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NEW STRATEGIES IN ASYMMETRIC SYNTHESIS BASED ON γ-ALKOXYBUTENOLIDES

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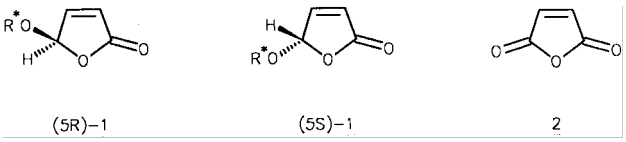
INTRODUCTION

Molecular chirality often is considered one of the distinctive elements in living organisms. The biological activity of numerous chemical compounds and the high selectivity of enzymes is related to well defined absolute configurations.[1] It is widely recognized that, in order to avoid unnecessary isomer contamination, the development of various drugs, plant protecting agents[2] and other physiologically active materials requires efficient routes to enantiomerically pure compounds. Chiral non-racemic molecules also play a crucial role in studies of enzyme-substrate interactions, chiral recognition phenomena, receptor chemistry and developments of many new materials.

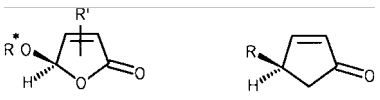
The challenge to prepare enantiomerically pure compounds led to remarkable new enantioselective and diastereoselective synthetic methodology. Chiral auxiliary based methods have met with high success among the various asymmetric transformations studied.[3] This is mainly due to reliable and often high and predictable absolute stereocontrol. Prerequisites for effective auxiliary based methods are *i*) diastereomeric excess (d.e.) >98%, *ii*) easy accessible and preferential cheap auxiliaries and *iii*) nondestructive ways to remove it after the asymmetric transformation i.e. chiral auxiliary recycling. A review of chiral auxiliaries for multistep enantioselective synthesis by Seebach[3] shows that the major part of these compounds is based on aminoacid, hydroxyacid and terpene derivatives and integral enforce conformational rigidity at the crucial stereogenic center forming step. It should be noted that several auxiliaries are still rather expensive or require multistep synthesis.

Our aim was to develop new chiral auxiliary based synthons that combine uniform high diastereoselectivity with chemical flexibility resulting in a variety of new asymmetric transformations. It appeared to us that enantiomerically pure furanones 1, with a chiral alkoxide as an auxiliary group at C5, would be very suitable. Enantiomers of 5-alkoxy-2(5H)-furanone (1) can be considered chiral analogs of maleic anhydride (2) although with slightly reduced reactivity due to the presence of an acetal functionality in 1 instead of the second carbonyl functionality in maleic anhydride (2).



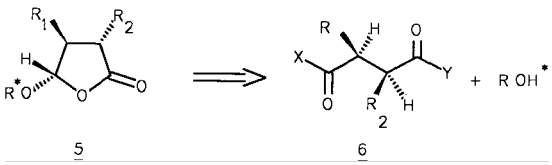
(5R)–1 (5S)–1 2

Furthermore substituted analogs such as 3 will broaden the scope of these asymmetric syntheses. Related strategies based on chiral cyclopentenoids 4 have been studied and in particular diastereoselective tandem additions to 4 were highly successful in the total synthesis of prostaglandins.



3 4

Major differences between chiral synthons 1 and 4 are the resolution that is required or the often laborious routes to enantiomerically pure 4, whereas 1 is auxiliary based. Furthermore mild hydrolysis of the chiral products 5, obtained from asymmetric additions to 1, allows easy auxiliary recycling and results in *acyclic* chiral building blocks 6. The different oxidation state of the carbonyl containing functionalities in 1, 3, 5 and 6 enhance the synthetic flexibility.

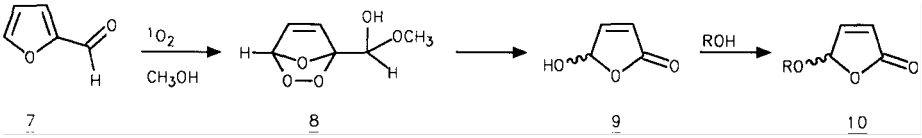


5 6

Reactivity studies of γ-alkoxyfuranones by Fariña and coworkers[4] and our group[5] have mainly been limited to racemic 5-methoxy-2(5H)-furanone 10 (R = CH_3) so far. A few applications in natural product synthesis have been reported.

SYNTHESIS OF ENANTIOMERICALLY PURE 5-MENTHYLOXY-2(5H)-FURANONES

The synthesis of pure enantiomers of 5-alkoxy-2(5H)-furanones 1 starts from 5-hydroxy-2(5H)-furanone 9 (Scheme 1). The photooxidation[6] of furfural (7) is probably most suitable for the preparation of 5-hydroxy-2(5H)-furanone (9) although a number of literature procedures are known.[7]



