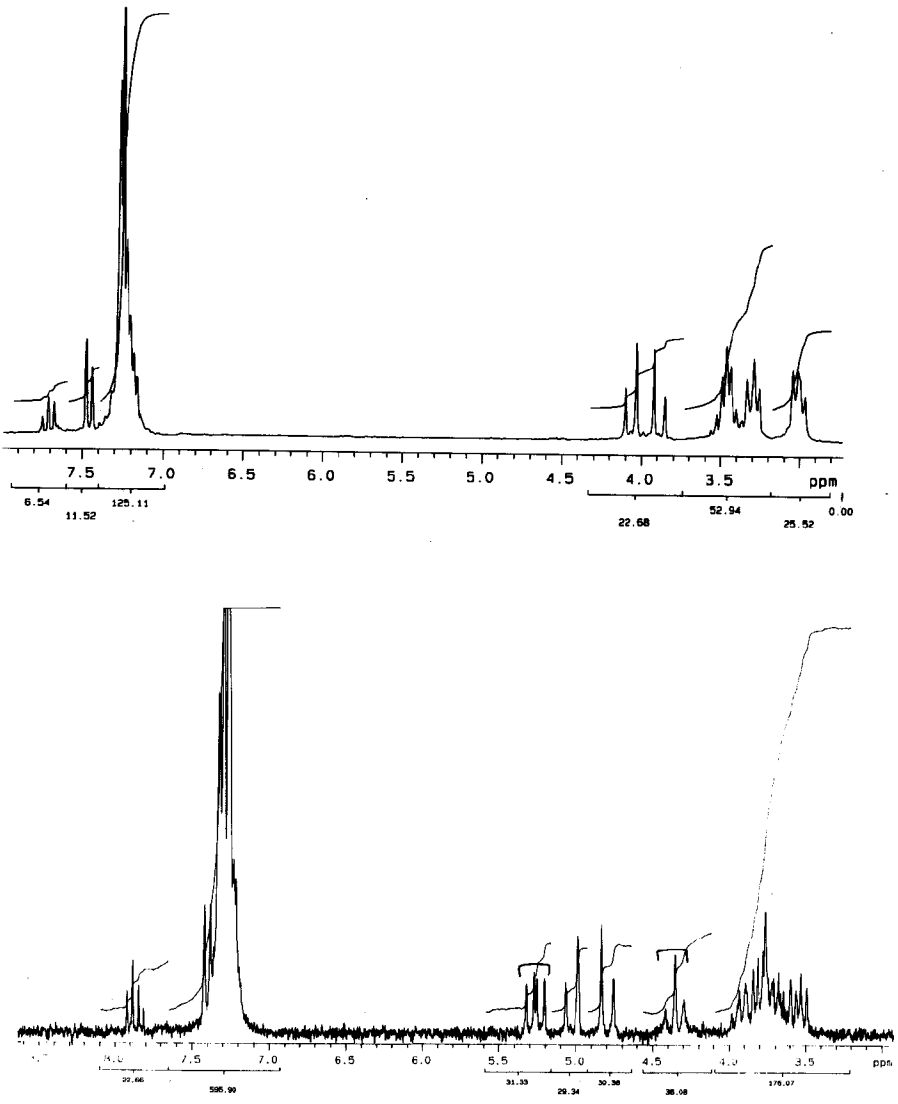


Figure 4.10 ^{1}H-NMR of **413** (top) and **413**.$RhCl_3$ (bottom) in $CDCl_3$

symmetry of the ligand. The benzylic protons (at δ 4 ppm) show an AB system and the aromatic region consists of a singlet for the aromatic hydrogens and a triplet (at δ 7.7 ppm) plus doublet (at δ 7.5 ppm) for the pyridine hydrogens. The rhodium complex again (bottom) shows C_2-symmetry. The pyrrolidine rings, as in the case of **411**·$ZnCl_2$ are locked, which results in six resonances for the six protons of the pyrrolidine ring. All resonances appear downfield relative to the free ligand. The benzylic protons are also shifted downfield (AB at δ 4.9 ppm). The resonances of the pyridine ring are also shifted (triplet at δ 7.9 ppm and doublet at 7.4 ppm), which proves that the pyridine nitrogen is also coordinated to the rhodium metal centre. As in the case of the pybox ligands, see figure 4.2[14], the rhodium coordination is probably octahedral.

In this section we have demonstrated that the ligands described in this chapter show high affinity towards transition metals and well-defined complexes are obtained. A general formulation of complexes of the ligand-metal complexes is depicted in figure 4.7.

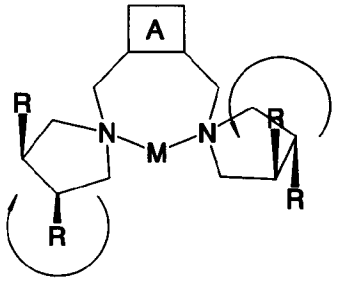


Figure 4.7

We have shown that the backbone **A** is easily modified, allowing variation in ring size and the possibility of extra binding sites. The substituent **R** creates a well-defined highly symmetrical cavity which will reduce the number of possible arrangements of the chiral catalyst with a coordinated substrate. Furthermore, both enantiomers of the 3,4-disubstitutedpyrrolidines are available on multi-gram scale (chapter 3). This will allow the synthesis of both enantiomers of the desired ligand.

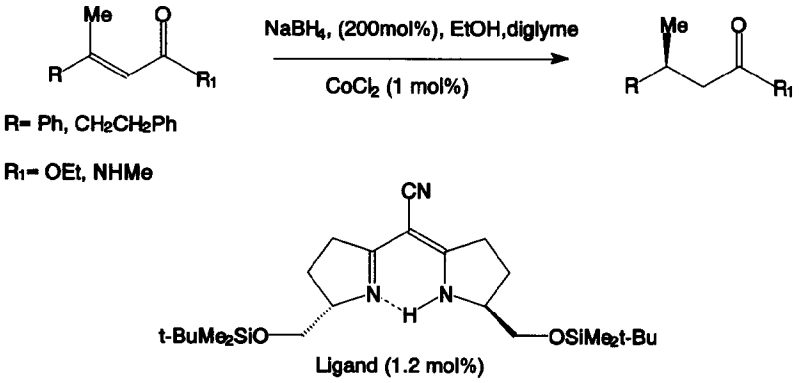
4.8 Enantioselective reduction of α,β-unsaturated carboxylic amides, with chiral cobalt-nitrogen ligands

In the previous sections we have described the synthesis of a variety of high symmetrical nitrogen ligands and have demonstrated the affinity of these ligands towards (transition) metal ions. We believe that the ligands described in this chapter might find use as catalysts in enantioselective reactions involving chiral ligand-metal complexes.

As a first example of such a metal catalysed process, we have investigated the enantioselective reduction of α,β-unsaturated carboxylic amides with chiral cobalt nitrogen ligands. The reasons we have chosen this reaction are threefold. First, the reaction is very

well documented[42], which makes it easy to synthesize the substrates used and analyze the products formed in the reaction. Secondly, we think that the ligands we have described in this chapter show great resemblance to the semicorrin ligands used by Pfaltz[42] for the same reaction. Thirdly, the non-catalyzed reaction is slow (<5% conversion after 48 hours).

Fischli[43] had already shown that α,ß-unsaturated carbonyl compounds can be reduced selectively at the double bond with zinc/acetic acid and cobalamine as catalyst with optical yields between 0 and 33%. Pfaltz[42] extended this work and found that the semicorrin cobalt catalysts are efficient and highly enantioselective in the conjugate reduction of α,ß-unsaturated carboxylic esters as well as amides with $NaBH_4$. Enantiomeric excesses up to 99%, essentially quantitative yields and high substrate/catalyst ratios were found (Scheme 4.16). A tentative model, to rationalize the stereoselectivity of the semicorrin/cobalt catalyst was proposed by Pfaltz.[44] Under the reaction conditions the precatalyst is reduced to a Co(I) complex. This complex then initiates the catalytic cycle by attacking the C=C bond, forming a π-complex. From labeling experiments using $NaBD_4$, Pfaltz found that the hydrogen atom introduced in the ß-position stems from borohydride, whereas the α-hydrogen comes from EtOH. These findings were interpreted to mean that $NaBH_4$ transfers a proton to the cobalt center, followed by an intermolecular proton shift from cobalt to the ß-carbon. The resulting cobalt enolate is then protonated by EtOH. The enantioselective step is therefore determined by the intramolecular proton shift.

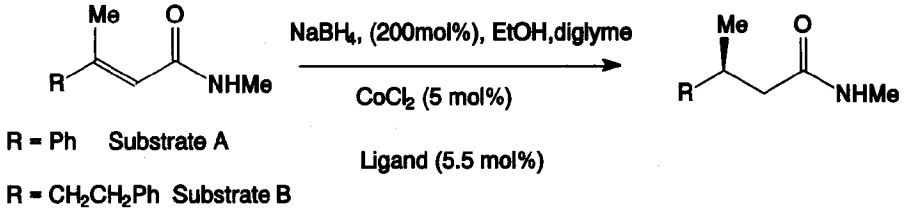


Scheme 4.16 reduction of α,ß-unsaturated esters and amides

[42] a) von Matt, P.; Pfaltz, A. *Tetrahedron Asymmetry* **1991**, *2*, 691; b) Leutenegger,U.; Madin, A.; Pfaltz, A. Angew. Chem. Int. Ed. **1989**, *28*, 60.

[43] a) Fischli, A.; Suss, D. *Helv. Chim. Acta* **1979**, **62**, 48; b) ibid, 2361; c) Fischli,A.; Daly, J. *Helv. Chim. Acta* **1980**, *63*, 1628.

[44] Pfaltz, A. *Chimia* **1990**, *44*, 202.



Scheme 4.17 Reduction of α,β-unsaturated amides

Table 4.2 Enantioselective reduction of α,ß-unsaturated amides

Entry	Ligand	Substrate	Conv.(48h)	o.p.	Conf.
1	**401** (*S,S*)	**A**	50	83	*S*
2	**411** (*S,S*)	**A**	40	25	*S*
3	**413** (*S,S*)	**A**	35	55	*S*
4	**415** (*S,S*)	**A**	40	30	*S*
5	**406** (*S,S*)	**A**	45	20	*S*
6	**414** (*R,R*)	**A**	35	50	*R*
7	**431** (*S,S*)	**A**	<5	-	-
8	**426** (*R,R*)	**A**	<5	-	-
9	**401** (*R,R*)	**B**	60	60	*S*
10	**401** (*S,S*)	**B**	55	58	*R*
11	**411** (*S,S*)	**B**	50	55	*R*
12	**413** (*S,S*)	**B**	40	50	*R*

The conversion was determined by GC. The optical purity (o.p.) was determined after purification of the products by column chromatography. In the case of substrate **A**, the ee was also determined by ^{1}H-NMR after derivatization with (*S*)-4-phenyl-2-oxazolidinone. The ee was consistent with the o.p..In the case of substrate **B**, the ee was also determined by chiral HPLC ((R,R Whelk-O). The results were comparable with those obtained by optical rotation measurements. The configuration was based upon the optical rotation.

We decided to use two substrates [(*E*)-3-phenyl-*N*-methyl-but-2-enamide **A** and (*E*)-*N*-3,4-dimethyl-5-phenylpent-2-enamide **B**] and the same reaction conditions used by

Pfaltz. The synthesis of the substrates was accomplished by the method described by Pfaltz[44a]. Since the *E* and *Z* isomers are converted to products of opposite configuration it is very important to use olefins of high isomeric purity. The substrates we used were more then 99.5% pure as determined GC. With these substrates we performed a series of reactions following the method depicted in scheme 4.17. The results are summarized in table 4.2

The chiral catalyst was prepared *in situ* by adding the ligand to a solution of $CoCl_2.6H_2O$ and substrate in EtOH. After dilution with diglyme, the clear blue solution was degassed three times. Sodium borohydride was then added which resulted in an instantaneous color change to brown. The resulting solution was again degassed and stirred at RT for 48 hours. From table 4.2 it can be seen that the ligand-cobalt catalyst is active in the reduction of α,ß-unsaturated amides **A** and **B**. The low conversion is probably caused by the fact that we did not perform these experiments with complete exclusion of oxygen. Substrate **B** gave better conversions then **A**, probably because of steric reasons. The optical purities observed were, however, better for substrate **A** then **B**, and varied between 83% (in the case of ligand **401**) and 25% (in the case of ligand **411**). Ligands **431** and **426** did not catalyze the reaction; no coordination with $CoCl_2$ was observed. The differences between bi- and tridentate (**413**, **414** and **415**) were not significant suggesting that only two of the nitrogens are involved in complexation.

As mentioned above the best result was obtained with ligand **401** and substrate **A**. The five membered chelate ring (after complexation with $CoCl_2$) creates the best defined chiral environment in which the phenyl groups on the pyrrolidine ring system reduce the number of possible transition states. In the other cases the chelate rings formed are too flexible, allowing more competing transition states. We have shown that the ligands described in this chapter can be used in the enantioselective reduction of α,ß-unsaturated carboxylic amides. The conversions were moderate and the enantioselectivities varied from moderate to good.

4.9 Conclusions

We have described the synthesis of a variety of high symmetrical polydentate nitrogen ligands based upon 3,4-diarylpyrrolidines. The size, shape, geometry and rigidity of the ligand can be adjusted to the specific acquirements of a particular application and provides a manner to optimize the selectivity of a metal catalyst in a systematic manner. The ligands show high affinity towards transition metals and show great similarity with the well described C_2-symmetrical bis(oxazoline) ligands.[45]

The ligands described in this chapter might find use in metal-catalyzed enantioselective reactions. A first example of such a reaction was discussed in section 4.8. More examples are needed to explore the applicability of these ligands in other reactions.

[45] For a review see: Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.

4.10 Experimental section

For general remarks see chapter 2.

(*R,R*)- and (*S,S*)-*N*[2-*N,N*-Dimethylaminoethyl]-3,4-diphenylpyrrolidine (406)
To a solution of anhydride **402** (25,2 g, 0,1 mol) (see chapter 3) in o-xylene (300 ml) was added *N,N*-dimethylethylenediamine (8.8 g, 0.1 mol). The resulting slurry was refluxed for 30 minutes with removal of the water formed. The clear solution was evaporated to afford succinimide **404** was a yellow oil. This oil was used without further purification in the next step. The oil was dissolved in THF (200 ml) and added dropwise to a suspension of $LiAlH_4$ (9.5 g, 0.25 mol) in THF (100 ml). The mixture was refluxed for 2 hours and hydrolysed with 10% KOH. The salts were filtered over Celite and washed. The combined filtrated were concentrated to dryness, to afford diamine **406** as a yellow oil. Yield 27 g (90%, pure by NMR)

Resolution of 406 with tartaric acid
To an solution of racemic amine **406** (18.71 g, 636 mmol) in EtOH (800 ml) was added L-(+)-tartaric acid (9.54 g,636 mmol). The mixture was refluxed and allowed to cool to RT in 2 hours. The solid was collected and recrystallized from EtOH to afford a salt (11.7 g, 40%) with $[\alpha]_{578}$= +95°(MeOH). Treatment of this salt with 10% NH_4OH/ether afforded (*S,S*)-**406** as a colourless oil. Yield 6,54 g (35%); $[\alpha]_{578}$= +121°($CHCl_3$); ^{1}H-NMR:δ 2.3 (s,6H), 2.5-2.9 (m,4H), 2.95 (m,2H), 3.2 (m,2H), 3.4 (m,2H), 7.2 (m,10H) ;^{13}C-NMR:δ 45.91 (CH_3), 52.76 (CH), 54.89 (CH_2), 58.41 (CH_2), 62.94 (CH_2), 126.18 (CH), 127.36 (CH), 128.28 (CH), 143.44 (C) HRMS calc. for $C_{20}H_{26}N_2$:294.210 Found:294.210; Anal. Calcd for $C_{20}H_{28}N_2Cl_2$: C 65.54 H 7.71 N 7.65 Found: C 64.23 H 7.64 N 7.48.
The combined mother liquors were evaporated and treated with 10% NH_4OH/ether. The enriched (*R,R*) amine **406** was treated with D-(-)tartaric acid (5.1 g) in EtOH. After one crystallisation from EtOH a salt was obtained with $[\alpha]_{578}$= -90°(MeOH). Treatment of this salt with 10 NH_4OH/ether afforded (*R,R*) **406** as a colourless oil. Yield 5,9 g, (32%); $[\alpha]_{578}$= -119°($CHCl_3$); Spectroscop data identical to (*S,S*) **406**.
Ee determination of **406**: (+)-di-*p*-toluoytartaric acid (1eq.) and (*S,S*) **406** (1eq.) were dissolved in $CDCl_3$ and a ^{1}H-NMR was taken (δ 2.48, s, CH_3); (racemic material δ 2.48-2.53, 2s, CH_3)

(*R,R*)- and (*S,S*)-*N*-[2-*N,N*-Dimethylaminoethyl]-3,4-bis(1-naphtyl)pyrrolidine (407) was prepared in the same way as described for amine **406**. Thus starting with anhydride **403** (12,5 g, 35,5 mmol) (see chapter 3) and *N-N*-dimethylethylenediamine (3.13 g, 35,5 mmol) imide **405** was obtained as a yellow solid which was used as such in the next step. This material was reduced with $LiAlH_4$ in THF in the same way as described for **406**, to afford racemic **407** as a yellow oil. Overall yield 9.0 g (70%).

