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A New Route to Enantiomerically Pure 4,4-Disubstituted Cyclohex-2-en-1-ones: Asymmetric Synthesis of (+)-Mesembrine

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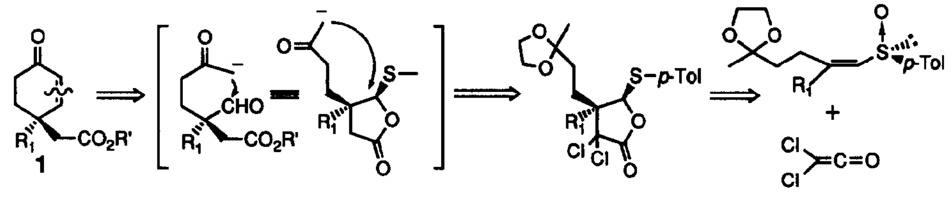
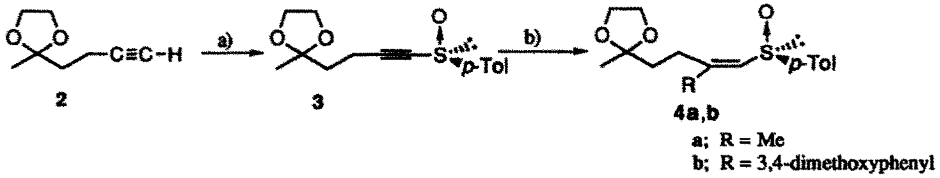
Abstract: Enantiomerically pure β,β-disubstituted vinyl sulfoxides undergo cycloaddition with dichloroketene to give β,β-disubstituted γ-lactones which are transformed into synthetically important 4,4-disubstituted cyclohex-2-enones in optically pure form. The present method is applied to the synthesis of enantiomerically pure (+)-mesembrine.

4,4-Disubstituted cyclohex-2-enones are useful intermediates in the synthesis of some natural products such as mesembrine or trichodermin.1) However, few reports of their preparation in optically pure form have been reported.2) Here we report the asymmetric synthesis of 4,4-disubstituted cyclohex-2-enones (**1**), based on the cycloaddition reaction between enantiomerically pure β,β-disubstituted vinyl sulfoxides with dichloroketene.

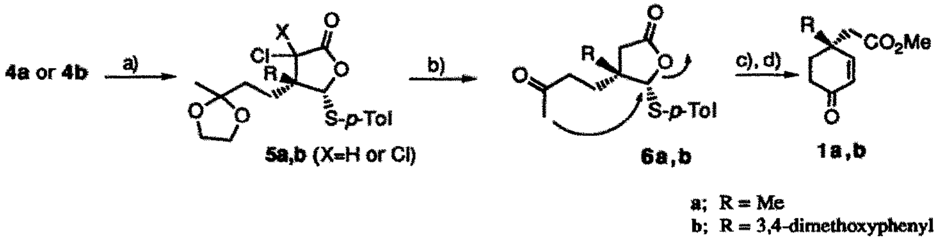
The reaction (additive Pummerer rearrangement) of vinyl sulfoxides with dichloroketene, originally developed by Marino,3) is a remarkably effective method for the preparation of variously substituted γ-lactones. Subsequent reports from some groups,4) including us,5) have shown that the chiral version of this method using enantiomerically pure vinyl sulfoxides leads to optically active γ-lactones in enantiomerically pure form. This method has proved to be quite effective for the preparation of both enantiomers of β-substituted γ-lactones5) since *E*- or Z-alkenyl sulfoxides are readily available from the same starting acetylenic sulfoxides via the stereoselective reduction.6) On the basis of our preliminary results, β,β-disubstituted vinyl sulfoxides were expected to be employed for the construction of chiral quaternary carbon centers. Furthermore, one advantage of the present strategy lies in the possibility of employing an appropriate β-side chain having an acetyl moiety to construct chiral 4,4-disubstituted cyclohex-2-enones via the intramolecular Aldol-type condensation with the γ-position (synthetically equivalent to an aldehyde) of the γ-lactone products, as shown in our retrosynthetic analysis (Scheme 1).

