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New Routes to enantioenriched substances through small organic molecules

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Abstract

In this thesis we will disclose the results obtained from the diastereoisomeric salt formation (*n* salt, *p* salt and p_1,n_1 salt) between non-racemic *trans*-chrysanthemic acid (*trans*-ChA) and pure enantiomers of *threo*-2-dimethylamino-1-phenyl-1,3-propanediol (DMPP). The occurrence of p_1,n_1 salt formation can have profound effects on enantiomer separation of scalemic (non-racemic) mixtures. This phenomenon when accompanied by substrate self-association impedes the complete recovery of the major enantiomer through formation of an inescapable racemate cage.

A synthetic sequence for the asymmetric synthesis of bicyclo[3.2.0]heptanones and bicyclo[3.2.0]hept-3-en-6-ones through a cycloaddition strategy is reported. The fundamental step is a [2+2]-cycloaddition of an enantiopure amide derived from the reaction between a set of acids and an oxazolidinone as the chiral auxiliary. The inter- and intramolecular cycloaddition of in situ-generated keteniminium salts gives bicycles with a good enantioselection.

A key intermediate of Iloprost, a chemically stable and biologically active mimic of prostacyclin PGI_2 is synthesized following a '*green* approach'. An example of simple optical resolution of this racemic intermediate involving the diastereoisomeric salt formation is described.

Chapter 1

Introduction

1.1 The importance of enantiopure compounds

One aim of synthetic organic chemistry is to provide discoveries and inventions that have a great impact in many areas like biology, medicine and agriculture. Many efficient procedures have been devised which allow the preparation of complex compounds with chemo- regio- stereo- and especially enantioselection. Asymmetric control of reaction is therefore essential every time biologically active molecules are involved. In the early 1960s the Thalidomide tragedy had brought to the public's attention the importance of producing drugs in enantiomeric pure form. In England, Thalidomide was marketed in racemic mixture and widely used to alleviate the undesired symptoms of pregnancy. Unfortunately too late, it was found that while the (*R*) enantiomer is the active analgesic principle, the opposite (*S*) enantiomer is teratogen and so responsible of birth deformities of numerous babies. The importance of enantiopure compounds results from the close relationship between the absolute configuration of a molecule and its biological properties and effects. Since then most drugs are now marketed as single enantiomers,[1] even if they are synthesized as racemic mixture. The required enantiomer has been achieved by optical resolution and purification of racemic mixture or by asymmetric reaction.

1.2 An industrial and *green* point of view

In the attempt to meet the evermore stringent social demands of new products with improved performance, lower financial price and lower environmental impact, the chemists have been focused on the development of new processes and products based

[1] In 1992, the US Food & Drug Administration (FDA) issued a policy on stereoisomeric drugs: 57 *Fed. Reg.* 22 249 (**1992**). According to this regulation, racemates can be sold, but both enantiomers must be characterized pharmacologically and toxicologically. This characterization is usually so long and expensive that the single enantiomer synthesis is often preferred.

on the so called '*green* chemistry'. In 1998, Anastas and Warner[2] exposed the twelve principles of *green* chemistry: 1) prevention, 2) atom economy, 3) less hazardous chemical synthesis, 4) designing safer chemicals, 5) safer solvent, 6) design for energy efficiency, 7) use of renewable feedstock, 8) reduce derivates, 9) catalysis, 10) design for degradation, 11) real-time analysis for pollution prevention, 12) inherently safer chemistry for accidental prevention. The goal of this chemistry is the optimization of production processes and of the resources exploitation. To be successful this technology should be applied in an economically viable manner, without side effects for environment following the concepts of 'intensification' and 'minimization' of the industrial process.

1.3 Chrysanthemic acid

Nature is the uncontested master in the design of biologically active compounds. From Nature we have discovered many compounds that have strongly enhanced life in the developed societies. For example, a famous and potent class of insecticides, the natural esters Pyrethrins, contains Chrysanthemic acid as the fundamental active constituent (Figure 1).

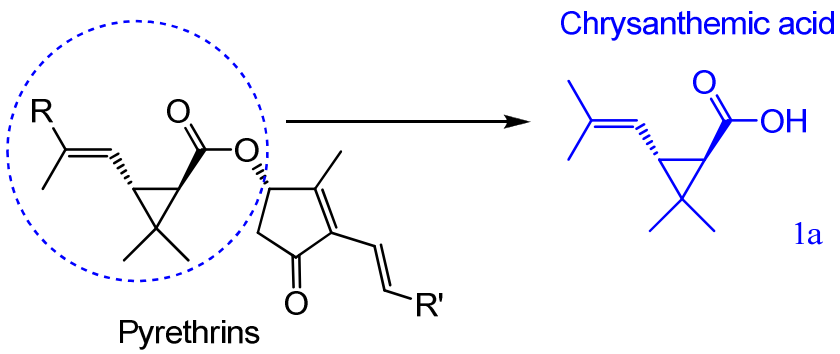


Figure 1

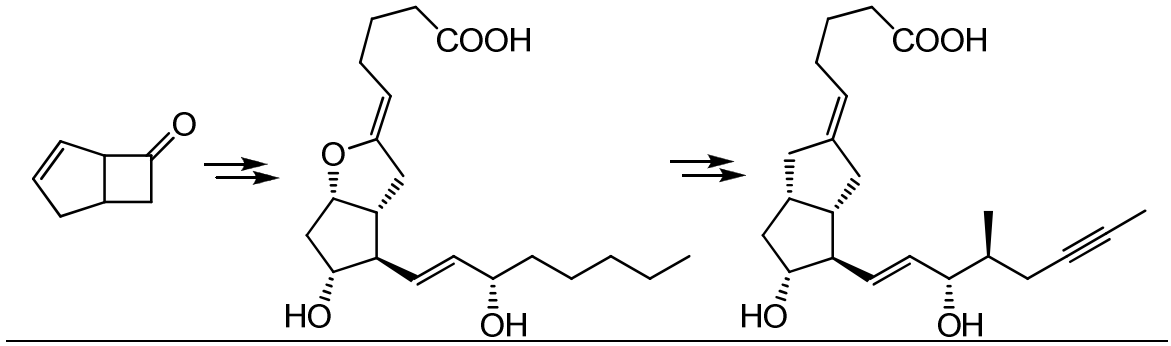
To improve the repellent activity and delete the photo instability of these esters a new generation of pyrethroids was developed. The biological properties of this repellents used in crop protection are related to the relative and absolute configuration of the

[2] Anastas, P. T., Warner, J. C. *Green Chemistry: theory and practice*, **1998**, Oxford University Press, p 30.

Chrysanthemic acid. Hence, again the necessity to develop efficient asymmetric resolution methods results evident.

1.4 Prostaglandin precursors and analogues

Prostaglandins have an immense biochemical importance because of their fascinating pharmacological properties. Several useful intermediates were synthesized in these years, and the bicycle-ketene here represented is just an example of these classes of attractive precursors (Scheme 1).



Scheme 1

Compounds belonging to this class have a versatile structure, a rigid skeleton and two fused rings with different functionalizable groups, therefore they are attractive precursors for the asymmetric synthesis of prostaglandin and their biosynthesized analogues, prostacyclins. Since the discovery of prostacyclins the search for more chemically and biologically stable mimics has been ongoing. The carbocyclic analogue Iloprost is a valuable drug for the treatment of pulmonary hypertension and it is a potent inhibitor of blood platelet aggregation.

1.5 Outline of the thesis

These reflections are at the basis of the work discussed in this thesis and of many efforts made in my group. In particular, the first topic deals with an optical resolution of a chrysanthemic acid scalemic mixture by formation of diastereomeric salts. In this case, the influence of the p_1,n_1 salt formation in the separation process is highlighted and

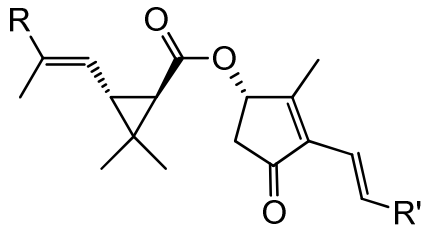
explained (Chapter 2). Then a method of synthesis of enantiopure bicycloketones based on [2+2]-cycloaddition of chiral amides will be discussed. First, synthetic route to these chiral intermediates will be described (Chapter 3). Finally the attention is focused on the total synthesis of Iloprost. The intensification of the synthetic process of a key racemic precursor is presented. The description of a new methodology for its enantiomeric resolution is explained (Chapter 4).

Chapter 2

Influence of p_1,n_1 salt in the enantiomeric separation of *trans*-Chrysanthemic acid

2.1 History

In 1924 Staudinger and Ruzicka[3] discovered that the pyrethrin natural active compounds are esters of chrysanthemic acid and pyrethric acid (Figure 2). Pyrethrins are natural insecticides obtained by dried flowers of pyrethrum (*Chrysanthemum cinerariaefolium* and *C. coccineum*). Those natural repellents and related synthetic analogues (first synthesized by Staudinger[4]) are instable in air and light, so this limit restricts and penalizes their use in agriculture crop protection against pests. Extensive research has product important industrial works and academic papers of a new and powerful class of esters.[5] Those pyrethroids are photostable, biodegradable and couple a high insecticidal activity with a low mammalian toxicity.[6]



	R	R'
Pyrethrin I	Me	$CH=CH_2$
Pyrethrin II	CO_2Me	$CH=CH_2$
Cinerin I	Me	CH_2Me
Cinerin II	CO_2Me	CH_2Me
Jasmolon I	Me	Me
Jasmolon II	CO_2Me	Me

Figure 2

[3] H. Staudinger, L. Ruzicka, *Helv. Chim. Acta* **1924**, *7*, 177, 201, 212, 236, 245, 377.
In 1939 L. Ruzicka was Nobel laureate in Chemistry and in 1953 H. Staudinger too.
[4] H. Staudinger, L. Ruzicka, *Helv. Chim. Acta* **1924**, *7*, 448.
[5] a) S. Jeanmart, *Aust. J. Chem*., **2003**, 56, 559 and references cited therein; b) A. Fishman, D. Kellner, D. Ioffe and E. Shapiro, *Org. Process Res. Dev*. **2000**, 4, 77 and references cited therein; c) J. Crosby, *Pestic. Sci*., **1996**, 46, 11; d) J. Martel, in *Chirality in Industry*, ed. A. N. Collins, G. N. Sheldrake and J. Crosby, John Wiley & Sons, Chichester, UK, **1992**, ch. 4 pp. 87–109; e) K. Naumann, in *Chemistry of Plant Protection*, ed. W. S. Bowers, W. Ebing, D. Martin and R. Wegler, Springer Verlag, Berlin, Germany, **1990**, vol. 5, ch.1, pp. 3–100; f) J. Tessier, *Chem. Ind*., **1984**, 199; g) *Pyrethrum–The Natural Insecticide*, ed. J. E. Casida, Academic Press, New York, USA, **1973**; h) D. Arlt, M. Jautelat and R. Lantzsch, *Angew. Chem., Int. Ed. Engl*., **1981**, 20, 703; i) M. Elliott and N. F. Janes, *Chem. Soc. Rev*. **1978**, 7, 473.
[6] M. Elliott, *ACS Symp. Ser.* **1977**, 42,1 and references cited therein.

trans- and *cis*-2,2-Dimethyl-3-(2-methylprop-2-enyl)cyclopropane carboxylic acids (Chrysanthemic acid, ChA) so are important starting material for the preparation of several natural and synthetic insecticides for the control of many kinds of undesired mites, insects, and spiders in agriculture crop and in the public health sector. The biologic activity is correlated to the chirality of the optical isomers: the more effective one is shown to be (+)-*trans* isomer, followed by (+)-*cis*, instead the (–)-*cis* and (–)-*trans* are almost ineffective[7] (Figure 3).

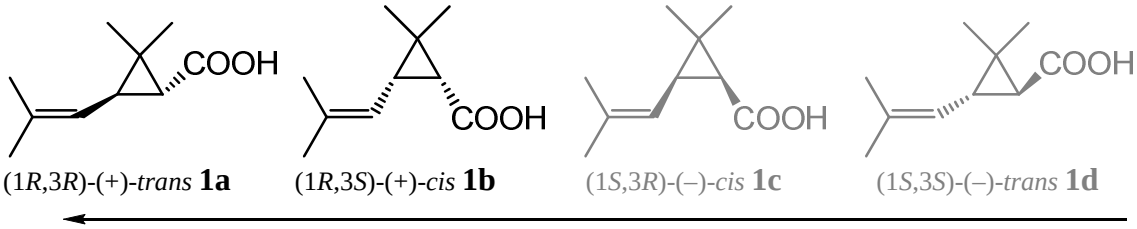
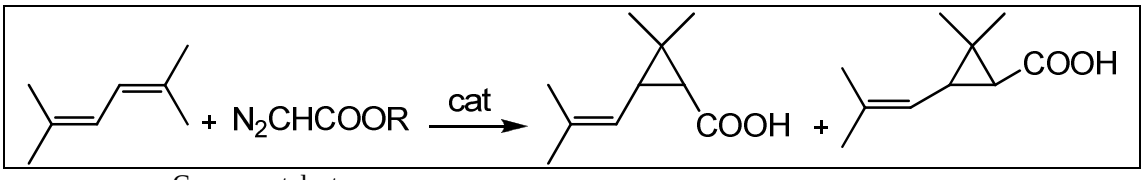
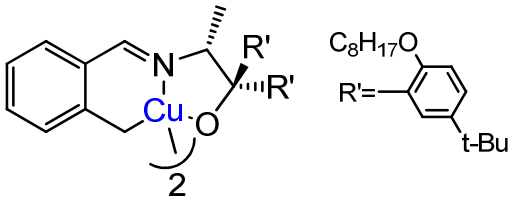


Figure 3

The first asymmetric synthesis was made by Aratani and co-workers[8] exploiting the reaction of alkyl diazoacetate with an olefin catalyzed by a chiral copper complex to obtain an optically active alkyl cyclopropanecarboxylate (Figure 4).



Copper catalyst



R	*trans-cis*	% ee (*trans*)	% ee (*cis*)
Et	51/49	68	62
t-Bu	75/25	75	46
l-adamantyl	84/16	85	46
l-menthyl (de)	93/7	94	46

Figure 4

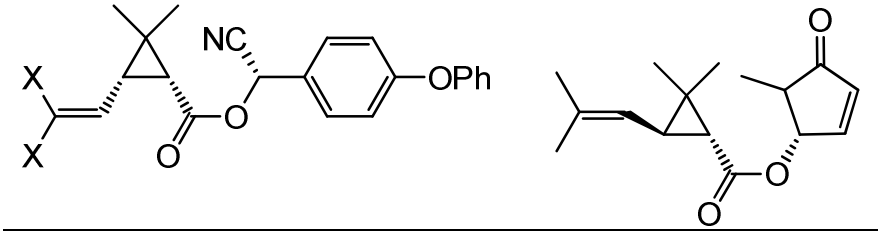
The asymmetric cyclopropanation is one of the most efficient methods to synthesize optically active chrysathemic acid esters.[9] To be employed in an industrially applicable

[7] For the racemization and epimerization of chrysanthemic acid isomers, see G. Suzukamo, M. Fukao and T. Nagase, *Chem. Letters* **1984**, 1799; G. Suzukamo, M. Fukao and M. Tamura, *Tetrahedron Letters 25*, **1984**, 1595.
[8] Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Letters* **1975**, 1707; **1977**, 2599; **1982**, 685. Aratani, T. **1985**, 1839.

process this reaction needs to proceed with good stereo- and enantioselectivity, and to use a simple alkyl diazoacetate and high catalyst efficiency: a panoramic summary of reactions and catalysts has been made by Itagaky and co-workers.[10] The use of ethyl diazoacetate (although a toxic and hazardous chemical product) allows a great atom economy, and still now many industries prepare tonnes of racemic chrysathemic acid in mixtures of *trans*- and *cis*-isomers in ratios ranging from 65:35 to 9:1 exploiting a metal catalyzed carbene insertion reaction of this starting material on 2,5-dimethyl-2,4-hexadiene.[11] Mixtures with a poor content of *trans*-ChA can be enriched by epimerization because of this isomer is the thermodynamically more stable and the equilibrium ratio (depending on the operative conditions) is on the order of 9:1.

2.2 Optical resolution

Enantiopure *trans*- and *cis*-ChA **1** are fundamental for the syntheses of pyrethroids with greater insecticidal and repellent activity like cypermethrin **2a**, deltamethrin **2b** and (*S*)-bioallethrin **2c** (Figure 5).



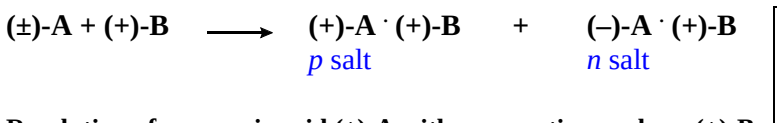
X= Cl, cypermethrin **2a** (*S*)-bioallethrin **2c**
X= Br, deltamethrin **2b**

Figure 5

Asymmetric catalysis is an elegant and fascinating route to the "chirality" but, many limits hamper the industrial use of catalysis in product, for example: a) the catalyst cost, stability, availability and efficiency; b) the costs resulting from licensing patents; c) the need of specialized equipment d) (frequently) the use of low temperatures, high

[9] Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, **1998**; Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, B. A. *Chem. Rev.* **2003**, *103*, 977.
[10] Itagaki, M.; Masumoto, K.; Suenobu, K.; Yamamoto, Y. *Org. Process & Rev.* **2006**, *10*, 245.
[11] Campbell, I. G. M.; Harper, S. H. *J. Chem. Soc.* **1945**, 283; Sanders, H. J.; Taff, A. W. *Ind. Eng. Chem.* **1954**, *46*, 414.

dilutions and purities of reagents and solvents.[12] Though progresses in this field during the last two decades are indubitable and impressive, the optical resolution of racemic acids and bases *via* formation of diastereomeric *p* and *n* salt[13] (Scheme 2), and their separation by crystallization, is still the preferred method to obtain a vast majority of enantiopure molecules that are pharmaceutical and agrochemical targets.



Resolution of a racemic acid (±)-A with an enantiopure base (+)-B

The letter *p* is used to designate the diasteroisomers resulting from reaction of two constituents having *like* sign of rotation, the letter *n* to *unlike* sign.

Scheme 2

The essence of this type of resolution (a substrate selective process) is the differential interaction of the enantiomers of a racemic mixture with the resolving agent to form a pair of diastereomers, which exhibit different physicochemical properties and can be separated by an achiral method. Finally the single diastereoisomers have to be decomposed to obtain the unchanged agent and the pure enantiomers.[14] Resolution can be yielded by formation of covalent or non-covalent diastereomers (Scheme 3); in the second case, for example, by salt formation (with acidic or basic substrate) or complex formation (with neutral racemate).

Optical Resolution

• Spontaneous resolution, induced crystallization • By Formation of Diasteromers • By substrate selective reactions • Combined with 2nd order asym. transformation: racemization and deracemization	# covalent # non -covalent	Salt Formation Complex Formation "Half equivalent" method With mixture or resolving agent With a derivate of the target compound Enantioselective chromatography Enantioselective phase-transfer

Scheme 3

Formation of *p* and *n* salt is the preferred methodology particularly when the undesired enantiomer can be recycled, as in the case, and when the goal is an industrial application

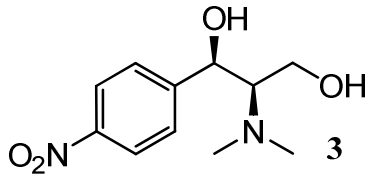
[12] Blaser, H. U. *Chem. Comm.* **2003**, 293.
[13] David Kozma *CRC Handbook of Optical Resolutions via Diastereoisomeric Salt formation*, CRC Press, London, **2001**; Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*, Wiley and Sons, New York, **1981**.
[14] Fogassy, E.; Nogradi, M.; Kozma, D.; Egri, G.; Palovics, E.; Kiss, V. *Org. Biomol. Chem.* **2006**, 3011.

(crystallization techniques is economical, scalable and in general no complex or expensive equipment is necessary).

2.3 The small molecule: DMPP

In the resolution of the *trans*-ChA **1a** Roussel-Uclaf has developed the most efficient process,[15] that uses as the resolving agent the enantiopure (1*R*,2*R*)-(–)-(*threo*-2-dimethylamino-1-(4-nitrophenyl)-1,3-propanediol) **3** (DMAD). The precipitation of the *n* salt occurs when this base is used with a crystallization co-solvent (*i*-Pr_2O/MeOH). Methanol is incorporated into the crystals of the less soluble salt, and promotes the nucleation and the crystal growth (Scheme 4).[16]

DMAD



3

solvent	Yield	Optical purity	S
i-Pr_2O/MeOH	84.4 %	96.7 %	0.82
di-*n*-butyl ether/MeOH	99.2 %	83.9 %	0.83
diethyl ether/MeOH	86.5 %	99.3 %	0.86

E. Fogassy, et al. *J. Chem. Soc., Perkin Trans. 2*, **2000**, 149.

Scheme 4

In the scheme a new parameter is highlighted: the Resolving Efficiency (S), also called *Fogassy*'s parameter. This is used for a numerical characterization of the resolution and so, it allows comparing the efficiency of different processes. Resolving Efficiency is the product of yield (*y*) times the enantiomeric purity (*e.e.*) (Equation 1).

[15] Inter alia: a) quinine: (i) I. C. M. Campbell and S. H. Harper, *J. Sci. Food Agric.* **1952**, 3, 189, (ii) L. Crombie, J. Crossley and D. A. Mitchard, *J. Chem. Soc*. **1963**, 4957; b) L-lysine: M. Matsui and F. Horiuchi, *Agric. Biol. Chem.* **1971**, 35, 1984; c) L-2-benzylaminopropanol: F. Horiuchi and M. Matsui, *Agric. Biol. Chem.* **1973**, 37, 1713; d) (–)-α-(1-naphthyl)ethylamine: (i) F. Horiuchi, A. Higo and H. Yoshioka, Sumitomo Chemical Co. Ltd., *German Pat.* 2 300 325, **1975**, (ii) K. Sasaki, Sumitomo Chem. Co. Ltd, *Japanese Pat.* 98–16789, **1999**; e) (*S*)-1-phenyl-2-(*p*-tolyl)ethylamine: (i) M. Itagaki, G. Suzukamo, K. Sasaki and K. Fujita, Sumitomo Chem. Co. Ltd, *Eur. Pat*. 933349 A1, **1999**, (ii) G. Suzukamo and K. Sasaki, Sumitomo Chemical Co.Ltd., *Eur. Pat*. 1236708 A1, **2002**; f) (*S*)-1-phenyl-2-methylpropylamine: H. Hagiya, Sumitomo Chemical Co. Ltd., *Japanese Pat*. 2001114728 A2, **2001**; g) L- or D-N-methyl-ephedrine: C. Pavan, J. Bulidon, Roussel Uclaf, *US Pat* 4 257 976, **1981**; h) phenylglycinamide or 2-phenylglycinonitrile: F. Faigl, E. Fogassy, L. Nagy, L. Csiz, I. Czudor and E. Kovacsne Kozsda, CHINOIN-Budapest, *PCT* WO 90/08126, **1990**.

[16] Kozsda-Kovács, E´., Keserü, G. M., Böcksei, Z., Szilágyi, I., Simon, K., Bertók, B., Fogassy, E. *J. Chem. Soc., Perkin Trans. 2* **2000**, 149.

Resolving Efficiency

$$S = (y \times e.e.)$$

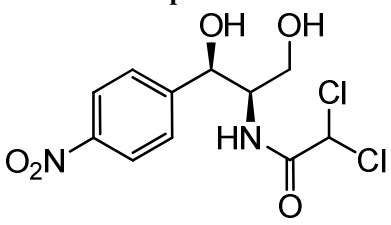
$y = (P_D + P_L)/0.5C_0$

P_D and P_L are the quantities (mol/l) of diastereomeric salts precipitated
C_0 in the initial concentration of the racemate

Equation 1

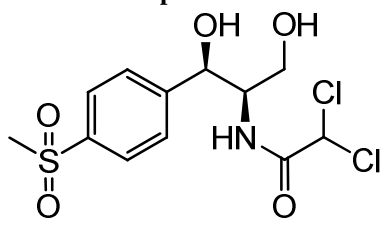
The use of a *threo*-2-dimethylamino-1-aryl-1,3-propanediol, like in our case the DMPP **4**, as resolving agent gives to the process a possible industrial and *green* application (in accordance to the principles of *green chemistry*[17]). The synthesis of those compounds exploits the synthesis process technologies of the base of chloramphenicol **5**[18], a potent bacteriostatic antimicrobial, isolated from bacterium *Streptomices venezuelae*. In the past, this antibiotic was produced and used in large scale until the discovery of its human toxicity. Due to this rare but serious side effect (aplastic anemia), it was bandit and a new similar drug was introduced in commerce: thiamphenicol **6**. It is the methyl-sulfonyl analogue of chloramphenicol **5**, but more potent and without the dangerous side effects. The limit of this compound is that only the levorotating (–)-enantiomer **(–)-6** is active. The industrial synthesis provides in large scale both the (+)- and the (–)-enantiomer of a racemic precursor of **6**. We could "recover" and exploit these optimized synthetic industrial technologies to obtained a wide set of chiral target compounds in both enantiomeric forms, that can be employed for example to obtain versatile and good resolving agents (Scheme 5).

Chloramphenicol 5



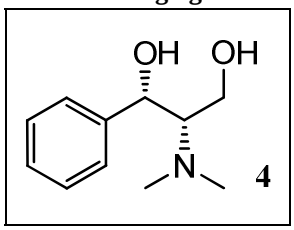
bandit drug

Thiamphenicol 6



6 (1*R*,2*R*)-(–) antibiotic
6 (1*S*,2*S*)-(+) inactive

Resolving agent



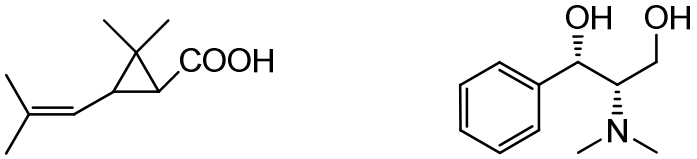
(DMPP)

Scheme 5

[17] Poliakoff, M.; Fittzpatrick, J. M.; Farren, T. R.; Anastas P. T. *Science* **2002**, *297*, 807.
[18] "Chloramphenicol" is the assigned generic name to the compound D-(–)-*threo*-*N*-(1,10-dihydroxy-1-*p*nitrophenylisopropyl)- dichloroacetamide for which Parke, Davis and Co. has adopted 'Chloromycetin' as its trademark; Bartz, Q. R. *J. Biol. Chem.* **1948**, *172*, 445.

2.4 The p_1,n_1 salt[19]

Due to this background, the aim of this work is to develop a practical process to resolve racemic ChA mixtures **1** of industrial origin by formation and separation of crystalline diastereomeric salts exploiting, like optically pure resolving agent, the *threo*-2-dimethylamino-1-phenyl-1,3-propanediol **4** (DMPP). Despite the innumerable qualities of the above described resolution method, some times unpredictable and exceptional results occur: a well-crystallized and poorly soluble mixture brings to a racemic acid, even after several recrystallizations. This phenomenon can be ascribed to the formation of a 1/1 double salt, a third salt (called p_1,n_1 salt) originating from a stable combination of the *p* and *n* salts. Ladenburg[20] has postulated the existence of those salts at the beginning of the last century, while the first structural evidence came later.[21] In our case racemic *trans*-ChA **1a** forms p_1,n_1 salts when treated with the pure enantiomers of DMPP **4**, where those new salts have the same rotation of the DMPP **4** enantiomer used (Scheme 6).



Trans-ChA **1a** (+)-DMPP **4**

(a) **(±)-ChA + 2 (+)-B** → **(+)-ChA · (+)-B** + **(–)-ChA · (+)-B**
p salt *n* salt

(b) **(±)-ChA + 2 (+)-B** → **[(±)-ChA · (+)-B$_2$]**
p_1,n_1 salt

Scheme 6

The single-crystal X-ray diffraction analysis (Figure 6) has proved the uniqueness of this salt, its supramolecular architecture and that it isn't a simple mechanical mixture of the *p* and *n* salts.[22]

[19] Rosini, G.; Borzatta, V.; Boschi, F.; Candido, G.; Marotta E.; Righi, P. *Chem. Commun*. **2007**, 2717.
[20] Ladenburg, A. *Justus Liebigs Ann. Chem.* **1908**, *340*, 227.
[21] Turkington, D. E.; MacLean, E. J.; Lough, A. J.; Ferguson G.; Glidewell, C. *Acta Crystallogr., Sect. B: Struct. Sci.* **2005**, *61*, 103.
[22] Rosini, G.; Ayoub, C.; Borzatta, V.; Mazzanti, A.; Marotta E.; Righi, P. *Chem. Commun*. **2006**, 4294.

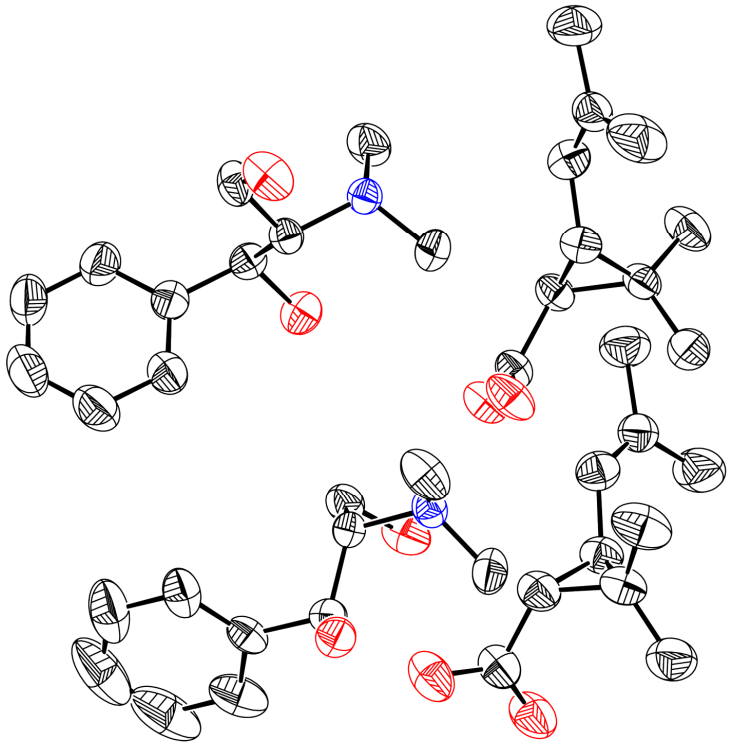


Figure 6

The presence of this salt can be exploited to recover the exceeding fraction of the major enantiomer from non-racemic mixture.[23] When a (+)-*trans*-ChA **(+)-1a** enriched mixture (50% ee) was treated with (+)-DMPP **(+)-4**, the first 0.5 equivalents of added base caused the precipitation of the p_1,n_1 salt (Figure 7).

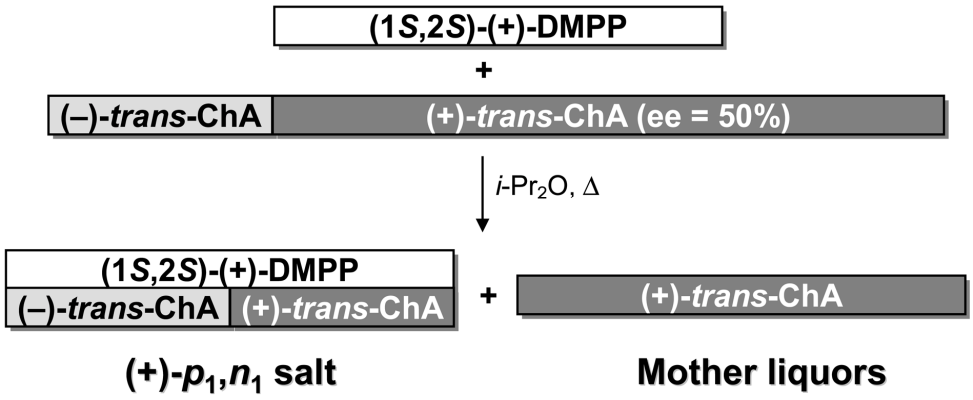


Figure 7

[23] For a very efficient resolution see: Rosini, G.; Ayoub, C.; Borzatta, V.; Marotta E.; Mazzanti, A.; Righi, P. *Green Chem*. **2007**, 441.

The same experiment was performed using the same 50% ee (+)-*trans*-ChA **(+)-1a** enriched mixture, but changing the base enantiomer. A completely different behavior was found: the addition of 0.5 equivalents of the (–)-DMPP **(–)-4** (that is stoichiometric to the excess of acid ee) caused the precipitation of *n* salt (Figure 8).

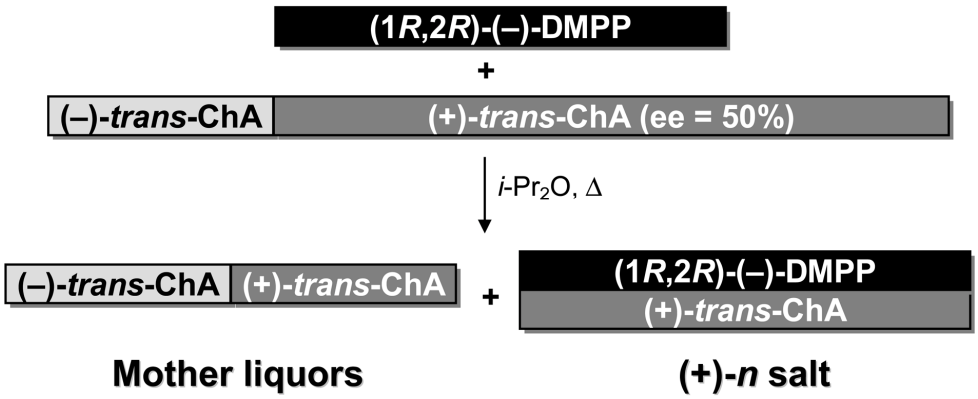


Figure 8

In summary, when a non-racemic mixture of *trans*-ChA **1a** is treated with the pure enantiomer of DMPP **4** with the same sign of rotation the p_1,n_1 salt is formed leaving the exceeding enantiomer in solution. On the other hand, when an enriched mixture of acid is treated with the pure enantiomer of base with opposite sign and stoichiometric to the exceeding fraction of the *trans*-ChA **1a** enantiomer, *n* salt always forms first, leaving the acid racemate in solution. Characterization and solubility data of the salts (Table 1,Table 2) did not fully explain this absolute specificity for *n* salt formation.

	DSC				
	Mp/°C	Peak/°C	ΔH^f/J g^{-1}	$[\alpha]_D$ (c/g (100mL)$^{-1}$) in $CHCl_3$ solution at 23°C	
(+)-*p* salt	90.0-92.0	88.81	-111.2	+39.7	(0.97)
(+)-*n* salt	132.6-134.0	131.27	-126.7	+12.3	(0.93)
(+)-p_1,n_1 salt	110.0-111.5	110.97	-146.4	+26.8	(1.04)

Table 1

Solubilities in *i*-Pr_2O/mg ml^{-1} (performed by equilibrating the solid/liquid mixture of the salt for 24h at the given temperature)				
T/°C	*n* salt	p_1,n_1 salt	*p* salt	
15	4.21	4.84	N.d.	*p* salt is soluble in refluxing *i*-Pr_2O. Once dissolved, it forms metastable solutions from which precipitation is achieved only by scratching the container's walls.
31	7.78	8.72	N.d.	
68	33.0	46.6	soluble	

Table 2

In the case depicted in Figure 7, the system has the opportunity to choose between the precipitation of the racemate as the p_1,n_1 salt and that of the *exceeding* enantiomer as the *n* salt. In such cases a specific and quantitative precipitation of the *n* salt has always been observed. Unfortunately, this great selectivity no allows a *quantitative* recovery of the major *trans*-ChA **1a**: the addition of 0.75 eq. (–)-DMPP **(–)-4** causes the precipitation of a salt with only 66% ee. This % ee value can be ascribed to 2 : 1 mixture of *n* and p_1,n_1 salts respectively.

To better understand this result we performed a set of ten crystallization experiments in a parallel reactor (Table 3). The ten vessels were charged with increasing amounts of (–)-DMPP **(–)-4** (from 0.1 equiv. in vessel #1 up to 1 equiv. in vessel #10, in linear steps of 0.1 equiv.). Then all the ten vessels were added with 1 equiv. of the scalemic mixture of (+)-*trans*-ChA **(+)-1a** with 50% ee in *i*-Pr_2O. The parallel reactor was heated at reflux for 30 min and then the ten mixtures were let to crystallize. Chrysanthemic acid obtained from solids and mother-liquors of each vessel was collected and separately analyzed. The analyses showed that *n* salt precipitation occurs first (vessels 1–5) up to the point were all the exceeding (+)-*trans*-ChA **(+)-1a** enantiomer is consumed (0.5 equiv. of base for a 50% ee of ChA) leaving in solution the *trans*-ChA **1a** racemate. Larger additions of the same DMPP **4** base enantiomer (vessels 6–10) cause the precipitation of the *trans*-ChA **1a** racemate as the p_1,n_1 salt.

vessel	(–)-DMPP **(–)-4** (equivalent)	Operation	Precipitate
1	0.1	# addiction of (+)-*trans*-ChA **(+)-1a** (50% ee) in *i*-Pr_2O # reflux for 30 min # crystallization # precipitate and mother liquor separation # analysis	*n* salt
2	0.2		
3	0.3		
4	0.4		
5	0.5		
6	0.6		p_1,n_1 salt
7	0.7		
8	0.8		
9	0.9		
10	1.0		

Table 3

This behavior may be explained by considering *trans*-ChA **1a** enantiomers self-association in solution.

2.5 The diastereomeric dimer

In solution, the enantiomers can give rise to the formation of three distinct dimers (Scheme 7), namely the diastereomeric heterodimer and the two enantiomeric homodimers.[24]

***Trans*-ChA self-association in solution**

m [(–)-ChA] + *n* [(+)-ChA] $m \geq n$	⇄	*n* [(+)-ChA· (–)-ChA] Heterodimer	+	*m* – *n* [(–)-ChA]
	⇌	*m*/2 $[(+)\text{-ChA}]_2$ Homodimer 1	+	*n*/2 $[(–)\text{-ChA}]_2$ Homodimer 2

Scheme 7

Three different situations can be considered. (a) Initial racemic composition ($m = n$): independently of the system preference, equal amounts of the two enantiomeric homodimers are always formed ($m = n$) and no free unmatched enantiomer is left after the formation of heterodimer ($m - n = 0$). (b) Initial non-racemic composition ($m \neq n$) with a preference for homodimers: the enantiomeric homodimers are formed in the same initial *m/n* ratio. (c) Initial non-racemic composition ($m \neq n$) with a preference for the heterodimer: after the formation of heterodimer, the exceeding fraction of the major enantiomer remains free in solution; this is the only case where the initial *m/n* ratio

[24] Gavezzotti, A.; Filippini, G. *Chem. Comm.* **1998**, 287.

between enantiomeric species is broken. This latter phenomenon has been exploited in a few cases for the achiral separation of the exceeding enantiomer from the racemate of a non-racemic mixture of a chiral substance.[25]

The assumption that, in solution, *trans*-ChA **1a** strongly prefers to form heterodimers, can explain the different results obtained with two enantiomers of DMPP **4**. This can also be implied by the fact that at room temperature racemic *trans*-ChA **1a** is solid (mp 54°C), while in enantiopure form is liquid (mp 17-21°C).

Thus, in a solution of enantioenriched *trans*-ChA **1a**, the heterodimer actually acts as a sequestrant of the minor enantiomer. Any base added to the system would preferentially react with the free fraction of the major enantiomer, without disrupting the stable heterodimer. Given this picture, the addition of either of the DMPP **4** enantiomers makes a big difference. If the DMPP **4** base added has the same rotation sign as the exceeding *trans*-ChA **1a** enantiomer [(–)-DMPP **(–)-4**, in Figure 7], reaction with the free (–)-ChA **(–)-1a** would form the *p* salt, which is soluble (Table 2) and does not precipitate. The only alternative for this base is to disrupt heterodimeric aggregate and form the p_1,n_1 salt. If the added enantiopure DMPP **4** has the opposite rotation sign with respect to the exceeding *trans*-ChA **1a** enantiomer [(+)-DMPP **(+)-4**, in Figure 8], reaction with the free (–)-ChA **(–)-1a** precipitates the less soluble *n* salt (Table 2). When the free fraction of (–)-ChA **(–)-1a** is consumed up to the n salt solubility level, further additions of the base would precipitate the heterodimer as the p_1,n_1 salt.

In an attempt to study the relative stability of the *n*, p_1,n_1 and *p* salts we performed the set of experiments depicted in Figure 9. In any case a salt was suspended in hot *i*-Pr2O, then 0.5 eq. of a pure enantiomer of *trans*-ChA **1a** were added. The mixture was kept at reflux for 30 min and then filtered. Enantiomer composition of *trans*-ChA **1a** obtained from the salts and the mother-liquors was determined.

[25] a) Tsai, W.-L.; Hermann, K.; Hug, E.; Rohde, B.; Dreiding, A. S. *Helv. Chim. Acta* **1985**, *68*, 2238; b) Fogassy, E.; Faigl, F.;A´cs, M. *Tetrahedron* **1985**, *41*, 2841; c) Nicoud, R.-M.; Jaubert, J.-N.; Rupprecht, I.; Kinkel, J. *Chirality* **1996**, *8*, 234.