Resolution of 407 with di-*p*-toluoyltartartic acid

To a solution of racemic amine **407** (4.8 g, 12 mmol) in 2-butanone (180 ml) was added (2*S*,3*S*)-(+)-di-*p*-toluyltartaric acid (4.0 g, 12 mmol) at reflux temperature. The mixture was refluxed and cooled to 35°C and the solid was collected and again refluxed in 2-butanone (100 ml). A salt was obtained (3.3 g, 35%) with $[\alpha]_{578}$= +5,5°(MeOH). The salt was treated with 10% NH_4OH/ether and (*R,R*) **407** was obtained as a yellow oil. Yield 1.1 g (23%); $[\alpha]_{578}$= -60°($CHCl_3$); ^{1}H-NMR: δ 2.5 (s,6H), 2.8 (m,2H), 3.0 (m,2H), 3.1 (m,2H), 3.6 (dd,2H), 4.65 (m,2H), 7.4 (m,6H), 7.5 (d,2H), 7.8 (d,2H), 8.1 (d,2H); ^{13}C-NMR: δ 44.51 (CH_3), 45.34 (CH), 52.71 (CH_2), 56.26 (CH_2), 71.79(CH_2), 123.30 (CH), 123.48 (CH), 125.39 (CH), 125.54 (CH), 125.91 (CH), 125.16 (CH), 128.70 (CH), 131.99 (C), 133.77 (C), 137.56 (C); HRMS calc. for $C_{28}H_{30}N_2$: 394.241 Found: 394.241

The combined mother liquors were evaporated and treated with 10% NH_4OH/ether to afford the enriched (*S,S*) enantiomer. This amine was treated with (2*R*,3*R*)-(-)-di-*p*-toluyltartaric acid to afford a salt, which afforded after treatment with 10% NH_4OH/ether (*S,S*) **407** as a yellow oil. Yield 1.1 g (23%); $[\alpha]_{578}$= +61,2°($CHCl_3$). Spectroscopic data identical to those of (*R,R*) **407**.

(All-*R*)- and (all-*S*)-*N,N*-ethylene-bis-(3,4-diphenylpyrrolidine) (401)

a) d,l-*N,N*-Ethylene-bis-(3,4-diphenylsuccinimide) 408

To a solution of anhydride **402** (20.0 g, 79 mmol) (see chapter 3) in THF (150 ml) was added ethylenediamine (2.38 g, 38 mmol). The mixture was stirred for 30 minutes at RT and evaporated, the resulting solid was treated with Ac_2O (150 ml) for 2 hours at reflux temperature. The clear solution was concentrated and iso-propanol (300 ml) was added. The mixture was refluxed and filtered while hot. The residue proved to be meso **408**. Yield 8 g (40 %). ^{1}H-NMR(DMSO-d6): δ 3.8 (s,4H), 4.25(s,4H), 7.3 (m,20H)

The filtrate was cooled and the crystals collected to afford d,l **408** as a white solid. Yield 8 g (40 %); mp 229-230^0 C; ^{1}H-NMR: δ 3.8 (s,2H), 4.15 (s,4H), 7.3 (m,20H); ^{13}C-NMR: δ 38.1 (CH_2), 56.0 (CH), 127.9 (CH), 128.1 (CH), 129.2 (CH), 135.6 (C), 176.8 (C=O) ; Anal. calc. for $C_{34}H_{28}N_2O_4$: C 77.24 H 5.34 N 5.30 Found: C 77.07 H 5.31 N 5.29.

b) d,l-401 was prepared from d,l-**408** via reduction with $LiAlH_4$ as described for racemic **406**. The crude diamine **401** was used in the resolution step without further purification. Yield 83%.

c) Resolution of 401 with dibenzoyltartaric acid

To a solution of racemic **401** (5 g, 10.5 mmol) in 2-butanone (200 ml) was added (2*R*,3*R*)-(-)-dibenzoyltartaric acid (3.8 g, 10.5 mmol) and the mixture was heated to reflux and allowed to cool to RT overnight. The solid was collected and recrystallized from 2-butanone/EtOH (10:1), to afford a salt with $[\alpha]_{578}$= -123°(DMF).This salt was treated with NH_4OH\ether and (all-*R*)-**401** was obtained as a colourless oil, which solified on standing. Yield 1.28g (26%); mp 84-85^{0}C (lit.[19c] 85-87^{0}C); $[\alpha]_{578}$= -144°($CHCl_3$); $[\alpha]_D$= -140°($CHCl_3$) (lit.[19c] $[\alpha]_D$= -143°($CHCl_3$)); ^{1}H-NMR: δ 2.7-3.0 (m,4H), 3.0 (m,4H), 3.3 (m,4H), 3.4 (m,4H), 7.3 (m,20H) ; ^{13}C-NMR: δ 53.07 (CH), 55.52 (CH_2),

63.11 (CH_2), 126.28 (CH), 127.45 (CH), 128.38 (CH), 143.82 (C); HRMS calculated for $C_{34}H_{36}N_2$: 472.288 Found: 472.288
The combined mother liquors were evaporated and treated with 10% NH_4OH/CH_2Cl_2. The enriched (*S*) enantiomer was purified with (2*S*,3*S*)-(+)-dibenzoyltartaric acid analogue to the procedure described above. Salt $[\alpha]_{578}$= +112°(DMF); (All-*S*)-**401**, Yield 22%; $[\alpha]_{578}$=+142°($CHCl_3$). Spectroscopic data identical with those of (all-*R*)-**401**.

(All-*S*)-3,3'-Bis-(3,4-diphenylpyrrolidine)-2,2'dimethylpropane (411)
a) Diamide 410
To a solution of (*S,S*)-3,4-diphenylpyrrolidine (1.12 g, 5.02 mmol) and Et_3N (1 ml) in CH_2Cl_2 (50 ml) was added dimethylmalonyldichloride* **409** (420 mg, 2.5 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred at RT for 2 hours and H_2O (50 ml) was added. The organic layer was washed with 10% HCl, 10% $NaHCO_3$ and dried (Na_2SO_4). Concentration afforded an oil which was crystallised from EtOH to afford **410** as a white solid. Yield 1.1 g (81%); mp 116-118°; $[\alpha]_{578}$= +107° ($CHCl_3$); ^{1}H-NMR: δ 1.5 (s,6H), 3.5 (m,6H), 3.75 (m,2H), 4.15 (m,4H), 7.2 (m,20H) ; ^{13}C-NMR: δ 23.38 (CH_3), 48.67 (CH), 48.8 (C), 52.27 (CH), 53.48 (CH_2), 54.24 (CH_2), 127.17 (CH), 127.29 (CH), 127.32 (CH), 127.4 (CH), 128.71 (CH), 128.77 (CH), 138 (C), 139.5 (C), 170,2 (C=O) ; Anal. Calcd for $C_{37}H_{38}N_2O_2.H_2O$: C 79.25 H 7.19 N 5.00 Found: C 78.88 H 7.17 N 4.93.
b) (All-*S*)-411
Reduction of diamide **410** (1.0 g, 1.84 mmol) was accomplished with $LiAlH_4$ as described for **401**. (All *S*)-**411** was obtained as a colourless oil. Yield 960 mg (90%); $[\alpha]_{578}$= +109° ($CHCl_3$); ^{1}H-NMR: δ 1.0 (s,6H), 2.45 (dd,4H), 3.0 (m,4H), 3.35 (m,6H), 7.2 (m,20H); ^{13}C-NMR: δ 25.8 (CH_3), 53.0 (CH), 62.26 (CH_2), 66.46 (CH_2), 126.59 (CH), 127.51 (CH), 128.51 (CH), 128.66 (C); HRMS calc. for $C_{37}H_{42}N_2$: 514.335 Found: 514.355.

* Dimethylmalonyldichloride was prepared from diethyl malonate in three steps according to ref.[24]. Yield 60%.

The (all-*R*) enantiomer was prepared in the same way, thus starting with (*R,R*)-diphenylpyrrolidine, **411** (all-*R*) was obtained in 70% overall yield. Spectroscopic data identical with those of **411** (all-*S*).

(All-*R*)-1,2-Bis-((-3,4-diphenylpyrrolidine)methyl)benzene (412) was prepared from phthaloyl chloride (5.3 g, 26 mmol) and (*RR*)-3,4-diphenylpyrrolidine (11.7 g, 52 mmol) (see chapter 3) following the same procedure as described for **411**. Yield 9.0 g (63 %); (All-*R*) diamide **412a**, white solid after crystallisation from EtOH. mp 112-115°C; $[\alpha]_{578}$= -26° ($CHCl_3$); ^{1}H-NMR: δ 3.6 (m,6H), 3.9 (m,4H), 4.3 (m,2H), 7.2 (m,20H), 7.4 (m,4H); ^{13}C-NMR: δ 49.89 (CH), 51.41 (CH), 52.86 (CH_2), 56.40 (CH_2), 126.55 (CH), 125.03 (CH), 127.58 (CH), 128.53 (CH), 129.1 (CH), 135.9 (C), 138.84 (C), 138.9 (C), 169 (C=O); HRMS calc. for $C_{40}H_{36}N_2O_2$: 576.278 Found: 576.278
(All-*R*) diamine **412**, colourless oil. $[\alpha]_{578}$= -74,2° ($CHCl_3$); ^{1}H-NMR: δ 2.9 (m,4H), 3.2 (m,4H), 3.4 (m,4H), 4.0 (dd,4H), 7.25 (m,22H), 7.5 (m,2H); ^{13}C-NMR: δ 53.51 (CH), 58.1 (CH_2), 62.96 (CH_2), 126.21 (CH), 126.87 (CH), 127.45 (CH), 128.4 (CH), 129.58

(CH), 137.95 (C), 144.61 (C) ; HRMS cal. for $C_{40}H_{40}N_2$: 548.319 Found: 548.319 Found: 548.319

(All-*R*)-*N*-2,6-Bis-(3,4-diphenylpyrrolidine)-methylpyridine (413) was prepared in the same way as described **411**. Thus starting with 2,6-dicarbonylchloro pyridine (2.6g, 11,2 mmol) and (*R,R*)-3,4-diphenylpyrrolidine (5g, 22,4mmol), the diamide **413a** was obtained as a white solid after crystallisation from 2-propanol. (All-*R*)-**413a**. mp 222-222.5^{0}C; $[\alpha]_{578}$= -343^0 ($CHCl_3$); ^{1}H-NMR: δ 3.45 (m,4H), 3.95 (m,4H), 4.25 (m,4H) 7.2 (m,20H), 8.0 (m,3H); ^{13}C-NMR: δ 49.09 (CH), 52.04 (CH), 54.05 (CH_2), 56.49 (CH_2), 125.67 (CH), 127.10 (CH), 127.25 (CH), 127.46 (CH), 128.62 (CH), 128.68 (CH), 139.95 (CH), 138. 58 (CH), 138.6 (C), 152.0 (C), 164 (C=O); Anal. Calcd for $C_{39}H_{35}N_3O_2$: C 81.07 H 6.11 N 7.28 Found: C 81.05 H 6.06 N 7.21.
Reduction of the diamide **413a** with $LiAlH_4$ in THF afforded after purification (column chromatography, silica/ether) the triamine **413** as an colourless oil. Yield 2,9 g (50%); $[\alpha]_{578}$= -191.5^{0}C ($CHCl_3$); ^{1}H-NMR: δ 3.0 (m,4H), 3.3 (m,4H), 3.5 (m,4H), 4.0 (dd,4H), 7.3 (m,20H), 7.5 (d,2H), 7.7 (t,1H); ^{13}C-NMR: δ 53.16 (CH), 62.16 (CH_2), 62.66 (CH_2), 121.10 (CH), 126.32 (CH), 127.46 (CH), 128.42 (CH), 136.9 (CH), 144.0 (C), 158.5 (C); HRMS calc. for $C_{39}H_{39}N_3$: 549.314 Found: 549.314
The (all-*S*) enantiomer was prepared in the same manner.

(All-*R*)-2,6-Bis-((3,4-bis-(1-naphthyl)pyrrolidine)methyl)pyridine (414) was prepared in the same way as described for **411**. Thus starting with 2,6-dicarbonylchloropyridine (383 mg, 1,9 mmol) and (*R,R*)-bis-(1-naphthyl)pyrrolidine (1,24 g, 3,83 mmol) (see chapter 3) the diamide **414a** was obtained as an orange solid, which was reduced with $LiAlH_4$ in THF to afford crude **414**. Purification (column-chromatography silica/CH_2Cl_2/MeOH (98:2)) afforded pure (all-*R*)-**414** as an orange foam. Yield 700 mg (50%); $[\alpha]_{578}$= -71^{0}C ($CHCl_3$); ^{1}H-NMR: δ 3.2 (dd,4H), 3.6 (t,4H), 4.1 (dd,4H), 4.6 (m,4H), 7.2-7.5 (m,14-H), 7.7 (dd,9H), 7.8 (d,4H), 8.1 (d,4H); ^{13}C-NMR: δ 46.62 (CH), 62.35 (CH_2), 121.13 (CH), 123.69 (CH), 125.31 (CH), 125.67 (CH), 126.91 (CH), 128.71 (CH), 132.11 (C), 133.88 (C), 137.03 (CH), 139.33 (C), 158 (C) HRMS calc. for $C_{55}H_{47}N_3$: 749.377 Found: Is currently under investigation

(All-*S*)-*N*-1,3,5-Tris-((3,4-diphenylpyrrolidine)methyl)benzene (415) was prepared in the same way as described for **411**. Thus starting with 1,3,5-benzenetricarboxylic acid chloride (820 mg, 3.1 mmol) and (*S,S*)-3,4-diphenylpyrrolidine (2.12 g, 9.5 mmol), the triamide was obtained as a beige solid (after crystallisation from 2-propanol) and reduced with $LiAlH_4$ in THF to afford **415** as a colourless oil. Yield 1.7 g (70 %). Triamide **415a**, mp 146-148^{0}C; $[\alpha]_{578}$= +90°($CHCl_3$); ^{1}H-NMR: δ 3.4-4.0 (m,15H), 4.25 (dd,3H), 7.1-7.3 (m,30H), 7.9 (s,3H); ^{13}C-NMR: δ 49.29 (CH), 51.80 (CH), 53.90 (CH_2), 57.80 (CH_2), 127.22 (CH), 127.41 (CH), 127.50 (CH), 127.61 (CH), 128.40 (CH), 128.66 (CH), 128.76 (CH), 136.66 (C), 137.82(C), 138.44 (C), 167.50 (C=O); Anal. Cald. for $C_{57}H_{51}N_3O_3.H_2O$: C 79.05 H 6.87 N 4.85 Found: C 80.00 H 6.27 N 4.84.
(All-*S*) Triamine **415**, $[\alpha]_{578}$= +62°($CHCl_3$); ^{1}H-NMR: δ 2.9 (t,6H), 3.25 (t,6H), 3.45 (m,6H), 3.8 (dd,6H), 7.25 (m,30H), 7.45 (s,3H); ^{13}C-NMR: δ 53.0 (CH), 60.5 (CH_2),

62.0 (CH_2), 126.36 (CH), 127.45 (CH), 128.40 (CH), 128.54 (CH), 128.60 (C), 128.74 (C); HRMS calc. for $C_{57}H_{57}N_3$: 783.455 Found: 783.455

1-Methoxybenzene-2,6-dicarboxylic acid (416)
To a cooled solution (0°C) of KOH (18,5 g, 85%, 0,21 mol) in EtOH (200 ml) was added 2,6-dimethylphenol (25 g, 0,2 mol) followed by MeI (20 ml, 0,4 mol). The mixture was stirred for 30 minutes at RT, water (600 ml) and ether (500 ml) were added. The organic layer was extracted with water, dried (Na_2SO_4) and concentrated to afford an oil which was used in the next step without further purification. This oil was added to H_2O (600 ml) and $KMnO_4$ (75 g) was added in one portion. The mixture was refluxed until the colour of $KMnO_4$ had disappeared (appr. 30 min.). Another portion of $KMnO_4$ (75 g, total 0,94 mol) was added and the mixture was refluxed for one hour. The mixture was filtered while hot and the colourless water layer was extracted with toluene (200 ml). The water layer was acidified and the solid collected and dried to afford **416** as a white solid. Yield 24 g (60%); mp 220-223°C(lit. Sprengling, G.R.; Freeman, J.H., *J. Am. Chem. Soc. 72,* 1982, **1950;** 222-223°C); ^{1}H-NMR ($CDCl_3/CD_3OD$): δ 4.38 (s,3H), 7.51-7.89 (m,1H), 8.45 (d,2H)

(All-*S*)-1-Hydroxy-2,6-bis((3,4-diphenylpyrrolidine)methyl)benzene (419) was prepared in the same way as described for **411**. Thus starting with 1-methoxy-2,6-dicarboxylchlorobenzene* (2.2 g, 9.8 mmol) and (*S,S*)-3,4-diphenylpyrrolidine (4.4 g, 19.7 mmol), diamide **417** was obtained as a yellow solid. Subsequent reduction with $LiAlH_4$ in THF afforded (all-*S*)-**418** as a yellow oil, which was used as such in the deprotection step.
(All-*S*)-**417**; mp 116-118°C; $[\alpha]_{578}$= +67,3° ($CHCl_3$); ^{1}H-NMR: δ 3.4-3.9 (m,10H), 4.05 (s,3H), 4.35 (dd,2H), 7.0-7.3 (m,21H), 7.45 (d,2H); ^{13}C-NMR: δ 50.06 (CH), 51.47 (CH), 52.62 (CH_2), 54.89 (CH_2), 63.0 (CH_3), 127.15 (CH), 127.27 (CH), 128.66 (CH), 129.27 (CH), 131.0 (C), 138.42 (C), 139.05 (C), 166.89 (C=O); HRMS calc. for $C_{41}H_{38}N_2O_3$: 606.288 Found: 606.288
(All-*S*)-**418**; ^{1}H-NMR: δ 3.0 (dd,4H), 3.3 (t,4H), 3.5 (m,4H), 3.9 (s,3H), 4.05 (s,4H), 7.2 (t,1H), 7.2-7.4 (m,20H), 7.55 (d,2H); ^{13}C-NMR: δ 53.5 (CH), 54.0 (CH_2), 62.1 (CH_3), 62.5 (CH_2), 124.0 (CH), 126.2 (CH), 127.5 (CH), 128.2 (CH), 129.5 (CH), 132 (C), 142 (C), 156.5 (C); HRMS calc. for $C_{41}H_{41}N_2O_2$: 577.321 Found: 577.321

* Obtained by reaction of **416** with $SOCl_2$ in toluene.