7 8 9 10

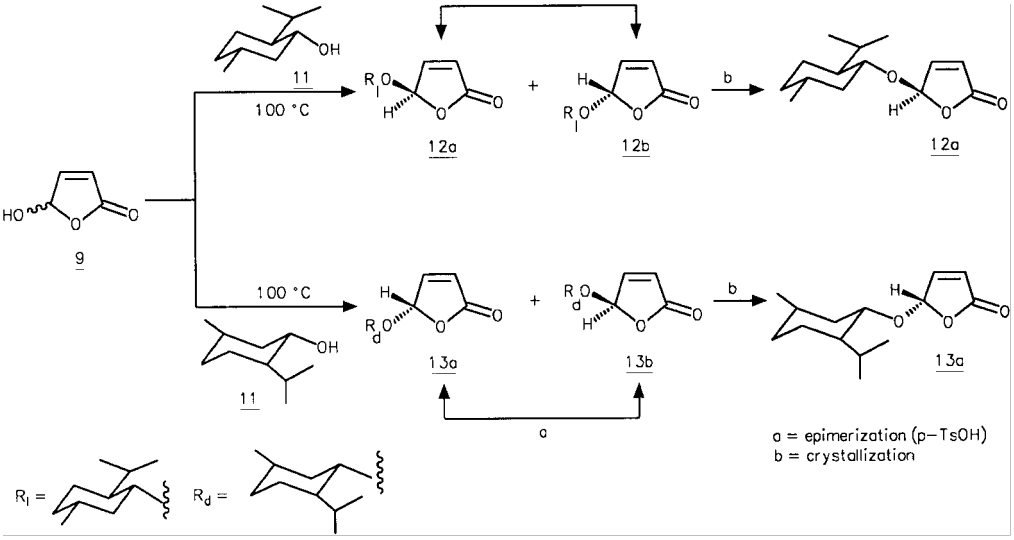
SCHEME 1.

We have performed several of these photooxidations on a 100 g scale without any difficulties providing the butenolide 9 in almost quantitative yields.[8] Racemic 5-methoxy-2(5H)-furanone (10) is obtained by refluxing 9 for 3 days in dry methanol. An essential feature of the asymmetric synthesis methods developed along the lines described here concerns the use of racemic 10 which allows easy optimization of reaction conditions and assessment of both scope and stereoselectivity of new reactions prior to the use of enantiomerically pure 1. On the basis of this approach the success of the subsequent enantioselective synthesis using 1 can readily be predicted.

For the preparation of enantiomerically pure synthons 1 and 3 several chiral alcohols were examined. In order to be synthetically useful the chiral auxiliary has to meet the following criteria:

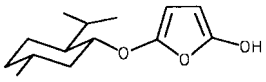
1. The 5-alkoxy-2(5H)-furanone should be a crystalline compound making it, in principle, possible to separate both diastereoisomers by means of crystallization.
2. Both enantiomers of the chiral alcohol have to be available allowing access to (5R)- and (5S)-1.
3. The auxiliary alcohol has to be relatively 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 synthesis of (5R)-12a is shown in Scheme 2. Acetalization of 5-hydroxy-2(5H)-furanone with *l*-menthol at 100°C for 20 h without solvent or at 120°C in refluxing toluene afforded a mixture of diastereoisomers 12a and 12b in a 60:40 ratio.



SCHEME 2.

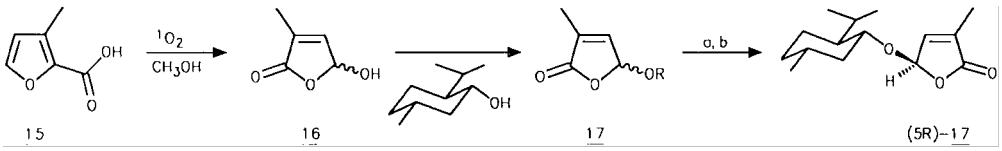
Enantiomerically pure 12a is readily obtained via a crystallization-epimerization procedure. The major diastereoisomer 12a readily crystallizes at -20°C from petroleum-ether solutions of the mixture of 12a and 12b. The crystallization process is accompanied by a remarkable *second order asymmetric transformation* of 12 in solution. The slow "crystallization" induced epimerization of 12b is driven by the continuous removal of the major crystalline isomer 12a from the solution. The epimerization can be catalyzed by *p*-toluenesulfonic acid but simple heating in petroleum ether (bp. 140-160°C) for 1 hour facilitates this process equally well resulting in a cleaner epimerization process. The epimerization presumably takes place *via* enolization of 12b (or 12a) to the unstable 2-hydroxy-5-(*l*-menthyloxy)-furan (14), which has lost it stereogenic center at C5. The epimerization-crystallization process allows the isolation of enantiomerically pure menthyloxybutenolides in high yields (up to 80%).



14

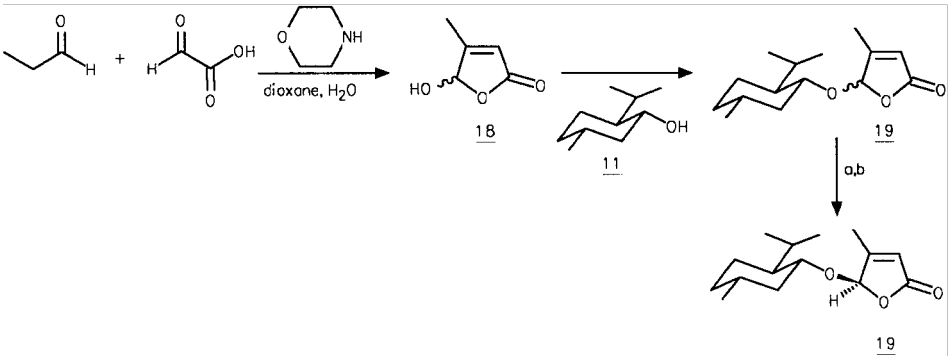
By a similar sequence (Scheme 2), using *d*-menthol as a chiral auxiliary alcohol, (5S)-5-(*d*-menthyloxy)-2(5H)-furanone (13a) is obtained. When enantiomerically pure 12a or 13a are heated for several hours in toluene with careful exclusion of acid no epimerization takes place. This property is essential for various asymmetric transformations.