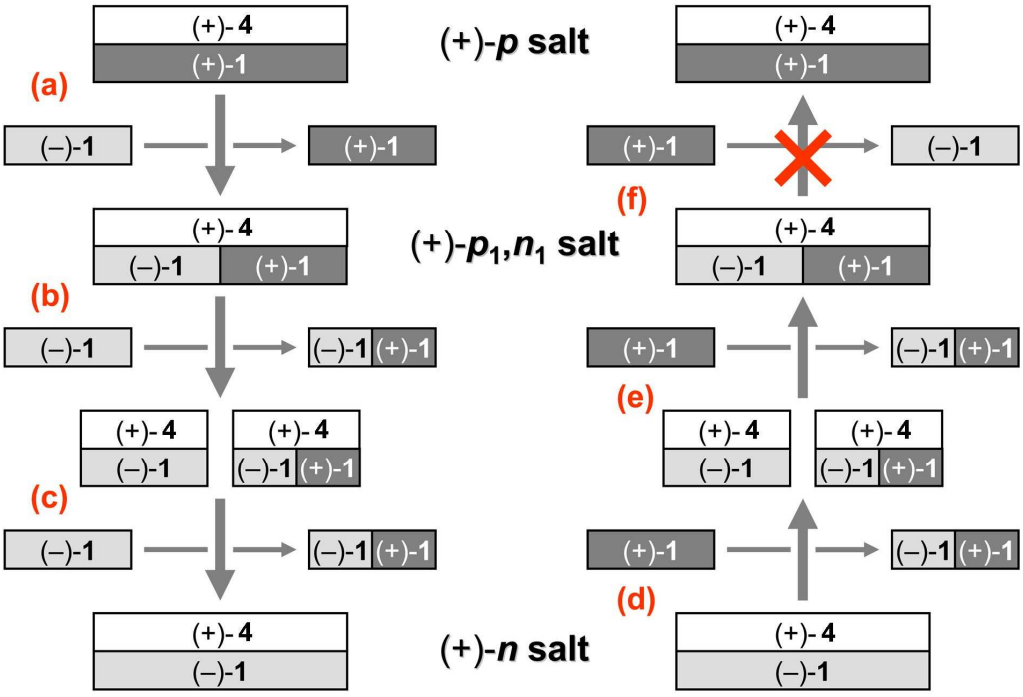


Figure 9

The results were the following: (a) addition of 0.5 eq. of (–)-ChA **(–)-1a** to (+)-*p* salt displaces 0.5 eq. of (+)-ChA **(+)-1a** from the salt to form the more stable and insoluble (+)-p_1,n_1 salt; (b) addition of 0.5 eq. of (–)-ChA **(–)-1a** to (+)-p_1,n_1 salt, does not displace the remaining 0.5 eq. of (+)-ChA **(+)-1a** from the salt to form the *n* salt: it only displaces half of the remaining (+)-ChA **(+)-1a** to form a 1 : 1 mixture of *n* and p_1,n_1 salts, so that a racemic composition is attained in solution; (c) *n* salt formation is completed by a addition of further 0.5 equiv. of (–)-ChA **(–)-1a** and again attaining a racemic composition in solution. Experiments (d)–(f) show that it is possible to convert the more stable and less soluble *n* salt into the p_1,n_1 salt, provided that a racemic composition of 1 is attained in solution: (d) addition of 0.5 eq. of (+)-ChA **(+)-1a** to n salt leads to the formation of the 1 : 1 mixture of *n* and p_1,$n_1$salts and a racemic solution of ChA **1a**; (e) addition of further 0.5 eq. of (+)-ChA **(+)-1a** to this mixture of salts leads to the p_1,n_1 salt and a racemic solution of ChA **1a**; and (f) addition of 0.5 eq. of (+)-ChA **(+)-1a** to p_1,n_1 salt causes no change since this would form the less stable and more soluble *p* salt without the possibility to achieve a racemic solution of 1.

2.5 Conclusion

Considering its behavior with respect to the base DMPP **4**, the major enantiomer in a *trans*-ChA **1a** non-racemic mixture it is not all the same. The part of the major enantiomer that exceeds the racemate forms the *n* salt, while the fraction of the major enantiomer that is part of the racemate behaves in a totally different way, forming the p_1,n_1 salt.

This salt formation influence the enantiomer separation process: when this phenomenon is accompanied by the substrate self-aggregation, an inescapable racemate ‘‘cage’’ may form both in the solid phase (the p_1,n_1 salt) on one side and in the solution phase self-aggregation of the substrate with preference for the heterodimer aggregate (Figure 10). This cage impedes the complete recovery of the major enantiomer of the substrate in an enantioenriched mixture, allowing to recover only the exceeding part of it.

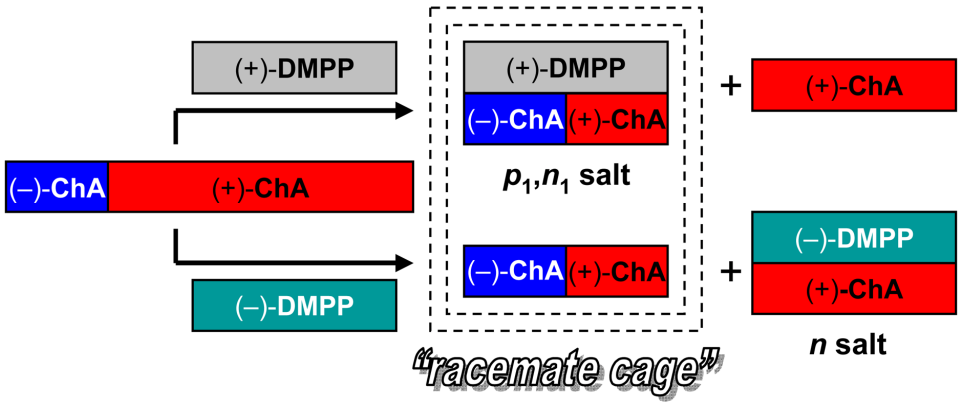


Figure 10

2.7 Experimental section

Enantiomeric composition of chrysathemic acid samples was determined by CSP GC (capillary column Rt-βDEXsm™-RESTEK Corp.; 30 m; 0.32 mmID; 0.25µm; injector 275 °C; FID detector 300 °C; 80 °C (2 min) then to 125 °C (1.5 °C/min): t_r[(+)*trans*-ChA] = 29.4min, t_r[(–)*trans*-ChA] = 30.3min. Differential scanning calorimetric measurements were performed with a TA-Instruments DSC-2920 apparatus adopting a temp. program consisting of one heating ramp starting from room temperature at a heating rate of 4°C/min under N_2.

Preparation of (+)-*n*, (+)-*p* and (+)-p_1,n_1 salts: General procedure

A 250 mL round-bottomed flask was fitted with a magnetic stirbar and a reflux condenser. The flask was charged with (1*S*,2*S*)-(+)-DMPP **(+)-4** (5.85 g, 30 mmol) and 100 mL of *i*Pr_2O. The suspension was heated to reflux until the base was completely dissolved, then the heating was stopped to add 30 mmol (5.04 g dissolved in 20 mL of *i*Pr_2O) of (–)-*trans*-ChA **(–)-1a**, (+)-*trans*-ChA **(+)-1a**, or (±)-*trans*-ChA **1a** in one portion to obtain, respectively, the (+)-*n* salt, the (+)-*p* salt and the (+)-p_1,n_1 salt. The addition of (–)-*trans*-ChA **(–)-1a** and (±)-*trans*-ChA **1a** produced the quick precipitation of, respectively the (+)-*n* salt and the (+)-p_1,n_1 salt. The mixtures were heated for one more hour, cooled to room temperature and the resulting microcrystalline solids were isolated by filtration, washed with *n*-hexane and dried *in vacuo* to give the (+)-*n* salt (95% yield) or the (+)-p_1,n_1 salt (94% yield). After the addition of (+)-*trans*-ChA **(+)-1a** no precipitation of (+)-*p* salt occurred, the solution was refluxed for one additional hour and then cooled at room temperature. It was necessary to scratch the walls of the flask to start the precipitation of the *p salt* as a white solid (80% yield).

(±)-*trans*-ChA•(1*S*,2*S*)-(+)-DMPP

[(+)-p_1,n_1 salt]

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (*s*, 3H); 1.22 (*s*, 3H); 1.30 (*dd*, 1H, J_1 = 5.4 Hz, J_2 =1.8 Hz); 1.68 (*s*, 6H); 1.94 (*dd*, 1H, J_1 = 8.0 Hz, J_2 =5.4 Hz); 2.71 (*s*, 6H); 2.94 (*m*, 1H); 3.33 (*dd*, 1H_a, J_1 = 12.9 Hz, J_2 =6.2 Hz); 3.52 (*dd*, 1H_b, J_1 = 12.9 Hz, J_2 = 2.8 Hz); 4.67 (*d*, 1H, J_1 = 9.5 Hz); 4.85 (*d*, 1H, J_1 = 5.2 Hz); 7.34 (*m*, 5H); 7,41 (*bs*, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 19.10; 21.35; 23.06; 26.16; 27.94; 32.31; 32.42; 37.49; 37.63; 42.06; 58.41; 71.51; 71.69; 122.80; 122.85; 127.68; 128.91; 129.27; 134.85; 141.86; 179.60; IR (KBr) υ: 3,151; 2,922; 1,568; 1,421 cm^{-1}. MS (ES+, *m/z*)**:** 196 (M^++1); 197 (M^++2); (ES-**,** *m/z*)**:**167 (M^--1); 168 (M^-). $[\alpha]_D^{20}$ + 26.8 (*c* 1.036, $CHCl_3$); m.p.: 109.7-111.5 °C; DSC: peak: 110.97 °C; ΔH_f -146.4 Jg^{-1}.

X-Ray crystal structure: orthorhombic, space group $P2_12_12_1$, *a* = 11.1297(6), *b* = 13.4914(7), *c* = 28.0333(14) Å, *V* = 4209.3(4) $Å^3$, T = 293(2) K, *Z* = 8, ρ_c = 1.147 g cm^{-3}, *F*(000) = 1584.0, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), μ($Mo_{K\alpha}$) = 0.078 mm^{-1}, colorless block (0.4 × 0.3 × 0.1 mm^3), empirical absorption correction with SADABS (transmission factors: 0.9694 – 0.9922), 2400 frames, exposure time 10

s, θ_{max} = 27.50, h_{max} = 14, k_{max} = 17, l_{max} = 36, 45793 reflections collected, 9681 independent reflections (R_{int} = 0.045), solution by direct methods (SHELXS97[26]) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (SHELX97[26]), hydrogen atoms refined with a riding model, data / parameters = 9681 / 495, $S(F^2)$ = 1.030, $R(F)$ = 0.0605 and $wR(F^2)$ = 0.1136 on all data, $R(F)$ = 0.0387 and $wR(F^2)$ = 0.1187 for 1652 reflections with $I > 2\sigma(I)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0567P)^2 + 0.2527P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference peak and hole 0.144 and –0.177 e Å^{-3}.

(–)-*trans*-ChA•1*S*,2*S*-(+)-DMPP

[(+)-*n* salt]

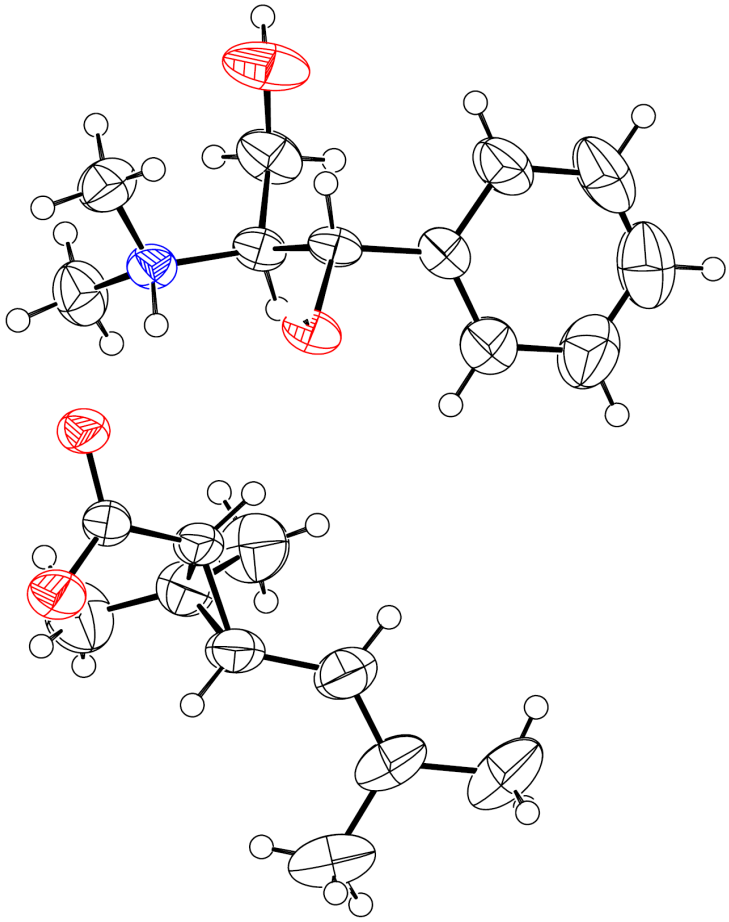
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.08 (*s*, 3H); 1.22 (*s*, 3H); 1.30 (*dd*, 1H, J_1 = 5.4 Hz, J_2 = 1.8 Hz); 1.69 (*s*, 6H); 1.94 (*dd*, 1H, J_1 = 7,9 Hz, J_2 =5.4 Hz); 2.71 (*s*, 6H); 2.94 (*m*, 1H); 3.31 (*dd*, 1H$_a$, J_1 = 12.9 Hz, J_2 = 6.2 Hz); 3.4 (*dd*, 1H$_b$, J_1 = 12.9 Hz, J_2 = 2.8 Hz); 4.68 (*d*, 1H, J_1 = 9.5 Hz); 4.85 (*d*, 1H, J_1 = 5.2 Hz); 7.32 (*m*, 5H); 7.67 (*bs*, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 18.60; 20.83; 22.57; 25.67; 27.33; 31.77; 37.56; 41.53; 57.83; 71.00; 122.37; 127.20, 128.42, 128.77; 134.32; 141.39; 179.20. IR (KBr) υ: 3,151; 2,922; 1,568; 1,421 cm^{-1}. MS: (ES+, *m/z*)**:** 196 (M^++1); 197 (M^++2); (ES-**,** *m/z*)**:** 167 (M^--1); 168 (M^-). $[\alpha]_D^{20}$ + 12.3 (*c* 0.9720, $CHCl_3$); m.p.: 132.6-134.0 °C. DSC: peak: 131.27 °C; ΔH_f -126.7 Jg^{-1}.

X-Ray crystal structure: orthorhombic, space group $P2_12_12_1$, *a* = 7.3883(8), *b* = 10.1582(11), *c* = 28.935(3) Å, *V* = 2171.6(4) Å^3, T = 293(2) K, *Z* = 4, ρ_c = 1.112 g cm^{-3}, *F*(000) = 792.0, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), μ($Mo_{K\alpha}$) = 0.076 mm^{-1}, empirical absorption correction with SADABS (transmission factors: 0.9694 – 0.9922), 2400 frames, exposure time 10 s, θ_{max} = 29.98, h_{max} = 10, k_{max} = 14, l_{max} = 40, 6299 reflections collected, 3606 independent reflections, solution by direct methods (SHELXS97[26]) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (SHELX97[26]), hydrogen atoms refined with a riding model, data / parameters = 3606 / 495, $S(F^2)$ = 1.045, $R(F)$ = 0.0560 and $wR(F^2)$ = 0.1441 on all data, $R(F)$ = 0.0387 and $wR(F^2)$ = 0.1187 for 1652 reflections with $I > 2\sigma(I)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0567P)^2 + 0.2527P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference peak and hole 0.144 and –0.177 e Å^{-3}.

[26] Sheldrick, G. M. *SHELX97*; Universität Göttingen, Germany, 1997.

X-ray crystal structure of the *n* salt

CCDC 287292 contains the supplementary crystallographic data for the *n* salt. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



A. L. Spek (2005) PLATON, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

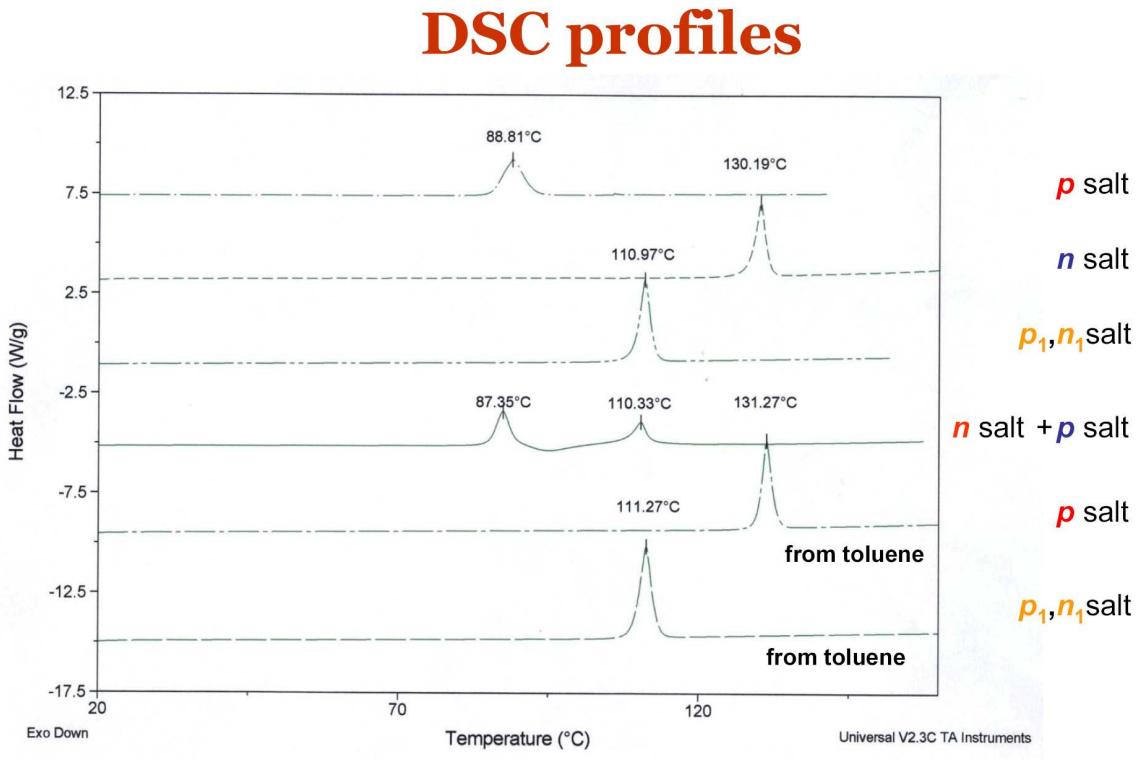
(+)-*trans*-ChA•1*S*,2*S*-(+)-DMPP

[(+)-*p* salt]

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.08 (*s*, 3H); 1.23 (*s*, 3H); 1.32 (*dd*, 1H, J_1 = 5.4 Hz, J_2 = 1.78 Hz); 1.69 (*s*, 6H); 1.94 (*dd*, 1H, J_1 = 8,0 Hz, J_2 =5.4 Hz); 2.70 (*s*, 6H); 2.94 (*m*, 1H); 3.33 (*dd*, $1H_a$, J_1 = 12.9 Hz, J_2 = 6.2 Hz); 3.51 (*dd*, $1H_b$, J_1 = 12.9 Hz, J_2 = 2.9 Hz); 4.65 (*d*, 1H, J_1 = 9.6 Hz); 4.87 (*d*, 1H, J_1 = 5.3 Hz); 7.32 (*m*, 5H); 7.50 (*bs*, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 18.41; 20.66; 22.37; 25.48; 27.32; 31.78; 36.76; 41.40; 57.82; 70.86; 71.13; 122.10; 126.98, 128.21, 128.59; 134.25; 141.19; 178.73. IR (KBr) υ: 3,151; 2,922; 1,568; 1,421 cm^{-1}. MS: (ES+, *m/z*)**:** 196 (M^++1); 197 (M^++2); (ES-,

m/z)**:** 167 (M^--1); 168 (M^-). $[\alpha]_D^{20}$ + 39.7 (*c* 0.9320, $CHCl_3$); m.p.: 93.7-96.6 °C. DSC: peak: 88.81 °C; ΔH_f -111.2 Jg^{-1}.

The levorotating enantiomers of *n*-, *p*- and p_1,n_1 salts were prepared by reacting (1*R*,2*R*)-(–)-DMPP and, respectively, (+)-*trans*-ChA *and* (–)-*trans*-ChA and (±)-*trans*-ChA.



General procedure for the recovery of the enantiomeric excess of (+)-*trans*-ChA (+)-1a from a scalemic mixture through formation of (+)-p_1,n_1 salt.

(1*S*,2*S*)-(+)-DMPP **(+)-4** (2.34 g, 12 mmol) was dissolved in 40 mL of hot *i*Pr_2O and to this solution was added a solution of 5.04 g (30 mmol) of a scalemic (+)-*trans*-ChA **(+)-1a** (ee = 60%) in 20 mL of *i*Pr_2O. The mixture was heated at 65 °C under stirring, then cooled to ambient temperature. When a solid started to precipitate heating was protracted for half an hour and then cooled to 0°C under stirring for 15 min. The solid is filtered and washed twice with *i*Pr_2O (10 mL).

The salt was dried and afforded 4.05 g (93 % yield) of (+)-p_1,n_1 salt with mp 110.0-111,5°C and $[\alpha]_D$ +26.3 (*c* 1.026, $CHCl_3$). From this salt, after the acidic/basic

treatment described previously, both racemic (±)-*trans*-ChA **1a** and the free base were recovered.

Washing of the mother liquors with an aqueous HCl solution until pH 3.5, drying and evaporation under vacuum (30 °C/24 mbar) afforded 2.66 g of (+)-*trans*-ChA (ee > 95%, 88% yield based on excess of (+)-*trans*-ChA **(+)-1a** of the starting mixture).

Recovery of the excess of (+)-*trans*-ChA, with (1*S*,2*S*)-(+)-DMPP through precipitation of (+)-p_1,n_1 salt.

(+)-*trans*-ChA (+)-1a	**(+)-DMPP (+)-4**	**p_1,n_1 salt**	**(+)-*trans*-ChA(+)-1a from ML**	
(+):(–), ee (%)[a]	(eq)	yield[b] (%)	ee (%)[a]	yield[c] (%)
75:25, 50	0.5	92	94	92
80:20, 60	0.4	93	96	94
85:15, 70	0.3	92	96	93
90:10, 80	0.2	88	94	90

a) Determined by CSP GC; b) Referred to (±)-*trans*-ChA **1a** present in the starting mixture; c) Referred to the excess of (+)-*trans*-ChA **(+)-1a** present in the starting mixture.

Chapter 3

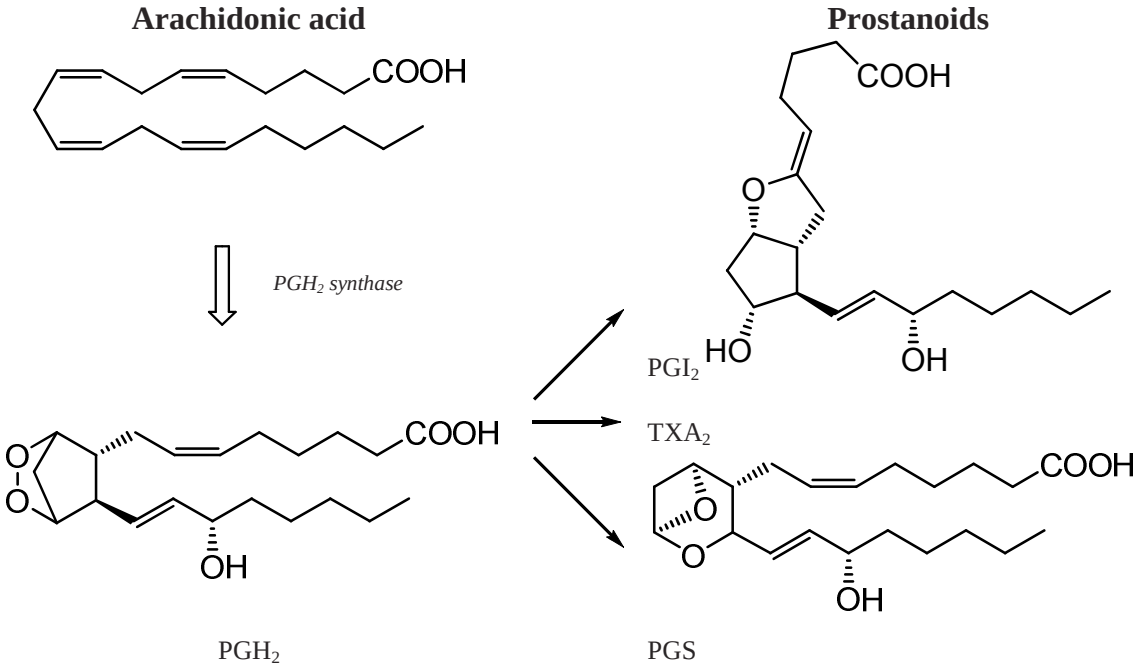
[2+2]-Cycloaddition reactions with chiral keteniminium salt

3.1 Background

3.1.1 First part

Prostaglandins (PGs), which are one of the classic example of lipid mediators acting as local hormones, were discovered[27] by Von Euler in the 1930s and their structures were elucidated in the mid-1960s by the pioneering study of Bergström[28] and his group. An extraordinary chemical and biological research[29] has been induced by the possible pharmacological utility of this type of lipids. They show a remarkable activity in a wide variety of mammalian tissues. Therefore they play a key role in immune response, inflammation and in tissue repair. These lipid mediators belong to the natural family of ecosanoids (derived from essential fatty acids oxidation). They are potent but very labile molecules, so they are not stored but biosynthesized. In the Scheme 8 the oxygenated metabolism of arachidonic acid is shown, where the biotransformation affords the key intermediate PGH2 by exploiting a *prostaglandine H_2 synthase* and two oxygen molecules. In turn, this is transformed into prostacyclin PGI2 (see chapter 4, paragraph 4.1), molecule with vasodilating and platelet antiaggregatory properties, and transformed into thromboxane TXA2 (vasoconstriction mediator) and different prostaglandins PGS as well.

[27] Von Euler, U. S. *Arch. Exp. Pathol. Pharmakol.* **1934**, *175*, 78.
[28] a) Bergström, S.; Sjövall, J. *Acta Chem. Scand.* **1957**, *11*, 1086; b) Bergström, S.; Sjövall, J. *Acta Chem. Scand*. **1960**, *14*, 1693 ; c) Bergström, S.; Sjövall, J. *Acta Chem. Scand*. **1960**, *14*, 1701; d) Bergström, S.; Ryhase, R.; Samuelsson, B.; Sjövall, J. *Acta Chem. Scand.* **1962**, *16*, 501; e) Bergström, S.; Ryhase, R.; Samuelsson, B.; Sjövall, J. *Biol. Chem*. **1963**, *238*, 3555.
[29] a) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*, Academic Press, New York, **1977**, 7 b) Mitra, A. *The Synthesis of Prostaglandins*; Wiley: New York, **1977** c) *New Synthetic Routes to Prostaglandins and Tromboxanes*; Roberts, S. M., Scheinmann, F., Eds.; Academic Press: New York, **1982** d) Newton, R. F.; Roberts, S. M. *Prostaglandins and Tromboxanes*; Butterworth: London, **1982** e) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley and Sons: New York, **1989** f) Nicolaou, K. C.; Sorensen, E. J. In *Classics in Total Synthesis- Targets, Strategies, Methods*; VCH: Weinheim, **1996**, 65 g) Das, S.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Chem. Rev.* **2007**, 3286.



Scheme 8

Prostanoids are obtained by total synthesis[30] following three main basic ideas: 1) the core structure cyclopentane is prepared with the right substituents in appropriate positions to add the chains later. In this elegant and versatile approach the *Corey lactone* **7** [31] can be considered a milestone in the prostaglandin synthesis (Figure 11); 2) a five-membered cyclic compound containing the first chain is coupled with the second one; 3) one pot procedure that exploits the three-component coupling.

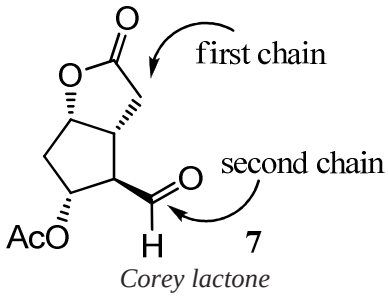
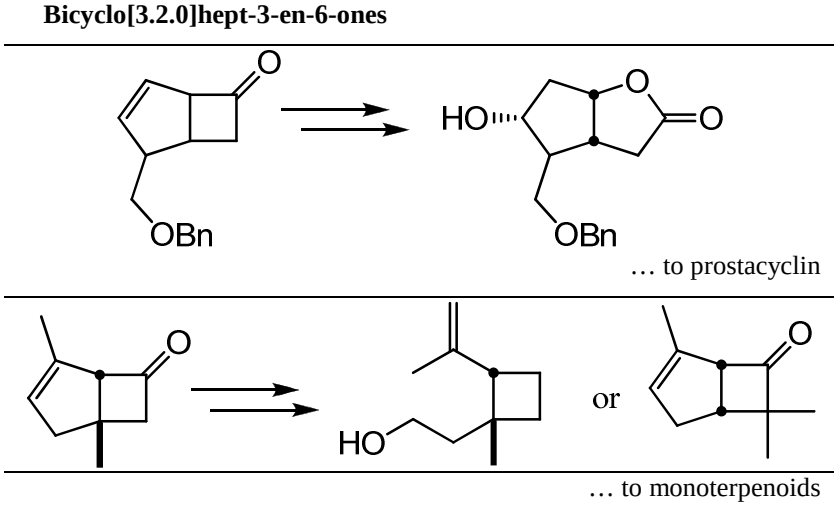


Figure 11

Like described above, the *Corey lactone* derivates are highly versatile intermediates for the synthesis of prostaglandins.[32] Bicyclo[3.2.0]heptanones and bicyclo[3.2.0]hept-3-

[30] Nicolaou, K. C.; Vourlomis, D.; Wissinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 45.
[31] Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc*. **1969**, *91*, 5675.
[32] a) Corey, E. J.; Andersen, N. H.; Cadson, R. M. ; Paust, J.; Vedejs, E.; Vlattas, I.; Winter, R. E. K. *J. Amer. Chem. Soc*. **1968**, *90*, 3245; b) Corey, E. J.; Vlattas, I.; Andersen, N. H.; Harding K.; *ibid*., **1968**, *90*, 3247; c) Corey, E. J.; Vlattas, I.; Harding K.; *ibid*., **1969**, *91*, 535.

en-6-ones[33] could be attractive building blocks to generate these important molecules and other natural biologically active compounds. In particular we can consider the 1,2-polysubstituted cyclobutanones[34] like the monoterpenoids grandisol, filifolone, raikovenal, and lineatin [35] (Scheme 9).



Scheme 9

These molecules are characterized by a rigid skeleton and the presence of two fused rings of different size that can be modified and functionalized in a straightforward manner. From a synthetic point of view, their attractive features appear to be: 1) the possession of two functional groups like the carbon-carbon double bond in the five-membered ring and the carbonyl group in the four-one, 2) the wedge form, that make possible selective modifications at the less hindered top-side (*exo*-side), 3) the possible reactivity that involves both groups at once since they are joined by a bridge-head carbon atom (Figure 12).

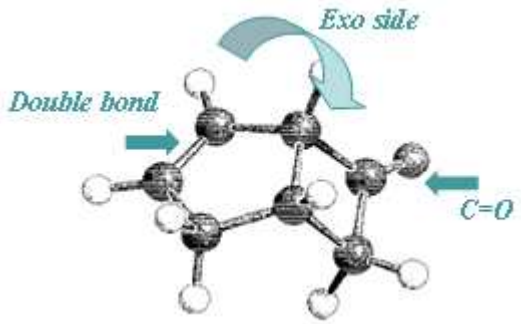
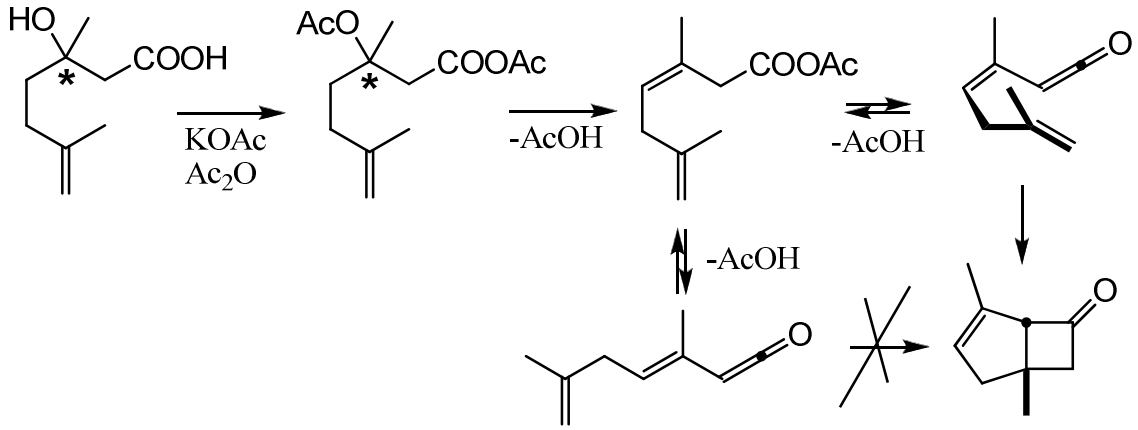


Figure 12

[33] Marotta, E.; Righi, P.; Rosini, G. *Org. Proc. Res. & Devel.* **1999**, *3*, 206 and references cited therein.
[34] Lee-Ruff, E.; Mladenova, G.; *Chem. Rev.* **2003**, *103*, 1449.
[35] Rosini, G.; Laffi, F.; Marotta, E.; Pagani, I.; Righi, P. *J. Org. Chem.* **1998**, *63*, 2389.

Due to the great importance of these cyclopentanic scaffolds, the last decades have seen many academic works devoted to find an efficient and versatile synthesis. For example, a general convenient and racemic approach to bicyclo[3.2.0]hept-3-en-6-ones exploits heptenoic acids like starting material. In the Scheme 10 the reaction conditions and the mechanism are shown: the sequence of events demonstrates the impossibility to obtain an enantiopure product even if starting with a optical pure acid. The loss of chirality occurs during the 1,2 elimination of acetic acid to generate an α,β-unsaturated mixed anhydride. Olefinic α,β-unsaturated ketene can be generated in two isomers (*E* and *Z*), but only the 3,4-*Z*-unsaturated intermediate can cyclize intramolecularly.



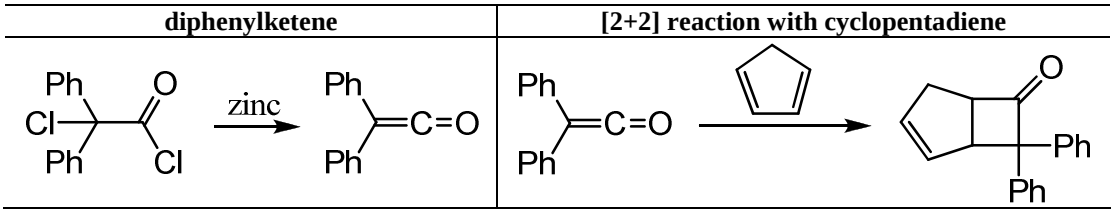
Scheme 10

Enantiopure targets can be obtained by following a different synthetic route or simply resolving the racemic compounds. For example an efficient method for the resolution is the stereoselective reduction to the corresponding alcohols, followed by the conversion into diastereoisomers using (–)-(1*S*,4*R*)-camphanic acid chloride as resolving agent and then chromatography separation. After a mild alkaline hydrolysis, the conversion to the enantiopure target is performed by oxidation. The $[\alpha]_D$ magnitudes of bicycles are consistent with the geometric structure of these unsaturated ketone chromophores.[36]

[36] Erman, W. F.; Treptw, R. S.; Bakuzis, P.; Wenkert, E. *J. Am. Chem. Soc.* **1971**, *93*, 657.

3.1.2 Second part

In the early years of the 20th century, Hermann Staudinger[37] has discovered ketene[38] and its reactions[39] starting from the [2+2]-cycloaddition of cyclopentadiene with diphenylketene, prepared by the dehalogenation of chlorodiphenylacetyl chloride with granulated zinc (Scheme 11). This discovery has been made two decades before the development of the Diels-Alder cycloaddition, and is still a fundamental mainstay of the organic chemistry.



Scheme 11

Ketenes are highly useful and versatile organic reactive intermediates that can undergo many possible transformations. They are characterized by an high electron density at the C2-substituted carbon and prefer to react with alkenes across the C=C rather than C=O bond. The traditional interpretation of the Staudinger reaction mechanism[40] is shown in Figure 13.

[37] Staudinger, H. *Chem. Ber.* **1905**, *38*, 1735.
[38] a) Staudinger, H. *Die Ketene*; Verlag Enke: Stuttgart, **1912**; b) Staudinger, H. *From Organic Chemistry to Macromolecules*; Wiley: New York, **1970**; c) Staudinger, H.; Klever, H. W. *Chem. Ber*. **1908**, *41*, 594; d) Staudinger, H.; Klever, H. W. *Chem. Ber*. **1908**, *41*, 1516.
[39] a) Staudinger, H. *Liebigs Ann. Chem*. **1907**, *356*, 51; b) Staudinger, H. *Chem. Ber*. **1907**, *40*, 1145; c) Staudinger, H.; Suter, E. *Chem. Ber*. **1920**, *53B*, 1092; d) Staudinger, H.; Rheiner, A. *Hel*v. *Chim. Acta* **1924**, *7*, 8.
[40] Machiguchi, T.; Hasegawa, T.; Ishiwata, A.; Terashima, S.; Yamabe, S.; Minato, T. *J. Am. Chem. Soc.* **1999**, *121*, 4771 and references cited therein.

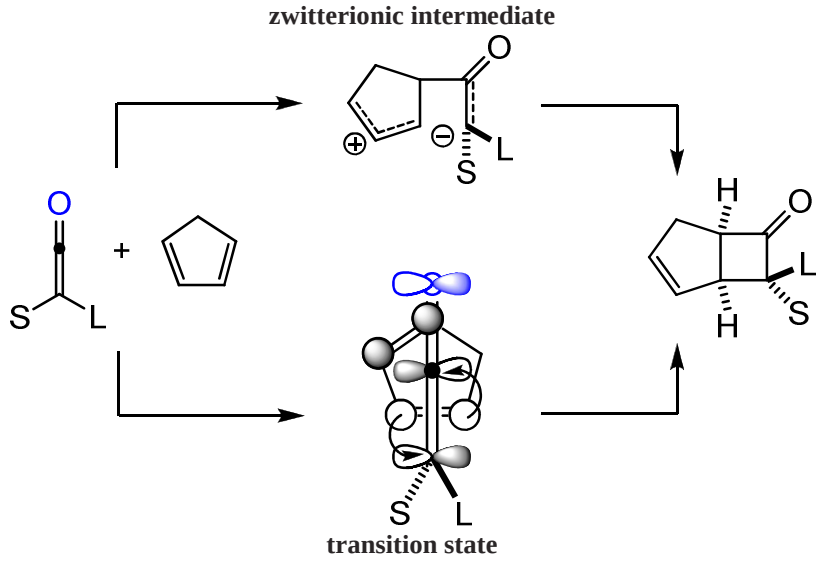


Figure 13

The bicycle can be formed through: 1) a two-step mechanism via a zwitterionic intermediate or 2) a concerted pathway via transition state, where the cyclopentadiene HOMO orthogonally interact with the ketene LUMO. It is well known that in thermal reaction ketenes are regarded as good antarafacial components. A large number of experiments[41] have followed the Staudinger pioneering studies, with important new discoveries from laboratories around the world. The most representative and remarkable development is found in a key initial stage of the total synthesis of prostaglandins[42] (see 3.1.1).

An alternative to ketenes cycloaddition involves the reaction of keteniminium salts with alkenes. The higher contribution to this field has been made by Ghosez[43] and co-workers.

Electronic structure

Ketene keteniminium ion

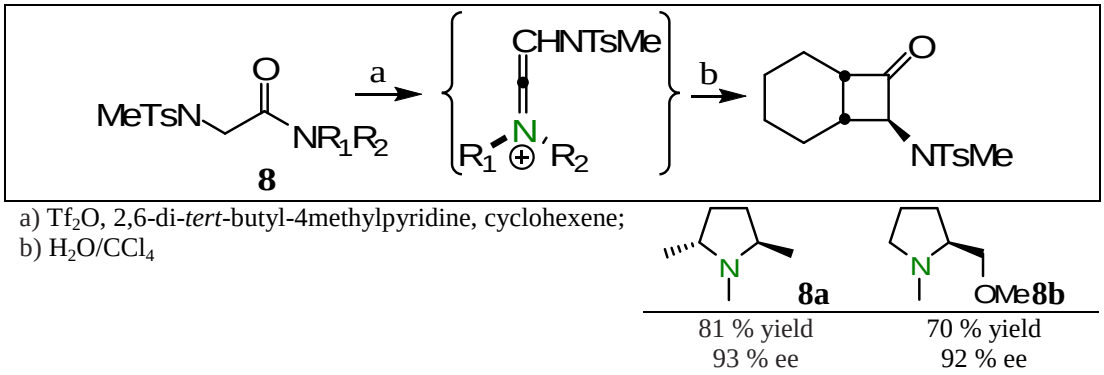
Figure 14

[41] a) Tidwell, T. T. *Ketenes*; Wiley: New York, NY, **1995**; b) Hyatt, J.; Raynolds, R. W. *Org. React.* **1994**, *45*, 159; Tidwell, T. T. *Eur. J. Org. Chem.* **2006**, 563.