Scheme 1





Scheme 2. a) EtMgBr/Et_2O, (S_S)-(-)-menthyl *p*-toluenesulfinate/toluene; b) RCu/THF, R=Me for **4a**; R=3,4-$(MeO)_2C_6H_3Cu$ for **4b**.

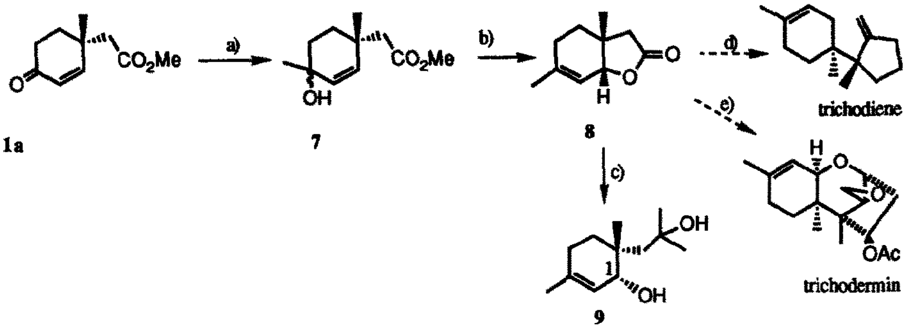


Scheme 3. a) Cl_3CCOCl, Zn-Cu/THF, 0 °C; b) Zn/AcOH, 0 °C and then AcOH/H_2O, 60 °C for 2 h; c) K_2CO_3/MeOH; d) CH_2N_2.

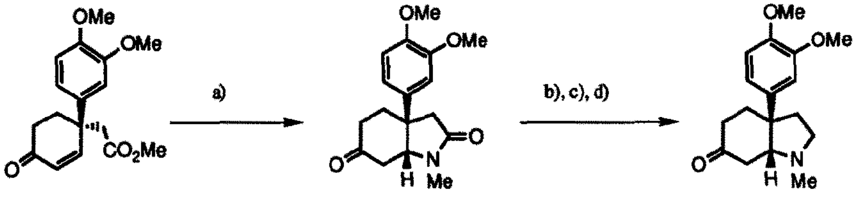
Our synthesis began with acetylenic sulfoxide (**3**), prepared from the known acetylene (**2**)[7] and (S_S)-(-)-menthyl *p*-toluenesulfinate as described previously[6] (Scheme 2). Conjugate addition[6] of **3** with MeCu or 3,4-$(MeO)_2C_6H_3Cu$[8] proceeded smoothly to give the corresponding vinyl sulfoxides **4a** (82%) and **4b** (73%), respectively.

Cycloaddition reaction of **4a** with dichloroketene was carried out by slow addition of a THF solution of trichloroacetyl chloride (3 equiv) to a THF solution of **4a** containing freshly prepared Zn-Cu (10 equiv) at 0 °C, furnishing a mixture of dichloro and monochloro lactones (**5a**). Without separation, the products were subjected to reductive dechlorination with Zn in acetic acid (r.t. for 1 h and then, after adding of H_2O, heated at 60 °C for 2 h) followed by concomitant deacetalization led to the desired lactone product **6a**, in 64% overall yield. When the cycloaddition reaction was conducted at lower temperature (-78 ~ -20 °C) previously employed[5] for mono-substituted vinyl sulfoxides, the yield dropped down and the main product was the reduced vinyl sulfide.

Intramolecular Aldol-type condensation between the acetyl moiety and the lactone γ-position in **5a** could be accomplished using usual alkaline conditions (K_2CO_3 in MeOH). Under the conditions, the concomitant desulfenylation furnished directly the enone carboxylic acid which was, after esterification with CH_2N_2, isolated as the corresponding enone ester (+)-**1a** ($[\alpha]_D^{23}$ +4.31 (*c* 1.72, $CHCl_3$)) in 82% yield. Following the procedure by Colvin and Raphael,[1d] (+)-**1a** was treated with 1 equiv MeLi to give a diastereomeric mixture of the alcohol (**7**), which was, in turn, transformed into the *cis*-bicyclolactone (**8**) in 61% from **1a** (Scheme 4). Establishment of the absolute configuration and the optical purity of the diol (**9**) derived from **8** led to the conclusion that (+)-**1a** was to be *R* and >98% ee.[9] Since trichodiene and trichodermin have been synthesized using the racemic **8**,[1d,10] the present result means the formal syntheses of these natural products.



