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A convergent asymmetric synthesis of γ-butenolides

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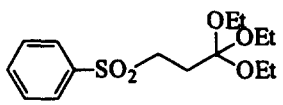
Abstract

Addition of aldehydes to the new enantiomerically pure lithiated sulfoxide **4** yielded γ-butenolides of high enantiomeric purities after elimination of phenylsulfinic acid. The reaction with ketones was less stereoselective.

Keywords: sulfoxides; γ-butenolides; annulation; asymmetric synthesis.

Enantiomerically pure γ-substituted α,β-unsaturated γ-lactones (γ-butenolides) are very useful building blocks for the synthesis of natural products and biologically active compounds. They have been prepared by enzymatic resolution,[1] by transformation of enantiomerically pure natural products[2] or by asymmetric synthesis using microbial[3] or chiral reagents.[4] In a continuing program aiming at the development of new 1,3-dipole equivalents for [3+2] annulation reactions, we had developed a connective synthesis of γ-butenolides based on the cyclocondensation of reagent **1** with aldehydes and ketones (Scheme 1).[5] A chiral homoenolate reagent **2** has been reported by the group of Bravo.[6] However, the addition of the dianion of **2** to aldehydes followed by lactonisation and elimination of *p*-tolylsulfinic acid gave only poor facial selectivities (ca. 20%). The chiral sulfonamide **3** seemed to us a more promising reagent since we had shown that the lithio derivative of **3** added to the C=C bond of cyclic enones with high facial selectivity.[7] However, in preliminary experiments, we found that reagent **3** could not be used for the synthesis of γ-butenolides as a result of a base-catalysed epimerisation of the newly formed stereogenic centre during the elimination step.[8]



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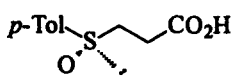

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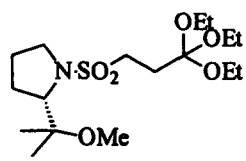

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Scheme 1.

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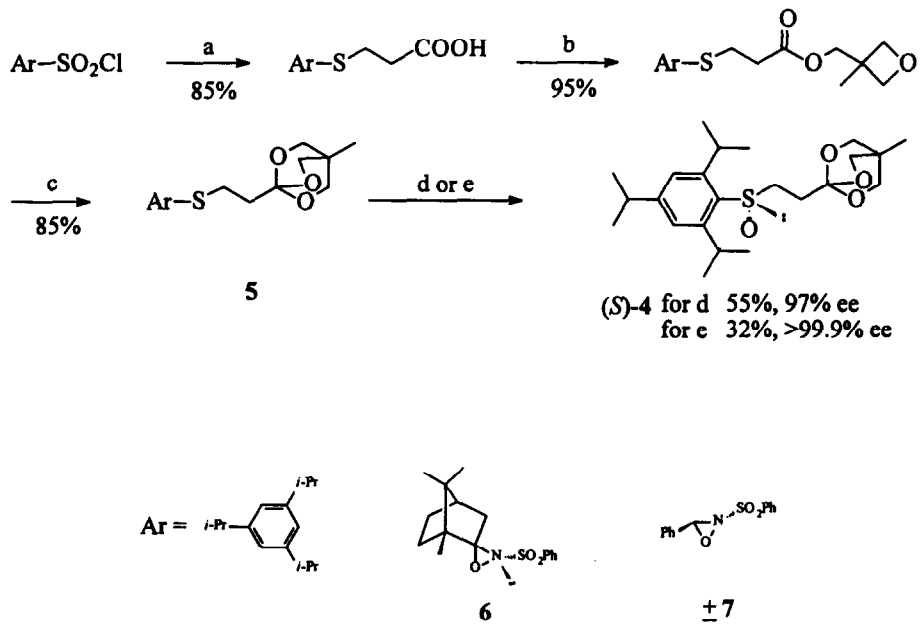
These observations led us to design a new reagent **4** which was expected to fulfil the following requirements: (a) to be readily available in enantiomerically pure form; (b) to ensure a high facial selectivity in the addition to prochiral carbonyl compounds; (c) to allow the generation of the double bond under non-racemising conditions. The bulky 2,4,6-triisopropylphenyl group was selected to guarantee a high facial discrimination in both the asymmetric oxidation of the sulfide precursor and the reaction of the resulting sulfoxide to the carbonyl group. Also, we expected that the elimination of phenylsulfenic acid would occur under very mild, non-racemising conditions.

The sulfide **5** which is the direct precursor of reagent **4** was readily prepared by the sequence outlined in Scheme 2.

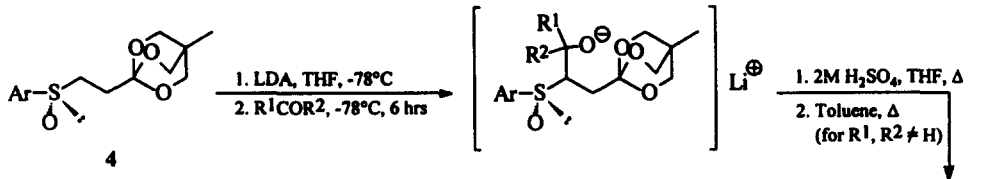


Scheme 2. Reagents and conditions: (a) $LiAlH_4$, Et_2O then methyl acrylate (3 equiv.), Et_3N (0.05%) in MeOH followed by LiOH in THF:H_2O (6:4); (b) *N,N*-carbonyldiimidazole (1.07 equiv.), CH_2Cl_2 then 3-methyl-3-oxetanemethanol (1.2 equiv.); (c) $BF_3.Et_2O$ (0.25 equiv.), CH_2Cl_2 ; (d) **6**, $(CH_2)_2Cl_2$, 6 days; (e) **7**[11] (1 equiv.), CH_2Cl_2 (85%) followed by resolution on HPLC