(All-*S*)-419
To a solution of (all-*S*)-**418** (2.9 g, 5 mmol) in acetic acid (100 ml) was added HBr (48%)(15 ml). The mixture was refluxed for 5 hours and concentrated to dryness. The residue was treated with 10% $NaHCO_3$ and the product extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated to afford all (*S*) **419**, which was purified by means of column chromatography (silicagel/CH_2Cl_2) to afford **419** as a yellow foam. Yield 2.7 g (50% overall); $[\alpha]_{578}$= +45° ($CHCl_3$); ^{1}H-NMR: δ 3.0 (m,4H), 3.35 (m,4H), 3.45 (m,4H), 4.0 (dd,4H), 6.8 (t,1H), 7.0-7.4 (m,20H), 7.45 (d,2H); ^{13}C-NMR: δ 53.5 (CH), 55.3 (CH_2), 62.0 (CH_2), 123.8 (C), 126.1 (CH), 127.5 (CH), 128.4 (CH), 129.5 (CH), 142.6 (C), 144.1 (C); HRMS calc. for $C_{40}H_{39}N_2O$: 564.314 Found: 564.314

(All-*R*)-1-Bromo-2,6-bis((3,4-diphenylpyrrolidine)methyl)benzene (420)
To a solution of (*R,R*)-3,4-diphenylpyrrolidine (4.0 g, 18 mmol), Et_3N (3 ml) in 250 ml benzene was added in one portion 2,6-bis(bromomethyl)-1-bromobenzene[30](3.0 g, 8.15 mmol). The mixture was stirred at RT overnight and filtered. The filtrate was evaporated and the residue was purified via column chromatography (silica/ether). The product was obtained as a yellow oil. Yield 4.3 g (84%); $[\alpha]_{578}$= -58.7^0 ($CHCl_3$); ^{1}H-NMR: δ 3.0 (dd,4H), 3.3 (t,4H), 3.4 (m,4H), 3.9 (dd,4H), 7.1-7.35 (m,21H), 7.5 (d,2H); ^{13}C-NMR: δ 53.38 (CH), 60.0 (CH_2), 62.77 (CH_2), 126.24 (CH), 127 (CH), 127.47 (CH), 128.4 (CH), 128.95 (CH), 138.5 (C), 144.26 (C); HRMS calc. for $C_{40}H_{39}N_2Br$: 626.230 Found: Anal. calc. for $C_{40}H_{41}N_2BrCl_2H_2O$: C 66.86 H 6.03 N 3.90 Br 11.12 Cl 9.87 Found: C 66.94 H 6.07 N 3.92 Br 11.06 Cl 9.83

1,10-Phenanthroline-2,9-dicarbonyl chloride (421) was synthesised according to ref. 33a. Yield 30%; mp 194-197^{0}C (lit.[33a] 196-198^{0}C);^{1}H-NMR (DMSO-d6): δ 8.15 (s,2H), 8.25 (d,2H), 8.75 (d,2H)

2,9-Bis(bromomethyl)-1,10-phenanthroline (422) was synthesised according to ref. 33b. Yield 35%; mp 108-110^{0}C (lit.[33b] 110-111^{0}C); ^{1}H-NMR: δ 4.95 (s,4H), 7.75 (d,2H), 7.85 (d,2H), 8.25 (s,2H)

2,2'-bipyridine-6,6'-dicarbonyl chloride (423) was synthesized according to ref. 33c. Yield 30%; mp 175-176^{0}C (lit.[33c] 177-178^{0}C); ^{1}H-NMR: δ 8.0-8.25 (m,4H), 8.6 (dd,2H)

(All-*R*)-2,9-Bis-[(3,4-diphenylpyrrolidine)carboxyl]-1,10-phenanthroline (424)
To a cooled solution of (*R,R*)-3,4-diphenylpyrrolidine (1.4 g, 6.28 mmol) in CH_2Cl_2 (50 ml) was added Et_3N (2 ml) followed by diacid chloride **421** (954 mg, 3.12 mmol). The mixture was stirred for two hours and water was added. The organic layer, after work-up was purified by means of column-chromatography over silica gel using CH_2Cl_2 and CH_2Cl_2/MeOH (9:1) as eluent. The product was obtained as a beige solid after crystallization from 2-propanol. Yield (40%); mp 150-154^{0}C; $[\alpha]_{578}$= -149^0 ($CHCl_3$); ^{1}H-NMR: δ 3.4 (m,4H), 3.8 (t,2H), 4.3 (m,4H), 4.75 (dd,2H), 7.2 (m,20H), 7.9 (s,2H), 8.35 (dd,4H); ^{13}C-NMR: δ 49.08 (CH), 51.23 (CH), 54.37 (CH_2), 56.18 (CH_2), 123.41 (CH), 127.08 (CH), 127.32 (CH), 127.60 (CH), 128.65 (CH), 129.58 (C), 136.93 (CH), 139.5 (C), 139.6 (C), 143.8 (C), 153 (C), 166 (C=O); HRMS calc. for $C_{46}H_{38}N_4O_2$: 678.299 Found: 678.299

(All-*S*)-2,9-Bis[(3,4-dibenzoyloxypyrrolidine)methyl]-1,10-phenanthroline (425)
To a solution of compound **421** (1.0 g, 2.7 mmol), Et_3N (2 g) in $CHCl_3$ (50 ml) was added (*S,S*)-3,4-dibenzoyloxypyrrolidine (1.85 g, 5.94 mmol) (see chapter 3) and the resulting mixture was stirred for 3 hours at RT. Water (50 ml) was added and the organic layer was washed with 10% $NaHCO_3$, brine and dried (Na_2SO_4). Concentration afforded the crude product which was purified by means of column chromatography over silica gel with $CHCl_3$/MeOH (99:1) as eluent. Yield (40%); $[\alpha]_{578}$= + 36^0 ($CHCl_3$); ^{1}H-NMR: δ 2.9 (dd,4H), 3.45 (dd,4H), 4.3 (dd,4H), 5.6 (t,4H), 7.2-7.6 (m,12H), 7.75 (s,2H), 7.95 (d,2H), 8.15 (m,8H), 8.25 (d,2H); ^{13}C-NMR: δ 58.34 (CH_2), 61.42 (CH_2), 78.08 (CH), 122.26 (CH), 125 97 (CH), 127.78 (C), 128.25 (CH), 129.49 (C), 129.68 (CH), 133.07

(CH), 136.79 (CH), 145.04 (C), 158.59 (C), 165.79 (C=O); No exact mass could be determined due to elimination of the benzoyl group (m=105).

(All-*R*)-6,6'-Bis[(3,4-diphenylpyrrolidene)carboxyl]-2,2'-bipyridine (426)
To a solution of (*R,R*)-3,4-diphenylpyrrolidine (2.23 g, 10 mmol) and Et_3N (3 ml) in CH_2Cl_2 (50 ml) was added compound **422** (1.40 g, 5 mmol). The resulting mixture was stirred for hours at RT. Water was added, the organic layer dried (Na_2SO_4) and evaporated. The crude product was crystallized from iso-propanol to afford **426** as a white solid. Yield 2.5 g (85%); mp 249-250^{0}C; $[\alpha]_{578}$= -165°($CHCl_3$); ^{1}H-NMR: δ 3.6 (m,4H), 3.9 (dd,2H), 4.2 (t,2H), 4.5 (ddd,4H), 7.2 (m,20H), 7.9 (m,4H), 8.4 (dd,2H); ^{13}C-NMR: δ 49.54 (CH), 52.30 (CH), 54.01 (CH_2), 56.45 (CH_2), 122.24 (CH), 124.49 (CH), 127.12 (CH), 127.51 (CH), 128.62 (CH), 138.01 (CH), 138.87 (C), 139.12 (C), 153.24 (C), 153.94 (C), 165.94 (C=O); HRMS calc. for $C_{44}H_{38}N_4O_2$: 654.299 Found: Anal. Calcd for $C_{44}H_{38}N_4O_2$: C 80.70 H 5.85 N 8.56 Found: C 80.00 H 5.87 N 8.48.

(All-*S*)-6,6'-Bis[(3,4-dibenzoyloxypyrrolidine)carboxyl]-2,2'-bipyridine (427)
To a solution of compound **422** (750 mg, 2.67 mmol) and Et_3N (2 ml) in $CHCl_3$ (50 ml) was added (*S,S*)-3,4-dibenzoyloxypyrrolidine (1.67 g, 5.4 mmol) in $CHCl_3$ (20 ml) over a 15 minutes period. The mixture was stirred for 3 hours at RT. Water was added, the organic layer dried (Na_2SO_4) and concentrated in vacuo. The crude product was crystallized from 2-propanol and obtained as a white solid. Yield 1.4 g (65%); mp 124,5-125^{0}C; $[\alpha]_{578}$= -19^0 ($CHCl_3$); ^{1}H-NMR: δ 4.2 (d,2H), 4.35 (d,2H), 4.45 (d,2H), 4.6 (d,2H), 5.65 (s,4H), 7.4-7.6 (m,12H), 7.9-8.1 (m,12H), 8.4 (d,2H); ^{13}C-NMR: δ 51.8 (CH_2), 52.6 (CH_2), 73.8 (CH), 122.3 (CH), 125.18 (CH), 128.56 (CH), 129.81 (C), 129.86 (CH), 133.60 (CH), 138.27 (CH), 152 (C), 153.89 (C), 165 (C=O), 165.86 (C=O); Anal. calc. for $C_{48}H_{38}N_4O_{10}$: C 69.38 H 4.61 N 6.75 Found: C 68.25 H 4.66 N 6.52

(*R,R*)-2,3-Bis-(benzyloxy)butanedioic acid diethylester (428) was prepared on a 500 mmol scale according to ref. 34 in 85% yield. The crude ester was used as such in the next step.

(*R,R*)-2,3-Bis-(benzyloxy)succinic anhydride (429)
To a solution of KOH (32 g, 500 mmol) in EtOH (200 ml) and H_2O (500 ml) was added diethylester **428** (90 g, 0.23 mol). The mixture was heated for 2 hours and 500 ml H_2O was added. The water layer was extracted with toluene and acidified with conc. HCl. The water layer was extracted with $CHCl_3$, the organic layer dried (Na_2SO_4) and concentrated in vacuo to give (*R,R*)-2,3-bis-(benzyloxy)butanedioic acid as a yellow oil. To this oil was added AcCl (200 ml) and the mixture was refluxed for two hours. After evaporation the crude anhydride was crystallized from ether to afford **429** as a colourless solid. Yield 30 g (40%); mp 104,2-104,7^0; $[\alpha]_{578}$= +134,6°($CHCl_3$); ^{1}H-NMR: δ 4.6 (s,2H), 4.9 (dd,4H), 7.4 (s,10H); ^{13}C-NMR: δ 73.8 (CH_2), 78.1 (CH), 128.4 (CH), 128.8 (CH), 135.9 (C), 166 (C=O); HRMS calc. for $C_{18}H_{16}O_5$: 312.100 Found: 312.100; Anal. Calcd for $C_{18}H_{16}O_5.H_2O$: C 65.45 H 5.49 Found: C 69.94 H 5.52.

(All-*S*)-1,2-Bis-[(3,4-benzyloxy)pyrrolidine]ethane (431)
A mixture of ethylenediamine (325 mg, 5.4 mmol), Et_3N (0.1 ml), anhydride **429** (3.5 g, 11.2 mmol) in toluene (50 ml) was refluxed for 10 hours. The clear solution was concentrated in vacuo and the crude product purified by means of column chromatography over silica gel with $CHCl_3$ as eluent, to afford diimide **430** as a colourless oil. Yield 2.5 g (71%); $[\alpha]_{578}$= +66°C ($CHCl_3$); ^{1}H-NMR: δ 3.75 (m,4H), 4.4 (s,4H), 4.8 (dd,8H), 7.3 (s,20H); ^{13}C-NMR: δ 36.59 (CH_2), 73.14 (CH_2), 78.70 (CH), 128.14 (CH), 128.46 (CH), 136.68 (C), 172.92 (C=O); HRMS calc. for $C_{38}H_{36}N_2O_8$: 648.247 Found: 648.247

Diimide **430** (2,3 g, 3,5 mmol) was reduced with $LiAlH_4$ in THF in the same way as described for **411**. The crude product was purified by means of column chromatography over silica gel with ether as eluent to afford (all-*S*)-**431** as a colourless oil. Yield 1,4 g (43% overall); $[\alpha]_{578}$= +18,69°($CHCl_3$); ^{1}H-NMR: δ 2.7 (m,8H), 3.0 (dd,4H), 4.1 (t,4H), 4.6 (dd,8H), 7.4 (m,20H);^{13}C-NMR: δ 54.55 (CH_2), 58.89 (CH_2), 71.45 (CH_2), 83.20 (CH), 127.71 (CH), 127.84 (CH), 128.39 (CH), 137.98 (C); HRMS calc. for $C_{38}H_{44}N_2O_4$: 592.330 Found: 592.330

(All-S) Hexamine (433)
A mixture of $DAB(PA)_4$* (3.16 g, 10 mmol) and anhydride **429** (12.5 g, 40 mmol) in toluene (200 ml) was refluxed for 16 hours. The mixture was evaporated to give the desired tetraimide in quantitative yield as a thick oil. The oil was dissolved in THF (200 ml) and added to $LiAlH_4$ (3.42 g, 90 mmol) in THF (100 ml). The mixture was refluxed for 2 hours and hydrolyzed with 10 % KOH. The resulting mixture was filtered over Celite and concentrated in vacuo the resulting red oil was purified by column chromatography using CH_2Cl_2, CH_2Cl_2/MeOH (10:1) and CH_2Cl_2/MeOH/NH_4OH (10:1:1) as eluent. The last fractions were combined to give **432** as a slightly red oil. Yield 6 g (43%); $[\alpha]_{578}$= +5° ($CHCl_3$); ^{1}H-NMR: δ 1.3 (m,4H), 1.6 (m,12H), 2.4 (m,16H), 2.7 (dd,8H), 3.9 (dd,4H), 4.1 (t,8H), 4.5 (dd,16H), 7.3 (s,40H); ^{13}C-NMR: δ 25.0 (CH_2), 25.9 (CH_2), 51.8 (CH_2), 54.0 (CH_2), 54.1 (CH_2), 58.78 (CH_2), 71.38 (CH_2), 83.40 (CH), 127.64 (CH), 127.80 (CH), 128.34 (CH), 138.0 (C); HRMS calc. for $C_{88}H_{112}N_6O8$: Found: Is currently under investigation
* $DAB(PA)_4$ was kindly supplied by E.M. Meyer (DSM research).

General procedure for the preparation of metal complexes
One equivalent of ligand was dissolved in THF, MeOH, EtOH and one equivalent of the appropriate metal salt was added. The mixture was stirred for 2 hours at RT, the solvent removed in vacuo and the remaining material was crystallized.

411·$ZnCl_2$ (all*S*) was recrystallized from THF/EtOH and obtained as a white solid.
mp 282-283°C; $[\alpha]_{578}$= +112° ($CHCl_3$); ^{1}H-NMR: δ 1.4 (s,6H), 3.0 (dd,2H), 3.3 (s,4H), .65 (dd,2H), 3.7 (dd,2H), 4.3 (m,2H), 4.4 (dd,2H), 4.6 (dd,2H), 7.4 (m,16H), 7.6 (d,4H); Anal. calc. for $C_{37}H_{42}N_2ZnCl_2$: C 68.50 H 6.53 N 4.32 Cl 10.79 Zn 9.86 Found: C 68.15 H 6.65 N 4.25 Cl 10.85 Zn 9.83.

Selected interatomic distances in Angstroms and angles in degrees with standard deviations of the last significant digets in parentheses.
Zn-Cl1 2.250(4); Zn-Cl2 2.252(4); Zn-N1 2.110(9); Zn-N23 2.078(9).
Cl1-Zn-Cl2 110.4(2); Cl1-Zn-N1 109.5(3); Cl1-Zn-N23 110.2(3); Cl2-Zn-N1 109.1(3); Cl2-Zn-N23 110.6(3); N1-Zn-N23 107.0(4); C2-N1-C5 106.8(9); C24-N23-C27 103.0(8); N1-C18-C19 120.(1); N1-C18-C190 121.(2).

413·$RhCl_3$ (all*R*) was purified by column chromatography (silica/CH_2Cl_2) and obtained as an orange solid. $[\alpha]_{578}$= -208^0 ($CHCl_3$); ^{1}H-NMR: δ 3.5-4.0 (m,10H), 4.45 (t,2H), 4.9 (dd,4H), 5.25 (dd,2H), 7.1-7.4 (m,20H), 7.4 (d,2H), 7.9 (t,1H)

(*E*)-3-Phenyl-*N*-methyl-but-2-enamide Substrate A was prepared according to the method described by von Matt (ref.44a). mp 111.5-113^{0}C (lit.[44a] 113^0); ^{1}H-NMR: δ 2.6 (s,3H), 2.9 (d,3H), 5.7 (br,1H), 6.0 (d,1H), 7.3-7.5 (m,5H). According to GC this material was more than 99.5% pure.

(*E*)-*N*-1,3-dimethyl-5-phenylpent-2-enamide Substrate B was prepared according to the method described by von Matt (ref. 44a). mp 82-83^{0}C (lit.[44a] 84^{0}C); ^{1}H-NMR: δ 2.2 (d,3H), 2.35-2.8 (2m,4H), 2.8 (d,3H), 5.4 (br,1H), 5.5 (s,1H), 7.1-7.3 (m,5H). According to GC this material was more than 99.5% pure.

General procedure for the enantioselective reduction of α,ß-unsaturated carboxylic amides
To substrate *A* (350 mg,2mmol) in EtOH (1ml) was added $CoCl_2.6H_2O$ (24 mg, 5mol%) followed by the addition ligand **401** (all *S*) (50mg, 6 mol%) in EtOH (1ml). To the deep blue solution was added diglyme (2ml) and the solution was degassed three times, while being kept under argon. $NaBH_4$ (76mg,2mmol) was added and the color immediately changed to brown. The resulting mixture was again degassed and stirred at RT for 48 hours. Water was added and the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with 10% HCl, brine, dried and concentrated in vacuo. The crude reaction mixture was purified by column chromatography (silica gel, EtOAc/hexane 1/5) to afford 50 mg 14% of (*S*)-3-phenyl-*N*-methyl-butanamide as a waxy solid.

