Pure & Appl. Chem., Vol. 64, No. 12, pp. 1865–1871, 1992.
Printed in Great Britain.

New approaches in asymmetric synthesis using γ-alkoxybutenolides

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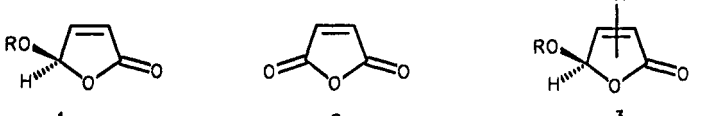
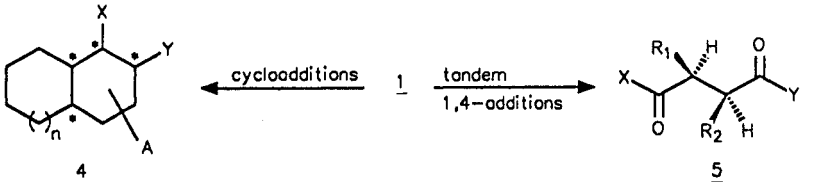
Abstract The synthesis of a new class of auxiliary based chiral synthons, γ-alkoxy-2(5H)-furanones, is described. The multifunctional compounds enter a variety of asymmetric transformations leading to acyclic- and cyclic-products with up to four new stereogenic centers in a single operation with stereoselectivities exceeding 98%. Applications in new routes to an enantiomerically pure ß-lactam and lignans are given.

Chiral non-racemic molecules play an essential role in numerous molecular recognition and interaction phenomena. It is well established now that the enantiomers of biological active compounds such as drugs or agrochemicals are chemically distinct species.[1] Although the use of pure enantiomers as starting materials or intermediates is generally considered a - *sine qua non* - in total synthesis of natural products the potential impact of molecular chirality in such area's as supramolecular chemistry and nanotechnology or in the design of new materials is far from fully realized.[2] There exists a tremendous challenge to develop efficient routes to enantiomerically pure compounds. New catalytic enantioselective methods rapidly emerge and are particular attractive when the *'chironomics'* of the stereoselective synthesis are considered.[3] Chiral auxiliary based asymmetric transformations are often highly successful due to the versatility and scope and because of the reliable and often predictable absolute stereocontrol that is offered in many cases.[4] We devised several new chiral auxiliary based synthons, i.e. 1 and 3, that combine high stereoselectivity (enantiomeric excess in general ≥98%) with synthetic flexibility. 5-Alkoxy-2(5H)-furanone 1 can be considered a chiral analog of maleic anhydride (2) with slightly reduced reactivity due to the presence of an acetal functionality in 1 instead of the second carbonyl functionality in 2.



1 2 3

As conformational rigidity is enforced by the cyclic structure and effective π-face shielding of the α,ß-unsaturated ester moiety in 1 is exerted by the OR group highly diastereoselective addition reactions are expected. The synthesis of enantiomerically pure 5-alkoxy-2(5H)-furanones will be described and several applications in the asymmetric synthesis of cyclic- (4) (*via* cycloadditions) and acyclic- (5) building blocks (*via* tandem 1,4-additions) are reported. Furthermore, the synthetic versatility is illustrated in the preparation of eudesmin and a ß-lactam in enantiomerically pure form.