The synthesis of *substituted γ-alkoxybutenolides* 3 is illustrated with two examples (Scheme 3 and Scheme 4). Enantiomerically pure (5R)-5-(*l*-menthyloxy)-3-methyl-2(5H)-furanone (17) was obtained in 78% yield from 5-hydroxy-3-methyl-2(5H)-furanone (16) following the acetalization-crystallization-epimerization sequence shown in Scheme 2.



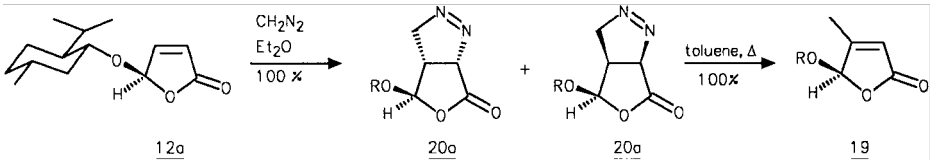
SCHEME 3.

A similar route to (5R)-5-(*l*-menthyloxy)-4-methyl-2(5H)-furanone (19) only resulted in 39% yield, mainly as a result of resistance to epimerization of the (5S)-epimer (Scheme 4).



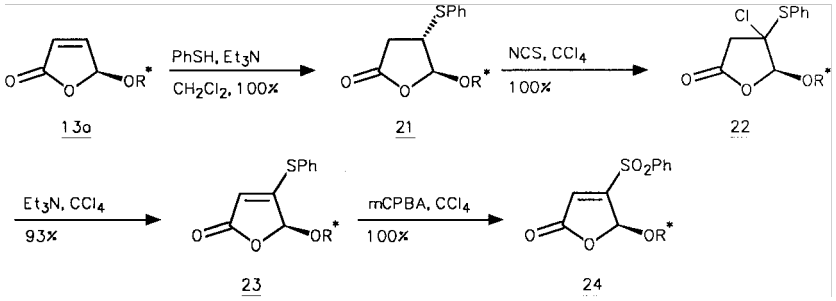
SCHEME 4.

An improved procedure for the preparation of (5R)-19 in quantitative overall yield from 12a was therefore developed (Scheme 5).[9] The sequence involves a 1,3-dipolar cycloaddition of diazomethane to 12a to yield a mixture of diastereoisomers 20a and 20b (60:40 ratio). Subsequent thermal N_2 elimination provides enantiomerically pure 19.



SCHEME 5.

When 12a and 13a were used as chiral dienophiles (*vide infra*) we could show that cycloadditions with less reactive dienes required rather long reaction times or high temperatures whereas trapping reactions with extremely reactive dienes such as *o*-xylylene are to slow to be synthetically useful. These observations inspired us to design 5-alkoxy-4-(phenylsulfonyl)-2(5H)-furanone 24 as a highly reactive chiral dienophile. The introduction of the electron withdrawing phenylsulfonyl substituent in the 4-position was achieved through a sequence shown in Scheme 6 starting with (5S)-butenolide 13a.



SCHEME 6.

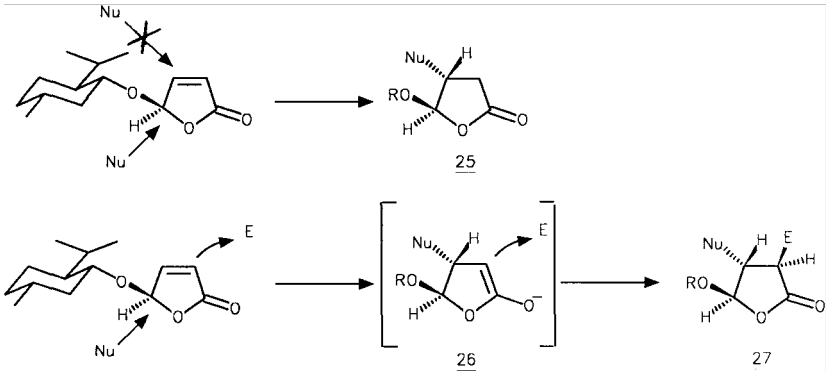
The 1,4-addition of thiophenol to 13a is followed by NCS chlorination and base-induced HCl elimination with Et_3N, to afford 23 in 93% yield. Special precautions are necessary to prevent epimerization at this stage as well as during the subsequent oxidation of 23 to the sulfone 24 using *m*-chloroperbenzoic acid. Enantiomerically pure 24 is stable towards epimerization under ambient conditions.

1,4-ADDITION REACTIONS

γ-Alkoxy-2-(5H)-furanones are excellent Michael type acceptors which can be applied in wide variety of 1,4-addition reactions. In (5R)-5-(*l*-menthyloxy)-2(5H)-furanone 12a effective π-face shielding is exerted by the bulky menthyloxy-moiety resulting in diastereoselective Si-face addition of nucleophiles (Scheme 7).

