Synthetic Application of Chiral Pool Derived Heterocycles

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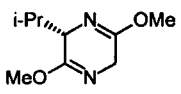
Optically active heterocycles have gained wide application in asymmetric synthesis as chiral building blocks, chiral auxiliaries and catalysts. Most often the chiral information found in such heterocycles is derived from natural products such as amino acids, carbohydrates, alkaloids or terpenes. We report here on the application of enantiopure α-alkylidenelactones, 3-ylidenepiperazine-2,5-diones and glycidic acids and derivatives in the synthesis of new optically active products, which often are analogues of natural products (Scheme 1). α-Alkylidenelactones are available by Wittig-reaction with enantiopure hydroxy or aminoaldehydes derived from carbohydrates or amino acids, respectively. Dehydrocostuslactone and Tulipan are naturally occurring, the latter is commercially available (Scheme 2). α-Alkylidenelactones are Michael-systems. Stereoselective additions of nucleophiles to the C-C double bond can be expected if chirality is found in the side chain. We envisaged to make use of such additions in ring transformation reactions of the α-alkylidenelactones with binucleophiles. The binucleophiles add to the C-C-double bond and subsequently open the starting lactone ring by attack of the second nucleophilic site to the lacton carbonyl carbon by forming a new ring. In this sequence a moiety consisting on a side chain and a heterocycle is transformed into a similar target with the side chain and heterocyclic subunit being exchanged (ring-chain transformation). Hydrazines as binucleophiles form

Scheme 1



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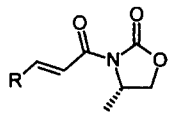
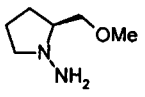


D. A. Evans



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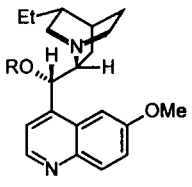
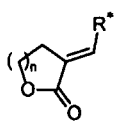
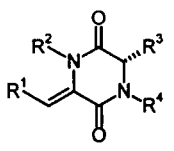
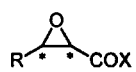


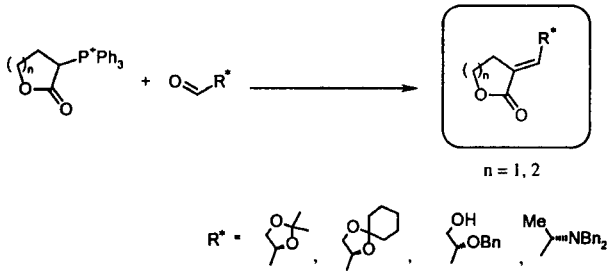
K. B. Sharpless



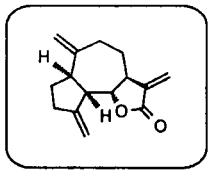




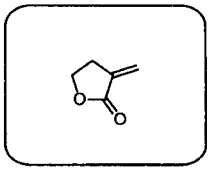
Scheme 2
α-Alkylidenelactones



Dehydrocostuslactone
In cooperation with
Prof. Berhanu Abegaz
University of Botswana

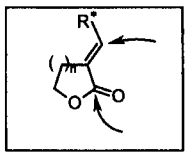


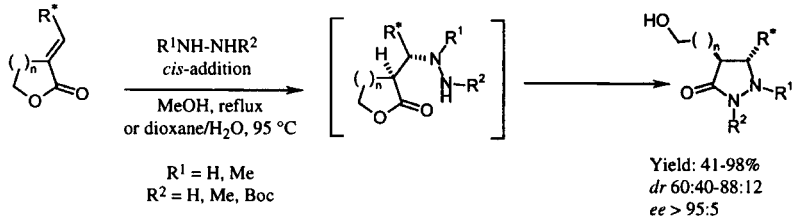
Tulipan
Commercially available,
synthetic and naturally
occurring



optically active 3-(ω-hydroxyalkyl)pyrazolidine-3-ones in this manner. The addition occurs in predominantly *syn*-fashion (Scheme 3) [1]. The stereochemical mode of attack of nucleophiles to α-alkylidenelactones can be interpreted by the *anti*-periplanar effect and Houk's outside crowded model (Scheme 4) implying primary adducts of the same configuration regardless whether (*R*)- or (*S*)-configuration is found in the starting α-alkylidenelactone. The stereoselectivity of the Michael-addition of nitromethane to α-alkylidenelactones is low. The diastereomers were separated by flash chromatography. Reduction of the nitro group causing ring-chain transformation gave access to enantiopure 3-(ω-hydroxyalkyl)-2-pyrrolidones as new γ-amino acid derivatives (Scheme 5). High stereoselectivity was observed in the analogous reaction of nitromethane with dehydrocostuslactone, where the starting chirality is found in a rigid ring system rather than in the side chain and where just one stereogenic center is created (Scheme 6). 1,3-Dipolar cycloaddition of diazoalkanes to α-alkylidenelactones occurs with much higher stereoselectivity as Michael-like additions. The resulting 1-pyrazolines provide access to spirocyclopropanes and to interesting 3-amino-3-(ω-hydroxyalkyl)-2-pyrrolinones which are interesting