(*S*)-3-Phenyl-*N*-methyl-butanamide
$[\alpha]_D$= +33^0 ($CHCl_3$); optical purity is 83% ;^{1}H-NMR: δ 1.2 (d,3H), 2.2-2.45 (m,2H), 2.6 (d,3H), 3.2 (m,1H), 6.1 (br,1H), 7.2 (m,5H).

(3(3*S*),4*S*)-4-Phenyl-3-(3-phenylbutanoyl)-2-oxazolidinone
The amide was hydrolysed in AcOH,H_2SO_4(50%) and the resulting (*S*)-3-phenylbutanoic acid was coupled with (*S*)-4-phenyl-2-oxazolidinone according to a literature procedure (Nicolas, E.; Rusell, K.C., Hruby, V.J. *J. Org. Chem.* **1993,** *58*, 766.). Integration of the H_4 proton allowed the determination of the enantiomeric excess (82% ee); δ 5.31 ppm (*S*) enantiomer, δ 5.4 ppm (*R*) enantiomer. ^{1}H-NMR: δ 1.2 (d,3H), 3.0-3.5 (m,3H), 4.2 (dd,1H), 4.6 (t,1H), 5.31 (dd,1H), 7.4 (m,10H).

(*S*)-*N*-1,3-Dimethyl-5-phenylpentanamide
mp 70-71^{0}C (lit.[44a] 72-73^{0}C); $[\alpha]_D$= -11.2^0 ($CHCl_3$); Optical purity is 60%; ^{1}H-NMR: δ 1,0 (d,3H), 1.4-1.55 (m,1H), 1.7 (m,1H), 2.0 (m,2H), 2.2 (m,1H), 2.8 (d,3H), 2.5-2.7 (m,2H), 5.4 (br,1H), 7.2 (m,5H).

CHAPTER 5

N-BROMOSUCCINIMIDE DERIVATIVES

5.1 Introduction

In this chapter we will describe two subjects, which have in common the synthesis and use of *N*-bromosuccinimide derivatives. The first part of this chapter describes the remote functionalisation of fatty acids and was the start of the work described in this thesis. The second part, C_2-symmetrical succinimides derived from tartaric acid, describes the synthesis of C_2-symmetrical *N*-bromosuccinimides and their use in enantioselective bromination reactions.

5.2 Remote functionalisation of unsaturated fatty acids

5.2.1 Introduction

The selective functionalisation of C-H bonds remains one of the major focuses of catalytic and organic chemistry. High selectivity is often achieved by the presence of activating groups which induce the reactivity of neighboring C-H bonds. The functionalisation of remote C-H bonds several carbon atoms away from the activating group represents a great challenge. Although such reactions are common to enzymes, which coordinate a functional group and geometrically select a specific site on the substrate. For example, heme-containing enzymes can selectively hydroxylate unactivated methyl groups while leaving double bonds of a substrate untouched. Relatively few cases, however, in solution chemistry have been reported.[1]

One of the best examples to show this capacity of enzymes to carry out selective functionalisation of simple substrates, is the conversion of stearic acid to oleic acid.

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[1] For selected reference: a) Breslow, R. *Chem. Soc. Rev.* **1972**, *1*, 553. b) Breslow, R.; Maresca, L.M. *Tetrahedron Lett.* **1977**, 623. c) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170. d) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146. e) Breslow, R. *Chemtracts: Org. Chem.* **1988**,*1*,333. f) Breslow, R. *Pure Appl. Chem.* **1994**, *66*, 1573. g)Czekay, G.; Drewello, T.; Schwarz, H. *J. Am. Chem. Soc.* **1989**, *111*, 456. h) Béqué, J.P. *J. Org. Chem.* **1982**, *47*, 4268. i) Kaufman, M.D.; Grieco, P.A.; Bougie, D.W. *J. Am. Chem. Soc.* **1993**, *115*, 11648. j) Isaacs, L.; Haldiman, R.F.; Diederich, F. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2339.

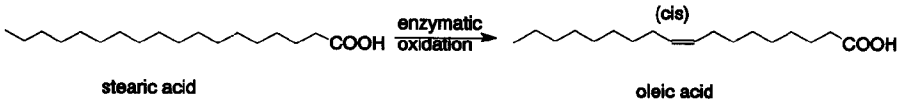
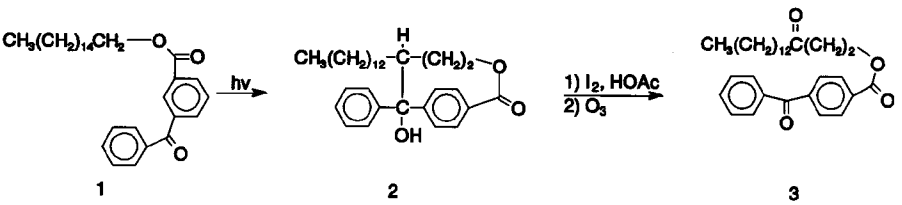


Figure 5.1. Selective functionalisation of stearic acid

The principle involved in this kind of transformation was stated as follows by Breslow *et al.*[2]; "any intrinsic reactivity of the substrate dictated by its own functional groups, can be overridden by combining the substrate with a reagent (i.e. the enzyme) whose selectivity is dominant. Thus even a single unactivated CH_2 group, in stearic acid for example, can be attacked selectively within a substrate-enzyme complex by steric approximation to the attacking atom." Breslow[1c] has coined the term 'remote functionalisation' for this kind of coordination of a functional group followed by selective reactions at sites away from the complexed functionality. The first chemical example of the application of this principle was described by the group of Breslow[2], scheme 5.1. They prepared a series of *p*-benzophenonecarboxylic esters **1** with long-chain alcohols. Irradiation of these esters resulted in a regiospecific intramolecular reaction to form alcohols **2**, dehydration of, which followed by ozonolysis furnished ketones **3**. In the case of the C_{16}-alcohol, considerable selectivity for C_{14} was observed. Other alcohols gave much less selectivity. But Breslow had proven that the functionalization of the substrate was dictated by geometric proximity as in enzymes.

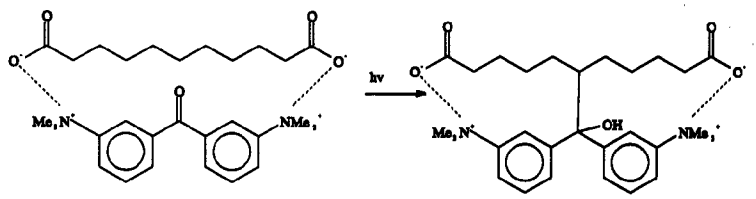


Scheme 5.1. Remote oxidation of unactivated methylene groups

Breslow turned to more rigid molecules, and successfully functionalized unactiva-

[2] Breslow, R.; Winnik, M.A. *J. Am. Chem. Soc.* **1969**, *91*, 3083.

ted C-H bonds in steroids.[3] Useful as the selective reactions proved to be in steroid chemistry, they entail a simplification of the challenge. Steroids have a rigid well-defined geometry, that place certain atoms in the site of reactivity and others not; moreover structural considerations lead to differences in reactivity (primary compared to secondary compared to tertiary C-H bonds). Breslow returned to the more flexible substrates (long chain alcohols) and found that the geometric control of the functionalisations is limited by their conformational randomness[4]. In order to solve this problem Breslow examined other phases, such as micelles and membranes in which the long flexible chains are more ordered. However, the chemical selectivity was not improved. The selectivity could be improved by double binding of a catalyst or reagent to both ends of the flexible chain (scheme 5.2).[4d]



Scheme 5.2 Double ion-pairing directs selectivity in flexible chains

Our goal within this field was the selective introduction of a bromine atom in a saturated, unsaturated or polyunsaturated fatty acid, utilizing the concept of remote functionalisation as introduced by Breslow. We wanted to achieve selective bromination of equally activated C-H bonds by combining the fatty acid with a carrier molecule, a *N*-bromosuccinimide derivative, as depicted in scheme 5.3, the selectivity of this remote bromination being geometrically controlled.

The reason that we wanted to use NBS derivatives as carrier molecules were threefold. First, NBS derivatives are readily available; secondly, other functionalizations like epoxidation and hydroxy-bromination are possible with the same reagent; thirdly the possibility to introduce chirality in the fatty acid chain by starting with chiral NBS reagents.

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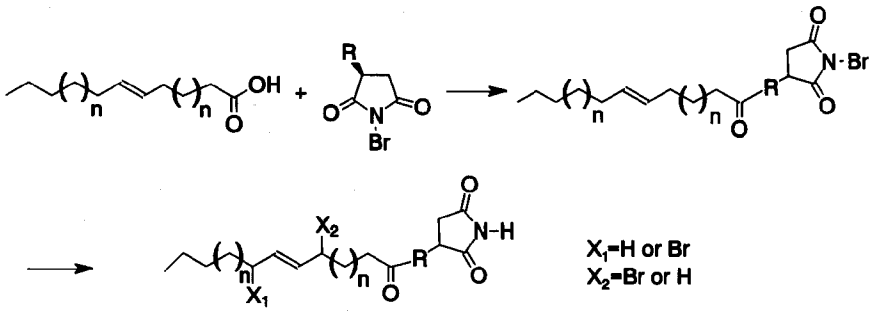
[3] a) Breslow, R.; Baldwin, S.; Flechter, T. Kalicky, P.; Liu, S.; Washburn, W. *J. Am. Chem. Soc.* **1973**, *95*, 325. b) Wife, R.L.; Prezant, D.; Breslow, R. *Tetrahedron Lett.* **1976**, 517. c) Breslow,R. *Acc. Chem. Res.* **1980**, *13*, 170 and references cited within. d) Breslow, R.; Brandl, M.; Hunger.J.;Adams, A.D. *J. Am. Chem. Soc.* **1987**, *109*, 3799. e) The functionalisation of unactivated C-H bonds in steroids was also studied by other groups. f) Burton, D.H.R.; Gokturk, A.N.; Morzycki,J.W.; Motherwell, W.B. *J. Chem. Soc., Perkin Trans 1* **1985**, 583. g) Rozen, S.; Brans, M.; Kol,M.J. *J. Am. Chem Soc.* **1989**, *111*, 8325. h) Groves, J.T.;Neumann, R. *J. Org. Chem.* **1988**, **53**,3891.i) ref. 1f)

[4] a) Breslow, R.; Rothbard, J.; Herman, F.; Rodriques, M.C. *J. Am. Chem. Soc.* **1978**, *100*, 1213. b) Breslow, R.; Kitabatake, S.; Rothbard, J. *J. Am. Chem. Soc.* **1978**, *100*, 8156. c) Czarniecki, M.F.; Breslow, R.*J. Am. Chem. Soc.* **1979**, *101*, 3675. d) Breslow, R.; Rajagopalan, R.; Schwarz, J. *J. Am. Chem Soc.***1981**, **103**, 2905.



Scheme 5.3. Remote bromination of unsaturated fatty acids

5.2.2 *Synthesis of carrier molecules*

The carrier molecules, succinimide derivatives should 'match' to several criteria. First, easy accessibility, secondly, the possibility to bind covalently or ionically to fatty acids and thirdly introduction of chirality should be possible. After careful study of the literature[5] we decided that 3-aminosuccinimide derivatives, depicted in figure 5.2, match to the criteria mentioned above. Compounds **501**, **502** and **504** have previously been described in the literature [7,9,10]. Starting materials for these substituted 3-aminosuccinimi-

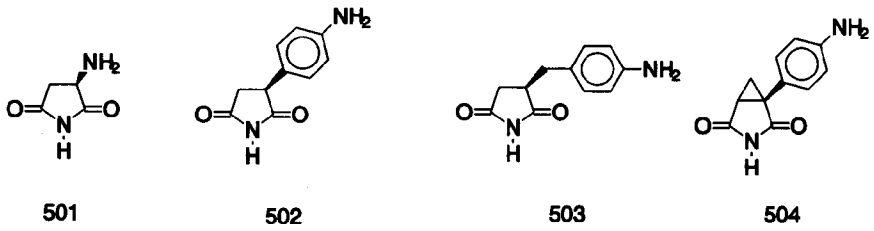
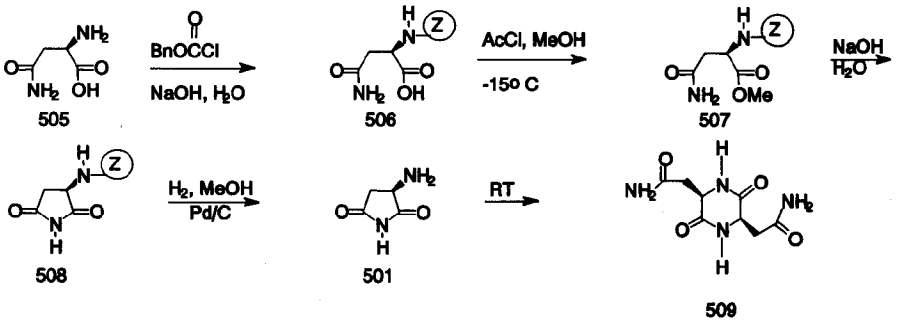


Figure 5.2 3-aminosuccinimides used as carrier molecules

des are the corresponding butanedioic acids, of which all four are available in enantiome-

[5] For the synthesis of various substituted succinimides see: a) Polonski, T. *J. Chem. Soc. Perkin Trans. 1* **1988**, 629. b) Polonski, T.; Milewska, M.J.; Katrusiak, A. *J. Org. Chem.* **1993**, *58*, 3411. c) ref. 20.

rically pure form.[6] We synthesized (*S*)-3-aminopyrrolidine-2,5-dione (**501**) according to a literature procedure.[7] L-Asparagine (**505**) was *N*-protected with benzyl chloroformate. The *N*-protected amino acid **506** was converted into its methyl ester **507** by careful control of esterification using 2M HCl in MeOH at -15°C, to prevent racemization. Cyclisation of the ester **507** with 0.5 M NaOH in H_2O afforded (*S*)-3-(benzyloxocarbonylamino)succinimide (**508**). Hydrogenation with H_2/Pd/C (10%) afforded succinimide **501** in 45% overall yield. We have been able to scale up this literature procedure to molar scale without difficulty. Succinimide **501** is very insoluble in organic solvents. It is not stable and cyclises to the corresponding piperazine-2,5-dione **509** in high yield.



Scheme 5.4. Synthesis of (S)-3-aminosuccinimide (501)

The solubility problem was solved by the introduction of a phenyl ring as in **502**, **503** and **504**. Succinimides that contain a *p*-aminophenyl group in the 2-position such as **502** are used as potential drugs for the inhibition of the conversion of androgens to estrogens.[8] They are of practical importance in the treatment of hormone dependent tumors, which comprise 30-40% of all cases of breast cancer. The synthesis of aminophenyl succinimides **502** and **504** are both described in the literature.[9,10] The general route we used to synthesize succinimides **502**, **503** and **504** is based upon the synthesis of 3-(4-aminophenyl)pyrrolidine-2,5-dione (**502**). Commercially available 2-phenylsuccinic acid (**510**) is converted to the corresponding succinimide **511** by reaction with urea at 180°C. The succinimide is nitrated with fuming nitric acid to afford after crystallization 3-(-4-

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6 (*R*)- and (*S*)-asparagine and (*R*)- and (*S*)-2-phenyl succinic acid are commercially available, 2-benzyl succinic acid and 1-phenyl-1,2-cyclopropanedicarboxylic acid are resolved with phenylethylamine.

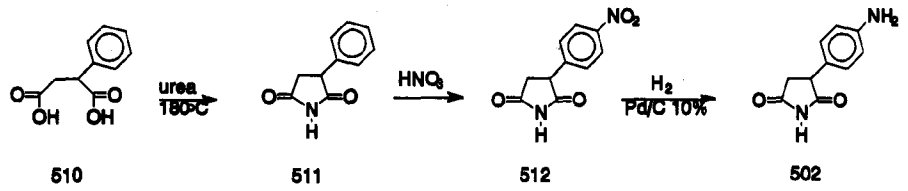
7 Howes, C.; Alcock, N.W.; Golding, B.T.; Mc Cabe, R.W. *J. Chem. Soc. Perkin Trans. 1* **1983**, 2287.

8 Stanek, J.; Alder, A.; Bellus, D.; Bhatnagar, A.S.; Häuster, A.; Schieweck, K.*J. Med. Chem.* **1991**, *34*, 1329.

9 Daly, M.J.; Jones, G.W.; Nicholls, P.J.; Smith, J.H.; Rowlands, M.G.; Bunnett, M.A. *J. Med. Chem.* **1986**, *29*, 520.

10 Rowlands, M.G.; Bunnett, M.A.; Foster, A.B.; Jorman, M.; Stanek, J.; Schweizer, E. *J. Med. Chem.* **1988**, *31*, 971.

nitrophenyl)succinimide (**512**) in 65% yield, the residue being ortho nitrated product. Reduction of the nitro group was accomplished by hydrogenation with H_2/Pd/C 10% to afford succinimide **502** in 35% overall yield.