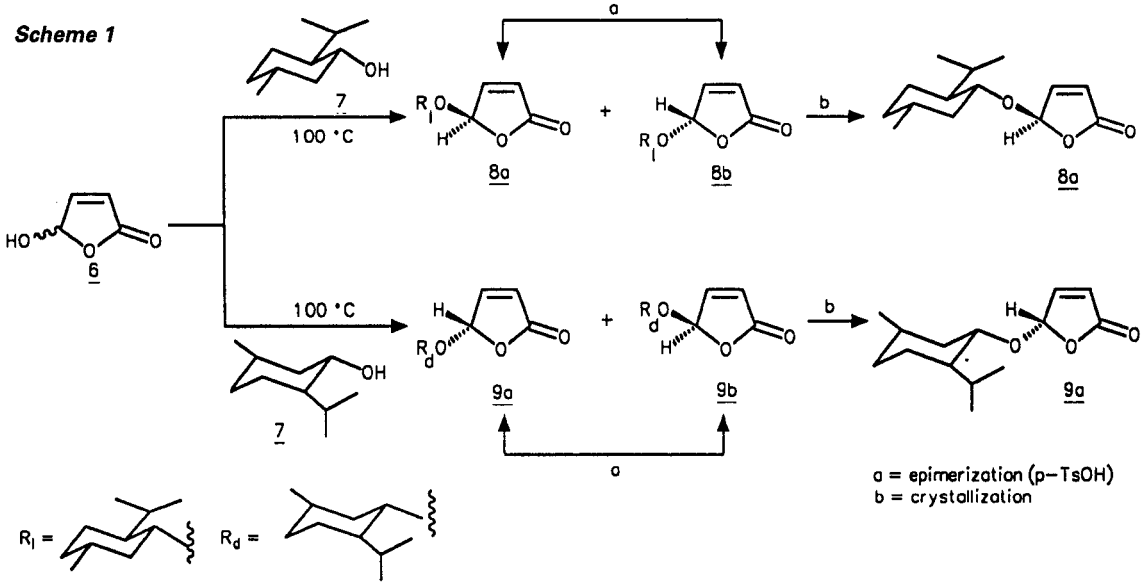
4 5

SYNTHETIC ROUTES TO ENANTIOMERICALLY PURE 5-ALKOXY-2(5H)-FURANONES

We considered the use of a chiral auxiliary alcohol in the preparation of the acetal moiety of butenolide 1 *via* acetalization of 5-hydroxyfuranone 6 an attractive route to the pure enantiomers. In order to be synthetically useful the chiral auxiliary has to meet the following criteria: *i.* The 5-alkoxy-2(5H)-furanone should be a crystalline compound making it, in principle, possible to separate both diastereoisomers by means of crystallization. *ii.* Both enantiomers of the chiral alcohol have to be available allowing access to (5R)- and (5S)-1. *iii.* The auxiliary alcohol has to be relatively inexpensive in order to prepare 5-alkoxy-2(5H)-furanones in large quantities.

The alcohol of choice, which meets all these criteria, is menthol. The asymmetric syntheses of (5R)-8a and (5S)-9a are depicted in Scheme 1. Acetalization of 5-hydroxy-2(5H)-furanone (6)[5] with *l*-menthol at 100 °C for 20 h without solvent or at 120 °C in refluxing toluene afforded a mixture of diastereoisomers 8a and 8b in a 60:40 ratio.[6]

Scheme 1



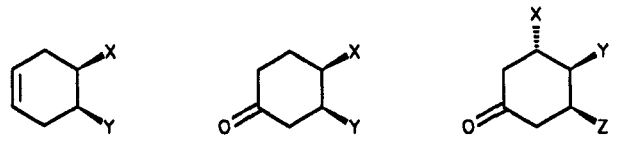
Enantiomerically pure 8a is easily obtained *via* a crystallization-epimerization procedure. The major diastereoisomer 8a readily crystallizes at -20 °C from petroleum ether solutions of the mixture of 8a and 8b. The crystallization process is accompanied by a remarkable *second order asymmetric transformation* of 8 in solution. The slow "crystallization induced epimerization" of 8b is driven by the continuous removal of the major crystalline isomer 8a from the solution. This epimerization-crystallization process allows the isolation of enantiomerically pure menthyloxybutenolides in high yields (up to 80%). By a similar sequence (Scheme 1), using *d*-menthol as a chiral auxiliary alcohol, (5S)-5-(*d*-menthyloxy)-2(5H)-furanone (9a) is obtained.

A number of 3- and 4-alkylsubstituted butenolides 3, as single enantiomers, have been prepared *via* related routes as shown in Scheme 1.

In an alternative approach we investigated the *catalytic kinetic resolution* of racemic γ-alkoxy butenolides 1 (RO = MeO, iPrO), an enantioselectivity >90% (at 75% conversion) has been reached sofar.

CYCLOADDITIONS

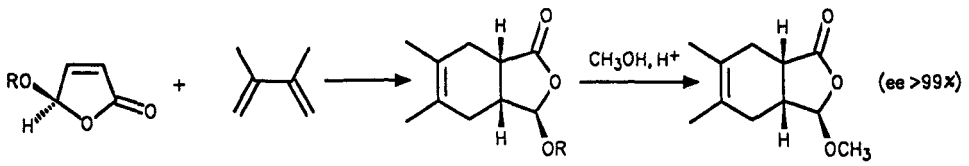
The thermal Diels-Alder reaction of dienes with (5R)-butenolide 8a is expected to proceed with high endo-selectivity and re-face diastereoselectivity. γ-Menthyloxy-butenolides 8a and 9a are extremely useful chiral dienophiles both for Diels-Alder reactions with cyclic- and acyclic 1,3-dienes. In particular the synthesis of a variety of optically active 3,4-disubstituted-cyclohexenes 10 and -cyclohexanones 11 is readily achieved but also the formation of trisubstituted derivatives 12 is feasible.[7]



