Tetrahedron Vol. 49, No. 41, pp. 9353-9372, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

A SIMPLE SYNTHESIS OF Δ^2-OXAZOLINES, Δ^2-OXAZINES, Δ^2-THIAZOLINES AND 2-SUBSTITUTED BENZOXAZOLES

Helmut Vorbrüggen and Konrad Krolikiewicz

Research Laboratories of Schering AG
D-1000 Berlin 65; Germany

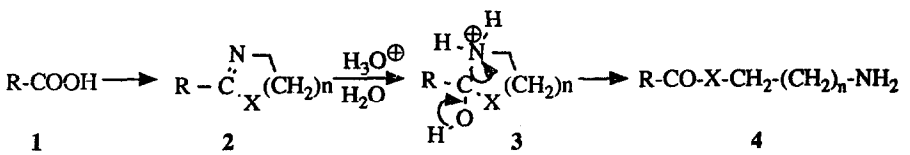
(*Received in USA* 14 *April* 1993; *accepted* 2 *June* 1993)

Dedicated to C. Djerassi on the occasion of his 70th birthday

Abstract: Carboxylic acids react readily at 0°→+24°C with amino alcohols, amino mercaptans and o-aminophenols in the presence of triphenylphosphine- or tributylphosphine dichloride (generated in situ from the reaction of the phosphines with hexachloroethane or CCl_4) and triethylamine in acetonitrile to form the corresponding Δ^2-oxazolines, Δ^2-oxazines, Δ^2-thiazolines and 2-substituted benzoxazoles in one reaction step in yields of up to 80%.

Many classes of drugs such as the nonsteroidal antiinflammatory drugs (NSAID) aspirin and naproxen, the diuretics furosemide and bumetanide or the biologically active natural eicosanoids prostaglandin $F_{2\alpha}$ and prostacyclins contain carboxylic groups, which determine their pharmacokinetic properties and biological actions.

Since it was anticipated that the modification of the carboxylic groups would change the resorption characteristics and pharmacokinetic properties of these drugs and might furthermore as in the case of the NSAID's diminish their erosive action on the mucosa of stomach and intestines, we became interested in the conversion of the carboxyl moieties of the NSAID's diuretics and eicosanoids **1** into their corresponding Δ^2-oxazolines **2a**, Δ^2-oxazines **2b** and Δ^2-thiazolines **2c** as potential prodrugs.[2] These derivatives **2** are expected to hydrolyse gradually under physiological conditions via **3** to the corresponding free or protonated ω-amino esters **4a** and **4b** and ω-amino thioesters **4c**, which would subsequently be saponified in vivo to the starting NSAID's, diuretics or eicosanoids **1**[3] or rearranged via their corresponding cyclols to ω-functionalized amides.



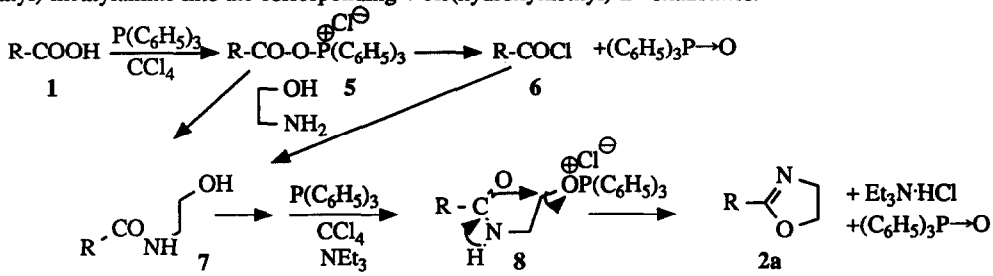
1 **2** **3** **4**

a) X = O; n = 1 b) X = O; n = 2 c) X = S; n = 1

In particular Δ^2-oxazolines **2a** and Δ^2-thiazolines **2c** have been described as structural entities in natural products [4] and as important synthetic intermediates [5] e.g. as chiral ligands for asymmetric synthesis [6] or as protecting groups for the carboxyl moiety [7] and as starting materials for the oxydative conversion into the corresponding aromatic oxazoles and thiazoles.[8]

The hitherto described methods for the conversion of carboxylic acids into the corresponding Δ^2-oxazolines,[3,5a] Δ^2-oxazines[9,10] and Δ^2-thiazolines [5e,11] require either heating to temperatures of up to 200-220°C or the repeated use of $SOCl_2$[12] to convert the carboxylic acids **1** via the acid chloride to the corresponding amides followed finally by cyclization of the ω-hydroxy- or ω-mercapto amides with $SOCl_2$ to the desired Δ^2-oxazolines **2a** or Δ^2-thiazolines **2c**.

Since all these methods require either drastic heating or aggressive reagents such as $SOCl_2$, these procedures did not appear to be applicable to sensitive NSAID's such as aspirin **28** and diclofenac **34** or to eicosanoids containing unprotected secondary or allylic alcoholic hydroxyl groups. The $SOCl_2$-procedure seemed furthermore not to be suitable to convert functionalized amino alcohols such as α,α,α-tris(hydroxymethyl)-methylamine into the corresponding 4-bis(hydroxymethyl)-Δ^2-oxazolines.



The ready conversion of carboxylic acids **1** with triphenylphosphine-CCl_4 into the corresponding acid chlorides **6** [13] and the preferential O-phosphorylation and activation of amino alcohols by the same reagents [14] prompted us to react **1** with ethanolamine in the presence of triphenylphosphine, CCl_4 and triethylamine to give via the corresponding O-triphenylphosphonium chlorides **5**, acid chlorides **6** and amides **7** finally the amide-O-triphenylphosphonium salts **8** (cf. however the later discussed intermediates **65**, **67** and **69**), which were expected to cyclize to the desired Δ^2-oxazolines **2a**. The anticipated reaction of the amino group of ethanolamine with triphenylphosphine dichloride to the corresponding amino triphenylphosphonium chloride was considered to be less likely, since the reaction of primary amines such as benzylamine with triphenylphosphine dichloride occurs only after 72 h heating to 40°C in CH_2Cl_2.[15]

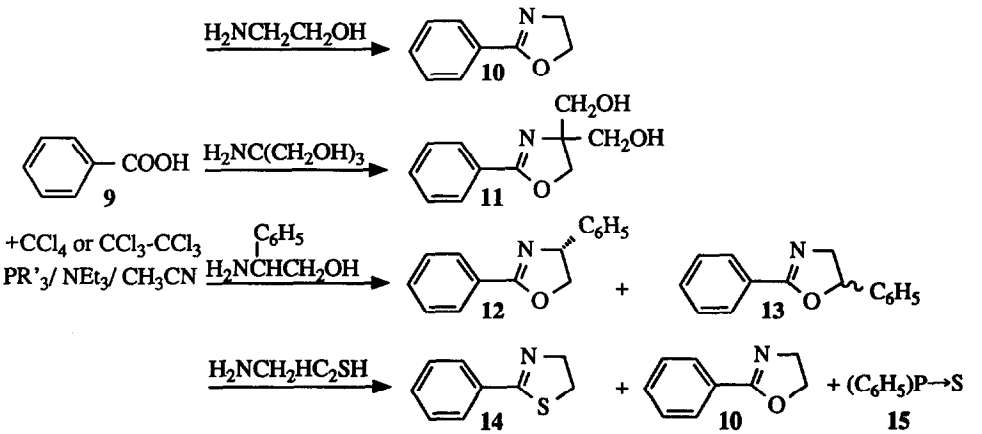
Scope of the Reaction

As briefly described in a preliminary publication,[1] we have found that aromatic and aliphatic carboxylic acids **1** can indeed be readily condensed with ω-amino alcohols, ω-amino mercaptans and o-aminophenols at 0°→24°C in one reaction step in acetonitrile in the presence of triphenylphosphine dichloride and triethylamine to afford the corresponding Δ^2-oxazolines **2a**, Δ^2-oxazines **2b**, Δ^2-thiazolines **2c** as well as 2-substituted benzoxazoles in yields of up to 80%. [16]

The triphenylphosphine dichloride is generated in situ from triphenylphosphine and CCl_4 [17] or cleaner and sometimes more effectively as we discovered later (cf. the subsequent discussion about side reactions) from triphenylphosphine and hexachloroethane.[18] Since the majority of our experiments were initially done with triphenylphosphine and the toxic CCl_4 producing besides triphenylphosphine dichloride all the products of the triphenylphosphine-CCl_4 cascade,[19] some of these yields can probably be improved on employing tri-

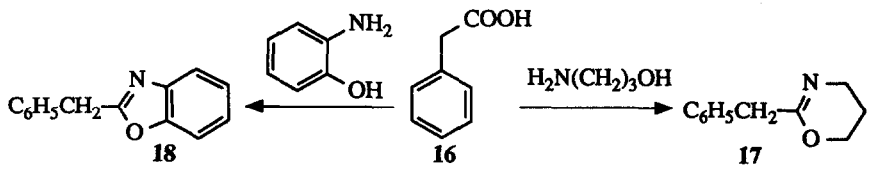
phenylphosphine in combination with hexachloroethane. Replacement of triphenylphosphine by tributylphosphine at 0°C resulted in a more exothermic reaction and in the formation of the water soluble tributylphosphine oxide, which can be extracted with water from an unpolar solvent or readily separated on silica gel containing 40% H_2O. This can be advantageous since on employing triphenylphosphine the removal or separation of triphenylphosphine oxide on workup is sometimes tedious. We furthermore used initially a 1:1 mixture of acetonitrile and pyridine as a solvent because the salts between the carboxylic acid **1** and the amino alcohols or amino mercaptans are usually precipitated from acetonitrile. But due to side reactions between pyridine and CCl_4, hexachloroethane or products of the triphenylphosphine-CCl_4-cascade[19] causing a rapid coloration of the reaction mixture, the use of pure acetonitrile is preferable since the ammonium carboxylates dissolve on gradual addition of neat triphenylphosphine, CCl_4 or crystalline hexachloroethane or a solution of triphenylphosphine, CCl_4 or hexachloroethane in CH_2Cl_2 or acetonitrile.

Benzoic acid **9** afforded with ethanolamine in the presence of 3 equiv. of triphenylphosphine, 10 equiv. of CCl_4 and 3.3 equiv. of triethylamine at 0°→24°C in acetonitrile 78% of pure redistilled 2-phenyl-Δ^2-oxazoline **10**. Reaction of benzoic acid **9** with α,α,α-tris(hydroxyymethyl)methylamine, triphenylphosphine, CCl_4 and triethylamine in acetonitrile-pyridine (1:1) at 0°C furnished 71% of the cristalline 4,4-bis(hydroxymethyl)2-phenyl-Δ^2-oxazoline **11** without any noticeable formation of products in which one or both hydroxylgroups in **11** had been replaced by chlorine.

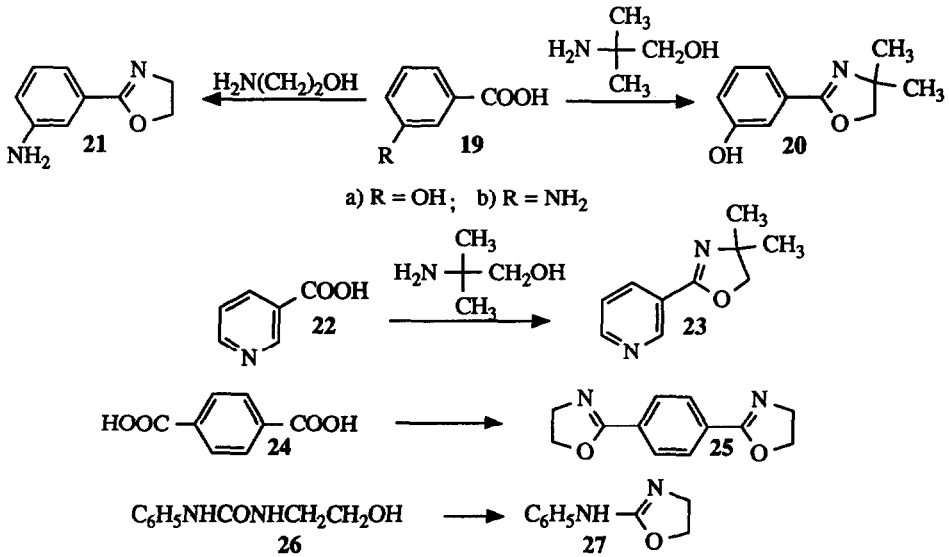


Optically active D(-)2-amino-2-phenylethanol furnished after chromatography 64% of the anticipated 2,4-diphenyl-Δ^2-oxazoline **12**, which gave on acid hydrolysis recovered crystalline D(-)2-amino-2-phenyl ethanol. Under modified reaction conditions there was isolated besides **12** the isomeric 2,5-diphenyl-Δ^2-oxazoline **13**, which originates from intermediate N-benzoyl-aziridine-formation. 2-Mercaptoethanol furnished with benzoic acid **9** the anticipated 2-phenyl-Δ^2-thiazoline **14** in 38% yield as well as ca. 10% of 2-phenyl-Δ^2-oxazoline **10** and triphenylphosphine sulfide **15**. The 2-phenyl-Δ^2-oxazoline **10** is probably formed by direct nucleophilic attack of the amide-carbonyl group on any intermediate S-triphenylphosphonium chloride to give **10** and **15**. Alternatively the mercapto group in the N(2-mercaptoethyl) benzamide intermediate can be transformed by chlorinative cleavage [20] into N(2-chloroethyl)-benzamide, which can also be generated by chloride attack on the alkylene-S-triphenylphosphonium chloride, followed by base catalyzed cyclization to the Δ^2-oxazoline **10** (Compare furthermore the later described reactions of p-nitrobenzoic acid

70 with threonine- and allo-threonine methylester hydrochloride to the 4,5-disubstituted Δ^2-oxazolines **72** and **75**).