Scheme 4 a) 1 equiv. MeLi; b) aq.NaOH and then H$^+$; c) excess MeLi; d) ref. 10; e) ref. 1d.



1b 10 11

Scheme 5 a) $MeNH_2$/THF; b)  PTS; c) $LiAlH_4$/THF; d)H$^+$ and then NH_4OH.

In a similar way, treatment of **4b** with dichloroketene afforded the lactone **5b**, which was followed by reductive dechlorination and deacetalization, producing the γ-tolylthio-γ-lactone **6b** in 47% overall yield. The subsequent conversion of **6b** to the key intermediate 4,4-disubstituted cyclohexenone **1b** was again effected by base-catalyzed cycloaldolization and esterification with diazomethane, **1b**: (65% overall yield); ($[\alpha]_D{}^{23}$ +47.5 (*c* 0.237, $CHCl_3$)).

The asymmetric synthesis of mesembrine (**11**) from **1b** was carried out using well established literature method.[1c,11] Heating of **1b** in THF containing excess $MeNH_2$ yielded the keto lactam (**10**) ($[\alpha]_D{}^{23}$ +55.6 (*c* 0.345, $CHCl_3$)) (83%). After protection of the carbonyl moiety, reduction of the amide with $LiAlH_4$, followed by deprotection gave (+)-mesembrine in 79% overall yield from **10**. Comparison of the specific rotation value with that of the literature establishes the absolute configuration and the optical purity of the synthesized mesembrine [$[\alpha]_D{}^{23}$ +60.0 (*c* 0.164, MeOH)] [lit.:$[\alpha]_D$ -55.4 (MeOH)[12a);$[\alpha]_D$ -59.0 (MeOH)[12b) for natural mesembrine]. Accordingly, the absolute stereochemistry of the cycloadducts between β,β-disubstituted vinyl sulfoxides and dichloroketene has been established as depicted in Scheme 3. Although not executed, it is anticipated that the use of commercially available (R_S)-(+)-menthyl *p*-toluenesulfinate should lead to natural (-)-mesembrine in this sequence.

In summary, we have shown that enantiomerically pure β,β-disubstituted vinyl sulfoxides undergo highly stereoselective cycloaddition with dichloroketene to give enantiomerically pure β,β-disubstituted γ-tolylthio-γ-lactones. Furthermore, the above results demonstrate the utility of the γ-tolylthioγ-lactones as chiral precursors to synthetically important 4,4-disubstituted cyclohexenones in high enantiomeric purity.

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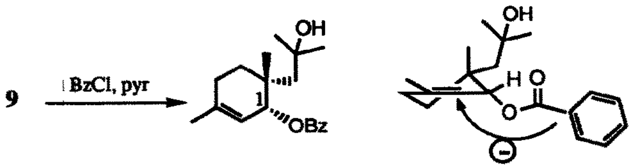
9. The absolute configuration and the optical purity of **9** were determined as follows. The CD spectrum of mono-benzoate from **9** shows the first negative Cotton effect (229.2 nm, Δε -8.16). Application of the CD exciton chirality method to the allylic benzoate system established the absolute configuration of the position 1 to be *R* (Harada, N; Nakanishi, K. *Circular Dichroic Spectroscopy - Exciton Coupling in Organic Stereochemistry-* ; University Science Books: California, U.S.A., 1983; pp. 260-273). The enantiomeric excess was determined to be >98% from the ^{1}H NMR of the MTPA esters of **9** (250 MHz, δ 3.49 and 3.57 for methoxy methyl signals; δ 5.52 and 5.63 for vinylic proton signals).



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