Pergamon

Tetrahedron Letters 40 (1999) 3071–3074

TETRAHEDRON LETTERS

# Asymmetric Synthesis of *Syn* and *Anti* 1,2-Diols from Diethyl oxalate using the Stereoselective Sulfoxide Directed Reduction of 1,2-Diketone derivatives.

**Guy Solladié*, Gilles Hanquet, Irene Izzo[a] and Robyn Crumbie[b]**

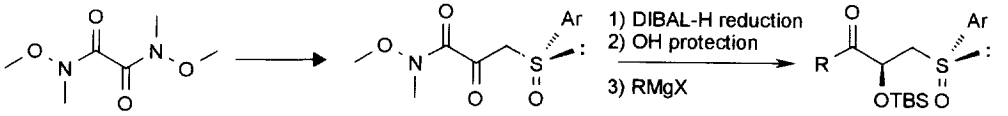
Laboratoire de Stéréochimie associé au CNRS, Université Louis Pasteur, ECPM,

25 Rue Becquerel, 67087-Strasbourg Cedex 2, France.

Received 18 December 1998; accepted 17 February 1999

**Abstract:** A new chiral Wittig reagent, a β-keto-γ-(*S*)-hydroxy-δ-(*R*)-*p*-tolylsulfinyl phosphonate, readily made from ethyl oxalate and stereoselective sulfoxide mediated reduction of the resulting β-ketosulfoxide, was used to prepare enantiomerically pure *syn* and *anti* 1,2-diols. This method was applied to the enantioselective synthesis of two acetogenin derivatives, (-)-(*R,R*)-muricatacin and its epimer (-)-(*R,S*)-epi-muricatacin. 

We previously reported[1] a straightforward synthesis of enantiomerically pure *syn* and *anti* 1,2-diols from the di-N-methyl-N-methoxyamide of oxalic acid **1** *via* the β-ketosulfoxide **2** which was stereoselectively reduced to the corresponding β-hydroxysulfoxide. Then the Weinreb amide was converted using Grignard reagents into the corresponding ketone **3** which can be stereoselectively reduced to enantiomerically pure *syn* or *anti* 1,2-diols. A major drawback of this method was the very low ketone yield in the case of long chain Grignards[2] (R=$C_{12}H_{25}$, yield between 10 to 25%).




**1** **2** **3**

Scheme 1

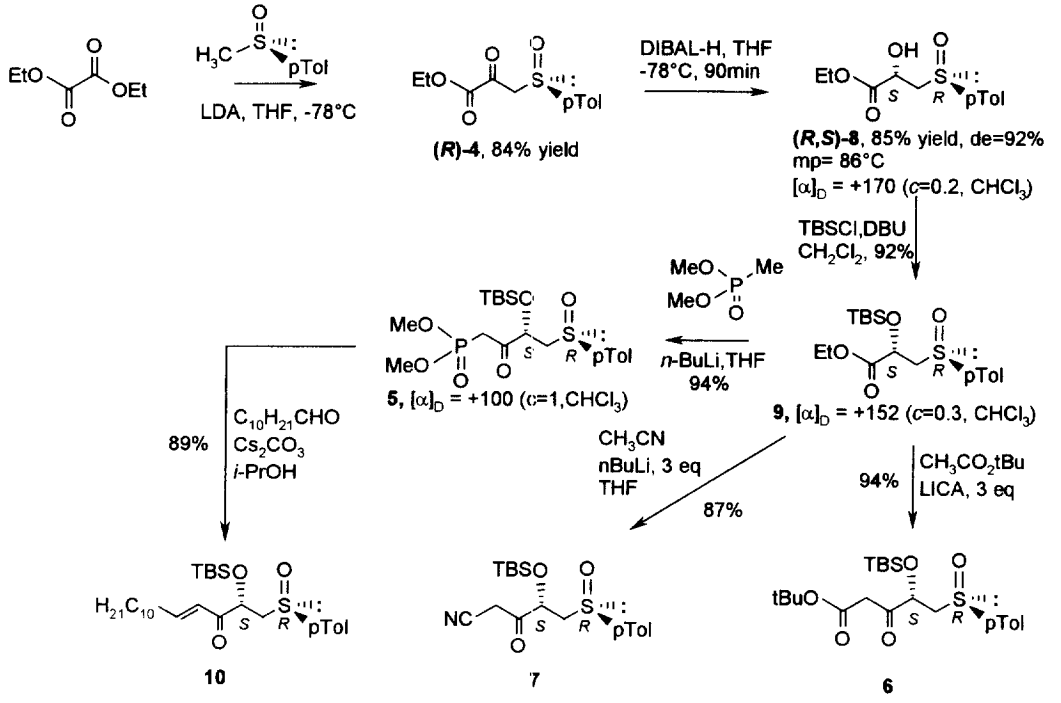
We report now a solution to this problem with the synthesis of the β-hydroxy-γ-ketosulfoxide **10** from diethyl oxalate *via* the α-keto β-sulfinyl ester **4** and the new chiral phoshonate **5** (Scheme 2). We report also the synthesis of the carboxylic and cyano analogues **6** and **7** and the stereoselective sulfoxide mediated reduction of all these compounds (Table I). Application to the synthesis of the natural product (-)-(*R,R*)-muricatacin containing a *syn* (*R,R*)-1,2-diol unit and its epimer (-)-(*R,S*)-epi-muricatacin having an *anti* (*R,S*)-1,2-diol unit confirms the absolute configurations of the 1,2-diols.