[42] a) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397; b) Corey, E. J.; Noyori, R.; Schaaf, T. K. *J. Am. Chem. Soc.* **1970**, *92*, 2586; c) Corey, E. J.; Shirahama, H.; Yamamoto, H.; Terashima, S.; Venkateswarlu, A.; Schaaf, T. K. *J. Am. Chem. Soc.* **1971**, *93*, 1490.

[43] Ghosez, L.; Marchand-Brynaert, J. *"Iminium Salts in Organic Chemistry Part 1"*; Bohme, J., Viehe, H. G., Eds., Wiley: New York, **1976**, 421.

These ketene equivalents are readily available from amide, more electrophilic than ketenes and avoid the dimerization problem often encountered in ketene reactions (Figure 14). The presence of a tetravalent iminium cation permits to hook a chiral auxiliary group on nitrogen to yield pure cyclic and polycyclic derivates that are important building blocks for the stereocontrolled construction of more complex carbon frameworks. Keteniminium salts can be easily synthesized by treatment, in an inert solvent, of an amide with triflic anhydride and a non-nucleophilic base or from α-halo enamine.[44] In a recent paper,[45] Ghosez has provided an efficient [2+2]-cycloaddition between olefins and chiral keteniminium salt, generated in-situ from N-tosylsarcosinamide **8** (
Scheme 12). This reaction involving ketenes bearing a chiral substituent led to asymmetric products. A model reaction with cyclohexene has been exploited to investigate the best auxiliary among various molecules with C_2 symmetry. In the scheme has been report two auxiliary examples arising from an asymmetric Baker's yeast reduction **8a**[46] and prolinol **8b**.[47] Ketenimium generated from these secondary amines has been tested in reaction of a wide variety of olefins with good yields and diastereoselection.



Scheme 12

The cycloaddition of a ketene or keteniminium salt can be regarded as the most successful way for the four-membered carbocyclic compounds preparation[48] and the

[44] a) Falmagne, J.-B.; Escudero, J.; Taleb-Sahraoui, S.; Ghosez, L. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 879; b) Saimoto, H.; Houge, C.; Hesbain-Frisque, A.-M.; Mockel, A.; Ghosez, L. *Tetrahedron Letters* **1983**, *24*, 2251.
[45] Ghosez, L.; Nahuteau-Betzer, F.; Genicot, C.; Vallribera, A.; Cordier, J. *Chem. Eur. J.* **2002**, *8*, 3411.
[46] Masamune, S.; Kennedy, M.; Short, P. *J. Org. Chem.* **1989**, *54*, 1755.
[47] Seebach, D.; Kalinowski, H.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; DuPreez, N.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H.; Schimdt, M. *Helv. Chim. Acta* **1977**, *60*, 301.
[48] Snider, B. B.; *Chem. Rev.*, **1988**, 793 and references cited therein.

regio- and stereo-controlled polycyclic compounds can be obtained by the [2+2] intramolecular version[49] (Figure 15).

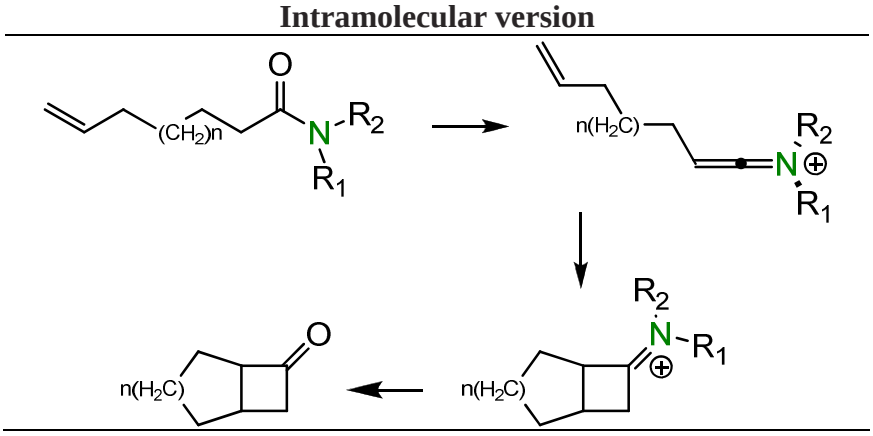
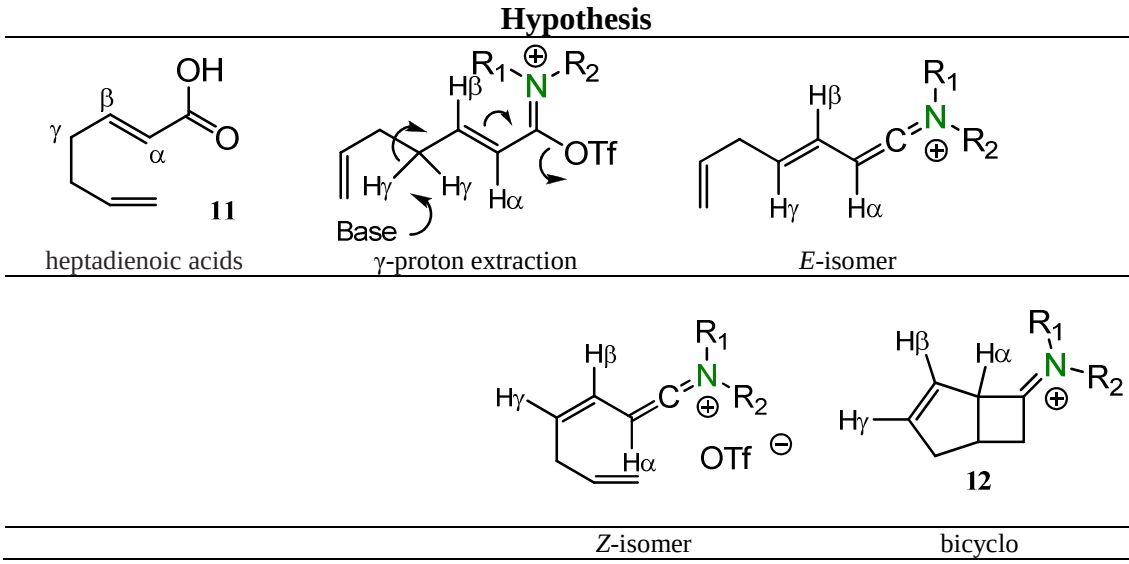


Figure 15

3.1.3 Third part

The above described highly selective asymmetric reaction could provide an attractive route to a wide variety of enantiopure prostanoids scaffolds.[50] To improve this methodology it could be interesting work with heptenoic acids **9** (to bicyclo[3.2.0]heptanones **10**) and, more attractive, with heptadienoic acids **11** (to bicyclo[3.2.0]hept-3-en-6-ones **12**). In this last hypothesis the base has to extract the γ-proton to create a new double bond and the ketenimium salt. The geometry of this new β,γ-double bond is fundamental for the reaction outcome: the *E*-unsaturated intermediates cannot undergo bicyclization while the starting material double bond configuration is independent because of the α,β-double bond is destroyed in the reaction evolution (Scheme 13).

[49] a) Mark6, I.; Ronsmans, B.; Hesbain-Frisque, A.; Dumas, S.; Ghosez, L. *J. Am. Chem. Soc.* **1985**, *107*, 2192; b) Ghosez, L.; O'Donnell, M. J. *Pericyclic Reactions;* Marchand, A. P., Lehr, R. E., Eds.; Academic: New York, **1977;** Vol. 11, 79; c) Frey, H. M.; Isaacs, N. S. *J. Chem.* Soc*B.* **1970**, 830; d) Brady, W. T. *Tetrahedron* **1981**, 2949. Brady, W. T. *Synthesis* **1971**, 415; e) Brady, W. T. *The Chemistry of Ketenes, Allenes and Related Compounds;* Patai, *S.*, Ed.; Interscience: New York, **1980;** 278.
[50] Adam, J.; Ghosez, L.; Houk, K. N. *Angew. Chem Int. Ed.* **1999**, *38*, 2728.



Scheme 13

This asymmetric [2+2] reaction has to be performed with a cheap, convenient and easily synthesized chiral auxiliary. We have decided to test the 5-benzyl-2,2,3-trimethylimidazolidin-4-one **13**[51] as auxiliary. This compound is a secondary amine that can be obtained in large scale and in both enantiomeric forms starting from the amino acid phenylalanine **14** (Figure 16). The synthetic procedure reported in literature has been modified to optimize the synthetic process. For example, we replaced the crystallization step of crude **13** in hot isopropyl alcohol with a simple washing in acetone.

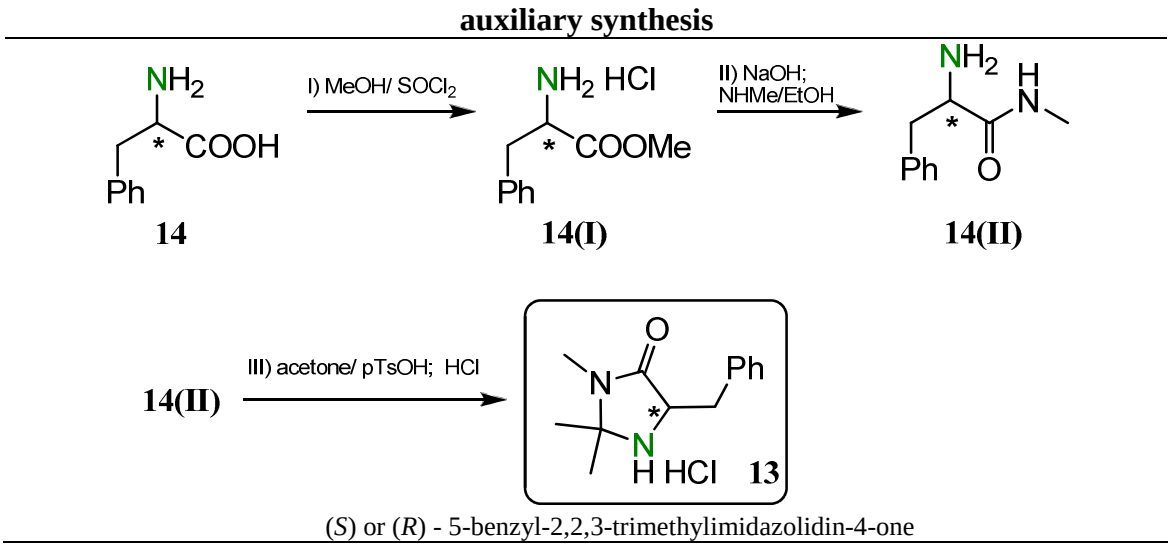
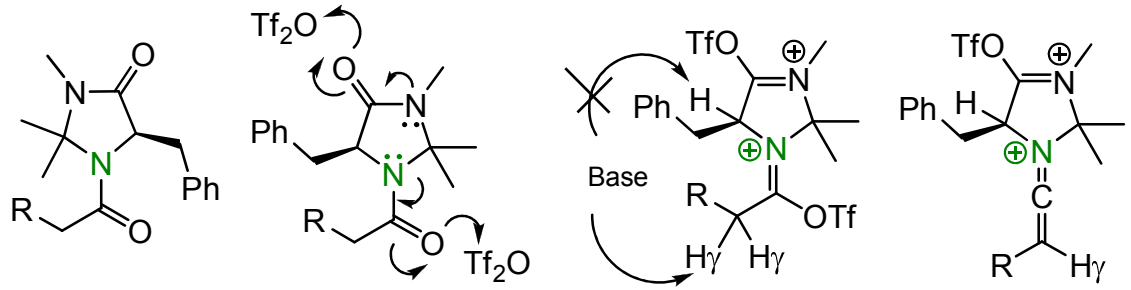


Figure 16

[51] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

It is often employed as an organocatalyst, and is effective for various class of cycloaddition through the LUMO-lowering activation of α,β-unsaturated carbonyls via the reversible formation of iminium ions.[52] In our case it could be able to enantioselect the cycloadduct inducing the closure of the cycle only from the favorite and less hindered side. The presence of a second amide group should not be a problem: if this group is attacked by the anhydride it can't be transformed into keteniminium ion (Figure 17).



Chiral amide | Anhydride attack | Proton extraction | Keteniminium ion

Figure 17

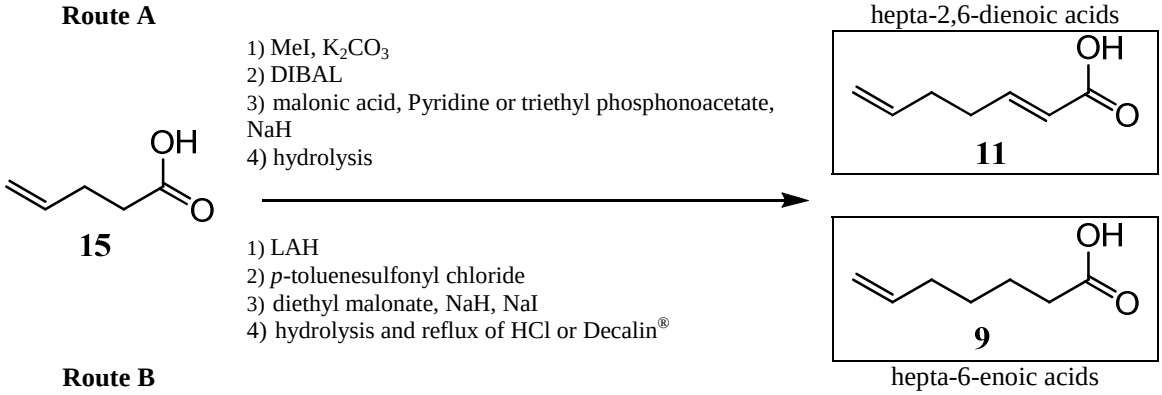
Differently by the standard reaction condition we have decided to use two equivalents of anhydride to be sure of obtain one equivalent of keteniminium ion.

3.2 Result and discussion

3.2.1 Acids and Amides synthesis

From these assumptions we have prepared a set of chiral amides with different substituents by reacting hepta-2,6-dienoic acids **11** or hepta-6-enoic acids **9** with the enantiopure *MacMillan* imidazolidinone **13** as auxiliary. Herein, we report the preparation of these classes of acids. Both synthetic strategies start from pent-4-enoic acids **15** (Scheme 14).

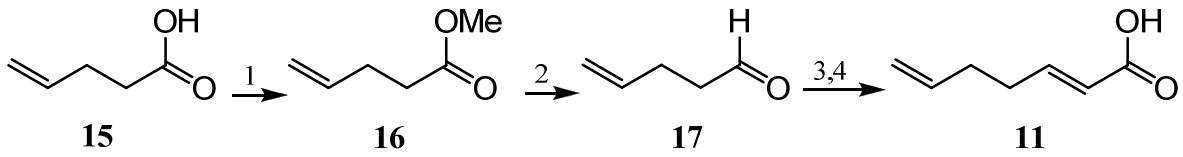
[52] a) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874, b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370, c) Austin, J. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172; d) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192; e) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.



Scheme 14

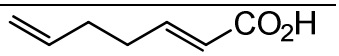
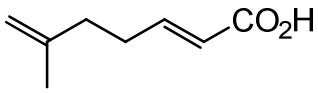
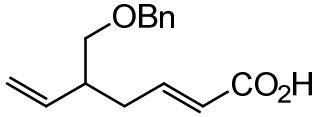
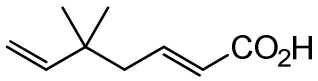
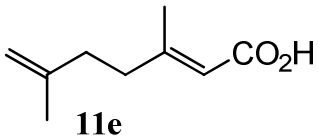
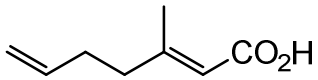
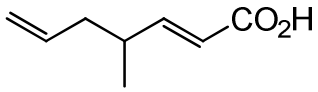
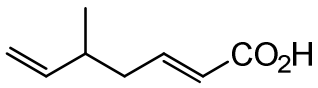
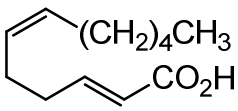
In the route A to obtain the acids **11** (Scheme 15), the pent-4-enoic acids **15** were transformed into the corresponding methylesters **16** by treating with MeI and K_2CO_3 in DMF at room temperature for 1h to obtain good reducible substrates. The esters **16** were converted into aldehydes **17** with a cold solution of DIBAL in dry dichloromethane under inert atmosphere. The 4-pentenylaldehydes **17** were refluxed with dry pyridine and malonic acid until the condensation was complete (method A). The reaction times were too long and the yields are not high so a new synthetic strategy was followed. In the method B the aldehydic derivates **17** were treated with triethyl phosphonoacetate and NaH in dry THF, then hydrolyzed. In the Table 4 yields of all steps are summarized.

Route A



1) MeI, K_2CO_3 2) DIBAL	3) malonic acid, Pyridine or triethyl phosphonoacetate, NaH 4) hydrolysis	***hepta-2,6-dienoic acids***

Scheme 15

Route A					
Reaction yields (%)					
Entry	Methylation	Reduction to aldehyde	Acid synthesis		***Hepta-2,6-dienoic acids***
			Method A	Method B	
1	**16a** (100)	**17a** (100)		73	 **11a**
2	commercial ethyl 4-methyl-4-pentenoate	**17b** (98)		74	 **11b**
3	available compound [a]	**17c** (99)		80	 **11c**
4	commercial methyl 3,3-dimethyl-4-pentenoate	**17d** (95)		52	 **11d**
5		commercial 5-methylhex-5-en-2-one		72	 **11e**
6		commercial hex-5-en-2-one		77	 **11f**
7	**16b** (95)	**17e** (87)	30		 **11g**
8	**16c** (91)	**17f** (99)	45		 **11h**
9		commercial cis-4-decenal	87		 **11i**

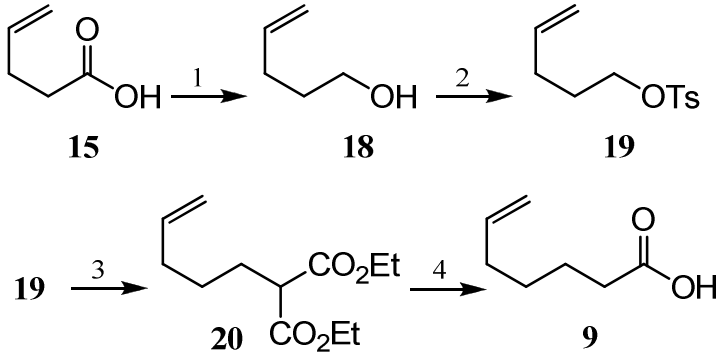
[a] Marotta, E.; Righi, P.; Rosini, G. *Org. Lett.* **2000**, *2*, 4145.

Table 4

To obtain the hepta-6-enoic acids **9** we followed the second route B (Scheme 16): the pent-4-enoic acids **15** were reduced using a solution of LAH in dry THF under inert atmosphere to give the corresponding alcohols **18**. These were converted in more reactive electrophiles **19** treating with *p*-toluenesulfonyl chloride and dry pyridine. Substituted 4-pentenylmalonates **20** were prepared in good yields by alkylation of

diethyl malonate with 4-pentyl tosylates using NaH as the base in presence of dry NaI. The desired acids **9** (Table 5) were obtained after a hydrolysis step conduced in decarboxylation conditions. The first approach was the removal of a molecule of carbon dioxide by treating with an excess of HCl at reflux. The moderate yields and the long reaction times (several days) suggested us to change decarboxylation agent. Decalin® was added to the diacids and heated until CO_2 gas evolution ceased. The Decalin® removal afforded the crude mono-acids.

Route B

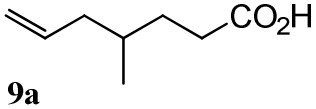
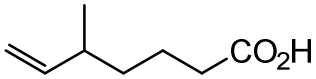
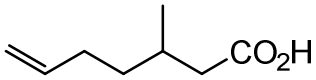
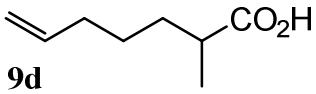
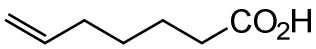


1) LAH
2) *p*-toluenesulfonyl chloride
3) diethyl malonate, NaH, NaI
4) hydrolysis and reflux of HCl or Decalin®

hepta-6-enoic acids

Scheme 16

Route B

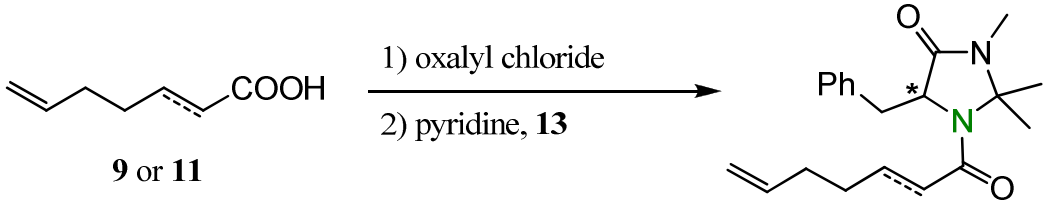
Entry	Reduction to alcohol	Tosylate	Malonate	Reaction yields (%) Decarboxylation HCl	Decarboxylation Decalin®	***Hepta-6-enoic acids***
1	**18a** (99)	**19a** (76)	**20a** (98)	58		 **9a**
2	**18b** (95)	**19b** (66)	**20b** (98)	61		 **9b**
3	**18c** (89)	**19c** (87)	**20c** (61)		87	 **9c**
4		Commercial 5-bromopent-1-ene	**20d** (100)		99	 **9d**
5[a]						 **9e**

[a] commercially available hept-6-enoic acid.

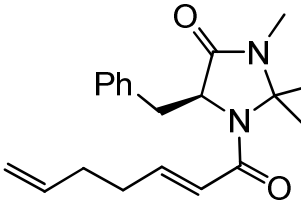
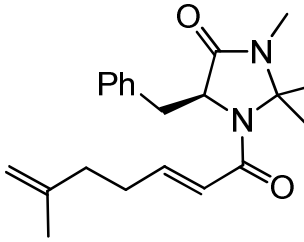
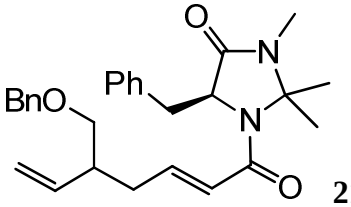
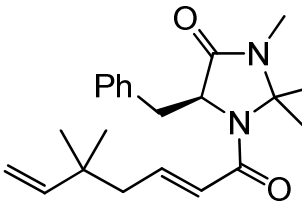
Table 5

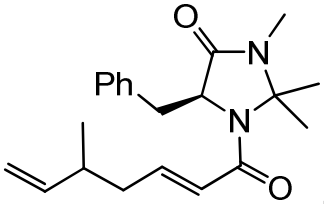
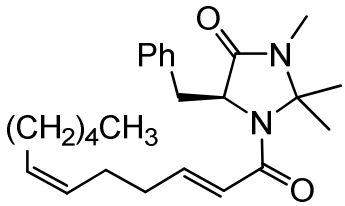
These resulting hepta-2,6-dienoic acids **11** and hepta-6-enoic acids **9** were successful converted into the corresponding acid chlorides by treatment with a cool solution of oxalyl chloride in anhydrous dichloromethane. Reaction of the chlorides with (*R*)- or (*S*)-imidazolidinone **13** in anhydrous dichloromethane, at room temperature and with pyridine presence gave in good yields the desired chiral amides **21** (Table 6).

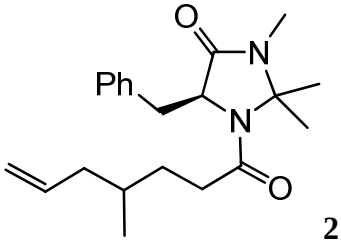
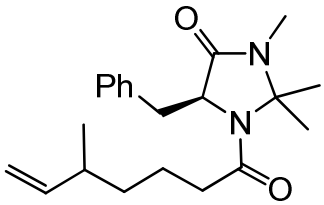
Synthetic amides

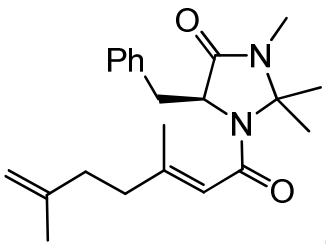
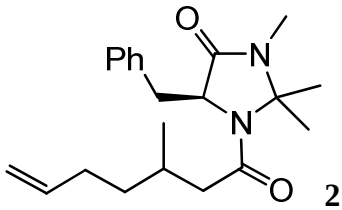
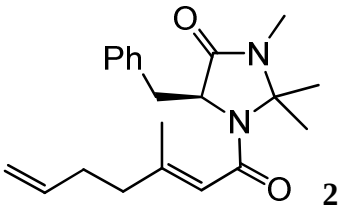
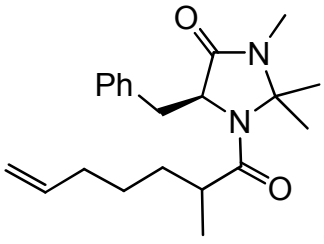
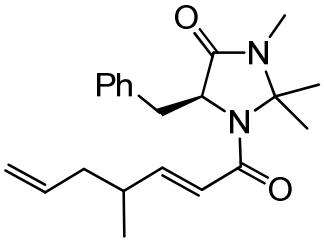
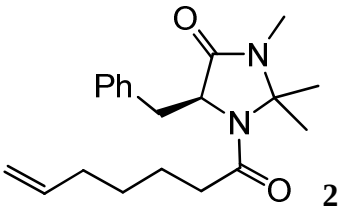


9 or **11** → **21**

Entry	yield	Amides from hepta-2,6-dienoic acids
1	37	 **21a**
2	66	 **21b**
3	86	 **21c**
4	26	 **21d**

Entry	yield	Amides from hepta-2,6-dienoic acids
8[a]	89	 **21h**
9	86	 **21i**

Entry	yield	Amides from hepta-6-enoic acids
10[a]	80	 **21l**
11	80	 **21m**

5	78	 **21e**	12	50	 **21n**
6[a]	63	 **21f**	13	61	 **21o**
7[a]	82	 **21g**	14	82	 **21p**

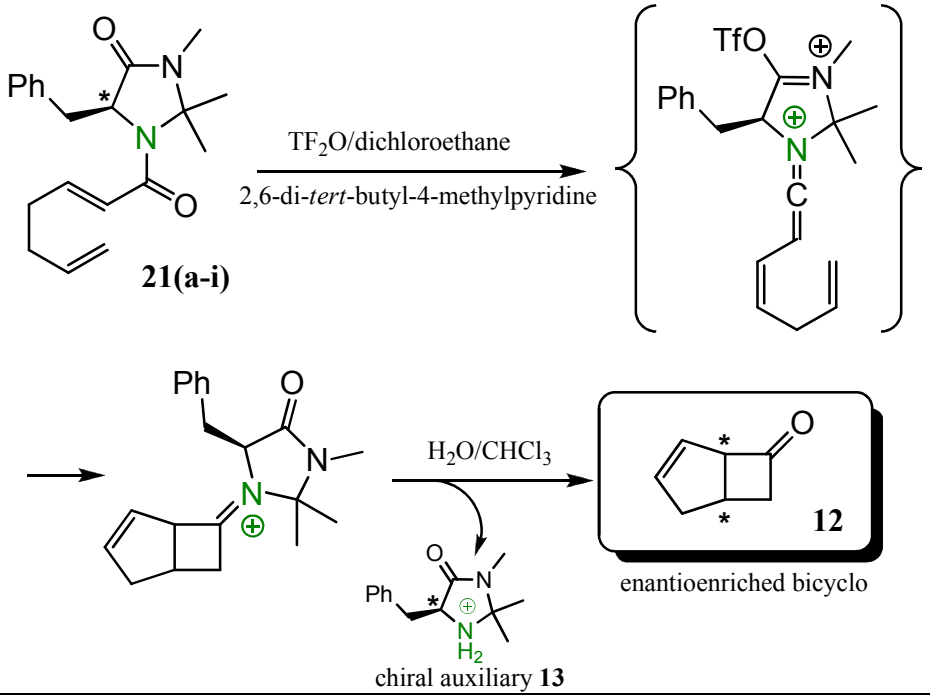
[a] Synthesized with (*R*) –imidazolidinone too.

Table 6

3.2.2 The [2+2] reaction and bicycles

As shown in Scheme 17, amides **21a-i** from hepta-2,6-dienoic acids can be converted into the corresponding ketene iminium triflate by treatment with two equivalents of triflic anhydride (added dropwise over one hour) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine as base (1.2 eq.). The bicyclo[3.2.0]hept-3-en-6-ones **12** can be obtained after hydrolysis ($H_2O/CHCl_3$, reflux, 4h) of the crude iminium salts, while the auxiliary **13** was recovered (*c.a.* 20 % yield) by the extraction of the aqueous layer at pH 14 with ether.

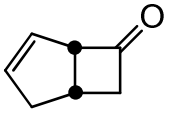
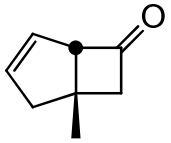
The [2+2] cycloaddition reaction



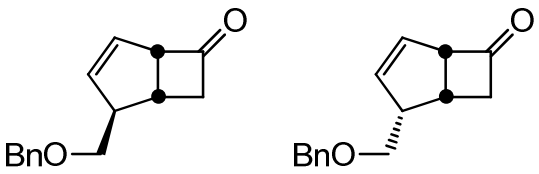
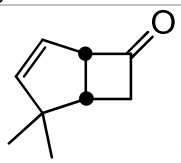
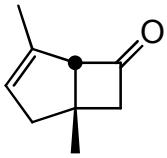
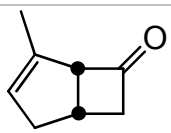
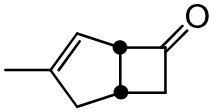
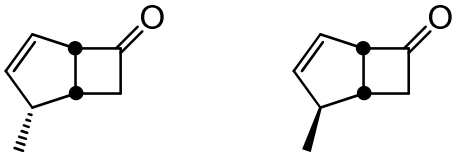
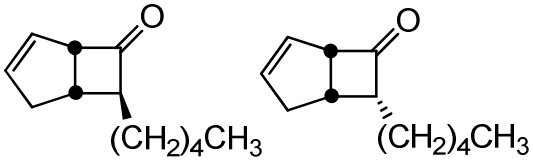
Scheme 17

The bicycle relative structure was established by NOESY1D experiments and the absolute structure was assigned comparing the $[\alpha]_D$ sign of these molecules with known compounds.[53] As indicated in Table 7, at room temperature the cycloaddition affords cyclobutanones **12** with moderate to good yields, a good diastereoselection and high enantiomeric excess. Because of the high volatility of the product yields were calculated by GC analysis on the crude after the hydrolysis step.

Bicyclo[3.2.0]hept-3-en-6-ones

Entry	Amide	Product	Dr [a]	Yield[a] (%)	Ee[b] (%)
1	**21a**	 **12a**		66	91
2	**21b**	 **12b**	-	-	-

[53] Pagani, I.; Righi, P.; Rosini, G.; Bertolasi, V.; Medici, A.; *Tetrahedron: Asymmetry* **1995**, *6*, 2319.

3	**21c**	 **12c** *Major* **12c** *Minor*	92/8	35	93 *Major*	67 *Minor*
4	**21d**	 **12d**		40	57	
5	**21e**	 **12e**	-	-	-	
6[c]	**21f**	 **12f**		71	93	
7[c]	**21g**	 **12g**		65	93	
8[c]	**21h**	 **12h** *Major* **12h** *Minor*	51/49	66	87 *Major*	84 *Minor*
9	**21i**	 **12i** *Major* **12i** *Minor*	88/22	70	92 *Major*	91 *Minor*

[a]Calculated to crude product by GC-analysis with an Agilent 19091Z-413E HP-1 Methyl siloxane column. [b]Determined by GC-analysis with a Restek 13104 Rt-betaDEXsm column. [c]Synthesized the opposite enantiomer with (*R*)- imidazolidinone.

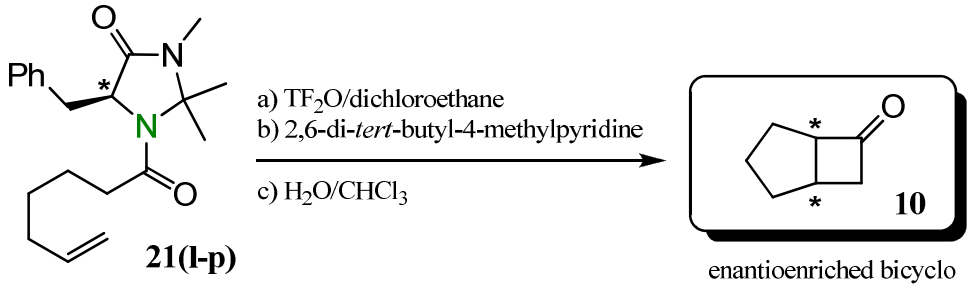
Table 7

The reaction is sensitive of substituents at the C6 position, in fact entry 2 and 5 were unsuccessful. Testing reaction conditions we have found that acetic anhydride and trifluoroacetic anhydride are not active to fulfill ketene generation and that, interestingly, the diastereo- and enantiocontrol does not improve at lower temperatures.

With optimized reaction conditions in hand, we set out to synthesize substituted bicyclo[3.2.0]heptanones trying intermolecular and intramolecular process (Table 8, Table 9) and oxa-bicyclo[3.2.0]heptanones (Table 10).

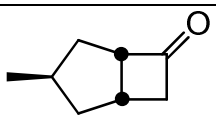
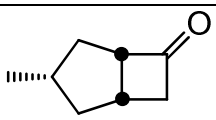
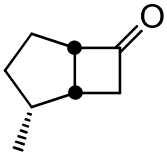
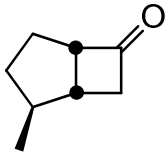
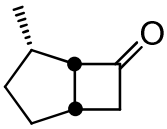
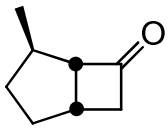
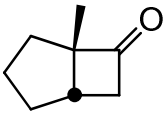
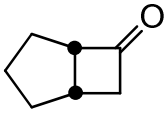
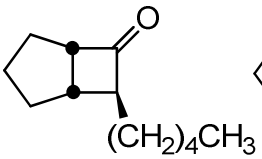
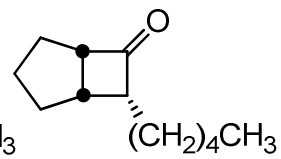
Bicyclo[3.2.0]heptan-6-ones

INTRAMOLECULAR



21(l-p)

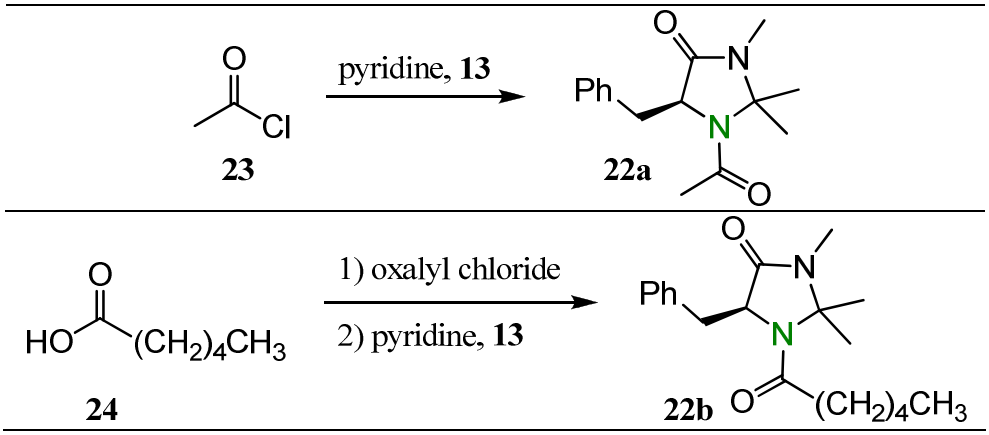
enantioenriched bicyclo

Entry	Amide	Product		Dr [a]	Yield[a] (%)	Ee[b] (%)	
1	**21l**	 **10a** *Major*	 **10a** *Minor*	55/45	32	85 *Major*	90 *Minor*
2	**21m**	 **10b** *Major*	 **10b** *Minor*	47/53	34	87 *Major*	92 *Minor*
3	**21n**	 **10c** *Major*	 **10c** *Minor*	67/33	28	79 *Major*	93 *Minor*
4	**21o**	 **10d**		-	-	-	
5	**21p**	 **10e**			25	88	
6	**21i** [c]	 **10f** *Major*	 **10f** *Minor*	88/22	70	92 *Major*	91 *Minor*

[a]Calculated to crude product by GC-analysis with an Agilent 19091Z-413E HP-1 Methyl siloxane column. [b]Determined by GC-analysis with a Restek 13104 Rt-betaDEXsm column. [c]Synthesized by hydrogenation with H_2 Pt/C of **12i** bicycle.

Table 8

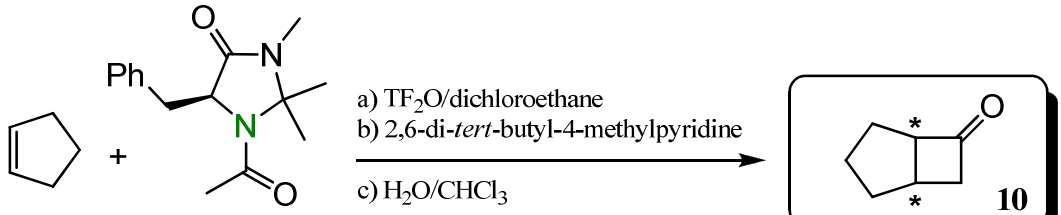
The amides **22a**, **22b** for the intermolecular sequence were prepared as described previously starting from acetyl chloride **23** (yield 97%) and heptanoic acid **24** (yield 81%) (Scheme 18).

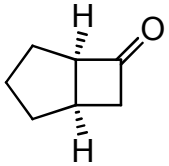
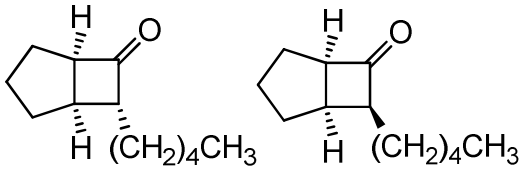


Scheme 18

Bicyclo[3.2.0]heptan-6-ones

INTERMOLECULAR



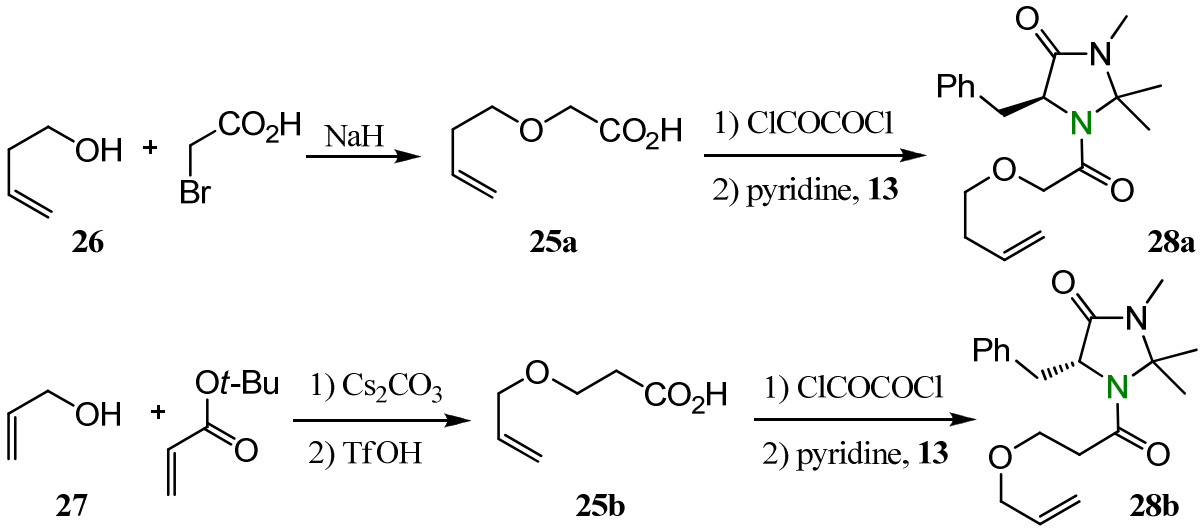
Entry	Amide	Product	Dr [a]	Yield[a] (%)	Ee[b] (%)
1	**22a**	 **10e**		3	96
2	**22b**	 **10f** *Major* **10f** *Minor*	65/35	5	63 (*Major*) 80 (*Minor*)

[a]Calculated to crude product by GC-analysis with an Agilent 19091Z-413E HP-1 Methyl siloxane column. [b]Determined by GC-analysis with a Restek 13104 Rt-betaDEXsm column.

Table 9

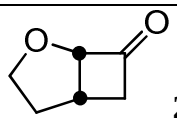
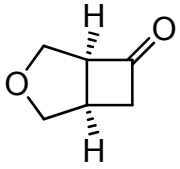
As shown in Table 8 the reaction proceed with moderate yields and high enantiomeric excess. The reaction with the amide **22a** and **22b** gave the corresponding bicycle in very low yields but with a high and opposite ee. So, starting from the same auxiliary [(*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one, **(*S*)-13**] the two mechanisms have an opposite enantioselectivity but the intermolecular process is disadvantage. The above results shown that the C2 is another denied position: the reaction critically depends on the no-replacement of the bridge head hydrogens. The resulting enantioselection is very good, instead diastereoselection is lower than bicyclo[3.2.0]hept-3-en-6-ones.

Because of the great importance of these bicycles we have thought that the synthesis of molecules containing a hetero atom (like oxygen) could be interesting to expand the products set. The hepta-6-enoic acids **25** for the oxa-products were synthesized with two new synthetic routes starting from 3-buten-1-ol **26** and prop-2-en-1-ol **27** and then converted into the corresponding amides **28** (Scheme 19).



Scheme 19

These chiral intermediates **28** gave oxa-bicycles in moderate yields and enantiomeric excess (Table 10).