Scheme 5.5 Synthesis of 3-(4-aminophenyl)pyrrolidine-2,5-dione (502)

The same procedure was also applied to the synthesis of aminosuccinimides **503** and **504**. Thus starting with 2-benzylsuccinic acid (**513**) and 1-phenyl-1,2-cyclopropanedicarboxylic acid (**514**) the corresponding imides **503** and **504**, respectively, were obtained in 30-40% overall yield. This route allows the synthesis of a variety of 3-(4-aminophenyl) substituted

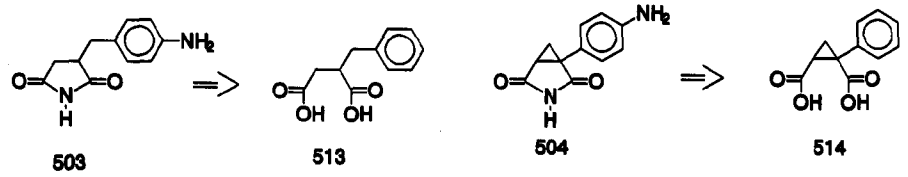


Figure 5.3. Retro synthetic scheme for the synthesis of succinimides 503 and 504

succinimides. The products **502**, **503** and **504** are crystalline compounds, as are all the intermediates, which makes it easy to perform the sequence on large scale. The butanedioic acids **513** and **514** were synthesized according to literature procedures.[11,12] Starting with ethyl acetoacetate, double alkylation with respectively benzylchloride and ethylchloroacetate followed by saponification afforded 2-benzylsuccinic acid (**513**) in 55% overall yield. Cis-1-phenyl-1,2-cyclopropanedicarboxylic acid (**514**) was obtained in a three step reaction sequence following McCoy's method.[12a] α-Bromoethylphenyl acetate was allowed to react with ethyl acrylate in a NaH-ether mixture to afford after saponification and crystallization the cis-acid in 78% yield. Since butanedioic acids **510**, **513**, and **514** are available in optically pure form, the synthesis of optically pure amino succinimides is possible via the same synthetic routes. It is also possible to resolve the aminosuccinimides

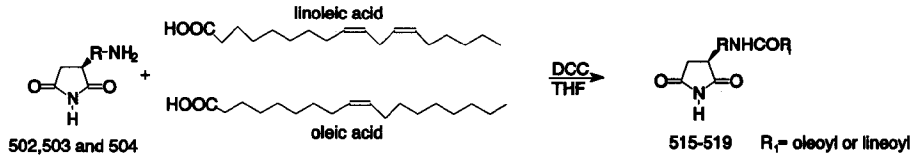
[11] Beech, W.F.; Legg, N. *J. Chem. Soc.* **1949**, 1887.

[12] a) Mc Coy, L.L. *J. Am. Chem. Soc.* **1962**, *84*, 2246. b) Epstein, J.W.; Brabander, H.J.; Fanshawe, W.J.; Hoffmann, C.M.; Mc Kenzie, T.C.; Safir, S.R.; Osterberg, A.C.; Cosulich, D.B.; Lowell, F.M. *J. Med. Chem.* **1981**, *24*, 481.

with chiral acids.[13]

5.2.3 *Remote bromination of oleic acid and linoleic acid*

The next step in the remote functionalisation of unsaturated fatty acids is to bind the aminosuccinimides **501-504** to fatty acids. We first examined the possibility to bind the carrier-molecules covalently to oleic and linoleic acid. There are, of course, several methods to form an amide bond.[14] After several unsuccessful experiments, caused by insolubility- and purification problems, we decided to use a coupling reagent to form the amide bond. Thus reaction of the appropriate aminosuccinimide with oleic acid or linoleic acid in the presence of dicyclohexylcarbodiimide (DCC)[15] in THF afforded the corresponding amides in reasonable yields after purification. The results are summarized in scheme 2.5.



Scheme 5.6 Synthesis of fatty acid-succinimide amides 515-519

Aminosuccinimide	acid	amide	yield (%)
502	oleic	**515**	20
502	linoleic	**516**	18
503	oleic	**517**	20
503	linoleic	**518**	16
504	oleic	**519**	25

The products **515-519** were all purified by crystallization, although with considerable reduction of yield. Chromatography is not possible with these compounds, because of the strongly polar character of the amide-succinimide fragment of the molecule. Aminosuccinimide **501** could not be used due to insolubility problems. With these amides in

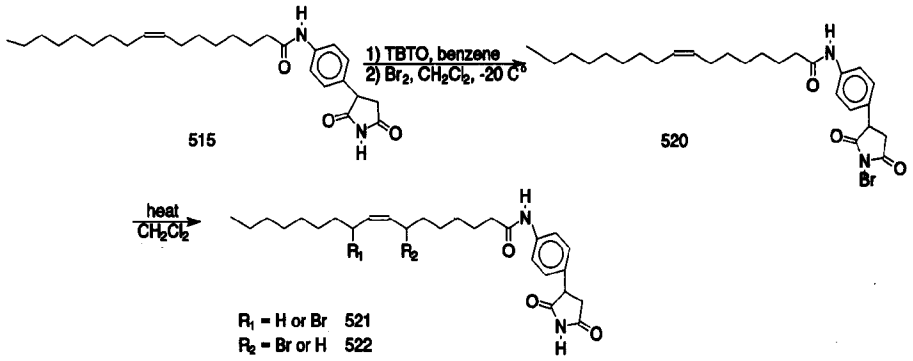
[13] We have been able to resolve compound **504** with 'chlocyphos' in a 5% yield. $[\alpha]_D$ = -66° (MeOH).

[14] March, J. *Advanced Organic Chemistry*, third ed. **1985**, John Wiley & Sons.

[15] DCC was first used by; Sheehan, ; Hess *J. Am. Chem. Soc.* **1955**, *77*, 1067.

hand, we were able to perform some remote bromination experiments. We decided to carry out these experiments according to scheme 5.7. The succinimide position of the amide **515** had to be converted to the corresponding *N*-bromo derivative **520** via a mild method that did not affect the double bond within the fatty acid part of the molecule. Remote bromination should afford the brominated compounds **521** and/or **522**. A mild method[16] for the synthesis of *N*-bromo succinimides makes use of a *N*-tri-*n*-butyltin intermediate,[17] which is converted to the *N*-bromosuccinimide by reaction with 1 eq. of Br_2.[18] This method has the advantage that the conditions are mild and only one equivalent of bromine is used. The *N*-butyltin intermediate is prepared by heating a mixture of bis(tri-n-butyltin)oxide (TBTO) and the appropriate succinimide with removal of the water formed.

Reaction of amide **515** with TBTO in benzene afforded in quantitative yield the *N*-tributyltin intermediate which was converted, without isolation, at -20°C to the *N*-bromosuccinimide derivative **520** by careful addition of 1 equivalent of bromine in CH_2Cl_2. The temperature was allowed to rise to reflux and the rate of allylic bromination reaction was followed by ^{1}H-NMR. We have, however, not been able to determine the selectivity because the research was interrupted by military service and subsequently the contract with Unilever stopped.



Scheme 5.7 Remote bromination of amide 515

[16] For other methods see references 36,37,38 and 39.

[17] a) Soundarajan, R.; Krishnamurthy, S.; Srivivasan, V.S.; Balasubramanian, T.R. *J. Organomet. Chem.* **1983**, *255*, 295. b) Also see section 2.3.

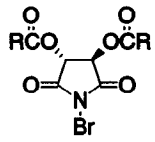
[18] Excess bromine will also brominate the double bond within the molecule.

5.3 C_2-symmetrical succinimides derived from tartaric acid

5.3.1 Introduction

Ever since the synthesis of succinimide,[19] one of the first organic molecules to be synthesized, cyclic imides have played an important role in organic chemistry.[20] Cyclic imides find use in a variety of applications including molecular clefts,[21] drugs,[22,23] peptide synthesis, protecting group,[24] amine synthesis,[25] chiral auxiliaries[26], as carriers for reactive entities like Br^+ and molecules with chiroptical properties.[5] Because of the work described in chapter 2 and section 5.2, we became interested in chiral *N*-bromosuccinimides. After some preliminary experiments on the synthesis of chiral *N*-bromosuccinimide derivatives we found that these compounds were easily accessible by starting with tartaric acid. Recently, various chiral C_2-symmetrical succinimides derived from tartaric acid have been used as chiral auxiliaries in enantioselective synthesis.[27] Another synthetic application of cyclic imides is that they are easily transformed to acyliminium ions, which can undergo a variety of nucleophilic addition reactions.[28]

Our intention was to use these C_2-symmetrical succinimides of general structure **A**, as chiral analogues of *N*-bromosuccinimide, figure 5.4.



A

Figure 5.4 Chiral C_2-symmetrical NBS derivatives

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19 Darcet, F. *Ann. Chim. Phys.* **1835**, *58*, 294.

20 For a review on cyclic imides see: Hargreaves, M.K.; Pritchard, J.G.; Dave, H.R. *Chem. Rev.* **1970**, *70*, 439.

21 Rebek Jr, J. *Science* **1987**, *235*, 1978.

22 Thalidomide; De Camp, W.H. *Chirality* **1989**, *1*,2.

23 Stanek, J.; Alder, A.; Bellus, D.; Bhatnagar, A.S.; Häuster, A.; Schieweck, K. *J. Med. Chem.* **1991**, *34*, 1329.

24 Phthalimide: Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2ed, **1991**, John Wiley & Sons, Inc.

25 Gabriel synthesis: Gibson; McBradshaw. *Angew. Chem., Int. Ed. Eng.* **1968**, *7*, 919-930.

26 Especially the work by Speckamp *et al.* should be mentioned: Speckamp, W.N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345.

27 For some nice examples see: a) Demer, J.M.; Hart, D.J.; Ramesh, S. *J. Org. Chem.* **1988**, *53*, 6022. b) Yoda, H.; Kitayama, H.; Yamada, W.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1451. c) Miller, S.A.; Chamberlin, A.R. *J. Org. Chem.* **1989**, *54*, 2502.

28 For a review see: Speckamp, W.N.; Hiemstra, H. *Tetrahedron* **1985**, *20*, 4367.

The idea of enantioselective halogenation is not new. *N*-bromocampheric imide and *N*-chlorocampheric imide were synthesized in optically pure form by Meyer. He performed some successful halogenation reactions with these compounds, but was not able to achieve any asymmetric induction.[29] The group of Duhamel has published the synthesis of several chiral brominating and chlorinating agents,[30] but no applications of these compounds have been described in the literature. The best results in this field have been obtained with the asymmetric fluorination of enolates with *N*-fluoro-2,10-(3,3-dichlorocamphorsulfone). The enantiomeric excesses obtained with this reagent vary from 10-75%.[31] There are several reasons why we wanted to use compounds of general structure **A** as chiral brominating reagent. First, the synthesis is straightforward and allows structural variations. Secondly, C_2-symmetrical chiral auxiliaries have proven to be successful in enantioselective synthesis,[32] and thirdly, at the time we started this research no succesfull enantioselective halogenation reactions had been reported in the literature. Chiral halo compounds are of great interest, since they are easily transformed into a variety of valuable derivatives, such as alcohols, thiols, amines, nitriles, etc. A disadvantage of compounds of general structure **A**, is that the chiral center is relatively far away from the bromine atom.

5.3.2 Synthesis of chiral C_2-symmetrical NBS derivatives

The general route to imides of general structure **A**, **536-541** is based upon the synthesis of (3*S*,4*S*)-3,4-diacetoxysuccinimide (**536**)[33] and is outlined in scheme 5.8. Although another method has been published[34], we found this method by far superior. Treatment of L-tartaric acid with an appropriate acid chloride affords the corresponding anhydrides **530-535** in high yield[35], after crystallization. Treatment of these anhydrides with gaseous ammonia in CH_2Cl_2, followed by ring closure of the salts obtained, affords in high yield (60-80%) the corresponding C_2-symmetrical succinimides **536-541** as crystalline compounds. The sequence is easily performed on 1 molar scale without difficulty. We prepared imides **540** and **541** in the hope that these might behave as chiral liquid crystals. The imide moiety might form a polar layer because of hydrogen bonding, and the two long aliphatic chains an apolar backbone as illustrated in figure 5.5. Although they are waxy solids , DSC experiments did not indicate liquid crystalline behaviour.

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[29] Meyer, E.W. *Ph. D. Thesis* **1982**, Groningen, chapter 2.

[30] a) Angibaud, P. *Ph. D. Thesis* **1991**, university of Rouen. b) Duhamel, L.; Angibaud, P.; Plé, G.; Desmurs, J.R. *Synth. Commun.* **1993**, *23*, 2423.

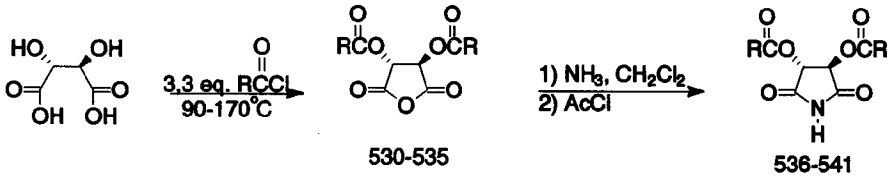
[31] Davis, F.A.; Zhou, P.; Murphy, C.K. *Tetrahedron Lett.* **1993**, *134*, 3971.

[32] a) Whitesell, J. *Chem. Rev.* **1989**, *89*, 581. b) see also chapters 3 and 4.

[33] Dener, J.M.; Hart, D.J.; Ranesh, S. *J. Org. Chem.* **1988**, *53*, 6022.

[34] Duhamel, L.; Herman, T.; Angibaud, P. *Synth. Commun.* **1992**, *22*, 735..

[35] a) Based upon: Shriner, R.L.; Furrow, R. *Org. Synth. Coll. Vol. IV* **1963**, 242. b) hydrolysis of these anhydrides affords the *O,O*-diacyltartaric acids, which are very useful resolving agents.



Scheme 5.8 Synthesis of chiral C $_2$-symmetrical succinimides derived from tartaric acid

config.		imide	overall yield(%)	$[\alpha]_{578}(CHCl_3)$	mp (°C)
(3*R*,4*R*)	**536**	R=CH_3	54	+ 113	144-146
(3*R*,4*R*)	**537**	R=tBu	62	+ 83	163-165
(3*R*,4*R*)	**538**	R=Ph	68	+ 196	92.5-93.5
(3*R*,4*R*)	**539**	R=$(CH_2)_2CH_3$	45	+ 137.7	61.8-63.9
(3*R*,4*R*)	**540**	R=$(CH_2)_8CH_3$	25	+ 80.5	43.6-44.4
(3*R*,4*R*)	**541**	R=$(CH_2)_{10}CH_3$	25	+ 108.8	55.2-56.8

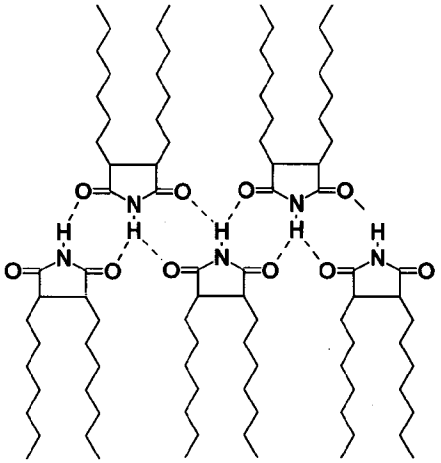
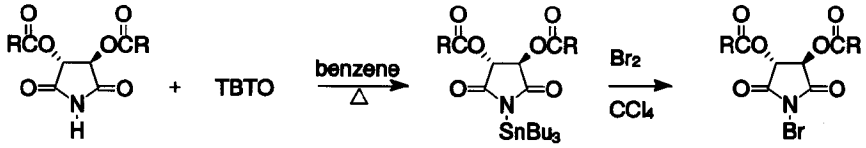


Figure 5.5. Possible orientation of compounds 540 and 541

Compounds **536-538** were converted to the corresponding *N*-bromo derivatives **542-544** by the procedure outlined in scheme 5.9. Reaction of the succinimides **536-538** with bis(tri-*n*-butyltin)oxyde (TBTO) afforded the corresponding stannyl derivatives. Treatment of these stannyl compounds with one equivalent of bromine in carbotetrachloride gave in high yield (80-95%) chiral *N*-bromosuccinimides **542-544**. They are obtained as solids which should be used immediatelly, due to low stability. The advantages of this



536 R = CH_3 542 95 %

537 R = Ph 543 90 %

538 R = t-Bu 544 80 %

Scheme 5.9 Synthesis of chiral C_2-symmetrical N-bromosuccinimides

method over other approaches, such as NaOH, Br_2, H_2O, t-butylhypobromite or acylhypobromite[36,37,38,39] is that it is very mild and no excess of bromine is needed. Furthermore, the method allows simple isolation, since the *N*-bromosuccinimides precipitate from the reaction mixture.

5.3.3 *Enantioselective bromination reactions with chiral C_2-symmetrical NBS derivatives 542-544*

With these chiral NBS derivatives in hand we decided to perform two reactions, allylic bromination of ethylbenzene[40] and the α-bromination of acid chlorides[41]. The first reaction is depicted in scheme 5.10. We chose ethylbenzene **545** because the product 1-phenylethylbromide **546** is known in optically pure form,[42] which makes the determination of optical purity easy. One equivalent of NBS derivative (**542-544**) and one equivalent of ethylbenzene were allowed to react in CCl_4 or CH_2Cl_2 at various temperatures without the addition of radical initiators. Although the reaction proceeded smoothly even at room temperature no asymmetric induction was observed. We also performed the allylic bromination of cyclohexene, but as in the case of ethylbenzene no asymmetric

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36 Beebe, T.R.; Wolfe, J.W. *J. Org. Chem.* **1970**, *35*, 2065.

37 Neale, R.S.; Marcus, N.L.; Schepers, R.G. *J. Am. Chem. Soc.* **1966**, *88*, 3051.

38 Olivetto, E.P.; Gerold, C. *Org. Synth.* **1951**, *31*, 177.

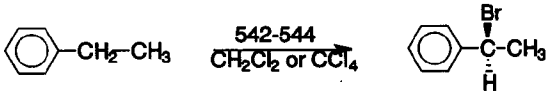
39 Ref. 30 b.

40 March, J. *Advanced Organic Chemistry*, 3rd, **1985**, 624, Wiley & Sons.

41 Harpp, D.N.; Bao, L.Q.; Black, C.J.; Geason, J.G.; Smith, R.A. *J. Org. Chem.* **1975**, *40*, 3420.

42 Hutchins, R.O.; Masilamani, D.; Maryanott, C.A. *J. Org. Chem.* **1976**, *41*, 1071.

induction was observed.