10 11 12

Cycloaddition of 2,3-dimethylbutadiene 13 for instance provided enantiomerically pure lactone-annulated cyclohexene 14 (Scheme 2).[8] Solvolysis in methanol under mild conditions resulted in lactone 15 with enantiomeric excess >99% whereas the auxiliary R menthol was recovered.[9]

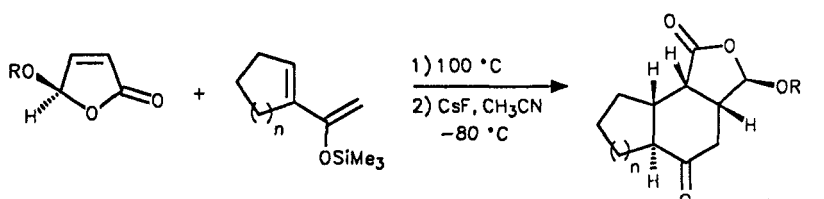
Scheme 2



8a 13 14 15

Enantiomerically pure decalines are particularly attractive targets for asymmetric cycloadditions as numerous natural products and biological active compounds contain the 6,6-ring system. Among these are various classes of steroids, the sesquiterpenes of the drimane class having insect antifeedant and plant growth regulation properties and the diterpenoids of the labdane class. Examples are forskolin with pronounced antihypertensive activity and compactin which has been shown to lower serum cholesterol levels. As our approach to the decaline and hydroindane skeletons is based on intermolecular cycloadditions with 1-ethenyl-cycloalkenes it might be possible to furnish, in a single operation enantiomerically pure decalines and indanes. The feasibility of this approach was confirmed using for instance 1-(1-trimethylsilyloxyethenyl)-cycloalkenes 16 and 17. Reaction of dienes 16 and 17 followed by in situ desilylation of the resulting adducts with CsF in wet acetonitrile at -80 °C afforded enantiomerically pure 18 and 19 respectively.[10] Four new stereogenic centers were introduced in a one pot operation under complete control of the regioselectivity, endo-selectivity and trans-selectivity with respect to the menthyloxy substituent. Furthermore, trans-decaline ring fusion was observed exclusively.

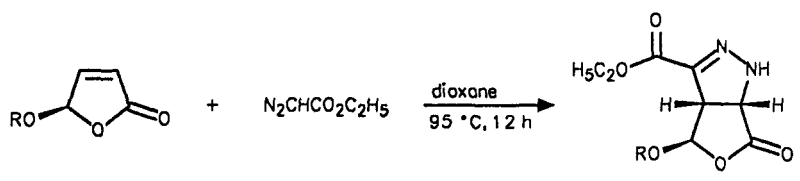
Scheme 3



8a 16 n = 1, 17 n = 2 18 n = 1, 19 n = 2

The prospect of preparing optically active multifunctional compounds by 1,3-dipolar cycloadditions to chiral γ-alkoxybutenolides in a high stereocontrolled fashion is particular attractive. The addition of ethyl diazoacetate for instance proceeds with complete regio- and diastereofacial control to yield enantiomerically pure 20 (Scheme 4).[11]

Scheme 4



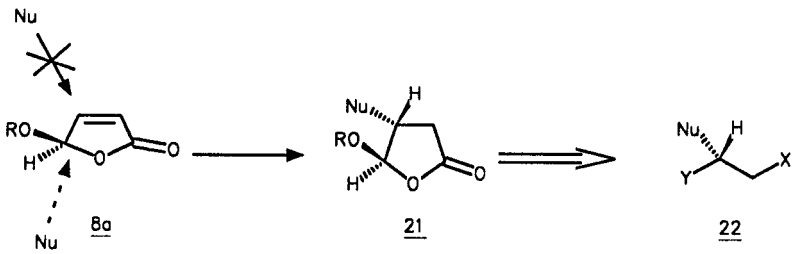
8a 20

Via asymmetric 1,3-dipolar cycloadditions carbon, oxygen and nitrogen functionalities are readily introduced into the α- and ß-positions of the lactone moiety. In this way useful precursors for natural product synthesis are accessible.