Analogous reactions of the "aliphatic" phenylacetic acid **16** with 3-aminopropanol gave rise to 51% of 2-phenyl-Δ^2-oxazine **17**, whereas condensation of **16** with o-aminophenol furnished at 24°C 78% of 2-benzyl-benzoxazole **18**. This synthesis of 2-substituted benzoxazoles proceeds under much milder conditions than any of the known literature methods.[21,22]

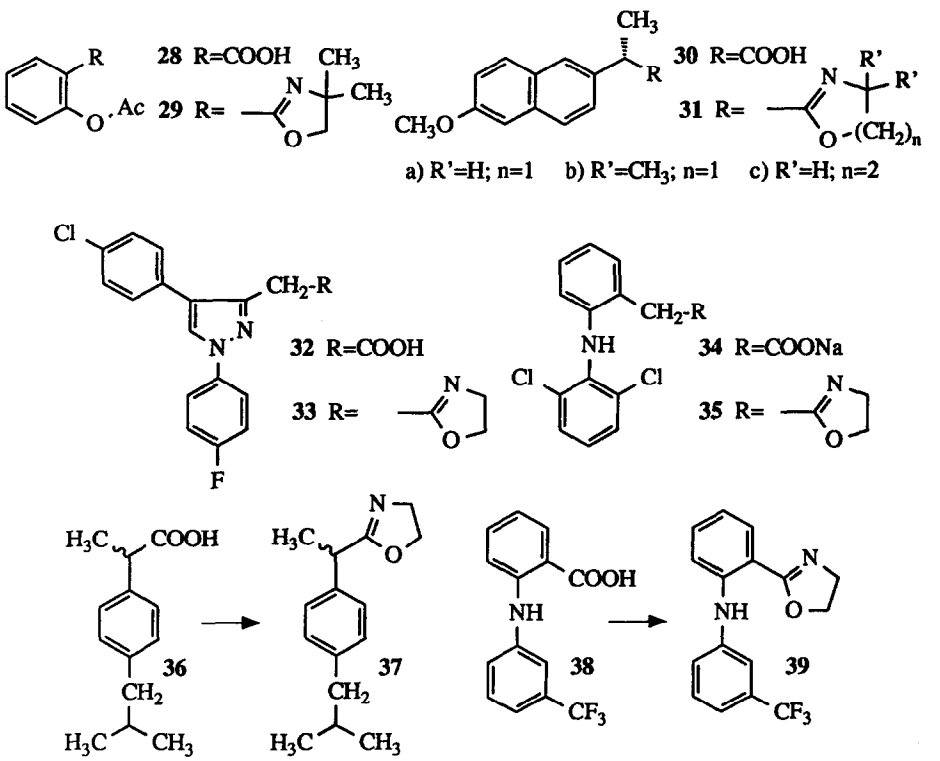


To test the influence of additional unprotected functional groups in carboxylic acids 3-hydroxy-benzoic acid **19a** was condensed with 2-amino-2-methyl-1-propanol to give in 68% yield 2(3-hydroxyphenyl)-4,4-dimethyl-Δ^2-oxazoline **20**. Since phenoxytriphenylphosphonium chloride is spontanously hydrolyzed with water,[23] any intermediate aryloxytriphenylphosphonium salt will not be detected on thin layer chromatography or isolated after workup. Analogously, 3-aminobenzoic acid **19b** afforded with ethanolamine 2(3-aminophenyl)-Δ^2-oxazoline **21** in 63% yield, without any interference of the aromatic amino group, since aniline only reacts with triphenylphosphine-CCl_4 after 7 days at 35°C.[15] Neither did the heterocyclic nitrogen in nicotinic acid **22** influence the formation of 2(3-pyridyl)-4,4-dimethyl-Δ^2-oxazoline **23** in 74% yield. The dicarboxylic acid terephthalic acid **24** furnished 50% of the crystalline bis-oxazoline **25**. Finally, the N'-hydroxyethyl-N''-phenylurea **26** cyclized readily to the crystalline 2-(phenylamino)-Δ^2-oxazoline **27** in 77% yield.

Application to nonsteroidal antiinflammatory drugs (NSAID).

As emphasized in the introduction, oral application of non steroidal antiinflammatory drugs (NSAID)

causes damage to the mucosa of stomach and intestines. We therefore transformed the carboxyl group of these NSAID's into their corresponding Δ^2-oxazolines **2a**, Δ^2-oxazines **2b** and Δ^2-thiazolines **2c** in order to change the pharmacokinetic properties (cf. the transformations **1**→**4**) and therefore the topical toxicity of these NSAID's. Thus aspirin **28** was transformed in 63% yield into the corresponding 4,4-dimethyl-Δ^2-oxazoline **29**, whereas S(+)naproxen **30** was modified in 55-70% yield to the optically active derivatives **31a-c**. Likewise, pyrazolac **32** afforded the Δ^2-oxazoline **33** in 72% yield. Diclofenac sodium **34** was readily converted in 51% yield into the corresponding crystalline Δ^2-oxazoline **35**, whereas racemic ibuprofen **36** afforded in 85% yield the Δ^2-oxazoline **37**. Finally, flufenamic acid **38** gave rise to 67% of the Δ^2-oxazoline **39**.

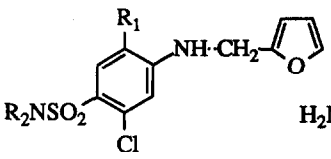


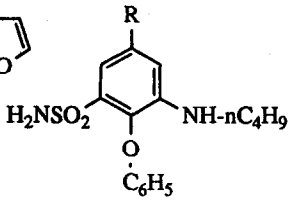
Although the initial biological tests demonstrated that the derivatives **29**, **31a-c**, **33**, **35**, **37** and **39** were potent antiinflammatory agents, which apparently did not induce the formation of stomach ulcers, the overall antiinflammatory potency of these derivatives was somewhat lower than that of the original NSAID's. When the dosage of these derivatives **29**, **31a-c**, **33**, **35**, **37** and **39** was raised in order to achieve the same antiinflammatory effects as the original drugs **28**, **30**, **34**, **36** and **38**, erosion of the mucosa of stomach and intestine was again observed so that this pharmacokinetic approach to obtain less ulcerogenic NSAID's was abandoned.[24]

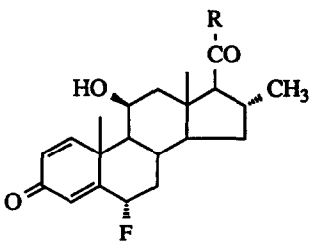
Miscellaneous Applications

The diuretic furosemide **40** was converted with triphenylphosphine/CCl_4/NEt_3 in 48% yield into the corresponding Δ^2-oxazoline **41**, whereas excess of triphenylphosphine caused the formation of the crystalline Δ^2-oxazoline-triphenylphosphine imine **42**. Analogously, the diuretic bumetanide **43** afforded the corresponding crystalline Δ^2-oxazoline **44** in 55% yield. Finally, the steroidal α-ketoacid **45** was only transformed into

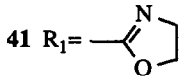
the corresponding Δ^2-oxazoline on employing DBU as base to give after chromatography on deactivated silica gel 28% of the very sensitive crystalline Δ^2-oxazoline **46b**. Using triethylamine as base furnished only the crystalline N-(2-chloroethyl)amide **46a**! Neither derivative showed any advantage compared to the original drugs.

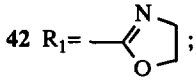




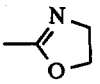


40 R_1=COOH; R_2=H_2

41 R_1=  ; R_2=H_2

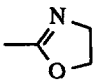
42 R_1=  ; R_2=$P(C_6H_5)_3$

43 R=COOH

44 R= 

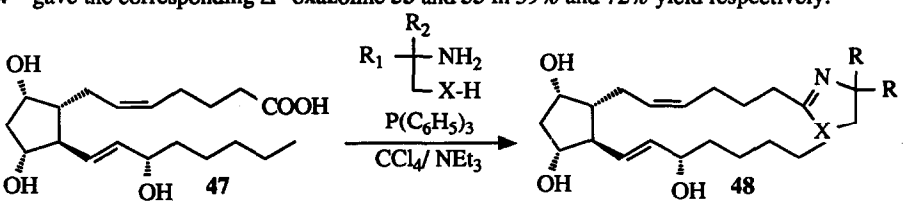
45 R=COOH

46a R=$CONHCH_2CH_2Cl$

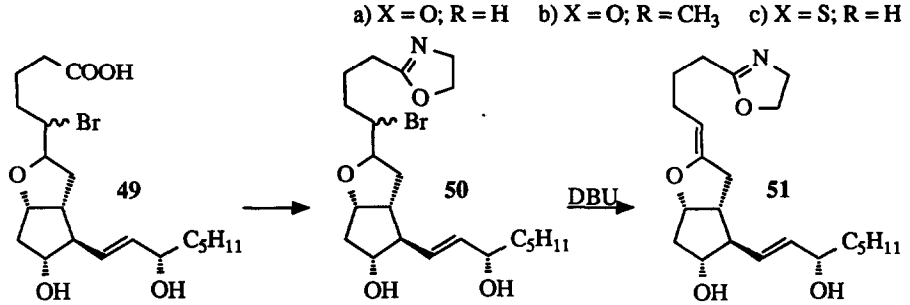
46b R= 

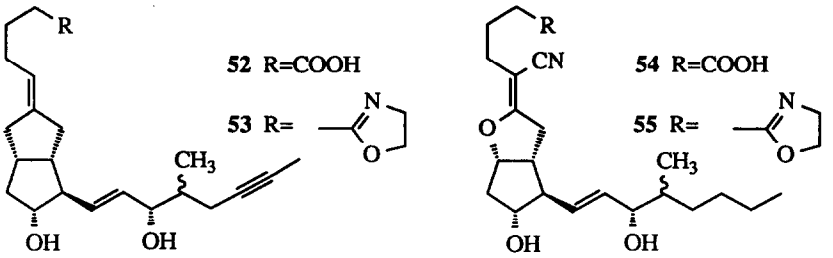
Application to Eicosanoids

Natural prostaglandin $PGF_{2\alpha}$ **47** containing three unprotected hydroxy groups could be selectively transformed with triphenylphosphine-CCl_4-triethylamine into the corresponding derivatives **48a-c**. Silylation of $PGF_{2\alpha}$ **47** with hexamethyldisilazane (HMDS) prior to the reaction with 2-amino-2-methyl-1-propanol and triphenylphosphine-CCl_4-triethylamine gave **48b** in 83% yield. The bromo-ether **49**,[25] derived from $PGF_{2\alpha}$ **47**, gave rise to 54% of the corresponding 5-bromo-Δ^2-oxazoline **50**, which afforded on dehydrobromination with DBU and separation on silica plates the rather stable Δ^2-oxazoline-derivative **51** of the very unstable free natural prostacyclin PGI_2. Finally, the very potent, chemically stable PGI_2-mimetics iloprost **52**[26] and nileprost **54**[27] gave the corresponding Δ^2-oxazoline **53** and **55** in 59% and 72% yield respectively.



a) X = O; R = H b) X = O; R = CH_3 c) X = S; R = H





Side Reactions

Although the conversion of primary and secondary hydroxy groups by triphenyl- and tributylphosphine dichloride (or dibromide) into the corresponding chlorides (or bromides) is a generally applied synthetic reaction,[19] we did only occasionally observe the formation of such ω-chloroalkylamides **57** (cf. the formation of **46a** and **73**), which can be gradually transformed in situ by the added triethylamine or DBU into the corresponding Δ^2-oxazolines **2a** and Δ^2-oxazines **2b**.

$$\underset{\mathbf{1}}{\text{R-COOH}} \longrightarrow \underset{\mathbf{56}}{\text{R-CO-NH-(CH}_2)_n\text{-O}\overset{\oplus}{\text{P}}\text{R'}_3\,\overset{\ominus}{\text{Cl}}} \longrightarrow \underset{\mathbf{57}}{\text{R-CO-NH-(CH}_2)_n\text{-Cl}} + \text{R'}_3\text{P}\rightarrow\text{O} \qquad n = 2, 3$$

The ω-chloroalkylamides **57**, however, become the main products, when no base such as triethylamine or DBU is added to cyclize the intermediate reactive phosphonium salts **56** (cf. also formula **8**) into the corresponding Δ^2-oxazolines **2a** and Δ^2-oxazines **2b**. Furthermore, the intermediate formation of such N(2-chloroethyl)amides **57** from the chlorinative cleavage of N(2-mercaptoethyl)amides followed by base catalyzed cyclization will yield the corresponding Δ^2-oxazolines **2a** and triphenylphosphine sulfide **15** besides the desired Δ^2-thiazolines **2c** (cf. the reaction of **9** to **14**, **15** and **10**). Employing β-mercaptoethylamine, the oxydative dimerization of the intermediate N(2-mercaptoethyl)amides to the corresponding disulfides can also occur, so that strict exclusion of oxygen should always be mandatory on using β-mercaptoethylamine.

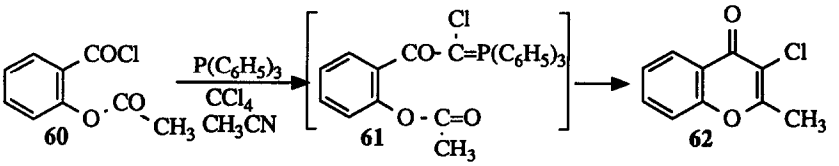
If the amino group in the 1,2-ethanolamine is sterically encumbered as in the case of the 2-amino-2-phenylethanol, the acylation of the amino group to the amide intermediate can be impeded so that the hydroxy group can partially be phosphorylated first. This can result in the formation of intermediate aziridines,[14] which give after N-acylation and rearrangement a mixture of the corresponding 4- or 5-substituted Δ^2-oxazolines (cf. the formation of **12** and **13**). In these cases slow addition of triphenylphosphine or hexachloroethane or CCl_4 at T<20°C is advisable to favor the initial formation of the corresponding amide-intermediates.