Diethyl oxalate reacts smoothly with (+)-(*R*)-methyl-*p*-tolyl sulfoxide anion[3] to give in 84% isolated yield (scheme 2) the β-ketosulfoxide (*R*)-**4**. DIBAL-H reduction of (*R*)-**4** provided the β-hydroxy sulfoxide (*R,S*)-**8** in high *S*-diastereoselectivity (85% isolated yield, d.e= 92%), showing thus that there was no significant effect of the vicinal ester function. A similar result has been also observed with an amide function.[1] The (*S*) configuration of C-2

* Fax : 33 3 88 13 69 49 - e-mail : solladie@chimie.u-strasbg.fr

0040-4039/99/$ - see front matter 
*PII:* S0040-4039(99)00368-8

was confirmed by chemical correlation with ethyl (+)-(*R*) silyloxy lactate described in literature[4] and obtained from **8** by desulfurization with Raney Ni. [$[\alpha]_D$ = + 30 (c=1, $CHCl_3$) ; lit.[4] +31 (c=2, $CHCl_3$)]. The protected β-hydroxysulfoxide (*R,S*)-**9** was quantitatively transformed into the ketophosphonate **5** by reaction with methylphosphonate anion (3 eq). The Wittig reaction of **5** was carried out with cesium carbonate in isopropanol and undecanal according to literature procedure[5] to give the α,β–unsaturated ketone (*R,S*)-**10** in 89% yield.