1,4-ADDITION REACTIONS

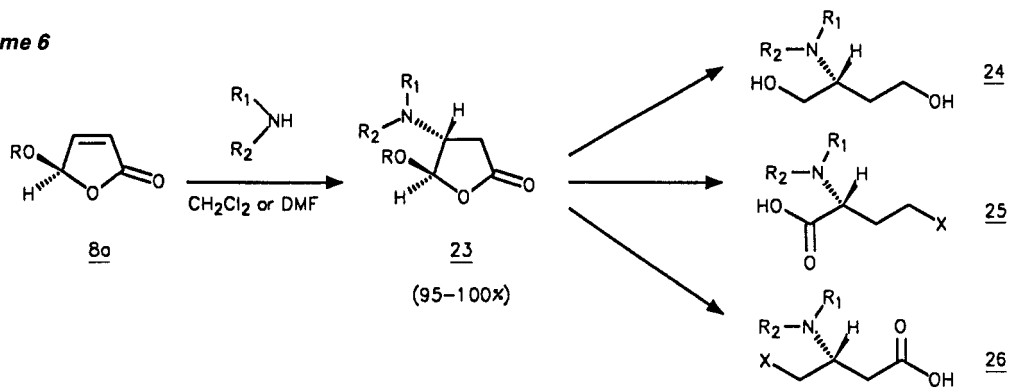
A variety of 1,4-addition reactions to γ-alkoxy-2(5H)-furanones both with carbon- and hetero-atom based nucleophiles take place. In (5R)-5-(*l*-menthyloxy)-2(5H)-furanone 8a effective π-face shielding is exerted by the bulky menthyloxy moiety resulting in trans diastereoselective additions of these nucleophiles (Scheme 5). 4-Substituted γ-alkoxybutyrolactones 21 give, after ringopening and removal of the auxiliary, acyclic products 22 in their enantiomerically pure form.[12]

Scheme 5



The 1,4-addition of primary and secondary amines proceeds trans diastereoselective with respect to the menthyloxy-group to give 4-amine-substituted lactones 23 in high yields (Scheme 6).[13]

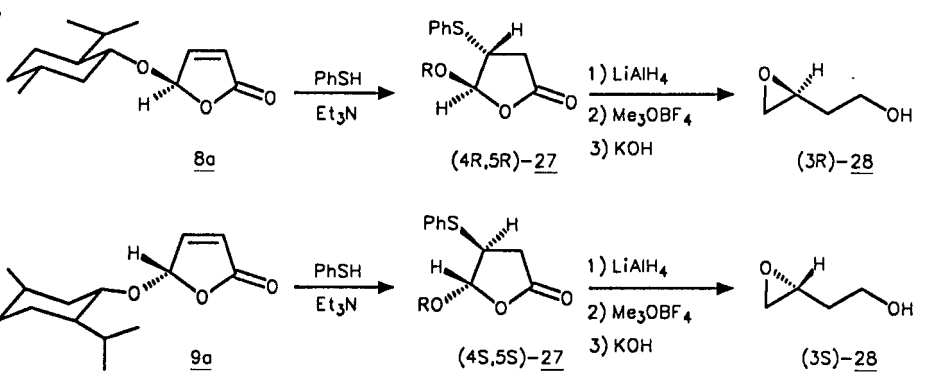
Scheme 6



The enantiomerically pure aminolactones 23 are extremely versatile synthons as illustrated in Scheme 6. It should be emphasized that the amine functionality is both in an α-relationship and a ß-relationship to two functional groups in different oxidation stages. Selective manipulations of the acetal and ester moieties in 23 give therefore access to both 1,2- and 1,3-aminoalcohols and α- (25) and ß-aminoacids (26) whereas $LiAlH_4$ reduction readily provides aminodiols 24.

The addition of thiols to γ-alkoxybutenolides, catalyzed by tert-amines, is also a fast and quantitative reaction (Scheme 7). The short synthetic route to both enantiomers of 3,4-epoxy-butanol[14] illustrates only one of the various application of 4-sulfide substituted lactones 27.