Another side reaction can be encountered during the synthesis of Δ^2-oxazolines **2a** of stronger carboxylic acids, such as trifluoro acetic acid, which are apparently converted much slower into the corresponding triphenylphosphonium ester chlorides **5** or acid chlorides **6**. As a consequence, the triphenylphosphine dichloride, formed in situ from triphenylphosphine and hexachloroethane or CCl_4, can react with the excess triethylamine to give via chlorination-dehydrochlorination the intermediate enamine **58**, which is converted by triphenylphosphine dichloride to E-diethylamino-vinyl-triphenylphosphonium chloride **59**. Thus traces of salts such as **59** can frequently be encountered on careful chromatography of the crude reaction mixtures. On performing these chlorinations-dehydrochlorinations of tert. amines such as triethylamine, diisopropylethylamine (Hünigbase) or N-ethylmorpholine in boiling tetrachloroethylene, the corresponding E-dialkylamino-vinyl-triphenylphosphonium chlorides such as **59** can be prepared in up to 70% yield.[28]

$$4\ \text{NEt}_3 \xrightarrow[\substack{2\ \text{Cl}_3\text{C-CCl}_3 \\ \text{CH}_3\text{CN/ 24°C}}]{\text{P(C}_6\text{H}_5)_3} \underset{\mathbf{58}}{[\text{Et}_2\text{N-CH=CH}_2]} \longrightarrow \underset{\mathbf{59}}{\text{Et}_2\text{N-CH=CH-}\overset{\oplus}{\text{P}}(\text{C}_6\text{H}_5)_3\,\overset{\ominus}{\text{Cl}}} + 3\ \text{Et}_3\text{N}\cdot\text{HCl}$$

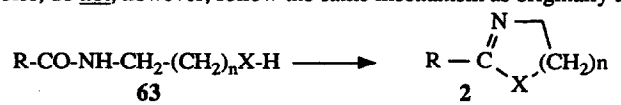
Finally, during experiments to convert 2-acetoxybenzoic acid (aspirin) **28** with triphenylphosphine-CCl_4-triethylamine into the corresponding acid chloride **60**, before adding the ethanolamine to generate the

corresponding Δ^2-oxazoline **29**, the acid chloride **60** was transformed at room temperature via **61** into 2-methyl-3-chloroflavone **62** in 66% yield. This and analogous Wittig-type cyclizations were published in detail elsewhere.[29]



Mechanisms

As aforediscussed, the preferential conversion of the carboxylic acids **1** into the corresponding triphenylphosphonium ester hydrochlorides **5** or the acid chlorides **6** is followed by formation of the amides **63**, which can always be detected as the first reaction intermediate by thin layer chromatography. The subsequent cyclization of the amides **63** to the corresponding Δ^2-oxazolines **2a**, Δ^2-oxazines **2b**, Δ^2-thiazolines **2c** and 2-substituted benzoxazoles, do not, however, follow the same mechanism as originally assumed.[1]

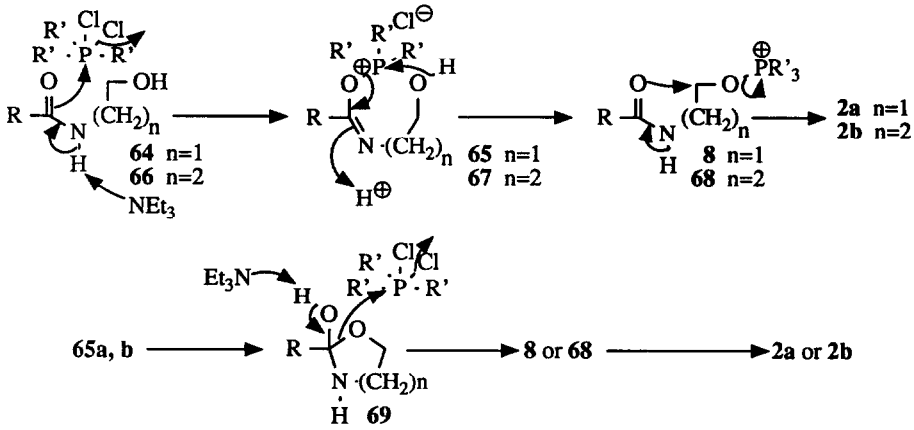


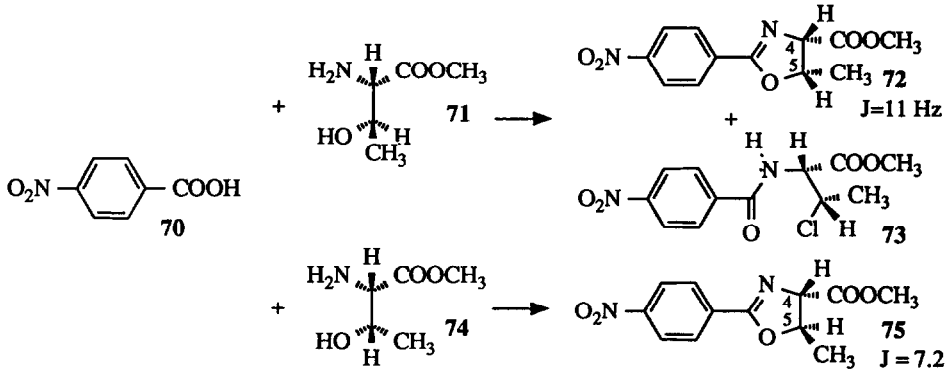
a) X = O; n = 1 b) X = O; n = 2 c) X = S; n = 1

Wheras the formation of triphenyl- or tributylphosphonium esters or acid chlorides as well as their conversion with ethanolamine or 3-aminopropanol to the corresponding amides **63a+b** are quite obvious, their subsequent reaction to the O-phosphonium salts **8** and **68** followed by cyclization to the Δ^2-oxazolines **2a** and **2b** is still not completely understood. Since the addition of tertiary bases such as triethylamine, N-ethylmorpholine or DBU is essential to prevent or minimize the conversion of any alcoholic hydroxyl-groups in the carboxyl- or amine moiety into the corresponding chloro compounds and the amide moiety is the most acidic group in the ω-hydroxyalkyl amides **63a,b**, the amide-O-phosphonium salts **65** or **67** will probably be formed first in the presence of tert. bases from the acidic amides **64** and **66** and possibly also in the case of the subsequently discussed mechanism of the formation of Δ^2-thiazolines. This is followed by proton catalyzed nucleophilic displacement of the amide-O-phosphonium groups by the ω-hydroxyalkylgroup to give via the 7- or 8-membered transition states **65** and **67** the final 5- or 6-membered intermediates **8** and **68**, which cyclize to the Δ^2-oxazolines **2a** and Δ^2-oxazines **2b** . An alternative, however, would imply the intermediate formation of the cyclic amide-hemiacetals or cyclols **69**,[30] which will react directly with triphenyl- or tributylphosphine dichloride to **8** or **68**. To complicate matters there can be distinctive differences in the mode of phosphorylation of two competing oxygen-nucleophiles on employing triphenylphosphine or tributylphosphine[31] so that the mechanistic results presented here are primarily valid for the application of triphenylphosphine.

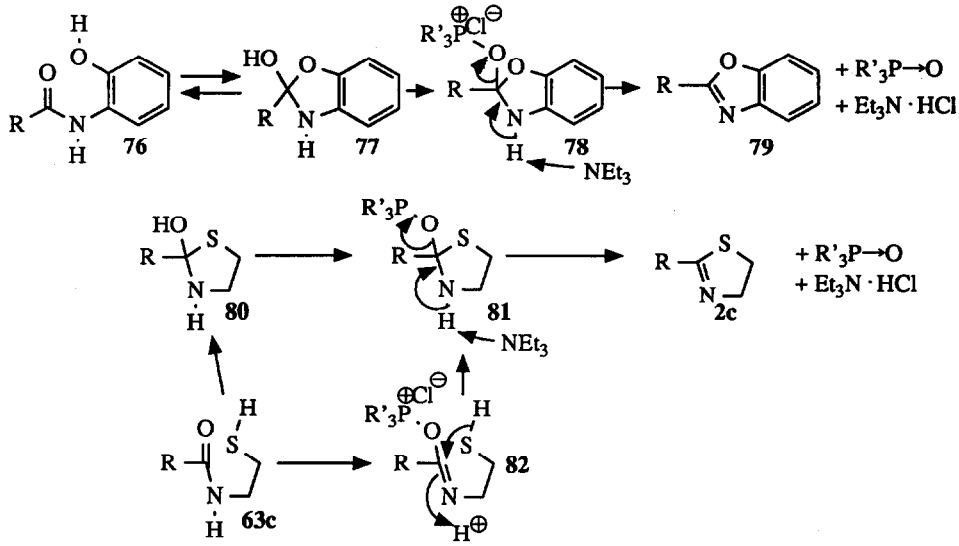
Due to the resulting O-phosphorylation [14] of the N(ω-hydroxyethyl)carboxyamides **63a+b** to **8** and **68**, the triethylamine or DBU induced cyclization of **8** and **68** occurs with Walden inversion of any chiral C-atom attached to the alcoholic hydroxy group to give the corresponding inverted 5-substituted Δ^2-oxazolines or 6-substituted Δ^2-oxazines. The reaction of p-nitrobenzoic acid **70** with L-threonine methylester hydrochloride **71** in the presence of triphenylphosphine, hexachloroethane and N-ethylmorpholine as base afforded in 52% yield the crystalline Δ^2-oxazoline **72**, in which the threonine-3-carbon atom had been inverted as well as 35%

of a crystalline chloride for which we assume structure **73**. The structure of **72** can be deduced from its ^{1}H-NMR spectrum with a coupling constant J=11 Hz[32] for the H_4, H_5 hydrogen atoms. L-Allothreonine methylester hydrochloride **74** gave 83% of the crystalline Δ^2-oxazoline **75**, with a H_4,H_5 coupling constant of J=7.2 Hz.[32] Analogous conclusions about the inversion of any chiral center of substituted ethanolamines and 3-aminopropanols at the C-atom carrying the hydroxygroups were reached by A. I. Meyers et al.[33] on applying our reaction conditions.





In the case of the N-acylated o-aminophenol **76**, which is the first intermediate in the synthesis of benzoxazoles, we assume that this amide **76** is in equilibrium with the cyclic amide-hemiacetal or cyclol **77**, which reacts with triphenylphosphine dichloride/triethylamine to **78** followed by elimination of triphenyl- or tributylphosphine oxide and triethylamine hydrochloride to give the 2-substituted benzoxazols **8**. Analogously the Δ^2-thiazolines **2c** might be formed from the amide-intermediates **63c** via reaction of the corresponding cyclic amide-hemiacetals or cyclols **80**[30] with triphenyl- or tributylphosphonium dichloride to **81**, which can, however, also be obtained by proton catalyzed 5-endo-trig cyclization of the ω-mercapto group in the corresponding imid-O-phosphonium salts **82**. Finally, elimination of '$R_3P\rightarrow O$ furnishes the corresponding Δ^2-thiazolines **2c**.



Summary

Although not all the different preparations in particular of the modified NSAID's, diuretics or eicosanoids were optimized, it can be assumed that following our procedures aromatic and aliphatic carboxylic acids or their salts (cf. **34**) can be routinely converted in 70-80% yield into the corresponding Δ^2-oxazolines **2a**, Δ^2-oxazines **2b**, and 2-substituted benzoxazoles, whereas usually only 40-50% of the Δ^2-thiazolines **2c**, which are accompanied by the corresponding Δ^2-oxazolines **2a** (cf. the formation of **14**, **10** and **15**) will be obtained. It can also be anticipated that the corresponding 2-substituted benzothiazoles will also be formed in less than 60-70% yield.

The experimental procedures are quite simple and reproducible if carefully dried and distilled acetonitrile, CH_2Cl_2, triethylamine, N-ethylmorpholine or DBU are employed and one follows the reactions by t.l.c. to make sure that the cyclizations are complete on workup. The choice of the right tertiary base is crucial. Whereas only DBU leads to Δ^2-oxazoline-formation in the case of the α-ketoacid **45**, the weaker tertiary base N-ethylmorpholine was used for the conversion of threonine- and allothreonine-methylester chlorides **71** and **74** to the corresponding Δ^2-oxazolines **72** and **75** to avoid any racemization of the protons α to the methylester groups resulting, however, in the formation of the chlorocompound **73**. It should furthermore be tested whether multifunctional carboxylic acids such as 3-hydroxybenzoic acid **19b** or $PGF_{2\alpha}$ **47** should be silylated by HMDS prior to their reaction with ethanolamines or mercaptoethylamines (cf. conversion of **47** into **48b**!). The separation from triphenylphosphine oxide can frequently be achieved by distillation. In many cases, however, the reaction products have to be isolated by rapid chromatography on deactivated silica gel or alumina to avoid ring opening of the desired end products.

Employing the Mitsunobu-reagent triphenylphosphine-azoester,[34] the Hendrickson reagent $[(C_6H_5)_3P^{\oplus}\text{-}O\text{-}P^{\oplus}(C_6H_5)_3]$-2 $CF_3SO_3^{\ominus}$/triethylamine[35] or the Mukaiyama reagent triphenylphosphine-2,2'-dipyridyldisulfide,[36] which all lead to the formation of intermediate alkoxytriphenylphosphonium salts **8**, gave, as described in our preliminary publication [1]about the same yields of Δ^2-oxazolines as with triphenylphosphine-CCl_4 or $Cl_3C\text{-}CCl_3$.[1] But we consider these procedures less practical since e. g. they generate additional reaction products such as the hydrazoesters and use more expensive reagents. These experiments are thus not described in the experimental part. Cyclizations of N'-(2-hydroxyalkyl-)amides and thioamides with

the Mitsunobu-reagent[37,38] or with the Hendrickson-reagent[39] to the corresponding Δ^2-oxazolines and Δ^2-thiazolines as well as analogous cyclizations with Burgess-reagent[38], o-chlorophenylphosphoro-bis-(1,2,4)triazolide[40] and dimethylaminosulfurtrifluoride[41] were recently described.