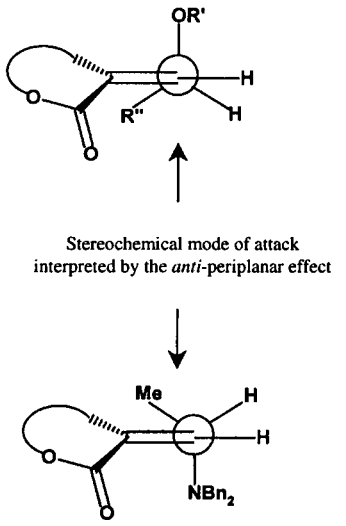
Scheme 3



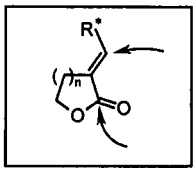


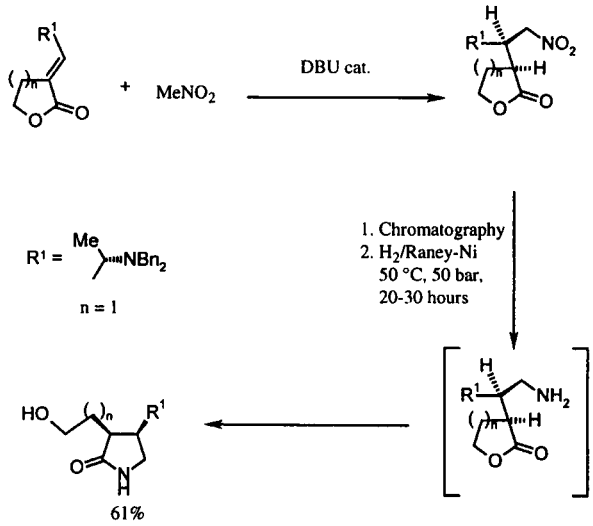
Ring-Chain Transformation

Scheme 4



Scheme 5

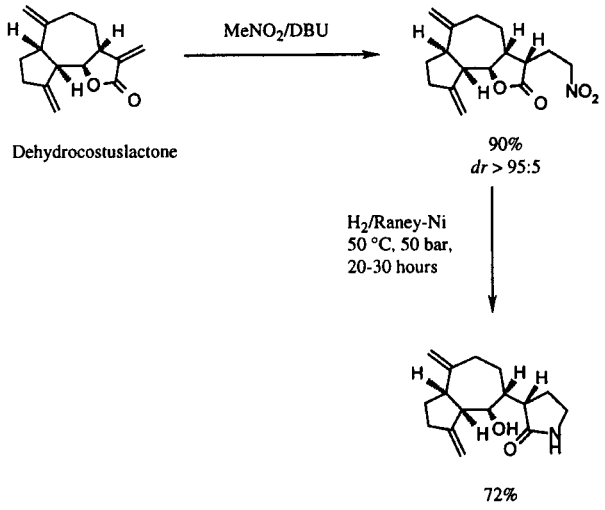




non-natural α,γ-diamino acid derivatives (Scheme 7) [2]. Cycloaddition of trimethylsilyldiazomethane requires high pressure reaction conditions affording 2-pyrazolines by the loss of the trimethylsilyl group.

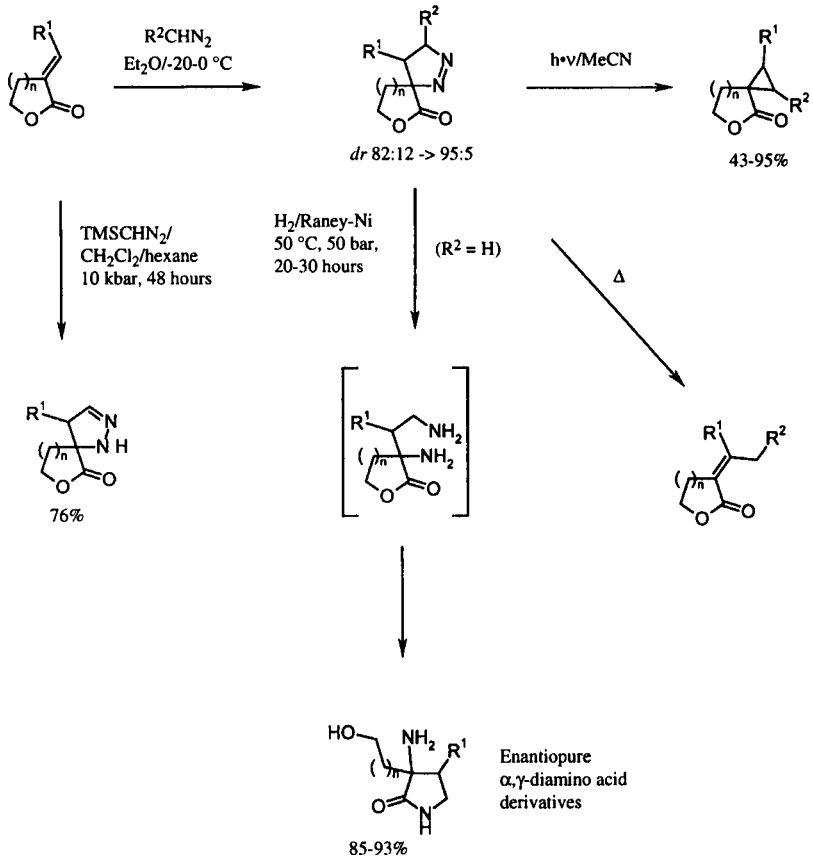
3-Ylidene-2,5-piperazinediones can occur in nature and are also available by a straight forward synthesis *via* Erlenmeyer azlactone route, formation of dipeptide and cyclisation, *i.e.* they are based on a chiral amino acid (*e.g.*