Scheme 2

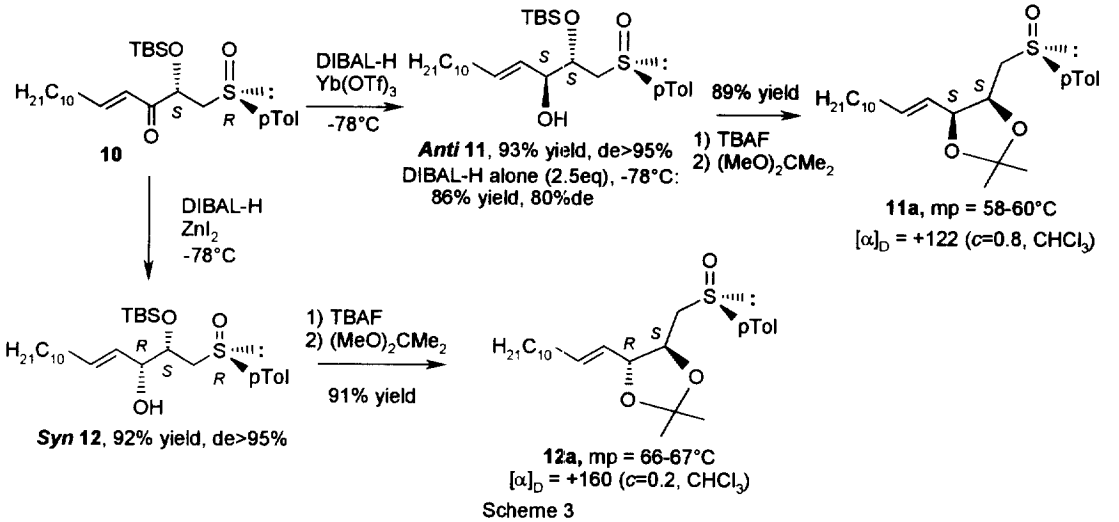
It was also possible to prepare the keto-ester **6** in 94% yield by reaction of **9** with *t*-butyl acetate enolate and the keto-cyanide **7** in 87% yield from **9** and acetonitrile anion.

Table I. Reduction of β-hydroxy-γ-ketosulfoxides.

| β-hydroxy-γ-keto-sulfoxide | Reduction conditions | Isolated yield % | de % | *syn* / *anti*[1] |
|---|---|---|---|---|
| **10** | DIBAL-H, 1h, -78°C | 84[2] | 80 | 10 / 90 |
| | + 1.1 eq of Yb(OTf)$_3$,30min, 78°C | 93 | >95 | 2 / 98 |
| | + 1.1 eq of $ZnI_2$, 45min, -78°C | 92 | 94 | 97 / 3 |
| **6** | DIBAL, 1h, -78°C | 55[3] | >95 | 2 / 98 |
| | + 1.1 eq of $ZnI_2$, 7h, -78°C | 45[4] | 56 | 22 / 78 |
| 7 | DIBAL, 2h, -78°C | 94 | >95 | 2 / 98 |
| | + 1.1 eq of $ZnI_2$, 2h, -78°C | 92 | 20 | 60 / 40 |

1) From $^1$H NMR; the relative configuration was determined from the corresponding acetonides by $^{13}$C NMR, 2) 12% of recovered starting material; 3) 18% of recovered starting material; 4) 43% of recovered starting material.

Following our previous results on the reduction of type **3** compounds,[1] we investigated the diastereoselectivity of the reduction of products **6**, **7** and **10** with DIBAL-H. Reduction of **10** (Table I) gave the *anti* diol **11** in 84% yield and 80% d.e. In presence of 1 eq. of $Yb(OTf)_3$ the yield and diastereoselectivity increased in favor of the *anti* diol, (93% yield and d.e. > 95%) while the *syn* diol **12** was obtained in presence of 1 eq. of $ZnI_2$ (92% yield and d.e.> 94%) in agreement with our previous results.[1] At this stage of the synthesis the absolute configuration of the created chiral center during the DIBAL-H reduction was assigned by comparison with our previous results.[1] After removing (Scheme 3) the protecting group in **11** and **12** with TBAF in THF and acetonide formation with dimethoxypropane in presence of PPTS, the relative configuration of the diol-acetonides **11a** and **12a** was determined by $^{13}C$ NMR.[1,6] That will be confirmed at the end of the synthesis by comparison with the known natural product. DIBAL-H reduction of the keto ester **6** gave a high d.e. (> 95%) in favor of the *anti* diol but a low yield (55%). In presence of $Yb(OTf)_3$ no reduction occurred. With 1 eq of $ZnI_2$, yield and diastereoselectivity were moderate ( 45% yield and 56% de) still in favor of the *anti* diol. In the case of the keto cyanide 7, DIBAL-H reduction is highly stereoselective (> 95%) giving the *anti* diol in high yield (94%). However in presence of $ZnI_2$ the diastereoselectivity was very low.