EXPERIMENTAL

The melting points were taken on a Kofler hot stage microscope. The acetonitrile was refluxed over P_2O_5, distilled and again refluxed over CaH_2 and distilled. The absolute pyridine (No 7463, E. Merck) was used as such. Furthermore, all reactions were performed under nitrogen or argon with exclusion of moisture. For column chromatography silica gel (SiO_2, E. Merck, Kieselgel 60.0.040-0.063 mm, containing 40% H_2O) as well as alumina (A IV) (Woelm, neutral or basic) were employed.

2-Phenyl-Δ^2-oxazoline (10):
To a suspension of 3.66 g (30 mmol) benzoic acid **9** and 18.89 g (72 mmol) triphenylphosphine in 100 ml abs. acetonitrile, 46.146 g (300 mmol) CCl_4 were added at +2°C and the reaction mixture stirred for 2 h at +2°C, whereupon a clear solution formed which smelled of benzoylchloride. A solution of 1.832 g (30 mmol) abs. redistilled ethanolamine and of 10.12 g (100 mmol) abs. triethylamine in 25 ml acetonitrile was added within 20 min at +2°C→+11°C whereupon triethylamine hydrochloride precipitated and an 1:1 mixture of N(2-hydroxyethyl)benzamide as well as **10** had formed (tlc, SiO_2, toluene:EtOAc (1:1)). Since the monoamide was still present after 1 h stirring at 24°C, the suspension was cooled to +3°C, additional 5.24 g (20 mmol) of triphenylphosphine were added and the ice bath removed, whereupon the reaction temperature rose to 29°C. Since all the intermediate monoamide had disappeared after 1 h, the reaction mixture was filtered (triethylamine hydrochloride), concentrated to 60 ml, cooled to 0°C, again filtered and the precipitate (triphenylphosphine oxide) washed with 50 ml cold (-10°C) acetonitrile. The filtrate was continuously extracted for 2 h with 500 ml hexane. After cooling to 0°C, the hexane extract was filtered and the crystalls (triphenylphosphine oxide) washed with 50 ml hexane. Since the residual acetonitrile phase still contained some 2-phenyl-Δ^2-oxazoline **10**, the acetonitrile-phase was again continuously extracted with 400 ml hexane. The combined hexane-extracts were concentrated to 10 ml, again filtered, the filtrate evaporated and the residue distilled in a Kugelrohr apparatus at 100-115°C/0.5 mbar to give 3.46 g (78.3%) of pure **10**, which crystallized on cooling, mp. 25-27°C (lit.[42] 27°C).

The workup can be simplified by evaporating the acetonitrile after filtering off the triethylamine hydrochloride, dissolving the residue in 200 ml CH_2Cl_2, washing with 200 ml ice cold 2 N NaOH and reextraction of the aqueous phase with 2 x 50 ml CH_2Cl_2. After drying (Na_2SO_4) and evaporation of the CH_2Cl_2 solution the residue is taken up in 60 ml toluene and 80 ml of hexane added. The yellowish precipitate of triphenylphosphine oxide is then filtered and the residue distilled as described above to give again ca 75-80% of pure 2-phenyl-oxazoline **10**. Rapid chromatography of crude **10** in hexane-methyl-tert. butylether (1:1) on a column with the 20 fold amount of SiO_2 (containing 40% H_2O) gives also ca 70% of **10**. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 3.9-4.2 (m, 2H), 4.25-4.6 (m, 2H), 7.3-7.5 (m, 3H), 7.8-8.1 (m, 2H). Found: C, 73.18; H, 6.08; N, 9.42 C_9H_9NO (141.17) requires C, 73.45; H, 6.19; N, 9.52.

2-Phenyl-4(bis-hydroxymethyl)-Δ^2-oxazoline (11):
To a stirred suspension of 1.21 g (10 mmol) of α,α,α-tris(hydroxymethyl)methylamine, 1.4 ml (10 mmol) triethylamine and 6.15 g (40 mmol) CCl_4 in 100 ml abs. acetonitrile-pyridine (1:1), a solution of 1.22 g (10 mmol) benzoic acid **9** and 2.62 g (10 mmol) of triphenylphosphine in 70 ml abs. acetonitrile-pyridine (1:1) was added within 4 h at 23-25°C. After stirring overnight a solution of 5.24 g (20 mmol) triphenylphosphine and 2.8 ml (20 mmol) triethylamine in 70 ml acetonitrile-pyridine (1:1) was added within 5 h to the reaction mixture, whereupon the temperature in the flask varied from 23-26°C. The yellow solution was kept over night, evaporated in vacuo, the residue taken up with 100 ml toluene and 100 ml ice cold 2 N NaOH and the aqueous phase reextracted with 3 x 50 ml toluene. The toluene phase gave after drying (Na_2SO_4) and evaporation 9.2 g of crystalline residue consisting mostly of triphenylphosphine oxide and some **11** (extract A). The aqueous NaOH phase was extracted with 4 x 50 ml CH_2Cl_2, the organic phase dried (Na_2SO_4) and evaporated to give 0.961 g yellow brownish residue (extract B), which was crystallized from 30 ml ethylacetate to furnish 0.499 g slightly colored **11**, mp 140°C. The mother liquor was evaporated to give on crystallization from 10 ml isopropanol additional 0.276 g **10** mp 139-140°C (lit[43] 138-140°C). The toluene extract (extract A) was treated subsequently at 100°C with 4 x 50 ml H_2O and the hot aqueous phase decanted. The cooled aqueous solution was saturated with NaCl and extracted with 4 x 50 ml CH_2Cl_2, which gave after drying (Na_2SO_4) and evaporation additional 1.1 g of crude **10**. Recrystallization from 15 ml isopropanol afforded 0.696 g pure **11**, mp 140°C. Combined yield of **11** = 1.471 g (71%). IR (KBr) 1640, 1580, 1500, 1365, 108,

1035, 980, 875, 780, 695, 680 cm^{-1}. ^{1}H-NMR (DMSO-D_6; 90 MHz) δ 3.45 (d, J=7 Hz, 4H), 4.25 (s, 2H), 4.75 (tr, J=7 Hz, 2H), 7.35-7.45 (m, 3H), 7.75-7.95 (m, 2H). Found: C, 63.44; H, 6.54; N, 6.69 $C_{11}H_{13}NO_3$ (207.22) requires: C, 63.75; H, 6.32; N, 6.76.

2,4-Diphenyl-Δ^2-oxazoline 12 and 2,5-diphenyl-Δ^2-oxazoline (13):
1) To a solution of 1.22 g (10 mmol) benzoic acid **9**, 1.37 g (10 mmol) of D-(-)-2-amino-2-phenylethanol 1.01 g (10 mmol) triethylamine and 3 ml (30 mmol) CCl_4 in 40 ml abs. acetonitrile-pyridine (1:1), a solution of 2.62 g (10 mmol) triphenylphosphine in 25 ml acetonitrile-pyridine (1:1) was added within 3 h (reaction temperature = 22-26°C) and stirring continued for 1 h to complete the formation of the intermediate amide. After addition of 2.8 ml (20 mmol) triethylamine a solution of 5.24 g (20 mmol) of triphenylphosphine in 50 ml abs. acetonitrile-pyridine (1:1) was added within 3 h, whereupon the reaction turned dark. After 18 h overnight, t.l.c. (toluene:EtOH=1:1) indicated that besides **12** traces of **13** had formed. The reaction mixture was evaporated and the dark sticky residue stirred with 150 ml toluene and 100 ml ice-cold 2 N NaOH, whereupon some sticky dark material remained undissolved. The aqueous alkaline phase was treated with 3 additional 50 ml portions of toluene, the toluene phase dried (Na_2SO_4) and evaporated to give a crystalline brown residue. After boiling with 200 ml diethyl ether, the insoluble triphenylphosphine oxide was filtered, washed with 50 ml diethyl ether and the combined filtrate evaporated to give 4.2 g crude product. Rapid chromatography in toluene over a column of 65 g of silica gel (40% H_2O) gave 1.43 g (64.1%) of pure 2,4-diphenyl-Δ^2-oxazoline **12** $[\alpha]_D$=+36.4° (c=1.04, $CHCl_3$), IR (KBr) 1650, 1495, 1450, 1560, 1083, 1065, 1062, 950, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 4.28 (tr, J=8 Hz, 1H), 4.80 (dd, J=8+10 Hz, 1H), 5.40 (dd, J=8+10 Hz, 1H), 7.15-8.15 (m, 8H), 7.90-8.15 (m, 2H). MS (CI) 224, (M+1; $C_{15}H_{13}NO$=223.26) 193, 154, 139.
On acid hydrolysis of 0.69 g of **12** with 4.5 N HCl for 3.5 h at 125°C bath temperature, cooling and extraction of benzoic acid **9** with diethyl ether and with 3 x 30 ml CH_2Cl_2, the aqueous acidic phase was treated at 0°C with 2 N NaOH until pH=9. Extraction with 3 x 50 ml CH_2Cl_2, drying (Na_2SO_4) evaporation and recrystallization from 25 ml diethyl ether gave 0.17 g of D(-)-2-amino-2-phenylethanol mp 75-77°C, $[\alpha]_D$=-25° (c= 0.79 in 1 N HCl).
2) To a stirred suspension of 3.66 g (30 mmol) benzoic acid **9** and 4.12 g (30 mmol) D-(-)-2-amino-2-phenylethanol in 100 ml abs. acetonitrile, 13.55 ml (90 mmol) of triethylamine and 7.91 ml (80 mmol) of CCl_4 were given followed by dropwise addition of a solution of 18.89 g (72 mmol) of triphenylphosphine in 300 ml abs. acetonitrile within 5 h , whereupon most of the precipitate had passed into solution and two new products had formed according to tlc (SiO_2; toluene:EtAc=1:1). After evaporation of the solvent, the yellowish residue was taken up in 300 ml CH_2Cl_2 and 200 ml ice cold 2 N NaOH. The continued CH_2Cl_2-extracts (600 ml) were dried (Na_2SO_4) and evaporated. The yellowish residue was extracted with 3 x 150 ml diethyl ether and the combined diethyl ether solution evaporated to give 14.1 g crystalline residue. Extraction for 3 h with 400 ml of boiling pentane afforded 3.77 g crude yellowish oil. Rapid chromatography in toluene on a column of 150 g SiO_2 (40% H_2O) gave after a forrun of 800 ml with the next 600 ml toluene 1.03 g of 2,4-diphenyl-Δ^2-oxazoline **12** and with the subsequent 1.4 l toluene 1.26 g of 2,5-diphenyl-Δ^2-oxazoline **13**. $[\alpha]_D$=-114.7° (c=1.02, $CHCl_3$) **13**: IR (KBr) 1650, 1494, 1448, 1255, 1080, 1060, 1025, 695 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 3.98 (dd, J=8+16 Hz, 1H), 4.50 (dd, J=9+16 Hz, 1H), 5.65 (dd, J=8+9 Hz, 1H), 7.20-7.60 (m, 8H), 7.90-8.10 (m, 2H). MS (CI) 224 (M+1; $C_{15}H_{13}NO$=223.26)117.

2-Phenyl-Δ^2-thiazoline (14), 2-phenyl-Δ^2-oxazoline (10) and triphenylphosphine sulfide (15):
To a stirred suspension of 3.66 g (30 mmol) benzoic acid **9**, 3.41 g (30 mmol) β-mercaptoethanol-hydrochloride a solution of 25.2 ml (180 mmol) abs. triethylamine was added within 45 min under argon at 22-24°C followed by 19.72 g (75 mmol) triphenylphosphine. To this mixture a solution of 15.62 g (66 mmol) hexachloroethane in 75 ml abs. CH_2Cl_2 was added slowly within 3.5 h at 22-26°C and the reaction kept over night at 22°C. On workup with 150 ml ice cold 2 N NaOH, the combined CH_2Cl_2-extracts were dried (Na_2SO_4) and evaporated in vacuo to give 27.9 g yellow crystalline residue. After dissolving the crude product in 75 ml toluene-ethyl acetate 9:1 + 10 ml CH_2Cl_2, the solution was chromatographed on a column of 220 g silica gel (40% H_2O) prepared with toluene-ethylacetate (9:1) and eluted with the same solvent mixture. The first 300 ml eluate afforded 2.82 g of crystalline triphenylphosphine sulfide **15**, mp 163°C, whereas the subsequent 200 ml furnished 2.18 g crude 2-phenyl-Δ^2-thiazoline **14**, containing some triphenylphosphine sulfide **15** to give on distillation in a Kugelrohr apparatus at $4 \cdot 10^{-2}$ mbar/90°C 1.86 g (38%) of pure **14**. **14**: IR (film) 1610, 1490, 1420, 1340, 1005, 945, 930, 765, 690 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 3.35-3.55 (tr, J= Hz, 2H), 4.38-4.6 (tr, J= Hz, 2H), 7.35-7.55 (m, 3H), 7.8-7.95 (m, 2H). Found: C, 66.08; H, 6.08; N, 8.24 C_9H_9NS (163.235) requires: C, 66.22; H, 5.56; N, 8.58. Further elution with toluene-ethylacetate 9:1 (120 ml) afforded 0.92 g crude 2-phenyl-Δ^2-oxazoline **10**, which furnished 0.4 g (9.4%) of pure **10** on distillation at 70-80°C/$4 \cdot 10^{-2}$ mbar.