Oxa-Bicyclo[3.2.0]heptan-6-ones				
Entry	Amide	Product	Yield[a] (%)	Ee[b] (%)
1	**28a**	 **29a**	50	40
2	**28b**	 **29b**	17	60

[a]Calculated to crude product by GC-analysis with an Agilent 19091Z-413E HP-1 Methyl siloxane column. [b]Determinated by GC-analysis with a Restek 13104 Rt-betaDEXsm column.

Table 10

To complete the study we have made a large number of experiments to obtain bicyclo[4.2.0]heptanones which, unexpectedly, have no success.

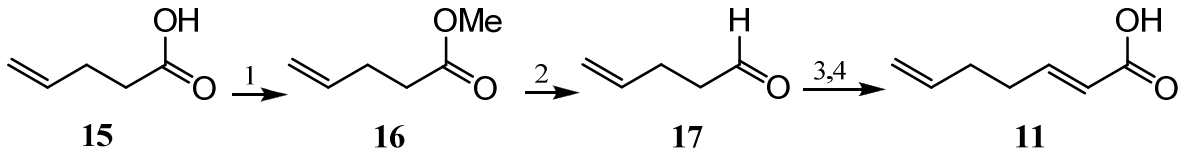
3.3 Conclusion

Several works followed the initial Corey route to the research of new syntheses of prostaglandins analogues and their intermediates. Because of the demonstrated importance of bicyclo[3.2.0]heptanones **10** and bicyclo[3.2.0]hept-3-en-6-ones **12** like versatile building blocks to generate these important molecules we decided to find an asymmetric synthesis. In this chapter, we have developed an efficient and simple method for preparing a large scale of bicycles with high regio- and stereoselectivity exploiting the [2+2]-cycloaddition of chiral keteniminium salts.

3.4 Experimental section

Route A: synthesis of hepta-2,6-dienoic acids

Route A



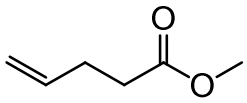
15 **16** **17** **11**

1) MeI, K_2CO_3
2) DIBAL
3) malonic acid, Pyridine or triethyl phosphonoacetate, NaH
4) hydrolysis

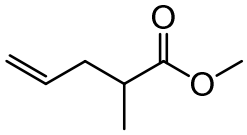
hepta-2,6-dienoic acids

(Scheme 15)

General Procedure[54] **for the synthesis of Methyl esters 16 :** Solid potassium carbonate (1.1 eq.) was added to a solution of acid **15** (1 eq.) in DMF (1.0 mL/mmol) cooled with an ice-water bath. After 10 min, methyl iodide (2 eq.) was added and the mixture was stirred at 0 °C for 30 min. The reaction was warmed to room temperature and stirred for an additional hour. Water was added to the mixture and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated under reduce pressure. The methyl ester was directly used in the next step without further purification.



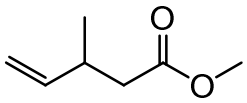
Methyl pent-4-enoate (16a): 5.0 g (49.9 mmol) of commercial pent-4-enoic acid afforded 5.7 g of product (49.9 mmol, 100 % yield). ^{1}H NMR (400MHz, $CDCl_3$): δ 2.40 (*m*, 4H), 3.68 (*s*, 3H), 5.00 (*m*, 1H), 5.06 (*m*, 1H), 5.82 (*m*, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ 28.7 (CH_2), 33.2 (CH_2), 51.4 (CH_3), 115.4 (CH_2), 136.5 (CH), 173.4 (C).



Methyl 2-methylpent-4-enoate (16b): 10.4 g (98.6 mmol) of commercial 2-methylpent-4-enoic acid afforded 10.9 g of product (85.0 mmol, 95 % yield). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.16 (*d*, 3H, *J* = 6.8Hz), 2.18 (*m*, 1H), 2.41 (*m*, 1H), 2.53 (*sext*,

[54] In according to literature: Garner, P.; Park, J. M. *Org. Syntheses* Coll. Vol. 9, **1998**, 300.

1H, *J* = 7.1Hz), 3.67 (*s*, 3H), 5.05 (*m*, 2H), 5.75 (*m*, 1H); ^{13}C NMR (75MHz, $CDCl_3$): δ 16.5 (CH_3), 37.7 (CH_2), 39.1 (CH), 51.4 (CH_3), 116.8 (CH_2), 135.4 (CH), 176.5 (C).



Methyl 3-methylpent-4-enoate (16c): 5.0 g (43.8 mmol) of commercial 3-methylpent-4-enoic acid afforded 5.2 g of product (40.1 mmol, 91 % yield). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.06 (*d*, 3H, *J* = 6.9Hz), 2.27 (*dd*, 1H, *J* = 7.4, 14.8Hz), 2.37 (*dd*, 1H, *J* = 7.1, 14.8Hz), 2.68 (*m*, 1H), 3.67 (*s*, 3H), 4.96 (*dt*, 1H, *J* = 1.3, 10.2Hz), 5.02 (*dt*, 1H, *J* = 1.3, 17.0Hz), 5.78 (*ddd*, 1H, *J* = 6.9, 10.2, 17.0Hz); ^{13}C NMR (75MHz, $CDCl_3$): δ 19.7 (CH_3), 34.4 (CH), 41.1 (CH_2), 51.4 (CH_3), 113.3 (CH_2), 142.4 (CH), 162.3 (C).

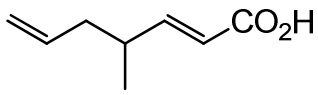
General Procedure[54] for the reduction to aldehydes 17 : In a dry three-necked flask, equipped with magnetic stirring bar, rubber septa and low temperature thermometer, was added the methyl ester **16** (1 eq.) in dry dichloromethane (2.0 mL/mmol). The solution was cooled to -78 °C and a solution of DIBAL 1M in dichloromethane (1.7 eq.) was added dropwise. The rate of addition is adjusted to keep the internal temperature below -65° C. The reaction mixture was stirred at -78 °C until it was complete by GC analyses. The reaction was quenched by slowly addition of cold methanol (0.4 mL/mmol) again keeping the internal temperature below -65° C. The emulsion was slowly poured into an ice-cold solution of HCl 1M (6.7 mL/mmol) and stirred for 15 min. The mixture was extracted three times with ether. The combined organic layers were washed with brine, dried with $MgSO_4$ and the solvent was evaporated under reduce pressure. The crude aldehyde was directly used without further purification for the hepta-2,6-dienoic acid formation.

General Procedure for the synthesis of hepta-2,6-dienoic acids 11 :

Method A[55] Malonic acid (1.2 eq.) and dry pyridine (1.6 eq.) were added to a stirred solution of the aldehyde **17** (1 eq.) in dry dichloromethane (2.0 mL/mmol). The mixture was heated to reflux until reaction was complete by GC analyses. The mixture was acidified to pH 1 with HCl 1M and washed three times with diethyl ether. The

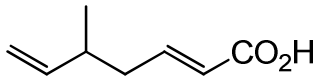
[55] In according to literature: Snyder, B. B.; Allentoff, A. J.; Kulkarni, y. S. *J. Org. Chem.* **1988**, *53*, 5320.

combined organic layers were dried with $MgSO_4$ and the solvent was evaporated. The crude products were purified by flash chromatography.



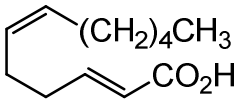
2-Methylpent-4-enal (17e): 10.0 g (78.0 mmol) of methyl ester **16b** afforded 6.7 g of product (67.8 mmol, 87 % yield).

4-Methylhepta-2,6-dienoic acid (11g): 17e (7.0 g, 71.3 mmol) afforded the corresponding acid (3.0 g, 21.4 mmol, 30 % yield); chromatographic conditions : petroleum ether/EtOAc/CH_2Cl_2/AcOH = 87/8/5/0.1 gradient to 75/15/10/0.2; colorless oil; [R_f (87/8/5/0.1) = 0.26]. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.08 (*d*, 3H, *J* = 6.6Hz), 2.16 (*m*, 1H), 2.44 (*m*, 1H), 5.04 (*m*, 2H), 5.73 (*m*, 1H), 5.80 (*dd*, 1H, *J* = 1.4, 15.6Hz), 7.02 (*dd*, 1H, *J* = 7.4, 15.6Hz), 10.26 (*s*, OH); ^{13}C NMR (75MHz, $CDCl_3$): δ 18.5 (CH_3), 36.2 (CH), 39.9 (CH_2), 116.8 (CH_2), 119.2 (CH), 135.6 (CH), 156.4 (CH), 172.2 (C).



3-Methylpent-4-enal (17f): 5.1 g (40.0 mmol) of methyl ester **16c** afforded 3.9 g of product (39.7 mmol, 99 % yield).

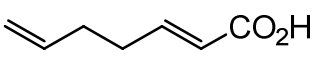
5-Methylhepta-2,6-dienoic acid (11h): 17f (3.9 g, 39.7 mmol) afforded the corresponding acid (2.5 g, 17.9 mmol, 45 % yield); chromatographic conditions : petroleum ether/EtOAc/CH_2Cl_2/AcOH = 87/8/5/0.1 gradient to 75/15/10/0.2; colorless oil; [R_f (87/8/5/0.1) = 0.17]. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.04 (*d*, 3H, *J* = 6.8Hz), 2.25 (*m*, 1H), 2.34 (*m*, 1H), 4.98 (*m*, 1H), 5.01 (*m*, 1H), 5.73 (*ddd*, 1H, *J* = 6.9, 10.4, 17.2Hz), 5.83 (*dt*, 1H, *J* = 1.5, 15.5Hz), 7.03 (*ddd*, 1H, *J* = 7.1, 7.7, 15.5Hz), 10.86 (*s*, OH); ^{13}C NMR (100MHz, $CDCl_3$): δ 19.6 (CH_3), 36.7 (CH), 39.1 (CH_2), 113.5 (CH_2), 121.9 (CH), 142.7 (CH), 150.3 (CH), 171.9 (C).



(6*E*)-Dodeca-2,6-dienoic acid (11i): commercial *cis*-4-decenal (850 mg, 4.4 mmol) afforded the corresponding acid (754 mg, 3.8 mmol, 87 % yield); chromatographic conditions : petroleum ether/EtOAc/CH_2Cl_2/AcOH = 75/15/10/0.2; colorless oil; [R_f (75/15/10/0.2) = 0.51]. IR (neat): ν 2957, 2927, 2857, 1696, 1651 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$): δ 0.89 (*m*, 3H), 1.30 (*m*, 6H), 2.01 (*m*, 2H), 2.25 (*m*, 4H), 5.38 (*m*, 2H), 5.84 (*m*, 1H), 7.08 (*m*, 1H); ^{13}C NMR (75MHz, $CDCl_3$): δ 14.0 (CH_3), 20.8 (CH_2), 22.5 (CH_2), 25.5 (CH_2), 27.2 (CH_2), 29.2 (CH_2), 31.4 (CH_2), 32.3 (CH_2), 120.8 (CH), 127.4 (CH), 131.5 (CH), 151.7 (CH), 175.0 (C).

General Procedure for the synthesis of hepta-2,6-dienoic acids 11 :

***Method B*[56]** Triethyl phosphonoacetate (1 eq.) in THF (0.2 mL/mmol) was added to a suspension of NaH (60 % wt, 1 eq.) in THF (1.0 mL/mmol) at room temperature. The mixture was stirred for 1h, then ketone or aldehyde **17** (1 eq.) was added to the solution and the reaction was stirred overnight. The THF was removed via distillation, the residue was washed with water and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed twice with brine and dried with $MgSO_4$. The solvent was evaporated to obtain the crude ester. To a stirred solution of this esters (1 eq.) in THF (0.2 mL/mmol), a solution of NaOH 10% in water (2.5 eq.) was added. The mixture was heated to reflux until reaction was complete by TLC. The mixture was washed once with diethyl ether and acidified to pH 1 with HCl 1M. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated to afford the crude acid that was directly engaged in the next step without further purification.

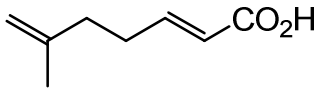


Pent-4-enal (17a): 5.7 g (49.9 mmol) of methyl ester **16a** afforded 4.2g of product (49.9 mmol, 100 % yield).

Hepta-2,6-dienoic acid (11a): 17a (4.2 g, 49.9 mmol) gave the corresponding acid (4.6 g, 36.8 mmol, 73 % yield) as a colorless oil. ^1H NMR (400MHz, $CDCl_3$): δ 2.24

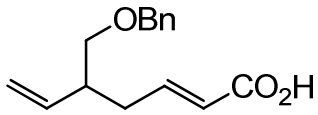
[56] In according to literature: Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, *98*, 4925.

(*m*, 2H), 2.34 (*m*, 2H), 5.02 (*m*, 1H), 5.06 (*m*, 1H), 5.80 (*ddt*, 1H, *J* = 6.4, 10.2, 23.5Hz), 5.85 (*dt*, 1H, *J* = 1.5, 15.6Hz), 7.08 (*dt*, 1H, *J* = 6.7, 15.6Hz), 9.14 (*s*, OH); ^{13}C NMR (100MHz, $CDCl_3$): δ 31.5 (CH_2), 31.8 (CH_2), 115.6 (CH_2), 121.0 (CH), 136.8 (CH), 151.3 (CH), 171.9 (C).



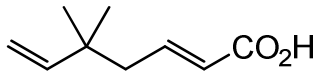
4-Methylpent-4-enal (17b): 1.5 g (10.5 mmol) of commercial ethyl 4-methylpent-4-enoate afforded 1.0 g of product (10.2 mmol, 98 % yield).

6-Methylhepta-2,6-dienoic acid (11b): aldehyde **17b** (1.0 g, 10.2 mmol) afforded the corresponding acid (1.2 g, 7.6 mmol, 74 % yield) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.73 (*s*, 3H), 2.18 (*t*, 2H, *J* = 7.7Hz), 2.38 (*m*, 2H), 4.73 (*m*, 1H), 5.85 (*dt*, 1H, *J* = 1.5, 15.6Hz), 7.08 (*dt*, 1H, *J* = 6.7, 15.6Hz), 11.86 (*s*, OH); ^{13}C NMR (100MHz, $CDCl_3$): δ 22.2 (CH_3), 30.2 (CH_2), 35.7 (CH_2), 110.8 (CH_2), 120.8 (CH), 143.9 (C), 151.4 (CH), 172.0 (C).



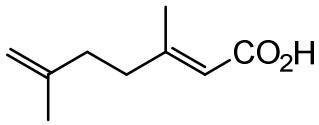
3-(Benzyloxymethyl)pent-4-enal (17c): 6.0 g (24.1 mmol) of ethyl 3-(benzyloxymethyl)pent-4-enoate afforded 4.9 g of product (24.0 mmol, 99 % yield).

5-(Benzyloxymethyl)hepta-2,6-dienoic acid (11c): aldehyde **17c** (4.9 g, 24.0 mmol) afforded the corresponding acid (4.7 g, 19.2 mmol, 80 % yield) as a colorless oil. IR (neat): υ 3030, 2858, 1695, 1651 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$): δ 2.28 (*m*, 1H), 2.50 (*m*, 1H), 2.54 (*m*, 1H), 3.37 (*dd*, 1H, *J* = 6.6, 9.2Hz), 3.45 (*dd*, 1H, *J* = 5.3, 9.2Hz), 4.50 (*s*, 2H), 5.08 (*m*, 1H), 5.11 (*m*, 1H), 5.69 (*ddd*, 1H, *J* = 7.7, 10.9, 16.8Hz), 5.83 (*m*, 1H), 7.03 (*dt*, 1H, *J* = 7.3, 15.5Hz), 7.32 (*m*, 5H); ^{13}C NMR (100MHz, $CDCl_3$): δ 34.1 (CH_2), 42.8 (CH), 72.7 (CH_2), 73.0 (CH_2), 116.5 (CH_2), 122.1 (CH), 127.5 (2CH), 127.6 (2CH), 128.3 (CH), 138.0 (CH), 138.1 (C), 149.9 (CH), 171.8 (C).

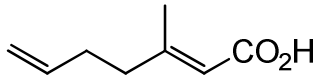


3,3-Dimethylpent-4-enal (17d): 4.0 g (28.1 mmol) of commercial methyl 3,3-dimethyl-4-pentenoate afforded 3.0 g of product (26.7 mmol, 95 % yield).

5,5-Dimethylhepta-2,6-dienoic acid (11d): aldehyde **17d** (3.0 g, 26.7 mmol) afforded the corresponding acid (2.1 g, 14.0 mmol, 52 % yield) as a colorless oil. IR (neat): υ 2954, 1697, 1651 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.04 (*s*, 6H), 2.22 (*dd*, 1H, *J* = 1.5, 7.8Hz), 4.96 (*dd*, 1H, *J* = 1.1, 17.2Hz), 4.98 (*dd*, 1H, *J* = 1.1, 17.2Hz), 5.79 (*dd*, 1H, *J* = 10.9, 17.2Hz), 5.82 (*dd*, 1H, *J* = 1.5, 15.5Hz), 7.02 (*dt*, 1H, *J* = 7.7, 15.5Hz); ^{13}C NMR (100MHz, $CDCl_3$): δ 26.7 ($2CH_3$), 36.9 (C), 45.2 (CH_2), 111.4 (CH_2), 122.7 (CH), 146.8 (CH), 149.2 (CH), 171.8 (C).



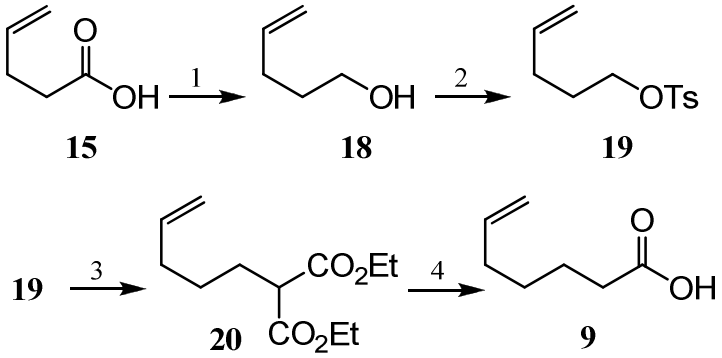
3,6-Dimethylhepta-2,6-dienoic acid (11e): commercial 5-methylhex-5-en-2-one (1.7 g, 15.4 mmol) afforded the corresponding acid (1.7 g, 11.0 mmol, 72 % yield) as a yellow oil. IR (neat): υ 2938, 1693, 1640 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.73 (*s*, 3H), 2.18 (*s*, 3H), 2.25 (*m*, 4H), 4.72 (*m*, 2H), 5.70 (*s*, 1H), 11.60 (*s*, OH); ^{13}C NMR (100MHz, $CDCl_3$): δ 19.0 (CH_3), 22.3 (CH_3), 35.4 (CH_2), 39.3 (CH_2), 110.7 (CH_2), 115.3 (CH), 144.3 (C), 162.7 (C), 172.5 (C).



3-Methylhepta-2,6-dienoic acid (11f): commercial hex-5-en-2-one (2.0 g, 20.4 mmol) afforded the corresponding acid (2.2 g, 15.6 mmol, 77 % yield) as a colorless oil. ^{1}H NMR (600MHz, $CDCl_3$): δ 2.17 (*s*, 3H), 2.26 (*m*, 4H), 5.02 (*dd*, 2H, *J* = 16.9, 32.8Hz), 5.70 (*m*, 1H), 5.78 (*m*, 1H); ^{13}C NMR (150MHz, $CDCl_3$): δ 19.0 (CH_3), 31.4 (CH_2), 40.3 (CH_2), 115.4 (CH_2), 115.5 (CH), 137.0 (CH), 162.3 (CH), 172.5 (C).

Route B: synthesis of hepta-6-enoic acids

Route B

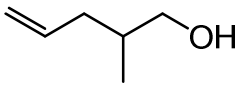


1) LAH
2) *p*-toluenesulfonyl chloride
3) diethyl malonate, NaH, NaI
4) hydrolysis and reflux of HCl or Decalin®

hepta-6-enoic acids

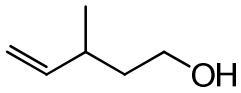
(Scheme 16)

General Procedure[57] **for the synthesis of alcohols 18:** A solution of acid **15** (1.0 eq.) in dry THF (0.2 mL/mmol) was slowly added to a stirred solution of $LiAlH_4$ (1 molar eq.) in dry THF (2.0 mL/mmol). The mixture was stirred overnight at room temperature. The reaction mixture was cooled to 0 °C and cautiously treated with water (0.038 mL/mmol), with a 15 % aqueous solution of NaOH (0.038 mL/mmol), and finally with water (0.11 mL/mmol). After 1 h at room temperature, the suspension was filtered through a pad of Celite. The solids were washed twice with diethyl ether. The filtrate was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was used directly in the next step without further purification.

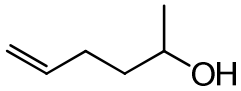


2-Methylpent-4-en-1-ol (18a): commercial 2-methylpent-4-enoic acid (10.0 g, 87.6 mmol) afforded the corresponding alcohol (8.7 g, 86.8 mmol, 99 % yield) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$): δ 0.92 (*d*, 3H, *J* = 6.6Hz), 1.72 (*m*, 1H), 1.91 (*m*, 1H), 2.18 (*m*, 1H), 2.36 (*s*, 1H), 3.46 (*m*, 1H), 5.00 (*m*, 1H), 5.72 (*ddt*, 1H, *J* = 7.1, 10.1, 17.1Hz); ^{13}C NMR (100MHz, $CDCl_3$): δ 16.2 (CH_3), 35.4 (CH), 37.7 (CH_2), 67.6 (CH_2), 115.9 (CH_2), 136.9 (CH).

[57] In according to literature: Taillier, C.; Gille, B.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2005**, *70*, 2097.

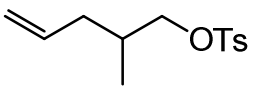


3-Methylpent-4-en-1-ol (18b): commercial 3-methylpent-4-enoic acid (4.5 g, 39.6 mmol) afforded the corresponding alcohol (3.8 g, 37.8 mmol, 95 % yield) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.02 (*d*, 3H, *J* = 6.8Hz), 1.57 (*q*, 2H, *J* = 6.8Hz), 2.30 (*hept*, 1H, *J* = 6.8Hz), 3.65 (*t*, 2H, *J* = 6.4Hz), 4.94 (*m*, 1H), 5.01 (*m*, 1H), 5.72 (*ddd*, 1H, *J* = 8.0, 10.4, 17.2Hz); ^{13}C NMR (100MHz, $CDCl_3$): δ 20.3 (CH_3), 34.7 (CH), 39.2 (CH_2), 61.0 (CH_2), 112.9 (CH_2), 144.0 (CH).



hex-5-en-2-ol[58] **(18c):** commercial hex-5-en-2-one (4.5 g, 45.8 mmol) afforded the corresponding alcohol (4.0 g, 40.6 mmol, 89 % yield) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.19 (*d*, 3H, *J* = 6.0Hz), 1.54 (*m*, 2H), 2.14 (*m*, 2H), 3.81 (*m*, 1H), 5.00 (*m*, 2H), 5.83 (*ddt*, 1H, *J* = 6.6, 10.1, 23.6Hz); ^{13}C NMR (75MHz, $CDCl_3$): δ 23.2 (CH_3), 30.0 (CH_2), 38.1 (CH_2), 67.3 (CH), 114.5 (CH_2), 138.4 (CH).

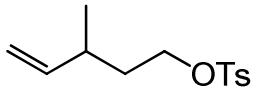
General Procedure[59] **for the synthesis of tosylates 19:** *p*-Toluenesulfonyl chloride (1.3 eq.) was added in small portions to a stirred solution of the alcohol **18** (1 eq.) in pyridine (6 eq.) at 0 °C. The suspension was stirred for 10 min, then it was warmed to room temperature and kept stirring for another 2 h. The mixture was poured in water and then it was extracted twice with Et_2O. The organic layers were washed with HCl 1 M, dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by flash chromatography.



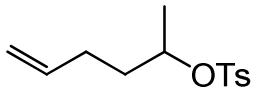
2-Methylpent-4-enyl 4-methylbenzenesulfonate (19a): 9.0 g (89.9 mmol) of alcohol **18a** afforded 17.4 g of product (68.2 mmol, 76 % yield). Flash chromatographic conditions : petroleum ether/ Et_2O = 4/1 gradient to 3/2; [R_f (3/2) = 0.46]. ^{1}H NMR

[58] Conti, P.; Dellanoce, C.; De Amici , M.; De Micheli, C.; Carrea, G.; Zambianchi F. *Tetrahedron: Asymmetry* **1998**, *9*, 657.
[59] In according to literature: Courchay, F. C.; Baughman, T. W.; Wagener, K. B. *J. of Organometallic Chem.* **2006**, 585.

(400MHz, $CDCl_3$): δ 0.90 (*d*, 3H, *J* = 6.8Hz), 1.90 (*m*, 2H), 2.10 (*m*, 1H), 2.45 (s, 3H), 3.83 (*dd*, 1H, *J* = 6.0, 9.6Hz), 3.89 (*dd*, 1H, *J* = 6.0, 9.6Hz), 4.97 (*m*, 2H), 5.65 (*m*, 1H), 7.35 (*d*, 2H, *J* = 8.4Hz), 7.79 (*d*, 2H, *J* = 8.4Hz); ^{13}C NMR (100MHz, $CDCl_3$): δ 16.0 (CH_3), 21.5 (CH_3), 32.6 (CH), 36.9 (CH_2), 74.3 (CH_2), 117.0 (CH_2), 127.8 (2CH), 129.7 (2CH), 133.0 (C), 135.2 (CH), 144.6 (C).



3-Methylpent-4-enyl 4-methylbenzenesulfonate (19b): 3.0 g (29.9 mmol) of alcohol **18b** afforded 5.0 g of product (19.7 mmol, 66 % yield). Flash chromatographic conditions : petroleum ether/ Et_2O = 2/1; [R_f (1/1) = 0.69]. ^1H NMR (400MHz, $CDCl_3$): δ 0.96 (*d*, 3H, *J* = 6.7Hz), 1.63 (*m*, 2H), 2.24 (*m*, 1H), 2.45 (s, 3H), 4.03 (*m*, 2H), 4.88 (*m*, 2H), 5.54 (*ddd*, 1H, *J* = 7.9, 10.5, 16.9Hz), 7.34 (*d*, 2H, *J* = 8.8Hz), 7.79 (*d*, 2H, *J* = 8.8Hz); ^{13}C NMR (100MHz, $CDCl_3$): δ 20.0 (CH_3), 21.6 (CH_3), 34.0 (CH), 35.1 (CH_2), 68.7 (CH_2), 114.0 (CH_2), 127.8 (2CH), 129.7 (2CH), 133.1 (C), 142.4 (CH), 144.6 (C).

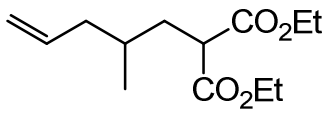


1-Methylpent-4-enyl 4-methylbenzenesulfonate (19c): 3.8 g (37.9 mmol) of alcohol **18c** afforded 8.4 g of product (33.1 mmol, 87 % yield). Flash chromatographic conditions : petroleum ether/ Et_2O = 2/1; [R_f (1/1) = 0.74]. ^1H NMR (400MHz, $CDCl_3$): δ 1.26 (*d*, 3H, *J* = 6.2Hz), 1.59 (*dddd*, 1H, *J* = 5.3, 6.2, 9.5, 14.4Hz), 1.72 (*dddd*, 1H, *J* = 6.0, 7.1, 9.0, 14.1Hz), 2.00 (*m*, 2H), 2.44 (s, 3H), 4.63 (*m*, 1H), 4.91 (*m*, 1H), 4.95 (*m*, 1H), 7.33 (*m*, 2H), 7.79 (*m*, 2H); ^{13}C NMR (100MHz, $CDCl_3$): δ 20.6 (CH_3), 21.4 (CH_3), 28.8 (CH_2), 35.5 (CH_2), 79.7 (CH), 115.2 (CH_2), 127.5 (2CH), 129.6 (2CH), 134.4 (C), 136.9 (CH), 144.4 (C).

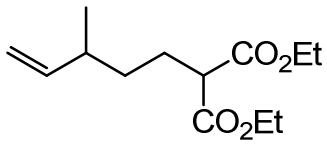
General Procedure[60] for the synthesis of substituted 4-pentenylmalonates 20: Diethyl malonate (2 eq.) was added at 0 °C to a suspension of NaH (60% wt in mineral oil, 1.5 eq.) in a dry 10:1 mL THF/DMF mixture (2.5 mL THF/mmol) under N_2. The reaction mixture was stirred for 30 min. Then the tosylate **19** (1 eq.) and anhydrous NaI

[60] In according to literature: Jahn, U.; Hartmann, P.; Dix, I.; Joneg, P. G. *Eur. J. Org. Chem.* **2001**, 3333.

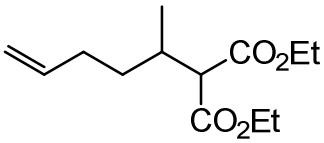
(0.4 eq.) were added at room temperature. The mixture was heated to reflux until reaction was complete by TLC. The mixture was quenched with a saturated NH_4Cl solution. The aqueous layer was extracted three times with ether. The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated. The crude product was purified by flash chromatography.



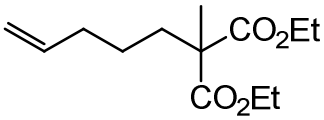
Diethyl 2-(2-methylpent-4-enyl)malonate (20a): 4.5 g (17.7 mmol) of tosylate **19a** afforded 4.2 g of product (17.4 mmol, 98 % yield). Chromatographic conditions : petroleum ether/Et_2O = 5/1; [R_f (4/1) = 0.62]. IR (neat): υ 1751, 1733 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$): δ 0.91 (*d*, 3H, *J* = 6.6Hz), 1.27 (*t*, 6H, *J* = 7.2Hz), 1.53 (*m*, 1H), 1.69 (*m*, 1H), 1.96 (*m*, 1H), 2.08 (*m*, 2H), 3.44 (*dd*, 1H, *J* = 6.6, 8.7Hz), 4.20 (2*q overlapped*, 4H, *J* = 7.2, 7.5Hz), 4.99 (*m*, 1H), 5.04 (*m*, 1H), 5.75 (*m*, 1H); ^{13}C NMR (75MHz, $CDCl_3$): δ 14.0 ($2CH_3$), 18.9 (CH_3), 30.7 (CH), 35.2 (CH_2), 40.9 (CH_2), 50.0 (CH), 61.2 ($2CH_2$), 116.3 (CH_2), 136.4 (CH), 169.5 (C), 169.7 (C).



Diethyl 2-(3-methylpent-4-enyl)malonate (20b): 3.1 g (12.2 mmol) of tosylate **19b** afforded 2.9 g of product (12.0 mmol, 98 % yield). Chromatographic conditions : petroleum ether/Et_2O = 4.5/0.5; [R_f (4/1) = 0.53]. IR (neat): υ 1749, 1732 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$): δ 1.00 (*d*, 3H, *J* = 6.8Hz), 1.27 (*t*, 6H, *J* = 7.2Hz), 1.32 (*m*, 2H), 1.88 (*m*, 2H), 2.14 (*hept*, 1H, *J* = 7.2Hz), 3.29 (*t*, 1H, *J* = 7.6Hz), 4.19 (2*q overlapped*, 4H, *J* = 7.2, 7.2Hz), 4.96 (*m*, 2H), 5.66 (*ddd*, 1H, *J* = 7.6, 10.4, 17.2Hz); ^{13}C NMR (100MHz, $CDCl_3$): δ 14.0 ($2CH_3$), 20.1 (CH_3), 26.5 (CH_2), 34.0 (CH_2), 37.5 (CH), 52.0 (CH), 61.2 ($2CH_2$), 113.2 (CH_2), 143.7 (CH), 169.5 (2C).



Diethyl 2-(1-methylpent-4-enyl)malonate (20c): 8.0 g (31.4 mmol) of tosylate **19c** afforded 4.7 g of product (19.2 mmol, 61 % yield). Chromatographic conditions : petroleum ether/Et_2O = 4.5/0.5; [R_f (4.5/0.5) = 0.38]. IR (neat): υ 1752, 1733 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$): δ 1.00 (*d*, 3H, *J* = 6.8Hz), 1.27 (2*t overlapped*, 6H, *J* = 7.1Hz), 1.32 (*m*, 1H), 1.54 (*m*, 1H), 2.04 (*m*, 1H), 2.15 (*m*, 1H), 2.28 (*m*, 1H), 3.24 (*d*, 1H, *J* = 7.9Hz), 4.19 (*q*, 4H, *J* = 7.1Hz), 5.78 (*ddt*, 1H, *J* = 6.8, 10.2, 17.0Hz); ^{13}C NMR (100MHz, $CDCl_3$): δ 14.0 (CH_3), 16.6 ($2CH_3$), 30.9 (CH_2), 32.6 (CH), 33.3 (CH_2), 57.5 (CH), 60.9 (CH_2), 61.0 (CH_2), 114.6 (CH_2), 138.0 (CH), 168.6 (C), 168.7 (C).

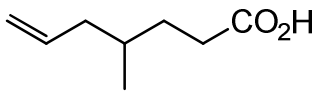


Diethyl 2-methyl-2-(pent-4-enyl)malonate (20d): Commercial 5-bromopent-1-ene (5.4 g; 34.4 mmol; 1.2 eq.) was used in place of the tosylate and reacted with 5.0 g (28.7 mmol, 1 eq.) of methyl diethyl malonate to afford 6.9 g of product (28.7 mmol, 100 % yield). [R_f (4.5/0.5) = 0.45]. ^1H NMR (400MHz, $CDCl_3$): δ 1.25 (*t*, 6H, *J* = 7.1Hz), 1.34 (*m*, 2H), 1.40 (*s*, 3H), 1.86 (*m*, 2H), 2.07 (*m*, 2H), 4.18 (*q*, 4H, *J* = 7.1Hz), 4.95 (*m*, 1H), 5.01 (*m*, 1H), 5.78 (*ddt*, 1H, *J* = 6.6, 10.2, 16.8Hz); ^{13}C NMR (100MHz, $CDCl_3$): δ 13.9 ($2CH_3$), 19.7 (CH_3), 23.5 (CH_2), 33.7 (CH_2), 34.8 (CH_2), 53.4 ($2CH_2$), 60.9 (C), 114.7 (CH_2), 137.9 (CH), 172.2 (2C).

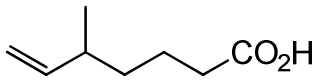
General Procedure for the decarboxylation step to hepta-6-enoic acids 9 :

Method A A solution of NaOH 10 % in water (2.5 eq.) was added to a stirred solution of the diester **20** (1 eq.) in THF (0.2 mL/mmol). The mixture was heated to reflux until the reaction was complete by TLC. The mixture was washed once with ether and acidified to pH=1 with HCl 1M. The aqueous layer was extracted three times with ether. The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated. THF (1.0 mL/mmol) and HCl 1M (2 eq.) were added to the crude product and the mixture was heated to reflux until decarboxylation was complete by TLC. The aqueous layer was extracted three times with ether. The combined organic layers were dried with

$MgSO_4$ and the solvent was evaporated. The crude product was purified by flash chromatography.

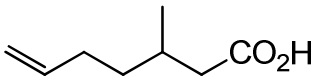


4-Methylhept-6-enoic acid (9a): 3.7 g (15.4 mmol) of diester **20a** afforded 1.3 g of product (8.9 mmol, 58 % yield). Chromatographic conditions : petroleum ether/Et_2O/AcOH = 3/2/0.1; [R_f (3/2/0.1) = 0.36]. IR (neat): υ 2960, 2928, 1710 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$): δ 0.90 (*d*, 3H, *J* = 6.5Hz), 1.46 (*m*, 1H), 1.56 (*m*, 1H), 1.71 (*m*, 1H), 1.94 (*m*, 1H), 2.08 (*m*, 1H), 2.37 (*m*, 2H), 5.01 (*m*, 2H), 5.77 (*m*, 1H); ^{13}C NMR (75MHz, $CDCl_3$): δ 18.9 (CH_3), 31.0 (CH), 31.8 (CH_2), 32.2 (CH_2), 41.0 (CH_2), 116.1 (CH_2), 136.8 (CH), 180.5 (C).

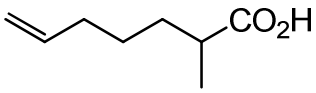


3-Methylhept-6-enoic acid (9b): 2.9 g (11.9 mmol) of diester **20b** afforded 1.0 g of product (7.3 mmol, 61 % yield). Chromatographic conditions : petroleum ether/Et_2O/AcOH = 4/1/0.1; [R_f (3/2/0.1) = 0.50]. ^1H NMR (300MHz, $CDCl_3$): δ 1.00 (*d*, 3H, *J* = 6.6Hz), 1.34 (*m*, 2H), 1.63 (*m*, 2H), 2.12 (*hept*, 1H, *J* = 6.9Hz), 2.34 (*t*, 2H, *J* = 7.4Hz), 4.92 (*m*, 1H), 4.97 (*m*, 1H), 5.67 (*ddd*, 1H, *J* = 7.7, 10.2, 17.3Hz), 11.1 (*s*, OH); ^{13}C NMR (75MHz, $CDCl_3$): δ 20.0 (CH_3), 22.3 (CH_2), 34.0 (CH_2), 35.8 (CH_2), 37.5 (CH), 112.8 (CH_2), 144.0 (CH), 180.3 (C).

Method B[59] A solution of NaOH 10% in water (2.5 eq.) was added to a stirred solution of the diester **20** (1 eq.) in THF (0.2 mL/mmol),. The mixture was heated to reflux until reaction was complete by TLC. The mixture was washed once with ether and acidified to pH=1 with HCl 1M. The aqueous layer was extracted three times with ether. The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated. Decalin® (1:1 wt%) was added to this crude product and the mixture heated to 185°C. CO_2 evolution was monitored with a mineral oil bubbler. The reaction was stirred vigorously until gas evolution ceased. Upon cooling, Decalin® was removed in vacuo affording acid.



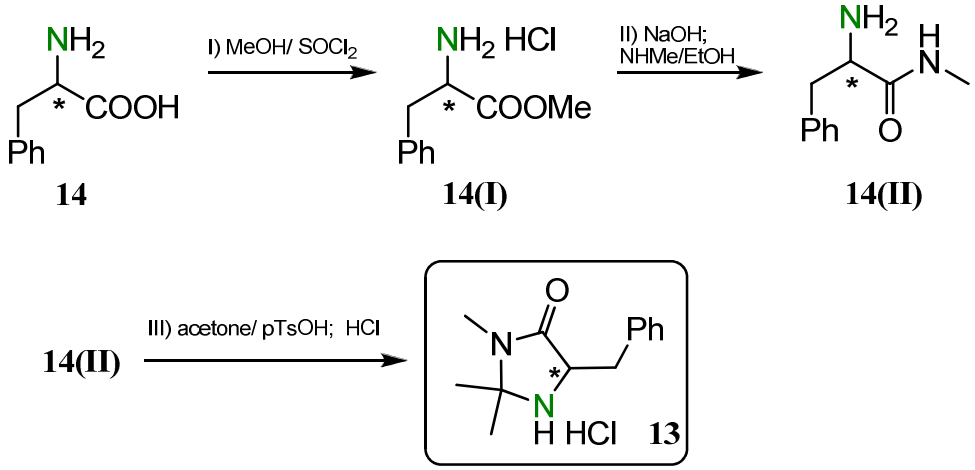
3-Methylhept-6-enoic acid (9c): 3.0 g (16.1mmol) of diester **20c** afforded 2.0 g of product (14.0 mmol, 87 % yield). ^{1}H NMR (400MHz, $CDCl_3$): δ 0.99 (*d*, 3H, *J* = 6.8Hz), 1.39 (*m*, 2H), 2.01 (*m*, 1H), 2.08 (*m*, 2H), 2.28 (*m*, 2H), 4.98 (*m*, 2H), 5.79 (*ddt*, 1H, *J* = 6.6, 10.1, 16.8Hz); ^{13}C NMR (100MHz, $CDCl_3$): δ 19.4 (CH_3), 29.6 (CH), 31.1 (CH_2), 35.7 (CH_2), 41.5 (CH_2), 114.6 (CH_2), 138.4 (CH), 179.8 (C).



2-Methylhept-6-enoic acid (9d): 3.0 g (16.1 mmol) of diester **20d** afforded 2.3 g of product (16.0 mmol, 99 % yield). ^{1}H NMR (400MHz, $CDCl_3$): δ 1.11 (*d*, 3H, *J* = 6.9Hz), 1.37 (*m*, 3H), 1.63 (*m*, 1H), 1.99 (*m*, 2H), 2.39 (*m*, 1H), 4.88 (*m*, 1H), 4.94 (*m*, 1H), 5.72 (*ddt*, 1H, *J* = 6.6, 10.2, 16.8Hz), 11.89 (*s*, OH); ^{13}C NMR (100MHz, $CDCl_3$): δ 16.7 (CH_3), 26.3 (CH_2), 32.9 (CH_2), 33.5 (CH_2), 39.3 (CH), 114.7 (CH_2), 138.3 (CH), 183.6 (C).