Scheme 6

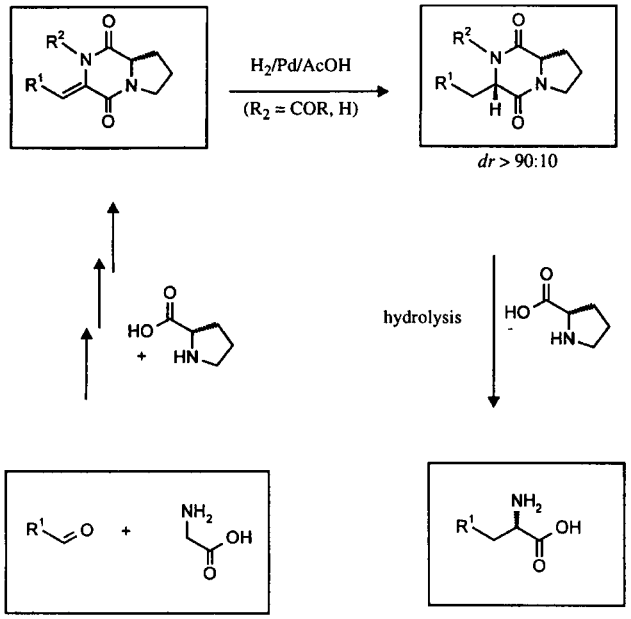


(*S*)-proline), glycine and an aldehyde (Scheme 8) [3,4]. The prochiral C-C-bond allowed highly stereoselective hydrogenation. After hydrolytic cleavage of the piperazinedione ring a new α-amino acid was obtained together with the starting chiral amino acid. As can be seen by the known reaction with thioacetic acid, the C-C-double bond of 3-ylidene-2,5-piperazindiones generally exhibits Michael as well as enamine reactivity (Scheme 9) [5]. In the latter case acid catalysis provides intermediate *N*-acyliminium salts that are further attacked by a nucleophile at the ring position. The 3-ylidene-2,5-piperazinediones investigated by us did not show Michael reactivity in reaction with nucleophiles. Thus we made use of the enamine properties and applied acid conditions. The resulting *N*-acyliminium salts react with electronically rich heterocycles by a Mannich-type reaction (Scheme 10 and 11) [6]. Thus derivatives of novel quaternary α-amino acids are formed. This is a very rare case where an aromatic substituent is introduced in the final step of the establishment of a quaternary center in an α-amino acid. In the case of indole as nucleophile an isomeric addition product appeared as by-