Scheme 7

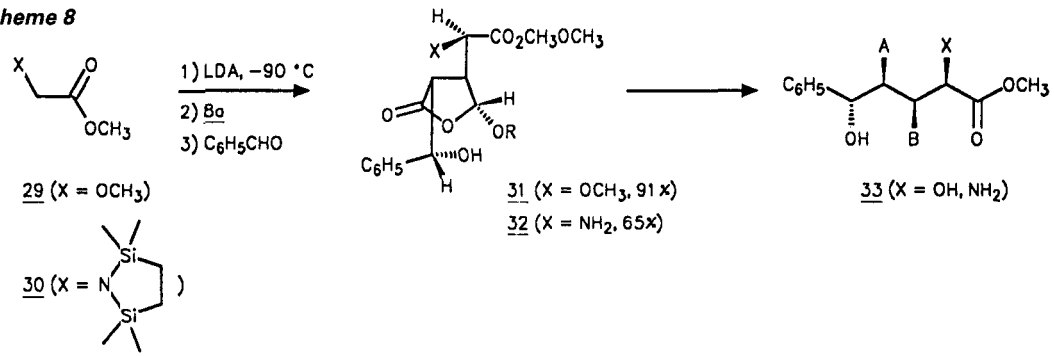


A very flexible synthetic protocol for the preparation of 4-alkyl- and 3,4-dialkyl substituted butyrolactones has been developed. Using lithiated bisthiophenyl dithianes as nucleophiles a variety of alkyl- and benzyl-substituents can readily be introduced *via* trans-diastereoselective 1,4-addition followed by desulfurization using Raney-nickel.

In a tandem approach the resulting lactone enolate, obtained after the initial 1,4-addition, is quenched with an alkyl- or benzyl-iodide. Subsequent Ra-Ni reduction provides 3,4-disubstituted lactones. The sequential introduction of the trismethylthiomethyl- or bisthiophenyldithiane-group at C_4 and an alkyl group at C_3 demonstrates that two new stereogenic centers are readily formed with complete trans vicinal stereocontrol.[15] The stereoselective sequential functionalization of the γ-butyrolactone ring with two benzyl-substituents forms the core of a new synthetic strategy to several classes of biologically active lignans (*vide infra*).

The stereoselective tandem addition-quenching reactions to 5-alkoxy-2(5H)-furanones was further extended using prochiral nucleophiles and prochiral electrophiles.

Scheme 8

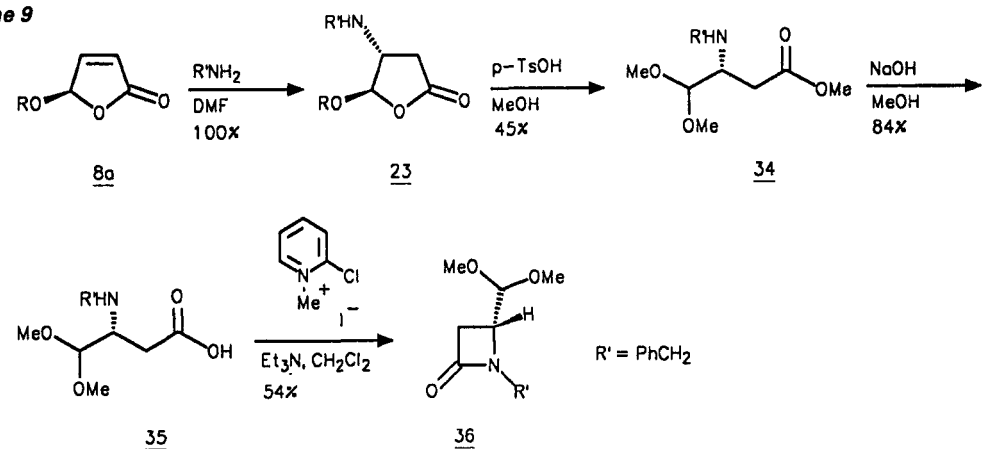


For instance when lithioenolates of the protected α-hydroxyesters or aminoesters are employed as nucleophiles and benzaldehyde as an electrophile lactones 31 and 32 are obtained as single enantiomers in high yield (Scheme 8). It should be noted that in order to reach high stereoselectivities at the exocyclic center the use of pure enolates, either E or Z, is essential. In the case of 29 and 30 presumably the chelated Z-enolate is involved leading to syn-adducts exclusively. The adducts 31 and 32 can serve as precursors for multifunctional α-hydroxyacids and α-aminoacids. As complete stereocontrol is found in the enolate addition and the subsequent aldol-reaction up to four contiguous stereogenic centers are introduced in a one pot operation resulting in enantiomerically pure products.