545 546

Scheme 5.10. Results of attempted asymmetric bromination of ethylbenzene

NBS derivative	Solvent	Temperature(°C)	Yield(%)	$[\alpha]_{578}$	$[\alpha]_{365}$
542	CCl_4	60	65	0.0	0.0
542	CH_2Cl_2	70	80	-	-
542	"	RT	85	-	-
542	"	-5	-	-	-
543	"	RT	85	-	-
544	"	RT	85	-	-

The mechanism of allylic bromination by NBS was established by Dauben and Mc Coy.[43] The reaction is initiated by small amounts of Br·. Once this is formed the main propagation steps are: Br· + RH --> R· + HBr and R· + Br_2 --> RBr + Br· Bromine (Br_2) is formed through an initiated ionic reaction between NBS and HBr liberated in the first step. NBS serves as a source of Br_2 and is itself not involved in the in the bromination step. Another mechanism, involving succinimidoyl radicals, was proposed by Skell[44]. The succinimidoyl radical, formed by radical initiators, reacts with the allyl compound forming succinimide and an allyl radical. This radical reacts with NBS to provide the allyl bromide and the succinimidoyl radical. In this mechanism NBS is used as the radical source. The (negative) results obtained in the enantioselective allylic bromination shows evidence for the mechanism proposed by McCoy. The reaction proceeds without adding radical initiators, during the transfer of bromine, the chiral succinimide plays no role, it is only used as a source of bromine, therefore no asymmetric induction is observed. In the mechanism proposed by Skell the chiral succinimide is the species which tranfers the bromine, therefore some induction would be expected. This experiment demonstrated us that if one wants to observe asymmetric induction in enantioselective bromination reactions, the reaction should proceed via an ionic pathway in which

[43] a) Dauben; Mc Coy *J. Am. Chem. Soc.* **1959**, *81*, 4863.

[44] a) Skell, P.S.; Day, J.C. *Acc. Chem. Res.* **1978**, *11*, 381. b) Skell, P.S. *J. Am. Chem. Soc.* **1984**, *106*, 1838.

the bromine is still attached to the chiral succinimide during the transfer of bromine to the substrate.

The α-bromination of acyl chlorides by NBS proceeds via an ionic pathway. Harpp *et al.*[41] suggest two possible mechanisms for this reaction as indicated in figure 5.6. In mechanism **A** it is suggested that NBS acts as a base to remove the α-hydrogen to form an enol intermediate. The enolate is then brominated by this $NBSH^+$ species giving the α-bromoacyl chloride. In the other mechanism **B**, it is postulated that the intermediate in the bromination of acid chlorides is a cationic complex in which the C_α-H bond of the conjugate acid is highly ionized, yet the proton is still associated with the α-carbon (see 2). In this proposal the rate-determining step would be that of an unusual electrophilic displacement of a proton of complex 2 by NBS. Both mechanisms allow the transfer of bromine to proceed with asymmetric induction.

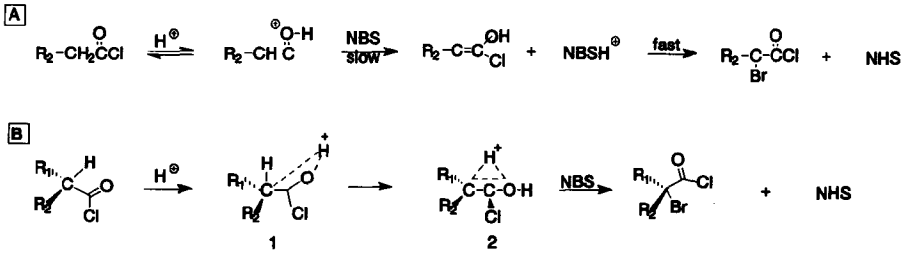


Figure 5.6. Possible mechanisms for bromination of acyl chlorides

Table 5.1. α-Bromination of acid chlorides.

Brominating agent	Acid	Yield*	$[\alpha]_{578}(CHCl_3)$
544	hexanoic	75	0.0
544	phenylacetic	69	0.0**
544	phenylpropanoic	74	0.0
543	phenylacetic	65	0.0
542	phenylacetic	63	0.0

* *Yield of α-bromoacyl halide after distillation*

** *To exclude racemisation during distillation, in one experiment we transformed the crude α-bromoacid chloride into the α-bromo amide and again no significant rotation was observed.*

We have performed this reaction with three substrates, hexanoic acid, phenylacetic acid and phenylpropanoic acid. The acid chlorides were prepared in situ by adding $SOCl_2$ to a mixture of the acid in CH_2Cl_2. After complete conversion (checked by ^{1}H-NMR, the chiral NBS derivative **542-544** together with a catalytic amount of HBr (48%) was added

and the mixture was refluxed overnight. The crude product was purified by distillation and the optical rotation was determined. The results are summarized in table 5.1.
These results are disappointing. Although the reaction proceeds smoothly, again no asymmetric induction was observed. The most likely explanation is that the reaction proceeds via mechanism *A*, the rate determining step being the formation of the enolate. The enolate is then brominated in a fast reaction by $NBSH^+$ in which no chirality is transferred. The results obtained by us and the fact that Duhamel published only the synthesis and no applications of chiral brominating and chlorinating reagents, indicate that enantioselective halogenations show very little potential in stereoselective synthesis.

5.4 Conclusions

In the first part of this chapter a start was made with the remote functionalisation of unsaturated fatty acids. The goal in this research was to design carrier molecules which would allow the regioselective introduction of a bromine atom in an unsaturated fatty acid. Although several carrier molecules were synthesized and coupled to unsaturated fatty acids (oleic acid and linoleic acid), the goal was not achieved because of external reasons (interruption by military service forced us to stop the contract with the sponsor, Unilever).

The second part of this chapter deals with the synthesis and use of chiral C_2-symmetrical *N*-bromosuccinimides derived from tartaric acid and their use in enantioselective brominations. A method is described which allows the synthesis of the chiral NBS derivatives. The NBS derivatives can be used in bromination reactions, however, no transfer of chirality was observed.

5.5 Experimental section

For general remarks, see chapter 2.

N-Benzyloxocarbonyl-L-asparagine (506)
A solution of L-asparagine (120 g, 0,9 mol) in 4 M NaOH (200 ml) and 1 M $NaHCO_3$ (400 ml) was cooled to 0°C. To this stirred solution was added simultaneously benzylchloroformate (200 g) in dioxane (250 ml) and 4 M NaOH (240 ml) while the temperature was maintained below 3°C. The reaction mixture was stirred for an additional 2 hours and the water layer was extracted with CH_2Cl_2 and subsequently acified with conc. HCl. The solid was collected, washed with cold water and dried, to yield **506** (242 g, 95%) as a white solid: mp 163-164°C (lit.[7] 163°C); $[\alpha]_D$= + 7,5° (AcOH) (lit.[7] $[\alpha]_D$= + 7,6°); ^{1}H-NMR(D_2O): δ 2.65 (d,2H), 4.45 (t,H), 5.15 (s,2H), 7.3 (s,5H).

N-Benzyloxocarbonyl-L-asparagine methylester (507)
A stirred suspension of **506** (100 g, 0,36 mol) in dry MeOH (1l.) was cooled to -60°C. Acetylchloride (140 ml) was added dropwise while maintaining the temperature below -50°C. The mixture was stirred for two days at -20°C and neutralized with a saturated $NaHCO_3$-solution. The precipitate was filtered off, washed with cold water and ether, to yield (96,8 g, 92%) **207** as a white solid: mp 155-156,5 (lit.[7] 153-153,5°C); $[\alpha]_D$= - 2,9°C (AcOH); ^{1}H-NMR(DMSO-d6): δ 2.5 (m,2H), 3.65 (s,3H); 4.49 (t,1H), 5.15 (s,2H), 7.3 (s, 5H).

(3*S*)-Benzyloxocarbonylamino-2,5-pyrrolidinedione (508)
To a suspension of **507** (92 g, 0,34 mol) in 500 ml of water was added 0,5 M NaOH (310 ml). The mixture was stirred for 30 minutes, filtered and acified with conc. HCl. After cooling for 30 minutes, the precipitate was collected and washed with ice water and dried, to yield (52 g, 74 %) **508** of a white solid: mp 80-81 (lit. 80-81°C); $[\alpha]_{578}$= -44° ($CHCl_3$) (lit.[7] $[\alpha]_D$= - 43°); ^{1}H-NMR: δ 2.6-3.05 (m,2H), 4.35 (dd,1H), 5.05 (s,2H), 6.12 (d,N-H), 7.3 (s,5H), 9.45 (b,NH); ^{13}C-NMR: δ 36.4 (CH_2), 51.0 (CH), 67.3 (CH_2), 128 (CH), 128.2 (CH), 128.4 (CH), 135.5 (C), 156.06 (C=O), 172.3 (C=O), 177 (C=O).

(3*S*)-3-Amino-2,5-pyrrolidinedione (501)
The protected imide **508** (20 g, 80 mmol) in 300 ml of MeOH containing 10% Pd/C (6 g) was hydrogenated in a Parr-apparatus for 3 hours. The resulting mixture was filtered and evaporated to give **501** as white solid, which was recrystallized from water/MeOH (5/95) to give **501** (8 g, 87%): mp 143°C (decomposition) (lit.[7] 144°C); $[\alpha]_D$= - 75° (MeOH); ^{1}H-NMR(D_2O): δ 2.3-2.4 (dd,1H), 2.8-3.0 (dd,1H), 3.8-3.9 (dd,1H); ^{13}C-NMR(D_2O): δ 37.08 (CH_2), 50.3 (CH), 179.7 (C=O), 182.79 (C=O).

(3*S*,6*S*)-3,6-Bis(carbanoylmethyl)-piperazine-2,5-dione (509)
When **508** was stirred in MeOH for several days (during the hydrogenation), **509** was obtained quantitively. All spectroscopical data were identical with literature[7] data.

3-Phenyl-2,5-pyrrolidinedione (511)
A mixture of 2-phenylbutanedioic acid (116 g, 0,60 mol) and urea (72 g, 1,80 mol) was heated until the temperature had reached 180°C. After 10 minutes at 180°C the solution was added to 2% $NaHCO_3$ (1500 ml) and the precipitate was extracted with CH_2Cl_2 (800 ml). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was crystallized from ether to afford **511** as a white solid (66 g, 63%): mp 89-90°C (lit.[9] 90-91°C); ^{1}H-NMR: δ 2.8 (dd,1H), 3.2 (dd,1H), 4.1 (dd,1H), 7.3 (m,5H), 9.05 (br,1H); ^{13}C-NMR: δ 38.22 (CH^2), 47.29 (CH), 127.41 (CH), 128.05 (CH), 129.22 (CH), 136.5 (C), 176.4 (C=O), 178.1 (C=O).

3-(4-Nitrophenyl)-2,5-pyrrolidinedione (512)
A solution of fuming nitric acid (100%) (210 ml) was cooled to -30°C and imide **511** (50 g, 10 mmol) was added portionwise over 30 minutes. The clear solution was stirred for another 30 minutes at -30°C and poured on ice-water (2 ltr). The precipitate was extracted with $CHCl_3$ (350 ml) and the organic layer was dried (Na_2SO_4) and evaporated. The crude product was recrystallized slowly with stirring from EtOH (96%). The solid was collected to obtain (25 g, 60%) **512** as a white solid: mp 149-151°C (lit.[9] 148-150°C); ^{1}H-NMR (DMSO-d6): δ 2.86 (dd,1H), 3.20 (dd,1H), 4.38 (dd,1H), 7.63 (d,2H), 8.19 (d,2H), 11.46 (br,1H); ^{13}C-NMR (DMSO-d6): δ 37.69 (CH_2), 46.93 (CH), 123.88 (CH), 129.68 (CH), 145.76 (C), 145.89 (C), 177.53 (C=O), 178.75 (C=O).

3-(4-Aminophenyl)-2,5-pyrrolidinedione (502)
A mixture of imide **512** (20 g, 90 mmol) Pd/C (10%) (2 g) and EtOAc (350 ml) was hydrogenated for 4 hours. The mixture was filtered, washed with EtOAc (100 ml) and evaporated to provide **502** (15 g, 89%) as a yellow solid: mp 171-173°C (lit.[9] 171,5-173,5°C); ^{1}H-NMR (DMSO-d6): δ 2.56 (dd,1H), 3.03 (dd,1H), 3.84 (dd,1H), 5.0 (br,2H), 6.47 (d,2H), 6.83 (d,2H), 11.12 (br,1H); ^{13}C-NMR (DMSO-d6): δ 38.42 (CH_2), 45.48 (CH), 114.2 (CH), 125.19 (C), 128.43 (CH), 147.99 (C), 178.27 (C=O), 180.37 (C=O).

2-(Phenylmethyl)butanedioic acid (513)
Sodium (38.3 g, 1,66 mol) was added to abs. EtOH (500 ml), the mixture was cooled to 10°C and ethyl acetoacetate (425 ml, 2 mol) was added dropwise, followed by benzyl chloride (192 ml, 1,66 mol) allowing the temperature to rise to 25-30°C. The mixture was refluxed until pH 7 was reached. Water was added and the product was extracted with toluene. The organic layer was dried (Na_2SO_4) and evaporated. The crude product was distilled (136-138°C/2 mm Hg) and benzyl ethyl acetoacetate was obtained as a colourless oil. Yield 347 g (90%). A solution of NaOEt was prepared by adding Na (28 g, 1,21 mol) to abs. EtOH (450 ml). The solution was cooled to RT and benzyl ethyl acetoacetate (250 g, 1,13 mol) was added dropwise followed by ethyl chloroacetate (140 g, 1,13 mol) and the mixture was refluxed to neutral pH. Water was added and the product extracted with toluene. The organic layer was dried (Na_2SO_4) and evaporated. The crude product was added to NaOH (80 g, 2 ml) in H_2O (1 ltr) and refluxed for 5 hours. The water layer was extracted with toluene and acified with conc. HCl. The aqeous layer was cooled, the precipitate collected washed with water and dried. 2-

(Phenylmethyl)butanedioic acid **513** was obtained as a slightly yellow solid. Yield (140 g, 63%); mp 159-161°C (lit.[11] 160°C); ^{1}H-NMR: δ 2.65 (t,2H), 2.7-2.9 (m,1H), 2.95 (t,2H), 7.15-7.4 (m,5H), 8.0-9.2 (br,2H); ^{13}C-NMR: δ 30.44 (CH_2), 35.49 (CH_2), 44.4 (CH), 126.19 (CH), 128.09 (CH), 128.39 (CH), 139.96 (C), 178.93 (C=O).

3-(Phenylmethyl)-2,5-pyrrolidinedione (513a) was prepared in the same way as described for **511**. Starting with acid **513** (100 g, 0,48 mol), imide **513a** was obtained as a white solid in 60% yield after crystallization from EtOH. mp 97-98°C (lit. Bryant, B.R.; Hauser, C.R. *J. Am. Chem. Soc.* **1961**, *83*, 3468; 97.5-98°C); ^{1}H-NMR: δ 2.4-3.35 (m,5H), 7.1-7.4 (m,5H), 9.4 (br,1H); ^{13}C-NMR: δ 34.33 (CH_2), 36.12 (CH_2), 42.6 (CH), 126.91 (CH), 128.15 (CH), 128.39 (CH), 136.94 (C), 176.86 (C=O), 179.83 (C=O).

3-(4-Nitrophenylmethyl)-2,5-pyrrolidinedione (513b) was prepared in the same way as described for **512**. Starting with imide **513a** (30 g, 0,2 mol), imide **513b** was obtained as a white solid in 60% yield after crystallization from EtOH. mp 168-169,5°C; ^{1}H-NMR(DMSO-d6): δ 2.3 (dd,1H), 2.6 (dd,1H), 2.9 (t,1H), 3.2 (m,2H), 7.4 (d,2H), 8.2 (d,2H) ; ^{13}C-NMR(DMSO-d6): δ 34.48 (CH_2), 35.10 (CH_2), 41.57 (CH), 123.35 (CH), 130.11 (CH), 146.17 (C), 146.98 (C), 177.57 (C=O), 180.32 (C=O); HRMS calculated for $C_{11}H_{10}N_2O_4$: 234.064 Found: 234.064; Anal. Calcd. C 56.41 H 4.30 N 11.96 Found: C 56.22 H 4.35 N 11.98.

3-(4-Aminophenylmethyl)-2,5-pyrrolidinedione (503) was prepared in the same manner as described for **502**. Starting with the imide **513b** (10 g, 42,5 mmol), imide **503** was obtained in 70% yield as a white solid. mp 144,5-145,1°C; ^{1}H-NMR: δ 2.48 (dd,1H), 2.70 (dd,1H), 2.83 (dd,1H), 3.04 (dd,1H), 3.12 (m,1H), 3.4-3.8 (br,2H), 6.6 (d,2H), 6.9 (d,2H), 8.2-8.5 (br,1H); ^{13}C-NMR: δ 34.1 (CH_2), 35.22 (CH_2), 42.8 (CH), 115.33 (CH), 126.36 (C), 129.78 (CH), 145.13 (C), 179 (C=O), 181.16 (C=O); HRMS calculated for $C_{11}H_{12}N_2O_2$: 204.090 Found: 204.090; Anal. Calc. C 64.69, H 5.92, N 13.72 Found: C 64.58 H 5.94 N 13.65.

(cis)-1-Phenyl-1,2-cyclopropanedicarboxylic acid (514)
To a suspension of NaH (50%, 24 g 0,5 mol) in ether (1200 ml) under a nitrogen stream was added 1 ml of EtOH. The mixture was cooled to 15°C and a mixture of α-bromoethyl phenylacetate, (12 g, 0,5 mol prepared by bromination of ethyl phenylacetate with NBS in tetra) ethylacrylate (100 ml, 1 mol) and EtOH (10 ml) was added dropwise over a 2 hour period. (The reaction is slightly exothermic.) The resulting mixture was stirred for 24 hours and H_2O was added. The organic layer was dried (Na_2SO_4) and evaporated. The crude product was distilled (155°C/0,9 mm Hg) and 1-phenyl-1,2-cyclopropanedicarboxylic acid diethyl ester was obtained as a colourless oil. The diester was treated with KOH (64 g) in EtOH (500 ml) and H_2O (200 ml) of reflux for 5 hours, while the EtOH was slowly distilled off. The remaining water layer was washed with toluene (200 ml) and acified with conc. HCl. The solid was filtered off, washed with water and dried to afford diacid **514** as white solid (80 g, 78%). mp 153-154°C (lit.[12b] 153-154 °C); ^{1}H-NMR (DMSO-d6): δ 1.46 (q,1H), 1.80 (q,1H), 2.17 (q,1H), 7.38 (m,5H).