Scheme 7

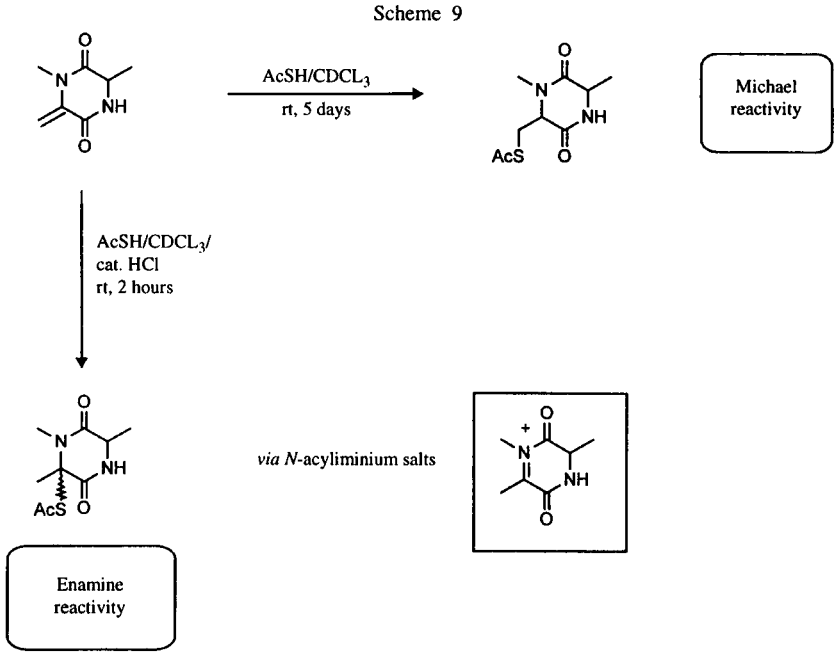


Scheme 8
3-Ylidene-2,5-piperazinediones

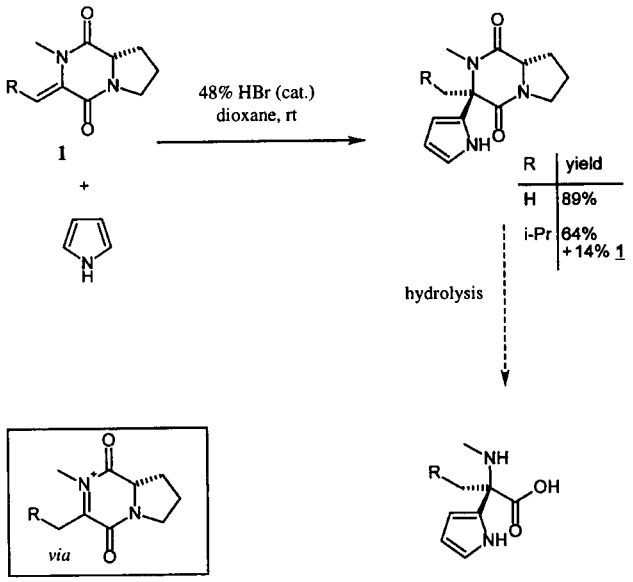


product which is formally derived from a 6-ylidene-2,5-piperazinedione rather than from a 3-ylidene-2,5-piperazinedione. An acid catalyzed isomerisation of the C-C-double bond of 3-ylidene-2,5-piperazinedione is responsible for this phenomenon (Scheme 12). This migration of the C-C-double bond is an unusual type of tautomerism which can be explained by a number of protonation and deprotonation steps (Scheme 13). The equilibrium is preferentially on the side of that tautomer which gives more conformational flexibility to the substituents attached at the nitrogen atoms and the adjacent carbon atom (Scheme 12, 14). If no steric interaction exists, such as in *N*-unsubstituted 3-ylidene-2,5-piperazinediones, no migration of the double bond occurs but just *E/Z* isomerisation (Scheme 14). 1,1-Diphenylethene can also act as a nucleophile in acid catalyzed additions to the ring position of 3-ylidene-2,5-piperazinediones. In addition to the expected optically active adducts, which again are interesting precursors for new quaternary α-amino acids, tricyclic cycloadducts are formed. This cycloaddition is likely to derive *via* mesoionic compounds (Scheme 13) or enols of *N*-acyliminium salts (Scheme 15). 3-Ylidene-2,5-piperazinediones can undergo highly stereoselective 1,3-dipolar cycloadditions with diazomethane [7] and epoxidation with dimethyldioxirane (Scheme 16) [8]. Remarkably the face selectivity of these reactions is opposite. The same was found in the corresponding reactions of 5-ylidene-1,3-dioxane-4-ones (Scheme 16). Epoxides [9] derived from 3-ylidene-2,5-piperazinediones can serve as precursors for optically active α-amino-β-hydroxy acids by rearrangement and catalytic hydrogenation, while the pyrazolines were used in the synthesis of allocoronamic acid (Scheme 17) [10].