Synthesis of (*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride[51]:

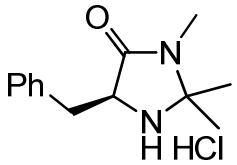
auxiliary synthesis



(*S*) or (*R*) - 5-benzyl-2,2,3-trimethylimidazolidin-4-one

Figure 16

(*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride (13)



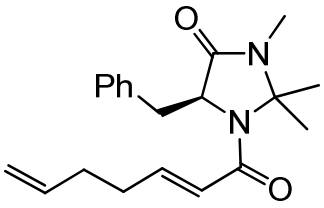
To a solution of ethanolic $MeNH_2$ (8 M, 46 mL) was added (*S*)-phenylalanine methyl ester[61] **14(I)** (22.1 g, 123 mmol) and the resulting mixture was stirred at room temperature for 15 h. The solvent and the excess of $MeNH_2$ were removed in vacuo. The obtained (*S*)-phenylalanine N-methyl amide hydrochloride was treated with an aqueous solution $NaHCO_3$ and the free amine was extracted three times with $CHCl_3$, dried and concentrated. To this amide **14(II)** (21.3 g, 119 mmol) was added MeOH (180 mL), acetone (180 ml) and *p*-TsOH (220 mg, 1.2 mmol). The reaction mixture was heated to reflux for 24 h, cooled to room temperature and concentrated. The residue was taken up in Et_2O and 119 mL of a HCl-Et_2O (2 M) solution was added to precipitate **13**. The yellow salt was washed with cool acetone and filtered to afford 30.3 g (yield 71%) as white solid.

^{1}H NMR (300MHz, d_6DMSO): δ 1.61 (*s*, 3H), 1.76 (*s*, 3H), 2.92 (*s*, 3H), 3.13 (*dd*, 1H, *J* = 10.5, 15.1Hz), 3.53 (*dd*, 1H, *J* = 3.5, 15.2Hz), 4.66 (*dd*, 1H, *J* = 3.6, 10.6Hz), 4.86 (*bs*, 2H), 7.23-7.51 (*m*, 5H); ^{13}C NMR (75MHz, d_6DMSO): δ 22.3 (CH_3), 24.4 (CH_3), 25.8 (CH_3), 35.0 (CH_2), 59.8 (CH), 79.2 (C), 128.8 (2CH), 130.3 (2CH), 130.4 (CH), 136.7 (C), 167.9 (C); HPLC (free amine) *Chiralcel*® OD-H, n-hexane/*i*-PrOH (96:4), flow 1 mL/min, λ= 254 nm, t_r(*R*) = 10.6 min, t_r(*S*) = 12.1 min.

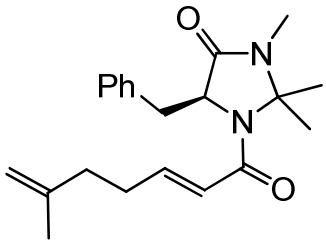
General Procedure for the synthesis of chiral amides 21: A solution of oxalyl chloride (3 eq.) in dry dichloromethane (4.0 mL/mmol) was added dropwise to a stirred solution of acid **11** or **9** (1 eq.) in dry dichloromethane (4.5 mL/mmol) at 0 °C and under a positive pressure of nitrogen. After 5h at 0 °C, the solvent and the excess of oxalyl chloride was removed in vacuo. The crude chloride was dissolved in anhydrous dichloromethane (2.8 mL/mmol) and the (*S*)- or (*R*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **13** (1.1 eq.) was added. The mixture was cooled to 0 °C and dry pyridine (2.2 eq.) was added. The mixture was allowed to warm to room temperature; after 24h TLC analysis revealed that the starting material was

[61] (*S*)-phenylalanine methyl ester hydrochloride: Effenberger, F ; Burkard, U. *Liebigs Ann. Chem.* **1986**, 334. (*R*)-phenylalanine methyl ester hydrochloride: commercially available.

consumed and water was added. The organic layer was washed twice with water, and then the aqueous layers were extracted three times with ether. The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated. The crude product was purified by flash chromatography.

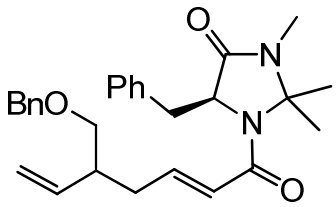


(*S*)-5-Benzyl-1-hepta-2,6-dienoyl-2,2,3-trimethylimidazolidin-4-one (21a): hept-2,6-dienoic acid **11a** (2.1 g, 16.6 mmol) gave the corresponding amide (2.0 g, 36.9 mmol, 37 % yield); chromatographic conditions : petroleum ether/Et_2O = 1/2; colorless oil; [R_f (1/1) = 0.28]. IR (neat): υ 1701, 1654 cm^{-1}. ^1H NMR (600MHz, $CDCl_3$): δ 0.65 (*s*, 3H), 1.55 (*s*, 3H), 2.28 (*m*, 2H), 2.40 (*m*, 2H), 2.67 (*s*, 3H), 3.16 (*m*, 1H), 3.35 (*m*, 1H), 4.57 (*m*, 1H), 5.03 (*m*, 1H), 5.09 (*m*, 1H), 5.83 (*m*, 1H), 6.16 (*m*, 1H), 7.04 (*m*, 1H), 7.05 (*m*, 2H), 7.21 (*m*, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 22.4 (CH_3), 23.8 (CH_3), 24.2 (CH_3), 31.6 (CH_2), 32.2 (CH_2), 38.1 (CH_2), 60.3 (CH), 79.0 (C), 115.7 (CH_2), 122.7 (CH), 127.3 (CH), 128.4 (2CH), 130.3 (2CH), 135.2 (C), 137.1 (CH), 146.6 (CH), 159.2 (C), 169.4 (C).

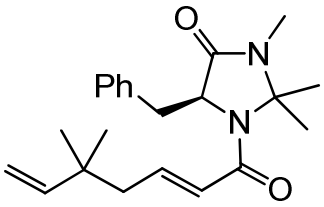


(*S*)-5-Benzyl-2,2,3-trimethyl-1-(6-methylhepta-2,6-dienoyl)imidazolidin-4-one (21b): hept-2,6-dienoic acid **11b** (536 mg, 3.8 mmol) gave the corresponding amide (844 mg, 2.5 mmol, 66 % yield); chromatographic conditions : petroleum ether/Et_2O = 1/2; colorless oil; [R_f (1/1) = 0.24]. IR (neat): υ 1704, 1660 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$): δ 0.64 (*s*, 3H), 1.10 (*s*, 3H), 1.11 (*s*, 3H), 1.57 (*s*, 3H), 2.31 (*dd*, 2H, *J* = 1.2, 7.6Hz), 2.68 (*m*, 3H), 3.17 (*dd*, 1H, *J* = 5.6, 13.8Hz), 3.38 (*dd*, 1H, *J* = 2.0, 13.8Hz), 4.60 (*m*, 1H), 4.99 (*m*, 1H), 5.01 (*m*, 1H), 5.86 (*dd*, 1H, *J* = 10.5, 17.3Hz), 6.17 (*d*, 1H, *J* = 15.0Hz), 7.04 (*m*, 1H), 7.06 (*m*, 2H), 7.22 (*m*, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ

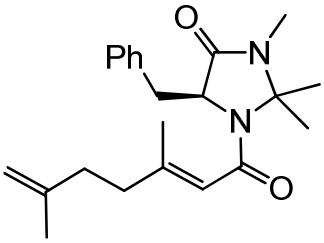
22.3 ($2CH_3$), 23.7 (CH_3), 24.1 (CH_3), 30.2 (CH_2), 36.0 (CH_2), 38.0 (CH_2), 60.2 (CH), 79.5 (C), 110.9 (CH_2), 122.5 (CH_2), 127.2 (CH), 128.3 (2CH), 130.2 (2CH), 135.2 (C), 144.1 (C), 146.7 (CH), 163.8 (C), 167.1 (C).



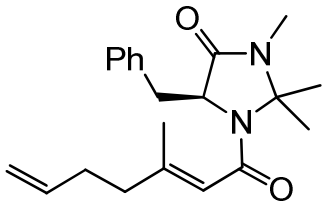
(*S*)-5-Benzyl-1-(5-(benzyloxymethyl)hepta-2,6-dienoyl)-2,2,3-trimethylimidazolidin-4-one (21c): hept-2,6-dienoic acid **11c** (2.2 g, 9.1 mmol) gave the corresponding amide (3.5 g, 7.8 mmol, 86 % yield); chromatographic conditions : petroleum ether/EtOAc= 1/1; colorless oil; [R_f (1/1) = 0.36]. IR (neat): υ 1704, 1661, 1626 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 0.63 (*s*, 3H*minor*), 0.64 (*s*, 3H*major*), 1.56 (*s*, 3H*minor* + 3H*major*), 2.37 (*m*, 1H*minor* + 1H*major*), 2.61 (*m*, 1H*minor* + 1H*major*), 2.68 (*m*, 1H*minor* + 1H*major*), 3.13 (*m*, 1H*minor*), 3.14 (*m*, 1H*major*), 3.34 (*m*, 1H*minor* + 1H*major*), 3.48 (*m*, 2H*minor* + 2H*major*), 4.53 (*s*, 2H*minor* + 2H*major*), 4.56 (*m*, 1H*minor* + 1H*major*), 5.15 (*m*, 2H*minor* + 2H*major*), 5.76 (*m*, 1H*minor* + 1H*major*), 6.17 (*m*, 1H*minor* + 1H*major*), 7.05 (*m*, 1H*minor* + 1H*major*), 7.28 (*m*, 10H*minor* + 10H*major*); ^{13}C NMR (75MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 21.9 (*minor*CH_3), 22.0 (*major*CH_3), 23.4 (*major*CH_3 + *minor*CH_3), 23.8 (*major*CH_3 + *minor*CH_3), 33.8 (*minor*CH_2), 34.1 (*major*CH_2), 42.8 (*minor*CH), 42.9 (*major*CH), 59.8 (*major*CH + *minor*CH), 72.5 (*minor*CH_2), 72.7 (*major*CH_2 + *minor*CH_2), 72.8 (*major*CH_2), 79.0 (*major*C + *minor*C), 116.2 (*major*CH_2), 116.4 (*minor*CH_2), 123.5 (*major*CH), 123.7 (*minor*CH), 126.9 (*minor*CH), 127.1 (*major*CH), 127.2 (*minor*CH), 127.3 (*major*CH), 128.0 (2*major*CH + 2*minor*CH), 129.9 (*major*CH), 130.0 (*minor*CH), 134.9 (*minor*C + *major*C), 137.9 (*major*CH), 138.2 (*minor*CH), 144.6 (*major*CH), 144.7 (*minor*CH), 163.3 (*minor*C + *major*C), 166.7 (*minor*C + *major*C).



(*S*)-5-benzyl-1-(5,5-dimethylhepta-2,6-dienoyl)-2,2,3-trimethylimidazolidin-4-one (21d): hept-2,6-dienoic acid **11d** (2.0 g, 12.9 mmol) gave the corresponding amide (1.2 g, 3.4 mmol, 26 % yield); chromatographic conditions : petroleum ether/EtOAc = 1/1; colorless oil; [R_f (1/1) = 0.40]. IR (neat): υ 1704, 1661, 1626 cm^{-1}. ^1H NMR (600MHz, $CDCl_3$): δ 0.64 (*s*, 3H), 1.10 (*s*, 3H), 1.11 (*s*, 3H), 1.57 (*s*, 3H), 2.31 (*dd*, 2H, *J* = 1.2, 7.6Hz), 2.68 (*m*, 3H), 3.17 (*dd*, 1H, *J* = 5.6, 13.8Hz), 3.38 (*dd*, 1H, *J* = 2.0, 13.8Hz), 4.60 (*m*, 1H), 4.99 (*m*, 1H), 5.01 (*m*, 1H), 5.86 (*dd*, 1H, *J* = 10.5, 17.3Hz), 6.17 (*d*, 1H, *J* = 15.0Hz), 7.04 (*m*, 1H), 7.06 (*m*, 2H), 7.22 (*m*, 3H); ^{13}C NMR (150MHz, $CDCl_3$): δ 22.2 (CH_3), 23.7 (CH_3), 24.0 (CH_3), 26.5 (CH_3), 26.9 (CH_3), 37.1 (C), 37.9 (CH_2), 45.4 (CH_2), 60.1 (CH), 79.4 (C), 111.3 (CH_2), 124.5 (CH), 127.1 (CH), 128.3 (2CH), 130.1 (2CH), 135.1 (C), 144.3 (CH), 146.9 (CH), 163.5 (C), 167.0 (C).

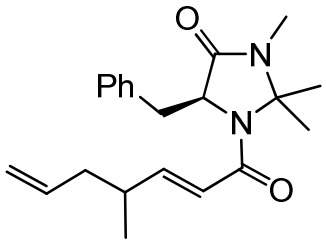


(*S*)-5-benzyl-1-(3,6-dimethylhepta-2,6-dienoyl)-2,2,3-trimethylimidazolidin-4-one (21e): hept-2,6-dienoic acid **11e** (1.0 g, 6.5 mmol) gave the corresponding amide (1.8 g , 5.1 mmol, 78 % yield); chromatographic conditions : petroleum ether/EtOAc = 3/2; colorless oil; [R_f (3/2) = 0.32]. IR (neat): υ 1704, 1651 cm^{-1}. ^1H NMR (600MHz, $CDCl_3$): δ 0.66 (*s*, 3H), 1.57 (*s*, 3H), 1.78 (*s*, 3H), 2.18 (*s*, 3H), 2.26 (*m*, 2H), 2.36 (*m*, 2H), 2.68 (*s*, 3H), 3.19 (*dd*, 1H, *J* = 5.9, 14.1Hz), 3.31 (*dd*, 1H, *J* = 2.0, 14.1Hz), 4.50 (*dd*, 1H, J = 1.7, 5.6Hz), 4.77 (*d*, 2H, *J* = 11.7Hz), 5.89 (*s*, 1H), 7.03 (*m*, 2H), 7.23 (*m*, 3H); ^{13}C NMR (150MHz, $CDCl_3$): δ 18.6 (CH_3), 22.3 (CH_3), 22.5 (CH_3), 23.7 (CH_3), 24.1 (CH_3), 35.4 (CH_2), 37.4 (CH_2), 38.3 (CH_2), 60.7 (CH), 79.3 (C), 110.9 (CH_2), 118.5 (CH), 127.1 (CH), 128.3 (2CH), 130.2 (2CH), 135.5 (C), 144.5 (C), 153.6 (C), 165.2 (C), 167.4 (C).



(*S*)-5-benzyl-2,2,3-trimethyl-1-(3-methylhepta-2,6-dienoyl)imidazolidin-4-one

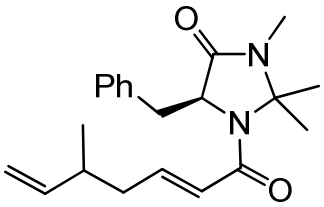
(21f): hept-2,6-dienoic acid **11f** (1.0 g, 7.1mmol) gave the corresponding amide (1.5 g , 4.5 mmol, 63 % yield); chromatographic conditions : petroleum ether/EtOAc = 3/2; colorless oil; [R_f (3/2) = 0.50]. ^{1}H NMR (400MHz, $CDCl_3$): δ 0.66 (*s*, 3H), 1.57 (*s*, 3H), 2.32 (*m*, 3H), 2.68 (*s*, 3H), 3.20 (*m*, 1H), 3.31 (*m*, 1H), 4.51 (*m*, 1H), 5.05 (*m*, 1H), 5.89 (*s*, 1H), 7.04 (*m*, 2H), 7.22 (*m*, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 18.5 (CH_3), 22.4 (CH_3), 23.6 (CH_3), 24.0 (CH_3), 31.4 (CH_2), 37.3 (CH_2), 39.5 (CH_2), 60.6 (CH), 79.2 (C), 115.5 (CH_2), 118.7 (CH), 127.0 (CH), 128.2 (2CH), 130.1 (2CH), 135.4 (C), 137.3 (CH), 153.3 (C), 165.0 (C), 167.3 (C).



(*S*)-5-benzyl-2,2,3-trimethyl-1-(4-methylhepta-2,6-dienoyl)imidazolidin-4-one

(21g): hept-2,6-dienoic acid **11g** (1.5 g, 10.7 mmol) gave the corresponding amide (3.0 g, 8.8 mmol, 82 % yield); chromatographic conditions : petroleum ether/EtOAc = 3/2; white solid, m.p. 114°C; [R_f (3/2) = 0.25]. IR (KBr): υ 1715, 1660, 1633 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 0.65 (*s*, 3H*minor*), 0.66 (*s*, 3H*major*), 1.14 (*d*, 3H*minor*, *J* = 5.5Hz), 1.16 (*d*, 3H*major*, *J* = 5.5Hz), 1.57 (2*s overlapped*, 3H*minor* + 3H*major*), 2.23 (*m*, 2H*minor* + 2H*major*), 2.53 (*hept*, 2H*minor* + 2H*major*, *J* = 6.8Hz), 2.69 (2*s overlapped*, 3H*minor* + 3H*major*), 3.17 (*dd*, 1H*minor*, *J* = 4.5, 14.0Hz), 3.18 (*dd*, 1H*major*, *J* = 5.5, 14.0Hz), 3.37 (2*dd overlapped*, 1H*minor* + 1H*major*, *J* = 2.2, 14.0Hz), 4.60 (*m*, 1H*minor* + 1H*major*), 5.07 (*m*, 2H*minor* + 2H*major*), 5.79 (*ddt*, 1H*minor*, *J* = 7.0, 10.3, 17.0Hz), 5.80 (*ddt*, 1H*minor*, *J* = 7.0, 10.3, 17.0Hz), 6.14 (*d*, 1H*minor* + 1H*major*, *J* = 15.0Hz), 6.96 (*dd*, 1H*minor*, *J* = 8.0, 15.0Hz), 7.03 (*dd*, 1H*major*, *J* = 7.0, 15.0Hz), 7.05 (*m*, 2H*minor* + 2H*major*), 7.22 (*m*, 3H*minor* + 3H*major*); ^{13}C NMR (100MHz, $CDCl_3$) (of the mixture

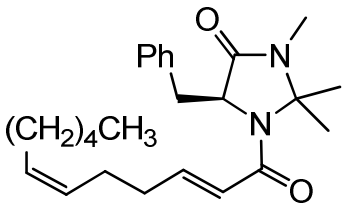
of the two diastereoisomers): δ 18.9 (*minor*CH_3), 19.3 (*major*CH_3), 22.2 (*major*CH_3 + *minor*CH_3), 23.6 (*major*CH_3 + *minor*CH_3), 24.0 (*major*CH_3 + *minor*CH_3), 36.0 (*minor*CH), 36.6 (*major*CH), 37.9 (*minor*CH_2), 38.0 (*major*CH_2), 40.0 (*minor*CH_2), 40.4 (*major*CH_2), 60.1 (*major*CH_2 + *minor*CH_2), 79.3 (*major*C + *minor*C), 116.7 (*major*CH_2 + *minor*CH_2), 120.7 (*minor*CH), 121.0 (*major*CH), 127.1 (*major*CH + *minor*CH), 128.2 (2*minor*CH), 128.3 (2*major*CH), 130.1 (2*minor*CH), 130.2 (2*major*CH), 135.1 (*minor*C + *major*C), 135.7 (*minor*CH), 136.0 (*major*CH), 151.6 (*minor*CH), 151.7 (*major*CH), 163.7 (*minor*C), 163.8 (*major*C), 166.9 (*minor*C + *major*C).



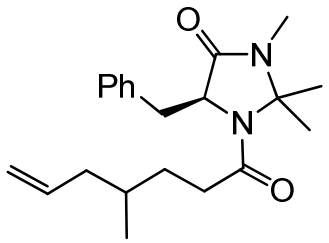
(*S*)-5-benzyl-2,2,3-trimethyl-1-(5-methylhepta-2,6-dienoyl)imidazolidin-4-one

(21h): hept-2,6-dienoic acid **11h** (770 mg, 5.5 mmol) gave the corresponding amide (1.7 g , 4.9 mmol, 89 % yield); chromatographic conditions : petroleum ether/EtOAc = 3/2; colorless oil; [R_f (3/2) = 0.26]. IR (neat): υ 1704, 1651 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 0.65 (2*s overlapped*, 3H*minor* + 3H*major*), 1.10 (*d*, 3H*minor*, *J* = 6.6Hz), 1.11 (*d*, 3H*major*, *J* = 6.6Hz), 1.57 (2*s overlapped*, 3H*minor* + 3H*major*), 2.33 (*m*, H*minor* + H*major*), 2.38 (*m*, 2H*minor* + 2H*major*), 2.69 (2*s overlapped*, 3H*minor* + 3H*major*), 3.17 (*dd*, 1H*minor* + 1H*major*, *J* = 5.6, 14.0Hz), 3.37 (*dd*, 1H*minor* + 1H*major*, *J* = 1.3, 14.0Hz), 4.60 (*m*, 1H*minor* + 1H*major*), 5.00 (*m*, H*minor* + H*major*), 5.06 (*m*, H*minor* + H*major*), 5.80 (*m*, H*minor* + H*major*), 6.19 (*m*, H*minor* + H*major*), 7.02 (*m*, H*minor* + H*major*), 7.06 (*m*, 2H*minor* + 2H*major*), 7.22 (*m*, 2H*minor* + 2H*major*); ^{13}C NMR (100MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 19.6 (*minor*CH_3), 19.9 (*major*CH_3), 22.2 (*major*CH_3 + *minor*CH_3), 23.6 (*major*CH_3 + *minor*CH_3), 24.0 (*major*CH_3 + *minor*CH_3), 36.8 (*minor*CH), 37.0 (*major*CH), 37.8 (*minor*CH_2), 37.9 (*major*CH_2), 39.1 (*minor*CH_2), 39.4 (*major*CH_2), 60.0 (*major*CH + *minor*CH), 79.3 (*major*C + *minor*C), 113.4 (*major*CH_2), 113.6 (*minor*CH_2), 127.0 (*major*CH + *minor*CH), 128.2 (2*minor*CH), 128.3 (2*major*CH), 130.1 (2*minor*CH), 130.2 (2*major*CH), 135.1 (*minor*C + *major*C),

142.9 (*major*CH + *minor*CH), 145.4 (*major*CH), 145.5 (*minor*CH), 163.5 (*minor*C + *major*C), 166.9 (*minor*C + *major*C).

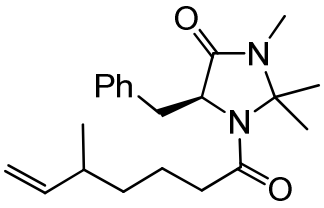


(*S*)-5-benzyl-1-((6Z)-dodeca-2,6-dienoyl)-2,2,3-trimethylimidazolidin-4-one (21i): hept-2,6-dienoic acid **11i** (0.52 g, 2.7 mmol) gave the corresponding amide (0.71 g, 1.8 mmol, 86 % yield); chromatographic conditions : petroleum ether/EtOAc = 3/2; colorless oil; [R_f (3/2) =0.37]. ^{1}H NMR (400MHz, $CDCl_3$): δ 0.67 (*s*, 3H), 0.89 (*m*, 3H), 1.30 (*m*, 6H), 1.57 (*s*, 3H), 2.05 (*m*, 2H), 2.32 (*m*, 4H), 2.69 (*s*, 3H), 3.17 (*dd*, 1H, *J* = 5.6, 14.1Hz), 3.37 (*dd*, 1H, *J* = 2.0, 14.1Hz), 4.59 (*dd*, 1H, *J* = 2.0, 5.5Hz), 5.42 (*m*, 2H), 6.16 (*d*, 1H, *J* = 16.0Hz), 7.06 (*m*, 2H), 7.23 (*m*, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 14.0 (CH_3), 22.3 (CH_3), 22.5 (CH_2), 23.7 (CH_3), 24.2 (CH_3), 25.8 (CH_2), 27.2 (CH_2), 29.2 (CH_2), 31.4 (CH_2), 32.5 (CH_2), 38.1 (CH_2), 60.2 (CH), 79.5 (C), 122.5 (CH), 127.2 (CH), 127.8 (CH), 128.3 (2CH), 130.3 (2CH), 131.4 (CH), 135.2 (C), 146.9 (CH), 163.8 (C), 167.2 (C).

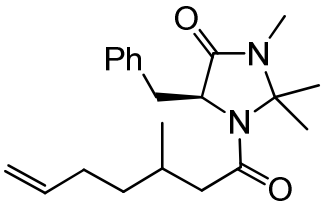


(*S*)-5-benzyl-2,2,3-trimethyl-1-(4-methylhept-6-enoyl)imidazolidin-4-one (21l): hept-6-enoic acid **9a** (0.9 g, 6.3 mmol) gave the corresponding amide (1.7 g, 5.1 mmol, 80 % yield); chromatographic conditions : petroleum ether/EtOAc = 3/2; colorless oil; [R_f (3/2) = 0.30]. IR (neat): υ 1706, 1655 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 0.69 (*s*, 6H), 0.94 (*d*, 6H, *J* = 6.3Hz), 1.54 (*s*, 6H), 1.58 (*m*, 4H), 1.79 (*m*, 2H), 1.98 (*m*, 2H), 2.09 (*m*, 2H), 2.40 (*m*, 4H), 2.69 (*s*, 6H), 3.16 (*dd*, 2H, *J* = 5.5, 14.0Hz), 3.36 (*m*, 2H), 4.51 (*m*, 2H), 5.03 (*m*, 4H), 5.80 (*m*, 2H), 7.09 (*m*, 4H), 7.24 (*m*, 6H); ^{13}C NMR (100MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 19.2 (CH_3), 19.4 (CH_3), 22.3 (CH_3), 22.4 (CH_3), 23.9 ($2CH_3$), 24.2

($2CH_3$), 31.6 (CH_2), 31.7 (CH_2), 32.3 (CH), 32.4 (CH), 33.1 (CH_2), 33.2 (CH_2), 38.0 ($2CH_2$), 41.0 (CH_2), 41.2 (CH_2), 61.6 (CH), 61.7 (CH), 79.5 (2C), 116.0 (CH_2), 116.1 (CH_2), 127.3 (2CH), 128.4 (4CH), 130.2 (4CH), 135.2 (2C), 136.8 (2CH), 167.2 (2C), 171.2 (C), 171.3 (C).

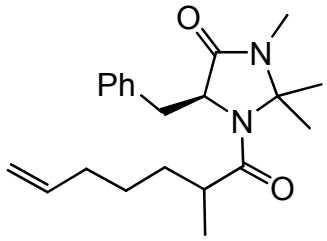


(*S*)-5-benzyl-2,2,3-trimethyl-1-(5-methylhept-6-enoyl)imidazolidin-4-one (21m): hept-6-enoic acid **9b** (0.51 g, 3.6 mmol) gave the corresponding amide (1.0 g, 2.9 mmol, 80 % yield); chromatographic conditions : petroleum ether/EtOAc = 3/2; colorless oil; [R_f (3/2) = 0.51]. IR (neat): υ 1707, 1656 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 0.68 (*s*, 3H), 1.02 (*dd*, 3H, *J* = 1.1, 6.7Hz), 1.37 (*m*, 2H), 1.54 (*s*, 3H), 1.73 (*m*, 2H), 2.16 (*hept*, 1H, *J* = 6.9Hz), 2.39 (*m*, 2H), 2.68 (*s*, 3H), 3.16 (*dd*, 1H, *J* = 5.3, 14.1Hz), 3.36 (*dd*, 1H, *J* = 1.8, 14.1Hz), 4.50 (*dd*, 1H, J = 2.2, 5.3Hz), 4.97 (*m*, 2H), 5.70 (*ddd*, 1H, *J* = 7.5, 10.2, 17.4Hz), 7.09 (*m*, 2H), 7.24 (*m*, 3H); ^{13}C NMR (100MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 20.1 (CH_3), 22.3 (CH_3), 22.8 (CH_2), 23.9 (CH_3), 24.2 (CH_3), 35.4 (CH_2), 36.0 (CH_2), 37.7 (CH), 37.8 (CH_2), 60.6 (CH), 79.5 (C), 112.9 (CH_2), 127.3 (CH), 128.4 (2CH), 130.2 (2CH), 135.1 (C), 144.1 (CH), 167.2 (C), 171.0 (C).

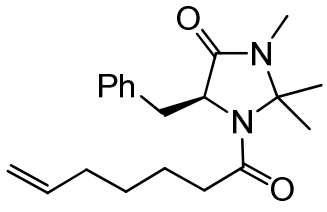


(*S*)-5-benzyl-2,2,3-trimethyl-1-(3-methylhept-6-enoyl)imidazolidin-4-one (21n): hept-6-enoic acid **9c** (1.1 g, 7.7 mmol) gave the corresponding amide (1.3 g, 3.7 mmol, 50 % yield); chromatographic conditions : petroleum ether/EtOAc = 3/2; colorless oil; [R_f (1/1) = 0.55]. IR (neat): υ 1704, 1658 cm^{-1}. ^1H NMR (600MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 0.67 (2*s overlapped*, 6H), 0.93 (*d*, 3H, *J* = 6.0Hz), 1.06 (*d*, 3H, *J* = 6.8Hz), 1.54 (*s*, 3H), 1.55 (*s*, 3H), 2.14 (*m*, 8H), 2.35 (*m*, 4H), 2.67 (*s*, 3H), 2.68 (*s*, 3H), 3.26 (*m*, 2H), 4.52 (*m*, 1H), 4.54 (*m*, 1H), 4.99 (*m*, 4H), 5.81

(*m*, 2H), 7.09 (*m*, 4H), 7.14 (*m*, 6H); ^{13}C NMR (150MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 19.0 (CH_3), 19.7 (CH_3), 22.0 (CH_3), 22.1 (CH_3), 23.6 ($2CH_3$), 23.9 ($2CH_3$), 29.7 (CH_3), 30.2 (CH_3), 30.9 (CH_2), 31.0 (CH_2), 35.3 (CH_2), 36.0 (CH_2), 37.8 ($2CH_2$), 42.5 (CH_2), 42.7 (CH_2), 60.4 (CH), 60.5 (CH), 79.3 (2C), 114.3 (CH_2), 114.4 (CH_2), 127.0 (2CH), 128.2 (4CH), 130.0 (4CH), 134.9 (C), 135.0 (C), 138.2 (2CH), 166.9 (C), 167.0 (C), 170.2 (C), 170.4 (C).



(*S*)-5-benzyl-2,2,3-trimethyl-1-(2-methylhept-6-enoyl)imidazolidin-4-one (21o): hept-6-enoic acid **9d** (1.3 g, 9.1 mmol) gave the corresponding amide (1.9 g, 5.6 mmol, 61 % yield); chromatographic conditions : petroleum ether/EtOAc = 3/2; white solid; m.p. 76°C; [R_f (3/2) = 0.20]. IR (KBr): υ 1699, 1649 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 0.73 (*s*, 3H), 1.28 (*d*, 3H, *J* = 6.5Hz), 1.42 (*m*, 3H), 1.54 (*s*, 3H), 1.63 (*m*, 1H), 2.03 (*m*, 2H), 2.67 (*m*, 1H), 2.68 (*s*, 3H), 3.08 (*dt*, 1H, *J* = 5.3, 14.0Hz), 3.37 (*dd*, 1H, *J* = 2.6, 14.0Hz), 4.56 (*dd*, 1H, *J* = 2.5, 5.3Hz), 4.97 (*m*, 1H), 4.99 (*m*, 1H), 5.75 (*ddt*, 1H, *J* = 6.7, 10.2, 23.8Hz), 7.11 (*m*, 2H), 7.24 (*m*, 3H); ^{13}C NMR (100MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 17.0 (CH_3), 22.5 (CH_3), 23.8 (CH_3), 24.1 (CH_3), 26.3 (CH_2), 33.5 (CH_2), 35.0 (CH_2), 38.0 (CH), 38.8 (CH_2), 60.4 (CH), 79.5 (C), 114.9 (CH_2), 127.2 (CH), 128.3 (2CH), 130.3 (2CH), 135.0 (C), 137.9 (CH), 167.1 (C), 175.1 (C).

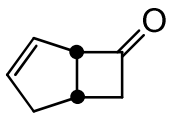


(*S*)-5-benzyl-1-hept-6-enoyl-2,2,3-trimethylimidazolidin-4-one (21p): commercial hept-6-enoic acid (1.1 g, 8.6 mmol) gave the corresponding amide (2.3 g, 7 mmol, 82 % yield), $[\alpha]_D^{20}$ +54.2 (*c* 1.000, CH_2Cl_2); chromatographic conditions : petroleum ether/EtOAc = 2/1; colorless oil; [R_f (2/1) = 0.43, 0.31]. IR (neat): υ 1704, 1660, 1647

cm^{-1}. ^1H NMR (600MHz, $CDCl_3$): δ 0.68 (*s*, 3H), 1.48 (*m*, 2H), 1.54 (*s*, 3H), 1.75 (*quintet*, 2H, *J* = 7.4Hz), 2.11 (*m*, 2H), 2.39 (*dt*, 1H, *J* = 7.6, 15.2Hz), 2.44 (*dt*, 1H, *J* = 7.3, 15.2Hz), 2.68 (*s*, 3H), 3.16 (*dd*, 1H, *J* = 5.6, 14.1Hz), 3.36 (*dd*, 1H, *J* = 2.3, 14.1Hz), 4.51 (*dd*, 1H, J = 2.1, 5.3Hz), 4.97 (*m*, 1H), 5.03 (*ddd*, 1H, *J* = 1.4, 3.5, 17.0Hz), 5.82 (*ddt*, 1H, *J* = 6.6, 10.0, 16.7Hz), 7.09 (*m*, 2H), 7.24 (*m*, 3H); ^{13}C NMR (150MHz, $CDCl_3$): δ 22.2 (CH_3), 23.8 (CH_3), 24.1 (CH_3), 24.5 (CH_2), 28.3 (CH_2), 33.4 (CH_2), 35.1 (CH_2), 37.8 (CH_2), 60.5 (CH), 79.4 (C), 114.6 (CH_2), 127.2 (CH), 128.3 (2CH), 130.1 (2CH), 135.0 (C), 138.2 (CH), 167.1 (C), 170.9 (C).

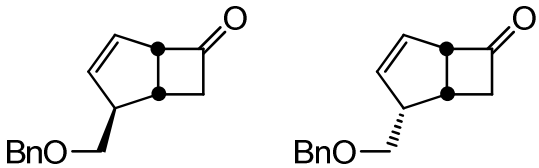
General Procedure[45] **for the [2+2] Intramolecular cycloaddition-hydrolysis sequence:** Under N_2**,** 2,6-di-*tert*-butyl-4-methylpyridine (1.2 eq.) was added to a stirring solution of amide **21** (1 eq.) in dry 1,2-dichloroethane (6.8 mL/mmol). A solution of triflic anhydride (2 eq.) in dry 1,2-dichloroethane (12.8 mL/mmol) was added dropwise in one hour to this mixture. Stirring was continued until reaction was complete by GC. The mixture was concentrated in vacuo and taken up in a biphasic system $CHCl_3/H_2O$ = 1/1 (9 mL/mmol). This mixture was refluxed for 5h, cooled, extracted with dichloromethane four times and dried over $MgSO_4$. The solvent was removed by distillation to give a brownish oil. This oil was taken up in *n*-pentane (1 mL/mmol), caused the precipitation of the 2,6-di-*tert*-butyl-4-methylpyridine. The liquid was charged into a column for the flash chromatographic purification. Because of the high volatility of the product yields were calculate by GC analysis on the crude after the hydrolysis step. The amine was recovered (*c.a.* 20 % yield) by extracting the aqueous layer at pH 14 with diethyl ether.

Bicyclo[3.2.0]hept-3-en-6-ones



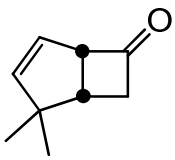
(1*S*,5*S*) Bicyclo[3.2.0]hept-3-en-6-one (12a): amide **21a** (1.9 g, 6.0 mmol) gave the corresponding highly volatile bicycle (434 mg, 4.0 mmol, 66 % yield, 91 % ee); chromatographic conditions : *n*-pentane/ CH_2Cl_2 = 1/0 gradient to 2/1; colorless oil; [R_f (2/1) = 0.20]. ^1H NMR (600MHz, $CDCl_3$): δ 1.59 (*m*, 1H), 1.63 (*m*, 1H), 1.75 (*m*, 1H), 1.84 (*m*, 2H), 2.04 (*m*, 1H), 2.68 (*m*, 3H), 2.49 (*ddd*, 1H, *J* = 3.2, 4.4, 18.2Hz), 2.89 (*m*,

1H), 3.19 (*ddd*, 1H, *J* = 4.4, 9.4, 18.5Hz), 3.55 (*m*, 1H); ^{13}C NMR (150MHz, $CDCl_3$): δ 25.6 (CH_2), 29.8 (CH), 40.2 (CH), 73.6 (CH), 125.1 (CH), 133.3 (CH), 207.6 (C); GC t_r(1*R*,5*R*) = 7.72min, t_r(1*S*,5*S*) = 8.46min.



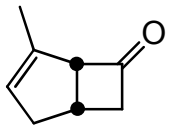
Major *Minor*

(1*R*,2*S*,5*S*) and (1*R*,2*R*,5*S*) -2-(Benzyloxymethyl) bicyclo[3.2.0]hept-3-en-6-one (12c): amide **21c** (2.3 g, 5.2 mmol) gave the corresponding bicycle (420 mg , 1.8 mmol, 35 % yield) in a *exo*:*endo* mixture (dr 92/8; ee *major* 93 %; ee *minor* 67 %); chromatographic conditions : *n*-pentane/Et_2O = 8/2; yellow oil; [R_f (7/3) = 0.48]. ^{1}H NMR (300MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 2.66-3.72 (*m*, 6H), 4.22 (*m*, 1H), 4.51 (*m*, 2H), 5.70 (*m*, 1H), 5.88 (*m*, 1H), 7.32 (*m*, 5H); ^{13}C NMR (75MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 28.8 (CH), 29.8 (CH), 46.7 (CH_2), 48.8 (CH), 52.8 (CH_2), 54.6 (CH), 69.3 (CH_2), 73.5 (CH), 73.6 (CH_2), 73.7 (CH_2), 73.8 (CH_2), 74.1 (CH), 127.3 (CH), 127.4 (4CH), 127.8 (CH), 128.9 (4CH), 134.8 (CH), 134.9 (CH), 138.7 (2C), 206.51 (2C); GC (column: Agilent 19091Z-413E, HP-1 Methyl siloxane column; (initial column temperature 50°C (2min); heating rate, 10°C/min (to 150°C), 25°C/min (to 275°C)): t_r(*major*) = 16.4min, t_r(*minor*) = 16.6min; GC (column: Restek 13104 Rt-βDEXsm; column temperature 180°C (30min)) *major*: t_r(1*S*,2*R*,5*R*) = 14.7min, t_r(1*R*,2*S*,5*S*) = 15.3min, *minor*: t_r(1*S*,2*S*,5*R*) = 12.9min, t_r(1*R*,2*R*,5*S*) = 13.4min.

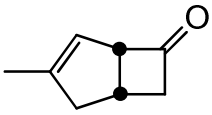


(1*S*,5*S*) 2,2-Dimethylbicyclo[3.2.0]hept-3-en-6-one (12d): amide **21d** (1.1 g, 1.2 mmol) gave the corresponding highly volatile bicycle (170 mg, 1.2 mmol, 40 % yield, 57 % ee); chromatographic conditions : *n*-pentane/ CH_2Cl_2 = 2/1; yellow oil; [R_f (2/1) = 0.28]. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.10 (*s*, 3H), 1.18 (*s*, 3H), 2.54 (*ddd*, 1H, *J* = 6.1, 6.2, 8.6Hz), 2.88 (*ddd*, 1H, *J* = 4.4, 8.4, 17.9Hz), 3.13 (*ddd*, 1H, *J* = 3.1, 6.3, 17.9Hz), 4.20 (*m*, 1H), 5.47 (*dd*, 1H, *J* = 2.6, 5.4Hz), 5.66 (*dd*, 1H, *J* = 2.2, 5.4Hz); ^{13}C

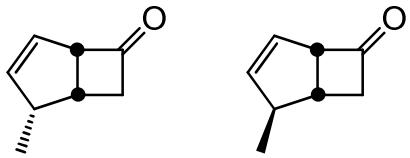
NMR (75MHz, $CDCl_3$): δ 21.2 (CH_3), 30.6 (CH_3), 37.5 (CH), 41.5 (C), 47.4 (CH_2), 73.2 (CH), 123.5 (CH), 144.7 (CH), 206.6(C); GC (column: Agilent 19091Z-413E, HP-1 Methyl siloxane column; (initial column temperature 50°C (2min); heating rate, 10°C/min (to 150°C), 25°C/min (to 275°C)): t_r = 7.3min; GC (column: Restek 13104 Rt-βDEXsm; column temperature 80°C (30min)): t_r(1*R*,5*R*) = 29.7min, t_r(1*S*,5*S*) = 31.3min.



(1*S*,5*R*) 4-Methylbicyclo[3.2.0]hept-3-en-6-one (12f): (*S*)-amide **21f** (1.4 g, 4.11 mmol) gave the corresponding bicycle (355 mg, 2.9 mmol, 71 % yield, 93 % ee); chromatographic conditions: *n*-pentane/CH_2Cl_2 = 4/1 gradient to 2/1; yellow oil; [R_f (2/1) = 0.28, permanganate]. ^{1}H NMR (600MHz, $CDCl_3$): δ 1.76 (*m*, 3H), 2.38 (*m*, 1H), 2.80 (*m*, 3H), 3.23 (*m*, 1H), 4.02 (*m*, 1H), 5.46 (*m*, 1H); ^{13}C NMR (150MHz, $CDCl_3$): δ 15.2 (CH_3), 26.7 (CH), 40.2 (CH_2), 53.3 (CH_2), 76.1 (CH), 126.6 (CH), 134.9 (C), 207.5 (C); GC (column: Agilent 19091Z-413E, HP-1 Methyl siloxane column; (initial column temperature 50°C (2min); heating rate, 10°C/min (to 150°C), 25°C/min (to 275°C)): t_r = 6.9min; GC (column: Restek 13104 Rt-βDEXsm; initial column temperature 120°C (20min); heating rate, 5°C/min (to 180°C)) : t_r(1*R*,5*S*) = 5.4min, t_r(1*S*,5*R*) = 5.5min.