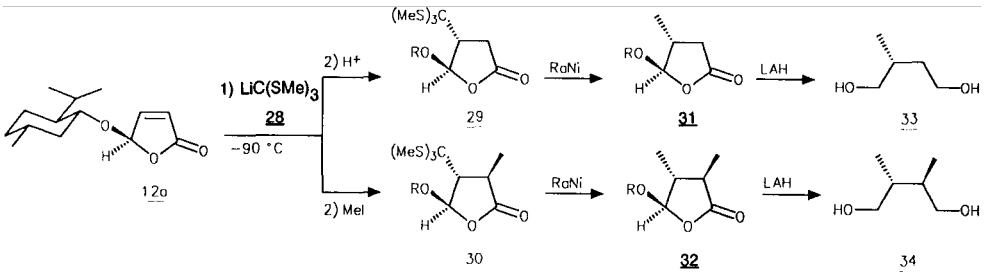
Using both carbon- and heteroatom-nucleophiles numerous 4-substituted γ-alkoxybutyrolactones are accessible in enantiomerically pure form.

In a tandem approach the resulting lactone enolate 26, obtained from the initial 1,4-addition, can be quenched in situ by various electrophiles. The face-selectivity in the enolate addition step is dictated by the substituent at C_4 leading to enantiomerically pure trans-3,4-disubstituted lactones 27.



SCHEME 7.

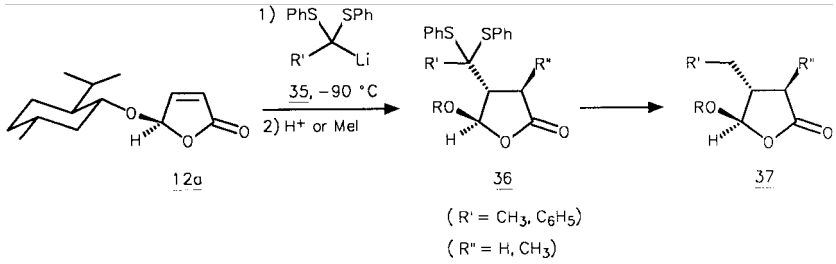
Several attempts to prepare 4-alkyl-substituted butyrolactones 25 (Nu = alkyl) via 1,4-additions of cuprate or zincate reagents failed so far.[10] We found however that lithiated trismethylthiomethane (28) is useful substitute for a methyl carbanion and a versatile Michael donor in conjugated additions to butenolides (Scheme 8). Addition of 28 to (5R)-5-(*l*-menthyloxy)-butenolide 12a is a facile process at -90°C resulting in adduct 29 in 84% yield as a single enantiomer.



SCHEME 8.

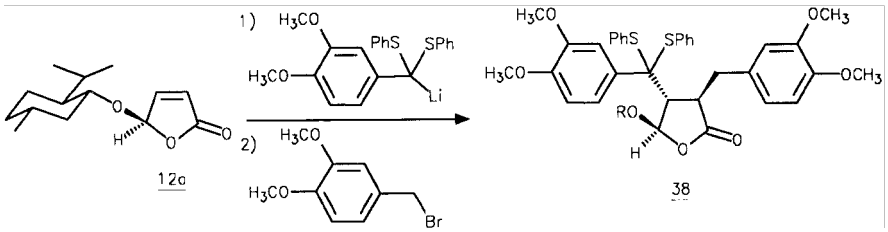
The sequential introduction of the trismethylthiomethane substituent at the 4 position and a methylgroup at C_3 by enolate quenching with MeI resulted in 30. Two new stereogenic centers are formed with complete trans vicinal stereocontrol.[11] The trismethylthiomethane group is readily converted into a methyl substituent by desulfurization using Raney Nickel. Subsequent $LiAlH_4$ reductions of 31 and 32 resulted in enantiomerically pure (2R)-2-methyl-butanediol 33 and (2R,3R)-2,3-dimethyl-butane-1,4-diol 34 respectively. The chiral auxiliary l-menthol is quantitatively recovered in this step.

Using a similar protocol as above, but with lithiated bisthiophenyl-dithianes 35 as nucleophiles, a variety of alkyl- and benzyl-substituents can readily be introduced in the lactone ring in a completely stereoselective manner (Scheme 9).[12]



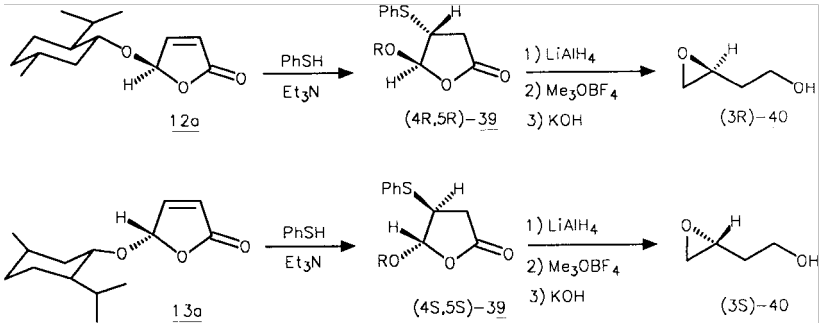
SCHEME 9.

These asymmetric tandem additions to 5-menthyloxybutenolides form the core of new synthetic strategies to several classes of biologically active lignans.[11,12,13,14,15] In particular dibenzylbutyrolactones are accessible via the asymmetric tandem addition as illustrated in Scheme 10. Butyrolactones, such as 38, are excellent precursors for many enantiomerically pure lignans.[16]



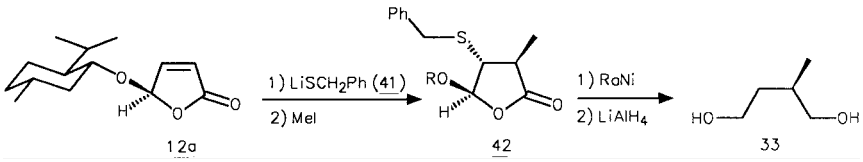
SCHEME 10.