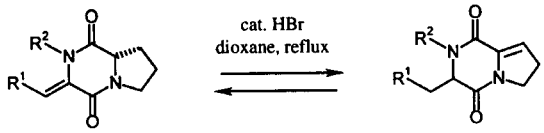
Scheme 9



Scheme 10

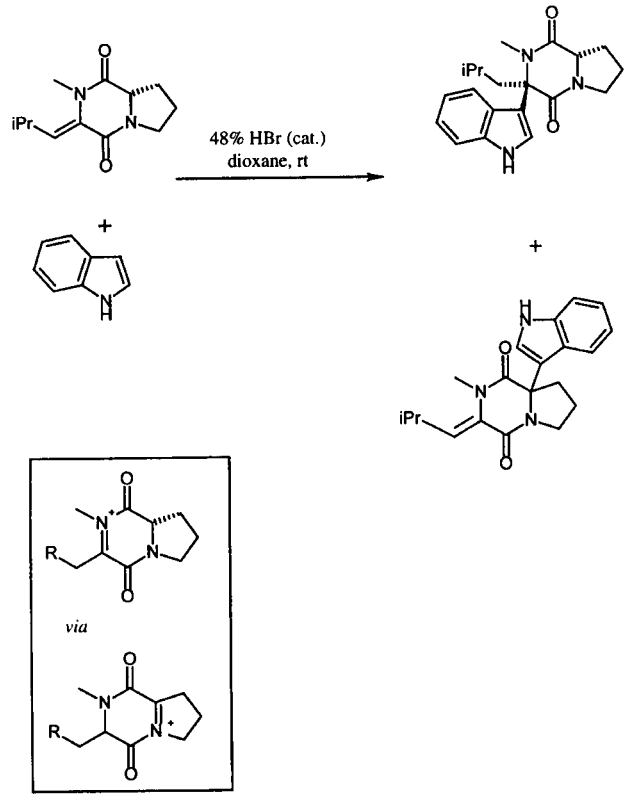


Scheme 12

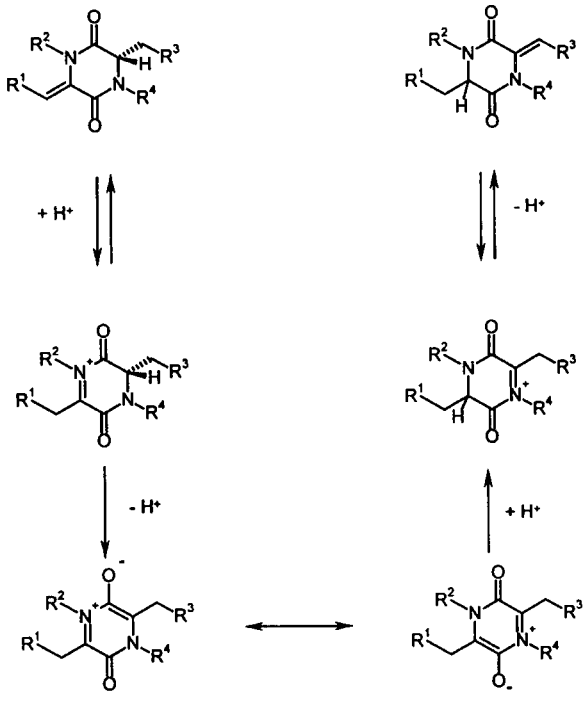


R^1	R^2	Yield II
H	Me	82%
i-Pr	Me	81%
i-Pr	H	39% + 60% racemate **I**
Ph	Me	93%
Ph	H	25% + 75% racemate **I** (starting from **I**) 28% + 78% racemate **I** (starting from **II**)

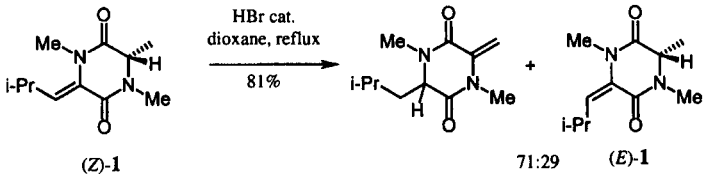
Scheme 11



Scheme 13

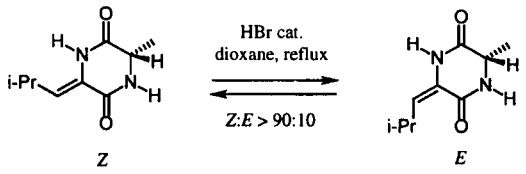


Scheme 14



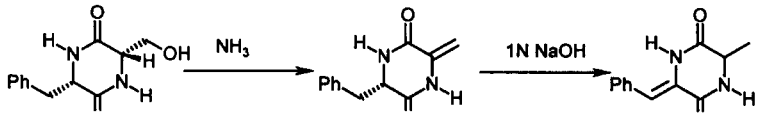
(Z)-1 (E)-1

Double bond migration and *E/Z* isomerisation
+ traces of (Z)-1
Exclusive *E/Z* isomerisation at rt