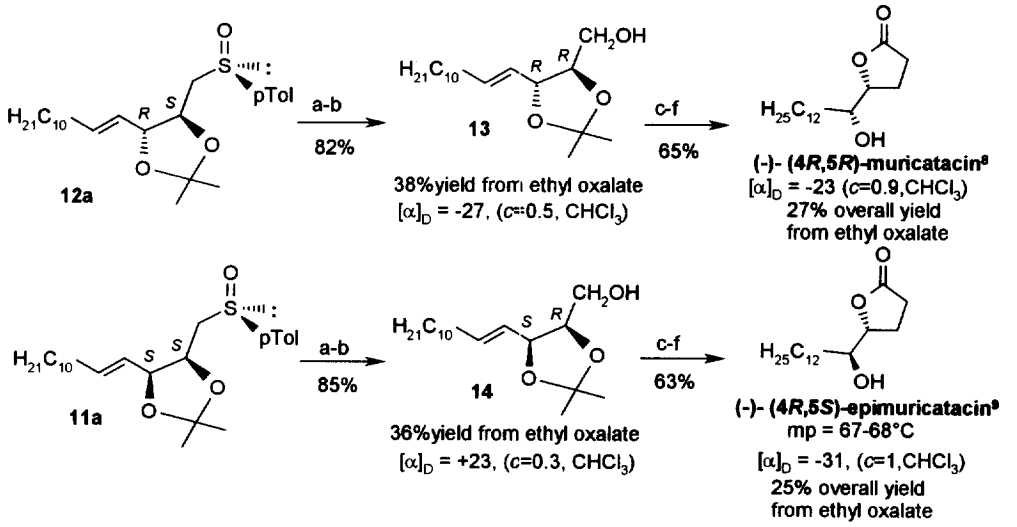



Scheme 3

(*R,R*) muricatacin, isolated from the seeds of *Annona muricata* is an acetogenin derivative with some cytotoxic activity on human tumors.[7] A few syntheses of this compound are already published.[8] The (4*S*,5*R*) *epi*-muricatacin which is not contained in the natural extract has been prepared and described a few years ago.[9] The acetonides **11a** and **12a** are good precursors of (*R,S*)-epimuricatacin and (*R,R*)-muricatacin (Scheme 4).

Pummerer rearrangement of the acetonides **11a** and **12a** and reduction with $LiAlH_4$ of the resulting intermediates gave the primary alcohols **13** and **14** in 82% and 85% overall yield. Finally Swern oxidation, Wittig homologation with triphenyphosphonium methylacetate under standard conditions, double-bond reduction with palladium in ethanol, and acetonide cleavage and lactonisation under acidic conditions gave (-)-(*R,R*)-muricatacin

and (*R,S*)-*epi*-muricatacin in 65% and 63% yields from **13** and **14,** respectively. (Scheme 4). The overall yield from diethyl oxalate is respectively 25% and 23% for (-)(*R,R*) muricatacin and (*R,S*) *epi*-muricatacin which show all the known characteristics of the known products,[8a,e,9] a result which confirms the configurations of the chiral centers.




a) $Ac_2O$, b) LAH, c) Swern, d) Wittig, $(Ph_3)P{=}CH\text{-}CO_2Me$, e) $H_2$ / Pd, f) THF / $H_2O$, TsOH,Δ

Scheme 4

In conclusion, DIBAL-H reduction of β-hydroxy-γ-ketosulfoxides is highly stereoselective although in the case of a carboxylate group β to the carbonyl the reduction yield is rather low probably due to the enolization of the ketone. However in presence of zinc iodide the diastereoselectivity is inverted only in the case of an alkenyl, aryl and alkyl substituent.