The addition of arylthiols to γ-alkoxybutenolides catalyzed by tert-amines, is a fast and quantitative reaction (Scheme 11). The addition of thiophenol to 12a and 13a was used in a short route to both enantiomers of 3,4-epoxy-butanol.



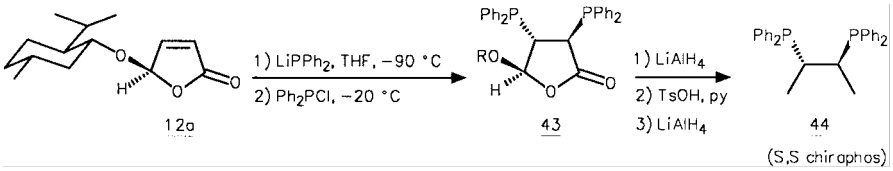
SCHEME 11.

It is remarkable that benzylthiol under thermodynamic controlled conditions and lithiated benzylthiol (41) under kinetic control both add to 12a. These findings were employed in the diastereoselective 1,4-addition of 41 to butenolide 12a followed by enolate alkylation with MeI (Scheme 12). Subsequent RaNi and $LiAlH_4$ reduction completed an alternative route (as compared to Scheme 8) to (2S)-2-methyl-butane-1,4-diol (33).



SCHEME 12.

Only limited use has been made of the Michael addition of phosphine anions to prepare substituted phosphines, but it turned out that the 1,4-addition of lithio-diphenylphosphine to butenolides is a facile and stereoselective process (Scheme 13). Also the subsequent quenching of the lactone-enolate with diphenylphosphine chloride is a smooth reaction. Combining the 1,4-addition of lithio-diphenylphosphine to (5R)-5-(*l*-menthyloxy)-2(5H)-furanone with the in situ quenching with diphenylphosphine chloride afforded bis-diphenylphosphine substituted lactone 43 in 92% yield as a single enantiomer.[17] A three step conversion, using standard methodology, resulted in enantiomerically pure (S,S)-chiraphos 44. The approach described here allows easy access to a variety of optically active phosphines which are widely used as chiral ligands in metal mediated asymmetric synthesis.



SCHEME 13.

CYCLOADDITIONS

High asymmetric induction has been achieved in a number of Diels Alder reactions using chiral dienophiles provided one of the π-faces of the dienophile is effectively shielded as is the case with 8-phenylmenthyl acrylates.[18] Thermal Diels Alder reactions with chiral dienophiles in general need further improvement as in most case complete diastereoselectivity is not reached.

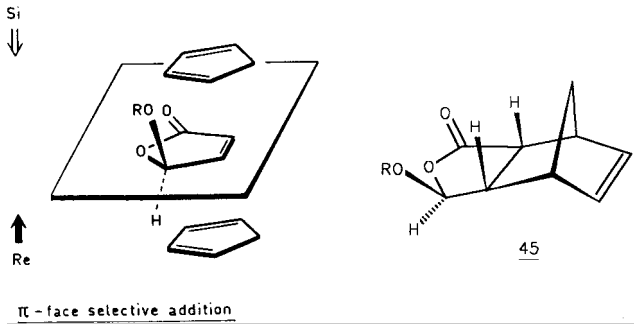
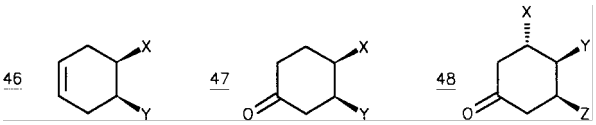
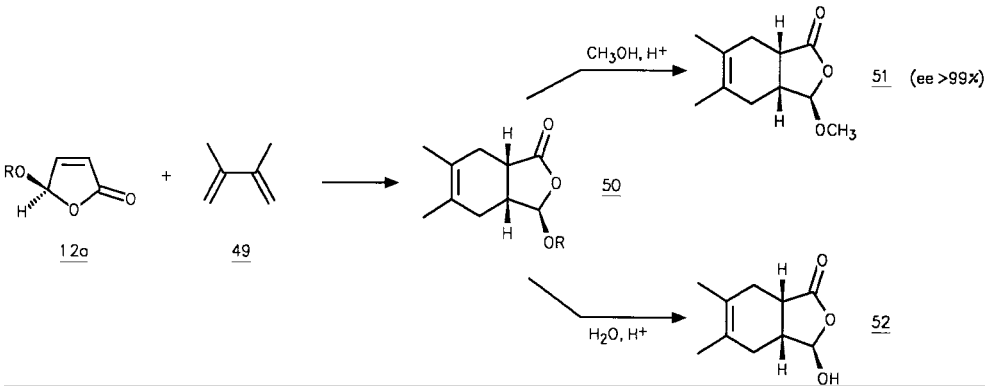


FIG. 1.

An inherent problem of many chiral dienophiles is their conformational flexibility leading to lower selectivity; a problem which can be circumvented in several cases using additional Lewis acid catalysis. As was already observed in the Michael additions the γ-menthyloxy-substituent effectively shields one of the π-faces in the chiral butenolides. The thermal Diels Alder reaction of dienes with (5S)-butenolide 12a is expected to proceed with high endo-selectivity and re-face diastereoselectivity (see Figure 1). In conformity herewith we could isolate adduct 45 in 90% yield as a single (endo-)isomer after heating 12a with excess cyclopentadiene in toluene for 4.5 hours. γ-Menthyloxy-butenolides 12a and 13a 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** 46 and **-cyclohexanones** 47 - is readily achieved but also the formation of trisubstituted derivatives 48 is feasible.