2-Benzyl-Δ^2-oxazine (17):
To a cooled (2-4°C) and stirred solution of 2.72 g (20 mmol) phenylacetic acid **16**, 1.53 ml (20 mmol)

3-amino-1-propanol, 14.688 g (56 mmol) triphenylphosphine and 22.2 ml triethylamine in 100 ml abs. acetonitrile, a solution of 3.9 ml (40 mmol) CCl_4 in 5 ml acetonitrile was added within 10 min. After 3 h at +4°C, the mixture was warmed to 22°C and kept for 72 h in a water bath at 24°C. The precipitate of triethylamine hydrochloride was filtered and washed with abs. acetonitrile. After evaporation of the filtrate, the residue was extracted with 4 x 150 ml boiling hexane, the pooled extracts cooled, the crystalls of triphenylphosphine oxide filtered and the filtrate evaporated. On distillation of the yellow-brownish residue in a Kugelrohr apparatus 1.8 g (51.4%) **17** $bp_{0.2\ mm}$=125°C was obtained. IR (Nujol) 1675, 1250, 1085 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.85 (m, 2H), 3.5 (m, 2H), 4.1 (m, 2H), 7.25 (s, 5H). Found: C, 75.33; H, 7.75; N, 7.81 $C_{11}H_{13}NO$ (175.23) requires: C, 75.40; H, 7.48; N, 7.99.

2-Benzyl-benzoxazole (18):
To a stirred suspension of 4.08 g (30 mmol) phenylacetic acid **16**, 3.27 g (30 mmol) of 2-aminophenol, 19.67 g (75 mmol) triphenylphosphine and 20.92 ml of triethylamine in 100 ml abs. acetonitrile a solution of 15.62 g (66 mmol) hexachloroethane in 60 ml abs. CH_2Cl_2 was added slowly under argon within 2.5 h while keeping the reaction temperature between 20-25°C with a cold water bath. After standing for 16 h at 22°C, the precipitated triethylamine hydrochloride was filtered and washed with 75 ml abs. acetone. After evaporation of the filtrate, the brownish partly crystalline residue was stirred for 30 min with 120 ml acetone and a further amount of crystalline triethylamine hydrochloride was filtered and washed with 50 ml acetone. The acetone phase gave on evaporation 28 g crude product, which was dissolved in 140 ml toluene and 10 ml ethylacetate and chromatographed on a column of 500 g basic Al_2O_3 (AIII): after a forrun of 400 ml toluene, the subsequent 300 ml toluene eluate furnished 7.8 g brownish oil, which was distilled at $4 \cdot 10^{-2}$ bar in a Kugelrohr apparatus to give 4.8 g (78%) of pure **18**, mp 31-33°C (lit.[21] 32°C). IR (Nujol) 1630, 1570, 1500, 1455, 1245, 1005, 845 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 4.25 (s, 2H), 7.25-7.4 (m, 9H). Found: C, 80.68; H, 5.33; N, 6.55 $C_{14}H_{11}NO$ (209.24) requires C, 80.36; H, 5.30; N, 6.69.

2-(3-Hydroxyphenyl)-4,4-dimethyl-Δ^2-oxazoline (20):
To a stirred solution of 1.38 g (10 mmol) 3-hydroxybenzoic acid **19a**, 0.89 g (10 mmol) 2-amino-2-methyl-1-propanol and 4.2 ml (30 mmol) triethylamine in 30 ml abs. acetonitrile and 20 ml abs. pyridine 3.9 ml (40 mmol) CCl_4 was given and subsequently a solution of 7.86 g (30 mmol) triphenylphosphine in 80 ml abs. acetonitrile-pyridine (1:1) added dropwise within 4 h while keeping the reaction temperature between 24-27°C. After 20 h at 24°C the solvents were evaporated, the residue taken up in 200 ml diethyl ether and 100 ml conc. aqueous ammonia. After extracting the aqueous phase with 3 x 100 ml diethyl ether, the combined diethyl ether phase was dried (Na_2SO_4) evaporated and the residue distilled in a Kugelrohr apparatus at 0.4 mbar/170°C. Since the distillate still contained some triphenylphosphine oxide, it was crystallized from 20 ml toluene to give on concentration of the filtrate in two batches 1.29 g (67.5%) of pure **20**, mp 159-161°C. IR (KBr) 1640, 1588, 1360, 1255, 1205, 1065, 980, 730 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.28 (s, 6H), 4.05 (s, 2H), 6.85-6.95 (m, 1H), 7.2-7.3 (m, 5H). Found C, 69.12; H, 6.87; N, 7.36 $C_{11}H_{13}NO_2$ (191.22) requires: C, 69.09; H, 6.85; N, 7.33.

2-(3-Aminophenyl)-Δ^2-oxazoline (21):
To a stirred solution of 1.37 g (10 mmol) 3-aminobenzoic acid **19b**, 0.6 ml ethanolamine and 3.9 ml (40 mmol) CCl_4 in 60 ml abs. acetonitrile-pyridine (1:1) a solution of 7.87 g (30 mmol) triphenylphosphine and 4.5 ml DBU in 100 ml acetonitrile-pyridine (1:1) was added dropwise within 6 h at 24-28°C reaction temperature. After 18 h at 24°C, the solvents were evaporated in vacuo, the residue taken up in 200 ml diethyl ether-100 ml H_2O and the aqueous phase extracted with 3 x 100 ml diethyl ether. After drying (Na_2SO_4) and evaporation, the residue was chromatographed in toluene-ethylacetate (1:1) on a column of 100 g silica gel (containing 40% H_2O). After 650 ml forrun containing the triphenylphosphine oxide, the subsequent 300 ml eluate furnished crude crystalline **21**, which gave on recrystallization from toluene 1.02 g (63%) of pure **21**, mp 125-126°C (lit.[44] 125-126°C). IR (KBr) 1650, 1465, 1085, 955, 730 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 3.85-4.05 (m, 2H), 4.25-4.5 (m, 2H), 6.7-6.9 (m, 1H), 7.10-7.45 (m, 3H). Found: C, 66.84; H, 6.01; N, 17.53 $C_9H_{10}N_2O$ (162.19) requires C, 66.65; H, 6.22; N, 17.27.

2-(3-Pyridyl)-4,4-dimethyl-Δ^2-oxazoline (23):
To a stirred suspension of 2.46 g (20 mmol) nicotinic acid **22**, 14.69 g (56 mmol) triphenylphosphine, 1.9 ml (20 mmol) 2-amino-2,2-dimethylethanol and 22.2 ml (160 mmol) triethylamine in 100 ml abs. acetonitrile, a mixture of 3.9 ml (40 mmol) CCl_4 and 6 ml acetonitrile was added under nitrogen within 10 min at +4°C. After 4 h at +9°C and 18 h at 24°C the precipitate was filtered from triethylamine hydrochloride and the dark brown filtrate evaporated at 30°C in vacuo. The residue was stirred subsequently with 4 x 150 ml portions of hexane. The insoluble residue was dissolved in 150 ml CH_2Cl_2, 350 ml hexane added and the resulting precipitate washed with 100 ml hexane. The pooled and filtered hexane extracts were evaporated and the residue distilled in vacuo to give 2.6 g (73.8%) of pure **23**. IR (Nujol) 1655, 1438, 1355, 1310, 1080, 1040, 710 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.35 (s, 6H), 4.13 (s, 2H), 7.25-7.4 (m, 1H), 8.15-8.25 (m, 1H),

8.65-8.75 (m, 1H), 9.1-9.15 (m, 1H). Found: C, 67.88; H, 7.05; N, 15.60; $C_{10}H_{12}N_2O$ (176.21) requires: C, 68.16; H, 6.86; N, 15.90.

1,4-bis(4,5-Dihydrooxazol-2-yl)benzene (25):
To a stirred suspension of 1.66 g (10 mmol) terephthalic acid **24**, 1.21 ml (20 mmol) ethanolamine, 9.8 ml (70 mmol) triethylamine and 6.79 ml (70 mmol) CCl_4 in 60 ml abs. acetonitrile-pyridine (1:1) a solution of 15.74 g (60 mmol) triphenylphosphine in 60 ml abs. acetonitrile-pyridine (1:1) was added slowly within 4 h at 22-26°C under argon, whereupon the yellow suspension passed into solution. After 20 h over night the dark brown mixture was filtered and the precipitated triethylamine hydrochloride washed with 20 ml acetonitrile-pyridine (1:1). After evaporation of the filtrate in vacuo, the residue was extracted with 3 x 100 ml portions of toluene and the extracts evaporated. The light brown crystalline residue (14 g) was recrystallized from 100 ml isopropanol to give in two portions 1.08 g (50%) of pure **25**, mp 231-233°C (lit.[42] 236-238°C). IR (KBr) 1645, 1420, 1365, 1325, 1250, 1080, 940, 870, 685 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 3.85-4.15 (m, 2H), 4.35-4.6 (m, 2H), 8.0 (s, 4H). Found: C, 66,67; H, 5.56; N, 12.76 $C_{12}H_{12}N_2O_2$ (216.23) requires: C, 66.65; H, 5.59; N, 12.96.

2-(Phenylamino)-Δ^2-oxazoline (27):
To a stirred suspension of 1.8 g (10 mmol) N-phenyl-N'-2-hydroxyethyl-urea **28**, 2.1 ml (15 mmol) triethylamine and 1.94 ml (20 mmol) CCl_4 in 50 ml abs. acetonitrile-pyridine (1:1) was added a solution of 3.93 g (15 mmol) triphenylphosphine in 50 ml abs. acetonitrile-pyridine (1:1) within 3.5 h under argon at 23-27°C. After 20 h at 2°C, the suspension was evaporated in vacuo at 30-35°C and the residue taken up in 200 ml CH_2Cl_2 and 150 ml H_2O, followed by extraction of the H_2O phase with 3 x 50 ml CH_2Cl_2. The combined CH_2Cl_2 phase was extracted with 150 ml of an aqueous phase solution of citric acid (pH=4), and the aqueous phase extracted with 2 x 70 ml CH_2Cl_2 to remove the last traces of triphenylphosphine oxide. The cooled aqueous solution was basified with ice cold 10% NaOH to pH=10 and extracted with 3 x 70 ml CH_2Cl_2. The combined extracts gave after drying (Na_2SO_4) and evaporation 1.42 g crude crystalline **27**, which was recrystallized from 60 ml diethyl ether to give in three crops 1.24 g (76.5%) of pure **27**, mp 119-121°C (lit.[45] 118-119°C). IR (Kbr) 1645, 1560, 1450, 1360, 1330, 1055, 935, 750, 695 cm^{-1}. ^{1}H-NMR (DMSO-D_6, 90 MHz) δ 3.65-3.85 (m, 2H), 4.15-4.35 (m, 2H), 6.8-6.95 (m, 1H), 7.1-7.3 (m, 2H), 7.4-7.6 (m, 1H9, 8.9 (br, NH). Found: C, 66.71; H, 6.20; N, 17.21 $C_9H_{10}N_2O$ (162.19) requires: C, 66.65; H, 6.22; N, 17.27.

2-(2-Acetoxyphenyl)-4,4-dimethyl-Δ^2-oxazoline (29):
To a stirred solution of 1.8 g (10 mmol) 2-O-acetylsalicylic acid **28** 5.6 ml (40 mmol) triethylamine, 0.89 g (10 mmol) 2-amino-2-methyl-1-propanol and 4.8 ml (50 mmol) CCl_4 in 60 ml abs. acetonitrile was added dropwise within 4 h and the yellow-brown reaction mixture kept for 21 h at 22°C. After evaporation in vacuo, the partly crystalline residue was taken up in 300 ml diethyl ether and 150 ml H_2O, the aqueous phase extracted with 3 x 100 ml portions of diethyl ether and the combined diethyl ether phase dried (Na_2SO_4) and concentrated to 100 ml. The precipitated material was filtered and the insoluble substance washed with 20 ml diethyl ether and 50 ml hexane. The combined filtrate was distilled at 0.4 mbar/110°C in a Kugelrohr apparatus to give 1.46 g (62.66%) of slightly yellowish **29**. IR (Nujol) 1730, 1460, 1120, 1070, 740 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.35 (s, 6H), 2.3 (s, 3H), 4.00 (s, 2H), 7.05-7.55 (m, 3H), 7.82-7.95 (m, 1H). MS (CI) 234 (M+1,$C_{13}H_{15}NO_3$=233.26) 216, 192, 176, 138, 114, 77.

2-[1-(6-Methoxy-2-naphthyl)-ethyl]-Δ^2-oxazoline (31a):
To a stirred and cooled (+8°C) suspension of 10 g (43.43 mmol) (S)-(+)-naproxen **30** 2.62 ml (43.43 mmol) ethanolamine, 14.5 ml (150 mmol) CCl_4 and 25.1 ml (180 mmol) triethylamine in 200 ml abs. acetonitrile-pyridine (1:1), a solution of 35.41 g (135 mmol) triphenylphosphine in 200 ml abs. acetonitrile-pyridine (1:1) was added at +8°C→+12°C within 4 h, whereupon everything passed into solution. After 16 h at 24°C, the precipitated triethylamine hydrochloride was filtered and washed with 75 ml abs. acetonitrile. The filtrate was evaporated in vacuo and the crystalline residue taken up in 250 ml CH_2Cl_2 and 150 ml ice cold 2 N NaOH. After extracting the aqueous phase with 2 x 150 ml portions of CH_2Cl_2, the combined CH_2Cl_2-extracts were dried (Na_2SO_4) and evaporated to give 49.5 g crystalline residue. On stirring with 300 ml abs. diethyl ether, the insoluble brown substance was filtered, washed with 75 ml diethyl ether and the combined filtrate concentrated to 75 ml, whereupon further material (triphenylphosphine oxide + colored impurity) separated, which was filtered and washed with 20 ml diethyl ether. The diethyl ether soluble material (14.9 g) was dissolved in 100 ml toluene and chromatographed on a column of 420 g basic Al_2O_3 (A IV). The first 300 ml toluene eluted 0.8 g triphenylphosphine whereas the next 1.5 l toluene eluted ca 10.8 g of crude **31a**, which was recrystallized from ca 150 ml hexane to give in several crops 7.75 g (69.9%) pure **31a**, mp 96.5°C, $[\alpha]_D$=+10.6° (c=1.06; $CHCl_3$). IR (KBr) 1660, 1605, 1270, 1235, 1178, 1060, 1030, 950, 925, 860, 825 cm^{-1}. ^{1}H-NMR (CD_2Cl_2, 90 MHz) δ 1.6 (d, J=6H), 3.7-4.9 (q, J=1H), 7.1-7.8 (m, 6H) MS (CI) 256 (M+1, $C_{16}H_{17}NO_2$=255.30) 185 ($C_{13}H_{13}O$).