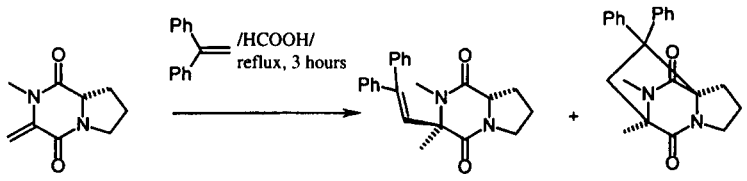


Z E

E/Z Isomerisation, no double bond migration



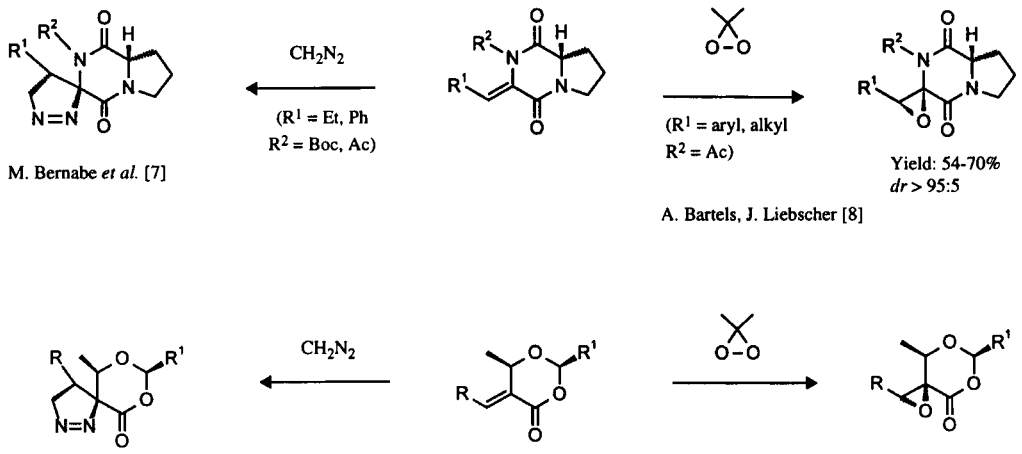
Scheme 15



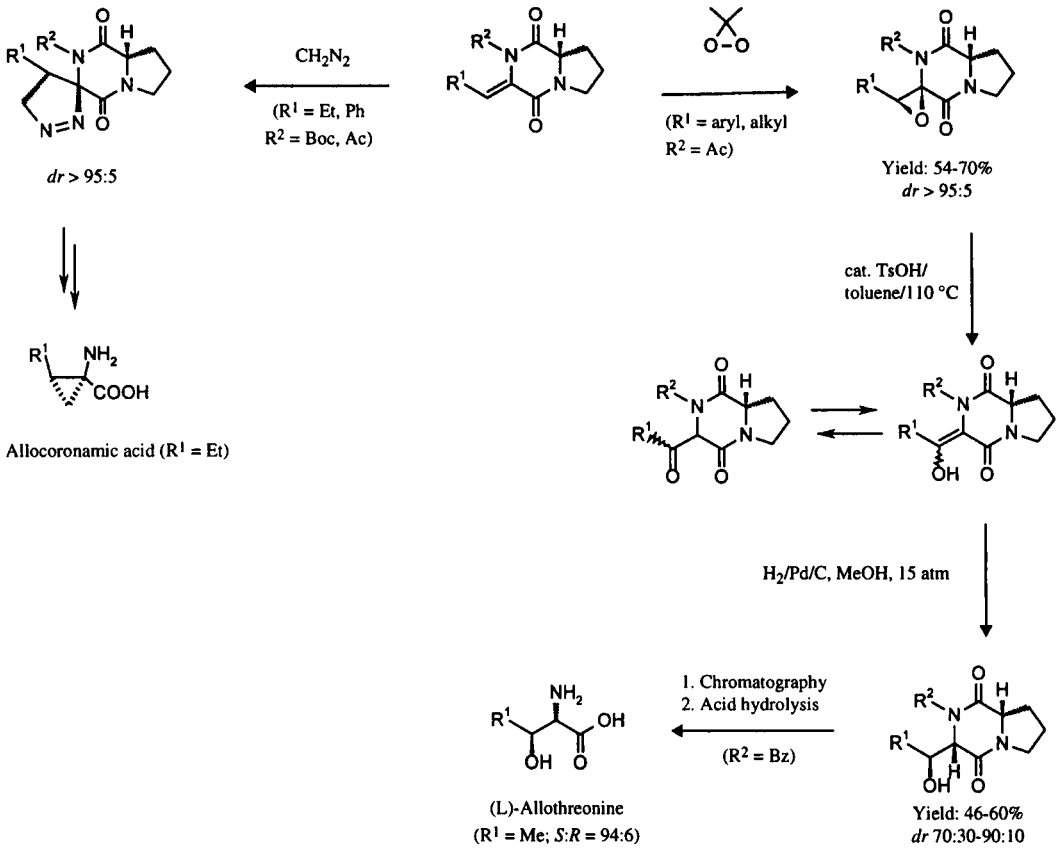
61% 21%
Racemate

Probable intermediates:

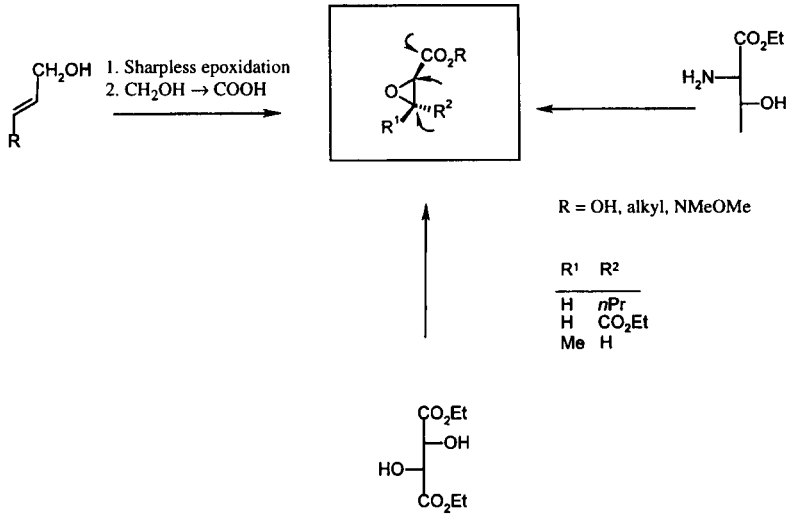
Scheme 16



Scheme 17

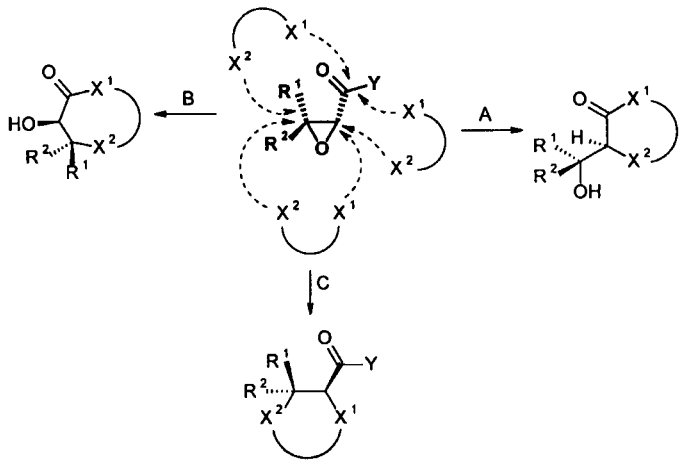


Scheme 18
Enantiopure Glycidates

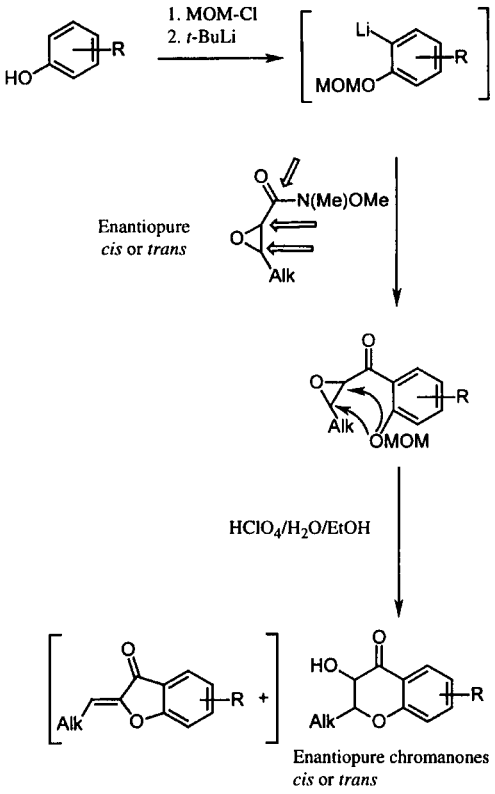


Enantiopure glycidic acids and derivatives are available by known routes starting from allylic alcohols by Sharpless epoxidation and oxidation or from threonine or diethyl tartrate (Scheme 18). They possess three electrophilic sites and can thus serve as C_2 or C_3-building blocks in reactions with binucleophiles (Scheme 19). Our investigations revealed that synthetic function of such glycidic acid derivatives depends on reaction conditions, type of binucleophile and type of leaving group at the carboxylic function. Weinreb amides of glycidic acids can serve as C_3-building block in reaction with *o*-lithiated MOM-protected phenols. Benzoyloxiranes are formed by primary attack at the amide function. Acidic deprotection generates *o*-hydroxybenzoyloxiranes which cyclize by attack at the β-position to new enantiopure hydroxychromanones, sometimes accompanied by aurones (attack at α-position) as by-products (Scheme 20) [11]. Alkyl-substituted glycidates react with 1,2-diaminobenzenes under neat conditions as C_3-building block, too, affording seven-membered enantiopure benzodiazepinones (Scheme 21). As shown by the isolation of 3-arylamino-2-hydroxycarboxylate the reaction sequence is likely to start with opening of the oxirane ring at β-position. In contrast the oxirane dicarboxylate acts as C_2-building block, *i.e.* 1,2-diaminobenzene reacts at one ester group and the adjacent carbon atom (Scheme 21). 2-Aminophenol as binucleophile similarly reacts with alkyl-substituted glycidates in the first step, *i.e.* by opening the oxirane ring in β-position (Scheme 22). The resulting β-(*o*-hydroxyarylamino)-α-hydroxy ester does not cyclize spontaneously by attack at