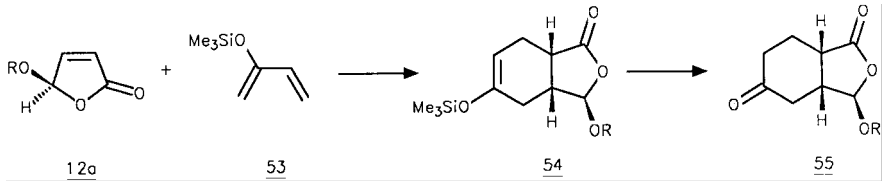
Cycloaddition of 2,3-dimethylbutadiene 49 for instance provided enantiomerically pure lactone-annulated cyclohexene 50 (Scheme 14).[19]



SCHEME 14.

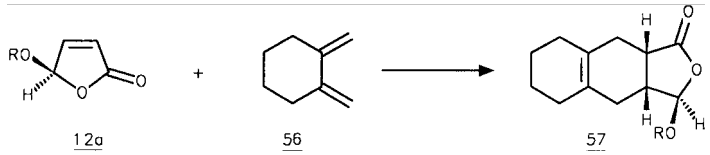
Solvolysis in methanol or hydrolysis, under mild conditions resulted in lactones 51 and 52 respectively with enantiomeric excesses >99% whereas the auxiliary l-menthol was recovered.[20]

Employing the highly reactive 2-trimethylsilyloxy-substituted butadiene 53 complete regio- and diastereocontrol was observed (Scheme 15).[21] Treatment of cycloadduct 54 with tetrabutylammonium fluoride provided lactone 55 as a single enantiomer.



SCHEME 15.

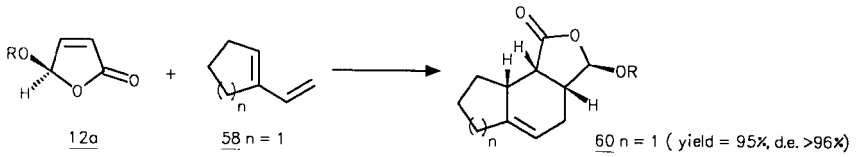
In an effort to prepare optically active **decalines** and **hydro indanes** the Diels Alder reactions of γ-alkoxybutenolides to exocyclic dienes and vinylcycloalkenes were studied. A typical example is the asymmetric cycloaddition of 1,2-bis(methylene) cyclohexane (56) resulting in cis 2,3-disubstituted-9,10-dehydro-decaline 57 as a single enantiomer.



12a 56 57

SCHEME 16.

A completely regio-, endo- and diastereo-selective route to 1,2-disubstituted 5,6- (60) and 6,6-membered (61) ring systems is based on the Diels Alder reactions of 12a (and 13a) to 1-vinylcyclopentene (58) and 1-vinylcyclohexene (59).



12a

58 n = 1

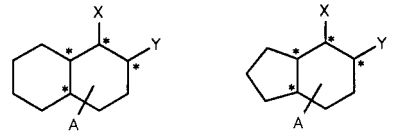
59 n = 2

60 n = 1 (yield = 95%, d.e. >96%)

61 n = 2 (yield = 70%, d.e. >96%)

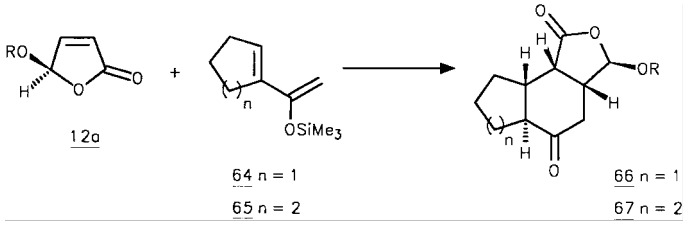
SCHEME 17.

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.



62 63

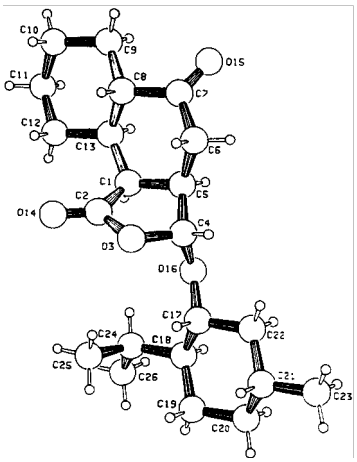
As our approach to the decaline and hydroindane skeletons is based on intermolecular cycloadditions with 1-ethenyl-cycloalkenes it might be possible to furnish, in a single operation enantiomerically pure decalines 62 and indanes 63 with up to four new stereogenic centers. The feasibility of this approach was confirmed using for instance 1-(1-trimethylsilyloxyethenyl)-cycloalkenes 64 and 65 (Scheme 18). Reaction of dienes 64 and 65 followed by in situ desilylation of the resulting adducts with CsF in wet acetonitrile at -80°C afforded enantiomerically pure 66 and 67 respectively. 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 18.

The relative and absolute configuration was established by X-ray analysis i.e. structure 67 of the Diels Alder products of 65 and 12a.