1-Phenyl-1,2-cyclopropanedicarboximide (514a) was prepared in the same way as described for **511**. Starting with diacid **514** (79,3 g, 0,34 mol), imide **514a** was obtained in 60% yield as a slightly pink solid after crystallization from MeOH. mp 135-136°C (lit.[10] 137-138°C); ^{1}H-NMR: δ 1.87 (dd,1H), 1.99 (dd,1H), 2.71 (ddd,1H), 7.38 (m,5H), 8.19 (br,1H); ^{13}C-NMR: δ 24.74 (CH_2), 25.30 (CH), 34.22 (C), 125.91 (CH), 126.26 (CH), 126.42 (CH), 128.98 (C), 172.25 (C=O), 173.10 (C=O).

1-(4-Nitrophenyl)-1,2-cyclopropanedicarboximide (514b) was prepared in the same way as described for **512**. Starting with imide **514a**, imide **514b** was obtained in 60% yield after crystallization from EtOAc. mp 172-174°C (lit.[10] 174-175°C).

1-(4-Aminophenyl)-1,2-cyclopropanedicarboximide (504) was prepared in the same way as described for **502**. Starting with imide **514[b]**, imide **502** was obtained in 65% yield, after crystallization from EtOH. mp 174-175°C (lit.[10] 174-175°C); ^{1}H-NMR(DMSO-d6): δ 1.5 (t,1H), 1.22 (t,1H), 1.9 (ddd,1H), 3.8 (br,2H), 6.6 (d,2H), 7.05 (d,2H), 10.2 (br,1H). ;

General procedure for the formation of amides 515-519.
The reactions were performed on a 20 mmol scale. The appropriate amino imide (1 eq.)(**502-504**) was dissolved in THF (100 ml) and the unsaturated fatty acid (1 eq.) was added followed by dicyclohexylcarbodiimide (DCC)(1 eq.). The mixture was stirred overnight and filtered to remove DHU. After evaporation the crude products were dissolved in CH_2Cl_2 and washed with 10% HCl and H_2O. After the organic layer was dried (Na_2SO_4) and evaporated. The crude products were recrystallized from EtOH (two or three times) to afford **515-519** as solids.

***N*-Oleoyl-3-(-4-aminophenyl)-2,5-pyrrolidinedione (515)** was obtained as a white solid. Yield 20%; mp 148,6-149.3°C ; ^{1}H-NMR: δ 0.8 (t,3H), 1.2 (m,21H), 1.65 (m,4H), 1.9 (m,4H), 2.35 (t,2H), 2.8 (dd,1H), 3.2 (dd,1H), 4.1 (dd,1H), 5.3 (m,2H), 7.15 (d,2H), 7.4 (s,1H), 7.45 (d,2H), 8.7 (br,1H); ^{13}C-NMR: δ ; HRMS calculated for $C_{28}H_{42}N_2O_3$: 454.304 Found: 454.304; Anal. Calcd. for C 73.96 H 9.32 N 6.16 Found: C 73.09 H 9.47 N 6.20.

***N*-Lineloyl-3-(4-aminophenyl)-2,5-pyrrolidinedione (516)** was obtained as a slightly yellow solid. Yield 18%; mp 119-122°C; $_1$H-NMR: δ 0.8 (t,3H), 1.2 (m,14H), 1.65 (m,2H), 2.0 (m,4H), 2.25 (t,2H), 2.7 (m,2H), 2.75 (dd,1H), 3.2 (dd,1H), 4.05 (dd,1H), 5.3 (m,4H), 7.15 (d,2H), 7.4 (br,1H), 7.5 (d,2H), 8.6 (br,1H); ^{13}C-NMR: δ ; HRMS calculated for $C_{28}H_{40}N_2O_3$: 452.304 Found: Is currently under investigation

***N*-Oleoyl-3-(4-aminophenylmethyl)-2,5-pyrrolidinedione (517)** was obtained as a yellow solid. Yield 20%; mp 70-75°C; ^{1}H-NMR: δ 0.8 (t,3H), 1.22 (m,21H), 1.65 (m,4H), 1.95 (m,4H), 2.3 (t,2H), 2.4 (dd,1H), 2.6 (dd,1H), 2.85 (dd,1H), 3.05 (m,2H), 5.35 (m,2H), 7.05 (d,2H), 7.45 (d,2H), 7.7 (br,1H), 9.0 (br, 1H); ^{13}C-NMR (only significant resonances are listed): δ 13.08 (CH_3), 41.61 (CH), 119.24 (CH), 119.32 (CH), 128.53 (CH), 128.98 (CH), 131.52 (C), 136.12 (C), 170.78 (C=O), 175.92 (C=O), 178.98 (C=O).

***N*-Lineoyl-3-(4-aminophenylmethyl)-2,5-pyrrolidinedione (518)** was obtained as a yellow solid. Yield 16%; mp 95-100°C; ^{1}H-NMR: δ 0.8 (t,3H), 1.2 (m,14H), 1.4-2.0 (m,8H), 2.25 (m,3H), 2.6 (m,1H), 2.85 (m,1H), 3.05 (m,2H), 5.35 (m,4H), 7.1 (d,2H), 7.45 (d,2H), 7.7 (br,1H), 8.8 (br,1H).

***N*-Oleoyl-1-(4-aminophenyl)-1,2-cyclopropanedicarboxamide (519)** was obtained as a slightly brown solid. Yield 25%; mp 149-152,5°C; ^{1}H-NMR: δ 0.8 (t,3H), 1.2 (m,21H), 1.4 (m,2H), 1.8 (dd,1H), 2.0 (m,3H), 2.3 (t,2H), 2.7 (dd,1H), 5.3 (m,2H), 7.3 (d,2H), 7.35 (s,1H), 7.5 (d,2H), 7.7 (br,1H);$_{13}$C-NMR (only significant resonances are listed): δ 14.06 (CH_3), 27.91 (CH), 120.08 (CH), 126.95 (C), 129.63 (CH), 129.99 (CH), 138.24 (C), 171.77 (C=O), 174.60 (C=O), 175.60 (C=O); HRMS calculated for $C_{29}H_{42}N_2O_3$: 466.319 Found: 466.319.

Remote bromination of amide 515

A mixture of amide **515** (2,26 g, 50 mmol) and bis(tri-n-butyltin)oxyde (1.5 g, 25mmol) in benzene (100ml) was refluxed with azeotropic removal of the water formed. After 3 hours, the reaction mixture was cooled and the solvent removed in vacuo. The residu was dissolved in CH_2Cl_2 (100 ml) and cooled to -20°C. To the clear solution was added a solution of bromine (50 mmol) in CH_2Cl_2. After the addition, the temperature was allowed to rise to RT and subsequent raised to reflux temperature. After one night the solvent was removed and ^{1}H-NMR clearly indicated that allylic bromination had taken place.

General procedure for the formation of (3*R*,4*R*)-3,4-diacyldihydro-2,5-furandiones (530-535)

A suspension of L-tartaric acid (75 g, 0,5 mol) and the appropriate acid chloride (3,3 equivalents) was heated at an ambient temperature (40-170°C) until a clear solution was obtained (2-30 hours). The reaction mixture was cooled, the crystals collected and recrystallized to afford anhydrides **530-535** as white solids.

(3*R*,4*R*)-3,4-Diacetyloxodihydro-2,5-furandione (530)

Recrystallization from CH_2Cl_2, afforded 130 g (92%) of **530**. mp 134.6-136.1°C (lit. [35] 133-134°C); $[\alpha]_D$= + 94.08 ($CHCl_3$) (lit. $[\alpha]_D$= 97.2); ^{1}H-NMR: δ 2.18 (s,6H), 5.62 (s,2H); ^{13}C-NMR: δ 19.7 (CH_3), 71.9 (CH), 163.2 (C=O), 169.5 (C=O).

(3*R*,4*R*)-3,4-Dipivaloyloxodihydro-2,5-furandione (531)

Recrystallization from CH_2Cl_2/hexane, afforded 119 g (80%) of **531**. ^{1}H-NMR: δ 1.25 (s,18H), 5.6 (S,2H); ^{13}C-NMR: δ 26.64 (CH_3), 72.18 (CH), 163.46 (C=O), 170.61 (C=O).

(3*R*,4*R*)-3,4-Dibenzoyloxodihydro-2,5-furandione (532)

Recrystallization from toluene, afforded 158 g (93%) of **532**. mp 192-193°C; ^{1}H-NMR: δ 6.1 (s,2H), 7.5 (t,4H), 7.6 (t,2H), 8.1 (d,4H); ^{13}C-NMR: δ 72.79 (CH), 127.04 (C), 128.69 (CH), 130.23 (CH), 134.53 (CH), 163.33 (C=O), 165.32 (C=O).

(3*R*,4*R*)-3,4-Dipropanoyloxodihydro-2,5-furandione (533)
Recrystallization from CH_2Cl_2/pentane, afforded 98 g (82%) of **533**. mp 60-61.7°C; ^{1}H-NMR: δ 0.95 (t,6H), 1.65 (m,4H), 2.4 (t,4H), 5.65 (s,2H); ^{13}C-NMR: δ 13.22 (CH_3), 17.93 (CH_2), 34.95 (CH_2), 71.88 (CH), 163.46 (C=O), 172.39 (C=O).

(3*R*,4*R*)-3,4-Didecanoyloxodihydro-2,5-furandione (534)
Recrystallization from ether/hexane (twice) afforded 110 g (50%) of **534**, still containing some decanoic acid (ca. 10%). This material was used as such in the next step. ^{1}H-NMR: δ 0.88 (t,6H), 1.2 (m,24H), 1.6 (m,4H), 2.4 (t,4H), 5.6 (s,2H).

(3*R*,4*R*)-3,4-Dilauroyloxodihydro-2,5-furandione (535)
Recrystallization from ether (twice) afforded 125 g (51%) of **535**, still containing some lauric acid (ca.10%). This material was used as such in the next step. ^{1}H-NMR: δ 0.88 (t,6H), 1.15 (m,32H), 1.6 (m,4H), 2.4 (t,4H), 5.6 (s,2H).

General procedure for the formation of (3*R*,4*R*)-3,4-dicarboxyloxo-2,5-pyrrolidinediones 536-541.
Ammonia (gaseous) was bubbled through a solution of the appropriate anhydride (**230-235**) (0,5 mol) in CH_2Cl_2 (500 ml) for 30 minutes. The CH_2Cl_2 was evaporated to afford a white solid. To this solid was added AcCl (500 ml) and the mixture was refluxed for 16 hours. Excess AcCl was removed and EtOAc (400 ml) added. The mixture was filtered over Celite and the filtrates concentrated to dryness. The crude products were purified via crystallization, to afford the pyrrolidinediones **536-541** as white solids.

(3*R*,4*R*)-3,4-Diacetyloxy-2,5-pyrrolidinedione (536)
Recrystallization from CH_2Cl_2/hexane afforded 65 g (60 %, reaction performed on 0,5 mol scale). mp 144-146 °C (lit.[33] 146-147°C); $[\alpha]_D$= + 104,82 ($CHCl_3$); ^{1}H-NMR δ 2,2 (s,6H), 5,5 (s,2H), 9,3 (br,1H); ^{13}C-NMR δ 20.2 (CH_3), 73.1 (CH), 169.2 (C=O), 169.9 (C=O).

(3*R*,4*R*)-3,4-Dipivaloyloxy-2,5-pyrrolidinedione (537)
Recrystallization from CH_2Cl_2/hexane, afforded 30 g (75%, reaction performed on 0,13 mol scale). mp 163-165°C (lit.[34] 166°C); $[\alpha]_{578}$= + 83^0 ($CHCl_3$) (lit.[34] $[\alpha]_D$= +83 ($CHCl_3$); ^{1}H-NMR: δ 1.2 (s,18H), 5.5 (s,2H), 8.6 (br,1H); ^{13}C-NMR: δ 26.94 (CH_3), 38.70 (C), 73.28 (CH), 168.87 (C=O), 178 (C=O).

(3*R*,4*R*)-3,4-Dibenzoyloxy-2,5-pyrrolidinedione (538)
Recrystallization from $CHCl_3$/hexane, afforded 24 g (70%), reaction performed on 0,1 mol scale). mp 92,5-93,5°C; $[\alpha]_D$= + 196,7 ($CHCl_3$); ^{1}H-NMR: δ 5.9 (s,2H), 7.4 (m,4H), 7.6 (m,2H), 8.0 (m,4H), 9.3 (br,1H); ^{13}C-NMR: δ 73.88 (CH), 127.93 (C), 128.42 (CH), 130.04 (CH), 133.86 (CH), 165.41 (C=O), 169.08 (C=O). HRMS calculated for $C_{18}H_{13}NO_6$: 339.075 Found: Could not be determined due to elimination of the benzoyl group; Anal. Calcd for $C_{18}H_{13}NO_6.H_2O$: C 60.51 H 4.23 N 3.92 Found: C 60.51 H 4.23 N 3.84.

(3*R*,4*R*)-3,4-Dipropanoyloxy-2,5-pyrrolidinedione (539)
Recrystallization from ether/pentane afforded 18 g (66%, reaction performed on 0,1 mol scale). mp 61,8-63,9°C ; $[\alpha]_{578}$= +137,7 (CH_2Cl_2) ; ^{1}H-NMR: δ 0.95 (t,6H), 1.6 (m,4H), 2.4 (t,4H), 5.65 (s,2H), 9.25 (br,1H); ^{13}C-NMR: δ 13.25 (CH_3), 17.96 (CH_2), 35.18 (CH_2), 169.38 (C=O), 172.55 (C=O).

(3*R*,4*R*)-3,4-Didecanoyloxy-2,5-pyrrolidinedione (540)
Recrystallization from ether/hexane (two times) afforded 26 g (49%, reaction performed on 0.1 mol). mp 43,6-44,4°C; $[\alpha]_{578}$= +80,5 (CH_2Cl_2); ^{1}H-NMR: δ 0.8 (t,6H), 1.3 (s,24H), 1.7 (m,4H), 2.5 (t,4H), 5.6 (s,2H), 9.0 (br,1H); ^{13}C-NMR: δ 14.0 (CH_3), 22.63, 24.56, 28.89, 29.20, 29.33, 31.82, 33.52 (all CH_2), 73.18 (CH), 169.09 (C=O), 172.76 (C=O); HRMS calculated for $C_{24}H_{41}NO_6$: 439.293 Found: Is currently under investigation

(3*R*,4*R*)-3,4-Dilauroyloxo-2,5-pyrrolidinedione (541)
Recrystallization from hexane (three times) afforded 25 g (51%, reaction performed on 0.1 mol scale). mp 55,2-56,8°C ; $[\alpha]_{578}$= +108.8 (CH_2Cl_2); ^{1}H-NMR: δ 0.85 (t,6H), 1.3 (s,32H), 1.6 (m,4H), 2.45 (t,4H), 5.55 (s,2H), 9.1 (br,1H); ^{13}C-NMR: δ 13.95 (CH_3), 22.54, 24.45, 28.79, 29.06, 29.20, 29.29, 29.46, 31.77, 33.41 (all CH_2), 73.09 (CH), 169.34 (C=O), 172.70 (C=O); Anal. Cald. for: C 67.83 H 9.97 N 2.83 Found: C 66.49 H 9.78 N 2.77.

General procedure for the formation of chiral *N*-bromosuccinimides 542-544
To a suspension of imides (**536-538**) (50 mmol) in benzene (300 ml) was added bis(tri-n-butyltin)oxide (TBTO) (25 mmol) and the mixture was refluxed for 3 hours with azeotropic removal of the water formed. The clear solution was evaporated and the resulting oil was dissolved in tetra (200 ml). The solution was cooled to 0°C and Br_2 (50 mmol) was added over a 30 minutes period, during which time the *N*-bromosuccinimides **242-244** precipitated from the reaction mixture. After stirring for an additional 15 minutes, the solid was collected and washed with tetra (50 ml) and pentane (200 ml). The products (**542-544**) can be used without further purification. Compounds **542-544** are unstable and should be prepared immediately before use.

(3*R*,4*R*)-3,4-Diacetyloxy-*N*-bromo-2,5-pyrrolidinedione (542)
Yield 95%, white solid.; ^{1}H-NMR: δ 2,2 (s,6H), 5,5 (s,2H).

(3*R*,4*R*)-3,4-Dibenzoyloxy-*N*-bromo-2,5-pyrrolidinedione (543)
Yield 90%, slightly yellow solid.; ^{1}H-NMR: δ 5,9 (s,2H), 7,5 (m,6H), 8,0 (m,4H);

(3*R*,4*R*)-3,4-Dipivaloyloxy-*N*-bromo-2,5-pyrrolidinedione (544)
Yield 80%, white solid.; ^{1}H-NMR: δ 1.25 (s,18H), 5.6 (s,2H)

Bromination of ethylbenzene with chiral *N*-bromosuccinimides 542-544.
A solution of ethylbenzene (2 g, 19 mmol) and the imide (**542-544**) (19 mmol) in CH_2Cl_2 (80 ml) was stirred for 4 hours. The mixture was concentrated and pentane (100 ml) was

added. The imide was filtered off and the organic layer evaporated. The yellow oil was distilled bulb-to-bulb to give α-methylbenzyl bromide as a colourless oil. $[\alpha]_D = 0$; $[\alpha]_{365} = 0$ (CH_2Cl_2); ^{1}H-NMR: δ 2,0 (d,3H), 5,1 (q,1H), 7,33 (m,5H).