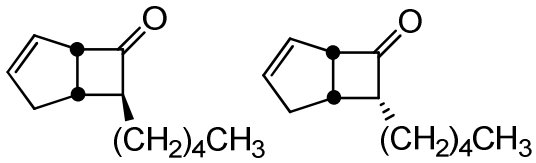


(1*S*,5*R*) 3-Methylbicyclo[3.2.0]hept-3-en-6-one (12g): (*S*)-amide **21g** (1.8 g, 5.3 mmol) gave the corresponding bicycle (422 mg, 3.5 mmol, 65 % yield, 93 % ee); $[\alpha]_D^{20}$ + 783.5 (*c* 0.500, $CHCl_3$); chromatographic conditions: *n*-pentane/CH_2Cl_2 = 100/0 gradient to 2/1; yellow oil; [R_f (2/1) = 0.15, permanganate]. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.80 (*m*, 3H), 2.29 (*m*, 1H), 2.75 (*m*, 1H), 2.80 (*m*, 2H), 3.21 (*m*, 1H), 4.18 (*m*, 1H), 5.21 (*m*, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ 16.5 (CH_3), 26.5 (CH), 44.4 (CH_2), 53.1 (CH_2), 73.5 (CH), 119.1 (CH), 134.9 (C), 208.6 (C); GC (column: Agilent 19091Z-413E, HP-1 Methyl siloxane column; (initial column temperature 50°C (2min); heating rate, 10°C/min (to 150°C), 25°C/min (to 275°C)): t_r = 7.3min; GC (column: Restek 13104 Rt-βDEXsm; initial column temperature 120°C (20min); heating rate, 5°C/min (to 180°C)) : t_r(1*R*,5*S*) = 6.5min, t_r(1*S*,5*R*) = 7.6min.



Major *Minor*

(1*R*,2*R*,5*S*) and (1*R*,2*S*,5*S*) 2-Methylbicyclo[3.2.0]hept-3-en-6-one (12h): (*S*)-amide **21h** (1.8 g, 5.3 mmol) gave the corresponding bicycle (422 mg, 3.5 mmol, 66 % yield) in a *endo*:*exo* mixture (dr 49/51; ee *major* 84 %; ee *minor* 87 %); chromatographic conditions: *n*-pentane/CH_2Cl_2 = 4/1 gradient to 2/1; yellow oil; [R_f (2/1) = 0.31, permanganate]. ^{1}H NMR (600MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 1.05 (*d*, 3H*minor*, *J* = 7.0Hz), 1.17 (*d*, 3H*major*, *J* = 7.3Hz), 2.41 (*dt*, 1H*minor*, *J* = 5.8, 9.0Hz), 2.75 (*m*, 1H*minor*), 2.80 (*m*, 1H*major*), 2.83 (*m*, 1H*minor*), 2.94 (*m*, 1H*major*), 3.17 (*dd*, 1H*minor*, *J* = 4.4, 9.0Hz), 3.20 (*m*, 1H*major*), 3.23 (*m*, 1H*major*), 4.19 (*m*, 1H*major*), 4.26 (*m*, 1H*minor*), 5.56 (*m*, 1H*minor*), 5.59 (*m*, 1H*major*), 5.69 (*m*, 1H*major*), 5.89 (*m*, 1H*minor*); ^{13}C NMR (150MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 13.4 (CH_3*major*), 21.5 (CH_3*minor*), 30.5 (CH_2*major*), 33.3 (CH_2*minor*), 41.9 (CH*minor*), 45.8 (CH_2*major*), 48.0 (CH*minor*), 52.1 (CH_2*minor*), 72.8 (CH*major*), 73.8 (CH*minor*), 124.3 (CH*major*), 124.9 (CH*minor*), 139.4 (CH*minor*), 139.5 (CH*major*), 207.4 (C*major*), 207.7 (C*minor*); GC (column: Agilent 19091Z-413E, HP-1 Methyl siloxane column; (initial column temperature 50°C (2min); heating rate, 10°C/min (to 150°C), 25°C/min (to 275°C)): t_r(*major*) = 6.9min, t_r(*minor*) = 6.4min; GC (column: Restek 13104 Rt-βDEXsm; initial column temperature 120°C (20min); heating rate, 5°C/min (to 180°C)) *major*: t_r(1*S*,2*S*,5*R*) = 5.1min, t_r(1*R*,2*R*,5*S*) = 5.6min; *minor*: t_r(1*S*,2*R*,5*R*) = 6.0min, t_r(1*R*,2*S*,5*S*) = 6.5min.



Major *Minor*

(1*S*,5*S*,7*S*) and (1*S*,5*S*,7*R*) 7-Pentylbicyclo[3.2.0]hept-3-en-6-one (12i): amide **21i** (460 mg, 1.2 mmol) gave the corresponding bicycle (178 mg , 0.8 mmol, 70 % yield) in mixture (dr 88/22; ee *major* 92 %; ee *minor* 91 %); chromatographic conditions : *n*-pentane/CH_2Cl_2 = 3/1 gradient to 2/1; yellow oil; [R_f (2/1) = 0.31]. IR (neat): υ 2956,

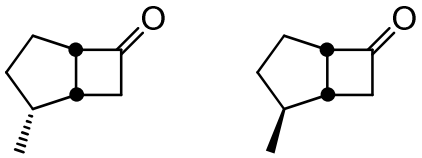
2926, 2855, 1774 cm^{-1}. ^1H NMR (600MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 0.89 (*t*, 3H*major*, *J* = 7.0Hz), 0.89 (*m*, 3H*minor*), 1.29 (*m*, 4H*major* + 4H*minor*), 1.38 (*m*, 2H*major* + 2H*minor*), 1.48 (*m*, 1H*minor*), 1.50 (*m*, 1H*major*), 1.60 (*m*, 1H*minor*), 1.70 (*m*, 1H*major*), 2.47 (*m*, 1H*major*), 2.50 (*m*, 1H*major*), 2.52 (*m*, 1H*minor*), 2.57 (*m*, 1H*minor*), 2.84 (*ddq*, 1H*major*, *J* = 2.3, 7.9, 15.6Hz), 2.95 (*ddt*, 1H*major*, *J* = 3.2, 5.98, 9.0Hz), 3.09 (*m*, 1H*minor*), 3.28 (*m*, 1H*minor*), 4.14 (*m*, 1H*major*), 4.25 (*m*, 1H*minor*), 5.60 (*m*, 1H*minor*), 5.65 (*dq*, 1H*major*, *J* = 2.6, 5.3Hz), 5.88 (*dq*, 1H*major*, *J* = 2.3, 4.7Hz), 5.91 (*m*, 1H*minor*); ^{13}C NMR (150MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 13.9 (CH_3*major*), 22.4 (CH_2*major*), 26.5 (CH_2*minor*), 26.8 (CH_2*major*), 28.0 (CH_2*minor*), 28.9 (CH_2*major*), 29.6 (CH_2*minor*), 30.1 (CH_3*minor*), 30.4 (CH*minor*), 31.6 (CH_2*minor*), 31.7 (CH_2*major*), 32.7 (CH_2*minor*), 33.3 (CH*major*), 40.5 (CH_2*major*), 61.7 (CH*minor*), 66.0 (CH*major*), 70.7 (CH*major*), 71.5 (CH*minor*), 116.1 (CH*minor*), 125.3 (CH*minor*), 126.2 (CH*major*), 133.3 (CH*major*), 211.2 (C*minor* + C*major*); GC (column: Agilent 19091Z-413E, HP-1 Methyl siloxane column; (initial column temperature 50°C (2min); heating rate, 10°C/min (to 150°C), 25°C/min (to 275°C)): t_r(*major*) = 11.2min, t_r(*minor*) = 11.5min; GC (column: Restek 13104 Rt-βDEXsm; initial column temperature 120°C (20min); heating rate, 5°C/min (to 180°C)) *major*: t_r(1*R*,5*R*,7*R*) = 22.8min, t_r(1*S*,5*S*,7*S*) = 23.2min, *minor*: t_r(1*R*,5*R*,7*S*) = 25.6min, t_r(1*S*,5*S*,7*R*) = 26.3min.

Bicyclo[3.2.0]heptan-6-ones

Major *Minor*

(1*S*,3*R*,5*S*) and (1*S*,3*S*,5*S*) 3-Methylbicyclo[3.2.0]heptan-6-one (10a): (*S*)-amide **21l** (1.17 g, 3.4 mmol) gave the corresponding bicycle (136 mg, 1.1 mmol, 32 % yield) in a *exo*:*endo* mixture (dr 55/45; ee *major* 85 %; ee *minor* 90 %); chromatographic conditions : *n*-pentane/ CH_2Cl_2 = 4/1 gradient to 3/2; colorless oil; [R_f (2/1) = 0.27, permanganate]. IR (neat): υ 2952, 2920, 2847, 1734 cm^{-1}. ^1H NMR (600MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 1.04 (*d*, 3H*major*, *J* = 6.7Hz), 1.05 (*d*, 3H*minor*, *J* = 6.0Hz), 1.18 (*ddd*, 1H*minor*, *J* = 6.0, 8.9, 13.0Hz), 1.26 (*m*, 1H*major*),

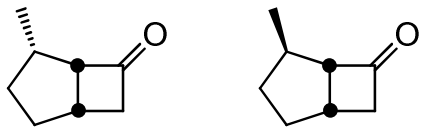
1.42 (*ddd*, 1H*major*, *J* = 7.2, 11.7, 12.7Hz), 1.54 (*ddd*, 1H*minor*, *J* = 5.6, 8.5, 13.0Hz), 1.89 (*dd*, 1H*major*, *J* = 5.9, 13.0Hz), 1.95 (*dddd*, 1H*minor*, *J* = 1.0, 6.9, 9.9, 13.0Hz), 2.09 (*m*, 1H*major*), 2.12 (*m*, 1H*major*), 2.18 (*m*, 1H*minor*), 2.26 (*m*, 1H*minor*), 2.56 (*ddd*, 1H*major*, *J* = 3.6, 4.3, 18.4Hz), 2.69 (*dt*, 1H*minor*, *J* = 3.5, 17.9Hz), 2.82 (*m*, 1H*minor*), 2.88 (*m*, 1H*major*), 3.19 (*m*, 1H*major* + 1H*minor*), 3.56 (*m*, 1H*major*), 3.63 (*m*, 1H*minor*); ^{13}C NMR (100MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 18.8 (*major*CH_3), 20.0 (*minor*CH_3), 29.4 (*major*CH), 30.1 (*minor*CH), 32.8 (*major*CH), 36.7 (*minor*CH_2), 38.0 (*major*CH_2), 39.9 (*minor*CH), 41.2 (*major*CH_2), 42.2 (*minor*CH_2), 51.9 (*major*CH_2), 52.6 (*minor*CH_2), 65.2 (*major*CH), 65.8 (*minor*CH), 214.1 (*major*C), 215.0 (*minor*C); GC (column: Agilent 19091Z-413E, HP-1 Methyl siloxane column; (initial column temperature 50°C (2min); heating rate, 10°C/min (to 150°C), 25°C/min (to 275°C)): t_r(*major*) = 6.86min, t_r(*minor*) = 7.1min; GC (column: Restek 13104 Rt-βDEXsm; column temperature 80°C (30min)) : *major*: t_r(1*R*,3*S*,5*R*) = 21.6min, t_r(1*S*,3*R*,5*S*) = 28.9min; *minor*: t_r(1*R*,3*R*,5*R*) = 23.7min, t_r(1*S*,3*S*,5*S*) = 28.1min.



Major *Minor*

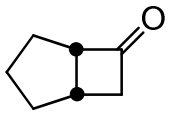
(1*R*,2*R*,5*S*) and (1*R*,2*S*,5*S*) 2-Methylbicyclo[3.2.0]heptan-6-one (10b): (*S*)-amide **21m** (0.95 g, 2.7 mmol) gave the corresponding bicycle (118 mg, 0.9 mmol, 34 % yield) in a *endo*:*exo* mixture (dr 53/47; ee *major* 87 %, ee *minor* 92 %); chromatographic conditions: *n*-pentane/CH_2Cl_2 = 2.5/1; colorless oil; [R_f (2/1) = 0.19, permanganate]. ^{1}H NMR (600MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 0.95 (*d*, 3H*minor*, *J* = 7.0Hz), 1.06 (*d*, 3H*major*, *J* = 6.7Hz), 1.56 (*m*, 2H*major*), 1.66 (*m*, 2H*minor*), 1.83 (*m*, 2H*major* + 2H*minor*), 2.17 (*m*, 1H*minor* + 1H*minor*), 2.52 (*m*, 1H*major* + 1H*minor*), 2.71 (*m*, 1H*major*), 2.77 (*m*, 1H*major*), 2.89 (*ddd*, 1H*major*, *J* = 4.7, 9.1, 18.2Hz), 3.17 (*ddd*, 1H*minor*, *J* = 4.7, 9.9, 19.0Hz), 3.52 (*m*, 1H*major*), 3.57 (*m*, 1H*minor*); ^{13}C NMR (100MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 14.7 (*major*CH_3), 20.0 (*minor*CH_3), 26.9 (*minor*CH_2), 28.6 (*major*CH_2), 31.6 (*minor*CH_2), 31.8 (*major*CH_2), 33.3 (*major*CH), 36.3 (*minor*CH), 37.2 (*major*CH), 39.6 (*minor*CH), 45.1 (*major*CH_2), 51.2 (*minor*CH_2), 64.2 (*minor*CH),

64.7 (*major*CH), 214.0 (*minor*C), 214.1 (*major*C); GC (column: Agilent 19091Z-413E, HP-1 Methyl siloxane column; (initial column temperature 50°C (2min); heating rate, 10°C/min (to 150°C), 25°C/min (to 275°C)): t_r(*major*) = 7.2min, t_r(*minor*) = 7.0min; GC (column: Restek 13104 Rt-βDEXsm; column temperature 80°C (30min)) : *major*: t_r(1*S*,2*S*,5*R*) = 25.9min, t_r(1*R*,2*R*,5*S*) = 28.6min; *minor*: t_r(1*S*,2*R*,5*R*) = 24.9min, t_r(1*R*,2*S*,5*S*) = 27.5min.

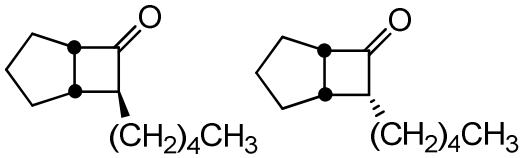


Major *Minor*

(1*S*,4*S*,5*S*) and (1*S*,4*R*,5*S*) 4-Methylbicyclo[3.2.0]heptan-6-one (19c): amide **21n** (1.28 g, 3.7 mmol) gave the corresponding bicycle (130 mg, 1.05 mmol, 28 % yield) in a *endo*:*exo* mixture (dr 67/33; ee *major* 79 %; ee *minor* 93 %); chromatographic conditions : *n*-pentane/CH_2Cl_2 = 4/1 gradient to 3/2; colorless oil; [R_f (2/1) = 0.22, permanganate]. ^{1}H NMR (600MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 0.89 (*d*, 3H*minor*, *J* = 7.3Hz), 1.13 (*d*, 3H*major*, *J* = 7.0Hz), 1.38 (*m*, 1H*major*), 1.55 (*dd*, 1H*minor*, *J* = 6.7, 12.9Hz), 1.82 (*m*, 2H*minor* + 2H*major*), 1.84 (*m*, 1H*major*), 2.00 (*m*, 1H*minor*), 2.11 (*m*, 1H*major*), 2.43 (*quintet*, 1H*minor*, *J* = 6.7Hz), 2.49 (*ddd*, 1H*major*, *J* = 3.5, 4.4, 18.4Hz), 2.51 (*m*, 1H*minor*), 2.83 (*m*, 1H*minor*), 2.91 (*m*, 1H*major*), 3.12 (*ddd*, 1H*major*, *J* = 4.7, 9.0, 18.4Hz), 3.17 (*ddd*, 1H*minor*, *J* = 4.4, 9.4, 18.4Hz), 3.23 (*m*, 1H*minor*), 3.41 (*m*, 1H*major*); ^{13}C NMR (150MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 15.3 (*major*CH_3), 19.7 (*minor*CH_3), 28.7 (*minor*CH), 29.3 (*major*CH), 30.2 (*major*CH_2), 31.8 (*minor*CH_2), 32.9 (*major*CH_2 + *minor*CH_2), 37.0 (*minor*CH), 39.2 (*major*CH), 51.1 (*minor*CH_2), 51.5 (*major*CH_2), 69.0 (*major*CH), 72.0 (*minor*CH), 213.1 (*major*C), 213.9 (*minor*C); GC (column: Agilent 19091Z-413E, HP-1 Methyl siloxane column; (initial column temperature 50°C (2min); heating rate, 10°C/min (to 150°C), 25°C/min (to 275°C)): t_r(*major*) = 13.5min, t_r(*minor*) = 13.7min; GC (column: Restek 13104 Rt-βDEXsm; column temperature 80°C (30min)): *major*: t_r(1*S*,4*S*,5*S*) = 26.2min, t_r(1*R*,4*R*,5*R*) = 29.0min; *minor*: t_r(1*R*,4*S*,5*R*) = 24.3min, t_r(1*S*,4*R*,5*S*) = 25.9min.



(1*S*,5*S*) Bicyclo[3.2.0]heptan-6-one (10e): amide **21p** (750 mg, 2.28 mmol) gave the corresponding highly volatile bicycle (63 mg, 0.57 mmol, 25 % yield, 88 % ee); $[\alpha]_D^{20}$ +182.6 (*c* 0.390, $CHCl_3$); chromatographic conditions : *n*-pentane/CH_2Cl_2 = 3/1 gradient to 2/1; colorless oil; [R_f (2/1) = 0.20, permanganate]. ^{1}H NMR (600MHz, $CDCl_3$): δ 1.59 (*m*, 1H), 1.63 (*m*, 1H), 1.75 (*m*, 1H), 1.84 (*m*, 2H), 2.04 (*m*, 1H), 2.49 (*ddd*, 1H, *J* = 3.2, 4.4, 18.2Hz), 2.89 (*m*, 1H), 3.19 (*ddd*, 1H, *J* = 4.4, 9.4, 18.5Hz), 3.55 (*m*, 1H); ^{13}C NMR (150MHz, $CDCl_3$): δ 24.7 (CH_2), 28.8 (CH), 29.8 (CH_2), 32.7 (CH_2), 51.5 (CH_2), 64.8 (CH), 214.8 (C); GC (column: Agilent 19091Z-413E, HP-1 Methyl siloxane column; (initial column temperature 50°C (2min); heating rate, 10°C/min (to 150°C), 25°C/min (to 275°C)): t_r = 4.3min; GC (column: Restek 13104 Rt-βDEXsm; column temperature 80°C (30min)) : t_r(1*R*,5*R*) = 16.7min, t_r(1*S*,5*S*) = 18.9min.

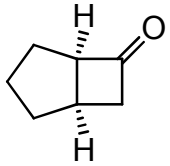


Major *Minor*

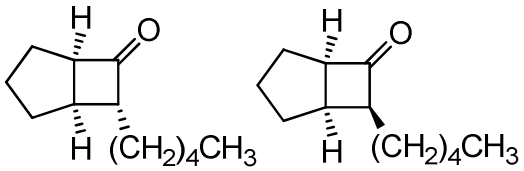
(1*R*,5*S*,7*S*) and (1*R*,5*S*,7*R*) 7-Pentylbicyclo[3.2.0]heptan-6-one (10f): 2-Methylbicyclo [3.2.0]hept-3-en-6-one **12i** (60 mg, 0.33 mmol, 1 eq.) was dissolved in methanol (2 mL/mmol) and the flask was saturated with nitrogen. To this solution Pd/C 5 % (13 mg, 0.04 g/ mmol) was added and the flask was saturated with hydrogen. At the flask was connected a gas-burette of hydrogen and the reaction was stirred until the H_2 adsorption end. After 3h the mixture was filtered through a pad of celite and the filtrate was concentrated under reduce pressure to afford 43 mg (0.24 mmol, 71 % yield) of product as colorless oil. IR (neat): υ 2953, 2929, 2857, 1771 cm^{-1}. ^{1}H NMR (600MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 0.90 (*t*, 3H, *J* = 7.0Hz), 1.33 (*m*, 4H), 1.53 (*m*, 1H), 1.64 (*m*, 2H), 1.77 (*m*, 1H), 1.86 (*m*, 2H), 2.00 (*m*, 1H), 2.55 (*m*, 1H), 2.60 (*m*, 1H); ^{13}C NMR (150MHz, $CDCl_3$) (of the mixture of the two diastereoisomers): δ 13.4 (CH_3*major* + CH_3*minor*), 22.0 (CH_2*major*), 22.9 (CH_2*minor*), 24.8 (CH_2*major*), 26.2 (CH_2*minor*), 26.3 (CH_2*minor*), 26.3 (CH_2*major*), 26.9 (CH_2*minor*), 28.5 (CH*minor*), 28.9 (CH_2*major*), 29.1 (CH*major*), 29.6 (CH_2*minor*),

31.2 (CH_2*major*), 31.3 (CH_2*minor*), 32.4 (CH_2*major*), 33.2 (CH_2*minor*), 36.1 (CH_2*major*), 60.3 (CH*minor*), 61.1 (CH*major*), 63.6 (CH*major*), 62.3 (CH*minor*), 119.4 (C*minor* + C*major*); GC (column: Agilent 19091Z-413E, HP-1 Methyl siloxane column; (initial column temperature 50°C (2min); heating rate, 10°C/min (to 150°C), 25°C/min (to 275°C)): t_r(*major*) = 11.8min, t_r(*minor*) = 11.5min; GC (column: Restek 13104 Rt-βDEXsm; initial column temperature 120°C (20min); heating rate, 5°C/min (to 180°C)) *major*: t_r(1*S*,5*R*,7*R*) = 23.8min, t_r(1*R*,5*S*,7*S*) = 24.1min, *minor*: t_r(1*S*,5*R*,7*S*) = 25.5min, t_r(1*R*,5*S*,7*R*) = 25.8min.

General Procedure[45] **for the [2+2] Intermolecular cycloaddition-hydrolysis sequence:** 2,6-Di-*tert*-butyl-4-methylpyridine (1.1 eq.) was added to a solution of amide **22a** or **22b** (1 eq.) in dry 1,2-dichloroethane (10 mL/mmol). This mixture was cooled at 0 °C and then a solution of triflic anhydride (2 eq.) in dry 1,2-dichloroethane (2 mL/mmol) was added dropwise in one hour. The mixture was stirred until reaction was complete by GC. It was concentrated in vacuo and taken up in a biphasic system $CHCl_3/H_2O$ = 1/1 (9 mL /mmol). This mixture was refluxed for 5h, cooled, extracted four times with dichloromethane and dried over $MgSO_4$. The solvent was removed by distillation to give a brownish oil. This oil was taken in *n*-pentane (1 mL/mmol), which caused the precipitation of the 2,6-di-*tert*-butyl-4-methylpyridine. The liquid was charged into column for the flash chromatographic purification. Because of the high volatility of the products the yields were calculate by GC analysis on the crude after the hydrolysis step. The chiral amine was recovered by extracting the aqueous layer at pH 14 with ether.

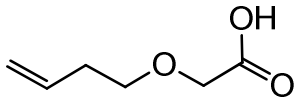


(1*R*,5*R*) Bicyclo[3.2.0]heptan-6-one (10e): amide **22a** (600 mg, 2.30 mmol) gave the corresponding bicycle (8 mg, 0.07 mmol, 3 % yield, 96 % ee); chromatographic conditions : *n*-pentane/CH_2Cl_2 = 3/1 gradient to 2/1; colorless oil; [R_f (2/1) = 0.20, permanganate].



Major *Minor*

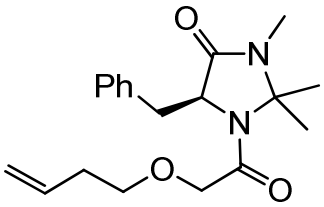
(1*S*,5*R*,7*R*) and (1*S*,5*R*,7*S*) 7-Pentylbicyclo[3.2.0]heptan-6-one (10f): amide **22b** (400 mg, 1.2 mmol) gave the corresponding bicycle (12 mg, 0.065 mmol, 5 % yield) in mixture (dr 65/35; ee *major* 63 %; ee *minor* 80 %); chromatographic conditions : *n*-pentane/CH_2Cl_2 = 1/0 gradient to 3/1; yellow oil; [R_f (3/1) = 0.23, permanganate].



2-(But-3-enyloxy)acetic acid 25a [62]**:** Sodium hydride (50% dispersion in mineral oil, 3.1 g, 65 mmol) was washed with hexanes and suspended in 50 mL of dry THF, and the mixture was cooled to 0 °C. 3-Buten-1-ol **26** (5.1g, 71 mmol) was added dropwise over 15 min. The resulting mixture was stirred at 0 °C for 15 min, warmed to 25 °C for 15 min, and then recooled to 0°C. In a second flask, sodium hydride (50% dispersion in mineral oil, 3.1 g, 65 mmol) was washed with hexanes and suspended in 25 mL of THF, and the mixture was cooled to 0 °C. Bromoacetic acid (9 g, 65 mmol) dissolved in 25 mL of THF was added into the second flask, and the mixture was stirred at 0 °C for 5 min. The sodium alkoxide of the alcohol was then added into the flask containing the sodium carboxylate of bromoacetic acid. The resultant mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched with water, and the THF was removed in vacuo. The aqueous layer was washed with diethyl ether, acidified and then extracted three times with diethyl ether. The extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The alkoxyacetic acid was obtained in 94% yield and was used without further purification.

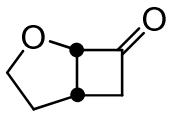
^{1}H NMR (400MHz, $CDCl_3$) : δ 2.39 (*tt*, 1H, *J* = 1.4, 6.7Hz), 2.41 (*tt*, 1H, *J* = 1.4, 6.7Hz), 3.63 (*t*, 2H, *J* = 6.7Hz), 4.15 (*s*, 2H), 5.08 (*m*, 1H), 5.13 (*m*, 1H), 5.82 (*ddt*, 1H, *J* = 6.7, 10.0, 17.0Hz), 10.9 (*s*, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ 33.8 (CH_2), 67.6 (CH_2), 71.1 (CH_2), 116.9 (CH_2), 134.3 (CH), 175.7 (C).

[62] Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653.



(*S*)-5-benzyl-1-(2-(but-3-enyloxy)acetyl)-2,2,3-trimethylimidazolidin-4-one 28a: A solution of oxalyl chloride (5.8 g, 46 mmol) in 12 mL of dry toluene was added dropwise to a stirred solution of acid **25a** (2 g, 15 mmol) in 60 mL of dry toluene at 0 °C and under a positive pressure of nitrogen. After 5min at 0 °C, few drops of dry DMF were added and the mixture was stirred at room temperature for 2h. The solvent and the excess of oxalyl chloride were removed in vacuo. The crude chloride was dissolved in 35 mL of anhydrous dichloromethane and the (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **13** (4.1 g, 16 mmol) was added. The mixture was cooled to 0 °C and dry pyridine (2.6 g, 32 mmol) was added. The mixture was allowed to warm to room temperature; after 24h TLC analysis revealed that the starting material was consumed and water was added. The organic layer was washed twice with water, and then the aqueous layers were extracted three times with ether. The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated. The crude was purified by flash column chromatography (CH_2Cl_2/MeOH 97:3) to afford the corresponding amide (3.1 g, yield 64 %).

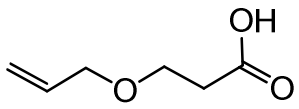
Colorless oil, R_f 0.38 (CH_2Cl_2/MeOH 97:3), ^{1}H NMR (400MHz, $CDCl_3$): δ 0.70 (*s*, 3H), 1.57 (*s*, 3H), 2.42 (*m*, 2H), 2.69 (*s*, 3H), 3.12 (*dd*, 1H, *J* = 5.6, 14.2Hz), 3.35 (*dd*, 1H, *J* = 2.5, 14.2Hz), 3.62 (*m*, 2H), 4.21 (*dd*, 1H, J = 13.8, 55.5Hz), 4.77 (*m*, 1H), 5.08 (*m*, 1H), 5.13 (*m*, 1H), 5.84 (*ddt*, 1H, *J* = 6.7, 10.2, 17.1Hz), 7.11 (*m*, 2H), 7.24 (*m*, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 22.5 (CH_3), 24.0 (CH_3), 24.4 (CH_3), 34.2 (CH_2), 37.6 (CH_2), 59.9 (CH), 71.4 (CH_2), 71.9 (CH_2), 80.1 (C), 117.2 (CH_2), 127.6 (CH), 128.7 (2CH), 130.4 (2CH), 134.8 (CH), 135.5 (C), 167.6 (C), 170.9 (C).



(1*S*,5*S*)-2-oxabicyclo[3.2.0]heptan-7-one 29a: Under N_2**,** 2,6-di-*tert*-butyl-4-methylpyridine (2.2 g, 11 mmol) was added to a stirring solution of amide **28a** (3.0 g, 9.1 mmol) in 53 mL of dry 1,2-dichloroethane. A solution of triflic anhydride (5.1 g, 18

mmol) in 18 mL of dry 1,2-dichloroethane was added dropwise in one hour to this mixture. Stirring was continued until reaction was complete by GC. The mixture was concentrated in vacuo and taken up in a biphasic system $CHCl_3/H_2O$ = 60/60. This mixture was refluxed for 5h, cooled, extracted with dichloromethane four times and dried over $MgSO_4$. The solvent was removed by distillation to give a brownish oil. This oil was taken up in *n*-pentane and the liquid was charged into a column for the flash chromatographic purification (CH_2Cl_2/*n*-pentane 4:1 gradient to 0:1) to afford 100 mg (yield 50%, ee 40%) of oxabicyclo.

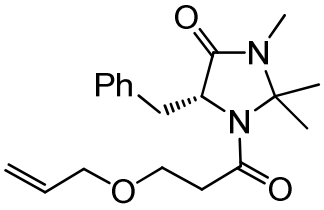
^{1}H NMR (400MHz, $CDCl_3$): δ 1.93 (*m*, 1H), 2.09 (*m*, 1H), 2.54 (*ddd*, 1H, *J* = 3.4, 4.0, 18.0Hz), 3.11 (*m*, 1H), 3.18 (*m*, 1H), 3.77 (*ddd*, 1H, *J* = 5.6, 9.2, 11.3Hz), 4.23 (*m*, 1H), 5.08 (*m*, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ 30.5 (CH), 31.7 (CH_2), 49.5 (CH_2), 68.8 (CH_2), 93.8 (CH), 210.9 (C); GC (column: Agilent 19091Z-413E, HP-1 Methyl siloxane column; (initial column temperature 50°C (2min); heating rate, 10°C/min (to 150°C), 25°C/min (to 275°C)): t_r = 6.5min; GC (column: Restek 13104 Rt-βDEXsm; initial column temperature 100°C (2min); heating rate, 1.5°C/min (to 180°C)) : t_r(1*R*,5*R*) = 9.6min, t_r(1*S*,5*S*) = 10.2min.



3-(Allyloxy)propanoic acid 25b [63]**:** Dry Cs_2CO_3 (3.2 g, 10 mmol) was suspended in 6 mL of dry DMF. The mixture was cooled to 0°C and *tert*-butyl acrylate (1.3 g, 10 mmol) was added dropwise. After 15min a solution of Prop-2-en-1-ol **27** (0.6 g, 10 mmol) in 4 mL of DMF was slowly added. The reaction was stirred overnight at 40°C. Then, brine was added and the product was extracted three times with diethyl ether. The organic phase was washed three times with brine, then the organic layer was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the *tert*-butyl ester as colorless oil (1.1 g, 58 % yield). This ester was dissolved in 20 mL of dry CH_2Cl_2, treated with 1.9 g (17.4 mmol) of trifluoroacetic acid and stirred overnight at 40°C. The solvent and the acid excess were removed under reduced pressure to afford 672 mg (89% yield) of acid.

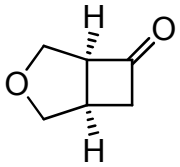
[63] In according to literature: Perrone, M. G.; Santandrea, E.; Dell'Uomo, N.; Giannessi, F.; Milazzo, F. M.; Sciarroni, A. F.; Scilimanti, A.; Tortorella, V. *Eur. J. Med. Chem.* **2005**, *40*, 143.

^{1}H NMR (400MHz, $CDCl_3$) : δ 2.62 (*m*, 2H), 3.70 (*m*, 2H), 3.99 (*m*, 2H), 5.17 (*m*, 1H), 5.25 (*m*, 1H), 5.87 (*m*, 1H), 10.3 (*s*, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ 35.0 (CH_2), 65.3 (CH_2), 72.2 (CH_2), 117.6 (CH_2), 134.5 (CH), 177.5 (C).



((*R*)-1-(3-(allyloxy)propanoyl)-5-benzyl-2,2,3-trimethylimidazolidin-4-one 28b: A solution of oxalyl chloride (3.8 g, 30 mmol) in 8 mL of dry dichloromethane was added dropwise to a stirred solution of acid **25b** (1.3 g, 10 mmol) in 40 mL of dry dichloromethane at 0 °C and under a positive pressure of nitrogen. After 5min at 0 °C, few drops of dry DMF were added and the mixture was stirred at room temperature for 2h. The solvent and the excess of oxalyl chloride were removed in vacuo. The crude chloride was dissolved in 30 mL of anhydrous dichloromethane and the (*R*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **13** (2.7 g, 10.3 mmol) was added. The mixture was cooled to 0 °C and dry pyridine (1.6 g, 20.7 mmol) was added. The mixture was allowed to warm to room temperature; after 24h TLC analysis revealed that the starting material was consumed and water was added. The organic layer was washed twice with water, and then the aqueous layers were extracted three times with ether. The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated. The crude was purified by flash column chromatography (CH_2Cl_2/MeOH 97:3) to afford the corresponding amide (1.8 g, yield 60 %).

Colorless oil, R_f 0.36 (CH_2Cl_2/MeOH 97:3), ^{1}H NMR (400MHz, $CDCl_3$): δ 0.66 (*s*, 3H), 1.54 (*s*, 3H), 2.67 (*s*, 3H), 2.70 (*m*, 2H), 3.21 (*dd*, 1H, *J* = 5.6, 14.0Hz), 3.38 (*dd*, 1H, *J* = 2.2, 14.0Hz), 3.85 (*m*, 2H), 4.03 (*m*, 2H), 4.59 (*m*, 1H), 5.18 (*m*, 1H), 5.28 (*m*, 1H), 5.91 (*ddt*, 1H, *J* = 5.5, 10.3, 17.1Hz), 7.14 (*m*, 2H), 7.22 (*m*, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 22.2 (CH_3), 23.7 (CH_3), 24.1 (CH_3), 35.9 (CH_2), 37.7 (CH_2), 60.5 (CH), 66.2 (CH_2), 72.1 (CH_2), 79.4 (C), 116.9 (CH_2), 127.1 (CH), 128.2 (2CH), 130.3 (2CH), 134.4 (CH), 135.1 (C), 167.0 (C), 169.2 (C).



(1*R*,5*S*)-3-oxabicyclo[3.2.0]heptan-6-one 29b: Under N_2**,** 2,6-di-*tert*-butyl-4-methylpyridine (1.3 g, 6.2 mmol) was added to a stirring solution of amide **28b** (1.7 g, 5.1 mmol) in 31 mL of dry 1,2-dichloroethane. A solution of triflic anhydride (2.9 g, 10 mmol) in 27 mL of dry 1,2-dichloroethane was added dropwise in one hour to this mixture. Stirring was continued until reaction was complete by GC. The mixture was concentrated in vacuo and taken up in a biphasic system $CHCl_3/H_2O$ = 34/34. This mixture was refluxed for 5h, cooled, extracted with dichloromethane four times and dried over $MgSO_4$. The solvent was removed by distillation to give a brownish oil. This oil was taken up in *n*-pentane and the liquid was charged into a column for the flash chromatographic purification (CH_2Cl_2/*n*-pentane 5:1 gradient to 0:1) to afford 100 mg (yield 17%, ee 60%) of oxabicyclo.

^{1}H NMR (400MHz, $CDCl_3$): δ 2.75 (*ddd*, 1H, *J* = 3.2, 4.6, 18.0Hz), 3.11 (*m*, 1H), 3.23 (*m*, 1H), 3.54 (*dd*, 1H, *J* = 6.9, 9.5Hz), 3.72 (*m*, 1H), 3.75 (*m*, 1H), 4.10 (*d*, 1H, *J* = 4.1Hz), 4.31 (*m*, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ 30.2 (CH), 51.9 (CH_2), 65.4 (CH), 70.7 (CH_2), 74.2 (CH_2), 210.1 (C); GC (column: Agilent 19091Z-413E, HP-1 Methyl siloxane column; (initial column temperature 50°C (2min); heating rate, 10°C/min (to 150°C), 25°C/min (to 275°C)): t_r = 6.3min; GC (column: Restek 13104 Rt-βDEXsm; initial column temperature 100°C (2min); heating rate, 1.5°C/min (to 180°C)) : t_r(1*S*,5*R*) = 8.2min, t_r(1*R*,5*S*) = 8.7min.

Chapter 4

A different process to Iloprost

4.1 The drug

In 1976 Prostacyclin (PGI_2) **30** was discovered by Vane *et al.*,[64] it is a metabolite of arachidonic acid (see chapter 3, paragraph 3.1.1), and has been shown to be a potent inhibitor of human platelet aggregation and a relaxer of vascular tissue. These important biological properties have attracted the attention of chemistry, medicine and biology[65] and make Prostacyclin per se an interesting drug for treatment of cardiovascular diseases. However, because of the labile enol ether linkage, PGI_2 **30** is a very unstable compound: under physiological conditions its chemical and metabolic instability is demonstrated by a half-life of only 3 seconds. The chemical instability is provoked by a fast hydration of the ring O-atom. The metabolic instability is caused by the enzymatic degradation of both α and ω-chain via a rapid oxidation in the α-position to the carboxy group (Figure 18).

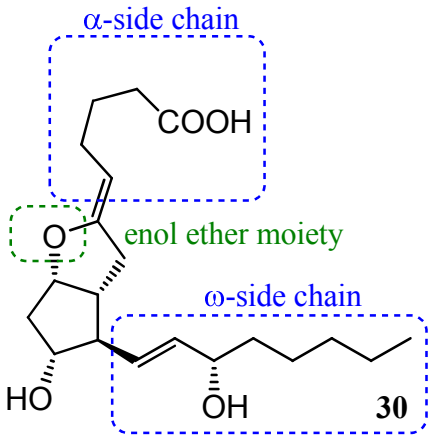
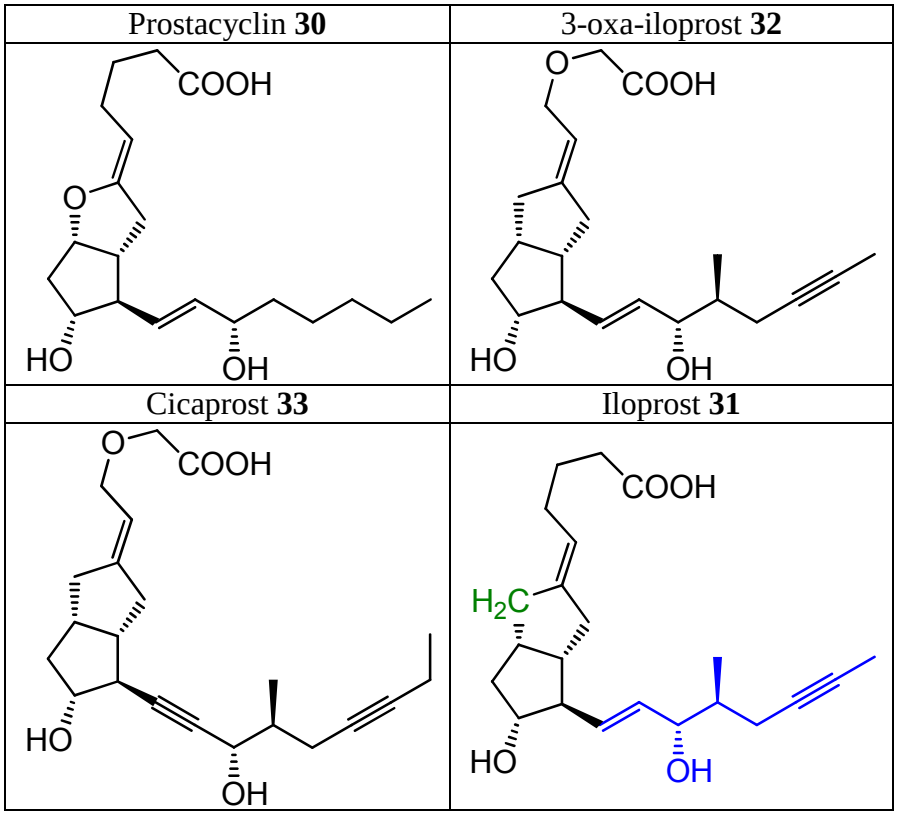


Figure 18

[64] a) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature* **1976**, 263, 663; b) Gryglewski, R. J.; Stock, G. *Prostacyclin and its Stable Analogue Iloprost*; Springer: Heidelberg, **1987**; c) Wise, H.; Jones, R. L.; *Prostacyclin and its Receptors*; Kluwer Academic Publishers: New York, **2000**.
[65] a) *Prostacyclin*; Vane, J. R., Bergström, S., Eds.; Raven Press: New York **1979**; b) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533; c) Schinzer, D. *In Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: New York, **1995**; p 301; d) *Platelets and Their Factors*; von Bruchhausen, F., Walter, U., Eds.; Springer-Verlag: Berlin, **1997**.