2-[1-(6-Methoxy-2-naphthyl)-ethyl]-4,4-dimethyl-Δ^2-oxazoline (31b):
To a stirred suspension of 1.15 g (5 mmol) (S)-(+)-naproxen **30** 0.446 g (5 mmol) 2-amino-2-methyl-1-propanol, 2.8 ml (20 mmol) triethylamine and 1.9 ml (20 mmol) CCl_4 in 50 ml abs. acetonitrile a solution of 3.93 g (15 mmol) triphenylphosphine in 80 ml abs. acetonitrile was added slowly within 3 h at 22-25°C. The clear yellow solution was kept for 20 h at 22°C, then evaporated in vacuo and the crystalline residue stirred for 30 min with 150 ml diethyl ether and 50 ml 2 N NaOH. The phases were separated and the aqueous phase extracted with 3 x 50 ml diethyl ether. The combined diethyl ether phase was washed with with 50 ml sat. NaCl-solution, dried (Na_2SO_4) and evaporated to give 5.7 g residue. After extraction with 30 ml diethyl ether there remained 3.4 g insoluble triphenylphosphine oxide. The diethyl ether extract was evaporated to give 2.3 g crude product, which was dissolved in 15 ml toluene and chromatographed on a column of 110 g basic Al_2O_3 (A IV). Elution with toluene gave 1.3 g crude **31b**, which yielded on recrystallization from 100 ml cyclohexane in two crops 0.953 g (67.3%) pure **31b**, mp 130-132°C, $[\alpha]_D$=+11.6° (c=0.99; $CHCl_3$). IR (KBr) 1665, 1610, 1270, 1235, 1180, 1145, 1055, 1030, 855, 820 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.25 (s, 6H), 1.6 (d, J=7Hz, 6H) 3.85 (q, J=7Hz, 3H)=3.88 (s,3H,$O\underline{CH_3}$),7.1-7.75 (m, 6H). Found; C, 76.55; H, 7.56; N,4.64 $C_{18}H_{21}NO_2$ (283.36) requires: C, 76.29; H, 7.47; N, 4.94.

2-[1-(6-methoxy-2-naphthyl)-ethyl)-Δ^2-oxazine (31c):
1.15 g (5 mmol) (S)-(+)-naproxen **30** was reacted with 3-amino-1-propanol exactly as described for the preparation of **31b** to give 2.4 g crude **33c**, which was chromatographed in toluene on 120 g basic Al_2O_3 (A IV) to give after 50 ml forrun with the subsequent 150 ml eluate 1.39 g crude **31c**. Recrystallization from 15 ml diethyl ether afforded in three crops 0.745 g (55.3%) pure **31c**, mp 112-114°C, $[\alpha]_D$=+32.5° (c=1.07, $CHCl_3$). IR (KBr) 1655, 1605, 1270, 1260, 1230, 1218, 1155, 1030, 860, 820 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.45 (d,J=7Hz, 3H), 1.6-1.9 (m, 2H), 3.4 (tr, J=6Hz, 2H), 3.6 (q, J=7Hz, 1H), 3.8 (s, 3H), 4.0 (tr, J=6Hz, 2H), 6.9-7.7 (m, 6H). Found: C, 75.84; H, 7.47; N, 4.92 $C_{17}H_{19}NO_2$ (269.33) requires C, 75.81; H, 7.11; N, 5.20.

2-[4-(4-chlorphenyl)-1-(4-fluorophenyl)-3-pyrazoyl-methyl]-Δ^2-oxazoline (33):
To a stirred suspension of 1.984 g (6 mmol) pyrazolac **32**, 0.36 ml (6 mmol) ethanolamine, 4.18 ml (30 mmol) triethylamine and 1.93 ml (20 mmol) CCl_4 in 100 ml abs. acetonitrile a solution of 4.72 g (18 mmol) triphenylphosphine in 70 ml abs. acetonitrile was added at 22-25°C within 3.5 h. After 3 days at 22°C the solvent was evaporated in vacuo and the yellow crystalline residue worked up with 120 ml diethyl ether and 70 ml 2N NaOH. After extraction and reextraction with diethyl ether, the combined diethyl ether phase was washed with 25 ml sat. NaCl-solution, dried (Na_2SO_4) and evaporated. The yellowish crystalline residue (7.6 g) was extracted with diethyl ether to give 2.8 g crystalline triphenylphosphine oxide. The resulting crude ethersoluble product (4.8 g) was dissolved in 20 ml toluene-ethylacetate (9:1) and chromatographed with this solvent mixture on a column of 200 g SiO_2 (40% H_2O). After a forrun of ca. 1.5 l yielding 0.25 g unreacted triphenylphosphine, the next 1.2 l afforded 0.958 g (44.9%) of crystalline **33**, which was obtained analytically pure on recrystallization from 150 ml cyclohexane, mp 126-128°C. Further elution with 1.5 l toluene-ethylacetate (9:1) afforded 0.6 g (26.8%) of the corresponding N-(2-hydroxyethyl)-amide of **33**. IR (KBr) 1670, 1555, 1520, 1485, 1215, 1005, 985, 835 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 3.7-3.9 (m, 4H), 4.1-4.4 (m, 2H), 7.05-7.4 (m, 6H), 7.55-7.75 (m, 2H), 7.9 (s, 1H). Found: C, 64.56; H, 4.49; N, 11.66 $C_{19}H_{15}ClFN_3O$ (355.81) requires: C, 64.14; H, 4.25; N, 11.81.

2-[2-(2,6-Dichloroanilino)-benzyl)-Δ^2-oxazoline (35):
To a stirred suspension of 1.59 g (5 mmol) dichlofenac sodium **34**, 0.305 g (5 mmol) ethanolamine, 28 ml (20 mmol) triethylamine and 1.9 ml (20 mmol) CCl in 70 ml abs. acetonitrile, a solution of 3.93 g (15 mmol) triphenylphosphine in 80 ml abs. acetonitrile was added slowly within 5 h at 23-26°C. After 22 h at 23°C the clear solution was worked up with 200 ml toluene and 100 ml ice cold 2 N NaOH and the concentrated toluene extract (40 ml) chromatographed on a column of 200 g basic Al_2O_3 (A IV) to give after 100 ml forrun with the following 150 ml toluene 1.12 g (69.7%) of crude crystalline **35**, which furnished on recrystallization from 30 ml ethanol in two crops 0.823 g (53%) of analytically pure **35**, mp 141°C. IR (KBr) 1660, 1510, 1455, 1305, 1150, 745 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 3.75 (s, 2H), 3.8-3.95 (m, 2H), 4.15-4.4 (m, 2H), 6.5-6.65 (m, 1H), 6.9-7.5 (m, 6H). Found: C, 59.68; H, 4.56; N, 8.44 $C_{16}H_{14}Cl_2N_2O$ (321.22) requires: C, 59.83; H, 4.39; N, 8.72.

2-([1-(4-Isobutylphenyl)-ethyl]-Δ^2-oxazoline (37):
To a stirred solution of 1.237 g (6 mmol) racemic ibuprofen **36**, 0.36 ml (6 mmol) ethanolamine, 3.5 ml (25 mmol) triethylamine and 1.93 ml (20 mmol) CCl_4 in 50 ml abs. acetonitrile a solution of 4.72 g (18 mmol) of triphenylphosphine in 70 ml abs. acetonitrile was added within 3.5 h at 22-26°C. After 18 h at 22°C evaporation and workup with diethyl ether-ice cold 2 N NaOH there was obtained 6.4 g crude product, which gave on extraction with 100 ml boiling diethyl ether in two crops 4.5 g triphenylphosphine oxide. The remai-

ning 1.9 g were chromatographed in toluene-ethylacetate (9:1) on a column of 80 g SiO_2 (40% H_2O) to give after a forrun of 250 ml subsequently 1.18 g (84.9%) pure oily **37**. IR (Nujol) 1660, 1515, 1470, 1370, 1240, 1170, 1080, 955, 915, 855 cm^{-1}. ^1H-NMR ($CDCl_3$, 90 MHz) δ 0.85-0.95 (d, J=6H), 1.48-1.58 (d, J=3H), 1.6-2.2 (m, 1H), 2.4-2.55 (d, 2H), 3.55-3.95 (m, 3H), 4.05-4.35 (m, 2H), 7.1-7.25 (m, 4H). Found: C, 77.87; H, 9.50; N, 6.02 $C_{15}H_{21}NO$ (231.0) requires C, 77.88; H, 9.15; N, 6.05.

2-(3'-Trifluoromethyldiphenylamino)-Δ^2-oxazoline (39):
To a stirred solution of 1.406 g (5 mmol) flufenamic acid **38**, 0.305 g (5 mmol) ethanolamine, 2.8 ml (20 mmol) triethylamine, 1.9 ml (20 mmol) CCl_4 in 60 ml abs. acetonitrile, a solution of 3.93 g (15 mmol) triphenylphosphine in 80 ml abs. acetonitrile was added at 22-25°C within 3 h. After 20 h at 22°C the reaction mixture was evaporated, worked up with 150 ml diethyl ether-70 ml ice cold 2 N NaOH. The diethyl ether extracts gave after drying (Na_2SO_4) and concentration to 50 ml crystalline triphenylphosphine oxide. The filtrate was evaporated, the residue (3.1 g) dissolved in 20 ml toluene and chromatographed in toluene on a column of 120 g basic Al_2O_3 (A IV) to give with the first eluate 1.02 g (66.6%) pure **39**. IR (Nujol) 1635, 1585, 1455, 1335, 1240, 1115, 1125, 1055, 950, 750, 700 cm^{-1}. ^1H-NMR ($CDCl_3$, 90 MHz) δ 4.0-4.5 (m, 4H), 6.75-6.95 (m, 1H), 7.2-7.5 (m, 4H), 7.8-8.0 (d, 1H), 10.5 (s, NH). Found: C, 63.02; H, 4.33; N, 8.93 $C_{16}H_{13}F_3N_2O$ (306.3) requires: C, 62.74; H, 4.28; N, 9.15.

2-Chloro-4-(2-furylmethylamino)-5-(Δ^2-oxazolin-2-yl)-benzene sulfonamide (41) and 2-chloro-4-(2-furylmethylamino)-5-(Δ^2-oxazolin-2-yl)benzene sulfone triphenylphosphine-imine (42):
To a stirred solution of 2.6 g (5 mmol) furosemide **40**, 0.305 g (5 mmol) ethanolamine, 2.1 ml (15 mmol) triethylamine and 1.9 ml (20 mmol) CCl_4 in 50 ml abs. acetonitrile-pyridine (1:1) a solution of 4.93 g (15 mmol) triphenylphosphine in 60 ml abs. acetonitrile-pyridine (1:1) was added within 5 h at 23-25°C. After 18 h at 23°C and evaporation in vacuo, the residue was taken up in 150 ml CH_2Cl_2-75 ml ice cold 2 N NaOH and the combined CH_2Cl_2 extracts dried (Na_2SO_4) and evaporated. The 6.3 g residue were dissolved in ca. 50 ml warm toluene and chromatographed in toluene on a column of 240 g silica gel (40% H_2O). After ca. 1 l forrun, the subsequent 700 ml eluted 1.05 g (59%) colorless crystals, which were recrystallized from 50 ml ethylacetate to give in two crops 0.86 g pure **41**, mp 187-188°C. IR (KBr) 1635, 1580, 1330, 1280, 1240, 1160, 1070, 930, 745, 685 cm^{-1}. ^1H-NMR (DMSO-D_6, 90 MHz) δ 3.95-4.5 (m, 4H), 4.55-4.65 (d, 2H), 6.25-6.45 (m, 2H), 7.1 (s, 1H), 7.32 (s, 2H), 7.6-7.65 (m, 1H), 8.22 (s, 1H), 9.25-9.5 (tr, NH). Found: C, 47.48; H, 3.95; N, 12.13 $C_{14}H_{14}ClN_3O_4S$ (355.81) requires: C, 47.26; H, 3.97; N, 11.81.
On utilizing a fourfold excess (5.23 g = 20 mmol) of triphenylphosphine and workup with CH_2Cl_2-150 ml ice cold H_2O evaporation of the collected and dried (Na_2SO_4) CH_2Cl_2-extracts gave a crude product, which crystallized on dissolving in ethylacetate to give in two crops 0.78 g (25%) of **42**, mp 216°C. The mother liquor contained acc. to t. l. c. in toluene-ethylacetate (1:1) still further amounts of **42** besides triphenylphosphine oxide and the oxazoline **41** . IR (KBr) 1635, 1580, 1440, 1280, 1245, 1220, 1060, 930, 720, 690, 600, 530, 510 cm^{-1}. ^1H-NMR ($CDCl_3$, 90 MHz) δ 4.9-4.35 (m, 4H), 4.35-4.45 (d, 2H), 6.15-6.35 (m, 2H), 6.6 (s,1 H), 7.2-7.85 (m, 17H), 8.95-9.15 (tr, NH). Found: C, 63.33; H, 4.57; N, 6.70, Cl, 5.98 $C_{32}H_{27}ClN_3O_4PS$ (616.08) requires: C, 62.38; H, 4.42; N, 6.82; Cl, 5.76.