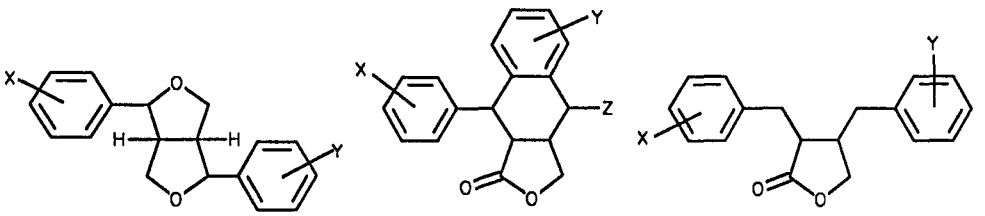
SYNTHETIC APPLICATION OF MENTHYLOXYBUTENOLIDES

A few applications of 1,4-addition reactions to 5-menthyloxybutenolides will be described here to demonstrate the synthetic potential in i.e. natural product chemistry.

Scheme 9



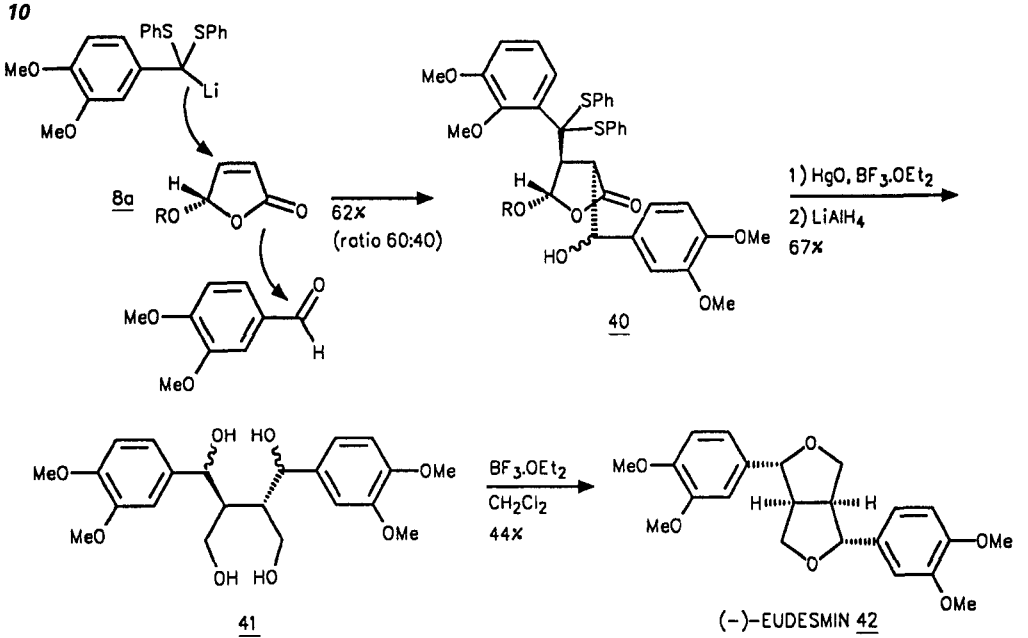
The 4-amine-substituted lactones 23 (*vide supra*) are versatile precursors for the preparation of optically active ß-aminoacids and ß-lactams.[16] Scheme 9 illustrates the conversion of 23 into ß-lactam 36, a potential carbapenem precursor. Essential steps involve ring-opening of 23 with in situ acetalization without epimerization and ringclosure of 35 using Mukayama's procedure.
The tandem 1,4-addition reactions provide short and stereoselective routes to the three major classes of lignans 37-39. New routes to enantiomerically pure lignans are highly warranted considering the biological activity of numerous lignans.[17]



37 38 39

The total synthesis of (-)-eudesmin (42) (Scheme 10) exemplifies a successful strategy with the formation of the dibenzyllactone moiety 40 as the key step.[18]

Scheme 10



Although the diastereoselectivity in the aldolstep is only modest, both epimers lead to (-)-eudesmin (42). Various other lignan syntheses as well as studies of further applications of cycloaddition and 1,4-addition products are currently in progress.

In conclusion efficient routes to chiral non-racemic γ-alkoxybutenolides have been developed . The compounds are versatile chiral building blocks in asymmetric synthesis due to their multifunctional nature, excellent stereocontrol and synthetic flexibility. Exploration of the acetal functionality in these butenolides will further increase the scope.

Acknowledgement

Part of these investigations were supported by the Netherlands Foundation of Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO).

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