This disadvantageous feature severely hampers the medicinal application. Intensive efforts were devoted to synthesize a wide number of analogs in the search for stable and therapeutically useful mimics as possible new antithrombotic drugs. The carba-prostacyclin analogues carbacyclin[66] and isocarbacyclin[67] show chemically and biologically stability but a reduced activity as compared to PGI_2 **30**. The Schering group headed by Vorbrüggen and Skuballa, successfully designed and developed carbocyclic prostacyclin analogue like Iloprost **31**, [64,68] 3-oxa-iloprost **32**,[69] and cicaprost **33**[70] (Scheme 20).

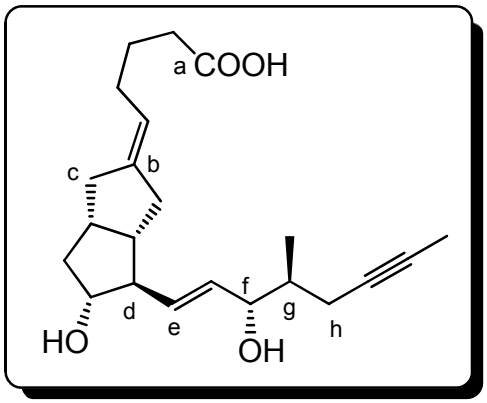


Scheme 20

[66] a) Kojima, K.; Sakai, K. *Tetrahedron Letters* **1978**, 3743; b) Nicolaou, K. C.; Sipio, W. J.; Magolda, R. L. Seitz, S.; Barnette, W. E. *J. Chem. Soc., Chem. Commun.* **1978**, 1067.
[67] Shibasaki, M.; Torisawa, Y.; Ikegami, S. *Tetrahedron Letters* **1983**, *24*, 3493.
[68] a) Skuballa, W.; Vorbrüggen, H. *Angew. Chem.* **1981**, *93*, 1080; b) Schenker, K. V.; von Philipsborn, W.; Evans, C. A.; Skuballa, W.; Hoyer, G. A. *Helv. Chim. Acta* **1986**, *69*, 1718; c) Kramp, G. J.; Kim, M.; Gais, H. J.; Vermeeren, C. *J. Am. Chem. Soc.* **2005**, *127*, 17910.
[69] a) Skuballa, W.; Raduechel, B.; Vorbrüggen, H.; Mannesmann, G.; Nieuweboer, B.; Town, M. H.; DE 3221193, **1983**; [*Chem. Abstr.* **1984**, *101*, 6931]; b) Tsai, A.-l.; Vijjeswarapu, H.; Wu, K. K. *Biochim. Biophys. Acta* **1988**, *942*, 220; c) Ashby, B. *Prostaglandins* **1992**, *43*, 255.
[70] a) Skuballa, W.; Schillinger, E.; Stuerzebecher, C. S.; Vorbrüggen, H. *J. Med. Chem.* **1986**, *29*, 313; b) Schneider, M. R.; Schirner, M.; Lichtner, R. B.; Graf, H. *Breast Cancer Res. Treat.* **1996**, *38*, 133; c) Harre, M.; Trabandt, J.; Westermann, J. *Liebigs Ann. Chem.* **1989**, 108; d) Lerm, M.; Gais, H. J.; Cheng, K.; Vermeeren, C. *J. Am. Chem. Soc.* **2003**, *125*, 9653.

Modification on the ω-chain proved to be the solution for the attainment of highly active and stable prostacyclin mimics. In Iloprost **31** a methylene group replaces the O atom at the c position, another one methylene group is introduced at Cg and a triple bond at Ch. This biologically highly potent and chemically stable analogue has already been commercialized for the treatment of peripheral arterial occlusive and Raynaud's disease as Ilomedin. The previous active compound has been also marketed as Ventavis with indications for the treatment of pulmonary arterial hypertension. The two drugs are introduced in commerce like a mixture of isomers. The mixture contains Cg-(*S*)-Iloprost **31** and its less active Cg-(*R*)-isomer approximately in ratio 1:1. Iloprost **31** is orally active, but it has a short duration, so Ilomedin is administered by intravenous infusion and Ventavis by inhalation (Scheme 21).

ILOPROST



31

Ilomedin

- 1 ml of Ilomedin contains 0.1mg of Iloprost.
- It promotes the healing of ulcerations secondary to ischemia (a blood vessel obstruction) and alleviates the pain in severe, long lasting disturbances of arterial circulation
- It widens narrow blood vessels in the lung, which in turn allows the heart to function more effectively

Ventavis

- 2 mL nebulizer solution contains 20 µg of Iloprost
- It is used to treat cases of pulmonary hypertension that may have been caused by some defect of the vessel walls, by connective tissue disease, or by blood clots in the lungs. It widens blood vessels, allowing more blood to reach the lungs and receive oxygen

Scheme 21

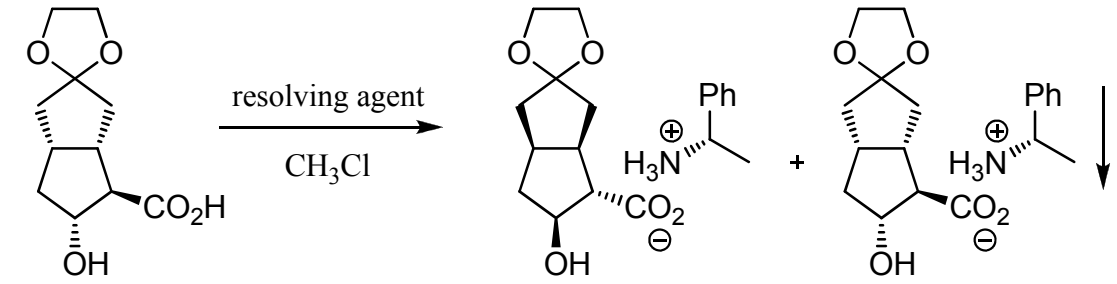
4.2 Literature

4.2.1 Papers

Prostacyclin **30** is the most potent endogenous blood platelet antiaggregantig and because of its considerable medicinal importance the last decades have witnessed a broad production of academic papers, that seek a fully stereocontrolled synthesis. Below, we report a panoramic summary of some synthetic strategies. In the 1985, Kojima and co-workers[71] reported a short synthesis of 9(O)-methanoprostacyclin in an

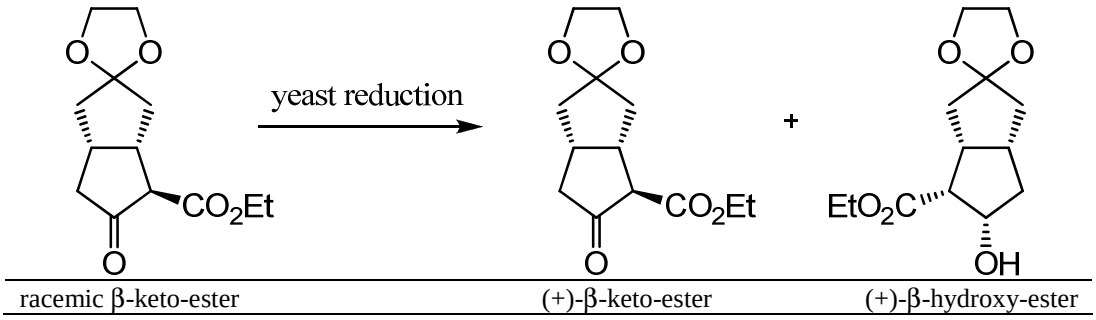
[71] Kojima, K.; Anemiya, S.; Koyama, K.; Sakai, K. *Chem. Pharm. Bull.* **1985**, *33*, 2688.

optically active form (Scheme 22). The target enantiopure molecule was obtained by the optical resolution of racemic acid with (*S*)-phenylethanamine as chiral resolving agent accomplished by recrystallization of its salt with the amine in CH_3Cl.



Scheme 22

Mori[72] synthesized a stable mimic of PGI_2 exploiting the kinetic resolution of a racemic β-keto-ester by yeast reduction (Scheme 23). The enantioselective reduction was carried out with wet yeast in a phosphate buffer containing glucose. This procedure gave the recovered (+)-β-keto-ester and the reduced (+)-β-hydroxy-ester simply separable under chromatographic conditions.

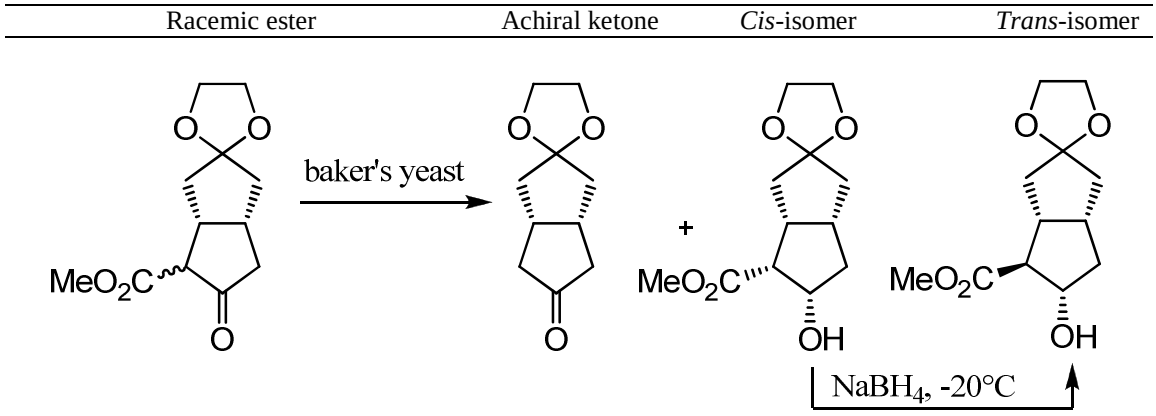


Scheme 23

In the 1987, Brooks and co-workers[73] developed a useful application of reduction by baker's yeast for the preparation of chiral target compounds for asymmetric synthesis of carbaprostaglandine (Scheme 24). They reported an enzymatic reaction of an enantiomeric pair involving a simultaneous dual kinetic resolution by two different enzymes in baker's yeast. This process involves ester hydrolysis by an esterase and a

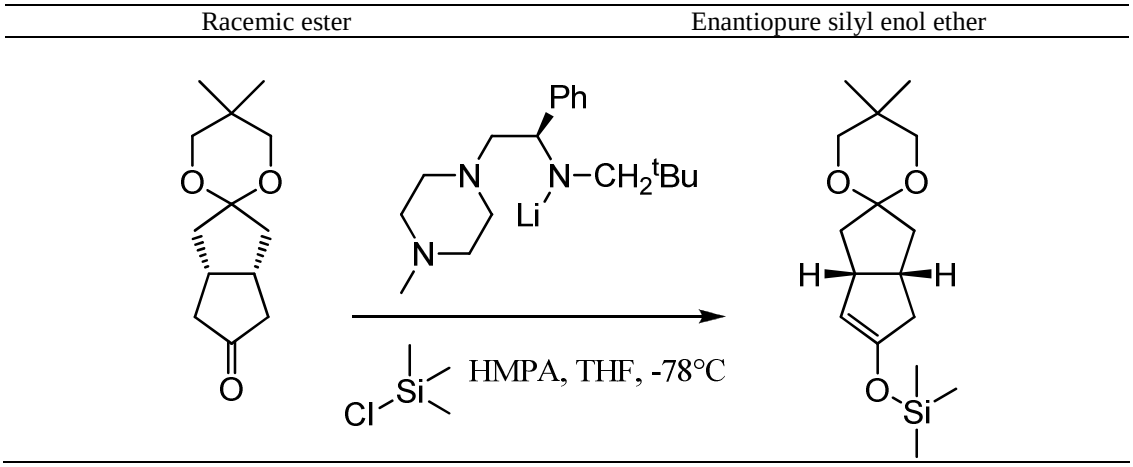
[72] Mori, K.; Tsuji, M. *Tetrahedron* **1986**, *42*, 435.
[73] Brooks, D. W.; Wilson, M.; Webb, M. *J. Org. Chem.* **1987**, *52*, 2244.

subsequent decarboxylation of the β-keto-acid intermediate to produce the achiral starting ketone. The reaction of the enantiopure β-hydroxy-ester with $NaBH_4$ at -20°C proceed stereo-selective to provide the active configuration *trans*.



Scheme 24

Another fascinating procedure is the kinetic deprotonation of prochiral cyclohexanones studied by Koga.[74] Chiral lithium amides in the presence of excess trimethylsilyl chloride afforded the corresponding enantiopure silyl enol ethers, that are important carbacyclin synthons (Scheme 25).

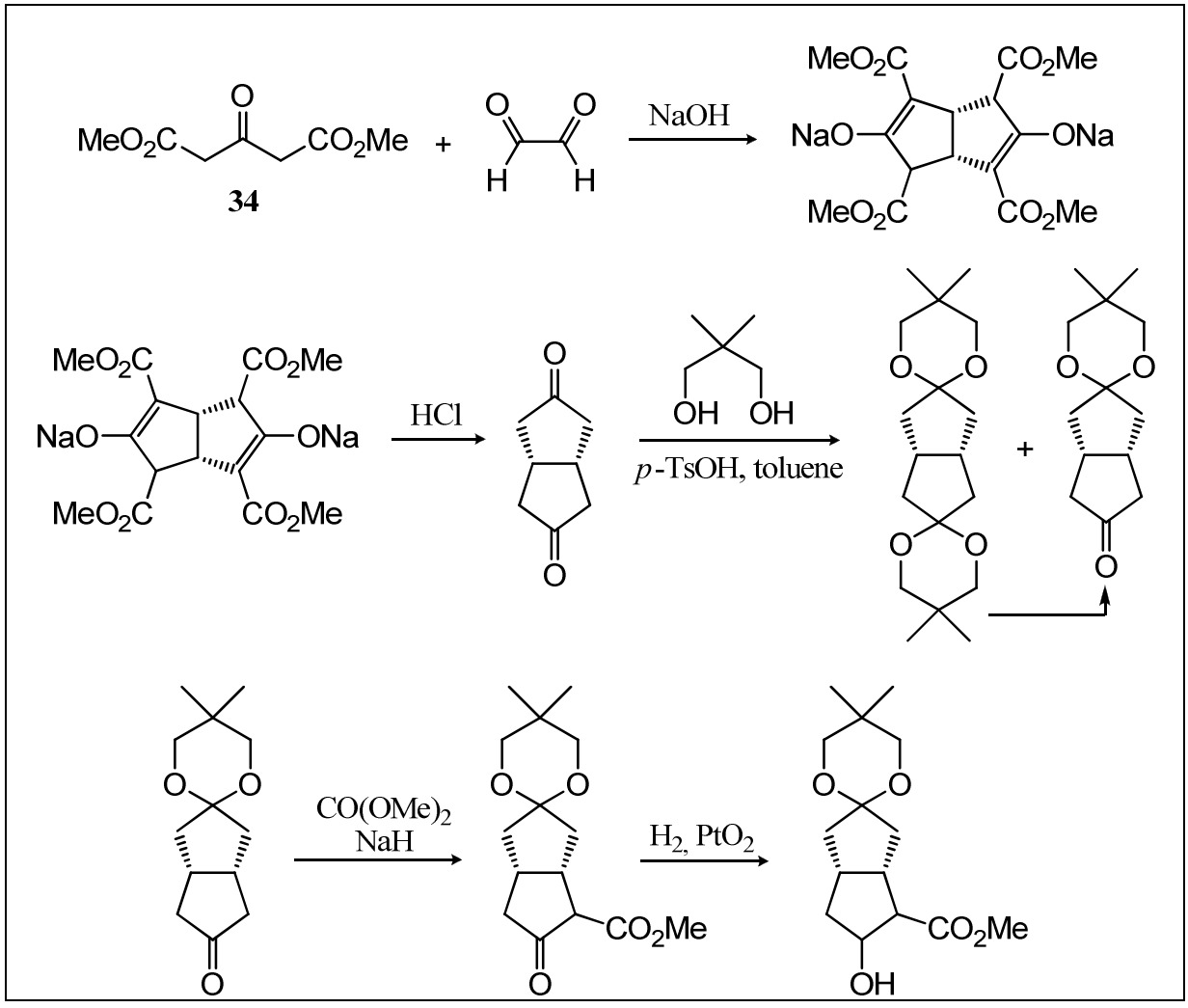


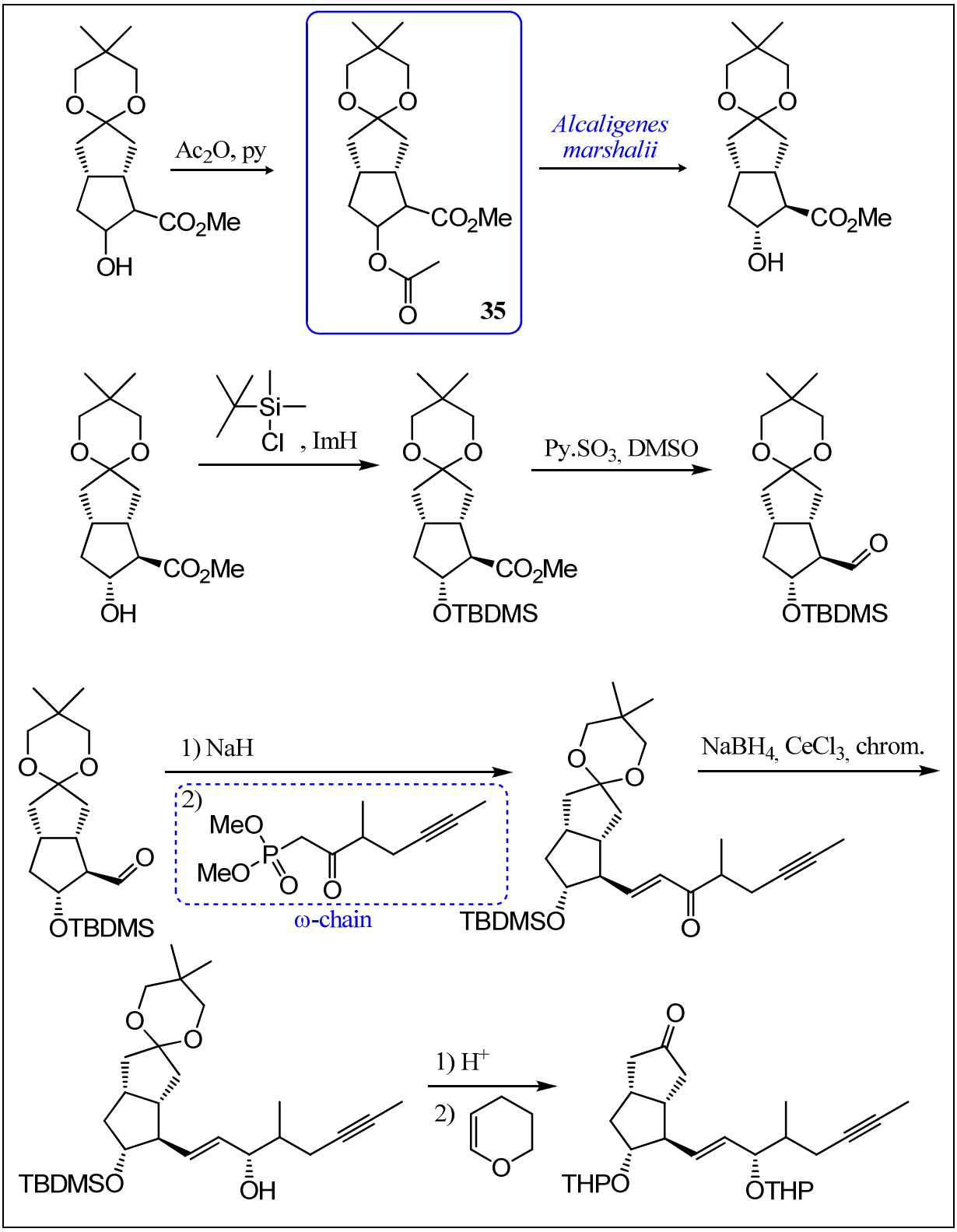
Scheme 25

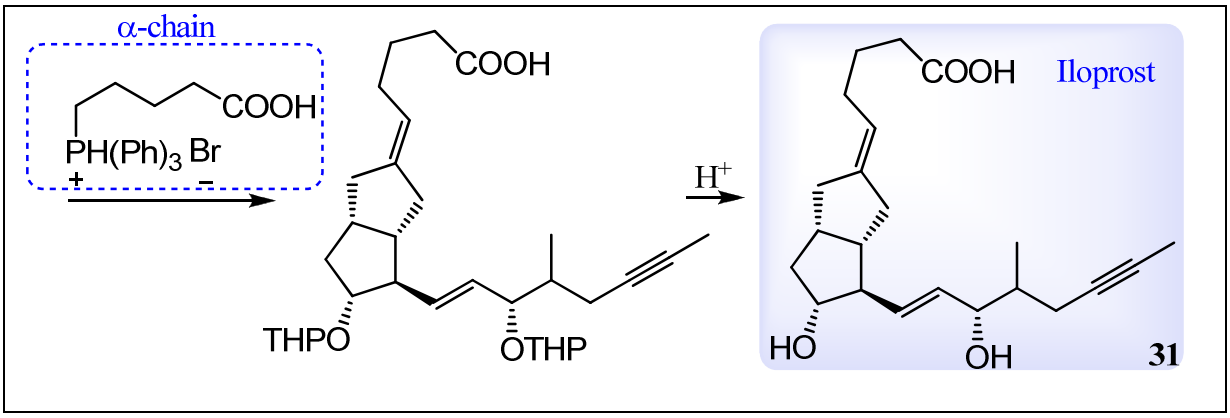
[74] Izaka, H.; Shirai, R.; Kawasaki, H.; Kim, H.; Koga, K. *Tetrahedron Letters* **1989**, 7221.

4.2.2 Patent

Herein, we report the synthesis of Iloprost **31** described in the DE 3816801 German patent (Scheme 26). This approach provides access to the drug in sufficient quantities and starts with the commercial dimethyl-1,3-acetonedicarboxylate **34**. In this synthetic route the racemic β-acyl-ester **35** is selected as the key intermediate for a highly stereo- and regio-controlled synthesis of the target molecule. This compound is asymmetric transformed into the corresponding chiral alcohol by a microbial resolution (*Alcaligenes Marshallii*). The unreduced enantiomer of β-acyl-ester **35** is separated from the desired enantiopure β-hydroxy-ester by chromatography on silica gel. In the following steps the ω and α-chains are introduced to the enantiopure bicyclic framework.




Ac2O, py
CO2Me
OH
35
Alcaligenes marshalii
Si
Cl
, ImH
OTBDMS
Py.SO3, DMSO
1) NaH
2)
MeO
MeO
P
O
ω-chain
NaBH4, CeCl3, chrom.
TBDMSO
1) H+
2)
THPO
OTHP



Scheme 26

Enzyme or microbial-catalyzed processes have various advantages like the selectivity (region, stereo and enantio) and the mild reaction conditions (aqueous solvent, room temperature). They present several negative factors that can limit the commercial utility too. Most organisms are active in mild conditions, but moving outside these temperature and pH ranges often they are destroyed. Frequently they need high dilutions and expensive recover at the end of a reaction. They are easily poisoned and they can have a high prize. All these factors plus the high initial price can dramatically increase the cost of using biocatalysts.

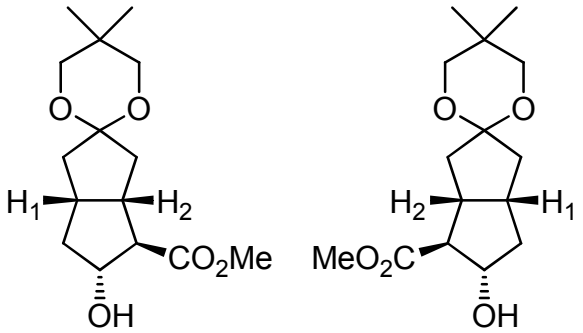
4.3 Process intensification

Green chemistry is often confused with 'environmental' chemistry; a science that study the effects of chemicals on the earth, like the contamination of land and water. In contrast, *green* chemistry is focused on the optimization of production processes, maximizing efficiency in the use of resources, avoiding the generation and use of hazardous composts, dramatically reducing the waste formation and environmental impact, redesigning a safer, cheaper and cleaner plant. Following all these guidelines, this new chemistry has to produce materials and products needed by the society in acceptable cost without causing damage to the environment. To obtain a greener and sustainable chemical process, process intensification is necessary. This concept is concerned with cost reduction, safety and product quality improvements, greater throughput, better process control and simplified reactors and ancillary equipment.

4.4 Result and Discussion

4.4.1 The racemic β-hydroxy-ester

The racemic β-hydroxy-ester **36** (Figure 19) appears to be an interesting starting building block to the development of an efficient and possible industrial synthetic process.



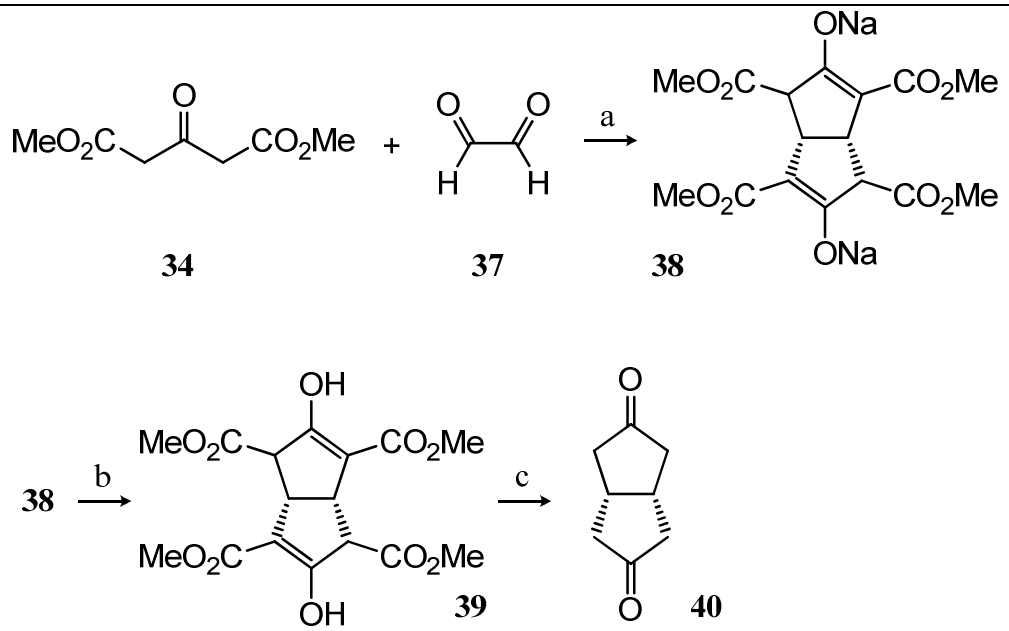
The β-hydroxy-ester **36** enantiomers

Figure 19

To provide the active Iloprost **31** isomer, this compound has to be a fixed relative structure, where the hydroxyl group has a *trans* correlation with both the ester and the bridge-head hydrogens. This attractive molecule contains four asymmetric centers, where the hydrogens H_1 and H_2 are closed in a *cis* structure. It possesses a *cis*-bicyclo[3.3.0]octane skeleton and carries functional groups in appropriate positions for the step-by-step insertion of the ω and α-side chains.

Our synthetic approach to this fundamental key substrate **36** began with the Weiss-Cook condensation[75] of glyoxal **37** and dimethyl-1,3-acetonedicarboxylate **34**. In the Weiss reaction the dicarboxylate was added to a cooled solution of NaOH and then the glyoxal **37** was slowly introduced at reflux condition. The obtained disodium-salt **38** was directly subjected to a hydrolysis step, following by a decarboxylation reaction. The reaction work up can be improved if the reaction co-product methanol is distilled off during the decarboxylation process. Crystallization of the tetracarboxylate diketone **39** in *n*-hexane was the only needed operation of purification. This methodology allowed the preparation of the corresponding diketone **40** on a large scale and in very good yield (Scheme 27).

[75] a) Bertz, S.; Cook, J. M.; Gawish, A.; Weiss, U. *Org. Synth.* **1985**,*64*, 27; b) Weiss, U.; Edwards, J. M.*Tetrahedron Letters* **1968**, 4885.



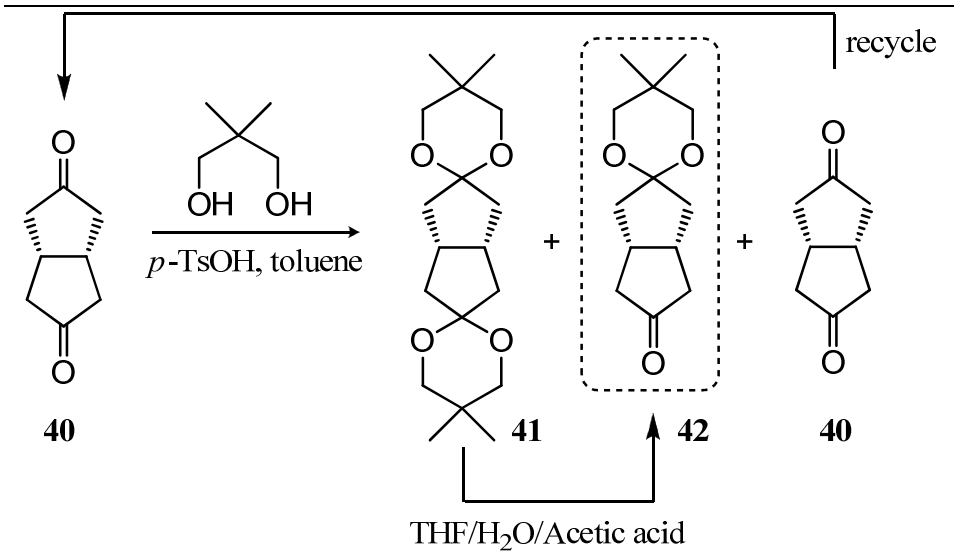
a) NaOH, MeOH; b) H_2O, $CHCl_3$, HCl; c) acetic acid, HCl

Diketone synthesis

Scheme 27

Following the work of Piers,[76] the mono-acetal **41** was obtained by the treatment with the protecting group in presence of a catalytic amount of TsOH. Monoacetalisation of diketone **40** gave a statistical 1:2:1 product mixture comprising bis-acetal **42**, mono-acetal **41** and recovered starting material **40**. After chromatographic separation on silica gel the bis-acetal **42** was transformed into mono-acetal **41** and the recovered diketone **40** was recycled. In contrast to the literature this reaction was conduced in toluene, not in benzene, and only in two hours (the described time is four hours). The bis-acetal **42** was hydrolyzed in two hours with a mixture of THF/H_2O/Acetic acid to gave a product mixture with a ratio of 5:1 in favor of the mono-acetal **41** (Scheme 28).

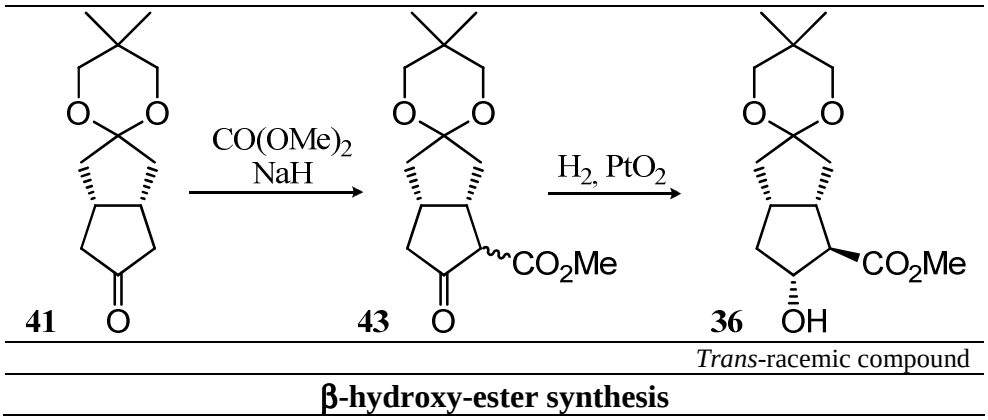
[76] Piers, E.; Karunaratne, V. *Can. J. Chem.* **1989**, *67*, 160.



Monoacetal synthesis

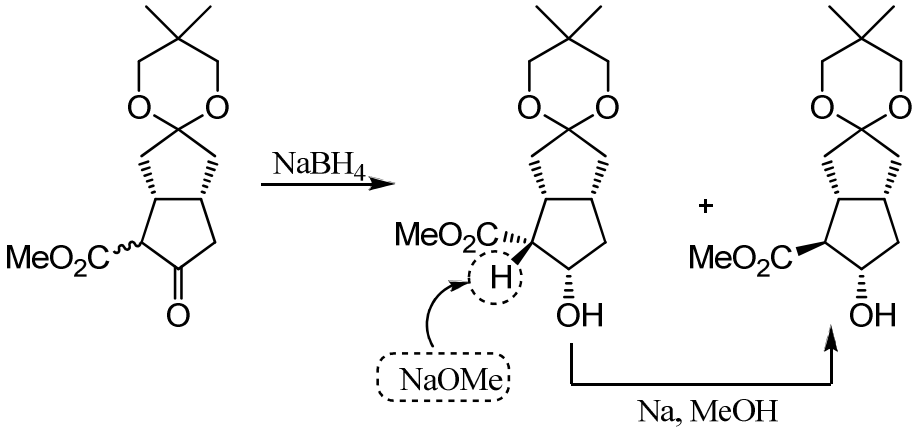
Scheme 28

The mono-protected ketone **41** has a concave-convex structure that allows a stereo-selective functionalization: the acylation was conduced in dimethylcarbonate as solvent in presence of NaH and a catalytic amount of MeOH like reaction starter. A simple filtration on silica gel afforded the purified β-keto-ester **43** as a mixture of racemic endo and exo isomers at the methoxycarbonyl group. Trying to improve the acylation process we found that it is possible halve the quantity of solvent and increase the yield conducing the reaction at 50°C. The reduction of the β-keto-ester **43** with molecular hydrogen using like catalyst PtO_2 proceeded stereoselectively to the racemic synthetic key β-hydroxy-ester **36** in quantitative yield with the appropriate relative structure *trans* (Scheme 29). To maximize this reaction we performed a set of reduction experiments. We have found that the catalyst quantity can be decrease allowing a minor reaction cost (1g of Pt_2O costs about 100€). The better compromise between time and cost is to work with 3.5 bar of pressure of H_2 for one night with 5% (w/w) of PtO_2.



Scheme 29

The *trans*-structure of the β-hydroxy-ester **36** was confirmed by NMR analysis comparing the H signals with literature.[73] Moreover, the *cis* and *trans* isomers can be obtained by the reduction of the ketone with $NaBH_4$ at room temperature. The *cis*-one can be converted into *trans* skeleton by the extraction of the acid hydrogen in α position at the carbonyl group. The treatment of the *cis* isomer with Na and MeOH gave the more stable *trans*. Our product does not change conformation under the above described reaction conditions (Scheme 30).



Scheme 30

The total synthesis described above is simple, efficient and scalable with a 14% overall yield in six steps. It is an example of improved eco-efficient product process that optimizes the use of resources, minimize waste simplifying the work up. Hence it is an example of process intensification.

4.4.2 Acids and optical resolution

We have described the preparation in racemic form of the β-hydroxy-ester **36**, that is a potential precursor for the synthesis of a broad range of natural and biologically active compounds. In our case, the right absolute structure is obtained by an optical resolution of diastereomeric salts (see chapter 2, paragraph 2.2), and their separation by crystallization. The three molecules **44**, **45** and **46** shown in Figure 20 were assumed like potential substrates for a good resolution.

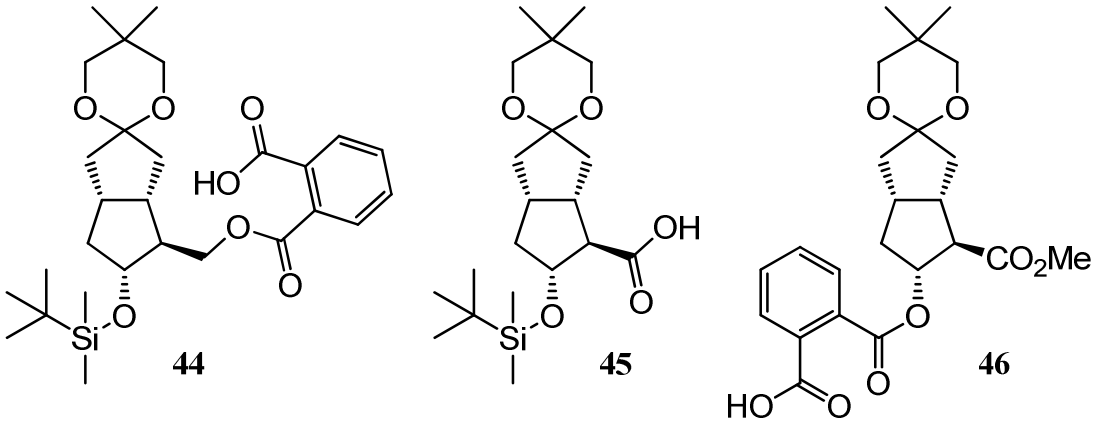
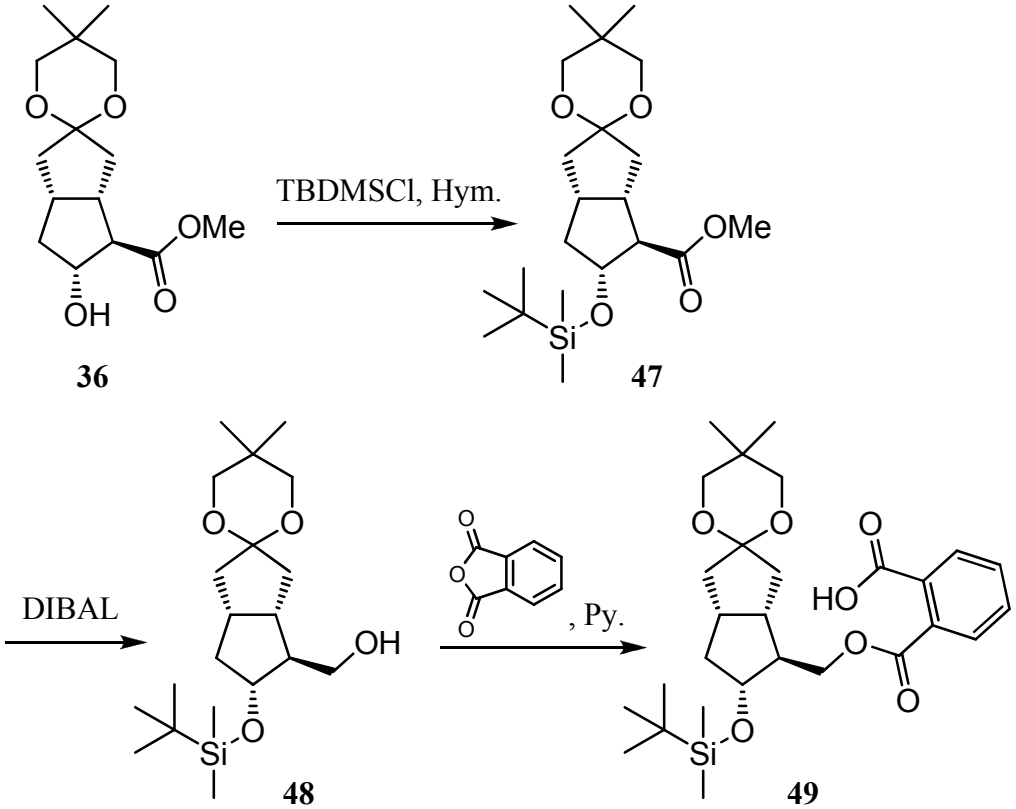


Figure 20

Acid **44** could be easily obtained in gram quantities with a minimum of synthetic transformations (Scheme 31). Starting from the β-hydroxy-ester **36**, after treatment with *tert*-butyldimethylsilyl chloride (to afford protected alcohol **47**) and reduction with DIBAL, primary alcohol **48** was obtained.[77] This alcohol was derivatized to carboxylic acid **49** by the reaction with phthalic anhydride in pyridine.

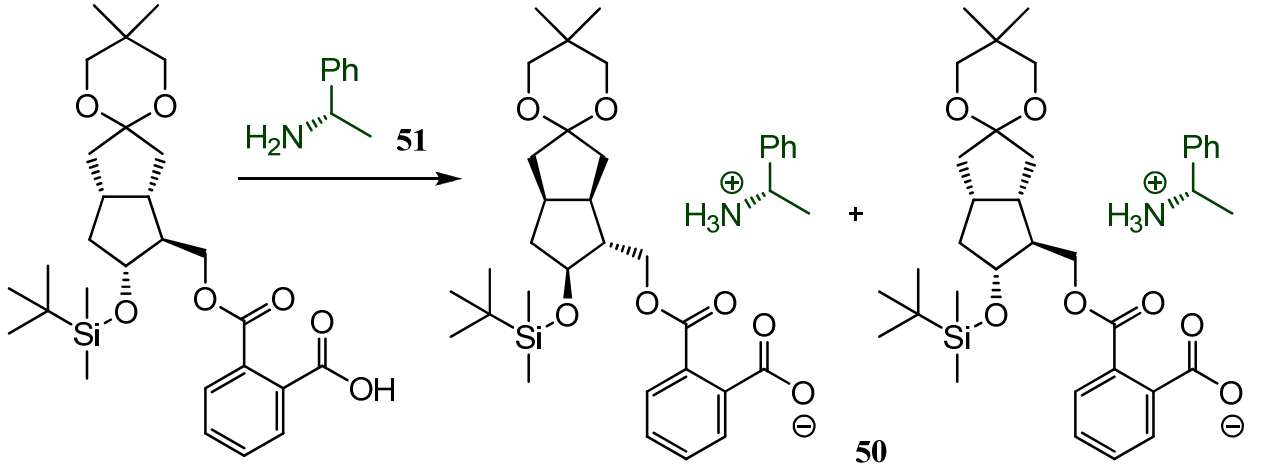
[77] Sheddan, N. A.; Mulzer, J. *Org. Letters* **2005**, *7*, 5115.