We choose the bicyclic orthoester group described by Corey et al.[9] for its greater stability to protic conditions and its easy preparation from carboxylic acid. The sulfoxide (*S*)-**4** was first prepared by asymmetric oxidation of **5** under neutral conditions using Davis' oxaziridine **6**.[10] The reaction was slow but gave a sulfoxide (*S*)-**4** of high enantiomeric purity. Best results were obtained at saturation of the solvent at room temperature. The reaction was complete after 6 days. Recrystallisation of the crude solid residue in THF yielded 55% of (*S*)-**4**, ee ~97%. We also converted sulfide **5** into racemic sulfoxide **4**. Resolution was effected by preparative HPLC on a 20 μm Chiralpac AD column using a 9:1 mixture of hexane:*i*-propanol as eluant. To minimise orthoester hydrolysis, *n*-hexane was dried over anhydrous $MgSO_4$ and HPLC-grade *i*-propanol was used. The separation gave the two enantiomers with ee >99.9% (32% yield for (*S*)-**4**[12] and 30% yield for (*R*)-**4**).

The optically active butenolides could be readily prepared by a one-pot cyclocondensation of enantiomerically pure reagent (*S*)-**4** (ee >99.9%) with aldehydes[13] and ketones (Scheme 3).

The crude product resulting from the addition of the carbonyl compound to the carbanion derived from (*S*)-**4** was quenched with 2 M H_2SO_4. With adducts derived from aldehydes, both cyclisation and elimin-



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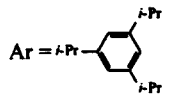
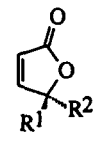
7	R1	R2	Yield %	ee %	Abs. config.
a	Ph	H	79	94	*R*
b	*n*-Pent	H	79	85	*S*
c	*c*-Hex	H	82	89	*S*
d	*i*-Pr	H	78	90	*S*
e	Ph	Me	65	32	*R*
f	*n*-But	Me	95	29	*S*





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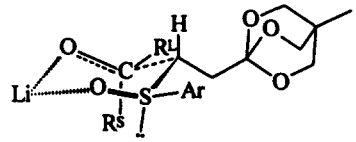
Scheme 3.

ation reactions were complete after a few hours in refluxing THF. With ketones adducts, the elimination step required further heating of the cyclised product in refluxing toluene. Facial selectivities were good for the cyclocondensations with aldehydes. On the other hand, reagent (*S*)-**4** did not discriminate well between the enantiotopic faces of acetophenone or 2-hexanone.

The absolute configuration of the γ-butenolides was assigned by comparison of the sign of their optical rotations with that of authentic samples (compounds **7a**,[6] **b**,[14] **d**[15] and **e**[6]). The configuration of C_5 in compound **7c** and **f** was assumed to be also *S* by analogy. The facial selectivity can be explained by considering a chair-like transition state where a lithium cation coordinates to oxygen atoms of the carbonyl and sulfoxide groups and where all large substituents are equatorial (Scheme 4).



Scheme 4.

We have thus developed an efficient one-pot method for the conversion of aldehydes into γ-butenolides of high enantiomeric purities. The method being highly convergent, it should provide an easy access to a wide variety of enantiomerically pure γ-butenolides which could serve as progenitors for many natural and non-natural biologically active substances.

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12. Sulfoxide **4**: m.p.:145–148°C; $[\alpha]_D^{25}$ −168.79 (*c* 1.48, THF). ^{1}H NMR (500 MHz, $CDCl_3$): 0.78 (s, 3H), 1.23 (d, *J*=6.2, 6H), 1.24 (d, *J*=6.7, 6H), 1.24 (d, *J*=6.8, 6H), 2.00 (ddd, *J*=6, *J*=10.3, *J*=14, 1H), 2.17 (ddd, *J*=5.2, *J*=10.4, *J*=14.1, 1H), 2.87 (hept, *J*=6.8, 1H), 3.03 (ddd, *J*=6.1, *J*=10.4, *J*=13.1, 1H), 3.45 (ddd, *J*=5.2, *J*=10.4, *J*=13.1, 1H), 3.85–4.09 (m, 2H), 3.86 (s, 6H), 7.05 (s_{br}, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 14.3, 23.6, 24.2, 24.4, 27.9, 30.3, 31.4, 34.2, 48.9, 72.7, 108.4, 123, 134.3, 150, 152. IR (cm^{-1}): 3048, 2959, 2879, 1598, 1460, 1398, 1047, 934, 887, 730. MS (CI-Q1MS):157, 209, 203, 234, 252, 393, 409, 437. Anal. calcd for $C_{23}H_{36}O_4S$: C 67.61%, H 8.88%, S 7.85%. Found: C 67.39%, H 9.00%, S 8.10%.
13. Sulfoxide **4** (1 mmol) in solution in THF was added dropwise to a solution of LDA (1.1 equiv.) in THF at −78°C. The reaction was stirred for 1 hour. The carbonyl compound (1.2 equiv.) was then added dropwise and the reaction mixture was stirred for 6 hours. The mixture was quenched by 6 mL of H_2SO_4 2 M, allowed to reach room temperature and then refluxed overnight. Extraction with dichloromethane gave a crude product which was purified by chromatography on silica gel to yield pure butenolides **7**. Enantiomeric purities were determined by GC analysis on a 25 m×0.25 mm (ID) Chrompack CP-Chirasil-DEX-CB column.
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