2-Phenoxy-3-n-butylamino-5-(Δ^2-oxazolin-2-yl)-benzenesulfonamide (44):
To a stirred solution of 1.82 g (0.05 mmol) bumetanide **43** 0.305 g (5 mmol) ethanolamine, 1.9 ml (20 mmol) CCl_4 and 2.1 ml (15 mmol) triethylamine in 50 ml abs. acetonitrile-pyridine (1:1) a solution of 1.52 g (15 mmol) triphenylphosphine in 50 ml abs. acetonitrile-pyridine (1:1) was added dropwise within 5 h at 23-25°C, whereupon a colorless compound crystallized from the yellow reaction mixture. Since there was still some bumetanide **43** present, a mixture of 0.276 ml (2 mmol) triethylamine and of 0.524 g (2 mmol) triphenylphosphine in 15ml abs. acetonitrile-pyridine (1:1) was added within 2.5 h, whereupon the starting material **43** had disappeared and a side product (triphenylphosphine imidosulfone?) had increased. After evaporation in vacuo at 35°C and workup with 200 ml CH_2Cl_2 and 150 ml sat. ice cold $NaHCO_3$-solution, the combined CH_2Cl_2-extracts were dried (Na_2SO_4) and evaporated to give 7.18 g orange colored crystalline residue, which was chromatographed in toluene-ethylacetate 9:1 and 8:2 on a column of 150 g silica gel (40% H_2O) to give 1.55 g (79.6%) crude **44**, which afforded on recrystallization from 50 ml ethylacetate in two crops 1.05 g (55.3%) analytically pure **44**, mp 202-204°C. IR (KBr) 1650, 1605, 1590, 1492, 1220, 1200, 1160, 750, 600 cm^{-1}. ^1H-NMR (DMSO-D_6, 90 MHz) δ 0.7-0.9 (m, 3H); 0.95-1.5 (m, 4H); 2.9-3.2 (q, $\underline{CH_2}$-NH); 3.85-4.15 (m, $\underline{CH_2}$N); 4.3-4.6 (m, $\underline{CH_2}$O); 4.9-5.1 (tr, NH); 6.8-7.4 (m, 6H); 7.6-7.65 (d, 1H). Found: C, 58.50; H, 5.86; N, 10.72; S, 8.51 $C_{19}H_{23}N_2O_4S$ (389.48) requires: C, 58.59; H, 5.95; N, 10.79; S, 8.23.

17β-(Δ^2-Oxazoline-2-yl-carbonyl)-6α-fluoro-(11β-hydroxy-16α-methyl-1,4-andra-1,4-diene-3-one (46b) and N-(2-chloroethyl)-6α-fluoro-11-β-hydroxy-16α-methyl-3,20-pregna-1,4-diene-3-one-21-amide (46a):
To a solution of 1.17 g (3 mmol) 6α-fluoro-11β-hydroxy-16α-methyl-3,20-dioxo-pregna-1,4-diene-

3-one-21-oic acid **45**, 0.183 g (3 mmol) abs. ethanolamine, 1.35 ml (9 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) and 1.54 g (10 mmol) CCl_4 in 40 ml abs. acetonitrile-pyridine (1:1) a solution of 2.36 g (9 mmol) triphenylphosphine in 40 ml abs. acetonitrile-pyridine (1:1) was added within 4 h at 20-23°C: After 16 h at 21°C the solvents were evaporated in vacuo at 35°C, the residue dissolved in 30 ml toluene-ethylacetate (2:1) and rapidly chromatographed on a column of 250 g silica gel (40% H_2O). After 4 l forrun, the subsequent 700 ml eluted 0.341 g (27.5%) crude **46b**, which was recrystallized from toluene to give 0.275 g **46b** as a toluene solvate, mp 117-121°C. Recrystallization from methanol furnished pure **46b**, mp 255°C. IR (KBr) 1705, 1655, 1635, 1235, 1045, 990, 970, 900, 825, 735 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 0.9-1.9 (m), 3.1-3.2 (d, H_{17}), 3.9-4.5 (m, 4H), 4.9-5.15 (m, H_6), 5.45.5.7 (m, H_6), 6.2-6.35 (m, 2H), 7.3 (m, H_1). Found: C, 73.30; H, 7.99; N, 2.22 $C_{24}H_{30}FNO_4$ (415.5) x C_7H_8 requires: C, 73.35; H, 7.54; N, 2.76.
On performing the same reaction employing 0.433 g (1 mmol) **45** with triethylamine instead of DBU, workup and chromatography of the crude residue (1.01 g) in toluene-ethylacetate 95:5 and 90:10 and finally 1:1 on a column of 50 g basic Al_2O_3 (A IV), the toluene-ethylacetate 1:1 mixture eluted 0.397 g (95.6%) of crude **46a**, which gave on recrystallization from 90 ml diethyl ether 0.170 g of pure **46a**, mp. 197-199°C. IR (KBr) 1688, 1660, 1622, 1600, 1528, 1450, 1120, 1050, 900, 822cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) 0.9-1.9 (m), 3.15-3.3 (d, C_{17}-H), 3.65-3.7 (m, CH_2-NH), 4.3-4.5 (m, C_{11}-H, 4.9-5.3+5.45-5.75 (m, C_6-H), 6.2-6.35 (m, 3H), 7.15 (m, C_1-H). Found: C, 63.79; H, 6.95; N, 3.10 $C_{24}H_{31}ClFNO_4$ (451.96) requires: C, 63.78; H, 6.91; N, 3.10.

(5Z,13E)-(8R,9S,11R,12R,15S)-2-(Δ^2-Oxazoline-2-yl)-1-nor-5,13-prostadiene-9,11,15-triol (48a):
To a stirred emulsion of 0.177 g (0.5 mmol) $PGF_{2\alpha}$ **47**, 0.5 mmol ethanolamine, 0.7 ml (5 mmol) triethylamine and 0.5 ml (5 mmol) CCl_4 in 15 ml abs. acetonitrile a solution of 0.655 g (2.5 mmol) triphenylphosphine in 15 ml abs. acetonitrile was added within 8 h at 20-22°C. After 20 h at 22°C the acetonitrile was evaporated in vacuo at 30-35°C, the residue worked up with 20 ml ethylacetate-15 ml ice cold H_2O. The combined ethylacetate extracts were dried (Na_2SO_4) and evaporated to give 1.03 g colored, partly crystalline residue, which was dissolved in 10ml ethylacetate (sat. with H_2O) and chromatographed on a column of 25 g basic Al_2O_3 (A IV) eluting with ethylacetate sat. with H_2O. After 150 ml forrun containing 0.71 g triphenylphosphine oxide, the subsequent 125 ml ethylacetate eluted 0.127 g (66.9%) slightly colored oily **48a**. IR (Nujol) 1660, 1455, 1236, 992, 965, 788, 760 cm^{-1}. ^{1}H-NMR (DMSO-D_6, 90 MHz) δ 0.8-2.4 (m), 3.5-4.3 (m), 5.2-5.5 (m, 4H). MS (EI) 379 ($M^{\oplus}$, $C_{22}H_{37}NO_2$ = 379.54) 362, 361 (M-H_2O), 343 (361-H_2O), 325 (343-H_2O), 308, 192, 98, 85.

(5Z,13E)-(8R,9S,11R,12R,15S)-2-(4,4-Dimethyl)-Δ^2-oxazoline-2-yl)-1-nor-5,13-prostadiene-9,11,15triol (49b):
0.177 g (0.5 mmol) $PGF_{2\alpha}$ **47** were suspended and heated for 2 h in 5 ml hexamethyldisilazane (HMDS) to 140°C oil bath temperature. After evaporation of the excess HMDS in vacuo at 0.2 mbar/40°C the oily residue was dissolved in 5 ml abs. acetonitrile containing 0.5 ml (0.5 mmol) 2-amino-2-methyl-1-propanol, 0.56 ml triethylamine and 0.525 g (2 mmol) triphenylphosphine and finally 2 mmol CCl_4 solution in 2 ml abs. acetonitrile added at 0°C. After 18 h warming up to 24°C, there had only ca 25-30% **48b** formed besides the intermediate amide. After cooling to 0°C, 1 mmol 2-amino-2-methyl-1-propanol, 4 mmol triethylamine as well as 1 mmol triphenylphosphine were added and the reaction mixture again kept for 72 h at 23°C. After evaporation in vacuo at 25°C, the residue (0.32 g) was treated for 1 h with 10 ml methanol and 5 ml 2 N NaOH, the methanol evaporated in vacuo and H_2O and ethylacetate added. The combined ethylacetate extracts were dried (Na_2SO_4) and evaporated. The crude **48b** containing still triphenylphosphine and triphenylphosphine oxide was purified by präparative t. l. c. on silica plates (20 x 20 cm) with $CHCl_3$-MeOH (9:1) to give 0.169 g (82.9%) **48b** containing still traces of the amide. Repeated präparative t. l. c. furnished 0.098 g analytically pure **51b**. IR (Nujol) 1665, 1460, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz). 0.8-2.4 (m), 3.2-4.3 (m), 4.7 (s), 5.2-5.6 (m), MS (EI) 407 ($M^{\oplus}$, $C_{24}H_{41}NO_4$ = 407.59), 389 (M-18), 371 (M-2H_2O), 336 (M-C_5H_{11}), 317 (336-18), 180, 126, 113.

(5Z,13E)-(8R,9S,11R,12R,15S)-2-(Δ^2-Thiazoline-2-yl)-1-nor-5,13-prostadiene-9,11,15-triol (48c):
0.177 g (0.5 mmol) $PGF_{2\alpha}$ **47** was silylated for 3 h at 140°C with 5 ml hexamethyldisilazane (HMDS) evaporated in vacuo and the residue dissolved with 0.057 g (0.5 mmol) β-mercaptoethylamine 0.7 ml (5 mmol) triethylamine and 0.384 g (2.5 mmol) CCl_4 in 15 ml abs. acetonitrile. A solution of 0.577 g (2.2 mol) triphenylphosphine in 20 ml abs. acetonitrile was added with stirring within 2.5 h at 24-26°C. After 18 h at 23°C and evaporation in vacuo, the redbrown crystalline residue was extracted with 3 x 50 ml pentane. On evaporation the residue (0.3 g) was stirred for 1 h with 15 ml methanol-2 N NaOH (2:1). After removal of the solvents the residue was treated with CH_2Cl_2-H_2O. The combined CH_2Cl_2-extracts were dried (Na_2SO_4) and evaporated. The residual 0.20 g were purified on präparative silica plates (20 x 20 cm) with $CHCl_3$-CH_3OH (9:1) to give 0.113 g (57%) light brownish **48c**. IR (Nujol) 1620, 1455, 1435, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 0.8-2.3 (m), 3.1-3.3 (m), 3.8-4.3 (v), 5.2-5.55 (m). MS (EI) 395 ($M^{\oplus}$, $C_{22}H_{37}NO_3S$=395.61) 378, 352, 338, 324, 294, 186, 182, 168, 154, 141, 114, 101.

(1S,5R,66,7R)-3-[(1R,S)-1-Bromo-4-(Δ^2-oxazolin-2-yl)-butyl]-6-[(E)-(3S)-3-hydroxy-1-octenyl]-2-oxabicyclo[3.3.0]octane-7-ol (50):
To a stirred suspension of 0.216 g (0.5 mmol) bromo-ether **49**,[25] 31 mg (0.5 mmol) ethanolamine, 0.7 ml (5 mmol) triethylamine and 0.5 ml (5 mmol) CCl_4 in 10 ml abs. acetonitrile, a solution of 0.655 g (2.5 mmol) triphenylphosphine in 15 ml abs. acetonitrile was addded within 8 h. After 20 h at 23°C, evaporation in vacuo and workup with 20 ml ethylacetate and 10 ml 2 N NaOH, the combined ethylacetate phase was dried (Na_2SO_4) and concentrated to 5 ml. After keeping over night at +4°C, the precipitated triphenylphosphine oxide was filtered and the concentrated filtrate (0.76 g) separated on präparative silica plates with ethylacetate-methanol 9:1 to give 0.125 g (54.4%) of **50**. IR (Nujol) 1665 cm^{-1}. ^{1}H-NMR (DMSO-D_6, 90 MHz) δ 1.1-2.4 (m), 3.6-4.8 (m), 5.35-5.55 (m, H_{13}+H_{14}). MS (CI) 459 (m+1) 458 ($M^{\oplus}$, $C_{22}H_{36}BrNO_4$=458.4), 442, 396, 378, 360, 279.

(1S,5R,6R,7R)-6-[(E)-(3S)-3-Hydroxy-1-octenyl]-3-[(E)-4-(Δ^2-oxazoline-2-yl)-butylidene]-2-oxabicyclo-[3.3.0]octane-7-ol (51):
On treatment of 0.125 g (0.27 mmol) **50** in 5 ml toluene for 8 h at 60-65°C with 0.26 ml (1.7 mmol) DBU, the mixture turned brown. After cooling and dilution with 20 ml toluene, the mixture was extracted with 5 x 15 ml ice-water. After drying (Na_2SO_4) of the toluene-phase and evaporation the 0.079 g residue were purified with ethylacetate-methanol 9:1 on präparative t. l. c. to give 0.043 g (42.3%) of pure **51**. IR (film) 1660, 1455, 1435, 1235, 1130, 1080, 1050, 965 cm^{-1}. ^{1}H-NMR (pyridine-D_6, 90 MHz) δ 0.8-2.8 (m), 3.6-5.1 (m), 5.85-6.05 (m, H_{13}+H_{14}) MS (CI) 378 (M + 1, $C_{22}H_{35}NO_4$=377.51) 279, 259, 171, 153, 110, 78.

(1S,2R,3R,5S)-2-[(E)-(3S,4RS)-3-Hydroxy-4-methyl-1-octen-6-ynyl]-7-[(E)-4-(2-oxazoline-2-yl)-butylidene]-bicyclo[3.3.0]octane-1-ol (53):
To a stirred solution of 0.110 g (0.3 mmol) iloprost **52**, 0.4 ml (3 mmol) abs. triethylamine, 0.3 mmol ethanolamine and 0.3 ml (3 mmol) CCl_4 in 10 ml abs. acetonitrile-pyridine (1:1) a solution of 0.3939 (1.5 mmol) triphenylphosphine in 10 ml abs. acetonitrile-pyridine (1:1) was added within 3.5 h. Afer 18 h at 23°C, evaporation and workup with CH_2Cl_2-ice cold 2 N NaOH, the residue (0.680 g) was chromatographed in ethylacetate on a column of 30 g Al_2O_3 (basic, A IV) to give on elution with ethylacetate-isopropanol (9:1) 0.68 g (58.8%) of pure iloprost-Δ^2-oxazoline **53**. IR (film) 1660, 1455, 1430, 1370, 1240, 1090, 990, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.8-2.5 (m), 3.65-4.3 (m), 5.1-5.3 (m, H_{15}), 5.4-5.55 (m, H_{13}, H_{14}). MS (CI) 386 (M+1, $M^{\oplus}$, $C_{24}H_{34}NO_3$=385.53) 378, 376, 368, 341, 296, 279, 161, 134, 105, 79, 74.