Scheme 31

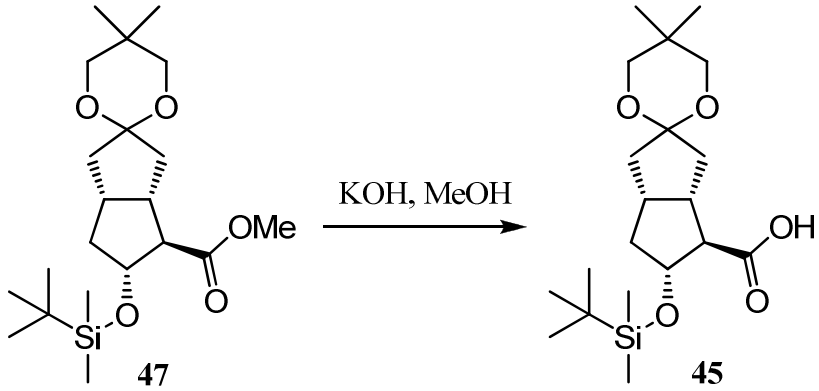
The corresponding diastereomeric salts **50** were obtained by a simple precipitation with one equivalent of (*S*)-phenylethanamine **51** (Scheme 32). Various solvents were tested but all the attempts to obtain the precipitation of only one enantiomer had no success.

Salt formation



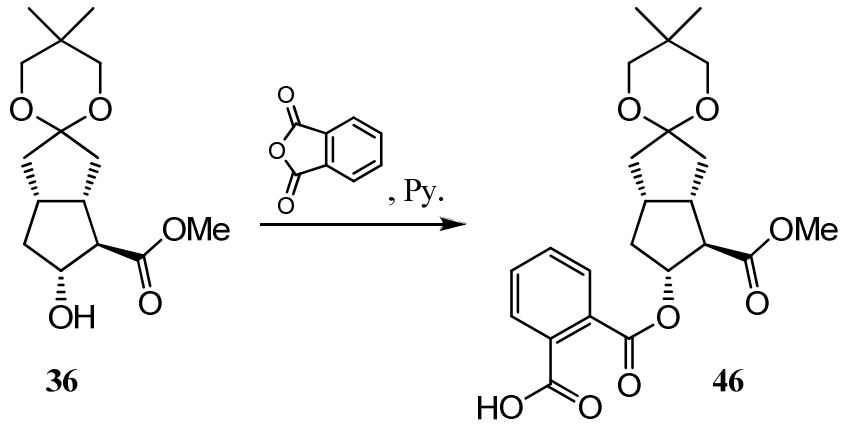
Scheme 32

The acid **45** was synthesized by saponification of the β-silyl-ester **47** in a KOH methanol solution (Scheme 33). The absence of a simple and efficient analytic method to analyze the acid enantiomeric excess like HPLC or GC with chiral columns convinced us to change molecule.



Scheme 33

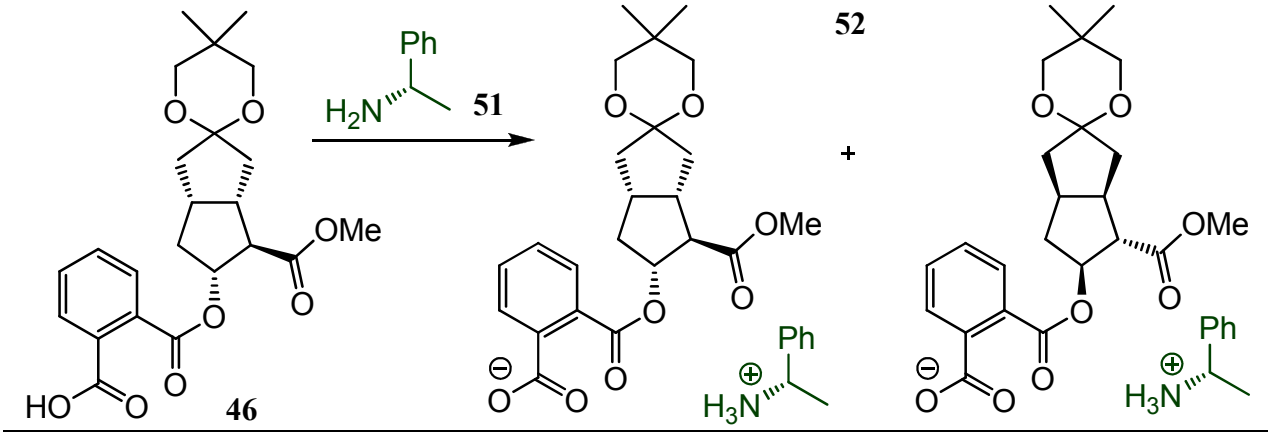
The introduction of the required carboxylic function directly into the β-hydroxy-ester **36** can be the best idea for a good optical resolution. The acid **46** was obtained by the treatment of the alcohol with phthalic anhydride and pyridine as solvent (Scheme 34).



Scheme 34

This acid **46** was dissolved in diisopropyl ether and (*S*)-phenylethanamine **51** was slowly added to the solution. The white precipitate **52** was filtered and submitted to a slow enantio-selective crystallization (Scheme 35). The HPLC analysis of the salt **52** showed the presence of the *cis* isomer in small quantity.

Salt formation



Scheme 35

Several tests were performed to find the best resolution conditions. Finally we found that the acid **46** can be resolved refluxing the salt in a solvent mixture *i*-Pr_2O:MeOH with a ratio 4:1 and allowing a slowly precipitation under mechanical agitation. We started with a racemic mixture of **46** with a diastereomeric ratio 94:6 in *trans*:*cis* isomers. In the first crystallization we obtained a salt **52** composition with a diastereomeric excess of 88% and an enantiomeric of 86% in the *trans* isomer. With the second crystallization we obtained only the *trans* acid **46** with an enantiomeric excess of 96% (Figure 21).

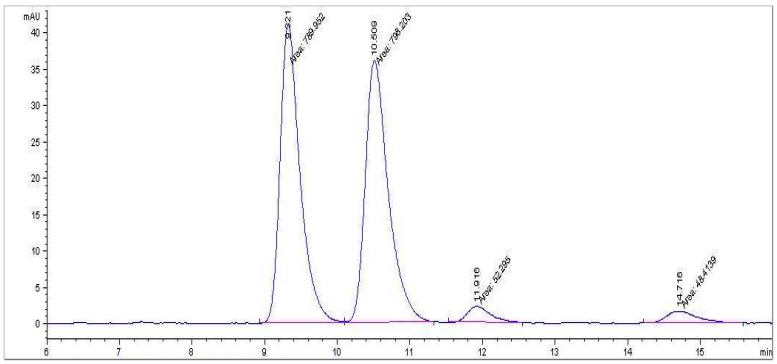
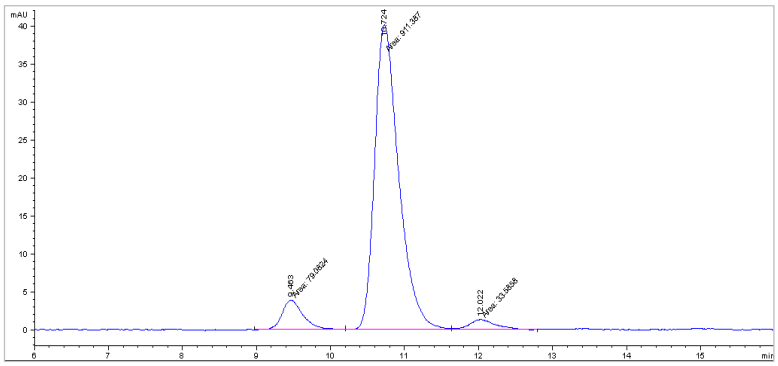
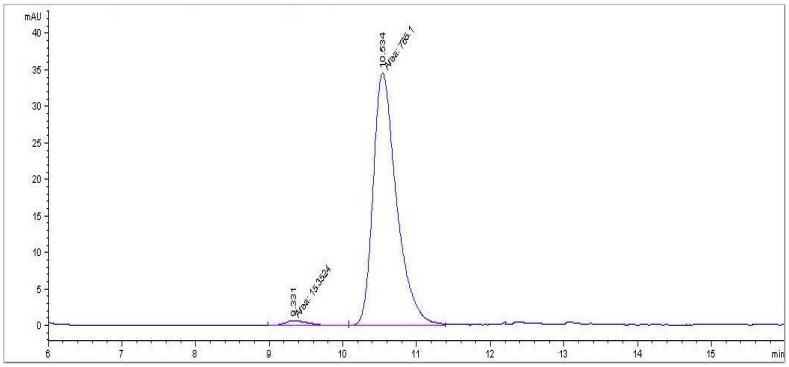
Optical Resolution	
 *trans* *cis*	Dr (*trans*/*cis*) = 94/6 Er (*trans*) = 50/50 *i*-Pr_2O/MeOH
 *trans* *cis*	Dr (*trans*/*cis*) = 97/3 Er (*trans*) = 7/93 Ee (*trans*) = 86% *i*-Pr_2O/MeOH
 *trans* *cis*	Dr (*trans*/*cis*) = 100/0 Er (*trans*) = 2/98 **Ee (*trans*) = 96%**

Figure 21

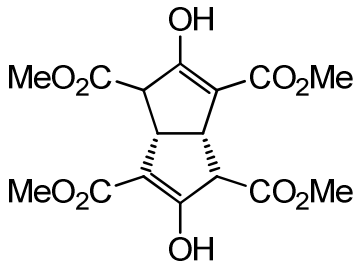
4.5 Conclusion

Taking into account the medicinal and biological importance of prostacyclin, new synthetic process and various types of significant intermediates have been discovered in the chemistry of these natural products and their mimic analogues. In this chapter we have described a methodology to intensify the synthetic process of the racemic β-hydroxy-ester **36**. This improved process obtains the required key intermediate with simple work up, cheap reactions and good yields. Moreover, we have described an

efficient asymmetric optical resolution of the corresponding carboxylic acid **46** highlighting a full stereo- and enantio-control of all stereogenic carbons. This practical synthesis and resolution is proven feasible on a large scale and can be considerate a good strategy to obtain, in according with the principles of *green* chemistry, only one enantiomer of a Iloprost precursor.

4.6 Experimental section

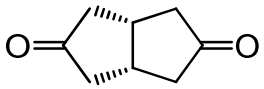
Tetramethyl 3,7-dihydroxybicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate (39)[75]



A 1-L, three-necked flask was equipped with a thermometer, mechanical stirrer and reflux condenser. To a stirred solution of 15.9 g (398 mmol) of NaOH in 280 mL of methanol, cooled in an ice bath, 68.1 g (191 mmol) of dimethyl 1,3-acetonedicarboxylate **34** was added dropwise. The resulting slurry was heated to reflux, at which point the white salt dissolved. Aqueous 40% glyoxal **37** (32.0 g, 221 mmol) was added at a rate sufficient to maintain the internal temperature at 65°C. The mixture was allowed to cool to room temperature and stirred overnight. The precipitate was filtrated, washed three times with 60 mL of methanol, and dried under reduced pressure. The yield of the white to light yellow disodium salt **38** was 72.8 g (76%). A 2-L Erlenmeyer flask equipped with a large magnetic stirring bar was charged with 500 mL of chloroform and a solution of 100 g of the disodium salt (231 mmol) in 400 mL of water. To the vigorously stirred mixture 463 mL of cold 1 M hydrochloric acid was added. After 20 minutes, the layers wee separated and the aqueous phase was extracted with three times with 100 mL of chloroform. The combined organic layers were washed once with saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure by rotary evaporation. Crystallization from 270 mL of a solution 2 : 1 hexane–ethyl acetate afford 55.8 g (65% based on dimethyl 1,3-acetonedicarboxylate) of the tetraester **39**.

White solid, mp 92-95°C, IR (KBr) υ 3010, 1743, 1674, 1636, 1444, 1332, 1274, 1198, 1163, 1051 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 3.65 (*m*, 2H), 3.79 (*s*, 6H), 3.81 (*s*, 6H), 3.87 (*m*, 2H), 10.32 (*broad s*, 2H); ^{13}C NMR (75MHz, $CDCl_3$): δ 43.8 ($2CH_3$), 51.7 (2CH), 52.6 (2CH), 55.2 ($2CH_3$), 103.7 (2C), 169.1 (2C), 170.6 (2C), 170.8 (2C).

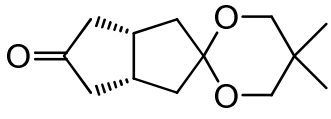
Cis-Bicyclo[3.3.0]octane-3,7-dione (40)[75]



A 1-L, three-necked flask equipped with two reflux condensers and mechanical stirrer was charged with 27 g (73 mmol) of the tetraester **39**, 15 mL of glacial acetic acid, and 150 mL of 1 M hydrochloric acid. The mixture was stirred vigorously and heated at reflux for 1.5 hours, then other 27 g (73 mmol) of the tetraester was added. The evolution of CO_2 was monitored with a mineral oil bubbler. The co-product methanol was distilled off at the end of the decarboxylation process. After 5.5 hours the solution was cooled in an ice bath and the product was extracted with five 100 mL portions of chloroform. The organic layers were combined, and the solution was concentrated by rotary evaporation. The residue was dissolved in 120 mL of fresh chloroform. The solution was washed with 40-mL of saturated sodium bicarbonate until the aqueous layer remains basic to litmus paper and dried with anhydrous sodium sulfate. The evaporation under reduced pressure afforded 19.0 g (137 mmol) of the bicycle with 94% yield..

White solid, mp 85-86°C, IR (KBr) υ cm^{-1} 2958, 1746, 1445, 1051; ^{1}H NMR (400MHz, $CDCl_3$): δ 2.16 (*dd*, 4H, *J* = 5.3, 19.6Hz), 2.58 (*dd*, 4H, *J* = 8.6, 19.6Hz), 3.06 (*m*, 2H); ^{13}C NMR (100MHz, $CDCl_3$): δ 36.3 (2CH), 43.5 ($4CH_2$), 217.8 (2C).

Cis-Bicyclo[3.3.0]octan-3,7-dione-(2',2'-dimethylpropylidene) acetal (41)



From dione **40** monoacetalisation[76]: To a 500-mL flask fitted with a Dean-Stark apparatus, condenser 16 g of dione **40** (116 mmol), 12 g (116 mmol) of 2,2-dimethyl-1,3-propanediol, 80 mg (0.4 mmol) of *p*-toluenesulphonic acid monohydrate were added to 180 mL of toluene. The reaction mixture was heated at the reflux until evolution of

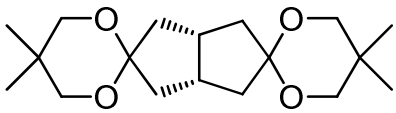
water ceased (2 hours). The solution was cooled to room temperature and K_2CO_3 was added. The suspension was filtered and the solvent removed in vacuo. The crude was purified by flash chromatography (2:1 petroleum ether/EtOAc to 1:2, crude mixture was loaded with 36 mL of 3:2:1 petroleum ether/EtOAc/CH_2Cl_2 solution). The first eluted compound was the bis-acetal **42** (5.8 g, 16% yield), obtained as a white crystalline solid. The second compound was the required mono-acetal **41** (11.5 g, 44% yield), obtained as a colorless solid. The last collected compound was the recovered starting material dione **40** (4.2 g, 26% yield).

From bis-acetal **42** hydrolysis: A 150-mL flask equipped with a reflux condenser and magnetic stirrer was charged with 8 g (25.8 mmol) of bis-acetal **42** and 50 mL of a 3:1:1 THF/H_2O/AcOH solution. The mixture was heated at the reflux for 2.5 hours, then cooled at room temperature. The solution was neutralized with NaOH 1M and the aqueous layer was extracted with three 50 mL portions of Et_2O. The combined organic layers were washed with 50-mL of brine, dried with anhydrous sodium sulfate and concentrated by rotary evaporation. The crude was purified by flash chromatography (2:1 petroleum ether/EtOAc to 1:2) to afford 3.4 g (60% yield) of the mono-acetal **41**.

Cis-Bicyclo[3.3.0]octan-3,7-dione-(2',2'-dimethylpropylidene) acetal (41)

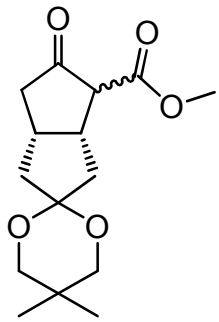
White solid, mp 49-51°C, R_f 0.24 (petroleum ether/Et_2O 1:1), IR (KBr) υ 2953, 2864, 1751, 1471, 1394, 1359, 1328, 1213, 1117, 1042, 1008, 906, 769 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 0.96 (*s*, 6H), 1.83 (*dd*, 2H, *J* = 5.1, 13.7Hz), 2.17 (*dd*, 2H, *J* = 4.6, 19.4Hz), 2.30 (*dd*, 2H, *J* = 8.7, 13.7Hz), 2.48 (*dd*, 2H, *J* = 9.8, 19.4Hz), 2.83 (*m*, 2H), 3.45 (*s*, 2H), 3.48 (*s*, 2H); ^{13}C NMR (100MHz, $CDCl_3$): δ 22.3 ($2CH_3$), 29.9 (C), 36.6 (2CH), 41.0 ($2CH_2$), 44.4 ($2CH_2$), 71.0 ($2CH_2$), 72.0 ($2CH_2$), 109.4 (C), 219.9 (C).

Cis-Bicyclo[3.3.0]octan-3,7-dione-_bis_-(2',2'-dimethylpropylidene) acetal (42)



White crystalline solid, mp 137-138°C, R_f 0.51 (petroleum ether/Et_2O 1:1), IR (KBr) υ 2953, 1472, 1393, 1359, 1306, 1222, 1116, 1018, 872, 789 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 0.96 (*s*, 12H), 1.72 (*dd*, 4H, *J* = 6.2, 13.2Hz), 2.20 (*dd*, 4H, *J* = 8.9, 13.2Hz), 2.54 (*m*, 2H), 3.46 (*s*, 4H), 3.47 (*s*, 4H); ^{13}C NMR (100MHz, $CDCl_3$): δ 22.5 ($4CH_3$), 30.0 (2C), 36.9 (2CH), 39.7 ($4CH_2$), 71.6 ($2CH_2$), 72.3 ($2CH_2$), 109.8 (2C).

Methyl-3-one-7,7-(2',2'-dimethylpropylidenedioxy) bicyclo[3.3.0]octane-2-carboxylate (43)[78]

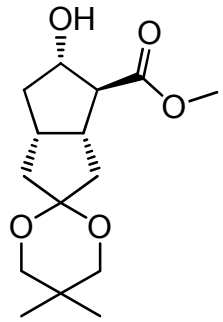


In a three-necked 500-mL flask equipped with a mechanical stirrer and a thermometer , 92mL of freshly distilled dimethyl carbonate were added to 9.6 g of NaH (60% wt in mineral oil, 400 mmol) under N_2. The solution was heated to 50°C. A solution with 15 g of mono-acetal **41** (66.9 mmol) in 55 mL of freshly distilled dimethyl carbonate was prepared, and 7.5 mL of this solution were added to the reaction mixture. Then 0.3 mL of methanol was added and the remaining mono-acetal **41** solution was added over 6.5 hours. The reaction was stirred at 50°C overnight. The mixture was cooled with an ice bath and 40mL of toluene were added. Methanol (30mL) was slowly added, followed by 8.3mL of acetic acid. Water (45mL) was added and the slurry was filtered by gooch. The organic layer was separated. The solid residue was washed twice with 50mL of toluene. The combined organic layers were washed twice with 20mL of water and concentrated by rotary evaporation. Toluene (20mL) was added and the solution was evaporated. The crude was purified by flash chromatography (3:1 petroleum ether/Et_2O) to afford 14 g (74% yield) of the required product as a diastereoisomers mixture.

White solid, mp 74-75°C, R_f 0.62 (petroleum ether/Et_2O 3:1), IR (KBr) υ 3008, 1669, 1618, 1440, 1337, 1276, 1145, 1114, 790 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) (of the mixture of two diastereoisomers): δ 0.94 (*s*, 3H), 0.95 (*s*, 3H), 0.96 (*s*, 3H), 0.99 (*s*, 3H), 1.63 (*m*, 1H), 1.71 (*ddd*, 1H, *J* = 0.9, 6.1, 13.6Hz), 1.83 (*m*, 1H), 2.04 (*m*, 1H), 2.22-2.43 (*m*, 7H), 2.61-2.80 (*m*, 3H), 2.94 (*m*, 1H), 3.17 (*m*, 1H), 3.28 (*m*, 2H), 3.44-3.54 (*m*, 8H), 3.74 (*s*, 3H), 3.76 (*s*, 3H); ^{13}C NMR (100MHz, $CDCl_3$) (of the mixture of two diastereoisomers): δ 22.3 ($2CH_3$), 22.4 (CH_3), 22.5 (CH_3), 30.0 (C), 30.1 (C), 33.2 (CH), 34.9 (CH), 38.7 (CH_2), 38.9 (CH_2), 40.2 (CH_2), 40.9 (CH_2), 41.0 (CH), 41.4 (CH), 42.0 (CH), 44.7 (CH_2), 51.0 (CH), 52.5 (CH), 60.6 (2CH), 71.6 (CH_3), 71.7 (CH_3), 72.3 (CH_2), 72.5 (CH_2), 108.6 (C), 109.1 (C), 169.7 (C), 174.8 (C), 211.8 (2C).

[78] German Patent DE 3816801.

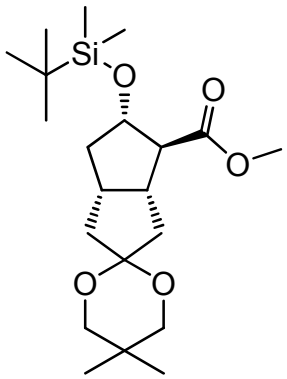
Methyl-3-hydroxy-7,7-(2',2'-dimethylpropylidenedioxy) bicyclo[3.3.0]octane-2-carboxylate (36)[78]



In a 300-mL batch reactor, 12.4 g (44 mmol) of β-keto-ester **43** were dissolved in 120 mL of ethyl acetate and the reaction system was saturated with argon. To this solution Platinum (IV) oxide (0.62 g, 5 % w/w) was added and the reactor was saturated with hydrogen. The reaction was mechanical stirred overnight with 3.5 bar of H_2 pressure. The mixture was filtered through a thin pad of celite and the filtrate was concentrated under reduce pressure to afford 12.5 g (100 % yield) of *trans*-alcohol.

Colorless oil, R_f 0.20 (petroleum ether/EtOAc 7:3), IR (neat) υ 2952, 2867, 1731 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 0.96 (*s*, 3H), 0.97 (*s*, 3H), 1.54 (*ddd*, 1H, *J* = 9.3, 10.2, 12.2Hz), 1.89 (*ddd*, 1H, *J* = 1.3, 4.7, 13.3Hz), 2.00-2.16 (*m*, 3H), 2.25 (*ddd*, 1H, *J* = 6.4, 8.2, 12.2Hz), 2.52 (*m*, 1H), 2.62 (*m*, 2H), 2.82 (*m*, 1H), 3.46 (*s*, 2H), 3.50 (*s*, 2H), 3.72 (*s*, 3H), 4.22 (*m*, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ 22.3 (CH_3), 22.4 (CH_3), 29.8 (C), 35.5 (CH), 38.7 (CH_2), 38.9 (CH_2), 40.4 (CH_2), 41.4 (CH), 51.6 (CH_3), 57.8 (CH), 71.6 (CH_2), 72.0 (CH_2), 75.6 (CH), 109.7 (C), 175.2 (C).

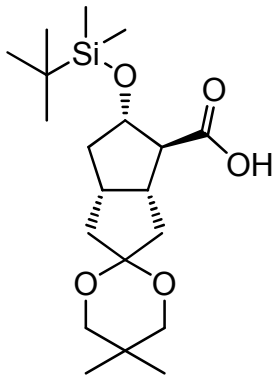
Methyl-3-(*tert*-butyldimethylsilyloxy)-7,7-(2',2'-dimethylpropylidenedioxy) bicyclo[3.3.0]octane-2-carboxylate (47)[77]



To a solution of β-hydroxy-ester **36** (16.0 g, 56 mmol) and imizadole (9.6 g, 141 mmol) in anhydrous DMF (41 mL), TBSCl (10 g, 68 mmol) in anhydrous DMF (30 mL) was dropwise added and the reaction mixture was stirred overnight. To the mixture 60 mL of water and 60 mL of Et_2O were added, and the solution was extracted with Et_2O (5 x 70 mL). Combined organic layers were washed with 50 mL of water and 35 mL of brine, dried over $MgSO_4$, filtered and concentrated. The crude was purified by flash column chromatography (petroleum ether/EtOAc 5:1) to afford the corresponding protected alcohol (18.2 g, 81%).

Colorless oil, R_f 0.59 (petroleum ether/EtOAc 5:1), IR (neat) υ cm^{-1} 1735, 1636, 1256, 116; ^1H NMR (600MHz, $CDCl_3$): δ 0.00 (*s*, 3H), 0.01 (*s*, 3H), 0.84 (*s*, 9H), 0.92 (*s*, 3H), 0.98 (*s*, 3H), 1.50 (*dt*, 1H, *J* = 9.1, 12.3Hz), 1.80 (*dd*, 1H, *J* = 5.3, 12.6Hz), 1.91 (*m*, 1H), 2.08-2.16 (*m*, 3H), 2.50 (*m*, 1H), 2.60 (*m*, 2H), 3.45 (*dd*, 2H, *J* = 11.4, 18.8Hz), 3.49 (*dd*, 2H, *J* = 11.7, 19.0Hz), 3.67 (*s*, 3H), 4.26 (*m*, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ -5.1 (CH_3), -4.8 (CH_3), 17.8 (C), 22.4 (CH_3), 22.5 (CH_3), 25.6 ($3CH_3$), 30.1 (C), 36.1 (CH), 38.3 (CH_2), 40.5 (CH_2), 41.7 (CH_2), 42.1 (CH), 51.5 (CH_3), 58.8 (CH), 71.9 (CH_2), 72.0 (CH_2), 77.5 (CH), 109.8 (C), 175.5 (C).

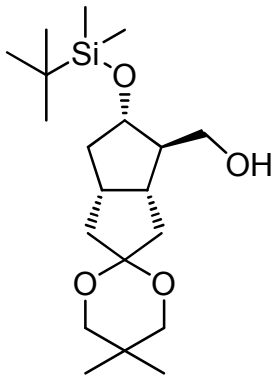
3-(*tert*-butyldimethylsilyloxy)-7,7-(2',2'-dimethylpropylidenedioxy) bicyclo[3.3.0]octane-2-carboxylic acid (45)



To a stirred solution of 1.0 g (2.5 mmol) of β-*tert*-butyldimethylsilyloxy ester **47** a solution of 10% KOH in methanol was added. The mixture was stirred overnight at room temperature. The mixture was concentrated and washed once with Et_2O. The aqueous layer was acidified to pH=5 with HCl 1M and extracted three times with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated to afford 0.9 g (2.3 mmol, 91%) of the crude acid that was directly engaged in the next step without further purification.

White solid, mp 87-90°C, R_f 0.33 (petroleum ether/EtOAc 5:1), IR (neat) υ cm^{-1} 2954, 1702, 1115; ^{1}H NMR (400MHz, $CDCl_3$): δ 0.01 (*s*, 3H), 0.02 (*s*, 3H), 0.84 (*s*, 9H), 0.91 (*s*, 3H), 0.98 (*s*, 3H), 1.51 (*dt*, 1H, *J* = 9.1, 12.2Hz), 1.81 (*dd*, 1H, *J* = 5.5, 13.7Hz), 1.98 (*m*, 1H), 2.06-2.19 (*m*, 3H), 2.51 (*m*, 1H), 2.62 (*m*, 2H), 3.45 (*m*, 2H), 3.49 (*m*, 2H), 4.26 (*m*, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ -5.0 (CH_3), -4.8 (CH_3), 17.9 (C), 22.4 (CH_3), 22.5 (CH_3), 25.7 ($3CH_3$), 30.0 (C), 36.0 (CH), 38.0 (CH_2), 40.7 (CH_2), 41.6 (CH_2), 42.0 (CH), 58.6 (CH), 71.9 (CH_2), 72.0 (CH_2), 77.3 (CH), 109.8 (C), 180.8 (C).

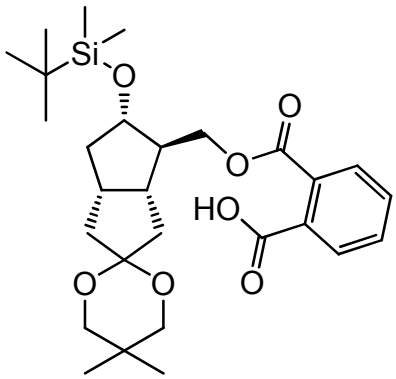
3-(*tert*-butyldimethylsilyloxy)-7,7-(2',2'-dimethylpropylidenedioxy) bicyclo[3.3.0]octane-2-methanol (48)[77]



Under nitrogen, to a stirred solution of 5.0 g (12.5 mmol) of β-*tert*-butyldimethylsilyloxy-ester **47** in 20 mL of dry CH_2Cl_2 a solution 1M of DIBAL (19 mL) was added dropwise at -78°C within 1.5 h. The reaction mixture was stirred at 0°C for 2 h, then 4 mL of MeOH and 45 mL of an aqueous potassium tartrate solution were added. The mixture was filtered through Celite which was washed with CH_2Cl_2. The combined organic phases were dried and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/EtOAc 3:1) gives 4.5 g (11.6 mmol, 92%) of alcohol.

Colorless solid, mp 79-82 °C, R_f 0.34 (petroleum ether/EtOAc 3:1), IR (neat) υ 3150, 1644, 1010 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 0.04 (*s*, 3H), 0.06 (*s*, 3H), 0.86 (*s*, 9H), 0.92 (*s*, 3H), 0.97 (*s*, 3H), 1.44 (*m*, 1H), 1.71-1.92 (*m*, 3H), 1.99-2.20 (*m*, 4H), 2.25 (*s*, 1H), 2.36 (*m*, 1H), 3.46 (*m*, 4H), 3.64 (*m*, 2H), 3.85 (*m*, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ -4.9 (CH_3), -4.1 (CH_3), 17.8 (C), 22.4 (CH_3), 22.5 (CH_3), 25.7 ($3CH_3$), 30.0 (C), 35.6 (CH), 38.5 (CH_2), 39.1 (CH), 40.6 (CH_2), 41.5 (CH_2), 55.1 (CH), 65.4 (CH_2), 71.9 (CH_2), 72.2 (CH_2), 78.3 (CH), 110.2 (C).

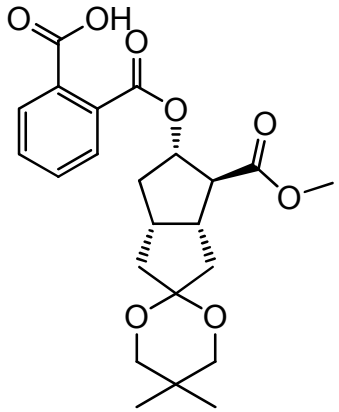
3-(*tert*-butyldimethylsilyloxy)-7,7-(2',2'-dimethylpropylidenedioxy) bicyclo[3.3.0]octane-2-methoxy- carbonyl benzoic acid (49)



In a 50-mL flask equipped with a magnetic stirrer and a reflux condenser 4.0 g (10.8 mmol) of alcohol **48** were dissolved in 4.3 mL of freshly distilled pyridine. Phthalic anhydride (1.6 g, 10.8 mmol) was added and the solution was heated to 70°C. After 24h the solution was cooled to room temperature and 25 mL of water were added. The mixture was washed once with Et_2O. The aqueous layer was acidified with HCl 1M and extracted three times with Et_2O. The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated to afford 3.9 g (7.6 mmol, 70%) of the required acid.

Colorless oil, IR (neat) υ 1727, 1633, 1258, 1118 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 0.00 (*s*, 6H), 0.84 (*s*, 9H), 0.92 (*s*, 3H), 0.93 (*s*, 3H), 1.46 (*m*, 1H), 1.75 (*dd*, 1H, *J* = 6.6, 13.1Hz), 1.85 (*dd*, 1H, *J* = 5.6, 12.8Hz), 2.14-1.99 (*m*, 2H), 2.34-2.16 (*m*, 3H), 2.40 (*m*, 1H), 3.45 (*s*, 2H), 3.46 (*s*, 2H), 3.88 (*m*, 1H), 4.22 (*dd*, 1H, *J* = 6.6, 10.9Hz), 4.41 (*dd*, 1H, *J* = 4.0, 10.9Hz) 7.55 (*m*, 2H), 7.69 (*m*, 1H), 7.88 (*m*, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ -4.9 (CH_3), -4.5 (CH_3), 17.9 (C), 22.4 ($2CH_3$), 25.7 ($3CH_3$), 30.0 (C), 35.7 (CH), 39.3 (CH_2), 40.1 (CH_2), 40.2 (CH), 41.4 (CH_2), 52.9 (CH), 66.3 (CH_2), 71.7 (CH_2), 72.2 (CH_2), 75.6 (CH), 110.3 (C), 128.7 (CH), 129.7 (CH), 130.8 (C), 130.9 (CH), 131.7 (CH), 132.9 (C), 168.2 (C), 170.7 (C).

2-(methoxycarbonyl)-7,7-(2',2'-dimethylpropylidenedioxy) bicyclo[3.3.0]octane-3-oxy- carbonyl benzoic acid (46)



In a 50-mL flask equipped with a magnetic stirrer and a reflux condenser 6.8 g (24.1 mmol) of β-hydroxy-ester **36** were dissolved in 10 mL of freshly distilled pyridine. Phthalic anhydride (3.6 g, 24.1 mmol) was added and the solution was heated to 70°C. After 24h the solution was cooled to room temperature and 50 mL of water were added to the reaction mixture. The reaction solution was acidified with 120 mL of HCl 1M and extracted twice with Et_2O. To completely remove the pyridine presence the combined organic layers were washed with 25 mL of saturated $CuSO_4$. The organic layer was dried with $MgSO_4$ and the solvent was evaporated to afford 8.3 g (19.1 mmol, 80%) of acid **46** with a diastereomeric ratio 94:6 in *trans*:*cis* isomers.

Colorless oil, R_f 0.48 (petroleum ether/EtOAc/AcOH 1:1:0.01), IR (neat) υ 1733, 1288, 1121 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 0.92 (*s*, 3H), 0.93 (*s*, 3H), 1.75 (*dt*, 1H, *J* = 7.8, 13.0Hz), 1.93 (*dd*, 1H, *J* = 5.1, 13.7Hz), 2.07 (*dd*, 1H, *J* = 4.6, 13.5Hz), 2.18 (*m*, 2H), 2.54 (*m*, 1H), 2.68 (*m*, 1H), 2.74 (*m*, 1H), 2.97 (*t*, 1H, *J* = 8.0Hz), 3.46 (*s*, 2H), 3.49 (*s*, 2H), 3.71 (*s*, 3H), 5.48 (*m*, 1H), 5.90 (*s*, 1H), 7.56 (*m*, 2H), 7.68 (*m*, 1H), 7.86 (*m*, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ 22.6 (CH_3), 22.7 (CH_3), 30.2 (C), 37.4 (CH), 37.7 (CH_2), 39.0 (CH_2), 40.3 (CH_2), 43.0 (CH), 52.3 (CH_3), 55.5 (CH), 72.2 (CH_2), 72.3 (CH_2), 79.5 (CH), 110.2 (C), 129.2 (CH), 129.6 (CH), 131.2 (CH), 131.8 (CH), 132.7 (2C), 167.6 (2C), 170.5 (C),174.5 (C).

The optical resolution: (*S*)-Phenylethanamine **51** (1.4 g, 11.6 mmol) is slowly added to a refluxed solution of acid **46** (5.0 g, 11.6 mmol) in 191 mL of a mixture *i*-Pr_2O:MeOH (4:1). The mixture is mechanical stirred at room temperature over night. The precipitate crystalline (2.0 g, ee 88%) is collected by filtration and re-crystallized from *i*-Pr_2O:MeOH (4:1) affording 1.4 g of enantiopure *trans*-acid **46** (ee 96%). HPLC (acid)

Chiralpak® AD-H, *n*-hexane/*i*-PrOH/*i*-PrOH(AcOH 4%) (80:10:10), flow 1 mL/min, λ= 254 nm, t_r(*trans*) = 9.3 min, t_r(*trans*) = 10.5 min, t_r(*cis*) = 11.9 min, t_r(*cis*) = 14.7 min.

Salt characterization (52): White solid, mp 154-156°C ,IR (KBr) υ 2096, 1640 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 0.93 (*s*, 3H), 0.94 (*s*, 3H), 1.49 (*d*, 3H, *J* = 6.7Hz), 1.61 (*m*, 1H), 1.78 (*dd*, 1H, *J* = 5.5, 13.3Hz), 1.96-2.18 (*m*, 3H), 2.34 (*m*, 1H), 2.49 (*m*, 1H), 2.67 (*m*, 1H), 2.90 (*t*, 1H, *J* = 8.2Hz), 3.43 (*s*, 4H), 3.64 (*s*, 3H), 4.26 (*q*, 1H, *J* = 6.7Hz), 5.28 (*m*, 1H), 7.17 (*m*, 3H), 7.26-7.37 (*m*, 5H), 7.54 (*m*, 1H), 8.30 (*s*, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 21.3 (CH_3), 22.4 ($2CH_3$), 29.9 (C), 36.6 (CH), 37.6 (CH_2), 38.8 (CH_2), 40.0 (CH_2), 42.3 (CH), 51.0 (CH), 51.8 (CH_3), 55.3 (CH), 71.8 (CH_2), 72.0 (CH_2), 78.0 (CH), 109.6 (C), 126.6 (2CH), 127.8 (2CH), 127.9 (2CH), 128.1 (2CH), 128.6 (CH), 130.1 (C), 130.7 (C), 139.9 (C) 167.8 (C), 173.8 (C), 174.2 (C).

Chapter 5

General considerations on Experimental sections

All moisture-sensitive reactions were performed in an inert, dry atmosphere of argon or nitrogen in oven-dried glassware. Reagent grade solvents were used for either chromatography or extraction. THF was distilled from Na/benzophenone under argon; CH2Cl2, acetonitrile, toluene, Et3N, dimethyl carbonate, 1,2-dichloroethane were distilled from CaH2 under argon; pyridine was distilled from KOH under argon and DMF was distilled over 4Å molecular sieves. Analytical thin-layer chromatography (TLC) was performed using Merck precoated tlc plates (Silica gel 60 GF254 0.25 mm). Flash chromatography was performed using Merck Silica gel 60 (230-400 mesh). The solvent compositions reported for all separations are on a volume/volume basis. Gas chromatography (GC) was performed using a Hewlett Packard HP6890 or an Agilent 6850 instruments. GC yield analyses were performed with an Agilent 19091Z-413E, HP-1 Methyl siloxane column, GC enantiomeric excess determinations were performed with a Restek 13104 Rt-βDEXsm column.

High performance liquid chromatography (HPLC) was performed using a Hewlett Packard 1100 or Agilent 1100 instruments equipped with a *Chiralpak*® AD-H (250 mm x 4.6 mm ID) or with a *Chiralcel*® OD-H (250 mm x 4.6 mm ID)

^{1}H NMR spectra were recorded at 300,400 or 600 MHz at 20 °C with either tetramethylsilane (δ 0.00), chloroform (δ 7.26) as the internal standard. ^{13}C NMR spectra were recorded at 75,100 or 150 MHz at 20 °C with either chloroform (δ 77.0) as the internal standard. Carbon assignments were based on DEPT, HMQC experiments. Melting points were determined through a *Büchi* instrument and are uncorrected. Specific optical rotations were determined at the D line through a *Perkin Elmer 341* polarimeter.

Abbreviations and acronyms

$[\alpha]_D^{20}$	Optical rotation at 589 nm	HOMO	highest occupied molecular orbital
Ac	Acetyl	HMPA	4-Hydroxymethyl-3-methoxyphenoxyacetic acid
B	base	HPLC	High performance liquid chromatography
Bn	Benzyl	IR	Infrared spectroscopy
c	concentration	LAH	$LiAlH_4$
cat	catalyst	LUMO	lowest unoccupied molecular orbital
ChA	Chrysanthemic acid	Me	methyl
CH_2Cl_2	Dichloromethane	MeOH	methanol
CH_3Cl	Chloroform	ML	Mother liquor
CCl_4	Methane tetrachloride	mp	Melting pot
$CO(OMe)_2$	Dimethyl carbonate	PGI_2	prostacyclin
DIBAL	Diisobutylaluminium hydride	n.d.	No date
DMAD	*threo*-2-dimethylamino-1-(4-nitrophenyl)-1,3-propanediol	NOESY	Nuclear Overhauser Effect Spectroscopy
DMF	N,N-dimethylformamide	Ph	Phenyl
DMPP	*threo*-2-dimethylamino-1-phenyl-1,3-propanediol	*i*-Pr	isopropyl
dr	Diastereoisomeric ratio	Py	pyridine
DSC	Differential scanning calorimetry	TFA	Trifluoroacetic acid
ee	Enantiomeric excess	TBDMS	*Tert*-butyldimethylsilyl
er	Enantiomeric ratio	*t*-Bu	*Tert*-Butyl
Et	Ethyl	Tf	triflic
Et_3N	Triethylamine	THF	tetrahydrofuran
Et_2O	Diethyl ether	THP	tetrahydropyran
EtOAc	Ethyl acetate	TLC	Thin layer chromatography
GC	Gas chromatography	t_r	Retention time
ImH	Imidazole	Ts	Tosyl (*p*-toluenesulfonyl)