Bromination of acid chlorides with chiral *N*-bromosuccinimides 542-544
A solution of the appropriate acid (13.3 mmol) and $SOCl_2$ (53 mmol) in CH_2Cl_2 (10 ml) is refluxed for 1 hour. The mixture is cooled to RT and a solution of imide (**242-244**) in CH_2Cl_2 (50 ml) is added, followed by two drops of HBr (48%). The resulting red solution is refluxed for until the red colour is dissappeared (appr. 5h) and the mixture is evaporated. n-Pentane is added and the imide is filtered off. The organic layer is concentrated to dryness and the crude α-bromo acid chloride purified via bulb-to-bulb distillation.

α-Bromophenylacetoyl chloride
$[\alpha]_{578} = 0$ (CH_2Cl_2); $[\alpha]_{365} = 0$ (CH_2Cl_2); Spectroscopic data were identical to those reported in the literature[41].

α-Bromohexanoyl chloride
$[\alpha]_{578} = 0$ (CH_2Cl_2); $[\alpha]_{365} = 0$ (CH_2Cl_2); Spectroscopic data were identical to those reported in the literature[41].

α-Bromophenylpropanoyl chloride
$[\alpha]_{578} = 0$ (CH_2Cl_2); $[\alpha]_{365} = 0$ (CH_2Cl_2); Spectroscopic data were identical to those reported in the literature[41].

Samenvatting

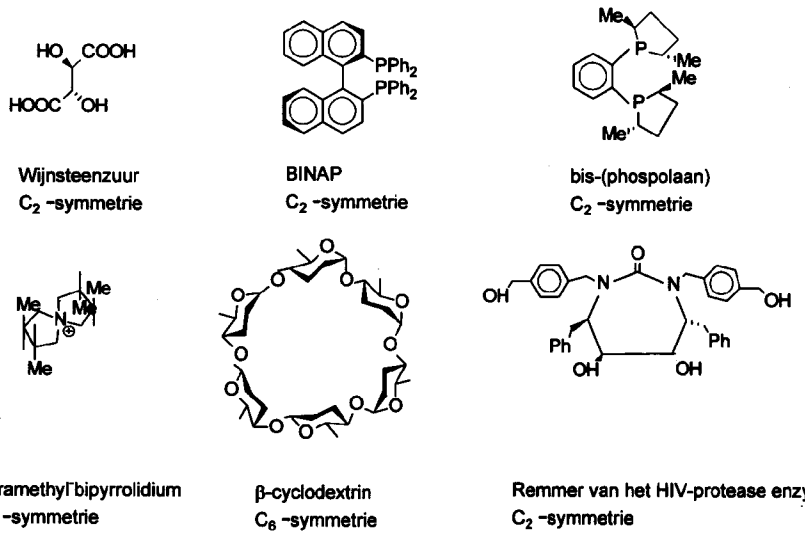
In dit proefschrift wordt de synthese en het gebruik van chirale cyclische derivaten van C_2-symmetrische butaandicarbonzuren beschreven. In het eerste gedeelte van deze samenvatting zullen de begrippen chiraliteit en symmetrie nader toegelicht worden.

Wanneer een object niet tot dekking te brengen is met zijn spiegelbeeld noemen we zo'n object chiraal. De meest bekende chirale objecten in onze omgeving zijn onze handen. Ze lijken identiek maar als je bijvoorbeeld probeert je linkerhand in een rechter handschoen te stoppen merk je dat dat slecht gaat. De relatie tussen een linker- en een rechterhand is dat ze elkaars spiegelbeeld zijn. Het zelfde geldt voor chirale molekulen, ze lijken identiek maar zijn elkaars spiegelbeeld. Het "linker- en rechter" molekuul noemen we enantiomeren van elkaar en deze hebben in een chirale omgeving (bv. het menselijk lichaam) verschillende eigenschappen. Daarom is het erg belangrijk om bij het gebruik van geneesmiddelen, bestrijdingsmiddelen, voedingsstoffen en andere biologisch aktieve moleculen één enantiomeer te gebruiken, omdat het andere enantiomeer ongewenste bijwerkingen kan vertonen. Er zijn binnen de chemie vele onderzoeksgroepen die zich bezig houden met de synthese (het bereiden) van enantiomeer zuivere verbindingen. De tak van de chemie die zich hier mee bezig houdt wordt vaak aangeduid met asymmetrische chemie. We zullen zien dat deze aanduiding tot verwarring kan lijden en daarom zullen wij de term stereoselectieve chemie gebruiken.

Symmetrie is een esthetisch prettige eigenschap van objecten. Binnen de kunst, architectuur en natuur speelt symmetrie een belangrijke rol. Iedereen is altijd aangenaam verrast bij de aanblik van een symmetrisch object zoals bijvoorbeeld, een vlinder, een bloem, een sneeuw kristal of een tekening van Escher. Een object dat symmetrie elementen bevat, bezit een as van symmetrie van multipliciteit n, dat er voor zorgt dat het object verkregen na rotatie om zijn as door $360^0/n$, tot dekking te brengen is met het origineel. Ook binnen de chemie speelt symmetrie een grote rol. Benzeen (C_6H_6), misschien wel het bekendste molekuul te wereld, is zeer symmetrisch (C_6-symmetrie). Het dankt zijn chemische en fysische eigenschappen (het verschil in smeltpunt tussen benzeen en tolueen is 100^0) aan de hoge symmetrie. Ook de opheldering van de structuur van benzeen is gebeurd aan de hand van symmetrie overwegingen. Een tweede belangrijk voorbeeld is de C_2-symmetrische structuur van het HIV-protease enzym. De symmetrie van het enzym heeft vele onderzoeksgroepen er toe gebracht om C_2-symmetrische remmers te ontwerpen.

De aanduiding asymmetrische chemie wordt vaak gebruikt om aan te geven dat we te maken hebben met chirale moleculen. Deze aanduiding suggereert dat chirale moleculen geen symmetrie elementen kunnen bezitten. De aanwezigheid van een symmetrieas in een molekuul sluit chiraliteit echter niet uit. De ontdekking van chiraliteit door Pasteur vond plaats met een C_2-symmetrisch molekuul, namelijk wijnsteenzuur. In de vroege literatuur werd vaak de term dissymmetrie gebruikt in plaats van asymmetrie als er gesproken werd over chirale moleculen. Pasteur was zich goed bewust van het verschil tussen dissymmetrie en asymmetrie. Dit blijkt ondermeer uit de Franse titel van een lezing die hij gaf in 1860; "Recherches sur la dissymmétrie moléculaire des produits organiques naturels". In de engelse vertaling werd dit: "researches on the molecular asymmetrie of natural organic products". Het woord dissymmetrie werd asymmetrie en het misverstand is eigenlijk nooit hersteld.

Zoals al eerder gezegd kunnen chirale moleculen symmetrie-elementen bevatten. Het is zelfs zo dat symmetrische chirale verbindingen een hele belangrijke rol spelen in de stereoselectieve chemie, als splitsingsmiddel, als chirale hulpgroep in stereoselectieve syntheses, als liganden in katalytische stereoselectieve synthese en als bouwstenen in de supramoleculaire chemie en in natuurstofsyntheses. Een van de redenen waarom vooral C_2-symmetrische verbindingen veelvuldig gebruikt worden in de stereoselectieve chemie is dat de interacties tussen moleculen makkelijker te begrijpen is als er symmetrische moleculen bij betrokken zijn. De inbreng van symmetrie in een probleem lijdt vaak tot snelle oplossingen en is vaak ook toepasbaar op andere soortgelijke problemen. Hoe hoger de symmetrie van een systeem hoe minder verschillende interacties er mogelijk zijn. In figuur 1 staan een aantal symmetrische chirale moleculen weergegeven die een belangrijke rol spelen in de stereoselectieve chemie.



Wijnsteenzuur
C_2 -symmetrie

BINAP
C_2 -symmetrie

bis-(phospolaan)
C_2 -symmetrie

tetramethylbipyrrolidium
D_2 -symmetrie

β-cyclodextrin
C_6 -symmetrie

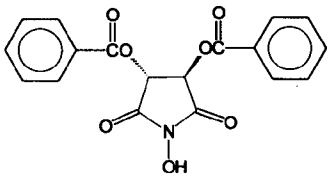
Remmer van het HIV-protease enzym
C_2 -symmetrie

Figuur 1 Symmetrische molekulen die gebruikt worden in de stereoselectieve chemie

Vooral het al eerder genoemde wijnsteenzuur (zie figuur 1) speelt een belangrijke rol in stereoselectieve chemie. Wijnsteenzuur wordt in grote hoeveelheden verkregen als afvalprodukt in de bereiding van wijn. Het is een van de goedkoopste en meest gebruikte chirale verbindingen in de chemie.

Twee observaties door ons gemaakt zijn belangrijk geweest voor het onderzoek beschreven in dit proefschrift. Ten eerste zijn er ondanks het veelvuldig gebruik van wijnsteenzuur (een C_2-symmetrische butaandicarbonzuur) relatief weinig andere C_2-symmetrische butaandicarbonzuren gebruikt in de stereoselectieve chemie. Ten tweede zijn er weinig cyclische derivaten van wijnsteenzuur toegepast in de stereoselectieve chemie. In dit proefschrift wordt de synthese en het gebruik van chirale cyclische derivaten van C_2-symmetrische butaandicarbonzuren beschreven.

Hoofdstuk 1 bevat een algemene inleiding over symmetrie, chiraliteit en het gebruik van wijnsteenzuur in de stereoselectieve chemie. In hoofdstuk 2 wordt de synthese beschreven van een tweetal chirale C_2-symmetrische *N*-hydroxysuccinimides (voorbeeld; zie figuur 2, verbinding **1**). Deze verbindingen zijn gebruikt als chirale derivatiserings reagentia, om de enantiomere overmaat van chirale carbonzuren te bepalen met behulp van ^{1}H-NMR spectroscopie. Reaktie van verbinding **1** met chirale carbonzuren gaf de overeenkomstige diastereomere esters. Op ^{1}H-NMR werden verschillende resonanties voor de twee diastereomere esters waargenomen. Door integratie van deze signalen is het mogelijk om de enantiomere overmaat van het chirale carbonzuur te bepalen. In hoofdstuk 3 wordt de synthese van een aantal chirale C_2-symmetrische 3,4-digesubstitueerde pyrrolidines beschreven (voorbeeld; zie figuur 3, verbinding **2**) uitgaande van de overeenkomstige butaandicarbonzuren. C_2-symmetrische pyrrolidines worden veelvuldig gebruikt in de stereoselectieve chemie, als chirale hulpgroep en bouwsteen voor liganden. Een aantal benaderingen worden besproken, die het mogelijk maken om deze 3,4-digesubstitueerde pyrrolidines (enantiomeer zuiver) op multi-gram schaal te synthetiseren. Tevens wordt er een methode beschreven om de enantiomere overmaat en absolute configuratie van deze amines te bepalen. Deze C_2-symmetrische pyrrolidines kunnen gebruikt worden als splitsingsmiddel, chirale hulpgroep en als bouwsteen in de synthese van liganden voor katalytische stereoselectieve chemie. Deze tak van de chemie houdt zich bezig met het ontwerpen van chirale liganden, die na complexatie met een metaal-ion in staat zijn een reaktie te katalyseren waarbij het produkt in hoge enantiomere overmaat gevormd wordt. Recentelijk is er veel aandacht voor liganden met één of meer stikstof atomen, aangezien deze een goede affiniteit hebben voor een groot aantal metaal-ionen.



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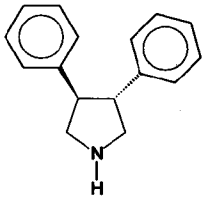
Figuur 2 Structuur van een chiraal N-hydroxysuccinimide



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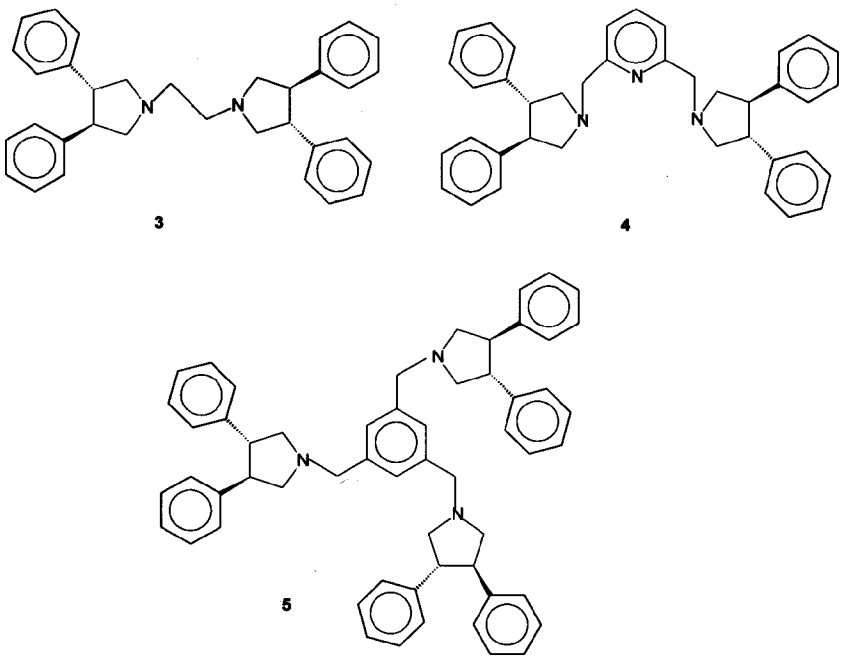
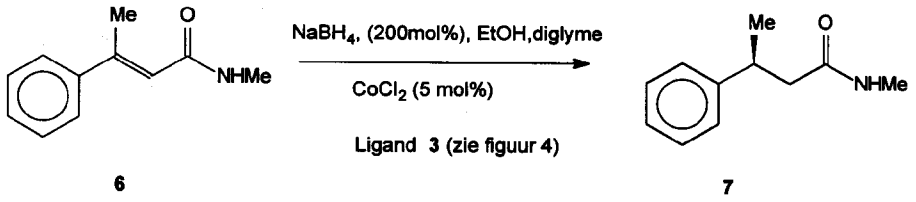
Figuur 3 Structuur van 3,4-diphenylpyrrolidine

In hoofdstuk 4 wordt de synthese beschreven van een groot aantal hoog symmetrische stikstof liganden, opgebouwd uit een of meerdere 3,4-digesubstitueerde pyrrolidines (voorbeeld; zie figuur 4, verbindingen **3**, **4** en **5**).



Figuur 4 Structuren van hoog symmetrische stikstof liganden

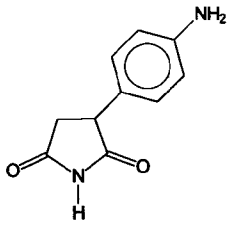
Het bleek mogelijk om een groot aantal nieuwe liganden (bi-, tri-, en tetradentaat met C_2-, D_2-, D_3,- of C_4-symmetrie) te synthetiseren via verschillende benaderingen. De coördinatie van deze liganden met een aantal metaal ionen wordt besproken en de structuur werd bepaald met behulp van ^{1}H-NMR spectroscopie en Röntgenanalyse. Een eerste toepassing van deze liganden in de katalytische stereoselectieve chemie wordt beschreven aan het eind van hoofdstuk 4 (zie figuur 4)



Figuur 5 Enantioselectieve reduktie van α,β–onverzadigd amide

De reductie van α,ß-onverzadigd amide **6** tot het verzadigd amide **7** werd uitgevoerd met behulp van ligand **3**, $CoCl_2$ en $NaBH_4$. Verbinding **7** werd in een enantiomere overmaat van 83% verkregen. Andere liganden gaven slechtere resultaten.

In het laatste hoofdstuk wordt het werk beschreven dat aan het begin van het onderzoek is uitgevoerd. Hier wordt de synthese beschreven van een aantal gesubstitueerde succinimides, derivaten van butaandicarbonzuren (voorbeeld; zie figuur 6, verbindingen **8** en **9**).



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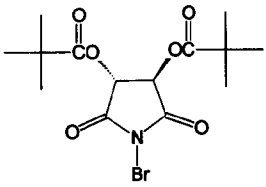

9

Figuur 6 Structuren van gesubstitueerde succinimides

Verbindingen van het type **8** werden gebruikt in de regio- en stereoselectieve functionalisering van onverzadigde vetzuren. Een (onverzadigd) vetzuur bestaat uit een groot aantal equivalente koolwaterstof atomen. Regio- of stereoselectieve functionalisering van een vetzuur is dan ook, chemisch gezien, erg moeilijk. Enzymen kunnen dit soort functionaliseringen echter wel perfect uitvoeren, een prachtig voorbeeld is de enzymatische oxidatie van stearinezuur tot oliëzuur. Door nu verbindingen zoals **9** te koppelen aan een onverzadigd vetzuur (oliezuur of linolzuur) is getracht op een regioselectieve wijze een broom atoom in te voeren in het onverzadigde vetzuur, waarbij de selectiviteit bepaald wordt door de geometrie van het systeem. De voortgang van dit onderzoek werd echter gedwarsboomd door het ministerie van Defensie; de auteur moest in militaire dienst en het onderzoek werd gestopt. Pas na anderhalf jaar kon de auteur weer aan de slag. Het onderzoek werd voortgezet op het gebied van gesubstitueerde succinimides en andere cyclische derivaten van butaandicarbonzuren. In de tweede helft van hoofdstuk 5 wordt de synthese en het gebruik van chirale C_2-symmetrische *N*-broomsuccinimides beschreven. Verbindingen van het type **9** zijn makkelijk te synthetiseren uitgaande van wijnsteenzuur. Het doel was, om deze verbindingen te gebruiken in enantioselectieve bromeringsreakties. Een tweetal reakties zijn onderzocht. Hoewel de verbindingen uitstekende bromeringsreagentia zijn werd er geen enkele enantioselectiviteit waargenomen. Dit wordt toegeschreven aan het radikalaire karakter van deze bromeringen.