(4S,5S)-2-(4-Nitrophenyl)-4-carbomethoxy-5-methyl-Δ^2-oxazoline (72) and methyl 2-(4-nitrobenzoylamido)-3-chlorobutyrate (73):
To a stirred suspension of 1.69 g (10 mmol) L-threonine methylester hydrochloride **71** in 60 ml abs. CH_2Cl_2, 1.26 ml abs. N-ethylmorpholine in 10 ml abs. CH_2Cl_2 was added slowly at 20°C within 10 min, whereupon a clear solution formed. On subsequent addition of 1.67 g (10 mmol) of p-nitrobenzoic acid **70** and 5.21 g (22 mmol) hexachloroethane a colorless salt precipitated. To this suspension a solution of 5.77 g (22 mmol) triphenylphosphine and 5.6 ml (44 mmol) of abs. N-ethylmorpholine in 50 ml abs. CH_2Cl_2 was added gradually within 4 h at 22-24°C. After 72 h at 23°C and workup of the dark red reaction mixture with ice cold sat. NaCl solution, the collected CH_2Cl_2-extracts were dried (Na_2SO_4) and evaporated to give 11.3 g orange-colored crystalline residue. Extraction with 3 x 50 ml diethyl ether afforded 6.8 g extract and residual crystalline triphenylphosphine oxide. The extract was dissolved in CH_2Cl_2 and chromatographed in CH_2Cl_2 on a column of 130 g silica gel (40% H_2O) to give after 400 ml forrun with the next 250 ml 1.05 g (34.8%) of the crystalline chloroamide **73**, mp 94-96°C followed on further elution by 1.37 g (51.9%) of crystalline **72**, mp 69.6°C (diethyl ether) $[\alpha]_D$-0.2°(c=1.015, $CHCl_3$) IR (KBr) 1755, 1643, 1520, 1342, 1202, 1187, 1080, 1035, 875, 852, 710 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.42 (d, 3H), 3.8 (s, 3H). Found: C, 54.67; H, 4.58; N, 10.70 $C_{12}H_{12}N_2O_5$ (264.23) requires: C, 54.54; H, 4.58; N, 10.60.
73 $[\alpha]_D$=+66.2° (c=0.53, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.72 (d, 3=7Hz, 3H), 3.9 (s, 3H), 4.45-4.55 (m, 1H), 5.01-5.06 (m,1H), 7.98-8.04 (m,2H), 8.31-8.36 (m, 2H), MS (CI) 318 (M + NH_3) 301 ($M^{\oplus}$, $C_{12}H_{13}N_2O_5Cl$ =300.7), 271, 265, 235, MS (EI) 265, 241, 237, 205, 167, 150, 134, 120, 104, 92, 76, 63, 50.

(4S,5R)-2-(4-Nitrophenyl)-4-carbomethoxy-5-methyl-Δ^2-oxazoline (75):
To a stirred suspension of 1.69 g (10 mmol) L-allo-threonine methylester hydrochloride **74** (Bachem AG, Switzerland) in 60 ml abs. CH_2Cl_2 a solution of 1.26 ml (10 mmol) of abs. N-ethylmorpholine in 10 ml abs. CH_2Cl_2, was added within 15 min. Then 1.67 g (10 mmol) neat p-nitrobenzoic acid **73** and 5.21 g (22 mmol) neat hexachloroethane was added followed within 3 h by a solution of 6.57 g (25 mmol) triphenylphosphine and 7.56 ml (60 mmol) N-ethylmorpholine in 60 ml abs. CH_2Cl_2 at 20-25°C. After 18 h at 23°C, there were still traces of another product. Thus 0.47 g (2 mmol) hexachloroethane in 10 ml abs. CH_2Cl_2 followed by 2.5 ml (20 mmol) N-ethylmorpholine in 10 ml abs. CH_2Cl_2 were added within 10 min and the reaction mixture worked up with 120 ml ice cold sat. NaCl-solution. The collected and dried (Na_2SO_4) CH_2Cl_2-extracts gave

11.8 g brown residue, which was boiled with 3 x 100 ml methyl-ther to afford 5.3 g light brown partly crystalline residue. Chromatography in CH_2Cl_2 on a column of 120 g silica gel (40% H_2O) gave after a forrun of 300 ml, 2.18 g (82.6%) of crystalline **75**, which furnished on recrystallization from methyl-t.butyl ether the analytical sample, mp 69-71°C. IR (KBr) 1755, 1730, 1520, 1345, 1200, 1085, 1025, 870, 695 cm^{-1}. ^1H-NMR ($CDCl_3$, 500 MHz) δ 1.57 (d, J=7Hz, 3H), 3.84 (s, 3H), 8.25-8.90 (m, 2H). MS (EI) = 264 ($M^{\oplus}$), 205 (M+1-$COOCH_3$). Found: C, 54.73; H, 4.49; N, 10.63 $C_{12}H_{12}N_2O_5$ (264.27) requires: C, 54.54; H, 4.58; N, 10.60.

Acknowledgements: We are obliged to Drs. D. Rosenberg and G. Michl for the measurements and interpretation of the NMR- and MS-spectra and especially to Mrs. M. Golde for competently and patiently writing and rewriting the English text.

REFERENCES

(1) Vorbrüggen,H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471-4474.

(2) Bodor, N.; Miller J. H. *Drugs of the Future* **1981**, *VI*, 165-182. *Prodrugs, Topical and Ocular Drug Delivery. Drugs and the Pharmac. Sci.*, Vol. **53**. Edited by K. B. Sloan, M. Dekker N. Y. 1992.

(3) Frump, J. A. *Chem. Rev.* **1971**, *71*, 483.

(4) (a) Toya Y.; Takagi M.; Kondo, T.; Nakata, H.; Isobe; M., Goto,T *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2604-2610. (b) White E. H.; McCapra F.; Field, G. F.; McElroy, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 2402-2403. (c) Bergeron, R. J.; Manis, J. S.; Dionis, J. B.; Garlich J. R. *J. Org. Chem.* **1985**, *50*, 2780-2782. (d) Hamada, Y.; Kato, S.; Shiori, T. *Tetrahedron Lett.* **1985**, *26*, 3223-3226. (e) Wipf, P.; Miller, Ch. P. *J. Am. Chem. Soc.* **1992**, *114*, 10975-10977. (f) Naegeli, H.-U.; Zähner,H. *Helv. Chim. Acta* **1980**, *63*, 1400-1406. (g) Cox, Ch. D.; Rinehart, Jr.,K. L.; Moore, M. L.; Cook, Jr., J. C. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 4256-426. (h) Jansen, R.; Kunze, B.; Reichenbach, H.; Jurkiewicz, E.; Hunsmann, G.; Höfle, G. *Liebigs Ann. Chem.* **1992**, 357-359. (i) Peterson, T.; Falk, K.-E.; Leong, S. A.; Klein, M. P.; Neilands, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 7715-7718. (j) Michael, J. P.; Pattenden, G. *Angew. Chem.* **1993**, *105*, 1-24. (k) Genet, J.-P.; Thorimbert, S.; Touzin, A.-M. *Tetrahedron Lett.* **1993**, *34*, 1159-1162. (l) Nagao, Y.; Miyasaka, T.; Hagiwara, Y.; Fujita, E. *J. Chem. Soc. Perkin Trans. I* **1984**, 183-187.

(5) (a) Meyers, A. I.; Mihelich, E. D. *Angew. Chem.***1976**, 321-332. (b) Meyers A. I. *J. Am. Chem. Soc.* **1978**, *11*, 375-381. (c) Reumann, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837-860. (d) Maryanoff, B.E. *The Chem. of Heterocycl. Comp.* **1986**, *45*, 963-1017; Editors: Weissberger, A.; Taylor, E. C.. (e) Meyers, A. I.; Durandetta,J. L. *J. Org. Chem.* **1975**, *40*, 2021-2029.

(6) (a) Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499-507. (b) Brunner, H.; Obermann, U.; Wimmer, P. *Organometallics* **1989**, *8*, 821-826. (c) Balavoine, G.; Clinet, J. C.; Lellouche, I. *Tetrahedron Lett.* **1989**, *30*, 5141-5144. (d) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846-848. (e) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005-6008. (f) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232-240. (g) Helmchen, G.; Krotz, A.; Ganz, K.-T.; Hansen, D. *Synlett* **1991**, 257-259. (h) Evans, D. A.; Woerpel, K. A.; Hinmann, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726-728.

(7) Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787-2793.

(8) Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, Jr., A. L.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497-501.

(9) (a) Schmidt, R. R. *Synthesis* **1972**, 333-350. (b) Kato, T.; Katagiri, N. *Heterocycles* **1980**, *14*, 1333-1401.

(10) Le Perchec, P. *Janssen Chim. Acta* **1986**, *4*, 3-17.

(11) Elderfield, R. C. *Heterocyclic Compounds* Vol. 5, 679-685.

(12) Wenker, H. *J. Am. Chem. Soc.* **1935**, *57*, 1079-1080.

(13) Lee, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 3440-3441.

(14) Appel, R.; Kleinstück, R. *Chem. Ber.* **1974**, *107*, 5-12.

(15) Appel, R.; Kleinstück, R.; Ziehn, K. D.; Knoll, F. *Chem. Ber.* **1970**, *103*, 3631-3639.

(16) Independent of us M. J. Miller, P. G. Mattingly, M. A. Morrison, and J. F. Kerwin, Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026-7032 reported on the cyclization of N(2-hydroxyethyl)amides with triphenylphosphine, CCl_4 and triethylamine to the corresponding Δ^2-oxazolines.

(17) Rabinowitz, R.; Marcus, R. *J. Am. Chem. Soc.***1962**, *84*, 1312-1313.

(18) Appel, R.; Schöler, H. *Chem. Ber.* **1977**, *110*, 2382-2384.
(19) Appel, R. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801-812.
(20) Dagani, M. J. *US-Pat. 3 624 159, C. A.* **1972**, *76*, 463 047.
(21) Higginbottom, R.; Suschitzky, H. *J. Chem. Soc.* **1962**, 2367-2370.
(22) (a) Seha, Z.; Weis, C. D. *Helv. Chim. Acta* **1980**, *63*, 413-419. (b) Doise, M.; Blondeau, D.; Sliwa, H. *Synth. Comm.* **1992**, *22*, 2891-1901.
(23) Appel, R.; Warning, K.; Ziehn, K.-D. *Liebigs Ann. Chem.* **1975**, 406-409.
(24) We thank Dr. I. Böttcher (present adress: Ciba-Geigy AG, Basel, Switzerland) for all the biological investigations with NSAID's.
(25) Tömösközi, I.; Galambos, G.; Simondesz, V.; Kovâcz, G. *Tetrahedron Lett.* **1977**, *18*, 2627-2630.
(26) Skuballa, W.; Vorbrüggen, H. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 1046.
(27) Skuballa, W.; Radüchel, B.; Vorbrüggen, H. *Tetrahedron Lett.* **1988**, *29*, 4285-4288.
(28) Vorbrüggen, H.; Krolikiewicz, K. *Helv. Chim. Acta* **1993**, *76*, 819.
(29) Vorbrüggen, H.; Bohn, B. D.; Krolikiewicz, K. *Tetrahedron* **1990**, *46*, 3489-3502.
(30) Vorbrüggen, H.; Krolikiewicz, K. *Chem. Ber.* **1975**, *108*, 2137-2148.
(31) Kodaka, M.; Tomohiro, T.; Okuno, H. *J. Chem. Soc. Chem. Comm.* **1993**, 81-82.
(32) For ^{1}H-NMR-spectra and coupling constants of the related 3-phenyl-Δ^2-isoxalines compare Binsch, G.; Huisgen, R.; König, H. *Chem. Ber.* **1964**, *97*, 2893-2902.
(33) Meyers, A. I.; Hoyer, D. *Tetrahedron Lett.* **1985**, *26*, 4687-4690.
(34) Misunobu, O. *Synthesis* **1981**, 1-28.
(35) (a) Hendrickson, J.B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, 277-280. (b) Aaberg,A.; Gramstad, T.; Huseby, S. *Tetrahedron Lett.* **1979**, 2263-2264. (c) Ramos, S.; Rosen, W. *Tetrahedron Lett.* **1981**, *22*,35-38.
(36) Mukaiyama, T. *Angew. Chem. Int. Ed. Eng.***1976**, *15*,94.
(37) Galéotti, N.; Montagne, C.; Poncet, J.; Jouin, P *Tetrahedron Lett.* **1992**, *33*, 2807-2810.
(38) Wipf, P.; Miller, Ch. P. *Tetrahedron Lett.* **1992**, *33*, 6267-6270.
(39) Yokokawa,F.; Hamada, Y.;Shioiri, T. *Synlett* **1992**, 153-155.
(40) Sund, Ch.; Ylikoski,J.; Kwiatkowski, M. *Synthesis*, **1987**, 853-854.
(41) Devi, N.; Threadgill, M.D.; Tendler, S. J. B. *Syn. Comm.* **1988**, *18*, 1545-1551.
(42) Neubold, K. *Ger. Offen.* **1971**, 2 158 615, *C. A.* **1973**, *79*, 92196a.
(43) Wehrmeister, H. L. *J. Org.Chem.* **1961**, *26*, 3821-3824.
(44) Leffler, M. T.; Adams, R. *J. Am. Chem. Soc.* **1937**, *59*, 2252-2258.
(45) Menne, E. *Ber. d. D. chem. Ges. Jahrg. XXXIII* **1900**, *33*, 657-665.