**References and notes**


a) On leave from the University of Salerno (Italy).

b) On leave from the University of Western Sydney Macarthur (Australia)

1) a) Solladié G, Hanquet, G.; Rolland, C. *Tetrahedron Lett.* **1997,** *38,* 5847-5850; b) Solladié G, Hanquet, G.; Rolland, C. *Tetrahedron Lett.* **1999,** *40,* 177-180.

2) For reaction of long chain Grignard reagents on Weinreb amids see Sharma, R.; Marquez, V.E.; *Org. Prep. Proc.*, Int., **1994**, *26,* 611-615.

3) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis*, **1987**, 173.

4) Solladié, G.; Almario, A. *Tetrahedron Lett.* **1994**, *35*, 1937-1940.

5) Yamanoi, T.; Akiyama, T.; Ishida, E.; Abe, H.; Amemiya, M.; Inazu, T. *Chem. Lett.*, **1989**, 335-336.

6) $^{13}C$ NMR ($CDCl_3$, 50 MHz): **11a** : 14.21 ($CH_3$), 21.51 ($CH_3$), 22.77 ($CH_2$), 25.54 (i-Pr $CH_3$), 28.88 (i-Pr $CH_3$), 29.19-29.78 ($CH_2$), 31.99 ($CH_2$), 31.37 ($CH_2$), 61.26 ($CH_2$-SO), 72.29 (CH-O), 79.04 (CH-O), 108.54 (i-Pr C), 123.56 (arom.CH), 124.16 (vinylic CH), 130.17 (arom. CH), 137.47 (vinylic CH), 141.59 ( arom. C), 141.67 (arom. C); **12a**: 14.24 ($CH_3$), 21.54 ($CH_3$), 22.80 ($CH_2$), 27.20 ( i-Pr $CH_3$), 27.29 (i-Pr $CH_3$), 28.86-29,72 ($CH_2$), 32.01 ($CH_2$), 32.43 ($CH_2$), 61.18 ($CH_2$-SO), 74.83 (CH-O), 82.38 (CH-O), 108.74 (i-Pr C), 123.93 (arom. CH), 125.12 (vinylic CH), 130.16 (arom. CH), 138.53 (vinylic CH), 141.36 (arom. C), 141.80 (arom. C).

7) Rieser, M.J.; Kozlowski, J.F.; Wood K.V.; Mc Laughlin, J.L. *Tetrahedron Lett.* **1991**, *32*, 1137-1140.

8) Previous syntheses : a) Rassu, G. ; Pinna, L. Spanu, P. ; Zanardi, F. ; Battistini, L. ; Casiraghi, G. *J. Org. Chem.* **1997**, *62*, 4513-4517; b) Somfai, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 817-819; c) Bonini, C.; Federici, C.; Rossi, L.; Righi, G. *J. Org. Chem.* **1995**, *60*, 4803-4812; c) Quayle, P.; Rahman, S.; Herbert, J. *Tetrahedron Lett.* **1995**, *36*, 8087-8088; d) Marshall, J.A. ; Welmaker, G.S. *J. Org. Chem.* **1994**, *59*, 4122-4125; e) Marshall, J.A. ; Welmaker, G.S. *Synlett* **1992**, 537-538;.f) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K.B.; Sinha, S.C.; Sinha-Bagchi,A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407-6410; g) Scholz, G.; Tochtermann, W. *Tetrahedron Lett.* **1991**, *32*, 5535-5538; h) Szlosek, M.S.; Franck, X.; Figadère, B.; Cavé, A. *J. Org. Chem.* **1998**, *63*, 5169-5172; i) Sanière, M.; Charvet, I.; Le Merrer, Y.; Depezay, J.C. *Tetrahedron* **1995**, *51*, 1653-1662.

9) a) Saïah, M.; Bessades, M. ;Antonakis, K. *Tetrahedron Lett.* **1993**, *34*, 1597-1598; b) . Figadère, B.; Harmange, J.-C.; Laurens, A.; Cavé, A. *Tetrahedron Lett.* **1991**, *32*, 7539-7542.