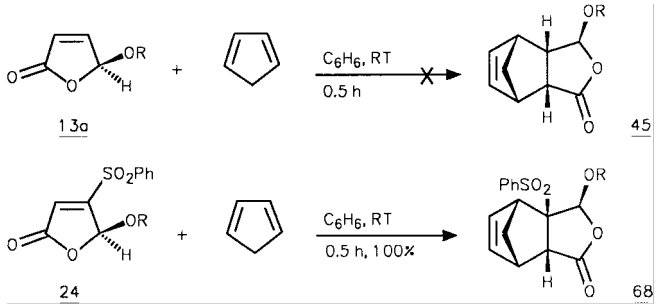
X-ray of compound 67



It should be emphasized that, using the asymmetric cycloaddition strategy given here, a large variety of multifunctional building blocks for natural product synthesis are readily available in enantiomerically pure form.

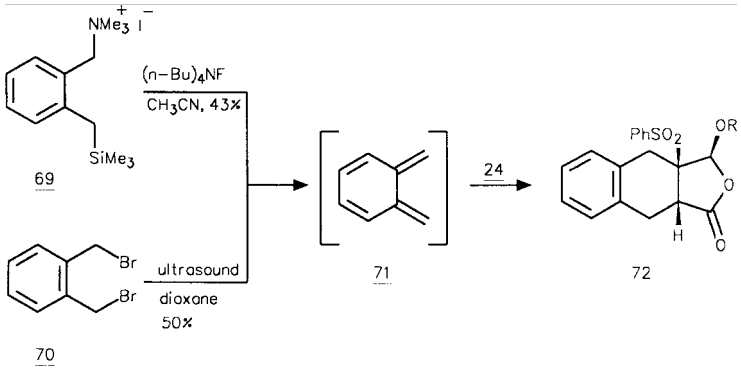
As already mentioned we had found that in some cases the reactivity of butenolides 12a and 13a was not high enough to be synthetically useful. Therefore we developed 5-alkoxy-4-(phenylsulfonyl)-2(5H)-furanones 24 (*vide supra*) as a new class of enantiomerically pure dienophiles. The reactivity of these compounds was studied by the Diels Alder reaction with cyclopentadiene. Both (5S)-5-(d-menthyloxy)-2(5H)-furanone (13a) and (5S)-5-(d-menthyloxy)-4-(phenylsulfonyl)-2(5H)-furanone (24) were reacted with cyclopentadiene for 0.5 h at RT in benzene (Scheme 19).

In the case of 24 complete conversion was observed (92% isolated yield) whereas with 13a only the starting materials were recovered. Product 68, obtained is a single isomer, most likely is the endo-adduct. This simple experiment clearly demonstrates that the introduction of a sulfonyl substituent enhances the reactivity in Diels Alder reactions considerably. Reaction with 2,3-dimethyl-1,3-butadiene afforded the corresponding cycloadduct in 70% yield, again as a single diastereoisomer.



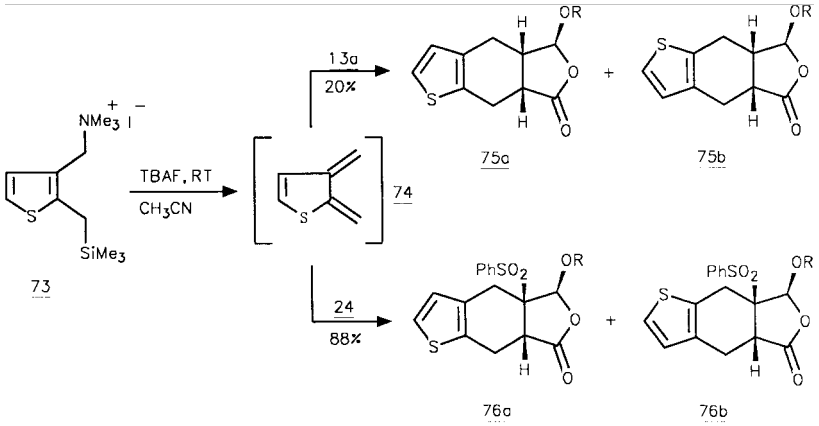
SCHEME 19.

Further support for the increased reactivity of 24 compared to 13a was found in the trapping experiments of the highly reactive dienes *o*-xylylene (71) and its heterocyclic analog 2,3-dimethylene-2,3-dihydrothiophene (73). No product was isolated when furanone 13a was reacted with *o*-xylylene. However, reaction of sulfone substituted furanone 24 with *o*-xylylene (71), generated according to the procedure of Saegusa and coworkers[22] or Boudjouk and Han,[23] afforded the expected cycloadduct in 43% and 50% respectively (Scheme 20). In both cases a single diastereoisomer was isolated.



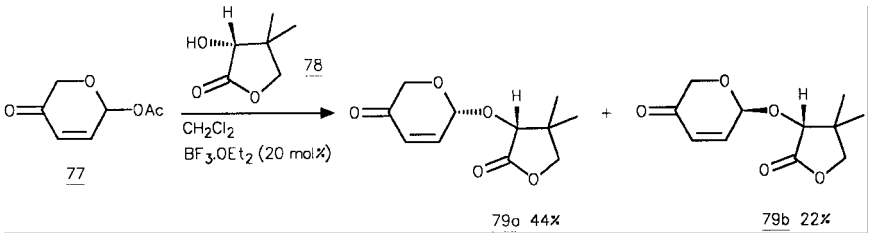
SCHEME 20.