Scheme 19

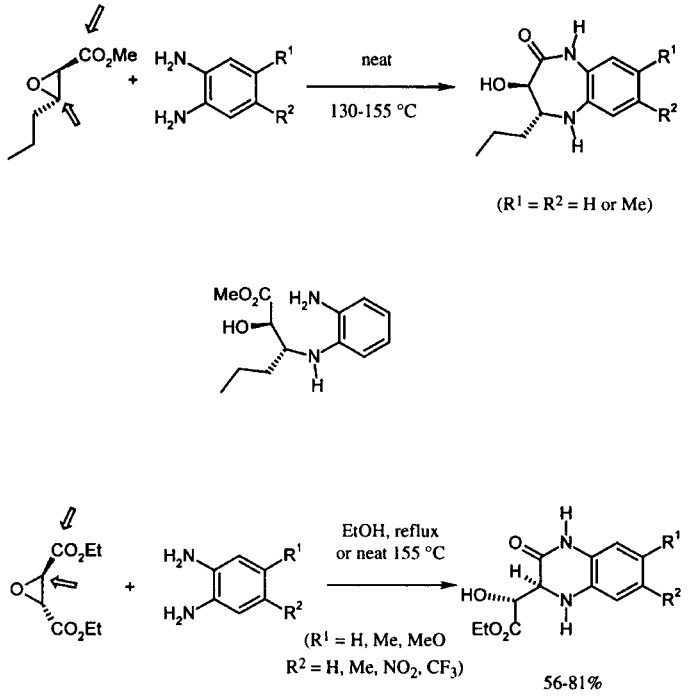


Scheme 20

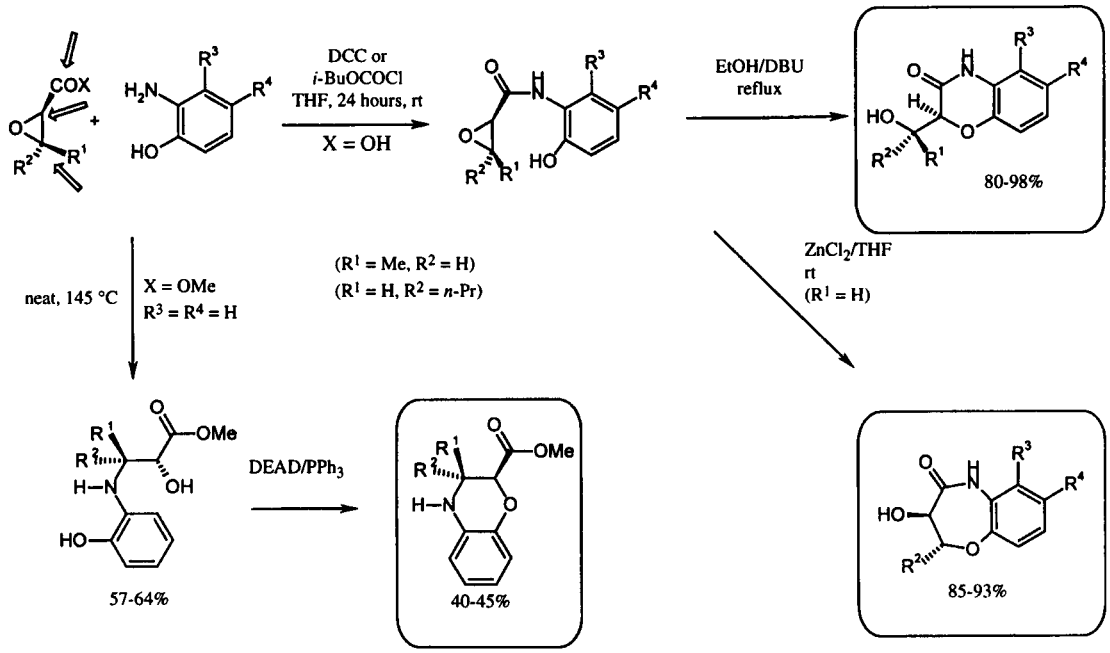


the ester function. However, the application of Mitsunobu-conditions allows cyclisation *via* nucleophilic displacement of the α-hydroxy group by the phenolic hydroxy group affording six-membered benzoxazinones. Alternatively oxirane carboxylic acids can react with *o*-aminophenols in the presence of dicyclohexylcarbodiimide or isobutyl chloroformate primarily at the carboxylic acid function (Scheme 22). The resulting oxirane carboxanilides cyclize to six-membered benzoxazepinones by attack of the phenolic hydroxy group at α-position under basic conditions. In contrast seven-membered hydroxybenzoxazepinones are obtained if the cyclisation is carried out in the presence of zinc chloride (Scheme 22) [12]. The change in regioselectivity probably is caused by chelation of the Lewis acid at the carbonyl oxygen atom and the oxirane oxygen atom. If the phenolic hydroxy group attacks the β-position this favorable chelation is maintained after the cleavage of the oxirane, while α-attack would destroy it. 3-Hydroxybenzoxazepinones are pharmaceutically interesting for the synthesis of *O*-analogous of Diltiazem®.

Scheme 21



Scheme 22



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