The same dramatic difference in reactivity was observed in the reaction of furanones 13a and 24 in the reaction with 2,3-dimethyl-2,3-dihydrothiophene (74).[24] Reaction of diene 74 with furanone 13a predominantly gave dimeric products of 74, in addition to unreacted furanone. However, formation of diene 74 in the presence of 24 resulted in the formation of cycloadducts 76a and 76b in 88% isolated yield as a mixture of regioisomers in a 1:1 ratio.



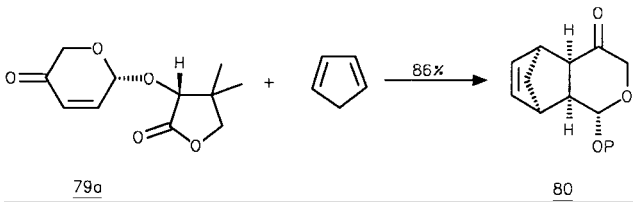
SCHEME 21.

Following the highly successful use of enantiomerically pure furanones 12a and 13a in various diastereoselective reactions, the related pyranone 79a was investigated as a chiral dienophile and Michael acceptor.[25] The coupling of 6-acetoxy-pyranone 77 with a chiral alcohol is promoted by the use of boron trifluoride etherate as Lewis acid. Of the various chiral alcohols tested (e.g. l-menthol, l-borneol) it appeared that d-pantolactone (78) was the only one which gave a diastereomeric mixture that was readily separated using chromatography (yield 79a 44%, 79b 22%) (Scheme 22). The major isomer was assigned the 6R-configuration by means of X-ray analysis.



SCHEME 22.

In asymmetric Diels Alder reactions of 79a nearly complete diastereoface selective additions take place. With cyclopentadiene only the endo-product 80, resulting from a trans-diastereoselective addition with respect to the 6-alkoxy substituent, was formed (Scheme 23). With butadiene and 2,3-dimethylbutadiene the cis/trans selectivity dropped to 10/90.

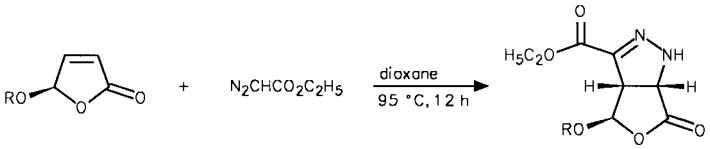


SCHEME 23.

In Michael additions with p-*t*-butyl-thiophenol and nitropropane comparable high selectivities were found (0/100 and 5/95 respectively).

These results show that the alkoxysubstituent at C6 results in a very effective π-face shielding of 79a although somewhat less when compared to 12a and 13a.

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. A complete regioselective addition of diazomethane to butenolide 12a was found.[26] However, in this reaction the π-face selectivity is very poor (trans/cis 60/40). The addition of ethyl diazoacetate proceeds with complete regio- and diastereofacial control to yield enantiomerically pure 81 (Scheme 23).

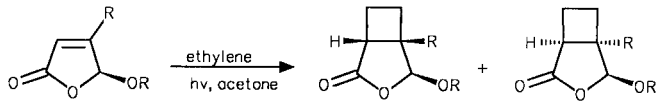


12a 81

SCHEME 24.

It must be noted that isomerization to the 2-pyrazoline structure has taken place. Also in the nitrone- and nitrileoxide-additions excellent stereocontrol is exerted by the menthyloxy substituent at C5 of 12a. These asymmetric 1,3-dipolar cycloadditions show that carbon, oxygen and nitrogen functionalities are readily introduced into the α- and β-positions of the lactone moiety. In this way useful precursors for natural product synthesis are accessible.

The [2 + 2] cycloaddition reactions with (5S)-5-(d-menthyloxy)-2(5H)-furanone (13a) and (5S)-5-(d-menthyloxy)4-methyl-2(5H)-furanone (82) were investigated by Scharf and coworkers.[27] Reaction of furanone 13a with ethylene afforded in high yield disubstituted cyclobutanes 83a and 83b but only with moderate diastereoselectivity. The maximum d.e. obtained in this reaction was 47%. Methylsubstituted furanone 82 was quantitatively converted into a diastereomeric mixture of 84a and 84b in the same way. This reaction takes place with a very low diastereoselectivity of only 9%. But the diastereomeric cyclobutanes can easily be separated by chromatography. In this way both enantiomers of grandisol were accessible (Scheme 24).[28]



13a (R = H)
82 (R = CH_3)

83a (R = H)
84a (R = CH_3)

83b (R = H)
84b (R = CH_3)

SCHEME 25.

CONCLUSIONS

In this paper we have shown that both enantiomers of 5-menthyloxy-2(5H)-furanone are readily available in enantiomerically pure form, starting from furfural and l-menthol. Because of the short synthetic route multigram quantities are readily available. Several substituted furanones like 3-methyl-, 4-methyl- and 4-(phenylsulfonyl)-5-menthyloxy-2(5H)-furanone are also readily prepared in enantiomerically pure form. These furanones have proven to be very versatile synthons with many applications in organic synthesis. During the last two years several papers concerning the synthesis of natural products, using

5-menthyloxy-2(5H)-furanone as chiral synthon, have appeared in literature. Michael additions and cycloadditions take place with high selectivity and complete trans addition with respect to the menthyloxy substituent is found. While in 1,3-dipolar cycloaddition reactions comparable high selectivities were found, only very moderate π-face selectivities were observed in the [2 + 2] cycloadditions with 5-menthyloxy-2(5H)-furanone.

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